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Development of DANDYs, New 3,5-Diaryl-7-azaindoles Demonstrating Potent DYRK1A Kinase Inhibitory Activity.

Stéphanie Gourdain,[1] Julien Dairou,[2] Clément Denhez,[3,4] Linh Chi Bui,[2] Fernando Rodrigues-Lima,[2] Nathalie Janel,[2] Jean M. Delabar,[2] Kevin Cariou,[1] and Robert H. Dodd[*,1]

[1] Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, UPR 2301, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

[2] Université Paris Diderot, Sorbonne Paris Cité, Unité de Biologie Fonctionnelle et Adaptative, CNRS EAC 4413, 75013, Paris, France

[3] ICMR UMR7312/ P3M, Université de Reims Champagne-Ardenne, UFR Pharmacie 3, rue du Maréchal Juin 51096 Reims Cedex, France

[4] Multiscale Molecular Modeling Platform, Université de Reims Champagne-Ardenne, rue du Maréchal Juin 51096 Reims Cedex, France

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ABSTRACT: A series of 3,5-diaryl-1*H*-pyrrolo[2,3-*b*]pyridines were synthesized and evaluated for inhibition of DYRKIA kinase in vitro. Derivatives having hydroxy groups on the aryl moieties (**2c**, **2j-l**) demonstrated high inhibitory potencies with K_i's in the low nanomolar

range. Their methoxy analogues were up to 100 times less active. Docking studies at the ATP binding site suggested that these compounds bind tightly to this site via a network of multiple H-bonds with the peptide backbone. None of the active compounds were cytotoxic to KB cells at 10^{-6} M. Kinase profiling revealed that compound **2j** showed significant selectivity for DYRK1A with respect to DYRK2 and DYRK3.

Introduction

Dual-specificity tyrosine phosphorylation-regulated kinase 1a (DYRK1A) belongs to the DYRK subfamily of protein kinases. The latter are related to the cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), glycogen synthase kinases (GSKs) and CDK-like kinases (CLKs), all of which constitute the CMGC group.[1] DYRK1A is expressed in human fetal and adult brains and its coding gene is located on chromosome 21 within the Down syndrome (DS) critical region.[2] The presence of an extra copy of whole or part of human chromosome 21[3] in DS results in an approximately 1.5-fold up-regulation of DYRK1A in DS brains[4] and this overexpression is strongly suspected to contribute to mental retardation. DS is also associated with other pathologies such as congenital heart defects, immune and endocrine system deregulations[5] and an increased risk of early Alzheimer's disease (AD).[6] AD is mainly caused by the intracellular aggregation of hyperphosphorylated forms of the microtubule-binding protein Tau responsible for the formation of neurofibrillary tangles (NFT).[7] Recent studies have suggested that DYRK1A phosphorylates Tau protein which, in the case of DS, leads to hyperphosphorylation at multiple Ser/Thr sites of the protein.[6] Moreover, DYRK1A has also been shown to phosphorylate amyloid precursor protein (APP) at the Thr668 residue which in turn increases β-amyloid production (notably in the forebrain and hippocampus), hence accounting for the early appearance of AD symptoms in DS patients.[8]

In view of the numerous deleterious consequences of the overexpression of DYRK1A in DS and its possible implications in AD, efforts have recently been made to develop inhibitors of this kinase (Figure 1).[9] Epigallocatechin-3-gallate (EGCG) and harmine have emerged as natural potent DYRK1A inhibitors. While EGCG, the major flavonoid in tea,[10,1c] is a non-competitive inhibitor, harmine, a β-carboline alkaloid isolated from *Peganum harmala,* is a specific and potent ATP-competitive inhibitor of DYRK1A (IC_{50} = 33-350 nM).[11] Although it represents a standard in terms of activity and selectivity, the numerous side effects of harmine have led to the development and study of various synthetic compounds. Not surprisingly, many of these DYRK1A inhibitors possess a heteroaromatic core. Examples are the purine derivative roscovitine,[10a] the quinazoline NCGC00010037,[12] the benzothiazoles TG003[13] and INDY,[14] aminopyrimidyl-indoles[15] or leucettine-derivatives (Figure 1).[16] A number of potent inhibitors structurally related to harmine incorporate indolic and aza-indolic scaffolds (meridianins,[17] meriolins,[18] 2-indoyl-pyridine derivatives[19] and lamellarin isosters[20]). Herein, we report the identification of new **D**iaryl-**A**zaindole i**N**hibitors of **DY**RK1A (**DANDY**) and the use of computer-guided molecular design for structural optimization.[21]

Selection of the target compounds

We began our study by screening our own chemical library for DYRK1A inhibitory activity (using an HPLC-based assay), focusing on 6-azaindole derivatives, a family to which harmine belongs and for which our group has a longstanding experience.[22] Two compounds, 3-phenyl-5-*p*-methoxyphenyl-6-azaindole **1a** and 3-phenyl-5-*p*-hydroxyphenyl-6-azaindole **2a**, emerged as potential hits with IC_{50} values of 17.0 μM and 27.4 μM, respectively (Figure 2). ~~Indeed, these values compare favorably with that of harmine (IC_{50} = 0.29 μM) determined under the same conditions.~~

~~Substrates **1a** and **2a** share a common 6-azaindole core with harmine.~~ Moreover, when comparing them to other competitive inhibitors of DYRK1A, several common structural characteristics emerge: an aromatic moiety on the indolic 3-position (see meridianin and meriolin) and a crescent-like shape (see leucettine and lamellarin). These analogies prompted us to further explore structural motifs based on 3,5-diphenolic 6- or 7-azaindoles of type **3**. Such compounds can in principle be easily prepared from the corresponding accessible 3,5-dihalo-6- or 7-azaindole **4** (Figure 3).

Virtual screening of a representative library of such compounds at the ATP binding site was thus initiated. Four DYRK1A crystal structures are available in the PDB: 3ANR (a DYRK1A-harmine complex), 3ANQ (a DYRK1A-INDY complex), 2VX3 (a DYRK1A-K00611A complex) and 2WO6 (a DYRK1A-K00611A complex associated with a peptide substrate).[14] All exhibit complete structural homology except for the presence of a chloride ion in the ATP site in the case of 2VX3 and 2WO6. Because 3ANQ is practically identical to 3ANR, it was excluded. Thus 3ANR, 2WO6 and 2VX3 were virtually prepared and validated using the Schrödinger suite 2012.™ Docking studies at the ATP binding site were then performed using the model 3,5-diaryl 6- and 7-azaindole substrates shown in Figure 4. These compounds were found to have docking scores within the same range as ATP regardless of the DYRK1A structure used, thus validating our initial structural design.

Several trends emerged from this virtual study. First, the 6-azaindole derivatives were found to bind somewhat more weakly than the 7-azaindoles (compare **1a**, **2a** with **1b**, **2b**). Furthermore, in the latter series, the hydroxy compounds appeared potentially more active than the corresponding methoxy compounds (compare **2b** with **1b** and **2c** with **1c**). Finally, increasing the number of hydroxy groups considerably improved the docking scores (compare tetrahydroxy **2d** with monohydroxy **2b** and dihydroxy **2c**).

From this information, a binding model of our proposed DYRK1A inhibitors at the ATP binding site could be defined (Figure 5). Thus, the two nitrogens of the 6- or 7-azaindole cores were found to fix the binding mode by establishing two H-bonds (one H-donating and one H-accepting) with the Glu239 carbonyl and the Leu241 NH, the 7-azaindole nucleus appearing better positioned to do so.[23] With the binding mode set in this way, the substituents at the C3 and C5 positions of the phenyl rings could be ideally allocated to generate further stabilizing interactions with Ser242, Ileu165 and Lys188. This is the case for the hydroxyphenyl derivatives **2d** which, by forming H-bonds with the carbonyl functions of Ser242 and Ileu165 and the ammonium center of Lys188 obtain the high docking scores noted above.

In order to verify these hypotheses, we then proceeded to synthesize the proposed diaryl 7-azaindole derivatives and assess their DYRK1A inhibitory potency.

Synthesis

For the preparation of the 3,5-diaryl-substituted 7-azaindole derivatives, a standard synthetic route was established.[24] Commercially available 5-bromo-7-azaindole **5** was iodinated in the presence of NIS and *N*-protected with a benzenesulfonyl group giving the common precursor **6** in almost quantitative yield (Scheme 1). Two successive Suzuki-Miyaura cross-couplings were then performed using various commercially available arylboronic acids to provide unsymmetrical compounds **7b,f-m** in good yields. Alternatively, symmetrical compounds **7c-e,n** were synthesized through a one-step double Suzuki-Miyaura cross-coupling reaction using two equivalents of the same arylboronic acid. Deprotection of the indole nitrogen was accomplished with sodium methanolate and led to the desired OMe-DANDYs **1b-d,f-n**, as well as the diphenyl derivative **1e** (n=0), with an average yield of 80%. De-*O*-methylation of the former compounds was performed with the adequate amount of BBr_3 (3.0 equivalents *per*

methyl group) to give the corresponding OH-DANDYs **2b-d,f-n**. All the desired derivatives were thus efficiently obtained in three to four steps from 3-iodo-5-bromo-7-azaindole.

Results and Discussion

DYRK1A inhibition studies

The DYRK1A inhibitory potencies of both the hydroxy and methoxy diaryl 7-azaindole derivatives were then evaluated *in vitro* (HPLC based assay carried out using a fluorescent peptide substrate of DYRK1A). The first set of data was collected for the 7-azaindoles bearing an unsubstituted phenyl group at C3 and a diversely substituted aryl group at C5 (Table 1). While the completely unsubstituted 3,5-diphenyl derivative **1e** exhibited an IC_{50} value in the submicromolar range (0.41 μM) *i.e.* four times more efficient than 6-aza-indole **1a** (1.70 μM, Figure 2), the incorporation of a *p*-OH function on the C5 phenyl (**2b**) afforded a slight improvement in inhibitory potency (IC_{50} = 0.33 μM). In contrast, activity was considerably decreased in the case of the *m*-OH and *o*-OH derivatives **2f** and **2g** (IC_{50} = 2.70 and 3.59 μM, respectively). Significantly, addition of a *p*-OH group to these latter compounds (i.e., **2i** and **2h**) doubled the DYRK1A inhibitory potencies with respect to the mono-OH derivative **2b** (IC_{50} = 0.16 and 0.15 μM, respectively *vs* 0.33 μM). In accordance with our binding model, the methoxy derivatives, in which H-bonding with the backbone peptide residues of the binding site is precluded, were found to be less potent than the corresponding hydroxy derivatives (compare **1b** *vs* **2b**; **1f** *vs* **2f**; **1g** *vs* **2g**; **1h** *vs* **2h; 1i** *vs* **2i**).

A second set of data was then obtained for compounds in which both aryl rings were substituted with various patterns of mono- and/or di-methoxy groups (Table 2). While the di-*p*-methoxy derivative **1c** was less active than the mono-*p*-methoxy analogue **1b** (IC_{50} = 1.74

μM and 0.96 μM, respectively), the trimethoxy compounds **1j** (IC_{50} = 0.28 μM) and **1k** (IC_{50} = 0.46 μM) were considerably more active than their corresponding dimethoxy derivatives **1h** and **1i** (IC_{50} = 1.17 μM and 3.08 μM, respectively). This advantage of an additional methoxy group was lost in the case of the tetramethoxy analogues **1l** (IC_{50} = 2.88 μM), **1m** (IC_{50} = 1.67 μM) and **1d** (IC_{50} = 57.78 μM). Thus, while good inhibitory activity was maintained with a *p*-methoxy group on the C3 aryl moiety, derivatives bearing a free hydroxy function on the C5 aryl still appeared to be superior inhibitors.

This observation also proved true for the derivatives having hydroxy rather than methoxy substituents on the C3 aryl ring. Indeed, these substrates were found to possess the highest activities toward DYRK1A of any inhibitors reported so far, with several compounds having IC_{50}s near or under the 10 nM threshold (Table 3). Thus, the presence of two *p*-hydroxy groups was found to be essential for high activity (compare **2c**, IC_{50} = 23.1 nM and **2n**, IC_{50} = 0.105 μM). A 2,4-dihydroxyphenyl group at C5 led to a lowering of the IC_{50} (**2j**, IC_{50} = 11.7 nM) while the closely related 3,4-dihydroxy analogue (**2k**) displayed an even higher inhibitory potency (IC_{50} = 3 nM). Addition of a *m*-hydroxy group to the C3 aryl moiety led to some loss of activity (**2l**, IC_{50} = 14.3 nM; **2d**, IC_{50} = 12.4 nM) though these remained excellent inhibitors. Finally, 2,5-dihydroxy substitution on the C5 phenyl led to some loss of activity (compare **2m**, IC_{50} = 39.1 nM and **2l**, IC_{50} = 14.3 nM).

In order to gain more insight into the mechanism of DYRK1A inhibition by these azaindole derivatives, kinetic experiments were conducted with the more potent compounds. Double-reciprocal plots were carried out with various concentrations of ATP and the peptide substrate. All inhibitors were found to be competitive with ATP but not with the peptide substrate. The exceptional DYRK1A inhibitory potencies of these DANDYs were confirmed, all K_i values being under 12 nM, and the most potent analogue, **2k**, demonstrating an $IC_{50} < 2$ nM (Table 3).

Detailed docking studies of the DANDYs

The putative binding modes at the ATP binding site of DYRK1A of the most active compounds of the series (**2c**, **2d**, **2j** and **2k)** were examined based on the structure of DYRK1A 2WO6.pdb available in the Protein Data Bank (PDB). The docking procedure was first evaluated by the direct docking of K00611A into this native structure of DYRK1A. The protein-ligand complex was correctly reproduced in direct docking with a rmsd of 0.45 Å, thus validating the procedure used for docking of our active compounds (Figure 6, A).

We then proceeded to dock a virtual ATP molecule with the prepared structure of DYRK1A. The adenine moiety was found to be oriented toward the back of the ATP binding site (Figure 6, B) allowing the NH_2 group to form an H-bond with the backbone Glu239 carbonyl while the N1 atom is H-bonded to the Leu241 NH. Two other H-bonded interactions between the sugar moiety 3'-OH and Asn244 and Glu291 side-chains were also observed. Finally, an H-bond and/or an electrostatic interaction between Lys289 and the pyrophosphate moiety extremity was evident.

Our 3,5-diaryl-7-azaindoles exhibit a similar binding mode with the ATP-binding site of DYRK1A. The 7-azaindole moiety mimics the adenine unit of ATP, forming two H-bonds between the Glu239 carbonyl and N1-H and between N7 and the Leu241 NH. Moreover, the heteroaromatic scaffold is tightly bound to the protein by hydrophobic interactions with Ileu165, Val173, Val222, Phe238, Leu241, Leu294 and Val306 side-chains (not shown in Figure 7). Finally, the aromatic unit at the 3-position of the 7-azaindole pharmacophore interacts deep within the ATP binding site *via* the Lys188 side-chain while the aromatic moiety on C5 interacts with the left edge of the active site.

The molecular modeling study also provides a rationale for the unfavorable impact of the methoxy groups on the biological activity. For instance, compound **1c** featuring a *p*-methoxy group on each of the two phenyl moieties of the 7-azaindole pharmacophore, demonstrates an IC_{50} of 1.74 μM, whereas its dihydroxy counterpart **2c** (Figure 7, A) is more active by almost two orders of magnitude (IC_{50} = 23.1 nM). While the docking experiment shows that the two compounds share the same general binding mode, the main difference lies in the possibility of formation, in the case of **2c**, of an extra H-bond with Ileu165 (1.71 Å) situated at the edge of the ATP binding site. Therefore, the H-bond donor character of the group borne by the C5 aromatic moiety appears to be essential for effective inhibition of DYRK1A. Further binding features of **2c** include a strong H-bond between the indole NH and both Glu239 and Leu241 (1.91 Å and 2.03 Å, respectively) and a weaker H-bond between the C3 phenyl OH group and Lys188 (2.98 Å).

Addition of an ortho-hydroxy function to the C5 phenyl group of **2c** (i.e., **2j**, Figure 7, B) allows formation of an additional H-bond with Leu241 (1.87 Å) with little perturbation of the overall binding mode. This supplementary H-bond translates into a doubling of the inhibitory potency of **2j** with respect to **2c**.

Compound **2d** (Figure 7, C) presents an interesting structural variation of **2c** in which a meta-OH has been added to each phenyl ring. Again, this substrate maintains the H-bonding pattern of the 7-azaindole pharmacophore with the Glu239 carbonyl and the Leu241 NH (1.86 Å and 2.06 Å, respectively). The diphenol residue at the C3 position now interacts with Lys188 by a 3-centered H-bond network (2.03 Å and 2.92 Å). However, the presence of the meta/para dihydroxy substitution on the C5 aromatic moiety leads to twisting of this phenyl ring such that now only the meta-hydroxy group is H-bonded to Ileu165. It can be speculated that the greater inhibitory potency of **2d** (IC_{50} = 12.4 nM) compared to **2c** (IC_{50} = 23.1 nM) is at least partly the consequence of this quite strong H-bond (1.85 Å).

Finally, removal of the meta-OH of the C3 aryl group of **2d** leads to compound **2k** (Figure 7, D) which demonstrates the highest inhibitory potency of all the DANDYs synthesized (IC_{50} = 3 nM) and of any compound reported so far. Surprisingly, no significant changes in the binding mode of this compound can be highlighted to rationalize the inhibition strength of this compound. Complementary studies implicating the water network surrounding the Lys188 side-chain residue[24] are under investigation.

The ATP binding site model of DYRK1A which we describe thus reasonably accounts for the observed DYRK1A inhibitory activities of the various DANDYs synthesized and should serve as a useful model for the preparation of more active and/or selective inhibitors.

Kinase profiling of selected DANDYs

The selectivities of four of the more active 7-azaindole derivatives (**2c**, **2d**, **2j** and **2k**) were evaluated at $5x10^{-8}$ M (ie between 5 and 15 times higher than their IC_{50}) for inhibitory activities on a panel of 13 different kinases belonging to several families: DYRK (DYRK2, DYRK3 as well as DYRK1A), the closely related CMGCs (CDK2, CDK5, CLK1, ERK2, GSK3β), other families of serine/threonine (AKT1, Pim1, CK1α) and tyrosine kinases (JAK3, TRKA) (Figure 8).[25] While **2d** was generally non-selective for the tested kinases (except AKT1), **2c**, **2j** and **2k** showed a more favorable selectivity profile. The latter three compounds were thus poor inhibitors of ERK2, GSK3β, Pim1 and TRKA. Moreover, **2j** only moderately inhibited (< 50%) CDK2, CK1α, DYRK2 and DYRK3. This selectivity of **2j** for DYRK1A compared to DYRK2 and DYRK3 is surprising in view of the close homology of these three kinases and suggests that these enzymes can indeed be differentiated by suitably engineered ligands.

Cytotoxicity Assessment of Active DANDYs

Since kinase inhibitory activity is often associated with cytotoxicity (a property that would be a deterrent in view of a potential DS or AD treatment), several DANDYs were evaluated for growth inhibition of KB cells *in vitro* (Table 4). While compounds **2c**, **2j** and **2k** inhibit between 83% to 95% of KB cell proliferation at 10^{-5} M concentrations, growth inhibition decreases to approximately 50% (**2c**, **2k**) and 21% (**2j**) when tested at 10^{-6} M concentrations. On the other hand, compounds **2d** and **2l** can be considered almost completely non-cytotoxic (11% and 9% growth inhibition, respectively, at 10^{-5} M). There thus appears to be no correlation between inhibition of KB cell growth and of DYRK1A by the DANDY derivatives and these can generally be considered to be only weakly cytotoxic.

Conclusion

Starting from a screening of 6-azaindole-based harmine lookalikes a new family of DYRK1A inhibitors was developed. *In silico* studies combined with a highly convergent synthetic strategy allowed the rapid synthesis of a relevant library of **D**iaryl-**A**zaindole i**N**hibitors of **DY**RK1A (**DANDY**) the activity of which was then evaluated *in vitro*. Among these, six compounds were found to exhibit Ki under the 15 nM threshold, making them the most potent inhibitors of DYRK1A reported to date.[26] Complementary studies showed that these compounds are non-cytotoxic, thus paving the way for studying their potential for treatment of neurodegenerative pathologies in appropriate animal models.

Experimental Section

Chemistry: General Methods. Commercial grade reagents and solvents were used without further purification except as indicated below. Analytical thin-layer chromatography was performed on silica gel 60 F_{254} on aluminum plates (Merck) and visualized under a UVP Mineralight UVLS-28 lamp (254 nm) and with 4-anisaldehyde and phosphomolybdic acid stains in ethanol. Infrared spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer (ATR). ^{1}H NMR was recorded at 300 or 500 MHz (Bruker Avance 300 / 500 MHz) for ^{1}H NMR and at 75 or 125 MHz for ^{13}C NMR. Chemical shifts are quoted in parts per million (ppm) referenced to the appropriate solvent peak. ^{13}C chemical shifts are reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-*d* and at 49.0 ppm of methanol-d_4. The following abbreviations are used to describe peak splitting patterns when appropriate: br = broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublet. Coupling constants *J* are reported in hertz units (Hz). Mass spectra were obtained either with an LCT (Micromass) instrument using electrospray ionization (ES), or from a Time of Flight analyzer (ESI-MS) for the high resolution mass spectra (HRMS). Flash chromatography was conducted on Merck silica gel 60 (40-63 μm) at medium pressure (300 mbar). Preparative thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} glass plates (Merck) and visualization on TLC was achieved by UV light (254 and 354 nm). Flash column chromatography was undertaken on silica gel SI60 40-63 μm (Merck). Melting points were obtained on a Buchi Melting Point B-540 apparatus. Ultra Performance Liquid Chromatography analyses for checking purity (> 95% area) of synthesized compounds were performed on a Waters UPLC instrument coupled with a Triple Quadrupole mass spectrometer detector (Acquity UPLC-TQD Waters) and equipped with a UPLC HSS C_{18} column (2.1 x 50

mm, 1.8 µm). Before UPLC/MS investigations, the samples were filtered through a 0.2 µm nylon membrane filter. The mobile Phase A was water and B was acetonitrile, both containing 0.1% formic acid. The gradient started at 20% B, was kept at 20% for ten minutes and was then increased linearly to 100% B over 0.2 minute. An equilibration time of 3 minutes was allowed before the next analysis. The flow rate was fixed at 0.6 mL/min and the column temperature was maintained at 40 °C.

3-Iodo-5-bromo-1H-pyrrolo[2,3-b]-pyridine. To a solution of the commercially available 5-bromo-1H-pyrrolo[2,3-b]-pyridine (1 g, 5.10 mmol) in CH_2Cl_2 (200 mL) was added KOH (145 mg, 2.55 mmol) at room temperature. After 30 min, N-iodosuccinimide (1.2 g, 5.10 mmol) was added, the mixture was stirred during 15 h, quenched with a saturated solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The desired product was obtained in quantitative yield and used in the next step without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.34 (s, 1H), 8.31 (d, J = 2.1 Hz, 1H), 7.86 (d, J = 2.1 Hz, 1H), 7.30 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 146.5 (Cq), 143.8 (CH), 132.5 (Cq), 129.9 (CH), 123.8 (Cq), 111.5 (CH), 53.6 (Cq). HRMS (ESI+) calcd for $C_7H_4{}^{79}BrIN_2$ $[M+H]^+$ 322.8681, found 322.8682, HRMS (ESI+) calcd for $C_7H_4{}^{81}BrIN_2$ $[M+H]^+$ 324.8660, found 324.8670. IR (neat, cm^{-1}): ν 3118, 2821, 1638.

3-Iodo-5-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (6). To a solution of 3-iodo-5-bromo-1H-pyrrolo[2,3-b]-pyridine (500 mg, 1.55 mmol) in CH_2Cl_2 (4.1 mL) were added sodium hydride 60% (186 mg, 4.66 mmol) and benzyltriethylammonium chloride (8 mg, 0.03 mmol) under argon, at 0°C. After 30 min, benzenesulfonyl chloride (240 µL, 1.86 mmol) was added at 0°C and the mixture was stirred at room temperature during 2 h. The mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried

($MgSO_4$) and concentrated in vacuo. The residue was precipitated in MeOH and filtered off to give **6** as a pale pink solid (97% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.46 (d, J = 2.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 2H), 7.88 (s, 1H), 7.82 (d, J = 2.5 Hz, 1H), 7.64-7.61 (m, 1H), 7.54-7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.7 (CH), 144.7 (Cq), 137.6 (Cq), 134.6 (CH), 132.5 (CH), 131.2 (CH), 129.2 (2CH), 128.2 (2CH), 126.7 (Cq), 116.0 (Cq), 60.6 (Cq). HRMS (ESI+) calcd for $C_{13}H_9N_2O_2S^{79}Br$ $[M+H]^+$ 462.8613, found 462.8605, HRMS (ESI+) calcd for $C_{13}H_9N_2O_2S^{81}Br$ $[M+H]^+$ 464.8592, found 464.8596. IR (neat, cm^{-1}): ν 2851, 1613, 1370.

Representative Procedure for Mono-Suzuki Coupling (RP1):

3-Phenyl-5-bromo-1-(phenylsulfonyl)- 1*H*-pyrrolo[2,3-*b*]pyridine. To solution of **6** (250 mg, 0.54 mmol) in toluene/ethanol 3:1 (17 mL) were added benzeneboronic acid (65 mg, 0.54 mmol), K_2CO_3 (1.6 mL of a 2M solution in water, 3.20 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) and the reaction was heated to 110°C for 3.5 h under argon. The reaction mixture was cooled to room temperature, concentrated in vacuo and then partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2 100%) to give the product as a white solid (89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, J = 2.1 Hz, 1H), 8.25-8.20 (m, 3H), 7.90 (s, 1H), 7.64-7.36 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.7 (Cq), 145.6 (CH), 137.9 (Cq), 134.3 (CH), 131.8 (Cq), 131.1 (CH), 129.1 (CH), 129.0 (CH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 123.9 (CH), 123.1 (Cq), 119.8 (Cq), 115.5 (Cq). HRMS (ESI+) calcd for $C_{19}H_{14}N_2O_2S^{79}Br$ $[M+H]^+$ 412.9959, found 412.9969, HRMS (ESI+) calcd for $C_{19}H_{14}N_2O_2S^{81}Br$ $[M+H]^+$ 414.9939, found 412.9958. IR (neat, cm^{-1}): ν 2919, 1605, 1383.

Representative Procedure for Double Suzuki Coupling (RP2):

3,5-Diphenyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7e). To a solution of **6** (200 mg, 0.43 mmol) in acetone (2 mL) were added benzeneboronic acid (98 mg, 0.86 mmol), Na_2CO_3 (1.3 mL of a 2M solution in water, 5.00 mmol), $Pd(OAc)_2$ (5 mol%), and triphenylphosphine (10 mol%). The reaction mixture was heated at 85 °C during 2 h under argon then cooled to room temperature, concentrated in vacuo and partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (heptane/ethyl acetate, gradient 97:3 to 95:5) to give **7e** as a white solid (72% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.72 (d, J = 2.0 Hz, 1H), 8.31-8.25 (m, 3H), 7.93 (s, 1H), 7.66-7.38 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.9 (Cq), 144.4 (CH), 138.3 (Cq), 138.2 (Cq), 134.1 (CH), 133.0 (Cq), 132.5 (Cq), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 123.2 (CH), 121.6 (Cq), 120.6 (Cq). HRMS (ESI+) calcd for $C_{25}H_{19}N_2O_2S$ $[M+H]^+$ 411.1167, found 411.1167. IR (neat, cm^{-1}): ν 2848, 1601, 1383.

3-Phenyl-5-(4-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7b). This compound was prepared according to RP1 using 3-phenyl-5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (333 mg, 0.81 mmol), 4-methoxybenzeneboronic acid (189 mg, 0.97 mmol), K_2CO_3 (2.6 mL of a 2M solution in water, 4.84 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (26 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 100%) to give **7b** as a white solid (98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (d, J = 2.1 Hz, 1H), 8.27-8.30 (m, 2H), 8.20 (d, J = 2.1 Hz, 1H), 7.92 (s, 1H), 7.65-7.58 (m, 3H), 7.55-7.47 (m, 6H), 7.42-7.37 (m, 1H), 7.01 (br d, J = 8.7 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5 (Cq), 146.6 (Cq), 144.1 (CH), 138.3 (Cq), 134.0 (CH), 132.7 (CH), 132.5 (Cq), 130.7 (Cq), 129.1 (2CH), 129.0 (2CH), 128.5 (2CH), 128.0 (2CH), 127.7 (CH),

127.5 (2CH), 126.7 (CH), 123.1 (CH), 121.6 (Cq), 120.6 (Cq), 114.5 (2CH), 55.3 (CH_3). HRMS (ESI+) calcd for $C_{26}H_{21}N_2O_3S$ $[M+H]^+$ 441.1273, found 441.1263. IR (neat, cm^{-1}): *ν* 2931, 1607, 1382.

3,5-Di-(4-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7c). This compound was prepared according to RP2 using **6** (300 mg, 0.65 mmol), 4-methoxybenzeneboronic acid (296 mg, 1.95 mmol), K_2CO_3 (1.9 mL of a 2M solution in water, 3.80 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (20 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 99:1) to give **7c** as a white solid (85% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 8.66 (d, *J* = 2.1 Hz, 1H), 8.26 (dd, *J* = 7.2 Hz, 2.1 Hz, 2H), 8.16 (d, *J* = 2.1 Hz, 1H), 7.83 (s, 1H), 7.60-7.48 (m, 7H), 7.05-6.99 (m, 4H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5 (Cq), 159.3 (Cq), 146.6 (Cq), 144.0 (CH), 138.3 (Cq), 134.0 (CH), 132.6 (Cq), 130.8 (Cq), 129.0 (2CH), 128.7 (2CH), 128.5 (2CH), 128.0 (2CH), 126.7(CH), 124.9 (Cq), 122.4 (Cq), 121.8 (Cq), 120.4 (Cq), 114.6 (CH), 114.5 (CH), 55.3 (2CH_3). HRMS (ESI+) calcd for $C_{27}H_{23}N_2O_4S$ $[M+H]^+$ 471.1379, found 471.1389. IR (neat, cm^{-1}): *ν* 2830, 1610, 1373.

3,5-Di-(3,4-Dimethoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7d). This compound was prepared according to RP2 using **6** (407 mg, 0.88 mmol), 3,4-dimethoxybenzeneboronic acid (480 mg, 2.64 mmol), K_2CO_3 (2.7 mL of a 2M solution in water, 5.4 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (20 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 98:2) to give **7d** as a white solid (91% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 8.66 (d, *J* = 2.1 Hz, 1H), 8.27 (d, *J* = 7.2 Hz, 2H), 8.17 (d, *J* = 2.4 Hz, 1H), 7.86 (s, 1H), 7.61-7.49 (m, 3H), 7.18 (dd, *J* = 8.2 Hz, 2.0 Hz, 1H), 7.13-6.95 (m, 5H), 3.69 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 3.65 (s, 3H); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 149.4 (Cq), 149.3 (Cq), 149.0 (Cq), 148.9 (Cq), 146.6 (Cq), 144.2 (CH), 138.3 (Cq), 134.0 (CH), 132.9 (Cq), 131.2 (Cq), 129.1 (2CH), 128.0 (2CH), 126.8 (CH), 125.2 (Cq), 122.6 (CH), 121.8 (Cq), 120.5 (Cq), 120.0 (CH), 119.8 (CH), 111.7 (2CH), 110.7 (CH), 110.6 (CH), 56.0 ($2CH_3$), 55.9 ($2CH_3$). HRMS (ESI+) calcd for $C_{29}H_{27}N_2O_6S$ $[M+H]^+$ 531.1590, found 531.1594. IR (neat, cm^{-1}): *ν* 2928, 1602, 1383.

3-Phenyl-5-(3-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7f). This compound was prepared according to RP1 using 3-phenyl-5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (155 mg, 0.38 mmol), 3-methoxybenzeneboronic acid (80 mg, 0.53 mmol), K_2CO_3 (1.2 mL of a 2M solution in water, 2.40 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (13 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 100%) to give **7f** as a white solid (98% yield). ^1H NMR ($CDCl_3$, 300 MHz) *δ* 8.70 (d, *J* = 2.1 Hz, 1H), 8.30-8.24 (m, 3H), 7.92 (s, 1H), 7.65-7.58 (m, 3H), 7.56-7.47 (m, 4H), 7.43-7.36 (m, 2H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.1 (t, *J* = 2.1 Hz, 1H), 6.94 (dd, *J* = 8.1 Hz, 2.4 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.1 (Cq) , 147.0 (Cq), 144.4 (CH), 139.8 (Cq) , 138.3 (Cq), 134.1 (CH), 132.9 (Cq), 132.5 (Cq), 130.1 (CH), 129.2 (2CH), 129.1 (2CH), 128.1 (2CH), 127.8 (CH), 127.5 (2CH), 127.3 (CH), 123.2 (CH), 121.6 (Cq), 120.7 (Cq), 119.9 (CH), 113.5 (CH), 112.9 (CH), 53.4 (CH_3). HRMS (ESI+) calcd for $C_{26}H_{21}N_2O_3S$ $[M+H]^+$ 441.1273, found 441.1260. IR (neat, cm^{-1}): *ν* 2913, 2851, 1607, 1355.

3-Phenyl-5-(2-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7g). This compound was prepared according to RP1 using 3-phenyl-5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (309 mg, 0.75 mmol), 2-methoxybenzeneboronic acid (125 mg, 0.83 mmol), K_2CO_3 (2.4 mL of a 2M solution in water, 4.50 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (24 mL). The residue was purified by flash chromatography on silica gel

(CH_2Cl_2 100%) to give **7g** as a clear oil (98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.66 (d, J = 2.1 Hz, 1H), 8.31-8.25 (m, 3H), 7.92 (s, 1H), 7.65-7.58 (m, 3H), 7.55-7.45 (m, 4H), 7.41-7.30 (m, 3H), 7.1-7.0 (m, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5 (Cq), 146.5 (Cq), 146.3 (CH), 138.4 (Cq), 134.0 (CH), 132.7 (Cq), 131.0 (CH), 130.1 (Cq), 129.6 (CH), 129.3 (CH), 129.0 (2CH), 129.0 (2CH), 128.0 (2CH), 127.6 (CH), 127.4 (2CH), 127.3 (Cq), 122.7 (CH), 121.1 (Cq), 121.0 (CH), 120.6 (Cq), 111.2 (CH), 55.5 (CH_3). HRMS (ESI+) calcd for $C_{26}H_{21}N_2O_3S$ $[M+H]^+$ 441.1273, found 441.1273. IR (neat, cm^{-1}): ν 2925, 1601, 1385.

3-Phenyl-5-(2,4-dimethoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7h). This compound was according to RP1 using 3-phenyl-5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (327 mg, 0.79 mmol), 2,4-dimethoxybenzeneboronic acid (159 mg, 0.87 mmol), K_2CO_3 (2.5 mL of a 2M solution in water, 4.76 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (25 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 100%) to give **7h** as a white solid (70% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.61 (d, J = 2.0 Hz, 1H), 8.30-8.26 (m, 2H), 8.21 (d, J = 2.0 Hz, 1H), 7.90 (s, 1H), 7.65-7.58 (m, 3H), 7.54-7.45 (m, 4H), 7.40-7.37 (m, 1H), 7.25-7.22 (m, 1H), 6.62-6.59 (m, 2H), 3.89 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8 (Cq), 157.5 (Cq), 146.4 (CH), 146.3 (CH), 138.4 (Cq), 134.0 (CH), 132.8 (Cq), 131.4 (CH), 130.0 (Cq), 129.4 (Cq), 129.0 (2CH), 129.0 (2CH), 128.0 (2CH), 127.6 (CH), 127.5 (2CH), 122.7 (CH), 121.1 (Cq), 120.6 (Cq), 120.1 (Cq), 104.9 (CH), 99.0 (CH), 55.5 (CH_3), 55.4 (CH_3). HRMS (ESI+) calcd for $C_{27}H_{23}N_2O_4S$ $[M+H]^+$ 471.1379, found 471.1392. IR (neat, cm^{-1}): ν 2931, 1611, 1383.

3-Phenyl-5-(3,4-dimethoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7i). This compound was prepared according to RP1 using 3-phenyl-5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (260 mg, 0.63 mmol), 3,4-dimethoxybenzeneboronic acid (126 mg,

0.69 mmol), K_2CO_3 (2.0 mL of a 2M solution in water, 4.00 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (20 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 99:1) to give **7i** as a white solid (67% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.67 (d, J = 2.0 Hz, 1H), 8.30-8.26 (m, 2H), 8.19 (d, J = 2.0 Hz, 1H), 7.92 (s, 1H), 7.65-7.59 (m, 3H), 7.55-7.48 (m, 4H), 7.43-7.41 (m, 1H), 7.11 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 6.67 (br d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4(Cq) , 149.0 (Cq), 146.7 (Cq), 144.3 (CH), 138.3 (Cq), 134.1 (CH), 133.0 (Cq), 132.6 (Cq), 131.3 (Cq), 129.2 (2CH), 129.1 (2CH), 128.1 (2CH), 127.8 (CH), 127.5 (2CH), 126.9 (CH), 123.2 (CH), 121.6 (Cq), 120.6 (Cq), 119.9 (CH), 111.7 (CH), 110.8 (CH), 56.1 (CH_3), 56.0 (CH_3). HRMS (ESI+) calcd for $C_{27}H_{23}N_2O_4S$ $[M+H]^+$ 471.1379, found 471.1384. IR (neat, cm^{-1}): ν 2824, 1604, 1382.

3-(4-Methoxyphenyl)-5-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine. This compound was prepared according to RP1 using **6** (725 mg, 1.57 mmol), 4-methoxybenzeneboronic acid (262 mg, 1.72 mmol), K_2CO_3 (5.0 mL of a 2M solution in water, 10.00 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (51 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 : 100%) to give the product as a white solid (71% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (d, J = 2.1 Hz, 1H), 8.23-8.18 (m, 3H), 7.82 (s, 1H), 7.62-7.54 (m, 1H), 7.54-7.46 (m, 4H), 7.02 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.3 (Cq), 145.8 (Cq), 145.7 (CH), 138.0 (Cq), 134.3 (CH), 131.1 (CH), 129.1 (2CH), 128.6 (2CH), 128.1 (2CH), 124.3 (Cq), 123.4 (Cq), 123.2 (CH), 119.7 (Cq), 115.5 (Cq), 114.7 (2CH), 55.4 (CH_3). HRMS (ESI+) calcd for $C_{20}H_{16}N_2O_3S^{79}Br$ $[M+H]^+$ 443.0065, found 443.0077, HRMS (ESI+) calcd for $C_{20}H_{16}N_2O_3S^{81}Br$ $[M+H]^+$ 445.0045, found 445.0056. IR (neat, cm^{-1}): ν 2848, 1611, 1373.

3-(4-Methoxyphenyl)-5-(2,4-dimethoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7j). This compound was prepared according to RP1 using 3-(4-methoxyphenyl)-5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (180 mg, 0.41 mmol), 2,4-dimethoxybenzeneboronic acid (104 mg, 0.61 mmol), K_2CO_3 (1.2 mL of a 2M solution in water, 2.40 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (14 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2: 100%) to give **7j** as a white solid (98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.60 (d, J = 2.1 Hz, 1H), 8.26 (dd, J = 8.5 Hz, 1.2 Hz, 2H), 8.16 (d, J = 2.1 Hz, 1H), 7.82 (s, 1H), 7.60-7.51 (m, 5H), 7.22 (d, J = 9.0 Hz, 1H,), 7.00 (d, J = 9.0 Hz, 2H), 6.60-6.58 (m, 2H), 3.86 (s, 6H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8 (Cq), 159.2 (Cq), 157.5 (Cq), 146.3 (Cq), 146.2 (CH), 138.5 (Cq), 133.9 (CH), 131.4 (CH), 129.9 (Cq), 129.4 (CH), 129.0 (2CH), 128.6 (2CH), 128.0 (2CH), 125.2 (Cq), 121.9 (CH), 121.3 (Cq), 120.3 (Cq), 120.2 (Cq), 114.5 (2CH), 104.9 (CH), 99.0 (CH), 55.5 (CH_3), 55.4 (CH_3), 55.3 (CH_3). HRMS (ESI+) calcd for $C_{28}H_{25}N_2O_5S$ $[M+H]^+$ 501.1484, found 501.1479. IR (neat, cm^{-1}): ν 2848, 1607, 1373.

3-(4-Methoxyphenyl)-5-(3,4-dimethoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7k). This compound was prepared according to RP1 using 3-(4-methoxyphenyl)-5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (326 mg, 0.74 mmol), 3,4-dimethoxybenzeneboronic acid (148 mg, 0.81 mmol), K_2CO_3 (2.4 mL of a 2M solution in water, 4.80 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (14 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 /MeOH: 100:0 to 98:2) to give the product as a white solid (78% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.66 (d, J = 2.1 Hz, 1H), 8.27 (br d, J = 8.1 Hz, 2H), 8.15 (d, J = 2.1 Hz, 1H), 7.84 (s, 1H), 7.63-7.50 (m, 5H), 7.13-6.96 (m, 5H), 3.94 (s, 3H), 3.93 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.3 (Cq), 149.4 (Cq), 149.0 (Cq), 146.7 (Cq), 144.2 (CH), 138.4 (Cq), 134.0 (CH), 132.9 (Cq), 131.3 (Cq), 129.1 (2CH), 128.7 (2CH), 128.0 (2CH), 126.8 (CH), 124.9 (Cq), 122.5 (CH), 121.8 (Cq),

120.3 (Cq), 119.9 (CH), 114.6 (2CH), 111.7 (CH), 110.8 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.4 (CH_3). HRMS (ESI+) calcd for $C_{28}H_{25}N_2O_5S$ $[M+H]^+$ 501.1484, found 501.1473. IR (neat, cm^{-1}): *ν* 2830, 1608, 1382.

3-(3,4-Dimethoxyphenyl)-5-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine. This compound was prepared according to RP1 using **6** (1 g, 2.16 mmol), 3,4-dimethoxybenzeneboronic acid (432 mg, 2.38 mmol), K_2CO_3 (7.0 mL of a 2M solution in water, 14.00 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (69 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2: 100%) to give the product as a white solid (88% yield). ^1H NMR ($CDCl_3$, 500 MHz) *δ* 8.49 (d, *J* = 2.5 Hz, 1H), 8.22 (d, *J* = 7.5 Hz, 2H), 8.19 (d, *J* = 2.0 Hz, 1H), 7.84 (s, 1H), 7.64-7.60 (m, 1H), 7.54-7.51 (m, 2H), 7.10 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.5 (Cq), 149.1 (Cq), 145.7 (CH+Cq), 138.0 (Cq), 134.3 (CH), 131.1 (CH), 129.1 (2CH), 128.1 (2CH), 124.5 (Cq), 123.3 (CH), 123.3 (Cq), 120.0 (CH), 119.8 (Cq), 115.5 (Cq), 111.7 (CH), 110.6 (CH), 56.1 (CH_3), 56.0 (CH_3). HRMS (ESI+) calcd for $C_{21}H_{18}N_2O_4S^{79}Br$ $[M+H]^+$ 473.0171, found 473.0172, HRMS (ESI+) calcd for $C_{21}H_{18}N_2O_4S^{81}Br$ $[M+H]^+$ 475.0150, found 475.0162. IR (neat, cm^{-1}): *ν* 2928, 1592, 1358.

3-(3,4-Dimethoxyphenyl)-5-(2,4-dimethoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7l). This compound was prepared according to RP1 using 3-(3,4-dimethoxyphenyl)-5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (315 mg, 0.68 mmol), 2,4-dimethoxybenzeneboronic acid (134 mg, 0.73 mmol), K_2CO_3 (2.1 mL of a 2M solution in water, 4.20 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (14 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 100%) to give **7l** as a clear oil (41% yield). ^1H NMR ($CDCl_3$, 300 MHz) *δ* 8.60 (br s, 1H), 8.27 (br d, *J* = 7.8 Hz, 2H), 8.19

(s, 1H), 7.83 (s, 1H), 7.60-7.48 (m, 3H), 7.24-7.15 (m, 2H), 7.11 (br s, 1H), 6.96 (br d, J = 8.1 Hz, 1H), 6.61-6.58 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8 (Cq), 157.5 (Cq), 149.4 (Cq), 148.8 (Cq), 146.3 (CH+Cq), 138.4 (Cq), 134.0 (CH), 131.4 (CH), 129.9 (Cq), 129.4 (CH), 129.0 (2CH), 128.0 (2CH), 125.5 (Cq), 122.1 (CH), 121.2 (Cq), 120.5 (Cq), 120.2 (Cq), 119.9 (CH), 111.6 (CH), 110.7 (CH), 104.9 (CH), 99.0 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.5 (CH_3), 55.4 (CH_3). HRMS (ESI+) calcd for $C_{29}H_{27}N_2O_6S$ $[M+H]^+$ 531.1590, found 531.1570. IR (neat, cm^{-1}): ν 2833, 1608, 1377.

3-(3,4-Dimethoxyphenyl)-5-(2,5-dimethoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**7m**). This compound was prepared according to RP1 using 3-(3,4-dimethoxyphenyl)-5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (500 mg, 1.06 mmol), 2,5-dimethoxybenzeneboronic acid (386 mg, 2.12 mmol), K_2CO_3 (3.3 mL of a 2M solution in water, 6.60 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (14 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 100%) to give an inseparable mixture of **7m** and 1,4-dimethoxybenzene (resulting from the protodeboration of the starting boronic acid) (41% yield of the desired compound). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.63 (d, J = 2.1Hz, 1H), 8.28 (br d, J = 7.2 Hz, 2H), 8.19 (d, J = 2.1 Hz, 1H), 7.85 (s, 1H), 7.60-7.49 (m, 3H), 7.17 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 7.11 (d, J = 1.8 Hz, 1H), 6.99-6.84 (m, 4H), 3.96 (s, 3H), 3.95 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8 (Cq), 150.7 (Cq), 149.4 (Cq), 148.8 (Cq), 146.5 (Cq), 146.1 (CH), 138.4 (Cq), 134.0 (CH), 129.8 (CH), 129.6 (CH), 129.0 (2CH), 128.3 (Cq), 128.0 (2CH), 125.3 (Cq), 122.2 (CH), 121.2 (Cq), 120.5 (Cq), 119.9 (CH), 116.9 (CH), 113.6 (CH), 112.5 (Cq), 111.7 (CH), 110.7 (CH), 56.2 (CH_3), 56.0 (CH_3), 55.9 (CH_3), 55.8 (CH_3). HRMS (ESI+) calcd for $C_{29}H_{27}N_2O_6S$ $[M+H]^+$ 531.1590, found 531.1588. IR (neat, cm^{-1}): ν 2833, 1608, 1377.

3,5-Di-(3-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**7n**). This compound was prepared according to RP2 using **6** (635 mg, 1.37 mmol), 3-methoxybenzeneboronic acid (521 mg, 3.43 mmol), K_2CO_3 (4.4 mL of a 2M solution in water, 8.80 mmol) and $Pd(PPh_3)_4$ (1.5 mol%) in toluene/ethanol 3:1 (20 mL). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 100%) to give **7n** as a yellow solid (77% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 7.2 Hz, 2H), 8.24 (d, J = 2.1 Hz, 1H), 7.93 (s, 1H), 7.62-7.50 (m, 3H), 7.42 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.14-7.13 (m, 2H), 7.10-7.08 (m, 1H), 6.94 (br d, J = 8.4 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.2 (Cq), 160.1 (Cq), 146.9 (Cq), 144.4 (CH), 139.8 (Cq), 138.3 (Cq), 134.1 (CH), 133.8 (Cq), 132.9 (Cq), 130.2 (CH), 130.1 (CH), 129.1 (2CH), 128.1 (2CH), 127.4 (CH), 123.4 (CH), 121.6 (Cq), 120.6 (Cq), 119.9 (2CH), 113.4 (CH), 113.3 (CH), 113.1 (CH), 112.9 (CH), 55.4 (CH_3), 55.3 (CH_3). HRMS (ESI+) calcd for $C_{27}H_{23}N_2O_4S$ $[M+H]^+$ 471.1379, found 471.1361. IR (neat, cm^{-1}): ν 2830, 1599, 1380.

Representative Procedure for *N*-Benzenesulfonyl Removal (RP3):

3-Phenyl-5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (**1e**). To a solution of **7e** (125 mg, 0.31 mmol) in MeOH (700 µL) was added NaOH (90 µL of a 2N solution in water, 0.18 mmol). The reaction mixture was heated at 80°C during 1 h, cooled to room temperature and concentrated in vacuo. It was then partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) to give **1e** as

a pale yellow solid (67% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.93 (s, 1H), 8.65 (d, J = 1.8 Hz, 1H), 8.45 (d, J = 1.8 Hz, 1H), 7.73-7.6 (m, 4H), 7.54 (s, 1H), 7.52-7.46 (m, 4H), 7.43-7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.7 (Cq), 142.4 (CH), 139.5 (Cq), 134.9 (Cq), 130.3 (Cq), 129.0 (2CH), 128.9 (2CH), 127.5 (2CH), 127.2 (2CH), 127.1 (CH), 126.9 (CH), 126.3 (CH), 122.9 (CH), 118.6 (Cq), 116.8 (Cq). HRMS (ESI+) calcd for $C_{19}H_{15}N_2$ $[M+H]^+$ 271.1235, found 271.1226. IR (neat, cm^{-1}): ν. 3136, 2884, 1602. UPLC R_t = 4.51 min; area 100%.

3-Phenyl-5-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**1b**). This compound was prepared according to RP3 using **7b** (100 mg, 0.23 mmol) in MeOH (520 µL) and NaOH (70 µL of a 2N solution in water, 0.14 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2/ MeOH, 99:1) to give **1b** as a white solid (72% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.24 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.40 (d, J = 2.1 Hz, 1H), 7.68 (d, J = 7.2 Hz, 2H), 7.60-7.56 (m, 3H), 7.52-7.46 (m, 2H), 7.37-7.34 (m, 1H), 7.03 (br d, J = 8.7 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2 (Cq), 147.6 (Cq), 141.5 (CH), 134.6 (Cq), 131.7 (Cq), 130.1 (Cq), 129.0 (2CH), 128.5 (2CH), 127.2 (2CH), 127.0 (CH), 126.5 (CH), 123.3 (CH), 118.9 (Cq), 116.9 (Cq), 114.5 (2CH), 55.4 (CH_3). HRMS (ESI+) calcd for $C_{20}H_{17}N_2O$ $[M+H]^+$ 301.1341, found 301.1337. IR (neat, cm^{-1}): ν 3097, 2830, 1604. UPLC R_t = 4.36 min; area 100%.

3,5-Di-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**1c**). This compound was prepared according to RP3 using **7c** (90 mg, 0.19 mmol) in MeOH (0.5 mL) and NaOH (60 µL of a 2N solution in water, 0.12 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 93:7) to give **1c** as a white solid (98% yield). Mp 190°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.60 (br s, 1H), 8.58 (d, J = 2.1 Hz, 1H), 8.33 (d, J = 2.1 Hz,

1H), 7.63-7.57 (m, 4H), 7.51 (s, 1H), 7.03 (d, J = 8.4 Hz, 4H) 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.1 (Cq), 158.3 (Cq), 148.3 (Cq), 142.1 (CH), 132.1 (Cq), 129.8 (Cq), 128.5 (2CH), 128.3 (2CH), 127.5 (Cq), 126.4 (CH), 122.1 (CH), 118.7 (Cq), 116.4 (Cq), 114.5 (2CH), 114.4 (2CH), 55.4 (CH_3), 55.3 (CH_3). HRMS (ESI-) calcd for $C_{21}H_{17}N_2O_2$ [M-H]$^-$ 329.1290, found 329.1282. IR (neat, cm^{-1}): ν 3143, 2853, 1606. UPLC R_t = 4.20 min; area 100%.

3,5-Di-(3,4-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1d). This compound was prepared according to RP3 using **7d** (475 mg, 0.90 mmol) in MeOH (2.1 mL) and NaOH (270 µL of a 2N solution in water, 0.54 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2/ MeOH, gradient 100:0 to 98:2) to give **1d** as a pale yellow solid (77% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.10 (br s, 1H), 8.54 (s, 1H), 8.42 (s, 1H), 7.54 (s, 1H), 7.24-7.11 (m, 4H), 7.01 (d, J = 8.1 Hz, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.96 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4 (2Cq), 148.8 (Cq), 148.2 (Cq), 146.9 (Cq), 140.9 (CH), 132.0 (Cq), 130.3 (Cq), 127.4 (CH), 127.3 (Cq), 122.7 (CH), 119.8 (CH), 119.7 (CH), 119.4 (Cq), 117.1 (Cq), 111.9 (CH), 111.8 (CH), 110.9 (CH), 110.8 (CH), 56.1 (4CH_3). HRMS (ESI+) calcd for $C_{23}H_{23}N_2O_4$ [M+H]$^+$ 391.1658, found 391.1663. IR (neat, cm^{-1}): ν 3124, 2833, 1604, 1247. UPLC R_t = 3.52 min; area 100%.

3-Phenyl-5-(3-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1f). This compound was prepared according to RP3 using **7f** (184 mg, 0.42 mmol) in MeOH (1.0 mL) and NaOH (125 µL of a 2N solution in water, 0.25 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 97:3) to give **1f** as a pale yellow solid (52% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.77 (br s, 1H), 8.62 (s, 1H), 8.43 (s, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.58 (s, 1H), 7.52-7.34 (m, 4H), 7.25-7.27 (m, 1H), 7.24-7.18 (m, 1H), 6.97-6.92 (m,

1H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.1 (Cq), 146.9 (Cq), 140.7 (Cq), 140.3 (Cq), 134.2 (Cq), 130.5 (Cq), 130.1 (CH), 129.1 (2CH), 128.2 (CH), 127.3 (2CH), 126.7 (CH), 123.3 (CH), 119.9 (CH), 119.5 (Cq), 117.4 (Cq), 113.4 (CH), 112.7 (CH), 55.4 (CH_3). HRMS (ESI+) calcd for $C_{20}H_{17}N_2O$ $[M+H]^+$ 301.1341, found 301.1346. IR (neat, cm^{-1}): *ν* 3115, 2854, 1604. UPLC R_t = 4.45 min; area 100%.

3-Phenyl-5-(2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1g). This compound was prepared according to RP3 using **7g** (374 mg, 0.85 mmol) in MeOH (2.3 mL) and NaOH (260 µL of a 2N solution in water, 0.51 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 98:2) to give **1g** as a yellow solid (42% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 11.50 (br s, 1H), 8.61 (s, 1H), 8.43 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 1H), 7.49-7.38 (m, 4H), 7.33-7.30 (m, 1H), 7.13-7.10 (m, 1H), 7.06 (br d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.7 (Cq), 148.3 (Cq), 143.9 (CH), 135.1 (Cq), 131.3 (CH), 129.4 (CH), 128.9 (2CH), 128.8 (CH), 128.7 (Cq), 127.1 (2CH+Cq), 126.1 (CH), 122.7 (CH), 121.0 (CH), 118.3 (Cq), 116.5 (Cq), 111.3 (CH), 55.6 (CH_3). HRMS (ESI+) calcd for $C_{20}H_{17}N_2O$ $[M+H]^+$ 301.1341, found 301.1337. IR (neat, cm^{-1}): *ν* 3124, 2833, 1599. UPLC R_t = 4.35 min; area 100%.

3-Phenyl-5-(2,4-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1h). This compound was prepared according to RP3 using **7h** (245 mg, 0.52 mmol) in MeOH (1.4 mL) and NaOH (160 µL of a 2N solution in water, 0.31 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 98:2) to give **1h** as a pale yellow solid (70% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 10.17 (br s, 1H), 8.51 (s, 1H), 8.34 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.56 (s, 1H), 7.49-7.43 (m, 2H), 7.34-7.28 (m, 2H), 6.64-6.61 (m, 2H), 3.89 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5 (Cq), 157.6 (Cq), 148.0 (Cq), 143.9

(CH), 135.1 (Cq), 131.6 (CH), 129.2 (CH), 128.8 (2CH), 127.0 (2CH), 126.9 (Cq), 126.1 (CH), 122.6 (CH), 121.4 (Cq), 118.3 (Cq), 116.4 (Cq), 104.7 (CH), 99.1 (CH), 55.6 (CH_3), 55.5 (CH_3). HRMS (ESI+) calcd for $C_{21}H_{19}N_2O_2$ $[M+H]^+$ 331.1447, found 331.1438. IR (neat, cm^{-1}): ν 3121, 2869, 1601. UPLC R_t = 4.25 min; area 85%.

3-Phenyl-5-(3,4-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1i). This compound was prepared according to RP3 using **7i** (190 mg, 0.40 mmol) in MeOH (1.1 mL) and NaOH (125 µL of a 2N solution in water, 0.24 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 98:2) to give **1i** as a pale yellow solid (57% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.36 (br s, 1H), 8.60 (d, J = 2.1 Hz, 1H), 8.39 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 6.9 Hz, 2H), 7.69 (s, 1H), 7.63-7.46 (m, 2H), 7.37-7.31 (m, 1H), 7.22-7.15 (m, 2H), 7.01 (d, J = 8.1 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4 (Cq), 148.6 (Cq), 148.4 (Cq), 141.9 (CH), 134.9 (Cq), 132.5 (Cq), 130.2 (Cq), 129.0 (2CH), 127.2 (2CH), 126.7 (CH), 126.3 (CH), 123.2 (CH), 119.8 (CH), 118.7 (Cq), 116.6 (Cq), 111.7 (CH), 110.9 (CH), 56.1 (CH_3), 56.0 (CH_3). HRMS (ESI+) calcd for $C_{21}H_{19}N_2O_2$ $[M+H]^+$ 331.1447, found 331.1448. IR (neat, cm^{-1}): ν 3109, 2824, 1590. UPLC R_t = 3.98 min; area 100%.

3-(4-Methoxyphenyl)-5-(2,4-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1j). This compound was prepared according to RP3 using **7j** (406 mg, 0.81 mmol) in MeOH (2.2 mL) and NaOH (245 µL of a 2N solution in water, 0.49 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 95:5) to give **1j** as a white solid (60% yield). Mp 90°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.21 (br s, 1H), 8.50 (s, 1H), 8.31 (d, J = 2.1 Hz, 1H), 7.61-7.58 (m, 2H), 7.48 (s, 1H), 7.32-7.29 (m, 1H), 7.03-7.00 (m, 2H), 6.65-6.61 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5

(CH), 158.3 (Cq), 157.6 (Cq), 147.5 (Cq), 143.9 (CH), 131.6 (CH), 129.3 (CH), 128.3 (2CH), 127.5 (Cq), 126.9 (Cq), 121.7 (CH), 121.4 (Cq), 118.4 (Cq), 116.5 (Cq), 114.4 (2CH), 104.8 (CH), 99.1 (CH), 55.6 (CH_3), 55.5 (CH_3), 55.3 (CH_3). HRMS (ESI+) calcd for $C_{22}H_{21}N_2O_3$ $[M+H]^+$ 361.1552, found 361.1557. IR (neat, cm^{-1}): ν 3312, 1998, 1616. UPLC R_t = 4.08 min; area 100%.

3-(4-Methoxyphenyl)-5-(3,4-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1k). This compound was prepared according to RP3 using **7k** (280 mg, 0.56 mmol) in MeOH (1.3 mL) and NaOH (170 µL of a 2N solution in water, 0.34 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 97:3) to give **1k** as a pale yellow solid (82% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.11 (br s, 1H), 8.56 (d, J = 2.1 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.52 (s, 1H), 7.20-7.14 (m, 2H), 7.06-6.99 (m, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.5 (Cq), 149.4 (Cq), 148.7 (Cq), 147.5 (Cq), 141.5 (CH), 132.3 (Cq), 130.2 (Cq), 128.4 (2CH), 127.1 (Cq), 127.0 (CH), 122.3 (CH), 119.8 (CH), 119.0 (Cq), 116.7 (Cq), 114.5 (2CH), 111.7 (CH), 110.9 (CH), 56.1 (CH_3), 56.0 (CH_3), 55.4 (CH_3). HRMS (ESI-) calcd for $C_{22}H_{19}N_2O_3$ $[M-H]^-$ 359.1396, found 359.1389. IR (neat, cm^{-1}): ν 3112, 2833, 1571, 1241. UPLC R_t = 3.85 min; area 100%.

3-(3,4-Dimethoxyphenyl)-5-(2,4-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1l). This compound was prepared according to RP3 using **7l** (213 mg, 0.40 mmol) in MeOH (1.0 mL) and NaOH (120 µL of a 2N solution in water, 0.24 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 98:2) to give **1l** as a yellow solid (78% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.70 (br s, 1H), 8.51 (s, 1H), 8.33 (d, J = 2.1 Hz, 1H), 7.51 (s, 1H), 7.33-7.29 (m, 1H), 7.24-7.18 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 6.65-

6.60 (m, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5 (Cq), 157.6 (Cq), 149.3 (Cq), 147.8 (Cq), 147.6 (Cq), 143.9 (CH), 131.5 (CH), 129.2 (CH), 128.0 (Cq), 126.9 (Cq), 122.0 (CH), 121.3 (Cq), 119.5 (CH), 118.4 (Cq), 116.5 (Cq), 111.8 (CH), 110.8 (CH), 104.8 (CH), 99.1 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.6 (CH_3), 55.5 (CH_3). HRMS (ESI+) calcd for $C_{23}H_{23}N_2O_4$ $[M+H]^+$ 391.1658, found 391.1657. IR (neat, cm^{-1}): *ν* 3124, 2934, 1611, 1248. UPLC R_t = 3.74 min; area 100%.

3-(3,4-Dimethoxyphenyl)-5-(2,5-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1m). This compound was prepared according to RP3 using **7m** (503 mg, 0.95 mmol) in MeOH (2.4 mL) and NaOH (280 µL of a 2N solution in water, 0.57 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 98:2) to give **1m** as a yellow solid (29% yield over two steps). ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 10.89 (br s, 1H), 8.56 (d, *J* = 1.5 Hz, 1H), 8.39 (d, *J* = 1.8 Hz, 1H), 7.54 (s, 1H), 7.25-7.18 (m, 2H), 7.00-6.97 (m, 3H), 6.93-6.88 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.9 (Cq), 150.9 (Cq), 149.3 (Cq), 147.9 (Cq), 147.8 (Cq), 143.8 (CH), 129.5 (Cq), 129.3 (CH), 127.8 (Cq), 126.8 (Cq), 122.1 (CH), 119.5 (CH), 118.4 (Cq), 117.1 (CH), 116.6 (Cq), 113.1 (CH), 112.6 (CH), 111.8 (CH), 110.7 (CH), 56.3 (CH_3), 56.0 (CH_3), 55.9 (CH_3), 55.8 (CH_3). HRMS (ESI+) calcd for $C_{23}H_{23}N_2O_4$ $[M+H]^+$ 391.1658, found 391.1648. IR (neat, cm^{-1}): *ν* 3130, 2830, 1582, 1245. UPLC R_t = 3.80 min; area 100%.

3,5-Di-(3-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**1n**). This compound was prepared according to RP3 using **7n** (472 mg, 1.00 mmol) in MeOH (2.7 mL) and NaOH (305 µL of a 2N solution in water, 0.60 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 99:1) to give **1n** as a pale yellow solid (59% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 10.64 (br s, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 8.44 (d, *J* = 2.1 Hz, 1H),

7.62 (s, 1H), 7.45-7.38 (m, 2H), 7.31-7.18 (m, 5H), 6.97-6.87 (m, 2H), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.1 (Cq), 160.0 (Cq), 148.4 (Cq), 142.1 (CH), 140.9 (Cq), 136.1 (Cq), 130.2 (Cq), 130.0 (2CH), 127.2 (CH), 123.2 (CH), 120.0 (CH), 119.7 (CH), 118.7 (Cq), 116.8 (Cq), 113.4 (CH), 113.1 (CH), 112.5 (CH), 111.7 (CH), 55.4 (CH_3), 55.3 (CH_3). HRMS (ESI+) calcd for $C_{21}H_{19}N_2O_2$ $[M+H]^+$ 331.1447, found 331.1443. IR (neat, cm^{-1}): *ν* 3109, 2830, 1607, 1207. UPLC R_t = 4.39 min; area 100%.

Representative Procedure for De-*O*-methylation (RP4):

3-Phenyl-5-(4-hydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**2b**). To a solution of **1b** (48 mg, 0.16 mmol) in CH_2Cl_2 (130 μL) was added BBr_3 (480 μL of a 1N solution in CH_2Cl_2, 0.48 mmol). The reaction mixture was stirred at room temperature during 15 h, then quenched at 0°C with MeOH and concentrated in vacuo. The residue was purified by preparative TLC (CH_2Cl_2/MeOH 90:10) to give compound **2b** as a pale yellow solid (46% yield). ^{1}H NMR (CD_3OD, 300 MHz) *δ* 8.40 (d, *J* = 2.1 Hz, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 7.64 (br d, *J* = 6.9 Hz, 2H), 7.61 (s, 1H) 7.48-7.39 (m, 4H), 7.28-7.25 (m, 1H), 6.89 (br d, *J* = 8.7 Hz, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 158.2 (Cq), 148.9 (Cq), 142.4 (CH), 136.3 (Cq), 131.8 (Cq), 131.3 (Cq), 129.9 (2CH), 129.4 (2CH), 127.9 (2CH), 127.1 (CH), 127.0 (CH), 124.7 (CH), 120.0 (Cq), 117.3 (Cq), 116.8 (2CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O$ $[M+H]^+$ 287.1184, found 287.1188. IR (neat, cm^{-1}): *ν* 3142, 2890, 1602, 1259. UPLC R_t = 3.44 min; area 100%.

3,5-Di-(4-hydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2c). This compound was prepared according to RP4 using **1c** (63 mg, 0.19 mmol) in CH_2Cl_2 (175 μL) with BBr_3 (1.2 mL of a 1N solution in CH_2Cl_2, 1.14 mmol). The residue was purified by preparative TLC (CH_2Cl_2/MeOH 85:15) to give **2c** as a pale yellow solid (70% yield). Mp 150-160°C. ^{1}H NMR (CD_3OD, 300 MHz) *δ* 8.38 (d, *J* = 1.5 Hz, 1H), 8.29 (d, *J* = 2.1 Hz, 1H), 7.52-7.46 (m, 5H), 6.92-6.88 (m,

4H); ^{13}C NMR (CD_3OD, 75 MHz) δ 158.1 (Cq), 157.1 (Cq), 148.8 (Cq), 142.2 (CH), 132.0 (Cq), 131.1 (Cq), 129.4 (2CH), 129.3 (2CH), 127.7 (Cq), 127.2 (CH), 123.9 (CH), 120.2 (Cq), 117.5 (Cq), 116.9 (2CH), 116.8 (2CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O_2$ $[M+H]^+$ 303.1134, found 303.1127. IR (neat, cm^{-1}): *ν* 3136, 2937, 1601, 1257. UPLC R_t = 2.47 min; area 100%.

3,5-Di-(3,4-dihydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2d). This compound was prepared according to RP4 using **1d** (225 mg, 0.59 mmol) in CH_2Cl_2 (480 µL) with BBr_3 (7.0 mL of a 1N solution in CH_2Cl_2, 7.04 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 95:5 to 85:15) and then by preparative TLC (CH_2Cl_2/MeOH 80:20) to give **2d** as a grey solid (61% yield). Mp 190°. ^1H NMR (CD_3OD, 300 MHz) δ 8.37 (d, *J* = 2.1 Hz, 1H), 8.31 (d, *J* = 2.1 Hz, 1H), 7.49 (s, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 7.09 (d, *J* = 2.1 Hz, 1H), 7.03-6.97 (m, 2H), 6.89 (d, *J* = 3.9 Hz, 1H), 6.86 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 148.8 (Cq), 146.8 (Cq), 146.6 (Cq), 146.0 (Cq), 145.1 (Cq), 142.2 (CH), 132.6 (Cq), 131.2 (Cq), 128.3 (Cq), 127.2 (CH), 123.8 (CH), 120.1 (Cq), 119.8 (CH), 119.6 (CH), 117.6 (Cq), 117.0 (2CH), 115.3 (2CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O_4$ $[M+H]^+$ 335.1032, found 335.1038. IR (neat, cm^{-1}): *ν* 3172, 3047, 1596, 1270. UPLC R_t = 1.99 min; area 100%.

3-Phenyl-5-(3-hydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2f). This compound was prepared according to RP4 using **1f** (51 mg, 0.17 mmol) in CH_2Cl_2 (140 µL) with BBr_3 (0.5 mL of a 1N solution in CH_2Cl_2, 0.51 mmol). The residue was purified by preparative TLC (CH_2Cl_2/MeOH 90:10) to give **2f** as a white solid (43% yield). ^1H NMR (CD_3OD, 300 MHz) *δ* 8.45 (d, *J* = 2.1 Hz, 1H), 8.38 (d, *J* = 2.1 Hz, 1H), 7.69-7.65 (m, 3H), 7.46-7.41 (m, 2H), 7.31-7.24 (m, 2H), 7.13-7.08 (m, 2H), 6.80 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) 159.1 (Cq), 149.4 (Cq), 142.7 (CH), 142.0 (Cq), 136.3 (Cq), 131.3 (Cq), 131.1 (CH),

129.9 (2CH), 128.0 (2CH), 127.6 (CH), 127.2 (CH), 125.0 (CH), 120.0 (Cq), 119.6 (CH), 117.5 (Cq), 115.2 (CH), 115.0 (CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O$ $[M+H]^+$ 287.1184, found 287.1182. IR (neat, cm^{-1}): *v* 3124, 2919, 1596. UPLC R_t = 3.64 min; area 100%.

3-Phenyl-5-(2-hydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2g). This compound was prepared according to RP4 using **1g** (113 mg, 0.38 mmol) in CH_2Cl_2 (325 μL) with BBr_3 (1.1 mL of a 1N solution in CH_2Cl_2, 1.13 mmol). The residue was purified by preparative TLC (CH_2Cl_2/MeOH 94:6) to give **2g** as a white solid (34% yield). ^1H NMR (CD_3OD, 300 MHz) *δ* 8.42 (s, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 7.63 (br d, *J* = 6.9 Hz, 2H), 7.58 (s, 1H) 7.40-7.35 (m, 2H), 7.31-7.28 (m, 1H), 7.24-7.14 (m, 2H), 6.95-6.89 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 155.6 (Cq), 148.5(Cq), 144.5 (CH), 136.3 (Cq), 131.9 (Cq), 130.3 (CH), 129.8 (2CH), 129.7 (CH), 128.6 (Cq), 127.9 (2CH), 127.6 (CH), 127.0 (CH), 124.4 (CH), 121.2 (CH), 119.6 (Cq), 117.4 (Cq), 117.0 (CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O$ $[M+H]^+$ 287.1184, found 287.1188. IR (neat, cm^{-1}): *v* 3267, 2869, 1602, 1262. UPLC R_t = 3.67 min; area 100%.

3-Phenyl-5-(2,4-dihydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2h). This compound was prepared according to RP4 using **1h** (100 mg, 0.30 mmol) in CH_2Cl_2 (260 μL) with BBr_3 (1.8 mL of a 1N solution in CH_2Cl_2, 1.82 mmol). The residue was purified by preparative TLC (CH_2Cl_2/MeOH 94:6) to give **2h** as a white solid (53% yield). ^1H NMR (CD_3OD, 300 MHz) *δ* 8.39 (s, 2H), 7.69 (br d, *J* = 9.3 Hz, 2H), 7.62 (s, 1H), 7.45-7.39 (m, 2H), 7.28-7.22 (m, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 6.45-6.41 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.2 (Cq), 156.5 (Cq), 148.3 (Cq), 144.5 (CH), 136.5 (Cq), 132.4 (CH), 130.1 (CH), 129.9 (2CH), 128.9 (Cq), 127.9 (2CH), 127.0 (CH), 124.3 (CH), 119.7 (Cq), 119.3 (Cq), 117.3 (Cq), 108.4 (CH), 104.1 (CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O_2$ $[M+H]^+$ 303.1134, found 303.1124. IR (neat, cm^{-1}): *v* 3252, 2833, 1605, 1259. UPLC R_t = 2.94 min; area 100%.

3-Phenyl-5-(3,4-dihydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2i). This compound was prepared according to RP4 using **1i** (70 mg, 0.21 mmol) in CH_2Cl_2 (185 µL) with BBr_3 (1.3 mL of a 1N solution in CH_2Cl_2, 1.27 mmol). The residue was purified by preparative TLC (CH_2Cl_2/MeOH 95:5) to give **2i** as a white solid (52% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.90 (br s, 1H), 9.01 (s, 1H), 9.00 (s, 1H), 8.44 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 2.1 Hz, 1H), 7.87 (s, 1H), 7.76 (d, J = 7.5 Hz, 2H), 7.48-7.43 (m, 2H), 7.28-7.23 (m, 1H), 7.09 (s, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 148.2 (Cq), 145.6 (Cq), 144.8 (Cq), 141.6 (CH), 135.1 (Cq), 131.3 (Cq), 130.3 (Cq), 129.2 (CH), 128.9 (2CH), 126.3 (2CH), 125.6 (CH), 124.4 (CH), 124.3 (Cq), 118.0 (CH), 117.2 (Cq), 116,2 (CH), 114.4 (CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O_2$ $[M+H]^+$ 303.1134, found 303.1143. IR (neat, cm^{-1}): ν 3112, 2830, 1601, 1254. UPLC R_t = 3.74 min; area 100%.

3-(4-Hydroxyphenyl)-5-(2,4-dihydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2j). This compound was prepared according to RP4 using **1j** (170 mg, 0.47 mmol) in CH_2Cl_2 (395 µL) with BBr_3 (4.1 mL of a 1N solution in CH_2Cl_2, 4.25 mmol). The residue was purified by flash chromatography on silica gel (CH_2Cl_2 / MeOH, gradient 100:0 to 95:5) and then by preparative TLC (CH_2Cl_2/MeOH 90:10) to give **2j** as a pale brown solid (75% yield). Mp 201-210°C. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.34 (d, J = 2.1 Hz, 1H), 8.31 (d, J = 2.1 Hz, 1H), 7.48-7.51 (m, 2H), 7.47 (s, 1H), 7.14 (d, J = 8.1 Hz, 1H), 6.88 (dd, J = 8.4 Hz, 2.1 Hz, , 2H), 6.44 (s, 1H), 6.41-6.45 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.1 (Cq), 157.0 (Cq), 156.5 (Cq), 148.3 (Cq), 144.4 (CH), 132.5 (CH), 130.0 (CH), 129.2 (2CH), 128.6 (Cq), 127.9 (Cq), 123.2 (CH), 119.8 (Cq), 119.4 (Cq), 117.4 (Cq), 116.7 (2CH), 108.4 (CH), 104.1 (CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O_3$ $[M+H]^+$ 319.1083, found 319.1087. IR (neat, cm^{-1}): ν 3189, 3008, 1605, 1260. UPLC R_t = 2.10 min; area 100%.

3-(4-Hydroxyphenyl)-5-(3,4-dihydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2k). This compound was prepared according to RP4 using **1k** (125 mg, 0.35 mmol) in CH_2Cl_2 (300 µL) with BBr_3 (3.1 mL of a 1N solution in CH_2Cl_2, 3.12 mmol). The residue was purified by preparative TLC (CH_2Cl_2/MeOH 90:10) to give **2k** as a pale grey solid (53% yield). Mp 275°C (degradation). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.37 (d, *J* = 2.1 Hz, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 7.52-7.49 (m, 3H), 7.08 (d, *J* = 2.1 Hz, 1H), 7.00-6.97 (m, 1H), 6.91-6.86 (m, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 157.1 (Cq), 148.9 (Cq), 146.8 (Cq), 146.1 (Cq), 142.2 (CH), 132.6 (Cq), 131.2 (Cq), 129.3 (2CH), 127.7 (Cq), 127.1 (CH), 123.8 (CH), 120.2 (Cq), 119.8 (CH), 117.5 (Cq), 117.0 (CH), 116.8 (2CH), 115.3 (CH). HRMS (ESI-) calcd for $C_{19}H_{13}N_2O_3$ $[M-H]^-$ 317.0926, found 317.0936. IR (neat, cm^{-1}): *ν* 3264, 3017, 1601, 1257. UPLC R_t = 2.22 min; area 100%.

3-(3,4-Dihydroxyphenyl)-5-(2,4-dihydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2l). This compound was prepared according to RP4 using **1l** (110 mg, 0.28 mmol) in CH_2Cl_2 (235 µL) with BBr_3 (3.4 mL of a 1N solution in CH_2Cl_2, 3.38 mmol). The residue was purified by preparative TLC (CH_2Cl_2/MeOH 80:20) to give **2l** as a black solid (53% yield). Mp 197°C. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.36-8.33 (m, 2H), 7.54 (s, 1H), 7.16-7.13 (m, 2H), 7.02-6.98 (m, 1H), 6.85 (br d, *J* = 8.1 Hz, 1H), 6.45-6.40 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.1 (Cq), 156.5 (Cq), 148.3 (Cq), 146.6 (Cq), 145.0 (Cq), 144.4 (CH), 132.5 (CH), 130.0 (CH), 128.6 (Cq), 128.5 (Cq), 123.2 (CH), 119.8 (Cq), 119.7 (CH), 119.5 (Cq), 117.5 (Cq), 116.9 (CH), 115.3 (CH), 108.4 (CH), 104.1 (CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O_4$ $[M+H]^+$ 335.1032, found 335.1025. IR (neat, cm^{-1}): *ν* 3136, 2842, 1604, 1259. UPLC R_t = 1.89 min; area 100%.

3-(3,4-Dihydroxyphenyl)-5-(2,5-dihydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2m). This compound was prepared according to RP4 using **1m** (150 mg, 0.38 mmol) in CH_2Cl_2 (320 μL) with BBr_3 (4.6 mL of a 1N solution in CH_2Cl_2, 4.61 mmol). The residue was purified by preparative TLC (CH_2Cl_2/MeOH 80:20) to give **2m** as a brown solid (41% yield). Mp 180°C. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.40 (m, 2H), 7.48 (s, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 8.1 Hz, 2.1 Hz, 1H), 6.87-6.77 (m, 3H), 6.68-6.64 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 151.7 (Cq), 148.6 (Cq), 148.4 (Cq), 146.6 (Cq), 145.0 (Cq), 144.3 (CH), 130.2 (CH), 128.4 (3Cq), 123.4 (CH), 119.7 (Cq), 119.6 (CH), 118.1 (CH), 118.0 (CH), 117.7 (Cq), 116.9 (CH), 116.1 (CH), 115.3 (CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O_4$ $[M+H]^+$ 335.1032, found 335.1023. IR (neat, cm^{-1}): *ν* 3216, 2916, 1605, 1276. UPLC R_t = 1.75 min; area 100%.

3,5-Di-(3-hydroxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2n). This compound was prepared according to RP4 using **1n** (158 mg, 0.48 mmol) in CH_2Cl_2 (400 μL) with BBr_3 (2.8 mL of a 1N solution in CH_2Cl_2, 2.87 mmol). The residue was purified by preparative TLC (CH_2Cl_2/MeOH 90:10) to give **2n** as a white solid (47% yield). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.45 (s, 1H), 8.42 (d, *J* = 2.1 Hz, 1H), 7.64 (s, 1H), 7.32-7.24 (m, 2H), 7.19-7.08 (m, 4H), 6.82-6.70 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.1 (Cq), 158.9 (Cq), 149.3 (Cq), 142.6 (CH), 142.0 (Cq), 137.6 (Cq), 131.2 (Cq), 131.1 (CH), 131.0 (CH), 127.7 (CH), 124.9 (CH), 119.9 (CH), 119.6 (CH), 119.3 (CH), 117.5 (CH), 115.2 (CH), 115.0 (CH), 114.7 (CH), 114.2 (CH). HRMS (ESI+) calcd for $C_{19}H_{15}N_2O_2$ $[M+H]^+$ 303.1134, found 303.1127. IR (neat, cm^{-1}): *ν* 3314, 3014, 1599, 1275. UPLC R_t = 2.91 min; area 100%.

Molecular Modeling Study

The putative binding mode between the ATP binding site of DYRK1A and the most active compounds of the series **2c**, **2d**, **2k** and **2j** was examined by molecular modeling experiments

using Schrodinger Suite™ 2012 Update 1.[27] The model used was based on the structure of DYRK1A 2WO6.pdb available in the Protein Data Bank (PDB). The structure was treated using Protein Preparation Wizard module, hydrogen atoms were added and refined using PROPKA algorithm at pH 7.0, restrained minimization was conducted with OPLS2005 forcefield with a convergence criterion for heavy atoms of 0.30 Å. All ligands were constructed and minimized using OPLS2005 force field. Structures were prepared for docking experiments with the LigPrep module with generation of all possible states using Epik algorithm (target pH of 7.0 ± 2.0). The grid was generated using Glide Receptor Grid Generation module from the prepared protein structure (volume of 20 $Å^3$ centered on the native ligand K00611A of 2WO6.pdb). The docking experiments were conducted with the Glide module of Schrodinger Suite™ with extra precision algorithm (XP Glide), flexible ligand sampling and adding Epik state penalties to docking score.

Expression and Purification of the Recombinant DYRK1A Catalytic Domain (DYRK1A-ΔC)

The cDNA coding for the catalytic domain (residues 1-502) of rat DYRK1A (99.6% amino acid identity with human DYRK1A) was a kind gift of Prof. W. Becker (Aachen University, Germany). This cDNA was subcloned into pET28 plasmid and used to produce recombinant 6xHis-tagged DYRK1A catalytic domain (DYRK1A-ΔC). The pET28-DYRK1A-ΔC plasmid was transformed into *E. coli* BL21(DE3) cells for production and purification of the protein. Briefly, transformed bacterial cells were grown at 37°C for 4h in the presence of 0.5 mM isopropyl β-D-1-thiogalactopyranoside and further grown at 4°C overnight. Cells were harvested by centrifugation and resuspended in phosphate buffered saline buffer (PBS) supplemented with protease inhibitors, 1 mg/ml lysozyme and 0.1% Triton X-100. After 30 min incubation at 4°C, the lysate was subjected to sonication on ice and pelleted (12,000xg, 30

min). The supernatant was incubated with His-select Nickel resin (Sigma) for 2h at 4°C. Resin was poured into a column and washed with Tris-HCl 20 mM, pH 7.5, 10 mM imidazole. Proteins were eluted in Tris-HCl 20 mM, pH 7.5, 300 mM imidazole. Proteins were reduced with 10 mM dithiothreitol (DTT) and dialyzed overnight against Tris-HCl 20 mM, pH 7.5. Proteins were quantified with Bradford's reagent (Bio-rad). Purity was assessed by SDS-PAGE. Proteins were kept at -80°C.

DYRK1A Inhibition Assay

Measurement of DYRK1A kinase activity was carried out using a high pressure liquid chromatography (HPLC)-based approach using a fluorescent peptide substrate of DYRK1A. The fluorescent peptide substrate was derived from the sequence of the human transcription factor FKHR which is known to be a physiological substrate of DYRK1A.[28] The peptide substrate is coupled to fluorescein by its N-terminal amino acid and has the following sequence: KISGRLSPIMTEQ (the serine residue that is phosphorylated by DYRK1A is underlined). DYRK1A-ΔC activity assays were performed in 96-well plates, in a total volume of 50 µl consisting of kinase buffer (Tris-HCl 50 mM, pH 7.5, 10 mM DTT, 5 mM $MgCl_2$), peptide substrates (ranging from 5-60 µM) and 20 ng of purified DYRK1A-ΔC. The reaction was initiated by addition of ATP (ranging from 50 to 800 µM) and the mixture was incubated for 30 min at 37 °C. Reactions were stopped by addition of 50 µl of 15% $HClO_4$ (v/v) and 20 µl of the mixture was analyzed by HPLC (Shimadzu) on a C8 reverse-phase column (Ascentis). Mobile phases used consisted of 0.12 % trifluoroacetic acid (TFA) (solvent A) and acetonitrile in 0.12% TFA. Phosphorylated and unphosphorylated peptides were separated by isocratic flow (85% solvent A/15% solvent B) at a flow rate of 1.5 ml/min. The peptides were monitored by fluorimetry (excitation at 485 nm, emission at 530 nm) and quantified by integration of the peak absorbance area. A calibration curve established with different known concentrations of

peptides was used for quantification. Initial velocities and kinetic parameters were determined by fitting the data iteratively to the following equation : $V_i = V_{max} [S_A][S_B]/(K_{AB} + K_{mB}[S_A] + K_{mA}[S_B] + [S_A][S_B])$ using the Prism 5 (GraphPad) program, where V_i is the initial velocity, V_m is the maximal velocity, K_{AB} is the dissociation constant and K_{mA} K_{mB} are the Michaelis-Menten constants.[29]

For inhibition studies, the compounds were added at different concentrations to the well prior to addition of ATP. Determination of the mode of inhibition (competitive/non competitive) of the compounds and inhibition constant (K_i) values were obtained by carrying out assays with different concentrations of inhibitors and fitting the data to the following equations: $V_i = V_{max} [S]/(K_m (1+[I]/K_I) + [S])$ and $V_i = (V_{max}/(1+[I]/K_I) [S])/(K_m + [S])$ for competitive and non competitive inhibition, respectively.[29] All experiments were done in triplicate, mean values are reported.

Cell Culture and Proliferation Assay

Cancer cell lines were obtained from the American Type Culture Collection (Rockville, MD, USA) and were cultured according to the supplier's instructions. Briefly, human KB epidermal carcinoma cells were grown in Dulbecco minimal essential medium (DMEM) containing 4.5 g/L glucose supplemented with 10% fetal calf serum (FCS) and 1% glutamine, 100 UI penicillin, 100 µg/ml streptomycin and 1.5 µg/ml fungizone and maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Cell viability was assessed using Promega CellTiter-Blue TM reagent according to the manufacturer's instructions. Briefly, cells were seeded in 96-well plates (5 x 10^3 cells/well) containing 50 ml growth medium. After 24h of culture, the cells were supplemented with 50 ml of the studied compound dissolved in DMSO (less than 0.1% in each preparation). After 72h of incubation, 20 ml of resazurin was added for

2h before recording fluorescence (λ_{ex} = 560nm, λ_{em} = 590nm) using a Victor microtiter plate fluorimeter (Perkin-Elmer, USA).

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Associated Content

Supporting Information

RP-HPLC traces showing the purity of the compounds tested. Copies of 1H NMR This material is available free of charge via the Internet at http://pubs.acs.org.

Author Information

Corresponding author

Tel.: 33-1-69824594; Fax: 33-1-69077247;

E-mail: robert.dodd@cnrs.fr

Abbreviations used

AKT, Protein Kinase B; Alk, alkyl; CK1α, casein kinase 1 α; CLKs, cdc2-like kinases; DANDYs, Diaryl-Azaindole iNhibitors of DYRK1A; DMEM, Dulbecco minimal essential medium; DYRKs, dual specificity, tyrosine phosphorylation regulated kinases; DS, Down Syndrome; EGCG, Epigallocatechin gallate; FCS, fetal calf serum; FKHR, Forkhead box protein O1; GSK, glycogen synthase kinase; INDY, (1Z)-1-(3-ethyl-5-hydroxy-1,3-benzothiazol-2-ylidene)propan-2-one; JAK, Janus Kinase; ND, Not Determined; NFTs, Neurofibrillary Tangles; NIS, *N*-Iodosuccinimide; Pim1, proto-oncogene serine/threonine-protein kinase; Rt, Retention time, TRK, tropomyosin-receptor kinase A.

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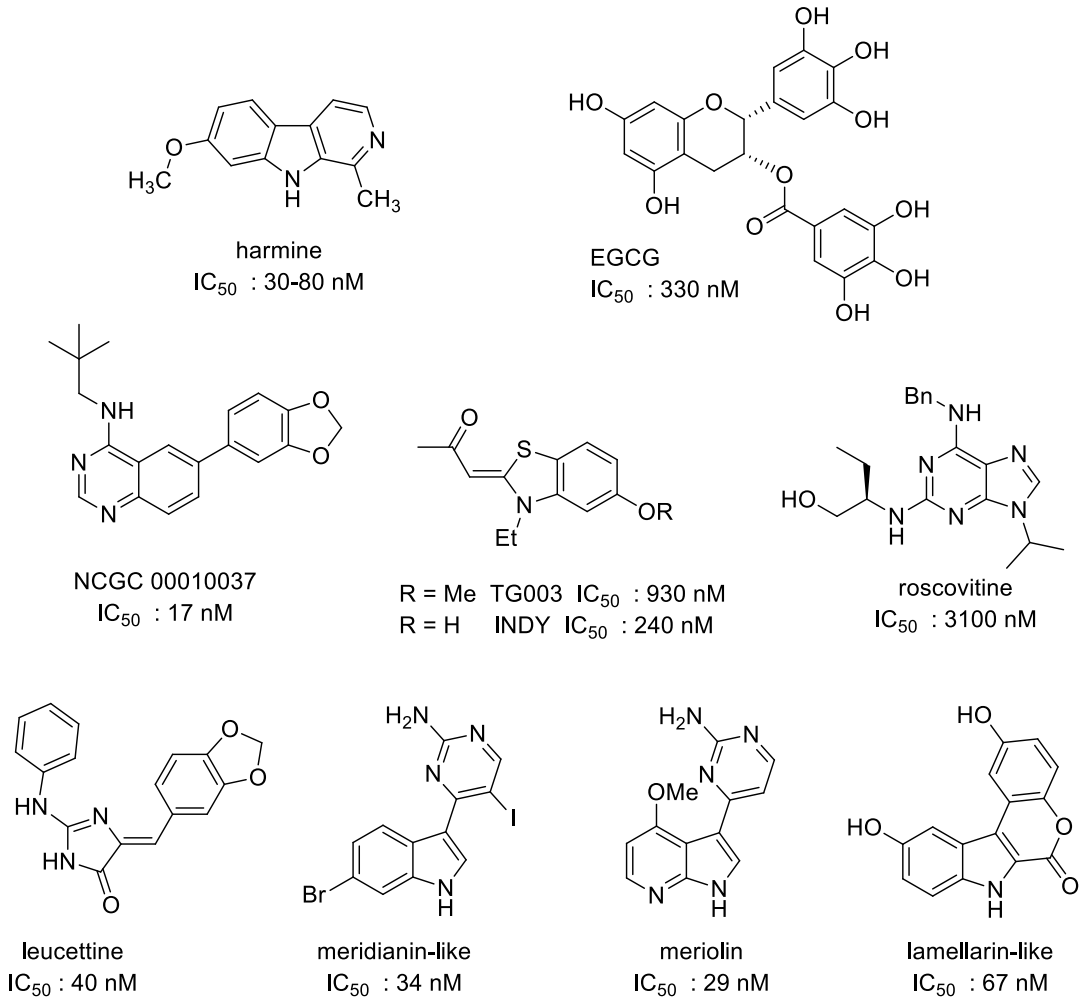
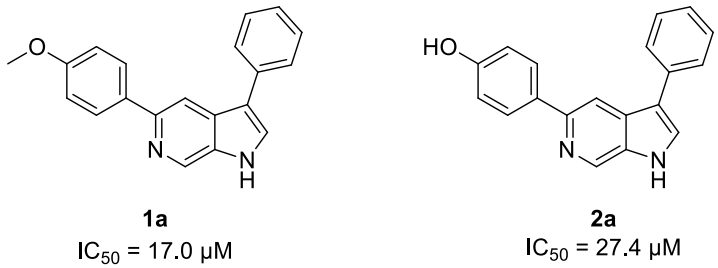


Figure 1: Known DYRK1A Inhibitors.



1a
IC_{50} = 17.0 μM

2a
IC_{50} = 27.4 μM

Figure 2. 3-Phenyl-5-aryl-6-azaindoles as Potential Hits

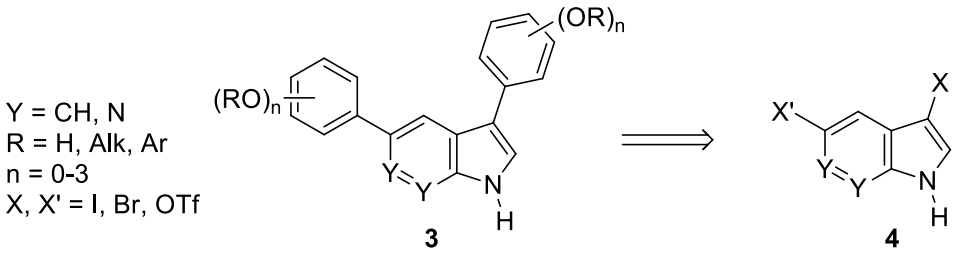


Figure 3: Initial Design.

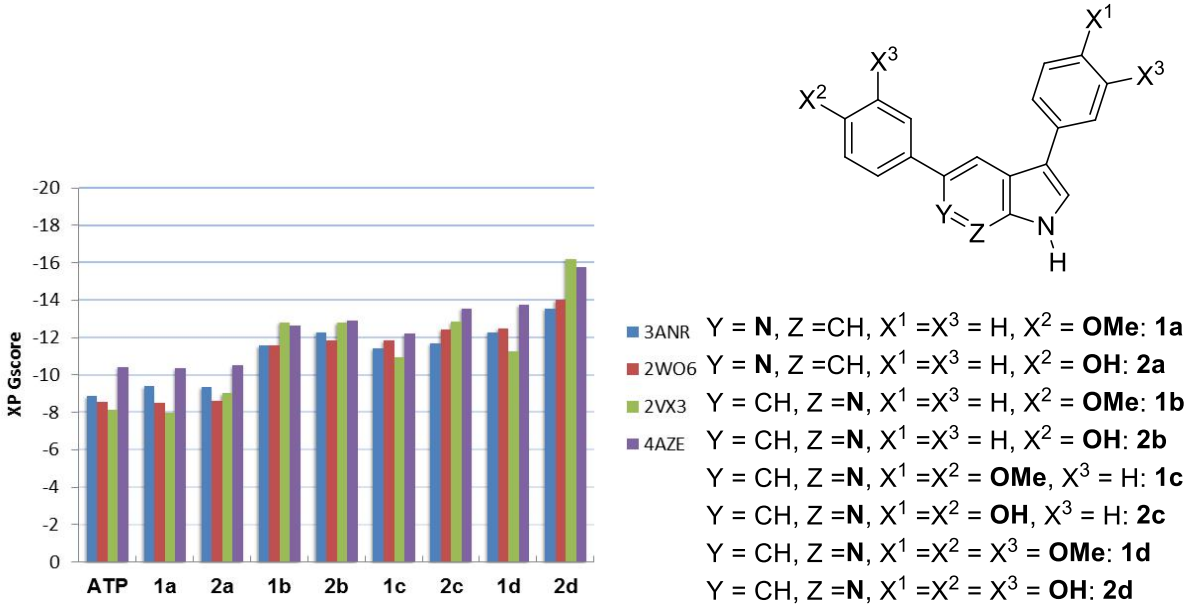


Figure 4: Comparison of Glide XP Docking Scores of Virtual Substrates.

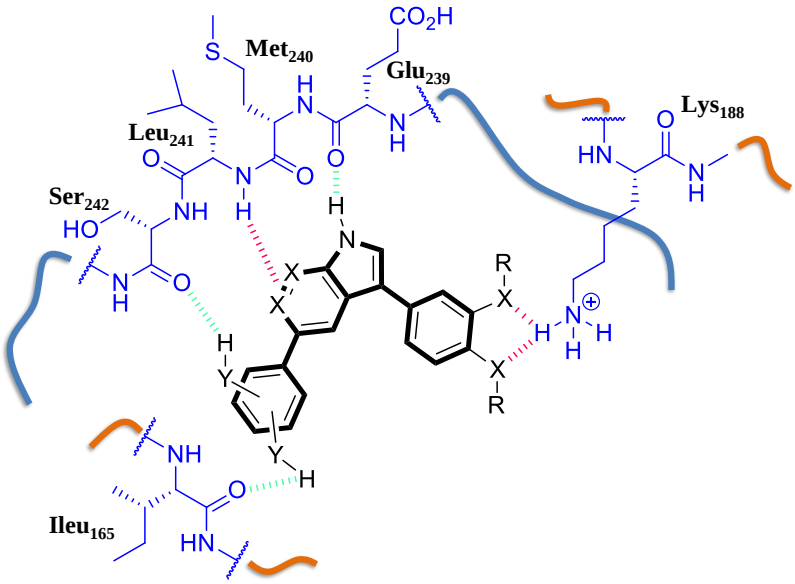
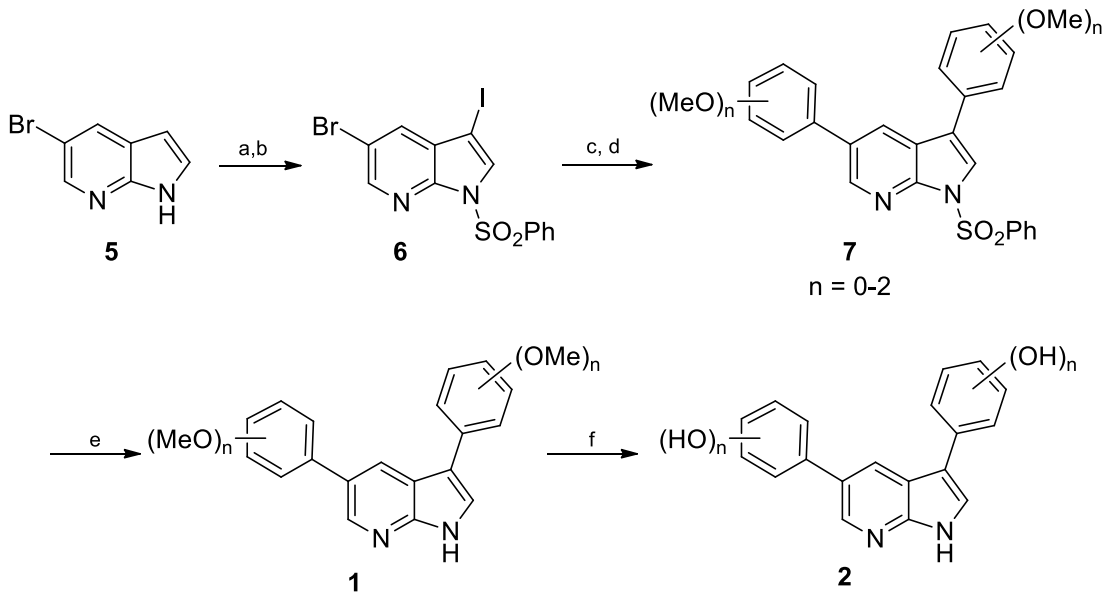


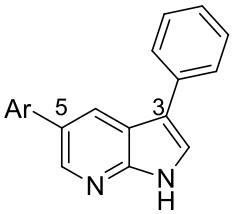
Figure 5: *In Silico* "Ideal Inhibitor" within the ATP-Binding Site .

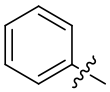
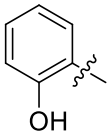
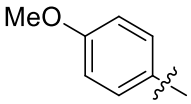
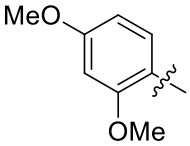
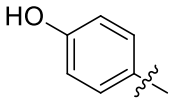
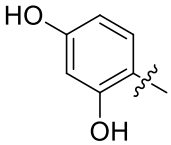
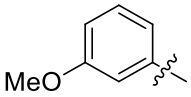
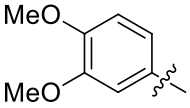
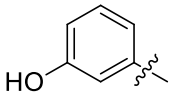
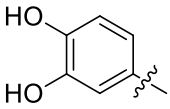
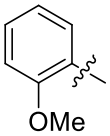
Scheme 1. Synthesis of 3,5-Diaryl-7-Azaindole Derivatives[a]



[a]Reagents and conditions: (a) NIS (1.0 equiv.), KOH (0.5 equiv.), DCM, rt, 15 h; (b) NaH (60% in mineral oil, 3equiv.), $PhSO_2Cl$ (1.2 equiv.), $BnEt_3NCl$ (cat.), DCM, rt, 15 h; 97% over two steps (c) or (d) arylboronic acid, $Pd(PPh_3)_4$ (cat.), K_2CO_3 2M (aqueous), toluene/EtOH 3:1, 110°C, 3.5 h (two successive steps with 1.0 equiv. of two different arylboronic acids or single step reaction with 2.0 equiv. of arylboronic acid, see materials and methods for details); 36-87% (e) NaOH 2N (aqueous), MeOH, 80°C, 2 h; 29-98% (f) BBr_3 (3.0 equiv. *per* Me), DCM, 0°C to rt, 15 h; 34-75%.

Table 1. *In Vitro* Activity of 3-Phenyl-5-Aryl-7-Azaindole Derivatives



Compd.	Ar	DYRK1A IC_{50} (μM)	Compd.	Ar	DYRK1A IC_{50} (μM)
1e		0.41	**2g**		3.59
1b		0.96	**1h**		1.17
2b		0.33	**2h**		0.15
1f		7.49	**1i**		3.08
2f		2.70	**2i**		0.16
1g		0.96			

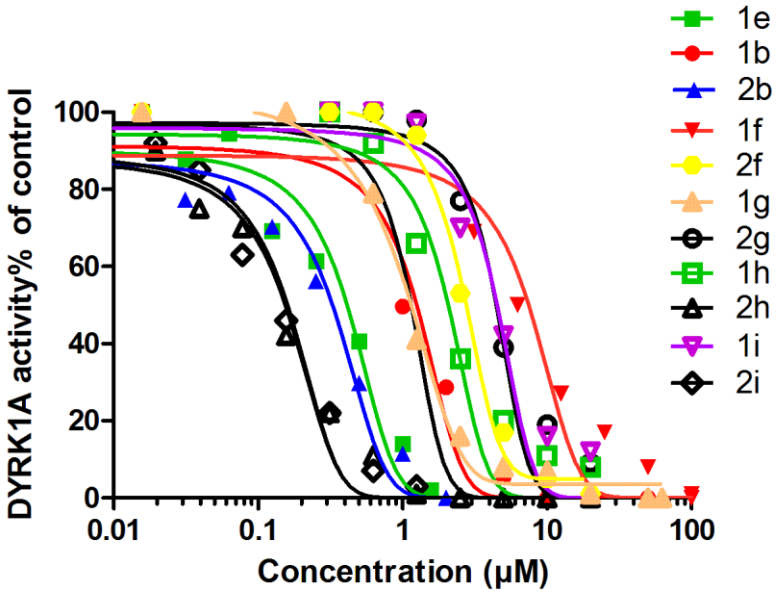
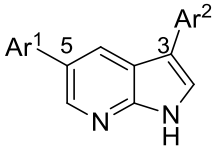
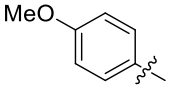
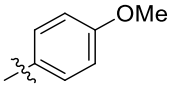
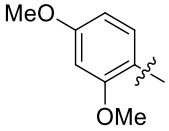
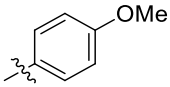
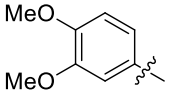
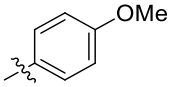
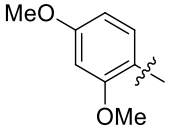
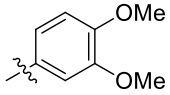
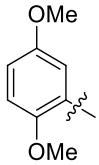
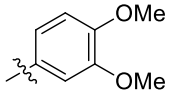
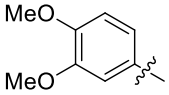
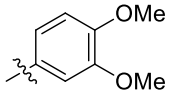
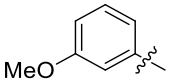
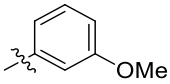


Figure 6: Dose-response of ΔDYRK1A activity (normalized in the absence of inhibitor, expressed as percentage) obtained with varied concentration of 3-phenyl-7-azaindole derivatives **1e,b,f-i** and **2b,f-i** (0.02 – 100 µM) with 50 µM of ATP.

Table 2. *In Vitro* Activity of Polymethoxy 3,5-Diaryl-7-Azaindole Derivatives



Compd	Ar^1	Ar^2	DYRK1A IC_{50} (μM)
1c			1.74
1j			0.28
1k			0.46
1l			2.88
1m			1.67
1d			57.78
1n			14.63

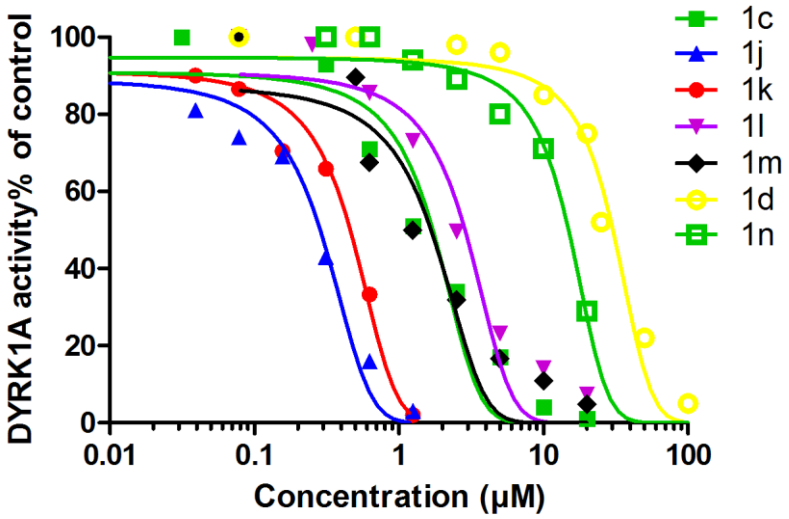
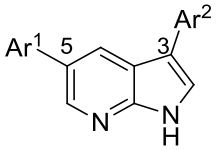
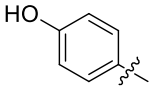
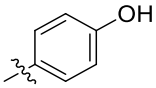
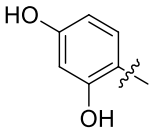
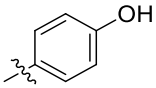
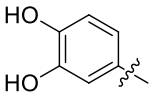
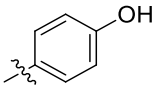
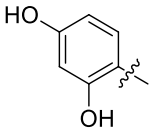
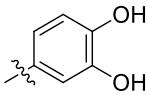
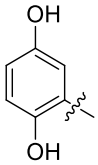
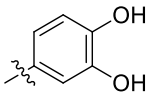
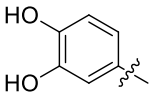
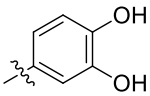
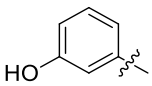
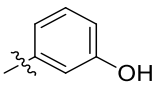


Figure 7: Dose-response of ΔDYRK1A activity (normalized in the absence of inhibitor, expressed as percentage) obtained with varied concentration of polmethoxy 3,5-diaryl-7-azaindole derivatives **1c,d,j-n** (0.02 – 100 µM) with 50 µM of ATP.

Table 3. ***In Vitro*** **Activity of Polyhydroxy 3,5-Diaryl-7-Azaindole Derivatives**



Compd	Ar[1]	Ar[2]	DYRK1A IC_{50} (µM)	Dyrk1A* IC_{50} (µM)	K_i (nM)
2c			0.0231	0.043	2.3
2j			0.0117	0.048	5.5
2k			0.0030	0.0055	<2
2l			0.0143	ND	7.6
2m			0.0391	ND	12.1
2d			0.0124	0.032	10.1
2n			0.1052	ND	ND

* IC_{50} were obtained with 1 mM ATP instead of 50 µM, ND: not determined.

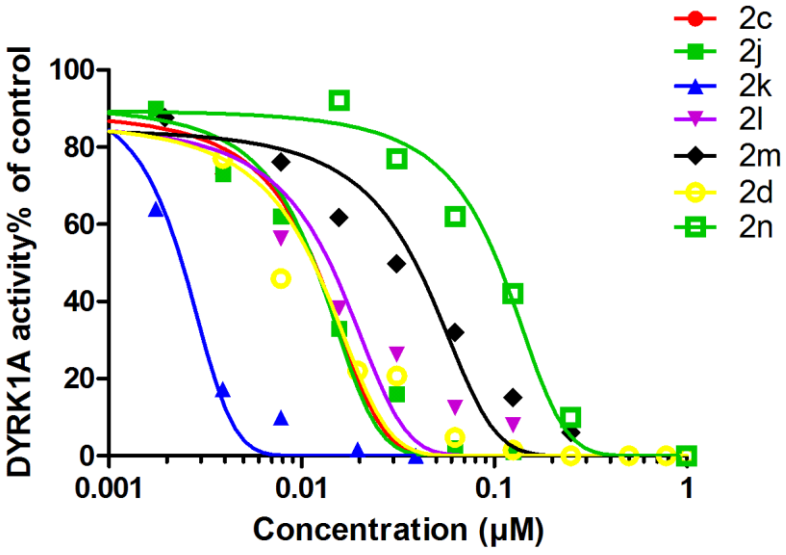


Figure 8: Dose-response of ΔDYRK1A activity (normalized in the absence of inhibitor, expressed as percentage) obtained with varied concentration of polyhydroxy 3,5-diaryl-7-azaindole derivatives **2c,d,j-n** (0.02 – 100 µM) with 50 µM of ATP.

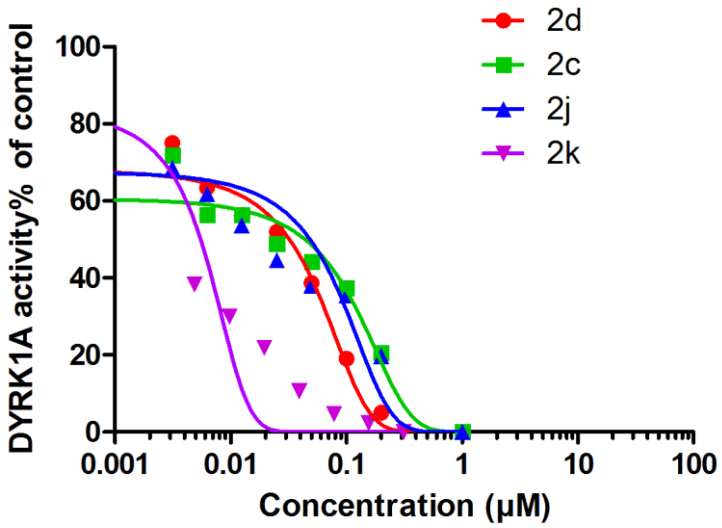


Figure 9: Dose-response of ΔDYRK1A activity (normalized in the absence of inhibitor, expressed as percentage) obtained with varied concentration of polyhydroxy 3,5-diaryl-7-azaindole derivatives **2c,d,j,k** (0.02 – 100 µM) with 1000 µM of ATP.

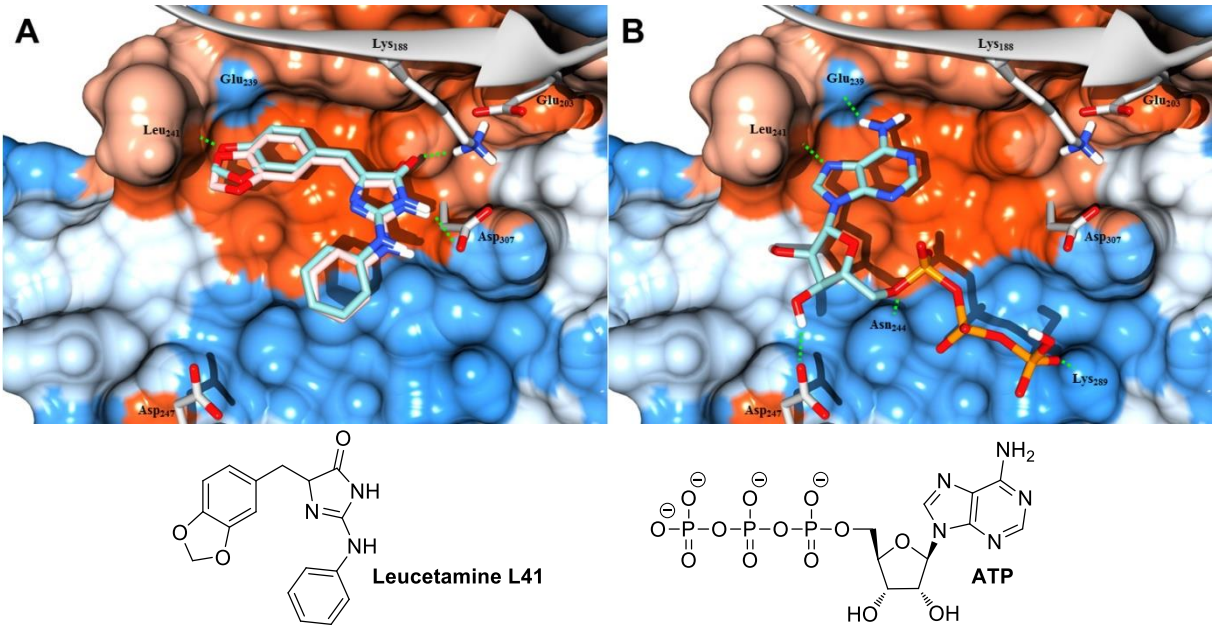


Figure 10. (A) Validation of the docking procedure *via* direct docking of L41 on 4AZE.pdb prepared structure (native ligand in purple (pink?) and top pose in green (blue?)). (B) Docking experiment using virtual ATP on the 4AZE.pdb prepared structure (Top residues 132 to 180 of the protein have been omitted for better clarity, pictures were made using Chimera and PovRay softwares).

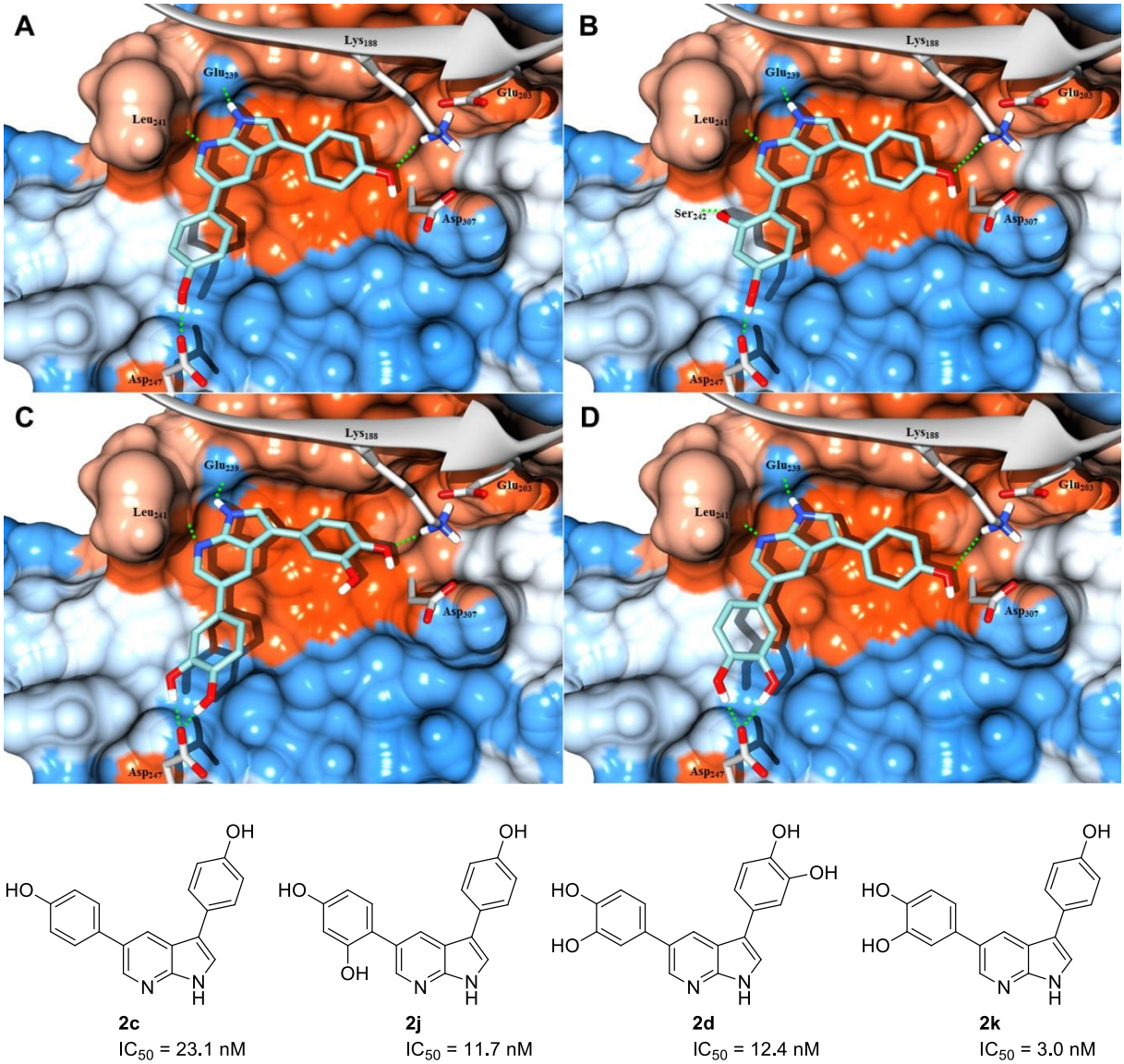


Figure 11. Top poses of compounds **2c** (A), **2j** (B), **2d** (C) and **2k** (D). Generated with GlideXP™ algorithm on the 4AZE.pdb prepared structure (Top residues 132 to 180 of the protein have been omitted for better clarity, pictures were made using Chimera and PovRay softwares)

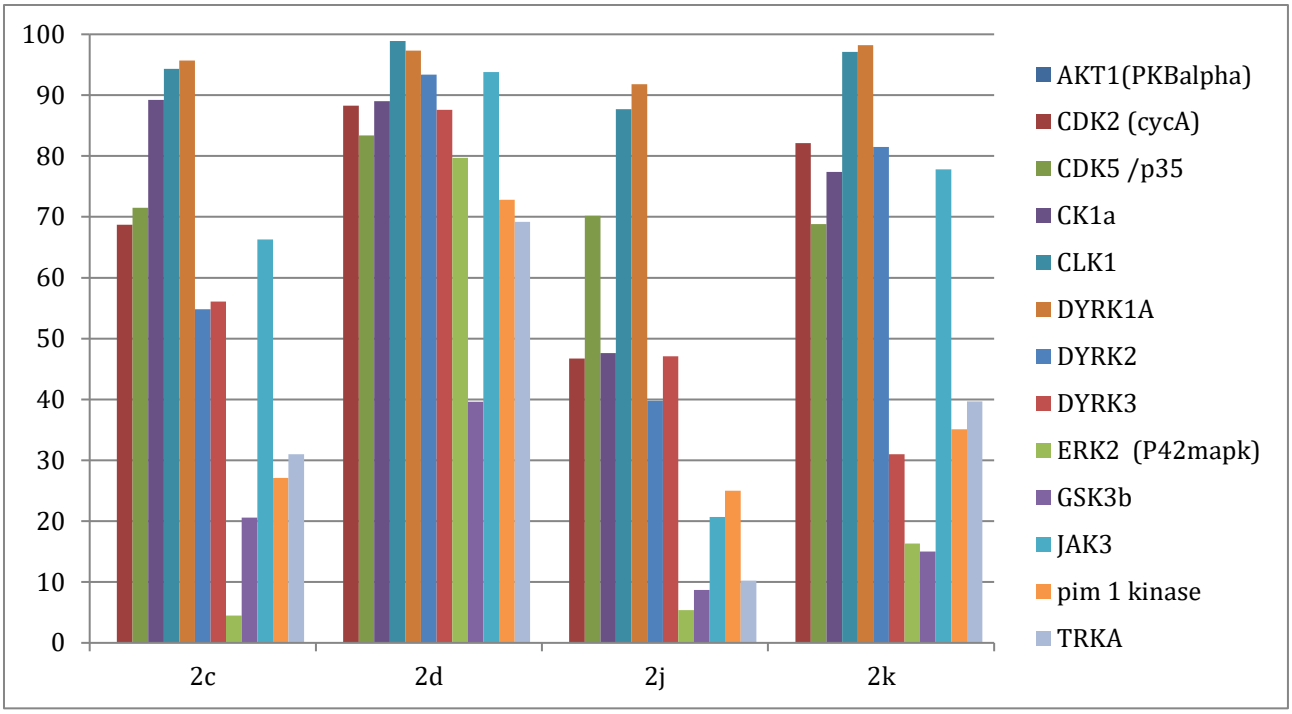
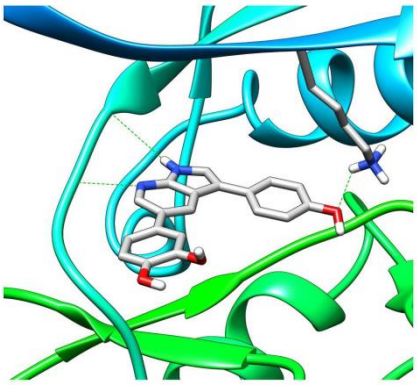


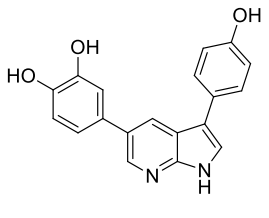
Figure 8. *In vitro* inhibition of a panel of kinases by compounds **2c**, **2d**, **2j** and **2k**, at 5.10^{-8}M concentration (100 represents full inhibition of the enzyme)

Table 4: Growth Inhibition of KB cells for compounds 2c, 2j, 2l, 2k and 2d (percentage)

compound	**At 10^{-5} M**	**At 10^{-6} M**
2c	95%	51%
2d	11%	2%
2j	83%	21%
2k	86%	56%
2l	9%	0%

Table of Contents Graphic





IC_{50} = 3 nM

Diaryl-Azaindole iNhibitors of DYRK1A (DANDY)