A catalyst-free and easy nucleophilic addition of certain isatins to sterically hindered 2,6-di-tert-butyl-4-methylenecyclohexa-2,5-dienone

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Abstract
Addition of substituted isatins to 2,6-di-tert-butyl-4-methylenecyclohexa-2,5-dienone, generated in situ from 3,5-di-tert-butyl-4-hydroxybenzyl acetate, to form 1-substituted hydroxybenzyl-isatins, is reported. On the basis of these isatins novel isatin-3-thiosemicarbazones as well as isoindigo derivatives bearing a 2,6-di-tert-butylphenol moiety were obtained. The structures of all novel compounds are confirmed by IR, ^1^H NMR and ^13^C NMR.

Keywords: Isatin, quinone methides, isoindigo, hydrazones, nucleophilic addition

Introduction

Isatin is a synthetically attractive substance due to its versatility in the chemistry of heterocycles.\(^1\)\(^-\)\(^5\) It is often used as a starting point in the synthesis of dyes and biologically active compounds.\(^6\)\(^-\)\(^10\) Isatin derivatives (Figure 1) also find applications in the field of solar energy,\(^11\)\(^-\)\(^13\) organic memory devices\(^14\) and organic field-effect transistors.\(^15\)\(^,\)\(^16\) Nevertheless there are only a few works that deal with investigations of the addition reactions of isatin derivatives with multiple carbon-carbon bonds. Thus, an addition of isatin and some of its derivatives to the C=N bond of isocyanates and C=C bond of diphenylketene to form 1-carbamoylisatins and 1-diphenylacetylisatin respectively, have been described.\(^17\)\(^,\)\(^18\) The presence of an organocatalyst (triphenylphosphine (arsine), triethyl phosphite, DABCO, isocyanides) allows the addition of isatin to double carbon-carbon bonds of fumaric and acrylic esters.\(^19\)\(^-\)\(^24\) In all cases formation of a carbon-nitrogen bond is realized.
Results and Discussion

Herein we report the synthesis of novel isatin derivatives containing sterically hindered 2,6-di-tert-butylphenol fragment. This approach is based on the condensation reaction of substituted isatins 1a-d with 3,5-di-tert-butyl-4-hydroxybenzyl acetate 2 to give corresponding benzylisatins 3a-d with high yields (Scheme 1).

Scheme 1. Synthesis of novel sterically hindered benzylisatins 3a-d.

The reaction proceeds in dipolar aprotic solvents such as DMF or DMSO. These conditions allows in situ generation of the highly reactive p-quinone methide 4 which immediately undergoes addition of corresponding isatin 1a-d with formation of a carbon-nitrogen bond (Scheme 2). It should be noted here that the reaction takes place despite the hindrance due to the methyl group at the 7 position of the isatin heterocycle.
Scheme 2. *In situ* generation of 2,6-di-tert-butyl-4-methylene cyclohexa-2,5-dienone.

Next, on the basis of novel isatins 3a-d we succeeded in obtaining the corresponding isatin-3-thiosemicarbazides 7a-d and acylhydrazones 8a-d (Scheme 3).

Scheme 3. Novel isatin-3-thiosemicarbazones 7a-d and acylhydrazones 8a-d.

The structures of the novel compounds 7a-d and 8a-d were determined by spectroscopic methods (IR, $^1$H and $^{13}$C NMR spectroscopy) and by elemental analyses. The presence of an NH-
proton signal at 12-13 ppm in the $^1$H NMR spectra of compounds 7 and 8 points to the existence of these compounds as $Z_{C=\text{N}}$ – isomers with strong intramolecular N-H-O bond.\textsuperscript{26} (Figure 2)

![cis, Z and trans, Z-isomers of compounds 7a-d and 8a-d.](image)

Figure 2. Representation of cis,Z and trans,Z-isomers of compounds 7a-d and 8a-d.

A doubling of the C(O)CH$_2$, H-4 and N-H – proton signals in $^1$H NMR spectra of compounds 8a-d proves the presence of cis- and trans-forms regarding C(O)-N – fragment\textsuperscript{26} (Table 1). Similar doubling of NH, H-4, H-6 and NH$_2$ – signals in $^1$H NMR spectra also takes place for compound 7c.

Table 1. Selected signals of cis-C(O)-N and trans-C(O)-N – forms of $E_{C=\text{N}}$ – isomers in $^1$H NMR spectra of compounds 8a-d

<table>
<thead>
<tr>
<th>Compd</th>
<th>C(O)CH$_2$, δ, ppm</th>
<th>H-4, δ, ppm</th>
<th>N-H, δ, ppm</th>
<th>cis-trans ratio</th>
</tr>
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<tr>
<td>8a</td>
<td>3.16 2.74</td>
<td>7.44 7.70</td>
<td>12.59 13.13</td>
<td>2.5/1</td>
</tr>
<tr>
<td>8b</td>
<td>3.12 2.72</td>
<td>7.69 7.96</td>
<td>12.51 13.02</td>
<td>3.8/1</td>
</tr>
<tr>
<td>8c</td>
<td>3.10 2.93</td>
<td>7.68 7.96</td>
<td>12.52 13.07</td>
<td>3/1</td>
</tr>
<tr>
<td>8d</td>
<td>3.17 2.73</td>
<td>7.51 7.76</td>
<td>12.58 13.16</td>
<td>2.5/1</td>
</tr>
</tbody>
</table>

In a development of our investigations on the reactivity of 1,2-diketones\textsuperscript{27-30} towards trivalent phosphorus derivatives, isatins 3b-d were treated with tris(diethylamino)phosphine. The reaction proceeds in mild conditions and after the addition of the phosphorus reactant at -60 °C immediately turns dark. Then on spontaneous warming to room temperature the reaction mixture become successively brown, dark-violet, dark-red and finally purple-colored, followed by precipitation of compounds 9b-d (Scheme 4).
Scheme 4. Synthesis of novel sterically-hindered isoindigo derivatives 9b-d.

The structures of novel compounds 9b-d were determined using IR, $^1$H and $^{13}$C NMR spectroscopy. Thus, for example, in compound 9d the most significant observation is the down-field shift of the H-4 signal from 7.51 ppm in the starting isatin 3d to 9.04 ppm in the corresponding isoindigo 9d. Probably this is due to the formation of intramolecular H-C=O bond. Additionally, as a result of deoxygenation and C=C bond formation the signal of the C-3 carbonyl carbon atom at 183.9 ppm shifts to a signal at 133.4 ppm.

Conclusions

In summary, a synthetic method for the preparation of novel highly functionalized benzylisatins was developed. It consists in nucleophilic addition of substituted isatins to an in situ generated highly reactive p-quinone methide. Furthermore, this approach allows access to various isatin-3-thiosemicarbazones and hydrazones as well as isoindigos which are interesting molecules for biological studies and radical-chain oxidation processes inhibitors.

Experimental Section

General. All melting points were measured with a Stuart digital SMP10 apparatus. Solvents were distilled and dried by standard literature procedures prior to use. Elemental analyses for C, H and N were performed using a CHNS-3 analyzer. IR spectra were measured with Bruker Vector-22 spectrometer as suspensions in Nujol. The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance-400 instrument (400 MHz for $^1$H and 100.6 MHz for $^{13}$C). Chemical shifts are
given in ppm (δ) relative to residual DMSO or CHCl₃ signals. Isatin derivatives 1a-d were prepared by known synthetic procedures.³¹⁻³³

Preparation of N-substituted 3,5-di-tert-butyl-4-hydroxybenzylindoline-2,3-diones 3a-c. A mixture of substituted isatin 1a-c (10 mmol), 3,5-di-tert-butyl-4-hydroxybenzylacetate 2 (1.73 g, 11 mmol) and triethylamine (a few drops) in absolute DMF (10 ml) was stirred under 70 °C for 5 h, and cooled to r.t. Resulted solution was treated with 10% aqueous NaCl (200 ml). Precipitate that formed was filtered off, washed with water and air-dried.

5-Butyl-1-(3,5-di-tert-butyl-4-hydroxybenzyl)indoline-2,3-dione (3a). Dark-orange solid, yield 83%, mp 106-107 °C, IR: (νmax, cm⁻¹): 3639 (OH), 1732 (C=O), 1619, 1595, 1488, 1436, 1336, 1285, 1236, 1179, 1162, 1124, 1026, 886. ¹H NMR (CDCl₃) δH 0.91 (t, 3JHH 8.5 Hz, 3H, CH₃), 1.32 (m, 2H, CH₂), 1.40 (s, 18H, t-Bu), 1.55 (m, 2H, CH₂), 2.56 (t, 2H, CH₂), 4.78 (s, 2H, CH₂), 5.21 (s, 1H, OH), 6.80 (d, 3JHH 8.4 Hz, 1H, H-7), 7.16 (s, 2H, H-10), 7.32 (dd, 3JHH 8.1 Hz, 4JHH 1.3 Hz, 1H, H-6), 7.42 (br s, 1H, H-4). ¹³C NMR (CDCl₃) δC 13.8, 22.1, 30.2, 30.9, 33.3, 34.7, 44.4, 110.7, 117.8, 124.8, 125.0, 125.5, 136.5, 138.1, 138.6, 149.2, 153.6, 158.4, 183.9. Anal. Calcd for C₂₇H₃₅NO₃ (421.26): C, 76.92; H, 8.37; N, 3.32%, Found: C, 76.86; H, 8.27; N, 3.18%.

5-Bromo-1-(3,5-di-tert-butyl-4-hydroxybenzyl)indoline-2,3-dione (3b). Orange solid, yield 92%, mp 178-180 °C, IR: (νmax, cm⁻¹): 3639 (OH), 1736 (C=O), 1604, 1331, 1237, 1178, 1159, 1127, 1033, 837. ¹H NMR (CDCl₃) δH 1.40 (s, 18H, t-Bu), 4.80 (s, 2H, CH₂), 5.24 (s, 1H, OH), 6.80 (d, 3JHH 8.4 Hz, 1H, H-7), 7.12 (s, 2H, H-10), 7.63 (dd, 3JHH 8.4 Hz, 4JHH 2.1 Hz, 1H, H-6), 7.70 (d, 4JHH 2.0 Hz, 1H, H-4). ¹³C NMR (CDCl₃) δC 30.2, 34.3, 44.5, 112.6, 116.5, 118.9, 124.7, 124.8, 128.1, 136.7, 140.3, 149.8, 153.8, 157.5, 182.4. Anal. Calcd for C₂₃H₂₆BrN₀₃ (443.11): C, 62.17; H, 5.90; N, 3.15%, Found: C, 61.96; H, 5.77; N, 3.08%.

5,7-Dibromo-1-(3,5-di-tert-butyl-4-hydroxybenzyl)indoline-2,3-dione (3c). Bright-orange solid, yield 88%, mp 155-157 °C, IR: (νmax, cm⁻¹): 3619 (OH), 1740 (C=O), 1598, 1406, 1360, 1336, 1310, 1275, 1223, 1144, 885. ¹H NMR (CDCl₃) δH 1.40 (s, 18H, t-Bu), 5.20 (s, 1H, OH), 5.32 (s, 2H, CH₂), 7.21 (s, 2H, H-10), 7.68 (dd, 4JHH 2.0 Hz, 1H, H-6), 7.85 (d, 4JHH 2.0 Hz, 1H, H-4). ¹³C NMR (CDCl₃) δC 30.2, 34.3, 44.5, 112.6, 116.5, 118.9, 124.7, 124.8, 128.1, 136.7, 140.3, 149.8, 153.8, 157.5, 182.8. Anal. Calcd for C₂₅H₂₅Br₂N₂O₃ (521.02): C, 52.79; H, 4.82; N, 2.68%, Found: C, 52.66; H, 4.70; N, 2.51%.

7-Methyl-1-(3,5-di-tert-butyl-4-hydroxybenzyl)indoline-2,3-dione (3d). A solution of 7-methylisatin 1d (909 mg, 6 mmol) and 3,5-di-tert-butyl-4-hydroxybenzylacetate 2 (1.58 g, 6 mmol) in DMF (50 ml) was stirred under 70 °C for 5 h and additionally for 5 days at r.t. Then resulted solution was treated with 10% aqueous NaCl (200 ml) followed by extraction with ether (100 ml). Combined organic extracts was rotary evaporated to form 1.54 g (72%) of compound 3d as orange solid, mp 165-168 °C, IR: (νmax, cm⁻¹): 3643 (OH), 1742 (C=O), 1725 (C=O), 1602, 1437, 1365, 1345, 1248, 1212, 1171, 1155, 1051, 769. ¹H NMR (CDCl₃) δH 1.37 (s, 18H, t-Bu), 2.36 (s, 3H, CH₃), 5.08 (s, 2H, CH₂), 5.15 (s, 1H, OH), 7.00 (m, 1H, H-5), 7.01 (s, 2H, H-10), 7.28 (d, 3JHH 7.7 Hz, 1H, H-6), 7.51 (d, 3JHH 7.4 Hz, 1H, H-4). ¹³C NMR (CDCl₃) δC 18.8, 30.2,
General procedure for the synthesis of substituted 1-(3,5-di-tert-butyl-4-hydroxybenzyl)-indoline-2,3-dione 3-thiosemicarbazones 7a-d. A mixture of substituted isatin 3a-d (10 mmol), thiosemicarbazide hydrochloride 5 (75 mg, 12 mmol) and triethylamine (0.05 ml, 0.4 mmol) in ethanol (10 ml) was stirred at 80 °C for 6 h, then cooled to r.t. The precipitate was collected by filtration, washed with ethanol (25 ml) and air-dried to give 7.

5-Butyl-1-(3,5-di-tert-butyl-4-hydroxybenzyl)indoline-2,3-dione 3-thiosemicarbazone (7a). Yellow solid, yield 52%, mp 208 °C, IR: (υ_max, cm⁻¹): 3577 (OH), 3413 (NH₂), 3245 (NH₂), 3157 (NH), 1685 (C=O), 1612 (C=N), 1446, 1310, 1240, 1191, 1140, 1127, 1027, 986, 850. ¹H NMR (CDCl₃) δH 0.92 (t, 3JHH 7.4 Hz, 3H, CH₃), 1.31-1.37 (m, 2H, CH₂), 1.40 (s, 18 H, t-Bu), 1.55-1.61 (m, 2H, CH₂), 2.59 (br t, 2H, CH₂), 4.79 (s, 2H, CH₂), 5.20 (br s, 1H, OH), 6.55 (br s, 1H, NH₂), 6.82 (d, 1H, 3JHH 8.1 Hz, H-7), 7.14-7.15 (m, 2H, H-10, 1H, H-6), 7.39 (br s, 1H, H-4), 7.54 (br s, 1H, NH₂), 12.93 (s, 1H, NH-O). ¹³C NMR (CDCl₃) δC 13.9, 22.2, 30.2, 33.7, 34.3, 35.2, 43.9, 109.9, 119.4, 120.7, 124.8, 125.8, 131.5, 132.6, 136.4, 138.0, 141.6, 153.5, 161.1, 180.1. Anal. Calcd for C₂₈H₃₈NaO₂S (494.27): C, 67.98; H, 7.74; N, 11.33%, Found: C, 67.71; H, 7.57; N, 11.19%.

5-Bromo-1-(3,5-di-tert-butyl-4-hydroxybenzyl)indoline-2,3-dione 3-thiosemicarbazone (7b). Yellow solid, yield 79%, mp 248-250 °C (dec.), IR: (υ_max, cm⁻¹): 3619 (OH), 3412 (NH₂), 3248 (NH₂), 3172 (NH), 1682 (C=O), 1599 (C=N), 1461, 1354, 1328, 1239, 1161, 1145, 1124, 1058, 1031, 971, 817. ¹H NMR (DMSO-d₆) δH 1.33 (s, 18H, t-Bu), 4.84 (s, 2H, CH₂), 6.93 (s, 1H, OH), 7.12 (s, 2H, H-10), 7.14 (d, 3JHH 8.3 Hz 1H, H-7), 7.57 (dd, 3JHH 8.4 Hz, 4JHH 2.0 Hz, 1H, H-6), 7.95 (d, 4JHH 2.0 Hz 1H, H-4), 8.87 (s, 1H, NH₂), 9.15 (s, 1H, NH₂), 12.23 (s, 1H, NH-…O). ¹³C NMR (DMSO-d₆) δC 30.2, 34.4, 43.0, 112.3, 114.8, 121.6, 123.3, 124.1, 126.4, 129.5, 133.0, 139.4, 141.8, 153.3, 160.3, 178.8. Anal. Calcd for C₂₄H₂₉Br₂N₄O₄S (516.12): C, 55.70; H, 5.65; N, 10.83%, Found: C, 55.53; H, 5.42; N, 10.68%.

5,7-Dibromo-1-(3,5-di-tert-butyl-4-hydroxybenzyl)indoline-2,3-dione 3-thiosemicarbazone (7c). Isomers ratio 3:1. Yellow solid, yield 96%, 220 mg, mp 240 °C (dec.), IR: (υ_max, cm⁻¹): 3623 (OH), 3414 (NH₂), 3248 (NH₂), 3156 (NH₂), 1694 (C=O), 1603 (C=N), 1554, 1463, 1444, 1343, 1320, 1237, 1151, 1127, 1074, 1038, 976, 861, 786, 725. ¹H NMR (DMSO-d₆) δH (major isomer) 1.31 (s, 18H, t-Bu), 5.21 (s, 2H, CH₂), 6.90 (s, 1H, OH), 7.02 (s, 2H, H-10), 7.81 (d, 4JHH 1.8 Hz, 1H, H-4), 8.09 (d, 4JHH 2.0 Hz, 1H, H-6), 8.99 (s, 1H, NH₂), 9.24 (s, 1H, NH₂), 12.13 (s, 1H, NH-O); (minor isomer) 1.31 (s, 18H, t-Bu), 5.21 (s, 2H, CH₂), 6.90 (s, 1H, OH), 7.02 (s, 2H, H-10), 7.77 (d, 4JHH 1.8 Hz, 1H, H-4), 7.91 (d, 4JHH 1.6 Hz, 1H, H-6), 8.87 (s, 1H, NH₂), 9.16 (s, 1H, NH₂), 12.23 (s, 1H, NH-O). ¹³C NMR (DMSO-d₆) δC 30.2, 34.5, 43.8, 103.6, 115.3, 122.7, 123.1, 124.7, 127.5, 128.1, 136.9, 139.0, 139.2, 153.0, 161.1, 178.8. Anal. Calcd for C₂₄H₂₉Br₂N₄O₄S (594.03): C, 48.33; H, 4.73; N, 9.39%, Found: C, 48.15; H, 4.49; N, 9.18%.
7-Methyl-1-(3,5-di-tert-butyl-4-hydroxybenzyl)indoline-2,3-dione 3-thiosemicarbazone (7d).

Yellow solid, yield 71%, mp 236 °C (dec.), IR: \((v_{\text{max}}, \text{cm}^{-1})\): 3631 (OH), 3396 (NH\(_2\)), 3291-3256 (NH\(_2\)), 3155 (NH), 1675 (C=O), 1604 (C=N), 1463, 1439, 1357, 1337, 1240, 1139, 1106, 1075, 1004, 869, 824, 799, 743, 704, 622. \(^1\)H NMR (DMSO-d\(_6\)) \(\delta_H\) 1.29 (s, 18H, \(t\)-Bu), 2.29 (s, 3H, CH\(_3\)), 5.08 (s, 2H, CH\(_2\)), 6.92 (s, 1H, OH), 6.93 (s, 2H, H-10), 7.05 (t, \(J_HH\) 7.6 Hz, 1H, H-5), 7.14 (d, \(J_HH\) 7.6 Hz, 1H, H-6), 7.66 (d, \(J_HH\) 7.6 Hz, 1H, H-4), 8.77 (s, 1H, NH\(_2\)), 9.09 (s, 1H, NH\(_2\)), 12.42 (s, 1H, NH-O). \(^13\)C NMR (DMSO-d\(_6\)) \(\delta_C\) 17.8, 30.2, 34.4, 44.1, 118.8, 120.1, 121.0, 122.0, 123.1, 127.9, 130.6, 134.8, 139.6, 140.8, 152.9, 161.6, 178.7. Anal. Calcd for C\(_{25}\)H\(_{32}\)N\(_2\)O\(_2\)S (452.22): C, 66.34; H, 7.13; N, 12.38%; Found: C, 66.15; H, 6.98; N, 12.05%.

General procedure for the synthesis of substituted 3-(3,5-di-tert-butyl-4-hydroxyphenyl)-propionic acid [1-(3,5-di-tert-butyl-4-hydroxybenzyl)-2-oxo-1,2-dihydroindol-3-ylidene]hydrazides 8a-d. A mixture of substituted isatin 3a-d (10 mmol), 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid hydrazide 6 (140 mg, 10 mmol) and trifluoroacetic acid (0.5 ml) in ethanol (10 ml) was stirred at 70 °C for 5 h, and cooled to r.t. The precipitate was filtered off, washed with ethanol (25 ml) and air-dried to give 8a-d.

3-(3,5-Di-tert-butyl-4-hydroxyphenyl)propionic acid [5-bromo-1-(3,5-di-tert-butyl-4-hydroxybenzyl)-2-oxo-1,2-dihydroindol-3-ylidene]hydrazide (8a). Isomers ratio 2.5:1. Yellow solid, yield 45%, mp 156-158 °C, IR: \((v_{\text{max}}, \text{cm}^{-1})\): 3643 (OH), 3210 (NH), 1692 (C=O), 1625 (C=N), 1611, 1466, 1435, 1349, 1319, 1248, 1212, 1172, 1154, 1133, 1044, 1021, 989, 865, 818, 802, 785, 739, 545. \(^1\)H NMR (CDCl\(_3\)) \(\delta_H\) (minor isomer) 0.94 (t, 3H, Me), 1.30-1.40 (m, 2H, CH\(_2\)), 1.42 (s, 18H, \(t\)-Bu), 1.47 (s, 18H, \(t\)-Bu), 1.55-1.63 (m, 2H, CH\(_2\)), 2.60 (t, 2H, CH\(_2\)Ar), 2.74 (br t, 2H, CH\(_2\)C(O)), 3.00 (br t, 2H, ArCH\(_2\)CH\(_2\)C(O)), 4.81 (s, 2H, NCH\(_2\)Ar), 5.08 (s, 1H, OH), 5.20 (s, 1H, OH), 6.82 (d, 1H, \(3_JHH\) 7.9 Hz, H-7), 7.05-7.19 (m, 5H, H-6, H-10, H-16), 7.70 (s,1H, H4), 13.13 (s,1H, NHO), \(\delta_H\) (major isomer) 0.94 (t, 3H, Me), 1.30-1.40 (m, 2H, CH\(_2\)), 1.42 (s, 18H, \(t\)-Bu), 1.45 (s, 18H, \(t\)-Bu), 1.55-1.63 (m, 2H, CH\(_2\)), 2.60 (t, 2H, CH\(_2\)Ar), 3.00 (br t, 2H, ArCH\(_2\)CH\(_2\)C(O)), 3.16 (br t, 2H, CH\(_2\)C(O)), 4.81 (s, 2H, NCH\(_2\)Ar), 5.10 (s, 1H, OH), 5.20 (s, 1H, OH), 6.82 (d, 1H, \(3_JHH\) 7.9 Hz, H-7), 7.05-7.19 (m, 5H, H-6, H-10, H-16), 7.44 (s, 1H, H-4), 12.59 (s, 1H, NHO), \(^13\)C NMR (CDCl\(_3\)) \(\delta_C\) 13.4, 21.8, 29.7, 29.9, 30.3, 33.4, 33.8, 33.9, 34.1, 34.8, 43.3, 109.1, 119.6, 120.0, 124.3, 124.6, 125.6, 130.3, 131.3, 132.7, 135.5, 135.8, 137.5, 140.6, 151.7, 153.0, 160.5, 175.2. Anal. Calcd for C\(_{46}\)H\(_{41}\)N\(_2\)O\(_3\) (695.47): C, 75.93; H, 8.83; N, 6.04%; Found: C, 75.75; H, 8.80; N, 5.85%.

3-(3,5-Di-tert-butyl-4-hydroxyphenyl)propionic acid [5-bromo-1-(3,5-di-tert-butyl-4-hydroxybenzyl)-2-oxo-1,2-dihydroindol-3-ylidene]hydrazide (8b). Isomers ratio 3.8:1. Yellow solid, yield 85%, mp 170 °C, IR: \((v_{\text{max}}, \text{cm}^{-1})\): 3647 (OH), 3615 (OH), 3213 (NH), 1686 (C=O), 1609 (C=N), 1589, 1463, 1436, 1376, 1352, 1318, 1235, 1161, 1121, 1043, 984, 807, 791, 725. \(^1\)H NMR (CDCl\(_3\)) \(\delta_H\) minor isomer 1.42 (s, 18H, \(t\)-Bu), 1.47 (s, 18H, \(t\)-Bu), 2.76 (br t, 2H, CH\(_2\)C(O)), 3.00 (br t, 2H, ArCH\(_2\)CH\(_2\)C(O)), 4.82 (s, 2H, NCH\(_2\)Ar), 5.10 (s, 1H, OH), 5.23 (s, 1H, OH), 6.80 (d, 1H, \(3_JHH\) 8.2 Hz, H-7), 7.11 (s, 2H, H-10), 7.13 (s, 2H, H-16), 7.99 (s, 1H, H-4), 13.02 (s, 1H, NHO), \(\delta_H\) major isomer 1.42 (s, 18H, \(t\)-Bu), 1.47 (s, 18H, \(t\)-Bu), 3.14 (br t,
2H, CH2C(O)), 3.00 (br t, 2H, ArCH2CH2C(O)), 4.82 (s, 2H, NCH2Ar), 5.10 (s, 1H, OH), 5.23 (s, 1H, OH), 6.80 (d, 1H, 3JHH 8.2 Hz, H-7), 7.11 (s, 2H, H-10), 7.13 (s, 2H, H-16), 7.44 (s, 1H, H-4), 12.51 (s, 1H, NH-O), 13C NMR (CDCl3) δC 29.7, 29.9, 30.2, 33.8, 33.9, 34.0, 43.4, 110.8, 115.4, 121.4, 123.0, 124.1, 124.5, 124.9, 130.9, 131.0, 132.7, 135.5, 136.0, 141.3, 151.7, 153.2, 160.0, 175.1. Anal. Calcd for C40H32BrN2O4 (717.31): C, 66.84; H, 7.29; N, 5.85%, Found: C, 66.65; H, 7.98; N, 5.62%.

3-(3,5-Di-tert-butyl-4-hydroxyphenyl)propionic acid [5,7-dibromo-1-(3,5-di-tert-butyl-4-hydroxybenzyl)-2-oxo-1,2-dihydroindol-3-ylidene]hydrazide (8e). Isomers ratio 3:1. Yellow solid, yield 83%, mp 218 °C, IR: (vmax, cm⁻¹): 3631 (OH), 3279 (NH), 1731 (C=O), 1686 (C=O), 1602 (C=N), 1553, 1460, 1358, 1329, 1269, 1234, 1121, 1081, 985, 873, 729. 1H NMR (CDCl3) δH minor isomer 1.39 (s, 18H, t-Bu), 1.44 (s, 18H, t-Bu), 2.71 (br s, 2H, CH2C(O)), 3.00 (br t, 2H, ArCH2CH2C(O)), 5.08 (s, 1H, OH), 5.17 (s, 1H, OH), 5.31 (s, 2H, NCH2Ar), 7.07 (s, 2H, H-10), 7.18 (s, 2H, H-16), 7.64 (s, 1H, H-4); 7.68 (s, 1H, H-6), 13.00 (s, trans-Z, 1H, NH O); δH major isomer 1.39 (s, 18H, t-Bu), 1.44 (s, 18H, t-Bu), 3.10 (br s, 2H, CH2C(O)), 3.00 (br t, 2H, ArCH2CH2C(O)), 5.08 (s, 1H, OH), 5.17 (s, 1H, OH), 5.31 (s, 2H, NCH2Ar), 7.07 (s, 2H, H-10), 7.18 (s, 2H, H-16), 7.64 (s, 1H, H-4); 7.69 (s, 1H, H-6), 12.44 (s, cis-Z, 1H, NH O). Due to the very low solubility of this compound in a wide range of organic solvents 13C NMR spectrum could not be recorded. Anal. Calcd for C40H31Br2N3O4 (795.22): C, 60.23; H, 6.44; N, 5.27%, Found: C, 60.07; H, 6.28; N, 5.19%.

3-(3,5-Di-tert-butyl-4-hydroxyphenyl)propionic acid [7-methyl-1-(3,5-di-tert-butyl-4-hydroxybenzyl)-2-oxo-1,2-dihydroindol-3-ylidene]hydrazide (8d). Isomers ratio 2.5:1. Yellow solid, yield 71%, mp 218-220 °C, IR: (vmax, cm⁻¹): 3627 (OH), 3285 (NH), 1713 (C=O), 1679 (C=O), 1596 (C=N), 1456, 1436, 1374, 1360, 1325, 1256, 1234, 1177, 1146, 1119, 1092, 1029, 875, 798, 741, 509. 1H NMR (CDCl3) δH minor isomer 1.38 (s, 18H, t-Bu), 1.44 (s, trans-Z, 18H, t-Bu), 2.38 (s, 3H, Me), 2.73 (br t, 2H, CH2C(O)), 3.01 (br t, 2H, ArCH2CH2C(O)), 5.08 (s, 1H, OH), 5.12 (s, 2H, NCH2Ar), 5.16 (s, 1H, OH), 6.95-7.15 (m, 6H, H-5, H-6, H-10, H-16), 7.75 (d, trans-Z, 1H, 3JHH 7.3 Hz, H-4), 13.16 (s, trans-Z, 1H, NH-O); major isomer 1.38 (s, 18H, t-Bu), 1.47 (s, cis-Z, 18H, t-Bu), 2.40 (s, 3H, Me), 3.17 (br t, 2H, CH2C(O)), 3.01 (br t, 2H, ArCH2CH2C(O)), 5.10 (s, 1H, OH), 5.12 (s, 2H, NCH2Ar), 5.16 (s, 1H, OH), 6.95-7.15 (m, 6H, H-5, H-6, H-10, H-16), 7.51 (d, cis-Z, 1H, 3JHH 7.3 Hz, H-4), 12.58 (s, cis-Z, 1H, NH-O), 13C NMR (CDCl3) δC 18.3, 29.7, 29.9, 30.1, 33.8, 33.9, 34.0, 44.3, 118.0, 120.3, 120.4, 122.3, 122.7, 124.5, 126.8, 131.2, 132.2, 134.4, 135.5, 135.9, 140.7, 151.7, 152.7, 161.4, 175.1. Anal. Calcd for C41H55N3O4 (653.42): C, 75.31; H, 8.48; N, 6.43%; Found: C, 75.09; H, 8.28; N, 6.29%.

5,5'-Dibromo-1,1'-(3,5-di-tert-butyl-4-hydroxybenzyl)-1H,1'H-[3,3']-biindolylidene-2,2'-dione (9b). Dark-cherry solid, yield 91%, 437 mg, mp > 300 °C, IR: (vmax, cm⁻¹): 3616 (OH), 1695 (C=O), 1605 (C=C), 1300, 1213, 1157, 1120, 801. 1H NMR (CDCl3) δH 1.32 (s, 18H, t-Bu), 4.90 (s, 2H, CH2), 6.92 (br s, 1H, OH), 7.11 (d, 3JHH 8.6 Hz, 1H, H-7), 7.14 (s, 2H, H-10), 7.64 (dd, 3JHH 8.5 Hz, 4JHH 1.6 Hz, 1H, H-6), 9.36 (d, 4JHH 1.6 Hz, 1H, H-4). Anal. Calcd for C46H52Br2N2O4 (854.23): C, 64.49; H, 6.12; N, 3.27%, Found: C, 64.28; H, 6.01; N, 3.18%. Due
to the very low solubility of this compound in a wide range of organic solvents. ¹³C NMR spectrum could not be recorded.

5,5',7,7'-Tetrabromo-1,1'-(3,5-di-tert-butyl-4-hydroxybenzyl)-1H,1'H-[3,3']-biindolylidene-2,2'-dione (9c). Light-purple solid, yield 83%, 215 mg, mp > 300 °C, IR: (v max, cm⁻¹): 3438 (OH), 1700 (C=O), 1608 (C=C), 1550, 1333, 1214, 1149, 1109, 1023. ¹H NMR (DMSO-d6) δH 1.40 (s, 18H, t-Bu), 5.15 (br s, 1H, OH), 5.41 (s, 2H, CH2), 7.20 (s, 2H, H-10), 7.67 (d, JHH 1.8 Hz, 1H, H-6), 9.37 (d, JHH 1.8 Hz, 1H, H-4). ¹³C NMR (DMSO-d6) δC 30.3, 34.4, 44.9, 102.5, 115.1, 124.3, 125.8, 127.2, 131.4, 133.1, 136.0, 140.5, 141.2, 153.2, 168.0.

7,7'-Dimethyl-1,1'-(3,5-di-tert-butyl-4-hydroxybenzyl)-1H,1'H-[3,3']-biindolylidene-2,2'-dione (9d). Dark-cherry crystals, yield 85%, 478 mg, mp 125 °C, IR: (v max, cm⁻¹): 3460 (OH), 1691 (C=O), 1600 (C=C), 1377, 1235, 1209, 1187, 1160, 1117, 1023, 787. ¹H NMR (CDCl3) δH 1.36 (s, 18H, t-Bu), 2.36 (s, 3H, CH3), 5.18 (s, 2H, CH2), 6.90 (t, 3JHH 7.8 Hz, 1H, H-5), 7.01 (s, 2H, H-10), 7.04 (d, 3JHH 7.4 Hz, 1H, H-6), 9.04 (d, 3JHH 7.8 Hz, 1H, H-4). ¹³C NMR (CDCl3) δC 19.2, 30.2, 34.3, 45.5, 119.1, 122.0, 122.6, 125.9, 127.3, 128.0, 133.4, 136.2, 136.6, 142.9, 152.9, 169.1. Anal. Calcd for C₄₆H₅₀Br₄N₂O₄ (1010.05): C, 54.46; H, 4.97; N, 2.76%. Found: C, 54.28; H, 4.91; N, 2.60%.

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