New One-Pot Synthesis of 3-Alkyl- and 3-(ω-Hydroxyalkyl)oxindoles from Isatins

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A new and efficient one-pot procedure has been developed for the synthesis of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles from isatins by treatment with alcohols and diols in the presence of Raney nickel, under hydrogen atmosphere.

Introduction

Oxindole derivatives are important targets in medicinal chemistry. In addition to already available drugs (ropinirole,[1] ziprasidone[2]), there are several representatives of this family in phase II or phase III clinical trials for various therapeutic purposes ranging from treatment of Alzheimer's disease (e.g. linopirdine[3]) to potassium channel openers[4,5] and VEGF-inhibitors with potential anti-cancer activity.[6]

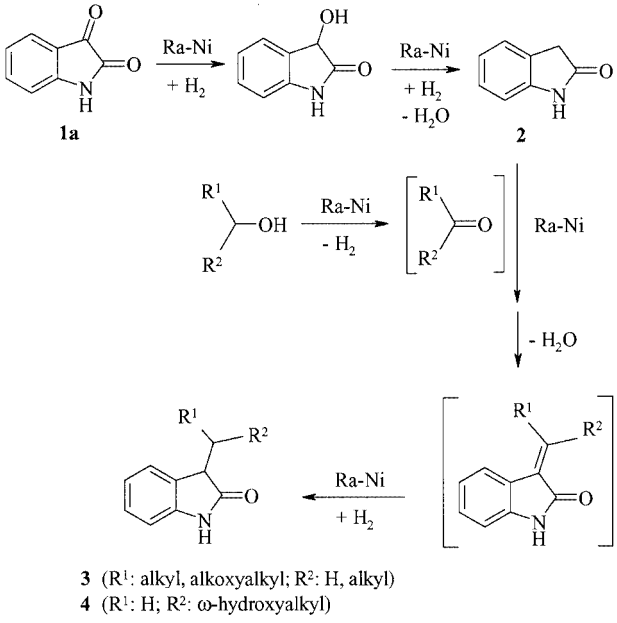
Since oxindole has two regiochemically distinct easily removable protons [N−H, C(3)−H] and the anions formed are ambident nucleophiles, any deprotonation/functionalization sequence can give rise to the formation of regioisomers. Thus, direct alkylation[7] and acylation[8] of deprotonated oxindoles have limited synthetic significance because of the lack of regioselectivity and the formation of di- and trialkylated (acylated) products.

The two-step reductive alkylation of oxindole with ketones and aromatic aldehydes is a convenient method for the preparation of 3-alkyloxindoles. However, in the case of aliphatic aldehydes the yields are moderate because of aldol-type side reactions.[9]

We set ourselves the task of developing efficient methods for the regioselective alkylation and acylation of oxindoles unsubstituted in the hetero ring. First we reported the synthesis of 1,3-bis[alkoxy(aryloxy)carbonyl]oxindoles with identical or different acyl groups in the two positions.[10] More recently, in an improvement of Wenkert's pioneer work,[11] we reported the synthesis of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles by treatment of oxindoles with alcohols and diols in the presence of Raney nickel.[12]

Results and Discussion

Since oxindoles can be prepared by the catalytic reduction of easily available isatins,[13−15] we investigated whether a complex reaction sequence (Scheme 1), which involves the reduction of isatin to oxindole via 3-hydroxyoxindole[16] and the regioselective alkylation of oxindole at the 3-position with alcohols in the presence of Raney nickel, might be carried out in one pot.



Scheme 1

Accordingly, we performed the reaction of isatin (**1a**) with ethanol by heating in an autoclave at 150 °C for 5 h in the presence of Raney nickel. As expected, we obtained 3-ethyloxindole (**3b**) as the main product. However, the conversion of isatin (**1a**) to 3-ethyloxindole (**3b**) was substan-

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Table 1. Reactions of isatins **1a**−**g** with alcohols affording 3-alkyloxindoles **3a**−**q**

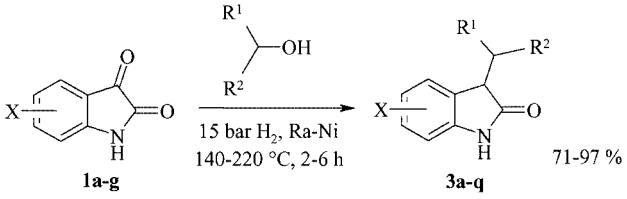
Entry	X	Starting material	R^1	R^2	Product[a]	Reaction time (h)	Temp. [°C]	Yield[b] [c] (%)	M.p. [°C]	Ref. m.p. [°C]
1	H	**1a**	H	H	**3a**[d]	2	190	71	122−123	123−124[12]
2	H	**1a**	Me	H	**3b**[d]	4	180	88	102−103	101−102[12]
3	H	**1a**	Et	H	**3c**[d]	3	180	94	82−83	81−82[19]
4	H	**1a**	Pr	H	**3d**[d]	4	180	97	62−63	62−63[12]
5	H	**1a**	*i*Pr	H	**3e**[d]	3	200	89	96−97	96−97[12]
6	H	**1a**	Ph	H	**3f**[d]	4	220	97	131−132	130−132[12]
7	H	**1a**	3-MeO−C_6H_4	H	**3g**[d]	5	140	93	89−90	–
8	H	**1a**	2-Me−C_6H_4	H	**3h**[d]	4	150	74	108−109	–
9	H	**1a**	$-(CH_2)_5-$		**3i**[d]	4	200	95	169−170	168−170[12]
10	H	**1a**	Me	Me	**3j**[d]	4	200	73	102−104	103−105[12]
11	5-F	**1b**	Me	H	**3k**[d]	4	210	71	105−106	–
12	6-F	**1c**	Me	H	**3l**[d]	5	210	89	96−97	–
13	5-Me	**1d**	Me	H	**3m**[d]	5	210	91	120−121	–[20]
14	7-Me	**1e**	Me	H	**3n**[d]	2	210	86	152−153	–
15	7-Et	**1f**	Me	H	**3o**[d]	3	200	83	112−113	–
16	7-MeO	**1g**	Me	H	**3p**[d]	3	170	94	144−146	–
17	H	**1a**	CH_2OMe	H	**3q**[d]	6	180	90	71−72	–
18	5-F	**1b**	Me	H	**3k**[e]	6	210	74	105−106	–
19	6-F	**1c**	Me	H	**3l**[f]	6	210	91	96−97	–
20	H	**1a**	$-(CH_2)_5-$		**3i**[g]	6	200	82	169−170	168−170[12]
21	H	**1a**	*i*Pr	H	**3e**[h]	8	200	85	96−97	96−97[12]
22	H	**1a**	Me	H	**3b**[i]	25	150	89	102−103	101−102[12]

[a] Satisfactory elemental analyses were obtained for all new compounds: calcd. C ± 0.28, H ± 0.15, N ± 0.13. Known compounds were identified with m.p. and ^1H NMR spectra. [b] Yields refer to spectroscopically pure products. [c] For recrystallization solvents, see the Exp. Sect. [d] Prepared according to the general procedure (see Exp. Sect.). [e] Starting from 5-fluoroisatin (**1b**; 9.9 g, 0.06 mol), EtOH (150 mL) and Raney Ni (3.0 g). [f] Starting from 6-fluoroisatin (**1c**; 16.5 g, 0.10 mol), EtOH (150 mL) and Raney Ni (5.0 g). [g] Starting from isatin (**1a**; 14.7 g, 0.10 mol), cyclohexanol (150 mL) and Raney Ni (5.0 g). [h] Starting from isatin (**1a**; 29.4 g, 0.20 mol), *i*BuOH (200 mL) and Raney Ni (5.0 g). [i] Starting from isatin (**1a**; 73.5 g, 0.50 mol), EtOH (500 mL) and Raney Ni (20.0 g).

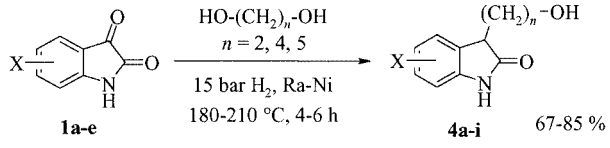
tially lower than the conversion of oxindole (**2**) to 3-ethyloxindole (**3b**) under the same conditions,[12] which indicates that the multistep reaction sequence suffers from the slow reduction of isatin (**1a**) to oxindole (**2**). Although longer reaction times and higher temperatures resulted in better conversions, the yield of the isolated product was unsatisfactory because of the formation of unidentified impurities. In order to accelerate the introductory reaction step, i.e. the reduction of isatin (**1a**) to oxindole (**2**), we carried out the reaction of isatin (**1a**) with ethanol in the presence of Raney nickel at 180 °C under 15 bar hydrogen. We obtained a high yield (88%) of 3-ethyloxindole (**3b**) after 4 h reaction time (Table 1, entry 2). It is remarkable that the overall reaction proceeds well in the reductive atmosphere, despite the fact that the supposed reaction sequence (Scheme 1) involves the oxidation of ethanol to acetaldehyde.

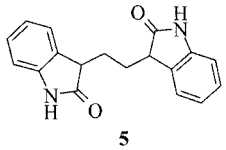
The reaction described above can be applied to other alcohols and isatins. Here we report the first convenient one-pot synthesis of 3-alkyloxindoles by treatment of isatins with alcohols in the presence of Raney nickel under hydrogen atmosphere. Multistep alternatives of the transformation of isatins to 3-alkyl- and 3-aryloxindoles involve the addition of carbanionic reagents to the 3-carbonyl group of isatins followed by reduction.[5,17]

We have successfully carried out the reactions of isatins **1a**−**g** with various primary and secondary alcohols in an autoclave at 140−220 °C for 2−5 h in the presence of less than one mass equivalent of Raney nickel under 15 bar hydrogen, and isolated the corresponding 3-alkyloxindoles **3a**−**p** in high yields (Scheme 2, Table 1, entries 1−16). The reaction of isatin with 2-methoxyethanol gave 3-(2-methoxyethyl)oxindole (**3q**) under similar conditions (entry 17). We



Scheme 2





Scheme 3

Table 2. Reactions of isatins **1a**−**e** with diols affording 3-(ω-hydroxyalkyl)oxindoles **4a**−**i**

Entry	X	Starting material	*n*	Product[a]	Reaction time (h)	Temperature [°C]	Yield[b][c] (%)	M.p. [°C]	Ref. m.p. [°C]
1	H	**1a**	2	**4a**[d]	5	180	69	111−112	110−111[12]
2	H	**1a**	4	**4b**[d]	4	190	75	86−87	86−87[12]
3	5-F	**1b**	4	**4c**[d]	5	190	81	130−131	−
4	6-F	**1c**	4	**4d**[d]	6	210	74	89−90	−
5	5-Me	**1d**	4	**4e**[d]	6	180	85	113−115	−
6	7-Me	**1e**	4	**4f**[d]	6	180	80	133−134	−
7	H	**1a**	5	**4g**[d]	5	190	83	78−80	−
8	5-F	**1b**	5	**4h**[d]	6	190	76	97−98	−
9	6-F	**1c**	5	**4i**[d]	6	190	67	86−87	−
10	H	**1a**	4	**4a**[e]	5	190	70	86−87	86−87[12]
11	5-F	**1b**	4	**4c**[f]	8	190	83	130−131	−
12	H	**1a**	4	**4b**[g]	25	150	78	86−87	86−87[12]

[a] Satisfactory elemental analyses were obtained for all new compounds: calcd. C ± 0.28, H ± 0.15, N ± 0.13. Known compounds were identified with m.p. and ^{1}H NMR spectra. [b] Yields refer to spectroscopically pure products. [c] For recrystallization solvents, see the Exp. Sect. [d] Prepared according to the general procedure (see Exp. Sect.). [e] Starting from isatin (**1a**; 14.7 g, 0.10 mol), butane-1,4-diol (150 mL, 1.69 mol) and Raney Ni (10.0 g). [f] Starting from 5-fluoroisatin (**1b**; 26.4 g, 0.16 mol), butane-1,4-diol (450 mL, 5.07 mol) and Raney Ni (15.0 g). [g] Starting from isatin (**1a**; 73.5 g, 0.50 mol), butane-1,4-diol (200 mL, 2.25 mol), THF (300 mL) and Raney Ni (20.0 g).

have also successfully performed scaled-up reactions starting from various isatins (entries 18−22).

Not surprisingly, the method does not tolerate the presence of chloro and bromo substituents: the reaction of 5-chloro- and 5-bromoisatin under the same conditions afforded product mixtures containing dehalogenated products.

We extended the alkylation reaction of isatins with alcohols under hydrogen in the presence of Raney nickel to the synthesis of 3-(ω-hydroxyalkyl)oxindoles.[18] The treatment of isatins **1a**−**e** with diols under the conditions shown above afforded 3-(ω-hydroxyalkyl)oxindoles **4a**−**i** in good yields (Scheme 3, Table 2, entries 1−9).

We isolated by-product **5** (≈10%, mixture of diastereomers) when we performed the reaction of isatin **1a** with five equivalents of ethylene glycol in tetrahydrofuran. The formation of compound **5** could be suppressed by using ethylene glycol as a solvent (Table 2, entry 1). We did not observe a similar by-product in the case of butane-1,4-diol (entry 12). Scaling up of the hydroxyalkylation reaction of isatin (**1a**) and 5-fluoroisatin (**1b**) with butane-1,4-diol also gave good results (entries 10 and 11, respectively).

Conclusion

The procedure described above provides a convenient one-pot access to a wide range of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles starting from isatins. It is noteworthy that a great diversity of reactions of different types (oxidation, condensation and varied reduction steps) proceeds consecutively in one pot. This method is apparently superior to earlier ones because the starting materials are readily available and the yields are good. The 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles obtained can be further functionalized, so they are valuable building blocks in medicinal and synthetic organic chemistry.

Experimental Section

General: All melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker IFS-113v FT spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Unity Inova 400 spectrometer (400 and 101 MHz for ^{1}H and ^{13}C NMR spectra, respectively) using TMS as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and Hz, respectively. Elemental analyses were performed on a Perkin−Elmer 2400 analyzer. The alkylation reactions were carried out in autoclaves (volume: 70, 250 or 850 mL, depending on the amount of reagents used), which were equipped with a temperature controller, a manometer (60 bar), a valve for gas inlet and a magnetic stirrer. All reactions were analyzed by TLC on silica gel 60 F_{254}.

Degussa's activated Raney nickel catalyst in water was used in the reactions. Isatin (**1a**) was purchased from Fluka Co., the substituted isatins **1b**−**g** were prepared from the corresponding anilines in two steps following the Sandmeyer procedure.[21]

Alkylation of Isatins, General Procedure: A mixture of the appropriate isatin (**1a**−**g**; 0.01 mol), alcohol or diol (20 mL) and Raney nickel (1.0 g, ca. 0.017 mol) was placed in an autoclave (volume 70 mL). It was flushed with nitrogen, charged with 15 bar hydrogen and heated while stirring (for temperatures and reaction times see Table 1 and 2). When the reaction was complete, the mixture was stirred with charcoal, filtered and the excess of alcohol was evaporated in vacuo.

(i) The residue was triturated with *n*-hexane (10 mL) to give **3c**−**g**, **3i**, **3l**−**m** and **3p**−**q** as colourless crystalline products.

(ii) The residue was triturated with *n*-hexane (10 mL) and the crude crystalline product was recrystallized from a mixture of *n*-hexane and EtOAc to give **3a**−**b**, **3h, 3j, 3n**−**o** and **4a** as colourless crystalline products.

(iii) The residue was triturated with Et_2O (10 mL) to give **4e** as a colourless crystalline product.

(iv) The oily residue was distilled under reduced pressure and the distillate was triturated with *n*-hexane (10 mL) to give **3k** as a colourless crystalline product.

(v) The oily residue was distilled under reduced pressure and the distillate was triturated with Et_2O (10 mL) to give **4b−d** and **4f−i** as colourless crystalline products.

Spectroscopic data for the new products **3g−h, 3k−q** and **4c−i** prepared according to the general procedure are shown below.

7-Ethyl-1*H*-indole-2,3-dione (1f): M.p. 193−194 °C (acetic acid/water) (ref.[22] m.p. 194−195 °C). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.15 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH_3), 2.56 (q, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2), 7.02 [t, $^3J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.35 [d, $^3J_{H,H}$ = 7.3 Hz, 1 H, C(4)-H], 7.45 [d, $^3J_{H,H}$ = 7.5 Hz, 1 H, C(6)-H], 11.1 (s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO, 25 °C): δ = 14.5 (CH_3), 22.5 (CH_2), 117.9 [C(3a)], 122.4 [C(4)], 123.1 [C(5)], 127.9 [C(7)], 138.3 [C(6)], 148.9 [C(7a)], 160.3 [C(2)], 185.0 [C(3)] ppm.

7-Methoxy-1*H*-indole-2,3-dione (1g): M.p. 240−242 °C (acetic acid/water) (ref.[23] m.p. 242−243 °C). IR (KBr): $\tilde{\nu}$ = 1738 cm^{-1} (C=O). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 3.87 (s, 3 H, CH_3), 7.04 [dd, $^3J_{H,H}$ = 8.1, $^3J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.11 [dt, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 0.9 Hz, 1 H, C(6)-H], 7.33 [dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.0 Hz, 1 H, C(4)-H], 11.1 (s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO, 25 °C): δ = 56.2 (CH_3), 116.5 [C(6)], 118.4 [C(3a)], 121.1 [C(4)], 123.5 [C(5)], 140.2 [C(7a)], 144.9 [C(7)], 159.5 [C(2)], 184.6 [C(3)] ppm.

3-(3-Methoxybenzyl)-1,3-dihydro-2*H*-indol-2-one (3g): Yield: 2.36 g (93%); m.p. 89−90 °C (EtOAc/*n*-hexane). IR (KBr): $\tilde{\nu}$ = 1698 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.90 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 9.3 Hz, 1 H, C*H*H), 3.47 [dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 4.4 Hz, 1 H, CH*H*], 3.72 (s, 3 H, CH_3), 3.75 [dd, $^3J_{H,H}$ = 9.3, $^3J_{H,H}$ = 4.4 Hz, 1 H, C(3)-H], 6.72−6.80 [m, 4 H, C(4)-H and 3 Ar-H], 6.85 [d, $^3J_{H,H}$ = 7.8 Hz, 1 H, C(7)-H], 6.90 [t, $^3J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.16 [t, $^3J_{H,H}$ = 7.8 Hz, 2 H, C(6)-H and Ar-H], 8.97 (s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 36.6 (CH_2), 47.5 [C(3)], 55.1 (CH_3), 109.7 [C(7)], 112.4, 114.7, 121.8, 122.0 [C(5)], 124.8 [C(4)], 127.9 [C(6)], 129.0 [C(3a)], 129.3, 139.4, 141.5 [C(7a)], 159.5, 179.8 [C(2)] ppm. $C_{16}H_{15}NO_2$ (253.3): calcd. C 75.87, H 5.97, N 5.53; found C 75.59, H 6.09, N 5.65.

3-(2-Methylbenzyl)-1,3-dihydro-2*H*-indol-2-one (3h): Yield: 1.75 g (74%); m.p. 108−109 °C (EtOAc/*n*-hexane). IR (KBr): $\tilde{\nu}$ = 1708 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.31 (s, 3 H, CH_3), 2.84 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 4.7 Hz, 1 H, C*H*H), 3.54 [dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 4.7 Hz, 1 H, CH*H*], 3.73 [dd, $^3J_{H,H}$ = 11.0, $^3J_{H,H}$ = 4.6 Hz, 1 H, C(3)-H], 6.55 [d, $^3J_{H,H}$ = 7.4 Hz, 1 H, C(7)-H], 6.85 [d, 1 H, $^3J_{H,H}$ = 7.5 Hz, C(5)-H], 6.85 [d, $^3J_{H,H}$ = 7.8 Hz, 1 H, C(7)-H], 7.17−7.21 [m, 5 H, C(6)-H and 4 Ar-H], 9.06 (s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 19.6 (CH_3), 34.3 (CH_2), 46.3 [C(3)], 109.8 [C(7)], 122.0 [C(5)], 125.0 [C(4)], 125.9, 126.8, 127.9 [C(6)], 129.2 [C(3a)], 130.0, 130.5, 136.5, 136.7, 141.4 [C(7a)], 180.1 ppm. $C_{16}H_{15}NO_2$ (237.3): calcd. C 80.98, H 6.37, N 5.90; found C 80.86, H 6.35, N 5.92.

3-Ethyl-5-fluoro-1,3-dihydro-2*H*-indol-2-one (3k): B.p. 114−118 °C (0.03 Torr). Yield: 1.27 g (71%); m.p. 105−106 °C (EtOAc/*n*-hexane). IR (KBr): $\tilde{\nu}$ = 1705 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH_3), 2.00−2.07 (m, 2 H, CH_2), 3.47 [t, $^3J_{H,H}$ = 5.5 Hz, 1 H, C(3)-H], 6.83 [dd, $^3J_{H,H}$ = 8.4, $^4J_{H,F}$ = 4.4 Hz, 1 H, C(7)-H], 6.89−6.95 [m, 1 H, C(6)-H], 6.98 [dd, $^3J_{H,F}$ = 8.1, $^4J_{H,H}$ = 2.0 Hz, 1 H, C(4)-H], 8.80 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 9.9 (CH_3), 23.5 (CH_2), 47.6 [d, $^4J_{C,F}$ = 1.9 Hz, C(3)], 110.1 [d, $^3J_{C,F}$ = 8.4 Hz, C(7)], 112.0 [d, $^2J_{C,F}$ = 24.8 Hz, C(4)], 114.1 [d, $^2J_{C,F}$ = 23.6 Hz, C(6)], 131.1 [d, $^3J_{C,F}$ = 8.0 Hz, C(3a)], 137.6 [d, $^4J_{C,F}$ = 2.3 Hz, C(7a)], 159.0 [d, $^1J_{C,F}$ = 240.3 Hz, C(5)], 180.3 [C(2)] ppm. $C_{10}H_{10}FNO$ (179.2): calcd. C 67.03, H 5.62, N 7.82; found C 66.97, H 5.61, N 7.72.

3-Ethyl-6-fluoro-1,3-dihydro-2*H*-indol-2-one (3l): Yield: 1.59 g (89%); m.p. 96−97 °C (EtOAc/*n*-hexane). IR (KBr): $\tilde{\nu}$ = 1690 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, CH_3), 2.02 (quintett, $^3J_{H,H}$ = 6.7 Hz, 2 H, CH_2), 3.43 [t, $^3J_{H,H}$ = 5.6 Hz, 1 H, C(3)-H], 6.65−6.75 [m, 2 H, C(5)-H and C(7)-H], 7.15 [dd, $^3J_{H,H}$ = 7.8, $^4J_{H,F}$ = 5.5 Hz, 1 H, C(4)-H], 9.28 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 9.9 (CH_3), 23.6 (CH_2), 46.7 [C(3)], 98.4 [d, $^2J_{C,F}$ = 27.1 Hz, C(7)], 108.5 [d, $^2J_{C,F}$ = 22.5 Hz, C(5)], 124.8 [d, $^4J_{C,F}$ = 3.0 Hz, C(3a)], 124.9 [d, $^3J_{C,F}$ = 9.5 Hz, C(4)], 143.1 [d, $^3J_{C,F}$ = 11.8 Hz, C(7a)], 162.6 [d, $^1J_{C,F}$ = 244.1 Hz, C(6)], 181.2 [C(2)] ppm. $C_{10}H_{10}FNO$ (179.2): calcd. C 67.03, H 5.62, N 7.82; found C 66.78, H 5.58, N 7.75.

3-Ethyl-5-methyl-1,3-dihydro-2*H*-indol-2-one (3m): Yield: 1.59 g (91%); m.p. 120−121 °C (EtOAc/*n*-hexane). IR (KBr): $\tilde{\nu}$ = 1706 cm^{-1} (C=O). ^{1}H and ^{13}C NMR spectra are in agreement with the data described in ref.[20]

3-Ethyl-7-methyl-1,3-dihydro-2*H*-indol-2-one (3n): Yield: 1.51 g (86%); m.p. 152−153 °C (*i*PrOH). IR (KBr): $\tilde{\nu}$ = 1703 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.94 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, CH_2CH_3), 1.99−2.06 (m, 2 H, CH_2), 2.29 (s, 3 H, $ArCH_3$), 3.46 [t, $^3J_{H,H}$ = 5.8 Hz, 1 H, C(3)-H], 6.95 [t, $^3J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.04 [d, $^3J_{H,H}$ = 7.7 Hz, 1 H, C(6)-H], 7.07 [d, $^3J_{H,H}$ = 7.3 Hz, 1 H, C(4)-H], 8.38 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 10.1 (CH_2CH_3), 16.5 ($ArCH_3$), 23.7 (CH_2), 47.5 [C(3)], 119.0 [C(7)], 121.4 [C(4)], 122.1 [C(5)], 129.1 [C(3a)], 129.1 [C(6)], 140.6 [C(7a)], 180.9 [C(2)] ppm. $C_{11}H_{13}NO$ (175.2): calcd. C 75.40, H 7.48, N 7.99; found C 75.31, H 7.36, N 7.96.

3,7-Diethyl-1,3-dihydro-2*H*-indol-2-one (3o): Yield: 1.57 g (83%); m.p. 112−113 °C (EtOAc/*n*-hexane). IR (KBr): $\tilde{\nu}$ = 1702 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.94 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, $ArCH_2CH_3$), 1.26 (t, $^3J_{H,H}$ = 7.6 Hz, 3 H, $CHCH_2CH_3$), 2.01−2.05 (m, 2 H, $CHCH_2$), 2.63 [q, $^3J_{H,H}$ = 7.6 Hz, 2 H, $ArCH_2$], 3.46 [t, $^3J_{H,H}$ = 5.9 Hz, 1 H, C(3)-H], 6.99 [t, $^3J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.07 [d, $^3J_{H,H}$ = 7.8 Hz, 1 H, C(6)-H], 7.08 [d, $^3J_{H,H}$ = 7.8 Hz, 1 H, C(4)-H], 9.01 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 10.1 ($CHCH_2CH_3$), 14.0 ($ArCH_2CH_3$), 23.7 ($CHCH_2$), 23.9 ($ArCH_2$), 47.4 [C(3)], 121.5 [C(4)], 122.3 [C(5)], 125.2 [C(7)], 127.3 [C(6)], 129.3 [C(3a)], 139.9 [C(7a)], 180.9 [C(2)] ppm. $C_{12}H_{15}NO$ (189.3): calcd. C 76.16, H 7.99, N 7.40; found C 76.05, H 7.97, N 7.32.

3-Ethyl-7-methoxy-1,3-dihydro-2*H*-indol-2-one (3p): Yield: 1.79 g (94%); m.p. 144−146 °C (EtOAc/*n*-hexane). IR (KBr): $\tilde{\nu}$ = 1710 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, CH_2CH_3), 1.99−2.06 (m, 2 H, CH_2), 3.47 [t, $^3J_{H,H}$ = 5.8 Hz, 1 H, C(3)-H], 3.87 (s, 3 H, OCH_3), 6.81 [d, $^3J_{H,H}$ = 8.2 Hz, 1 H, C(4)-H], 6.86 [dq, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 0.5 Hz, 1 H, C(6)-H], 6.99 [t, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(5)-H], 8.31 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 10.0 (CH_2CH_3), 23.5 ($CHCH_2$), 47.7 [C(3)], 55.6 (OCH_3), 110.2 [C(4)], 116.4 [C(6)], 122.6 [C(5)], 130.3 [C(7a)], 130.5 [C(3a)], 143.7 [C(7)], 179.4 [C(2)] ppm. $C_{11}H_{13}NO_2$ (191.2): calcd. C 69.09, H 6.85, N 7.32; found C 68.97, H 6.70, N 7.29.

3-(2-Methoxyethyl)-1,3-dihydro-2*H*-indol-2-one (3q): Yield: 1.72 g (90%); m.p. 71−72 °C (EtOAc/*n*-hexane). IR (KBr): $\tilde{\nu}$ = 1704 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.17−2.26 (m, 2 H, CHC*H*$_2$), 3.31 (s, 3 H, CH_3), 3.54−3.60 (m, 3 H, CH_2O and CH), 6.92 [d, $^3J_{H,H}$ = 7.7 Hz, 1 H, C(7)-H], 7.02 [t, $^3J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.18−7.25 [m, 2 H, C(4)-H and C(6)-H], 9.29 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 30.2 (CH*C*H$_2$), 43.2 [C(3)], 58.5 (CH_3), 69.1 [CH_2O], 109.8 [C(7)], 122.1 [C(5)], 124.2 [C(4)], 127.8 [C(6)], 129.3 [C(3a)], 141.7 [C(7a)], 180.9 [C(2)] ppm. $C_{11}H_{13}NO_2$ (191.2): calcd. C 69.09, H 6.85, N 7.32; found C 68.89, H 6.77, N 7.28.

3-(4-Hydroxybutyl)-1,3-dihydro-2*H*-indol-2-one (4b): B.p. 184−186 °C (0.15 Torr). Yield: 1.54 g (75%); m.p. 86−87 °C (EtOAc/*n*-heptane). For spectroscopic data, see ref.[12]

5-Fluoro-3-(4-hydroxybutyl)-1,3-dihydro-2*H*-indol-2-one (4c): B.p. 206−208 °C (0.03 Torr). Yield: 1.81 g (81%); m.p. 130−131 °C (EtOAc/*n*-heptane). IR (KBr): $\tilde{\nu}$ = 1683 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.36−1.64 (m, 4 H, 2 × CH_2), 1.96−2.05 (m, 2 H, CH_2), 3.50 [t, $^3J_{H,H}$ = 5.9 Hz, 1 H, C(3)-H], 3.63 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, C*H*$_2$OH), 6.81 [dd, $^3J_{H,H}$ = 8.5, $^4J_{H,F}$ = 4.4 Hz, 1 H, C(7)-H], 6.92 [m, 1 H, C(6)-H], 6.98 [dd, $^3J_{H,F}$ = 8.1, $^4J_{H,H}$ = 2.3 Hz, 1 H, C(4)-H], 8.51 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 21.9 (CH_2), 30.1 (CH_2), 32.5 (CH_2), 46.4 [C(3)], 62.4 (CH_2OH), 110.1 [d, $^3J_{C,F}$ = 8.4 Hz, C(7)], 112.1 [d, $^2J_{C,F}$ = 24.8 Hz, C(4)], 114.2 [d, $^2J_{C,F}$ = 23.7 Hz, C(6)], 131.2 [d, $^3J_{C,F}$ = 8.0 Hz, C(3a)], 137.4 [C(7a)], 159.1 [d, $^1J_{C,F}$ = 240.0 Hz, C(5)], 180.0 [C(2)] ppm. $C_{12}H_{14}FNO_2$ (223.3): calcd. C 64.56, H 6.32, N 6.27; found C 64.52, H 6.34, N 6.17.

6-Fluoro-3-(4-hydroxybutyl)-1,3-dihydro-2*H*-indol-2-one (4d): B.p. 204−206 °C (0.02 Torr). Yield: 1.65 g (74%); m.p. 89−90 °C (diisopropyl ether). IR (KBr): $\tilde{\nu}$ = 1699 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34−1.50 (m, 2 H, CH_2), 1.54−1.62 (m, 2 H, CH_2), 1.90−2.00 (m, 2 H, CH_2), 2.16 (br. s, 1 H, OH), 3.45 [t, $^3J_{H,H}$ = 6.0 Hz, 1 H, C(3)-H], 3.61 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, C*H*$_2$OH), 6.65 [dd, $^3J_{H,F}$ = 8.7, $^4J_{H,H}$ = 2.3 Hz, 1 H, C(7)-H], 6.70 [ddd, $^3J_{H,F}$ = 9.7, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 2.3 Hz, 1 H, C(5)-H], 7.14 [dd, $^3J_{H,H}$ = 8.0, $^4J_{H,F}$ = 5.3 Hz, 1 H, C(4)-H], 9.19 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 21.9 (CH_2), 30.2 (CH_2), 32.4 (CH_2), 45.5 [C(3)], 62.3 (CH_2OH), 98.4 [d, $^2J_{C,F}$ = 27.1 Hz, C(7)], 108.5 [d, $^2J_{C,F}$ = 22.5 Hz, C(5)], 124.9 [C(3a)], 124.9 [d, $^3J_{C,F}$ = 6.1 Hz, C(4)], 142.9 [d, $^3J_{C,F}$ = 11.8 Hz, C(7a)], 162.6 [d, $^1J_{C,F}$ = 244.1 Hz, C(6)], 181.1 [C(2)] ppm. $C_{12}H_{14}FNO_2$ (223.3): calcd. C 64.56, H 6.32, N 6.27; found C 64.57, H 6.47, N 6.40.

3-(4-Hydroxybutyl)-5-methyl-1,3-dihydro-2*H*-indol-2-one (4e): Yield: 1.86 g (85%); m.p. 113−115 °C (EtOAc/*n*-hexane). IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.36−1.48 (m, 2 H, CH_2), 1.57 (quintett, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2), 1.96 (q, $^3J_{H,H}$ = 7.4 Hz, 2 H, CH_2), 2.31 (s, 3 H, CH_3), 2.50 (br. s, 1 H, OH), 3.43 [t, $^3J_{H,H}$ = 5.8 Hz, 1 H, C(3)-H], 3.59 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, C*H*$_2$OH), 6.78 [d, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(7)-H], 6.98 [d, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(6)-H], 7.02 [s, 1 H, C(4)-H], 9.27 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 21.1 (CH_3), 21.9 (CH_2), 30.1 (CH_2), 32.5 (CH_2), 46.1 [C(3)], 62.2 (CH_2OH), 109.5 [C(7)], 124.7 [C(4)], 128.0 [C(6)], 129.7 [C(3a)], 131.6 [C(5)], 139.2 [C(7)], 180.9 [C(2)] ppm. $C_{13}H_{17}NO_2$ (219.3): calcd. C 71.21, H 7.81, N 6.39; found C 71.15, H 7.79, N 6.35.

3-(4-Hydroxybutyl)-7-methyl-1,3-dihydro-2*H*-indol-2-one (4f): B.p. 206−208 °C (0.20 Torr). Yield: 1.75 g (80%); m.p. 133−134 °C (EtOAc/*n*-heptane). IR (KBr): $\tilde{\nu}$ = 1698 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.36−1.54 (m, 2 H, CH_2), 1.54−1.63 (m, 2 H, CH_2), 1.76 (t, $^3J_{H,H}$ = 5.0 Hz, 1 H, OH), 1.98−2.05 (m, 2 H, CH_2), 2.29 (s, 3 H, CH_3), 3.50 [t, $^3J_{H,H}$ = 6.0 Hz, 1 H, C(3)-H], 3.60 (q, $^3J_{H,H}$ = 5.5 Hz, 2 H, C*H*$_2$OH), 6.94 [t, $^3J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.03 [d, $^3J_{H,H}$ = 7.3 Hz, 1 H, C(6)-H], 7.06 [d, $^3J_{H,H}$ = 7.3 Hz, 1 H, C(4)-H], 9.15 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 16.5 (CH_3), 22.0 (CH_2), 30.2 (CH_2), 32.6 (CH_2), 46.4 [C(3)], 62.4 (CH_2OH), 119.1 [C(7)], 122.2 [C(4)], 122.4 [C(5)], 129.1 [C(6)], 129.2 [C(3a)], 140.4 [C(7a)], 181.0 [C(2)] ppm. $C_{13}H_{17}NO_2$ (219.3): calcd. C 71.21, H 7.81, N 6.39; found C 71.08, H 7.69, N 6.41.

3-(5-Hydroxypentyl)-1,3-dihydro-2*H*-indol-2-one (4g): B.p. 206−210 °C (0.04 Torr). Yield: 1.82 g (83%); m.p. 78−80 °C (EtOAc/diisopropyl ether). IR (KBr): $\tilde{\nu}$ = 1701 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.29−1.40 (m, 4 H, 2 × CH_2), 1.41−1.59 (m, 2 H, CHC*H*$_2$), 1.86−2.00 (m, 2 H, C*H*$_2$CH$_2$OH), 2.62 (br. s, 1 H, OH), 3.46 [t, $^3J_{H,H}$ = 5.4 Hz, 1 H, C(3)-H], 3.59 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, C*H*$_2$OH), 6.91 [d, $^3J_{H,H}$ = 7.5 Hz, 1 H, C(7)-H], 7.01 [t, $^3J_{H,H}$ = 7.6 Hz, 1 H, C(5)-H], 7.19 [t, $^3J_{H,H}$ = 7.3 Hz, 1 H, C(6)-H], 7.20 [d, $^3J_{H,H}$ = 7.3 Hz, 1 H, C(4)-H], 9.23 (s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 25.5 (CHCH$_2$*C*H$_2$), 25.8 (CHCH$_2$CH$_2$*C*H$_2$), 30.5 (CH*C*H$_2$), 32.5 (*C*H$_2$CH$_2$OH), 46.2 [C(3)], 62.7 (CH_2OH), 110.0 [C(7)], 122.4 [C(5)], 124.2 [C(4)], 128.0 [C(6)], 130.0 [C(3a)], 141.9 [C(7a)], 181.1 [C(2)] ppm. $C_{13}H_{17}NO_2$ (219.3): calcd. C 71.21, H 7.81, N 6.39; found C 71.16, H 7.93, N 6.49.

5-Fluoro-3-(5-hydroxypentyl)-1,3-dihydro-2*H*-indol-2-one (4h): B.p. 204−208 °C (0.025 Torr). Yield: 1.80 g (76%); m.p. 97−98 °C (EtOAc/diisopropyl ether). IR (KBr): $\tilde{\nu}$ = 1684 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.30−1.44 (m, 4 H, 2 × CH_2), 1.51−1.59 (m, 2 H, C*H*$_2$CH$_2$OH), 1.89−1.99 (m, 3 H, CHC*H*$_2$ and OH), 3.47 [t, $^3J_{H,H}$ = 6.0 Hz, 1 H, C(3)-H], 3.61 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, CH_2OH), 6.83 [dd, $^3J_{H,H}$ = 8.5, $^4J_{H,F}$ = 4.4 Hz, 1 H, C(7)-H], 6.91 [dt, $^3J_{H,H} \approx {}^3J_{H,F}$ = 8.5, $^4J_{H,H}$ = 2.6 Hz, 1 H, C(6)-H], 6.96 (dd, $^3J_{H,F}$ = 8.1, $^4J_{H,H}$ = 1.9 Hz, 1 H, C(4)-H), 9.09 (s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 25.3 (CHCH$_2$*C*H$_2$), 25.6 (CHCH$_2$CH$_2$*C*H$_2$), 30.2 (CH*C*H$_2$), 32.3 (*C*H$_2$CH$_2$OH), 46.4 [d, $^4J_{C,F}$ = 1.5 Hz, C(3)], 62.5 (CH_2OH), 110.2 [d, $^3J_{C,F}$ = 8.0 Hz, C(7)], 112.0 [d, $^2J_{C,F}$ = 24.4 Hz, C(4)], 114.1 [d, $^2J_{C,F}$ = 23.7 Hz, C(6)], 131.3 [d, $^3J_{C,F}$ = 8.0 Hz, C(3a)], 137.6 [C(7a)], 159.0 [d, $^1J_{C,F}$ = 240.0 Hz, C(5)], 180.6 [C(2)] ppm. $C_{13}H_{16}FNO_2$ (237.3): calcd. C 65.81, H 6.80, N 5.90; found C 65.98, H 6.89, N 5.83.

6-Fluoro-3-(5-hydroxypentyl)-1,3-dihydro-2*H*-indol-2-one (4i): B.p. 200−204 °C (0.05 Torr). Yield: 1.59 g (67%); m.p. 86−87 °C (EtOAc/diisopropyl ether). IR (KBr): $\tilde{\nu}$ = 1706 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.25−1.39 (m, 4 H, 2 × CH_2), 1.40−1.58 (m, 2 H, C*H*$_2$CH$_2$OH), 1.60−1.90 (br. s, 1 H, OH), 1.90−1.99 (m, 2 H, CHC*H*$_2$), 3.44 [t, $^3J_{H,H}$ = 6.1 Hz, 1 H, C(3)-H], 3.61 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, CH_2OH), 6.65 [dd, $^3J_{H,F}$ = 8.5, $^4J_{H,H}$ = 2.4 Hz, 1 H, C(7)-H], 6.71 [dt, $^3J_{H,H} \approx {}^3J_{H,F}$ = 8.9, $^4J_{H,H}$ = 2.4 Hz, 1 H, C(5)-H], 7.14 (dd, $^3J_{H,H}$ = 8.2, $^4J_{H,F}$ = 5.3 Hz, 1 H, C(4)-H), 8.82 (s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 25.3 (CHCH$_2$*C*H$_2$), 25.6 (CHCH$_2$CH$_2$*C*H$_2$), 30.4 (CH*C*H$_2$), 32.3 (*C*H$_2$CH$_2$OH), 45.4 [C(3)], 62.6 (CH_2OH), 98.3 [d, $^2J_{C,F}$ = 27.1 Hz, C(7)], 108.5 [d, $^2J_{C,F}$ = 22.5 Hz, C(5)], 124.9 [C(3a)], 125.0 [C(4)], 142.8 [d, $^3J_{C,F}$ = 12.2 Hz, C(7a)], 162.6 [d, $^1J_{C,F}$ = 244.5 Hz, C(6)], 180.8 [C(2)] ppm. $C_{13}H_{16}FNO_2$ (237.3): calcd. C 65.81, H 6.80, N 5.90; found C 65.73, H 6.79, N 5.91.

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