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# Polycyclic imidazo[1,2-*a*]pyridine analogs – synthesis *via* oxidative intramolecular C–H amination and optical properties†

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A novel and straightforward approach to synthesize 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles has been developed. The key step is C–H amination of easily available 2-(2'-aminophenyl)imidazo[1,2-*a*]pyridines by the use of copper(II) triflate, trifluoroacetic acid and (diacetoxyiodo)benzene. The entire strategy consists of just four steps, starting from 2-aminopyridines and acetophenones, giving the target compounds in an overall yield of 20–35%. The optical properties of a library of  $\pi$ -expanded imidazo[1,2-*a*]pyridines were for the first time fully characterized, showing that these ladder-type compounds strongly absorb UV radiation and exhibit fluorescence in the 415–461 nm region.

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## Introduction

Imidazo[1,2-*a*]pyridines are a group of very important heterocycles possessing strong and diverse biological activity. Their structural motif can be found in several marketed drugs, such as anxiolytic alpidem,<sup>1</sup> necopidem and saripidem and in drugs used for the treatment of insomnia and brain disorders (zolpidem).<sup>2</sup> Their antiviral,<sup>3–5</sup> antiparasitic,<sup>6</sup> antibacterial,<sup>7</sup> anti-inflammatory,<sup>8</sup> analgesic and antipyretic<sup>9,10</sup> properties are also well documented, as well as their ability to inhibit  $\beta$ -amyloid formation.<sup>11</sup> Not surprisingly, methodology of their synthesis has attracted significant attention in the last decade.<sup>12–21</sup> Besides the pharmacological importance, imidazo[1,2-*a*]pyridines exhibit interesting optical properties. In particular, they typically possess high fluorescence quantum yields.<sup>22–28</sup>

With the advent of interest in ladder-type aromatic heterocycles,<sup>29,30</sup> we reasoned that  $\pi$ -expanded imidazo[1,2-*a*]pyridines being analogues of recently explored systems such as indolo[3,2-*b*]indoles<sup>31,32</sup> can offer new opportunities once an efficient synthetic methodology is developed. Indolo[3,2-*b*]indoles (1), benzofuroindoles (2) and benzothioindoles (3) were recently reported as highly active sex steroid hormone receptor modulators<sup>33</sup> and anticancer agents (Fig. 1).<sup>34</sup> Indolo[3,2-*b*]indoles and their analogues were also investigated in optoelectronics.<sup>35,36</sup> Only three inefficient synthetic method-



Fig. 1 Comparison of the chemical structures of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles, indoloindoles (1), benzofuroindoles (2) and benzothioindoles (3).

ologies leading to our targeted 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles were reported: Cadogan cyclization,<sup>37–39</sup> multicomponent Bienaymé reaction followed by *N*-arylation<sup>40,41</sup> and ionic liquid promoted cyclization of *N*-methylisatin and 2-aminopyridine.<sup>42</sup> The synthesis of a library of pyridoimidazoindoles and the analysis of the relationship between their structure and spectroscopic properties might open the door to their future optoelectronic applications. In this paper we propose a novel strategy towards this class of nitrogen containing heterocycles, with the key step being oxidative C–H bond amination.

## Results and discussion

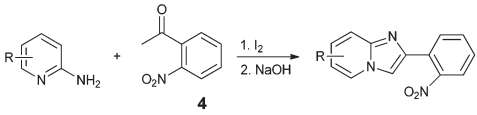
An analysis of possible synthetic routes towards 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles led us to the conclusion that oxidative C–H amination of easily available 2-(2'-aminophenyl)


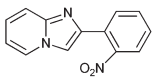
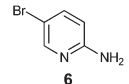
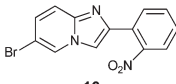
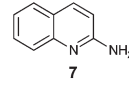
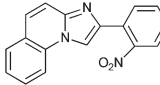

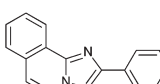
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†Electronic supplementary information (ESI) available: Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra. See DOI: 10.1039/c4qo00248b



**Table 1** Synthesis of 2-(2'-nitrophenyl)imidazo[1,2-*a*]pyridines<sup>a</sup>


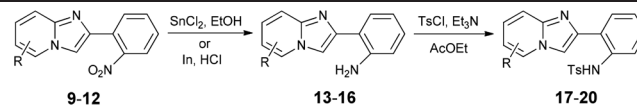
| Entry | Amine   | Product   | Yield (%) |
|-------|---|---|-----------|
| 1     |  |  | 69        |
| 2     |  |  | 64        |
| 3     |  |  | 24        |
| 4     |  |  | 49        |

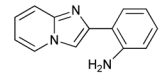
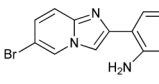
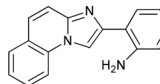
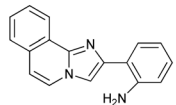
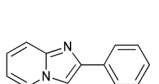
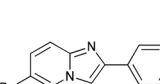
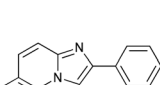
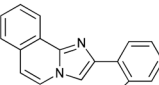
<sup>a</sup> Reaction conditions: (1) amine (20 mmol), 2-nitroacetophenone (10 mmol), I<sub>2</sub> (10 mmol), 110 °C, 12 h; (2) NaOH aq.

substituted imidazo[1,2-*a*]pyridines should be a straightforward strategy towards these compounds. This atom-economical process has attracted significant attention in recent years, because it avoids arene preactivation in the synthesis of industrially important heterocycles, *e.g.* carbazoles. The proposed mechanism for oxidative C–H amination requires the attacked carbon atom to possess a certain electron density. For this reason our strategy should benefit from the fact that the most electron-rich position in imidazo[1,2-*a*]pyridines is C-3, which remains unsubstituted if the classical Chichibabin method is employed. Thus, we synthesized a series of 2-(2'-nitrophenyl)imidazo[1,2-*a*]pyridines using the one-pot, tandem Ortoleva–King–Chichibabin process<sup>25</sup> (Table 1). Both 2-aminopyridines and their expanded analogs gave the expected imidazopyridines **9–12** in good yield (24–69%).

The previously reported reduction of nitroarenes using H<sub>2</sub> and Pd on charcoal did not work in our hands (we observed hydrogenation of the pyridine ring).<sup>43</sup> The reaction with iron powder in concentrated hydrochloric acid solution failed too; however the procedure developed by Kundu and co-workers, involving tin(II) chloride, gave the desired 2-(2'-aminophenyl) substituted imidazo[1,2-*a*]pyridines **13–16** in good yields.<sup>44</sup> Even better results could be obtained using indium powder in hydrochloric acid which seems to be the best but a bit expensive reductant (Table 2).

Having 2-(2'-aminophenyl)imidazo[1,2-*a*]pyridine (**13**) as a key substrate, we started to search for suitable conditions for oxidative C–H amination. Literature data revealed that *N*-substituted 2-aryl-1-aminobenzenes possessing various electron-withdrawing groups on the nitrogen atom have been trans-

**Table 2** Synthesis of *N*-tosyl-2-(2'-aminophenyl)imidazo[1,2-*a*]pyridines


| Structure   | Yield (%)   |
|---|---|
|    | <b>13</b> (69%) <sup>a</sup>                      |
|  | <b>14</b> (49%) <sup>a</sup> , (85%) <sup>b</sup> |
|  | <b>15</b> (61%) <sup>a</sup>                      |
|    | <b>16</b> (48%) <sup>a</sup> , (88%) <sup>b</sup> |
|  | <b>17</b> (80%) <sup>c</sup>                      |
|  | <b>18</b> (32%) <sup>c</sup>                      |
|   | <b>19</b> (88%) <sup>c</sup>                      |
|  | <b>20</b> (47%) <sup>c</sup>                      |

<sup>a</sup> Reaction conditions: Reaction conditions: Nitroimidazopyridine (10 mmol), SnCl<sub>2</sub> (40 mmol), EtOH, 100 °C, 1.5 h. <sup>b</sup>Nitroimidazopyridine (1 mmol), indium powder (4 mmol), THF, 3 h, rt. <sup>c</sup>Amine (1 mmol), TsCl (2 mmol), Et<sub>3</sub>N (2 mmol), AcOEt, 50 °C, 16 h.

formed into corresponding carbazoles.<sup>45–48</sup> In the preliminary phase of our studies it was found that amination reactions of acetyl- and trifluoromethanesulfonyl-protected amine **13** were sluggish regardless of the conditions, occasionally giving the expected product in very low yields. Given that subsequently we discovered that the tosyl protecting group is the most effective in C–H bond amination we transformed all amines into tosylamides **17–20**.

We decided to test four procedures published for carbazoles<sup>45–48</sup> in oxidative coupling of amide **17** as a model compound. Buchwald's methodology using palladium(II) acetate as a catalyst and copper(II) acetate/oxygen as a reoxidant did not lead to the expected product (Table 3, entry 1).<sup>45</sup> Thus, we adopted the Youn procedure which requires oxone or (diacetoxyiodo)benzene (PIDA) as a reoxidant of palladium(II) acetate (entries 2–5).<sup>46</sup> The latter reoxidant allowed us to isolate the desired tetracyclic compound **21**; however, the yield was still not satisfactory (entry 4). Finally, we decided to apply Chang's method, which uses copper(II) triflate in combination with PIDA in ethylene chloride.<sup>47</sup> This allowed us to isolate **21** in excellent yield and purity (entry 7). There are some reports on an analogous transformation that could be achieved without the use of any metal catalyst source (intramolecular organocatalytic C–H bond amination). Antonchick and co-workers found that *N*-substituted carbazoles can be obtained by treatment of *N*-protected diphenylamines with PIDA.<sup>48</sup> They also observed the positive effect of a fluorinated co-solvent. As this approach offers a number of advantages over a transition-metal-catalyzed amination, we tried to apply these conditions



**Table 3** Optimization of oxidative C–H amination of *N*-tosyl-2-(2-aminophenyl)imidazo[1,2-*a*]pyridines


| Entry | Catalyst             | Reoxidant                            | Additives   | Solvent   | Time (h)         | Yield <sup>a</sup> (%) |
|-------|----------------------|--------------------------------------|-------------|-----------|------------------|------------------------|
| 1     | Pd(OAc) <sub>2</sub> | Cu(OAc) <sub>2</sub> /O <sub>2</sub> | Mol. sieves | Toluene   | 12 <sup>b</sup>  | 0                      |
| 2     | Pd(OAc) <sub>2</sub> | Oxone                                |             | PivOH–DMF | 12 <sup>c</sup>  | 0                      |
| 3     | Pd(OAc) <sub>2</sub> | Oxone                                | TsOH        | PivOH–DMF | 12 <sup>c</sup>  | 0                      |
| 4     | Pd(OAc) <sub>2</sub> | PIDA                                 |             | AcOH–DMF  | 12 <sup>c</sup>  | 40                     |
| 5     | Pd(OAc) <sub>2</sub> | PIDA                                 | TsOH        | AcOH–DMF  | 12 <sup>c</sup>  | 32                     |
| 6     | —                    | PIDA                                 |             | HFIP–DCM  | 16 <sup>c</sup>  | 62                     |
| 7     | Cu(OTf) <sub>2</sub> | PIDA                                 | TFA         | DCE       | 0.5 <sup>d</sup> | 93                     |
| 8     | —                    | PIFA                                 | TFA         | DCE       | 0.5 <sup>d</sup> | 77                     |

<sup>a</sup> Isolated yields. <sup>b</sup> 120 °C. <sup>c</sup> Room temperature. <sup>d</sup> 50 °C.

**Table 4** Synthesis of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles

<sup>a</sup> Reaction conditions: Reaction conditions: Tosylamide (0.2 mmol), PIDA (0.3 mmol), Cu(OTf)<sub>2</sub> (0.01 mmol), TFA (0.6 mmol), DCE, 50 °C, 0.5 h. <sup>b</sup> Tosylamide (0.2 mmol), PIFA (0.3 mmol), TFA (0.6 mmol), DCE, 50 °C, 0.5 h. <sup>c</sup> 22 (0.27 mmol), 4-ethynyl-*N,N*-dimethylaniline (0.69 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.76 mmol), Pd(OAc)<sub>2</sub> (0.035 mmol), PPh<sub>3</sub> (0.14 mmol), DMSO, 80 °C, 24 h.

for oxidation of tosylamide **17** which afforded fused compound **21** in fairly good yield (62%, entry 6). Finally, it was found that the second procedure published by Chang and co-workers,<sup>47</sup> *i.e.* bis-(trifluoroacetoxy)iodobenzene (PIFA) in the presence of trifluoroacetic acid (TFA), could also be applied, albeit the yield of compound **21** was slightly lower (77%, entry 8).

Following the well-supported Chang's proposition<sup>47</sup> we think that the copper species works as a Lewis acid to activate PIFA, which is the main oxidant inducing the formation of radical intermediates. Having optimized the C–H bond amination, we tried to transform the other sulfonamides. Although bromoderivative **22** smoothly undergoes this reaction, in the case of benzo-fused analogues **19** and **20** we observed the formation of many by-products (Table 4). Therefore we changed

**Table 5** Spectroscopic properties of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles<sup>a</sup>

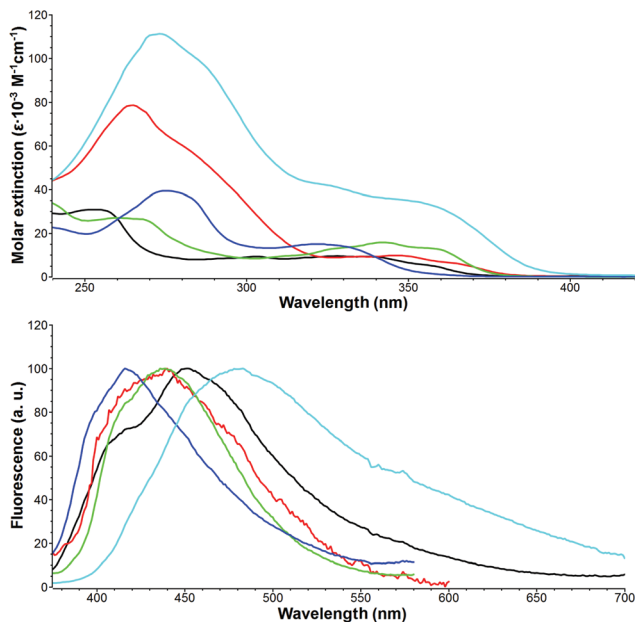
| Compd                  | Abs <sub>max</sub> (nm) | $\epsilon$ ( $\times 10^{-3}$ M <sup>-1</sup> cm <sup>-1</sup> ) | Emission <sub>max</sub> (nm) | Stokes shift (cm <sup>-1</sup> ) | $\Phi_f^c$         |
|------------------------|-------------------------|--|------------------------------|----------------------------------|--------------------|
| <b>IP</b> <sup>b</sup> | 318                     |  | 376                          | 4800                             |                    |
| <b>21</b>              | 254                     | 31.1   | 444                          | 8000                             | 0.034 <sup>d</sup> |
|                        | 303                     | 9.28   |                              |                                  |                    |
|                        | 328                     | 9.51   |                              |                                  |                    |
| <b>22</b>              | 265                     | 78.9   | 434                          | 5700                             | 0.025 <sup>d</sup> |
|                        | 348                     | 9.76   |                              |                                  |                    |
| <b>23</b>              | 260                     | 27.2   | 432                          | 6100                             | 0.006 <sup>e</sup> |
|                        | 342                     | 15.8   |                              |                                  |                    |
| <b>24</b>              | 275                     | 39.7   | 415                          | 7000                             | 0.008 <sup>e</sup> |
|                        | 322                     | 15.1   |                              |                                  |                    |
| <b>25</b>              | 274                     | 134  | 461                          | 6500                             | 0.009 <sup>d</sup> |
|                        | 355                     | 33.2   |                              |                                  |                    |

<sup>a</sup> Measured in DCM. <sup>b</sup> **IP** = unsubstituted imidazo[1,2-*a*]pyridine (data taken from ref. 49). <sup>c</sup> Measured with quinine sulphate as a standard. <sup>d</sup> Excited at 360 nm. <sup>e</sup> Excited at 310 nm.

the catalytic system to a copper-free PIFA–TFA mixture which gave a much cleaner conversion and higher yields of compounds **23** and **24**. The presence of a bromine atom in compound **22** gives an opportunity for further extension of the  $\pi$ -system using palladium catalyzed Sonogashira coupling. This reaction proceeded smoothly, resulting in the formation of compound **25**.

The successful synthesis of a small library of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles and their  $\pi$ -expanded analogs gave us an excellent opportunity for measuring their photophysical properties for the first time. In the case of ladder-type fused heterocycles it is well-known that extending the  $\pi$ -system alters some of the photophysical properties but usually it does not lead to a bathochromic shift of absorption.<sup>29,30</sup> The spectroscopic data collected for compounds **21**–**25** are presented in Table 5. The electronic spectra of indole-fused imidazopyridines typically consist of two strong bands in the 254–355 nm region, whereas a single band was observed in their fluorescence spectra (Fig. 2). Comparison of the properties of compounds **21** and **22** with unsubstituted imidazo[1,2-*a*]pyridine





**Fig. 2** Absorption (top) and normalized fluorescence (bottom) spectra of **21** (black), **22** (red), **23** (green), **24** (blue) and **25** (cyan) measured in DCM.

IP led to a conclusion that fusion with an indole scaffold results in 10–30 nm and 58–68 nm bathochromic shift of absorption and emission maxima, respectively. Due to the angular type of fusion of an additional benzene ring in derivatives **23** and **24**, their optical properties strongly resemble those of compound **21**. On the other hand, *N,N*-dimethylphenylethynyl substituted imidazopyridine **25** exhibits well pronounced red-shifted absorption and emission maxima at 355 and 461 nm, respectively. As expected, this compound displays the most intense absorption bands (with  $\epsilon$  reaching  $130\,000\text{ M}^{-1}\text{ cm}^{-1}$ ) as a result of high  $\pi$ -conjugation and strong dipolar character. The largest Stokes shift was observed for compound **21**, which was almost two times higher than that calculated for unsubstituted imidazopyridine. In contrast to imidazo[1,2-*a*]pyridines compounds **21**–**25** display very weak fluorescence. Interestingly, the highest fluorescence quantum yield was measured for compound **21**. Substitution with a heavy atom (bromo-derivative **22**), according to expectations, led to a further decrease in fluorescence intensity. Extension of the  $\pi$ -system probably opens the non-radiative deactivation pathways, which resulted in the lower fluorescence quantum yield observed for compounds **21**–**25**.

## Conclusions

It has been proven that intramolecular oxidative C–H amination can also occur with heterocycles bearing a basic nitrogen atom. A new, straightforward, four-step synthesis of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles was developed. Two sets of suitable reaction conditions were found for the key step, *i.e.* intramolecular C–H bond amination: Cu(OTf)<sub>2</sub>–PIDA–TFA and

organocatalytic PIFA–TFA combinations. In contrast to many analogous structures, the fluorescence quantum yields of the prepared blue-emitting  $\pi$ -expanded imidazo[1,2-*a*]pyridine analogs turned out to be low.

## Experimental section

### General information

All the reported NMR spectra (<sup>1</sup>H NMR and <sup>13</sup>C NMR) were recorded on a Varian 500 spectrometer. Chemical shifts ( $\delta$  ppm) were determined with TMS as the internal reference; *J* values are given in Hz. High resolution mass spectra (HRMS) were obtained *via* electron ions (EI). IR spectra were recorded on a JASCO FT/IR-6200 Spectrometer. UV-Vis absorption spectra were recorded on a PerkinElmer Lambda 25 Spectrometer. Fluorescence spectra were recorded on a HITACHI F-7000 Fluorescence Spectrophotometer. Chromatography was performed on silica gel 60 (230–400 mesh) and thin layer chromatography was performed on TLC plates (Merck, silica gel 60 F<sub>254</sub>). Compound **13** was prepared according to a previously reported procedure.<sup>44</sup>

### General procedure for the synthesis of 2-(2-nitrophenyl)imidazo[1,2-*a*]pyridines

A mixture of 1-(2'-nitrophenyl)ethanone (10 mmol), 2-aminopyridine (20 mmol) and iodine (10 mmol) was heated at 110 °C. After 4 h the temperature of the oil bath was reduced to 70 °C and stirring was continued for an additional 12 h. The resulting waxy solid was dissolved in distilled water and an excess of conc. aqueous sodium hydroxide (45%) was added. Then the reaction mixture was stirred at 100 °C for 1 h, cooled and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The pH of the resulting mixture was adjusted to neutral using aqueous HCl (10%) and layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Column chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>–AcOEt 95 : 5, gradually increasing the amount of AcOEt) followed by crystallization from AcOEt–hexanes afforded products of analytical purity.

**2-(2'-Nitrophenyl)*H*-imidazo[1,2-*a*]pyridine (9)**. Yellow solid, 2.02 g, 69% yield. The spectroscopic properties were in good agreement with published data.<sup>44</sup>

**6-Bromo-2-(2'-nitrophenyl)*H*-imidazo[1,2-*a*]pyridine (10)**. Yellow solid, 1.865 g, 64% yield. M.p. 151 °C. <sup>1</sup>H NMR (DMSO, 500 MHz):  $\delta$  8.99–8.87 (m, 1H), 8.30 (s, 1H), 7.96 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.77 (td, *J* = 7.7, 1.2 Hz, 1H), 7.60–7.65 (m, 2H), 7.44 (dd, *J* = 9.5, 1.9 Hz, 1H). <sup>13</sup>C NMR (DMSO, 125 MHz):  $\delta$  106.4, 111.4, 117.9, 123.7, 126.3, 127.2, 128.5, 129.2, 130.6, 132.1, 140.5, 143.0, 148.8. IR (KBr, cm<sup>-1</sup>): 729, 811, 1059, 1342, 1366, 1511, 3026, 3166. HRMS (EI): *m/z* calculated for C<sub>13</sub>H<sub>8</sub>BrN<sub>3</sub>O<sub>2</sub> [M<sup>+</sup>] = 316.9800; found: 316.9809. Elemental analysis (%): calculated for C<sub>13</sub>H<sub>8</sub>BrN<sub>3</sub>O<sub>2</sub>: C, 49.08; H, 2.53; N, 13.21; found: C, 48.97; H, 2.35; N, 13.16.



**2-(2'-Nitrophenyl)-*H*-imidazo[1,2-*a*]quinoline (11).** Yellow solid, 0.761 g, 24% yield. M.p. 190 °C. <sup>1</sup>H NMR (DMSO, 500 MHz): δ 9.08 (s, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.88 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.74–7.80 (m, 3H), 7.55–7.62 (m, 3H). <sup>13</sup>C NMR (DMSO, 125 MHz): δ 111.4, 116.4, 117.0, 123.3, 124.3, 125.8, 127.4, 127.4, 129.3, 129.7, 129.8, 130.9, 132.5, 132.6, 140.0, 143.6, 149.1. IR (KBr, cm<sup>-1</sup>): 741, 760, 810, 1355, 1523, 1611, 3154. HRMS (EI): *m/z* calculated for C<sub>17</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub> [M<sup>+</sup>] = 289.0851; found: 289.0851. Elemental analysis (%): calculated for C<sub>17</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>: C, 70.58; H, 3.83; N, 14.53; found: C, 70.50; H, 3.96; N, 14.40.

**2-(2'-Nitrophenyl)-*H*-imidazo[2,1-*a*]isoquinoline (12).** Yellow solid, 1.30 g, 49% yield. M.p. 138–140 °C. <sup>1</sup>H NMR (DMSO, 500 MHz): δ 8.40 (d, *J* = 7.3 Hz, 2H), 8.30 (s, 1H), 8.01 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.86–7.91 (m, 2H), 7.75 (td, *J* = 7.6, 1.1 Hz, 1H), 7.59 (td, *J* = 7.6, 1.3 Hz, 1H), 7.64–7.71 (m, 2H), 7.31 (d, *J* = 7.3 Hz, 1H). <sup>13</sup>C NMR (DMSO, 125 MHz): δ 113.5, 113.7, 123.0, 123.2, 124.0, 124.7, 127.2, 127.8, 128.7, 129.1, 129.1, 129.8, 130.7, 132.5, 138.3, 142.5, 149.2. IR (KBr, cm<sup>-1</sup>): 698, 733, 792, 1360, 1508, 1606, 3169. HRMS (EI): *m/z* calculated for C<sub>17</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub> [M<sup>+</sup>] = 289.0851; found: 289.0853.

### General procedure for the reduction of nitro-imidazo[1,2-*a*]pyridines

**Method A:** A solution of nitroimidazopyridine (10 mmol) and SnCl<sub>2</sub> (40 mmol) in ethanol was stirred at 100 °C for 1.5 h under argon. Then the reaction mixture was cooled to rt and 5% aqueous NaHCO<sub>3</sub> was added until the pH was made slightly basic (pH 8). The resulting slurry was then filtered through a pad of Celite, washed with a small amount of ethanol and concentrated. The aqueous solution was extracted with AcOEt and the combined organic layers were washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by column chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>–AcOEt 3:1) and crystallization from AcOEt–hexanes gave the expected product of analytical purity.

**Method B:** To a solution of nitroimidazopyridine (0.56 mmol) in aq. THF (3 mL), indium powder (260 mg, 2.26 mmol) was added, followed by concentrated HCl (300 μL). After stirring for 3 h at r.t., 5% aqueous NaHCO<sub>3</sub> was added until the pH was neutral. After evaporation the crude product was used in the next step without any further purification.

**2-(6-Bromo-*H*-imidazo[1,2-*a*]pyridine-2-yl)benzenamine (14).** Yellow-cream solid, 0.823 g, 49% yield. M.p. 158–159 °C. <sup>1</sup>H NMR (DMSO, 500 MHz): δ 8.89–8.87 (m, 1H), 8.26 (s, 1H), 7.59 (d, *J* = 9.5 Hz, 1H), 7.55 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.37 (dd, *J* = 9.4, 2.0 Hz, 1H), 7.03 (td, *J* = 6.9, 1.4 Hz, 1H), 6.75 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.59 (td, *J* = 6.8, 1.2 Hz, 1H), 6.54 (s, 2H). <sup>13</sup>C NMR (DMSO, 125 MHz): δ 106.0, 109.2, 114.6, 115.6, 116.1, 117.1, 126.2, 127.2, 127.7, 128.7, 142.1, 146.5, 146.7. IR (KBr, cm<sup>-1</sup>): 745, 789, 1056, 1232, 1610, 3384. HRMS (EI): *m/z* calculated for C<sub>13</sub>H<sub>10</sub>BrN<sub>3</sub> [M<sup>+</sup>] = 287.0058; found: 287.0054. Elemental analysis (%): calculated for C<sub>13</sub>H<sub>10</sub>BrN<sub>3</sub>: C, 54.19; H, 3.50; N, 14.58; found: C, 54.42; H, 3.63; N, 14.79.

**2-(*H*-Imidazo[2,1-*a*]quinolin-2-yl)benzenamine (15).** Yellow-cream solid, 0.408 g, 61% yield. M.p. 168–169 °C. <sup>1</sup>H NMR (DMSO, 500 MHz): δ 9.06 (s, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.71–7.79 (m, 3H), 7.62 (d, *J* = 9.3 Hz, 1H), 7.56 (t, *J* = 7.1 Hz, 1H), 7.04 (td, *J* = 7.6, 1.3 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.63 (t, *J* = 8.0 Hz, 1H), 6.57 (s, 2H). <sup>13</sup>C NMR (DMSO, 125 MHz): δ 108.9, 115.7, 116.0, 116.5, 116.6, 116.7, 123.3, 125.4, 126.3, 128.1, 128.7, 129.6, 132.3, 142.3, 145.5, 146.9. IR (KBr, cm<sup>-1</sup>): 740, 815, 1443, 1610, 3331, 3450. HRMS (EI): *m/z* calculated for C<sub>17</sub>H<sub>13</sub>N<sub>3</sub> [M<sup>+</sup>] = 259.1109; found: 259.1113. Elemental analysis (%): calculated for C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>: C, 78.74; H, 5.05; N, 16.20; found: C, 78.52; H, 4.93; N, 16.21.

**2-(*H*-Imidazo[2,1-*a*]isoquinolin-2-yl)benzenamine (16).** Off-white solid, 0.511 g, 48% yield. M.p. 184–185 °C. <sup>1</sup>H NMR (DMSO, 500 MHz): δ 8.51 (d, *J* = 7.9 Hz, 1H), 8.37 (d, *J* = 7.3 Hz, 1H), 8.32 (s, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.69 (td, *J* = 7.0, 0.9 Hz, 1H), 7.64 (td, *J* = 7.3, 1.0 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.03 (td, *J* = 6.9, 1.4 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 6.58 (s, 2H). <sup>13</sup>C NMR (DMSO, 125 MHz): δ 111.3, 113.1, 115.9, 116.2, 116.6, 122.9, 123.0, 124.4, 127.8, 127.9, 128.5, 128.6, 128.6, 129.5, 141.2, 144.3, 146.8. IR (KBr, cm<sup>-1</sup>): 746, 795, 1320, 1511, 1610, 3310, 3453. HRMS (EI): *m/z* calculated for C<sub>17</sub>H<sub>13</sub>N<sub>3</sub> [M<sup>+</sup>] = 259.1109; found: 259.1096. Elemental analysis (%): calculated for C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>: C, 78.74; H, 5.05; N, 16.20; found: C, 78.66; H, 5.01; N, 16.09.

### Typical procedure for the preparation of sulfonamides

A solution of toluenesulphonyl chloride (2 mmol) in AcOEt (15 mL) was slowly added to the mixture of aminoimidazo[1,2-*α*]pyridines (1 mmol) and dry Et<sub>3</sub>N (2 mmol) in AcOEt (15 mL). The reaction mixture was stirred at 50 °C for 12 h under argon. The resulting suspension was diluted with AcOEt and extracted with H<sub>2</sub>O. The organic layer was subsequently washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Crystallization from MeOH afforded pure products.

***N*-Tosyl-2-(*H*-imidazo[1,2-*a*]pyridine-2-yl)benzenamine (17).** White solid, 0.704 g, 80% yield. M.p. 181–182 °C. <sup>1</sup>H NMR (DMSO, 500 MHz): δ 12.69 (s, 1H), 8.58 (d, *J* = 6.7 Hz, 1H), 8.38 (s, 1H), 7.75 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.73 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.51, 7.14 (AA'BB', *J* = 8.3 Hz, 4H), 7.43–7.38 (m, 1H), 7.27 (td, *J* = 8.5, 1.3 Hz, 1H), 7.12–7.10 (m, 1H), 7.04 (td, *J* = 6.7, 0.8 Hz, 1H), 2.24 (s, 3H). <sup>13</sup>C NMR (DMSO, 125 MHz): δ 21.3, 110.9, 113.9, 116.7, 120.6, 121.6, 124.6, 126.8, 127.0, 127.3, 128.0, 129.1, 129.9, 136.0, 136.6, 143.3, 143.8. IR (KBr, cm<sup>-1</sup>): 544, 568, 676, 736, 748, 916, 1092, 1157, 1289, 1417, 1495, 1585, 3055, 3145. HRMS (EI): *m/z* calculated for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S [M<sup>+</sup>] = 363.1041; found: 363.1048. Elemental analysis (%): calculated for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S: C, 66.10; H, 4.71; N, 11.56; found: C, 66.02; H, 4.70; N, 11.53.

***N*-Tosyl-2-(6-bromo-*H*-imidazo[1,2-*a*]pyridine-2-yl)benzenamine (18).** Cream solid, 0.401 g, 32% yield. M.p. 203–204 °C. <sup>1</sup>H NMR (DMSO, 500 MHz): δ 12.32 (s, 1H), 8.95–8.93 (m, 1H), 8.30 (s, 1H), 7.76–7.71 (m, 2H), 7.53–7.48 (m, 4H), 7.29 (td, *J* = 8.3, 1.1 Hz, 1H), 7.12–7.16 (m, 3H), 2.24 (s, 3H). <sup>13</sup>C NMR



(DMSO, 125 MHz):  $\delta$  21.3, 107.5, 111.3, 117.8, 121.0, 121.5, 124.8, 127.0, 127.3, 128.2, 129.4, 129.5, 129.9, 135.9, 136.5, 142.4, 143.8, 144.0. IR (KBr,  $\text{cm}^{-1}$ ): 568, 743, 918, 1092, 1155, 1279, 1495, 1584, 3099, 3136. HRMS (EI):  $m/z$  calculated for  $\text{C}_{20}\text{H}_{16}\text{N}_3\text{BrO}_2\text{S}$  [ $\text{M}^+$ ] = 441.0147; found: 441.0157. Elemental analysis (%): calculated for  $\text{C}_{20}\text{H}_{16}\text{N}_3\text{BrO}_2\text{S}$ : C, 54.31; H, 3.65; N, 9.50; found: C, 54.45; H, 3.67; N, 9.40.

***N*-Tosyl-2-(*H*-imidazo[1,2-*a*]quinolin-2-yl)benzenamine (19).** Cream solid, 0.545 g, 88% yield. M.p. 264–265 °C.  $^1\text{H}$  NMR (DMSO, 500 MHz):  $\delta$  11.47 (br s, 1H), 9.18 (s, 1H), 8.44 (d,  $J$  = 8.4 Hz, 1H), 8.19 (d,  $J$  = 7.8 Hz, 1H), 8.14 (d,  $J$  = 8.8 Hz, 1H), 7.95 (t,  $J$  = 7.7 Hz, 1H), 7.80, 7.00 (AA'BB',  $J$  = 8.5 Hz, 4H), 7.74 (t,  $J$  = 7.5 Hz, 1H), 7.39–7.49 (m, 4H), 7.33 (t,  $J$  = 7.2 Hz, 1H), 2.06 (s, 3H).  $^{13}\text{C}$  NMR (DMSO, 125 MHz):  $\delta$  21.2, 111.9, 113.7, 116.7, 123.0, 123.6, 126.2, 126.8, 127.0, 129.3, 129.7, 130.2, 131.1, 131.7, 135.3, 137.1, 140.8, 143.5. IR (KBr,  $\text{cm}^{-1}$ ): 549, 661, 760, 817, 913, 1158, 1338, 1427, 1492, 2654, 2687, 2730, 3057, 3087. HRMS (EI):  $m/z$  calculated for  $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$  [ $\text{M}^+$ ] = 413.1198; found: 413.1200.

***N*-Tosyl-2-(*H*-imidazo[2,1-*a*]isoquinolin-2-yl)benzenamine (20).** Cream solid, 0.483 g, 47% yield. M.p. 202–203 °C.  $^1\text{H}$  NMR (DMSO, 500 MHz):  $\delta$  12.94 (s, 1H), 8.50 (d,  $J$  = 7.9 Hz, 1H), 8.45 (s, 1H), 8.40 (d,  $J$  = 7.2 Hz, 1H), 7.99 (d,  $J$  = 7.9 Hz, 1H), 7.84 (t,  $J$  = 8.1 Hz, 1H), 7.79 (dd,  $J$  = 7.8, 1.2 Hz, 1H), 7.75 (td,  $J$  = 8.1, 1.1 Hz, 1H), 7.55–7.59 (m, 3H), 7.43 (d,  $J$  = 7.2 Hz, 1H), 7.28 (td,  $J$  = 8.5, 1.3 Hz, 1H), 7.12–7.16 (m, 3H), 2.23 (s, 3H).  $^{13}\text{C}$  NMR (DMSO, 125 MHz):  $\delta$  21.2, 114.3, 115.9, 123.5, 124.5, 125.9, 126.9, 128.4, 128.5, 129.7, 130.7, 135.3, 137.2, 143.5. IR (KBr,  $\text{cm}^{-1}$ ): 549, 553, 663, 811, 920, 1092, 1155, 1328, 2774, 3012. HRMS (EI):  $m/z$  calculated for  $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$  [ $\text{M}^+$ ] = 413.1198; found: 413.1208. Elemental analysis (%): calculated for  $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$ : C, 69.71; H, 4.63; N, 10.16; found: C, 69.52; H, 4.62; N, 10.01.

### Typical procedure for the oxidative coupling of tosylamides

**Method A:**  $\text{CF}_3\text{COOH}$  (46  $\mu\text{L}$ , 0.6 mmol) was slowly added to the mixture of tosylamides **17** or **18** (0.2 mmol),  $\text{Cu}(\text{OTf})_2$  (0.01 mmol) and  $\text{PhI}(\text{OAc})_2$  (0.3 mmol) in 1,2-dichloroethane (2 mL) and the whole reaction mixture was stirred at 50 °C for 30 minutes under argon. The resulting solution was cooled, filtered through a pad of Celite and washed with AcOEt. Purification by column chromatography (silica, AcOEt–hexanes 6 : 4) followed by crystallization from AcOEt–hexanes afforded pure products.

**Method B:**  $\text{CF}_3\text{COOH}$  (46  $\mu\text{L}$ , 0.6 mmol) was slowly added to the mixture of tosylamide **19** or **20** (0.2 mmol) and  $\text{PhI}(\text{CF}_3\text{COO})_2$  (0.3 mmol) in 1,2-dichloroethane (2 mL) and the whole reaction mixture was stirred at 50 °C for 30 minutes under argon. The product was purified according to the procedure described in Method A.

***N*-Tosyl-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole (21).** Off-white solid, 0.067 g, 93% yield. M.p. 177–178 °C.  $^1\text{H}$  NMR (DMSO, 500 MHz):  $\delta$  9.14 (d,  $J$  = 6.8 Hz, 1H), 8.21 (d,  $J$  = 8.4 Hz, 1H), 7.80–7.76 (m, 2H), 7.54–7.42 (m, 3H), 7.38, 7.18 (AA'BB',  $J$  = 8.3 Hz, 4H), 7.24 (t,  $J$  = 6.9 Hz, 1H), 2.20 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (DMSO, 125 MHz):  $\delta$  21.4, 113.8, 117.6, 118.2, 119.9,

123.3, 125.7, 126.2, 126.4, 126.9, 127.2, 130.5, 131.0, 138.2, 141.6, 146.4. IR (KBr,  $\text{cm}^{-1}$ ): 539, 677, 740, 971, 1173, 1364, 1529, 1592, 1706, 3057, 3141. HRMS (EI):  $m/z$  calculated for  $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$  [ $\text{M}^+$ ] = 361.0885; found: 361.0881.

***N*-Tosyl-(5-bromo-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole (22).** Off-white solid, 0.170 g, 48% yield. M.p. 182–183 °C.  $^1\text{H}$  NMR (DMSO, 500 MHz):  $\delta$  9.23–9.21 (m, 1H), 8.17 (d,  $J$  = 8.5 Hz, 1H), 7.79 (d,  $J$  = 7.3 Hz, 1H), 7.75 (d,  $J$  = 9.8 Hz, 1H), 7.56 (dd,  $J$  = 9.8, 1.9 Hz, 1H), 7.52 (t,  $J$  = 7.8 Hz, 1H), 7.40–7.45 (m, 3H), 7.18 (d,  $J$  = 8.2 Hz, 2H), 2.20 (s, 3H).  $^{13}\text{C}$  NMR (DMSO, 125 MHz):  $\delta$  21.4, 107.3, 117.5, 119.8, 120.1, 123.5, 125.5, 126.5, 127.2, 127.4, 128.3, 130.5, 130.9, 141.6, 146.5. IR (KBr,  $\text{cm}^{-1}$ ): 537, 573, 664, 756, 787, 1169, 1365, 1502, 1594, 3137. HRMS (EI):  $m/z$  calculated for  $\text{C}_{20}\text{H}_{14}\text{N}_3\text{O}_2\text{SBr}$  [ $\text{M}^+$ ] = 438.9990; found: 438.9991.

***N*-Tosyl-5*H*-quinolino[1',2':2,3]imidazo[4,5-*b*]indole (23).** Off-white solid, 0.097 g, 29% yield. M.p. 191–193 °C.  $^1\text{H}$  NMR (DMSO, 500 MHz):  $\delta$  8.77 (d,  $J$  = 8.5 Hz, 1H), 8.10 (d,  $J$  = 8.1 Hz, 1H), 8.06 (d,  $J$  = 7.8 Hz, 1H), 7.88 (d,  $J$  = 9.5 Hz, 1H), 7.81 (td,  $J$  = 8.5, 1.2 Hz, 1H), 7.67 (d,  $J$  = 9.5 Hz, 1H), 7.63 (t,  $J$  = 7.5 Hz, 1H), 7.58 (d,  $J$  = 7.5 Hz, 1H), 7.46 (td,  $J$  = 8.4, 1.2 Hz, 1H), 7.39 (td,  $J$  = 7.5, 1.0 Hz, 1H), 7.00, 6.84 (AA'BB',  $J$  = 8.3 Hz, 4H), 2.17 (s, 3H).  $^{13}\text{C}$  NMR (DMSO, 125 MHz):  $\delta$  21.4, 117.9, 119.30, 119.34, 120.5, 123.9, 126.0, 126.1, 126.3, 127.6, 127.7, 127.9, 128.1, 128.7, 128.9, 129.4, 131.0, 132.2, 140.6, 144.4, 146.0, 147.4. IR (KBr,  $\text{cm}^{-1}$ ): 535, 573, 665, 750, 808, 1173, 1360, 3052. HRMS (EI):  $m/z$  calculated for  $\text{C}_{24}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$  [ $\text{M}^+$ ] = 411.1041; found: 411.1038. Elemental analysis (%): calculated for  $\text{C}_{24}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$ : C, 70.05; H, 4.16; N, 10.21; found: C, 69.99; H, 4.28; N, 10.10.

***N*-Tosyl-5*H*-isoquinolino[1',2':2,3]imidazo[4,5-*b*]indole (23).** Off-white solid, 0.101 g, 62% yield. M.p. 188–191 °C.  $^1\text{H}$  NMR (DMSO, 500 MHz):  $\delta$  8.96 (d,  $J$  = 7.5 Hz, 1H), 8.62–8.58 (m, 1H), 8.21 (d,  $J$  = 8.1 Hz, 1H), 8.01–7.97 (m, 1H), 7.83 (dd,  $J$  = 7.5, 0.8 Hz, 1H), 7.77–7.72 (m, 2H), 7.54 (d,  $J$  = 7.5 Hz, 1H), 7.49 (td,  $J$  = 7.4, 1.2 Hz, 1H), 7.47–7.41 (m, 3H), 7.17 (d,  $J$  = 8.1 Hz, 2H), 2.19 (s, 3H).  $^{13}\text{C}$  NMR (DMSO, 125 MHz):  $\delta$  21.4, 113.8, 117.6, 119.5, 123.0, 123.5, 123.6, 123.9, 126.2, 126.4, 127.2, 127.8, 128.2, 129.0, 129.3, 129.4, 130.5, 131.2, 136.5, 141.2, 145.6, 146.4. IR (KBr,  $\text{cm}^{-1}$ ): 541, 574, 672, 738, 795, 1176, 1378, 1442, 1740, 3061, 3146. HRMS (EI):  $m/z$  calculated for  $\text{C}_{24}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$  [ $\text{M}^+$ ] = 411.1041; found: 411.1044.

***N*-Tosyl-(5-(4-*N,N*-dimethylaminophenylethynyl)-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole (25).** The mixture of compound **22** (120 mg, 0.27 mmol), 4-ethynyl-*N,N*-dimethylaniline (100 mg, 0.69 mmol),  $\text{Cs}_2\text{CO}_3$  (247 mg, 0.76 mmol),  $\text{Pd}(\text{OAc})_2$  (7.8 mg, 0.035 mmol) and  $\text{PPh}_3$  (36 mg, 0.14 mmol) in 10 mL of DMSO was stirred at 80 °C for 24 h under argon. The resulting solution was diluted with AcOEt and extracted with  $\text{H}_2\text{O}$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. Purification by column chromatography (silica, hexanes–AcOEt 7 : 3) followed by crystallization from AcOEt–hexanes afforded **25** as yellow crystals (0.059 g, 43% yield). M.p. 229–232 °C.  $^1\text{H}$  NMR (DMSO, 500 MHz):  $\delta$  9.21–9.19 (m, 1H), 8.19 (d,  $J$  = 8.2 Hz, 1H), 7.79 (d,  $J$  = 7.7 Hz, 1H), 7.76 (dd,  $J$  = 9.5, 0.8 Hz, 1H), 7.54–7.48



(m, 2H), 7.46–7.41 (m, 5H), 7.19 (d,  $J = 8.2$  Hz, 2H), 6.75 (d,  $J = 9.0$  Hz, 2H), 2.89 (s, 6H), 2.21 (s, 3H).  $^{13}\text{C}$  NMR (DMSO, 125 MHz):  $\delta$  21.4, 84.2, 92.8, 108.2, 109.9, 112.3, 117.6, 118.5, 120.0, 123.4, 126.3, 126.5, 127.1, 127.3, 127.4, 128.0, 130.5, 130.8, 133.0, 139.5, 141.6, 146.5, 147.0, 150.8. IR (KBr,  $\text{cm}^{-1}$ ): 539, 574, 673, 815, 931, 1172, 1371, 1536, 1604, 2211, 3037, 3131. HRMS (EI):  $m/z$  calculated for  $\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2\text{S}$  [ $\text{M}^+$ ] = 504.1620; found: 504.1622.

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