Synthesis of 3,3-Disubstituted Oxindoles *via* a Three-Component Condensation Reaction in H_2O

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An efficient method has been developed for the synthesis of a novel series of unsymmetrically 3,3-disubstituted oxindoles in good-to-high yields by a one-pot three-component condensation reaction of 2-hydroxynaphthalene-1,4-dione, an isatin, and a barbituric acid derivative, in H_2O, and with *p*-toluenesulfonic acid as a catalyst, at 90°. The effects of solvent, temperature, and the amount of catalyst on the yield of the reaction have been investigated. Additionally, the influence of hydrophilicity and hydrophobicity of the reactants on the selectivity of products has been examined.

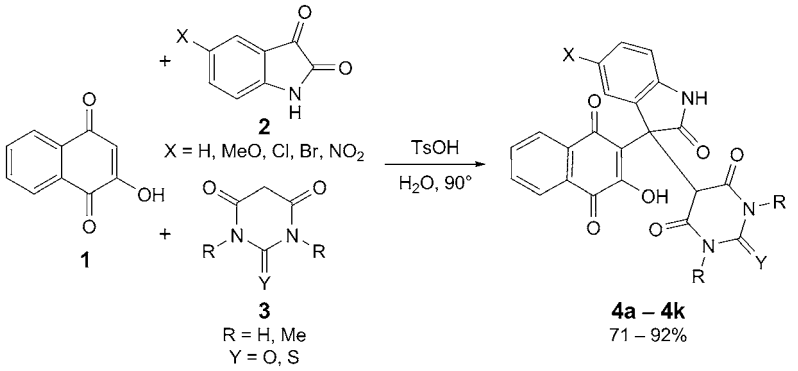
Introduction. – Among oxindoles, the 3,3-disubstituted oxindole system is a core structure for many pharmacological agents and natural products [1–3]. Substructures of this type have also been used as synthetic intermediates for the indole alkaloid synthesis [4]. Due to these interesting properties many efforts toward the synthesis of 3,3-disubstituted oxindoles were made. The successful syntheses include the reaction of malonic esters with 3-halogeno-3-oxindoles in the presence of base [5], the formation of indolenines and subsequent oxidation of them [6], the *Michael* addition of oxindoles to α,β-unsaturated aldehydes [7], the *Friedel–Crafts* reaction [8], an aldol-type reaction [9], the *Mannich* reaction [10], an intramolecular cyanoamidation reaction [11], the rearrangement of indolyl acetate and carbonates [12], the *Heck* reaction [13][14], the intramolecular α-arylation of amides [15], and intramolecular cyclization *via* Ar–H and activated C–H bonds by copper catalyst [16–18].

Barbituric acid and its derivatives are known to show biological activities [19], and have been used for the clinical treatment of epilepsy [20].

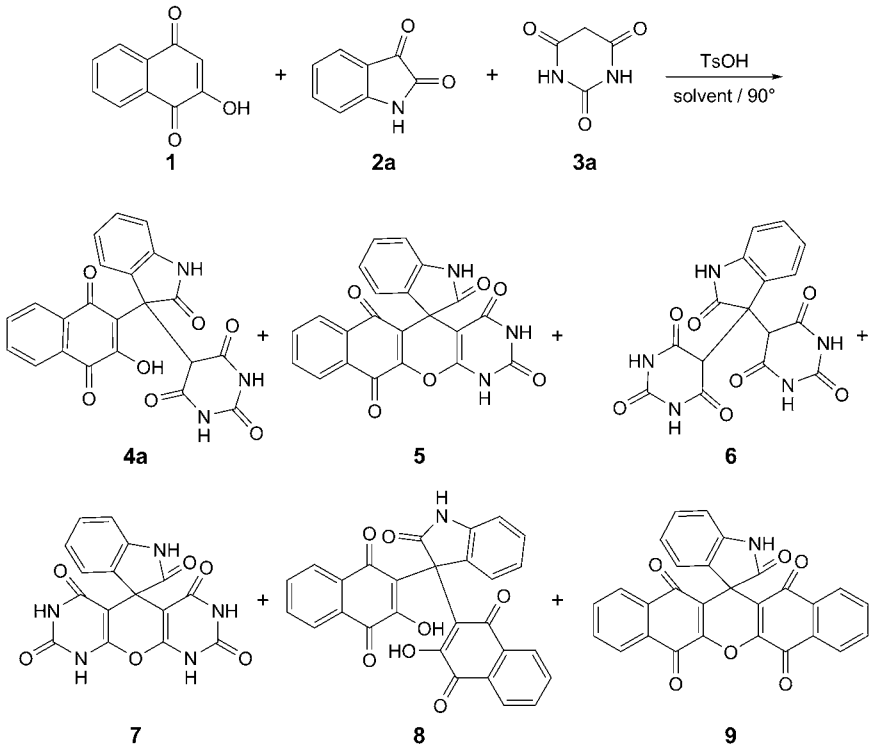
Recently, a new series of hybrid compounds, containing indole and barbituric acid moieties, which evidently show anticancer activities, have been synthesized through C–C bond formation [21]. Due to the biological and pharmaceutical importance of hybrid compounds containing oxindole and barbituric acid moieties, and in continuation of our investigations on multicomponent reactions [22–24], we report on the synthesis of a new series of unsymmetrically 3,3-disubstituted oxindoles containing barbituric or thiobarbituric acid (*Scheme 1*).

Results and Discussion. – To prepare the hybrid compound **4a**, the reaction of 2-hydroxynaphthalene-1,4-dione (**1**), isatin (**2a**), and barbituric acid (**3a**) as simple model substrates was carried out in MeOH with TsOH as catalyst. A number of products (**4a**, **5**–**9**) could be expected in the course of this reaction (*Scheme 2*). However, only the

Scheme 1. *Synthesis of Compounds* **4**



Scheme 2. *A Series of Possible Products that Can Be Expected from the Reaction of Compounds* **1**, **2a**, *and* **3a**



two compounds **4a** and **9** were obtained under these conditions. The compounds **9** and **6** have been reported earlier by *Bazgir et al.* [25] and by *Jursic* and *Stevens* [26], respectively.

With the goal of the selective formation of **4a**, in the presence of TsOH as catalyst, a variety of solvents was tested (*Table 1*, *Entries 1–8*). High yields of **4a** were obtained using H_2O and DMF. With DMF, both products **4a** and **9** were obtained. With H_2O, compound **4a** was the only product. Subsequently, to improve the yields, the reaction was performed in H_2O at various temperatures, times, and with different amounts of catalyst (*Entries 9–21*). The best yield was obtained at 90° after 24 h (*Entry 20*). When the reaction was carried out under solvent-free conditions, the yield of **4a** was only 11% (*Entry 22*). Application of other solvents, such as ionic liquid (TBAB) and PEG 400, not only had no significant effect on the yield of **4a**, but also increased the yield of **9** (*Table 1*, *Entries 6* and *7*). This process seriously depended on the catalyst, because, in its absence, the yields of the reaction decreased (*Entries 9*, *18*, and *23*).

Table 1. *Optimization of the Formation of* **4a**[a])

Entry	Solvent	Catalyst TsOH [mol-%]	Temperature [°]	Time [h]	Yield of **4a** [%][b])	Yield of **9** [%][b])
1	AcOEt	20	reflux	30	0	51
2	MeCN	20	reflux	30	0	78
3	MeOH	20	reflux	30	27	23
4	EtOH	20	reflux	30	24	26
5	DMF	20	90	30	60	15
6	PEG 400	20	90	30	11	31
7	TBAB	20	90	30	10	30
8	H_2O	20	90	30	75	–
9	H_2O	–	90	30	23	–
10	H_2O	20	70	30	60	–
11	H_2O	20	50	30	25	–
12	H_2O	20	r.t.	30	–	–
13	H_2O	20	90	6	14	–
14	H_2O	20	90	12	31	–
15	H_2O	20	90	18	51	–
16	H_2O	20	90	24	75	–
17	H_2O	20	90	36	75	–
18	H_2O	–	90	24	19	–
19	H_2O	5	90	24	55	–
20	H_2O	10	90	24	75	–
21	H_2O	40	90	24	75	–
22	–	20	90	30	11	20
23	–	–	90	30	–	23

[a]) Isatin (**2a**; 1 mmol), barbituric acid (**3a**; 1.5 mmol), 2-hydroxynaphthalene-1,4-dione (**1**; 1 mmol). [b]) Yield of isolated compound.

Additionally, we found that the yield was significantly influenced by the substrate ratios. In MeOH, an increased ratio of **1** and/or isatin (**2a**) let the yield of **9** increase, however, increasing the amount of barbituric acid (**3a**) did not have a notable effect on the yield. In H_2O, on the other hand, the yield of **4a** improved by increasing the amount of **3a**, while it remained unaffected with increased ratios of **1** and/or **2a**. Finally, the best results were obtained when the molar ratio of 1:1:1.5 was employed for **1**/**2a**/**3a**. It is

worth mentioning that the concentration of **3a** plays a key role in this reaction; by increasing the amount of **3a** to 2.5 equiv., product **9** was observed again.

To explore the scope and limitations of this reaction, we extended the setup to a series with various substituted isatins **2** and barbituric acids **3**. It can be seen from *Table 2* that the substituents in **3** had no significant effect on the yield of the products (*Entries 1*, *6*, and *9*).

Table 2. *Unsymmetrical 3,3-Disubstituted Oxindoles* **4** *Synthesized under Optimized Conditions*[a])

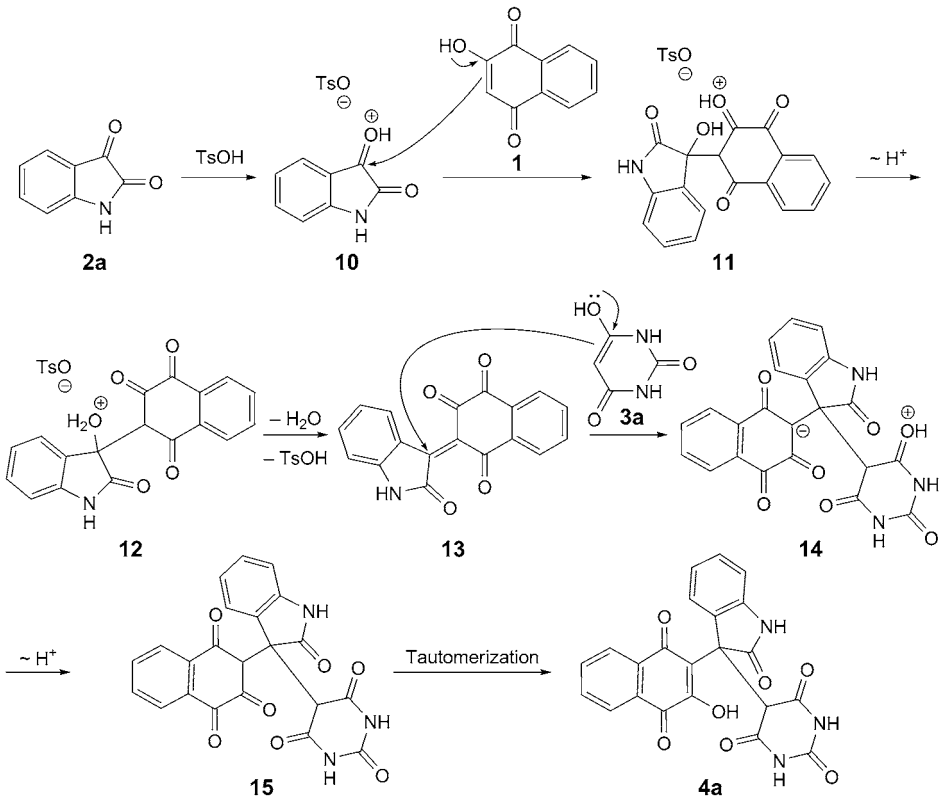
Entry	X	R	Y	Product	Yield [%][b])
1	H	H	O	**4a**	75
2	MeO	H	O	**4b**	72
3	Cl	H	O	**4c**	71
4	Br	H	O	**4d**	73
5	NO_2	H	O	**4e**	88
6	H	Me	O	**4f**	81
7	Br	Me	O	**4g**	72
8	NO_2	Me	O	**4h**	79
9	H	H	S	**4i**	81
10	Br	H	S	**4j**	92
11	NO_2	H	S	**4k**	79

[a]) Isatin (**2**; 1 mmol), barbituric acid derivative (**3**; 1.5 mmol), 2-hydroxynaphthalene-1,4-dione (**1**; 1 mmol) and TsOH (0.1 mmol) at 90° in H_2O (10 ml) for 24 h. [b]) Yield of isolated **4**.

Different to previous reports, where it was shown that multicomponent reactions of isatin with active methylene compounds in H_2O give spiro-oxindoles through cyclization [27–32], under our reaction conditions only hybrid compounds **4a**–**4k** were produced. The structures of products **4a**–**4k** were deduced from their IR, ^{1}H- and ^{13}C-NMR, and mass spectra, as well as by elemental analysis. The IR spectrum of **4a** showed absorptions at 3354, 3219 (NH), 1752, 1739, 1696, 1669, 1655 (C=O), 1341 (C–N), and 1236 (C–O) cm^{-1}, indicating the presence of the functional groups in the proposed structure. The mass spectrum of **4a** displayed a molecular-ion peak at *m*/*z* 431, which is consistent with a 1:1:1 adduct of the starting materials with loss of H_2O. For some of the products, where the molecular-ion peak was not observed, the elemental analysis was used to prove the chemical formula. The ^{1}H-NMR spectrum of **4a** exhibited a *singlet* for a CH group at δ(H) 5.42 and a *multiplet* corresponding to eight aromatic H-atoms appearing at δ(H) 6.74–8.06. The signals for the H-atoms of the NH groups appeared each as a *singlet* at δ(H) 10.65, 11.07, and 11.20. A *singlet* at δ(H) 11.38 could be readily identified as arising from the OH group of the 2-hydroxynaphthalene-1,4-dione moiety. The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 22 distinct resonances in agreement with the suggested structure. The ^{1}H- and ^{13}C-NMR spectra of the related compounds **4** are similar to those of **4a**, except for the signals of the substitutents, which exhibit characteristic signals with appropriate chemical shifts. As a result of rapid H^+-exchange, the OH signal from the 2-hydroxynaphthalene-1,4-dione moiety was not observed in some of the ^{1}H-NMR spectra of the products.

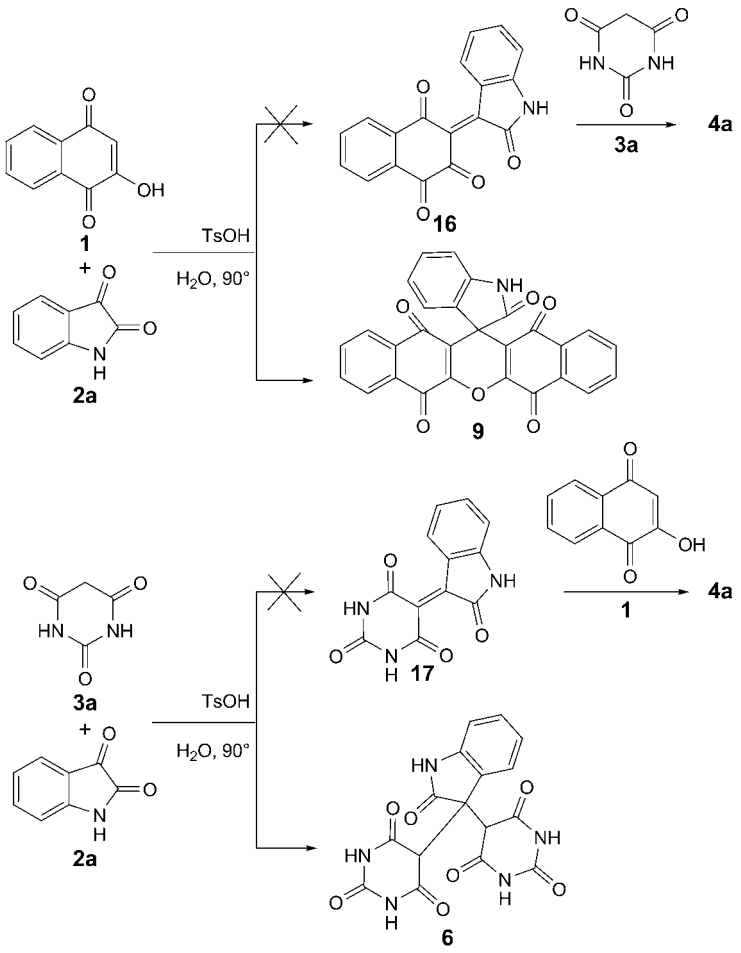
A possible mechanism for the formation of the unsymmetrically 3,3-disubstituted oxindoles **4** shown in *Scheme 3*, with **4a** as an example. In a first step, the isatin C=O group is activated by TsOH. Then, reaction between **1** and protonated **2a** (*i.e.*, compound **10**) gives intermediate **11**, which in turn converts to **12**. Elimination of H_2O and TsOH from **12** results in α,β-unsaturated compound **13**. *Michael* addition of barbituric acid (**3a**) to **13** gives intermediate **14**. Subsequent H^+-transfer leads to compound **15**, which undergoes tautomerization to product **4** (*Scheme 3*).

Scheme 3. *Mechanism of the Reaction of Compounds* **1**, **2a**, *and* **3a**



In order to confirm the above mechanism and the selective formation of product **4a**, several reactions have been performed in H_2O in the presence of TsOH at 90°. First, we tried to prepare intermediates **6** and **8**, and to reacted them subsequenty with the third partner to give product **4a**. However, our efforts for the preparation of these intermediates were not conclusive. When **1** and isatin (**2a**) were reacted in an equal molar ratio under the optimized conditions, only product **9** was obtained after 9 h, whereas after conversion of **2a** with barbituric acid (**3a**) under the same conditions for five days, only low yields of **6** were obtained (*Scheme 4*). These results showed that the role of H_2O as a solvent, as well as the solubility, hydrophilicity, hydrophobicity, and reactivity of organic reactants, are important in this process. During various experi-

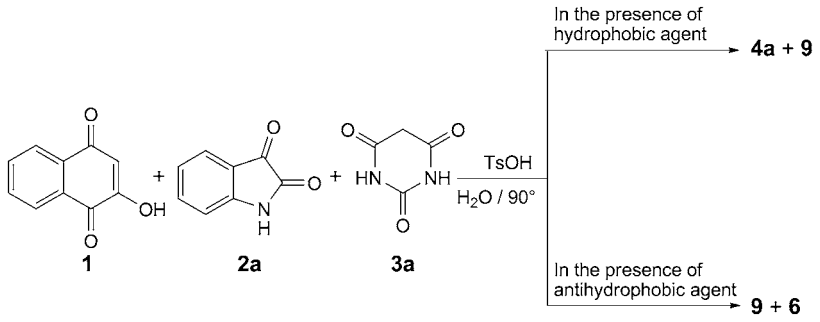
Scheme 4. *Reactions Designed to Prove the Mechanism*



ments, it was found that the reactivity of **1** is higher than that of barbituric acid, but its solubility is low at 90°. Probably due to the low solubility of **1**, only small amounts of **1** are solved in a suspension, and the solved molecules react with **2a** to produce compound **16**, which reacts immediately with barbituric acid **3**. From these results, it can be depicted that intermediates **16** and **17** are highly reactive, and as soon as they are generated they react rapidly with the third partner.

Breslow and co-workers showed that antihydrophobic cosolvents, such as urea, guanidinium salts, and its derivatives, increase the hydrophilicity of organic compounds in H_2O, while Li salts increase the hydrophobicity [33][34]. As barbituric acid derivatives possess an urea moiety, they can have a similar influence on antihydrophobic agents. Therefore, it is possible that they might increase the solubility of 2-hydroxynaphthalene-1,4-dione (**1**). For this reason, in the present reaction, **1** dissolves

Scheme 5. *Effects of Hydrophobic and Antihydrophobic Agents*



slowly in H_2O, reacts then with isatin (**2a**) instantly due to its high reactivity. For further understanding, LiCl was added to the mixture. We observed a decrease in the yield of **4a** as a result of hydrophobic effects. In addition, when TBAB and antihydrophobic cosolvents were added to H_2O, the yield of **9** increased (*Scheme 5*).

In summary, a novel, efficient, and simple three-component condensation reaction for the synthesis of unsymmetrically 3,3-disubstituted oxindoles using easily available starting materials have been developed. The simple one-pot procedure, good yields, and easy workup of the reaction are among the advantages of this new reaction.

Experimental Part

General. All reagents and catalysts were commercially available and used as received. M.p.: *Electrothermal 9100* apparatus, uncorrected. IR Spectra: *JASCO FT/IR-6300* model spectrometer; KBr discs; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker-Avance-400* (tope spine) NMR instrument, in (D_6)DMSO; δ in ppm, *J* in Hz. MS: *Shimadzu QP 1100 EX* mass spectrometer, at 70 eV; in *m*/*z* (%). Elemental analyses: *Heraeus* CHNS rapid analyzer.

General Procedure for the Synthesis of Unsymmetrically 3,3-Disubstituted Oxindoles **4a**–**4k**. A soln. of isatin derivative (**2**; 1 mmol), barbituric acid derivative (**3**; 1.5 mmol), 2-hydroxynaphthalene-1,4-dione (**1**; 1 mmol), and TsOH (0.1 mmol) was heated at 90° in H_2O (10 ml) for 24 h. After completion of the reaction, as indicated by TLC (MeOH/AcOEt 1:5), the mixture was filtered hot. The filtered residue was washed with H_2O (2 × 20 ml). The solid product was recrystallized from acetone/EtOH or acetone/MeOH.

*5-[3-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-2-oxo-1*H*-indol-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4a**). Yellow powder. 0.323 g (75%). M.p. 265–267°. IR (KBr): 3354, 3219, 1752, 1739, 1696, 1669, 1655, 1341, 1236, 749. ^{1}H-NMR (300 MHz, (D_6)DMSO): 5.42 (*s*, 1 CH); 6.74–8.06 (*m*, 8 arom. H); 10.65 (*s*, 1 NH); 11.07 (*s*, 1 NH); 11.20 (*s*, 1 NH); 11.38 (*s*, 1 OH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 49.1; 55.5; 109.6; 122.1; 122.3; 125.7; 126.0; 126.6; 128.5; 129.7; 130.7; 133.7; 133.9; 135.3; 143.1; 151.2; 152.9; 167.4; 168.8; 176.2; 181.1; 185.3. MS: 431 (8, M^+), 429 (3, $[M-2]^+$), 219 (9), 105 (24), 76 (42), 69 (100). Anal. calc. for $C_{22}H_{13}N_3O_7$ (431.35): C 61.26, H 3.04, N 9.74; found: C 61.25, H 3.17, N 9.35.

*5-[3-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-5-methoxy-2-oxo-1*H*-indol-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4b**). Yellow powder. 0.332 g (72%). M.p. 242°. IR (KBr): 3321, 3213, 1757, 1739, 1702, 1662, 1648, 1608, 1355, 1293, 720. ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.63 (*s*, MeO); 5.32 (*s*, 1 CH); 6.64 (*s*, 1 arom. H); 6.70 (*s*, 1 arom. H); 7.03 (*s*, 1 arom. H); 7.79–8.01 (*m*, 4 arom. H); 10.44 (br. *s*, 1 NH); 10.99 (*s*, 1 NH); 11.05 (*s*, 1 NH); 11.31 (*s*, 1 OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 49.0; 55.7; 55.9; 109.7; 112.7; 113.0; 122.0; 126.0; 126.6; 129.7; 131.9; 133.6; 134.0; 135.2;

136.6; 151.1; 152.9; 155.2; 167.4; 168.7; 176.0; 181.1; 186.4. MS: 435 (8, $[M-26]^+$), 149 (9), 101 (40), 76 (41), 57 (100). Anal. calc. for $C_{23}H_{15}N_3O_8$ (461.38): C 59.87, H 3.28, N 9.11; found: C 59.98, H 3.41, N 9.15.

*5-[5-Chloro-3-(1,4-dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-2-oxo-1*H*-indol-3-yl]-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4c**). Yellow powder. 0.330 g (71%). M.p. 271–273°. IR (KBr): 3351, 3213, 1739, 1696, 1668, 1644, 1619, 1422, 1347, 1226, 724. ^{1}H-NMR (300 MHz, (D_6)DMSO): 5.39 (*s*, 1 CH); 6.77 (*d*, $J = 8.2$, 1 arom. H); 7.21 (*d*, $J = 8.1$, 1 arom. H); 7.42 (*s*, 1 arom. H); 7.78–8.06 (*m*, 4 arom. H); 10.80 (*s*, 1 NH); 11.10 (*s*, 1 NH); 11.15 (*s*, 1 NH); 11.50 (br. *s*, 1 OH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 49.0; 55.4; 111.0; 121.1; 125.6; 126.0; 126.6; 128.4; 129.8; 132.8; 133.7; 133.9; 135.2; 142.1; 151.1; 153.2; 167.5; 168.5; 176.0; 181.0; 186.4. MS: 470 (4, $[M+5]^+$), 352 (3), 105 (9), 79 (17), 77.18 (46), 69 (100), 50 (91). Anal. calc. for $C_{22}H_{12}ClN_3O_7$ (465.80): C 56.73, H 2.60, N 9.02; found: C 56.65, H 2.54, N 9.12.

*5-[5-Bromo-3-(1,4-dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-2-oxo-1*H*-indol-3-yl]-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4d**). Yellow powder. 0.371 g (73%). M.p. 245°. IR (KBr): 3364, 3219, 1732, 1711, 1672, 1633, 1620, 1335, 1277, 727. ^{1}H-NMR (400 MHz, (D_6)DMSO): 5.35 (*s*, 1 CH); 6.70 (*d*, $J = 5.7$, 1 arom. H); 7.32 (*d*, $J = 5.4$, 1 arom. H); 7.53 (*s*, 1 arom. H); 7.78–8.03 (*m*, 4 arom. H); 10.78 (*s*, 1 NH); 11.06 (*s*, 1 NH); 11.12 (*s*, 1 NH); 11.50 (*s*, 1 OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 49.1; 55.3; 111.5; 113.8; 121.1; 126.0; 126.6; 128.2; 129.8; 131.2; 133.7; 133.9; 135.2; 142.5; 144.5; 151.1; 153.2; 167.5; 168.5; 176.0; 181.0; 186.4. MS: 174 (100, $[M-335]^+$), 128 (21), 105 (66), 89 (41), 77 (87), 74 (43), 50 (66). Anal. calc. for $C_{22}H_{12}BrN_3O_7$ (510.25): C 51.79, H 2.37, N 8.24; found: C 52.01, H 2.44, N 8.37.

*5-[(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-5-nitro-2-oxo-1*H*-indol-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4e**). Yellow powder. 0.419 g (88%). M.p.: 211°. IR (KBr): 3509, 3278, 1749, 1721, 1683, 1655, 1626, 1599, 1341, 1236, 724. ^{1}H-NMR (400 MHz, (D_6)DMSO): 5.53 (*s*, 1 CH); 6.96 (*d*, $J = 8.4$, 1 arom. H); 7.79–8.36 (*m*, 7 arom. H); 11.17 (*s*, 1 NH); 11.23 (*s*, 1 NH); 11.41 (*s*, 1 NH); 11.44 (*s*, 1 OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 49.1; 54.8; 109.8; 120.5; 121.1; 126.0; 126.1; 126.7; 127.9; 129.8; 132.0; 133.8; 135.3; 142.7; 149.6; 151.0; 153.3; 167.7; 168.3; 177.0; 180.9; 186.4. MS: 481 (14, $[M+5]^+$), 147 (30), 108 (37), 105 (63), 84 (91), 73 (44), 57 (83), 53 (100). Anal. calc. for $C_{22}H_{12}N_4O_9$ (476.35): C 55.47, H 2.54, N 11.76; found: C 55.62, H 2.61, N 11.84.

*5-[3-(1,4-dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-2-oxo-1*H*-indol-3-yl]-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4f**). Yellow powder. 0.371 g (81%). M.p. 176–178°. IR (KBr): 3213, 1712, 1693, 1686, 1613, 1364, 1279, 756. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.96 (*s*, MeN); 3.03 (*s*, MeN); 5.61 (*s*, 1 CH); 6.75 (*d*, $J = 7.6$, 1 arom. H); 6.94 (*dd*, $J = 7.4, 7.4$, 1 arom. H); 7.16 (*dd*, $J = 7.5, 7.5$, 1 arom. H); 7.45 (*d*, $J = 7.4$, 1 arom. H); 7.79–8.00 (*m*, 4 arom. H); 10.64 (*s*, 1 NH); 11.55 (*s*, 1 OH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 28.5; 49.8; 56.5; 109.7; 122.3; 126.1; 126.6; 128.8; 124.7; 133.8; 135.4; 142.8; 152.0; 165.6; 165.9; 166.2; 166.6; 175.8; 181.1. MS: 464 (3, $[M+5]^+$), 425 (3), 341 (5), 287 (9), 174 (20), 105 (19), 87 (22), 74 (72), 69 (82), 58 (50), 57 (41), 56 (56), 51 (44). Anal. calc. for $C_{24}H_{17}N_3O_7$ (459.41): C 62.75, H 3.73, N 9.15; found: C 62.49, H 3.59, N 9.22.

*5-[5-Bromo-3-(1,4-dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-2-oxo-1*H*-indol-3-yl]-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4g**). Yellow powder. 0.388 g (72%). M.p. 181–183°. IR (KBr): 3396, 3286, 1752, 1668, 1366, 1277, 724. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.96 (*s*, MeN); 3.02 (*s*, MeN); 5.57 (*s*, 1 CH); 6.72 (*s*, 1 arom. H); 7.33–7.99 (*m*, 6 arom. H); 10.80 (*s*, 1 NH); 11.69 (br. *s*, 1 OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 28.6; 49.7; 56.2; 111.7; 112.2; 113.5; 113.9; 119.8; 120.6; 125.9; 126.2; 126.7; 129.9; 131.6; 132.7; 133.8; 135.3; 142.2; 151.9; 165.6; 166.7; 175.8; 180.6; 183.7. MS: 536 (3, $[M-2]^+$), 367 (17), 207 (50), 76 (68), 69 (82), 57 (100), 55 (97). Anal. calc. for $C_{24}H_{16}BrN_3O_7$ (538.30): C 53.55, H 3.00, N 7.81; found: C 53.69, H 2.91, N 7.98.

*5-[3-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-5-nitro-2-oxo-1*H*-indol-3-yl]-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4h**). Yellow powder. 0.398 g (79%). M.p. 248–249°. IR (KBr): 3260, 1735, 1682, 1660, 1629, 1602, 1337, 1079, 724. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.97 (*s*, MeN); 3.04 (*s*, MeN); 5.73 (*s*, 1 CH); 6.98 (*d*, $J = 6.6$, 1 arom. H); 7.81–8.30 (*m*, 6 arom. H); 11.40 (*s*, 1 NH); 11.90 (br. *s*, 1 OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 28.6; 49.8; 55.7; 110.0; 120.1; 121.4; 126.2; 126.7; 129.9; 131.5; 133.8; 135.3; 142.8; 149.3; 151.7; 154.0; 165.8; 166.4; 176.9; 180.9; 186.5. MS: 509 (53, $[M+5]^+$), 388 (25), 163 (39), 107 (47), 101 (70), 67 (57), 57 (66), 56 (100), 54 (81), 53 (91), 50 (61). Anal. calc. for $C_{24}H_{16}N_4O_9$ (504.41): C 57.15, H 3.20, N 11.11; found: C 56.94, H 3.33, N 10.97.

*5-[3-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-2-oxo-1*H-*indol-3-yl]dihydro-2-thioxopyrimidine-4,6(1*H,*5*H*)-dione* (**4i**). Yellow powder. 0.362 g (81%). M.p. >300°. IR (KBr): 3333, 3064, 1711, 1676, 1655, 1623, 1599, 1328, 1236, 754. ^{1}H-NMR (300 MHz, (D_6)DMSO): 5.40 (*s*, 1 CH); 6.73–8.00 (*m*, 8 arom. H); 10.62 (*s*, 1 NH); 11.00 (*s*, 1 NH); 11.08 (*s*, 1 NH); 11.34 (*s*, 1 OH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 49.0; 55.5; 109.6; 122.1; 122.2; 125.7; 126.0; 126.6; 128.5; 129.7; 130.7; 133.7; 133.9; 135.2; 143.1; 151.2; 152.8; 167.4; 168.8; 176.2; 181.1; 186.2. MS: 452 (11, $[M+5]^+$), 231 (24), 174.0 (32), 162 (26), 107 (15), 89 (22), 74 (53), 69 (57), 53 (75), 50 (100). Anal. calc. for $C_{22}H_{13}N_3O_6S$ (447.42): C 59.06, H 2.93, N 9.39, S 7.17; found: C 59.74, H 3.02, N 9.48, S 7.31.

*5-[3-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-2-oxo-1*H-*indol-3-yl]dihydro-2-thioxopyrimidine-4,6(1*H,*5*H*)-dione* (**4j**). Yellow powder. 0.484 g (92%). M.p. 242–250°. IR (KBr): 3407, 1701, 1678, 1637, 1611, 1596, 1318, 1264, 780. ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.59 (*s*, 1 CH); 6.77 (*s*, 1 arom. H); 7.32–7.99 (*m*, 6 arom. H, NH); 10.86 (*s*, 2 NH); 12.55 (br. *s*, 1 OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 30.6; 48.5; 111.0; 113.3; 113.9; 125.2; 126.6; 127.9; 129.0; 129.5; 130.9; 131.6; 132.6; 135.8; 140.5; 143.7; 157.3; 176.2; 177.1; 177.7. MS: 446 (50, $[M-Br]^+$), 262 (11), 195 (10), 150 (60), 148 (41), 120 (39), 52 (100). Anal. calc. for $C_{22}H_{12}BrN_3O_6S$ (526.32): C 50.20, H 2.30, N 7.98, S 6.09; found: C 49.95, H 2.32, N 8.08, S 6.22.

*5-[3-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yl)-2,3-dihydro-5-nitro-2-oxo-1*H-*indol-3-yl]dihydro)-2-thioxopyrimidine-4,6(1*H,*5*H*)-dione* (**4k**). Yellow powder. 0.389 g (79%). M.p. >300°. IR (KBr): 3346, 3115, 1704, 1681, 1628, 1606, 1575, 1339, 1226, 773. ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.45 (*s*, 1 CH); 6.99 (*s*, 1 arom. H); 7.00 (*s*, 1 arom. H); 7.74–8.15 (*m*, 5 arom. H); 8.21 (*s*, 1 NH); 11.42 (br. *s*, 2 NH); 12.62 (*s*, 1 OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 46.2; 56.5; 109.1; 113.5; 121.2; 125.3; 126.5; 129.0; 131.0; 132.6; 133.0; 135.5; 142.4; 150.9; 153.0; 156.4; 159.8; 174.2; 176.2; 177.1; 177.7. MS: 497 (29, $M+5]^+$), 319 (30), 162 (41), 121 (61), 55 (100). Anal. calc. for $C_{22}H_{12}N_4O_8S$ (492.42): C 53.66, H 2.46, N 11.38, S 6.51; found: C 53.69, H 2.54, N 11.47, S 6.39.

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