3,5-Dialkoxyypyridine analogues of bedaquiline are potent antituberculosis agents with minimal inhibition of the hERG channel

Hamish S. Sutherlanda, Amy S.T. Tonga, Peter J. Choia, Adrian Blaser, Daniel Conoleb,c,d, Scott G. Franzblau, Manisha U. Lotlikard, Christopher B. Cooperd, Anna M. Uptond, William A. Denny,⁎, Brian D. Palmera,b

a Auckland Cancer Society Research Centre, School of Medical Sciences, New Zealand
b Maurice Wilkins Centre, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
c Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL 60612, USA
d Global Alliance for TB Drug Development, 40 Wall St, New York, NY 10005, USA

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ABSTRACT

Bedaquiline is a new drug of the diarylquinoline class that has proven to be clinically effective against drug-resistant tuberculosis, but has a cardiac liability (prolongation of the QT interval) due to its potent inhibition of the cardiac potassium channel protein hERG. Bedaquiline is highly lipophilic and has an extremely long terminal half-life, so has the potential for more-than-desired accumulation in tissues during the relatively long treatment durations required to cure TB. The present work is part of a program that seeks to identify a diarylquinoline that is as potent as bedaquiline against Mycobacterium tuberculosis, but with lower lipophilicity, higher clearance, and lower risk for QT prolongation. Previous work led to the identification of compounds with greatly-reduced lipophilicity compounds that retain good anti-tubercular activity in vitro and in mouse models of TB, but has not addressed the hERG blockade. We now present compounds where the C-unit naphthalene is replaced by a 3,5-dialkoxy-4-pyridyl, demonstrate more potent in vitro and in vivo anti-tubercular activity, with greatly attenuated hERG blockade. Two examples of this series are in preclinical development.

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⁎ Corresponding author at: Auckland Cancer Society Research Centre, School of Medical Sciences, The University of Auckland, New Zealand.
E-mail address: b.denny@auckland.ac.nz (W.A. Denny).

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1. Introduction

Bedaquiline (TMC207, Sirturo, Janssen Pharmaceuticals; 1; Table 2), a diarylquinoline, is the first example of a new class of drug that has proven clinically effective against drug-resistant tuberculosis (TB).\textsuperscript{1} It has a novel mechanism of action, selectively inhibiting the mycobacterial ATP synthase enzyme.\textsuperscript{2} In attempts to develop improved second-generation analogues of 1, we have focused on two areas. One is to lower its very high lipophilicity (clogP 7.25), which may contribute to its long terminal elimination half-life and tissue accumulation at high doses.\textsuperscript{3} The other aim is to attenuate its inhibition (IC\textsubscript{50} 1.6 µM) of the cardiac potassium channel protein coded by the human ether-a-go-go-related gene (hERG).\textsuperscript{4} This forms the pore-forming subunit of the rapidly activating delayed rectifier potassium channel (IKr), which is important for cardiac repolarization. Dysfunction of hERG causes long QT syndrome and can increase the risk of sudden death in patients with cardiac ischemia - a potential safety issue that all drug candidates seeking regulatory approval must currently address. In our attempts to develop analogues of lower lipophilicity, we have reported on the utility of replacing the 6-Br substituent on the A-unit quinoline with a more polar cyano group,\textsuperscript{5} replacing the B-unit phenyl with heterocycles,\textsuperscript{6} and replacing the C-unit naphthalene with either bicyclic heterocycles\textsuperscript{7} or substituted pyridines.\textsuperscript{8} These studies provided a diverse range of potent diarylquinolines with much lower lipophilicity, and defined structure-activity relationships between antitubercular activity and lipophilicity. While they were, in the main, less successful in identifying active compounds with significantly attenuated potency against the hERG channel, we recently\textsuperscript{9} reported encouraging results (hERG IC\textsubscript{50} values around or > 10 µM) in a small number of compounds containing a 4-pyridyl-3,5-dialkoxy C-unit, suggesting this substitution is a promising one for mitigation of hERG potency. In the present paper, we follow up on that observation with a more extensive structure-activity study of this motif, which has allowed selection of two candidate compounds for preclinical development.

2. Results and discussion

2.1. Chemistry

The bedaquiline analogues of Table 2 were prepared as previously described,\textsuperscript{5–9} by LDA-mediated coupling of the appropriate benzyliquinolone A/B-units and 1-(2,6-dialkoxypyridin-4-yl)-3-(dimethylamino)propan-1-one (Mannich base) C/B-units (Scheme 1). The 6-cyano derivatives were prepared by palladium-catalyzed cyanation of the corresponding bromo analogues. The resulting diarylquinolines were formed as a racemic mixture of four diastereomers, and the desired 1R,2S diastereomer (depicted) was isolated by super-critical fluid HPLC at BioDuro LLC (Beijing).

Having previously established the utility of a range of substituted pyridyl B- and/or C-units\textsuperscript{6–8} in lowering overall clogP values, in the present SAR study we report 3,5-dialkoxy-4-pyridyl C-unit analogues bearing a wide range of different B-unit substitutions, with the focus on mitigation of hERG potency. Thirty-four different A/B-units were used, apart from the unsubstituted parent; syntheses of many of these (for compounds 7, 9, 10, 13, 14, 16, 17, 23–26, 34, 40–42, 48, 50 of Table 2) have already been reported.\textsuperscript{5–8} The remainder were prepared as outlined in Scheme 1 and Table 1.

The acid chlorides derived from I were reacted with N,O-di-methylhydroxylamine to give the N-methoxyacetamides (Weinreb amides) (II), which were converted to the required Mannich bases (III) in high yields by reaction with vinyl magnesium bromide to generate an intermediate (IIa), followed by reaction with dimethylamine. Mannich bases IV to VII were prepared to evaluate the role of varying D unit pKa on hERG inhibition (see Table 4). In the absence of an additional dialkylamine source, the desired 1R,2S diastereomer (depicted) was isolated by super-critical fluid HPLC at BioDuro LLC (Beijing).

Reagents and conditions: (i) LiTMP, THF, −75 °C, 1.5 h then the appropriate aldehyde B, −75 °C, 4 h; (ii) Et3SiH, TFA, DCM, (iii) Me3Si, Et,N, DMF, then NaBH4; (iv) Cs2CO3, Pd(PPh3)4, PhMe/DMF, 110 °C (sealed tube), 5 h; (v) LDA, THF, −75 °C, 1.5 h then the appropriate ketone C/D (sealed tube), 5 h; (vi) Zn/Zn (CN)2, Pd2(dbcat)2(P(o-tol)2)2, DMF, 50 °C, then separation of the diastereomers by SFC HPLC.
triazole (VII) derivatives required the isolation of crude before subsequent reaction with imidazole or triazole, this avoided the competitive reaction between IIa and the more nucleophilic N,O-dimethylhydroxylamine.

2.2. Structure-activity relationships

In previous work, we demonstrated the ability of a range of analogues with substituted pyridyl C-units to significantly lower lipophilicity (clogP values between about 5.5–4.0) while producing compounds only slightly less effective than I against both replicating and non-replicating cultures of M.\(\text{tb}\) in vitro, and in a mouse TB infection model. While these compounds, as a class, did not show useful reduc-

Table 1 provides data on analogues of hERG potassium channel inhibition. Of the 33 compounds evaluated, 19 had I\(C_{50}\) values of \(\leq 10 \mu M\), in strong contrast with previous studies of different sets of analogues, where no compound had I\(C_{50}\) values even approaching 10 \(\mu M\). The data suggest that, for this series, potent hERG inhibition is broadly related to higher compound lipophilicity; the 14 analogues with hERG values \(\geq 10 \mu M\) had an average clogP of 6.17, whereas the 19 analogues with hERG values \(\leq 10 \mu M\) had an average clogP of 4.57, whereas the 14 analogues with hERG values \(\geq 10 \mu M\) had an average clogP of 6.17 (Table 2). Put another way, 15/17 compounds with clogP \(\geq 5.5\) had hERG I\(C_{50}\) > 10 \(\mu M\) for CYP2A4 inhibition (bedaquiline I\(C_{50}\) > 40 \(\mu M\)), however, compounds 3–7, 11, 19–21, 24, 27–28, 30–31, 33, 36, 41–42, 45–49, 51–52 were not tested in this assay.

The most interesting result of this study was the very positive effect of the 3,5-dialkoxypyridyl C-unit substitution on hERG potassium channel inhibition. Of the 33 compounds evaluated, 19 had I\(C_{50}\) values of \(\geq 10 \mu M\), in strong contrast with previous studies of different sets of analogues, where no compound had I\(C_{50}\) values even approaching 10 \(\mu M\). The data suggest that, for this series, potent hERG inhibition is broadly related to higher compound lipophilicity; the 14 analogues with hERG values \(\geq 10 \mu M\) had an average clogP of 6.17, whereas the 19 analogues with hERG values \(\leq 10 \mu M\) had an average clogP of 4.57, whereas the 14 analogues with hERG values \(\geq 10 \mu M\) had an average clogP of 6.17 (Table 2). Put another way, 15/17 compounds with clogP \(\geq 5.5\) had hERG I\(C_{50}\) > 10 \(\mu M\) for CYP2A4 inhibition (bedaquiline I\(C_{50}\) > 40 \(\mu M\)), however, compounds 3–7, 11, 19–21, 24, 27–28, 30–31, 33, 36, 41–42, 45–49, 51–52 were not tested in this assay.

Table 3 also provides data on the in vitro clearance of the analogues from human and mouse liver microsomes. The very slow clearance (CL\(\text{int}\) 3 \(\mu L/min/mg\)) and concomitantly long half-life (231 min) of 1 in human liver microsomes is improved upon 2-fold by many of the analogues but a 3-fold or more increase in human microsomal clearance was seen for a handful of analogues only. The mouse liver microsome data may better predict the human clearance of these compounds versus 1 for CYP isoforms in human versus mouse microsomes. The human microsome data may better predict the human clearance of these compounds, if microsomal metabolism is representative of metabolism overall, for these compounds. Studies of pharmacokinetics in several species, followed by modelling work, will be needed to provide a better prediction of human PK.

The pharmacokinetics in mice were evaluated after administration of a single oral dose and a single intravenous injection. Clearance in vivo between 6.25 and 4.25 (Table 2). Nearly all have MIC\(_{90}\) values significantly superior (many by > 10-fold) to 1 against both replicating and non-replicating cultures of M.\(\text{tb}\). As shown previously, the more lipophilic compounds appear more potent, but as so many had indeterminate endpoint values (below the testing range of the assay), this could not be quantified. We have previously shown that different B-units have little specific effect on inhibitory activity (MIC\(_{90}\)) apart from their contribution to overall lipophilicity. This appears to also be the case for the analogues tested here.

Representative compounds in the series were evaluated in vitro for a range of ADMET and toxicological properties (Table 3). Compounds were tested for cytotoxicity in Vero green monkey-derived epithelial kidney cells, and for inhibition of CYP 3A4, the major metabolising enzyme for 1. All tested compounds had I\(C_{50}\) > 10 \(\mu M\) in the Vero assay, except for compound 9, which had a value of 7.3, and compounds 28 and 34, and where this was not measured. In comparison, the value for 1 in repeat assays was between 4 and 16 \(\mu M\). Where tested, compounds had I\(C_{50}\) > 10 \(\mu M\) for CYP2A4 inhibition (bedaquiline I\(C_{50}\) > 40 \(\mu M\)), however, compounds 3–7, 11, 19–21, 24, 27–28, 30–31, 33, 36, 41–42, 45–49, 51–52 were not tested in this assay.

Scheme 2. Synthesis of dialkoxyypyridyl Mannich bases (III–VII) Reagents and conditions: (i) COCl\(_2\), DMF, DCM, then MeNH(OMe).HCl, pyridine; (ii) vinylmagnesium bromide, THF; (iii) dimethylamine, water; (iv) for IV, water; V, morpholine, water; VI and VII, isolation of crude IIa then imidazole or triazole.

Table 1

| Y     | Name             | Steps | Overall yield (%) | For Table 3 compounds |
|-------|------------------|-------|-------------------|-----------------------|
| 2,3-(CH\(_2\))\(_3\)_ | AB-1  | 3     | 84                | 2.3                   |
| 2,3-(CH\(_3\))\(_2\)_ | AB-2  | 3     | 41                | 4                     |
| 2-3, 3-Me     | AB-3  | 1     | 76                | 5-7                   |
| 2,3, 4-OMe   | AB-4  | 3     | 37                | 11                    |
| 2,3-OCH\(_2\)_ | AB-5  | 1     | 76                | 15, 16                |
| 2,3-OCH\(_2\)=CH– | AB-6  | 3     | 52                | 21                    |
| 3-aza, 4-NEBT | AB-7  | 2     | 43                | 24-26                 |
| 3-aza, 2-Ome, 5-OPr | AB-8  | 4     | 20                | 29, 30                |
| 3-aza, 2,3-O(3\(_2\)=CH–) | AB-9  | 5     | 40                | 31, 32                |
| 4-aza, 2,3-diOme | AB-10 | 5     | 16                | 34                    |
| 4-aza, 3,5-diOMe | AB-11 | 3     | 21                | 36                    |
| 4-aza, 3,5-diSeEt | AB-12 | 4     | 37                | 37                    |
| 4-aza, 2-Ome, 5-OPr | AB-13 | 9     | 11                | 38, 39                |
| 4-aza, 3-Ome, 5-O\(_2\)=Bu | AB-14 | 5     | 55                | 43                    |
| 4-aza, 3-OEt, 5-OPr | AB-15 | 5     | 58                | 44, 45                |
| 4-aza, 2,3,5-triOme | AB-16 | 8     | 13                | 46                    |
| 4-aza, 3-Ome, 5-NMe\(_2\) | AB-17 | 2     | 51                | 47, 48                |
| 4-aza, 3-OEt, 5-NMe\(_2\) | AB-18 | 3     | 42                | 49, 50                |
| 4-aza, 3-SeEt, 5-NMe\(_2\) | AB-19 | 4     | 37                | 51                    |
| 4-aza, 2-F, 3-0me | AB-20  | 5      | 12                | 52                   |
Table 2

Inhibitory properties of 3,5-dialkoxy-4-pyril analogues of bedaquiline.

| No | X       | Y        | Z      | Yld (%) | MIC<sub>90</sub> (µg/mL)<sup>a</sup> | clogP<sup>c</sup> |
|----|---------|----------|--------|---------|-------------------------------------|-----------------|
| 1  | Br      | 2,3-(CH<sub>2</sub>)<sub>2</sub> | Me | 24 | 0.01 | 0.02 | 6.81 |
| 2  | Br      | 2,3-(CH<sub>2</sub>)<sub>2</sub> | Me | 71<sup>b</sup> | 0.02 | 0.02 | 5.45 |
| 3  | Br      | 2,3-(CH<sub>2</sub>)<sub>2</sub> | Me | 13 | <0.004 | 0.01 | 7.38 |
| 5  | Br      | 2,3-OCH<sub>2</sub>O-Me | Me | 61 | <0.01 | <0.01 | 6.44 |
| 6  | Br      | 2,3-OCH<sub>2</sub>O-Me | Et | 67 | <0.02 | <0.02 | 7.50 |
| 7  | CN      | 2,3-OCH<sub>2</sub>O-Me | Et | 74<sup>c</sup> | <0.02 | <0.02 | 6.14 |
| 8  | Br      | 2,3-OCH<sub>2</sub>O-Me | Me | 52 | 0.006 | 0.02 | 5.80 |
| 9  | CN      | 2,3-OCH<sub>2</sub>O-Me | Me | 80<sup>d</sup> | 0.09 | 0.09 | 4.44 |
| 10 | Br      | 2,3-OCH<sub>2</sub>O-Me | Et | 70 | 0.02 | 0.08 | 6.86 |
| 11 | Br      | 3,4-OCH<sub>2</sub>O-Me | Me | 38 | 0.01 | 0.01 | 5.80 |
| 12 | Br      | 3,4-OCH<sub>2</sub>O-Me | Me | 63 | <0.01 | <0.01 | 5.06 |
| 13 | CN      | 3,4-OCH<sub>2</sub>O-Me | Me | 80<sup>d</sup> | 0.12 | 0.14 | 3.70 |
| 14 | Br      | 3,4-diOMe | Et | 64 | <0.02 | <0.02 | 6.11 |
| 15 | Br      | 2,3-OCH<sub>3</sub>O-Me | Me | 66 | <0.02 | 0.06 | 5.76 |
| 16 | CN      | 2,3-OCH<sub>3</sub>O-Me | Me | 85<sup>d</sup> | 0.06 | 0.07 | 4.41 |
| 17 | Br      | 2,3-(CH<sub>2</sub>)<sub>2</sub>O-Me | Me | 72 | 0.02 | 0.02 | 5.72 |
| 18 | CN      | 2,3-(CH<sub>2</sub>)<sub>2</sub>O-Me | Me | 76<sup>c</sup> | 0.02 | 0.02 | 4.90 |
| 19 | Br      | 2,3-(CH<sub>2</sub>)<sub>2</sub>O-Me | Et | 52 | 0.07 | 0.13 | 6.78 |
| 20 | CN      | 2,3-(CH<sub>2</sub>)<sub>2</sub>O-Me | Et | 62<sup>d</sup> | 0.03 | 0.03 | 5.42 |
| 21 | Br      | 2,3-OCH=CH–Me | Me | 16 | <0.004 | 0.01 | 6.36 |
| 22 | Br      | 3,4-OCH<sub>2</sub>O-Me | Me | 65 | <0.02 | <0.02 | 4.72 |
| 23 | CN      | 3,4-OCH<sub>2</sub>O-Me | Me | 68<sup>d</sup> | 0.04 | 0.25 | 3.36 |
| 24 | Br      | 3,4-NEt<sub>2</sub> Me | Et | 26 | <0.02 | <0.02 | 7.13 |
| 25 | Br      | 4,5-NEt<sub>2</sub> Me | Me | 46 | 0.003 | 0.08 | 6.07 |
| 26 | CN      | 3,4-NEt<sub>2</sub> Me | Me | 68<sup>d</sup> | <0.01 | <0.01 | 4.71 |
| 27 | Br      | 3,4-NEt<sub>2</sub> Me | Me | 38 | <0.02 | <0.02 | 5.12 |
| 28 | CN      | 3,4-NEt<sub>2</sub> Me | Me | 44<sup>d</sup> | 0.02 | 0.04 | 3.76 |
| 29 | Br      | 3,4-NEt<sub>2</sub> Me | Me | 38 | <0.004 | 0.04 | 5.96 |
| 30 | CN      | 3,4-NEt<sub>2</sub> Me | Me | 56 | <0.004 | 0.004 | 4.60 |
| 31 | Br      | 3,4-NEt<sub>2</sub> Me | Me | 38 | <0.01 | <0.01 | 5.15 |
| 32 | CN      | 3,4-NEt<sub>2</sub> Me | Me | 39<sup>d</sup> | <0.01 | <0.01 | 3.79 |
| 33 | Br      | 4,5-NEt<sub>2</sub> Me | Me | 62 | <0.02 | 0.07 | 4.77 |
| 34 | Br      | 2,3-NEt<sub>2</sub> Me | Me | 77 | 0.07 | 0.13 | 6.78 |
| 35 | Br      | 3,4-NEt<sub>2</sub> Me | Et | 32 | <0.02 | <0.02 | 5.83 |
| 36 | Br      | 3,5-diSMe | Me | 26 | <0.01 | <0.01 | 6.18 |
| 37 | Br      | 3,5-diSMe | Me | 28 | <0.02 | <0.02 | 7.24 |
| 38 | Br      | 3,5-diSMe | Me | 54 | <0.004 | 0.008 | 5.96 |
| 39 | Br      | 2,3-OMe | 5-OPr | Me | 39<sup>d</sup> | 0.05 | 0.09 | 4.60 |
| 40 | Br      | 3,4-OMe | 5-OPr | Me | 57 | <0.01 | <0.01 | 6.36 |
| 41 | CN      | 3,4-OMe | 5-OPr | Me | 57<sup>d</sup> | 0.01 | 0.01 | 5.00 |
| 42 | Br      | 3,4-OMe | 5-OPr | Me | 52 | 0.01 | 0.01 | 6.58 |
| 43 | Br      | 3,4-OMe | 5-OPr | Me | 16 | 0.01 | 0.12 | 6.43 |
| 44 | Br      | 3,5-OMe | 5-OPr | Me | 61 | <0.01 | <0.01 | 6.88 |
| 45 | CN      | 3,4-OMe | 5-OPr | Me | 80<sup>d</sup> | 0.01 | 0.01 | 5.53 |
| 46 | Br      | 2,3,5-triOMe | Me | 47 | 0.004 | 0.006 | 5.15 |
| 47 | Br      | 3,4-OMe | 5-NMe<sub>2</sub> | Me | 21 | 0.01 | 0.03 | 5.83 |
| 48 | CN      | 3,4-OMe | 5-NMe<sub>2</sub> | Me | 71<sup>d</sup> | 0.03 | 0.09 | 4.48 |
| 49 | Br      | 3,4-OMe | 5-NMe<sub>2</sub> | Me | 78 | <0.004 | 0.03 | 6.36 |
| 50 | CN      | 3,4-OMe | 5-NMe<sub>2</sub> | Me | 90<sup>d</sup> | 0.03 | 0.05 | 5.01 |
| 51 | Br      | 3,4-OMe | 5-NMe<sub>2</sub> | Me | 52 | 0.01 | 0.01 | 6.68 |
| 52 | Br      | 2,4,3-OMe | Me | 54 | <0.01 | <0.05 | 5.10 |

<sup>a</sup> Yields (Yld) in the AB/CD coupling step to give bedaquiline analogues (as racemic mixtures). The desired 1R, 2S diastereomer was then isolated by SFC HPLC at BioDuro LLC, Beijing. <sup>b</sup>MIC<sub>90</sub> (µg/mL); minimum inhibitory concentration for 90% inhibition of growth of M.<i>tb</i> strain H37Rv, determined under aerobic (replicating; MABA) (ref. 10) or non-replicating (LORA) (ref. 11) conditions, determined at the Institute for Tuberculosis Research, University of Illinois at Chicago. <sup>c</sup>clogP calculated by ChemDraw Ultra v12.0.2. (CambridgeSoft). <sup>d</sup>Yields for the Br/CN conversion.
Several compounds presented here, namely 3, 8, 10, 18, 22, 24, 27, 28, 30, 31, 33, 41 45, 46, 50 and 51 demonstrated 4 log unit CFU reductions in mice, at an AUC at least approximately 4-fold lower than that of bedaquiline. This suggests these analogues may have potential to demonstrate efficacy against TB in patients at lower plasma levels than bedaquiline. Of these compounds, 8, 10, 24, 41, 45, 46, 49 and 51 exhibited hERG IC50s of 9.9 µM or higher, compared to 1.6 µM for bedaquiline. Taken together, a higher IC50 against hERG along with a lower efficacious exposure may predict a lower risk of QTc prolongation in patients for these analogues compared to bedaquiline. Although not all of these compounds showed higher human microsome Clint than bedaquiline, the possible lower risk of QTc prolongation along with potential for lower overall adverse effects based on a lower efficacious exposure, resulted in selection of these compounds, as well as others in Table 3 that demonstrated similar efficacy to bedaquiline with lower potency against hERG, for further evaluation. Electrocardiography studies in animals and ultimately in human subjects will be needed to determine whether the decreases in potency against hERG seen here, along with the decreased plasma levels needed for efficacy for some of these compounds, translates into an absence of QTc prolongation at a therapeutic dose and exposure.

Finally, the overall good activity profile of this series of 3,5-dialkoxy-4-pyridyl analogues was utilized to explore the results of changes in the pKa values of the α-unit side chain. This was explored previously by Guillemont et al. in their original paper, where they concluded that a sidechain with a pKa of > 8 was needed to retain activity against the related mycobacterium, M. smegmatis. We were thus motivated by the idea that utilising a much weaker base in the side chain in analogue series with intrinsically higher potency might further attenuate hERG blockade while retaining good M.tb potency. The results in Table 4 suggest that a weaker base did lead to reduced hERG inhibition (compare hERG data for 12 and 54, 33 and 61), but there was also a large increase in the MICs for inhibition of M.tb.

3. Conclusions

In previous publications in this series, we have shown that less lipophilic analogues of 1 (clogP 7.25) retain substantial in vitro and in vivo activity against M.tb, down to compounds with a clogP of about 4; this shows that one of the potential drawbacks of 1 can be ameliorated. In the present paper, we show that substitution of the C-unit naphthylthio-1-yl group (TBAJ-876)16 as compounds for pre-clinical development. Based on the preliminary data presented in this paper, several compounds (including 8 and 46), with activity against murine TB similar to bedaquiline at the same dose, with lower clogP, higher IC50 against hERG, and, in most cases, higher Cl values in human microsomes, were
was dried with Na2SO4 and concentrated under reduced pressure to obtain 2,3-dihydro-1H-inden-4-yl)methanol (2.45 g, 99%) as a yellow oil. 1H NMR (CDCl3) δ 7.22–7.12 (m, 3H), 4.67 (s, 2H), 2.93 (t, J = 7.6 Hz, 2H), 2.91 (t, J = 7.4 Hz, 2H), 2.09 (p, J = 7.6 Hz, 2H). Found: [M + H–18] = 131.5.

To a solution of 2,3-dihydro-1H-inden-4-yl)methanol (4.33 g, 36.4 mmol) in DCM (50 mL) at 0 °C was added thionyl chloride (2.45 g, 16.5 mmol). The reaction mixture was stirred at 20 °C for 24 h and solvent was removed under reduced pressure. The residue was diluted with DCM (100 mL) and quenched with ice-water (100 mL). The organic phase was washed with sat. aq. NaHCO3, dried with Na2SO4 and concentrated to give a yellow residue. Purification by flash column chromatography using hexanes:EtOAc (1:1) gave 4-(choloromethyl)-2,3-dihydro-1H-indene (2.36 g, 86%) as a colourless oil. 1H NMR (CDCl3) δ 7.22–7.13 (m, 3H), 4.59 (s, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.11 (p, J = 7.6 Hz, 2H). Found: [M + H] = 167.5.

A mixture of (6-bromo-2-methoxyquinolin-3-yl)-boronic acid (3.69 g, 12.9 mmol), 4-(chloromethyl)-2,3-dihydro-1H-indene (2.36 g, 14.2 mmol) and Cs2CO3 (9.67 g, 29.7 mmol) in toluene:DMF (60 mL, 2:1) was degassed under N2, then Pd(PPh3)4 (0.82 mmol) was added and the mixture was heated at 90 °C for 3 h. The reaction mixture was cooled to 20 °C, filtered through a plug of Celite, water (150 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na2SO4 and filtered. The residue was concentrated to obtain a yellow residue. Purification by flash column chromatography using hexanes:EtOAc (9:1) gave 6-bromo-3-(2,3-dihydro-1H-inden-4-yl)-methyl)-2-methoxyquinoline (AB-1) (4.70 g, 99%) as a yellow oil. 1H NMR (CDCl3) δ 7.71 (d, J = 2.2 Hz, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.60 (dd, J = 8.9, 2.2 Hz, 1H), 7.33 (s, 1H), 7.18–7.11 (m, 2H), 6.95 (d, J = 7.2 Hz, 1H), 4.11 (s, 3H), 3.98 (s, 2H), 2.96 (t, J = 7.5 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 2.04 (p, J = 7.6 Hz, 2H). Found: [M + H] = 368.5.

4.1.2. 6-Bromo-2-methoxyquinolin-1-yl)methylquinoline (AB-2).

To a solution of 1-tetrahydronaphthalene (5.70 g, 32.3 mmol) in THF (100 mL) at 0 °C was added lithium aluminium hydride (2.46 g, 64.7 mmol) in small portions. The reaction mixture was stirred at 0 °C for 30 min and then stirred for further 24 h at 20 °C. The reaction mixture was washed with water (100 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was dried with Na2SO4 and concentrated under reduced pressure to obtain 5-(chloromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)quinoline (AB-2) (3.69 g, 86%) as a yellow oil. 1H NMR (CDCl3) δ 7.18 (d, J = 7.4 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 4.67 (s, 2H), 2.80 (t, J = 6.2 Hz, 2H), 2.76 (t, J = 6.4 Hz, 2H), 1.88–1.77 (m, 4H). Found: [M + H–18] = 145.5.

To a solution of (5,6,7,8-tetrahydronaphthalen-1-yl)methanol (5.24 g, 32.3 mmol) in DCM (200 mL) at 0 °C was added thionyl chloride (8.45 g, 71.1 mmol). The reaction mixture was stirred at 20 °C for 24 h, then solvent was removed under reduced pressure. The residue was diluted with DCM (100 mL) and quenched with ice-water (100 mL). The organic phase was washed with sat. aq. NaHCO3, dried with Na2SO4 and concentrated to give 5-(choloromethyl)-1,2,3,4-tetrahydronaphthalene (3.25 g, 56%) as a brown oil. 1H NMR (CDCl3) δ 7.16–7.05 (m, 3H), 4.59 (s, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.79 (t, J = 6.4 Hz, 2H), 1.88–1.77 (m, 4H). Found: [M + H] = 181.6.

The organic phase was washed with sat. aq. NaHCO3, dried with Na2SO4 and concentrated to give 5-(choloromethyl)-1,2,3,4-tetrahydronaphthalene (3.25 g, 56%) as a brown oil. 1H NMR (CDCl3) δ 7.16–7.05 (m, 3H), 4.59 (s, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.79 (t, J = 6.4 Hz, 2H), 1.88–1.77 (m, 4H). Found: [M + H] = 181.6.

A mixture of (6-bromo-2-methoxyquinolin-3-yl)-boronic acid (4.69 g, 16.4 mmol), 5-(chloromethyl)-1,2,3,4-tetrahydronaphthalene (3.25 g, 18.0 mmol) and Cs2CO3 (12.29 g, 37.7 mmol) in toluene:DMF (60 mL, 2:1) was degassed under N2, then Pd(PPh3)4 (0.948 g, 0.82 mmol) was added and the mixture was heated at 90 °C for 3 h. The reaction mixture was cooled to 20 °C, filtered through a plug of Celite, water (150 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na2SO4 and filtered. The residue was concentrated to obtain a yellow residue. Purification by flash column chromatography using...
hexanes:EtOAc (9:1) gave 6-bromo-2-methoxy-3-(5,6,7,8-tetrahydroanthralen-1-yl)methylquinoline (AB-2) (4.64 g, 74%) as a white solid. 1H NMR (CDCl3) δ 7.71–7.69 (m, 2H), 7.60 (dd, J = 8.9, 2.2 Hz, 1H), 7.23 (s, 1H), 7.12–7.04 (m, 2H), 6.92 (d, J = 6.9 Hz, 1H), 4.11 (s, 3H), 3.96 (s, 2H), 2.83 (bs, 2H), 2.57 (bs, 2H), 1.76 (p, J = 3.5 Hz, 4H). Found: [M + H] = 382.1.

4.1.1.3. 6-Bromo-3-(2-fluoro-3-methylbenzyl)-2-methoxyquinoline (AB-3). A mixture of 6-bromo-2-methoxyquinolin-3-yl)boric acid (3.00 g, 10.55 mmol), 1-(bromomethyl)-2-fluoro-3-methylbenzene (S7) (4.24 g, 20.9 mmol) and Cs2CO3 (7.87 g, 24.2 mmol) in toluene:DMF (60 mL, 2:1) was degassed under N2, then Pd(PPh3)4 (0.607 g, 0.525 mmol) was added, and the mixture was heated at 90°C for 2 h. The reaction mixture was cooled to 20°C, filtered through a plug of Celite, water (150 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The organic layer was washed with brine (100 mL), dried over Na2SO4, filtered and concentrated under reduced pressure to obtain a yellow residue. Purification by flash column chromatography using hexanes:EtOAc (9:1) gave 6-bromo-3-(2-fluoro-3-methylbenzyl)-2-methoxyquinoline (AB-3) (2.87 g, 76%) as a white solid. 1H NMR (CDCl3) δ 7.71 (d, J = 2.2 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.60 (dd, J = 8.9, 2.2 Hz, 1H), 7.50 (s, 1H), 7.11–6.96 (m, 3H), 4.09 (s, 3H), 4.03 (s, 2H), 2.28 (d, J = 2.1 Hz, 3H). Found: [M + H] = 360.6.

4.1.1.4. 6-Bromo-3-(3-fluoro-4-methoxybenzyl)-2-methoxyquinoline (AB-4). Borane – dimethylsulfide complex (2.79 mL, 29.40 mmol) and trimethyl borate (3.34 mL, 29.40 mmol) were added to a solution of 3-fluoro-4-methoxybenzoic acid (2.50 g, 14.69 mmol) in THF (80 mL, dist. Na) at 0°C, and the solution warmed to 20°C and stirred overnight. The mixture was then cooled to 0°C, and quenched with MeOH (10 mL). The solvent was then evaporated and the residue was partitioned between EtOAc and water. The organic layer was then dried and evaporated to afford (3-fluoro-4-methoxyphenyl)methanol, (2.35 g, 95%), 1H NMR (CDCl3) δ 7.11 (1H, dd, J = 2.0, 11.9 Hz), 7.06 (1H, dd, J = 0.9, 2.0, 9.1 Hz), 6.94 (1H, dd, J = 8.4, 8.4 Hz), 4.61 (2H, s), 3.89 (3H, s), 1.73 (1H, s). Found: [M – OH] = 139.7.

To a solution of 3-fluoro-4-methoxyphenyl)methanol (2.35 g, 15.05 mmol) and triethylamine (3.15 mL, 22.58 mmol) in DCM (50 mL) at 0°C anhydrous) at 20°C was added mesyl chloride (1.414 mL, 18.06 mmol) and Cs2CO3 (18.5 g, 56.7 mmol) in toluene (100 mL) and DMF (50 mL) was purged with nitrogen. Pd(PPh3)4 (0.31 g, 0.27 mmol) was added, the mixture was refluxed for 0.5 h and then evaporated. The residue was partitioned between DCM and water; the organic fraction was dried and evaporated and the residue was dissolved in acetone (200 mL), LiBr (27.6 g, 318 mmol) was added and the mixture was refluxed for 0.5 h and then evaporated. The residue was partitioned between DCM and water; the organic fraction was dried and evaporated. Column chromatography (DCM) gave 7-(bromomethyl)benzofuran (6.08 g, 90%), 1H NMR (CDCl3) δ 7.69 (d, J = 8.9 Hz, 1H), 7.56 (dd, J = 7.7, 1.2 Hz, 1H), 7.31 (dd, J = 7.3, 0.6 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 6.80 (dd, J = 2.2 Hz, 1H), 5.02 (d, J = 6.2 Hz, 2H), 1.93 (t, J = 6.2 Hz, 3H).

A solution of benzofuran-7-ylmethanol (4.72 g, 31.8 mmol) in DCM (100 mL, anhydrous) at 0°C was treated sequentially with triethylamine (8.9 mL, 63.9 mmol) then mesyl chloride (3.70 mL, 47.8 mmol), the mixture was stirred at 0°C for 1 h then partitioned between DCM and water. The organic fraction was dried and evaporated and the residue was dissolved in acetone (200 mL), LiBr (27.6 g, 318 mmol) was added and the mixture was refluxed for 0.5 h and then evaporated. The residue was partitioned between DCM and water; the organic fraction was dried and evaporated. Column chromatography (DCM) gave 7-(bromomethyl)benzofuran (6.08 g, 90%). 1H NMR (CDCl3) δ 7.69 (d, J = 2.2 Hz, 1H), 7.57 (dd, J = 7.7, 1.2 Hz, 1H), 7.32 (dd, J = 7.4, 0.7 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 6.80 (dd, J = 2.2 Hz, 1H), 4.81 (s, 2H).

A mixture of 6-bromo-2-methoxyquinolin-3-yl)boric acid (8.00 g, 28.4 mmol), 7-(bromomethyl)benzofuran (5.99 g, 28.4 mmol) and Cs2CO3 (18.5 g, 56.7 mmol) in toluene (100 mL) and DMF (50 mL) was purged with nitrogen. Pd[PPh3]4 (0.66 g, 0.57 mmol) was added, the mixture was purged with nitrogen then heated to 80°C under nitrogen for 3 h. The reaction was partitioned between EtOAc and water and the organic fraction was dried and evaporated. Column chromatography with 3:1 hexanes:DCM eluted impurities, then elution with 1:1 hexanes:DCM then benzofuran-7-ylmethanol (6.95 g, 67%). 1H NMR (CDCl3) δ 7.71 (d, J = 2.2 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.58–7.62 (m, 2H), 7.50–7.54 (m, 2H), 7.20 (t, J = 7.4 Hz, 1H), 7.13 (dd, J = 7.4, 0.6 Hz, 1H), 6.79 (d, J = 2.2 Hz, 1H), 4.32 (s, 2H), 4.10 (s, 3H). Found: [M + H] = 368.8.

4.1.1.7. 5-((6-Bromo-2-methoxyquinolin-3-yl)methyl)-N,N-diethylpyridin-2-amine (AB-7). To a solution of freshly distilled N,N,N,N,N'-pentamethylenepiperidine (1.60 mL, 9.56 mmol) in freshly distilled THF (13 mL) was added at −30°C under nitrogen, n-Buli (4.40 mL, 8.76 mmol) dropwise. The mixture was maintained at about −30°C for 15 min, then cooled to −78°C. A solution of 6-bromo-2-methoxyquinoline (1.90 g, 7.96 mmol) in dry THF (15 mL) was added dropwise at −78°C. The resultant organic mixture was stirred at the same temperature for 75 min. A solution of 6-diethyldiamino nicotinaldehyde (1.42 g, 7.96 mmol) in dry THF (6 mL) was added dropwise at −78°C, the reaction mixture remained orange brown, stirred at −78°C for 2.5 h. The mixture was quenched with acetic acid (0.68 mL) at −65°C. Water was added, the aqueous mixture was extracted with ethyl acetate (2x), and the combined extract was
washed with brine, dried (MgSO₄) and concentrated in vacuo to give the crude product as a yellow solid. Flash chromatography of the crude product using 10–100% ethyl acetate in hexane as eluent afforded product (6-bromo-2-methoxyquinolin-3-yl)(6-(diethylamino)pyridin-3-yl)methanol (1.90 g, 57%) as an off-white solid. ¹H NMR (CDCl₃) δ 8.15 (d, J = 2.4 Hz, 1H), 8.01 (s, 1H), 7.88 (d, J = 2.1 Hz, 1H), 7.70–7.64 (m, 2H), 7.39 (dd, J = 8.9, 2.5 Hz, 1H), 6.43 (d, J = 8.9 Hz, 1H), 5.94 (d, J = 3.7 Hz, 1H), 4.04 (s, 3H), 3.53–3.47 (m, 4H), 2.65 (d, J = 3.9 Hz, 1H), 1.17 (t, J = 7.0 Hz, 6H).

To a sparsely soluble solution of 2-methoxyquinolin-3-yl)(6-(diethylamino)pyridin-3-yl)methanol (1.90 g, 4.57 mmol) in freshly distilled THF (19 mL) was added at 2°C under nitrogen sodium borohydride (0.86 g, 23.0 mmol) was stirred at 2°C for 1 h. The resultant solution was diluted with water cautiously to 2°C until gas evolution ceased. The white slurry was filtered through celite. The milky white filtrate was diluted in water, and the organic phase was collected. The aqueous phase was extracted with ethyl acetate (3x). The organic extract was washed with brine, dried (MgSO₄) and concentrated in vacuo to furnish the crude product as a brownish residue. Flash chromatography of the crude product using 10% ethyl acetate in hexane as eluent afforded product 5-((6-bromo-2-methoxyquinolin-3-yl)methyl)boronic acid (1.39 g, 76%) as a white solid. ¹H NMR (CDCl₃) δ 7.07 (1H, d, J = 8.2 Hz), 6.13 (1H, d, J = 8.2 Hz), 3.92 (3H, s), 3.86 (3H, s), 1.27–1.18 (3H, m), 1.08 (18H, d, J = 7.1 Hz). Found: [M + H] = 312.8.

To a solution of 2,6-dimethoxy-3-((trisopropylsilyl)oxy)pyridine (8.00 g, 25.69 mmol) and N,N-diisopropylamine (0.18 mL, 1.28 mmol) in THF (100 mL, dist. Na) at −40°C under nitrogen was added n-BuLi (15.41 mL, 30.83 mmol) dropwise. The resultant solution was stirred at −40°C for 5 min, and then warmed to 0°C and stirred at this temperature for a further 3 h. The solution was then again cooled to −40°C, and formylpiperidine (4.28 mL, 38.54 mmol) was added dropwise, and the mixture stirred at 20°C for another 1 h. Acetic acid (8 mL) was added and the solvent was removed in vacuo. The resultant mixture was partitioned between EtOAc and water, and the organic fraction dried and evaporated. Column chromatography with 49:1 hexanes/EtOAc afforded the product 2,6-dimethoxy-3-((trisopropylsilyl)oxy)nicotinaldehyde (7.55 g, 87%). ¹H NMR (CDCl₃) δ 10.17 (1H, s), 7.51 (1H, s), 4.02 (3H, s), 4.01 (3H, s), 1.30–1.19 (18H, m), 1.08 (18H, d, J = 7.3 Hz). Found: [M − CHO]⁻ = 312.8.

Tetrabutylammonium fluoride in THF (1 N, 33.36 mL, 33.36 mmol) was added to a solution of 2,6-dimethoxy-3-((trisopropylsilyl)oxy)nicotinaldehyde (7.55 g, 22.24 mmol) in THF (35 mL, dist. Na) at 0°C. The reaction was then warmed to 20°C and stirred for 4 h. The solvent was removed and the residue partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc three times, and the organic layer dried and evaporated. Column chromatography with 36:1 hexanes/EtOAc afforded the product 2,6-dimethoxy-3-((trisopropylsilyl)oxy)nicotinaldehyde (3.35 g, 77%). ¹H NMR (CDCl₃) δ 10.20 (1H, s), 7.59 (1H, s), 5.15–4.80 (1H, br s), 4.10 (3H, s), 4.01 (3H, s).

A mixture of 5-hydroxy-2,6-dimethoxynicotinaldehyde (3.15 g, 17.20 mmol) and potassium carbonate (3.57 g, 25.80 mmol) in DMF (80 mL, anhydrous) was heated at 50°C for 10 min. Methyl iodide (1.29 mL, 20.64 mmol) was then added and the mixture stirred at this temperature for 2 h. The resultant solution was diluted with EtOAc and washed with brine three times. The organic layer was dried and evaporated. Column chromatography with 2:1 DCM/EtOAc afforded the product 5-hydroxy-2,6-dimethoxynicotinaldehyde (3.15 g, 100%). ¹H NMR (CDCl₃) δ 10.21 (1H, s), 7.53 (1H, s), 4.10 (3H, s), 4.02 (3H, s), 3.87 (3H, s).

A solution of N,N,N,N-tetramethylpiperidine (3.59 mL, 21.03 mmol) in THF (40 mL, dist. Na) was cooled to −40°C, n-BuLi (10.52 mL, 21.03 mmol) was added and the solution was stirred at −40°C for 15 min, then cooled to −78°C. A solution of 6-bromo-2-methoxyquinoline (17.53 mmol) in THF (40 mL, dist. Na) was added dropwise,
the orange solution was stirred at −78 °C for 1.5 h, then a solution of 2,5,6-trimethoxy nicotinaldehyde (3.42 g, 17.53 mmol) in THF (40 mL, dist. Na) was added. The mixture was stirred at −78 °C for 2 h, then acetic acid (2.5 mL) was added and the solution was allowed to warm to 20 °C. The solvent was removed and the residue partitioned between EtOAc and water, and the organic fraction was dried and evaporated. Column chromatography with 9:1 hexanes/EtOAc followed by 4:1 hexanes/EtOAc gave the product (6-bromo-2-methoxyquinolin-3-yl) methanol (5.50 g, 72%) as a white solid.

To a solution of 2,5,6-trimethoxy nicotinaldehyde (5.35 g, 12.35 mmol) in DCM (125 mL) and the solution was stirred for 1 h at 20 °C, then ice water was added. The mixture was partitioned between sat. aq. NaHCO3 and DCM and the aqueous fraction was dried and evaporated. Column chromatography with 9:1 hexanes/EtOAc gave 6-bromo-2-methoxy-3-((2,5-dimethoxypyridin-3-yl) methoxy)quinoline (4.09 g, 87%). 1H NMR (CDCl3): δ 7.70 (1H, s), 7.69 (1H, d, J = 6.9 Hz, 2H), 7.78 (1H, s), 7.75 (1H, d, J = 2.2 Hz, 1H), 6.72 (1H, d, J = 7.0 Hz, 2H), 4.03 (3H, s), 3.79 (3H, s), 3.89 (5H, s). Found: [M + H] = 389.7.

A mixture of 5-(ethoxymethoxy)-2-methoxypyridine (2.20 g, 51%) and potassium carbonate, dried and evaporated. The residue was recrystallized from methanol and was used without further purification for the next step. 1H NMR (CDCl3): δ 7.75 (s, 1H), 6.75 (s, 1H), 4.40 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H). Found: [M + H] = 216.5.

A solution of 5-(ethoxymethoxy)-2-methoxy pyridine (6.20 g, 33.84 mmol) and diisopropylamine (0.24 mL, 1.69 mmol) in THF (100 mL, dist. Na) at −40 °C under nitrogen was added n-BuLi (25.4 mL, 50.76 mmol) dropwise. The resultant mixture stirred at −40 °C for 5 min, and then warmed to 0 °C and stirred at this temperature for a further 3 h. The solution was then again cooled to −40 °C, and n-formylpiperidine (6.76 mL, 60.91 mmol) was added dropwise, and the mixture stirred at 20 °C for another 1 h. Acetic acid (15 mL) was added and the solvent was removed in vacuo. The resultant mixture was partitioned between EtOAc and water, and the organic fraction was dried and evaporated. Column chromatography with 9:1 X4:EtOAc afforded 5-ethoxy-2-methoxy nicotinaldehyde (4.00 g, 56%). 1H NMR (CDCl3): δ 10.43 (s, 1H), 8.27 (s, 1H), 7.07 (d, J = 0.4 Hz, 1H), 5.30 (s, 2H), 3.92 (s, 3H), 3.78 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H).

A solution of 5-(ethoxymethoxy)-2-methoxy nicotinaldehyde (4.00 g, 18.85 mmol) and 3 M HCl (60 mL) in THF (40 mL, dist. Na) was heated at 40 °C for 3 h. The solution was then cooled, diluted with water, and the pH adjusted to 7 using potassium carbonate. The aqueous layer was then extracted with EtOAc three times, and the organic layer dried and evaporated. Column chromatography with 9:1 X4:EtOAc afforded 5-hydroxy-2-methoxy nicotinaldehyde (2.50 g, 87%). 1H NMR (CDCl3): δ 9.97 (d, J = 0.7 Hz, 1H), 9.46 (s, 1H), 8.08 (s, 1H), 6.93 (d, J = 0.6 Hz, 1H), 3.94 (s, 3H).

A mixture of 5-hydroxy-2-methoxy nicotinaldehyde (2.50 g, 16.33 mmol) and potassium carbonate (3.39 g, 24.45 mmol) in DMF (80 mL, anhydrous) was heated at 50 °C for 10 min. Methyl iodide (1.22 mL, 19.59 mmol) was then added and the mixture stirred at this temperature for 2 h. The resultant solution was diluted with EtOAc and washed with brine three times. The organic layer was dried and evaporated to afford 2,5-dimethoxy nicotinaldehyde (2.25 g, 82%). 1H NMR (CDCl3): δ 10.4 (s, 1H), 8.01 (s, 1H), 7.07 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H). Found: [M + MeOH] = 200.4.

A mixture of 2,5-dimethoxy nicotinaldehyde (2.25 g, 13.46 mmol) and sodium borohydride (1.02 g, 26.92 mmol) in MeOH (50 mL, anhydrous) was stirred at 20 °C for 1 h. The solvent was then removed and the residue partitioned between EtOAc and water. The organic layer was dried and evaporated to afford (2,5-dimethoxy pyridin-4-yl)methanol (2.17 g, 95%). 1H NMR (CDCl3): δ 7.70 (s, 1H), 6.77 (s, 1H), 4.66 (d, J = 6.0 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 2.23 (t, J = 6.4 Hz, 1H). To a solution of (2,5-dimethoxy pyridin-4-yl)methanol (2.05 g, 12.12 mmol) and triethylamine (2.53 mL, 18.18 mmol) in DCM (35 mL, anhydrous) at 20 °C was added methanesulfonyl chloride (1.13 mL, 14.50 mmol) dropwise. After 15 min, the reaction was diluted with DCM (20 mL) and the organic layer washed with sat. sodium hydrogen carbonate, dried and evaporated. The residue was redissolved in acetone (70 mL, anhydrous), Lithium bromide (10 g, excess) added, and the mixture heated at reflux for 30 min. The solution was then cooled and the solvent evaporated, and the residue partitioned between EtOAc and water. The aqueous layer was extracted twice with EtOAc and the organic layer was dried and evaporated to afford 4-(bromomethyl)-2,5-dimethoxy pyridineline (2.54 g, 90%). 1H NMR (CDCl3): δ 7.75 (s, 1H), 6.75 (s, 1H), 4.40 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H).

A mixture of (2-bromo-2-methoxy nicotinolin-3-yl)boronic acid (2.80 g, 9.95 mmol), 4-(bromomethyl)-2,5-dimethoxy pyridine (2.54 g, 10.94 mmol) and cesium carbonate (6.50 g, 19.9 mmol) in toluene (50 mL, anhydrous) and DMF (25 mL, anhydrous) was purged with nitrogen. Pd(PPh3)4 (0.646 g, 0.40 mmol) was then added, the mixture purged with nitrogen then heated to 80 °C under nitrogen for 4 h. The reaction was partitioned between EtOAc and water and the organic fraction was dried and evaporated. Column chromatography (19:1 X4:EtOAc) gave 6-bromo-3-(2,5-dimethoxypyridin-4-yl)-2methoxy quinoline (2.20 g, 51%). 1H NMR (CDCl3): δ 7.77 (d, J = 2.2 Hz, 1H), 7.75 (s, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.62 (dd, J = 8.9, 2.2 Hz, 1H), 7.53 (s, 1H), 6.48 (s, 1H), 4.07 (s, 3H), 3.97 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H). Found: [M + H] = 389.7.
Phosphorus tribromide (2.97 mL, 31.4 mmol) was added to a solution of (2,6-bis(methylthio)pyridin-4-yl)methanol (5.26 g, 26.1 mmol) in DCM (300 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 18 h then solvent was evaporated. The residue was diluted with DCM (100 mL) and quenched with ice, the organic layer was washed with sat. NaHCO₃, dried with MgSO₄, filtered and the solvent was evaporated. Column chromatography (6:1 hexanes:EtOAc) gave 4-(bromo-methyl)-2,6-bis(methylthio)pyridine (3.44 g, 50%) as a white solid. M.p. 100 – 102 °C. ¹H NMR (CDCl₃) δ 6.86 (s, 2H), 4.23 (s, 2H), 2.58 (s, 6H). Found: [M + H] = 266.4.

A mixture of 4-(bromomethyl)-2,6-bis(methylthio)pyridine (3.44 g, 15.0 mmol), (6-bromo-2-methoxyquinolin-3-yl)boronic acid (4.31 g, 15.0 mmol), and Cs₂CO₃ (11.24 g, 34.5 mmol) in toluene-DMF (60 mL, 2:1) was degassed under N₂, then added Pd(PPh₃)₄ (0.867 g, 0.750 mmol), and heated at 90 °C for 2 h. Reaction mixture was cooled to 20 °C, filtered through a plug of celite, added water and extracted with EtOAc (x4). Organic layer washed with brine, dried with Na₂SO₄, filtered and the solvent was evaporated to give a yellow residue.

Purification by flash column chromatography with silica using hexane:EtOAc (9:1) to give 3-((2,6-bis(methylthio)pyridin-4-yl)methyl)-6-bromo-2-methoxyquinoline (AB-11) (2.90 g, 46%) as a white solid. M.p. 129 – 131 °C. ¹H NMR (CDCl₃) δ 7.80 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.65 (dd, J = 8.9, 2.2 Hz), 7.57 (s, 1H), 6.72 (s, 2H), 4.05 (s, 3H), 3.87 (s, 2H), 2.57 (s, 6H). Found: [M + H] = 241.8.

A mixture of (6-bromo-2-methoxyquinolin-3-yl)boronic acid (2.56 g, 9.10 mmol), 4-(chloromethyl)-2,6-bis(ethylthio)pyridine (2.25 g, 9.10 mmol) and Cs₂CO₃ (5.93 g, 18.19 mmol) in toluene-DMF (60 mL, 2:1) was degassed under N₂, then added Pd(PPh₃)₄ (0.52 g, 0.45 mmol), and heated at 90 °C for 1.5 h. Reaction mixture was cooled to 20 °C, filtered through a plug of celite, added water and extracted with EtOAc (x4). Organic layer washed with brine, dried with Na₂SO₄, filtered and the solvent was evaporated to give a yellow residue.

Purification by flash column chromatography with silica using hexane:EtOAc (9:1) to give 3-((2,6-bis(ethylthio)pyridin-4-yl)methyl)-6-bromo-2-methoxyquinoline (AB-12) (1.80 g, 47%) as a white solid. ¹H NMR (CDCl₃) δ 7.80 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.65 (dd, J = 8.9, 2.2 Hz), 7.57 (s, 1H), 6.72 (s, 2H), 4.05 (s, 3H), 3.87 (s, 2H), 2.57 (s, 6H). Found: [M + H] = 211.5.

A mixture of 6-bromo-3-((2-isopropoxy-5-methoxypyridin-4-yl)methyl)-2-methoxyquinoline (AB-13). Sodium metal (2.04 g, 85.0 mmol) was added to a solution of isopropanol (150 mL) and the mixture stirred at reflux for 3 h. The solution was then cooled to room temperature and 5-bromo-2-fluoropyridine (10.0 g, 56.67 mmol) was added, and the reaction heated at 80 °C for 0.5 h. The solvent was then removed and the residue partitioned between EtOAc and water, and the organic extract was dried and evaporated to afford 5-bromo-2-isopropoxypyridine (10.9 g, 89%). ¹H NMR (CDCl₃) δ 8.16 (d, J = 2.5 Hz, 1H), 7.60 (dd, J = 8.8, 2.6 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 5.23 (sep, J = 6.2 Hz, 1H), 1.34 (s, 3H), 1.32 (s, 3H). Found: [M + H] = 215.5.

To a solution of 5-bromo-2-isopropoxypyridine (9.85 g, 45.6 mmol) in THF (200 mL, dist. Na) at ~78 °C was added n-BuLi (2.0 M in cyclohexane, 36.48 mL, 72.96 mmol) dropwise over 10 min. The reaction was stirred for 20 min and then trimethyl borate (15.24 mL, 72.96 mmol) was added dropwise over 5 min. The resulting mixture was stirred for 2 h at ~78 °C, then peracetic acid solution (32 wt% in dilute acetic acid, 25.69 mL, 72.96 mmol) was added. After 10 min at ~78 °C, the reaction was warmed to 0 °C and stirred for 1 h. The reaction was then quenched with aqueous sodium bisulfite and stirred for 15 min at 0 °C. The solvent was then concentrated, sodium bicarbonate added and the aqueous layer extracted with EtOAc. The organic extract was dried and evaporated. Column chromatography with 4.1 xEtOAc afforded 6-isopropanylpyridin-3-ol (5.40 g, 65%). ¹H NMR (CDCl₃) δ 7.76 (dd, J = 3.1, 0.4 Hz, 1H), 7.17 (dd, J = 8.9, 3.1 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 6.16 (br s, 1H), 5.09 (sep, J = 6.1 Hz, 1H), 1.34 (s, 3H), 1.32 (s, 3H). Found: [M + H] = 237.1.

To a solution of 6-isopropanylpyridin-3-ol (6.00 g, 32.97 mmol) in DMF (80 mL, anhydrous) at 0 °C was added sodium hydride (60% in mineral dispersion, 1.57 g, 39.54 mmol) in portions. The mixture was then stirred at 20 °C for another 1 h. The mixture was cooled to −40 °C for 5 min, and then warmed to 0 °C and stirred at this temperature for a further 3 h. The solution was then again cooled to −40 °C, and n-formylpiperidine (4.49 mL, 40.46 mmol) was added dropwise, and the mixture stirred at 20 °C for another 1 h. Acetic acid was added and the aqueous layer extracted with EtOAc. The organic extract was dried and evaporated. Column chromatography with 4.1 xEtOAc afforded 5-(ethoxymethoxy)-2-isopropoxypyridine (6.50 g, 54.2%). ¹H NMR (CDCl₃) δ 7.94 (d, J = 3.0 Hz, 1H), 7.33–7.30 (m, 1H), 6.61 (d, J = 8.9 Hz, 1H), 5.20 (sep, J = 6.2 Hz, 1H), 5.14 (s, 2H), 3.73 (q, J = 7.0 Hz, 2H), 1.33 (s, 3H), 1.32 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H). Found: [M + H] = 213.1.

To a solution of 5-(ethoxymethoxy)-2-isopropoxypyridine (6.50 g, 26.97 mmol) and diisopropylamine (0.19 mL, 1.35 mmol) in THF (80 mL, dist. Na) at −40 °C under nitrogen was added n-BuLi (2.0 M in cyclohexane, 16.18 mL, 32.36 mmol) dropwise. The resultant solution was stirred at −40 °C for 5 min, and then warmed to 0 °C and stirred at this temperature for a further 3 h. The solution was then again cooled to −40 °C, and n-formylpiperidine (4.49 mL, 40.46 mmol) was added dropwise, and the mixture stirred at 20 °C for another 1 h.
(12 mL) was added and the solvent was removed in vacuo. The resultant mixture was partitioned between EtOAc and water, and the organic fraction dried and evaporated. Column chromatography with 19:1 x4-EtOAc afforded 5-(ethoxymethoxy)-2-isopropoxyisonicotinaldehyde (5.51 g, 76%).1H NMR (CDCl3) δ 10.41 (s, 1H), 8.25 (s, 1H), 7.01 (d, J = 0.5 Hz, 1H), 5.29 (s, 2H), 5.23–5.16 (m, 1H), 3.79 (q, J = 7.1 Hz, 2H), 1.34 (s, 3H), 1.32 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

A solution of 5-(ethoxymethoxy)-2-isopropoxyisonicotinaldehyde (5.51 g, 20.48 mmol) and 3 M HCl (65 mL) in THF (45 mL, dist. Na) was heated at 40 °C for 1.5 h. The solution was then cooled, diluted with water, and the pH adjusted to 7 using sodium hydrogen carbonate. The aqueous layer was then extracted with EtOAc (x3), and the organic layer dried and evaporated to afford 5-hydroxy-2-isopropoxyisonicotinic acid (3.00 g, 16.4 mmol) in DMF (100 mL, anhydrous). Potassium carbonate (8.65 g, 125 mmol) and bromocyclobutane (2.00 mL, 25.0 mmol). The mixture was stirred at 20 °C for 4 h, partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc. The combined organic fractions were washed with water, dried and evaporated. Column chromatography (DCM) gave methyl 2-cyclobutoxy-6-methoxisonicotinate (2.215 g, 57%) as a colourless oil.1H NMR (CDCl3) δ 6.84 (d, J = 1.0 Hz, 1H), 6.79 (d, J = 1.0 Hz, 1H), 5.08 (pd, J = 7.4, 0.8 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.42–2.52 (m, 2H), 2.12–2.24 (m, 2H), 1.80–1.90 (m, 1H), 1.62–1.75 (m, 1H). Found: [M + H] = 238.2.

A solution of LiOH (0.71 g, 29.6 mmol) in water (20 mL) was added to a solution of methyl 2-cyclobutoxy-6-methoxisonicotinate (2.205 g, 9.29 mmol) in MeOH (20 mL) and THF (20 mL); the solution was stirred at 20 °C for 18 h and then evaporated. The residue was dissolvet in water (80 mL) and acidified to pH 3 with 2 M HCl. The resulting precipitate was filtered and dried to give 2-cyclobutoxy-6-methoxisonicotinic acid (2.02 g, 97%) as a white solid. M.p. 170–171 °C.1H NMR (DMSO-d6) δ 13.56 (bs, 1H), 6.74 (d, J = 1.0 Hz, 1H), 6.67 (d, J = 1.0 Hz, 1H), 5.07 (pd, J = 7.1, 0.7 Hz, 1H), 3.85 (s, 3H), 3.27–3.46 (m, 2H), 2.14–2.22 (m, 2H), 1.74–1.83 (m, 1H), 1.59–1.72 (m, 1H). Found: [M + H] = 224.2.

Trimethyl borate (1.03 mL, 9.0 mmol) and borane dimethyl sulfide complex were added sequentially to a solution of 2-cyclobutoxy-6-methoxisonicotinic acid (1.01 g, 4.52 mmol) in anhydrous THF (20 mL) at 0 °C. The solution was stirred at 20 °C for 18 h and then quenched with MeOH. Removal of the solvent gave an oil, chromatography (3.1 hexanes:EtOAc) of the crude product gave 2-cyclobutoxy-6-methoxypropyridin-4-yl)methanol (0.91 g, 96%) as a colourless oil.1H NMR (CDCl3) δ 6.29 (d, J = 0.9 Hz, 1H), 6.23 (d, J = 0.9 Hz, 1H), 5.06 (pd, J = 7.2, 0.9 Hz, 1H), 4.62 (d, J = 6.2 Hz, 2H), 3.88 (s, 3H), 2.41–2.49 (m, 2H), 2.11–2.22 (m, 2H), 1.79–1.89 (m, 1H), 1.63–1.75 (m, 2H). Found: [M + H] = 210.2.

A solution of (2-cyclobutoxy-6-methoxypropyridin-4-yl)methanol 0.842 g, 4.04 mmol) in DCM (25 mL) at 0 °C was treated sequentially with Et3N (2.25 mL, 16.1 mmol) and mesyl chloride (0.47 mL, 6.1 mmol), the solution was stirred for 1 h at 0 °C and then partitioned with water, the organic fraction was dried and evaporated. The residue was dissolved in acetone (50 mL), LiBr (3.50 g, 40.3 mmol) was added and the mixture was refluxed for 0.5 h and then evaporated. The residue was partitioned between DCM and water and the organic fraction was dried and evaporated. Column chromatography (DCM) gave 4-(bromomethyl)-2-cyclobutoxy-6-methoxypropyridine (0.994 g, 90%) as a colourless oil.1H NMR (CDCl3) δ 6.30 (d, J = 1.0 Hz, 1H), 6.25 (d, J = 1.0 Hz, 1H), 5.07 (pd, J = 7.1, 0.9 Hz, 1H), 4.27 (s, 2H), 3.88 (s, 3H), 2.41–2.49 (m, 2H), 2.11–2.22 (m, 2H), 1.79–1.89 (m, 1H), 1.61–1.75 (m, 1H). Found: [M + H] = 272, 274.

A mixture of (6-bromo-2-methoxyquinolin-3-yl)boronic acid (1.010 g, 3.58 mmol), 4-(bromomethyl)-2-cyclobutoxy-6-methoxypropyridine (0.975 g, 3.58 mmol) and Cs2CO3 (2.33 g, 7.2 mmol) in toluene/DMF (2:1, 50 mL) was purged with nitrogen. Pd(PPh3)4 (0.083 g, 0.072 mmol) was added and the mixture was heated to 80 °C for 3 h under an atmosphere of nitrogen. The mixture was partitioned between EtOAc and water, the organic fraction was dried and evaporated. Column chromatography using a gradient of 3:1 hexanes:DCM to DCM gave 6-bromo-3-(2-cyclobutoxy-6-methoxypropyridin-4-yl)methyl)-2-methoxyquinoline (AB-14) (1.195 g, 78%) as a white solid. M.p. 101–102 °C.1H NMR (CDCl3) δ 7.77 (d, J = 2.2 Hz, 1H), 7.72 (s, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.62 (dd, J = 8.9, 2.2 Hz, 1H), 7.54 (s, 1H), 6.38 (s, 1H), 5.17 (sep, J = 6.2 Hz, 1H), 4.07 (s, 3H), 3.96 (s, 2H), 3.83 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H).

4.1.1.14. 6-Bromo-3-((2-cyclobutoxy-6-methoxypropyridin-4-yl)methyl)-2-methoxyquinoline (AB-14). A solution of methyl 2-hydroxy-6-methoxisonicotinate (3.00 g, 16.4 mmol) in DMF (50 mL, anhydrous) was treated with K2CO3 (4.52 g, 32.7 mmol) and bromocyclobutane (2.00 mL, 25.0 mmol). The mixture was stirred at 20 °C for 48 h, partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc. The combined organic fractions were washed with water, dried and evaporated. Column chromatography (DCM) gave methyl 2-cyclobutoxy-6-methoxisonicotinate (2.215 g, 57%) as a colourless oil.1H NMR (CDCl3) δ 6.84 (d, J = 1.0 Hz, 1H), 6.79 (d, J = 1.0 Hz, 1H), 5.08 (pd, J = 7.4, 0.8 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.42–2.52 (m, 2H), 2.12–2.24 (m, 2H), 1.80–1.90 (m, 1H), 1.62–1.75 (m, 1H). Found: [M + H] = 429.1, 431.1.

4.1.1.15. 6-Bromo-3-((2-ethoxy-6-methoxypropyridin-4-yl)methyl)-2-methoxyquinoline (AB-15). Potassium carbonate (8.65 g, 125 mmol) and 2-isopropanol (12.8 mL, 128 mmol) were added to a solution of
ethyl 2-ethoxy-6-hydroxyisonicotinate (10.82 g, 51.2 mmol) in anhydrous DMF (125 mL) and the mixture was stirred at 20 °C for 48 h. 2-Iodopropane (12.8 mL, 128 mmol) and potassium carbonate (8.65 g, 125 mmol) were added and the mixture was stirred for a further 24 h and then partitioned between DCM and water. The organic fraction was dried and evaporated, chromatography using DCM as an eluent gave ethyl 2-ethoxy-6-isopropoxyisonicotinate (11.557 g, 89%) as a colourless oil. 1H NMR (CDCl3) δ 6.61 (s, 2H), 5.23 (sp, J = 6.2 Hz, 1H), 4.36 (t, J = 7.2 Hz, 2H), 4.32 (t, J = 7.1 Hz, 2H), 1.33–1.42 (m, 12H). Found: [M + H] = 254.2.

A solution of LiOH (3.25 g, 136 mmol) in water (60 mL) was added to a solution of ethyl 2-ethoxy-6-isopropoxyisonicotinate (11.424 g, 45.1 mmol) in THF (60 mL) and MeOH (60 mL), the solution was stirred at 20 °C for 60 h then evaporated. The residue was dissolved in water (200 mL) and the solution was adjusted to pH 6 with 2 M HCl. The oily solid was extracted with EtOAc, the organic fractions were washed with water, dried and evaporated to give ethyl 2-ethoxy-6-isopropoxyisonicotinic acid (10.034 g, 99%) as a white solid. M.p. > 300 °C. 1H NMR (DMSO-d6) δ 13.48 (bs, 1H), 6.66 (d, J = 1.0 Hz, 1H), 6.46 (d, J = 1.0 Hz, 1H), 5.17 (sp, J = 6.2 Hz, 2H), 4.50 (q, J = 7.0 Hz, 2H), 1.28–1.34 (m, 9H). No diagnostic peak in the mass spectrum.

Trimethylborate (3.03 mL, 26.7 mmol) and then borane-dimethylsulfide (2.53 mL, 26.7 mmol) were added to a solution of 2-ethoxy-6-isopropoxyisonicotinic acid (3.00 g, 13.3 mmol) in THF (50 mL, dist. Na) at 0 °C and the mixture was stirred at 20 °C for 18 hr. The solution was cooled to 0 °C and methanol was cautiously added to quench the reaction. Removal of the solvent gave a solid, this was partitioned between EtOAc and water, and the organic fraction was dried and evaporated. Column chromatography (3:1 hexanes:EtOAc) gave (2-ethoxy-6-isopropoxy-4-yl)methanol (2.60 g, 12.3 mmol) in DCM (50 mL, anhydrous) at 0 °C was treated sequentially with triethylamine (4.43 mL, 26.6 mmol) then mesyl chloride (1.43 mL, 18.5 mmol), the mixture was stirred at 0 °C for 1 h then partitioned between DCM and water. The organic fraction was dried and evaporated and the residue was dissolved in acetone (100 mL), LiBr (10.7 g,18.78 mmol) in THF (200 mL, dist. Na) at −40 °C and triisopropylborate (24.87 mL, 107.76 mmol) was added dropwise. The resultant solution was stirred at −40 °C for 5 min, and then warmed to 0 °C and stirred at this temperature for a further 3 h. The solution was then again cooled to −40 °C, and triisopropylborate (24.87 mL, 107.76 mmol) was added dropwise, and the mixture stirred at 20 °C for another 1 h. Water (50 mL) was added and the solvent was removed in vacuo. To the residue was added 1 M NaOH (100 mL) and the aqueous layer was washed with EtOAc (2 × 100 mL). The aqueous layer was then acidified to pH 3 and a solid precipitated. This solid was filtered and dried to afford 2,6-dimethoxypropyridin-3-yl)boronic acid (8.10 g, 61%). 1H NMR (DMSO-d6) δ 7.87 (1H, d, J = 7.9 Hz), 6.36 (1H, d, J = 7.9 Hz), 3.90 (3H, s), 3.87 (3H, s).

To a solution of 2,6-dimethoxypropyridin-3-ol (6.45 g, 40.97 mmol) in DMF (70 mL, anhydrous) at 0 °C was added 60% sodium hydride in mineral oil (41.97 g, 9.16 mmol) in portions. The mixture was warmed to 20 °C and stirred for 1 h. 1-Chloro-2-methyloxethane (4.37 mL, 47.11 mmol) was then added, and the resultant mixture stirred at 20 °C for a further 2 h. The reaction was diluted with brine (100 mL) and extracted with EtOAc three times. The organic layer was washed with brine three times, dried and evaporated. Column chromatography with 9:1 hexanes/EtOAc afforded 2,6-dimethoxypropyridin-3-ol (6.05 g, 90%), 1H NMR (CDCl3) δ 7.12 (1H, d, J = 8.3 Hz), 6.21 (1H, d, J = 8.2 Hz), 4.90 (1H, s), 7.00 (3H, s), 3.86 (3H, s). Found: [M + H] = 156.7.

To a solution of 2,6-dimethoxypropyridin-3-ol (6.45 g, 40.97 mmol) in DMF (70 mL, anhydrous) at 0 °C was added 60% sodium hydride in mineral oil (41.97 g, 9.16 mmol) in portions. The mixture was warmed to 20 °C and stirred for 1 h. 1-Chloro-2-methyloxethane (4.37 mL, 47.11 mmol) was then added, and the resultant mixture stirred at 20 °C for a further 2 h. The reaction was diluted with brine (100 mL) and extracted with EtOAc three times. The organic layer was washed with brine three times, dried and evaporated. Column chromatography with 9:1 hexanes/EtOAc afforded 2-(ethylmethoxy)-2,6-dimethoxypropyridin-9.1 H NMR (CDCl3) δ 7.54 (7.9 Hz), 3.78 (2H, dq, J = 1.8, 7.1 Hz), 1.22 (3H, dt, J = 2.9, 7.0 Hz).
washed with brine three times. The organic layer was dried and evaporated to afford the product 2,3,6-trimethoxyisonicotinaldehyde (1.40 g, 96%). 1H NMR (CDCl3) δ 10.40 (1H, s), 6.58 (1H, s), 4.04 (3H, s), 3.93 (3H, s), 3.91 (3H, s).

A mixture of 2,3,6-trimethoxyisonicotinaldehyde (1.40 g, 7.11 mmol) and sodium borohydride (0.54 g, 14.21 mmol) in MeOH (30 mL, anhydrous) was stirred at 20 °C for 1 h. The solvent was then removed and the residue partitioned between EtOAc and water. The organic layer was dried and evaporated to afford the product (2,3,6-trimethoxypyridin-4-yl)methyl)quinoline (1.44 g, 54%). 1H NMR (CDCl3) δ 6.30 (1H, s), 4.68 (2H, d, J = 5.6 Hz), 3.99 (3H, s), 3.88 (3H, s), 3.79 (3H, s), 2.21 (1H, t, J = 5.9 Hz).

To a solution of (2,3,6-trimethoxypyridin-4-yl)methanol (1.35 g, 6.78 mmol) and triethylamine (1.42 mL, 10.78 mmol) in DCM (20 mL, anhydrous) at 20 °C was added mesyl chloride (0.63 mmol, 8.14 mmol) dropwise. After 15 min, the reaction was diluted with DCM (20 mL) and the organic layer washed with sat. aq. NaHCO3, dried and evaporated. The residue was dissolved in acetone (40 mL, anhydrous), lithium bromide (excess) was added, and the mixture heated at reflux for 30 min. The solution was then cooled and the solvent evaporated, and the residue partitioned between EtOAc and water. The aqueous layer was extracted twice with EtOAc and the organic layer was dried and evaporated to give the product 4-(bromomethyl)-2,3,6-trimethoxyquinoline (1.69 g, 95%). 1H NMR (CDCl3) δ 6.67 (1H, s), 4.40 (2H, s), 3.98 (3H, s), 3.87 (3H, s), 3.87 (3H, s). Found: [M + H] = 420.2

A mixture of (6-bromo-2-methoxyquinolin-3-yl)boronic acid (1.89 g, 6.69 mmol), 4-(bromomethyl)-2,3,6-trimethoxyquinoline (1.67 g, 6.37 mmol) and cesium carbonate (4.15 g, 12.74 mmol) in toluene (40 mL, anhydrous) and DMF (20 mL, anhydrous) was purged with nitrogen. Pd(PPh3)4 (0.29 g, 0.26 mmol) was then added, the mixture purged with nitrogen and heated at 85 °C under nitrogen for 4 h. The reaction was partitioned between EtOAc and water and the organic fraction was dried and evaporated. Column chromatography (19:1 hexanes/EtOAc) gave the product 6-bromo-2-methoxy-3-(2,3,5-trimethoxyquinolin-4-yl)methyl)quinoline (AB-16) (1.44 g, 54%). 1H NMR (CDCl3) δ 7.76 (1H, d, J = 2.2 Hz), 7.68 (1H, d, J = 8.9 Hz), 7.61 (1H, dd, J = 2.2, 8.8 Hz), 7.54 (1H, s), 6.04 (1H, s), 4.07 (3H, s), 4.00 (3H, s), 3.93 (2H, s), 3.85 (3H, s), 3.72 (3H, s). Found: [M + H] = 420.2

4.1.1.7. 4-((6-Bromo-2-methoxyquinolin-3-yl)methyl)-6-methoxy-N,N-dimethylpyridin-2-amine (AB-17). To a solution of (2-(dimethylamino)-6-methoxyisonicotinyl)-4-yl)methanol (1.6 mL, 20.0 mmol) was added, then the mixture purged with nitrogen then heated to 80 °C under nitrogen for 4 h. The reaction was partitioned between EtOAc and water and the organic fraction was dried and evaporated. Column chromatography (19:1 hexanes/EtOAc) gave the product 6-bromo-2-methoxy-3-(2,3,5-trimethoxyquinolin-4-yl)methyl)quinoline (AB-16) (1.44 g, 54%). 1H NMR (CDCl3) δ 7.76 (1H, d, J = 2.2 Hz), 7.54 (1H, s), 5.90 (1H, s), 4.31 (2H, s), 3.87 (3H, s), 3.79 (3H, s). Found: [M + H] = 420.2

4.1.1.18. 4-((6-Bromo-2-methoxyquinolin-3-yl)methyl)-6-ethoxy-N,N-dimethylpyridin-2-amine (AB-18). To a tube was charged ethyl 2-chloro-6-ethoxyisonicotinate (1.00 g, 4.37 mmol), diphenylphosphino-1,1′-binaphthol (0.44 g, 0.70 mmol) and cesium carbonate (1.99 g, 6.12 mmol) under continuous nitrogen flow. Anhydrous toluene (24 mL) was added. The mixture was purged with nitrogen 5 min. Palladium acetate (0.079 g, 0.35 mmol) was added, the mixture was purged again with nitrogen. Dimethylamine in THF (2N, 2.6 mL, 5.246 mmol) was added and the mixture was sealed in the tube and heated at 80 °C overnight. The mixture was filtered through Celite, washing with EtOAc and the filtrate was concentrated in vacuo to yield the crude product as a dark red liquid. Flash chromatography using 2–4% Et2O in hexanes gave ethyl 2-(dimethylaminomethyl)-6-ethoxyisonicotinate (88.5%, 82%) as a light yellow oil. 1H NMR (CDCl3) δ 6.60 (1H, d, J = 0.8 Hz), 6.51 (1H, d, J = 0.8 Hz), 4.35 (2H, q, J = 7.0 Hz), 4.33 (2H, q, J = 7.1 Hz), 3.09 (6H, s), 1.38 (3H, t, J = 7.2 Hz), 1.37 (3H, t, J = 7.2 Hz).

To a solution of ethyl 2-(dimethylaminomethyl)-6-ethoxyisonicotinate (4.40 g, 18.50 mmol) in freshly distilled THF (90 mL) was added at −78 °C under nitrogen lithium aluminium hydride (0.91 g, 24.0 mmol) and 30 drops of degassed THF. The mixture was stirred at −78 °C for 15 min then at 20 °C for 1 h. The mixture was quenched cautiously with water at 2 °C until gas evolution ceased. 1 N NaOH (32 mL) was added and the mixture was stirred for 1 h, then the aqueous mixture was diluted with water and extracted with EtOAc (3x). The combined organic extract was washed with brine, dried (Na2SO4) and concentrated to give the product, which was purified via flash chromatography eluting with mixtures of 6:1 then 4:1 hexanes/EtOAc to give the alcohol intermediate (3.27 g, 90%) as a light yellow oil. The material was used directly in the next step without further characterisation.

To a solution of the alcohol intermediate (3.27 g, 16.7 mmol) in anhydrous DCM (50 mL) was added at 2 °C under nitrogen triethylamine (3.5 mL, 25.0 mmol) dropwise, followed by mesyl chloride (1.6 mL, 20.0 mmol). The mixture was stirred from 2 °C for 10 min, then at 20 °C for 0.5 h. The mixture was quenched with sat. aq. NaHCO3 solution. The aqueous mixture was extracted with DCM (3x) and the combined extract was washed with water, dried and concentrated to afford the crude product as a brown solid. This was triturated in acetone (60 mL), lithium bromide (1.42 g) was added. The suspension was refluxed for 1 h. Flash chromatography using a mixture of 3–5% EtO in hexanes as eluent gave 4-(bromomethyl)-6-ethoxy-N,N-dimethylpyridin-2-amine (3.84 g, 89%) as a mobile yellow oil. 1H NMR (CDCl3) δ 6.011 (1H, s), 5.99 (1H, s), 4.30 (2H, q, J = 6.8 Hz), 4.27 (2H, s), 3.05 (6H, s), 1.37 (3H, t, J = 7.2 Hz).

A mixture of (6-bromo-2-methoxyquinolin-3-yl)boronic acid (4.13 g, 14.7 mmol), 4-(bromomethyl)-6-ethoxy-N,N-dimethylpyridin-2-amine (3.80 g, 14.7 mmol) and cesium carbonate (9.58 g, 29.4 mmol) in a mixture of toluene (40 mL) and DMF (20 mL) was purified with nitrogen. Pd(PPh3)4 (0.68 g) was added. The mixture was purged again with nitrogen and heated at 85 °C under nitrogen for 3 h. The mixture was partitioned between water and EtOAc and the aqueous mixture was extracted with EtOAc (2x). The extract was washed with water (2x), brine, dried (MgSO4) and concentrated to afford the crude product as a brown solid which was chromatographed using 3–10% Et2O in hexanes as eluent to yield the product 4-((6-bromo-2-methoxyquinolin-3-yl)methyl)-6-ethoxy-N,N-dimethylpyridin-2-amine (AB-18) (3.51 g, 57%) as a pale yellow solid.
(1H, d, J = 8.8 Hz), 7.61 (1H, dd, J = 2.2, 8.8 Hz), 7.55 (1H, s), 5.91 (1H, s), 5.84 (1H, s), 4.30 (2H, q, J = 7.1 Hz), 4.07 (3H, s), 3.87 (2H, s), 3.03 (6H, s), 1.36 (3H, t, J = 7.1 Hz).

4.1.1.19. 4-((6-Bromo-2-methoxyquinolin-3-yl)methyl)-6-(ethylthio)-N,N-dimethylpyridin-2-amine (AB-19). To a glass tube was charged methyl 2-chloro-6-(dimethylamino)isonicotinate (WO 2010/100475) (2.44 g, 1.140 mmol) and cesium carbonate (4.43 g, 13.60 mmol) under continuous nitrogen flow. Anhydrous toluene (30 mL) was added. The mixture was purged with nitrogen, then heated to 80 °C under nitrogen for 2.5 h. The mixture was partitioned between water and EtOAc. The aqueous layer was then acidified to pH 1 and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried and evaporated to afford 2,3-difluoroisonicotinic acid (2.39 g, 35%).

1H NMR (CDCl3) δ 153.2 (1H, br s), 8.14 (1H, dd, J = 1.2, 5.0 Hz), 7.70 (1H, dd, J = 4.8, 4.8 Hz). Found: [M − H] = 158.5.

Sodium (0.79 g, 33.09 mmol) was added portion wise to MeOH (60 mL) over 0.5 h. 2,3-difluoroisonicotinic acid (2.39 g, 15.04 mmol) was then added and the reaction refluxed for 2 h. The solution was cooled and the solvent evaporated. The residue was taken up into water (100 mL) and washed with EtOAc (2 × 50 mL). The aqueous layer was then acidified to pH 1 and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried and evaporated to afford 3-fluoro-2-methoxyisonicotinic acid (2.23 g, 87%).

1H NMR (CDCl3) δ 7.92 (1H, d, J = 5.2 Hz), 7.02 (1H, dd, J = 4.7, 4.9 Hz), 3.97 (3H, s). Found: [M − H] = 170.5.

Borane – dimethylsulfide complex (2.47 mL, 26.07 mmol) and triethylborate (2.96 mL, 26.07 mmol) were added to a solution of 3-fluoro-2-methoxyisonicotinic acid (13.03 mmol) in THF (80 mL, dist. Na) at 0 °C, and the solution warmed to 20 °C and stirred overnight. The mixture was then cooled to 0 °C, and quenched with methanol (10 mL). The solvent was then evaporated and the residue was partitioned between EtOAc and water. The organic layer was then dried and evaporated to afford the product (3-fluoro-2-methoxypropyridin-4-yl)methanol (1.89 g, 92%).

1H NMR (CDCl3) δ 7.91 (1H, d, J = 5.2 Hz), 7.02 (1H, dd, J = 4.5, 5.1 Hz), 4.81 (2H, s), 4.03 (3H, s). Found: [M + H] = 158.5.

To a solution of (3-fluoro-2-methoxypropyridin-4-yl)methanol (1.89 g, 12.03 mmol) and triethylamine (2.52 mL, 18.05 mmol) in DCM (30 mL, anhydrous) at 20 °C was added mesyl chloride (1.12 mL, 14.44 mmol) dropwise. After 15 min, the reaction was diluted with DCM (20 mL) and the organic layer washed with sat. NaHCO3, dried and evaporated. The residue was dissolved in acetone (60 mL, anhydrous), lithium bromide (excess) added, and the mixture heated at reflux for 30 min. The solution was then cooled and the solvent evaporated, and the residue partitioned between EtOAc and water. The aqueous layer was extracted twice with EtOAc and the organic layer was dried and evaporated to give the product 4-(bromomethyl)-3-fluoro-2-methy propyridine (2.20 g, 83%).

1H NMR (CDCl3) δ 7.90 (1H, d, J = 5.2 Hz), 6.90 (1H, dd, J = 4.8, 4.9 Hz), 4.43 (2H, s), 4.02 (3H, s). Found: [M + H] = 220.2.

A mixture of (6-bromo-2-methoxyquinolin-3-yl)boronic acid (2.56 g, 9.09 mmol), 4-(bromomethyl)-3-fluoro-2-methy pyridine (2.20 g, 10.00 mmol) and cesium carbonate (5.92 g, 18.18 mmol) in toluene (45 mL, anhydrous) and DMF (22.5 mL, anhydrous) was purged with nitrogen. 1H NMR (CDCl3) (0.42 g, 0.363 mmol) was then added, the mixture purged with nitrogen, then heated to 80 °C under nitrogen for 4 h. The reaction was partitioned between EtOAc and water and the aqueous mixture was extracted with EtOAc (2x). The extract was washed with water, brine, dried (MgSO4) and concentrated to afford the crude product as an orange oil which was chromatographed using 2–5% EtO in hexanes as eluent to yield the product as a light yellow solid. Recrystallisation from DCM/MeOH provided 4-((6-bromo-2-methoxyquinolin-3-yl)methyl)-6-(ethylthio)-N,N-dimethylpyridin-2-amine (AB-19) (1.25 g, 57%) as a white solid.

1H NMR (CDCl3) δ 7.79 (1H, d, J = 2.4 Hz), 7.70 (1H, d, J = 8.8 Hz), 7.64 (1H, dd, J = 2.4, 9.2 Hz), 7.56 (1H, s), 6.34 (1H, s), 6.06 (1H, s), 4.09 (3H, s), 3.86 (2H, s), 6.15 (2H, q, J = 7.2 Hz), 3.07 (6H, s), 1.39 (3H, t, J = 7.2 Hz). Found [M + H] = 432.1.
organic fraction was dried and evaporated. Column chromatography (19:1 hexanes/EtOAc) gave the product 6-bromo-3-((3-fluoro-2-methoxy-pyridin-4-yl)methyl)-2-methoxyquinoline (AB-20) (1.76 g, 51%).

1H NMR (CDCl3) δ 7.82 (1H, d, J = 5.2 Hz), 7.79 (1H, d, J = 2.1 Hz), 7.69 (1H, d, J = 8.8 Hz), 7.64 (1H, dd, J = 2.2, 8.9 Hz), 7.60 (1H, s), 6.69 (1H, dd, J = 4.8, 5.0 Hz), 4.07 (3H, s), 4.06 (2H, s), 4.03 (3H, s). Found: [M + H] = 377.2

4.1.2. Scheme 2. New C/D units

4.1.2.1. 1-(2,6-Diethoxypyridin-4-yl)-3-(dimethylamino)propan-1-one (IIa). Oxalyl chloride (1.34 mL, 15.8 mmol) was added to a suspension of 2,6-diethoxypyridin-4-yl-methylammonium chloride (24.2 g, 12.3 mmol) in DCM (70 mL) and DMF (0.20 mL, 2.6 mmol) at 20 °C. The mixture was stirred for 1 h to give a colourless solution which was cooled to 0 °C. N,N-dimethylhydroxylamine hydrochloride (1.42 g, 14.6 mmol) and pyridine (3.51 mL, 28.9 mmol) were added sequentially and the mixture was stirred at 20 °C for 18 h, then partitioned between EtOAc and sat. aq. NaHCO3. Column chromatography with hexanes:EtOAc (2:1) gave N2,6-trimethoxy-N-methylisonicotinamide (II (Z = Me), 2.49 g, 83%). 1H NMR (CDCl3) δ 6.47 (s, 2H), 0.11 (s, 6H), 3.58 (br s, 3H), 3.32 (s, 3H). Found: [M + H] = 227.2.

Vinylmagnesium bromide (42.5 mL of a 1 M solution in THF, 42.5 mmol) was added to a solution of N2,6-trimethoxy-N-methylisonicotinamide (II (Z = Me), 4.81 g, 21.3 mmol) in dry THF (200 mL) at 0 °C. The brown solution was warmed to 20 °C for 1 h then dimethoxypyridin-4-yl)-3-(1H-1,2,4-triazol-1-yl)propan-1-one (VI) (0.045 g, 0.044 mmol) as an oil. 1H NMR (CDCl3) δ 6.73 (s, 2H), 3.95 (s, 6H), 3.70 (t, J = 7.4 Hz, 2H), 3.08 (t, J = 7.1 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 2.48 (t, J = 4.4 Hz, 4H). Found: [M + H] = 281.6.

24 h, then partitioned between EtOAc and water. The solution was dried and evaporated and column chromatography with hexanes:EtOAc (9:1) gave 1-(2,6-dimethoxypyridin-4-yl)-3-(methyl(methyl)amino)propan-1-one (IV) (5.50 g, 72%) as an oil. 1H NMR (CDCl3) δ 6.76 (s, 2H), 3.96 (s, 6H), 3.46 (s, 3H), 3.16 (t, J = 6.6 Hz, 2H), 3.04 (t, J = 6.5 Hz, 2H), 2.61 (s, 3H). Found: [M + H] = 255.6.

4.1.2.4. 1-(2,6-Dimethoxypyridin-4-yl)-3-morpholinopropan-1-one (V). Vinyleнизарин bromide (18.6 mL of a 1 M solution in THF, 18.6 mmol) was added to a solution of N2,6-trimethoxy-N-methylisonicotinamide (II (Z = Me), 2.00 g, 8.80 mmol) in dry THF (30 mL) at 0 °C. The yellow/orange solution was warmed to 20°C for 1 h then morpholine (3.23 mL, 37.1 mmol) was added. The solution was stirred at 20 °C for 1 h, the solvent removed in vacuo, and the resultant mixture then partitioned between EtOAc and water. The solution was dried and evaporated to afford 1-(2,6-dimethoxypyridin-4-yl)-3-morpholinopropan-1-one (V) (2.40 g, 97%) as an oil. 1H NMR (CDCl3) δ 6.72 (s, 2H), 3.95 (s, 6H), 3.70 (t, J = 4.4 Hz, 4H), 3.08 (t, J = 7.1 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 2.48 (t, J = 4.4 Hz, 4H). Found: [M + H] = 281.6.

4.1.2.5. 1-(2,6-Dimethoxypyridin-4-yl)-3-(1H-imidazol-1-yl)propan-1-one (VI). Vinyleнизарин bromide (0.93 mL of a 1 N solution in THF, 0.93 mmol) was added to a solution of N2,6-trimethoxy-N-methylisonicotinamide (II (Z = Me), 0.10 g, 0.44 mmol) in dry THF (3 mL) at 0 °C. The yellow/orange solution was warmed to 20 °C for 1 h. The solvent was removed in vacuo and the residue partitioned between EtOAc and water, and the pH adjusted to 3 with 1 M HCl. The combined organic extracts were dried and the solvent removed in vacuo. The crude residue was redissolved in THF (3 mL), cooled to 0 °C, and imidazole (0.18 g, 2.65 mmol) was added followed by water (1 mL). The solution was then stirred at 20 °C for 1 h, then partitioned between EtOAc and water. The solution was dried and evaporated and column chromatography with hexanes:EtOAc (1:2) gave 1-(2,6-dimethoxypyridin-4-yl)-3-(1H-imidazol-1-yl)propan-1-one (VI) (0.045 g, 39%) as an oil. 1H NMR (CDCl3) δ 7.54 (s, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 6.68 (s, 2H), 4.41 (t, J = 6.4 Hz, 2H), 3.95 (s, 6H), 3.35 (t, J = 6.4 Hz, 2H). Found: [M + H] = 262.6.

4.1.2.6. 1-(2,6-Dimethoxypyridin-4-yl)-3-(1H,1,2,4-triazol-1-yl)propan-1-one (VII). Vinyleнизарин bromide (27.9 mL of a 1 N solution in THF, 27.9 mmol) was added to a solution of N2,6-trimethoxy-N-methylisonicotinamide (II (Z = Me), 3.00 g, 13.3 mmol) in dry THF (30 mL) at 0 °C. The yellow/orange solution was warmed to 20 °C for 1.5 h. The solvent was removed in vacuo and the residue partitioned between chloroform and water, and the pH adjusted to 1 with 1 M HCl. The combined organic extracts were dried and the solvent removed in vacuo. The crude residue was redissolved in chloroform (150 mL) and 1H-1,2,4-triazole (2.67 g, 39.8 mmol) and the resultant mixture stirred at 60 °C for 3 h. The solution cooled to 20 °C and partitioned between chloroform and water. The solution was dried and evaporated and column chromatography with hexanes:EtOAc (1:2) gave 1-(2,6-dimethoxypyridin-4-yl)-3-(1H,1,2,4-triazol-1-yl)propan-1-one (VII) (1.54 g, 44%) as an oil. 1H NMR (CDCl3) δ 8.20 (s, 1H), 7.91 (s, 1H), 6.70 (s, 2H), 4.61 (t, J = 6.2 Hz, 2H), 3.94 (s, 6H), 3.51 (t, J = 6.1 Hz, 2H). Found: [M + H] = 263.6.

4.1.3. Example of the synthesis of the bromo analogues of Table 1

4.1.3.1. 1-(6-Bromo-2-methoxynicotin-3-yl)-1-(2,5-dimethoxypyridin-3-yl)-2-(2,5-dimethoxypyridin-4-yl)-4-(dimethylamino)butan-2-ol (27). n-BuLi (2.92 mL of a 2 N solution in cyclohexane, 5.83 mmol) was added at −40 °C under dry nitrogen to a solution of dry disopropylamine (0.813 mL, 5.83 mmol) in dry THF (6 mL) and the solution was stirred at this temperature for 10 min, then cooled to −78 °C. A solution of 6-bromo-3-(2,5-dimethoxypyridin-3-yl)methyl)-2-methoxynicotinamide (AB-10) (1.90 g, 4.86 mmol) in dry THF (6 mL)
was added dropwise and the mixture was stirred at \( -78 \) °C for 90 min, to give a dark, wine-red coloured solution. A solution of 1-(2,6-dimethoxyphenyl-4-yl)-3-(dimethylamino)propan-1-one (IIIa) (1.15 g, 4.86 mmol) in dry THF (7 mL) was added and the reaction mixture was stirred at this temperature for 4 h. HOAc (0.90 mL) was added and the mixture was heated to 55 °C for 4 h. The reaction was diluted with water and extracted with EtOAc (2x). The combined organic extract was washed with sat. aq. NaHCO\(_3\) solution, and brine, then dried (Na\(_2\)SO\(_4\)) and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. Elution with 0–10% MeOH/DCM afforded isomer A of 27 (1.11 g, 36%) followed by isomer B of 27 (1.03 g, 34%) as white solids.

Isomer A. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.12 (d, \( J = 3.3 \) Hz, 2H), 7.82 (d, \( J = 2.2 \) Hz, 1H), 7.68 (d, \( J = 8.9 \) Hz, 1H), 7.60 (dd, \( J = 8.9, 2.2 \) Hz, 1H), 7.48 (d, \( J = 3.0 \) Hz, 1H), 6.56 (br s, 2H), 5.31 (s, 1H), 4.19 (s, 3H), 3.88 (s, 6H), 3.74 (s, 3H), 3.63 (s, 3H), 2.30–2.04 (m, 1H), 2.02–1.96 (m, 1H), 1.97 (s, 6H), 1.83–1.68 (m, 2H). Found: [M + H] = 627.8.

Isomer B. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.63 (s, 1H), 7.78 (d, \( J = 1.7 \) Hz, 1H), 7.68 (d, \( J = 3.0 \) Hz, 1H), 7.55–7.47 (m, 3H), 6.56 (br s, 2H), 5.32 (s, 1H), 4.04 (s, 3H), 3.84 (s, 3H), 3.83 (s, 6H), 3.71 (s, 3H), 2.40–2.32 (m, 1H), 2.08 (s, 6H), 2.03–1.98 (m, 1H), 1.87–1.79 (m, 1H), 1.76–1.70 (m, 1H). Found: [M + H] = 627.8.

The mixture was resolved into its four optical isomers using preparative supercritical fluid HPLC at BioDuro LLC (Beijing). The data in Table 1 are for the most active \( R,S \)-diastereomers. The other 6-cyano compounds in Table 1 were prepared and purified similarly.

### 4.1.4. Example of cyanation reaction to give the cyano compounds of Table 1

1. **hydroxybutyl)-2-methoxyquinoline-6-carbonitrile (28)**. A solution of compound 27 (Table 1) (0.61 g, 0.969 mmol) in DMF (6 mL, anhydrous) was purged with nitrogen and heated to 55 °C for 10 min. Tri(o-tolyl)phosphine (0.044 g, 0.145 mmol), zinc dust (0.006 g, 0.073 mmol) were then added, and the reaction was again purged with nitrogen and heated for another 10 min at 55 °C. Zinc cyanide (0.063 g, 0.533 mmol) was then added and the reaction mixture was heated to 65 °C for 4 h. The reaction was diluted with water and extracted with EtOAc three times. The organic layer was washed with brine three times, dried and evaporated. Column chromatography with 1:1 hexane/EtOAc followed by 1:3 hexane/EtOAc afforded 28 (0.41 g, 74%); isomer A as a white solid.

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.23 (s, 1H), 8.10 (d, \( J = 3.0 \) Hz, 1H), 8.05 (d, \( J = 1.7 \) Hz, 1H), 7.86 (d, \( J = 8.7 \) Hz, 1H), 7.71 (dd, \( J = 8.6, 1.8 \) Hz, 1H), 7.49 (d, \( J = 3.0 \), 1H), 6.56 (br s, 2H), 5.31 (s, 1H), 4.23 (s, 3H), 3.89 (s, 6H), 3.74 (s, 3H), 3.63 (s, 3H), 2.31–2.24 (m, 1H), 2.02–1.96 (m, 1H), 1.97 (s, 6H), 1.78–1.68 (m, 2H). Found: [M + H] = 574.6.

Followed by isomer B, (7%), foamy white solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.76 (s, 1H), 8.01 (d, \( J = 1.7 \) Hz, 1H), 7.70–7.60 (m, 3H), 7.48 (d, \( J = 3.0 \) Hz, 1H), 6.55 (br s, 2H), 5.30 (s, 1H), 4.04 (s, 3H), 3.88 (s, 3H), 3.83 (s, 6H), 3.72 (s, 3H), 2.32–2.25 (m, 1H), 2.05 (s, 6H), 2.04–2.00 (m, 1H), 1.88–1.80 (m, 1H), 1.71–1.64 (m, 1H). Found: [M + H] = 574.6.

The mixtures were resolved into their four optical isomers using preparative supercritical fluid HPLC at BioDuro LLC (Beijing). The data in Table 1 are for the most active \( R,S \)-diastereomers. The other 6-cyano compounds in Table 1 were prepared and purified similarly.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2019.02.026. These data include MOL files and InChIKeys of the most important compounds described in this article.

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