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## AMINOPHENYLPYRROLE SYNTHESIS AND APPLICATION TO PYRROLO[1,2-*c*]QUINAZOLINONE SYNTHESIS

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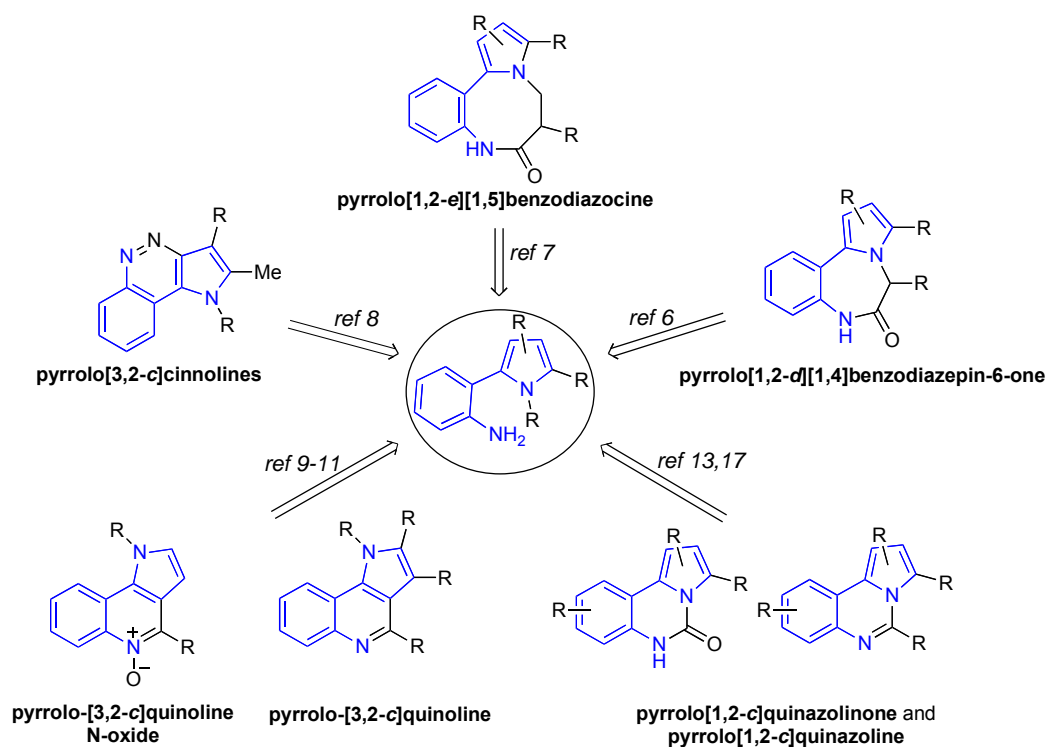
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**Abstract** – Aminophenylpyrroles have been synthesized by a three-step route from methyl *N*-(Boc)anthranilate (**2**). Amine protection of commercially available methyl anthranilate (**1**) gave Boc-protected methyl ester **2**, which reacted with vinylmagnesium bromide in the presence of a catalytic amount of copper (I) cyanide to yield 1-[2-*N*-(Boc)aminophenyl]pent-4-en-1-one (**3**) in 43% yield. Oxidation of homoallylic ketone **3** using either a mixture of OsO<sub>4</sub>•NaIO<sub>4</sub> and 2,6-lutidine, or PdCl<sub>2</sub>-CuCl under oxygen atmosphere gave respectively aldehyde **4** and ketone **5**. Treatment of 1,4-dicarbonyl compounds **4** and **5** with ammonium formate as well as primary amines under Paal-Knorr conditions afforded a set of eight 2-[2-*N*-(Boc)aminophenyl]pyrroles **6a-d** and **7a-d**. In addition, treatment of 2-[2-*N*-(Boc)aminophenyl]-1*H*-pyrrole **6a** with NaH provided a novel entry to pyrrolo[1,2-*c*]quinazolin-5(6*H*)-one **8**.

### INTRODUCTION

Pyrrole derivatives have considerable synthetic importance due to their abundance in natural products and extensive applications in materials science and drug discovery.<sup>1</sup> Pyrroles containing a 2-aminophenyl unit are present in a variety of molecules exhibiting interesting biological activity, including nitric oxide synthase (NOS) inhibitors,<sup>2</sup> and α<sub>1</sub> adrenergic receptor agonists,<sup>3</sup> as well as antifungal,<sup>4,5</sup> antibacterial,<sup>5</sup> and antimicrobial agents.<sup>5</sup> Furthermore, the 2-(2-aminophenyl)pyrrole skeleton is an integral component of various biologically active heterocycles: pyrrolo[1,2-*d*][1,4]benzodiazepin-6-ones,<sup>6</sup> which exhibit antiviral activity against HIV-1; pyrrolo[1,2-*e*][1,5]benzodiazocin-7-ones,<sup>7</sup> which have CNS activity; pyrrolo[3,2-*c*]cinnolines,<sup>8</sup> which show anti-germinative properties; pyrrolo-[3,2-*c*]quinolines,<sup>9-11</sup> which have antitumor, hypotensive and anti-inflammatory activities; and pyrrolo[1,2-*c*]quinazolines,<sup>12,13</sup> which have anti-hypertensive, antiviral, antimalarial, and antibacterial activity (Figure 1). Although the

2-(2-aminophenyl)pyrrole unit may appear to be a useful building block for making such interesting targets, to the best of our knowledge, all approaches to date have employed the corresponding 2-(2-nitrophenyl)pyrrole analogs, which are subsequently reduced to afford the 2-(2-aminophenyl)pyrrole counterpart. Procedures involving the 2-(2-nitrophenyl)pyrrole precursors have entailed multiple steps employing cyclisations<sup>2a,9,10,13-15</sup> and condensations<sup>6-8,11</sup> onto the pyrrole ring. For example, a one-pot gold-catalyzed nitro-Mannich/hydroamination cascade reaction provided moderate yields of 2-(2-nitrophenyl)pyrrole analogs.<sup>16</sup> Pyrrole arylation with nitroaromatic derivatives has also been achieved using Pd-catalyzed cross-coupling reactions in alkaline, super-basic and ionic liquid media to afford 2-(2-nitrophenyl)pyrroles.<sup>3,17-22</sup>

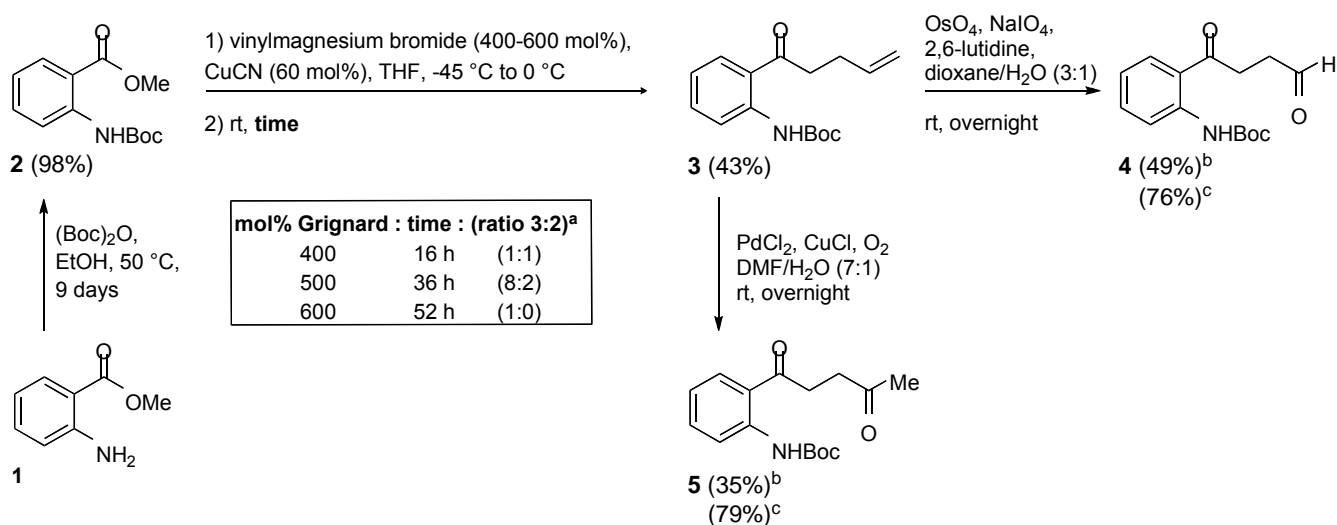


**Figure 1.** 2-(2-Aminophenyl)pyrroles as components of diverse bioactive heterocycles

Considering the utility of an approach which introduces the amino group at a lower oxidation state, we describe the synthesis of 2-(2-aminophenyl)pyrroles from relatively inexpensive methyl anthranilate (**1**). Employing *N*-(Boc)anthranilate **2** in a copper-catalyzed cascade addition of vinyl Grignard reagent, followed by olefin oxidation, this route affords 1,4-diketone **4** and 1,4-ketoaldehyde **5** precursors, which were found suitable for Paal-Knorr condensations to deliver a variety 2-(2-aminophenyl)pyrrole analogs.

## RESULTS AND DISCUSSION

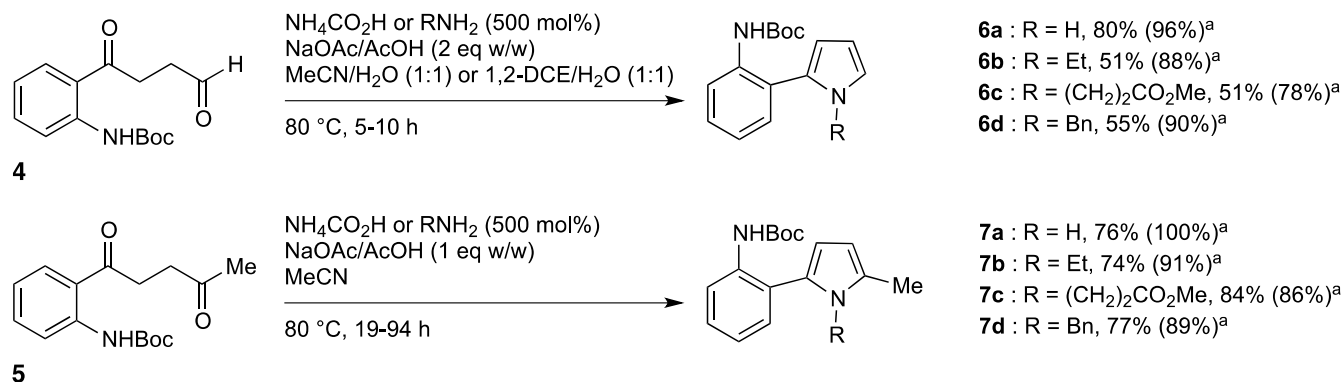
Methyl anthranilate (**1**) was converted into 1,4-diketone **4** and 1,4-ketoaldehyde **5** by a common route featuring *N*-protection, copper-catalyzed cascade addition of vinylmagnesium bromide to the ester and olefin oxidation (Scheme 1). Heating anthranilate **1** and excess di-*tert*-butyl dicarbonate (Boc<sub>2</sub>O) in ethanol at 50 °C for 9 days afforded methyl *N*-(Boc)anthranilate (**2**) in 98% yield, after destruction of excess of Boc<sub>2</sub>O with imidazole, and chromatography.<sup>23,24</sup> Treatment of methyl ester **2** with vinylmagnesium bromide (400 mol%) in the presence of a catalytic amount of CuCN (60 mol%) in THF at –45 °C followed by stirring at room temperature for 16 h gave the desired homoallylic ketone **3** contaminated with starting material in a 1:1 ratio as determined by <sup>1</sup>H NMR spectroscopy by comparison of the integrations of the methyl singlet of **2** at 3.92 ppm and the vinyl multiplet of **3** in CDCl<sub>3</sub> at 5.91 ppm.<sup>25</sup> Augmenting the amount of Grignard reagent to 500 mol% and the reaction time to 36 h gave an improved 4:1 ratio favoring homoallylic ketone **3**. Although ketone **3** and ester **2** were inseparable by chromatography, oxidation of the terminal olefin could be performed on the crude mixture and the ester could be recovered thereafter. For example, oxidation of olefin **3** [ratio 4:1] using a mixture of OsO<sub>4</sub>•NaIO<sub>4</sub> and 2,6-lutidine in dioxane/water gave 4-ketoaldehyde **4** in 49% yield over two steps along with 15% recovered **2**.<sup>26</sup> On the other hand, Tsuji-Wacker oxidation of olefin **3** [ratio 1:1] using PdCl<sub>2</sub> and CuCl in a DMF/water mixture under oxygen atmosphere afforded 1,4-diketone **5** in 35% over two steps with 44% recovered ester **2**.<sup>27</sup> Finally, by augmenting the amount of Grignard reagent to 600 mol% and the reaction time to 52 h, only the desired homoallylic ketone **3** was obtained in 43% yield after purification. Subsequent oxidations of pure **3** as described above gave respectively 4-ketoaldehyde **4** and 1,4-diketone **5** in 76% and 79% yields.



a) Ratio determined by <sup>1</sup>H NMR spectroscopy. b) Yield over two steps from **2**. c) Yield from **3**.

**Scheme 1.** Syntheses of ketoaldehyde **4** and diketone **5**

To demonstrate the utility of 1,4-dicarbonyl compounds **4** and **5**, a set of pyrrole targets were prepared employing diverse Paal-Knorr reaction conditions using ammonia and three different primary amines: ethylamine,  $\beta$ -alanine methyl ester and benzylamine (Scheme 2).



a) Crude purity as determined by reverse-phase HPLC with monitoring at 280 nM.

### Scheme 2. Synthesis of 2-(2-*N*-(Boc)aminophenyl)pyrroles **6a-d** and **7a-d**.

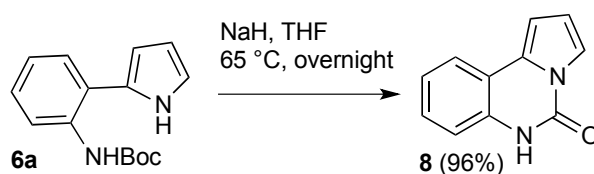
First, ketoaldehyde **4** was respectively treated with ammonium formate and ethylamine hydrochloride (500 mol%) with  $\text{NaOAc/AcOH}$  (1 equiv w/w) in acetonitrile at  $65\text{ }^\circ\text{C}$  for 5-6 h, which afforded pyrroles **6a** and **6b** in 39% and 19% yields. On the other hand, no pyrrole **6c** was obtained from  $\beta$ -alanine methyl ester hydrochloride (300 mol%) under the same conditions for 2 days; instead, degradation of starting ketoaldehyde **4** was observed.<sup>25a,28</sup> Employing 1,4-diketone **5** under the same conditions, pyrroles **7a-c** were obtained in 51-66% yields after 3-5 days. Improved yields (74-84%) of pyrroles **7a-d** were obtained by increasing the reaction temperature to  $80\text{ }^\circ\text{C}$ , which shortened reaction times, and which gave 86-100% crude purities as determined by reversed-phase HPLC at 280 nM.

Attempting to improve pyrrole yields from ketoaldehyde **4**, a biphasic mixture of 1,2-dichloroethane and  $\text{AcOH/H}_2\text{O}$  (1:1) at  $85\text{ }^\circ\text{C}$  was employed using ammonium formate,  $\beta$ -alanine methyl ester hydrochloride and benzylamine (500 mol%).<sup>28</sup> Only *N*-benzylpyrrole **6d** was however isolated in 44%. Analysis of the other reactions by thin layer chromatography indicated trace amounts of pyrrole **6a** and no pyrrole **6c** contaminated with many impurities from degradation of starting ketoaldehyde **4**.

Pyrrole **6a** was isolated in 80% yield by chromatography of the condensation product (93% crude HPLC purity) of ketoaldehyde **4** and ammonium formate (500 mol%) using  $\text{NaOAc/AcOH}$  (2 equiv w/w) in a mixture of  $\text{MeCN/H}_2\text{O}$  (1:1) at  $80\text{ }^\circ\text{C}$  for 6 h. Similarly, better yields (51%) of pyrroles **6b** and **6c** were obtained from purification of condensation products (88 and 78% crude HPLC purities) of ketoaldehyde **4** respectively with ethylamine hydrochloride and  $\beta$ -alanine methyl ester hydrochloride for 10 h and 7 h. On the contrary, *N*-benzylpyrrole **6d** was obtained in lower quality (58% crude purity) from the  $\text{MeCN/H}_2\text{O}$

(1:1) conditions, which led to an insoluble product and degradation as observed by TLC. Employing benzylamine in the Paal-Knorr conditions using a biphasic mixture of 1,2-dichloroethane and H<sub>2</sub>O (1:1) for 5 h gave *N*-benzylpyrrole **6d** in 55% yield (90% crude HPLC purity). On the other hand, attempts to synthesize pyrroles **7** using a mixture of MeCN/H<sub>2</sub>O (1:1) with NaOAc/AcOH (2 equiv w/w) at 80 °C afforded only recovered starting diketone **5** after 3 days.

To further demonstrate the utility of the 2-aminophenylpyrrole structure, pyrrolo[1,2-*c*]quinazolinone **8** was prepared in 96% yield by treatment of 2-[2-*N*-(Boc)aminophenyl]-1*H*-pyrrole **6a** with NaH in THF at 65 °C overnight (Scheme 3). In spite of growing interest in this tricyclic system because of medically relevant biological activity,<sup>12</sup> few pyrrolo[1,2-*c*]quinazolinone syntheses have been reported to date.<sup>12,13,17,29</sup>



**Scheme 3.** Synthesis of pyrrolo[1,2-*c*]quinazolin-5(6*H*)-one **8**

Eight 2-(2-*N*-(Boc)aminophenyl)pyrroles were synthesized from methyl *N*-(Boc)anthranilate (**2**) using a three-step protocol featuring the copper-catalyzed cascade addition of vinyl Grignard reagent to the ester, olefin oxidation of the resulting  $\gamma,\delta$ -unsaturated ketone and Paal-Knorr condensation. From the Paal-Knorr reaction of ketoaldehyde **4** with ammonium formate and primary amines (500 mol%), pyrroles **6a-d** were isolated in 51-80% yields using NaOAc/AcOH (2 equiv w/w) in MeCN/H<sub>2</sub>O (1:1) or 1,2-dichloroethane/H<sub>2</sub>O (1:1) at 80 °C. On the other hand, 5-methylpyrroles **7a-d** were prepared in 74-84% yields from treatment of 1,4-diketone **5** with ammonium formate and primary amines (500 mol%) using NaOAc/AcOH (1 equiv w/w) in MeCN at 80 °C. In addition, the parent pyrrolo[1,2-*c*]quinazolinone skeleton has been assembled from exposure of 2-[2-*N*-(Boc)aminophenyl]-1*H*-pyrrole **6a** to sodium hydride. Effective access to aminophenylpyrroles and potential for constructing various heterocycle systems from common building blocks makes this practical approach useful for the synthesis of pyrrole analogs for multiple applications.

## EXPERIMENTAL

Anhydrous conditions refer to reactions performed in flame-dried glassware under a positive pressure of argon using dry solvent transferred by syringe. Anhydrous solvents (THF and MeCN) were obtained by passage through solvent filtration systems (GlassContour, Irvine, CA). Final isolated compounds, all were purified by flash column chromatography on silica gel (230-400 mesh).<sup>30</sup> TLC was performed on

glass-backed silica gel plates. Silica gel was pre-treated with 1% Et<sub>3</sub>N in hexane before purification of pyrroles **6** and **7**, and with 1% Et<sub>3</sub>N in chloroform before purification of pyrroloquinazolinone **8** respectively. <sup>1</sup>H NMR spectra were measured in CDCl<sub>3</sub>, acetone-*d*<sub>6</sub> and DMSO-*d*<sub>6</sub> at 400 MHz and referenced to CDCl<sub>3</sub> (7.26 ppm), acetone-*d*<sub>6</sub> (2.05 ppm) and DMSO-*d*<sub>6</sub> (2.50 ppm). <sup>13</sup>C NMR spectra were measured in CDCl<sub>3</sub>, acetone-*d*<sub>6</sub> and DMSO-*d*<sub>6</sub> at 100 MHz and referenced to CDCl<sub>3</sub> (77.2 ppm), acetone-*d*<sub>6</sub> (29.9 ppm) and DMSO-*d*<sub>6</sub> (39.5 ppm). HRMS measurements were made on a LC-MSD TOF (Agilent) mass analyzer. HPLC analyses were performed on a Gemini Analytical C18 reverse-phase analytical column (Prevail column from Phenomenex, 5μm, 4.6 x 150 mm, Part No. 00F-4435-E0). Analytical elution was performed using a flow rate of 0.5 mL/min and gradients from 60:40 to 90:10 A/B over 20 min (method A), and 70:30 to 90:10 A/B over 20 min (method B), in which A = CH<sub>3</sub>OH (0.1% formic acid) and B = H<sub>2</sub>O (0.1% formic acid). Retention times (R<sub>t</sub>) are reported in minutes followed by elution conditions.

**Starting Materials.** Vinylmagnesium bromide was freshly prepared or purchased from Aldrich and titrated before use. All commercially available chemicals were employed without further purification.

**Methyl 2-*N*-(Boc)anthranilate (2).** A solution of methyl anthranilate (**1**, 5 g, 33.07 mmol) in dry EtOH (60 mL) was treated with (Boc)<sub>2</sub>O (21.75 g, 99.65 mmol) stirred for 9 days at 50 °C, cooled to rt, and treated with imidazole (9 g, 132.3 mmol) to destroy excess (Boc)<sub>2</sub>O. After 30 min, the volatiles were evaporated, the residue was dissolved in CHCl<sub>3</sub> (150 mL), washed with 1% HCl (2 × 300 mL, 0 °C), dried (MgSO<sub>4</sub>), and evaporated to give an oil, that was purified by column chromatography on silica gel (10-20% EtOAc in hexane). Evaporation of the collected fractions gave 2-*N*-(Boc)anthranilate **2** (8.19 g, 98%) as white crystalline solid; mp 77-79 °C; R<sub>f</sub> 0.65 (20:80 EtOAc/hexane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.54 (s, 9H), 3.92 (s, 3H), 7.97-7.03 (m, 1H), 7.47-7.54 (m, 1H), 7.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 10.28 (br s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 28.5, 52.4, 80.7, 114.5, 119.0, 121.3, 131.1, 134.7, 142.6, 153.1, 168.8; HRMS (ESI) Calcd *m/z* for C<sub>13</sub>H<sub>17</sub>NNaO<sub>4</sub> [(M + Na)<sup>+</sup>] 274.1050, found 274.1059.

**1-[2-*N*-(Boc)Aminophenyl]pent-4-en-1-one (3).** A flask containing CuCN (1.60 g, 18 mmol, 60 mol%), was briefly flame-dried under a stream of argon and filled with dry THF (36 mL; 2.0 mL per 1 mmol of CuCN). The suspension was cooled to -45 °C under argon atmosphere and treated via syringe with a commercially available solution of 1.3 M vinylmagnesium bromide in THF (139 mL, 180 mmol, 600 mol%). The slurry was stirred for 2 h at -45 °C then treated dropwise with a solution of methyl ester **2** (7.53 g, 30 mmol, 100 mol%) in dry THF (60 mL; 2.0 mL per 1 mmol of methyl ester). The resultant mixture was stirred for 1 h at -45 °C. The cold bath was replaced with an ice bath, stirring was maintained for 1 h at 0 °C, and the ice bath was removed. The reaction mixture was allowed to stir and warm to room temperature for 52 h, cooled to 0 °C, quenched on treatment with 1M aqueous NaH<sub>2</sub>PO<sub>4</sub>

solution (500 mL, 200% *v/v* based on total reaction volume) and diluted with Et<sub>2</sub>O (500 mL). The biphasic solution was vigorously stirred at 0 °C. When a white precipitate had formed, the layers were separated. The aqueous phase was extracted with Et<sub>2</sub>O (2 × 500 mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> solution (1 × 500 mL), brine (1 × 500 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated to a residue, which was purified by column chromatography on silica gel (5-10% EtOAc in hexane). Evaporation of the collected fractions gave homoallylic ketone **3** (3.56 g, 43%) as pale yellow oil; *R<sub>f</sub>* 0.43 (EtOAc-hexane 10:90); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.53 (s, 9H), 2.45-2.53 (m, 2H), 3.13 (t, *J* = 7.4 Hz, 2H), 5.02-5.06 (ddd, *J* = 10.2, 3.0, 1.4 Hz, 1H), 5.07-5.14 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1H), 5.85-5.97 (m, 1H), 7.00-7.06 (m, 1H), 7.48-7.55 (m, 1H), 7.90 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.49 (dd, *J* = 8.4, 1.2 Hz, 1H), 10.95 (br s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 28.6, 39.2 (2C), 80.7, 115.7, 119.6, 121.2, 121.3, 130.9, 144.0, 137.3, 142.1, 153.4, 203.6; HRMS (ESI) Calcd *m/z* for C<sub>16</sub>H<sub>21</sub>NNaO<sub>3</sub> [M + Na]<sup>+</sup> 298.1414, found 298.1413.

**1-[2-*N*-(Boc)Aminophenyl]-4-oxobutanal (4)**. A solution of homoallylic ketone **3** (1.68 g, 6.10 mmol) in 3:1 dioxane/H<sub>2</sub>O (60 mL) was treated with 2,6-lutidine (1.50 mL, 12.65 mmol), OsO<sub>4</sub> (4% in H<sub>2</sub>O, 0.80 mL, 12.65 × 10<sup>-2</sup> mmol) and NaIO<sub>4</sub> (5.41 g, 25.31 mmol), stirred at room temperature overnight, and partitioned between H<sub>2</sub>O (60 mL) and CH<sub>2</sub>Cl<sub>2</sub> (150 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 75 mL). The combined organic layers were washed with brine (150 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to a residue, which was purified by column chromatography on silica gel (20-80% EtOAc in hexane). Evaporation of the collected fractions gave ketoaldehyde **4** (1.29 g, 76%) as pale-grey crystalline solid: mp 98-100 °C; *R<sub>f</sub>* 0.37 (30:70 EtOAc-hexane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.53 (s, 9H), 2.91 (t, *J* = 6.3 Hz, 2H), 3.39 (t, *J* = 6.2 Hz, 2H), 7.02-7.08 (m, 1H), 7.50-7.57 (m, 1H), 7.95 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.50 (dd, *J* = 8.6, 1.0 Hz, 1H), 9.92 (s, 1H), 10.83 (br s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 28.6, 32.5, 37.8, 80.8, 119.5, 120.9, 121.2, 130.9, 135.3, 142.2, 153.3, 200.7, 201.5; HRMS (ESI) Calcd *m/z* for C<sub>15</sub>H<sub>19</sub>NNaO<sub>4</sub> [M + Na]<sup>+</sup> 300.1206, found 300.1206.

**1-[2-*N*-(Boc)Aminophenyl]pentane-1,4-dione (5)**. In a two-necked flask fitted with a septum and a three-way stopcock connected to an oxygen-filled rubber balloon, PdCl<sub>2</sub> (228 mg, 1.29 mmol) and CuCl (638 mg, 6.44 mmol) were placed in 7:1 DMF/H<sub>2</sub>O (10 mL). The flask was evacuated and flushed with oxygen three times, during which the initial black solution turned gradually to green. After stirring 40 min at room temperature, the mixture was treated via syringe with a solution of homoallylic ketone **3** (1.77 g, 6.44 mmol) in 7:1 dioxane/H<sub>2</sub>O (22 mL). The reaction mixture was stirred vigorously at room temperature under oxygen overnight, poured into cold 1 *M* aqueous KHSO<sub>4</sub> (150 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> solution (1 × 200 mL) and brine (1 × 200 mL), dried (MgSO<sub>4</sub>), filtered and evaporated to a residue, which was purified by column chromatography on silica gel (15% EtOAc in hexane) to give diketone **5** (1.47 g,

79%) as viscous pale-yellow oil:  $R_f$  0.38 (EtOAc-hexane 30:70);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.53 (s, 9H), 2.28 (s, 3H), 2.87 (t,  $J = 6$  Hz, 2H), 3.34 (t,  $J = 6$  Hz, 2H), 7.00-7.07 (m, 1H), 7.48-7.55 (m, 1H), 7.96 (dd,  $J = 8.2, 1.4$  Hz, 1H), 8.48 (d,  $J = 7.6$  Hz, 1H), 10.85 (br s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  28.5, 30.3, 33.7, 37.3, 80.7, 119.4, 121.1, 121.2, 131.0, 135.1, 142.1, 153.3, 202.2, 207.3; HRMS (ESI) Calcd  $m/z$  for  $\text{C}_{16}\text{H}_{21}\text{NNaO}_4$  [ $\text{M} + \text{Na}$ ] $^+$  314.1363, found 314.1363.

**1-[2-*N*-(Boc)Aminophenyl]-4-oxobutanal (4) from methyl 2-*N*-(Boc)anthranilate (2).** Methyl ester **2** (4.62 g, 18.37 mmol) was treated with a solution of freshly prepared 1.25 *M* vinylmagnesium bromide (74 mL, 92.50 mmol, 500 mol%) and CuCN (981 mg, 11.02 mmol, 60 mol%) in THF for 36 h at room temperature as described above to give after work-up, 4.95 g of a 4:1 mixture of homoallylic ketone **3** and starting **2**, as measured by  $^1\text{H}$  NMR spectroscopy and integration of the methyl singlet of **2** at 3.92 ppm and the vinyl multiplet of **3** at 5.91 ppm. Without further purification, 1.25 g of the mixture in 3:1 dioxane/ $\text{H}_2\text{O}$  (40 mL) was treated with 2,6-lutidine (0.85 mL, 7.26 mmol),  $\text{OsO}_4$  (4% in  $\text{H}_2\text{O}$ , 440  $\mu\text{L}$ ,  $7.26 \times 10^{-2}$  mmol) and  $\text{NaIO}_4$  (3.11 g, 14.52 mmol), stirred at room temperature overnight, and partitioned between  $\text{H}_2\text{O}$  (75 mL) and  $\text{CH}_2\text{Cl}_2$  (150 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 75$  mL). The combined organic layers were washed with brine (150 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to a residue, which was purified by column chromatography on silica gel (10-20% EtOAc in hexane). First to elute was **2** (517 mg, 15%) followed by ketoaldehyde **4** (637 mg, 49% over 2 steps).

**1-[2-*N*-(Boc)Aminophenyl]pentane-1,4-dione (5) from methyl-2-*N*-(Boc)-anthranilate (2).** Methyl ester **2** (1.5 g, 5.98 mmol) was treated with a solution of freshly prepared 1.3 *M* vinylmagnesium bromide (18.5 mL, 24.05 mmol, 400 mol%) and CuCN (320 mg, 3.59 mmol, 60 mol%) in THF for 16 h at room temperature as described above to give after work-up, 1.21 g of a 1:1 mixture homoallylic ketone **3** and starting **2**. Without further purification, 604 mg of the mixture in 7:1 dioxane/ $\text{H}_2\text{O}$  (5 mL) was added to a two-necked flask fitted with a septum and a three-way stopcock connected to an oxygen-filled rubber balloon, in which  $\text{PdCl}_2$  (39 mg, 0.22 mmol) and CuCl (109 mg, 1.10 mmol) in 7:1 DMF/ $\text{H}_2\text{O}$  (2 mL) had been pre-treated with oxygen for 1h at room temperature. After stirring vigorously at room temperature under oxygen overnight, the mixture was poured into cold 1 *M* aqueous  $\text{KHSO}_4$  (25 mL) and extracted with EtOAc ( $4 \times 25$  mL). The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  solution ( $1 \times 25$  mL), brine ( $1 \times 25$  mL), dried ( $\text{MgSO}_4$ ), filtered and evaporated to a residue, which was purified by column chromatography on silica gel (10-20 AcOEt in hexane). First to elute was ester **2** (331 mg, 44%) followed by diketone **5** (305 mg, 35% over 2 steps).

**2-[2-*N*-(Boc)Aminophenyl]-1*H*-pyrrole (6a).** A mixture of ketoaldehyde **4** (200 mg, 0.73 mmol), ammonium formate (229 mg, 3.63 mmol) and NaOAc/AcOH (prepared by mixing equimolar quantities of NaOAc and AcOH; 2 eq w/w, 400 mg) in MeCN/ $\text{H}_2\text{O}$  (1:1, 10 mL) was heated to 80 °C with rapid stirring for 6 h, when complete consumption of the starting material was observed by TLC (30:70



EtOAc/hexane). After cooling to room temperature, the reaction mixture was partitioned between 2:1 Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and 5 % aqueous Na<sub>2</sub>CO<sub>3</sub> (25 mL). The layers were separated, and the aqueous phase was extracted with Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> (2:1, 2 × 20 mL). The combined organic phases were washed with pH 6.8 phosphate buffer (25 mL) and brine (25 mL), dried (MgSO<sub>4</sub>), filtered, evaporated and purified by column chromatography on silica gel (10% EtOAc in hexane). Evaporation of the collected fractions yielded pyrrole **6a** (151 mg, 80%) as colorless oil: R<sub>f</sub> 0.58 (30:70 EtOAc/hexane); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) δ 1.47 (s, 9H), 6.23-6.27 (m, 1H), 6.31-6.35 (m, 1H), 6.93-6.97 (m, 1H), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H), 7.21-7.27 (m, 1H), 7.35 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.46 (br s, 1H), 8.01 (br d, *J* = 8.0 Hz, 1H), 10.36 (br s, 1H); <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>) δ 28.6, 80.5, 108.7, 110.1, 120.3, 121.4, 124.0, 125.2, 128.2, 128.7, 129.6, 136.5, 153.8; HRMS (ESI) Calcd *m/z* for C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub> [MH]<sup>+</sup> 259.1441, found 259.1443; HPLC R<sub>t</sub> 12.6 (method A).

**1-Ethyl-2-[2-*N*-(Boc)aminophenyl]pyrrole (6b).** Prepared using the procedure described for the synthesis of **6a** from ketoaldehyde **4** (20.9 mg, 7.54 × 10<sup>-2</sup> mmol), ethylamine hydrochloride (31 mg, 3.77 × 10<sup>-1</sup> mmol) and NaOAc/AcOH (42 mg) in MeCN/H<sub>2</sub>O (1:1, 2 mL) for 10 h, pyrrole **6b** (11 mg, 51%) was isolated by chromatography on silica gel (10% EtOAc in hexane) as colorless oil: R<sub>f</sub> 0.74 (30:70 EtOAc/hexane); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) δ 1.19 (t, *J* = 7.2 Hz, 3H), 1.44 (s, 9H), 3.75 (q, *J* = 7.2 Hz, 2H), 6.07 (dd, *J* = 3.6, 2.0 Hz, 1H), 6.20 (dd, *J* = 3.6, 2.8 Hz, 1H), 6.91-7.00 (br s at 6.96 partially overlapped with dd, *J* = 2.8, 1.6 Hz, 2H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 (ddd, *J* = 7.6, 1.6, 0.4 Hz, 1H), 7.33-7.40 (m, 1H), 8.16 (br d, *J* = 8.4 Hz, 1H); <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>) δ 17.0, 28.5, 42.2, 80.7, 109.1, 110.1, 119.8, 122.5, 123.2, 123.5, 128.6, 129.7, 132.2, 138.9, 153.3; HRMS (ESI) Calcd *m/z* for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>2</sub> [M + Na]<sup>+</sup> 309.1574, found 309.1571; HPLC R<sub>t</sub> 12.2 (method B).

**Methyl 3-{2-[2-*N*-(Boc)aminophenyl]-1*H*-pyrrolyl}propanoate (6c).** Prepared using the procedure described for the synthesis of **6a** from ketoaldehyde (**4**) (20.4 mg, 7.34 × 10<sup>-2</sup> mmol), β-alanine methyl ester hydrochloride (51 mg, 3.67 × 10<sup>-1</sup> mmol) and NaOAc/AcOH (40 mg) in MeCN/H<sub>2</sub>O (1:1, 2 mL) for 7 h, pyrrole **6c** (13 mg, 51%) was isolated by chromatography on silica gel (10% EtOAc in hexane) as colorless gum: R<sub>f</sub> 0.66 (30:70 EtOAc/hexane); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) δ 1.45 (s, 9H), 2.59 (t, *J* = 7 Hz, 2H), 3.55 (s, 3H), 4.05 (t, *J* = 7 Hz, 2H), 6.09 (dd, *J* = 3.6, 1.6 Hz, 1H), 6.18 (dd, *J* = 3.6, 2.8 Hz, 1H), 6.93 (dd, *J* = 2.8, 1.6 Hz, 1H), 7.02 (br s, 1H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H), 7.23 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.34-7.40 (m, 1H), 8.16 (br d, 8.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>) δ 28.5, 51.3, 80.6, 109.3, 110.7, 119.6, 123.0 (C2), 124.1, 127.7, 128.2, 129.3, 129.4, 129.8, 132.3, 139.0, 139.6, 153.1; HRMS (ESI) Calcd *m/z* for C<sub>22</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub> [MH]<sup>+</sup> 349.1911, found 349.1901; HPLC R<sub>t</sub> 13.6 (method B). <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>) δ 28.5, 36.2, 43.3, 52.0, 80.6, 109.2, 110.5, 120.1, 123.2, 123.3, 128.9, 129.8, 132.3, 139.0, 153.4, 171.8; HRMS (ESI) Calcd *m/z* for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub> [MH]<sup>+</sup> 345.1809, found 345.1808; HPLC R<sub>t</sub> 14.2 (method A).

**1-Benzyl-2-[2-*N*-(Boc)aminophenyl]pyrrole (6d).** Prepared using a modification of the procedure described for the synthesis of **6a** from ketoaldehyde (**4**) (20.8 mg,  $7.50 \times 10^{-2}$  mmol), benzylamine (42  $\mu$ L,  $3.75 \times 10^{-1}$  mmol) and NaOAc/AcOH (42 mg) in 1,2-dichloroethane/H<sub>2</sub>O (1:1, 2 mL) for 5 h. pyrrole **6d** (14.4 mg, 55%) was isolated by chromatography on silica gel (10% EtOAc in hexane) as pale yellow gum:  $R_f$  0.72 (30:70 EtOAc-hexane); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>)  $\delta$  1.44 (s, 9H), 4.97 (s, 2H), 6.16 (dd,  $J = 3.4, 1.8$  Hz, 1H), 6.25 (dd,  $J = 3.4, 3.2$  Hz, 1H), 6.87 (br s, 1H), 6.88-6.92 (m, 2H), 6.97-7.00 (m, 1H), 7.00-7.04 (dd,  $J = 7.2, 1.2$  Hz, 1H), 7.11-7.16 (ddd,  $J = 7.7, 1.9, 0.5$  Hz, 1H), 7.17-7.26 (m, 3H), 7.29-7.36 (m, 1H), 8.40 (br d,  $J = 8.4$  Hz, 1H); <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>)  $\delta$  28.5, 51.3, 80.6, 109.3, 110.7, 119.6, 123.0 (C2), 124.1, 127.7, 128.2, 129.3, 129.4, 129.8, 132.3, 139.0, 139.6, 153.1; HRMS (ESI) Calcd  $m/z$  for C<sub>22</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub> [MH]<sup>+</sup> 349.1911, found 349.1901; HPLC  $R_f$  13.6 (method B).

**2-[2-*N*-(Boc)Aminophenyl]-5-methyl-1*H*-pyrrole (7a).** A mixture of diketone **5** (200 mg, 0.68 mmol), ammonium formate (218 mg, 3.46 mmol), and NaOAc/AcOH (prepared by mixing equimolar quantities of NaOAc and AcOH; 1 eq w/w, 210 mg) in MeCN (10 mL) was heated at 80 °C with rapid stirring for 94 h, when complete consumption of the starting material was observed by TLC (30:70 EtOAc/hexane). After cooling to room temperature, the reaction mixture was partitioned between 2:1 Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and a mixture of pH 6.8 phosphate buffer solution (30 mL) and brine (10 mL). The layers were separated. The organic phase was washed with a mixture of pH 6.8 phosphate buffer (10 mL) and brine (5 mL). The combined aqueous phase was extracted with Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> (2:1, 3  $\times$  30 mL). The combined organic phases were washed with brine (1  $\times$  30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and evaporated to a residue, which was purified by column chromatography on silica gel (10% EtOAc in hexane) to yield pyrrole **7a** (142 mg, 76%) as pale yellow crystalline solid: mp 125-126 °C;  $R_f$  0.72 (30:70 EtOAc/hexane); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>)  $\delta$  1.48 (s, 9H), 2.29 (d,  $J = 0.8$  Hz, 3H), 5.89-5.94 (m, 1H), 6.19 (t,  $J = 3$  Hz, 1H), 7.04 (td,  $J = 7.5, 1.0$  Hz, 1H), 7.20 (td,  $J = 7.8, 1.1$  Hz, 1H), 7.32, (dd,  $J = 7.8, 1.4$  Hz, 1H), 7.52 (br s, 1H), 8.00 (br d,  $J = 8.0$  Hz, 1H), 10.06 (br s, 1H); <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>)  $\delta$  13.0, 28.6, 80.4, 108.2, 108.8, 121.2, 123.9, 125.3, 127.2, 127.7, 129.1, 130.3, 136.1, 153.8; HRMS (ESI) Calcd  $m/z$  for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>NaO<sub>2</sub> [M + Na]<sup>+</sup> 295.1417, found 295.1417; HPLC  $R_f$  10.6 (method B).

**1-Ethyl-2-[2-*N*-(Boc)aminophenyl]-5-methylpyrrole (7b).** Prepared by the same protocol as described for the synthesis of **7a** from diketone **5** (200 mg, 0.68 mmol), ethylamine hydrochloride (282 mg, 3.45 mmol) and NaOAc/AcOH (216 mg) in MeCN (10 mL) for 29 h, pyrrole **7b** (152 mg, 74%) was isolated by column chromatography (10% EtOAc in hexane) as viscous colorless oil:  $R_f$  0.71 (30:70 EtOAc/hexane); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>)  $\delta$  1.03, (t,  $J = 7.2$  Hz, 3H), 1.44 (s, 9H), 2.29 (d,  $J = 0.4$  Hz, 3H), 3.72 (q,  $J = 7.2$  Hz, 2H), 5.92-5.95 (dd,  $J = .2, 0.8$  Hz, 1H), 5.95-5.99 (d,  $J = 3.2$  Hz, 1H), 7.01 (br s, 1H), 7.07 (td,  $J = 7.4, 1.2$  Hz, 1H), 7.19 (dd,  $J = 7.6, 1.6$  Hz, 1H), 7.32-7.40 (m, 1H), 8.18 (br d,  $J = 8.4$  Hz, 1H); <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>)  $\delta$  12.6, 16.5, 28.5, 39.3, 80.7, 108.0, 109.2, 119.4, 123.0,

123.9, 127.5, 129.6, 130.3, 132.4, 139.0, 153.3; HRMS (ESI) Calcd  $m/z$  for  $C_{18}H_{25}N_2O_2 [MH]^+$  301.1911, found 301.1907; HPLC  $R_f$  13.1 (method B).

**Methyl 3-{2-[2-*N*-(Boc)aminophenyl]-5-methyl-1*H*-pyrrolyl}propanoate (7c).** Prepared by the same protocol as described for the synthesis of **7a** from diketone **5** (200 mg, 0.68 mmol),  $\beta$ -alanine methyl ester hydrochloride (482 mg, 3.45 mmol) and NaOAc/AcOH (211 mg) in MeCN (10 mL) for 19 h, pyrrole **7c** (190 mg, 77%) was isolated by column chromatography (10% EtOAc in hexane) as viscous pale yellow oil:  $R_f$  0.60 (30:70 EtOAc/hexane);  $^1H$  NMR (400 MHz, acetone- $d_6$ )  $\delta$  1.45 (s, 9H), 2.30 (d,  $J = 0.8$  Hz, 3H), 2.41 (t,  $J = 7.6$  Hz, 2H), 3.51 (s, 3H), 4.04 (t,  $J = 7.6$  Hz, 2H), 5.92-5.95 (dd,  $J = 3.6, 0.8$  Hz, 1H), 5.98-6.01 (d,  $J = 3.2$  Hz, 1H), 7.05-7.13 (br s totally overlapped with td,  $J = 7.4, 1.2$ , 2H), 7.20 (dd,  $J = 7.6, 1.6$  Hz, 1H), 7.32-7.39 (m, 1H), 8.18 (br d,  $J = 8.4$  Hz, 1H);  $^{13}C$  NMR (100 MHz, acetone- $d_6$ )  $\delta$  12.6, 28.5, 35.7, 40.4, 51.9, 80.6, 108.2, 109.9, 119.7, 123.2, 123.7, 127.8, 129.7, 130.9, 132.2, 139.0, 153.4, 171.6; HRMS (ESI) Calcd  $m/z$  for  $C_{20}H_{26}N_2NaO_4 [M + Na]^+$  381.1785, found 381.1788; HPLC  $R_f$  11.8 (method B).

**1-Benzyl-2-[2-*N*-(Boc)aminophenyl]-5-methyl-pyrrole (7d).** Prepared by the same protocol as described for the synthesis of **7a** from diketone **5** (200 mg, 0.68 mmol), benzylamine (375  $\mu$ L, 3.43 mmol) and NaOAc/AcOH (209 mg) in MeCN (10 mL) for 24 h, pyrrole **7d** (208 mg, 84%) was isolated by column chromatography (10% EtOAc in hexane) as yellow solid: mp 76-78 °C;  $R_f$  0.71 (30:70 EtOAc/hexane);  $^1H$  NMR (400 MHz, acetone- $d_6$ )  $\delta$  1.45 (s, 9H), 2.18 (d,  $J = 0.4$  Hz, 3H), 4.98 (s, 2H), 6.04-6.07 (dd,  $J = 3.2, 0.8$  Hz, 1H), 6.09-6.13 (d,  $J = 3.2$  Hz, 1H), 6.79 (br d,  $J = 6.8$  Hz, 2H), 6.96 (td,  $J = 7.4, 1.2$  Hz, 1H), 7.07 (br s, 1H), 7.11 (dd,  $J = 7.6, 1.6$  Hz, 1H), 7.15-7.31 (m, 4H), 8.11 (br d,  $J = 8.4$  Hz, 1H);  $^{13}C$  NMR (100 MHz, acetone- $d_6$ )  $\delta$  12.8, 28.5, 48.0, 80.6, 108.4, 109.7, 119.4, 122.9, 123.4, 126.7, 127.9, 128.8, 129.4, 129.6, 131.4, 132.2, 138.9, 139.8, 153.1; HRMS (ESI) Calcd  $m/z$  for  $C_{23}H_{26}N_2NaO_2 [M + Na]^+$  385.1886, found 385.1890; HPLC  $R_f$  14.5 (method B).

**Pyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (8).** Sodium hydride (60% dispersion in mineral oil, 8.7 mg,  $21.75 \times 10^{-2}$  mmol) was added to a solution of pyrrole **6a** (46.7 mg,  $18.08 \times 10^{-2}$  mmol) in THF (3 mL) under an argon atmosphere. The mixture was stirred at 65 °C overnight, and partitioned between H<sub>2</sub>O (10 mL) and CHCl<sub>3</sub> (20 mL). The aqueous phase was extracted with CHCl<sub>3</sub> (2  $\times$  10 mL). The combined organic layers were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to a crude residue, which was purified by crystallisation from MeOH to give pyrroloquinazolinone **8** (32.1 mg, 96%) as white solid: mp 264-265 °C;  $R_f$  0.32 (30:70 EtOAc/hexane);  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  6.67 (t,  $J = 3.2$  Hz, 1H), 7.00 (dd,  $J = 3.4, 1.4$  Hz, 1H), 7.17-7.22 (m, 1H), 7.23-7.26 (dd,  $J = 8.0, 0.8$ , 1H), 7.30-7.35 (m, 1H), 7.59 (dd,  $J = 3.2, 1.6$ , 1H), 7.92 (br d,  $J = 8.0$  Hz, 1H), 11.48 (br s, 1H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  104.4, 113.8, 114.3, 115.5 (2C), 122.2, 123.1, 127.5, 129.2, 132.5, 145.5; HRMS (ESI) Calcd  $m/z$  for  $C_{11}H_9N_2O [MH]^+$  185.0709, found 185.0715.

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## SUPPLEMENTARY MATERIAL

Reversed phase HPLC profiles of pyrroles **6a-d** and **7a-d**, and <sup>1</sup>H and <sup>13</sup>C NMR spectra of all compounds.