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

Andrei V. Bogdanov,*[a] Sergei V. Bukharov,[b] Yulia N. Oludina,[b] Lenar I. Musin,[a] Gulnara N. Nugumanova,[b] Viktor V. Syakaev,[a] and Vladimir F. Mironov[a]

[a]*A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of Russian Academy of Sciences, Arbuzov str. 8, Kazan 420088, Russian Federation*
[b]*Kazan National Research Technological University, Karl Marx str. 68, Kazan 420015, Russian Federation*
E-mail: bogdanov@iopc.ru

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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.

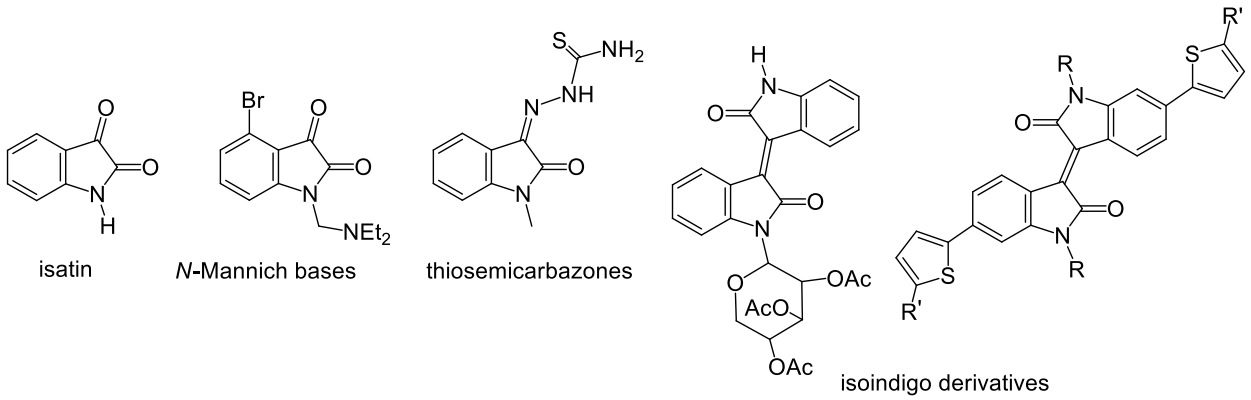
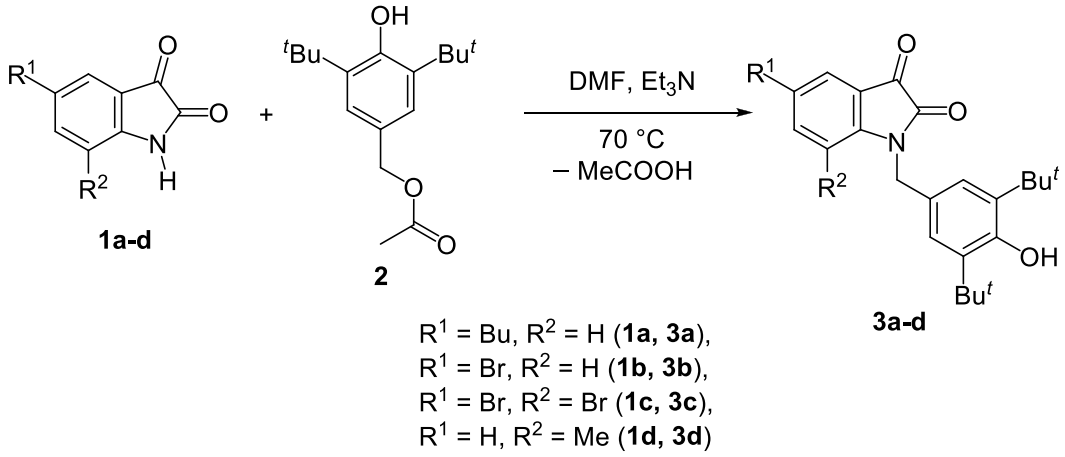


Figure 1. Isatin and its derivatives.

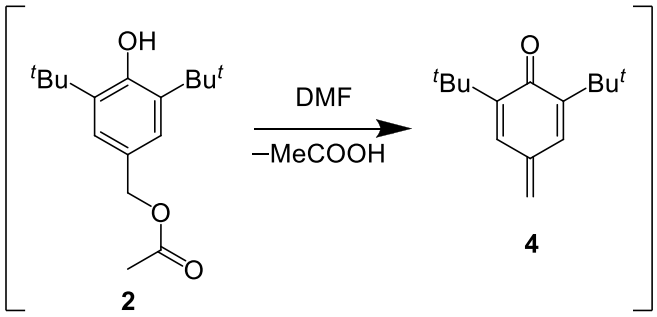
Results and Discussion

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).



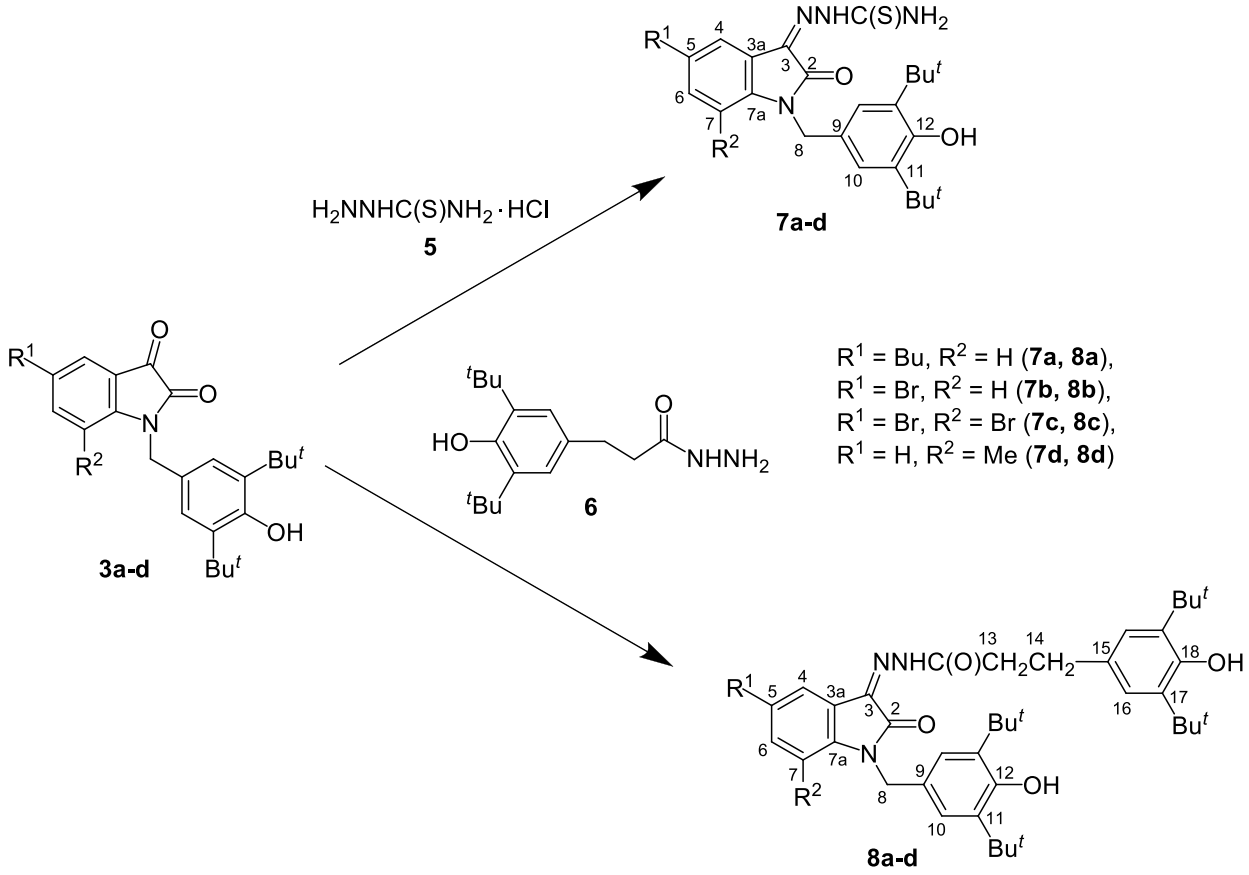
Scheme 1. Synthesis of novel sterically hindered benzylisatins **3a-d**.

The reaction proceeds in dipolar aprotic solvents such as DMF or DMSO. These conditions[25,26] 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-methylenecyclohexa-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 $Z_{C=N}$ – isomers with strong intramolecular N-H·O bond.[26] (Figure 2)

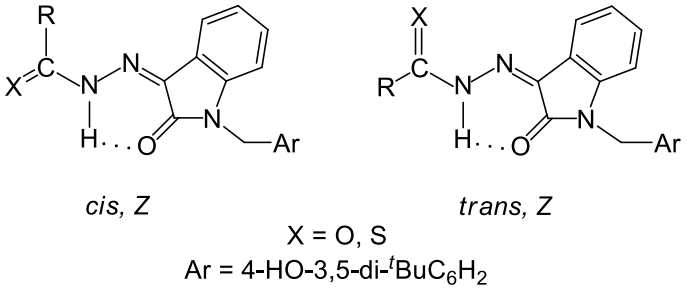


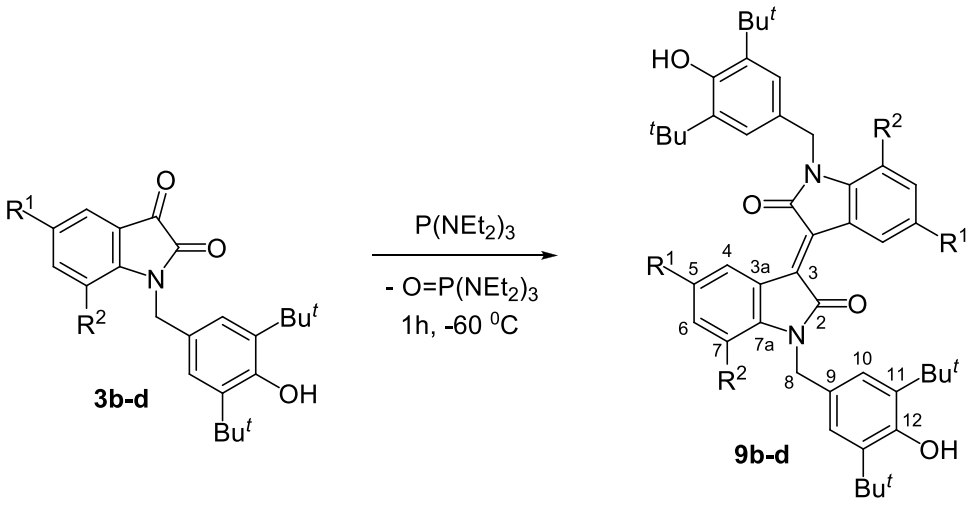
Figure 2. Representation of *cis,Z* and *trans,Z*-isomers of compounds **7a-d** and **8a-d.**

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[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 $E_{C=N}$ – isomers in ^{1}H NMR spectra of compounds **8a-d**

Compd	C(O)CH_2, δ, ppm		H-4, δ, ppm		N-H, δ, ppm		*cis*-/ *trans*
	cis	*trans*	*cis*	*trans*	*cis*	*trans*	ratio
8a	3.16	2.74	7.44	7.70	12.59	13.13	2.5/1
8b	3.12	2.72	7.69	7.96	12.51	13.02	3.8/1
8c	3.10	2.93	7.68	7.96	12.52	13.07	3/1
8d	3.17	2.73	7.51	7.76	12.58	13.16	2.5/1

In a development of our investigations on the reactivity of 1,2-diketones[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 $CHCl_3$ 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 ºC 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: (ν_{max}, cm^{-1}): 3639 (OH), 1732 (C=O), 1619, 1595, 1488, 1436, 1336, 1285, 1236, 1179, 1162, 1124, 1026, 886. ^{1}H NMR ($CDCl_3$) δ_H 0.91 (t, $^3J_{HH}$ 8.5 Hz, 3H, CH_3), 1.32 (m, 2H, CH_2), 1.40 (s, 18H, *t*-Bu), 1.55 (m, 2H, CH_2), 2.56 (t, 2H, CH_2), 4.78 (s, 2H, CH_2), 5.21 (s, 1H, OH), 6.80 (d, $^3J_{HH}$ 8.1 Hz, 1H, H-7), 7.16 (s, 2H, H-10), 7.32 (dd, $^3J_{HH}$ 8.1 Hz, $^4J_{HH}$ 1.3 Hz, 1H, H-6), 7.42 (br s, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ_C 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 $C_{27}H_{35}NO_3$ (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: (ν_{max}, cm^{-1}): 3639 (OH), 1736 (C=O), 1604, 1331, 1237, 1178, 1159, 1127, 1033, 837. ^{1}H NMR ($CDCl_3$) δ_H 1.40 (s, 18H, *t*-Bu), 4.80 (s, 2H, CH_2), 5.24 (s, 1H, OH), 6.80 (d, $^3J_{HH}$ 8.4 Hz, 1H, H-7), 7.12 (s, 2H, H-10), 7.63 (dd, $^3J_{HH}$ 8.4 Hz, $^4J_{HH}$ 2.1 Hz, 1H, H-6), 7.70 (d, $^4J_{HH}$ 2.0 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ_C 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 $C_{23}H_{26}BrNO_3$ (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: (ν_{max}, cm^{-1}): 3619 (OH), 1740 (C=O), 1598, 1406, 1360, 1336, 1310, 1275, 1223, 1144, 885. ^{1}H NMR ($CDCl_3$) δ_H 1.40 (s, 18H, *t*-Bu), 5.20 (s, 1H, OH), 5.32 (s, 2H, CH_2), 7.21 (s, 2H, H-10), 7.68 (dd, $^4J_{HH}$ 2.0 Hz, 1H, H-6), 7.85 (d, $^4J_{HH}$ 2.0 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ_C 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 $C_{23}H_{25}Br_2NO_3$ (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 ºC 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: (ν_{max}, cm^{-1}): 3643 (OH), 1742 (C=O), 1725 (C=O), 1602, 1437, 1365, 1345, 1248, 1212, 1171, 1155, 1051, 769. ^{1}H NMR ($CDCl_3$) δ_H 1.37 (s, 18H, *t*-Bu), 2.36 (s, 3H, CH_3), 5.08 (s, 2H, CH_2), 5.15 (s, 1H, OH), 7.00 (m, 1H, H-5), 7.01 (s, 2H, H-10), 7.28 (d, $^3J_{HH}$ 7.7 Hz, 1H, H-6), 7.51 (d, $^3J_{HH}$ 7.4 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ_C 18.8, 30.2,

34.3, 45.5, 118.9, 122.2, 122.7, 123.5, 123.9, 126.7, 136.5, 142.4, 149.1, 153.2, 159.8, 183.9. Anal. Calcd for $C_{24}H_{29}NO_3$ (379.21): C, 75.96; H, 7.70; N, 3.69%, Found: C, 75.83; H, 7.58; N, 3.58%.

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 ºC 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: (ν_{max}, cm^{-1}): 3577 (OH), 3413 (NH_2), 3245 (NH_2), 3157 (NH), 1685 (C=O), 1612 (C=N), 1446, 1310, 1240, 1191, 1140, 1127, 1027, 986, 850. ^{1}H NMR ($CDCl_3$) δ_H 0.92 (t, $^3J_{HH}$ 7.4 Hz, 3H, CH_3), 1.31-1.37 (m, 2H, CH_2), 1.40 (s, 18 H, *t*-Bu), 1.55-1.61 (m, 2H, CH_2), 2.59 (br t, 2H, CH_2), 4.79 (s, 2H, CH_2), 5.20 (br s, 1H, OH), 6.55 (br s, 1H, NH_2), 6.82 (d, 1H, $^3J_{HH}$ 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, NH_2), 12.93 (s, 1H, NH·O). ^{13}C NMR ($CDCl_3$) δ_C 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 $C_{28}H_{38}N_4O_2S$ (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: (ν_{max}, cm^{-1}): 3619 (OH), 3412 (NH_2), 3248 (NH_2), 3172 (NH), 1682 (C=O), 1599 (C=N), 1461, 1354, 1328, 1239, 1161, 1145, 1124, 1058, 1031, 971, 817. ^{1}H NMR (DMSO-d_6) δ_H 1.33 (s, 18H, *t*-Bu), 4.84 (s, 2H, CH_2), 6.93 (s, 1H, OH), 7.12 (s, 2H, H-10), 7.14 (d, $^3J_{HH}$ 8.3 Hz 1H, H-7), 7.57 (dd, $^3J_{HH}$ 8.4 Hz, $^4J_{HH}$ 2.0 Hz, 1H, H-6), 7.95 (d, $^4J_{HH}$ 2.0 Hz 1H, H-4), 8.87 (s, 1H, NH_2), 9.15 (s, 1H, NH_2), 12.23 (s, 1H, NH···O). ^{13}C NMR (DMSO-d_6) δ_C 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 $C_{24}H_{29}BrN_4O_2S$ (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: (ν_{max}, cm^{-1}): 3623 (OH), 3414 (NH_2), 3248 (NH_2), 3156 (NH),1694 (C=O), 1603 (C=N), 1554, 1463, 1444, 1343, 1320, 1237, 1151, 1127, 1074, 1038, 976, 861, 786, 725. ^{1}H NMR (DMSO-d_6) δ_H (major isomer) 1.31 (s, 18H, *t*-Bu), 5.21 (s, 2H, CH_2), 6.90 (s, 1H, OH), 7.02 (s, 2H, H-10), 7.81 (d, $^4J_{HH}$ 1.8 Hz, 1H, H-4), 8.09 (d, $^4J_{HH}$ 2.0 Hz, 1H, H-6), 8.99 (s, 1H, NH_2), 9.24 (s, 1H, NH_2), 12.13 (s, 1H, NH·O); (minor isomer) 1.31 (s, 18H, *t*-Bu), 5.21 (s, 2H, CH_2), 6.90 (s, 1H, OH), 7.02 (s, 2H, H-10), 7.77 (d, $^4J_{HH}$ 1.8 Hz, 1H, H-4), 7.91 (d, $^4J_{HH}$ 1.6 Hz, 1H, H-6), 8.87 (s, 1H, NH_2), 9.16 (s, 1H, NH_2), 12.23 (s, 1H, NH·O). ^{13}C NMR (DMSO-d_6) δ_C 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 $C_{24}H_{28}Br_2N_4O_2S$ (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: (ν_{max}, 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) δ_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, $^3J_{HH}$ 7.6 Hz, 1H, H-5), 7.14 (d, $^3J_{HH}$ 7.6 Hz, 1H, H-6), 7.66 (d, $^3J_{HH}$ 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) δ_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 $C_{25}H_{32}N_4O_2S$ (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 ºC 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-butyl-1-(3,5-di-*tert*-butyl-4-hydroxy-benzyl)-2-oxo-1,2-dihydroindol-3-ylidene]hydrazide (8a). Isomers ratio 2.5:1. Yellow solid, yield 45%, mp 156-158 °C, IR: (ν_{max}, 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 ($CDCl_3$) δ_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_2Ar), 2.74 (br t, 2H, CH_2C(O)), 3.00 (br t, 2H, ArCH_2CH$_2$C(O)), 4.81 (s, 2H, NCH_2Ar), 5.08 (s, 1H, OH), 5.20 (s, 1H, OH), 6.82 (d, 1H, $^3J_{HH}$ 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, NH·O), δ_H (major isomer) 0.94 (t, 3H, Me), 1.30-1.40 (m, 2H, CH_2), 1.42 (s, 18 H, *t*-Bu), 1.45 (s, 18 H, *t*-Bu), 1.55-1.63 (m, 2H, CH_2), 2.60 (t, 2H, CH_2Ar), 3.00 (br t ,2H, ArCH_2CH$_2$C(O)), 3.16 (br t, 2H, CH_2C(O)), 4.81 (s, 2H, NCH_2Ar), 5.10 (s, 1H, OH), 5.20 (s, 1H, OH), 6.82 (d, 1H, $^3J_{HH}$ 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, NH·O), ^{13}C NMR ($CDCl_3$) δ_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 $C_{44}H_{61}N_3O_4$ (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: (ν_{max}, 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 ($CDCl_3$) δ_H minor isomer 1.42 (s, 18H, *t*-Bu), 1.47 (s, 18H, *t*-Bu), 2.76 (br t, 2H, CH_2C(O)), 3.00 (br t, 2H, ArCH_2CH$_2$C(O)), 4.82 (s, 2H, NCH_2Ar), 5.10 (s, 1H, OH), 5.23 (s, 1H, OH), 6.80 (d, 1H, $^3J_{HH}$ 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, NH·O), δ_H major isomer 1.42 (s, 18H, *t*-Bu), 1.47 (s, 18H, *t*-Bu), 3.14 (br t,

2H, C*H*$_2$C(O)), 3.00 (br t, 2H, ArC*H*$_2$CH$_2$C(O)), 4.82 (s, 2H, NC*H*$_2$Ar), 5.10 (s, 1H, OH), 5.23 (s, 1H, OH), 6.80 (d, 1H, $^3J_{HH}$ 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), ^{13}C NMR (CDCl$_3$) δ_C 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 $C_{40}H_{52}BrN_3O_4$ (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 (8c). Isomers ratio 3:1. Yellow solid, yield 83%, mp 218 °C, IR: (ν_{max}, 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. ^{1}H NMR (CDCl$_3$) δ_H minor isomer 1.39 (s, 18H, *t*-Bu), 1.44 (s, 18H, *t*-Bu), 2.71 (br s, 2H, C*H*$_2$C(O)), 3.00 (br t, 2H, ArC*H*$_2$CH$_2$C(O)), 5.08 (s, 1H, OH), 5.17 (s, 1H, OH), 5.31 (s, 2H, NC*H*$_2$Ar), 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); δ_H major isomer 1.39 (s, 18H, *t*-Bu), 1.44 (s, 18H, *t*-Bu), 3.10 (br s, 2H, C*H*$_2$C(O)), 3.00 (br t, 2H, ArC*H*$_2$CH$_2$C(O)), 5.08 (s, 1H, OH), 5.17 (s, 1H, OH), 5.31 (s, 2H, NC*H*$_2$Ar), 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 ^{13}C NMR spectrum could not be recorded. Anal. Calcd for $C_{40}H_{51}Br_2N_3O_4$ (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: (ν_{max}, 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. ^{1}H NMR (CDCl$_3$) δ_H 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, C*H*$_2$C(O)), 3.01 (br t, 2H, ArC*H*$_2$CH$_2$C(O)), 5.08 (s, 1H, OH), 5.12 (s, 2H, NC*H*$_2$Ar), 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, $^3J_{HH}$ 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, C*H*$_2$C(O)), 3.01 (br t, 2H, ArC*H*$_2$CH$_2$C(O)), 5.10 (s, 1H, OH), 5.12 (s, 2H, NC*H*$_2$Ar), 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, $^3J_{HH}$ 7.3 Hz, H-4), 12.58 (s, cis-*Z*, 1H, NH·O), ^{13}C NMR (CDCl$_3$) δ_C 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 $C_{41}H_{55}N_3O_4$ (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: (ν_{max}, cm^{-1}): 3616 (OH), 1695 (C=O), 1605 (C=C), 1300, 1213, 1157, 1120, 801. ^{1}H NMR (CDCl$_3$) δ_H 1.32 (s, 18H, *t*-Bu), 4.90 (s, 2H, CH$_2$), 6.92 (br s, 1H, OH), 7.11 (d, $^3J_{HH}$ 8.6 Hz, 1H, H-7), 7.14 (s, 2H, H-10), 7.64 (dd, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 1.6 Hz, 1H, H-6), 9.36 (d, $^4J_{HH}$ 1.6 Hz, 1H, H-4). Anal. Calcd for $C_{46}H_{52}Br_2N_2O_4$ (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 ^{13}C 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: (ν_{max}, cm^{-1}): 3438 (OH), 1700 (C=O), 1608 (C=C), 1550, 1333, 1214, 1149, 1109, 1023. ^1H NMR (DMSO-d_6) δ_H 1.40 (s, 18H, *t*-Bu), 5.15 (br s, 1H, OH), 5.41 (s, 2H, CH_2), 7.20 (s, 2H, H-10), 7.67 (d, $^4J_{HH}$ 1.8 Hz, 1H, H-6), 9.37 (d, $^4J_{HH}$ 1.8 Hz, 1H, H-4). ^{13}C NMR (DMSO-d_6) δ_C 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. Anal. Calcd for $C_{46}H_{50}Br_4N_2O_4$ (1010.05): C, 54.46; H, 4.97; N, 2.76%, Found: C, 54.28; H, 4.91; N, 2.60%.

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: (ν_{max}, cm^{-1}): 3460 (OH), 1691 (C=O), 1600 (C=C), 1377, 1235, 1209, 1187, 1160, 1117, 1023, 787. ^1H NMR ($CDCl_3$) δ_H 1.36 (s, 18H, *t*-Bu), 2.36 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 6.90 (t, $^3J_{HH}$ 7.8 Hz, 1H, H-5), 7.01 (s, 2H, H-10), 7.04 (d, $^3J_{HH}$ 7.4 Hz, 1H, H-6), 9.04 (d, $^3J_{HH}$ 7.8 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ_C 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 $C_{48}H_{58}N_2O_4$ (726.44): C, 79.30; H, 8.04; N, 3.85%, Found: C, 79.18; H, 7.95; N, 3.68%.

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