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# Synthesis and structure activity relationships of cyanopyridone based anti-tuberculosis agents

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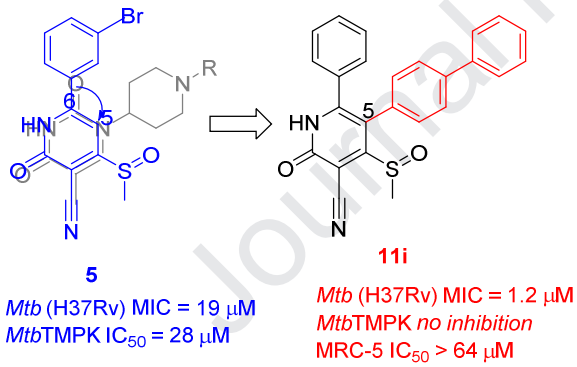
## Abstract

*Mycobacterium tuberculosis*, the causative agent of tuberculosis, relies on thymidylate kinase (*Mtb*TMPK) for the synthesis of thymidine triphosphates and thus also DNA synthesis. Therefore, this enzyme constitutes a potential Achilles heel of the pathogen. Based on a previously reported *Mtb*TMPK 6-aryl-substituted pyridine inhibitor and guided by two co-crystal structures of *Mtb*TMPK with pyridone- and thymine-based inhibitors, we report the synthesis of a series of aryl-shifted cyanopyridone analogues. These compounds generally lacked significant *Mtb*TMPK inhibitory potency, but some analogues did exhibit promising antitubercular activity. Analogue **11i** demonstrated a 10-fold increased antitubercular activity (MIC H37Rv, 1.2 μM) compared to literature compound **5**. Many analogues with whole-cell antimycobacterial activity were devoid of significant cytotoxicity.


## Graphical abstract




**5**

*Mtb* (H37Rv) MIC = 19 μM
*Mtb*TMPK $IC_{50}$ = 28 μM

**11i**

*Mtb* (H37Rv) MIC = 1.2 μM
*Mtb*TMPK *no inhibition*
MRC-5 $IC_{50}$ > 64 μM

## Introduction

Tuberculosis (TB), a communicable disease caused by the infectious agent *Mycobacterium tuberculosis* (*Mtb*), still ranks as one of the top 10 causes of death worldwide with around 10 million people contracting TB every year.[1] Though a 27% reduction of TB-related death rate was achieved since 2000 due to improved control, more than 1.2 million TB deaths were reported in 2018.[1] In particular, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis threatens global efforts to combat TB.[2]

The first-line treatment of TB consists of a 6-month combination regimen, comprised of isoniazid, ethambutol, pyrazinamide and rifampicin, while for resistant TB, the treatment duration is longer and the employed drugs have a narrow therapeutic index, leading to poor patient adherence and high economic burden.[2-4] The newly approved antitubercular drugs bedaquiline,[5] delamanid[6] and pretomanid[7] open new prospects for the cure of MDR TB. Nevertheless, the first bedaquiline-resistant *Mtb* isolate was already observed in 2014,[8] and resistance to delamanid related to the poor bio-activation by mutations of the deazaflavin (F420)-dependent nitroreductase (Ddn) was also reported.[9] Thus, there remains a pressing need for new antitubercular chemical entities.

Thymidylate kinase (TMPK) catalyzes the phosphorylation of thymidine 5'-monophosphate to the corresponding 5'-diphosphate in *Mtb* and is indispensable for *Mtb* growth and survival,[10] earmarking this enzyme as an attractive target to develop inhibitors as potential anti-TB agents. Additionally, several co-crystal structures of *Mtb*TMPK with substrates/inhibitors have been published,[11-14] enabling rational drug design.

Previously reported *Mtb*TMPK inhibitors mainly arose from either substrate modifications[15-18] or derivatisation of the thymine base.[19-21] Nevertheless, none of these derivatives displayed adequate whole-cell activity (Figure 1, analogues **1**-**3**).[18-21]

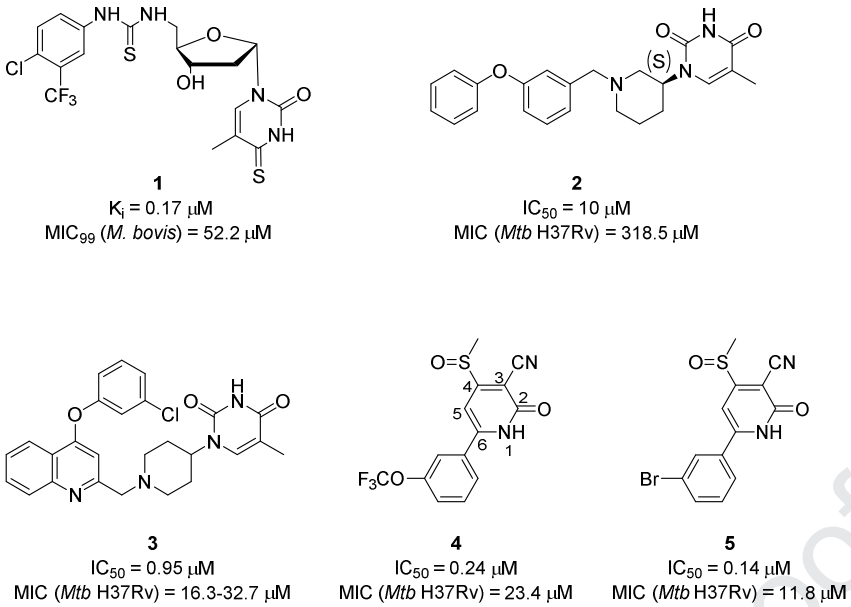



**Figure 1**. Structures of thymidine-like and non-nucleoside *Mtb*TMPK inhibitors.

In 2015 AstraZeneca reported on a series of non-nucleoside *Mtb*TMPK inhibitors featuring a cyanopyridone moiety as a potential thymine isostere.[22] Their work resulted in the identification of several analogues with reasonable antitubercular activity (Figure 1, **4** and **5**). Comparison of the co-crystal structure of *Mtb*TMPK with our previously reported inhibitor **2** (PBD: 5NQ5[20]) to that with compound **4** (PDB:4UNQ[22]), shows that the thymine and pyridine rings superimpose in such a way that key interactions with the enzyme are conserved (Figure 2A). This marks the cyanopyridone ring as a suitable thymine bioisostere. Although the phenyl ring of **4** and the substituted piperidine ring of **2** protrude in different directions, the latter fits perfectly in the big groove surrounded by helix α2, α3 and α5 through a bent conformation of the biphenylether tail. This led us to explore a shift of the phenyl ring from the 6 position of the cyanopyridone ring to the 5 position. First, compound **11a**, featuring such aryl shift, was docked into the catalytic pocket of enzyme to gain insight in the putative binding mode (Figure 2B). As expected, the cyanopyridone ring adopts an identical pose to that observed with compound **4**, with the aromatic tail pointing to a different direction, reminiscent of the piperidine ring of compound **2**.

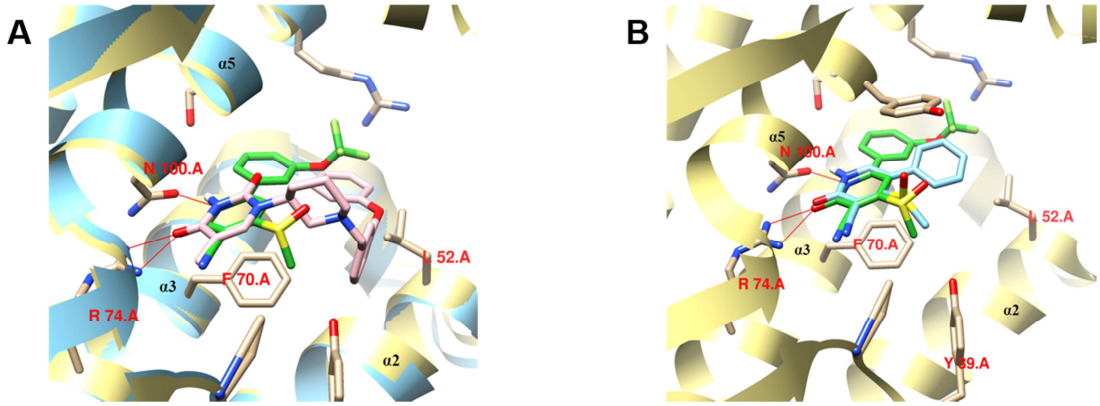



**Figure 2**. A. Structure overlay of compound **2** (PDB 5NQ5) and compound **4** (PDB 4UNQ) in the *Mtb*TMPK active site. *Mtb*TMPK is shown in a blue (PDB 5NQ5) and yellow (PDB 4UNQ) cartoon representation with selected side chains labelled and shown as sticks with carbon atoms colored grey. Ligands are drawn in stick representation with carbon atoms in pink (ligand **2**) and green (ligand **4**), hydrogen-bonding interactions are shown as red lines. B. Structure overlay of compound **4** and docking pose of compound **11a** in the *Mtb*TMPK (PDB 4UNQ) active site. *Mtb*TMPK is shown in a yellow cartoon representation with selected side chains labelled and shown as sticks with carbon atoms colored grey. Ligands are drawn in stick representation with carbon atoms in green (ligand **4**) and blue (ligand **11a**), hydrogen-bonding interactions are shown as red lines.

In this manuscript, we describe our optimization efforts starting from the designed aryl-shifted cyanopyridone analogue **11a**, arriving at compounds with whole cell activity, which surprisingly failed to elicit enzyme inhibitory potency. An overview of the synthesized analogues is presented in Figure 3.

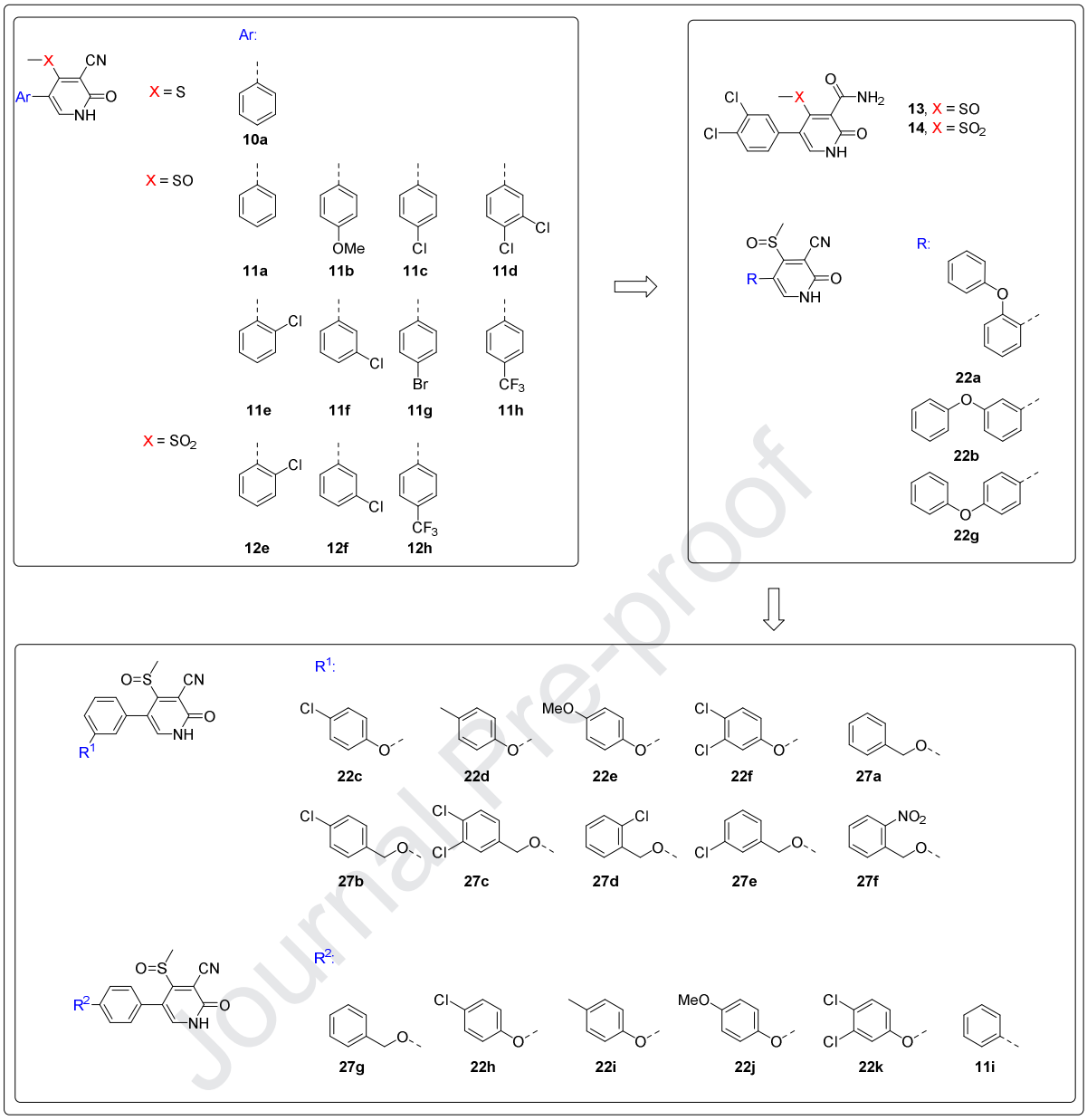
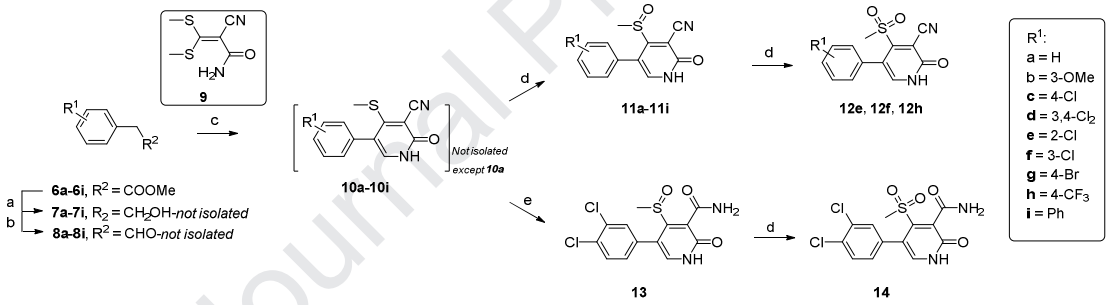



**Figure 3**. An overview of synthesized compounds in this study.

**Chemistry**

To obtain the envisioned 5-aryl-substituted cyanopyridones, commercially available substituted methyl phenylacetates were reduced with $LiAlH_4$[23] and re-oxidized by PCC to the corresponding aldehyde,[24,25] followed by condensation[22] with **9**[26] to give intermediate **10a**-**10i** (Scheme 1). Next, oxidation[27] of the resulting methylthiopyridones with 1 eq. of mCPBA afforded the precipitate sulfoxides, while further oxidation of the resulting sulfoxides with another 1 eq. of mCPBA furnished the sulfone analogues. For the synthesis of sulfoxide **13** and sulfone **14** analogues, intermediate **10d** was first hydrolyzed with aq. sulfuric acid[28] to give the corresponding 3-carboxamide thioether, which was then oxidized by mCPBA to yield the desired analogues.

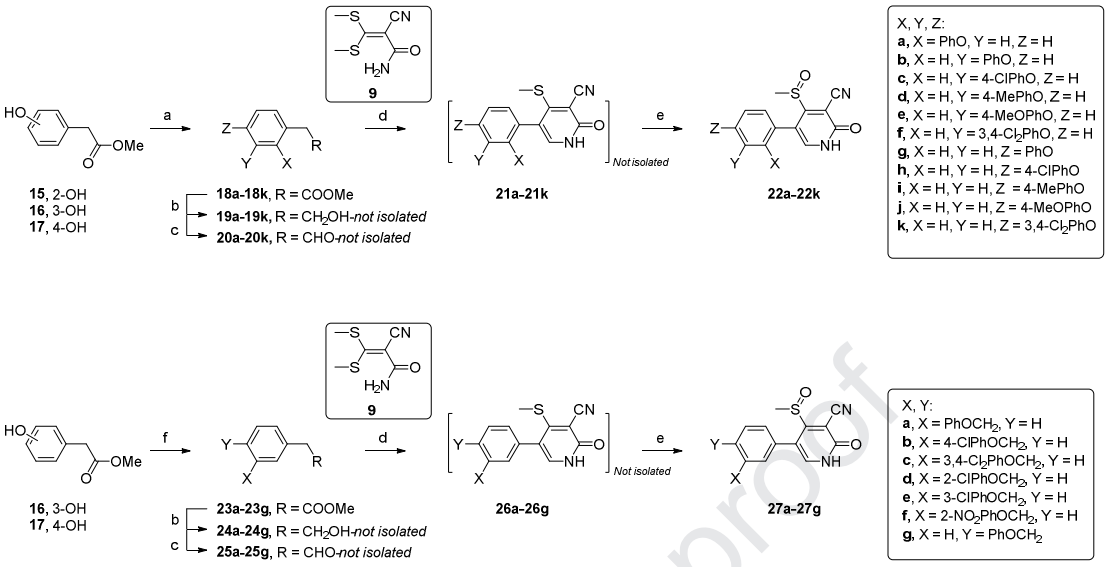
Scheme 1.




**Reagents and conditions**: (a) $LiAlH_4$, THF; (b) PCC, $CH_2Cl_2$; (c) **9**, NaOH, DMSO; (d) mCPBA, THF; (e) (i) con.$H_2SO_4$, 100 □; (ii) mCPBA, THF.

The synthesis of substituted phenoxy- or benzyloxyaryl analogues **22a**-**22k** and **27a**-**27g** was achieved from commercially available hydroxyphenylacetic ester derivatives (Scheme 2). First, the phenolic group of hydroxyphenylacetates was functionalized by either Chan-Lam coupling with boronic acids.[29] Alternatively, it was alkylated with benzyl bromides under basic conditions.[30] Then, reduction of the ester to the corresponding alcohol, followed by re-oxidation resulted in the desired arylacetaldehyde intermediate, which was subsequently condensed with **9** to enable cyanopyridone ring formation. Finally, mCPBA-mediated oxidation afforded analogues **22a**-**22k** and **27a**-**27g**.

Scheme 2




**Reagents and conditions**: (a) substituted phenylboronic acid, pyridine, molecular sieves, $Cu(OAc)_2$, 1,2-dichloroethane; (b) $LiAlH_4$, THF; (c) PCC, $CH_2Cl_2$; (d) **9**, NaOH, DMSO; (e) mCPBA, THF; (f) substituted benzyl bromide, hydroxyphenylacetic ester derivative, $K_2CO_3$, NaI, DMF.

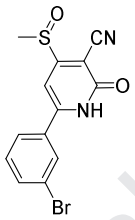
## Biological results

To validate our design strategy, representative analogues **10a**, **11a**, **22a, 22b** and **22g** were evaluated for their capacity to inhibit *Mtb*TMPK activity. As shown in Table 1, methylthiopyridone analogue **10a** was 7-fold less active than reported compound **5**. Surprisingly, the sulfoxide-modified analogues **11a, 22a**, **22b** and **22g** failed to exhibit any enzyme inhibitory potency, contradicting our docking result and the remarkable inhibitory activity observed for several 5,6-disubstituted analogues reported earlier by AstraZeneca.[22] The inconsistency of the experimental results with the *in-silico* model are likely attributable to the 5-phenyl ring, which unlike the 3-functionalized piperidine in **2** is unable to adapt a chair conformation, which favours hydrophobic interactions with the relevant residues in the active site of *Mtb*TMPK (Figure 2A).

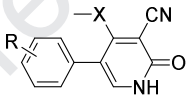
Despite the lack of enzyme inhibitory potency, these compounds do exert significant antimycobacterial activity *in vitro* (Table 1), suggesting that they might interact with another

protein. Methylthiopyridone analogue **10a** did not display *in vitro* antimycobacterial activity, but oxidation to the sulfoxide **11a** resulted in modest activity, comparable to the 6-substitued analogue **5**.[22] Interestingly, the phenoxy analogues of **11a** (**22a**, **22b** and **22g**) retained antimycobacterial activity, regardless of the position of the phenoxy substituent on the phenyl ring. These analogues proved more potent in minimal (GAST/Fe) medium possibly reflecting increased metabolic dependence of the cells on the activity of the putative target under these growth conditions. Importantly, the active compounds **11a, 22a**, **22b** and **22g** did not display severe cytotoxicity with compound **22g** showing selectivity index (SI) over 20 for minimal (GAST/Fe) condition.

Table 1. The *Mtb*TMPK enzymatic activity, antimycobacterial activity (H37Rv) and cytotoxicity against MRC-5 fibroblasts of representative compounds.




**5**




**10a**, **11a**, **22a**, **22b**, **22g**

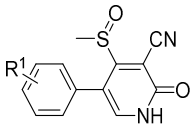
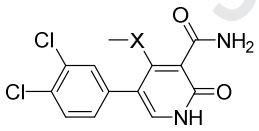
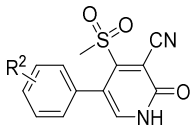
| | | | | *M. tuberculosis* MIC[a] (μM) | | |
|---|---|---|---|---|---|---|
| Comp. | R | X | *Mtb*TMPK $IC_{50}$ (μM) | 7H9/glucose | GAST/Fe | MRC-5 (μM) |
| **5** | | | 28 | 19 | 19 | - |
| **10a** | H | S | 206 | 100 | ≥100 | 64 |
| **11a** | H | SO | NI | 25 | 37 | >64 |
| **22a** | 2-PhO | SO | NI | 50 | 9.4 | 30 |
| **22b** | 3-PhO | SO | NI | 37 | 6.25 | 32 |
| **22g** | 4-PhO | SO | NI | 25 | 3.13 | >64 |
| Isoniazid | | | | 0.15 | 0.2 | - |

[a]Minimum inhibitory concentration (MIC) is the minimum concentration required to inhibit >99% growth of *M. tuberculosis* H37Rv in liquid culture. NI: no inhibition at 0.2 mM

Further substitution of the phenyl ring of **11a** indicated that sterically demanding and moderately electron withdrawing substituents, such as the 4-bromo substituent in **11g**,

contribute favourably to the whole-cell activity (Table 2), while strongly electron withdrawing substituents negatively affected the activity (**11h**). In addition, the use of polar electron donating groups such as a methoxy group as found in analogue **11b** appears to have a negative effect on the activity. On the other hand, the position (*o*, *m*, *p*) of the substituent only had a small effect on the *in vitro* activity against the organism. None of the analogues (**11b**-**11h**) displayed appreciable cytotoxicity against human fibroblasts.

Table 2. Antimycobacterial activity (H37Rv) and cytotoxicity against MRC-5 fibroblasts of compounds.

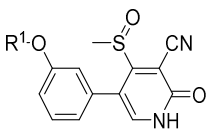
| | | | *M. tuberculosis* MIC[a] (μM) | | |
|---|---|---|---|---|---|
| Structure | Substituent | Comp. | 7H9/glucose | GAST/Fe | MRC-5 (μM) |
|  | $R^1$ = H | **11a** | 25 | 37 | >64 |
| | $R^1$ = 2-Cl | **11e** | 12.5 | 37 | >64 |
| | $R^1$ = 3-Cl | **11f** | 19 | 37 | >64 |
| | $R^1$ = 4-Cl | **11c** | 19 | 25 | >64 |
| | $R^1$ = 4-Br | **11g** | 12.5 | 19 | >64 |
| | $R^1$ = 4-$CF_3$ | **11h** | 37 | 19 | >64 |
| | $R^1$ = 3,4-$Cl_2$ | **11d** | 19 | 12.5 | >64 |
| | $R^1$ = 4-OMe | **11b** | >100 | >100 | >64 |
|  | X = SO | **13** | 50 | ≥50 | 16.44 |
| | X = $SO_2$ | **14** | 37 | 19 | >64 |
|  | $R^2$ = 2-Cl | **12e** | 37 | >50 | >64 |
| | $R^2$ = 3-Cl | **12f** | >50 | >50 | >64 |
| | $R^2$ = 4-$CF_3$ | **12h** | >50 | >50 | >64 |
| | | Isoniazid | 0.15 | 0.2 | - |

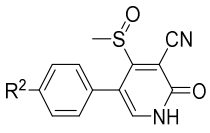
[a]Minimum inhibitory concentration (MIC) is the minimum concentration required to inhibit >99% growth of *M. tuberculosis* H37Rv in liquid culture.

Hydrolysing the cyano group of **11d** into a carboxyamide (**13**) was at the expense of antimycobacterial activity and selectivity, which could be partially restored by oxidation of the sulfoxide to a sulfone (**14**), suggesting that a sulfone moiety could be a favourable factor for the whole-cell activity. However, the favourable influence of a sulfone was found not to be a general rule since oxidation of sulfoxides **11e**, **11f** and **11h** to their corresponding sulfones (**12e**, **12f** and **12h**), resulted in loss of antimycobacterial activity.

Since modification on both cyanopyridone core and phenyl ring of compound **11a** failed to afford substantial improvements in antimycobacterial activity, we shifted our attention to scaffolds **22b** and **22g** (Table 3). Introduction of different substituents on the distal phenyl ring of **22b**, resulted in analogues with improved antimycobacterial activity (e.g. **22c** and **22f**). Also, replacing the phenoxy substituent of **22b** by a benzyloxy was found to be beneficial for the whole-cell activity, with several analogues exhibiting MIC values below 10 μM upon further substitution (**27b**-**27e**). Also, several substituted *p*-aryloxy analogues (derived from **22g**) showed promising activity. These results indicated that *p*-aryloxy analogues (**22g**) slightly higher activity than their *meta* congeners (**22b**). Moreover, in agreement with our previous statement, polar and electron rich moieties have a negative impact on antimycobacterial activity (**22j**). Interestingly, a further increase of the lipophilicity by elimination of the oxygen of the diarylether motif of **22g** led to biphenyl analogue **11i,** which showed significantly improved activity and was the most potent antimycobacterial analogue in both media. Additionally, the switch from a diphenylether to a biphenyl motif reduced cytotoxicity with selectivity indices of 27.8 and 50 depending on the assay conditions.

Table 3. The antimycobacterial activity (H37Rv) and cytotoxicity against MRC-5 fibroblasts of compounds.

| | | | *M. tuberculosis* MIC[a] (μM) | | |
|---|---|---|---|---|---|
| Structure | Substituent | Comp. | 7H9/glucose | GAST/Fe | MRC-5 (μM) |
|  | $R^1$ = Ph | **22b** | 37 | 6.25 | 32 |
| | $R^1$ = 4-ClPh | **22c** | 12.5 | 9.5 | 24 |
| | $R^1$ = 4-$CH_3$Ph | **22d** | 25 | 6.25 | 30 |
| | $R^1$ = 4-OMePh | **22e** | 25 | 6.25 | 30 |

| | | | | | |
|---|---|---|---|---|---|
| | $R^1$ = 3,4-$Cl_2$Ph | **22f** | 12.5 | 19 | 8 |
| | $R^1$ = $PhCH_2$ | **27a** | 19 | 6.25 | 25 |
| | $R^1$ = 4-Cl$PhCH_2$ | **27b** | 9.4 | 9.4 | 31 |
| | $R^1$ = 3,4-$Cl_2PhCH_2$ | **27c** | 9.4 | 9.4 | >64 |
| | $R^1$ = 2-Cl$PhCH_2$ | **27d** | 9.4 | 4.7 | 25 |
| | $R^1$ = 3-Cl$PhCH_2$ | **27e** | 9.4 | 9.4 | >64 |
| | $R^1$ = 2-$NO_2PhCH_2$ | **27f** | 37 | 19 | 64 |
|  | $R^2$ = PhO | **22g** | 25 | 3.13 | >64 |
| | $R^2$ = 4-ClPhO | **22h** | 9.4 | 9.4 | 25 |
| | $R^2$ = 4-MePhO | **22i** | 9.4 | 4.7 | 28 |
| | $R^2$ = 4-OMePhO | **22j** | 19 | 9.4 | 23 |
| | $R^2$ = 3,4-$Cl_2$PhO | **22k** | 9.4 | 19 | 28 |
| | $R^2$ = $PhCH_2O$ | **27g** | 9.4 | 4.7 | 25 |
| | $R^2$ = Ph | **11i** | 1.2 | 2.3 | >64 |
| | | Isoniazid | 0.15 | 0.2 | - |

[a]Minimum inhibitory concentration (MIC) is the minimum concentration required to inhibit >99% growth of *M. tuberculosis* H37Rv in liquid culture.

## Conclusion

Guided by the co-crystal structures of *Mtb*TMPK with compounds **2** and **4**, 33 readily synthesized pyridone analogues were prepared and evaluated for their antimycobacterial activity. Despite the fact that a first subset of analogues showed no inhibition of the *Mtb*TMPK enzyme, these compounds displayed cellular activity against *M. tuberculosis*, implying a different or additional mode of action of these compounds. Structure activity relationships analysis revealed that the cyanopyridone moiety and sulfoxide group were indispensable for antimycobacterial activity. Lipophilic and moderately electron withdrawing substituents on the phenyl ring positively influence the whole-cell activity. Substitution of the phenyl ring of **11a** or the distal phenyl rings of **22b** or **22g** afforded analogues with MIC-values just above or under 10 μM. Moreover, these results showed that *p*-aryloxy scaffold is superior to *m*-aryloxy scaffold.

Importantly, removal of the ether linkage between the phenyl rings of **22g** afforded more lipophilic biphenyl analogue **11i** with reduced cytotoxicity, showing 10-fold more potent antimycobacterial activity than the literature compound **5**, and therefore represents a promising lead compound for further investigation.

## Experimental part

### Molecular modelling

Starting from publicly available complex crystal structure of *Mtb*TMPK (PDB entry 4UNQ[22]), the molecular modelling was conducted using AutoDock vina and AutodockTools-1.5.6.[31] After having minimized the energy in ChemDraw 3D 16.0, PDB files of ligands were generated. All PDBQT files of receptor and ligands were generated in AutodockTools-1.5.6. Centered on *Mtb*TMPK active site PHE70 CE2 (the coordinates x, y, z were 24.089, 33.504, −4.478 correspondingly), the prepared PDBQT files of ligands and receptor were docked using a default grid spacing of 0.375 and 60 x 60 x 60 number of grid points. Through Lamarckian 4.2 method, each ligand was docked 3 times in autodock vina, affording total 60 possible conformations. All vinadock results were viewed and analyzed in Chimera and LigPlus.

### *Mtb*TMPK assay

*Mycobacterium tuberculosis* thymidylate kinase (*Mtb*TMPK) was expressed and purified as previously reported[20]. The synthesized compounds were dissolved in DMSO and evaluated by serial dilution at fixed concentration of dTMP (0.05 mM) and ATP (0.5 mM) according to the spectrophotometric assay reported by Blondin et al.[32] The components of the reaction medium were 50 mM Tris-HCl, pH 7.4, 50 mM KCl, 2 mM $MgCl_2$, 0.2 mM NADH, 1 mM phosphoenol pyruvate, and 2 units each of coupling enzymes (lactate dehydrogenase, pyruvate kinase and nucleoside diphosphate kinase). $IC_{50}$ value of each compound was calculated with KaleidaGraph.

### *In vitro* cytotoxicity assay

*In vitro* cytotoxicity on the MRC-5 *Homo sapiens* long fibroblast cell line (ATCC CCL-171) was assessed for each analogue by a resazurin assay. The assay was conducted as previously reported.[20]

**Whole cell activity against *M. tuberculosis***

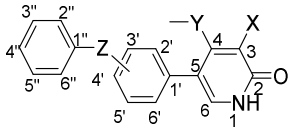
MIC values were determined as previously described.[33] Briefly, compounds were dissolved in DMSO as 10 mM stocks. Isoniazid was used as a positive control, and DMSO as negative control. *M. tuberculosis* H37Rv cells (ATCC 27294) were cultured to $OD_{650nm}$ 0.2-0.3 in the respective medium and diluted 1000-fold in the medium for the MIC determination. Compounds were 2-fold serially diluted in the required medium in clear, sterile round-bottom 96-well plates (Nunclon) at 50 mL per well in duplicates in a concentration range spanning 100-0.049 mM. An equal volume of the diluted cells equating to approximately $1\times 10^4$ bacteria per well was added to each well. Plates were incubated at 37 □ for 1 week after which plates were read with enlarging inverted mirror plate reader. The MIC was taken as the lowest concentration that completely inhibited growth. The media was either GAST/Fe or 7H9/glucose/casitone/Tyloxapol. GAST/Fe medium (per liter) consisted of 0.3 g of Bacto Casitone (Difco), 4.0 g of dibasic potassium phosphate, 2.0 g of citric acid, 1.0 g of L-alanine, 1.2 g of magnesium chloride hexahydrate, 0.6 g of potassium sulfate, 2.0 g of ammonium chloride, 1.80 mL of 10 N sodium hydroxide, 10.0 mL of glycerol, 0.05% Tween 80, and 0.05 g of ferric ammonium citrate adjusted to pH 6.6. The 7H9/glucose/casitone/Tyloxapol medium (per liter) consisted of 4 g glucose, 4.7 g Middlebrook 7H9 broth base, 0.8 g NaCl, 0.3 g Bacto casitone and 0.5 mL Tyloxapol.

**Chemistry**

All reagents and solvents were purchased from standard commercial sources and were of analytical grade. All synthetic compounds described in this study were checked with analytical TLC (Machery−Nagel precoated F254 aluminum plates), visualized under UV light at 254 nm, and purified by column chromatography (CC) on a Reveleris X2 (Grace) automated flash unit. All compounds were measured with Varian Mercury 300/75 MHz or a Bruker Avance Neo® 400/101 MHz spectrometer at 298.15 K using TMS as an internal standard. The analysis and confirmation of final compounds were conducted with $^1H$, $^{13}C$, HSQC and HMBC NMR spectral data, in assistant with high resolution mass spectrometry which was performed on a Waters LCT Premier XETM time of flight (TOF) mass spectrometer equipped with a standard electrospray ionization (ESI) and modular LockSpray TM interface. The purity of the tested compounds was determined by LC - MS analysis (Waters AutoPurification system: a Waters

Cortecs C18 column (2.7 μm, 100 × 4.6 mm); a gradient system of formic acid in $H_2O$ (0.2%, v/v)/MeCN; a flow rate of 1.44 mL/min; a gradient of 95:5 to 0:100 in 10 min.).

Atom numbering throughout the NMR follows the scheme below, atoms in the aryl ring of ester intermediates are not explicitly assigned:




X = CN; $CONH_2$
Y = S; S(O); $SO_2$
Z = O; $OCH_2$

*General procedure for the synthesis of aldehyde intermediates***.** To a solution of methyl phenyl acetates (1.0 eq.) in dry THF (5 mL) was added $LiAlH_4$ (2 eq.) at 0 □ under $N_2$ atmosphere, and the resulting mixture was stirred at room temperature for 1 h.[23] After complete consumption of starting material, the reaction mixture was quenched with $Na^+/K^+$ tartrate solution (~10 mL), and the mixture was filtered after being stirred at room temperature overnight. The collected filtrate was dried and concentrated to afford crude alcohol intermediate, which was oxidized by PCC (2 eq.) for 2 h in $CH_2Cl_2$ (5-10 mL).[24,25] The reaction mixture was filtered through short silica column to remove brown side-product. The collected filtrate was concentrated *in vacuo* for next step without any purification.

*General procedure for the synthesis of final compounds.* The obtained aldehyde intermediate was treated with NaOH (2 eq.) and **9** in DMSO (1 mL) for 2 h to furnish key intermediate methylthiopyridones,[22] which was oxidized by mCPBA in THF (4 mL) for 2-4 h to afford desired compounds.

*4-(Methylthio)-2-oxo-5-phenyl-1,2-dihydropyridine-3-carbonitrile* (**10a**) The suspension of 2-phenylacetaldehyde (0.2 g, 1.1 mmol) and NaOH (85 mg, 2.1 mmol) in DMSO (1 mL) was added **9** (0.13 g, 1.1 mmol), and the reaction mixture was stirred at room temperature for 2 h to give **10a** (eluent system: 5% methanol in $CH_2Cl_2$, 0.16 g, 0.66 mmol, 62% yield). $^1$H NMR (300 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.37 (s, 3 H, $SCH_3$), 7.32 - 7.46 (m, 5 H, H-2', H-3', H-4', H-5', H-6'), 7.52 (s, 1 H, H-6), 12.58 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-$d_6$*) $\delta$ ppm 17.5 (1 C, $SCH_3$), 102.6 (1 C, C-3), 115.8 (1 C, CN), 120.8 (1 C, C-5), 128.0 (1 C, C-4'), 128.4 (2 C, C-3', C-5'), 129.8 (2 C, C2', C-6'), 134.9 (1 C, C-1'), 138.1 (1 C, C-6), 159.7 (1 C, C-2), 161.2 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{13}H_{10}N_2OS - H]^-$ 241.0441, found 241.0431.

*4-(Methylsulfinyl)-2-oxo-5-phenyl-1,2-dihydropyridine-3-carbonitrile* (**11a**) To a solution of **10a** (0.13 g, 0.54 mmol) in dry THF (5 mL) was added mCPBA (75%, 0.12 g, 0.54 mmol), and the reaction mixture was stirred at room temperature for 3 h to afford **11a** (eluent system: 5% methanol in $CH_2Cl_2$, 89 mg, 0.34 mmol, 64% yield). $^1$H NMR (300 MHz, *DMSO-d$_6$*) *δ* ppm 2.75 (s, 3 H, $SCH_3$), 7.25 - 7.51 (m, 5 H, H-2', H-3', H-4', H-5', H-6'), 7.75 (s, 1 H, H-6), 13.13 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-d$_6$*) *δ* ppm 39.6 (1 C, $SCH_3$), 112.4 (1 C, CN), 117.2 (1 C, C-5), 128.5 (3 C, C-3', C-4', C-5'), 130.2 (2 C, C-2', C-6'), 132.6 (1 C, C-1'), 140.6 (1 C, C-6), 160.4 (1 C, C-2), 165.7 (1 C, C-4), C (C-3) could not be observed. HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{13}H_{10}N_2O_2S - H]^-$ 257.0390, found 257.0392.

*5-(4-Methoxyphenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**11b**) Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(4-methoxyphenyl)acetate (0.80 g, 4.4 mmol) was treated with $LiAlH_4$ (0.34 g, 8.8 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (1.2 g, 5.3 mmol) in $CH_2Cl_2$ (10 mL) to yield aldehyde. The suspension of aldehyde and NaOH (0.13 g, 3.3 mmol) in DMSO (1 mL) was added **9** (0.31 g, 1.7 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 0.26 g, 1.2 mmol) to afford **11b** (eluent system: 5% methanol in $CH_2Cl_2$, 0.12 g, 0.42 mmol, 10% yield). $^1$H NMR (300 MHz, *DMSO-d$_6$*) *δ* ppm 2.75 (s, 3 H, $SCH_3$), 3.79 (s, 3 H, $OCH_3$), 6.91 - 7.05 (m, 2 H, Ph, H-3', H-5'), 7.20 - 7.37 (m, 2 H, H-2', H-6'), 7.70 (s, 1 H, H-6), 13.07 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-d$_6$*) *δ* ppm 39.6 (1 C, $SCH_3$), 55.2 (1 C, $OCH_3$), 99.2 (1 C, C-3), 112.4 (1 C, CN), 113.9 (2 C, C-3', C-5'), 116.9 (1 C, C-5), 124.5 (1 C, C-1'), 131.5 (2 C, C-2', C-6'), 140.4 (1 C, C-6), 159.4 (1 C, ($CH_3O$)C-4'), 160.4 (1 C, C-2), 166.1 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{14}H_{12}N_2O_3S - H]^-$ 287.0496, found 287.0495.

*5-(4-Chlorophenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**11c**) Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(4-chlorophenyl)acetate (0.6 g, 3.3 mmol) was treated with $LiAlH_4$ (0.25 g, 6.5 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.99 g, 4.6 mmol) in $CH_2Cl_2$ (10 mL) to yield aldehyde. The suspension of aldehyde and NaOH (0.14 mg, 3.7

mmol) in DMSO (1 mL) was added **9** (0.35 g, 1.8 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 0.33 g, 1.4 mmol) to afford **11c** (eluent system: 5% methanol in $CH_2Cl_2$, 0.27 g, 0.92 mmol, 29% yield). $^1$H NMR (300 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.75 (s, 3 H, $SCH_3$), 7.39 (d, *J* = 7.4 Hz, 2 H, H-2', H-6'), 7.48 (d, *J* = 7.4 Hz, 2 H, H-3', H-5'), 7.76 (s, 1 H, H-6), 13.14 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 99.4 (1 C, C-3), 112.3 (1 C, CN), 115.9 (1 C, C-5), 128.5 (2 C, C-3', C-5'), 131.5 (1 C, C-1'), 132.2 (2 C, C-2', C-6'), 133.5 (1 C, (Cl)C-4'), 140.9 (1 C, C-6), 160.3 (1 C, C-2), 165.6 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{13}H_9ClN_2O_2S - H]^-$ 291.0000, found 291.0007.

*5-(3,4-Dichlorophenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**11d**) Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3,4-dichlorophenyl)acetate (0.54 g, 2.5 mmol) was treated with $LiAlH_4$ (0.19 g, 4.9 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.63 g, 2.9 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (88 mg, 2.2 mmol) in DMSO (1 mL) was added **9** (0.21 g, 1.1 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 0.13 g, 0.58 mmol) to afford **11d** (eluent system: 5% methanol in $CH_2Cl_2$, 89 mg, 0.27 mmol, 11% yield). $^1$H NMR (300 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.77 (s, 3 H, $SCH_3$), 7.39 (dd, *J* = 8.2, 2.1 Hz, 1 H, H-6'), 7.68 (d, *J* = 8.2 Hz, 1 H, H-5'), 7.74 (d, *J* = 2.1 Hz, 1 H, H-2'), 7.82 (s, 1 H, H-6), 13.19 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.5 (1 C, $SCH_3$), 99.3 (1 C, C-3), 112.2 (1 C, CN), 114.7 (1 C, C-5), 130.4 (1 C, C-5'), 130.8 (1 C, C-6'), 131.1 (1 C, (Cl)C-3'), 131.4 (1 C, (Cl)C-4'), 132.3 (1 C, C-2'), 133.3 (1 C, C-1'), 141.3 (1 C, C-6), 160.3 (1 C, C-2), 165.6 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{13}H_8Cl_2N_2O_2S - H]^-$ 324.9611, found 324.9604.

*5-(2-Chlorophenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**11e**) Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(2-chlorophenyl)acetate (0.3 g, 1.6 mmol) was treated with $LiAlH_4$ (0.12 g, 3.3 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.63 g, 2.9 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (0.12 g, 2.9 mmol) in DMSO (1 mL) was added **9** (0.27 g, 1.5 mmol) to give methylthiopyridone intermediate,

followed by oxidation with mCPBA (75%, 0.21 g, 0.92 mmol) to afford **11e** (eluent system: 5% methanol in $CH_2Cl_2$, 0.16 g, 0.55 mmol, 32% yield). $^1$H NMR (400 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.75 (d, *J* = 9.9 Hz, 3 H, $SCH_3$), 7.41 - 7.47 (m, 2 H, H-3', H-6'), 7.47 - 7.52 (m, 1 H, H-4'), 7.57 - 7.64 (m, 1 H, H-5'), 7.85 (d, *J* = 10 Hz, 1 H, H-6), 13.25 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 99.4 (1 C, C-3), 111.9 (1 C, CN), 113.7 (1 C, C-5), 127.46 (d, *J* = 47.0 Hz, 1 C, C-3'), 129.35 (d, *J* = 20.0 Hz, 1 C, C-5'), 131.0 (1 C, C-1'), 131.1 (1 C, C-4'), 133.21 (d, *J* = 16.1 Hz, 1 C, C-6'), 133.80 (d, *J* = 7.5 Hz, 1 C, (Cl)C-2'), 141.65 (d, *J* = 71.2 Hz, 1 C, C-6), 160.4 (1 C, C-2), 166.0 (d, *J* = 59.9 Hz, 1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{13}H_9ClN_2O_2S - H]^-$ 291.0000, found 291.0006.

*5-(3-Chlorophenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**11f**) Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-chlorophenyl)acetate (0.3 g, 1.6 mmol) was treated with $LiAlH_4$ (0.12 g, 3.3 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.70 g, 3.3 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (0.13 g, 3.2 mmol) in DMSO (1 mL) was added **9** (0.30 g, 1.6 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 0.31 g, 1.3 mmol) to afford **11f** (eluent system: 5% methanol in $CH_2Cl_2$, 0.15 g, 0.51 mmol, 32% yield). $^1$H NMR (400 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.79 (s, 3 H, $SCH_3$), 7.36 (dt, *J* = 7.1, 1.6 Hz, 1 H, H-6'), 7.43 - 7.52 (m, 2 H, H-4', H-5'), 7.54 (t, *J* = 1.6 Hz, 1 H, H-2'), 7.83 (s, 1 H, H-6), 13.20 (br. s.,1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 99.4 (1 C, C-3), 112.3 (1 C, CN), 115.7 (1 C, C-5), 128.5 (1 C, C-4'), 129.2 (1 C, C-6'), 130.1 (1 C, C-2'), 130.3 (1 C, C-5'), 133.1 (1 C, (Cl)C-3'), 134.7 (1 C, C-1'), 141.1 (1 C, C-6), 160.3 (1 C, C-2), 165.6 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{13}H_9ClN_2O_2S - H]^-$ 291.0000, found 290.9987.

*5-(4-Bromophenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**11g**) Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(4-bromophenyl)acetate (0.3 g, 1.3 mmol) was treated with $LiAlH_4$ (99 mg, 2.6 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.56 g, 2.6 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (90 mg, 2.2 mmol)

in DMSO (1 mL) was added **9** (0.21 g, 1.1 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 0.13 g, 0.58 mmol) to afford **11g** (eluent system: 5% methanol in $CH_2Cl_2$, 0.14 g, 0.42 mmol, 32% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) *δ* ppm 2.78 (s, 3 H, $SCH_3$), 7.32 - 7.39 (m, 2 H, H-2', H-6'), 7.61 - 7.67 (m, 2 H, H-3', H-5'), 7.78 (s, 1 H, H-6), 13.18 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) *δ* ppm 39.7 (1 C, $SCH_3$), 99.4 (1 C, C-3), 112.3 (1 C, CN), 116.0 (1 C, C-5), 122.2 (1 C, (Br)C-4'), 131.4 (2 C, C-3', C-5'), 131.9 (1 C, C-1'), 132.5 (2 C, C-2', C-6'), 140.8 (1 C, C-6), 160.3 (1 C, C-2), 165.6 (1 C, C-4). HRMS (ESI): m/z $[M + H]^+$ Calcd. for $[C_{13}H_9BrN_2O_2S + H]^+$ 336.9641, found 336.9644.

*4-(Methylsulfinyl)-2-oxo-5-(4-(trifluoromethyl)phenyl)-1,2-dihydropyridine-3-carbonitrile* (**11h**) Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(4-(trifluoromethyl)phenyl)acetate (0.3 g, 1.4 mmol) was treated with $LiAlH_4$ (0.10 g, 2.8 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.59 g, 2.8 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (0.11 g, 2.7 mmol) in DMSO (1 mL) was added **9** (0.26 g, 1.4 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 0.21 g, 0.93 mmol) to afford **11h** (eluent system: 5% methanol in $CH_2Cl_2$, 0.15 g, 0.46 mmol, 35% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) *δ* ppm 2.81 (s, 3 H, $SCH_3$), 7.64 (d, *J* = 8.1 Hz, 2 H, H-2', H-6'), 7.81 (d, *J* = 8.3 Hz, 2 H, H-3', H-5'), 7.86 (s, 1 H, H-6), 13.24 (br. s., 1 H, NH). $^{19}$F NMR (377 MHz, *DMSO-d$_6$*) *δ* ppm -61.1. $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) *δ* ppm 39.7 (1 C, $SCH_3$), 99.6 (1 C, C-3), 112.3 (1 C, CN), 115.9 (1 C, C-5), 124.11 (q, *J* = 273.0 Hz, 1 C, $CF_3$), 125.30 (d, *J* = 3.7 Hz, 2 C, C-3', C-5'), 128.86 (q, *J* = 32.0 Hz, 1 C, ($CF_3$)C-4'), 131.3 (2 C, C-2', C-6'), 137.0 (1 C, C-1'), 141.2 (1 C, C-6), 160.3 (1 C, C-2), 165.4 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{14}H_9F_3N_2O_2S - H]^-$ 325.0264, found 325.0256.

*5-([1,1'-Biphenyl]-4-yl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**11i**) Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-([1,1'-biphenyl]-4-yl)acetate (0.3 g, 1.3 mmol) was treated with $LiAlH_4$ (0.10 g, 2.7 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.56 g, 2.6 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and

NaOH (91 mg, 2.3 mmol) in DMSO (1 mL) was added **9** (0.22 g, 1.1 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 0.11 g, 0.47 mmol) to afford **11i** (eluent system: 5% methanol in $CH_2Cl_2$, 77 mg, 0.23 mmol, 17% yield). $^1$H NMR (300 MHz, *DMSO-d$_6$*) $\delta$ ppm 2.80 (s, 3 H, $SCH_3$), 7.33 - 7.52 (m, 5 H, H-2', H-6', H-3'', H-4'', H-5''), 7.71 (t, *J* = 7.5 Hz, 4 H, H-3', H-5', H-2'', H-6''), 7.80 (s, 1 H, H-6), 13.15 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-d$_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 99.4 (1 C, C-3), 112.4 (1 C, CN), 116.8 (1 C, C-5), 126.7 (4 C, C-3', C-5', C-2'', C-6''), 127.8 (1 C, C-4''), 129.0 (2 C, C-3'', C-5''), 130.8 (2 C, C-2', C-6'), 131.7 (1 C, C-1'), 139.2 (1 C, C-1''), 140.1 (1 C, C-4'), 140.8 (1 C, C-6), 160.4 (1 C, C-2), 165.7 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. For $[C_{19}H_{14}N_2O_2S - H]^-$ 333.0703, found 333.0702.

*5-(2-Chlorophenyl)-4-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**12e**) To a solution of **11e** (90 mg, 0.31 mmol) in dry THF (5 mL) was added mCPBA (75%, 71 mg, 0.31 mmol), and the reaction mixture was stirred at room temperature for 2 h to afford **12e** (eluent system: 5% methanol in $CH_2Cl_2$, 32 mg, 0.10 mmol, 34% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) $\delta$ ppm 3.25 (s, 3 H, $SCH_3$), 7.34 - 7.47 (m, 3 H, H-3', H-4', H-6'), 7.48 - 7.53 (m, 1 H, H-5'), 7.98 (s, 1 H, H-6), 13.66 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) $\delta$ ppm 43.4 (1 C, $SCH_3$), 102.7 (1 C, C-3), 113.5 (1 C, CN), 114.7 (1 C, C-5), 126.7 (1 C, C-3'), 128.7 (1 C, C-5'), 130.3 (1 C, C-4'), 132.5 (1 C, C-6'), 133.3 (1 C, C-1'), 134.3 (1 C, (Cl)C-2'), 144.9 (1 C, C-6), 155.1 (1 C, C-4), 160.3 (1 C, C-2). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{13}H_9ClN_2O_3S - H]^-$ 306.9949, found 306.9952.

*5-(3-Chlorophenyl)-4-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**12f**) To a solution of **11f** (80 mg, 0.27 mmol) in dry THF (5 mL) was added mCPBA (75%, 62 mg, 0.27 mmol), and the reaction mixture was stirred at room temperature for 4 h to afford **12f** (eluent system: 5% methanol in $CH_2Cl_2$, 20 mg, 0.065 mmol, 23% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) $\delta$ ppm 3.16 (s, 3 H, $SCH_3$), 7.34 (dt, *J* = 7.5, 1.4 Hz, 1 H, H-6'), 7.38 - 7.51 (m, 3 H, H-2', H-4', H-5'), 7.93 (s, 1 H, H-6), 13.61 (s, 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) $\delta$ ppm 43.9 (1 C, $SCH_3$), 113.4 (1 C, CN), 116.2 (1 C, C-5), 128.2 (1 C, C-2'), 129.6 (2 C, C-5', C-6'), 130.5 (1 C, C-4'), 132.3 (1 C, (Cl)C-3'), 136.5 (1 C, C-1'), 144.6 (1 C, C-6), 155.0 (1 C, C-4),

160.2 (1 C, C-2). C (C-3) could not be observed. HRMS (ESI): m/z [M - H]$^-$ Calcd. for [$C_{13}H_9ClN_2O_3S$ - H]$^-$ 306.9949, found 306.9934.

*4-(Methylsulfonyl)-2-oxo-5-(4-(trifluoromethyl)phenyl)-1,2-dihydropyridine-3-carbonitrile* (**12h**) To a solution of **11h** (60 mg, 0.18 mmol) in dry THF (5 mL) was added mCPBA (75%, 42 mg, 0.18 mmol), and the reaction mixture was stirred at room temperature for 4 h to afford **12h** (eluent system: 5% methanol in $CH_2Cl_2$, 20 mg, 0.058 mmol, 23% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) $\delta$ ppm 3.20 (s, 3 H, $SCH_3$), 7.59 (d, *J* = 8.0 Hz, 2 H, H-2', H-6'), 7.77 (d, *J* = 8.1 Hz, 2 H, H-3', H-5'), 7.95 (br. s., 1 H, H-6), 13.59 (br. s., 1 H, NH). $^{19}$F NMR (377 MHz, *DMSO-d$_6$*) $\delta$ ppm -61.1. $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) $\delta$ ppm 44.0 (1 C, $SCH_3$), 103.6 (1 C, C-3), 113.5 (1 C, CN), 116.2 (1 C, C-5), 124.22 (q, *J* = 273.0 Hz, 1 C, $CF_3$), 124.59 (q, *J* = 3.8 Hz, 2 C, C-3', C-5'), 128.58 (q, *J* = 31.0 Hz, 1 C, ($CF_3$)C-4'), 131.6 (2 C, C-2', C-6'), 139.0 (1 C, C-1'), 144.5 (1 C, C-6), 154.9 (1 C, C-4), 160.3 (1 C, C-2). HRMS (ESI): m/z [M - H]$^-$ Calcd. for [$C_{14}H_9F_3N_2O_3S$ - H]$^-$ 341.0213, found 341.0217.

*5-(3,4-Dichlorophenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carboxamide* (**13**) Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3,4-dichlorophenyl)acetate (0.54 g, 2.5 mmol) was treated with $LiAlH_4$ (0.19 g, 4.9 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.63 g, 2.9 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (88 mg, 2.2 mmol) in DMSO (1 mL) was added **9** (0.21 g, 1.1 mmol) to give methylthiopyridone intermediate, followed by hydrolysis in con. $H_2SO_4$ (10 mL) at 100 □ for 2 h to afford amide intermediate.[28] Oxidation of the intermediate with mCPBA (75%, 82 mg, 0.36 mmol) in dry THF (4 mL) for 2 h afforded compound **13** (eluent system: 5% methanol in $CH_2Cl_2$, 79 mg, 0.23 mmol, 9% yield). $^1$H NMR (300 MHz, *DMSO-d$_6$*) $\delta$ ppm 2.87 (s, 3 H, $SCH_3$), 7.31 (dd, *J* = 8.2, 2.1 Hz, 1 H, H-6'), 7.45 (s, 1 H, H-6), 7.54 - 7.61 (m, 2 H, H-2', H-5'), 7.63 (br. s., 1 H, (CO)$NH_2$), 8.36 (br. s., 1 H, (CO)$NH_2$), 12.59 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-d$_6$*) $\delta$ ppm 42.4 (1 C, $SCH_3$), 115.5 (1 C, C-5), 123.7 (1 C, C-3), 129.4 (1 C, C-5'), 130.0 (1 C, (Cl)C-3'), 130.1 (1 C, (Cl)C-4'), 131.0 (1 C, C-6'), 132.4 (1 C, C-2'), 135.9 (1 C, C-1'), 138.7 (1

C, C-6), 158.2 (1 C, C-4), 169.9 (1 C, C-2), 165.1 (1 C, $CO(NH_2)$). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{13}H_{10}Cl_2N_2O_3S - H]^-$ 342.9716, found 342.9702.

*5-(3,4-Dichlorophenyl)-4-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide* (**14**) To a solution of **13** (40 mg, 0.12 mmol) in dry THF was added mCPBA (75%, 27 mg, 0.12 mmol), and the reaction mixture was stirred for 3 h to afford **14** (eluent system: 5% methanol in $CH_2Cl_2$, 33 mg, 0.091 mmol, 79% yield). $^1$H NMR (300 MHz, *DMSO-$d_6$*) $\delta$ ppm 3.15 (s, 3 H, $SCH_3$), 7.30 (dd, *J* = 8.4, 1.6 Hz, 1 H, H-6'), 7.44 - 7.62 (m, 4 H, $(CO)NH_2$, H-6, H-2', H-5'), 7.71 (br. s., 1 H, $(CO)NH_2$), 12.55 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-$d_6$*) $\delta$ ppm 45.4 (1 C, $SCH_3$), 114.1 (1 C, C-5), 129.6 (1 C, C-5'), 130.1 (1 C, (Cl)C-3'), 130.4 (1 C, (Cl)C-4'), 131.0 (1 C, C-6'), 132.3 (1 C, C-2'), 136.9 (1 C, C-1'), 138.1 (1 C, C-6), 145.2 (1 C, C-4), 159.7 (1 C, C-2), 165.5 (1 C, $CO(NH_2)$), C (C-3) could not be observed. HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{13}H_{10}Cl_2N_2O_4S - H]^-$ 358.9665, found 358.9662.

*4-(Methylsulfinyl)-2-oxo-5-(2-phenoxyphenyl)-1,2-dihydropyridine-3-carbonitrile* (**22a**) According to a literature report,[29] methyl 2-(2-hydroxyphenyl)acetate (1.1 g, 8.1 mmol), phenylboronic acid (2.9 g, 24 mmol), $Cu(OAc)_2$ (2.9 g, 16 mmol), molecular sieves (1.5 g) and pyridine (1.9 mL, 24 mmol) in 1,2-dichloroethane (50 mL) afforded the ester intermediate methyl 2-(2-phenoxyphenyl)acetate **18a** (eluent system: 10% ethylacetate in petroleum ether, 0.40 g, 1.6 mmol, 21% yield). $^1$H NMR (300 MHz, *$CDCl_3$*) $\delta$ ppm 3.63 (s, 3 H, $OCH_3$), 3.72 (s, 2 H, $CH_2$), 6.90 (dd, *J* = 8.1, 1.0 Hz, 1 H, Ph), 6.95 - 7.01 (m, 2 H, Ph), 7.06 - 7.15 (m, 2 H, Ph), 7.21 - 7.37 (m, 4 H, Ph). $^{13}$C NMR (75 MHz, *$CDCl_3$*) $\delta$ ppm 35.6 (1 C, $CH_2$), 51.8 (1 C, $OCH_3$), 118.3 (2 C, Ph), 118.8 (1 C, Ph), 123.0 (1 C, Ph), 123.6 (1 C, Ph), 125.8 (1 C, Ph), 128.6 (1 C, Ph), 129.6 (2 C, Ph), 131.4 (1 C, Ph), 155.0 (1 C, Ph), 157.2 (1 C, Ph), 171.7 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(2-phenoxyphenyl)acetate (0.2 g, 0.83 mmol) was treated with $LiAlH_4$ (63 mg, 1.7 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.34 g, 1.6 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (57 mg, 1.4 mmol) in DMSO (1 mL) was added **9** (0.13 g, 0.71 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 0.10 g, 0.46 mmol)

to afford **22a** (eluent system: 5% methanol in $CH_2Cl_2$, 68 mg, 0.19 mmol, 23% yield). $^1$H NMR (300 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.78 (br. s., 3 H, $SCH_3$), 6.88 (d, *J* = 7.9 Hz, 1 H, H-5'), 6.95 (d, *J* = 7.9 Hz, 2 H, H-2'', H-6''), 7.12 (t, *J* = 8.0 Hz, 1 H, H-4''), 7.21 (t, *J* = 7.4 Hz, 1 H, H-3'), 7.27 - 7.48 (m, 4 H, H-4', H-6', H-3'', H-5''), 7.75 (br. s., 1 H, H-6), 13.10 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.5 (1 C, $SCH_3$), 99.1 (1 C, C-3), 112.2 (1 C, CN), 117.8 (1 C, C-5'), 118.8 (2 C, C-2'', C-6''), 123.6 (1 C, C-1'), 123.8 (1 C, C-3'), 123.9 (1 C, C-4''), 130.1 (2 C, C-3'', C-5''), 131.0 (1 C, C-6'), 132.7 (1 C, C-4'), 141.4 (1 C, C-6), 154.4 (1 C, C-2'), 155.8 (1 C, C-1''), 160.3 (1 C, C-2), C (C-4) and C (C-5) could not be observed. HRMS (ESI): m/z [M - H]$^-$ Calcd. for [$C_{19}H_{14}N_2O_3S$ - H]$^-$ 349.0652, found 349.0638.

*4-(Methylsulfinyl)-2-oxo-5-(3-phenoxyphenyl)-1,2-dihydropyridine-3-carbonitrile* (**22b**)

According to a literature report,[29] methyl 2-(3-hydroxyphenyl)acetate (1.1 g, 8.1 mmol), phenylboronic acid (2.9 g, 24 mmol), $Cu(OAc)_2$ (2.9 g, 16 mmol), molecular sieves (1.5 g) and pyridine (1.9 mL, 24 mmol) in 1,2-dichloroethane (50 mL) afforded the ester intermediate methyl 2-(3-phenoxyphenyl)acetate **18b** (eluent system: 10 % ethylacetate in petroleum ether, 0.80 g, 3.3 mmol, 41% yield). $^1$H NMR (300 MHz, *$CDCl_3$*) $\delta$ ppm 3.62 (s, 2 H, $CH_2$), 3.71 (s, 3 H, $OCH_3$), 6.90 - 6.95 (m, 1 H, Ph), 6.98 (t, *J* = 2.1 Hz, 1 H, Ph), 7.01 - 7.07 (m, 3 H, Ph), 7.13 (tt, *J* = 7.4, 1.14 Hz, 1 H, Ph), 7.26 - 7.40 (m, 3 H, Ph). $^{13}$C NMR (75 MHz, *$CDCl_3$*) $\delta$ ppm 40.9 (1 C, $CH_2$), 52.0 (1 C, $OCH_3$), 117.3 (1 C, Ph), 119.0 (2 C, Ph), 119.7 (1 C, Ph), 123.3 (1 C, Ph), 124.0 (1 C, Ph), 129.7 (3 C, Ph), 135.7 (1 C, Ph), 156.9 (1 C, Ph), 157.4 (1 C, Ph), 171.6 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-phenoxyphenyl)acetate (0.2 g, 0.83 mmol) was treated with $LiAlH_4$ (63 mg, 1.7 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.35 g, 1.6 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (60 mg, 1.5 mmol) in DMSO (1 mL) was added **9** (0.14 g, 0.74 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 87 mg, 0.38 mmol) to afford **22b** (eluent system: 5% methanol in $CH_2Cl_2$, 57 mg, 0.16 mmol, 20% yield). $^1$H NMR (300 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.75 (s, 3 H, $SCH_3$), 6.99 - 7.07 (m, 4 H, H-2', H-4', H-2'', H-6''), 7.09 - 7.19 (m, 2 H, H-6', H-4''), 7.34 - 7.48 (m, 3 H, H-5', H-3'', H-5''), 7.77 (s, 1 H, H-6), 13.12 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 99.3 (1 C, C-3), 112.3

(1 C, CN), 116.4 (1 C, C-5), 118.6 (1 C, C-2'), 118.8 (2 C, C-2'', C-6''), 120.3 (1 C, C-4'), 123.7 (1 C, C-4''), 125.2 (1 C, C-6'), 130.1 (2 C, C-3'', C-5''), 130.3 (1 C, C-5'), 134.4 (1 C, C-1'), 140.7 (1 C, C-6), 156.3 (1 C, C-3'), 156.6 (1 C, C-1''), 160.4 (1 C, C-2), 165.6 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{19}H_{14}N_2O_3S - H]^-$ 349.0652, found 349.0649.

*5-(3-(4-Chlorophenoxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**22c**) According to a literature report,[29] methyl 2-(3-hydroxyphenyl)acetate (0.60 g, 4.4 mmol), (4-chlorophenyl)boronic acid (2.1 g, 13 mmol), $Cu(OAc)_2$ (1.6 g, 8.8 mmol), molecular sieves (0.82 g) and pyridine (1.1 mL, 13 mmol) in 1,2-dichloroethane (50 mL) afforded the ester intermediate methyl 2-(3-(4-chlorophenoxy)phenyl)acetate **18c** (eluent system: 10% ethylacetate in petroleum ether, 0.40 g, 1.4 mmol, 33% yield). $^1$H NMR (300 MHz, *$CDCl_3$*) *δ* ppm 3.62 (s, 2 H, $CH_2$), 3.71 (s, 3 H, $OCH_3$), 6.87 - 6.99 (m, 4 H, Ph), 7.05 (d, *J* = 7.3 Hz, 1 H, Ph), 7.25 - 7.34 (m, 3 H, Ph). $^{13}$C NMR (75 MHz, *$CDCl_3$*) *δ* ppm 40.9 (1 C, $CH_2$), 52.1 (1 C, $OCH_3$), 117.4 (1 C, Ph), 119.8 (1 C, Ph), 120.2 (2 C, Ph), 124.5 (1 C, Ph), 128.4 (1 C, Ph), 129.8 (2 C, Ph), 129.9 (1 C, Ph), 136.0 (1 C, Ph), 155.7 (1 C, Ph), 157.1 (1 C, Ph), 171.6 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-(4-chlorophenoxy)phenyl)acetate (0.2 g, 0.72 mmol) was treated with $LiAlH_4$ (55 mg, 1.5 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.31 g, 1.5 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (42 mg, 1.1 mmol) in DMSO (1 mL) was added **9** (99 mg, 0.53 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 55 mg, 0.24 mmol) to afford **22c** (eluent system: 5% methanol in $CH_2Cl_2$, 41 mg, 0.11 mmol, 15% yield). $^1$H NMR (300 MHz, *DMSO-$d_6$*) *δ* ppm 2.75 (s, 3 H, $SCH_3$), 7.01 - 7.10 (m, 4 H, H-2', H-4', H-2'', H-6''), 7.14 (dt, *J* = 7.6, 1.3 Hz, 1 H, H-6'), 7.36 - 7.49 (m, 3 H, H-5', H-3'', H-5''), 7.76 (s, 1 H, H-6), 13.12 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-$d_6$*) *δ* ppm 39.7 (1 C, $SCH_3$), 99.3 (1 C, C-3), 112.3 (1 C, CN), 116.3 (1 C, C-5), 118.9 (1 C, C-2'), 120.4 (2 C, C-2'', C-6''), 120.5 (1 C, C-4'), 125.7 (1 C, C-6'), 127.4 (1 C, (Cl)C-4''), 130.0 (2 C, C-3'', C-5''), 130.4 (1 C, C-5'), 134.5 (1 C, C-1'), 140.7 (1 C, C-6), 155.3 (1 C, C-1''), 156.2 (1 C, C-3'), 160.3 (1 C, C-2), 165.7 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{19}H_{13}ClN_2O_3S - H]^-$ 383.0262, found 383.0248.

*4-(Methylsulfinyl)-2-oxo-5-(3-(p-tolyloxy)phenyl)-1,2-dihydropyridine-3-carbonitrile* (**22d**) According to a literature report,[29] methyl 2-(3-hydroxyphenyl)acetate (0.60g, 4.4 mmol), p-tolylboronic acid (1.8 g, 13 mmol), $Cu(OAc)_2$ (1.6 g, 8.8 mmol), molecular sieves (0.8 g) and pyridine (1.1 mL, 13 mmol) in 1,2-dichloroethane (50 mL) afforded the ester intermediate methyl 2-(3-(p-tolyloxy)phenyl)acetate **18d** (eluent system: 10% ethylacetate in petroleum ether, 0.34 g, 1.3 mmol, 30% yield). $^1$H NMR (300 MHz, *CDCl$_3$*) $\delta$ ppm 2.37 (s, 3 H, (Ph)$CH_3$), 3.62 (s, 2 H, $CH_2$), 3.72 (s, 3 H, $OCH_3$), 6.89 - 6.99 (m, 4 H, Ph), 7.00 - 7.05 (m, 1 H, Ph), 7.14 - 7.21 (m, 2 H, Ph), 7.25 - 7.32 (m, 1 H, Ph). $^{13}$C NMR (75 MHz, *CDCl$_3$*) $\delta$ ppm 20.6 (1 C, (Ph)$CH_3$), 40.9 (1 C, $CH_2$), 51.9 (1 C, $OCH_3$), 116.7 (1 C, Ph), 119.1 (3 C, Ph), 123.5 (1 C, Ph), 129.6 (1 C, Ph), 130.1 (2 C, Ph), 132.9 (1 C, Ph), 135.6 (1 C, Ph), 154.4 (1 C, Ph), 157.9 (1 C, Ph), 171.6 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-(p-tolyloxy)phenyl)acetate (0.2 g, 0.78 mmol) was treated with $LiAlH_4$ (59 mg, 1.6 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.28 g, 1.3 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (46 mg, 1.2 mmol) in DMSO (1 mL) was added **9** (0.11 g, 0.58 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 78 mg, 0.34 mmol) to afford **22d** (eluent system: 5% methanol in $CH_2Cl_2$, 54 mg, 0.15 mmol, 19% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) $\delta$ ppm 2.29 (s, 3 H, (Ph)$CH_3$), 2.76 (s, 3 H, $SCH_3$), 6.92 - 7.05 (m, 4 H, H-2', H-4', H-2'', H-6''), 7.10 (d, *J* = 7.6 Hz, 1 H, H-6'), 7.15 - 7.26 (m, 2 H, H-3'', H-5''), 7.42 (t, *J* = 7.7 Hz, 1 H, H-5'), 7.77 (s, 1 H, H-6), 13.12 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) $\delta$ ppm 20.3 (1 C, (Ph)$CH_3$), 39.7 (1 C, $SCH_3$), 99.5 (1 C, C-3), 112.3 (1 C, CN), 116.5 (1 C, C-5), 118.1 (1 C, C-2'), 119.1 (2 C, C-2'', C-6''), 119.7 (1 C, C-4'), 124.8 (1 C, C-6'), 130.2 (1 C, C-5'), 130.5 (2 C, C-3'', C-5''), 133.0 (1 C, ($CH_3$)C-4''), 134.3 (1 C, C-1'), 140.6 (1 C, C-6), 153.7 (1 C, C-1''), 157.2 (1 C, C-3'), 160.4 (1 C, C-2), 165.7 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{20}H_{16}N_2O_3S - H]^-$ 363.0809, found 363.0810.

*5-(3-(4-Methoxyphenoxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**22e**) According to a literature report,[29] methyl 2-(3-hydroxyphenyl)acetate (0.60 g, 4.4 mmol), (4-methoxyphenyl)boronic acid (2.0 g, 13 mmol), $Cu(OAc)_2$ (1.6 g, 8.8 mmol), molecular sieves (0.8 g) and pyridine (1.1 mL, 13 mmol) in 1,2-dichloroethane (50 mL)

afforded the ester intermediate methyl 2-(3-(4-methoxyphenoxy)phenyl)acetate **18e** (eluent system: 10% ethylacetate in petroleum ether, 0.33 g, 1.2 mmol, 28% yield). $^{1}$H NMR (300 MHz, *CDCl$_3$*) $\delta$ ppm 3.60 (s, 2 H, $CH_2$), 3.70 (s, 3 H, $OCH_3$), 3.82 (s, 3 H, (Ph)$OCH_3$), 6.82 - 6.87 (m, 1 H, Ph), 6.88 - 6.94 (m, 3 H, Ph), 6.95 - 7.03 (m, 3 H, Ph), 7.22 - 7.29 (m, 1 H, Ph). $^{13}$C NMR (75 MHz, *CDCl$_3$*) $\delta$ ppm 41.0 (1 C, $CH_2$), 52.0 (1 C, $OCH_3$), 55.6 (1 C, (Ph)$OCH_3$), 114.8 (2 C, Ph), 116.0 (1 C, Ph), 118.4 (1 C, Ph), 120.9 (2 C, Ph), 123.2 (1 C, Ph), 129.6 (1 C, Ph), 135.6 (1 C, Ph), 149.8 (1 C, Ph), 155.9 (1 C, Ph), 158.6 (1 C, Ph), 171.7 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-(4-methoxyphenoxy)phenyl)acetate (0.2 g, 0.74 mmol) was treated with $LiAlH_4$ (56 mg, 1.5 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.32 g, 1.5 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (46 mg, 1.2 mmol) in DMSO (1 mL) was added **9** (0.11 g, 0.58 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 95 mg, 0.42 mmol) to afford **22e** (eluent system: 5% methanol in $CH_2Cl_2$, 0.12 g, 0.32 mmol, 42% yield). $^{1}$H NMR (300 MHz, *DMSO-d$_6$*) $\delta$ ppm 2.74 (s, 3 H, $SCH_3$), 3.75 (s, 3 H, $OCH_3$), 6.89 - 7.08 (m, 7 H, H-2', H-4', H-6', H-2'', H-3'', H-5'', H-6''), 7.38 (t, *J* = 7.7, 1.3 Hz, 1 H, H-5'), 7.74 (s, 1 H, H-6), 13.09 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-d$_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 55.4 (1 C, $OCH_3$), 99.4 (1 C, C-3), 112.4 (1 C, CN), 115.2 (2 C, C-3'', C-5''), 116.6 (1 C, C-5), 117.3 (1 C, C-2'), 118.9 (1 C, C-4'), 120.9 (2 C, C-2'', C-6''), 124.4 (1 C, C-6'), 130.1 (1 C, C-5'), 134.3 (1 C, C-1'), 140.6 (1 C, C-6), 148.9 (1 C, C-1''), 155.8 (1 C, ($CH_3O$)C-4''), 158.0 (1 C, C-3'), 160.4 (1 C, C-2), 165.6 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{20}H_{16}N_2O_4S - H]^-$ 379.0758, found 379.0753.

*5-(3-(3,4-Dichlorophenoxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**22f**) According to a literature report,[29] methyl 2-(3-hydroxyphenyl)acetate (0.60 g, 4.4 mmol), (3,4-dichlorophenyl)boronic acid (2.5 g, 13 mmol), $Cu(OAc)_2$ (1.6 g, 8.8 mmol), molecular sieves (0.8 g) and pyridine (1.1 mL, 13 mmol) in 1,2-dichloroethane (50 mL) afforded the ester intermediate methyl 2-(3-(3,4-dichlorophenoxy)phenyl)acetate **18f** (eluent system: 10% ethylacetate in petroleum ether, 0.73 g, 2.3 mmol, 53% yield). $^{1}$H NMR (300 MHz, *CDCl$_3$*) $\delta$ ppm 3.63 (s, 2 H, $CH_2$), 3.71 (s, 3 H, $OCH_3$), 6.86 (dd, *J* = 8.9, 2.8 Hz, 1 H, Ph), 6.90 - 6.99 (m, 2 H, Ph), 7.06 - 7.12 (m, 2 H, Ph), 7.31 (d, *J* = 7.9 Hz, 1 H, Ph), 7.37 (d, *J* = 8.8 Hz, 1

H, Ph). $^{13}$C NMR (75 MHz, *CDCl$_3$*) $\delta$ ppm 40.8 (1 C, $CH_2$), 52.1 (1 C, $OCH_3$), 117.8 (1 C, Ph), 118.0 (1 C, Ph), 120.2 (1 C, Ph), 120.3 (1 C, Ph), 125.1 (2 C, Ph), 130.0 (1 C, Ph), 130.9 (1 C, Ph), 133.1 (1 C, Ph), 136.1 (1 C, Ph), 156.1 (1 C, Ph), 156.3 (1 C, Ph), 171.5 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-(3,4-dichlorophenoxy)phenyl)acetate (0.2 g, 0.64 mmol) was treated with $LiAlH_4$ (49 mg, 1.3 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.23 g, 1.1 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (28 mg, 0.71 mmol) in DMSO (1 mL) was added **9** (0.11 g, 0.58 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 32 mg, 0.14 mmol) to afford **22f** (eluent system: 5% methanol in $CH_2Cl_2$, 41 mg, 0.098 mmol, 16% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) $\delta$ ppm 2.77 (s, 3 H, $SCH_3$), 7.05 (dd, *J* = 8.8, 2.6 Hz, 1 H, H-6''), 7.16 (br. s., 2 H, H-2', H-4'), 7.21 (d, *J* = 7.5 Hz, 1 H, H-6'), 7.34 (d, *J* = 2.6 Hz, 1 H, H-2''), 7.50 (t, *J* = 8.2 Hz, 1 H, H-5'), 7.66 (d, *J* = 8.9 Hz, 1 H, H-5''), 7.80 (br. s., 1 H, H-6), 13.12 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 99.1 (1 C, C-3), 112.4 (1 C, CN), 116.2 (1 C, C-5), 118.9 (1 C, C-6''), 119.3 (1 C, C-2'), 120.5 (1 C, C-2''), 120.9 (1 C, C-4'), 125.6 (1 C, (Cl)C-4''), 126.3 (1 C, C-6'), 130.5 (1 C, C-5'), 131.6 (1 C, C-5''), 132.1 (1 C, (Cl)C-3''), 134.7 (1 C, C-1'), 141.0 (1 C, C-6), 155.6 (1 C, C-3'), 156.1 (1 C, C-1''), 160.5 (1 C, C-2), 165.5 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{19}H_{12}Cl_2N_2O_3S - H]^-$ 416.9873, found 416.9875.

*4-(Methylsulfinyl)-2-oxo-5-(4-phenoxyphenyl)-1,2-dihydropyridine-3-carbonitrile* (**22g**)

According to a literature report,[29] methyl 2-(4-hydroxyphenyl)acetate (0.60 g, 4.4 mmol), phenylboronic acid (1.6 g, 13 mmol), $Cu(OAc)_2$ (1.6 g, 8.8 mmol), molecular sieves (0.8 g) and pyridine (1.1 mL, 13 mmol) in 1,2-dichloroethane (50 mL) afforded the ester intermediate methyl 2-(4-phenoxyphenyl)acetate **18g** (eluent system: 10% ethylacetate in petroleum ether, 0.66 g, 2.7 mmol, 62% yield). $^1$H NMR (300 MHz, *CDCl$_3$*) $\delta$ ppm 3.63 (s, 2 H, $CH_2$), 3.72 (s, 3 H, $OCH_3$), 6.95 - 7.06 (m, 4 H, Ph), 7.08 - 7.15 (m, 1 H, Ph), 7.23 - 7.29 (m, 2 H, Ph), 7.31 - 7.39 (m, 2 H, Ph). $^{13}$C NMR (75 MHz, *CDCl$_3$*) $\delta$ ppm 40.3 (1 C, $CH_2$), 52.0 (1 C, $OCH_3$), 118.8 (4 C, Ph), 123.2 (1 C, Ph), 128.7 (1 C, Ph), 129.6 (2 C, Ph), 130.5 (2 C, Ph), 156.3 (1 C, Ph), 157.0 (1 C, Ph), 172.0 (1 C, CO). Following the *General procedure for the synthesis of aldehyde*

*intermediates and final compounds*, methyl 2-(4-phenoxyphenyl)acetate (0.2 g, 0.83 mmol) was treated with $LiAlH_4$ (63 mg, 1.6 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.3 g, 1.4 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (50 mg, 1.3 mmol) in DMSO (1 mL) was added **9** (0.12 g, 0.63 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 67 mg, 0.29 mmol) to afford **22g** (eluent system: 5% methanol in $CH_2Cl_2$, 76 mg, 0.22 mmol, 26% yield). $^1$H NMR (400 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.79 (s, 3 H, $SCH_3$), 7.00 - 7.05 (m, 2 H, H-3', H-5'), 7.06 - 7.10 (m, 2 H, H-2'', H-6''), 7.20 (t, *J* = 7.2 Hz, 1 H, H-4''), 7.35 - 7.40 (m, 2 H, H-2', H-6'), 7.41 - 7.46 (m, 2 H, H-3'', H-5''), 7.76 (s, 1 H, H-6), 13.13 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.6 (1 C, $SCH_3$), 99.3 (1 C, C-3), 112.3 (1 C, CN), 116.6 (1 C, C-5), 117.9 (2 C, C-3', C-5'), 119.3 (2 C, C-2'', C-6''), 124.1 (1 C, C-4''), 127.3 (1 C, C-1'), 130.2 (2 C, C-3'', C-5''), 132.0 (2 C, C-2', C-6'), 140.6 (1 C, C-6), 155.9 (1 C, C-1''), 157.2 (1 C, C-4'), 160.4 (1 C, C-2), 165.9 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{19}H_{14}N_2O_3S - H]^-$ 349.0652, found 349.0654.

*5-(4-(4-Chlorophenoxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**22h**) According to a literature report,[29] methyl 2-(4-hydroxyphenyl)acetate (0.30 g, 2.2 mmol), (4-chlorophenyl)boronic acid (1.0 g, 6.6 mmol), $Cu(OAc)_2$ (0.80 g, 4.4 mmol), molecular sieves (0.40 g) and pyridine (0.53 mL, 6.6 mmol) in 1,2-dichloroethane (25 mL) afforded the ester intermediate methyl 2-(4-(4-chlorophenoxy)phenyl)acetate **18h** (eluent system: 10% ethylacetate in petroleum ether, 0.30 g, 1.1 mmol, 49% yield). $^1$H NMR (400 MHz, *$CDCl_3$*) $\delta$ ppm 3.62 (s, 2 H, $CH_2$), 3.72 (s, 3 H, $OCH_3$), 6.92 - 6.98 (m, 4 H, Ph), 7.23 - 7.31 (m, 4 H, Ph). $^{13}$C NMR (101 MHz, *$CDCl_3$*) $\delta$ ppm 40.3 (1 C, $CH_2$), 52.1 (1 C, $OCH_3$), 118.9 (2 C, Ph), 120.0 (2 C, Ph), 128.3 (1 C, Ph), 129.2 (1 C, Ph), 129.7 (2 C, Ph), 130.7 (2 C, Ph), 155.8 (1 C, Ph), 156.0 (1 C, Ph), 172.0 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(4-(4-chlorophenoxy)phenyl)acetate (0.2 g, 0.72 mmol) was treated with $LiAlH_4$ (55 mg, 1.5 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.26 g, 1.2 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (39 mg, 0.97 mmol) in DMSO (1 mL) was added **9** (91 mg, 0.48 mmol) to give methylthiopyridone intermediate, followed by oxidation

with mCPBA (75%, 61 mg, 0.27 mmol) to afford **22h** (eluent system: 5% methanol in $CH_2Cl_2$, 91 mg, 0.24 mmol, 33% yield). $^1$H NMR (400 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.79 (s, 3 H, $SCH_3$), 7.04 - 7.13 (m, 4 H, H-3', H-5', H-2'', H-6''), 7.36 - 7.43 (m, 2 H, H-2', H-6'), 7.45 - 7.51 (m, 2 H, H-3'', H-5''), 7.77 (s, 1 H, H-6), 13.13 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.6 (1 C, $SCH_3$), 99.3 (1 C, C-3), 112.3 (1 C, CN), 116.5 (1 C, C-5), 118.2 (2 C, C-3', H-5'), 120.9 (2 C, C-2'', C-6''), 127.7 (1 C, C-1'), 127.8 (1 C, (Cl)C-4''), 130.0 (2 C, C-3'', C-5''), 132.2 (2 C, C-2', C-6'), 140.7 (1 C, C-6), 154.9 (1 C, C-1''), 156.7 (1 C, C-4'), 160.4 (1 C, C-2), 165.9 (1 C, C-4). HRMS (ESI): m/z [M - H]$^-$ Calcd. for [$C_{19}H_{13}ClN_2O_3S$ - H]$^-$ 383.0262, found 383.0258.

*4-(Methylsulfinyl)-2-oxo-5-(4-(p-tolyloxy)phenyl)-1,2-dihydropyridine-3-carbonitrile* (**22i**)

According to a literature report,[29] methyl 2-(4-hydroxyphenyl)acetate (0.30 g, 2.2 mmol), *p*-tolylboronic acid (0.90 g, 6.6 mmol), $Cu(OAc)_2$ (0.80 g, 4.4 mmol), molecular sieves (0.40 g) and pyridine (0.53 mL, 6.6 mmol) in 1,2-dichloroethane (25 mL) afforded the ester intermediate methyl 2-(4-(*p*-tolyloxy)phenyl)acetate **18i** (eluent system: 10% ethylacetate in petroleum ether, 0.18 g, 0.70 mmol, 32% yield). $^1$H NMR (400 MHz, *$CDCl_3$*) $\delta$ ppm 2.35 (s, 3 H, (Ph)$CH_3$), 3.61 (s, 2 H, $CH_2$), 3.71 (s, 3 H, $OCH_3$), 6.90 - 6.97 (m, 4 H, Ph), 7.15 (d, *J* = 8.1 Hz, 2 H, Ph), 7.23 (d, *J* = 8.8 Hz, 2 H, Ph). $^{13}$C NMR (101 MHz, *$CDCl_3$*) $\delta$ ppm 20.7 (1 C, (Ph)$CH_3$), 40.3 (1 C, $CH_2$), 52.0 (1 C, $OCH_3$), 118.3 (2 C, Ph), 119.1 (2 C, Ph), 128.3 (1 C, Ph), 130.2 (2 C, Ph), 130.5 (2 C, Ph), 133.0 (1 C, Ph), 154.6 (1 C, Ph), 156.9 (1 C, Ph), 172.1 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(4-(p-tolyloxy)phenyl)acetate (0.2 g, 0.78 mmol) was treated with $LiAlH_4$ (59 mg, 1.6 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.29 g, 1.3 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (54 mg, 1.4 mmol) in DMSO (1 mL) was added **9** (0.13 g, 0.67 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 72 mg, 0.32 mmol) to afford **22i** (eluent system: 5% methanol in $CH_2Cl_2$, 0.11 g, 0.30 mmol, 38% yield). $^1$H NMR (400 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.31 (s, 3 H, (Ph)$CH_3$), 2.79 (s, 3 H, $SCH_3$), 6.98 (dx2, *J* = 8.5 Hz, 4 H, H-3', H-5', H-2'', H-6''), 7.24 (d, *J* = 8.1 Hz, 2 H, H-3'', H-5''), 7.35 (d, *J* = 8.6 Hz, 2 H, H-2', H-6'), 7.75 (s, 1 H, H-6), 13.12 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-$d_6$*) $\delta$ ppm 20.3 (1 C, (Ph)$CH_3$), 39.7 (1 C, $SCH_3$), 99.3 (1 C, C-3), 112.4 (1 C, CN), 116.6 (1 C, C-5), 117.4 (2 C,

C-3', C-5'), 119.5 (2 C, C-2'', C-6''), 126.8 (1 C, C-1'), 130.6 (2 C, C-3'', C-5''), 132.0 (2 C, C-2', C-6'), 133.4 (1 C, $(CH_3)$C-4''), 140.7 (1 C, C-6), 153.4 (1 C, C-1''), 157.8 (1 C, C-4'), 160.4 (1 C, C-2), 165.9 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{20}H_{16}N_2O_3S - H]^-$ 363.0809, found 363.0810.

*5-(4-(4-Methoxyphenoxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**22j**) According to a literature report,[29] methyl 2-(4-hydroxyphenyl)acetate (0.30 g, 2.2 mmol), (4-methoxyphenyl)boronic acid (1.0 g, 6.6 mmol), $Cu(OAc)_2$ (0.80 g, 4.4 mmol), molecular sieves (0.40 g) and pyridine (0.53 mL, 6.6 mmol) in 1,2-dichloroethane (25 mL) afforded the ester intermediate methyl 2-(4-(4-methoxyphenoxy)phenyl)acetate **18j** (eluent system: 10% ethylacetate in petroleum ether, 0.38 g, 1.4 mmol, 63% yield). $^1$H NMR (400 MHz, *CDCl$_3$*) $\delta$ ppm 3.60 (s, 2 H, $CH_2$), 3.71 (s, 3 H, $OCH_3$), 3.81 (s, 3 H, (Ph)$OCH_3$), 6.86 - 6.93 (m, 4 H, Ph), 6.96 - 7.01 (m, 2 H, Ph), 7.19 - 7.24 (m, 2 H, Ph). $^{13}$C NMR (101 MHz, *CDCl$_3$*) $\delta$ ppm 40.3 (1 C, $CH_2$), 52.0 (1 C, $OCH_3$), 55.6 (1 C, (Ph)$OCH_3$), 114.8 (2 C, Ph), 117.6 (2 C, Ph), 120.8 (2 C, Ph), 127.9 (1 C, Ph), 130.4 (2 C, Ph), 150.0 (1 C, Ph), 155.9 (1 C, Ph), 157.7 (1 C, Ph), 172.2 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(4-(4-methoxyphenoxy)phenyl)acetate (0.2 g, 0.74 mmol) was treated with $LiAlH_4$ (56 mg, 1.5 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.32 g, 1.5 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (37 mg, 0.93 mmol) in DMSO (1 mL) was added **9** (87 mg, 0.46 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 31 mg, 0.13 mmol) to afford **22j** (eluent system: 5% methanol in $CH_2Cl_2$, 0.14 g, 0.37 mmol, 15% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) $\delta$ ppm 2.78 (s, 3 H, $SCH_3$), 3.76 (s, 3 H, (Ph)$OCH_3$), 6.91 - 6.96 (m, 2 H, H-3', H-5'), 6.97 - 7.02 (m, 2 H, H-3'', H-5''), 7.03 - 7.09 (m, 2 H, H-2'', H-6''), 7.23 - 7.41 (m, 2 H, H-2', H-6'), 7.74 (s, 1 H, H-6), 13.11 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) $\delta$ ppm 39.6 (1 C, $SCH_3$), 55.4 (1 C, (Ph)$OCH_3$), 99.4 (1 C, C-3), 112.4 (1 C, CN), 115.2 (2 C, C-3'', C-5''), 116.7 (3 C, C-5, C-3', C-5'), 121.3 (2 C, C-2'', C-6''), 126.4 (1 C, C-1'), 131.9 (2 C, C-2', C-6'), 140.6 (1 C, C-6), 148.6 (1 C, C-1''), 156.0 (1 C, ($CH_3O$)C-4''), 158.5 (1 C, C-4'), 160.4 (1 C, C-2), 166.0 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{20}H_{16}N_2O_4S-H]^-$ 379.0758, found 379.0739.

*5-(4-(3,4-Dichlorophenoxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**22k**) According to a literature report,[29] methyl 2-(4-hydroxyphenyl)acetate (0.30 g, 2.2 mmol), (3,4-dichlorophenyl)boronic acid (1.3 g, 6.6 mmol), $Cu(OAc)_2$ (0.80 g, 4.4 mmol), molecular sieves (0.40 g) and pyridine (0.53 mL, 6.6 mmol) in 1,2-dichloroethane (25 mL) afforded the ester intermediate methyl 2-(4-(3,4-dichlorophenoxy)phenyl)acetate **18k** (eluent system: 10% ethylacetate in petroleum ether, 0.40 g, 1.3 mmol, 58% yield). $^1$H NMR (400 MHz, *CDCl$_3$*) $\delta$ ppm 3.63 (s, 2 H, $CH_2$), 3.73 (s, 3 H, $OCH_3$), 6.86 (dd, *J* = 8.8, 2.8 Hz, 1 H, Ph), 6.95 - 7.01 (m, 2 H, Ph), 7.09 (d, *J* = 2.9 Hz, 1 H, Ph), 7.27 - 7.31 (m, 2 H, Ph), 7.38 (d, *J* = 8.8 Hz, 1 H, Ph). $^{13}$C NMR (101 MHz, *CDCl$_3$*) $\delta$ ppm 40.3 (1 C, $CH_2$), 52.1 (1 C, $OCH_3$), 117.9 (1 C, Ph), 119.4 (2 C, Ph), 120.3 (1 C, Ph), 126.5 (1 C, Ph), 129.9 (1 C, Ph), 130.9 (2 C, Ph), 131.0 (1 C, Ph), 133.2 (1 C, Ph), 155.2 (1 C, Ph), 156.5 (1 C, Ph), 171.9 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(4-(3,4-dichlorophenoxy)phenyl)acetate (0.2 g, 0.65 mmol) was treated with $LiAlH_4$ (49 mg, 1.3 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.24 g, 1.1 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (46 mg, 1.1 mmol) in DMSO (1 mL) was added **9** (0.11 g, 0.57 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 34 mg, 0.15 mmol) to afford **22k** (eluent system: 5% methanol in $CH_2Cl_2$, 41 mg, 0.098 mmol, 15% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) $\delta$ ppm 2.80 (s, 3 H, $SCH_3$), 7.07 (dd, *J* = 8.9, 2.9 Hz, 1 H, H-6''), 7.10 - 7.16 (m, 2 H, H-3', H-5'), 7.38 (d, *J* = 2.8 Hz, 1 H, H-2''), 7.40 - 7.45 (m, 2 H, H-2', H-6'), 7.68 (d, *J* = 8.9 Hz, 1 H, H-5''), 7.78 (s, 1 H, H-6), 13.14 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 99.3 (1 C, C-3), 112.4 (1 C, CN), 116.4 (1 C, C-5), 118.7 (2 C, C-3', C-5'), 119.2 (1 C, C-6''), 120.9 (1 C, C-2''), 125.9 (1 C, (Cl)C-4''), 128.4 (1 C, C-1'), 131.7 (1 C, C-5''), 132.1 (1 C, (Cl)C-3''), 132.3 (2 C, C-2', C-6'), 140.8 (1 C, C-6), 155.7 (1 C, C-1''), 156.1 (1 C, C-4'), 160.4 (1 C, C-2), 165.8 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{19}H_{12}Cl_2N_2O_3S - H]^-$ 416.9873, found 416.9865.

*5-(3-(Benzyloxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**27a**) According to a literature report[30] with minor revision, methyl 2-(3-hydroxyphenyl)acetate

(0.30 g, 2.2 mmol), benzyl bromide (0.26 mL, 2.2 mmol), $K_2CO_3$ (0.61 g, 4.4 mmol), sodium iodide (33 mg, 0.22 mmol) in DMF (10 mL) afforded the ester intermediate methyl 2-(3-(benzyloxy)phenyl)acetate **23a** (eluent system: 10% ethylacetate in petroleum ether, 0.33 g, 1.3 mmol, 58% yield). $^1$H NMR (300 MHz, *CDCl$_3$*) *δ* ppm 3.65 (s, 2 H, $CH_2$), 3.73 (s, 3 H, $OCH_3$), 5.10 (s, 2 H, (Ph)$CH_2$), 6.83 - 7.05 (m, 3 H, Ph), 7.21 - 7.52 (m, 6 H, Ph). $^{13}$C NMR (75 MHz, *CDCl$_3$*) *δ* ppm 41.1 (1 C, $CH_2$), 52.0 (1 C, $OCH_3$), 69.8 (1 C, (Ph)$CH_2$), 113.4 (1 C, Ph), 115.8 (1 C, Ph), 121.8 (1 C, Ph), 127.5 (2 C, Ph), 127.9 (1 C, Ph), 128.5 (2 C, Ph), 129.5 (1 C, Ph), 135.4 (1 C, Ph), 136.9 (1 C, Ph), 158.9 (1 C, Ph), 171.8 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-(benzyloxy)phenyl)acetate (0.2 g, 0.78 mmol) was treated with $LiAlH_4$ (59 mg, 1.6 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.34 g, 1.6 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (48 mg, 1.2 mmol) in DMSO (1 mL) was added **9** (0.11 g, 0.60 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 69 mg, 0.30 mmol) to afford **27a** (eluent system: 5% methanol in $CH_2Cl_2$, 92 mg, 0.25 mmol, 32% yield). $^1$H NMR (300 MHz, *DMSO-d$_6$*) *δ* ppm 2.73 (s, 3 H, $SCH_3$), 5.11 (s, 2 H, (Ph)$CH_2$), 6.92 (dt, *J* = 7.6, 1.2 Hz, 1 H, H-6'), 7.01 - 7.10 (m, 2 H, H-2', H-4'), 7.26 - 7.48 (m, 6 H, H-5', H-2'', H-3'', H-4'', H-5'', H-6''), 7.74 (s, 1 H, H-6), 13.12 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-d$_6$*) *δ* ppm 39.8 (1 C, $SCH_3$), 69.3 (1 C, (Ph)$CH_2$), 99.3 (1 C, C-3), 112.3 (1 C, CN), 115.1 (1 C, C-2'), 116.5 (1 C, C-4'), 117.0 (1 C, C-5), 122.6 (1 C, C-6'), 127.8 (2 C, C-2'', C-6''), 127.9 (1 C, C-4''), 128.4 (2 C, C-3'', C-5''), 129.7 (1 C, C-5'), 133.9 (1 C, C-1'), 136.8 (1 C, C-1''), 140.5 (1 C, C-6), 158.3 (1 C, C-3'), 160.4 (1 C, C-2), 165.9 (1 C, C-4). HRMS (ESI): m/z [M - H]$^-$ Calcd. for [$C_{20}H_{16}N_2O_3S$ - H]$^-$ 363.0809, found 363.0821.

*5-(3-((4-Chlorobenzyl)oxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**27b**) According to a literature report[30] with minor revision, methyl 2-(3-hydroxyphenyl)acetate (0.40 g, 2.9 mmol), 4-chlorobenzyl bromide (0.60 g, 2.9 mmol), $K_2CO_3$ (0.81 g, 5.9 mmol), sodium iodide (44 mg, 0.29 mmol) in DMF (20 mL) afforded the ester intermediate methyl 2-(3-((4-chlorobenzyl)oxy)phenyl)acetate **23b** (eluent system: 10% ethylacetate in petroleum ether, 0.50 g, 1.7 mmol, 5% yield). $^1$H NMR (400 MHz, *CDCl$_3$*) *δ* ppm 3.61 (s, 2 H, $CH_2$), 3.70 (s, 3 H, $OCH_3$), 5.03 (s, 2 H, (Ph)$CH_2$), 6.85 - 6.93 (m, 3 H, Ph), 7.22 -

7.29 (m, 1 H, Ph), 7.36 - 7.39 (m, 4 H, Ph). $^{13}$C NMR (101 MHz, *CDCl$_3$*) $\delta$ ppm 41.2 (1 C, $CH_2$), 52.1 (1 C, $OCH_3$), 69.1 (1 C, (Ph)$CH_2$), 113.5 (1 C, Ph), 115.8 (1 C, Ph), 122.1 (1 C, Ph), 128.7(2 C, Ph), 128.8 (2 C, Ph), 129.6 (1 C, Ph), 133.7 (1 C, Ph), 135.4 (1 C, Ph), 135.5 (1 C, Ph), 158.7 (1 C, Ph), 171.9 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-((4-chlorobenzyl)oxy)phenyl)acetate (0.2 g, 0.69 mmol) was treated with $LiAlH_4$ (52 mg, 1.4 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.29 g, 1.3 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (48 mg, 1.2 mmol) in DMSO (1 mL) was added **9** (0.11 g, 0.60 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 58 mg, 0.25 mmol) to afford **27b** (eluent system: 5% methanol in $CH_2Cl_2$, 84 mg, 0.21 mmol, 31% yield). $^1$H NMR (400 MHz, *DMSO-d$_6$*) $\delta$ ppm 2.75 (s, 3 H, $SCH_3$), 5.13 (s, 2 H, (Ph)$CH_2$), 6.95 (d, *J* = 7.5 Hz, 1 H, H-6'), 7.07 (br. s., 2 H, H-2', H-4'), 7.36 (t, *J* = 8.3 Hz, 1 H, H-5'), 7.43 - 7.56 (m, 4 H, H-2'', H-3'', H-5'', H-6''), 7.76 (s, 1 H, H-6), 13.14 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-d$_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 68.5 (1 C, (Ph)$CH_2$), 99.3 (1 C, C-3), 112.3 (1 C, CN), 115.2 (1 C, C-2'), 116.5 (1 C, C-4'), 116.9 (1 C, C-5), 122.8 (1 C, C-6'), 128.5 (2 C, C-3'', C-5''), 129.6 (2 C, C-2'', C-6''), 129.8 (1 C, C-5'), 132.5 (1 C, (Cl)C-4''), 133.9 (1 C, C-1'), 135.9 (1 C, C-1''), 140.4 (1 C, C-6), 158.1 (1 C, C-3'), 160.4 (1 C, C-2), 165.9 (1 C, C-4). HRMS (ESI): m/z [M - H]$^-$ Calcd. for [$C_{20}H_{15}ClN_2O_3S$ - H]$^-$ 397.0419, found 397.0417.

*5-(3-((3,4-Dichlorobenzyl)oxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**27c**) According to a literature report[30] with minor revision, methyl 2-(3-hydroxyphenyl)acetate (0.40 g, 2.9 mmol), 3,4-dichlorobenzyl bromide (0.70 g, 2.9 mmol), $K_2CO_3$ (0.81 g, 5.9 mmol), sodium iodide (44 mg, 0.29 mmol) in DMF (20 mL) afforded the ester intermediate methyl 2-(3-((3,4-dichlorobenzyl)oxy)phenyl)acetate **23c** (eluent system: 10% ethylacetate in petroleum ether, 0.75 g, 2.3 mmol, 84% yield). $^1$H NMR (300 MHz, *CDCl$_3$*) $\delta$ ppm 3.62 (s, 2 H, $CH_2$), 3.70 (s, 3 H, $OCH_3$), 5.01 (s, 2 H, (Ph)$CH_2$), 6.87 (d, *J* = 8.2 Hz, 1 H, Ph), 6.93 (br. s., 2 H, Ph), 7.21 - 7.30 (m, 2 H, Ph), 7.41 - 7.48 (m, 1 H, Ph), 7.54 (s, 1 H, Ph). $^{13}$C NMR (75 MHz, *CDCl$_3$*) $\delta$ ppm 41.1 (1 C, $CH_2$), 52.1 (1 C, $OCH_3$), 68.4 (1 C, (Ph)$CH_2$), 113.4 (1 C, Ph), 115.8 (1 C, Ph), 122.3 (1 C, Ph), 126.5 (1 C, Ph), 129.2 (1 C, Ph), 129.7 (1 C, Ph), 130.5 (1 C, Ph), 131.8 (1 C, Ph), 132.6 (1 C, Ph), 135.6 (1 C, Ph), 137.3 (1 C, Ph), 158.4

(1 C, Ph), 171.7 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-((3,4-dichlorobenzyl)oxy)phenyl)acetate (0.2 g, 0.62 mmol) was treated with $LiAlH_4$ (47 mg, 1.2 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.26 g, 1.2 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (48 mg, 1.2 mmol) in DMSO (1 mL) was added **9** (0.11 g, 0.60 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 58 mg, 0.26 mmol) to afford **27c** (eluent system: 5% methanol in $CH_2Cl_2$, 80 mg, 0.18 mmol, 30% yield). $^1$H NMR (300 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.73 (s, 3 H, $SCH_3$), 5.13 (s, 2 H, (Ph)$CH_2$), 6.94 (d, *J* = 7.3 Hz, 1 H, H-6'), 7.00 - 7.09 (m, 2 H, H-2', H-4'), 7.29 - 7.46 (m, 2 H, H-5', H-6''), 7.64 (d, *J* = 8.5 Hz, 1 H, H-5''), 7.69 (s, 1 H, H-2''), 7.74 (s, 1 H, H-6), 13.14 (br. s., 1 H, NH). $^{13}$C NMR (75 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.8 (1 C, $SCH_3$), 67.7 (1 C, (Ph)$CH_2$), 99.3 (1 C, C-3), 112.3 (1 C, CN), 115.2 (1 C, C-2'), 116.6 (1 C, C-4'), 116.9 (1 C, C-5), 122.9 (1 C, C-6'), 127.9 (1 C, C-6''), 129.5 (1 C, C-2''), 129.8 (1 C, C-5'), 130.4 (1 C, (Cl)C-4''), 130.7 (1 C, C-5''), 131.1 (1 C, (Cl)C-3''), 134.0 (1 C, C-1'), 138.1 (1 C, C-1''), 140.5 (1 C, C-6), 157.9 (1 C, C-3'), 160.4 (1 C, C-2), 165.8 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{20}H_{14}Cl_2N_2O_3S - H]^-$ 431.0029, found 431.0031.

*5-(3-((2-Chlorobenzyl)oxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**27d**) According to a literature report[30] with minor revision, methyl 2-(3-hydroxyphenyl)acetate (0.40 g, 2.9 mmol), 1-(bromomethyl)-2-chlorobenzene (0.60 g, 2.9 mmol), $K_2CO_3$ (0.81 g, 5.9 mmol), sodium iodide (44 mg, 0.29 mmol) in DMF (20 mL) afforded the ester intermediate methyl 2-(3-((2-chlorobenzyl)oxy)phenyl)acetate **23d** (eluent system: 10% ethylacetate in petroleum ether, 0.26 g, 0.89 mmol, 30% yield). $^1$H NMR (300 MHz, *$CDCl_3$*) $\delta$ ppm 3.63 (s, 2 H, $CH_2$), 3.71 (s, 3 H, $OCH_3$), 5.17 (s, 2 H, (Ph)$CH_2$), 6.86 - 7.01 (m, 3 H, Ph), 7.23 - 7.36 (m, 3 H, Ph), 7.41 (dd, *J* = 7.0, 2.1 Hz, 1 H, Ph), 7.53 - 7.63 (m, 1 H, Ph). $^{13}$C NMR (75 MHz, *$CDCl_3$*) $\delta$ ppm 41.2 (1 C, $CH_2$), 52.1 (1 C, $OCH_3$), 67.1 (1 C, (Ph)$CH_2$), 113.4 (1 C, Ph), 116.0 (1 C, Ph), 122.1 (1 C, Ph), 126.9 (1 C, Ph), 128.8 (1 C, Ph), 129.0 (1 C, Ph), 129.3 (1 C, Ph), 129.6 (1 C, Ph), 132.6 (1 C, Ph), 134.7 (1 C, Ph), 135.5 (1 C, Ph), 158.7 (1 C, Ph), 171.8 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-((2-chlorobenzyl)oxy)phenyl)acetate (0.2 g, 0.69 mmol) was treated

with $LiAlH_4$ (52 mg, 1.4 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.25 g, 1.2 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (43 mg, 1.1 mmol) in DMSO (1 mL) was added **9** (0.10 g, 0.53 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 89 mg, 0.39 mmol) to afford **27d** (eluent system: 5% methanol in $CH_2Cl_2$, 90 mg, 0.23 mmol, 33% yield). $^1$H NMR (400 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.77 (s, 3 H, $SCH_3$), 5.19 (s, 2 H, (Ph)$CH_2$), 6.97 (dd, *J* = 7.7, 1.2 Hz, 1 H, H-6'), 7.06 - 7.13 (m, 2 H, H-2', H-4'), 7.33 - 7.44 (m, 3 H, H-5', H-4'', H-5''), 7.49 - 7.56 (m, 1 H, H-3''), 7.59 - 7.65 (m, 1 H, H-6''), 7.79 (s, 1 H, H-6), 13.15 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 67.0 (1 C, (Ph)$CH_2$), 99.3 (1 C, C-3), 112.4 (1 C, CN), 115.2 (1 C, C-2'), 116.4 (1 C, C-4'), 116.9 (1 C, C-5), 122.9 (1 C, C-6'), 127.4 (1 C, C-5''), 129.4 (1 C, C-3''), 129.8 (1 C, C-5'), 129.9 (1 C, C-4''), 130.2 (1 C, C-6''), 132.6 (1 C, (Cl)C-2''), 134.0 (1 C, C-1'), 134.1 (1 C, C-1''), 140.5 (1 C, C-6), 158.1 (1 C, C-3'), 160.4 (1 C, C-2), 165.9 (1 C, C-4). HRMS (ESI): m/z [M - H]$^-$ Calcd. for [$C_{20}H_{15}ClN_2O_3S$ - H]$^-$ 397.0419, found 397.0411.

*5-(3-((3-Chlorobenzyl)oxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**27e**) According to a literature report[30] with minor revision, methyl 2-(3-hydroxyphenyl)acetate (0.40 g, 2.9 mmol), *m*-chlorobenzyl bromide (0.60 g, 2.9 mmol), $K_2CO_3$ (0.81 g, 5.9 mmol), sodium iodide (44 mg, 0.29 mmol) in DMF (20 mL) afforded the ester intermediate methyl 2-(3-((3-chlorobenzyl)oxy)phenyl)acetate **23e** (eluent system: 10% ethylacetate in petroleum ether, 0.62 g, 2.1 mmol, 73% yield). $^1$H NMR (400 MHz, *$CDCl_3$*) $\delta$ ppm 3.61 (s, 2 H, $CH_2$), 3.70 (s, 3 H, $OCH_3$), 5.03 (s, 2 H, (Ph)$CH_2$), 6.84 - 6.94 (m, 3 H, Ph), 7.23 - 7.28 (m, 1 H, Ph), 7.29 - 7.32 (m, 3 H, Ph), 7.35 - 7.48 (m, 1 H, Ph). $^{13}$C NMR (101 MHz, *$CDCl_3$*) $\delta$ ppm 41.2 (1 C, $CH_2$), 52.1 (1 C, $OCH_3$), 69.1 (1 C, (Ph)$CH_2$), 113.4 (1 C, Ph), 115.8 (1 C, Ph), 122.1 (1 C, Ph), 125.3 (1 C, Ph), 127.4 (1 C, Ph), 128.0 (1 C, Ph), 129.6 (1 C, Ph), 129.8 (1 C, Ph), 134.5 (1 C, Ph), 135.5 (1 C, Ph), 139.0 (1 C, Ph), 158.6 (1 C, Ph), 171.9 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-((3-chlorobenzyl)oxy)phenyl)acetate (0.2 g, 0.69 mmol) was treated with $LiAlH_4$ (52 mg, 1.4 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.26 g, 1.2 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (42 mg,

1.0 mmol) in DMSO (1 mL) was added **9** (98 mg, 0.52 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 58 mg, 0.26 mmol) to afford **27e** (eluent system: 5% methanol in $CH_2Cl_2$, 74 mg, 0.19 mmol, 27% yield). $^1$H NMR (400 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.75 (s, 3 H, $SCH_3$), 5.15 (s, 2 H, (Ph)$CH_2$), 6.95 (d, *J* = 7.6 Hz, 1 H, H-6'), 7.02 - 7.12 (m, 2 H, H-2', H-4'), 7.31 - 7.48 (m, 4 H, H-5', H-4'', H-5'', H-6''), 7.52 (s, 1 H, H-2''), 7.77 (s, 1 H, H-6), 13.15 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.8 (1 C, $SCH_3$), 68.4 (1 C, (Ph)$CH_2$), 99.4 (1 C, C-3), 112.3 (1 C, CN), 115.1 (1 C, C-2'), 116.5 (1 C, C-4'), 116.9 (1 C, C-5), 122.8 (1 C, C-6'), 126.2 (1 C, C-6''), 127.3 (1 C, C-2''), 127.8 (1 C, C-4''), 129.8 (1 C, C-5'), 130.4 (1 C, C-5''), 133.1 (1 C, (Cl)C-3''), 133.9 (1 C, C-1'), 139.4 (1 C, C-1''), 140.4 (1 C, C-6), 158.0 (1 C, C-3'), 160.4 (1 C, C-2), 165.9 (1 C, C-4). HRMS (ESI): m/z $[M + H]^+$ Calcd. for $[C_{20}H_{15}ClN_2O_3S + H]^+$ 399.0565, found 399.0544.

*4-(Methylsulfinyl)-5-(3-((2-nitrobenzyl)oxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**27f**) According to a literature report[30] with minor revision, methyl 2-(3-hydroxyphenyl)acetate (0.40 g, 2.9 mmol), 2-nitrobenzyl bromide (0.64 g, 2.9 mmol), $K_2CO_3$ (0.81 g, 5.9 mmol), sodium iodide (44 mg, 0.29 mmol) in DMF (20 mL) afforded the ester intermediate methyl 2-(3-((2-nitrobenzyl)oxy)phenyl)acetate **23f** (eluent system: 10% ethylacetate in petroleum ether, 0.60 g, 2.0 mmol, 88% yield). $^1$H NMR (300 MHz, *$CDCl_3$*) $\delta$ ppm 3.62 (s, 2 H, $CH_2$), 3.71 (s, 3 H, $OCH_3$), 5.49 (s, 2 H, (Ph)$CH_2$), 6.85 - 6.99 (m, 3 H, Ph), 7.27 (t, *J* = 7.8 Hz, 1 H, Ph), 7.42 - 7.55 (m, 1 H, Ph), 7.69 (td, *J* = 7.6, 1.2 Hz, 1 H, Ph), 7.85 - 7.96 (m, 1 H, Ph), 8.18 (dd, *J* = 8.2, 1.2 Hz, 1 H, Ph). $^{13}$C NMR (75 MHz, *$CDCl_3$*) $\delta$ ppm 41.1 (1 C, $CH_2$), 52.1 (1 C, $OCH_3$), 66.7 (1 C, (Ph)$CH_2$), 113.4 (1 C, Ph), 116.1 (1 C, Ph), 122.5 (1 C, Ph), 124.9 (1 C, Ph), 128.3 (1 C, Ph), 128.5 (1 C, Ph), 129.7 (1 C, Ph), 133.8 (1 C, Ph), 134.0 (1 C, Ph), 135.6 (1 C, Ph), 149.2 (1 C, Ph), 158.3 (1 C, Ph), 171.8 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(3-((2-nitrobenzyl)oxy)phenyl)acetate (0.2 g, 0.66 mmol) was treated with $LiAlH_4$ (50 mg, 1.3 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.13 g, 0.61 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (20 mg, 0.49 mmol) in DMSO (1 mL) was added **9** (46 mg, 0.25 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 17 mg, 0.080 mmol) to afford **27f**

(eluent system: 5% methanol in $CH_2Cl_2$, 7.0 mg, 0.017 mmol, 3% yield). $^1$H NMR (400 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.72 (s, 3 H, $SCH_3$), 5.50 (s, 2 H, (Ph)$CH_2$), 6.97 (d, *J* = 7.6 Hz, 1 H, H-6'), 7.03 - 7.12 (m, 2 H, H-2', H-4'), 7.37 (t, *J* = 8.1 Hz, 1 H, H-5'), 7.58 - 7.67 (m, 1 H, H-4''), 7.74 - 7.84 (m, 3 H, H-6, H-5'', H-6''), 8.14 (d, *J* = 7.9 Hz, 1 H, H-3''), 13.14 (s, 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-$d_6$*) $\delta$ ppm 39.7 (1 C, $SCH_3$), 66.4 (1 C, (Ph)$CH_2$), 99.3 (1 C, C-3), 112.3 (1 C, CN), 115.3 (1 C, C-2'), 116.3 (1 C, C-4'), 123.1 (1 C, C-6'), 124.9 (1 C, C-3''), 129.2 (2 C, C-4'', C-6''), 129.9 (1 C, C-5'), 132.3 (1 C , C-1''), 134.0 (2 C, C-1', C-5''), 140.5 (1 C, C-6), 147.5 (1 C, ($NO_2$)C-2''), 157.8 (1 C, C-3'), 160.4 (1 C, C-2), 166.1 (1 C, C-4). C (C-5) could not be observed. HRMS (ESI): m/z [M - H]$^-$ Calcd. for [$C_{20}H_{15}N_3O_5S$ - H]$^-$ 408.0659, found 408.0661.

*5-(4-(Benzyloxy)phenyl)-4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* (**27g**) According to a literature report[30] with minor revision, methyl 2-(4-hydroxyphenyl)acetate (0.30 g, 2.2 mmol), benzyl bromide (0.26 mL, 2.2 mmol), $K_2CO_3$ (0.61 g, 4.4 mmol), sodium iodide (33 mg, 0.22 mmol) in DMF (10 mL) afforded the ester intermediate methyl 2-(4-(benzyloxy)phenyl)acetate **23g** (eluent system: 10% ethylacetate in petroleum ether, 0.38 g, 1.5 mmol, 67% yield). $^1$H NMR (400 MHz, *$CDCl_3$*) $\delta$ ppm 3.59 (s, 2 H, $CH_2$), 3.71 (s, 3 H, $OCH_3$), 5.07 (s, 2 H, (Ph)$CH_2$), 6.93 - 6.98 (m, 2 H, Ph), 7.19 - 7.25 (m, 2 H, Ph), 7.31 - 7.37 (m, 1 H, Ph), 7.38 - 7.47 (m, 4 H, Ph). $^{13}$C NMR (101 MHz, *$CDCl_3$*) $\delta$ ppm 40.3 (1 C, $CH_2$), 52.0 (1 C, $OCH_3$), 70.0 (1 C, (Ph)$CH_2$), 114.9 (2 C, Ph), 126.3 (1 C, Ph), 127.4 (2 C, Ph), 127.9 (1 C, Ph), 128.5 (2 C, Ph), 130.3 (2 C, Ph), 137.0 (1 C, Ph), 157.9 (1 C, Ph), 172.3 (1 C, CO). Following the *General procedure for the synthesis of aldehyde intermediates and final compounds*, methyl 2-(4-(benzyloxy)phenyl)acetate (0.2 g, 0.78 mmol) was treated with $LiAlH_4$ (59 mg, 1.6 mmol) in dry THF (5 mL) to give alcohol intermediate, which was oxidized with PCC (0.33 g, 1.5 mmol) in $CH_2Cl_2$ (5 mL) to yield aldehyde. The suspension of aldehyde and NaOH (57 mg, 1.42 mmol) in DMSO (1 mL) was added **9** (0.13 g, 0.71 mmol) to give methylthiopyridone intermediate, followed by oxidation with mCPBA (75%, 48 mg, 0.21 mmol) to afford **27g** (eluent system: 5% methanol in $CH_2Cl_2$, 29 mg, 0.080 mmol, 10% yield). $^1$H NMR (400 MHz, *DMSO-$d_6$*) $\delta$ ppm 2.76 (s, 3 H, $SCH_3$), 5.14 (s, 2 H, (Ph)$CH_2$), 7.04 - 7.09 (m, 2 H, H-3', H-5'), 7.26 - 7.37 (m, 3 H, H-2', H-6', H-4''), 7.38 - 7.44 (m, 2 H, H-3'', H-5''), 7.44 - 7.50 (m, 2 H, H-2'', H-6''), 7.70 (s, 1 H, H-6), 13.08 (br. s., 1 H, NH). $^{13}$C NMR (101 MHz, *DMSO-$d_6$*)

$\delta$ ppm 39.6 (1 C, $SCH_3$), 69.3 (1 C, (Ph)$CH_2$), 99.2 (1 C, C-3), 112.4 (1 C, CN), 114.7 (2 C, C-3', C-5'), 116.9 (1 C, C-5), 124.8 (1 C, C-1'), 127.8 (2 C, C-2'', C-6''), 127.9 (1 C, C-4''), 128.5 (2 C, C-3'', C-5''), 131.5 (2 C, C-2', C-6'), 136.8 (1 C, C-1''), 140.5 (1 C, C-6), 158.5 (1 C, C-4'), 160.4 (1 C, C-2), 166.1 (1 C, C-4). HRMS (ESI): m/z $[M - H]^-$ Calcd. for $[C_{20}H_{16}N_2O_3S - H]^-$ 363.0809, found 363.0796.

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- 5-aryl-substituted cyanopyridone analogues were prepared and evaluated as anti-*M. tuberculosis* agents.
- Biphenyl analogue **11i** demonstrated promising antitubercular activity (MIC H37Rv, 1.2 μM) and reasonable selectivity.
- The lack of a clear correlation between thymilylate kinase inhibitory potency and in vitro antimycobacterial activity points towards a new, yet unknown mode of action.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: