

# Titanium(IV) Chloride Promoted Syntheses of New Imidazo[1,2-*a*]pyridine Derivatives under Microwave Conditions

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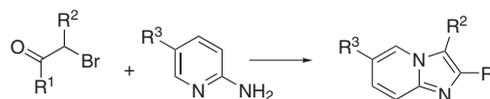
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Received 6 May 2005

**Abstract:** A new method is described for the synthesis of imidazo[1,2-*a*]pyridine derivatives from the reaction of 2-aminopyridines with  $\alpha$ -haloketones. The critical reagent is titanium(IV) chloride, which appears to serve as a strong dehydrating agent to promote formation of putative Schiff base intermediates, which cyclize subsequently to form the products. The reactions were performed rapidly under microwave conditions. Multiple reaction conditions were evaluated, including reaction temperature, solvent and other Lewis acids. Various combinations of substitution patterns in both the  $\alpha$ -haloketone and 2-aminopyridine substrates were examined to evaluate the scope of the reaction. The reaction is quite sensitive to substituents in both substrates, especially those with basicity or coordination ability.

**Keywords:** titanium(IV) chloride, imidazo[1,2-*a*]pyridine, polycyclic, condensation, Schiff base formation, microwave

We<sup>1</sup> and others<sup>2</sup> have been exploring imidazo[1,2-*a*]pyridine derivatives as ligands that potentially may bind selectively to  $\beta$ -amyloid aggregates,<sup>3–5</sup> benzodiazepine receptors<sup>6</sup> or peripheral benzodiazepine receptors (PBR),<sup>6</sup> and which may therefore be converted into radiolabeled probes for imaging these proteins in living brain with positron emission tomography (PET).<sup>7,8</sup> Usually the synthesis of an imidazo[1,2-*a*]pyridine makes use of the condensation between an  $\alpha$ -bromocarbonyl compound and a 2-aminopyridine derivative under weak basic conditions. Three types of bromocarbonyls have been used, including primary  $\alpha$ -bromoketones,<sup>1</sup> secondary  $\alpha$ -bromoketones,<sup>6</sup> and activated  $\alpha$ -bromoamides (Scheme 1).<sup>9–11</sup> A mechanism for the reaction has been proposed,<sup>1</sup> which includes the nucleophilic substitution of the bromide by the pyridine-nitrogen in the 2-aminopyridine derivative. Other possibilities exist, such as pre-formation of a Schiff base before ring-closure to form the final product. These reaction conditions only work when bromo is on a primary carbon or occasionally on a secondary carbon. However, when steric hindrance on the secondary carbon is large or when the products are fused-polycyclic compounds there is no desired condensation. Reitmann<sup>12</sup> condensed 2-aminopyridine with 2-bromo-1-tetralone under the typical weak basic conditions and the structure of the product was proved later.<sup>13</sup> However, analogous reaction of the 6-amino-2-bromo-1-tetralone derivatives did not generate any

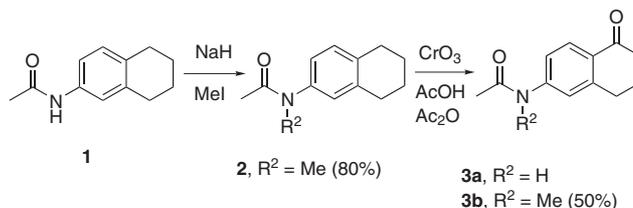


**Scheme 1**

isolable products in the identical conditions or other variations of its kind. Here we report our success in overcoming these limitations by using titanium(IV) chloride as an auxiliary reagent under microwave conditions. A wide range of new substituted imidazo[1,2-*a*]pyridines were rapidly accessed by this approach.

## 6-Amino-3,4-dihydronaphthalen-1(2*H*)-one Derivatives

An *N*-methyl group was introduced at the amido group of **1** by pretreating it with sodium hydride and then reacting with iodomethane, to generate **2** (Scheme 2).<sup>14</sup> Oxidation of the amide with chromium(VI) oxide gave the ketone **3b**,<sup>15</sup> with the ketone group *para* to the amido methyl group. Dimethylation of the amino group of **4**<sup>15–18</sup> was accomplished with iodomethane under basic conditions to give **3g** (Scheme 3).<sup>19–22</sup> Formylation of the amino group of **4** was achieved by heating the compound in formic acid to generate **3e**. Mono-methylation of **4** was possible by controlling the amount of iodomethane used and the reaction time to give **6**.<sup>19,21</sup> For the synthesis of both **5** and **7** (Scheme 4), a bromo group was introduced at the sterically demanding *ortho* position by using NBS as a selective brominating agent, as confirmed by the disappearance of the singlet <sup>1</sup>H NMR peak in the aromatic region for both **4** and **6**. *N*-Acylation of **5** and **7** with acetyl chloride under basic conditions gave **3c** and **3d**, respectively. Formylation of the amino group in **6** was also accomplished with formic acid, but only in the presence of DCC, reflecting the reduction of reactivity of the amino group caused by the attached methyl group.



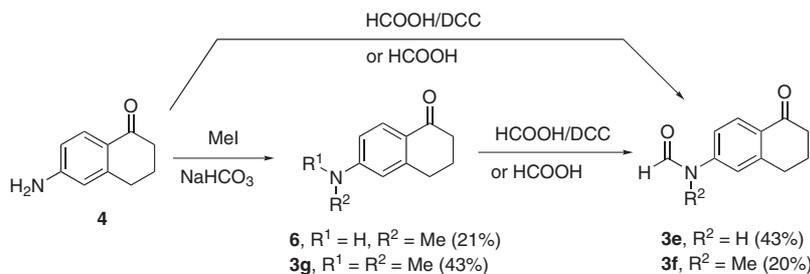
**Scheme 2**

SYNTHESIS 2006, No. 1, pp 0133–0145

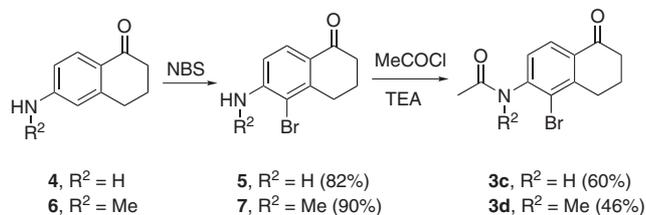
Advanced online publication: 24.11.2005

DOI: 10.1055/s-2005-918490; Art ID: M03405SS

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Scheme 3



Scheme 4

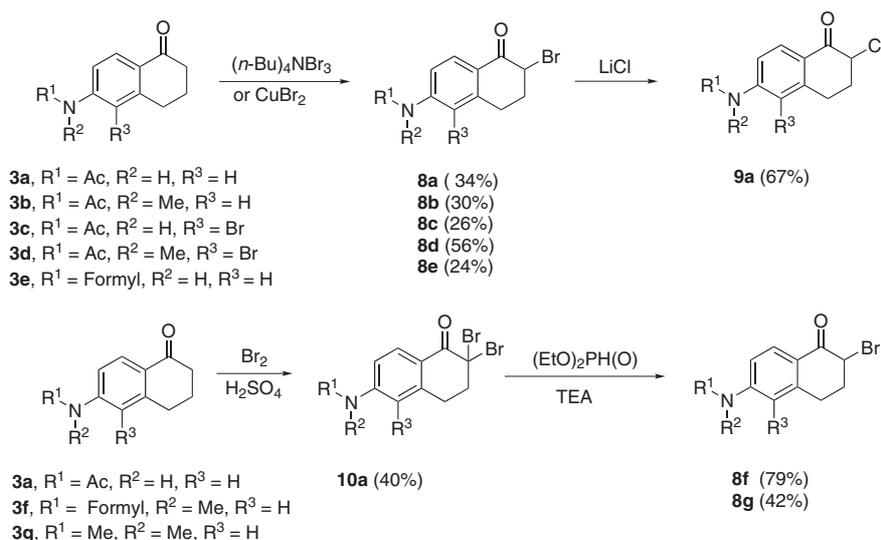
### 6-Amino-2-bromo-3,4-dihydro-1(2H)-one Derivatives

Three types of brominating agents were adopted for the synthesis of this type of  $\alpha$ -bromo compounds (Scheme 5). The first brominating agent was tetra-*n*-butylammonium tribromide ( $\text{Bu}_4\text{NBr}_3$ ),<sup>23</sup> which was used successfully in the syntheses of **8a**,<sup>24</sup> **8c**,<sup>24</sup> and **8d**. The mixed solvent of dichloromethane and methanol is critical for the selective formation of the mono-bromides. Either pure dichloromethane or methanol promoted dibromide formation. When tetra-*n*-butylammonium tribromide failed to give the desired monobromides, a second brominating agent was used, namely copper(II) bromide.<sup>25,26</sup> This method was used for the synthesis of **8b** and **8e**. When both methods described above failed, a third strategy was used. This

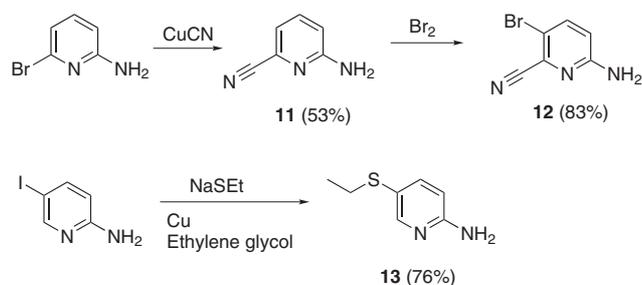
involves a two-step sequence.<sup>27</sup> The first is the formation of  $\alpha,\alpha$ -dibromoketone, such as **10a**. The second is the selective reduction of the dibromide to the mono-bromide. The  $\alpha$ -chloro derivative **9a** was synthesized by the displacement of bromide by chloride under anhydrous conditions. Lithium chloride is the agent of choice for this reaction with negligible by-product formation.

### 2-Aminopyridine Derivatives

Except for some commercially available 2-aminopyridines, others were synthesized through electrophilic substitution or nucleophilic substitution of halide in the pyridine ring (Scheme 6). Copper(I) cyanide was used to introduce the cyano group in the synthesis of **11**.<sup>28–30</sup> Bromination of **11** affords **12**, showing the dominant *para* directing effect of the amino group. Although the syntheses of **13**<sup>31,32</sup> have been reported, these made use of copper as catalyst and methanol as solvent at 150 °C under pressure.<sup>11</sup> The inconvenience of the procedure prompted us to evaluate other solvents to replace the low boiling methanol. Ethylene glycol was an excellent choice for this reaction, giving high yield in a short reaction time. The benefits of ethylene glycol as solvent in other copper or copper(I)-catalyzed reaction have been noted.<sup>33</sup>



Scheme 5



Scheme 6

### Reaction of $\alpha$ -Bromotetralone with 2-Aminopyridine Derivatives

Taking the condensation reaction of **8c** and 5-bromo-2-aminopyridine as an example (Table 1), the effect of varying the temperature (microwave), Lewis acids, and solvent on the reaction was evaluated to establish optimal conditions for other substrates. A microwave device was utilized as a convenient and practical source of energy for the condensation reactions. Two conditions (Method A:

170 °C, 30 s, 300 W, 300 psi; Method B: 110 °C, 30 min, 300 W, 300 psi) were used. The Lewis acids examined included zinc chloride, tin(IV) chloride, tetra(dimethylamino)titanium(IV) and titanium(IV) chloride. The first two gave no products at all. The third gave a complicated mixture. Only titanium(IV) chloride gave appreciable amounts of product. This will be the only agent to be discussed. A group of chlorinated solvents was selected and evaluated. A high boiling solvent was desirable to enhance the solubility of the substrates and to allow the reaction at elevated temperatures. Among the evaluated chlorinated solvents (CHCl<sub>3</sub>, CCl<sub>3</sub>CH<sub>2</sub>Cl, CHCl<sub>2</sub>CH<sub>2</sub>Cl, CHCl<sub>2</sub>CHCl<sub>2</sub>, and CHCl<sub>2</sub>CCl<sub>3</sub>), both chloroform and 1,1,2-trichloroethane gave better results, and were used in subsequent reactions. TiCl<sub>4</sub> in dichloromethane was used, with no effort to remove the small amount of dichloromethane.

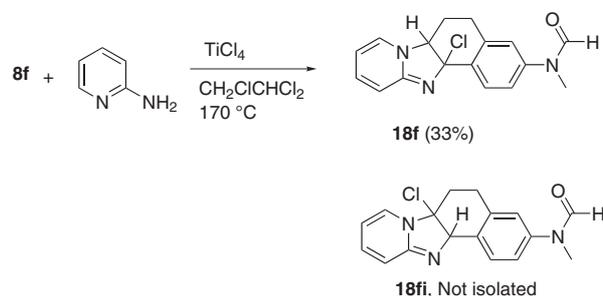
The reactions are shown in Table 1. Most of the reactions go smoothly, giving low to moderate yields. Substituents in either the tetralone or the 2-aminopyridine have a significant effect on the yield and speed of the reaction. 2-Aminopyridine and substituted 2-aminopyridines, includ-

**Table 1** Reaction of  $\alpha$ -Bromotetralones with 2-Aminopyridine Derivatives

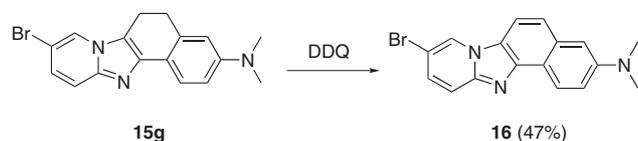


R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Method	Product	Yield (%)
6-Br	Ac	H	H	A or B		0
6-CN	Ac	H	H	A or B		0
6-CN, 5-Br	Ac	H	H	A or B		0
5-CN	Ac	H	H	A or B		0
5-NO <sub>2</sub>	Ac	H	H	A or B		0
5-I	Ac	H	H	B	<b>14a</b>	22
5-I	Ac	H	Br	A	<b>14c</b>	9
5-Br	Ac	H	H	B	<b>15a</b>	17
5-Br	Ac	H	Br	B	<b>15c</b>	22
5-Br	Me	Me	H	B	<b>15g</b>	46
5-SEt	Ac	H	Br	A	<b>17c</b>	24
H	Ac	H	H	B	<b>18a</b>	30
H	Ac	H	Br	B	<b>18c</b>	32
4-OEt	Ac	H	H	B	<b>19a</b>	45
4-OEt	Ac	H	Br	B	<b>19c</b>	18
3-OBn	Ac	H	H	A	<b>20a</b>	0
3-OBn	Ac	H	Br	B	<b>20c</b>	22

ing 5-iodo, 5-bromo, 5-ethylthio, 4-ethoxy and 3-benzyl-oxo derivatives, undergo the reactions, with the electron-donating substituents giving better yields and faster reactions. Electron-withdrawing groups, such as cyano and nitro groups inhibit the reaction and so does any substituent in 6-position, such as 6-bromo or 6-cyano group. The effect of substituents in the bromotetralone derivatives differs according to their positions in the ring system. A substituent in 5-position of the dihydronaphthalene ring appears to have minimal effect on the reaction, except for a change in solubility of the starting materials and products. However, substituents on the 6-amino group have significant impact on the reaction. We have evaluated acetyl, formyl and methyl substituents. Changing from an acetyl group to a formyl group alters the reactivity dramatically. Substrates with a formyl group gave much more complicated reactions. At least in one case, instead of the normal product, we isolated **18f**, an hydrogen chloride addition product of the expected tetracyclic compound (Scheme 7). Hydrochloride adducts of expected products were also observed in small amount in other reactions. When the substituents on 6-amino group were dimethyl groups, the reaction shifted in a different direction. Except for the expected product, **15g**, we also observed the dehydrogenated aromatized product, **16**, with the ratio of 3:1 (**15g**:**16**). The mixture of **15g** and **16** was transformed cleanly to pure **16** with DDQ (Scheme 8). It appears that the strong electron-releasing dimethylamino group favors the dehydrogenation of the newly formed ring. The mechanism is unclear at this time.



Scheme 7

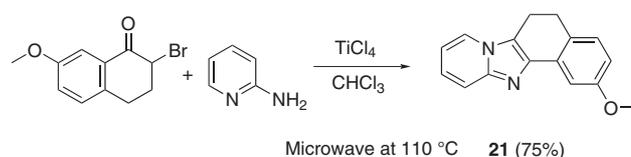


Scheme 8

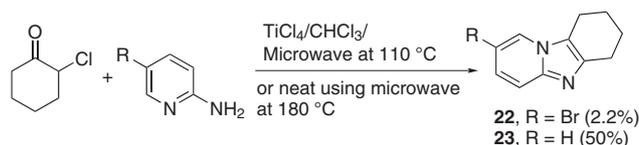
### Reaction of Other $\alpha$ -Bromoketones with 2-Aminopyridine Derivatives

Other  $\alpha$ -bromo tetralones gave analogous reactions in the presence of titanium(IV) chloride. For example, 2-bromo-3,4-dihydro-7-methoxynaphthalen-1(2*H*)-one reacted with 2-aminopyridine to give the desired product, **21**, in

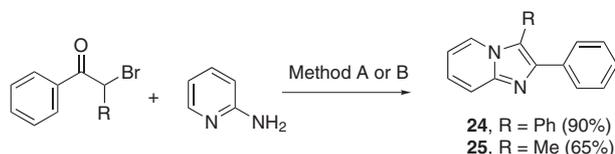
high yield (Scheme 9). Other six-membered  $\alpha$ -bromo and  $\alpha$ -chloroketones reacted with 2-aminopyridine derivatives to give the desired products **22** and **23** (Scheme 10) at low to moderate yield. Compound **23** could also be generated without  $\text{TiCl}_4$ , without or with a variety of solvents (incl. EtOH, *n*-BuOH, MeCN, DMF, or DMSO). However, five-membered  $\alpha$ -bromoketones did not give any products, although analogous compounds have been synthesized using other methods.<sup>34–40</sup> The preference of fused six- and five-membered rings over two five-membered rings in the expected products is reflected in part in the reactions involving  $\alpha$ -bromoketones in open chains (Scheme 11). These reactions gave overall much better yield, up to 90% in selected cases, such as **24**<sup>41–44</sup> and **25**.<sup>45–47</sup> Tertiary  $\alpha$ -bromoketones did not give any products, even with a secondary bromo group at the  $\beta$ -position.



Scheme 9



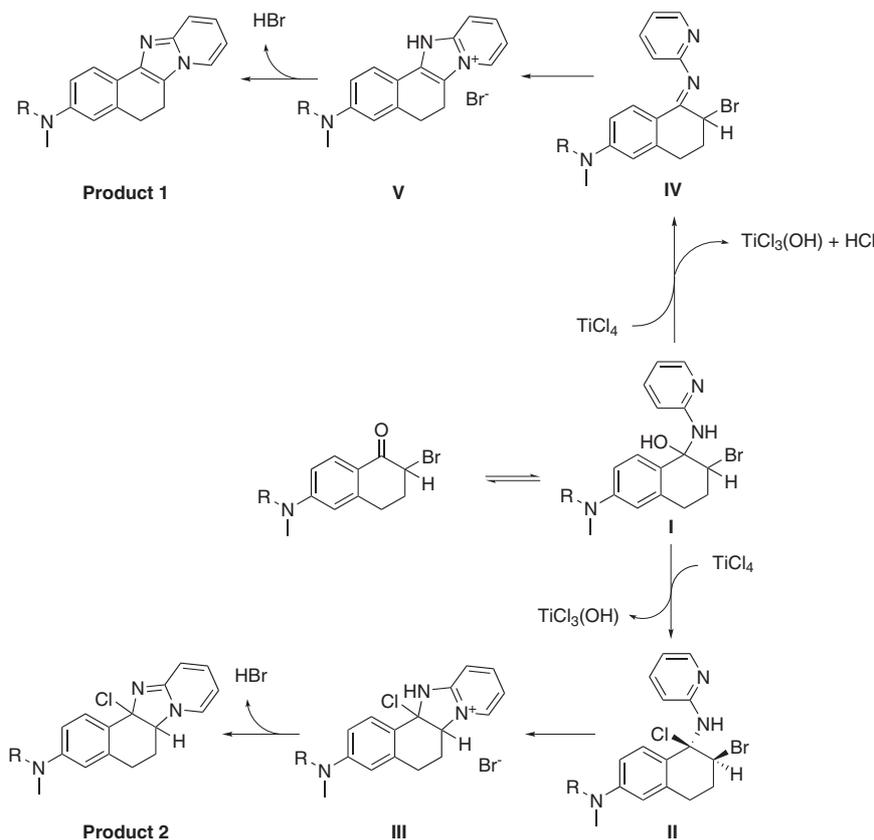
Scheme 10



Scheme 11

### Mechanistic Implications

The proposed mechanistic model for  $\text{TiCl}_4$ -promoted condensation is shown in Scheme 12. This model differs from that proposed previously for the normal synthesis of imidazo[1,2-*a*]pyridines under slightly basic conditions.<sup>1</sup> Titanium(IV) chloride has been shown to be an efficient promoter for Schiff base formation from ketones and amino-compounds under mild conditions.<sup>48–50</sup> The presumed first intermediate **I** in Scheme 12 can proceed in two possible routes, to generate either **II** or the Schiff base intermediate **IV**. Intermediate **IV** undergoes cyclization to give intermediate **V**, which would generate the normal 'Product 1'. Intermediate **II** would react similarly to give abnormal 'Product 2'. Both pathways are possible routes for semi-ketal chemistry. It appears that higher temperature favors the second route, as Method A (in experimental section) normally gave various amounts of 'Product



Scheme 12

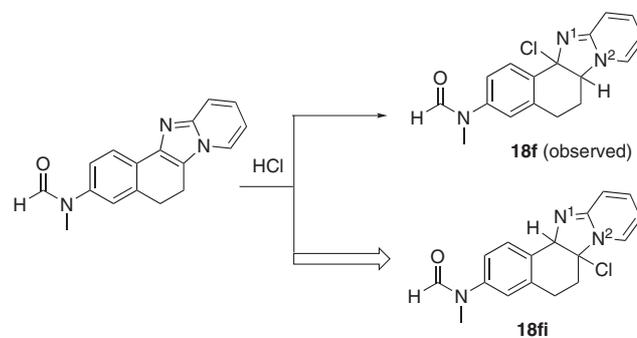
**2'**. Under basic conditions, such as treatment with aqueous potassium carbonate solution, '**Product 2**' transforms into '**Product 1**'.

An alternative mechanism, such as an elimination-addition mechanism with subsequent enamine-enamine rearrangement,<sup>51,52</sup> is unlikely, since the elimination intermediate would rearrange into a naphthol, which would be inactive under the reaction conditions. The elimination reaction would be possible as a pathway to by-products, rationalizing the relative low yields of the present reaction.

An alternative explanation for the observation of '**Product 2**' may be that '**Product 1**' reacts with hydrogen chloride generated in the reaction media, to form the hydrogen chloride adduct. If that is the case, we should expect to observe a different product, as shown in Scheme 13, since the nitrogen at the N<sup>2</sup> position should stabilize the developing charge on adjacent carbon more efficiently than that at the N<sup>1</sup> position. However, the <sup>1</sup>H NMR spectrum of the isolated product showed clearly strongly coupled protons, as expected for **18f**. Compound **18fi** was not observed as a product. This is against the argument that the product **18f** arises from hydrogen chloride addition.

In conclusion, we have developed a new method for the synthesis of imidazo[1,2-*a*]pyridines, in terms of reaction conditions and reaction scope. Good reaction conditions were established, with respect to reaction solvent, temperature and Lewis acid. Chloroform and 1,2,2-trichloro-

ethane are the best solvents, 110–170 °C the optimal temperature range and titanium(IV) chloride the best Lewis acid of those so far tested. A variety of substrates have been examined, giving poor to moderately high reaction yields. Based on the isolated products, we have proposed an overall reaction mechanism to explain the experimental facts. The main feature of this proposal is that the titanium(IV) chloride promotes Schiff base formation preceding cyclization on to the final product. In selected cases, a novel semi-ketal intermediate was trapped before proceeding to new imidazo[1,2-*a*]pyridines. Several of these derivatives, especially the quite rigid and almost planar tetracyclic compounds, are now of further interest for potential conversion into radioligands for PET imaging.



Scheme 13

*N*-(1,2,3,4-Tetrahydronaphthalen-7-yl)acetamide<sup>53,54</sup> (**1**), *N*-(1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide<sup>53</sup> (**3a**) and 6-amino-3,4-dihydronaphthalen-1(2*H*)-one<sup>53</sup> (**4**) were synthesized as reported or purchased from Pharmaron (Louisville, KY). 2-Bromo-3,4-dihydro-7-methoxynaphthalen-1(2*H*)-one and 6-bromo-2-aminopyridine were purchased from Aldrich (Milwaukee, WI). All compounds synthesized have been purified by either column chromatography or preparative HPLC until their purity was greater than 95% as judged by analytical HPLC. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were acquired on a 300, 400 or 500 MHz spectrometer (Bruker) using the chemical shifts of residual deuterated solvent as internal standard; chemical shifts ( $\delta$ ) for proton and carbon resonances are reported in parts per million (ppm) relative to the internal standard. High-resolution mass spectra (HRMS) were acquired from Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign (Urbana, IL). Low-resolution mass spectra were acquired with either LCQ<sup>DECA</sup> LC-MS (Thermo Finnigan) equipped with an MS-HPLC column: (Luna C18; 5  $\mu$ m; 2.0  $\times$  150 mm; Phenomenex) eluted at 150  $\mu$ L/min with a MeOH–H<sub>2</sub>O mixture or with a PolarisQC GC-MS (Thermo Finnigan) equipped with a capillary RTX-5ms column (30 m  $\times$  0.25 mm) and helium (1 mL/min) as carrier gas. Melting points were determined using Electrothermal Mel-Temp Manual Melting Point Apparatus (Fisher Scientific) and are uncorrected. Elemental analyses were performed by Midwest Microlab (Indianapolis, IN) or Galbraith Laboratories, Inc. (Knoxville, TN). A CEM Discover microwave system was used (Matthews, NC).

#### ***N*-(1,2,3,4-Tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylacetamide (**3b**)<sup>15</sup>**

*N*-(1,2,3,4-Tetrahydronaphthalen-7-yl)-*N*-methylacetamide (**2**; 15.8 g, 83.5 mmol) was dissolved in AcOH (38 mL) plus Ac<sub>2</sub>O (50 mL) to form solution A. Chromium(VI) oxide (7.90 g, 79.0 mmol) was dissolved in H<sub>2</sub>O (8.7 mL) and AcOH (34.8 mL) to form solution B. Solution B was added dropwise to solution A at 0 °C, stirred at that temperature for 1 h, and then stirred at r.t. overnight. The reaction mixture was filtered and the filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was collected. After drying and removal of the solvent, the crude solid was purified using column chromatography on silica gel (EtOAc–hexanes, 3:1) to afford **3b** as a white solid (8.4 g, 50% yield). The unreacted starting material was recovered from chromatography and reused; mp 80–82 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.08 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.1 Hz, 1 H, ArH), 7.14 (s, 1 H, ArH), 7.10 (d, <sup>3</sup>*J*<sub>HH</sub> = 5.6 Hz, 1 H, ArH), 3.28 (s, 3 H, NCH<sub>3</sub>), 2.98 (t, <sup>3</sup>*J*<sub>HH</sub> = 5.9 Hz, 2 H, CH<sub>2</sub>), 2.68 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.4 Hz, 2 H, CH<sub>2</sub>), 2.17 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.96 (s, 3 H, COCH<sub>3</sub>).

EI-MS: *m/z* (%) = 217.1 (70) [M]<sup>+</sup>, 175.1 (100) [M + H – CH<sub>3</sub>CO]<sup>+</sup>, 147.1 (45) [M + H – CH<sub>3</sub>CO – CO]<sup>+</sup>, 56.0 (30) [CH<sub>2</sub>CO – N]<sup>+</sup>.

HRMS (TOF<sup>+</sup>): *m/z* calcd for C<sub>13</sub>H<sub>15</sub>NO<sub>2</sub>: 217.1103; found: 217.1097.

#### ***N*-(5-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**3c**)**

6-Amino-5-bromo-3,4-dihydronaphthalen-1(2*H*)-one (**5**; 34.0 g, 142 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (500 mL). The solution was cooled to 0 °C with an ice bath. Acetyl chloride (16.7 g, 213 mmol) and Et<sub>3</sub>N (TEA; 21.4 g, 212 mmol) were added dropwise to the above solution. The reaction mixture was allowed to warm to r.t. and stirred for 2 h. H<sub>2</sub>O was added to wash the organic phase. The collected organic phase was dried and the solvent was removed. The obtained solid was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>–petroleum ether to afford **3c** as a white solid (24 g, yield: 60%); mp 174–176 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.41 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.7 Hz, 1 H, ArH), 8.06 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.8 Hz, 1 H, ArH), 7.91 (br s, 1 H, NH), 3.02 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.1 Hz, 2 H, CH<sub>2</sub>), 2.63 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.6 Hz, 2 H, CH<sub>2</sub>), 2.28 (s, 3 H, CH<sub>3</sub>), 2.17 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

EI-MS: *m/z* (%) = 283.0 (15), 281.0 (15), [M]<sup>+</sup>, 241.0 (40), 239.0 (40) [M + H – CH<sub>3</sub>CO]<sup>+</sup>, 213.0 (48), 211.0 (48) [M + H – CH<sub>3</sub>CO – CO]<sup>+</sup>, 202.1 (100) [M – Br]<sup>+</sup>, 130.1 (11), 104.1 (22), 77.0 (11), 56.0 (30) [CH<sub>2</sub>CO – N]<sup>+</sup>.

HRMS (TOF<sup>+</sup>): *m/z* calcd for C<sub>12</sub>H<sub>12</sub>BrNO<sub>2</sub>: 283.0031; found: 283.0031.

#### ***N*-(5-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylacetamide (**3d**)**

5-Bromo-3,4-dihydro-6-(methylamino)naphthalen-1(2*H*)-one (**7**; 15.4 g, 60.6 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (200 mL). TEA (8.30 g, 82.2 mmol) was added. Acetyl chloride (5.70 g, 72.6 mmol) was added dropwise. The progress of the reaction was monitored by TLC. After the reaction had ended, the organic layer was washed with H<sub>2</sub>O and dried. The solvent was removed and the residue was separated by column chromatography on silica gel (EtOAc–hexanes; 1:1) to afford **3d** as a white solid (8.2 g, yield: 46%); mp 114–116 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.12 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.3 Hz, 1 H, ArH), 7.29 (d, <sup>3</sup>*J*<sub>HH</sub> = 6.1 Hz, 1 H, ArH), 3.20 (s, 3 H, NCH<sub>3</sub>), 3.10 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.1 Hz, 2 H, CH<sub>2</sub>), 2.69 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.6 Hz, 2 H, CH<sub>2</sub>), 2.50 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.83 (s, 3 H, CH<sub>3</sub>).

EI-MS: *m/z* (%) = 283.0 (15), 281.0 (15) [M]<sup>+</sup>, 241.0 (40), 239.0 (40) [M + H – CH<sub>3</sub>CO]<sup>+</sup>, 255.0 (32), 253.0 (32) [M + H – CH<sub>3</sub>CO]<sup>+</sup>, 241.0 (81), 239 (81) [M + H – CH<sub>3</sub>CO – CH<sub>3</sub> + H]<sup>+</sup>, 227.0 (32), 225.0 (32) [M + H – CH<sub>3</sub>CONCH<sub>3</sub> + H]<sup>+</sup>, 216.0 (64) [M – Br]<sup>+</sup>, 213.0 (100), 211.0 (100) [M + H – CH<sub>3</sub>CO – CH<sub>3</sub> – CO + H]<sup>+</sup>, 185.0 (11), 183.0 (11) [M + H – CH<sub>3</sub>CO – CH<sub>3</sub> – CO – C<sub>2</sub>H<sub>4</sub> + H]<sup>+</sup>, 161.1 (10), 149.0 (46), 130.1 (21), 115.1 (12), 104.1 (55), 77.0 (24), 62.0 (84).

HRMS (TOF<sup>+</sup>): *m/z* calcd for C<sub>13</sub>H<sub>15</sub>BrNO<sub>2</sub>: 296.0286; found: 296.0296.

#### ***N*-(1,2,3,4-Tetrahydro-1-oxonaphthalen-6-yl)formamide (**3e**)**

6-Amino-3,4-dihydronaphthalen-1(2*H*)-one (**4**; 30.0 g, 0.186 mol) was added to formic acid (150 mL). The reaction mixture was refluxed for 3 h. After the reaction ended, formic acid was removed under reduced pressure. Crunched ice was added. Oily material precipitated and solidified. The crude material was extracted into CH<sub>2</sub>Cl<sub>2</sub> and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvent was removed to afford the crude product. The compound was further purified by column chromatography on silica gel (CHCl<sub>3</sub>–MeOH, 50:1) to obtain **3e** as a white solid (15 g, yield: 43%), as a mixture of *cis* and *trans* isomers; mp 134–136 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.87 (d, <sup>3</sup>*J*<sub>HH</sub> = 11.2 Hz, 0.5 H, ArH), 8.44 (s, 1 H, HCO), 8.04 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.6 Hz, 0.5 H, ArH), 8.01 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.5 Hz, 0.5 H, ArH), 7.72 (br s, 1 H, NH), 7.36 (br s, 0.5 H, ArH), 6.99 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.3 Hz, 0.5 H, ArH), 6.92 (s, 0.5 H, ArH), 2.94–2.98 (m, 2 H, CH<sub>2</sub>), 2.62–2.67 (m, 2 H, CH<sub>2</sub>), 2.09–2.18 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

EI-MS: *m/z* (%) = 189.1 (86) [M]<sup>+</sup>, 161.1 (100) [M + H – HCO]<sup>+</sup>, 147.0 (27) [M + H – HCONH + H]<sup>+</sup>, 133.1 (22), 105.1 (20), 77.0 (15), 62.0 (67).

HRMS (TOF<sup>+</sup>): *m/z* calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>: 189.0790; found: 189.0790.

#### ***N*-(1,2,3,4-Tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylformamide (**3f**)**

Formic acid (4.40 g, 95.6 mmol) was dissolved in CHCl<sub>3</sub> (42 mL). The solution was cooled to 5 °C using an ice-bath. *N,N'*-Dicyclohexylcarbodiimide (DCC, 7.00 g, 33.9 mmol) in CHCl<sub>3</sub> (34 mL) was added dropwise. After addition, the solution was stirred for another 5 min and produced a white precipitate. 3,4-Dihydro-6-(methylamino)naphthalen-1(2*H*)-one (**6**; 3.00 g, 17.1 mmol) in pyridine (15 mL) was added dropwise. The mixture was warmed to r.t. and

stirred for 4 h. The mixture was filtered and the solvent was removed from the filtrate to give the crude product, which was further purified by column chromatography on silica gel (EtOAc–hexanes, 1:5) to afford **3f** as a white solid (1.0 g, yield: 20%); mp 71–73 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.67 (s, 1 H, HCO), 8.10 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 1 H, ArH), 7.14 (dd, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, <sup>4</sup>J<sub>HH</sub> = 2.0 Hz, 1 H, ArH), 7.05 (s, 1 H, ArH), 3.36 (s, 3 H, CH<sub>3</sub>), 3.01 (t, <sup>3</sup>J<sub>HH</sub> = 6.0 Hz, 2 H, CH<sub>2</sub>), 2.69 (t, <sup>3</sup>J<sub>HH</sub> = 6.5 Hz, 2 H, CH<sub>2</sub>), 2.18 (pent, <sup>3</sup>J<sub>HH</sub> = 6.3 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

EI-MS: *m/z* (%) = 203.1 (100) [M]<sup>+</sup>, 175.1 (71), [M + H – HCO]<sup>+</sup>, 162.1 (12), 147.1 (26) [M + H – HCONCH<sub>3</sub> + H]<sup>+</sup>, 134.1 (25), 118.1 (17), 91.1 (10).

HRMS: (TOF<sup>+</sup>): *m/z* calcd for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>: 203.0946; found: 203.0944.

### 6-(Dimethylamino)-3,4-dihydronaphthalen-1(2H)-one (3g)

6-Amino-3,4-dihydronaphthalen-1(2H)-one (**4**; 3.80 g, 23.6 mmol), iodomethane (8.32 g, 58.6 mmol) and NaHCO<sub>3</sub> (4.40 g, 52.4 mmol) were suspended in EtOH (100 mL). The reaction mixture was refluxed in the dark until TLC showed complete conversion. The solvents were removed under reduced pressure. The residue was extracted using CH<sub>2</sub>Cl<sub>2</sub> and washed with H<sub>2</sub>O. The organic layer was dried (MgSO<sub>4</sub>). The solvent was removed to afford **3g** as a white solid (1.9 g, yield: 43%); mp 73–75 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.95 (d, <sup>3</sup>J<sub>HH</sub> = 8.9 Hz, 1 H, ArH), 6.59 (d, <sup>3</sup>J<sub>HH</sub> = 5.6 Hz, 1 H, ArH), 6.39 (s, 1 H, ArH), 3.05 (s, 6 H, NCH<sub>3</sub>), 2.87 (t, <sup>3</sup>J<sub>HH</sub> = 6.0 Hz, 2 H, CH<sub>2</sub>), 2.56 (t, <sup>3</sup>J<sub>HH</sub> = 6.3 Hz, 2 H, CH<sub>2</sub>), 2.08 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

EI-MS: *m/z* (%) = 189.1 (100) [M]<sup>+</sup>, 161.1 (100) [M + H – 2 × CH<sub>3</sub> + H]<sup>+</sup>, 147.1 (7) [M + H – 2 × CH<sub>3</sub> + H]<sup>+</sup>, 133.1 (11), 62.1 (21).

HRMS: (TOF<sup>+</sup>): *m/z* calcd for C<sub>12</sub>H<sub>15</sub>NO: 189.1154; found: 189.1158.

### 6-Amino-5-bromo-3,4-dihydronaphthalen-1(2H)-one (5)

6-Amino-3,4-dihydronaphthalen-1(2H)-one (**4**; 28.0 g, 174 mmol) was suspended in CH<sub>2</sub>Cl<sub>2</sub> (1 L) and the mixture was cooled to 0 °C. NBS (31.0 g, 174 mmol) was added in portions. The reaction was allowed to warm to r.t. After 2 h, a solid precipitated out. H<sub>2</sub>O was added into the mixture, and the organic layer was separated and dried. Removal of the solvent generated a pale brown solid **5** (34 g, yield: 82%); mp 186–188 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.93 (d, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, 1 H, ArH), 6.75 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 1 H, ArH), 3.00 (t, <sup>3</sup>J<sub>HH</sub> = 6.2 Hz, 2 H, CH<sub>2</sub>), 2.59 (t, <sup>3</sup>J<sub>HH</sub> = 6.6 Hz, 2 H, CH<sub>2</sub>), 2.14 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

EI-MS: *m/z* (%) = 241.0 (90), 239.0 (90) [M]<sup>+</sup>, 213.0 (100) [M – CO]<sup>+</sup>, 185.0 (12), 183.0 (12) [M – CO – C<sub>2</sub>H<sub>4</sub>]<sup>+</sup>, 160.1 (5), 143.1 (8), 130.1 (16), 117.1 (5), 104.1 (49), 77.0 (17), 65.0 (12).

HRMS: (TOF<sup>+</sup>): *m/z* calcd for C<sub>10</sub>H<sub>10</sub>BrNO: 238.9946; found: 238.9949.

### 5-Bromo-3,4-dihydro-6-(methylamino)naphthalen-1(2H)-one (7)

3,4-Dihydro-6-(methylamino)naphthalen-1(2H)-one (**6**; 12.0 g, 68.5 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (300 mL). The solution was heated under reflux. NBS (12.0 g, 68.2 mmol) was added in portions. After addition, the reaction mixture was stirred at r.t. for 20 min. The solution was washed with H<sub>2</sub>O. The organic layer was dried and the solvent was removed. The solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with H<sub>2</sub>O again. The organic layer was dried, and the solvent was removed to afford **7** as a white solid (15.6 g, yield: 90%); mp 187–189 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.02 (d, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, 1 H, ArH), 6.58 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 1 H, ArH), 2.99 (t, <sup>3</sup>J<sub>HH</sub> = 6.2 Hz, 2 H, CH<sub>2</sub>),

2.99 (s, 3 H, NCH<sub>3</sub>), 2.65 (t, <sup>3</sup>J<sub>HH</sub> = 6.6 Hz, 2 H, CH<sub>2</sub>), 2.14 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

EI-MS: *m/z* (%) = 255.0 (27), 253.0 (27) [M]<sup>+</sup>, 241.0 (79), 239.0 (79) [M + H – CH<sub>3</sub> – H]<sup>+</sup>, 227 (22), 225 (22) [M – CO]<sup>+</sup>, 213.0 (100), 211.0 (100) [M + H – CO – C<sub>2</sub>H<sub>4</sub>]<sup>+</sup>, 185.0 (10), 183.0 (10) [M + H – CO – 2 × C<sub>2</sub>H<sub>4</sub>]<sup>+</sup>, 175.1 (15), 147.1 (12), 130.1 (17), 104.1 (51), 77.1 (20), 62.1 (63).

HRMS: (TOF<sup>+</sup>): *m/z* calcd for C<sub>11</sub>H<sub>12</sub>BrNO: 253.0102; found: 253.0095.

### *N*-(2-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (8a)<sup>24</sup>

*N*-(1,2,3,4-Tetrahydro-1-oxonaphthalen-6-yl)acetamide (**3a**; 7.20 g, 35.4 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>–MeOH (1:1, 200 mL). Tetra-*n*-butylammonium tribromide (18.8 g, 39.0 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 1 h. Progress of the reaction was monitored by TLC. As soon as by-products began to appear, the reaction was stopped. The solvent was removed and the product was separated by column chromatography on silica gel (EtOAc–hexanes, 4:1) to afford **8a** as a pale brown solid (3.4 g, yield: 34%); mp 166–168 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.03 (d, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, 1 H, ArH), 7.75 (s, 2 H, ArH, NH), 7.25 (d, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, 1 H, ArH), 4.70 (t, <sup>3</sup>J<sub>HH</sub> = 4.3 Hz, 1 H, CHBr), 3.27 (m, 1 H, CH<sub>2</sub>), 2.89 (m, 1 H, CH<sub>2</sub>), 2.47 (m, 2 H, CH<sub>2</sub>), 2.22 (s, 3 H, CH<sub>3</sub>).

EI-MS: *m/z* (%) = 283.1 (3), 281.1 (3) [M]<sup>+</sup>, 241.0 (79), 239.0 (7) [M + H – CH<sub>3</sub>CO]<sup>+</sup>, 213.1 (5), 211.1 (5) [M + H – CH<sub>3</sub>CO – CO]<sup>+</sup>, 203.1 (13) [M – Br]<sup>+</sup>, 161.1 (15) [M + H – Br – CH<sub>3</sub>CO + H]<sup>+</sup>, 133.1 (21), [M + H – Br – CH<sub>3</sub>CO + H – CO]<sup>+</sup>, 103.1 (6), 77.1 (6), 62.0 (100).

HRMS: (TOF<sup>+</sup>): *m/z* calcd for C<sub>12</sub>H<sub>12</sub>BrNO<sub>2</sub>: 283.0031; found: 283.0035.

### *N*-(2-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylacetamide (8b)

*N*-(1,2,3,4-Tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylacetamide (**3b**; 1.00 g, 4.60 mmol) was dissolved in THF (10 mL). Copper(II) bromide (2.06 g, 9.22 mmol) was added. The reaction mixture was refluxed for 2.5 h. After cooling to r.t., the mixture was filtered and the solid was washed with THF. After removing the solvent, the residue was purified using silica gel column chromatography (EtOAc–hexanes, 3:1) to give **8b** as a pale brown solid (0.30 g, yield: 30%); mp 72–74 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.15 (d, <sup>3</sup>J<sub>HH</sub> = 8.3 Hz, 1 H, ArH), 7.19 (d, <sup>3</sup>J<sub>HH</sub> = 8.4 Hz, 1 H, ArH), 7.14 (s, 1 H, ArH), 4.74 (t, <sup>3</sup>J<sub>HH</sub> = 3.9 Hz, 1 H, CHBr), 3.31 (s, 3 H, NCH<sub>3</sub>), 3.10–3.15 (m, 1 H, CH<sub>2</sub>), 2.91–2.97 (m, 1 H, CH<sub>2</sub>), 2.49–2.56 (m, 2 H, CH<sub>2</sub>), 2.00 (s, 3 H, CH<sub>3</sub>).

### *N*-(2,5-Dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (8c)<sup>24</sup>

*N*-(5-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**3c**; 17.4 g, 61.7 mmol) and tetra-*n*-butylammonium tribromide (29.7 g, 61.6 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub>–MeOH (1:1, 500 mL). The reaction was refluxed for 3 h and monitored by TLC. At the end of the reaction, the solvent was removed and the solid was extracted (EtOAc–hexanes, 1:1). After removing the solvent, the residue was purified using silica gel column chromatography (EtOAc–hexanes, 1:1) to give **8c** as a pale brown solid; (5.7 g, yield: 26%); mp 141–143 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.46 (d, <sup>3</sup>J<sub>HH</sub> = 8.8 Hz, 1 H, ArH), 8.09 (d, <sup>3</sup>J<sub>HH</sub> = 8.8 Hz, 1 H, ArH), 7.94 (br s, 1 H, NH), 4.68 (t, <sup>3</sup>J<sub>HH</sub> = 4.1 Hz, 1 H, CHBr), 3.04–3.24 (m, 2 H, CH<sub>2</sub>), 2.48–2.58 (m, 2 H, CH<sub>2</sub>), 2.29 (s, 3 H, CH<sub>3</sub>).

EI-MS:  $m/z$  (%) = 363.0 (3), 361.0 (7), 359.0 (3) [M]<sup>+</sup>, 321.0 (8) 319.0 (17), 317.0 (8) [M + H - CH<sub>3</sub>CO]<sup>+</sup>, 282.0 (37), 280.0 (37) [M - Br]<sup>+</sup>, 241.0 (65), 239.0 (65) [M + H - Br - CH<sub>3</sub>CO + H]<sup>+</sup>, 213.0 (100), 211.0 (100) [M + H - Br - CH<sub>3</sub>CO + H - CO]<sup>+</sup>, 202.0 (84) [M - 2 × Br]<sup>+</sup>, 185.0 (7), 183.0 (7) [M + H - Br - CH<sub>3</sub>CO + H - CO - C<sub>2</sub>H<sub>4</sub>]<sup>+</sup>, 174.1 (7), 159.1 (8), 130.1 (32), 104.1 (42), 77.0 (22), 62.0 (67).

HRMS: (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>12</sub>H<sub>11</sub>Br<sub>2</sub>NO<sub>2</sub>: 358.9157; found: 358.9155.

#### *N*-(2,5-Dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylacetamide (**8d**)

*N*-(5-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylacetamide (**3d**; 8.00 g, 27.0 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>-MeOH (1:1, 200 mL). Tetra-*n*-butylammonium tribromide (16.0 g, 33.2 mmol) was added in one portion. The reaction was monitored by TLC and stirred at r.t. for 1 h. After the reaction ended, the solvent was removed and the residue was separated by column chromatography on silica gel (EtOAc-hexanes, 1:1) to give **8d** as a pale brown solid (5.7 g, yield: 56%); mp 128–130 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.15 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 1 H, ArH), 7.31 (d, <sup>3</sup>J<sub>HH</sub> = 8.2 Hz, 1 H, ArH), 4.72 (t, <sup>3</sup>J<sub>HH</sub> = 4.1 Hz, 1 H, CHBr), 3.20 (s, 3 H, NCH<sub>3</sub>), 3.18 (m, 2 H, CH<sub>2</sub>), 2.56 (m, 2 H, CH<sub>2</sub>), 1.84 (s, 3 H, CH<sub>3</sub>).

EI-MS:  $m/z$  (%) = 335.0 (3), 333.0 (7), 331.0 (3) [M + H - CH<sub>3</sub>CO]<sup>+</sup>, 296.1 (65), 294.1 (65) [M - Br]<sup>+</sup>, 253.0 (7), 251.0 (7) [M - Br - CH<sub>3</sub>CO]<sup>+</sup>, 239.0 (37), 237.0 (37) [M + H - Br - CH<sub>3</sub>CO - CH<sub>3</sub>]<sup>+</sup>, 227.0 (30), 225.0 (30) [M + H - Br - CH<sub>3</sub>CO + H - CO]<sup>+</sup>, 216.1 (100) [M + H - 2 × Br]<sup>+</sup>, 213.0 (40), 211.0 (40) [M + H - Br - CH<sub>3</sub>CO + H - CH<sub>3</sub> + H - CO]<sup>+</sup>, 186.1 (11), 144.1 (10), 130.1 (10), 115.1 (17), 104.1 (23), 89.1 (8), 77.1 (12), 62.1 (20).

HRMS: (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>13</sub>H<sub>13</sub>Br<sub>2</sub>NO<sub>2</sub>: 371.9235; found: 371.9242.

#### *N*-(2-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)formamide (**8e**)

*N*-(1,2,3,4-Tetrahydro-1-oxonaphthalen-6-yl)formamide (**3e**; 25.0 g, 132 mmol) and copper(II) bromide (55.0 g, 246 mmol) were dissolved in THF (500 mL). The reaction mixture was refluxed overnight. After cooling to r.t., the solution was filtered and the solvent was removed from the filtrate. The solid was purified by column chromatography on silica gel (EtOAc-hexanes, 1:1) to give **8e** as a pale brown solid (8.6 g, yield: 24%); mp 124–126 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.46 (s, 1 H, HCO), 8.08 (d, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, 1 H, ArH), 7.79 (s, 1 H, ArH), 7.41 (br s, 1 H, NH), 7.30 (d, <sup>3</sup>J<sub>HH</sub> = 8.4 Hz, 1 H, ArH), 4.72 (t, <sup>3</sup>J<sub>HH</sub> = 4.1 Hz, 1 H, CHBr), 3.29–3.35 (m, 1 H, CH<sub>2</sub>), 2.89–2.94 (m, 1 H, CH<sub>2</sub>), 2.47–2.54 (m, 2 H, CH<sub>2</sub>).

EI-MS:  $m/z$  (%) = 269.0 (14), 267.0 (14), [M]<sup>+</sup>, 241.0 (27), 239.0 (27) [M + H - HCO]<sup>+</sup>, 213.0 (34), 211.0 (34) [M + H - HCO - CO]<sup>+</sup>, 189.1 (54) [M + H - Br]<sup>+</sup>, 161.1 (92) [M + H - Br - CO]<sup>+</sup>, 133.1 (23) [M + H - Br - 2 × CO + H]<sup>+</sup>, 104.1 (33), 77.1 (22), 62.1 (100).

HRMS: (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>11</sub>H<sub>10</sub>BrNO<sub>2</sub>: 266.9895; found: 266.9888.

#### *N*-(2-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylformamide (**8f**)

*N*-(1,2,3,4-Tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylformamide (**3f**; 3.00 g, 14.8 mmol) was added portionwise into concd H<sub>2</sub>SO<sub>4</sub> (30 mL) cooled by an ice bath. Bromine (2.60 g, 16.3 mmol) was added dropwise to the above solution. After the addition, the reaction mixture was stirred at r.t. for 3 h. When the reaction was complete, the reaction mixture was added slowly to ice-water. A green precipitate generated was collected by filtration and dried to afford *N*-(2,2-dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)-*N*-meth-

ylformamide as a pale brown solid (5.0 g, yield: 94%). This compound (3.90 g, 10.8 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0 °C with an ice bath. Diethyl phosphonate (1.80 g in 10 mL THF, 13.0 mmol) and TEA (1.80 g, 17.8 mmol) were added dropwise. The reaction mixture was stirred at r.t. for 6 h. After the reaction was complete, the solvent was removed. Ice-water was added to wash the solid. The collected solid was purified by column chromatography on silica gel (CHCl<sub>3</sub>) to give **8f** as a pale brown solid (2.4 g, yield: 79%); mp 104–106 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.70 (s, 1 H, HCO), 8.16 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 1 H, ArH), 7.19 (d, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, 1 H, ArH), 7.07 (s, 1 H, ArH), 4.74 (br s, 1 H, CHBr), 3.37 (s, 3 H, NCH<sub>3</sub>), 3.10–3.15 (m, 1 H, CH<sub>2</sub>), 2.92–2.97 (m, 1 H, CH<sub>2</sub>), 2.48–2.56 (m, 2 H, CH<sub>2</sub>).

LC-MS:  $m/z$  (%) = 586.5 (34), 365.4 (14), 363.4 (16), 300.7 (98) [M + H<sub>2</sub>O]<sup>+</sup>, 298.7 (85), 284.1 (100) [M + H]<sup>+</sup>, 282.2 (92).

HRMS: (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>Br: 282.0130; found: 282.0131.

#### 2-Bromo-6-(dimethylamino)-3,4-dihydronaphthalen-1(2H)-one (**8g**)

6-(Dimethylamino)-3,4-dihydronaphthalen-1(2H)-one (**3g**; 0.500 g, 2.64 mmol) was dissolved in H<sub>2</sub>SO<sub>4</sub> (1.0 mL). The solution was cooled down to 0 °C. Bromine (0.840 g, 5.25 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 4 h. At the end of the reaction, the mixture was poured into ice-water, to precipitate the dibromide intermediate as a pale brown solid (0.7 g, 2.02 mmol, yield: 76%). The solid was then dissolved in THF (5 mL) and cooled to 0 °C. Diethyl phosphonate (0.260 g, 1.88 mmol) and TEA (0.200 g, 1.98 mmol) were added dropwise. The reaction mixture was stirred at r.t. for 6 h. After removal of the solvent, ice-water was added to afford a pale solid which was purified by column chromatography on silica gel (EtOAc-hexanes, 1:2) to give **8g** as a pale brown solid (0.3 g, yield: 55% based on the dibromide, overall yield: 42%); mp 142–144 °C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.99 (d, <sup>3</sup>J<sub>HH</sub> = 8.9 Hz, 1 H, ArH), 6.64 (d, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, 1 H, ArH), 6.40 (s, 1 H, ArH), 4.68 (t, <sup>3</sup>J<sub>HH</sub> = 3.6 Hz, 1 H, CHBr), 3.30–3.21 (m, 1 H, CH<sub>2</sub>), 3.07 (s, 6 H, NCH<sub>3</sub>), 2.84–2.76 (m, 1 H, CH<sub>2</sub>), 2.49–2.40 (m, 2 H, CH<sub>2</sub>).

#### *N*-(2-Chloro-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**9a**)<sup>55</sup>

2-Bromo-6-acetamidotetralone (**8a**, 28 mg, 0.10 mmol) and LiCl (28 mg, 0.67 mmol) were loaded into a microwave vessel with a stirrer-bar. DMF (1.0 mL) was added and the mixture was irradiated (150 W) for 5 min at 150 psi and 150 °C (actual temperature rose to 186 °C). After the reaction, the solution was filtered and loaded directly onto a reverse-phase (C18) HPLC column to afford **9** as a white solid (16 mg, yield: 67%); mp 179–181 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.02 (d, <sup>3</sup>J<sub>HH</sub> = 8.8 Hz, 1 H, ArH), 7.73 (s, 1 H, ArH), 7.43 (br s, 1 H, NH), 7.20 (dd, <sup>3</sup>J<sub>HH</sub> = 8.4 Hz, <sup>4</sup>J<sub>HH</sub> = 1.6 Hz, 1 H, ArH), 4.57–4.60 (m, 1 H, CH), 3.21–3.24 (m, 1 H, CH<sub>2</sub>), 2.93–2.95 (m, 1 H, CH<sub>2</sub>), 2.51–2.55 (m, 1 H, CH<sub>2</sub>), 2.41–2.44 (m, 1 H, CH<sub>2</sub>), 2.20 (s, 3 H, CH<sub>3</sub>).

<sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ = 189.8 (1 C, CO), 168.6 (1 C, CO), 145.1 (1 C, ArC), 142.9 (1 C, ArC), 130.0 (1 C, ArCH), 126.3 (1 C, ArC), 118.2 (1 C, ArCH), 117.7 (1 C, ArCH), 59.6 (1 C, CCl), 32.4 (1 C, CH<sub>2</sub>), 26.5 (1 C, CH<sub>2</sub>), 24.9 (1 C, CH<sub>3</sub>).

LC-MS:  $m/z$  (%) = 240.2 (24), 239.1 (16), 238.1 (100) [M + H]<sup>+</sup>.

#### *N*-(2,2-Dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**10a**)

6-Acetamidotetralone (**3a**; 20.7 mg, 0.10 mmol) was dissolved in AcOH (1.0 mL) and bromine (12 μL, 0.24 mmol) was added. The mixture was stirred for 1 h and then partitioned between sat. NaHCO<sub>3</sub> and EtOAc. The separated organic layer was washed with

H<sub>2</sub>O and dried. The solvent was removed in vacuo. The crude product was dissolved in DMSO and loaded onto HPLC. The product fraction was collected and the solvent was removed in vacuo. The product was dried azeotropically with MeCN (2 ×) to yield **10** as an off-white solid (15 mg, yield: 40%); mp > 200 °C (decomp.).

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ = 8.02 (d, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, 1 H, ArH), 7.68 (d, <sup>4</sup>J<sub>HH</sub> = 1.8 Hz, 1 H, ArH), 7.52 (dd, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, <sup>4</sup>J<sub>HH</sub> = 2.1 Hz, 1 H, ArH), 3.04–3.10 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>), 2.16 (s, 3 H, CH<sub>3</sub>).

LC-MS: *m/z* (%) = 380.5 (40), 378.6 (100), 376.5 (40) [M + H<sub>2</sub>O]<sup>+</sup>, 363.9 (32), 361.9 (64), 360.0 (32) [M]<sup>+</sup>.

### 6-Amino-3-bromopyridine-2-carbonitrile (**12**)

6-Aminopyridine-2-carbonitrile (**11**; 4.20 g, 21.2 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>–MeOH (1:1, 84 mL). Tetra-*n*-butylammonium tribromide (11.8 g, 24.5 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 45 min. The solvent was removed to afford a yellowish oil. Under constant stirring, H<sub>2</sub>O was added to generate a white precipitate, which was collected by filtration to give the crude product (4.0 g). The solid was further purified by washing (EtOAc–hexanes, 1:1) to give **12** as an off-white solid (3.5 g, yield: 83%); mp 184–186 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 7.75 (d, <sup>3</sup>J<sub>HH</sub> = 9.1 Hz, 1 H, ArH), 6.68 (d, <sup>3</sup>J<sub>HH</sub> = 9.1 Hz, 1 H, ArH).

EI-MS: *m/z* (%) = 199.0 (24), 197.0 (24) [M]<sup>+</sup>, 172.0 (14), 170.0 (14) [M – CN]<sup>+</sup>, 118.1 (33) [M – Br]<sup>+</sup>, 92.0 (33), 62.0 (100).

HRMS (TOF<sup>+</sup>): *m/z* calcd for C<sub>6</sub>H<sub>4</sub>BrN<sub>3</sub>: 196.9589; found: 196.9595.

### 5-Ethylthiopyridin-2-amine (**13**)<sup>31,32</sup>

2-Amino-5-iodo-pyridine (2.20 g, 10 mmol), sodium ethanethiolate (80%, 1.7 g, 16 mmol) and copper powder (190 mg, 3.00 mmol) were loaded into a 100 mL round bottom flask under N<sub>2</sub>. Ethylene glycol (40 mL, 0.25 mol) was added and the solution was stirred at 150 °C for 26 h. The cooled solution was filtered and partitioned between EtOAc and H<sub>2</sub>O twice. The organic layer was dried over barium oxide, filtered and the solvent was removed in vacuo to yield **13** as yellow oil (1.2 g, yield: 76%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.06 (d, <sup>4</sup>J<sub>HH</sub> = 2.1 Hz, 1 H, ArH), 7.48 (dd, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, <sup>4</sup>J<sub>HH</sub> = 2.4 Hz, 1 H, ArH), 6.42 (dd, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, <sup>5</sup>J<sub>HH</sub> = 0.6 Hz, 1 H, ArH), 2.68 (q, <sup>3</sup>J<sub>HH</sub> = 7.3 Hz, 2 H, CH<sub>2</sub>), 1.15 (t, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 3 H, CH<sub>3</sub>).

### Microwave Reaction; General procedure

*Method A:* An α-bromotetralone derivative (1 equiv) and a 2-aminopyridine derivative (1.2 equiv) were put into a microwave reaction tube. Anhyd 1,1,2-trichloroethane was added to give a solution (≤ 0.1 M) under N<sub>2</sub>. Titanium(IV) chloride (0.75 equiv, 1 M) in CH<sub>2</sub>Cl<sub>2</sub> and anhyd TEA (0.6 equiv) were added under the same conditions. The reaction tube was sealed and the mixture was irradiated (300 W) at 170 °C for 30 s with stirring. CAUTION: Pressure may build up in the reaction tube. The mixture was cooled to r.t. and partitioned twice between CHCl<sub>3</sub> and 2 M K<sub>2</sub>CO<sub>3</sub> solution. The combined organic solvent was removed in vacuo to leave a solid.

*Method B:* An α-bromotetralone derivative (1 equiv) and a 2-aminopyridine derivative (4.0 equiv) were put into a microwave reaction vessel. Anhyd CHCl<sub>3</sub> was added to give a solution (≤ 0.1 M) under N<sub>2</sub>. Titanium(IV) chloride (0.75 equiv, 1 M) in CH<sub>2</sub>Cl<sub>2</sub> and anhyd TEA (0.6 equiv) were added under the same conditions. The reaction vessel was sealed and the mixture was irradiated (300 W) with stirring at 110 °C for 30 min. The workup was the same as in Method A.

The crude product was dissolved in a minimal amount of DMSO for HPLC separation. On a C18 column, the mixture was eluted at 30 mL/min with a gradient (buffered with 0.25% of 50% aq NH<sub>3</sub>) run-

ning from H<sub>2</sub>O–MeCN (4:1) to pure MeCN over 20 min. The elution was continued for another 20 min with pure MeCN. The fractions were checked for purity with TLC. The solvent was removed from pure fractions in vacuo and the solid was azeotropically dried twice with added MeCN.

### *N*-(5,6-Dihydro-9-iodonaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)acetamide (**14a**)

*Method B:* *N*-(2-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**8a**; 28.2 mg, 0.100 mmol), 2-amino-5-iodo-pyridine (88.0 mg, 0.400 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75 μL), and CHCl<sub>3</sub> (1.0 mL) were used to afford **14a** as a white solid (9.0 mg, yield: 22%); mp > 296 °C (decomp.).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 9.94 (br s, 1 H, NH), 8.66 (d, <sup>4</sup>J<sub>HH</sub> = 1.5 Hz, 1 H, ArH), 7.68 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 1 H, ArH), 7.54 (s, 1 H, ArH), 7.50 (dd, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, <sup>3</sup>J<sub>HH</sub> = 2.1 Hz, 1 H, ArH), 7.41 (d, AB system, <sup>3</sup>J<sub>HH</sub> = 9.3 Hz, <sup>3</sup>J<sub>HH</sub> = 0.9 Hz, 1 H, ArH), 7.37 (d, AB system, <sup>3</sup>J<sub>HH</sub> = 9.6 Hz, <sup>3</sup>J<sub>HH</sub> = 1.5 Hz, 1 H, ArH), 3.09–3.11 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>), 2.05 (s, 3 H, CH<sub>3</sub>).

<sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ = 168.1 (1 C, CO), 143.3 (1 C, ArC), 139.8 (1 C, ArC), 138.5 (1 C, ArC), 135.8 (1 C, ArC), 130.9 (1 C, ArC), 128.9 (1 C, ArCH), 125.8 (1 C, ArC), 122.3 (1 C, ArC), 119.5 (1 C, ArC), 118.9 (1 C, ArCH), 117.6 (1 C, ArCH), 117.3 (1 C, ArCH), 75.6 (1 C, ArI), 28.1 (1 C, CH<sub>2</sub>), 24.0 (1 C, CH<sub>2</sub>), 18.1 (1 C, CH<sub>3</sub>).

LC-MS: *m/z* (%) = 405.2 (10), 404.2 (100) [M + H]<sup>+</sup>.

HRMS: (TOF<sup>+</sup>): *m/z* calcd for C<sub>17</sub>H<sub>15</sub>ION<sub>3</sub>: 404.0260; found: 404.0265.

### *N*-(4-Bromo-5,6-dihydro-9-iodonaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)acetamide (**14c**)

*Method A:* *N*-(2,5-Dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (36.1 mg, 0.10 mmol), 5-iodo-2-aminopyridine (26.4 mg, 0.12 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75 μL), TEA (60 μL, 0.43 mmol) and 1,1,2-trichloroethane (1.0 mL) were used. Aq K<sub>2</sub>CO<sub>3</sub> solution (2 M, 5.0 mL) was added to the product fraction collected from HPLC. The mixture was heated at 70 °C for 30 min. After removal of the solvent, the residue was partitioned between EtOAc and de-ionized H<sub>2</sub>O (2 ×). After drying and filtration, the organic solvent was removed. The solid was washed with Et<sub>2</sub>O (3 ×) or until the Et<sub>2</sub>O layer was clear. The solid was dried in vacuo to afford **14c** as an off-white powder (6.1 mg, yield: 13%); mp > 250 °C (decomp.).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 9.60 (br s, 1 H, NH), 9.46 (s, 1 H, ArH), 8.68 (d, <sup>4</sup>J<sub>HH</sub> = 0.9 Hz, 1 H, ArH), 7.78 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 1 H, ArH), 7.50 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 1 H, ArH), 7.44 (AB system, <sup>2</sup>J<sub>HH</sub> = 10.3 Hz, 1 H, ArH), 7.37 (AB system, <sup>2</sup>J<sub>HH</sub> = 10.3 Hz, 1 H, ArH), 3.20–3.27 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>), 2.09 (s, 3 H, CH<sub>3</sub>).

<sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ = 168.5 (1 C, CO), 143.7 (1 C, ArC), 139.0 (1 C, ArC), 135.7 (1 C, ArC), 135.0 (1 C, ArC), 131.4 (1 C, ArC), 129.2 (1 C, ArCH), 125.6 (1 C, ArC), 121.0 (1 C, ArC), 120.0 (1 C, ArC), 117.9 (1 C, ArCH), 76.0 (1 C, ArI), 28.6 (1 C, CH<sub>2</sub>), 23.2 (1 C, CH<sub>2</sub>), 17.7 (1 C, CH<sub>3</sub>).

LC-MS: *m/z* (%) = 485.1 (14), 484.1 (100), 483.1 (22), 482.1 (100) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>): *m/z* calcd for C<sub>17</sub>H<sub>14</sub>N<sub>3</sub>OBrI: 481.9365; found: 481.9368.

### *N*-(5,6-Dihydro-9-bromonaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)acetamide (**15a**)

*Method B:* *N*-(2-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**8a**; 28.2 mg, 0.100 mmol), 2-amino-5-bromo-pyridine (69.2 mg, 0.400 mmol), titanium(IV) chloride (0.075 mmol,

1.0 M) in  $\text{CH}_2\text{Cl}_2$  (75  $\mu\text{L}$ ), and  $\text{CHCl}_3$  (1.0 mL) were used to afford **15a** as a white solid (6.1 mg, yield: 17%); mp > 380 °C (decomp.).

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 9.18 (br s, 1 H, NH), 8.45 (dd,  $^4J_{\text{HH}} = 1.8$  Hz,  $^5J_{\text{HH}} = 0.72$  Hz, 1 H, ArH), 7.81 (d,  $^3J_{\text{HH}} = 8.2$  Hz, 1 H, ArH), 7.66 (d,  $^4J_{\text{HH}} = 1.5$  Hz, 1 H, ArH), 7.54 (dd,  $^3J_{\text{HH}} = 8.2$  Hz,  $^4J_{\text{HH}} = 2.0$  Hz, 1 H, ArH), 7.49 (dd,  $^3J_{\text{HH}} = 9.5$  Hz,  $^4J_{\text{HH}} = 0.74$  Hz, 1 H, ArH), 7.27 (dd,  $^3J_{\text{HH}} = 9.5$  Hz,  $^4J_{\text{HH}} = 1.9$  Hz, 1 H, ArH), 3.19 (m, 4 H,  $\text{CH}_2\text{CH}_2$ ), 2.10 (s, 3 H,  $\text{CH}_3$ ).

$^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 168.7 (1 C, CO), 143.8 (1 C, ArC), 141.0 (1 C, ArC), 139.1 (1 C, ArC), 136.3 (1 C, ArC), 126.6 (1 C, ArC), 126.3 (1 C, ArC), 124.9 (1 C, ArC), 122.8 (1 C, ArC), 120.6 (1 C, ArC), 119.4 (1 C, ArC), 117.8 (1 C, ArCH), 117.8 (1 C, ArCH), 106.2 (1 C, CBr), 28.6 (1 C,  $\text{CH}_2$ ), 24.5 (1 C,  $\text{CH}_2$ ), 18.7 (1 C,  $\text{CH}_3$ ).

LC-MS:  $m/z$  (%) = 359.7 (18), 358.7 (96) [ $\text{M} + \text{H}$ ] $^+$ , 357.7 (20) [ $\text{M} + \text{H}$ ] $^+$ , 356.7 (100) [ $\text{M} + \text{H}$ ] $^+$ .

HRMS (TOF $^+$ ):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{15}\text{BrON}_3$ : 356.0398; found: 356.0399.

#### ***N*-(4-Bromo-5,6-dihydro-9-bromonaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)-acetamide (15c)**

*Method B*: *N*-(2,5-Dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**8d**; 36.1 mg, 0.100 mmol), 2-amino-5-bromopyridine (21.4 mg, 0.120 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in  $\text{CH}_2\text{Cl}_2$  (75  $\mu\text{L}$ ), and  $\text{CHCl}_3$  (1.0 mL) were used to afford **15c** as a white solid (9.7 mg, yield: 22%); mp > 300 °C (decomp.).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.30 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 1 H, ArH), 8.00 (s, 1 H, ArH), 7.95 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 1 H, ArH), 7.74 (br s, 1 H, NH), 7.51 (d,  $^3J_{\text{HH}} = 9.5$  Hz, 1 H, ArH), 7.21 (dd,  $^3J_{\text{HH}} = 9.5$  Hz,  $^4J_{\text{HH}} = 1.8$  Hz, 1 H, ArH), 3.38 (t,  $^3J_{\text{HH}} = 7.9$  Hz, 2 H,  $\text{CH}_2$ ), 3.13 (t,  $^3J_{\text{HH}} = 7.9$  Hz, 2 H,  $\text{CH}_2$ ), 2.26 (s, 3 H,  $\text{CH}_3$ ).

$^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  = 168.5 (1 C, CO), 143.6 (1 C, ArCH), 139.4 (1 C, ArC), 135.7 (1 C, ArC), 135.0 (1 C, ArC), 129.7 (1 C, ArC), 126.8 (1 C, ArCH), 125.6 (1 C, ArC), 124.8 (1 C, ArCH), 121.0 (1 C, ArCH), 120.9 (1 C, ArC), 120.6 (1 C, ArC), 117.6 (1 C, ArCH), 106.0 (1 C, ArCH), 28.6 (1 C,  $\text{CH}_2$ ), 23.3 (1 C,  $\text{CH}_2$ ), 17.7 (1 C,  $\text{CH}_3$ ).

LC-MS:  $m/z$  (%) = 438.1 (48), 436.1 (100), 434.1 (52) [ $\text{M} + \text{H}$ ] $^+$ .

HRMS (TOF $^+$ ):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{14}\text{Br}_2\text{ON}_3$ : 433.9504; found: 433.9496.

#### **9-Bromo-3-(dimethylamino)-5,6-dihydronaphth[1',2':4,5]imidazo[1,2-*a*]pyridine (15g)**

*Method B*: 2-Bromo-6-(dimethylamino)-3,4-dihydronaphthalen-1(2*H*)-one (**8g**; 27.3 mg, 0.10 mmol), 5-bromo-2-aminopyridine (21.4 mg, 0.12 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in  $\text{CH}_2\text{Cl}_2$  (75  $\mu\text{L}$ ), and  $\text{CHCl}_3$  (1.0 mL) were used to afford **15g** and the dehydrogenated derivative **16** in a ratio of 3:1 as a white solid (15.7 mg, yield: 46%); mp 222–224 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 8.23 (d,  $^4J_{\text{HH}} = 1.5$  Hz, 1 H, ArH), 7.54 (d,  $^3J_{\text{HH}} = 8.1$  Hz, 1 H, ArH), 7.34 (d,  $^3J_{\text{HH}} = 9.3$  Hz, 1 H, ArH), 7.22 (dd,  $^3J_{\text{HH}} = 1.8$ , 9.3 Hz, 1 H, ArH), 6.58 (dd,  $^3J_{\text{HH}} = 2.4$ , 8.1 Hz, 1 H, ArH), 6.55 (s, 1 H, ArH), 2.99–3.06 (m, 4 H,  $\text{CH}_2\text{CH}_2$ ), 2.93 [s, 6 H,  $\text{N}(\text{CH}_3)_2$ ].

LC-MS:  $m/z$  (%) = 345.3 (15), 344.2 (86) [ $\text{M} + \text{H}$ ] $^+$ , 343.2 (18), 342.3 (100) [ $\text{M} + \text{H}$ ] $^+$ , 329.4 (6), 328.4 (22) [ $\text{M} - \text{CH}_3$ ] $^+$ , 327.4 (6), 326.4 (26) [ $\text{M} - \text{CH}_3$ ] $^+$ .

HRMS (TOF $^+$ ):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{17}\text{BrN}_3$ : 342.0606; found: 342.0587.

#### **9-Bromo-3-(dimethylamino)naphth[1',2':4,5]imidazo[1,2-*a*]pyridine (16)**

To a solution of **15g** and **16** (6.90 mg, 0.020 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) in a small vial was added 2,3-dichloro-5,6-dicyanoquinone (DDQ; 96%, 5.70 mg, 0.024 mmol). The mixture was stirred for 2 h. After the reaction was complete, the mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$  (2  $\times$ ) and the organic layer was separated and dried over barium oxide. The slurry was filtered and the solvent was removed in vacuo to yield **16** as a reddish-brown solid (3.2 mg, yield: 47%); mp 112–114 °C.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.59 (d,  $^3J_{\text{HH}} = 9.0$  Hz, 1 H, ArH), 8.53 (d,  $^4J_{\text{HH}} = 1.2$  Hz, 1 H, ArH), 7.54 (d,  $^3J_{\text{HH}} = 8.1$  Hz, 1 H, ArH), 7.70 (d,  $^3J_{\text{HH}} = 9.0$  Hz, 1 H, ArH), 7.68 (d,  $^3J_{\text{HH}} = 9.6$  Hz, 1 H, ArH), 7.55 (d,  $^3J_{\text{HH}} = 8.7$  Hz, 1 H, ArH), 7.38 (dd,  $^3J_{\text{HH}} = 9.6$  Hz,  $^4J_{\text{HH}} = 1.8$  Hz, 1 H, ArH), 7.26 (dd,  $^3J_{\text{HH}} = 9.0$  Hz,  $^4J_{\text{HH}} = 2.4$  Hz, 1 H, ArH), 7.05 (d,  $^4J_{\text{HH}} = 2.7$  Hz, 1 H, ArH), 3.04 (s, 6 H,  $\text{NCH}_3$ ).

$^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 151.4 (1 C, ArC), 146.1 (1 C, ArC), 141.1 (1 C, ArC), 135.8 (1 C, ArC), 133.0 (1 C, ArCH), 127.3 (1 C, ArCH), 124.5 (1 C, ArCH), 124.2 (1 C, ArCH), 123.9 (1 C, ArC), 118.7 (1 C, ArC), 117.7 (1 C, ArCH), 117.2 (1 C, ArCH), 111.9 (1 C, ArCH), 109.8 (1 C, ArCH), 107.3 (1 C, ArC), 41.2 (1 C,  $\text{CH}_3$ ).

LC-MS:  $m/z$  (%) = 344.2 (16), 343.2 (16), 342.2 (100), [ $\text{M} + \text{H}$ ] $^+$ , 341.2 (8), 340.4 (88, [ $\text{M} + \text{H}$ ] $^+$ ), 327.4 (6), 326.4 (34) [ $\text{M} - \text{CH}_3$ ] $^+$ , 325.4 (8), 324.5 (26) [ $\text{M} - \text{CH}_3$ ] $^+$ , 299.5 (4), 298.5 (10) [ $\text{M} - \text{NMe}_2$ ] $^+$ , 297.5 (8), 296.5 (10) [ $\text{M} - \text{NMe}_2$ ] $^+$ .

HRMS (TOF $^+$ ):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{15}\text{BrN}_3$ : 340.0449; found: 340.0463.

#### ***N*-(4-Bromo-5,6-dihydro-9-ethylthionaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)-acetamide (17c)**

*Method A*: *N*-(2,5-Dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**8d**; 36.1 mg, 0.100 mmol), 5-ethylthio-2-aminopyridine (21.4 mg, 0.120 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in  $\text{CH}_2\text{Cl}_2$  (75  $\mu\text{L}$ ), and 1,1,2-trichloroethane (1.0 mL) were used to afford **17c** as a brown solid (10 mg, yield: 24%); mp 184–186 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.22 (d,  $^3J_{\text{HH}} = 8.2$  Hz, 1 H, ArH), 7.90 (d,  $^3J_{\text{HH}} = 7.5$  Hz, 1 H, ArH), 7.89 (dd,  $^4J_{\text{HH}} = 1.5$  Hz,  $^5J_{\text{HH}} = 0.9$  Hz, 1 H, ArH), 7.66 (br s, 1 H, NH), 7.49 (d,  $^3J_{\text{HH}} = 9.6$  Hz, 1 H, ArH), 7.15 (dd,  $^3J_{\text{HH}} = 9.3$  Hz,  $^3J_{\text{HH}} = 1.8$  Hz, 1 H, ArH), 3.32 (t,  $^3J_{\text{HH}} = 8.0$  Hz, 2 H,  $\text{CH}_2$ ), 3.07 (t,  $^3J_{\text{HH}} = 8.0$  Hz, 2 H,  $\text{CH}_2$ ), 2.82 (q,  $^3J_{\text{HH}} = 7.3$  Hz, 2 H,  $\text{CH}_2$ ), 2.19 (s, 3 H,  $\text{CH}_3$ ), 1.23 (t,  $^3J_{\text{HH}} = 7.4$  Hz, 3 H,  $\text{CH}_3$ ).

$^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 168.1 (1 C, CO), 145.0 (1 C, ArCH), 140.2 (1 C, ArC), 134.8 (1 C, ArCH), 134.4 (1 C, ArC), 128.7 (1 C, ArC), 128.4 (1 C, ArCH), 125.0 (1 C, ArCH), 122.1 (1 C, ArCH), 120.6 (1 C, ArC), 119.9 (1 C, ArC), 118.8 (1 C, ArC), 117.2 (1 C, ArCH), 116.0 (1 C, ArC), 29.9 (1 C,  $\text{CH}_2$ ), 29.1 (1 C,  $\text{CH}_2$ ), 24.9 (1 C,  $\text{CH}_2$ ), 18.4 (1 C,  $\text{CH}_3$ ), 14.7 (1 C,  $\text{CH}_3$ ).

LC-MS:  $m/z$  (%) = 420.1 (6), 419.1 (20), 418.2 (100) [ $\text{M} + \text{H}$ ] $^+$ , 417.2 (25), 416.2 (100) [ $\text{M} + \text{H}$ ] $^+$ .

HRMS (TOF $^+$ ):  $m/z$  calcd for  $\text{C}_{19}\text{H}_{19}\text{OSBrN}_3$ : 416.0432; found: 416.0434.

#### ***N*-(5,6-Dihydronaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)acetamide (18a)**

*Method B*: *N*-(2-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**8a**; 28.2 mg, 0.100 mmol), 2-aminopyridine (11.3 mg, 0.120 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in  $\text{CH}_2\text{Cl}_2$  (75  $\mu\text{L}$ ), and  $\text{CHCl}_3$  (1.0 mL) were used to afford **18a** as a white solid (8.2 mg, yield: 30%); mp > 300 °C (decomp.).

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 8.46 (br s, 1 H, NH), 8.13 (d,  $^3J_{\text{HH}} = 6.8$  Hz, 1 H, ArH), 7.70 (d,  $^3J_{\text{HH}} = 8.2$  Hz, 1 H, ArH), 7.52 (s,

1 H, ArH), 7.47 (d,  $^3J_{\text{HH}} = 9.1$  Hz, 1 H, ArH), 7.34 (dd,  $^3J_{\text{HH}} = 8.2$  Hz,  $^4J_{\text{HH}} = 2.0$  Hz, 1 H, ArH), 7.21 (ddd,  $^3J_{\text{HH}} = 9.1$  Hz,  $^3J_{\text{HH}} = 6.8$  Hz,  $^4J_{\text{HH}} = 1.2$  Hz, 1 H, ArH), 6.88 (td,  $^3J_{\text{HH}} = 6.8$  Hz,  $^4J_{\text{HH}} = 1.0$  Hz, 1 H, ArH), 3.05–3.16 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>), 2.09 (s, 3 H, CH<sub>3</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 167.7$  (1 C, CO), 144.3 (1 C, ArCH), 139.0 (1 C, ArC), 137.8 (1 C, ArC), 135.1 (1 C, ArC), 125.8 (1 C, ArC), 123.7 (1 C, ArCH), 123.0 (1 C, ArC), 121.6 (1 C, ArCH), 118.7 (1 C, ArC), 118.4 (1 C, ArCH), 116.8 (1 C, ArCH), 115.9 (1 C, ArCH), 111.3 (1 C, ArCH), 27.7 (1 C, CH<sub>2</sub>), 23.5 (1 C, CH<sub>2</sub>), 17.6 (1 C, CH<sub>3</sub>).

LC-MS:  $m/z$  (%) = 279.4 (16), 278.3 (100) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>17</sub>H<sub>16</sub>ON<sub>3</sub>: 278.1293; found: 278.1293.

#### ***N*-(4-Bromo-5,6-dihydronaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)acetamide (18c)**

*Method B:* *N*-(2,5-Dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**8d**); 36.1 mg, 0.100 mmol), 2-aminopyridine (11.3 mg, 0.120 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75  $\mu$ L), and CHCl<sub>3</sub> (1.0 mL) were used to afford **18c** as a white solid (11.4 mg, yield: 32%); mp 208–210 °C.

$^1\text{H}$  NMR (300 MHz, CD<sub>3</sub>OD):  $\delta = 8.18$  (d,  $^3J_{\text{HH}} = 6.9$  Hz, 1 H, ArH), 7.85 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 1 H, ArH), 7.56 (d,  $^3J_{\text{HH}} = 9.0$  Hz, 1 H, ArH), 7.55 (d,  $^3J_{\text{HH}} = 9.0$  Hz, 1 H, ArH), 7.31 (t,  $^3J_{\text{HH}} = 7.6$  Hz, 1 H, ArH), 6.96 (t,  $^3J_{\text{HH}} = 6.9$  Hz, 1 H, ArH), 3.40 (t,  $^3J_{\text{HH}} = 7.8$  Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>), 3.19 (t,  $^3J_{\text{HH}} = 7.8$  Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>), 2.20 (s, 3 H, CH<sub>3</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz, CD<sub>3</sub>OD):  $\delta = 172.3$  (1 C, CO), 147.4 (1 C, ArC), 139.8 (1 C, ArC), 136.9 (1 C, ArC), 136.7 (1 C, ArC), 131.6 (1 C, ArC), 126.7 (1 C, ArCH), 126.5 (1 C, ArCH), 125.3 (1 C, ArCH), 122.5 (1 C, ArCH), 122.2 (1 C, ArC), 121.7 (1 C, ArC), 117.3 (1 C, ArCH), 114.1 (1 C, ArCH), 30.3 (1 C, CH<sub>2</sub>), 23.4 (1 C, CH<sub>2</sub>), 19.0 (1 C, CH<sub>3</sub>).

LC-MS:  $m/z$  (%) = 359.2 (16), 358.2 (95) [M + H]<sup>+</sup>, 357.2 (21), 356.2 (100) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>17</sub>H<sub>15</sub>BrON<sub>3</sub>: 356.0398; found: 356.0408.

#### ***N*-(12a-Chloro-6a,5,6,12a-tetrahydronaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)acetamide (18f)**

*Method A:* *N*-(2-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)-*N*-methylformamide (**8f**); 28.2 mg, 0.100 mmol), 2-aminopyridine (11.3 mg, 0.120 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75  $\mu$ L), and 1,1,2-trichloroethane (1.0 mL) were used to afford **18f** as a white solid (10.4 mg, yield: 33%); mp > 200 °C (decomp.).

$^1\text{H}$  NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>):  $\delta = 9.27$  (s, 1 H, HCO), 8.31 (ddd,  $^3J_{\text{HH}} = 4.5$  Hz,  $^4J_{\text{HH}} = 1.8$  Hz,  $^5J_{\text{HH}} = 0.9$  Hz, 1 H, ArH), 8.04 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 1 H, ArH), 7.69 (td,  $^3J_{\text{HH}} = 7.5$  Hz,  $^4J_{\text{HH}} = 2.1$  Hz, 1 H, ArH), 7.40 (dd,  $^3J_{\text{HH}} = 8.7$  Hz,  $^4J_{\text{HH}} = 2.4$  Hz, 1 H, ArH), 7.35 (d,  $^4J_{\text{HH}} = 2.1$  Hz, 1 H, ArH), 7.04–7.08 (m, 2 H, ArH), 4.82 (dd,  $^3J_{\text{HH}} = 8.1$  Hz,  $^3J_{\text{HH}} = 3.9$  Hz, 1 H, CH), 3.30 (ABdd,  $^2J_{\text{HH}} = 17.4$  Hz,  $^3J_{\text{HH}} = 7.8$  Hz,  $^3J_{\text{HH}} = 4.5$  Hz, 1 H, CH<sub>2</sub>), 3.15 (dd, AB system  $^2J_{\text{HH}} = 17.1$  Hz,  $^3J_{\text{HH}} = 6.9$  Hz,  $^3J_{\text{HH}} = 4.8$  Hz, 1 H, CH<sub>2</sub>), 2.81 (s, 3 H, CH<sub>3</sub>), 2.61–2.72 (m, 1 H, CH<sub>2</sub>), 2.38–2.52 (m, 1 H, CH<sub>2</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz, CD<sub>3</sub>COCD<sub>3</sub>):  $\delta = 189.2$  (1 C, HCO), 161.2 (1 C, ArC), 152.2 (1 C, ArCH), 149.5 (1 C, ArC), 148.6 (1 C, ArCH), 145.7 (1 C, ArC), 138.0 (1 C, ArCH), 129.9 (1 C, ArCH), 126.3 (1 C, ArC), 119.6 (1 C, ArCH), 119.1 (1 C, ArCH), 117.8 (1 C, ArCH), 117.3 (1 C, CHCl), 60.4 (1 C, CH), 33.0 (1 C, NCH<sub>3</sub>), 32.6 (1 C, CH<sub>2</sub>), 26.9 (1 C, CH<sub>2</sub>).

LC-MS:  $m/z$  (%) = 317.1 (7), 316.1 (35) [M + H]<sup>+</sup>, 315.1 (20), 314.2 (100) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>17</sub>H<sub>17</sub>OCIN<sub>3</sub>: 314.1060; found: 314.1059.

#### ***N*-(5,6-Dihydro-10-ethoxynaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)acetamide (19a)**

*Method B:* *N*-(2-Bromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**8a**); 28.2 mg, 0.10 mmol), 2-amino-4-ethoxypyridine (55.2 mg, 0.40 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75  $\mu$ L), and CHCl<sub>3</sub> (1.0 mL) were used to afford **19a** as a white solid (5.7 mg, yield: 18%); mp > 258 °C (decomp.).

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.78$  (d,  $^3J_{\text{HH}} = 8.2$  Hz, 1 H, ArH), 7.64 (d,  $^3J_{\text{HH}} = 7.4$  Hz, 1 H, ArH), 7.58 (s, 1 H, ArH), 7.17 (dd,  $^3J_{\text{HH}} = 8.2$  Hz,  $^4J_{\text{HH}} = 1.9$  Hz, 1 H, ArH), 6.84 (d,  $^4J_{\text{HH}} = 2.3$  Hz, 1 H, ArH), 6.49 (dd,  $^3J_{\text{HH}} = 7.4$  Hz,  $^4J_{\text{HH}} = 2.4$  Hz, 1 H, ArH), 4.05 (q,  $^3J_{\text{HH}} = 7.0$  Hz, 2 H, OCH<sub>2</sub>), 3.17 (t,  $^3J_{\text{HH}} = 7.0$  Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>), 3.00 (t,  $^3J_{\text{HH}} = 7.0$  Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>), 2.17 (s, 3 H, CH<sub>3</sub>CO), 1.45 (t,  $^3J_{\text{HH}} = 7.0$  Hz, 3 H, OCH<sub>2</sub>CH<sub>3</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 168.1$  (1 C, CO), 155.8 (1 C, ArC), 146.1 (1 C, ArC), 139.0 (1 C, ArC), 137.9 (1 C, ArC), 135.2 (1 C, ArC), 126.7 (1 C, ArC), 124.9 (1 C, ArCH), 121.7 (1 C, ArCH), 118.9 (1 C, ArCH), 118.0 (1 C, ArC), 117.3 (1 C, ArC), 106.3 (1 C, ArCH), 95.0 (1 C, ArCH), 63.5 (1 C, OCH<sub>2</sub>), 28.4 (1 C, CH<sub>2</sub>CH<sub>2</sub>), 24.0 (1 C, CH<sub>2</sub>CH<sub>2</sub>), 18.2 (1 C, COCH<sub>3</sub>), 14.3 (1 C, OCH<sub>2</sub>CH<sub>3</sub>).

LC-MS:  $m/z$  (%) = 324.3 (2), 323.3 (18), 322.3 (100) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>19</sub>H<sub>20</sub>O<sub>2</sub>N<sub>3</sub>: 322.1556; found: 322.1556.

#### ***N*-(4-Bromo-5,6-dihydro-10-ethoxynaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)acetamide (19c)**

*Method B:* *N*-(2,5-Dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**8d**); 36.1 mg, 0.100 mmol), 4-ethoxy-2-aminopyridine (55.2 mg, 0.400 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75  $\mu$ L), and CHCl<sub>3</sub> (1.0 mL) were used to afford **19c** as a brown solid (18 mg, yield: 45%); mp > 256 °C (decomp.).

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 8.24$  (d,  $^3J_{\text{HH}} = 6.2$  Hz, 1 H, ArH), 7.89 (d,  $^3J_{\text{HH}} = 6.3$  Hz, 1 H, ArH), 7.71 (br s, 1 H, NH), 7.67 (d,  $^3J_{\text{HH}} = 5.5$  Hz, 1 H, ArH), 6.87 (d,  $^4J_{\text{HH}} = 1.7$  Hz, 1 H, ArH), 6.53 (dd,  $^3J_{\text{HH}} = 5.5$  Hz,  $^4J_{\text{HH}} = 1.8$  Hz, 1 H, ArH), 4.07 (q,  $^3J_{\text{HH}} = 7.9$  Hz, 2 H, OCH<sub>2</sub>), 3.34 (t,  $^3J_{\text{HH}} = 6.0$  Hz, 2 H, CH<sub>2</sub>), 3.07 (t,  $^3J_{\text{HH}} = 6.0$  Hz, 2 H, CH<sub>2</sub>), 2.25 (s, 3 H, COCH<sub>3</sub>), 1.46 (t,  $^3J_{\text{HH}} = 5.2$  Hz, 3 H, CH<sub>3</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 168.3$  (1 C, ArC), 156.8 (1 C, ArC), 147.6 (1 C, ArC), 139.1 (1 C, ArC), 134.4 (1 C, ArC), 134.1 (1 C, ArC), 129.4 (1 C, ArC), 123.4 (1 C, ArCH), 121.8 (1 C, ArCH), 120.8 (1 C, ArCH), 117.8 (1 C, ArC), 116.3 (1 C, ArC), 107.7 (1 C, ArCH), 95.5 (1 C, ArCH), 64.0 (1 C, OCH<sub>2</sub>), 29.3 (1 C, CH<sub>2</sub>CH<sub>2</sub>), 25.1 (1 C, CH<sub>2</sub>CH<sub>2</sub>), 18.5 (1 C, COCH<sub>3</sub>), 14.6 (1 C, OCH<sub>2</sub>CH<sub>3</sub>).

LC-MS:  $m/z$  (%) = 404.2 (3), 403.2 (19), 402.2 (100) [M + H]<sup>+</sup>, 401.2 (20), 400.2 (96) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>19</sub>H<sub>19</sub>BrO<sub>2</sub>N<sub>3</sub>: 400.0661; found: 400.0649.

#### ***N*-(4-Bromo-5,6-dihydro-11-benzoxynaphth[1',2':4,5]imidazo[1,2-*a*]pyridin-3-yl)acetamide (20c)**

*Method B:* *N*-(2,5-Dibromo-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl)acetamide (**8d**); 36.1 mg, 0.100 mmol), 3-(benzyloxy)pyridin-2-amine (24 mg, 0.12 mmol), a solution of titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75  $\mu$ L), and CHCl<sub>3</sub> (1.0 mL) were used to afford **20c** as a brown solid (10 mg, yield: 22%); mp 202–204 °C.

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 8.26$  (d,  $^3J_{\text{HH}} = 6.4$  Hz, 1 H, ArH), 8.12 (d,  $^3J_{\text{HH}} = 6.3$  Hz, 1 H, ArH), 7.72 (br s, 1 H, NH), 7.52–7.47 (m, 2 H, ArH), 7.36–7.40 (m, 2 H, ArH), 7.30–7.33 (m, 1 H, ArH), 6.63 (t,  $^3J_{\text{HH}} = 5.4$  Hz, 1 H, ArH), 6.43 (d,  $^3J_{\text{HH}} = 5.4$  Hz, 1 H, ArH), 5.41 (s, 2 H, CH<sub>2</sub>Ph), 3.36 (t,  $^3J_{\text{HH}} = 6.0$  Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>), 3.11 (t,  $^3J_{\text{HH}} = 6.0$  Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>), 2.25 (s, 3 H, COCH<sub>3</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz, DMSO- $d_6$ ):  $\delta$  = 169.1 (1 C, CO), 147.1 (1 C, ArCH), 140.3 (1 C, ArC), 138.4 (1 C, ArC), 137.2 (1 C, ArCH), 136.0 (1 C, ArC), 135.4 (1 C, ArC), 130.9 (1 C, ArC), 129.2 (2 C, ArCH), 128.9 (2 C, ArCH), 126.3 (1 C, ArC), 121.0 (1 C, ArCH), 121.4 (1 C, ArC), 118.2 (1 C, ArCH), 112.7 (1 C, ArCH), 103.6 (1 C, ArCH), 70.7 (1 C, OCH<sub>2</sub>), 29.4 (1 C, CH<sub>2</sub>), 24.0 (1 C, CH<sub>2</sub>), 18.6 (1 C, CH<sub>3</sub>).

LC-MS:  $m/z$  (%) = 466.0 (3), 465.1 (22), 464.1 (94) [M + H]<sup>+</sup>, 463.1 (32), 462.1 (100) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>24</sub>H<sub>21</sub>BrO<sub>2</sub>N<sub>3</sub>: 462.0817; found: 462.0819.

### 2-Methoxy-5,6-dihydro-naphth[1',2':4,5]imidazo[1,2-*a*]pyridine (21)

*Method B*: 2-Bromo-3,4-dihydro-7-methoxynaphthalen-1(2*H*)-one (25.5 mg, 0.10 mmol), 2-aminopyridine (11.3 mg, 0.12 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75  $\mu$ L), and CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) were used to afford **21** as a white solid (19.0 mg, yield: 75%); mp 292–294 °C. The compound was dissolved in MeOH and HCl (1.0 equiv) in Et<sub>2</sub>O was added. The salt was recrystallized by slow diffusion of Et<sub>2</sub>O into a solution in MeOH.

$^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  = 8.69 (dt,  $^3J_{\text{HH}} = 6.6$  Hz,  $^4J_{\text{HH}} = 1.2$  Hz, 1 H, ArH), 7.95 (m, 2 H, ArH), 7.53 (ddd,  $^3J_{\text{HH}} = 6.2$  Hz,  $^3J_{\text{HH}} = 6.0$  Hz,  $^4J_{\text{HH}} = 2.7$  Hz, 1 H, ArH), 7.32 (m, 2 H, ArH), 6.95 (dd,  $^3J_{\text{HH}} = 8.4$  Hz,  $^4J_{\text{HH}} = 2.7$  Hz, 1 H, ArH), 3.87 (s, 3 H, OCH<sub>3</sub>), 3.26 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz, CD<sub>3</sub>OD):  $\delta$  = 160.8 (1 C, ArC), 141.7 (1 C, ArC), 134.2 (1 C, ArCH), 132.1 (1 C, ArC), 131.3 (1 C, ArCH), 129.0 (1 C, ArC), 127.9 (1 C, ArCH), 126.2 (1 C, ArC), 124.3 (1 C, ArC), 118.7 (1 C, ArCH), 116.6 (1 C, ArCH), 113.1 (1 C, ArCH), 109.5 (1 C, ArCH), 56.2 (1 C, OCH<sub>3</sub>), 28.0 (1 C, CH<sub>2</sub>), 19.3 (1 C, CH<sub>2</sub>).

LC-MS:  $m/z$  (%) = 252.4 (15) [M + H]<sup>+</sup>, 251.3 [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>16</sub>H<sub>15</sub>ON<sub>2</sub>: 251.1184; found: 251.1178.

Anal. Calcd for C<sub>16</sub>H<sub>15</sub>ClN<sub>2</sub>O: C, 67.02; H, 5.27; Cl, 12.36; N, 9.77. Found: C, 66.68; H, 5.33; Cl, 12.30; N, 9.60.

### 2-Bromo-6,7,8,9-tetrahydrobenzoimidazo[1,2-*a*]pyridine (22)

*Method B*: 2-Chlorocyclohexanone (13.3 mg, 0.100 mmol), 5-bromopyridin-2-amine (21.4 mg, 0.102 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75  $\mu$ L), and CHCl<sub>3</sub> (1.0 mL) were used to afford **22** as a brown solid (5.5 mg, yield: 2.2%); mp > 320 °C (decomp.).

$^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  = 8.31 (d,  $^4J_{\text{HH}} = 1.2$  Hz, 1 H, ArH), 7.39 (AB system,  $^2J_{\text{HH}} = 12.8$  Hz, 1 H, ArH), 7.31 (d, AB system,  $^2J_{\text{HH}} = 12.4$  Hz,  $^4J_{\text{HH}} = 2.4$  Hz, 1 H, ArH), 2.79 (t,  $^3J_{\text{HH}} = 8.2$  Hz, 4 H, CH<sub>2</sub>), 1.98 (m, 4 H, CH<sub>2</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, CD<sub>3</sub>OD):  $\delta$  = 143.7 (1 C, ArC), 143.5 (1 C, ArC), 128.3 (1 C, ArCH), 124.9 (1 C, ArCH), 121.5 (1 C, ArC), 117.4 (1 C, ArCH), 107.5 (1 C, ArC), 25.5 (1 C, CH<sub>2</sub>), 24.3 (1 C, CH<sub>2</sub>), 23.6 (1 C, CH<sub>2</sub>), 21.0 (1 C, CH<sub>2</sub>).

LC-MS:  $m/z$  (%) = 253.4 (100), 251.3 (96) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>11</sub>H<sub>12</sub>BrN<sub>2</sub>: 251.0184; found: 251.0171.

### 6,7,8,9-Tetrahydropyrido[1,2-*a*]benzimidazole (23)

2-Chlorocyclohexanone (13.3 mg, 0.10 mmol), 2-aminopyridine (21.4 mg, 0.120 mmol), and a variety of solvents (1.0 mL), including EtOH, *n*-BuOH, MeCN, DMF, and DMSO were used. The reaction temperature ranged from 110 °C to 175 °C, with isolated yield from 5% to 45%. Method A was also used to give 24% isolated yield of **23** as a white solid; mp > 360 °C (decomp.).

$^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.80 (dt,  $^3J_{\text{HH}} = 6.8$  Hz,  $^4J_{\text{HH}} = 1.2$  Hz, 1 H, ArH), 7.52 (dt,  $^3J_{\text{HH}} = 9.0$  Hz,  $^4J_{\text{HH}} = 2.2$  Hz, 1 H, ArH), 7.10 (ddd,  $^3J_{\text{HH}} = 9.0$  Hz,  $^3J_{\text{HH}} = 6.8$  Hz,  $^4J_{\text{HH}} = 1.3$  Hz, 1 H, ArH), 6.76 (td,  $^3J_{\text{HH}} = 6.7$  Hz,  $^4J_{\text{HH}} = 1.1$  Hz, 1 H, ArH), 2.86 (t,  $^3J_{\text{HH}} = 6.0$  Hz, 2 H, CH<sub>2</sub>), 2.75 (t,  $^3J_{\text{HH}} = 6.1$  Hz, 2 H, CH<sub>2</sub>), 2.01–1.92 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz, acetone- $d_6$ ):  $\delta$  = 144.7 (1 C, ArC), 142.8 (1 C, ArC), 123.8 (1 C, ArCH), 123.2 (1 C, ArCH), 119.4 (1 C, ArC), 117.1 (1 C, ArCH), 111.7 (1 C, ArC), 25.6 (1 C, CH<sub>2</sub>), 24.1 (1 C, CH<sub>2</sub>), 23.2 (1 C, CH<sub>2</sub>), 20.6 (1 C, CH<sub>2</sub>).

GC-MS:  $m/z$  (%) = 172.12 (60) [M]<sup>+</sup>, 144.17 (100) [M – C<sub>2</sub>H<sub>4</sub>]<sup>+</sup>.

The compound was dissolved in Et<sub>2</sub>O and precipitated with HCl in Et<sub>2</sub>O to give a white solid.

$^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.51 (br s, 1 H, NH), 7.94 (dd,  $^3J_{\text{HH}} = 6.8$  Hz,  $^4J_{\text{HH}} = 0.8$  Hz, 1 H, ArH), 7.86 (dd,  $^3J_{\text{HH}} = 9.1$  Hz,  $^4J_{\text{HH}} = 0.9$  Hz, 1 H, ArH), 7.39 (td,  $^3J_{\text{HH}} = 8.0$  Hz,  $^4J_{\text{HH}} = 1.1$  Hz, 1 H, ArH), 7.02 (td,  $^3J_{\text{HH}} = 6.8$  Hz,  $^4J_{\text{HH}} = 1.0$  Hz, 1 H, ArH), 2.88 (t,  $^3J_{\text{HH}} = 6.0$  Hz, 2 H, CH<sub>2</sub>), 2.76 ( $^3J_{\text{HH}} = 6.1$  Hz, 2 H, CH<sub>2</sub>), 1.93–2.02 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>).

LC-MS:  $m/z$  (%) = 174.4 (10), 173.4 (100) [M + H]<sup>+</sup>, 172.7 (3).

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>: 173.1079; found: 173.1073.

### 2,3-Diphenyl-1*H*-imidazo[1,2-*a*]pyridine (24)

*Method B*: 2-Bromo-1,2-diphenylethanone (28.4 mg, 0.100 mmol), 2-aminopyridine (11.3 mg, 0.120 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75  $\mu$ L), and CHCl<sub>3</sub> (1.0 mL) were used to afford **24** as a white solid (24.0 mg, yield: 90%); mp 150–152 °C.

$^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.88 (d,  $^3J_{\text{HH}} = 6.6$  Hz, 1 H, ArH), 7.58–7.63 (m, 3 H, ArH), 7.36–7.49 (m, 5 H, ArH), 7.10–7.24 (m, 4 H, ArH), 6.66 (td,  $^3J_{\text{HH}} = 6.6$  Hz,  $^4J_{\text{HH}} = 1.2$  Hz, 1 H, ArH).

$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 145.0 (1 C, ArC), 142.6 (1 C, ArC), 134.3 (1 C, ArC), 130.9 (2 C, ArCH), 130.1 (1 C, ArC), 129.7 (2 C, ArCH), 129.1 (1 C, ArCH), 128.5 (2 C, ArCH), 128.3 (2 C, ArCH), 127.7 (1 C, ArCH), 124.9 (1 C, ArCH), 123.5 (1 C, ArCH), 121.3 (1 C, ArC), 117.7 (1 C, ArCH), 112.5 (1 C, ArCH).

LC-MS:  $m/z$  (%) = 272.5 (14) [M + H]<sup>+</sup>, 271.4 (100) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>19</sub>H<sub>15</sub>N<sub>2</sub>: 271.1235; found: 271.1223.

### 3-Methyl-2-phenyl-1*H*-imidazo[1,2-*a*]pyridine (25)

*Method A*: 2-Bromo-1-phenylpropan-1-one (15.0  $\mu$ L, 0.100 mmol), 2-aminopyridine (11.3 mg, 0.120 mmol), titanium(IV) chloride (0.075 mmol, 1.0 M) in CH<sub>2</sub>Cl<sub>2</sub> (75  $\mu$ L), and CHCl<sub>3</sub> (1.0 mL) were used to afford **25** as a white solid (13.6 mg, yield: 65%); mp 238–240 °C.

$^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.84 (d,  $^3J_{\text{HH}} = 6.9$  Hz, 1 H, ArH), 7.74 (dd,  $^3J_{\text{HH}} = 8.4$  Hz,  $^4J_{\text{HH}} = 1.5$  Hz, 2 H, ArH), 7.59 (dd,  $^3J_{\text{HH}} = 8.4$  Hz,  $^4J_{\text{HH}} = 1.2$  Hz, 2 H, ArH), 7.40 (td,  $^3J_{\text{HH}} = 7.2$  Hz,  $^4J_{\text{HH}} = 1.8$  Hz, 2 H, ArH), 7.28 (td,  $^3J_{\text{HH}} = 6.6$  Hz,  $^4J_{\text{HH}} = 1.2$  Hz, 1 H, ArH), 7.12 (ddd,  $^3J_{\text{HH}} = 9.0$  Hz,  $^3J_{\text{HH}} = 6.9$  Hz,  $^4J_{\text{HH}} = 1.2$  Hz, 1 H, ArH), 6.79 (td,  $^3J_{\text{HH}} = 6.9$  Hz,  $^4J_{\text{HH}} = 1.2$  Hz, 1 H, ArH), 2.58 (s, 3 H, CH<sub>3</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 144.5 (1 C, ArC), 142.5 (1 C, ArC), 134.9 (1 C, ArC), 128.8 (2 C, ArCH), 128.6 (2 C, ArCH), 127.7 (1 C, ArCH), 123.9 (1 C, ArCH), 123.1 (1 C, ArCH), 117.7 (1 C, ArCH), 116.2 (1 C, ArCH), 116.2 (1 C, ArC), 112.4 (1 C, ArCH), 29.9 (1 C, CH<sub>3</sub>).

LC-MS:  $m/z$  (%) = 210.4 (11) [M + H]<sup>+</sup>, 209.3 (100) [M + H]<sup>+</sup>.

HRMS (TOF<sup>+</sup>):  $m/z$  calcd for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>: 209.1079; found: 209.1083.

## Acknowledgment

We are grateful to Dr. Shuiyu Lu (MIB, NIMH) for his help with microwave reactions, to Dr. Umesh Shetty for some MS analysis and NMR experiments.

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