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I_2-Triggered N–O cleavage of ketoxime acetates for the synthesis of 3-(4-pyridyl)indoles†

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A facile and complementary [3 + 2 + 1] annulation of aryl ketoxime acetates and 3-formylindoles to give pyridine derivatives is reported. The condensation reaction demonstrated that I_2 was capable of triggering N–O bond cleavage of ketoxime acetates to generate iminyl radicals *via* a single electron transfer pathway. This direct and operationally simple protocol provides a fundamental platform to synthesize 3-(4-pyridyl)indoles with high functional group compatibility and high regioselectivity.

Introduction

The construction of bis-heterocyclic scaffolds is highly appreciated in modern drug discovery to achieve specific drug–receptor interactions.[1] Heteroaryl-indoles are such an unprecedented class of bis-heterocycles. For example, pimprinine displayed a range of biological activities such as antiepileptic activity, monoamine oxidase inhibition, and anticonvulsant activity.[2] Meridianin D analogues showed antibiofilm activity against MRSA and increased colistin efficacy in Gram-negative bacteria.[3] Pyrazolyl–indole has been reported to be a strong inhibitor of *h*CA XII.[4] Especially, recent studies revealed that incorporation of the pyridine nucleus into the C3 position of indoles leaded to diverse biological activities such as antiproliferative activity, inhibition of IMPDH and Rho-kinase[5] (Fig. 1).

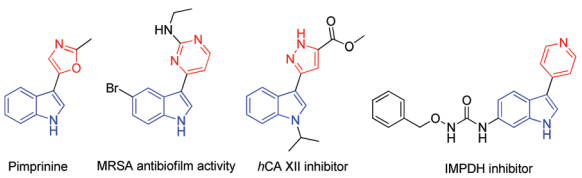
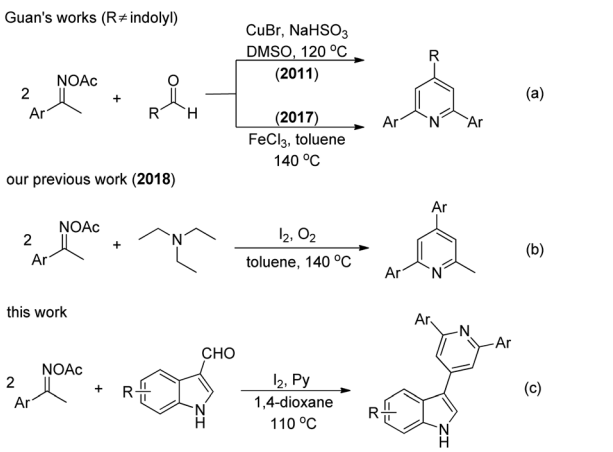


Fig. 1 Selected bioactive heteroaryl-indoles.

However, most of the reported methods for the synthesis of 3-(4-pyridyl)indoles have suffered from limited diversity of products and the requirement of multistep procedures.[5a,6] Herein, we sought to develop an efficient and complementary strategy to directly obtain a diverse range of 3-(4-pyridyl)indoles.

Recently, transition-metal catalysis has been demonstrated as a powerful tool for breaking the N–O bond of oximes to give iminyl radicals through single-electron reduction and formation of various multisubstituted heterocycles.[7] The strategy of using readily available ketoximes bearing α-protons to construct pyridines is appealing.[8] Guan and co-workers developed Cu- and Fe-catalyzed coupling reactions of ketoxime acetates and aldehydes, wherein both the nitrogen and α-carbon atoms were incorporated into the final pyridine rings (Scheme 1a).[9] However, the introduction of important indolyl into pyridine was not reported *via* this approach, which substantially limited the accessible substitution patterns of the resulting pyridines.



Scheme 1 Synthesis of pyridines from ketoximes and aldehydes.

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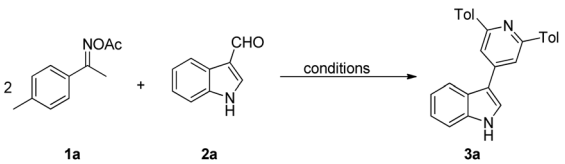
Very recently, our group disclosed a metal-free pyridine-forming reaction, in which two molecules of ketoxime acetates are condensed with triethylamine as the C1 source (Scheme 1b).[10] Inspired by the reaction, we now report an I_2-triggered effective formation of indole-linked pyridines through [3 + 2 + 1] annulation of aryl ketoxime acetates and 3-formylindoles (Scheme 1c). The method features simple and mild reaction conditions and enables the regioselective synthesis of a broad range of 3-(4-pyridyl)indoles.

Results and discussion

On the basis of our previous work,[10,11] initial experiments were carried out with 4-methylacetophenone oxime acetate (**1a**) and 1*H*-indole-3-carbaldehyde (**2a**) in the presence of I_2 and Et_3N in chlorobenzene at 130 °C (Table 1). To our delight, the desired 3-(4-pyridyl)indole (**3a**) was obtained in 65% yield (entry 1). Different solvents such as toluene, 1,4-dioxane, CH_3CN, NMP, THF, DCE, DMF, and DMSO were screened first (entries 2–9), revealing that 1,4-dioxane was superior to chlorobenzene for this transformation. Subsequently, investigation into the effect of the loading of I_2 disclosed that reducing the amount of I_2 was negative to the results (entries 11 and 12). By replacing I_2 with NIS or NH_4I, the desired product was isolated in 59% and 42% yields, respectively (entries 13 and 14). However, no desired product was obtained in the presence of KI, or TBAI (entries 16 and 17), and no reaction occurred in the absence of iodine reagents, indicating that I_2 is essential for the reaction (entry 18). Surprisingly, the yield of **3a** was improved to 82% when using pyridine instead of Et_3N as the electron donor (entry 23). Note that the reaction, when performed using Et_3N as an electron donor, was accompanied by homocoupling of **1a** to produce methyl-containing pyridine as a byproduct.[10] Moreover, this reaction could still proceed successfully when conducted at 110 °C (entry 25).

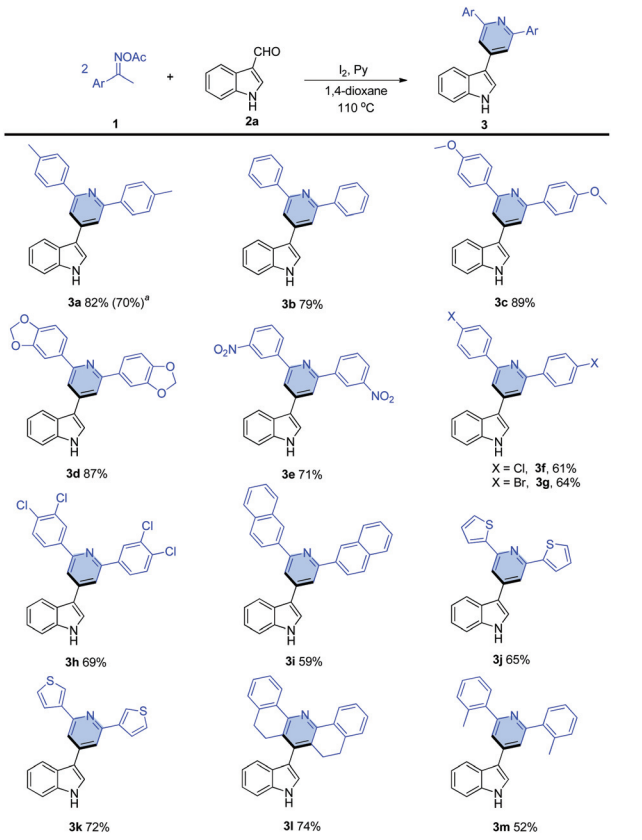
With the optimized reaction conditions in hand, the generality and scope of this facile and complementary [3 + 2 + 1] annulation for the synthesis of 3-(4-pyridyl)indoles was explored. The reaction demonstrated a wide substrate scope of the ketoxime acetates (Scheme 2). Aryl ketone *O*-acetyloximes bearing electron-neutral (*e.g.*, 4-Me, 4-H), electron-rich (*e.g.*, 4-OMe, 3,4-OCH_2O), and electron-deficient (*e.g.*, 3-NO_2) groups on the phenyl ring were converted to the corresponding products in good yields (71–89%; **3a–3e**). The reaction of **1a** could

Table 1 Optimization of reaction conditions[a]



Entry	[I]	Donor	Solvent	Yield[b] (%)
1	I_2	Et_3N	PhCl	65
2	I_2	Et_3N	Toluene	60
3	I_2	Et_3N	1,4-Dioxane	76
4	I_2	Et_3N	CH_3CN	72
5	I_2	Et_3N	NMP	n.d.
6	I_2	Et_3N	THF	69
7	I_2	Et_3N	DCE	23
8	I_2	Et_3N	DMF	48
9	I_2	Et_3N	DMSO	n.d.
10[c]	I_2	Et_3N	1,4-Dioxane	77
11[d]	I_2	Et_3N	1,4-Dioxane	63
12[e]	I_2	Et_3N	1,4-Dioxane	39
13	NIS	Et_3N	1,4-Dioxane	59
14	NH_4I	Et_3N	1,4-Dioxane	42
15	CuI	Et_3N	1,4-Dioxane	13
16	KI	Et_3N	1,4-Dioxane	n.r.
17	TBAI	Et_3N	1,4-Dioxane	Trace
18		Et_3N	1,4-Dioxane	n.r.
19	I_2	Et_2NH	1,4-Dioxane	68
20	I_2	DABCO	1,4-Dioxane	64
21	I_2	DBU	1,4-Dioxane	43
22	I_2	Quinoline	1,4-Dioxane	41
23	I_2	Py	1,4-Dioxane	82
24	I_2		1,4-Dioxane	23
25[f]	**I_2**	**Py**	1,4-Dioxane	**82**
26[g]	I_2	Py	1,4-Dioxane	73

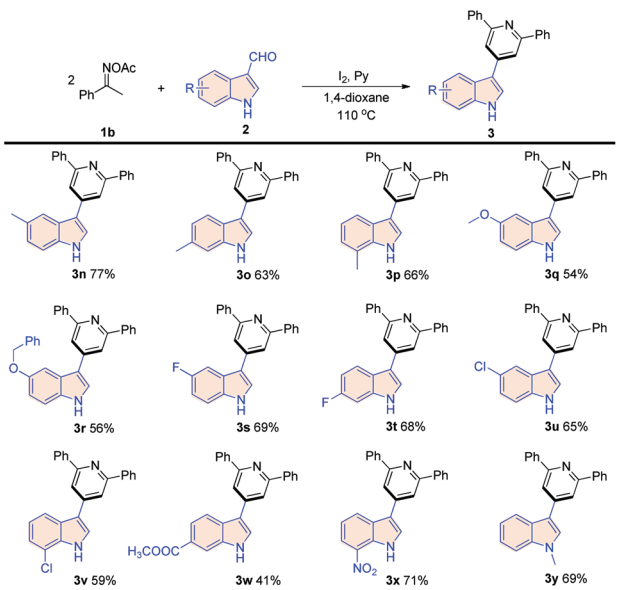
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), [I] (0.5 mmol), donor (0.5 mmol), solvent (2 mL), at 130 °C. [b] Isolated yield; n.d. = no desired product; n.r. = no reaction. [c] I_2 (0.75 mmol). [d] I_2 (0.25 mmol). [e] I_2 (0.1 mmol). [f] At 110 °C. [g] At 100 °C.



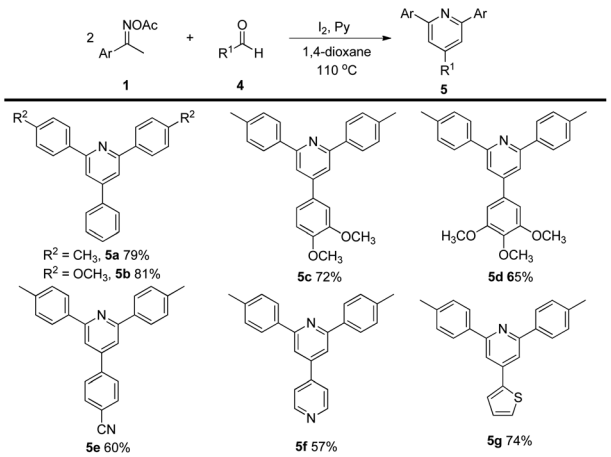
Scheme 2 Scope of ketoxime acetates. Reaction conditions: **1** (1.0 mmol), **2a** (0.5 mmol), I_2 (0.5 mmol) and pyridine (0.5 mmol) in 1,4-dioxane (2 mL) at 110 °C. Isolated yield. [a] Conducted on 10 mmol scale, isolated yield.

be scaled up to 10 mmol scale without a problem. In general, acetophenone oxime acetates with an electron-donating group showed higher reactivity than those with an electron-withdrawing group. Much to our satisfaction, the optimized conditions were mild enough to allow a broad range of halogenated (*e.g.*, 4-Cl, 4-Br, 3,4-Cl_2) substrates to be reacted (61–69%; **3f–3h**). Naphthalen-2-yl ethanone oxime acetate was also a suitable substrate for this reaction to provide the target product (**3i**) in 59% yield. Meanwhile, the optimized conditions could be applied to thiophene-2-yl methyl ketoxime acetate and thiophene-3-yl methyl ketoxime acetate, delivering the annulation products in 65% and 72% yields, respectively (**3j–3k**). It is noteworthy that ketoxime acetate derived from α-tetralone underwent the desired reaction to afford the symmetrical indolyl pyridine (**3l**) in good yield (74%). In addition, *ortho*-methyl substituted substrates reacted smoothly and resulted in the target pyridine (**3m**) in 52% yield. Unfortunately, no reaction occurred when alkyl ketoxime acetate 3,3-dimethylbutan-2-one oxime acetate was employed as the substrate.

The scope of this reaction was subsequently extended to the representative 3-formylindoles (Scheme 3). Indoles substituted with various useful substituents such as methyl, methoxy, benzyloxy, and halogens (F and Cl) at the C5, C6, and C7 positions of the aromatic ring showed good reactivity with acetophenone oxime acetate **1b**, leading to the corresponding pyridines **3n–3v** in 54–77% yields. In the case of a 6-methyl substituted substrate, the structure of the desired product (**3o**) was unambiguously confirmed by single-crystal X-ray diffraction (CCDC 1844843†). These results indicated that the position of the substituents on the aromatic ring of the indoles had little effect on the yields of the products. Notably, the strong electron-withdrawing groups 6-$COOCH_3$ and 7-NO_2 could be accessed through this route to generate the desired products (41–71%; **3w–3x**). In addition, the protocol was also effective with an *N*-protected indole, furnishing the expected product (**3y**) in 69% yield.



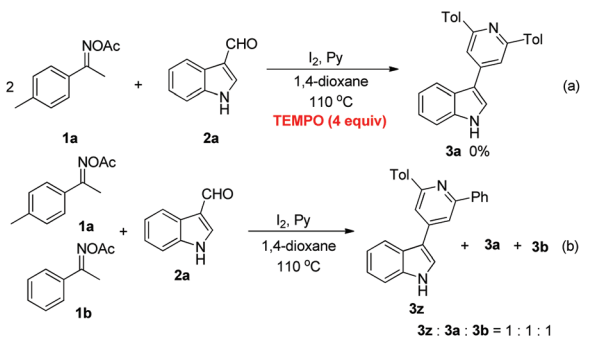
Scheme 3 Scope of 3-formylindoles. Reaction conditions: **1b** (1.0 mmol), **2** (0.5 mmol), I_2 (0.5 mmol) and pyridine (0.5 mmol) in 1,4-dioxane (2 mL) at 110 °C. Isolated yield.



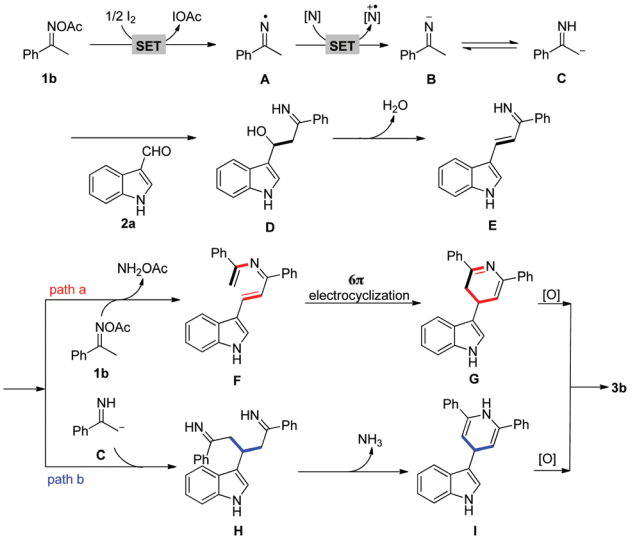
Scheme 4 Scope of aldehydes and ketoxime acetates. Reaction conditions: **1** (1.0 mmol), **4** (0.5 mmol), I_2 (0.5 mmol) and pyridine (0.5 mmol) in 1,4-dioxane (2 mL) at 110 °C. Isolated yield.

Next, we were naturally interested in the general scope of the present reaction system using other types of aldehydes. As expected, several (het)aryl aldehydes (**4**) and ketoxime acetates were subjected to the procedure, and the corresponding pyridines (**5**) were obtained in 57–81% yields (Scheme 4). However, no reaction occurred when isobutyraldehyde was used as the substrate.

To understand the role of molecular iodine in this process, an inhibition experiment for the radical was carried out. As expected, when TEMPO was introduced into the reaction system, the formation of **3a** was completely suppressed (Scheme 5a). This result indicated that molecular iodine was capable of reducing the N–O bond of the ketoxime acetates to generate iminyl radicals *via* a single-electron transfer (SET) process. Finally, we investigated the cross reaction between two representative substrates 4-methylacetophenone oxime acetate (**1a**) and acetophenone oxime acetate (**1b**) under standard conditions. Fortunately, all the products were successfully



Scheme 5 Control experiments.



Scheme 6 Proposed mechanism.

identified by HRMS analysis of the crude reaction extract, and the ratio of **3a**, **3b** and **3z** was further calculated using ^{1}H NMR analysis (Scheme 5b).

On the basis of the above results and previous reports,[12] a possible mechanism has been proposed using acetophenone oxime acetate (**1b**) and 3-formylindole (**2a**) as examples (Scheme 6). Initially, the single-electron reduction of the N–O bond of ketoxime acetate **1b** with molecular iodine produced the iminyl radical intermediate **A** and hypervalent iodine species (I^+).[10] Subsequently, the highly active iminyl radical **A** was reductively quenched by an electron donor to generate the corresponding anion **B** which could isomerize to a strong nucleophile α-carbanion **C**.[11] Then, nucleophilic addition of **C** to the formyl of **2a** and dehydration would afford the imine intermediate **E**. Next, condensation of the intermediate **E** with a second ketoxime acetate **1b** gave an aza-hexa-1,3,5-triene intermediate **F**. Finally, the intermediate **F** underwent sequential thermal electrocyclization and rapid oxidative aromatization reactions to provide the desired product **3b**. Another possible pathway involves Michael addition of species **C** to the α,β-unsaturated imine **E** followed by intramolecular imine/enamine condensation and oxidative aromatization.

Conclusions

In summary, we have developed a facile and efficient I_2-triggered [3 + 2 + 1] annulation of aryl ketoxime acetates and 3-formylindoles to produce diverse 3-(4-pyridyl)indoles that are challenging to prepare by traditional methods. With the easily accessible starting materials, operational simplicity, functional group compatibility and high regioselectivity, the present method not only effectively complements other existing and emerging methods for pyridine synthesis but also enables the construction of a diverse array of indole-linked pyridines. Significantly, this work provides an example for applying molecular iodine as a promising alternative to transition metal catalysts for single-electron reduction coupling reactions. Further mechanistic investigations and exploration of new transformations of oxime acetates with I_2 are underway and will be reported in due course.

Experimental

General information

All reagents were commercially available and used without further purification. TLC analysis was performed using precoated glass plates. Column chromatography was performed using silica gel (200–300 mesh). ^{1}H spectra were recorded in DMSO-d_6/$CDCl_3$ on 400 MHz NMR spectrometers and resonances (δ) are given in parts per million relative to tetramethylsilane. ^{13}C spectra were recorded in DMSO-d_6/$CDCl_3$ on 100 MHz NMR spectrometers and resonances (δ) are given in ppm. HRMS were obtained on a Bruker 7-tesla FT-ICR MS equipped with an electrospray source. The X-ray crystal-structure determinations of **3o** were obtained on a Bruker SMART APEX CCD system. Melting points were determined using XT-4 apparatus and not corrected.

General procedure for the synthesis of 3

A mixture of ketoxime acetates **1** (1.0 mmol), 1*H*-indole-3-carbaldehydes **2** (0.5 mmol), iodine (0.5 mmol), and pyridine (0.5 mmol) in 1,4-dioxane (2 mL) was stirred at 110 °C. After disappearance of the reactant (monitored by TLC), 50 mL of water was added to the mixture, and then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the product **3**.

General procedure for the synthesis of 5

A mixture of ketoxime acetates **1** (1.0 mmol), aldehydes **4** (0.5 mmol), iodine (0.5 mmol), and pyridine (0.5 mmol) in 1,4-dioxane (2 mL) was stirred at 110 °C. After disappearance of the reactant (monitored by TLC), 50 mL of water was added to the mixture, and then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the product **5**.

3-(2,6-Di-*p*-tolylpyridin-4-yl)-1*H*-indole (3a). Yield 82% (153.3 mg); white solid; mp 231–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.79 (s, 1H), 8.29 (d, J = 2.8 Hz, 1H), 8.21 (d, J = 8.0 Hz, 4H), 8.15 (s, 2H), 8.13–8.08 (m, 1H), 7.58–7.50 (m, 1H), 7.36 (d, J = 8.0 Hz, 4H), 7.26–7.22 (m, 2H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.1, 145.4, 138.4, 137.2, 136.5, 129.3, 126.7, 126.5, 124.8, 121.9, 120.5, 119.3, 115.0, 113.4, 112.3, 20.9; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{27}H_{22}N_2Na$: 397.1675; found: 397.1676.

3-(2,6-Diphenylpyridin-4-yl)-1*H*-indole (3b). Yield 79% (136.7 mg); white solid; mp 225–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.81 (s, 1H), 8.32 (d, J = 7.6 Hz, 5H), 8.22 (s, 2H), 8.14 (d, J = 4.4 Hz, 1H), 7.64–7.53 (m, 5H), 7.52–7.45 (m, 2H), 7.29–7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.3, 145.6, 139.2, 137.2, 129.0, 128.7, 126.8, 126.6, 124.8, 121.9, 120.6, 119.4, 115.7, 113.3, 112.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{25}H_{19}N_2$: 347.1543; found: 347.1545.

3-(2,6-Bis(4-methoxyphenyl)pyridin-4-yl)-1*H*-indole (3c). Yield 89% (180.6 mg); white solid; mp 224–227 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.78 (s, 1H), 8.27 (d, J = 7.6 Hz, 5H), 8.16–8.02 (m, 3H), 7.56 (d, J = 5.6 Hz, 1H), 7.25 (d, J = 3.6 Hz, 2H), 7.11 (d, J = 8.4 Hz, 4H), 3.83 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.1, 155.9, 145.3, 137.2, 131.9, 128.1, 126.4, 124.9, 121.9, 120.5, 119.4, 114.2, 114.1, 113.6, 112.4, 55.2; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{27}H_{23}N_2O_2$: 407.1754; found: 407.1757.

3-(2,6-Bis(benzo[*d*][1,3]dioxol-5-yl)pyridin-4-yl)-1*H*-indole (3d). Yield 87% (188.8 mg); yellow solid; mp 210–214 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.76 (s, 1H), 8.28 (s, 1H), 8.10 (s, 1H), 8.07 (s, 2H), 7.87 (s, 3H), 8.84 (s, 1H), 7.53 (d, J = 4.4 Hz, 1H), 7.23 (d, J = 2.8 Hz, 2H), 7.08 (d, J = 7.6 Hz, 2H), 6.12 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 155.5, 148.1, 147.9, 145.4, 137.2, 133.7, 126.5, 124.8, 121.9, 120.9, 120.5, 119.5, 114.7, 113.4, 112.3, 108.4, 107.0, 101.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{27}H_{19}N_2O_4$: 435.1339; found: 435.1338.

3-(2,6-Bis(3-nitrophenyl)pyridin-4-yl)-1*H*-indole (3e). Yield 71% (154.7 mg); brown solid; mp 258–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.84 (s, 1H), 9.03 (s, 2H), 8.70 (d, J = 7.6 Hz, 2H), 8.36 (d, J = 2.8 Hz, 1H), 8.34 (s, 2H), 8.31 (d, J = 2.0 Hz, 1H), 8.29 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 7.2 Hz, 1H), 7.82 (t, J = 8.0 Hz, 2H), 7.55–7.50 (m, 1H), 7.28–7.18 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 154.0, 148.4, 146.4, 140.4, 137.2, 133.1, 130.3, 127.4, 124.6, 123.7, 122.0, 121.2, 120.6, 119.5, 116.9, 112.7, 112.3; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{25}H_{16}N_4NaO_4$: 459.1064; found: 459.1069.

3-(2,6-Bis(4-chlorophenyl)pyridin-4-yl)-1*H*-indole (3f). Yield 61% (126.5 mg); brown solid; mp 182–185 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.89 (s, 1H), 8.43 (s, 2H), 8.40 (s, 3H), 8.31 (s, 2H), 8.23–8.18 (m, 1H), 7.68 (d, J = 8.4 Hz, 4H), 7.64–7.59 (m, 1H), 7.35–7.28 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 155.0, 145.9, 137.8, 137.2, 133.9, 128.7, 128.6, 126.9, 124.7, 122.0, 120.6, 119.4, 115.8, 113.0, 112.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{25}H_{17}Cl_2N_2$: 415.0763; found: 415.0764.

3-(2,6-Bis(4-bromophenyl)pyridin-4-yl)-1*H*-indole (3g). Yield 64% (161.3 mg); brown solid; mp 223–225 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.81 (s, 1H), 8.31 (d, J = 2.8 Hz, 1H), 8.28–8.20 (m, 6H), 8.14–8.09 (m, 1H), 7.73 (d, J = 8.4 Hz, 4H), 7.56–7.51 (m, 1H), 7.28–7.19 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 155.1, 145.9, 138.2, 137.2, 131.6, 128.9, 126.9, 124.7, 122.7, 122.0, 120.6, 119.4, 115.8, 113.0, 112.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{25}H_{17}Br_2N_2$: 502.9753; found: 502.9758.

3-(2,6-Bis(3,4-dichlorophenyl)pyridin-4-yl)-1*H*-indole (3h). Yield 69% (167 mg); brown solid; mp 179–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.81 (s, 1H), 8.43 (s, 2H), 8.30 (d, J = 4.4 Hz, 1H), 8.24–8.15 (m, 4H), 8.08 (d, J = 7.2 Hz, 1H), 7.74–7.67 (m, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.28–7.17 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 153.6, 146.1, 139.3, 137.2, 131.7, 131.6, 130.7, 128.4, 127.2, 126.8, 124.6, 121.9, 120.5, 119.5, 116.3, 112.8, 112.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{25}H_{15}Cl_4N_2$: 482.9984; found: 482.9988.

3-(2,6-Di(naphthalen-2-yl)pyridin-4-yl)-1*H*-indole (3i). Yield 59% (131.5 mg); yellow solid; mp 219–221 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.86 (s, 1H), 8.93 (s, 2H), 8.57 (d, J = 8.4 Hz, 2H), 8.43 (s, 2H), 8.40 (d, J = 2.4 Hz, 1H), 8.26–8.21 (m, 1H), 8.17 (d, J = 7.2 Hz, 2H), 8.12 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 6.8 Hz, 2H), 7.63–7.55 (m, 5H), 7.32–7.25 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.3, 145.7, 137.3, 136.7, 133.3, 133.2, 128.7, 128.2, 127.6, 126.7, 126.6, 126.4, 126.1, 124.8, 122.0, 120.6, 119.5, 116.2, 113.4, 112.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{33}H_{23}N_2$: 447.1856; found: 447.1859.

3-(2,6-Di(thiophen-2-yl)pyridin-4-yl)-1*H*-indole (3j). Yield 65% (116.3 mg); brown solid; mp 165–169 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.82 (s, 1H), 8.28 (s, 1H), 8.19–8.05 (m, 3H), 7.98 (s, 2H), 7.66 (d, J = 4.4 Hz, 2H), 7.55 (d, J = 5.2 Hz, 1H), 7.29–7.10 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 151.8, 145.4, 144.6, 137.2, 128.4, 128.3, 126.8, 125.4, 124.7, 122.0, 120.6, 119.5, 113.5, 112.7, 112.4; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{14}N_2NaS_2$: 381.0491; found: 381.0492.

3-(2,6-Di(thiophen-3-yl)pyridin-4-yl)-1*H*-indole (3k). Yield 72% (128.9 mg); brown solid; mp 182–186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.78 (s, 1H), 8.38 (d, J = 2.0 Hz, 2H), 8.25 (d, J = 2.8 Hz, 1H), 8.16–8.12 (m, 1H), 8.08 (s, 2H), 7.97 (d, J = 5.2 Hz, 2H), 7.70–7.66 (m, 2H), 7.57–7.52 (m, 1H), 7.29–7.19 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 152.8, 145.3, 142.4, 137.2, 126.8, 126.7, 126.5, 124.8, 124.2, 121.9, 120.5, 119.6, 115.1, 113.1, 112.3; HRMS (ESI): m/z [M − H]$^-$ calcd for $C_{21}H_{13}N_2S_2$: 357.0526; found: 357.0521.

7-(1*H*-Indol-3-yl)-5,6,8,9-tetrahydrodibenzo[*c*,*h*]acridine (3l). Yield 74% (147.3 mg); brown solid; mp 133–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.52 (s, 1H), 8.47 (d, J = 7.2 Hz, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 7.34–7.28 (m, 2H), 7.23 (d, J = 7.2 Hz, 2H), 7.20–7.13 (m, 2H), 7.00 (t, J = 7.2 Hz, 1H), 2.86–2.73 (m, 4H), 2.73–2.66 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 149.1, 141.3, 137.8, 136.1, 134.9, 130.5, 128.6, 127.6, 126.8, 126.5, 125.0, 124.7, 121.4, 119.4, 118.9, 111.9, 110.1, 27.5, 25.6; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{29}H_{23}N_2$: 399.1856; found: 399.1855.

3-(2,6-Di-*o*-tolylpyridin-4-yl)-1*H*-indole (3m). Yield 52% (97.2 mg); white solid; mp 270–273 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.74 (s, 1H), 8.17 (d, J = 2.8 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.76 (s, 2H), 7.56–7.52 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.36–7.29 (m, 6H), 7.23–7.14 (m, 2H), 2.45 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 159.0, 144.3, 140.7, 137.2, 135.4, 130.6, 129.7, 128.1, 126.5, 125.9, 124.7, 121.9,

120.5, 119.1, 118.7, 112.9, 112.4, 20.4; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{23}N_2$: 375.1856; found: 375.1856.

3-(2,6-Diphenylpyridin-4-yl)-5-methyl-1*H*-indole (3n). Yield 77% (138.6 mg); brown solid; mp 187–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.66 (s, 1H), 8.30 (d, J = 7.6 Hz, 4H), 8.22 (d, J = 2.8 Hz, 1H), 8.17 (s, 2H), 7.85 (s, 1H), 7.57 (t, J = 7.6 Hz, 4H), 7.49 (t, J = 7.2 Hz, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.2, 145.8, 139.3, 135.5, 129.2, 129.0, 128.8, 126.8, 126.6, 125.0, 123.6, 118.8, 115.7, 112.8, 112.1, 21.6; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{20}N_2Na$: 383.1519; found: 383.1518.

3-(2,6-Diphenylpyridin-4-yl)-6-methyl-1*H*-indole (3o). Yield 63% (113.4 mg); brown solid; mp 157–160 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.64 (s, 1H), 8.31 (d, J = 7.2 Hz, 4H), 8.23 (d, J = 2.4 Hz, 1H), 8.19 (s, 2H), 7.99 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.6 Hz, 4H), 7.48 (t, J = 7.2 Hz, 2H), 7.32 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.2, 145.7, 139.3, 137.7, 131.1, 129.0, 128.7, 126.8, 126.0, 122.7, 122.3, 119.1, 115.5, 113.1, 112.1, 21.3; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{20}N_2Na$: 383.1519; found: 383.1520.

3-(2,6-Diphenylpyridin-4-yl)-7-methyl-1*H*-indole (3p). Yield 66% (118.8 mg); brown solid; mp 192–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.34–8.29 (m, 5H), 8.21 (s, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.4 Hz, 4H), 7.49 (t, J = 7.2 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 6.8 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.2, 145.7, 139.2, 136.7, 129.0, 128.7, 126.8, 126.4, 124.5, 122.5, 121.6, 120.8, 116.9, 115.6, 113.7, 16.9; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{21}N_2$: 361.1699; found: 361.1696.

3-(2,6-Diphenylpyridin-4-yl)-5-methoxy-1*H*-indole (3q). Yield 54% (101.5 mg); brown solid; mp 169–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.33–8.28 (m, 4H), 8.22 (d, J = 2.4 Hz, 1H), 8.16 (s, 2H), 7.56 (t, J = 7.4 Hz, 4H), 7.51–7.46 (m, 3H), 7.43 (d, J = 8.8 Hz, 1H), 6.94–6.87 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.2, 154.4, 145.7, 139.2, 132.3, 129.0, 128.8, 127.1, 126.8, 125.2, 115.5, 113.1, 113.0, 111.6, 101.4, 55.4; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{20}N_2NaO$: 399.1468; found: 399.1468.

5-(Benzyloxy)-3-(2,6-diphenylpyridin-4-yl)-1*H*-indole (3r). Yield 56% (126.5 mg); brown solid; mp 154–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.69 (s, 1H), 8.29 (d, J = 7.2 Hz, 4H), 8.24 (d, J = 2.8 Hz, 1H), 8.12 (s, 2H), 7.61–7.55 (m, 5H), 7.52–7.44 (m, 5H), 7.37–7.28 (m, 3H), 7.04–6.97 (m, 1H), 5.26 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.3, 153.4, 145.7, 139.3, 137.9, 132.4, 129.0, 128.7, 128.4, 127.6, 127.3, 127.2, 126.8, 125.1, 115.5, 113.1(3), 113.0(9), 112.7, 102.9, 69.8; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{25}N_2O$: 453.1961; found: 453.1962.

3-(2,6-Diphenylpyridin-4-yl)-5-fluoro-1*H*-indole (3s). Yield 69% (125.6 mg); yellow solid; mp 232–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.91 (s, 1H), 8.37 (s, 1H), 8.33 (d, J = 6.8 Hz, 4H), 8.16 (s, 2H), 7.83 (d, J = 10.0 Hz, 1H), 7.56 (d, J = 6.4 Hz, 5H), 7.49 (d, J = 6.4 Hz, 2H), 7.10 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 159.0, 156.7, 156.3, 145.1, 139.2, 133.9, 129.0, 128.7, 128.5, 126.9, 125.0, 124.9, 115.6, 113.7, 113.6, 113.4, 113.3, 110.3, 110.0, 104.5, 104.2; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{17}FN_2Na$: 387.1268; found: 387.1271.

3-(2,6-Diphenylpyridin-4-yl)-6-fluoro-1*H*-indole (3t). Yield 68% (123.7 mg); yellow solid; mp 223–226 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.87 (s, 1H), 8.37–8.28 (m, 5H), 8.20 (s, 2H), 8.16–8.09 (m, 1H), 7.57 (t, J = 7.6 Hz, 4H), 7.49 (t, J = 7.2 Hz, 2H), 7.38–7.32 (m, 1H), 7.14–7.06 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.2, 157.8, 156.3, 145.1, 139.2, 137.3, 137.2, 129.0, 128.7, 126.9, 121.7, 120.7, 120.6, 115.7, 113.6, 109.0, 108.8, 98.4, 98.2; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{17}FN_2Na$: 387.1268; found: 387.1270.

5-Chloro-3-(2,6-diphenylpyridin-4-yl)-1*H*-indole (3u). Yield 65% (123.8 mg); yellow solid; mp 219–221 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.98 (s, 1H), 8.34 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 8.0 Hz, 4H), 8.14 (s, 2H), 8.04 (s, 1H), 7.56 (t, J = 7.6 Hz, 5H), 7.48 (t, J = 7.2 Hz, 2H), 7.28–7.20 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.4, 144.9, 139.2, 135.7, 129.1, 128.7, 128.2, 126.9, 125.8, 125.1, 122.0, 118.4, 115.9, 113.9, 113.3; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{17}ClN_2Na$: 403.0972; found: 403.0976.

7-Chloro-3-(2,6-diphenylpyridin-4-yl)-1*H*-indole (3v). Yield 59% (112.4 mg); brown solid; mp 168–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.15 (s, 1H), 8.39 (d, J = 2.8 Hz, 1H), 8.33 (d, J = 7.2 Hz, 4H), 8.22 (s, 2H), 8.10 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.4 Hz, 4H), 7.48 (t, J = 7.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.4, 144.9, 139.1, 134.0, 129.1, 128.7, 127.8, 126.9, 126.7, 121.5(4), 121.5(1), 118.5, 116.7, 116.0, 114.6; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{18}ClN_2$: 381.1153; found: 381.1152.

Methyl 3-(2,6-diphenylpyridin-4-yl)-1*H*-indole-6-carboxylate (3w). Yield 41% (82.8 mg); brown solid; mp 240–243 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.19 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.32 (d, J = 7.6 Hz, 4H), 8.23–8.17 (m, 4H), 7.85–7.81 (m, 1H), 7.57 (t, J = 7.4 Hz, 4H), 7.49 (t, J = 7.2 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 167.0, 156.4, 144.8, 139.1, 136.5, 130.2, 129.1, 128.8, 128.2, 126.9, 122.9, 121.1, 119.4, 115.9, 114.1, 113.9, 52.0; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2O_2$: 405.1598; found: 405.1596.

3-(2,6-Diphenylpyridin-4-yl)-7-nitro-1*H*-indole (3x). Yield 71% (138.8 mg); red solid; mp 209–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.47 (s, 1H), 8.58 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 2.8 Hz, 1H), 8.36–8.30 (m, 4H), 8.25–8.18 (m, 3H), 7.56 (t, J = 7.4 Hz, 4H), 7.48 (t, J = 7.2 Hz, 2H), 7.42 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 156.4, 143.9, 139.0, 133.0, 129.4, 129.3, 129.1, 129.0, 128.7, 128.1, 127.0, 120.2, 119.3, 116.6, 115.3; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{18}N_3O_2$: 392.1394; found: 392.1394.

3-(2,6-Diphenylpyridin-4-yl)-1-methyl-1*H*-indole (3y). Yield 69% (124.2 mg); yellow solid; mp 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.32 (d, J = 7.6 Hz, 4H), 8.15 (d, J = 7.6 Hz, 1H), 8.02 (s, 2H), 7.63 (t, J = 7.4 Hz, 4H), 7.58–7.52 (m,

2H), 7.47–7.34 (m, 4H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.1, 144.7, 139.8, 137.6, 128.7, 128.6, 128.0, 127.0, 125.6, 122.3, 120.6, 119.7, 116.5, 114.1, 109.9, 32.8; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{21}N_2$: 361.1699; found: 361.1701.

4-Phenyl-2,6-di-*p*-tolylpyridine (5a). Yield 79% (132.3 mg); white solid; mp 150–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (d, J = 8.0 Hz, 4H), 7.83 (s, 2H), 7.75–7.71 (m, 2H), 7.51 (t, J = 7.4 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H), 7.31 (d, J = 8.0 Hz, 4H), 2.42 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.3, 150.0, 139.2, 139.0, 136.8, 129.4, 129.0, 128.8, 127.2, 127.0, 116.5, 21.3; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{25}H_{21}NNa$: 358.1566; found: 358.1566.

2,6-Bis(4-methoxyphenyl)-4-phenylpyridine (5b). Yield 81% (148.6 mg); white solid; mp 158–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16 (d, J = 8.8 Hz, 4H), 7.78 (s, 2H), 7.76–7.71 (m, 2H), 7.53 (t, J = 7.2 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 8.8 Hz, 4H), 3.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.5, 156.9, 150.2, 139.2, 132.1, 129.1, 128.9, 128.4, 127.2, 115.8, 114.0, 55.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{22}NO_2$: 368.1645; found: 368.1648.

4-(3,4-Dimethoxyphenyl)-2,6-di-*p*-tolylpyridine (5c). Yield 72% (142.2 mg); pink solid; mp 93–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.09 (d, J = 8.0 Hz, 4H), 7.78 (s, 2H), 7.32 (d, J = 8.0 Hz, 5H), 7.23 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 3.99 (s, 3H), 3.96 (s, 3H), 2.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.3, 149.8(3), 149.7(9), 149.4, 138.9, 136.9, 132.0, 129.4, 127.0, 119.8, 116.2, 111.5, 110.1, 56.1, 56.0, 21.3; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{27}H_{25}NNaO_2$: 418.1778; found: 418.1780.

2,6-Di-*p*-tolyl-4-(3,4,5-trimethoxyphenyl)pyridine (5d). Yield 65% (138.1 mg); violet solid; mp 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.09 (d, J = 8.0 Hz, 4H), 7.77 (s, 2H), 7.32 (d, J = 8.0 Hz, 4H), 6.90 (s, 2H), 3.97 (s, 6H), 3.93 (s, 3H), 2.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.4, 153.7, 150.3, 139.1, 138.8, 136.8, 135.2, 129.4, 127.0, 116.6, 104.5, 61.0, 56.4, 21.3; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{28}H_{27}NNaO_3$: 448.1883; found: 448.1881.

4-(2,6-Di-*p*-tolylpyridin-4-yl)benzonitrile (5e). Yield 60% (108 mg); white solid; mp 211–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.08 (d, J = 8.0 Hz, 4H), 7.81 (s, 4H), 7.78 (s, 2H), 7.32 (d, J = 8.0 Hz, 4H), 2.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.8, 148.0, 143.7, 139.4, 136.3, 132.8, 129.5, 127.9, 126.9, 118.5, 116.2, 112.5, 21.3; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{26}H_{20}N_2Na$: 383.1519; found: 383.1517.

2,6-Di-*p*-tolyl-4,4′-bipyridine (5f). Yield 57% (95.7 mg); black solid; mp 190–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.78 (d, J = 3.6 Hz, 2H), 8.10 (d, J = 8.4 Hz, 4H), 7.83 (s, 2H), 7.65 (d, J = 5.6 Hz, 2H), 7.33 (d, J = 8.0 Hz, 4H), 2.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.9, 150.4, 147.2, 146.9, 139.4, 136.3, 129.5, 127.0, 121.7, 116.0, 21.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{21}N_2$: 337.1699; found: 337.1701.

4-(Thiophen-2-yl)-2,6-di-*p*-tolylpyridine (5g). Yield 74% (126.2 mg); pink solid; mp 163–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (d, J = 8.4 Hz, 4H), 7.80 (s, 2H), 7.58 (dd, J = 3.6, 1.2 Hz, 1H), 7.40 (dd, J = 5.2, 0.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 4H), 7.16–7.13 (m, 1H), 2.42 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.5, 142.8, 142.1, 139.0, 136.6, 129.4, 128.3, 126.9, 126.7, 125.1, 114.7, 21.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{20}NS$: 342.1311; found: 342.1314.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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