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# Br<sub>2</sub>- or HBr-catalyzed synthesis of asymmetric 3,3-di(indolyl)indolin-2-ones

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**Abstract:** Under the catalysis of 1 mol% of Br<sub>2</sub> or HBr at room temperature, indoles undergo a rapid reaction with 3-hydroxy-3-(indol-3-yl)indolin-2-ones to give asymmetric 3,3-di(indol-3-yl)indolin-2-ones with high efficiency and wide substrate scope. This is a rare example of Br<sub>2</sub> acting as a Lewis acid catalyst. Theoretical calculations suggest that both the catalytic activity of the catalysts and the stability of reaction intermediates are responsible for the high efficiency of this reaction.

**Keywords:** alcohols; alkylation; C–C coupling; halogens; homogeneous catalysis.

## Introduction

The indole system is a ubiquitous feature of alkaloids and represents a privileged structural motif for pharmaceutically active compounds [1–6]. In this context, 3,3-di(indolyl)indolin-2-ones, frequently referred to as trisindolines, are a class of natural products isolated from marine-derived bacteria [7–9] and terrestrial plants [10]. They exhibit activities as anticancer [11–13], antimicrobial, anticonvulsant [14] and spermicidal agents [15].

Despite the plethora of preparations of symmetric trisindolines from indoles and isatins [16], reports on

the synthesis of asymmetric 3,3-di(indolyl)indolin-2-ones are rare. In 2006, Ji and co-workers disclosed a facile synthesis of such compounds from 3-hydroxy-3-(indolyl)indolin-2-ones and indoles catalyzed by ceric ammonium nitrate (CAN). The reaction was run under ultrasound irradiation with a rather high catalyst content of 10 mol% [17]. More recently, an elegant synthesis of asymmetric 3,3-di(indolyl)indolin-2-ones in the ionic liquid *N,N,N,N*-tetramethylguanidinium trifluoroacetate (TMGT) as the solvent was realized by Rad-Moghadam and co-workers. This reaction featured a narrow substrate scope [18]. Mamaghani and co-workers reported the successful preparation of the title compounds from indoles and isatins by using montmorillonite KSF clay as a recyclable heterogeneous catalyst, however, both a high temperature and a high catalyst load were required [19]. There were two additional attempts in which no substrate scope was explored. Thus, one asymmetric 3,3-di(indolyl)indolin-2-one was afforded in a 40% yield under the catalysis of 5 mol% of toxic Hg(ClO<sub>4</sub>)<sub>2</sub>·3H<sub>2</sub>O [20]. The Lewis acids Sn(OTf)<sub>2</sub> and Cu(OTf)<sub>2</sub> were also reported to catalyze the reaction but at a high load of 10 mol% and a long reaction time was required [21]. Given our ongoing interest in the bromine effect [16, 22–26], we examined the catalytic activity of Br<sub>2</sub> in this dehydrative C–C coupling reaction and found that bromine is an excellent catalyst. It should be noted that in a sharp contrast to the wide application of molecular iodine in organic synthesis, elemental bromine is under-rated and has rarely been used as a Lewis acid catalyst, which is partly due to its high vapor pressure and corrosiveness [27, 28]. The use of hydrobromic acid as catalyst was also explored in this work.

## Results and discussion

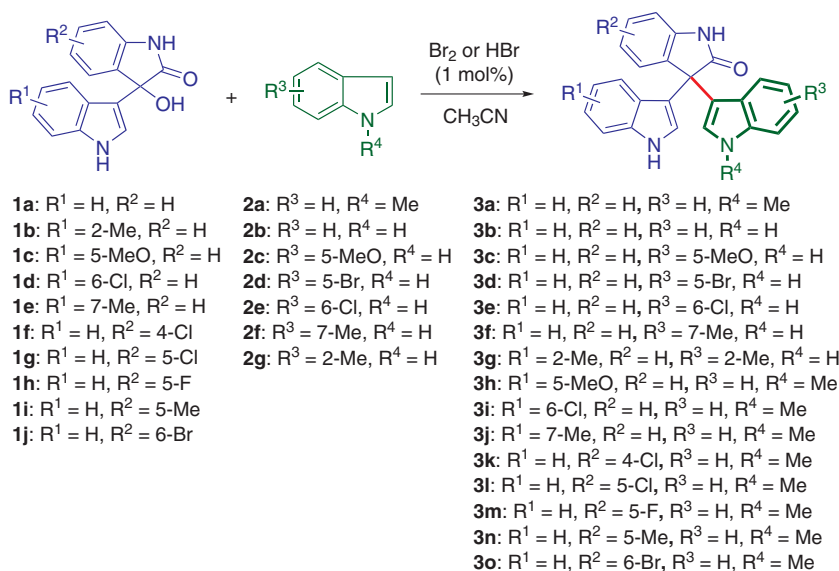
The dehydrative coupling of 3-hydroxy-3-(indol-3-yl)indolin-2-one (**1a**) and 1-methylindole (**2a**) was investigated as the model reaction. We were pleased to find that in the presence of only 1 mol% of Br<sub>2</sub> in MeCN at room temperature, this reaction was completed rapidly within 6 min and asymmetric 3,3-di(indol-3-yl)indolin-2-one **3a** was obtained in a nearly quantitative yield. An excellent

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Scheme 1 Substrate scope.

yield was still achieved after 50 min in the presence of a reduced catalyst loading of 0.5 mol%. The remarkable role of  $\text{Br}_2$  could not be replaced by the use of *N*-bromosuccinimide (NBS), a well-known alternative to  $\text{Br}_2$ . The trisindoline **3a** was obtained in 96% yield within 10 min in a HBr-catalyzed reaction using 48% hydrobromic acid [29, 30]. With  $\text{CuBr}_2$  [31–33] as the catalyst, the product **3a** was obtained in 93% yield after a much longer reaction time of 6 h. Notably, the reaction catalyzed by  $\text{Br}_2$  was hardly affected by the addition of water, whereas aqueous HBr was less active when 4 Å molecular sieves were added, probably due to adsorption of the catalyst. In the presence of  $\text{I}_2$  as catalyst, trisindoline **3a** was obtained in 94% yield within 20 min. The reaction was also catalyzed by a 47% aqueous HI but it took 6 h for the reaction to be completed. Product **3a** was obtained after prolonged reaction times in the presence of  $\text{H}_2\text{SO}_4$ , TsOH,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{AlCl}_3$  or  $\text{SnCl}_4$  as the catalyst. Next, the solvents were screened. No reaction occurred in  $\text{CH}_2\text{Cl}_2$  under the catalysis of 1 mol% of  $\text{Br}_2$  and only trace amounts of **3a** was observed in toluene after 12 h under otherwise similar conditions. Reactions performed in tetrahydrofuran and ethanol were completed in 6 h and 12 h, respectively. Product **3a** was obtained in low yield in *N,N*-dimethylformamide after 12 h.

Under optimal conditions the reaction was conducted in MeCN at ambient temperature in the presence of 1 mol% of  $\text{Br}_2$  as the catalyst. Aqueous HBr is also a good catalyst. Both catalysts were used to evaluate the substrate scope with respect to both coupling partners (Scheme 1). In general, the HBr-catalyzed reactions proceed slower and with slightly lower yields than the reactions catalyzed

by  $\text{Br}_2$ . As can be seen from Scheme 1, many substituents in substrates **1** and **2** are tolerated and products **3** are obtained in high yields after short reaction times. The only exceptions are the reactions of substrate **1f** which are conducted in the presence of 5 mol% of the catalyst, proceed efficiently at 50°C and require much longer reaction times.

In an effort to gain insights into the extraordinary performances of  $\text{Br}_2$  and HBr, theoretical calculations of natural population atomic (NPA) charges on C(3) of 3-hydroxy-3-(indol-3-yl)indolin-2-one (**1a**) upon activation by a series of Brønsted and Lewis acids were carried out (Figure 1). Upon coordination of the hydroxyl oxygen atom to acid, the positivity of  $\alpha$ -carbon is enhanced. The results at the M062X/def2TZVP level [34, 35] demonstrate that while all acids function in molecular forms, in terms of acidity,  $\text{Br}_2$ , HBr or  $\text{I}_2$  are not superior to other selected acids, including HI,  $\text{H}_2\text{SO}_4$ , TFA,  $\text{BF}_3$  and  $\text{AlCl}_3$ . In addition, the positivity of the  $\alpha$ -carbon is enhanced only slightly when the solvent effect of MeCN is considered (M062X/def2TZVP + MeCN) [36]. It can be suggested that acidity is not the primary cause of the robust catalytic activities of  $\text{Br}_2$  and HBr in this reaction; the origin of which remains

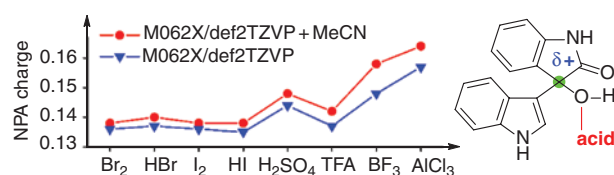
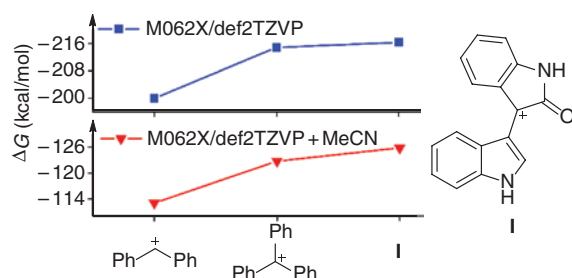


Figure 1 NPA charge calculations for C(3) of **1a** at the M062X/def2TZVP and SMD-MeCN-M062X/def2TZVP levels of theory.



**Figure 2** Stabilities of diphenylmethylium, triphenylmethylium and 3-(indol-3-yl)-2-oxoindolin-3-ylum I at the M062X/def2TZVP level.

unclear at this stage. Further exploration still needs to be carried out and is ongoing in our laboratory.

Next, the stabilities of diphenylmethylium cation, triphenylmethylium cation and 3-(indol-3-yl)-2-oxoindolin-3-ylum cation **I** were analyzed (Figure 2). DFT calculations at the M062X/def2TZVP level revealed that intermediate cation **I** is more stable than the triphenylmethylium cation, and that the solvent greatly stabilizes all these cations (M062X/def2TZVP + MeCN). Thus, it can be suggested that both the catalytic activity of the catalysts and the stability of reaction intermediates are responsible for the extremely high efficiency of this reaction.

## Conclusions

A novel Br<sub>2</sub>- or HBr-catalyzed dehydrative coupling of indoles with 3-hydroxy-3-(indol-3-yl)indolin-2-ones was developed. This reaction provides direct access to biologically important asymmetric 3,3-di(indolyl)indolin-2-ones at low cost and high efficiency, with good functional group tolerance. Bromine is a novel Lewis acid in this study, examples of which are scarce [16, 22–26]. The results of DFT calculations suggest that both the catalytic activity of the catalyst and the stability of the reaction intermediate are responsible for the high efficiency of this reaction.

## Experimental

Thin-layer chromatography (TLC) was carried out using silica gel GF254 plates. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded in DMSO-*d*<sub>6</sub> at 25°C on a Bruker Ascend 400 spectrometer (Bruker, Karlsruhe, Baden-Württemberg, Germany) using TMS as internal standard. High-resolution mass spectra (HR-MS) were obtained on a Bruker micro TOF II Focus spectrometer (Bruker Daltronics, Bremen, Germany) using electrospray ionization (ESI).

Optimization of all molecular geometries and vibrational analyses were calculated at M06-2X functions with the def2-TZVP basis set by using Gaussian 09 program (Gaussian, Wallingford, Connecticut, USA) [37]. A natural bonding orbital (NBO) analysis for structures

was also performed to determine NPA charges by using the NBO 3.1 package implemented in Gaussian 09. All calculated structures were true minima (no imaginary frequencies). Solvent effect at the M062X/def2TZVP level was calculated using the solvent model density (SMD) approach [36]. The Gibbs free energy change (ΔG) of reactions of 'ROH + H<sup>+</sup> = R<sup>+</sup> + H<sub>2</sub>O' was used to compare the stabilities of different cations [38–42].

### General procedure with Br<sub>2</sub> as the catalyst (method A)

To a stirred solution of 3-hydroxy-3-(indol-3-yl)indolin-2-one **1** (0.5 mmol) and indole **2** (0.55 mmol) in MeCN (2.5 mL) was added a solution of Br<sub>2</sub> (0.026 mL, 0.5 mmol) in MeCN (0.5 mL), and the mixture was stirred at ambient temperature. After substrate **1** was consumed, as indicated by TLC, the reaction mixture was quenched with saturated aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (0.5 mL) and water (20 mL), and stirred for an additional 10 min. The precipitated solid was filtered, washed with water (20 mL) and then with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and dried under reduced pressure to afford asymmetric 3,3-di(indol-3-yl)indolin-2-one **3**.

### General procedure with HBr as the catalyst (method B)

To a stirred solution of 3-hydroxy-3-(indol-3-yl)indolin-2-one **1** (0.5 mmol) and indole **2** (0.55 mmol) in MeCN (2.5 mL) was added a solution of HBr (0.073 mL, 0.5 mmol) in MeCN (0.5 mL), and the mixture was stirred at ambient temperature. After substrate **1** was consumed, as indicated by TLC, the reaction mixture was quenched with saturated aqueous solution of NaHCO<sub>3</sub> (0.5 mL) and water (20.0 mL), and stirred for an additional 10 min. The precipitated solid was filtered, washed with water (20 mL) and then with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and dried under reduced pressure to afford asymmetric 3,3-di(indol-3-yl)indolin-2-one **3**.

**1-Methyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'(1'*H*)-one (3a)** This compound was obtained from **1a** and **2a**; yield 97%, 6 min, method A; yield 96%, 10 min, method B; off-white solid; mp 310–311°C (dec.); <sup>1</sup>H NMR: δ 3.71 (s, 3H), 6.77–6.86 (m, 4H), 6.92 (dd, *J* = 7.4, 7.2 Hz, 1H), 6.97–7.03 (m, 2H), 7.08 (dd, *J* = 7.0, 7.0 Hz, 1H), 7.19–7.25 (m, 4H), 7.36 (dd, *J* = 8.2, 9.8 Hz, 2H), 10.60 (s, 1H), 10.96 (s, 1H); <sup>13</sup>C NMR δ 179.1, 141.8, 137.8, 137.4, 135.0, 128.9, 128.3, 126.6, 126.1, 125.4, 124.8, 122.0, 121.6, 121.5, 121.4, 121.1, 118.8, 118.7, 114.7, 114.0, 112.1, 110.2, 110.1, 53.0, 32.8. HR-MS. Calcd for C<sub>25</sub>H<sub>20</sub>N<sub>3</sub>O<sup>+</sup> ([M+H]<sup>+</sup>): *m/z* 378.1601. Found: *m/z* 378.1602.

**1*H*,1'*H*-[3,3':3',3''-terindol]-2'(1'*H*)-one (3b)** This compound was obtained from **1a** and **2b**; yield 92%, 60 min, method A; yield 92%, 180 min, method B; off-white solid; mp 319–320°C (dec.); <sup>1</sup>H NMR: δ 6.78–7.03 (m, 8H), 7.23 (d, *J* = 4.8 Hz, 4H), 7.35 (d, *J* = 6.7 Hz, 2H), 10.60 (s, 1H), 10.95 (s, 2H); <sup>13</sup>C NMR: δ 179.2, 141.8, 137.4, 135.1, 128.3, 126.2, 125.4, 124.8, 121.9, 121.4, 121.3, 118.7, 114.8, 112.1, 110.0, 53.1. HR-MS. Calcd for C<sub>24</sub>H<sub>18</sub>N<sub>3</sub>O<sup>+</sup> ([M+H]<sup>+</sup>): *m/z* 364.1444. Found: *m/z* 364.1447.

**5-Methoxy-1*H*,1'*H*-[3,3':3',3''-terindol]-2'(1'*H*)-one (3c)** This compound was obtained from **1a** and **2c**; yield 95%, 5 min, method A; yield 92%, 15 min, method B; off-white solid; mp 307–308°C (dec.); <sup>1</sup>H NMR: δ 3.52 (s, 3H), 6.67–6.71 (m, 2H), 6.79–6.83 (m, 2H), 6.89 (d, *J* = 2.5 Hz,

1H), 6.94 (ddd,  $J=0.8, 7.6, 7.5$  Hz, 1H), 6.99–7.04 (m, 2H), 7.22–7.27 (m, 4H), 7.37 (d,  $J=8.1$  Hz, 1H), 10.61 (s, 1H), 10.83 (d,  $J=1.9$  Hz, 1H), 10.98 (d,  $J=1.7$  Hz, 1H);  $^{13}\text{C}$  NMR:  $\delta$  179.2, 152.9, 141.9, 137.4, 135.1, 132.6, 128.3, 126.6, 126.2, 125.6, 125.4, 124.9, 121.9, 121.4, 121.2, 118.7, 114.6, 114.3, 112.5, 112.1, 110.9, 110.0, 103.8, 55.6, 53.1. HR-MS. Calcd for  $\text{C}_{25}\text{H}_{20}\text{N}_3\text{O}_2^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  394.1550. Found  $m/z$  394.1546.

**5-Bromo-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3d)** This compound was obtained from **1a** and **2d**; yield 86%, 10 min, method A; yield 87%, 30 min, method B; white solid; mp 302–303°C (dec.);  $^1\text{H}$  NMR:  $\delta$  6.79–7.04 (m, 6H), 7.13–7.27 (m, 4H), 7.35 (dd,  $J=6.1, 6.1$  Hz, 2H), 7.44 (s, 1H), 10.65 (s, 1H), 10.97 (s, 1H), 11.20 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  179.1, 141.8, 137.4, 136.2, 134.6, 128.5, 128.0, 126.3, 126.0, 125.4, 124.8, 124.0, 123.7, 122.1, 121.5, 120.7, 118.9, 114.6, 114.5, 114.2, 112.2, 111.4, 110.2, 52.8. HR-MS. Calcd for  $\text{C}_{24}\text{H}_{17}\text{BrN}_3\text{O}^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  442.0550. Found:  $m/z$  442.0551.

**6-Chloro-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3e)** This compound was obtained from **1a** and **2e**; yield 93%, 10 min, method A; yield 90%, 30 min, method B; white solid; mp 281–282°C (dec.);  $^1\text{H}$  NMR:  $\delta$  6.77–7.02 (m, 7H), 7.15–7.25 (m, 4H), 7.35 (d,  $J=7.8$  Hz, 1H), 7.41 (s, 1H), 10.63 (s, 1H), 10.98 (s, 1H), 11.14 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  179.0, 141.8, 137.8, 137.4, 134.8, 128.4, 126.2, 126.1, 125.8, 125.3, 125.0, 124.7, 122.8, 122.0, 121.4, 120.9, 119.0, 118.8, 115.1, 114.6, 112.1, 111.7, 110.2, 52.9. HR-MS. Calcd for  $\text{C}_{24}\text{H}_{17}\text{ClN}_3\text{O}^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  398.1055. Found:  $m/z$  398.1056.

**7-Methyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3f)** This compound was obtained from **1a** and **2f**; yield 95%, 2 min, method A; yield 93%, 10 min, method B; yellow solid; mp 220–221°C;  $^1\text{H}$  NMR:  $\delta$  2.45 (s, 3H), 6.73 (dd,  $J=7.1, 7.3$  Hz, 1H), 6.80–6.87 (m, 4H), 6.94 (dd,  $J=6.8, 7.0$  Hz, 1H), 7.00–7.06 (m, 3H), 7.22–7.31 (m, 3H), 7.37 (d,  $J=7.8$  Hz, 1H), 10.62 (s, 1H), 10.95 (s, 1H), 10.98 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  179.3, 141.8, 137.4, 136.9, 135.2, 128.3, 126.2, 125.9, 125.4, 124.7, 124.5, 121.9, 121.5, 121.4, 121.0, 119.0, 118.8, 118.7, 115.3, 114.8, 112.1, 110.0, 53.1, 17.2. HR-MS. Calcd for  $\text{C}_{25}\text{H}_{20}\text{N}_3\text{O}^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  378.1601. Found:  $m/z$  378.1606.

**2,2''-Dimethyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3g)** This compound was obtained from **1b** and **2g**; yield 90%, 60 min, method A; yield 90%, 120 min, method B; pinkish solid; mp 290–291°C;  $^1\text{H}$  NMR:  $\delta$  1.93 (s, 3H), 2.07 (s, 3H), 6.45 (d,  $J=7.3$  Hz, 1H), 6.58–6.70 (m, 3H), 6.84–6.95 (m, 4H), 7.13–7.23 (m, 4H), 10.51 (s, 1H), 10.83 (s, 1H), 10.86 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  179.8, 141.7, 136.1, 135.5, 135.4, 134.4, 132.5, 128.3, 128.2, 127.5, 125.9, 121.7, 120.2, 120.0, 119.8, 119.8, 118.4, 118.4, 110.9, 110.8, 109.9, 52.9, 13.6, 13.4. HR-MS. Calcd for  $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  392.1757. Found:  $m/z$  392.1749.

**5''-Methoxy-1-methyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3h)** This compound was obtained from **1c** and **2a**; yield 91%, 10 min, method A; yield 90%, 30 min, method B; off-white solid; mp 303–304°C;  $^1\text{H}$  NMR:  $\delta$  3.52 (s, 3H), 3.72 (s, 3H), 6.65–6.71 (m, 2H), 6.84–7.01 (m, 5H), 7.10 (dd,  $J=7.1, 6.6$  Hz, 1H), 7.22–7.28 (m, 4H), 7.39 (d,  $J=7.7$  Hz, 1H), 10.63 (s, 1H), 10.83 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  179.1, 152.9, 141.8, 137.8, 135.0, 132.6, 129.0, 128.4, 126.6, 126.5, 125.6, 125.4, 122.0, 121.5, 118.8, 114.1, 113.9, 112.6, 110.9, 110.2, 110.0, 103.6, 55.6, 52.9, 32.8. HR-MS. Calcd for  $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_2^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  408.1707. Found:  $m/z$  408.1710.

**6''-Chloro-1-methyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3i)** This compound was obtained from **1d** and **2a**; yield 93%, 20 min, method A; yield 93%, 30 min, method B; off-white solid; mp

283–284°C;  $^1\text{H}$  NMR:  $\delta$  3.71 (s, 3H), 6.82–6.86 (m, 2H), 6.88 (s, 1H), 6.91 (d,  $J=2.4$  Hz, 1H), 6.92–7.00 (m, 2H), 7.09 (ddd,  $J=0.8, 7.2, 7.2$  Hz, 1H), 7.18 (d,  $J=8.0$  Hz, 1H), 7.22–7.26 (m, 3H), 7.38 (d,  $J=8.3$  Hz, 1H), 7.41 (d,  $J=1.8$  Hz, 1H), 10.65 (s, 1H), 11.12 (d,  $J=1.6$  Hz, 1H);  $^{13}\text{C}$  NMR:  $\delta$  178.9, 141.7, 137.8, 137.7, 134.7, 128.9, 128.5, 126.4, 126.3, 125.8, 125.3, 125.0, 122.7, 122.1, 121.6, 121.2, 119.1, 118.9, 115.0, 113.9, 111.7, 110.3, 110.2, 100.0, 52.8, 32.8. HR-MS. Calcd for  $\text{C}_{25}\text{H}_{19}\text{ClN}_3\text{O}^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  412.1211. Found:  $m/z$  412.1213.

**1,7''-Dimethyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3j)** This compound was obtained from **1e** and **2a**; yield 95%, 2 min, method A; yield 93%, 10 min, method B; off-white solid; mp 311–312°C (dec.);  $^1\text{H}$  NMR:  $\delta$  2.44 (s, 3H), 3.71 (s, 3H), 6.72 (dd,  $J=7.1, 7.3$  Hz, 1H), 6.81–6.86 (m, 4H), 6.93 (dd,  $J=7.0, 7.0$  Hz, 1H), 7.01 (dd,  $J=7.7, 12.8$  Hz, 2H), 7.09 (dd,  $J=7.3, 6.7$  Hz, 1H), 7.21–7.30 (m, 3H), 7.38 (d,  $J=8.0$  Hz, 1H), 10.61 (bs, 1H), 10.95 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  179.1, 141.8, 137.8, 136.8, 135.1, 128.9, 128.3, 126.6, 125.8, 125.4, 124.5, 121.9, 121.8, 121.5, 121.1, 119.0, 118.8, 118.6, 115.2, 114.0, 110.2, 110.0, 53.0, 32.8, 17.2. HR-MS. Calcd for  $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  392.1757. Found:  $m/z$  392.1759.

**4'-Chloro-1-methyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3k)** This compound was obtained from **1f** and **2a**; yield 88%, 12 h, method A but using 5 mol% of catalyst at 50°C; yield 83%, 24 h, method B but using 5 mol% of catalyst at 50°C; off-white solid; mp 270–271°C (dec.);  $^1\text{H}$  NMR:  $\delta$  3.73 (s, 3H), 6.84–6.97 (m, 5H), 7.01 (d,  $J=7.5$  Hz, 1H), 7.06 (dd,  $J=7.3, 7.3$  Hz, 1H), 7.13 (dd,  $J=7.4, 7.3$  Hz, 1H), 7.21 (d,  $J=8.0$  Hz, 1H), 7.27–7.33 (m, 2H), 7.40 (dd,  $J=8.4, 10.4$  Hz, 2H), 10.81 (s, 1H), 11.03 (d,  $J=1.7$  Hz, 1H);  $^{13}\text{C}$  NMR:  $\delta$  178.4, 144.2, 137.7, 137.2, 131.5, 130.5, 130.4, 130.3, 126.6, 126.3, 125.9, 123.4, 121.5, 121.4, 120.6, 118.9, 112.1, 111.0, 110.3, 110.3, 109.1, 53.8, 32.9. HR-MS. Calcd for  $\text{C}_{25}\text{H}_{19}\text{ClN}_3\text{O}^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  412.1211. Found:  $m/z$  412.1205.

**5'-Chloro-1-methyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3l)** This compound was obtained from **1g** and **2a**; yield 92%, 10 min, method A; yield 90%, 15 min, method B; off-white solid; mp 273–274°C;  $^1\text{H}$  NMR:  $\delta$  3.72 (s, 3H), 6.82–6.89 (m, 2H), 6.93 (s, 2H), 7.01–7.06 (m, 2H), 7.11 (dd,  $J=7.6, 7.1$  Hz, 1H), 7.21–7.41 (m, 6H), 10.79 (s, 1H), 11.05 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  178.8, 140.7, 137.9, 137.4, 137.0, 129.0, 128.4, 126.4, 126.0, 125.9, 125.2, 125.0, 121.7, 121.6, 121.4, 120.8, 119.0, 113.9, 113.2, 112.2, 111.6, 110.4, 53.2, 32.8. HR-MS. Calcd for  $\text{C}_{25}\text{H}_{19}\text{ClN}_3\text{O}^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  412.1211. Found:  $m/z$  412.1210.

**5'-Fluoro-1-methyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3m)** This compound was obtained from **1h** and **2a**; yield 94%, 10 min, method A; yield 95%, 20 min, method B; off-white solid; mp 289–290°C (dec.);  $^1\text{H}$  NMR:  $\delta$  3.72 (s, 3H), 6.80–7.11 (m, 9H), 7.20 (d,  $J=7.5$  Hz, 1H), 7.25 (d,  $J=7.6$  Hz, 1H), 7.38 (dd,  $J=8.8, 8.5$  Hz, 2H), 10.65 (bs, 1H), 11.02 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  179.0, 158.3 (d,  $^3J_{\text{C-F}}=235.3$  Hz), 138.0 (d,  $^4J_{\text{C-F}}=1.4$  Hz), 137.8, 137.4, 136.7 (d,  $^3J_{\text{C-F}}=7.6$  Hz), 129.0, 126.4, 126.0, 125.0, 121.6, 121.5, 121.5, 120.8, 118.9, 118.9, 114.7 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 114.1, 113.3, 112.9 (d,  $^2J_{\text{C-F}}=24.3$  Hz), 112.2, 110.9 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 110.3, 53.5 (d,  $^4J_{\text{C-F}}=1.2$  Hz), 32.8. HR-MS. Calcd for  $\text{C}_{25}\text{H}_{19}\text{FN}_3\text{O}^+$  ( $[\text{M}+\text{H}]^+$ )  $m/z$  396.1507. Found:  $m/z$  396.1510.

**1,5'-Dimethyl-1*H*,1'*H*-[3,3':3',3''-terindol]-2'-(1'*H*)-one (3n)** This compound was obtained from **1i** and **2a**; yield 94%, 30 min, method A; yield 92%, 60 min, method B; off-white solid; mp 310–311°C (dec.);  $^1\text{H}$  NMR:  $\delta$  2.18 (s, 3H), 3.71 (s, 3H), 6.80–6.89 (m, 5H), 7.00–7.11 (m, 4H), 7.23–7.27 (m, 2H), 7.37 (dd,  $J=7.8, 7.8$  Hz, 2H), 10.51 (s, 1H), 10.97 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  179.1, 139.3, 137.8, 137.4, 135.1, 130.7, 128.9, 128.6,



126.6, 126.2, 125.9, 124.9, 121.7, 121.5, 121.4, 121.1, 118.8, 118.7, 114.8, 114.2, 112.1, 110.2, 109.8, 53.0, 32.8, 21.3. HR-MS. Calcd for  $C_{26}H_{22}N_3O^+$  ( $[M+H]^+$ ):  $m/z$  392.1757. Found:  $m/z$  392.1755.

**6'-Bromo-1-methyl-1H,1'H-[3,3':3',3''-terindol]-2'(1'H)-one (3o)** This compound was obtained from **1j** and **2a**; yield 92%, 20 min, method A; yield 90%, 45 min, method B; off-white solid; mp 285–286°C (dec.);  $^1H$  NMR:  $\delta$  3.71 (s, 3H), 6.80–6.88 (m, 4H), 7.02 (dd,  $J=6.7$ , 6.8 Hz, 1H), 7.08–7.16 (m, 4H), 7.19 (d,  $J=7.8$  Hz, 1H), 7.24 (d,  $J=7.6$  Hz, 1H), 7.34–7.40 (m, 2H), 10.72 (bs, 1H), 11.01 (s, 1H);  $^{13}C$  NMR:  $\delta$  179.0, 143.6, 137.8, 137.4, 134.3, 128.9, 127.2, 126.4, 126.0, 124.9, 124.6, 121.6, 121.5, 121.5, 120.8, 120.8, 118.9, 114.0, 113.3, 113.9, 112.2, 110.3, 52.7, 32.8. HR-MS. Calcd for  $C_{25}H_{19}BrN_3O^+$  ( $[M+H]^+$ ):  $m/z$  456.0706. Found:  $m/z$  456.0701.

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