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# Expansion of the aromatic part of *Cinchona* alkaloids. Annulation of quinolines with phenoxazine motifs

Małgorzata Wąsińska-Kałwa, Mirosław Giurg, Przemysław J. Boratyński, Jacek Skarżewski*

*Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, 50-370 Wrocław, Poland*

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ABSTRACT

An oxidative cross-coupling strategy for quinoline ring annulation in *Cinchona* alkaloids has been developed. Key-reaction optimization by changing oxidants and adjusting the nucleophilicity of the 2-aminophenols led to cupreine and cupreidine expanded with the phenoxazinone unit in 56–75% yield. The stereochemical integrity of the obtained alkaloid structures was confirmed by combined experimental and computed CD and NMR data. The conformational study revealed a fast equilibrium of the three conformers, differing in the orientation of the pyrido[*a*-3,2]phenoxazine moiety.



## 1. Introduction

*Cinchona* alkaloids constitute a privileged class of easily available natural compounds widely used in organic synthesis.[1] In particular, the last decades have witnessed a remarkable development of their applications in asymmetric reactions in the roles of chiral ligands,[2] organocatalysts,[3] and phase-transfer catalysts.[4] A unique chiral architecture and multiple functional groups render them interesting targets for structural modifications. Catalytically valuable ethers,[5] thioureas,[6] and squaramides[7] were obtained by transforming the 9-OH group. Modifications of the quinoline moiety are much less abundant. Specifically, conversion of the C-6′ methoxy group into an OH group[8] and $NR_2$ groups,[9] and transformations at C-2′ and C-3′ with organometallic compounds were performed.[10] Moreover, the C-5′ position was modified by installation of nitrogen substituents[11] such as urea and thiourea[12] that resulted in the formation of fused oxazolinone ring.[11a,13] Recently, annulation of the quinoline has led to a tetrazole alkaloid derivative, which was an effective organocatalyst.[14] However, other aromatic annulations have not been reported so far.

Beside their extraordinary catalytic potency, *Cinchona* alkaloids are known for their medicinal applications.[15] Moreover, conjugation of quinine with other biologically active compounds has introduced promising cytotoxic and inhibitory properties.[16]

On the other hand, various phenoxazinones are well known for their biological activities.[17] A notable example is actinomycin D, a natural polypeptide antibiotic containing a phenoxazinone moiety, which is an approved anti-cancer drug.[18] Additionally, some phenoxazinone compounds are used as synthetic dyes and fluorophores.[19] All of these prompted us to develop new *Cinchona* alkaloid derivatives with an extended aromatic system incorporating the phenoxazinone fragment.

## 2. Results and discussion

We decided to focus on the annulation of cupreine and cupreidine in order to extend their quinoline moieties and obtain phenoxazinone hybrids (Fig. 1).

The well established synthetic route to phenoxazinones relies on the intramolecular oxidative coupling of two *ortho*-aminophenols (Scheme 1). Many different oxidants have been used for the efficient self-condensation of various substituted 2-aminophenols, including $K_2Cr_2O_7$, $PbO_2$,[20] $K_3Fe(CN)_6$,[21,22] $NaIO_3$,[22,23] benzoquinones,[24] as well as oxygen and peroxides in the presence of activators[22,25] or laccase.[26] In nature, the oxidative dimerization is catalyzed by phenoxazinone synthase.[27] A mechanism of the formation of the phenoxazinone system has been proposed (Scheme 1).[28]

* Corresponding author.
*E-mail address:* jacek.skarzewski@pwr.wroc.pl (J. Skarżewski).

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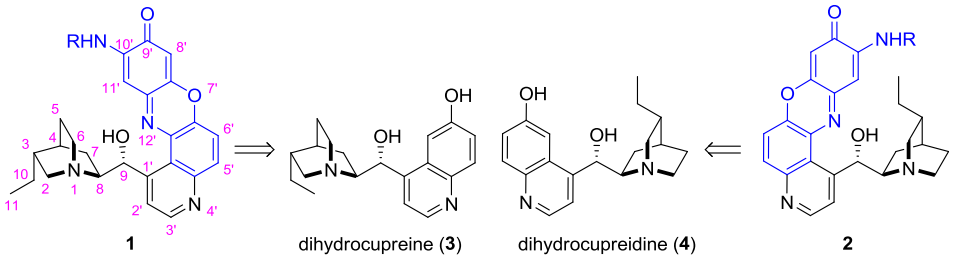
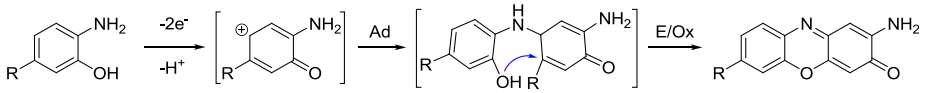



**Fig. 1.** Phenoxazine-based *Cinchona* alkaloid derivatives **1** and **2**.



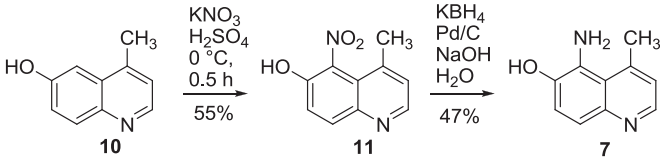

**Scheme 1.** Simplified mechanism for oxidative homo-condensation of substituted *o*-aminophenols.

However, the synthesis of unsymmetrical condensation products by the oxidative cross-coupling between two different derivatives of 2-aminophenol still presents a challenge. As proved by the Takusagawa,[21] Moody,[22] and Gu[23] groups it requires a specific oxidant and strictly controlled reaction conditions. Nonetheless the desired products were obtained in modest yields only.

Thus, prior to modification of *Cinchona* alkaloids, we explored the feasibility of cross-coupling of simple reactants using $H_2O_2$/ebselen or horseradish peroxidase, and $MnO_2$/ligand oxidations (51–91% yield, for the details, see Supplementary material). When these conditions were applied in the reaction of 2-aminophenol with 5-amino-6-hydroxyquinoline (**6**) the outcome was homo-coupling of 2-aminophenol only. By lowering the nucleophilicity of *o*-aminophenol by acetylation at nitrogen (as in **5a**), we obtained up to 1% of the heterocoupled product **8**. However, the desired product **8** was isolated in 10% yield when sodium iodate ($NaIO_3$) was used as an oxidant. Thus, for further tests we applied $NaIO_3$ to run the reaction with substituted *N*-acetyl-*o*-aminophenols (Scheme 2). The use of 5-methoxy-aminophenol (**5b**) resulted in better yields, presumably because of higher stability of the oxidized intermediate (*cf.* Scheme 1).

We also synthesized 5-amino-6-hydroxy-4-methyl-quinoline (**7**) (Scheme 3), which is chemically closer to the *Cinchona* alkaloid aromatic unit. The oxidative cyclocondensation proceeded with even higher yield than for **6** (Scheme 2).

Overall, these model experiments confirmed that sodium iodate was a suitable oxidant in the cross-coupling reaction. Moreover, it seems that the presence of a substituent at the 4 position of the quinoline ring significantly improves the reaction efficiency. With this consideration in mind, we prepared modified *Cinchona* alkaloids amenable for the coupling. The derivatives **13** and **15** with 5′-amino and 6′-hydroxyl groups were prepared in 3–4 step procedures (Scheme 4). 10,11-Dihydrocupreine (**3**) and 10,11-dihydrocupreidine (**4**) were obtained by treating commercially



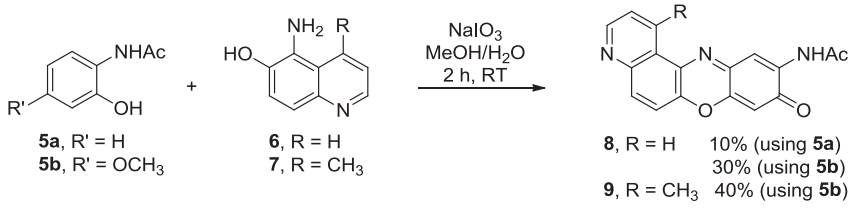

**Scheme 3.** Synthesis of **7**.

available 10,11-dihydroquinine and 10,11-dihydroquinidine with an aqueous solution of hydrobromic acid at reflux.[29] Then, nitration with fuming nitric acid was carried out affording the 5′-nitro derivatives **12** and **14** in 68% and 81% yields, respectively. Subsequent catalytic hydrogenation of the nitro compounds gave the corresponding 5′-amino alkaloids **13** and **15**. For each corresponding step of the syntheses noticeably higher yields were obtained for the quinidine-derived products (Scheme 4).

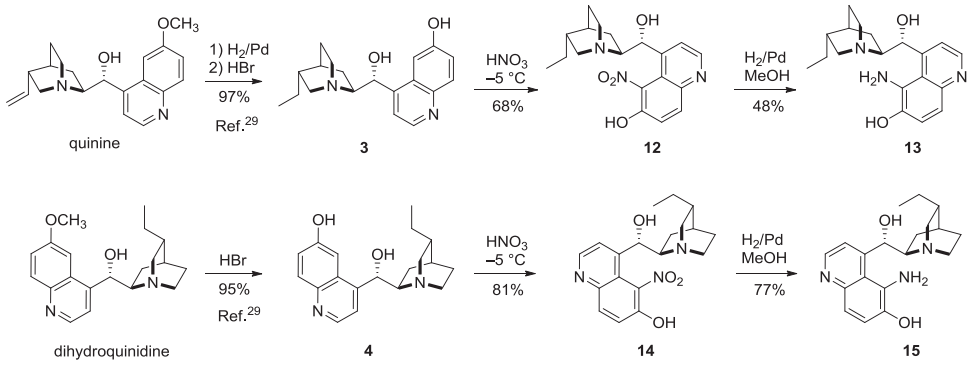
Ultimately, we carried out the oxidative cross-coupling reaction in the same manner as for the model experiments. The 5′-amino derivatives of cupreine **13** and cupreidine **15** when subjected to the reaction with the selected aminophenol **5b** afforded the desired cross-coupling products in good yields (Scheme 5).

In prospect of further modifications of new *Cinchona* analogs, a free amino group at the 10′ position of the phenoxazinone moiety is desirable. For this purpose the amino group in 2-amino-5-methoxyphenol was protected with a Boc group giving **5c**. Using the same protocol, we obtained the condensation products **1b** and **2b** in 72–75% yield, the highest in the series. Deprotection was carried out with an excess of trifluoroacetic acid in dichloromethane and furnished the desired 10′-amines **1c** and **2c** in good yields.

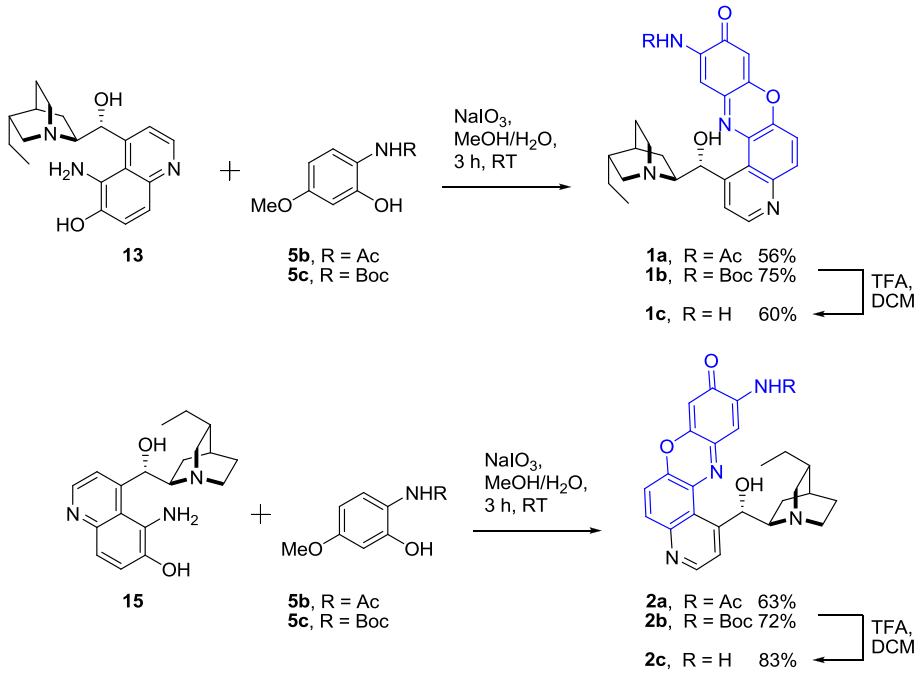
A preliminary test showed that the free amine **1c** exhibited some stereoselectivity in the copper-catalyzed Henry reaction (see Supplementary material). Biological assays of the *Cinchona*




**Scheme 2.** Oxidative coupling of **5a-b** with 5-amino-6-hydroxyquinolines **6** and **7** giving pyrido[3,2-*a*]phenoxazin-9-ones **8** and **9**.




**Scheme 4.** Synthesis of 5′-amino-10,11-dihydrocupreine (**13**) and 5′-amino-10,11-dihydrocupreidine (**15**).




**Scheme 5.** Aromatic oxidative cross-coupling of *Cinchona* alkaloid derivatives.

alkaloid-phenoxazinone hybrids for cytotoxic and inhibitory properties are under-way.

### 2.1. Conformation

The stereodifferentiating and catalytic properties of *Cinchona* alkaloids depend on their conformation. Therefore, it was interesting to examine how a substantial alteration to the aromatic ring system of the alkaloids would affect their conformational properties. Thus, we employed NMR and CD spectroscopy combined with DFT calculation. It was found that for the obtained phenoxazine hybrids **1a** and **2a** there exists an equilibrium of three conformers. Their proposed structures differing only slightly in energy calculated at the DFT/B3LYP/CC-pVDZ level of theory are shown in Fig. 2. Their presence was consistent with the observed NOESY interactions. Similar conformations were observed for unmodified quinine and quinidine.[30]

The best fit of experimental and GIAO/DFT chemical shifts for $^{13}C$ and $^{1}H$ nuclei was obtained for a 0.1:0.6:0.3 ratio of *syn-closed(1), anti-open,* and *syn-closed(2)* conformer populations (for more details, see Supplementary material). The interconversion of the rotamers was fast on the NMR time-scale down to 190 K. Consequently, an upper limit for the rotational barrier was estimated at 9 kcal/mol. This is in agreement with the results of a PM6 geometry scan (see Supplementary material), and very close to the value reported for unmodified alkaloids (8.3 kcal/mol by dynamic NMR).[31]

To confirm the stereochemical identity of the two diastereoisomers, CD spectra of **1a** and **2a** were recorded. For each of the compounds, both long-wavelength (450, 355 nm) and short-wavelength (315, 290, 270 nm) Cotton effects revealed nearly perfect mirror-images (Fig. 3). The CD spectra remain in qualitative agreement with TD-DFT calculation (see Supplementary material).

## 3. Conclusion

In conclusion, an unprecedented quinoline moiety annulation in *Cinchona* alkaloids has been developed. The method is based on simple oxidative cross-coupling of electron rich *N*-acylated 2-aminophenols with quinoline-derived aminophenols by application of sodium iodate. The analysis of a series of theoretical and experimental data showed that enlargement of the quinoline ring

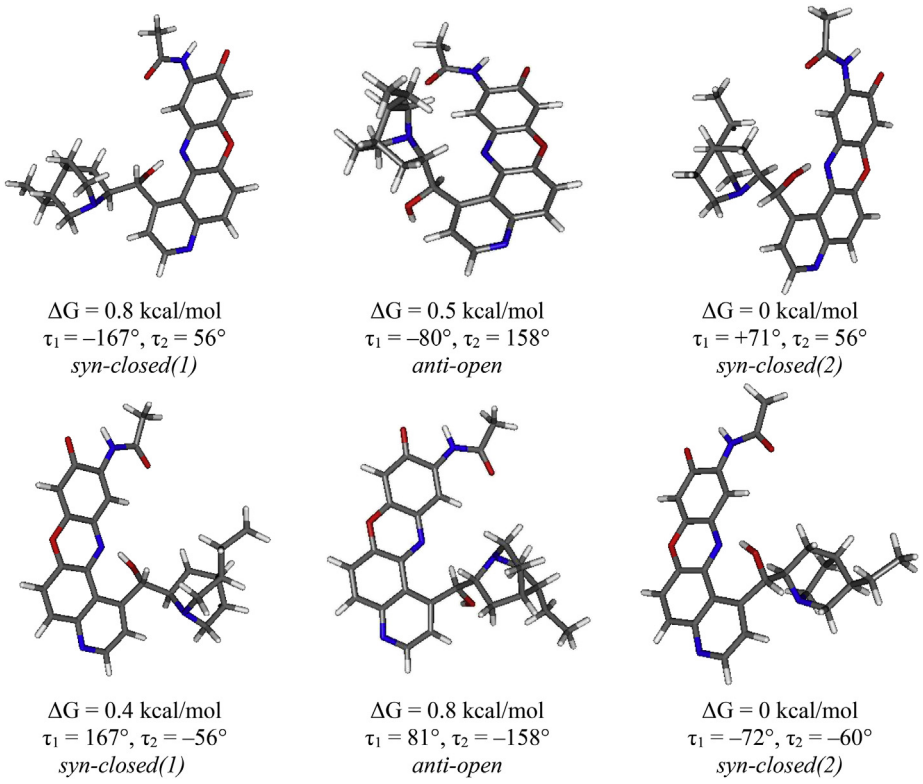



**Figure 2.** Computed low energy conformers and dihedral angles $\tau_1$: C2′–C1′–C9–C8 and $\tau_2$: C1′–C9–C8–N1 for **1a** (top) and **2a** (bottom) at the DFT/B3LYP/CC-pVDZ level of theory.

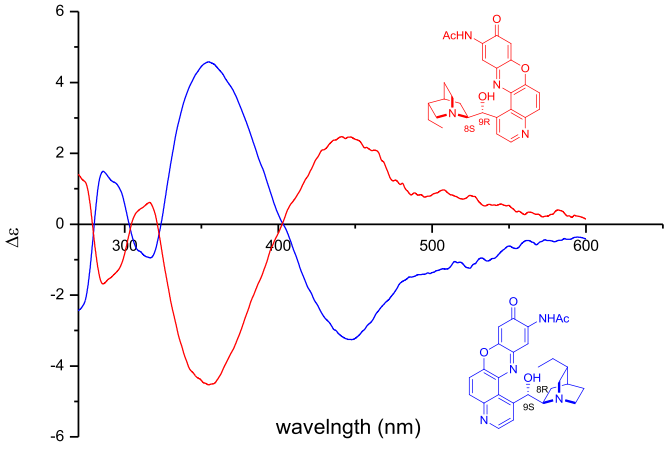



**Fig. 3.** Comparison of experimental CD spectra of **2a** (blue) and **1a** (red).

by 5,6-annulation does not affect the conformation or dynamics significantly as compared to the native *Cinchona* alkaloids.

## 4. Experimental section

### 4.1. General

Melting point were determined using an Electrothermal IA 91100 digital melting-point apparatus using the standard open capillary method and are uncorrected. $^1$H and $^{13}$C NMR spectra (400, 600 MHz and 100, 151 MHz, respectively) were collected on Jeol 400yh and Bruker Avance II 600 instruments. NMR spectra recorded in $CDCl_3$, methanol-$d_4$, DMSO-$d_6$, and $CF_3CO_2D$ were referenced to the respective residual $^1$H or $^{13}$C signals of the solvents. CD and UV spectra were recorded for $4 \times 10^{-4}$ M solutions in dichloromethane in 2-mm quartz cuvettes on a JASCO J-1500 circular dichroism spectrophotometer. Infrared spectra (4000-400 $cm^{-1}$) were collected on a Fourier transform, Bruker VERTEX 70V spectrometer using diamond ATR accessory. High resolution mass spectra were collected using electrospray ionization on Waters LCT Premier XE TOF instrument. Quinine and dihydroquinidine hydrochloride were purchased from Buchler GmbH. Compounds **5b**,[32] **5c**,[33] and **6**[34] were prepared according to the literature procedures.

### 4.2. General procedure for nitration of *3* and *4*. Preparation of *12* and *14*

A 100 mL flat bottomed flask was charged with fuming nitric acid (4.0 mL) and cooled to −5 °C. Dihydrocupreine (**3**) or dihydrocupreidine (**4**) (1.0 g, 3.2 mmol) was carefully added in small portions, keeping the temperature below 0 °C. The reaction mixture was allowed to stir for 15 min at ca. −5 °C, then poured onto 20 g of crushed ice. The pH was brought to 8–9 using 25% NaOH aqueous solution. The precipitate was filtered, and dissolved in 3/1 v/v chloroform/methanol solution. The aqueous filtrate was evaporated to dryness under reduced pressure, and the residual solid was extracted several times with 3/1 v/v chloroform/methanol solution. The combined organic phases were dried over $Na_2SO_4$, evaporated under reduced pressure and subjected to column chromatography on silica gel (70–230 mesh) with 3/1 v/v chloroform/methanol.

#### 4.2.1. 10,11-Dihydro-5′-nitro-cupreine (*12*)[13]

Dark red solid (0.77 g, 68%) mp 140–142 °C (dec). $R_f$ = 0.48 (3/1, v/v chloroform/methanol); $\nu_{max}$ (ATR)/$cm^{-1}$ 2200–3500 (br), 3039,

2957, 2931, 2877, 1608, 1504 (s), 1416, 1315 (br), 1257, 1118, 975, 822, 746, 542, 468; $\delta_H$ (400 MHz, $CD_3OD$) 8.59 (d, $J = 4.7$ Hz, 1H), 7.94 (d, $J = 9.3$ Hz, 1H), 7.92 (d, $J = 4.7$ Hz, 1H), 7.36 (d, $J = 9.3$ Hz, 1H), 5.45 (d, $J = 0.8$ Hz, 1H), 4.24–4.13 (m, 1H), 3.60–3.49 (m, 2H), 3.15–3.25 (m, 1H), 2.99 (ddd, $J = 12.8$, 4.4, 2.8 Hz, 1H), 2.13–2.0 (m, 3H), 1.99–1.89 (m, 1H), 1.88–1.77 (m, 1H), 1.40–1.23 (m, 3H), 0.84 (t, $J = 7.4$ Hz, 3H); $\delta_C$ (100 MHz, $CD_3OD$) 158.7, 146.4, 142.7, 141.8, 134.6, 134.2, 127.5, 122.5, 120.3, 67.9, 62.2, 57.8, 46.0, 36.8, 27.9, 25.8, 25.7, 19.0, 11.9; HRMS (ESI-TOF) calcd for $C_{19}H_{24}N_3O_4$ $[M+H]^+$: 358.1761, found: 358.1755.

#### 4.2.2. 10,11-Dihydro-5′-nitro-cupreidine (**14**)

Dark red solid (0.93 g, 81%), mp 145–146 °C (dec) $R_f = 0.48$ (3/1, v/v chloroform/methanol); $\nu_{max}$ (ATR)/$cm^{-1}$ 3322 (br), 2959, 2934, 1618, 1515, 1423, 1311, 1243, 1116, 989, 837, 750, 450, 443; $\delta_H$ (600 MHz, $CD_3OD$) 8.50 (d, $J = 4.6$ Hz, 1H), 7.86 (d, $J = 4.6$ Hz, 1H), 7.85 (d, $J = 9.4$ Hz, 1H), 7.28 (d, $J = 9.4$ Hz, 1H), 5.50 (s, 1H), 3.83 (ddd, $J = 12.5$, 8.8, 2.2 Hz, 1H), 3.54–3.45 (m, 2H), 3.39 (dd, $J = 12.8$, 9.9 Hz, 1H), 3.26 (ddd, $J = 12.2$, 9.4, 9.4 Hz, 1H), 2.24 (dd, $J = 12.8$, 10.4 Hz, 1H), 1.94 (s, br, 1H), 1.91–1.80 (m, 3H), 1.62–1.51 (m, 2H), 1.03 (ddd, $J = 13.4$, 9.3, 5.3 Hz, 1H), 0.94 (t, $J = 7.4$ Hz, 3H); $\delta_C$ (150 MHz, $CD_3OD$) 161.2, 145.3, 142.1, 141.0, 135.0, 133.8, 129.2, 122.0, 120.6, 68.1, 62.3, 52.2, 50.5, 36.2, 26.6, 25.3, 24.4, 18.4, 11.8; HRMS (ESI-TOF) calcd for $C_{19}H_{24}N_3O_4$ $[M+H]^+$: 358.1761, found: 358.1763.

### 4.3. General procedure for the synthesis of 5′-amino derivatives of alkaloids, **13** and **15**

To a 100 mL pressure vessel equipped with a stir bar, 5′-nitro derivative **12** or **14** (1.0 equiv) in methanol and 5% palladium on charcoal (0.08 equiv) were added. The reactor was then flushed with argon and the atmosphere was replaced with 3 bar of hydrogen. The mixture was stirred for three hours, and palladium was removed by filtration through Celite. The reaction was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (70–230 mesh) with 3/1, v/v chloroform/methanol.

#### 4.3.1. 5′-Amino-10,11-dihydro-cupreine (**13**)[13]

Following the general procedure above **12** (1.0 g, 2.8 mmol) in methanol (10.0 mL) was converted into the title compound **13** as a dark brown solid (0.44 g, 1.34 mmol, 48%), mp 125–127 °C (dec) $R_f = 0.77$ (3/1, v/v chloroform/methanol); $\nu_{max}$ (ATR)/$cm^{-1}$ 2300–3500 (br), 2956, 2926, 1573 (v), 1459, 1382, 1260 (br), 1144, 1115, 1044, 944, 830, 804, 519, 437; $\delta_H$ (600 MHz, $CD_3OD$) 8.57 (d, $J = 4.6$ Hz, 1H), 7.70 (d, $J = 4.6$ Hz, 1H), 7.53 (d, $J = 8.9$ Hz, 1H), 7.40 (d, $J = 8.9$ Hz, 1H), 6.1 (d, $J = 2.5$ Hz, 1H), 4.18 (ddd, $J = 10.7$, 7.2, 3.0 Hz, 1H), 4.00–4.10 (m, 1H), 3.53 (dd, $J = 12.7$, 10.5 Hz, 1H), 3.21 (ddd, $J = 12.5$, 11.6, 5.4 Hz, 1.2 Hz, 1H), 2.87 (ddd, $J = 12.5$, 5.6, 2.8 Hz, 1H), 2.19–2.04 (m, 3H), 2.02–1.94 (m, 1H), 1.92–1.81 (m, 1H), 1.71–1.60 (m 1H), 1.48–1.30 (m, 2H), 0.87 (t, $J = 7.4$ Hz, 3H); $\delta_C$ (100 MHz, $CD_3OD$) 147.8, 147.3, 146.4, 145.2, 129.5, 122.2, 121.0, 120.9, 120.2, 71.6, 62.6, 57.6, 45.0, 36.7, 27.6, 25.7, 25.6, 18.4, 11.9; HRMS (ESI-TOF) calcd for $C_{19}H_{26}N_3O_2$ $[M+H]^+$: 328.2020; found: 328.2015.

#### 4.3.2. 5′-Amino-10,11-dihydro-cupreidine (**15**)

Following the general procedure above **14** (923 mg, 2.58 mmol) in methanol (9.0 mL) was converted into the title compound **15** as a dark brown solid (656 mg, 2.0 mmol, 77%), mp 120–121 °C (dec) $R_f = 0.77$, (3/1, v/v chloroform/methanol); $\nu_{max}$ (ATR)/$cm^{-1}$3131 (br), 3042, 2958, 2934, 2876, 1572 (v), 1460, 1400, 1382, 1291, 1143, 1115, 1038, 946, 826, 795, 520, 441; $\delta_H$ (600 MHz, $CD_3OD$) 8.57 (d, $J = 4.5$ Hz, 1H), 7.75 (d, $J = 4.5$ Hz, 1H), 7.53 (d, $J = 8.9$ Hz, 1H), 7.39 (d, $J = 8.9$ Hz, 1H), 6.30 (s, 1H), 4.10 (dd, $J = 9.9$, 9.4 Hz, 1H), 3.76 (ddd, $J = 12.5$, 8.3, 1.8 Hz, 1H), 3.46–3.36 (m, 2H), 3.26 (ddd, $J = 12.5$, 9.1, 9.1 Hz, 1H), 2.26 (dd, $J = 13.1$, 9.9 Hz, 1H), 1.97 (s, 1H), 1.95–1.89 (m, 1H), 1.88–1.83 (m, 2H), 1.68–1.51 (m, 2H), 1.21 (ddd, $J = 13.1$, 9.4, 4.9 Hz, 1H), 0.96 (t, $J = 7.4$ Hz, 3H); $\delta_C$ (150 MHz, $CD_3OD$) 147.9, 147.4, 146.6, 145.3, 129.2, 122.7, 121.1, 120.9, 119.7, 71.2, 62.8, 51.4, 50.5, 36.3, 26.4, 25.5, 24.7, 19.0, 11.8; HRMS (ESI-TOF) calcd. for $C_{19}H_{26}N_3O_2$ $[M+H]^+$: 328.2020, found: 328.2011.

### 4.4. General procedure for the synthesis of phenoxazinone derivatives of Cinchona alkaloids **1a**, **1b** and **2a**, **2b**

To a mixture of the amino alkaloid derivative **13** or **15** (1.0 equiv) and *N*-acyl-2-amino-5-methoxyphenol **5b** or **5c** (1.5 equiv) in methanol, a solution of $NaIO_3$ (1.5 equiv) in water was added dropwise at room temperature. The resulting mixture was stirred for three hours, and extracted with chloroform. The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered, and the solvent was evaporated at 30 °C under reduced pressure. The products were purified by column chromatography on silica gel (70–230 mesh) with chloroform/methanol 10:1 or 20:1 v/v.

#### 4.4.1. (R)-(10-Acetamino-9-oxo-pyrido[3,2-a]phenoxazin-1-yl)((1S,2S,5R)-5-ethylquinuclidin-2-yl)methanol (**1a**)

Prepared according to the general procedure using **13** (82.0 mg, 0.25 mmol) and 2-hydroxy-5-metoxyacetanilide (**5b**, 68.0 mg, 0.38 mmol), in methanol (3.0 mL) and solution of $NaIO_3$ (73.8 mg, 0.38 mmol) in water (3.0 mL). The crude was subjected to column chromatography (10/1, v/v chloroform/methanol) giving desired product **1a** as a dark red solid (66.0 mg, 0.14 mmol, 56%) mp 241.5–243.5 °C (dec) $R_f = 0.36$ (10/1, v/v chloroform/methanol); $\nu_{max}$ (ATR)/$cm^{-1}$ 3265, 2955, 2926, 2875, 1611, 1585, 1565, 1488, 1437, 1366, 1338, 1158, 1004, 873, 835, 591, 522, 469; $\delta_H$ (600 MHz, $CDCl_3$) 8.92 (d, $J = 4.6$ Hz, 1H), 8.56 (s, 1H), 8.54 (s, 1H), 8.24 (d, $J = 9.2$ Hz, 1H), 8.12 (d, $J = 4.6$ Hz, 1H), 7 0.69 (d, $J = 9.2$ Hz, 1H), 6.99 (s, 1H), 6.46 (s, 1H) 4.55 (dd, $J = 17.7$, 10.9 Hz, 1H) 4.09 (dd, $J = 10.9$, 9.6 Hz, 1H), 3.58 (dd, $J = 13.3$, 10.5 Hz, 1H), 3.25 (ddd, $J = 17.7$, 6.4, 2.9 Hz, 1H), 2.96 (d, $J = 13.3$ Hz, 1H) 2.26 (s, 3H), 2.13–2.02 (m, 3H), 1.82 (m, 1H), 1.72 (ddd, $J = 12.0$, 12.0, 6.7 Hz, 1H), 1.32–1.24 (m, 1H) 1.17–1.13 (m, 2H), 0.72 (t, $J = 7.4$ Hz, 3H); $\delta_C$ (100 MHz, $CDCl_3$) 178.7, 169.1, 150.3, 147.94, 147.92, 146.9, 146.6, 142.4, 137.7, 136.0, 129.1, 123.2, 122.6, 119.0, 113.0, 103.5, 68.6, 59.6, 57.1, 44.7, 36.2, 27.4, 25.5, 24.9, 24.4, 19.9, 11.7; HRMS (ESI-TOF) calcd for $C_{27}H_{29}N_4O_4$ $[M+H]^+$: 473.2183, found: 473.2190.

#### 4.4.2. (R)-(10-tert-Butyloxycarbonyl-amino-9-oxo-pyrido[3,2-a] phenoxazin-1-yl)((1S,2S,5R)-5-ethylquinuclidin-2-yl)methanol (**1b**)

Prepared according to the general procedure using **13** (0.22 g, 0.67 mmol), *tert*-butyl-(2-hydroxy-5-methoxyphenyl)carbamate (**5c**, 0.24 g, 1.0 mmol) in methanol (8.0 mL) and solution of $NaIO_3$ (0.198 g, 1.0 mmol) in water (8.0 mL). The crude product was purified on column chromatography (10/1 v/v chloroform/methanol) giving desired product as a dark red solid (0.267 g, 0.50 mmol, 75%) mp 189.0–191.5 °C (dec) $R_f = 0.45$ (20/1 v/v chloroform/methanol). $\nu_{max}$ (ATR)/$cm^{-1}$ 3352, 2928, 2871, 1732, 1616, 1588, 1565, 1493, 1339, 1142, 1013, 841, 642, 602, 523, 436; $\delta_H$ (400 MHz, $CDCl_3$) 8.94 (d, $J = 4.6$ Hz, 1H), 8.27 (d, $J = 9.2$ Hz, 1H), 8.14 (s, 1H), 8.07 (d, $J = 4.6$ Hz, 1H), 7.98 (s, 1H), 7.74 (d, $J = 9.2$ Hz, 1H), 6.82 (br., 1H), 6.52 (s, 1H), 5.09 (s, br, 1H) 4.40–4.25 (m, 1H), 4.03 (ddd, $J = 9.6$, 9.6, 3.7 Hz, 1H), 3.41 (dd, $J = 13.0$, 10.5 Hz, 1H), 3.14 (ddd, $J = 12.1$, 12.1, 3.6 Hz, 1H), 2.83 (d, $J = 13.1$ Hz, 1H), 2.10–1.95 (m, 3H), 1.83–1.63 (m, 2H), 1.56 (s, 9H), 1.50–1.40 (m, 1H), 1.21 (dq, $J = 8.7$, 7.3 Hz, 2H), 0.76 (t, $J = 7.3$ Hz, 3H); $\delta_C$ (100 MHz, $CDCl_3$) 178.4, 151.7, 150.3, 148.0, 147.9, 147.1, 146.5, 142.5, 139.0, 135.7, 129.0, 123.4, 123.0, 119.1, 109.9, 103.6, 82.4, 77.2, 59.5, 57.3, 44.5, 36.5, 28.2, 27.5, 26.0, 24.6, 24.0,

11.8; HRMS (ESI-TOF) calcd for $C_{30}H_{35}N_4O_5$ $[M+H]^+$: 531.2602, found: 531.2614.

#### 4.4.3. (S)-(10-Acetamino-9-oxo-pyrido[3,2-a]phenoxazin-1-yl)((1S,2R,5R)-5-ethylquinuclidin-2-yl)methanol (**2a**)

Prepared according to the general procedure using **15** (82.0 mg, 0.25 mmol), 2-hydroxy-5-metoxyacetanilide (**5b**, 68.0 mg, 0.375 mmol) in methanol (3.0 mL) and solution of $NaIO_3$ (73.8 mg, 0.375 mmol) in water (3.0 mL). The crude product was purified on column chromatography (10/1, v/v chloroform/methanol) giving desired product as a dark red solid (81.0 mg, 0.17 mmol, 68%) mp 211–212 °C (dec) $R_f$ = 0.42 (20/1, v/v chloroform/methanol); $\nu_{max}$ (ATR)/$cm^{-1}$ 3259, 2956, 2926, 2878, 1689, 1607, 1586, 1565, 1493, 1436, 1368, 1338, 1158, 1005, 875, 838, 590, 520, 469; $\delta_H$ (600 MHz, $CD_3OD$) 9.01 (d, $J$ = 4.8 Hz, 1H), 8.54 (d, $J$ = 1.3 Hz, 1H), 8.31 (dd, $J$ = 9.2, 2.3 Hz, 1H), 8.28 (d, $J$ = 4.8 Hz, 1H), 7.96 (dd, $J$ = 9.2, 2.3 Hz, 1H), 6.98 (d, $J$ = 1.3 Hz, 1H), 6.58 (d, $J$ = 2.9 Hz, 1H), 4.20–4.28 (m, 1H), 4.18 (ddd, $J$ = 12.5, 8.9, 2.2 Hz, 1H), 3.59 (dd, $J$ = 12.5, 10.2 Hz, 1H), 3.54–3.52 (m, 1H), 3.46–3.41 (m, 1H), 2.39–2.33 (m, 1H), 2.32 (s, 3H), 2.03–1.99 (m, 1H), 1.98–1.93 (m, 1H), 1.89–1.85 (m, 2H), 1.71–1.62 (m, 2H), 1.18–1.13 (m, 1H), 1.01 (t, $J$ = 7.4 Hz, 3H); $\delta_C$ (100 MHz, $CD_3OD$) 180.6, 172.9, 151.2, 150.4, 150.2, 148.7, 148.0, 144.7, 139.8, 135.8, 131.2, 124.1, 123.4, 121.3, 114.5, 104.4, 70.7, 61.4, 53.0, 51.5, 36.3, 26.5, 25.4, 24.6, 24.4, 18.9, 11.8; HRMS (ESI-TOF) calcd for $C_{27}H_{29}N_4O_4$ $[M+H]^+$: 473.2183, found: 473.2201.

#### 4.4.4. (S)-(10-tert-Butyloxycarbonyl-amino-9-oxo-pyrido[3,2-a]phenoxazin-1-yl)((1S,2R,5R)-5-ethylquinuclidin-2-yl)methanol (**2b**)

Prepared according to the general procedure using **15** (1.08 g, 3.30 mmol), *tert*-butyl-(2-hydroxy-5-methoxyphenyl)carbamate (**5c**, 1.18 g, 4.93 mmol) in methanol (20.0 mL) and solution of $NaIO_3$ (0.976 g, 4.93 mmol) in water (20.0 mL). The crude product was purified on column chromatography (10/1, v/v chloroform/methanol) giving desired product as a dark red solid (1.26 g, 2.37 mmol, 72%) mp 148–149 °C (dec) $R_f$ = 0.45 (20/1, v/v chloroform/methanol); $\nu_{max}$ (ATR)/$cm^{-1}$ 3339, 2956, 2931, 2876, 1726, 1614, 1587, 1565, 1493, 1340, 1141, 1014, 840, 648, 602, 521, 435; $\delta_H$ (600 MHz, $CDCl_3$) 8.91 (d, $J$ = 4.6 Hz, 1H), 8.24 (d, $J$ = 9.2 Hz, 1H), 8.11 (s, 1H), 8.09 (d, $J$ = 4.6 Hz, 1H), 7.87 (s, 1H), 7.69 (d, $J$ = 9.2 Hz, 1H), 7.22 (br., 1H), 6.37 (s, 1H), 5.56 (br., 2H), 4.03 (dd, $J$ = 10.5 Hz, 1H), 3.50 (dd, $J$ = 12.6, 10.4 Hz, 1H), 3.31–3.42 (m, 1H), 3.23–3,12 (m, 1H), 2.17 (dd, $J$ = 12.0 Hz, 1H), 1.98–1.86 (m, 1H), 1.80–1.70 (m, 3H), 1.55 (s, 9H), 1.66–1.49 (m, 2H), 1.07–0.98 (m, 1H), 0.93 (t, $J$ = 7.4 Hz, 3H); $\delta_C$ (100 MHz, $CDCl_3$) 178.2, 151.7, 150.3, 147.7, 147.4, 147.0, 146.4, 142.3, 138.8, 135.6, 129.2, 122.8, 122.5, 119.1, 110.0, 103.5, 82.5, 77.2, 60.4, 51.8, 49.8, 35.6, 28.2, 25.5, 24.4, 24.3, 19.5, 11.6; HRMS (ESI-TOF) calcd for $C_{30}H_{35}N_4O_5$ $[M+H]^+$: 531.2602, found: 531.2596.

### 4.5. General procedure for Boc deprotection of **1b** and **2b** to **1c** and **2c**

Deprotection of 1 mmol of Boc was performed using trifluoroacetic acid (TFA) (15 equiv) in dichloromethane for two hours at room temperature. After evaporation of solvent at 30 °C under reduced pressure, the residue was dissolved with 10/1 chloroform/methanol solution (10 mL), neutralized with 5% aqueous $NaHCO_3$ (15 mL) and extracted with $CHCl_3$ (5 × 30 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (10/1, v/v chloroform/methanol) gave products **1c** and **2c** in the form of dark red solids.

#### 4.5.1. (R)-(10-Amino-9-oxo-pyrido[3,2-a]phenoxazin-1-yl)((1S,2S,5R)-5-ethylquinuclidin-2-yl)methanol (**1c**)

Prepared according to the general procedure using **1b** (0.267 g, 0.5 mmol) in dichloromethane (1.0 mL) and trifluoroacetic acid (0.67 mL, 8.8 mmol). Followed by purification was furnished the desired product as a dark red solid (0.125 g, 2.9 mmol, 59%), mp 231.1–233.0 °C $R_f$ = 0.45 (15/1 v/v chloroform/methanol); $\nu_{max}$ (ATR)/$cm^{-1}$ 3305, 3176, 2961, 2878, 1670, 1582, 1566, 1385, 1260, 1178 (br.), 1114 (br.), 1008, 828, 798, 719, 598, 521; $\delta_H$ (400 MHz, $CDCl_3$) δ 8.89 (d, $J$ = 4.6 Hz, 1H), 8.11 (d, $J$ = 4.6 1H), 8.10 (d, $J$ = 9.1 Hz, 1H), 7.60 (d, $J$ = 9.1 Hz, 1H), 7.17 (br., 1H), 6.93 (s, 1H), 6.11 (s, 1H), 5.62 (br., 2H), 4.67 (dd, $J$ = 18.2, 12.0 Hz, 1H), 3.84 (t, $J$ = 9.9 Hz, 1H), 3.55 (t, $J$ = 11.8 Hz, 1H), 3.30 (ddd, $J$ = 12.4, 11.9, 3.0 Hz, 1H), 2.66–2.58 (m, 1H), 2.19–2.09 (m, 1H), 2.07–1.98 (m, 2H), 1.87–1.70 (m, 2H), 1.13–0.93 (m, 3H), 0.66 (t, $J$ = 7.4 Hz, 3H); $\delta_C$ (100 MHz, $CDCl_3$) 178.8, 149.5, 147.9, 147.4, 147.2, 146.6, 146.5, 140.8, 132.0, 129.2, 121.6, 121.6, 119.4, 103.3, 99.1, 69.0, 60.2, 57.5, 45.3, 35.8, 27.3, 25.0, 24.0, 18.9, 11.6; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_4O_3$ $[M+H]^+$: 431.2078, found: 431.2078.

#### 4.5.2. (S)-(10-Amino-9-oxo-pyrido[3,2-a]phenoxazin-1-yl)((1S,2R,5R)-5-ethylquinuclidin-2-yl)methanol (**2c**)

Prepared according general procedure using **2b** (0.950 g, 1.8 mmol) in dichloromethane (2.5 mL) and trifluoroacetic acid (0.86 mL, 27.0 mmol). Followed by purification was furnished the desired product as a dark red solid (0.645 g, 1,5 mmol, 83%), mp 275.6–276.9 °C (dec); $R_f$ = 0.42 (15/1 v/v $CHCl_3$/MeOH); $\nu_{max}$ (ATR)/$cm^{-1}$ 3200–3600 (br), 3130, 2957, 2933, 2880, 1572 (br), 1515, 1461, 1382, 1277 (br), 1141, 1117, 1040, 826, 790, 720, 607, 520, 438; $\delta_H$ (400 MHz, $CDCl_3$) 8.89 (d, $J$ = 4.6 Hz, 1H), 8.12 (d, $J$ = 4.6 Hz, 1H), 8.09 (d, $J$ = 9.2 Hz, 1H), 7.59 (d, $J$ = 9.2 Hz, 1H), 7.28 (br., 1H), 7.21 (s, 1H), 6.05 (s, 1H), 5.82 (br., 1H), 5.45 (s, br, 2H), 4.23 (ddd, $J$ = 13.0, 9.1, 2.1 Hz, 1H), 3.79 (dd, $J$ = 10.1, 9.6 Hz, 1H), 3.68 (dd, $J$ = 12.5, 10.6 Hz, 1H), 3.37 (ddd, $J$ = 12.2 9.6, 9.6 Hz, 1H), 3.11 (dd, $J$ = 12.2, 11.0 Hz 1H), 2.23 (dd, $J$ = 10.1, 7.1 Hz, 1H), 1.92–1.88 (m, 1H), 1.82–1.70 (m, 2H), 1.70–1.50 (m, 3H), 0.95 (t, $J$ = 4.6 Hz, 3H), 0.82 (ddd, $J$ = 9.6, 7.1, 3.9 Hz, 1H); $\delta_C$ (100 MHz, $CDCl_3$) 178.7, 149.9, 147.4, 147.11, 147.07, 147.0, 146.1, 140.7, 132.6, 129.2, 121.5, 121.3, 119.1, 103.2, 99.3, 68.9, 60.8, 51.5, 50.3, 35.2, 25.4, 24.2, 23.6, 18.3, 11.5; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_4O_3$ $[M+H]^+$: 431.2078, found: 431.2078.

### 4.6. 5-Amino-4-methylquinolin-6-ol (**7**)

To a solution of NaOH (6.3 g, 0.16 mol) in methanol and water (76 mL, 1:1, v/v), $KBH_4$ (2.12 g, 39.3 mmol) and 5% Pd on charcoal (0.098 g, 0.046 mmol, 0.6 mol%) was added. To the vigorously stirred mixture, a solution of 6-hydroxy-4-methyl-5-nitroquinoline (**11**) (1.59 g, 7.80 mmol) in methanol (40 mL) was added dropwise over 3 h at room temperature (+25 °C). The resulting mixture then was allowed to stir for 15 min. When the reaction was completed the palladium was removed by filtration through a Celite pad and washed with methanol. The reaction mixture was evaporated under vacuum and the residue was treated with water (60 mL) and concentrated HCl (22 mL). The pH was brought to 8–9 value using $NaHCO_3$ (6.0 g). The insoluble material was filtered and the aqueous layer was extracted with ethyl acetate (5 × 100 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, and the solvent was removed *in vacuo* to give the desired product as a brown solid (0.635 g, 3.64 mmol, 47%), mp 251–252 °C, $R_f$ = 0.3 (AcOEt); $\nu_{max}$ (ATR)/$cm^{-1}$ 3376, 2924, 2852, 1606, 1575, 1515, 1383, 1298, 1272, 1255, 1194, 1139, 916, 819, 811, 548; $\delta_H$ (600 MHz, DMSO-$d_6$) 9.58 (br., 1H), 8.36 (d, $J$ = 4.2 Hz, 1H), 7.27 (d, $J$ = 8.8 Hz, 1H), 7.23 (d, $J$ = 8.8 Hz, 1H), 6.98 (d, $J$ = 4.2 Hz, 1H), 4.71 (br., 2H), 2.92 (s, 3H); $\delta_C$ (100 MHz, DMSO-$d_6$) 146.5, 144.2, 143.2, 140.6, 130.6, 121.7, 120.0, 119.1, 118.6, 23.4; HRMS (ESI-TOF) calcd for $C_{10}H_{11}N_2O$ $[M + H]^+$: 175.0866, found: 175.0877.

### 4.7. General procedure for preparation of **8** and **9**

To a mixture of 5-aminoquinoline **6** or **7** (1.0 equiv) and *N*-acethyl-2-aminophenol derivative **5a** or **5b** (1.5 equiv) in methanol, a solution of $NaIO_3$ (1.5 equiv) in water was added dropwise at room temperature. The resulting mixture was stirred for up to three hours at room temperature, then the organic solvent was removed under reduced pressure (20 mmHg). The precipitate was filtered and the residue extracted with hot methanol and concentrated to afford pure product.

#### 4.7.1. 10-Acetaminopyrido[3,2-a]phenoxazin-9-one (**8**)

Prepared according to the general procedure using 5-amino-6-hydroxyquinoline (**6**, 40.0 mg, 0.25 mmol), *N*-(2-hydroxy-5-methoxyphenyl)acetamide (**5b**) (68.0 mg, 0.375 mmol) in methanol (3.0 mL) and $NaIO_3$ (74.0 mg, 0.375 mmol) in water (3.0 mL). **8** was obtained as orange solid (23.0 mg, 0.075 mmol, 30%), mp > 300 °C (dec), $R_f$ = 0.6 (20/1 v/v chloroform/methanol). For **8**·TFA: $\nu_{max}$ (ATR)/$cm^{-1}$ 3330, 3199, 2918, 2850, 1673, 1580 (s), 1483, 1379, 1182 (s), 1131 (s), 813, 799, 717, 498, 479; $\delta_H$ (600 MHz, $CF_3COOD$) 10.17 (d, $J$ = 8.5 Hz, 1H), 9.17 (br., 1H), 8.80 (s br, 1H), 8.49 (dd, $J$ = 9.2, 2.9 Hz, 1H), 8.27 (dd, $J$ = 8.7, 5.6 Hz, 1H), 8.24 (d, $J$ = 9.2 Hz, 1H), 6.90 (s, 1H), 2.43 (s, 3H); $\delta_C$ (150 MHz, $CF_3COOD$) 183.6, 177.7, 152.2, 151.9, 146.3, 145.9, 145.7, 140.2, 138.0, 131.2, 130.2, 128.2, 126.4, 125.8, 119.2, 106.8, 24.7; HRMS (ESI-TOF) calcd for $C_{17}H_{12}N_3O_3$ $[M + H]^+$: 306.0873, found: 306.0886.

#### 4.7.2. 10-Acetamino-1-methylpyrido[3,2-a]phenoxazin-9-one (**9**)

Prepared according general procedure using 5-amino-6-hydroxy-4-methylquinoline (**7**, 44.0 mg, 0.25 mmol), *N*-(2-hydroxy-5-methoxyphenyl)acetamide (**5b**, 68.0 mg, 0.375 mmol) in methanol (3.0 mL) and $NaIO_3$ (74.0 mg, 0.375 mmol) in water (3.0 mL). **9** was obtained as a red solid (32.0 mg, 0.1 mmol, 40%), mp > 300 °C (dec); $R_f$ = 0.62 (20/1 v/v chloroform/methanol); $\nu_{max}$ (ATR)/$cm^{-1}$3292, 2961, 2923, 2851, 1688, 1598, 1548, 1513, 1489, 1386, 1260, 1160, 1015 (br), 796, 762, 469; $\delta_H$ (600 MHz, $CF_3COOD$) 8.90 (d, $J$ = 4.8 Hz, 1H), 8.79 (s, 1H), 8.45 (d, $J$ = 9.1 Hz, 1H), 8.21 (d, $J$ = 9.1 Hz, 1H), 8.03 (d, $J$ = 4.8 Hz, 1H), 6.90 (s, 1H), 3.60 (s, 3H), 2.43 (s, 3H); $\delta_C$ (150 MHz, $CF_3COOD$) 183.4, 177.5, 166.2, 151.3, 150.3, 146.4, 143.9, 140.2, 138.7, 133.7, 129.1, 128.6, 127.8, 127.5, 118.8, 106.0, 28.4, 24.8; HRMS (ESI-TOF) calcd for $C_{18}H_{14}N_3O_3$ $[M + H]^+$: 320.1030, found: 320.1046.

### 4.8. 4-Methylquinolin-6-ol (**10**)

Using a modified patent procedure,[35] to a solution of *p*-hydroxyaniline (1.36 g, 12.5 mmol) and anhydrous zinc(II)chloride (0.260 g, 1.59 mmol) in ethanol/water 95/5 v/v (7.0 mL) at 40 °C, dry iron(III) chloride (5.4 g, 34 mmol) was added and the temperature was increased to 80 °C. Then, methyl vinyl ketone (1.0 mL, 0.876 g, 12.5 mmol) was slowly injected with a syringe over 1 h. The reaction was stirred at 80 °C for an additional 15 h before cooling to room temperature and quenching with 10% aqueous sodium hydroxide (25 mL). The insoluble material was filtered off through a pad of Celite and rinsed several times with ethyl acetate. The aqueous layer was extracted with ethyl acetate (5 × 50 mL), and dried over anhydrous $Na_2SO_4$, and filtered. The solvent was removed *in vacuo*, and the residue was purified by column chromatography using ethyl acetate to give the desired product **10** as a pale yellow solid (1.03 g, 6.5 mmol, 54%), mp 217–218 °C (lit.[36] mp 222–224 °C); $\nu_{max}$ (ATR)/$cm^{-1}$ 2983, 2909, 2844, 2546 (br), 1616, 1467, 1404, 1245, 1230, 896, 842, 741, 539, 422; $\delta_H$ (600 MHz, $CD_3OD$) 8.46 (d, $J$ = 4.2 Hz, 1H), 7.32 (dd, $J$ = 9.0, 2.3 Hz, 1H), 7.27 (d, $J$ = 2.3 Hz, 1H), 7.26 (d, $J$ = 4.2 Hz, 1H), 2.62 (s, 3H); $\delta_C$ (150 MHz, $CD_3OD$) 157.4, 147.5, 145.3, 143.5, 131.1, 130.9, 123.1, 123.0, 106.3, 18.8.

### 4.9. 4-Methyl-5-nitroquinolin-6-ol (**11**)

To conc. $H_2SO_4$ (17.0 mL), 6-hydroxy-4-methylquinoline (**10**) (2.00 g, 12.6 mmol) was added in portions at 0 °C. After 5 min, $KNO_3$ (1.88 g, 18.5 mmol, 1.5 equiv) was added and the reaction mixture was stirred at 0 °C for 30 min. Then it was poured onto 60 g of crushed ice. The pH was brought to 8–9 using 25% aq $NH_4OH$. The precipitate was filtered to give **11** as a green solid (1.41 g, 6.90 mmol, 55%), mp 249–250 °C; $R_f$ = 0.5 (ethyl acetate); $\nu_{max}$ (ATR)/$cm^{-1}$ 3046, 2984, 2366 (br), 1591, 1521, 1508, 1380, 1304, 1279, 1249, 1225, 1155, 1100, 974, 843, 782, 711, 567, 519, 422; $\delta_H$ (600 MHz, DMSO-$d_6$) 11.57 (br., 1H), 8.66 (d, $J$ = 4.4 Hz, 1H), 8.09 (d, $J$ = 9.2 Hz, 1H), 7.55 (d, $J$ = 9.2 Hz, 1H), 7.43 (d, $J$ = 4.4 Hz, 1H), 2.45 (s, 3H); $\delta_C$ (150 MHz, DMSO-$d_6$) 148.3, 148.1, 141.7, 138.7, 133.6, 132.6, 125.7, 120.9, 120.0, 17.7; HRMS (ESI-TOF) calcd for $C_{10}H_9N_2O_3$ $[M + H^+]$: 205.0608, found: 205.0621.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.11.072.

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