

## Synthesis of 8-aminoquinoline chelating moieties for chemosensor molecules

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This paper is dedicated to Professor György Keglevich on the occasion of his 65th birthday

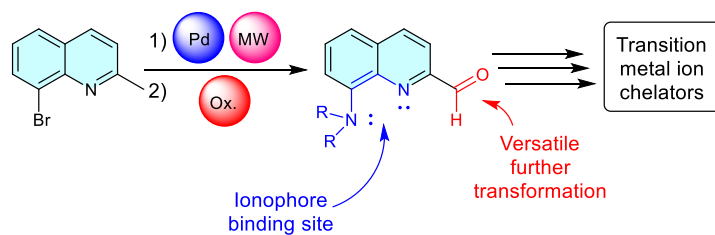
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### Abstract

8-Aminoquinolines are useful molecular motifs for ion sensors. To encourage chemosensor development, new building blocks containing these motifs are essential. 8-Aminoquinoline-2-carbaldehydes are proposed as useful building blocks since their aldehyde group offers the possibility for further transformations. We present a general method for the preparation of these compounds starting from commercially available 8-bromo-2-methylquinoline. Different sidechains for fine-tuning their affinity and selectivity were introduced by a microwave-aided *N*-arylation using Pd(0) and P-ligands; the desired products were achieved by oxidation. An alternative method is also presented when the product shows high affinity towards the catalyst limiting the effectiveness of the Pd-catalysed the *N*-arylation.



- ✓ Commercially available starting material
- ✓ High overall yields
- ✓ Mild reaction conditions

**Keywords:** Chemosensor ligands, *N*-arylation, P-ligand, Buchwald-Hartwig amination, microwave, ionophores

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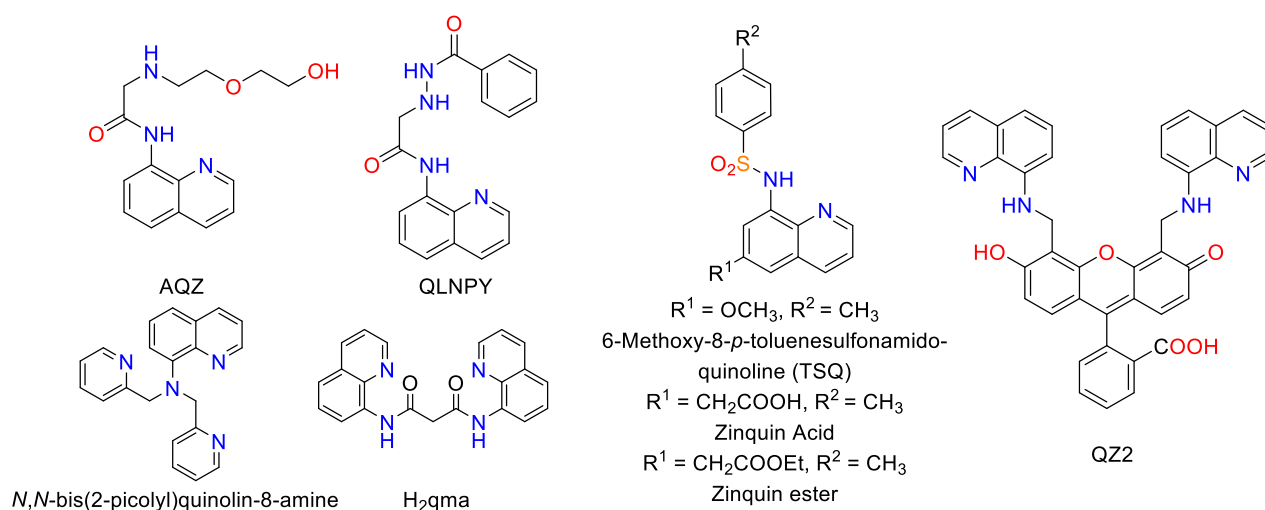
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## Introduction

Detection of metal ions is an important area of modern analytical chemistry.<sup>1</sup> Molecular sensors are useful tools to solve challenges in different fields such as neurobiology<sup>2</sup>, cancer therapy<sup>3-6</sup>, wastewater analysis<sup>1</sup>, etc.<sup>2</sup> The functions of these ion sensors are based on different molecular mechanisms, e.g., the alteration of their fluorescent, optical (absorbance), electrochemical or magnetic properties.<sup>7</sup>

Chemosensor molecules all contain a well-defined binding site, which is responsible for the stable and selective chelation of the analyte. A wide variety of selective binding moieties have been reported previously for various target analytes. 8-Aminoquinolines have been proven to be potent ionophores, used in many metal-ion chelators, especially for Cu<sup>2+</sup>, Ni<sup>2+</sup>, Zn<sup>2+</sup> and Cd<sup>2+</sup> ions (see examples in *Figure 1*).<sup>8-13</sup> These analytes have gained significant importance recently, owing to their roles in neurobiology, immunology, and even in infectious diseases such as COVID-19.<sup>14-19</sup>



**Figure 1.** Selected examples of metal sensors with 8-aminoquinoline motifs.<sup>20-26</sup>

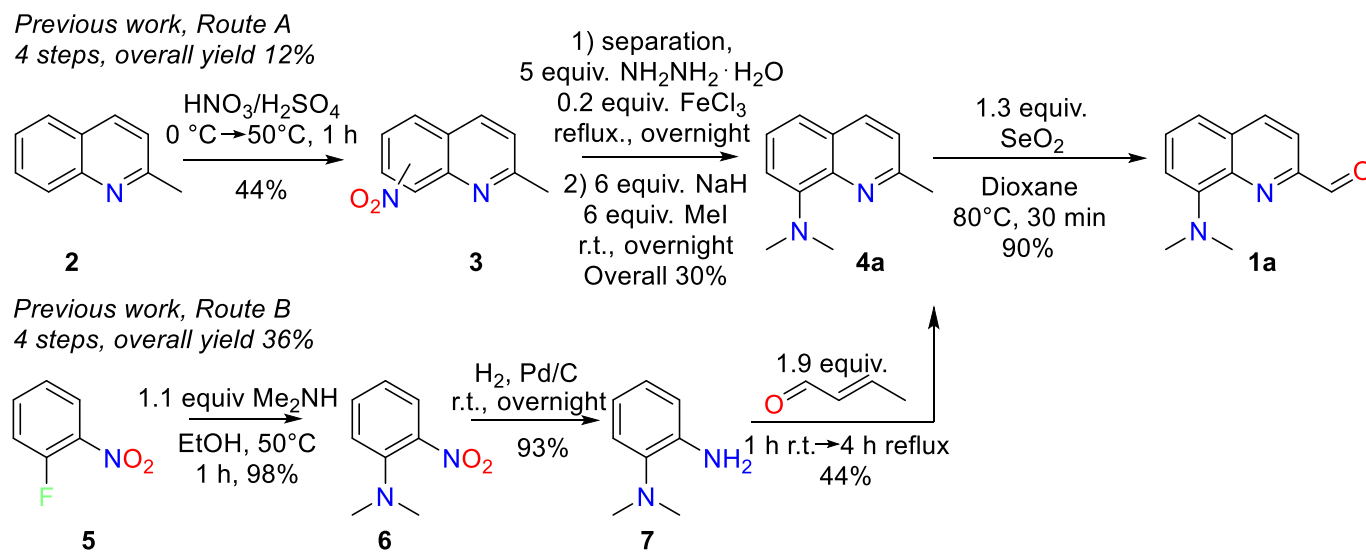
Preparation of these quinoline-based ion sensors is challenging for chemists. The availability of precursor-building blocks would encourage more extensive research in the field of chemosensor development. Our aim was the development of a simple, general synthetic route for substituted 8-aminoquinoline-2-carbaldehydes as promising building blocks for future chemosensor compounds. These derivatives contain a tuneable motif for binding to the analytes. In addition, they contain a reactive aldehyde group. Therefore, a versatile functionalization would have a high impact on the characteristics of the achieved chemosensors. Position 2 on the quinoline ring was chosen as the placement of the aldehyde function since it is sterically close to the binding site. On one hand, this affords the possibility for further fine tuning of the affinity of the resulting compounds. On the other hand, it also offers the possibility of modifying spectroscopic properties of the chemosensors or the possibility of conjugating them to biomolecules, for example. Currently no chemosensors take advantage of functionalization at this position. Thus, hopefully, the described synthetic method will help to explore the effects of different substituents at position 2 in the future.

The degree of substitution of the amines also plays an essential role in selective metal-ion chelating.<sup>13,26</sup> The syntheses of tertiary amines can be carried out simply in different ways which have been previously published, such as *N*-alkylation of primary or secondary amines by alkyl halides or tosylates and mesylates,<sup>27-29</sup> intramolecular Mitsunobu reaction of amino alcohols,<sup>30,31</sup> or *N*-arylation reactions.<sup>32</sup> One of the most effective

methods for *N*-arylation is the microwave-assisted Buchwald-Hartwig or Ullman-Goldberg coupling reaction.<sup>33-36</sup> These transition-metal-catalysed coupling processes have revolutionized the entire field of organic chemistry in general. Although this synthetic route offers a straightforward strategy to obtain the desired 8-aminoquinolines in a systematic manner, syntheses of 8-aminoquinolines bearing ionophore side chains employing this method have not been reported previously. Keglevich and co-workers have presented several times in the last few years, the unique effectiveness of microwave irradiation, combined with transition metal catalysis, on various types of coupling reactions.<sup>36-42</sup> Therefore, a general method using similar reactions is presented in this research work.

Previously, the transformations of 8-aminoquinolines (**4**) into the desired aldehydes (**1**) have been reported using a Riley oxidation.<sup>33</sup> Two synthetic routes were described for the desired compound, 8-*N,N*-dimethylaminoquinoline-2-carbaldehyde (**1a**). Route A (Scheme 1, top) has a low yield due to the formation of undesired regioisomers during nitration of 2-methylquinoline (**2**). After chromatography, the proper nitro derivative was reduced, then bis-alkylated using methyl iodide, to form **4a** in low yield. Finally, the intermediate **4a** was transformed into the desired product **1a**.

A different strategy has been carried out in Route B (Scheme 1, bottom), starting with arylation of dimethylamine by 2-fluoronitrobenzene (**5**) followed by the reduction of **6** to obtain **7** in high overall yield. The quinoline ring was formed in a Doebner-von Miller reaction using crotonaldehyde. We have carried out and confirmed the synthesis of **1a** *via* route B with similar yields as published,<sup>33</sup> however, for further target molecules, this method offers relatively low yields. Moreover, preparing 8-aminoquinolines (e.g., **4a**) *via* this route also requires three steps, which would become laborious when a larger library of these compounds is needed.

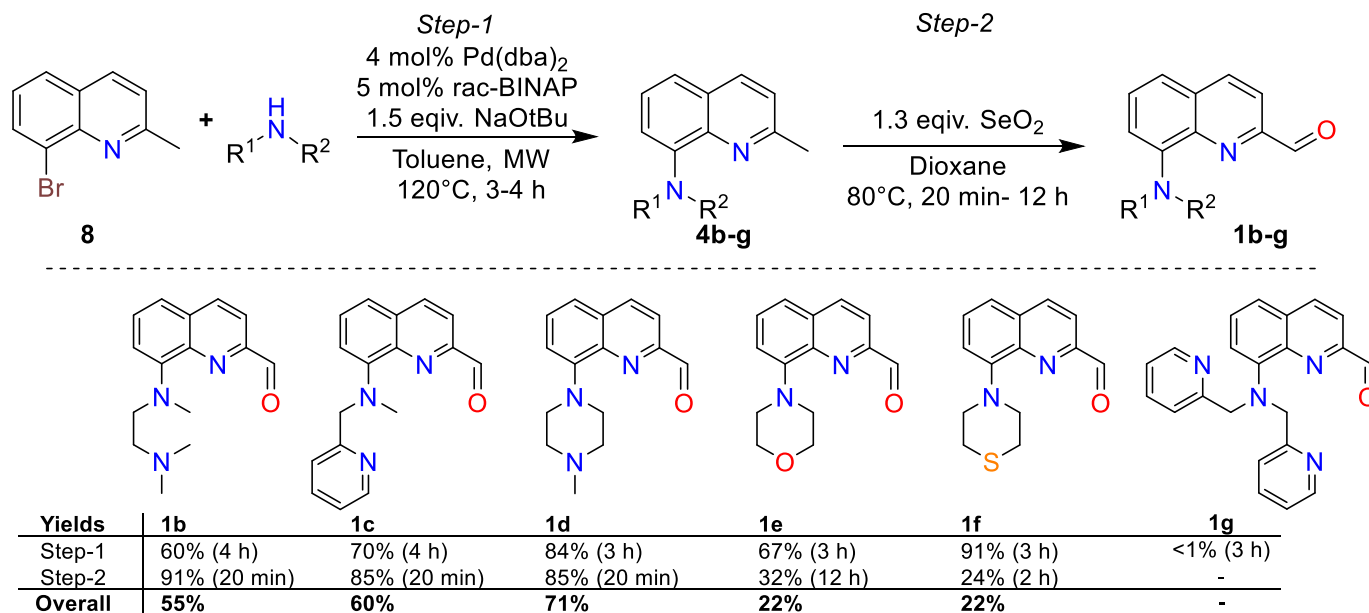


**Scheme 1.** Previously reported synthetic routes for the synthesis of 8-dimethylamino-2-carbaldehyde **1a**.<sup>33</sup>

## Results and Discussion

For preparing the 8-aminoquinolines (**4b-4g**), we proposed a more versatile, single-step alternative involving the previously mentioned Buchwald-Hartwig (BH) amination (Scheme 2). This palladium-catalysed, cross-coupling step provided good yields and simple reaction setup using 2,2'-

bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)-ligand and microwave irradiation. The intermediates were transformed into aldehydes similarly as described using SeO<sub>2</sub>.

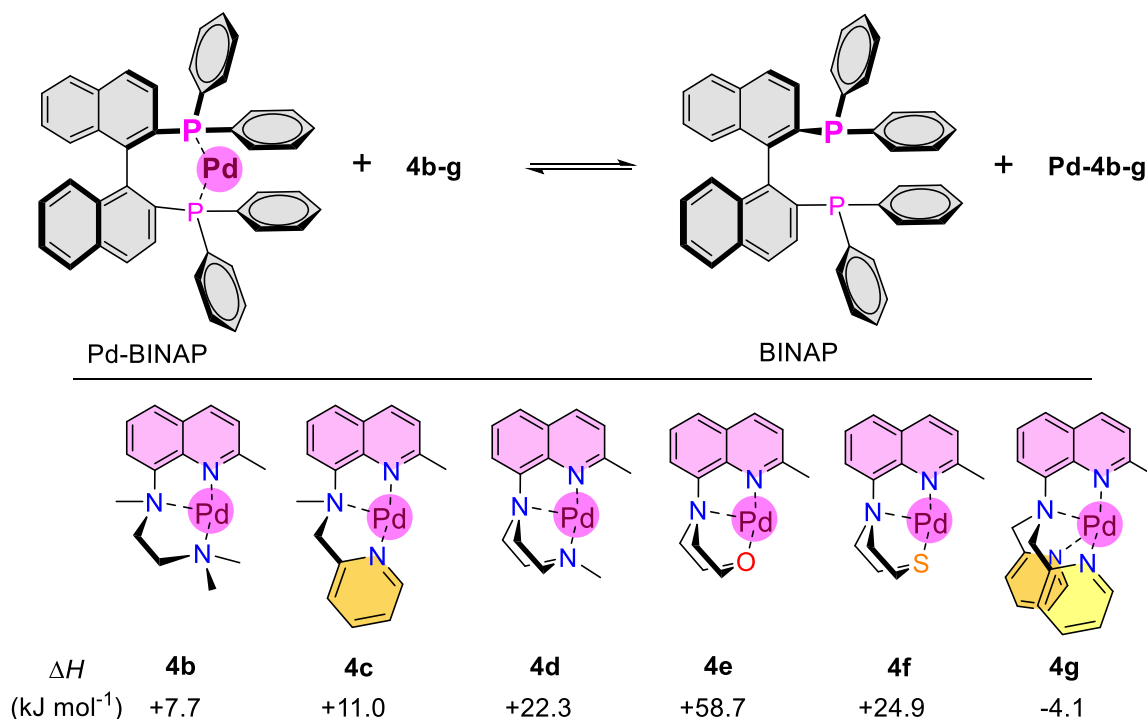


**Scheme 2.** Synthetic route to prepare 8-aminoquinoline-2-carbaldehyde (**1b-g**) chemosensor precursors (top) and the structures of the synthesized molecules (bottom). BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, dba = dibenzylideneacetone.

Five examples of the desired aldehydes (**4b-4f**) were prepared *via* this route in good overall yields, which were limited mainly by the oxidation step, highlighting the efficiency of our simpler method to obtain 8-aminoquinolines.

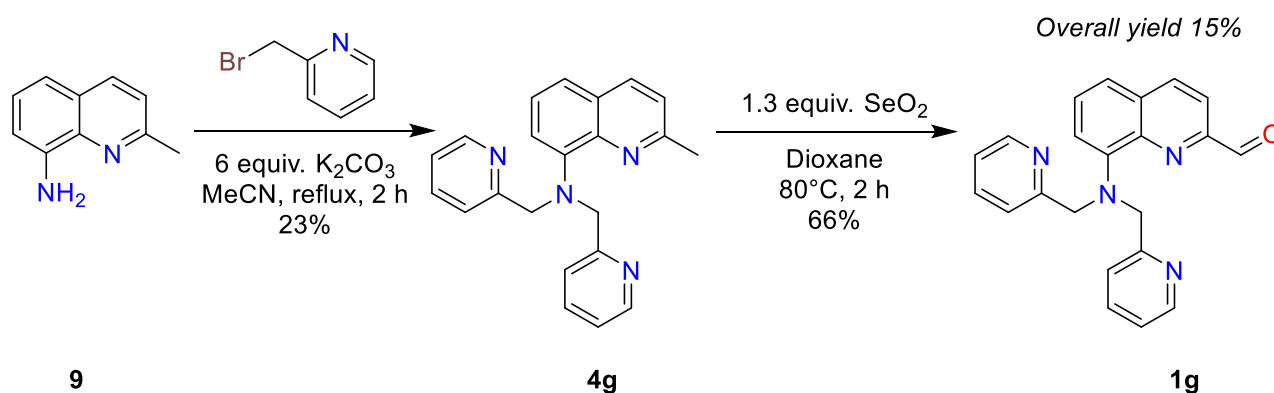
High affinity towards analytes is often a requirement for chemosensors, which can be achieved by incorporating additional side chains containing further ionophore parts and heteroatoms. An example of this would be a di-(2-picolyl)amine (DPA) sidechain (**1g**), which is also a strong ionophore itself. We attempted to extend the scope of our method to produce (**1g**), however, unlike in the other cases, the reaction mixture became green instead of brownish, and no conversion was observed. A possible reason for this result is that the product or the DPA exhibits a high affinity towards the catalytically-active Pd(0) species as well, forming a highly-stable, sterically-saturated complex that blocks the Pd(0), thereby, acting as a catalyst poison. Consequently, a limitation of the presented method is the synthesis of scaffolds containing additional powerful ionophores.

In order to confirm this hypothesis, DFT calculations were carried out on the complexation equilibrium of Pd-BINAP with **4b-g** at M06-2X/6-31G(d,p)//PCM(toluene) level of theory as shown in Scheme 3.<sup>43</sup> According to the computed enthalpy values ( $\Delta H$ ), all of these equilibria are significantly endothermic towards Pd-**4**, except for **4g**. This means that **4b-4f** are weaker chelating agents towards Pd(0) than the BINAP. However, the formation of Pd-**4g** is an exothermic process, which supports our theory that the product poisons the catalyst by capturing Pd(0), stopping the BH reaction. While this is unfortunate with regards to the presented synthetic route, it may hold the promise that further functionalization of the presented products may also be useful in developing new catalysts.



**Scheme 3.** DFT study of the complexation equilibrium between BINAP and **4b-g** for Pd(0) computed at M06 2X/6 31G(d,p)//PCM(toluene) level of theory.<sup>44</sup>

Since the DPA and similar moieties are widely used in chemosensors, an alternative method for the preparation of **1g** was carried out by the alkylation of **9** using 2-(bromomethyl)pyridine, followed by Riley oxidation (Scheme 4).

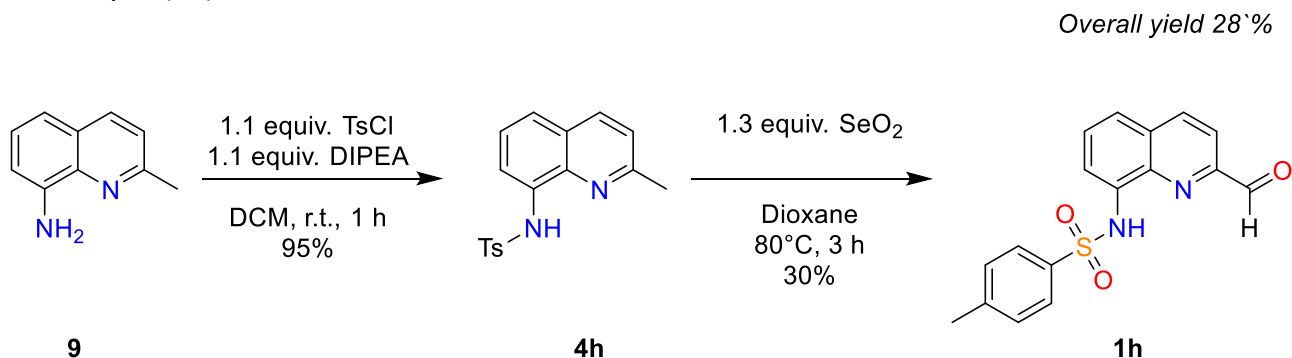


**Scheme 4.** Synthesis of **1g** from **9** via a bis-alkylation followed by an oxidation step.

After the optimization of the alkylation step, the reaction towards **4g** provided a moderate isolated yield after separation from the other alkylated products. The product **1g** was also prepared by a simple oxidation step.

The pioneering sensor for Zn<sup>2+</sup>, TSQ<sup>24</sup>, contains a similar chelating moiety, however, it contains a sulphonamide instead of an amine in position 8. Similarly, the widely used analogue, Zinquin, contains sulphonamide as well (Figure 1). Since these sulphonamides are also useful building blocks for other ionophores, we explored a similar two-step synthesis, based on previously reported reactions, to obtain them,

effectively. Although both steps are well explored, no previous work has investigated the preparation of 8-toluenesulphonamido-quinoline-2-carbaldehydes using this route. 8-Aminoquinoline (**9**) was tosylated with excellent yield,<sup>45</sup> then oxidized to **1h** in moderate yield using the previously presented protocol (Scheme 5). This experiment confirms that the succession of these reactions is a straightforward way to prepare the desired aldehyde (**1h**).



**Scheme 5.** Synthesis of toluenesulphonamide derivative **1h** from **9** in two steps.

The overall yield of this synthesis was 28%, making the proposed route appealing for the versatile preparation of sulphonamide analogues similar to **1h**.

## Conclusions

In summary, an efficient, scalable method has been developed for the preparation of a number of 8-(*N,N*-dialkylamino)quinoline-2-carbaldehydes using microwave-assisted Pd-catalysed *N*-arylation followed by a Riley oxidation. Using this protocol, several novel quinolines have been synthesized in moderate-to-high yields. We have also demonstrated the possible limitations of Buchwald-Hartwig coupling in cases in which the product possesses excellent chelating character; thereby, capturing the catalytic Pd(0) from the original ligands, and quenching the reaction. Alternative reaction routes were used to prepare *N,N*-bis(pyridyl-2-ylmethyl) 8-aminoquinoline-2-carbaldehydes and *N*-tosyl analogues successfully. The prepared compounds are useful metal-ion chelators and offer promising perspectives in metal-ion-sensor synthesis.

## Experimental Section

**General.** Reagents and solvents were purchased from Sigma-Aldrich and Fluorochem in reagent grade and used as received, while NMR solvents were purchased from Eurisotop. Thin-layer chromatography (TLC) was performed on commercially available pre-coated TLC plates (Merck Silica gel 60 F<sub>254</sub> aluminium sheets or Merck Aluminium oxide 60 F<sub>254</sub> plates). Visualisation was achieved by UV-light irradiation at 254 nm. For flash-column chromatography, an Interchim PuriFlash XS 520 Plus system was employed using gradient elution on normal phase (silica or aluminium oxide column; hexane–EtOAc or DCM–MeOH as eluents). Reactions were monitored by a Shimadzu LC-MS 2020 system. Preparative HPLC was applied for purification in many cases using an Armen SPOT Prep II instrument with UV detector (200–600 nm scan) equipped with a Phenomenex Gemini C18, 250×50.00 mm; 10 μm, 110A column. Gradient elution was employed using 0.08 g NH<sub>4</sub>HCO<sub>3</sub> in 1 L

water (A) and acetonitrile (B) or 2 mL TFA in 1 L water (A) and acetonitrile (B) as eluent systems. NMR spectra were recorded on Varian Unity INOVA spectrometers operating at an equivalent  $^1\text{H}$  frequency of 400, 500 or 600 MHz. Notations for the  $^1\text{H}$  NMR spectral splitting patterns include singlet (s), doublet (d), triplet (t), doublet of doublets (dd), doublet of triplets (dt), broad (br) and multiplet/overlapping peaks (m). Chemical shifts of the resonances are given as  $\delta$  values in ppm, and coupling constants ( $J$ ) are expressed in Hertz. Exact mass measurements were performed on a high-resolution Q-Exactive Focus hybrid quadrupole-orbitrap mass spectrometer (Thermo Fisher Scientific, Bremen, Germany) equipped with a heated electrospray ionization source. Samples were dissolved in an acetonitrile-water 1:1 (V/V) solvent mixture containing 0.1% (V/V) formic acid. Flow-injection analysis was performed using a 50  $\mu\text{L}/\text{min}$  eluent flow provided by a Thermo Scientific UPLC. Under the applied conditions, the compounds form protonated molecules,  $[\text{M} + \text{H}]^+$  or radical cations,  $[\text{M}]^+$  in positive ionization ESI. Microwave-assisted reactions were carried out in an Anton-Paar Monowave 450 microwave reactor (Anton-Paar, Austria) equipped with a MAS-24 autosampler and an IR temperature probe. Temperatures of the reactions were monitored on the surface and the reactions were carried out in a closed tube.

### General procedure 1 for the synthesis of 8-amino-2-methylquinolines

333 mg (1.5 mmol, 1.25 equiv.) 8-bromo-2-methylquinoline (**8**) was dissolved in 5 mL toluene and 1.20 mmol (1 equiv.) of the corresponding amine was added to the solution. The solution was transferred into a closed microwave reaction tube equipped with a stir bar and 216 mg (2.25 mmol, 1.5 equiv.) NaOtBu, 47 mg (0.08 mmol, 0.05 equiv.) BINAP and 28 mg Pd(dba)<sub>2</sub> (0.05 mmol, 0.04 equiv.) were also added to it. The tube was flushed with Argon and the reaction mixture was heated to 120 °C as fast as possible, then stirred at that temperature for 2-4 hours. After cooling to room temperature, the mixtures were diluted with 15 mL DCM and extracted with water (3  $\times$  15 mL).<sup>46</sup> The organic phase was washed with brine (15 mL) and dried over MgSO<sub>4</sub>, then concentrated under reduced pressure. The crude product was purified by flash chromatography or by preparative HPLC.

### General procedure 2 for the synthesis of 8-aminoquinoline-2-carbaldehydes

111 Mg (1 mmol, 1.3 equiv.) of selenium dioxide were suspended in a mixture of 5 mL dioxane and 0.5 mL of water. The mixture was stirred at 80 °C for 10 minutes. 0.80 Mmol (1 equiv.) of the previously prepared 8-amino-2-methylquinoline was then added to the mixture, with continued stirred at 80 °C for 10 min - 12 hours. The mixture was cooled to room temperature and then either purified by preparative HPLC or filtered through celite and washed with DCM. After evaporation of the solvent, the compounds were purified by flash chromatography.

**Preparation of *N,N*-dimethyl-2-nitroaniline (**6**).** A 5.6 M solution of dimethylamine (4 mL, 22.4 mmol, 1.1 equiv.) in EtOH was added to a flask containing stirring 2-fluoronitrobenzene (2.8 g, 2.08 mL, 20.3 mmol). The reaction was heated to 50 °C for 1 hour. The mixture was then cooled to room temperature, diluted with dichloromethane and extracted with a solution of 8% NaHCO<sub>3</sub> in water. The organic layer was washed with brine and dried over MgSO<sub>4</sub>. After filtration, the solvent was removed *in vacuo* yielding a dark orange oil (3.55 g, 96%). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the product are in good agreement with the reported one (Supplementary Material, Figures S36, S37).<sup>33</sup>

**Preparation of 2-(*N,N*-dimethylamino)-aniline (**7**).** 1 g of **6** (6 mmol, 1 equiv.) was suspended in EtOH and placed into an autoclave containing a stir bar, then 35 mg of Pd/C 10% (0.033 mmol, 0.55 mol %) was added to the solution. The autoclave was flushed with Argon, then charged with 5 bar H<sub>2</sub> gas, and the mixture was stirred at room temperature overnight. The mixture was then filtered on celite, and the solvent was removed *in vacuo* to obtain the product as a brown oil (0.76 g, 94%). The product was used without further purification.

The spectroscopic characterization of the product is in good agreement with previously reported results (Supplementary Material, Figures S38, S39).<sup>33</sup>

**Preparation of 8-(*N,N*-dimethylamino)-quinaldine (4a).** 500 mg of **7** (3.67 mmol, 1.0 equiv.) was dissolved in 6.6 mL of 6M hydrochloric acid, then 0.6 mL of crotonaldehyde (495 mg, 7.07 mmol, 1.9 equiv.) was added, and the mixture was stirred for 1 h at ambient temperature. Then, 5 mL of toluene was added before heating the reaction mixture to reflux temperature for 4 h. The mixture was cooled to room temperature, then the organic layer was separated, and the aqueous layer was neutralized by addition of NaOH. The solution was extracted using dichloromethane and the organic layer was washed with brine, and then dried over MgSO<sub>4</sub>. After filtration of the drying agent, the solvent was removed *in vacuo*, and the resulting residue was purified by flash chromatography on silica gel using DCM/Cyclohexane 1/1 as eluents to obtain the product. The product was obtained as a yellow oil (124 mg, 42%). The spectroscopic characterization of the product was in good agreement with the previously reported spectra (Supplementary Material, Figures S40, S41).<sup>33</sup>

**Preparation of 8-(*N,N*-dimethylamino)-quinoline-2-carbaldehyde (1a).** General procedure 2 was followed starting from **4a** to obtain the product. The reaction time was 30 minutes, and purification was carried out by flash chromatography on silica gel using 2% MeOH in DCM as eluent.

The product was obtained as a brown oil (144 mg, 90%) The spectroscopic characterization of the product was in good agreement with the previously reported spectra (Supplementary Material, Figures S42, S43).<sup>33</sup>

**Preparation of 8-(*N*<sup>1</sup>,*N*<sup>1</sup>,*N*<sup>2</sup>-trimethylethane-1,2-diamino)-quinaldine (4b).** General procedure 1 was followed starting from *N*<sup>1</sup>,*N*<sup>1</sup>,*N*<sup>2</sup>-trimethylethane-1,2-diamine to obtain the product. The reaction time was 4 hours, and purification was performed by flash chromatography on neutral aluminium oxide using gradient elution (Hexane/EtOAc 0 → 10% in 8 CV). The resulting product was a brown oil (219 mg, 60%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.11 (d, *J* 8.4 Hz, 1H, 10), 7.37 – 7.28 (m, 3H, 1, 6, 9), 6.97 (dd, *J* 6.7, 2.3 Hz, 1H, 2), 3.63 (t, *J* 7.4 Hz, 2H, 14), 2.93 (s, 3H, 13), 2.64 (s, 3H, 11), 2.61 (t, *J* 7.5 Hz, 2H, 15), 2.13 (s, 6H, 17, 18). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 155.3, 148.8, 141.3, 136.9, 127.9, 126.1, 121.8, 119.2, 114.8, 57.6, 54.5, 46.1, 46.0, 40.7, 25.5. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>22</sub>N<sub>3</sub><sup>+</sup> 244.1808, found 244.1804. TLC (Al<sub>2</sub>O<sub>3</sub> neut., DCM/MeOH 10:1) *R*<sub>f</sub> = 0.68

**Preparation of 8-(*N*<sup>1</sup>,*N*<sup>1</sup>,*N*<sup>2</sup>-trimethylethane-1,2-diamino)-quinoline-2-carbaldehyde (1b).** General procedure 2 was followed starting from **4b** to obtain the product. The reaction time was 20 minutes, purification was performed using preparative HPLC with TFA buffer. The resulting product was a brown oil (186 mg, 91%). <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.19 (d, *J* 0.8 Hz, 1H, 18), 8.52 (d, *J* 8.3 Hz, 1H, 7), 8.01 (d, *J* 8.4 Hz, 1H, 8), 7.63 (t, *J* 7.9 Hz, 1H, 6), 7.56 (dd, *J* 8.1, 1.3 Hz, 1H, 1), 7.27 (dd, *J* 7.7, 1.3 Hz, 1H, 5), 4.78 (s, 6H), 3.87 (t, 2H, 13), 3.68 (t, 2H, 14), 3.05 (s, 3H, 12), 2.94 (s, 6H, 16, 17). <sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>) δ 193.4, 149.3, 148.8, 140.6, 138.2, 131.2, 129.6, 119.5, 117.8, 115.8, 54.5, 51.6, 43.0, 39.6. HRMS-ESI *m/z* [M•]<sup>+</sup> calcd for C<sub>15</sub>H<sub>19</sub>N<sub>3</sub>O•<sup>+</sup> 257.1522, found 257.1517. TLC (Al<sub>2</sub>O<sub>3</sub> neut., DCM/MeOH 10:1) *R*<sub>f</sub> = 0.75

**Preparation of 8-(*N*-methyl-*N*-picolylamino)-quinaldine (4c).** General procedure 1 was followed starting from *N*-methyl-*N*-picolylamine to obtain the product. The reaction time was 4 hours, and purification was performed by flash chromatography on neutral aluminium oxide using gradient elution (Hexane/EtOAc 0 → 10% in 8 CV). The resulting product was a brown oil (184 mg, 70%). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.55 (ddd, *J* 4.9, 1.8, 0.9 Hz, 1H, Ar), 7.94 (d, *J* 8.4 Hz, 1H, Ar), 7.70 (d, *J* 7.9 Hz, 1H, Ar), 7.59 (td, *J* 7.6, 1.8 Hz, 1H, Ar), 7.37 – 7.26 (m, 2H, Ar), 7.19 (d, *J* 8.4 Hz, 1H, Ar), 7.12 (ddd, *J* 7.4, 4.8, 1.3 Hz, 1H, Ar), 7.05 (dd, *J* 7.1, 1.9 Hz, 1H, Ar), 4.95 (s, 2H, 13), 2.99 (s, 3H, 14), 2.60 (s, 3H, 11).

<sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 160.3, 156.0, 148.5, 148.1, 141.7, 136.5, 136.1, 127.7, 125.6, 122.9, 121.7, 121.5, 120.0, 115.5, 62.7, 40.2, 25.3. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>18</sub>N<sub>3</sub><sup>+</sup> 264.1495, found 264.1490. TLC (Silica gel, DCM/MeOH 10:1) *R*<sub>f</sub> = 0.5



**Preparation of 8-(*N*-methyl-*N*-picolylamino)-quinoline-2-carbaldehyde (1c).** General procedure 2 was followed starting from **4c** to obtain the product. The reaction time was 20 minutes, and purification was performed using preparative HPLC with TFA buffer. The resulting product was an orange oil (188 mg, 85%). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 9.68 (d, *J* 1.0 Hz, 1H, 11), 8.59 (dd, *J* 3.5, 1.4 Hz, 1H, Ar), 8.21 (dd, *J* 8.4, 0.9 Hz, 1H, Ar), 7.94 (d, *J* 8.5 Hz, 1H, Ar), 7.74 – 7.65 (m, 2H, Ar), 7.56 (t, *J* 7.9 Hz, 1H, Ar), 7.37 (dd, *J* 8.2, 1.2 Hz, 1H, Ar), 7.22 – 7.18 (m, 1H, Ar), 7.14 (dd, *J* 7.8, 1.3 Hz, 1H, Ar), 5.04 (s, 2H, 13), 3.12 (s, 3H, 14). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 193.5, 160.3, 149.8, 149.5, 148.9, 137.6, 136.4, 131.8, 129.9, 122.1, 121.9, 118.9, 117.4, 117.0, 115.0, 62.9, 40.4. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>16</sub>N<sub>3</sub>O<sup>+</sup> 278.1288, found 278.1284 TLC (Silica gel, DCM/MeOH 10:1) *R*<sub>f</sub> = 0.25

**Preparation of 8-(4-methylpiperazin-1-yl)-quinaldine (4d).** General procedure 1 was followed starting from *N*-methylpiperazine to obtain the product. The reaction time was 3 hours, and purification was performed by flash chromatography on neutral aluminium oxide using gradient elution (Hexane/EtOAc 40 → 100% in 12 CV then 4 CV 100% MeOH). The resulting product was a brown powder (162 mg, 84%). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.02 (d, *J* 8.4 Hz, 1H, 10), 7.46 (dd, *J* 7.8, 1.4 Hz, 1H, 2), 7.39 (t, *J* 7.8 Hz, 1H, 1), 7.28 (d, *J* 8.4 Hz, 1H, 9), 7.13 (dd, *J* 7.8, 1.4 Hz, 1H, 6), 3.74 (s, 4H, 13, 17), 3.35 (s, 4H, 14, 16), 2.79 (s, 3H, 18), 2.73 (s, 3H, 11). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 157.4, 146.8, 141.7, 137.1, 127.9, 125.9, 122.8, 122.0, 116.8, 54.4, 49.5, 44.4, 26.1. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>20</sub>N<sub>3</sub><sup>+</sup> 242.1652, found 242.1647. TLC (Silica gel, DCM/MeOH 10:1) *R*<sub>f</sub> = 0.20

**Preparation of 8-(4-methylpiperazin-1-yl)-quinoline-2-carbaldehyde (1d).** General procedure 2 was followed starting from **4d** to obtain the product. The reaction time was 20 minutes, and purification was performed using preparative HPLC with TFA buffer. The resulting product was an orange oil (173 mg, 85%). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 12.59 (s, 1H, NH), 10.15 (s, 1H, 11), 9.03 (s, 1H, NH), 8.33 (d, *J* 8.4 Hz, 1H, 10), 8.06 (d, *J* 8.4 Hz, 1H, 9), 7.66 – 7.57 (m, 2H, 1, 6), 7.30 – 7.22 (m, 1H, 2), 4.13 (d, *J* 12.0 Hz, 2H, 14', 18''), 3.83 (d, *J* 10.8 Hz, 2H, 15'', 17'), 3.53 – 3.34 (m, 4H, 14'', 15', 17'', 18'), 2.99 (s, 3H, 19). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 193.0, 150.6, 147.6, 141.6, 138.4, 131.7, 129.7, 123.0, 117.8, 117.6, 54.1, 49.0, 43.7. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>18</sub>N<sub>3</sub>O<sup>+</sup> 256.1445, found 256.1439. TLC (Silica gel, DCM/MeOH 10:1) *R*<sub>f</sub> = 0.25

**Preparation of 8-(morpholinyl)-quinaldine (4e).** General procedure 1 was followed starting from morpholine to obtain the product. The reaction time was 3 hours, and purification was performed by flash chromatography on silica gel using gradient elution (Hexane/EtOAc 0 → 10% in 8 CV). The product obtained was a brown powder (229 mg, 67%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.16 (d, *J* 8.4 Hz, 1H, 10), 7.46 (dd, *J* 8.1, 1.4 Hz, 1H, 6), 7.39 (t, *J* 8.3 Hz, 2H, 1, 9), 7.07 (dd, *J* 7.5, 1.4 Hz, 1H, 2), 3.85 (t, *J* 4.6 Hz, 4H, 13, 16), 3.39 – 3.31 (m, 4H, 12, 14), 2.64 (s, 3H, 17).

<sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 155.8, 148.0, 141.1, 136.7, 127.4, 125.8, 121.6, 121.0, 115.4, 66.3, 51.8, 25.3. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>N<sub>2</sub>O<sup>+</sup> 229.1336, found 229.1332. TLC (Silica gel, EtOAc/Hexane 1:1) *R*<sub>f</sub> = 0.63

**Preparation of 8-(morpholinyl)-quinoline-2-carbaldehyde (1e).** General procedure 2 was followed starting from **4e** to obtain the product. The reaction time was 12 hours, purification was performed using preparative HPLC with NH<sub>4</sub>HCO<sub>3</sub> buffer. The resulting product was a yellow powder (120 mg, 33%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.05 (s, 1H, 18), 8.50 (dd, *J* 8.5, 0.9 Hz, 1H, 6), 7.95 (d, *J* 8.4 Hz, 1H, 10), 7.69 – 7.59 (m, 2H, 1, 9), 7.23 (dd, *J* 7.0, 2.0 Hz, 1H, 2), 3.89 (t, *J* 4.7 Hz, 4H, 16), 3.47 – 3.39 (m, 4H, 14). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 193.7, 149.5, 149.5, 141.0, 138.3, 131.3, 130.0, 120.7, 116.8, 116.4, 66.3, 51.8. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup> 243.1128, found 243.1124. TLC (Silica gel, EtOAc/Hexane 1:1) *R*<sub>f</sub> = 0.70

**Preparation of 8-(thiomorpholinyl)-quinaldine (4f).** General procedure 1 was followed starting from thiomorpholine to obtain the product. The reaction time was 3 hours, the product was used without further purification. The product obtained was a brown oil (333 mg, 91%).

**Preparation of 8-(thiomorpholinyl)-quinoline-2-carbaldehyde (1f).** General procedure 2 was followed starting from **4f** to obtain the product. The reaction time was 2 hours, purification was performed using preparative HPLC with TFA buffer. After the distillation of MeCN from the collected fractions, the product precipitated in the form of yellowish crystals. The solid was collected by filtration after purification yielding yellow-green, fluorescent crystals (50 mg, 24%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.07 (s, 1H, 18), 8.49 (d, *J* 8.5 Hz, 1H, 10), 7.94 (d, *J* 8.4 Hz, 1H, 9), 7.66 – 7.56 (m, 2H, 1, 6), 7.26 (dd, *J* 7.1, 2.1 Hz, 1H, 2), 3.68 – 3.61 (m, 4H, 12, 14), 2.93 – 2.87 (m, 4H, 13, 16). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 193.8, 150.4, 149.6, 141.2, 138.3, 131.3, 129.9, 120.7, 117.4, 116.8, 54.1, 27.1. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>OS<sup>+</sup> 259.0900, found 259.0896. TLC (Silica gel, EtOAc/Hexane 1:4) *R*<sub>f</sub> = 0.54

**Attempted preparation of 4g via Buchwald-Hartwig amination.** General procedure 1 was followed starting from di-(2-picolyl)amine (DPA). After 3 hours, usually a brown solution is found, however, in this case, the solution was a deep green color and HPLC-MS analysis indicated no conversion, but just the presence of starting materials.

**Preparation of 8-(di-(2-picolyl)amino)-quinaldine (4g) via alkylation.** In a two-necked round bottom flask equipped with a condenser and magnetic stir bar, a solution of 8-Aminoquinaldine (**9**, 1 g, 6.32 mmol, 1 equiv.) in MeCN (10 mL) was added. 6.12 g K<sub>2</sub>CO<sub>3</sub> (44.2 mmol, 7 equiv.) was also added, the system was flushed with nitrogen and stirring was started. A solution of 4.8 g (19 mmol, 3 equiv.) of 2-(bromomethyl)pyridine hydrobromide in 20 mL MeCN was added dropwise, then the reaction mixture was heated to reflux for 2 hours. The obtained orange coloured solution was concentrated using a rotavapor and the dry residue was diluted with DCM (30 mL), then washed with water (20 mL). The aqueous phase was extracted with DCM (2x15 mL), then the organic phases were dried over MgSO<sub>4</sub>. After filtration, the solvent was removed, and the red crude product was purified by preparative HPLC using TFA as a buffer. The collected fractions were lyophilized to obtain the product which was obtained as a brown oil (830 mg, 23%).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.28 (bs, 1H, NH<sup>+</sup>), 8.83 (d, *J* 5.3 Hz, 2H, 18, 24), 8.51 (d, *J* 8.5 Hz, 1H, 4), 8.13 (td, *J* 7.8, 1.6 Hz, 2H, 16, 22), 7.74 (d, *J* 8.0 Hz, 2H, 15, 21), 7.68 – 7.57 (m, 4H, 7, 8, 17, 23), 7.55 – 7.46 (m, 2H, 3, 9), 4.97 (s, 4H), 2.45 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 156.7, 156.2, 144.7, 143.5, 141.6, 140.0, 138.0, 127.7, 126.5, 124.4, 124.0, 122.7, 121.4, 118.4, 117.0, 114.1, 57.0, 22.7. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>21</sub>N<sub>4</sub><sup>+</sup> 341.1754, found 341.1761. TLC (Al<sub>2</sub>O<sub>3</sub> neut., EtOAc/Hexane 1:1) *R*<sub>f</sub> = 0.52

**Preparation of 8-(di-(2-picolyl)amino)-quinoline-2-carbaldehyde (1g).** General procedure 2 was followed starting from **4g** to obtain the product. The reaction time was 2 hours, and purification was performed using preparative HPLC with TFA buffer. The product obtained was a yellow oil (187 mg, 66%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.81 (bs, 1H, NH<sup>+</sup>), 8.92 (s, 1H, 11), 8.88 (d, *J* 5.3 Hz, 2H, 19, 24), 8.48 (d, *J* 8.5 Hz, 1H, 10), 8.27 (td, *J* 7.8, 1.6 Hz, 2H, 21, 26), 7.95 (d, *J* 8.0 Hz, 2H, 22, 27), 7.87 (d, *J* 8.4 Hz, 1H, 9), 7.72 (t, *J* 6.5 Hz, 2H, 20, 25), 7.61 – 7.48 (m, 2H, 1, 6), 7.34 (dd, *J* 7.2, 2.0 Hz, 1H, 2), 5.28 (s, 4H, 14, 15).

<sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 191.9, 157.1, 148.8, 145.8, 144.6, 141.9, 140.0, 138.2, 131.2, 129.6, 124.2, 123.9, 119.4, 117.0, 115.4, 114.0, 56.9. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>19</sub>N<sub>4</sub>O<sup>+</sup> 355.1554, found 355.1548. TLC (Silica gel, MeOH/DCM 1:4) *R*<sub>f</sub> = 0.13

**Preparation of 8-(toluenesulphonamido)-quinaldine (4h).** To a solution of 8-aminoquinaldine (**9**, 1 g, 6.32 mmol, 1 equiv.) in 30 mL DCM 1.3 g (6.96 mmol, 1.1 equiv.) tosyl chloride was added with stirring. 2.7 mL (3.6 g, 20.8 mmol, 3 equiv.) DIPEA was also added, then the reaction mixture was stirred at room temperature for 1 hour. Then the reaction mixture was extracted with 30 mL of water, then 100 mL of a 0.5M HCl solution. The

aqueous phase containing HCl was extracted with 2 x 40 mL DCM, and then the organic phases were extracted with 60 mL 8% NaHCO<sub>3</sub> solution, followed by brine. The organic phase was dried over MgSO<sub>4</sub> and concentrated after filtration to obtain the product. The product, a yellow powder (2.05 g, 95%), was not further purified. The product matches the one described earlier. (Supplementary Material, Figures S44, S45)<sup>45</sup>

**Preparation of 8-(toluenesulphonamido)-quinoline-2-carbaldehyde (1h).** General procedure 2 was followed starting from **4h** to obtain the product. The reaction time was 3 hours, and purification was performed using preparative HPLC with TFA buffer. Upon the distillation of MeCN from the collected fractions, the product precipitated in the form of grey crystals. Instead of lyophilization, the greenish-grey crystals were collected by filtration (71 mg, 29%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.27 (1 H, s, 13), 10.19 – 10.10 (1 H, m, 11), 8.54 (1 H, d, *J* 8.5, 10), 7.97 (1 H, d, *J* 8.4, 9), 7.86 – 7.79 (2 H, m, 18, 22), 7.80 – 7.73 (2 H, m, 2, 6), 7.73 – 7.64 (1 H, m, 1), 7.27 (2 H, d, *J* 8.0, 19, 21), 2.25 (3 H, s, 23). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 193.4, 150.7, 143.6, 138.6, 138.3, 136.4, 134.7, 129.9, 129.7, 129.6, 127.1, 123.1, 118.2, 117.7, 20.9. HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>S<sup>+</sup> 327.0798.

### Theoretical calculations

Gaussian 16 program package (G16),<sup>47</sup> using default convergence criteria were used, respectively. Computations were carried out at M06-2X/6-31G(d,p) level of theory<sup>44</sup> for nuclei CHNOP and MWB28 for Pd<sup>48</sup>, using integral equation formalism-polarisable continuum model (IEFPCM) method with the parameters of toluene. The method and basis sets were chosen for their reliability shown in earlier studies.<sup>49,50</sup>

The vibrational frequencies were computed at the same levels of theory as used for geometry optimisation to properly confirm that all structures reside at minima on their potential energy hypersurfaces (PESs). Thermodynamic functions, such as energy (*U*), enthalpy (*H*), Gibbs free energy (*G*), and entropy (*S*) were computed for 398.15 K, using the quantum chemical, rather than the conventional thermodynamic reference state.

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## Supplementary Material

<sup>1</sup>H and <sup>13</sup>C NMR spectra and high-resolution mass spectra are provided in the Supplementary Material associated with this manuscript.

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