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ARTICLE TYPE

Synthesis of 7-Hydroxy-6,7-dihydro-indole and 6',7'-Dihydro-3,7'-biindole Derivatives from Domino Reactions of Arylglyoxals or Methyl Ketones with Enamines†

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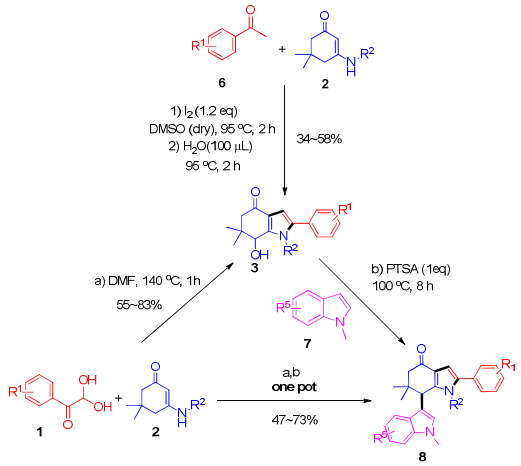
A series of interesting 7-hydroxy-2-aryl-6,7-dihydro-indol-4(5*H*)-ones 3 was successfully synthesized in moderate to good yields by the domino reactions of different arylglyoxals 1 with enamines 2 under catalyst-free conditions. 7-Hydroxy-2-aryl-6,7-dihydro-indol-4(5*H*)-ones 3 could also be prepared in moderate yields by the iodine-promoted one pot-two steps reactions of methyl ketones 6 with enamines 2. The reaction of 3a with N-methyl indole 7a in the presence of PTSA afforded 2'-aryl-6',7'-dihydro-[3,7'-biindol]-4'(5'*H*)-ones 8a in 81% yield. In addition, 3,7'-bis-indoles 8 could also be observed in 47-73% yields by one pot domino reaction of arylglyoxals 1 with enamines 2 and indoles 7 over two steps. This protocol provides a simple and practical method to construct diverse 7-hydroxy-6,7-dihydro-indole derivatives 3 and 3,7'-bis-indoles 8 from easily obtained starting materials.

Introduction

Tetrahydroindoles have attracted great attention for their important physiological activity and their wide applications in pharmaceutical synthesis. For example, they were used as antibiotics,[1] antipsychotics,[2] antiproliferative, cytotoxic agents,[3] GABAA-a5 receptors,[4] blood-platelet aggregation inhibitors,[5] and selec-tive Kv1.5 blockers.[6] In addition, they are the key intermediates for the preparation of acetylcholineserase inhibitors,[7] as well as for the synthesis of indole derivatives.[8] In view of the importantance of tetrahydroindoles derivatives, some multistep synthetic methods have been developed to construct the relative compounds.[9-12] Such methods include the intramolecular 1,3-dipolar cycloaddition from amino acid methyl esters,[9] the oxidation of hydroxy-enamines derived from cyclohexane-1,3-diones,[10] the condensation of 2-azido-1,1-diethoxyethane with cyclohexane-1,3-diones followed by cyclization,[11] and the iodocyclization of β-allyl-dimedone and subsequent dehydroiodination.[12] However, these reactions often required long reaction time, multi steps, poor overall yields and used starting materials that are difficult to synthesize. Domino reaction is an efficient and powerful tool to construct complicated molecules with several new bonds formation in one step. Recently, Tu, Li and coworkers have reported the synthesis of polyfunctionalized indoles by domino reactions of arylglyoxals with enamines and amines or indoles under microwave irradiation conditions.[13, 14] More recently, Pramanik group have reported a domino reaction of arylglyoxals with enamines to give 7-hydroxy-2-aryl-6,7-dihydro-indol-4(5*H*)-ones[15] or 7-ethoxy-2-aryl-6,7-dihydro-indol-4(5*H*)-one derivatives, respectively.[16] To the best of our knowledge, the sysnthesis of 7-hydroxy-2-aryl-6,7-dihydro-indol-4(5*H*)-ones from methyl ketones and 6',7'-dihydro-3,7'-biindole derivatives from arylglyoxals utilizing domino reaction strategy have not been reported yet. Herein, we demonstrate two methods to construct hydroxy-2-aryl-6,7-dihydro-indol-4(5*H*)-ones **3** in moderate to good yields. **3** can be achieved via the domino reactions of different arylglyoxals **1** with enamines **2** under catalyst-free conditions. The iodine-promoted one pot-two steps reactions of methyl ketones **6** with enamines **2** is another way to synthesize **3**. The reaction of **3** with indoles **7** in the presence of PTSA afforded 2'-aryl-6',7'-dihydro-[3,7'-biindol]-4'(5'*H*)-ones **8** in good yields. In addition, **8** could also be observed in 47-73% yields by reacting arylglyoxals **1** with enamines **2**, and subsequently indoles **7** in the same pot over 2 steps. This protocol provides a simple and practical way to construct diverse 7-hydroxy-6,7-dihydro-indole derivatives **3** and 3,7'-bis-indoles **8** from easily obtained starting materials(Scheme 1).



Scheme1. our new work

Results and Discussion

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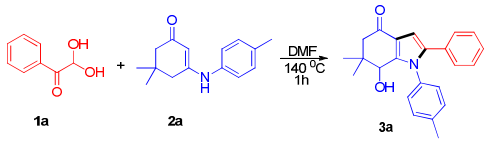
We began our investigations by the model reaction of 2,2-dihydroxy-1-phenylethanone **1a** and 5,5-dimethyl-3-(p-tolylamino)cyclohex-2-enone **2a** in CH_2Cl_2, which afforded 7-hydroxy-6,6-dimethyl-2-phenyl-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one (**3a**) in 24% LC-yield (Table 1, entry 1). The structure of **3a** was confirmed by IR, NMR as well as single-crystal X-ray analysis. When the reaction was carried out in DMA, DMSO or DMF instead of CH_2Cl_2, the LC-yield of **3a** was increased to 33%, 35% and 37%, respectively (Table 1, entries 2-4). Other solvents such as CH_3CN, dioxane, CH_3NO_2, and THF led to poor yields of **3a**. Different reaction temperatures were also screened. It was found that 140 °C was the optimal reaction temperature, which resulted **3a** in 55% LC-yield (Table 1, entry 6). Further screening of different ratios of **1a**: **2a** revealed that the ratios of **1a**: **2a** = 1:1.5 could improve the LC-yield of **3a** to 88% (83% isolated yield). Therefore, the optimal reaction condition was determined to be **1a** (0.5 mmol), **2a** (0.75 mmol) in DMF at 140 °C.

Table 1. Optimization of reaction conditions[a]

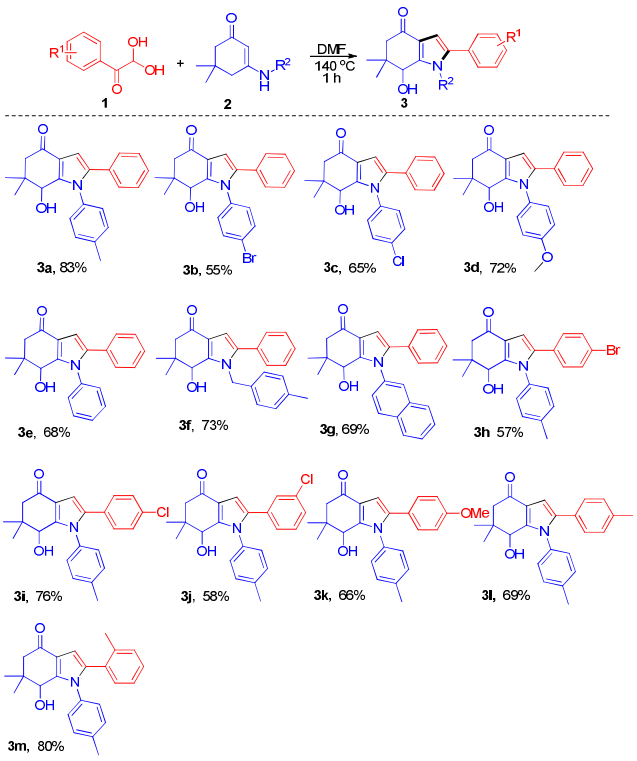


entry	**1a**:**2a**	solvent	T (°C)[b]	time(h)	yield (%)[c]
1	1:1	CH_2Cl_2	80	2	24
2	1:1	DMA	80	2	33
3	1:1	DMSO	80	2	35
4	1:1	DMF	80	2	37
5	1:1	DMF	120	2	49
6	1:1	DMF	140	2	55
7	1:1	DMF	reflux	2	51
8	1:1	DMF	140	0.5	48
9	1:1	DMF	140	1	57
10	1:1.2	DMF	140	1	60
11	1:1.5	DMF	140	1	88(83[d])
12	1:2	DMF	140	1	49

[a]Reaction conditions: **1a** (0.5 mmol), **2a**, solvent (2.5 mL). [b]The temperature of the reaction in solvent. [c]Yields were determined by LC analysis with biphenyl (0.5 mmol) as the internal standard. [d]Isolated yield.

With the optimized conditions in hand, reactions were carried out with a variety of 2,2-dihydroxy-1-phenylethanone **1** and 5,5-dimethyl-3-(p-tolylamino)cyclohex-2-enones **2**. All the reactions proceeded smoothly to afforded the desired products in moderate to good yields and the results were summarized in Table 2. Generally, enamines bearing either electron-withdrawing or electron-donating substituents reacted with **1a** favorably to give the products in moderate to good yields under the reaction conditions (**3a-g**). The reaction of 5,5-dimethyl-3-(naphthalen-2-ylamino)cyclohex-2-enone **2g** with **1a** could also led to the desired product **3g** in 69% yield. To our delight, the desired products were obtained in moderate to good yields when arylglyoxals with diverse substituents (such as bromo, chloro , methyl and methoxy) reacted with enamines **2a** under the reaction condition to yield (**3h-m**).

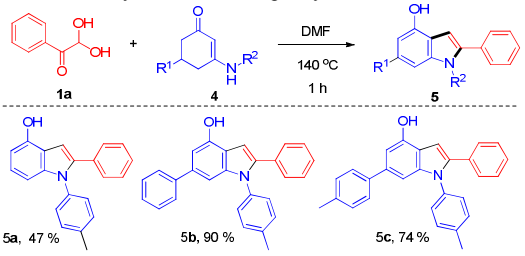
Table 2. Synthesis of 7-hydroxy-6,6-dimethyl-6,7-dihydro-1*H*-indol-4(5*H*)-one **3** [a,b]



[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75mmol) in DMF (2.5 mL), 140 °C for 1 hour. [b]Isolated yield.

As anticipated, the reaction of **1a** and 3-(phenylamino)cyclohex-2-enone **4a** led to the formation of 2-phenyl-1-(p-tolyl)-1*H*-indol-4-ol of **5a** in 47% yield under the same reaction condition (Table 3). We then investigated the scope of 3-(p-tolylamino)cyclohex-2-enone under the unanimous conditions. The reaction of 5-(p-tolylamino)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one **4b** with **1a** afforded the desired product **5b** in 90% yield, whereas 4'-methyl substituted **4c** gave the expected product **5c** in 74% yield.

Table 3. Synthesis of 1,2-diphenyl-1*H*-indol-4-ol **5** [a,b]



[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75mmol) in DMF (2.5 mL), 140 °C for 1 hour. [b]Isolated yield.

It is well known that arylglyoxals could be prepared by treating the corresponding methyl ketones with excess iodine in DMSO.[17] We thus reasoned that arylglyoxals could be generated in situ from ketones and subjected to the reactions with enamine **2** to construct **3**. As such, we move on to optimize iodine-promoted one pot-two step reactions of methyl ketone **6a** with enamine **2a** in DMSO (see the supporting information for details). To our delight, the reaction of acetophenone (**6a** , 0.5 mmol) and

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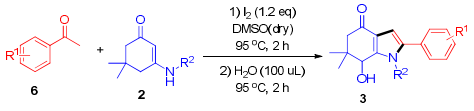
enamine (**2a** , 0.6 mmol) with I_2 (0.6 mmol) also led to the desired product **3a** in 58% yield at 95 °C for 4 h with 100 μL H_2O in DMSO (Table S2, entry 1). With this successful result in hand, the scope of substituted aryl methyl ketones and enamines were investigated (Details see supporting information). The reactants with electron-withdrawing or electron-donating group on the aryl ring, such as methyl, methoxy, chloro, bromo groups on either the enaminone or acetophenone ring, also resulted in the desired product **3** in moderate yields (Table S2, entries 2-9).

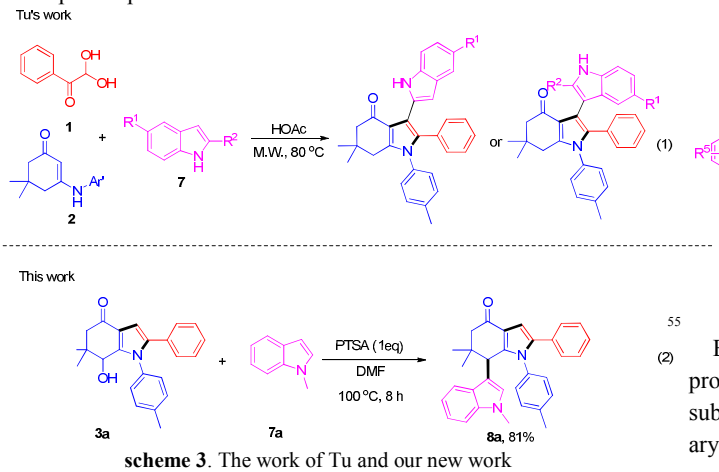
Scheme 2. Synthesis of 7-hydroxy-6,6-dimethyl-6,7-dihydro-1*H*-indol-4(5*H*)-one **3** from differents acetophenone and enamines[a,b]



[a]Reaction conditions: **6** (0.5 mmol) , **2** (0.6 mmol) , I_2 (0.6 mmol), and H_2O (100 μL) in DMSO (2 mL) at 95 °C for 4 hours. [b]Isolated yield.

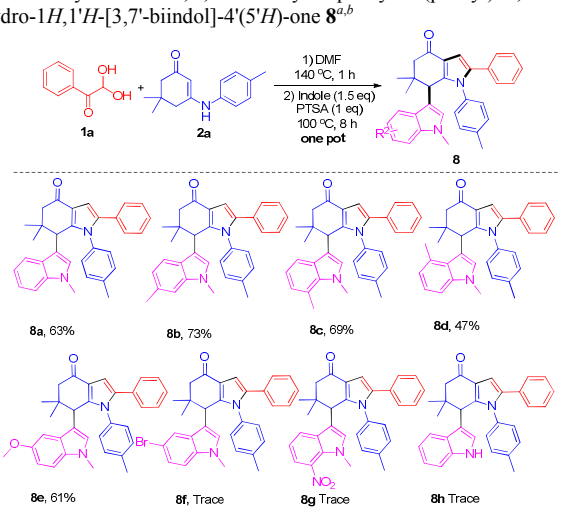
Recently, Tu and coworkers reported a microwave-assisted domino reaction of arylglyoxal monohydrate, diverse N-aryl enaminones, and indoles to furnish 3,2-bis-indoles and 3,3-bis-indoles (Scheme 3, eq. 1).[14] With hydroxy-2-aryl-6,7-dihydro-indol-4(5*H*)-ones **3** in hand, we further investigated the reaction between 7-hydroxy-6,6-dimethyl-2-phenyl-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one **3a** and 1-methyl-1*H*-indole **7a**. To our delight, the presence of 1equiv PTSA improve the yield of 2'-aryl-6',7'-dihydro-[3,7'-biindol]-4'(5'*H*)-ones **8a** to 81% (Scheme 3, eq. 2).

Next, we tried the one pot-two steps domino reactions of arylglyoxals **1a** with enamines **2a**, followed by indoles **7** to construct 3,7'-bis-indoles **8** based on the above optimal reaction conditions. As expected, **8a** was obtained in 63% yield by this one pot-two steps domino synthetic approach. We then investigated the scope of 1-methyl-1*H*-indole **7** under the identical conditions (Table 5). The indole **7** with electron-donating group on the indole ring afforded the expected product **8b, 8c, 8d** and **8e** in 73%, 69%, 47% and 61% yields, respectively. Unfortunately, N-H indole gave only a trace amount of desired product **8h**, likely due to the electron poor nature of N-H indole. Electron withdrawing groups substituted on the indole ring such as bromo and nitro groups, also gave trace amount of the expected products.



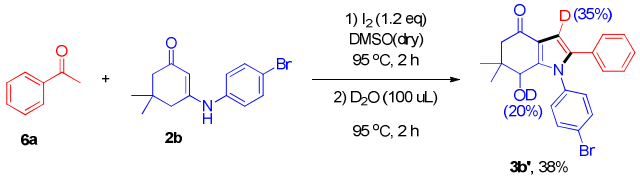
scheme 3. The work of Tu and our new work

Table 5. Synthesis of 1,6',6'-trimethyl-2'-phenyl-1'-(p-tolyl)-6',7'-dihydro-1*H*,1'*H*-[3,7'-biindol]-4'(5'*H*)-one **8**[a,b]

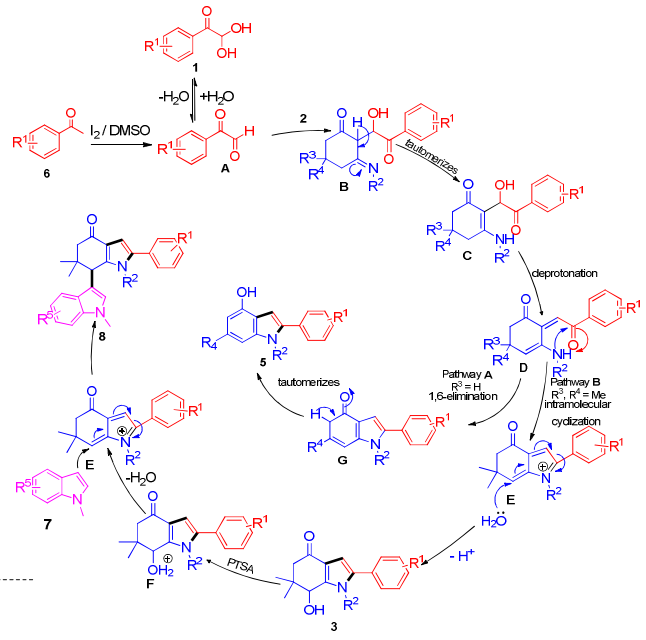


[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol) in DMF (2.5 mL) at 140 °C for 1 hours. PTSA (0.5 mmol), Indole (0.75 mmol), 100 °C, 8 h. For details, see the typical experimental procedure (**8a-e**). [b]Isolated yield.

To better understand the mechanism of the reaction, the reaction of **6a** and **2b** was carried out in DMSO(dry) in the presence of 1.2 equiv I_2 and D_2O (100 μL). It was found that the deuterated product **3b'** could be isolated in 38% yield (scheme 4).



Scheme 4. **6a** (0.5 mmol) , **2b** (0.6 mmol) , I_2 (0.6 mmol), and D_2O (100 μL) in DMSO (2 mL) at 95 °C for 4 hours. [b]Isolated yield.



Scheme 5. A plausible mechanism.

Based on the above results and the literature reports,[13-19] we proposed a possible reaction mechanism (Scheme 5). First, the substituted aryl methyl ketones **6** reacts with I_2 in DMSO to give arylglyoxal **A**. Enamines **2** or **4** reacts with **A** to afford the

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intermediate **B** following a consecutive tautomerization to furnish intermediate **C**. After deprotonation of intermediate **C**, the intermediate enamino-ketone **D** is formed. When R^3 = H, 1,6-elimination of water results in the intermediate **G**, following a subsequent tautomerization to give aromatized compound **5** (Scheme 5, Pathway A). When R^3, R^4 = Me, intramolecular cyclization of the intermediate **D** furnish **E** and subsquently nucleophilic attack of water leds to **3** (Scheme 5, Pathway B). In the presence of PTSA, **3** is transformed to furnish the intermediate **E**, following the reaction with indoles to afford 3,7'-bis-indole **8.**

Conclusions

In summary, we have developed the domino reactions of different arylglyoxals **1** with enamines **2** under catalyst-free conditions and the iodine-promoted one pot two step reactions of methyl ketones **6** with enamines **2** to construct hydroxy-2-aryl-6,7-dihydro-indol-4(5*H*)-ones **3** in up to 83% yield and 58% yield, respectively. The reaction of **3** with indoles in the presence of PTSA afforded 2'-aryl-6',7'-dihydro-[3,7'-biindol]-4'(5'*H*)-ones **8** in 81% yield. In addition, 3,7'-bis-indoles **8** could also be observed in 47-73% yields by one pot domino reaction of arylglyoxals **1** with enamines **2** and indoles **7** over two steps. This protocol provides a simple practical method to construct diverse 7-hydroxy-6,7-dihydro-indole derivatives **3** and 3,7'-bis-indoles **8** from easily obtained starting materials.

Experimental

General

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All reactions were carried out in air and using undistilled solvent, without any precautions to exclude air and moisture unless otherwise noted. Melting points were recorded on an Electrothermal digital melting point apparatus and were uncorrected. IR spectra were recorded on a spectrophotometer using KBr optics. ^{1}HNMR and ^{13}CNMR spectra were recorded on a 400 MHz (^{1}HNMR) and 100 MHz (^{13}CNMR) spectrumeter using $CDCl_3$, DMSO-d6 as solvent and TMS as internal standard. High resolution mass spectra were obtained using a high resolution ESI-TOF mass.

General procedure for the preparation of the 7-hydroxy-6,6-dimethyl-2-phenyl-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one derivatives 3 (3a as an example):

A mixture of arylglyoxal **1a** (0.5 mmol) and enamine **2a** (0.75 mmol) was stirred at 140 °C in DMF (2.5 mL) for 1 h and the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was diluted with 10 mL of ethyl acetate and washed with 10 mL of brine. The aqueous layer was extracted with ethyl acetate (10 mL x 2). The organic layer was combined and dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=10:1) to yield the desired product **3a** as a yellow solid (143 mg, 83% yield) .

General procedure for the preparation of the 7-hydroxy-6,6-dimethyl-2-phenyl-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one derivatives from different substituted aryl methyl ketones and enaminone (3a-b, 3d, 3g, 3h-m, 3a as an example):

A mixture of acetophenone **6a** (0.5 mmol) and I_2 (0.6 mmol) was stirred at 95 °C in DMSO (2 mL) for 2 h. After cooling to the room temperature, H_2O (100 uL), enaminone **2a** (0.6 mmol) were added and further stirred at 95 °C for 2 h. Then the resulting mixture was diluted with 10 mL of ethyl acetate and washed with 10 mL of sodium thiosulfate saturated solution. The aqueous layer was extracted with ethyl acetate (10 mL x 2). The organic layer was combined and dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=10:1) to yield the desired product **3a** as a yellow solid (100 mg, 58% yield).

General procedure for the preparation of the 1,2-diphenyl-1*H*-indol-4-ol derivatives 5 (5a as an example):

A mixture of arylglyoxal **1a** (0.5 mmol) and enamine **4a** (0.75 mmol) was stirred at 140 °C in DMF (2.5 mL) for 1 h and the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was diluted with 10 mL of ethyl acetate and washed with 10 mL of brine. The aqueous layer was extracted with ethyl acetate (10 mL x 2). The organic layer was combined and dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=20:1) to yield the desired product **5a** as a purple solid (70 mg, 47% yield).

General procedure for the preparation of the 1,6',6'-trimethyl-2'-phenyl-1'-(p-tolyl)-6',7'-dihydro-1*H*,1'*H*-[3,7'-biindol]-4'(5'*H*)-one derivatives 8 (8a as an example):

A mixture of arylglyoxal **1a** (0.5 mmol) and enamine **2a** (0.75 mmol) was stirred at 140 °C in DMF (2.5 mL) for 1 h. The reaction mixture was then cooled to room temperature, followed by addition of 1-methyl-1*H*-indole **7** (0.75 mmol) and PTSA (0.5 mmol). Then, the mixture was stirred for 8 h at 100 °C monitored by TLC. The resulting mixture was diluted with 10 mL of ethyl acetate and washed with 10 mL of brine. The aqueous layer was extracted with ethyl acetate (10 mL x 2). The organic layer was combined and dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc=8:1) to yield the desired product **8a** as a yellow solid (144 mg, 63% yield).

7-hydroxy-6,6-dimethyl-2-phenyl-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one(3a): yellow solid (143 mg, 83%). m. p.: 178-180 ºC. **IR** (neat, v, cm-1): 3065, 2961, 2878, 1714, 1606, 745, 726, 693 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.30 – 7.15 (m, 6H), 7.11 (d, *J* = 6.9 Hz, 3H), 6.63 (s, 1H), 5.39 (d, *J* = 7.3 Hz, 1H), 3.84 (d, *J* = 7.1 Hz, 1H), 2.78 (d, *J* = 16.4 Hz, 1H), 2.35 (s, 3H), 1.98 (d, *J* = 16.4 Hz, 1H), 1.03 (s, 3H), 0.87 (s, 3H).

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^{13}CNMR (101 MHz, DMSO) δ 193.4, 146.0, 138.4, 136.8, 134.9, 132.1, 130.2, 128.7, 128.5, 128.2, 127.5, 119.5, 105.2, 68.0, 47.2, 26.4, 25.9, 21.1. **HRMS (ESI-TOF)** Calcd for $C_{23}H_{24}NO_2^+$ ([M+H]$^+$) 346.1807. Found 346.1811.

1-(4-bromophenyl)-7-hydroxy-6,6-dimethyl-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one(3b): yellow solid (112 mg, 55%). m. p.: 153-155 ºC. **IR** (neat, ν, cm^{-1}): 3372, 2958, 1649, 1600, 1522, 763, 696, 673 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.66 (d, *J* = 5.1 Hz, 2H), 7.33 – 7.17 (m, 4H), 7.12 (d, *J* = 6.8 Hz, 3H), 6.64 (s, 1H), 5.45 (d, *J* = 7.3 Hz, 1H), 3.89 (d, *J* = 7.1 Hz, 1H), 2.76 (d, *J* = 16.3 Hz, 1H), 2.00 (d, *J* = 16.0 Hz, 1H), 1.03 (s, 3H), 0.89 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.4, 145.8, 136.8, 132.7, 131.7, 130.6, 128.9, 128.6, 127.7, 122.0, 119.8, 105.5, 68.0, 47.3, 26.2, 25.9. **HRMS (ESI-TOF)** Calcd for $C_{22}H_{21}BrNO_2^+$ ([M+H]$^+$) 410.0756. Found 410.0760.

1-(4-chlorophenyl)-7-hydroxy-6,6-dimethyl-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one(3c): yellow solid (119 mg, 65%). m. p.: 139-141 ºC. **IR** (neat, ν, cm-1): 2955, 2852, 1726, 1633, 1556, 762, 695, 638 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.66 (d, *J* = 5.1 Hz, 2H), 7.35 – 7.01 (m, 7H), 6.64 (s, 1H), 5.45 (d, *J* = 7.3 Hz, 1H), 3.89 (d, *J* = 7.1 Hz, 1H), 2.76 (d, *J* = 16.3 Hz, 1H), 2.00 (d, *J* = 16.0 Hz, 1H), 1.03 (s, 3H), 0.89 (s, 3H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 194.1, 144.0, 137.6, 135.8, 134.4, 131.3, 129.5, 129.2, 128.5, 128.4, 127.5, 120.1, 105.9, 69.3, 46.8, 39.5, 29.7, 25.8, 16.3. **HRMS (ESI-TOF)** Calcd for $C_{22}H_{21}ClNO_2^+$ ([M+H]$^+$) 366.1261. Found 366.1262.

7-hydroxy-1-(4-methoxyphenyl)-6,6-dimethyl-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one(3d): yellow solid (130 mg, 72%). m. p.: 149-151 ºC. **IR** (neat, ν, cm-1): 3068, 2963, 2873, 1719, 1606, 741, 724, 691 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.29 – 7.15 (m, 4H), 7.12 (d, *J* = 6.7 Hz, 2H), 7.00 (s, 3H), 6.62 (s, 1H), 5.37 (d, *J* = 7.4 Hz, 1H), 3.83 (d, *J* = 7.3 Hz, 1H), 3.79 (s, 3H), 2.76 (d, *J* = 16.4 Hz, 1H), 1.98 (d, *J* = 16.3 Hz, 1H), 1.03 (s, 3H), 0.88 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ193.4, 159.3, 146.1, 136.9, 132.1, 130.1, 129.7, 128.7, 128.4, 127.5, 119.3, 114.8, 104.9, 68.0, 55.8, 47.2, 26.4, 25.9. **HRMS (ESI-TOF)** Calcd for $C_{23}H_{24}NO_3^+$ ([M+H]$^+$)362.1756. Found 362.1758.

7-hydroxy-6,6-dimethyl-1,2-diphenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one(3e): yellow solid (113 mg, 68%). m. p.: 162-163 ºC. **IR** (neat, ν, cm-1): 3298, 2972, 2956, 2887, 1716, 1698, 1684, 1576, 737, 665 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.45 (s, 4H), 7.20 (d, *J* = 6.5 Hz, 4H), 7.09 (d, *J* = 6.6 Hz, 2H), 6.64 (s, 1H), 5.43 (d, *J* = 7.3 Hz, 1H), 3.85 (d, *J* = 7.1 Hz, 1H), 2.77 (d, *J* = 16.4 Hz, 1H), 1.99 (d, *J* = 16.3 Hz, 1H), 1.03 (s, 3H), 0.88 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.4, 145.9, 137.4, 136.8, 132.0, 129.7, 128.9, 128.7, 128.5, 128.5, 127.6, 119.5, 105.3, 68.1, 47.2, 26.4, 25.9. **HRMS (ESI-TOF)** Calcd for $C_{22}H_{22}NO_2^+$ ([M+H]$^+$) 332.1651. Found 332.1658.

7-hydroxy-6,6-dimethyl-1-(4-methylbenzyl)-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one(3f): yellow solid (131 mg, 73%). m. p.: 163-164 ºC. **IR** (neat, ν, cm-1): 2957, 2921, 2869, 1644, 1607, 1561, 760, 718, 677 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.34 (dt, *J* = 10.7, 6.9 Hz, 5H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.78 (d, *J* = 7.9 Hz, 2H), 6.46 (s, 1H), 5.56 (d, *J* = 7.2 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.24 (d, *J* = 17.1 Hz, 1H), 4.07 (d, *J* = 7.0 Hz, 1H), 2.70 (d, *J* = 16.2 Hz, 1H), 2.24 (s, 3H), 2.04 – 1.94 (m, 1H), 1.03 (s, 3H), 0.84 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.0, 144.8, 137.0, 136.7, 135.5, 132.2, 129.6, 129.1, 129.1, 128.3, 125.8, 119.3, 105.0, 68.3, 47.6, 47.4, 26.3, 26.0, 21.1. **HRMS (ESI-TOF)** Calcd for $C_{24}H_{26}NO_2^+$ ([M+H]$^+$) 360.1964. Found 360.1967.

7-hydroxy-6,6-dimethyl-1-(naphthalen-2-yl)-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one(3g): yellow solid (132 mg, 69%). m. p.: 101-102 ºC. **IR** (neat, ν, cm-1): 2955, 2922, 2863, 1644, 1599, 1556, 752, 696, 660 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.99 (s, 4H), 7.60 (s, 3H), 7.16 (s, 5H), 6.71 (s, 1H), 5.47 (s, 1H), 3.97 (d, *J* = 35.0 Hz, 1H), 2.80 (d, *J* = 16.3 Hz, 1H), 2.02 (d, *J* = 16.9 Hz, 1H), 0.97 (d, *J* = 42.4 Hz, 6H). ^{13}CNMR (101 MHz, DMSO) δ 193.5, 146.2, 135.0, 133.1, 132.7, 132.0, 129.4, 128.8, 128.4, 128.2, 127.6, 127.5, 127.4, 126.9, 126.6, 119.7, 105.4, 68.1, 47.3, 45.7, 26.3, 25.9. **HRMS (ESI-TOF)** Calcd for$C_{26}H_{24}NO_2^+$ ([M+H]$^+$) 382.1807. Found 382.1834.

2-(4-bromophenyl)-7-hydroxy-6,6-dimethyl-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one(3h): yellow solid (121 mg, 57%). m. p.: 179-181ºC. **IR** (neat, ν, cm-1): 3354, 2963, 2934, 1672, 1644, 1545, 743, 708, 661 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.49 – 7.18 (m, 5H), 7.05 (d, *J* = 8.1 Hz, 3H), 6.69 (s, 1H), 5.42 (d, *J* = 6.6 Hz, 1H), 3.85 (s, 1H), 2.78 (d, *J* = 16.4 Hz, 1H), 2.36 (s, 3H), 1.99 (d, *J* = 16.4 Hz, 1H), 1.03 (s, 3H), 0.87 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.4, 146.3, 138.5, 135.5, 134.6, 131.7, 131.3, 130.4, 130.3, 128.2, 120.9, 119.6, 105.7, 68.0, 47.2, 26.4, 25.8, 21.2. **HRMS (ESI-TOF)** Calcd for $C_{23}H_{23}BrNO_2^+$ ([M+H]$^+$) 424.0912. Found 424.0902.

2-(4-chlorophenyl)-7-hydroxy-6,6-dimethyl-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one(3i): yellow solid (144 mg, 76%). m. p.: 187-189 ºC. **IR** (neat, ν, cm-1): 3264, 2963, 1673, 1645, 1555, 749, 720, 657 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.28 (d, *J* = 8.5 Hz, 5H), 7.11 (d, *J* = 8.5 Hz, 3H), 6.68 (s, 1H), 5.41 (d, *J* = 7.3 Hz, 1H), 3.84 (d, *J* = 7.2 Hz, 1H), 2.77 (d, *J* = 16.4 Hz, 1H), 2.36 (s, 3H), 1.99 (d, *J* = 16.4 Hz, 1H), 1.03 (s, 3H), 0.87 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.4, 146.2, 138.5, 135.5, 134.6, 132.3, 131.0, 130.3, 130.1, 128.8, 128.2, 119.5, 105.7, 68.0, 47.2, 26.4, 25.8, 21.2. **HRMS (ESI-TOF)** Calcd for$C_{23}H_{23}ClNO_2^+$ ([M+H]$^+$) 380.1417. Found 380.1419.

2-(3-chlorophenyl)-7-hydroxy-6,6-dimethyl-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one(3j): yellow solid (110 mg, 58%). m. p.: 165-167 ºC. **IR** (neat, ν, cm-1): 2957, 2931, 1639, 1597, 1567, 726, 690, 663 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.23 (dd, *J* = 26.7, 21.4 Hz, 7H), 7.03 (d, *J* = 4.3 Hz, 1H), 6.75 (s, 1H), 5.43 (d, *J* = 7.3 Hz, 1H), 3.86 (d, *J* = 7.2 Hz, 1H), 2.78 (d, *J* = 16.4 Hz, 1H), 2.36 (s, 3H), 2.00 (d, *J* = 16.4 Hz, 1H), 1.03 (s, 3H), 0.88 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.4, 146.4, 138.6, 135.1, 134.6, 134.1, 133.4, 130.5, 130.3, 128.2, 128.0, 127.3, 126.9, 119.5, 106.1, 89.4, 68.0, 47.2, 26.4, 25.8, 21.2, 15.9. **HRMS (ESI-TOF)** Calcd for $C_{23}H_{23}ClNO_2^+$ ([M+H]$^+$) 380.1417. Found 380.1419.

7-hydroxy-2-(4-methoxyphenyl)-6,6-dimethyl-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one(3k): yellow solid (124 mg, 66%). m. p.: 198-200 ºC. **IR** (neat, ν, cm-1): 3414, 2969, 1634, 1613, 1560, 732, 691, 675 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.25 (s, 3H), 7.04 (d, *J* = 8.5 Hz, 3H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.53 (s, 1H), 5.36 (d, *J* = 7.3 Hz, 1H), 3.83 (d, *J* = 7.2 Hz, 1H), 3.69 (s, 3H), 2.77 (d, *J* = 16.4 Hz, 1H), 2.35 (s, 3H), 1.97 (d, *J* = 16.0 Hz, 1H), 1.02 (s, 3H), 0.87 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.4, 158.8, 145.5, 138.3, 136.7, 135.0, 130.2, 129.9, 128.3, 124.5, 119.3, 114.2, 104.3, 68.1, 55.5, 47.2, 26.4, 25.9, 21.2. **HRMS (ESI-TOF)** Calcd for $C_{24}H_{26}NO_3^+$ ([M+H]$^+$) 376.1913. Found 376.1914.

7-hydroxy-6,6-dimethyl-1,2-di-p-tolyl-6,7-dihydro-1*H*-indol-4(5*H*)-one(3l): yellow solid (124 mg, 69%). m. p.: 180-182 ºC. **IR** (neat, ν, cm-1): 3372, 2958, 1649, 1600, 1555, 763, 637 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.25 (s, 3H), 7.01 (d, *J* = 2.6 Hz, 5H), 6.58 (s, 1H), 5.38 (s, 1H), 3.84 (s, 1H), 2.77 (d, *J* = 16.4 Hz, 1H), 2.35 (s, 3H), 2.22 (s, 3H), 1.98 (d, *J* = 16.4 Hz, 1H), 1.03 (s, 3H), 0.87 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.4, 145.8, 138.3, 136.9, 134.9, 130.2, 129.3, 129.3, 128.4, 128.2, 119.4, 104.71, 68.1, 47.2, 26.4, 25.9, 21.1, 21.1. **HRMS (ESI-TOF)** Calcd for $C_{24}H_{26}NO_2^+$ ([M+H]$^+$) 360.1964. Found 360.1960.

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7-hydroxy-6,6-dimethyl-2-(o-tolyl)-1-(p-tolyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one(3m): yellow solid (144 mg, 80%). m. p.: 95-96 ºC. **IR** (neat, ν, cm-1): 3332, 2956, 1642, 1557, 761, 681, 638 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 7.18 – 7.02 (m, 8H), 6.42 (s, 1H), 5.41 (d, *J* = 7.5 Hz, 1H), 3.88 (d, *J* = 7.5 Hz, 1H), 2.79 (d, *J* = 16.5 Hz, 1H), 2.27 (s, 3H), 2.07 (s, 3H), 1.99 (d, *J* = 16.4 Hz, 1H), 1.04 (s, 3H), 0.89 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.5, 144.6, 137.9, 137.6, 135.8, 134.6, 132.0, 131.7, 130.3, 129.8, 128.7, 128.6, 127.7, 125.8, 119.1, 105.7, 68.2, 47.3, 39.7, 26.4, 25.9, 21.0, 20.5. **HRMS (ESI-TOF)** Calcd for $C_{24}H_{26}NO_2^+$ ([M+H]$^+$) 360.1964. Found 360.1960.

2-phenyl-1-(p-tolyl)-1*H*-indol-4-ol (5a): purple solid (70 mg, 47%). m. p.: 125-127 ºC. **IR** (neat, ν, cm-1): 2970, 2925, 2869, 1660, 1603, 1555, 753, 711, 655 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 9.64 (s, 1H), 7.34 – 7.19 (m, 7H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.91 (dd, *J* = 20.5, 12.6 Hz, 2H), 6.59 (d, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 2.35 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 151.1, 141.2, 138.7, 137.3, 136.2, 130.4, 128.8, 128.8, 128.1, 127.6, 123.9, 118.3, 105.2, 102.2, 101.3, 100.4, 21.1. **HRMS (ESI-TOF)** Calcd for $C_{21}H_{18}NO^+$ ([M+H]$^+$) 300.1388. Found 300.1393.

2,6-diphenyl-1-(p-tolyl)-1*H*-indol-4-ol(5b): green solid (169 mg, 90%). m. p.: 136-138 ºC. **IR** (neat, ν, cm-1): 3450, 3120, 1586, 1571, 761, 658 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.38 (dd, *J* = 10.4, 4.8 Hz, 2H), 7.30 – 7.21 (m, 8H), 7.18 – 7.13 (m, 2H), 7.06 (s, 1H), 6.85 – 6.83 (m, 2H), 2.40 (s, 3H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 148.8, 142.1, 141.4, 140.4, 137.3, 137.1, 135.8, 132.5, 130.0, 128.8, 128.6, 128.2, 127.8, 127.4, 127.3, 126.75, 117.1, 104.9, 102.7, 99.4, 21.2. **HRMS (ESI-TOF)** Calcd for $C_{27}H_{22}NO^+$ ([M+H]$^+$) 376.1701. Found 376.1701.

2-phenyl-1,6-di-p-tolyl-1*H*-indol-4-ol(5c): green solid (144 mg, 74%). m. p.: 200-201 ºC. **IR** (neat, ν, cm-1): 3540, 3103, 2875, 1585, 1515, 761, 725, 650 cm^{-1}. ^{1}HNMR (400 MHz, DMSO) δ 9.82 (s, 1H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.33 – 7.13 (m, 11H), 6.91 (s, 1H), 6.80 (d, *J* = 2.0 Hz, 2H), 2.35 (s, 3H), 2.30 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 151.3, 141.7, 139.3, 139.1, 137.4, 136.6, 136.3, 136.1, 132.6, 130.5, 129.8, 128.8, 128.7, 128.1, 127.7, 126.9, 117.7, 104.5, 101.3, 100.3, 21.2, 21.1. **HRMS (ESI-TOF)** Calcd for $C_{28}H_{24}NO^+$ ([M+H]$^+$) 390.1858. Found 390.1848.

1,6',6'-trimethyl-2'-phenyl-1'-(p-tolyl)-6',7'-dihydro-1*H*,1'*H*-[3,7'-biindol]-4'(5'*H*)-one (8a): yellow solid (144 mg, 63%). m. p.: 198-199 ºC. **IR** (neat, ν, cm-1): 2951, 2926, 1656, 1604, 761, 641 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 20.7, 13.4 Hz, 4H), 7.07 – 6.89 (m, 8H), 6.79 (s, 2H), 6.55 (s, 1H), 3.72 (s, 1H), 3.63 (s, 3H), 2.83 – 2.64 (m, 1H), 2.13 (s, 3H), 2.06 (d, *J* = 17.1 Hz, 1H), 1.17 (s, 3H), 0.73 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 192.5, 169.5, 140.6, 138.9, 138.0, 134.3, 133.3, 131.6, 130.6, 130.2, 129.7, 129.0, 128.7, 128.6, 128.4, 128.1, 127.9, 121.1, 105.1, 69.0, 60.2, 48.2, 39.1, 26.0, 25.364, 21.172, 20.8. **HRMS (ESI-TOF)** Calcd for $C_{32}H_{31}N_2O^+$ ([M+H]$^+$) 459.2436. Found 459.2438.

1,6,6',6'-tetramethyl-2'-phenyl-1'-(p-tolyl)-6',7'-dihydro-1*H*,1'*H*-[3,7'-biindol]-4'(5'*H*)-one(8b): yellow solid (172 mg, 73%). m. p.: 227-228 ºC. **IR** (neat, ν, cm-1): 2956, 2921, 1661, 1602, 1550, 760, 642 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.99 (dt, *J* = 5.9, 5.4 Hz, 9H), 6.83 – 6.71 (m, 3H), 6.47 (s, 2H), 3.68 (s, 1H), 3.58 (s, 3H), 2.77 (d, *J* = 17.1 Hz, 1H), 2.40 (s, 3H), 2.14 (s, 3H), 2.04 (d, *J* = 15.8 Hz, 1H), 1.15 (s, 3H), 0.72 (s, 3H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 194.7, 137.8, 137.3, 136.4, 134.9, 132.0, 131.3, 129.4, 128.1, 127.9, 127.8, 127.5, 127.2, 126.7, 125.8, 120.8, 118.9, 113.0, 109.1, 105.2, 60.4, 39.3, 32.8, 28.5, 28.4, 21.9, 21.1, 14.2. **HRMS (ESI-TOF)** Calcd for $C_{33}H_{33}N_2O^+$ ([M+H]$^+$) 473.2593. Found 473.2588.

1,6',6',7-tetramethyl-2'-phenyl-1'-(p-tolyl)-6',7'-dihydro-1*H*,1'*H*-[3,7'-biindol]-4'(5'*H*)-one(8c): purple solid (163 mg, 69%). m. p.: 183-185 ºC. **IR** (neat, ν, cm-1): 2951, 2925, 1660, 1602, 759, 642 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.01 (dt, *J* = 7.2, 4.4 Hz, 8H), 6.78 (t, *J* = 6.5 Hz, 5H), 6.45 (s, 1H), 3.91 (s, 3H), 3.68 (s, 1H), 2.78 (d, *J* = 17.1 Hz, 1H), 2.69 (s, 3H), 2.16 (s, 3H), 2.05 (d, *J* = 17.1 Hz, 1H), 1.15 (s, 3H), 0.72 (s, 3H). ^{13}CNMR (101 MHz, DMSO) δ 193.0, 137.8, 136.0, 135.4, 134.9, 132.1, 129.8, 129.0, 128.6, 128.1, 127.2, 124.0, 121.3, 119.1, 117.1, 111.8, 105.3, 48.2, 36.6, 31.4, 28.3, 28.1, 22.5, 21.0, 19.7, 14.4. **HRMS (ESI-TOF)** Calcd for $C_{33}H_{33}N_2O^+$ ([M+H]$^+$) 473.2593. Found 473.2591.

1,4,6',6'-tetramethyl-2'-phenyl-1'-(p-tolyl)-6',7'-dihydro-1*H*,1'*H*-[3,7'-biindol]-4'(5'*H*)-one(8d): purple solid (111 mg, 47%). m. p.: 184-186 ºC. **IR** (neat, ν, cm-1): 2851, 1657, 1600, 1552, 738,671 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.09 – 6.92 (m, 9H), 6.77 (s, 2H), 6.68 – 6.60 (m, 2H), 6.46 (s, 1H), 4.11 (s, 1H), 3.63 (s, 3H), 2.83 (d, *J* = 17.3 Hz, 1H), 2.33 (s, 1H), 2.17 (s, 3H), 2.00 (s, 3H), 1.18 (s, 3H), 0.70 (s, 3H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 194.5, 150.2, 138.3, 137.1, 136.4, 135.1, 132.0, 130.4, 128.4, 128.1, 128.0, 127.9, 127.8, 126.7, 126.1, 121.4, 121.4, 118.8, 113.8, 107.3, 104.8, 48.0, 41.2, 39.1, 33.0, 28.6, 27.7, 21.0, 20.7. **HRMS (ESI-TOF)** Calcd for $C_{33}H_{33}N_2O^+$ ([M+H]$^+$) 473.2593 . Found 473.2602.

5-methoxy-1,6',6'-trimethyl-2'-phenyl-1'-(p-tolyl)-6',7'-dihydro-1*H*,1'*H*-[3,7'-biindol]-4'(5'*H*)-one(8e): purple solid (149 mg, 61%). m. p.: 158-160ºC. **IR** (neat, ν, cm-1): 2951, 2942, 1658, 1511, 1420, 769, 643 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.24 – 7.00 (m, 8H), 6.89 (s, 3H), 6.63 (d, *J* = 20.0 Hz, 3H), 3.87 – 3.62 (m, 7H), 2.89 (d, *J* = 17.1 Hz, 1H), 2.34 – 2.02 (m, 4H), 1.29 (s, 3H), 0.85 (s, 3H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 194.6, 153.8, 149.7, 137.8, 136.4, 134.9, 132.2, 132.0, 129.4, 128.2, 128.1, 127.9, 127.8, 127.6, 126.7, 118.9, 112.7, 111.8, 109.8, 105.1, 100.8, 55.9, 47.9, 41.2, 39.3, 33.0, 28.4, 28.2, 21.0. **HRMS (ESI-TOF)** Calcd for $C_{33}H_{33}N_2O_2^+$ ([M+H]$^+$) 489.2542. Found 489.2540.

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Notes and references

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1 W. A. Remers and M. J. Weiss, *J. Org. Chem*., 1965, **30**, 5232.
2 C. F. Masaguer and E. Ravina, *Tetrahedron Lett*., 1996, **37**, 5171.
3 (*a*) L. Chacon-Garcia and R. Martinez, *J. Med. Chem*., 2002, **37**, 261; (*b*) L. Chun-chatprasert and P. V. R. Shannon, *J. Chem. Soc. Perkin Trans. 1*., 1996, 1787.
4 C. L. Shaffer, M. Gunduz, T. N. O'Connell, R. S. Obach and S. Yee, *Drug Metab. Dispos*., 2005, **33**, 1688.

View Article Online
DOI: 10.1039/C5RA09478J

5 L. Sun, N. Tran, C. Liang, S. Hubbard, F. Tang, K. Lipson, R. Schreck , Y. Zhou, G. McMahon and C. Tang, *J. Med. Chem*., 2000, **43**, 2655.
6 A. Fluxe, S. Wu, J. B. Sheffer, J. M. Janusz, M. Murawsky, G. M. Fadayel, B. Fang and M. Hare, *Bioorg. Med. Chem. Lett*., 2006, **16**, 5855.
7 S. Naruto, J. Sugano, Y. Ueda, T. Kaneko and Y. Kumagai. Jpn. Jp 07133274A, 19950523. Kokai Tokkyo Koho (1995).
8 (*a*) W. A. Remers, R. H. Roth and M. J. Weiss, *J. Med. Chem*., 1971, **14**, 860; (*b*) W. A. Remers, R. H. Roth, G. J. Gibs and M. J. Weiss, *J. Org. Chem*., 1971, **36,** 1232
9 (*a*) D. R. Hutchison, N. K. Nayyar and M. J. Martinelli, *Tetrahedron Lett*., 1996, **37**, 2887; (*b*) N. K. Nayyar and D. R. Hutchison, M. J. Martinelli, *J. Org. Chem*., 1997, **62**, 982.
10 Y. Aoyagi, T. Mizusaki, M. Shishikura, T. Komine, T. Yoshinaga, H. Inaba, A. Ohta and K. Takeya, *Tetrahedron.* 2006, **62**, 8533.
11 E. Bellur and P. Langer, *Tetrahedron Lett*., 2006, **47**, 2151.
12 H. M. C. Ferraz, F. L. C. Pereira and F. S. Leite, *Tetrahedron*. 1999, **55**, 10915.
13 (*a*) B. Jiang, Q.-Y. Li, S.-J. Tu and G.-G. Li, *J. Org. Chem*., 2012, **77**, 7497; (*b*) B. Jiang, M.-S. Yi, F. Shi, S.-J. Tu, S. Pindi, P. McDowell and G.-G. Li, *Chem. Commun*., 2012, **48**, 808.
14 L.-P. Fu, Q.-Q. Shi, Y. Shi, B. Jiang and S.-J. Tu, *ACS Comb. Sci*., 2013, **15**, 135.
15 S. Maity, S. Pathak and A. Pramanik, *Eur. J. Org. Chem*., 2013, **6**, 2479.
16 S. Maity, A. Pramanik, *Synthesis*., 2013, **45**, 2853.
17 (*a*) Y.-P. Zhu, M-C. Liu, F.-C. Jia and A.-X. Wu, *Org. Lett*., 2012, **14**, 3392; (*b*) Y-P. Zhu, F-C. Jia, M-C. Liu and A.-X. Wu, *Org. Lett*., 2012, **14**, 4414; (*c*) W.-J. Xue, Y.-Q. Guo, F.-F. Gao and A.-X. Wu, *Org. Lett*., 2013, **15**, 890; (*d*) Q.-G. Gao, J.-J. Zhang, X. Wu and A.-X. Wu, *Org. Lett*., 2015, **17**, 134.
18 H.-Y. Wang and D.-Q. Shi, *ACS Comb. Sci*., 2013, **15**, 261.
19 W.-J. Hao, S.-Y. Wang and S.-J. Ji, *ACS Catal*., 2013, **3**, 2501.