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Hydroxymethylation of quinolines *via* iron promoted oxidative C–H functionalization: synthesis of arsindoline-A and its derivatives†

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Herein, we report a mild and efficient hydroxymethylation of quinolines *via* an iron promoted cross-dehydrogenative coupling reaction under external acid free conditions. Various hydroxyalkyl substituted quinolines were achieved in excellent yields with well tolerated functional groups. Importantly, a few of the hydroxylmethylated quinolines were further transformed into respective aldehydes, and were successfully utilized for the synthesis of alkaloid arsindoline-A and its derivatives.

Introduction

Methanol is one of the most important raw materials in both organic chemistry and drug discovery. It is also used as a common solvent and reagent in synthetic organic chemistry and is a sustainable feedstock for value-added chemicals, pharmaceuticals and materials.[1] In addition, it has been successfully used as a C_1 source for various organic transformations such as methylation, methoxylation, formylation and hydroxymethylation.[2] Among these transformations, hydroxymethylation of azaarenes has attracted remarkable interest from medicinal chemists due to the common occurrence of hydroxymethyl(alkyl)units in various important pharmaceutically active compounds (Fig. 1).[3–5] Along similar lines, *N*-heterocycles are also key scaffolds in several biologically active natural products and pharmaceutical agents.[6] Owing to the significance of these units, the hydroxymethylation of *N*-heteroarenes has gained much attention in modern synthetic chemistry.

Despite the significance of hydroxymethylated heteroarenes, only a few reports on their synthesis have been documented so far. For example, in 1971, Minisci and co-workers proposed a method for the introduction of the hydroxymethyl group into 4-methylquinoline by employing $(NH_4)_2S_2O_8$ as an oxidant and H_2SO_4 as an additive under thermal conditions.[7] Interestingly, Togo *et al.* reported a metal free hydroxymethylation of quinolines by using $Na_2S_2O_8$ in a mixture of methanol and water at 70 °C.[8] Later, Wang's group described a silver promoted hydroxyalkylation of quinolines by utilizing Selectfluor as an oxidant under reflux conditions.[9] Recently, Lei *et al.* demonstrated a visible-light-induced protocol for the synthesis of hydroxy alkylated quinoline derivatives in the presence of Selectfluor and TFA as an additive.[10] However, these methods suffer from the requirement of relatively expensive reagents/catalysts and the need for longer reaction times. In addition, the Minisci-type of transformation always requires external acid additives and extensive high energetic conditions. Hence, eco-friendly/green-chemistry protocols for the development of hydroxyalkylated heterocycles using inexpensive, environmentally benign and easy handling reagents would be highly desirable.

On the other hand, iron-catalyzed/-mediated oxidative C–H bond functionalization is a powerful strategy for the construction of C–C and C-hetero atom bonds.[11] This promising strategy is more economic and doesn't require pre-functionalized starting materials. In continuation of our efforts towards the development of iron-catalyzed/-mediated organic transformations,[12] herein, we wish to report an efficient iron mediated rapid hydroxyalkylation of heteroarenes, in which H_2O_2 is used as a cheap and mild oxidant under external acid free con-

Fig. 1 Examples of bioactive compounds possessing hydroxyalkyl groups.

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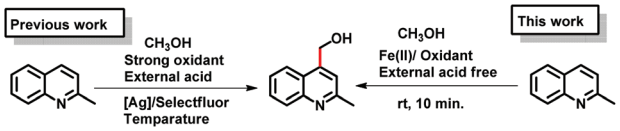


Scheme 1 Hydroxy alkylation of heteroarenes.

ditions. Notably, this reaction was complete within 10 minutes at room temperature (Scheme 1).

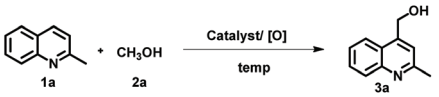
Results and discussion

To find the optimum reaction conditions, we initiated our investigation with 2-methylquinoline (**1a**) as the model substrate in excess quantity of methanol (**2a**), which acted as both as a hydroxymethylating agent and solvent. First, we performed the reaction of **1a** and excess amount of **2a** in the presence of $Fe(ClO_4)_2{\cdot}xH_2O$ (1.0 equiv.) and TBHP (70% in water, 2.0 equiv.) as an oxidant at room temperature for 10 min, giving the desired product (2-methylquinolin-4-yl)methanol (**3a**) in 66% yield (Table 1, entry 1), whereas the use of H_2O_2 (50% in water) instead of TBHP increased the yield of the product (**3a**) up to 78% (Table 1, entry 2). Encouraged by these results, a series of iron salts, namely, $FeCl_2$, $FeBr_2$, $FeSO_4$ and $Fe(acac)_2$, were examined for this reaction. But they were found to be ineffective for this transformation, and provided very low yields (Table 1, entries 3–6). Furthermore Fe^{III} catalysts resulted in low yields (Table 1, entries 7–9). Among all the tested iron catalysts, $Fe(ClO_4)_2{\cdot}xH_2O$ showed the best results for this transformation. Other metal salts like $CuCl_2$, $Cu(ClO_4)_2$, $PdCl_2$ and $Co(ClO_4)_2$ proved to be inadequate for this protocol (Table 1, entries 10–13). Meanwhile, the reaction could not be induced in the presence of other oxidants, for instance DTBP, DCP, $PhI(OAc)_2$ and O_2 (Table 1, entries 14–17). Furthermore, the absence of either $Fe(ClO_4)_2{\cdot}xH_2O$ or H_2O_2 did not produce the desired product (Table 1, entries 18 and 19).

These results explain that both $Fe(ClO_4)_2{\cdot}xH_2O$ and H_2O_2 are necessary for this transformation. In addition, the reaction under reflux conditions resulted in 59% yield (Table 1, entry 20). Although the reaction time was prolonged up to 12 h, a satisfactory increment in the yield was not observed (Table 1, entry 21). Based on the optimization studies, we conclude that 1.0 equivalent of $Fe(ClO_4)_2{\cdot}xH_2O$ and 2.0 equivalents of H_2O_2 (50% in water) at room temperature are the optimal conditions for this transformation.

With these optimal reaction conditions in hand, the scope of the quinolines was investigated and the results are shown in Table 2. Quinolines bearing electron-donating (–Me and –OMe) and electron-withdrawing (–F, –Cl, and –Br) groups were well tolerated in the reaction and afforded the corresponding products (**3a–3n**) in good yields. Electron-withdrawing groups on 2-methyl quinolines (**1e–1g**) gave **3e–3g** in slightly higher yields than electron-donating groups (**3a–3d**). Notably,

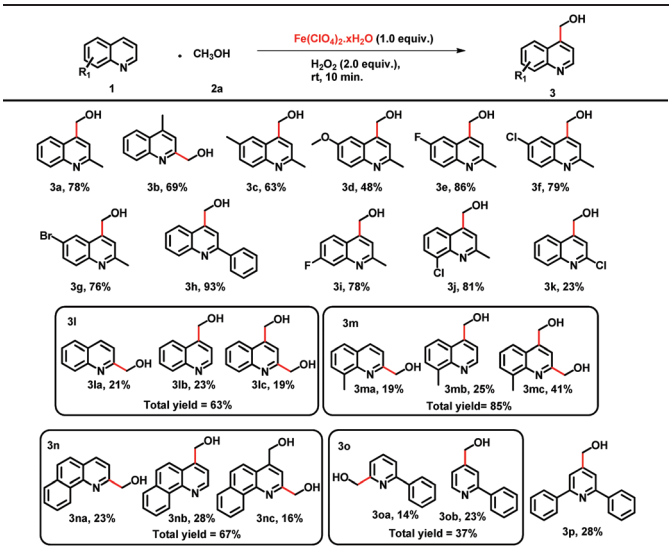
Table 1 Screening of the reaction conditions for the hydroxyl methylation of 2-methyl quinoline[a]



Entry	Catalyst	Oxidant	Yield[b] (%)
1	$Fe(ClO_4)_2{\cdot}xH_2O$	TBHP	66
2	**$Fe(ClO_4)_2{\cdot}xH_2O$**	**H_2O_2**	**78**
3	$FeCl_2$	H_2O_2	33
4	$FeBr_2$	H_2O_2	28
5	$FeSO_4$	H_2O_2	Trace
6	$Fe(acac)_2$	H_2O_2	Trace
7	$FeCl_3$	H_2O_2	13
8	$Fe(ClO_4)_3$	H_2O_2	18
9	$Fe(acac)_3$	H_2O_2	Trace
10	$CuCl_2$	H_2O_2	0[c]
11	$Cu(ClO_4)_2$	H_2O_2	0
12	$PdCl_2$	H_2O_2	0
13	$Co(ClO_4)_2$	H_2O_2	0
14	$Fe(ClO_4)_2{\cdot}xH_2O$	DTBP	0
15	$Fe(ClO_4)_2{\cdot}xH_2O$	DCP	0
16	$Fe(ClO_4)_2{\cdot}xH_2O$	$PhI(OAc)_2$	0
17	$Fe(ClO_4)_2{\cdot}xH_2O$	O_2	0
18	—	H_2O_2	0
19	$Fe(ClO_4)_2{\cdot}xH_2O$	—	0
20	$Fe(ClO_4)_2{\cdot}xH_2O$	H_2O_2	59[d]
21	$Fe(ClO_4)_2{\cdot}xH_2O$	H_2O_2	76[e]

[a] Reactions were performed with **1a** (1.0 mmol), catalyst (1.0 equiv.), and oxidant (2.0 equiv.) in methanol **2a** (2.0 mL) at rt for 10 min. [b] Isolated yields. [c] 0% yield means no reaction. [d] Under reflux conditions. [e] Reaction time increased to 12 h.

Table 2 Scope of the quinoline derivatives[a,b]



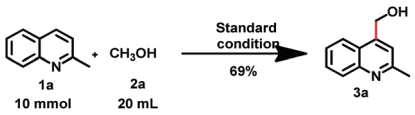
[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mL), H_2O_2 (2.0 equiv.), Fe $(ClO_4)_2{\cdot}xH_2O$ (1.0 equiv.), rt, 10 min. [b] Isolated yields.

2-phenyl substituted quinoline **1h** smoothly furnished the respective product (**3h**) in excellent yield. 7-Fluoro-2-methylquinoline and 8-chloro-2-methylquinolines (**1i** and **1j**) reacted well and gave the corresponding products (**3i** and **3j**) in good

yields. However, 2-chloroquinoline (**1k**) gave the desired product **3k** in 23% yield. Furthermore, unsubstituted quinoline (**1l**) gave three regioisomers, namely, quinolin-2-ylmethanol (**3la**), quinolin-4-ylmethanol (**3lb**) and quinoline-2,4-diyldimethanol (**3lc**), in 21%, 23% and 19% (overall yield 63%) yield respectively. Moreover, these isomers were separated by column chromatography. Similarly, 8-methylquinoline (**1m**) and benzo[*h*]quinoline (**1n**) gave a mixture of regioisomers (**3ma–3mc**) in 85% and (**3na–3nc**) 67% overall yields respectively. 2-Phenyl pyridine (**1o**) also produced two regioisomers (**3oa** and **3ob**) in 37% overall yield. Subsequently, 2,6-diphenyl pyridine (**1p**) furnished the desired product (**3p**) in low yield.

Furthermore, we also extended our investigation to explore the possibility of this strategy using higher alcohols (like ethanol **2b**, propanol (**2c**), butanol (**2d**), isobutanol (**2e**), and hexanol (**2f**)) other than methanol and the results are summarised in Table 3. In this sequence, the reaction with 2-methyl quinoline **1a** in ethanol **2b** under the standard conditions failed to give the expected product **4a**, and the starting materials remained as such. A longer reaction time (12 h) also failed to give product **4a**. Gratifyingly, switching over to other oxidants, like TBHP (2.0 equiv.) instead of H_2O_2, under the same reaction conditions gave the desired product **4a** in 66% yield. In order to improve the yield of the reaction, the reaction time was prolonged to 12 h, and we observed a trace amount of acylated quinoline (**4a′**) along with the desired product (**4a**). Furthermore, reactions with 2-phenyl quinoline and 8-chloro-2-methyl quinoline (**1h** and **1j**) in ethanol **2b** afforded **4b** and **4c** in 57% and 52% yields, respectively. Later, substituted quinolines with propanol **2c** produced **4d–4f** in 34–42% yields. Similarly, 4-methyl/2,6-dimethyl quinolines (**1b**/**1c**) with butanol **2d** gave the corresponding products **4g–4h** in low yields. These results explain that increasing the chain lengths of alcohols decreases their reactivity for this transformation. Furthermore, the reaction of 2-methyl quinoline **1a** with a branched alcohol, iso-butanol **2e**, successfully afforded the product **4i** in 33% yield. Similarly, reaction with hexanol gave **4j** in 31% yield.

Moreover, due to the easy availability of the starting materials and the operational simplicity of this protocol, we performed a gram scale reaction with 2-methylquinoline **1a** in methanol **2a** under the optimized conditions and obtained **3a** in 69% yield (Scheme 2).



Scheme 2 Gram scale synthesis.

Quinoline bearing a formyl group at the 4-position is a key intermediate for the synthesis of various bioactive compounds[13] and sensing agents,[14] for example, arsindoline-A alkaloid, which is a representative molecule of anticancer agents.[15]

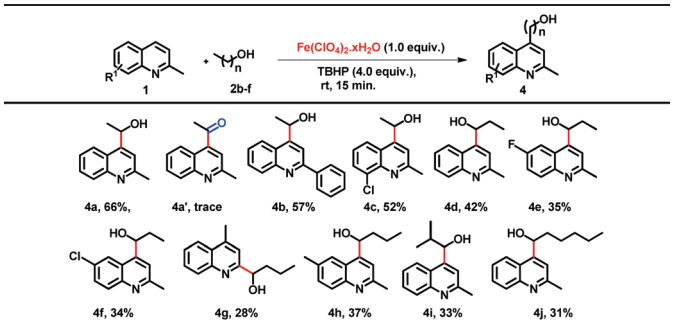
Owing to the importance of this intermediate, some of the 4-hydroxymethyl quinolines **3** were successfully converted into the corresponding 4-formyl quinolines **5** using the Dess–Martin oxidant.

Furthermore, the formyl group (compound **5**) was involved in a mineral acid (conc. H_2SO_4 (1.0 equiv.) mediated condensation reaction with indole (**6**) in H_2O at room temperature for 1 h, giving the arsindoline-A alkaloid **7a** in 83% yield and its derivatives **7b** and **7c** in 73 and 76% yields, respectively (Table 4).

In order to gain insights into the reaction mechanism, we performed a control experiment with **1a** and **2a** in the presence of the radical scavenger TEMPO under optimized reaction conditions, and product **3a** was not obtained (Scheme 3). This result suggests that the reaction proceeds through a radical pathway. Furthermore, the reaction was also examined with different catalytic systems, such as 10 mol% of $Fe(ClO_4)_2{\cdot}xH_2O$ and 2.0 equiv. of H_2O_2, at room temperature; we did not observe any desired product, and the starting material (95%) was recovered (Scheme 3b). Similarly, loading of 30 mol% and 50 mol% of catalyst gave low yields (Scheme 3c and d), whereas the use of 75 mol% of $Fe(ClO_4)_2{\cdot}xH_2O$ resulted in 58% isolated yield along with 30% of the unreacted starting material (Scheme 3e). These catalytic experiments suggest that the reaction necessarily required a stoichiometric amount of $Fe(ClO_4)_2{\cdot}xH_2O$.

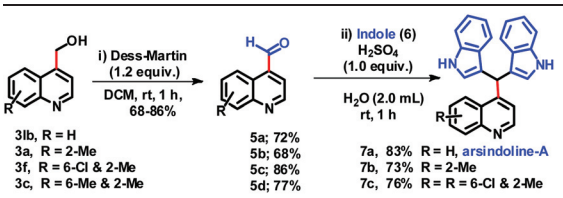
Based on previous reports[9,16] and our own control experimental results, we have proposed a plausible mechanism as shown in Scheme 4. Initially, Fe(II) is oxidised to Fe(III) *via* a single electron transfer (SET) process in the presence of H_2O_2,

Table 3 Scope of various alcohols[a,b]

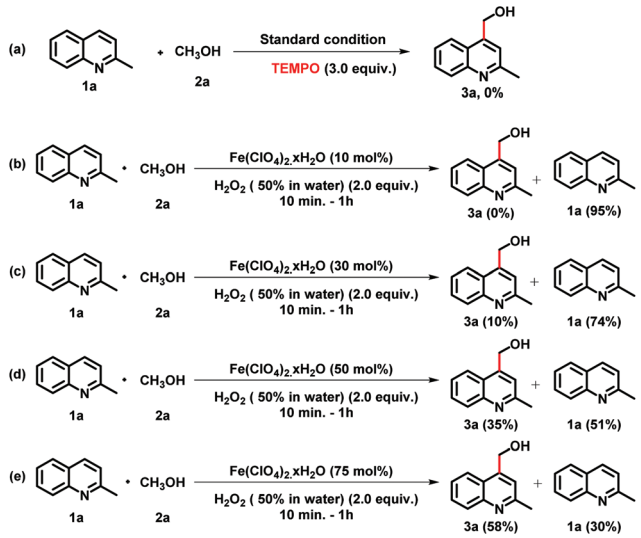


[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mL), TBHP (2.0 equiv.), $Fe(ClO_4)_2{\cdot}xH_2O$ (1.0 equiv.), rt, 15 min. [b] Isolated yields.

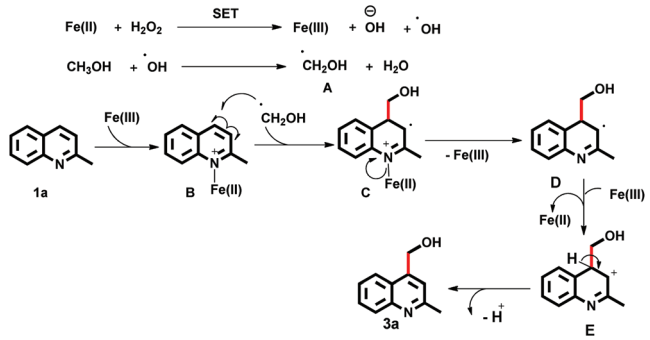
Table 4 Synthesis of arsindoline-A alkaloid and its derivatives[a,b]



[a] Reaction conditions for compounds **5** and **7**: (i) Compound **3** (1.0 mmol), Dess–Martin (1.2 equiv.), DCM (2.0 mL), rt, 1 h. (ii) Compound **5** (0.5 mmol), indole **6** (1.0 mmol), conc. H_2SO_4 (1.0 equiv.), H_2O (2.0 mL), rt, 1 h. [b] Isolated yields are provided.



Scheme 3 Control experiments of **3a–3e**.



Scheme 4 Plausible mechanism.

generating a hydroxyl radical and a hydroxyl ion. The corresponding hydroxyl radical abstracts the hydrogen radical from the α-CH of methanol and generates a hydroxymethyl radical (**A**). Meanwhile, Fe(III) coordinates with the *N*-atom of quinoline to form a more electron deficient intermediate (**B**). Afterwards, hydroxymethyl radical (**A**) attacks the 4th position of intermediate **B** to afford the radical cation intermediate **C**. Intermediate **D** is obtained from intermediate **C** *via* the removal of Fe(III). Furthermore, intermediate **D** is oxidised by Fe(III) to generate a cationic intermediate **E**, which is similar to that reported by Wang *et al.* in the Ag-promoted α-C–H arylation of alcohols.[9] Finally, intermediate **E** readily undergoes rearomatization followed by the loss of a proton, resulting in product **3a**. Probably, the corresponding proton is abstracted by an *in situ* generated hydroxyl anion.

Conclusions

In summary, we have developed a simple, mild and efficient protocol for the hydroxymethylation of *N*-heteroarenes *via* an iron mediated oxidative CDC strategy under ambient conditions. The main features of the present transformation are that it does not require external acid additives, uses inexpensive and commercially available H_2O_2 as an oxidant, and has shorter reaction time. In addition, various alcohols were also tolerated by this reaction to furnish the respective hydroxylalkylated *N*-heteroarenes. Moreover, we have shown synthetic utility of the isolated hydroxymethylated quinolines for the generation of the corresponding formyl quinolines, which were further employed for the synthesis of bioactive arsindoline-A alkaloid and its derivatives.

Experimental section

All the chemicals and solvents were purchased from Sigma-Aldrich, Alfa Aesar and S. D. Fine Chemicals Pvt. Ltd, India and used without further purification. Silica gel (100–200 mesh) was used for column chromatography, and thin-layer chromatography was performed on pre-coated silica gel 60-F_{254} plates and visualized by UV-light and developed by iodine. The IR values are reported in reciprocal centimeters (cm^{-1}). All the ^1H and ^{13}C {^1H} NMR spectra were recorded on Avance-300, Avance-400, and Avance-500 MHz spectrometers. Chemical shifts (δ) are reported in ppm, using TMS (δ = 0) as an internal standard in $CDCl_3$. The peak patterns are indicated as follows: bs, broad singlet; s, singlet; d, doublet; t, triplet; dd, doublet of doublets; sep, septet; and m, multiplet. The coupling constants (J) are reported in hertz (Hz). LC–MS measurements were carried out with an Agilent 1200 series (DAD; diode array detector) instrument using a Zorbax (SB-C18, 3.0 mm × 50 mm × 1.8 μm) column. Low- and high-resolution mass spectrometry was carried out using the electrospray ionisation method.

General procedure and characterization data for the hydroxymethylation of quinolines (3a–3p)

To a stirring solution of quinolines (**1**) (1.0 mmol) and Fe$(ClO_4)_2{\cdot}xH_2O$ (1.0 equiv.) in 2.0 mL of methanol (**2a**) was added dropwise 2.0 equivalents of 50% H_2O_2 at room temperature. The progress of the reaction was monitored by TLC. After the completion of the reaction (10 min), the reaction mixture was extracted with ethyl acetate and washed with saturated $NaHCO_3$ and brine solution. The organic layer was dried over Na_2SO_4 and concentrated in vacuum. The mixture was purified by column chromatography over silica gel (100–200 mesh size), and using a hexane/ethyl acetate mixture as the eluent gave the desired products **3**.

(2-Methylquinolin-4-yl)methanol (3a). White solid (136 mg, 78% yield), mp 143–145 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.67 (t, J = 8.4 Hz, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.41 (s, 1H), 5.19 (s, 2H), 2.70 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.0, 147.4, 146.4, 129.3, 128.9, 125.8, 124.1, 122.7, 119.1, 61.4, 25.2. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{12}NO$: 174.0913, found: 174.0917.

(4-Methylquinolin-2-yl)methanol (3b). Yellow solid (121 mg, 69% yield), mp 78–80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.71 (t, J = 8.4 Hz, 1H), 7.55 (t, J = 8.2 Hz, 1H), 7.12 (s, 1H), 4.87 (s, 2H), 2.70 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.6, 146.4, 145.3, 129.5, 129.1, 127.6, 126.1, 123.8, 119.0, 64.0, 18.8. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{12}NO$: 174.0913, found: 174.0920.

(2,6-Dimethylquinolin-4-yl)methanol (3c). White solid (119 mg, 63% yield), mp 150–152 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.6 Hz, 1H), 7.63 (s, 1H), 7.49 (d, J = 10.4 Hz, 1H), 7.36 (s, 1H), 5.14 (s, 2H), 2.66 (s, 3H), 2.51 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.0, 146.0, 145.6, 135.6, 131.4, 128.7, 124.1, 121.7, 119.1, 61.5, 25.1, 21.8. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{12}H_{14}NO$: 188.1070, found: 188.1069.

(6-Methoxy-2-methylquinolin-4-yl)methanol (3d). Yellow solid (98 mg, 48% yield), mp 163–165 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, J = 9.2 Hz, 1H), 7.36–7.32 (m, 2H), 7.14 (d, J = 2.8 Hz, 1H), 5.11 (s, 2H), 3.92 (s, 3H), 2.68 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$ + DMSO) δ 161.7, 160.9, 150.7, 148.2, 135.1, 129.9, 125.8, 124.2, 106.2, 65.6, 60.3, 29.7. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{12}H_{14}NO_2$: 204.1019, found: 204.1019.

(6-Fluoro-2-methylquinolin-4-yl)methanol (3e). White solid (167 mg, 86% yield), mp 162–164 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (dd, J = 9.2, 5.5 Hz, 1H), 7.52 (dd, J = 9.8, 2.8 Hz, 1H), 7.48–7.42 (m, 2H), 5.12 (s, 2H), 2.73 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$ + DMSO) δ 159.7 (d, J = 244.5 Hz), 158.2, 146.6 144.5, 144.6, 131.3, 131.2, 124.9 (d, J = 9.4 Hz), 119.9, 118.8 (d, J = 25.5 Hz), 106.9, 106.6, 60.8, 25.1. **^{19}F NMR** (377 MHz, $CDCl_3$) δ −109.3 (s). **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{11}FNO$: 192.0819, found: 192.0827.

(6-Chloro-2-methylquinolin-4-yl)methanol (3f). Pale yellow solid (166 mg, 79% yield), mp 158–160 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 2.3 Hz, 1H), 7.60 (dd, J = 9.0, 2.3 Hz, 1H), 7.43 (s, 1H), 5.13 (s, 2H), 2.70 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 146.0, 145.3, 131.7, 130.7, 130.2, 124.9, 122.0, 120.0, 61.5, 25.3. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{11}ClNO$: 208.0524, found: 208.0529.

(6-Bromo-2-methylquinolin-4-yl)methanol (3g). Pale yellow solid (192 mg, 76% yield), mp 163–165 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, J = 2.1 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.74 (dd, J = 9.0, 2.2 Hz, 1H), 7.43 (s, 1H), 5.13 (s, 2H), 2.71 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$ + DMSO) δ 159.5, 146.2, 132.4, 130.8, 125.6, 125.4, 120.0, 119.5, 60.7, 25.4. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{11}BrNO$: 252.0019, found: 252.0029.

(2-Phenylquinolin-4-yl)methanol (3h). White solid (219 mg, 93% yield), mp 106–108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 1H), 7.97–7.87 (m, 2H), 7.72 (d, J = 9.2 Hz, 2H), 7.68–7.61 (m, 1H), 7.47–7.33 (m, 4H), 5.00 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 147.9, 146.9, 139.5, 130.1, 129.5, 129.4, 128.8, 127.6, 126.4, 122.7, 116.1, 61.7. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{16}H_{14}NO$: 236.1070, found: 236.1081.

(7-Fluoro-2-methylquinolin-4-yl)methanol (3i). White solid (151 mg, 78% yield), mp 172–174 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 9.2, 6.0 Hz, 1H), 7.67 (dd, J = 10.3, 2.6 Hz, 1H), 7.38 (s, 1H), 7.32–7.28 (m, 1H), 5.16 (s, 2H), 2.72 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (d, J = 250.4 Hz), 160.5, 149.0, 146.0, 124.9 (d, J = 9.9 Hz), 121.2, 118.7, 116.0 (d, J = 24.2 Hz), 113.1, 112.9 61.8, 25.4. **^{19}F NMR** (377 MHz, $CDCl_3$) δ −110.3 (s). **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{11}FNO$: 192.0819, found: 192.0829.

(8-Chloro-2-methylquinolin-4-yl)methanol (3j). Pale yellow solid (151 mg, 78% yield), mp 141–143 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82–7.77 (m, 2H), 7.44–7.37 (m, 2H), 5.15 (s, 2H), 2.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.3, 146.3, 144.0, 133.3, 129.5, 125.6, 125.5, 121.9, 120.0, 61.7, 25.8. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{11}ClNO$: 208.0524, found: 208.0530.

(2-Chloroquinolin-4-yl)methanol (3k). Yellow solid (46 mg, 23% yield), mp 148–150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.74 (t, J = 8.4 Hz, 1H), 7.61–7.55 (m, 2H), 5.22 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.1, 149.5, 147.7, 130.4, 129.3, 127.1, 124.4, 122.7, 119.2, 61.3. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{10}H_9ClNO$: 194.0367, found: 194.0369.

Quinolin-2-ylmethanol (3la). Pale yellow oil (34 mg, 21% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.75–7.69 (m, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 4.92 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.2, 145.7, 135.9, 128.8, 127.5, 126.6, 126.5, 125.3, 117.4, 63.2. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{10}H_{10}NO$: 160.0757, found: 160.0765.

Quinolin-4-ylmethanol (3lb). Pale yellow oil (37 mg, 23% yield); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10–8.76 (m, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.58–7.50 (t, J = 6.3 Hz, 2H), 5.23 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$ + DMSO) δ 160.5, 146.3, 136.1, 136.07, 129.0, 127.9, 127.1, 125.5, 118.2, 64.3. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{10}H_{10}NO$: 160.0757, found: 160.0765.

Quinoline-2,4-diyldimethanol (3lc). Brown oil (36 mg, 19% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 9.2 Hz, 1H), 7.73 (t, J = 8.4 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.45 (s, 1H), 5.23 (s, 2H), 4.92 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$ + DMSO) δ 161.5, 147.4, 146.0, 128.4, 128.3, 125.1, 124.2, 122.6, 115.3, 64.5, 59.5. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{12}NO_2$: 190.0863, found: 190.0865.

(8-Methylquinolin-2-yl)methanol (3ma). Brick red solid (35 mg, 19% yield), mp 121–123 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.46–7.40 (m, 1H), 7.27–7.22 (m, 1H), 4.92 (s, 2H), 2.81 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 145.5, 137.2, 136.4, 130.1, 127.6, 126.1, 125.7, 117.9, 63.9, 17.8. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{12}NO$: 174.0913, found: 174.0921.

(8-Methylquinolin-4-yl)methanol (3mb). Pale yellow solid (44 mg, 25% yield), mp 134–136 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (d, J = 4.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.0 Hz, 1H), 7.54 (d, J = 4.3 Hz, 1H), 7.48–7.43 (m, 1H), 5.22 (s, 2H), 2.83 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2, 147.1, 146.1, 137.8, 129.6, 126.5, 125.7, 120.7, 117.9, 61.9, 18.7. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{12}NO$: 174.0913, found: 174.0920.

(8-Methylquinoline-2,4-diyl)dimethanol (3mc). Pale yellow solid (84 mg, 41% yield), mp 126–128 °C; **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 7.0 Hz, 2H), 7.47–7.42 (m, 2H), 7.40 (s, 2H), 5.20 (s, 4H), 4.90 (s, 5H), 2.80 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 147.0, 145.2, 137.1, 129.9, 126.2, 125.0, 120.5, 114.7, 63.9, 61.8, 18.3. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{12}H_{14}NO_2$: 204.1019, found: 204.1029.

Benzo[*h*]quinolin-2-ylmethanol (3na). Pale yellow oil (49 mg, 23% yield); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.29 (d, J = 8.9 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.94–7.90 (m, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.79–7.66 (m, 3H), 7.40 (d, J = 8.2 Hz, 1H), 5.01 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.4, 144.8, 136.8, 133.9, 130.8, 128.3, 127.9, 127.5, 127.1, 125.5, 125.1, 124.2, 118.8, 64.2. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{14}H_{12}NO$: 210.0913, found: 210.0922.

Benzo[*h*]quinolin-4-ylmethanol (3nb). Yellow oil (60 mg, 28% yield); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.29 (d, J = 9.1 Hz, 1H), 8.94 (d, J = 4.5 Hz, 1H), 7.93–7.88 (m, 1H), 7.82 (s, 2H), 7.78–7.66 (m, 2H), 7.61 (d, J = 4.5 Hz, 1H), 5.23 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.8, 146.1, 145.8, 133.3, 131.6, 128.3, 128.0, 127.8, 127.3, 124.7, 123.7, 120.3, 119.2, 62.0. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{14}H_{12}NO$: 210.0913, found: 210.0922.

Benzo[*h*]quinoline-2,4-diyldimethanol (3nc). Brown oil (40 mg, 16% yield); **^{1}H NMR** (400 MHz, $CDCl_3$ + DMSO) δ 9.22 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.78–7.71 (M, 2H), 7.66–7.57 (M, 3H), 5.11 (s, 2H), 4.91 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$ + DMSO) δ 158.4, 148.2, 144.4, 133.3, 131.1, 128.0, 127.7, 127.0, 126.9, 124.5, 122.8, 120.5, 116.3, 64.7, 61.1. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{15}H_{14}NO_2$: 240.1019, found: 240.1030.

(6-Phenylpyridin-2-yl)methanol (3oa). Yellow liquid (26 mg, 14% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04–8.00 (m, 2H), 7.75 (t, J = 7.7 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.52–7.41 (m, 3H), 7.16 (d, J = 8.2 Hz, 1H), 4.82 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5, 156.1, 138.8, 137.5, 129.2, 128.8, 126.9, 119.1, 118.8, 63.9. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{12}H_{12}NO$: 186.0913, found: 186.0923.

(2-Phenylpyridin-4-yl)methanol (3ob). Yellow liquid (44 mg, 23% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.60 (d, J = 5.0 Hz, 1H), 7.97–7.92 (m, 2H), 7.69 (s, 1H), 7.48–7.38 (m, 3H), 7.18 (d, J = 6.5 Hz, 1H), 4.75 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7, 151.0, 149.6, 139.3, 129.1, 128.8, 127.0, 119.7, 118.1, 63.6. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{12}H_{12}NO$: 186.0913, found: 186.0923.

(2,6-Diphenylpyridin-4-yl)methanol (3p). White solid (75 mg, 28% yield) mp 103–104 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15–8.12 (4, 2H), 7.63 (s, 1H), 7.52–7.46 (m, 4H), 7.45–7.40 (m, 2H), 4.78 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.1, 151.4, 139.4, 129.1, 128.7, 127.1, 116.2, 64.0. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{18}H_{16}NO$: 262.1226, found: 262.1239.

General procedure and characterization data for the hydroxyalkylated quinolines (4a–4j)

To a stirring solution of quinolines (**1**) (1.0 mmol) and Fe $(ClO_4)_2{\cdot}xH_2O$ (1.0. equiv.) in 2.0 mL of alcohols (**2b–f**) was dropwise added TBHP (4.0 equiv.) at room temperature. The progress of the reaction was monitored by TLC. After the completion of the reaction (15 min), the reaction mixture was extracted with ethyl acetate and washed with saturated $NaHCO_3$ and brine solution. The organic layer was dried over Na_2SO_4 and concentrated in vacuum. The mixture was purified by column chromatography over silica gel (100–200 mesh size), and using a mixture of hexane/ethyl acetate as the eluent gave the desired product **4**.

1-(2-Methylquinolin-4-yl)ethan-1-ol (4a). Pale yellow solid (115 mg, 66% yield) mp 109–111 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.67–7.59 (m, 1H), 7.44 (dd, J = 8.9, 5.4 Hz, 2H), 5.59 (s, 1H), 2.69–2.58 (m, 3H), 1.67–1.56 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.1, 151.5, 147.7, 129.2, 129.1, 125.6, 123.6, 122.8, 117.6, 65.9, 25.9, 24.6. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{12}H_{14}NO$: 188.1070, found: 188.1150.

1-(2-Methylquinolin-4-yl)ethan-1-one (4a′). Yellow liquid (18 mg, 9% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.49 (s, 1H), 2.80 (s, 3H), 2.74 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.6, 158.5, 148.9, 143.2, 129.9, 129.2, 127.4, 125.3, 122.0, 120.8, 30.2, 25.4. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{12}H_{12}NO$: 186.0913, found: 186.0913.

1-(2-Phenylquinolin-4-yl)ethan-1-ol (4b). Yellow liquid (144 mg, 57% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 6.2 Hz, 2H), 7.82 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.44–7.38 (m, 4H), 5.42 (q, J = 6.4 Hz, 1H), 1.55 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 152.3, 148.0, 139.3, 130.1, 129.4, 129.3, 128.7, 127.5, 126.1, 124.2, 122.8, 114.4, 66.1, 24.5. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{17}H_{16}NO$: 250.1226, found: 250.1360.

1-(8-Chloro-2-methylquinolin-4-yl)ethan-1-ol (4c). White solid (116 mg, 52% yield) mp 124–126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.46 (s, 1H), 7.39–7.33 (m, 1H), 5.54 (q, J = 6.2 Hz, 1H), 2.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.3, 151.5, 144.2, 133.5, 129.2, 125.4, 125.0, 121.9, 118.4, 66.3, 25.9, 24.6. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{12}H_{13}ClNO$: 222.0680, found: 222.0759.

1-(2-Methylquinolin-4-yl)propan-1-ol (4d). Yellow liquid (82 mg, 42% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 8.2 Hz, 1H), 7.44 (t, J = 8.2 Hz, 1H), 7.39 (s, 1H), 5.33 (dd, J = 7.7, 4.4 Hz, 1H), 2.64 (s, 3H), 2.09–1.91 (m, 1H), 1.89–1.76 (m, 1H), 1.03 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9, 150.3, 147.8, 129.2, 129.0, 125.5, 123.9, 122.8, 118.4, 71.1, 31.3, 25.3, 10.3. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{13}H_{16}NO$: 202.1226, found: 202.1291.

1-(6-Fluoro-2-methylquinolin-4-yl)propan-1-ol (4e). Yellow liquid (77 mg, 35% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02–7.94 (m, 1H), 7.53 (d, J = 10.2 Hz, 1H), 7.45–7.35 (m, 2H), 5.24–5.16 (m, 1H), 2.66 (s, 3H), 2.00–1.89 (m, 1H), 1.89–1.77 (m, 1H), 1.03 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8 (d, J = 247.5 Hz), 158.5, 150.0, 144.8, 131.3, 131.2, 124.5 (d, J = 9.1 Hz), 119.2, 119.0 (d, J = 25.3 Hz), 107.0, 106.8, 71.3, 31.0, 25.0, 10.3. **^{19}F NMR** (377 MHz, $CDCl_3$) δ −113.6 (s). **HRMS** (ESI): calcd for $[M + H]^+$ $C_{13}H_{15}FNO$: 220.1132, found: 220.1236.

1-(6-Chloro-2-methylquinolin-4-yl)propan-1-ol (4f). Yellow liquid (81 mg, 34% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.8, 5.6 Hz, 2H), 7.55 (dd, J = 9.0, 2.3 Hz, 1H), 7.39 (s, 1H), 5.22 (dd, J = 7.7, 4.6 Hz, 1H), 2.65 (s, 3H), 1.99–1.88 (m, 1H), 1.86–1.77 (m, 1H), 1.03 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.2, 148.4, 145.2, 130.4, 129.8, 128.9, 123.6, 121.1, 118.3, 30.1, 24.3, 9.2. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{13}H_{15}ClNO$: 236.0837, found: 236.0895.

1-(4-Methylquinolin-2-yl)butan-1-ol (4g). Brown liquid (61 mg, 28% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 22.7, 8.4 Hz, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.55–7.48 (m, 1H), 7.20 (s, 1H), 3.72–3.64 (m, 2H), 3.41–3.29 (m, 1H), 2.69 (s, 3H), 2.13–2.04 (m, 1H), 2.03–1.94 (m, 1H), 1.41 (d, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.7, 146.9, 145.2, 129.3, 129.0, 126.9, 125.8, 123.6, 120.7, 60.1, 40.0, 38.2, 20.5, 18.9. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{14}H_{18}NO$: 216.1382, found: 216.1382.

1-(2,6-Dimethylquinolin-4-yl)butan-1-ol (4h). Brown liquid (85 mg, 36% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 1H), 7.65 (s, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.36 (s, 1H), 5.38 (dd, J = 7.9, 4.3 Hz, 1H), 2.65 (s, 3H), 2.51 (s, 3H), 1.91–1.73 (m, 2H), 1.62–1.44 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9, 149.9, 146.4, 135.2, 131.2, 128.9, 123.8, 121.8, 118.2, 69.6, 40.4, 25.2, 21.9, 19.2, 14.0. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{15}H_{20}NO$: 230.1539, found: 230.1539.

2-Methyl-1-(2-methylquinolin-4-yl)propan-1-ol (4i). Brown liquid (71 mg, 33% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 8.2 Hz, 1H), 7.38 (s, 1H), 5.19 (d, J = 5.2 Hz, 1H), 2.69 (s, 3H), 2.23–2.13 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7, 149.6, 147.9, 129.3, 129.0, 125.4, 124.2, 123.1, 119.3, 74.8, 34.4, 25.4, 20.1, 16.7. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{14}H_{18}NO$: 216.1383, found: 216.1429.

1-(2-Methylquinolin-4-yl)hexane-1-ol (4j). Brown liquid (76 mg, 31% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.39 (s, 1H), 5.38 (dd, J = 8.2, 4.0 Hz, 1H), 2.63 (s, 3H), 1.92–1.73 (m, 2H), 1.62–1.40 (m, 2H), 1.39–1.23 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.8, 151.2, 147.5, 129.1, 129.0, 125.6, 123.8, 122.8, 118.3, 69.8, 38.5, 31.7, 25.8, 25.1, 22.6, 14.1. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{16}H_{22}NO$: 244.1696, found: 244.1813.

General procedure and characterization data for the quinoline-4-carbaldehydes (5)

To a stirring solution of hydroxymethylated quinoline **3a** (1.0 mmol) in 2.0 mL of DCM, Dess–Martin periodinane (1.2 equiv.) was added slowly at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with saturated sodium thiosulphate solution and extracted with DCM (5.0 mL × 3). The organic layer was washed with saturated sodium bicarbonate solution, dried with anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography over silica gel (100–200 mesh size) and using a hexane/ethyl acetate mixture as the eluent gave the desired product **5**.

Quinoline-4-carbaldehyde (5a). White solid (114 mg, 72% yield), mp 79–81 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 9.21 (d, J = 4.2 Hz, 1H), 9.03 (d, J = 9.5 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 7.83 (m, 2H), 7.75 (t, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 150.5, 149.3, 136.8, 130.2, 130.1, 129.4, 125.9, 124.5, 123.9. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{10}H_8NO$: 158.0600, found: 158. 158.0601.

2-Methylquinoline-4-carbaldehyde (5b). White solid (117 mg, 68% yield), mp 84–86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.95 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.78 (t, J = 8.4 Hz, 1H), 7.71–7.63 (m, 2H), 2.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.0, 159.2, 149.0, 137.1, 130.2, 129.2, 128.3, 127.1, 124.2, 122.3, 25.3. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_{10}NO$: 172.0757, found: 172.0757.

6-Chloro-2-methylquinoline-4-carbaldehyde (5c). Pale yellow solid (178 mg, 86% yield), mp 113–115 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.99 (s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.73–7.66 (m, 2H), 2.85 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.7, 159.5, 147.4, 136.2, 134.7, 131.2, 130.6, 128.5, 123.7, 122.6, 25.2. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{11}H_9ClNO$: 206.0367, found: 206.0368.

2,6-Dimethylquinoline-4-carbaldehyde (5d). Pale yellow solid (145 mg, 77% yield), mp 118–120 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.72 (s, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.63–7.57 (m, 2H), 2.83 (s, 3H), 2.58 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.2, 158.0, 147.7, 138.7, 136.5, 132.4, 128.8, 127.2, 123.2, 122.30, 25.1, 22.0. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{12}H_{12}NO$: 186.0913, found: 186.0913.

General procedure characterization data for the arsindoline-A and its derivatives (7a–c)

To a stirred solution of quinoline-4-carbaldehyde **5** (0.5 mmol) and indole **6** (1.0 equiv.) in H_2O (2 mL), H_2SO_4 (1.0 equiv.) was added dropwise at 0 °C. After the completion of the reaction, the reaction mixture was diluted with water and extracted with DCM twice. The organic layer was washed with saturated sodium bicarbonate solution, dried with anhydrous Na_2SO_4 and concentrated. The crude reaction mixture was purified by column chromatography using EtOAc/hexane as eluents to obtain the product **7**.

4-(Di(1*H*-indol-3-yl)methyl)quinoline (7a). Pale yellow solid (313 mg, 83% yield), mp 108–110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (d, J = 4.5 Hz, 1H), 8.16 (d, J = 8.3 Hz, 2H), 8.06 (s, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.37 (dd, J = 8.2, 2.8 Hz, 4H), 7.20 (t, J = 7.6 Hz, 2H), 7.16 (d, J = 4.5 Hz, 1H), 7.02 (t, J = 7.6 Hz, 2H), 6.65 (s, 1H), 6.58 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.4, 149.8, 148.4, 136.8, 129.9, 129.0, 127.4, 126.8, 126.6, 124.4, 124.2, 122.3, 121.0, 119.6, 119.5, 117.7, 111.3, 35.6. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{26}H_{20}N_3$: 374.1651, found: 374.1654.

4-(Di(1*H*-indol-3-yl)methyl)-2-methylquinoline (7b). Brick red solid (286 mg, 73% yield), mp 251–252 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.9, 4.4 Hz, 2H), 8.02 (s, 2H),

7.64 (t, J = 7.7 Hz, 1H), 7.42–7.34 (m, 5H), 7.21 (t, J = 7.2 Hz, 2H), 7.04 (dd, J = 15.4, 8.4 Hz, 3H), 6.66–6.57 (m, 3H), 2.59 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$ + DMSO) δ 158.6, 150.3, 147.6, 136.8, 128.8, 128.6, 126.6, 125.6, 125.4, 124.6, 123.9, 121.5, 121.4, 119.0, 118.7, 116.8, 111.4, 35.4, 25.2. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{27}H_{22}N_3$: 388.1808, found: 388.1811.

6-Chloro-4-(di(1*H*-indol-3-yl)methyl)-2-methylquinoline (7c). Brick red solid (324 mg, 76% yield), mp 163–165 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09–7.99 (m, 4H), 7.57 (dd, J = 9.0, 2.1 Hz, 1H), 7.36 (dd, J = 12.2, 8.1 Hz, 4H), 7.20 (t, J = 7.6 Hz, 2H), 7.09 (s, 1H), 7.02 (t, J = 7.3 Hz, 2H), 6.58 (d, J = 1.6 Hz, 2H), 6.51 (s, 1H), 2.56 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 149.1, 146.5, 136.8, 130.7, 130.0, 126.7, 124.3, 122.9, 122.6, 122.4, 119.6, 119.5, 117.3, 111.3, 35.6, 25.3. **HRMS** (ESI): calcd for $[M + H]^+$ $C_{27}H_{21}ClN_3$: 422.1419, found: 422.1412.

Conflicts of interest

There are no conflicts to declare.

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