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2*H*-[1,3]Oxazino[3,2-α]indolin-4(3*H*)-ones: A New Class Of Polyheterocyclic Indole-based Compounds

Jan M. Hartmann,[a] Marita de Groot,[a] Katja Schäringer,[a] Kira Henke,[a] Kari Rissanen[b] and Markus Albrecht*[a]

Abstract: A methodology for the synthesis of 2*H*-[1,3]oxazino[3,2-α]indolin-4(3*H*)-ones is reported. They are obtained from readily available materials by a facile synthetic procedure following either a two step cascade reaction or a step by step transformation. The target compounds represent a hitherto unreported class of indole derivatives with a novel kind of tris- or tetracyclic backbone.

Introduction

The indole-alkaloids represent an important class of natural products with a broad structural versatility and remarkable biochemical or pharmacological activities.[1] Especially, fused polycyclic indoline derivatives are important bioactive natural products.[2] Well-known members of this class include the chloride channel modulator strychnine **1**,[3] cholinesterase inhibitor (–)-physostigmine **2**[4] and the microtubule inhibitor (+)-vinblastine **3**[5] (Figure 1).

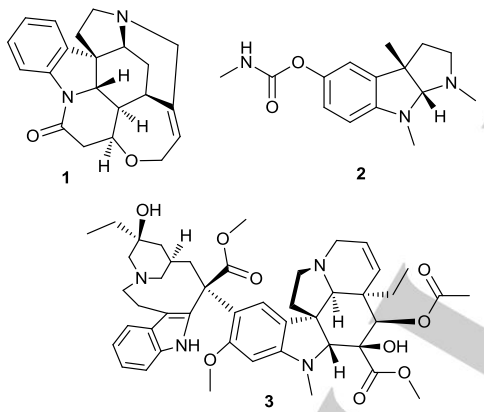

Figure 1. Important indoline based natural products.

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Synthetic access to a wide palette of highly functionalized indoline derivatives is therefore of high interest for synthetic organic chemistry with a high impact in medicine, pharmacology as well as molecular biology.[6]

To the best of our knowledge, 5a*H*-benzo[5,6][1,3]oxazino[3,2-α]indol-12(6*H*)ones **4** and even more generally 2*H*-[1,3]oxazino[3,2-α]indolin-4(3*H*)-ones **5** have not previously been reported[7] in the literature while the corresponding aromatic indole **6a** as well as derivatives thereof have been synthesiszed by copper-catalyzed domino intramolecular cyclization.[8] Recently the tetracycles **6b** bearing an alkyl group R^1 as well as an exocyclic double bond (ketone or alkene) in 3 position of the indoline have been prepared by a Pd(II)-catalyzed Wacker-type cyclization (Figure 2).[9] The high importance of indole derivatives in nature as well as their high biological activity makes the synthesis of unknown indole based structures desirable.[1] In this paper we report the facile preparation of 2,3-sp^3 hybridized 2*H*-[1,3]oxazino[3,2-α]indolin-4(3*H*)-one derivatives **4** and **5** from readily available starting materials.

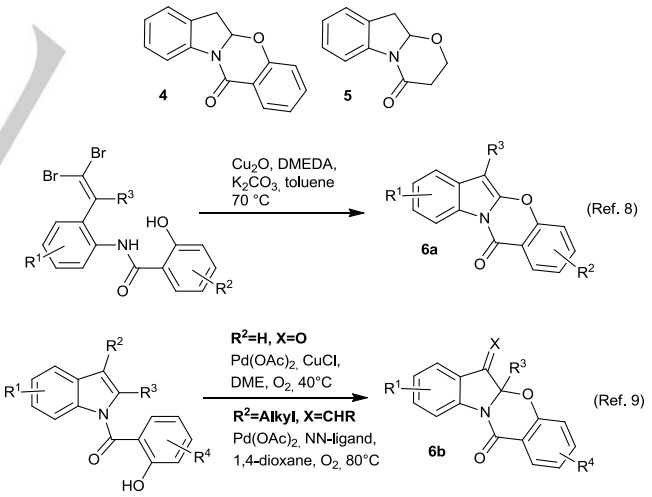
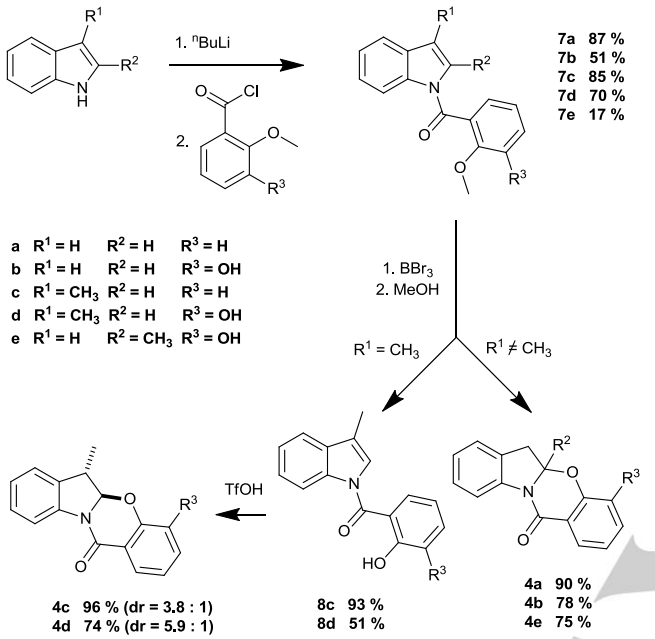


Figure 2. 5a*H*-benzo[5,6][1,3]oxazino[3,2-*a*]indol-12(6*H*)one **4**, 2*H*-[1,3]oxazino[3,2-*a*]indolin-4(3*H*)-ones **5**, and the preparation of the aromatic analogues **6a,b**[8,9].

Results and Discussion

The synthesis of the target compounds starts with *N*-(2-methoxybenzoyl)-1*H*-indoles **7** which are conveniently prepared from the respective indole and acyl chloride precursors.[10] Subsequent demethylation with boron tribromide[11] leads in case of the skatole derivatives **7c,d** to the expected *N*-

(2-hydroxybenzoyl)-1*H*-indoles **8c** and **8d**.[12] In case of the parent indole **7a,b** or of 2-methylindole **7e** demethylation is followed by cyclization[13] and 5a*H*-benzo[5,6][1,3]oxazino[3,2-α]indol-12(6*H*)ones **4a,b,e** are obtained. Similar cyclization can be achieved for the skatole derivatives **8c,d** by the use of triflic acid resulting in **4c,d** *(Scheme 1).*



Scheme 1. Synthesis of 5a*H*-benzo[5,6][1,3]oxazino[3,2-α]indol-12(6*H*)ones **4a-e**, starting from the respective indoles and acyl chlorides.

The tetracyclic compounds are characterized by standard analytical methods. As an example the unsubstituted derivative **4a** shows a characteristic ^{1}H NMR spectrum revealing the signals of two aryl units at δ = 8.14 (d, *J* = 7.9 Hz, 1 H), 8.08 (dd, *J* = 7.7 Hz, 1.7 Hz, 1 H), 7.49 – 7.53 (m, 1 H), 7.24 – 7.33 (m, 2 H), 7.20 (pt, *J* = 7.5 Hz, 1 H) and 7.05 – 7.12 (m, 2 H) and of the CH_2CH moiety at δ = 6.06 (dd, *J* = 8.2 Hz, 6.9 Hz, 1 H, CH), 3.60 (dd, *J* = 16.5 Hz, 8.2 Hz, 1 H, CH_2) and 3.49 (dd, *J* = 16.5 Hz, 6.9 Hz, 1 H, CH_2) (Figure 3, top).

The methyl-hydroxy substituted compound **4e** crystallizes in the space group P21/n. The structure in the solid state obtained by X-ray diffraction is shown in Figure 4. The tetracycle adopts a corrugated structure with pyramidalization at the methyl substituted sp^3 carbon of the indoline skeleton.

A catalyst screening revealed triflic acid and sulfuric acid to be suitable to induce the cyclisation reaction while acetic acid, trifluoroacetic acid and *p*-toluenesulfonic acid did not lead to a transformation of the precursors **8c,d**. Phosphoric acid based chiral Brønsted acids were also included in the screening,[14] but resulted in no reaction. If cyclization does not take place, starting material can be recovered quantitatively.

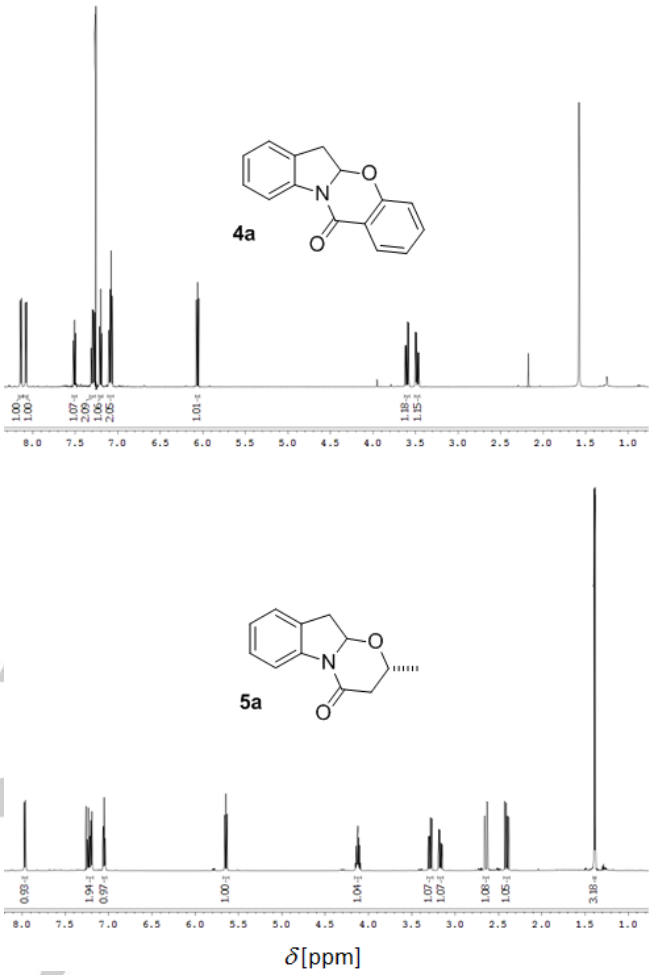


Figure 3. Proton NMR spectra of **4a** and **5a**.

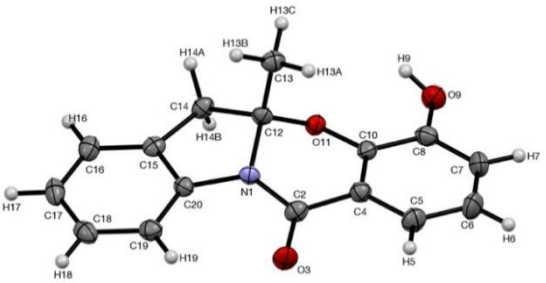
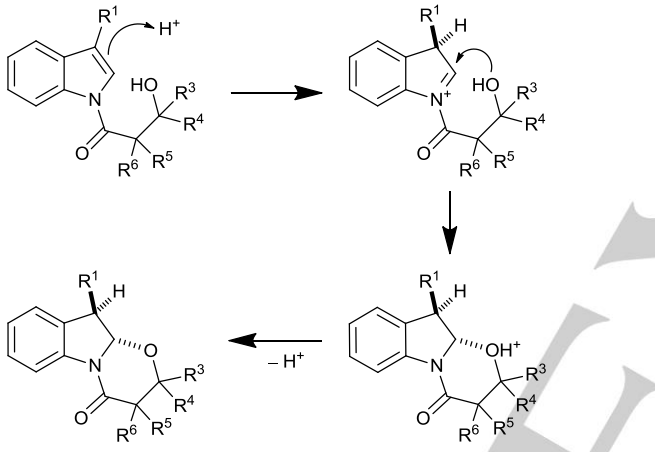


Figure 4. Molecular structure of **4e** in the crystal.

The described method is limited to N-acylindoles. No analogous reaction with BBr_3 could be observed for 2-methoxybenzoyl derivatives of pyrrole, benzotriazole or carbazole or for the 2,3-dimethoxybenzoyl of benzimidazole. The addition reaction also appears to proceed only intramolecularly; attempting the triflic acid-catalyzed addition of phenol to N-benzoylindole failed.

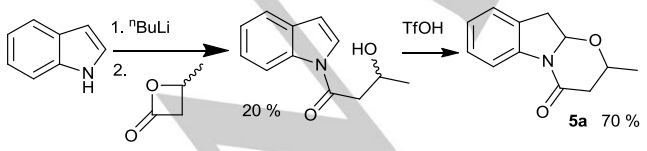
With substituents in 3-position of the indole ring, a mixture of diastereoisomers of **4c,d** is formed. The NOE contacts show the favoured diastereoisomer to have trans-configuration along the indoline C2-C3 bond. Triflic acid gives a marginally higher diastereomeric ratio than sulfuric acid (e.g. **8c**: TfOH: 3.8:1, H_2SO_4: 3.3:1).

The skatole starting materials bearing a substituent in the nucleophilic 3-position of the indole require Brønsted acids to initiate the cyclization reaction but do not work with BBr_3. This points to the addition of an acid (BBr_3 or proton) to C3 as the initial step in the mechanism, which appears to be sterically restricted to sterically undemanding derivatives at C3 (e.g. **7a,b,e**) with boron tribromide. Steric effects may favour the ring closing trans attack of the phenolic oxygen on C2. A mechanism as shown in scheme 2 can be deduced from this. With BBr_3, the mechanism is similar but the Lewis acid is removed upon hydrolytic work up.



Scheme 2. Postulated mechanism for the Brønsted acid-catalyzed addition reaction.

The described synthetic approach is not limited to aromatic acyl groups, as exemplified by the triflic acid-catalyzed cyclization of 3-hydroxybutyryl indole **7f** yielding tricyclic 2*H*-[1,3]oxazino[3,2-α]indolin-4(3*H*)-one **5a** (Scheme 3). Despite the notable differences in reactivity of phenols and secondary aliphatic alcohols, the reaction proceeds just as smoothly and yields are comparable.



Scheme 3. Synthesis of 2*H*-[1,3]oxazino[3,2-α]indolin-4(3*H*)-one **5a**, starting from indole and rac-β-butyrolactone.

Compound **5a** easily can be characterized by its spectroscopic data showing in the 1H NMR spectrum signals of the aromatic (δ = 7.96 (d, *J* = 8.0 Hz, 1 H), 7.14 – 7.31 (m, 2 H), 7.05 (pt, *J* = 7.5 Hz, 1 H),) as well as aliphatic protons (δ = 5.65 (dd, *J* = 8.5 Hz, 7.5 Hz, 1 H), 4.03 – 4.19 (m, 1 H), 3.29 (dd, *J* = 15.7 Hz, 7.5 Hz, 1 H, CH_2), 3.18 (dd, *J* = 15.7 Hz, 8.5 Hz, 1 H, CH_2), 2.64 (dd, *J* = 17.6 Hz, 4.8 Hz, 1 H, CH_2), 2.40 (dd, *J* = 17.5 Hz, 10.5 Hz, 1 H, CH_2), 1.39 (d, *J* = 6.2 Hz, 3 H, CH_3); Figure 3, bottom).

Conclusions

In summary, we presented a facile synthesis of a novel indoline based polycyclic structure which is easily obtained by acid catalysed intramolecular nucleophilic addition of hydroxyl groups to the 2 position of indole.[15] Hereby, the deprotection/cyclization procedure utilising BBr_3 as deprotecting as well as cyclizating reagent represents a two step cascade reaction.[16] The obtained tricyclic and tetracyclic structures are structurally interesting and might provide an entry to a new class of functional molecules.

Experimental Section

Anhydrous diethyl ether and DCM were obtained from a solvent purification system. 2,3-dimethoxybenzoyl chloride was prepared from the corresponding acid by refluxing with excess thionyl chloride. All other solvents and chemicals were used as obtained from commercial suppliers. Chloroform contained < 1 % ethanol for stabilization. Air and moisture sensitive reactions were carried out using air-free technique under nitrogen. NMR spectra were measured on Varian Mercury 300, VNMRS 400 and VNMRS 600 instruments. EI mass spectra were measured on a Finnigan SSQ 7000. HR-ESI mass spectra were measured on a ThermoFisher Scientific LTQ Orbitrap XL on samples in acidified methanol. FTIR spectra were measured on a PerkinElmer Spectrum 100 *via* ATR. Elemental analysis was performed using vario EL and vario EL cube instruments from elementar. Melting points were determined on a Büchi B-540 melting point apparatus. TLC was carried out on silica F_{254} TLC plates from Macherey-Nagel, Düren.

General Procedure 1 – Synthesis of *N*-Acylindoles To a solution of the indole in anhydrous Et_2O (50 mL) under nitrogen was added ^{n}BuLi (1.6 M in hexanes, 1.0 equiv.). The reaction mixture was stirred for 5 min. The acid chloride (1.1 equiv.) was added, resulting in a voluminous precipitate. The reaction mixture was stirred for 24 h and washed with water (50 mL). The organic phase was separated off and the aqueous phase extracted with DCM (3 × 50 mL). The combined organic phases were dried with sodium sulfate and the solvent was removed *in vacuo*. Chromatographic purification of the residue (silica, 35 × 5 cm, DCM) yielded the *N*-acylindole.

***N*-(2-Methoxybenzoyl)-1*H*-indole (7a).** Indole (430 mg, 3.67 mmol), ^{n}BuLi (1.6 M in hexanes, 2.3 mL, 37 mmol, 1.0 equiv.) and 2-methoxybenzoyl chloride (0.60 mL, 40 mmol, 1.1 equiv.) were used. *N*-(2-Methoxybenzoyl)-1*H*-indole (**7a**, 809 mg, 3.21 mmol, 87 %) was obtained as a yellowish oil. **Molecular formula:** $C_{16}H_{13}NO_2$. **Molecular mass:** 251.280 g/mol. $\mathbf{R_f}$ (DCM): 0.66. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.44 (*d*, J = 7.9 Hz, 1 H, CH), 7.60 – 7.27 (*m*, 5 H, CH), 7.12 – 6.99 (*m*, 3 H, CH), 6.55 (*d*, J = 3.8 Hz, 1 H, CH), 3.79 (*s*, 3 H, OCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.4 (CO), 156.5 (C), 135.7 (C), 132.3 (CH), 131.1 (C), 129.2 (CH), 127.6 (CH), 125.0 (CH), 124.0 (CH), 122.1 (C),

120.9 (CH), 120.9 (CH), 116.7 (CH), 111.6 (CH), 108.8 (CH), 55.9 (OCH_3). **MS** (EI^+, 70 eV) *m/z* (%): 252.1 (32), 251.0 (100) M^+, 136.1 (13), 135.0 (100) $[M–C_8H_6N]^+ = [C_8H_7O_2]^+$, 117.1 (17) $[M–C_8H_8O_2]^+ = [C_8H_7N]^+$. **HRMS** ($ESI^+$) *m/z:* calcd. for $[M+Na]^+ = [C_{16}H_{13}NO_2Na]^+$: 274.0839, found: 274.0842. **IR** (ATR): ν = 3372 (*br w*), 3058 (*w*), 2945 (*w*), 2319 (*br w*), 2095 (*w*), 1908 (*br w*), 1685 (*vs*), 1594 (*m*), 1537 (*w*), 1449 (*vs*), 1338 (*vs*), 1248 (*m*), 1114 (*w*), 1021 (*s*), 937 (*w*), 880 (*s*), 748 cm^{-1} (*vs*).

***N*-(2,3-Dimethoxybenzoyl)-1*H*-indole (7b).** Indole (1.17 g, 10.0 mmol), ^{n}BuLi (1.6 M in hexanes, 6.3 mL, 10 mmol, 1.0 equiv.) and 2,3-dimethoxybenzoyl chloride (2.21 g, 11.0 mmol, 1.1 equiv.) were used. *N*-(2,3-Dimethoxybenzoyl)-1*H*-indole (**7b**, 1.45 g, 5.15 mmol, 51 %) was obtained as a brown oil. **Molecular formula:** $C_{17}H_{15}NO_3$. **Molecular mass:** 281.306 g/mol. R_f (chloroform): 0.55. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.55 – 8.41 (*br*, 1 H, CH), 7.58 (*d*, J = 7.7 Hz, 1 H, CH), 7.38 (*pt*, J = 7.5 Hz, 1 H, CH), 7.32 (*pt*, J = 7.5 Hz, 1 H, CH), 7.18 (*pt*, J = 7.9 Hz, 1 H, CH), 7.13 – 7.04 (*m*, 2 H, CH), 7.01 (*dd*, J = 7.7 Hz, 1,5 Hz, 1 H, CH), 6.55 (*d*, J = 3.8 Hz, 1 H, CH), 3.93 (*s*, 3 H, OCH_3), 3.84 (*s*, 3 H, OCH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 166.9 (CO), 152.9 (C), 146.3 (C), 135.7 (C), 131.2 (C), 130.3 (C), 127.6 (CH), 125.0 (CH), 124.6 (CH), 124.1 (CH), 121.0 (CH), 119.9 (CH), 116.6 (CH), 114.6 (CH), 108.9 (CH), 61.9 (OCH_3), 56.1 (OCH_3). **MS** (EI^+, 70 eV) *m/z* (%): 282.1 (22), 281.1 (92) M^+, 166.0 (10), 165.0 (100) $[M–C_8H_6N]^+ = [C_9H_9O_3]^+$. **IR** (ATR): ν = 3376 (*br w*), 3011 (*w*), 2942 (*m*), 2834 (*w*), 2327 (*br m*), 2097 (*m*), 1914 (*br w*), 1690 (*vs*), 1586 (*m*), 1535 (*w*), 1454 (*vs*), 1338 (*vs*), 1266 (*m*), 1200 (*m*), 1048 (*s*), 1002 (*s*), 930 (*m*), 878 (*w*), 824 (*m*), 750 (*vs*), 666 cm^{-1} (*w*). **CHN analysis** calcd. for $C_{17}H_{15}NO_3$: C 72.58 %, H 5.37 %, N 4.98 %; found: C 72.39 %, H 5.38 %, N 5.45 %.

***N*-(2-Methoxybenzoyl)-3-methyl-1*H*-indole (7c).** 3-Methylindole (1.31 g, 10.0 mmol), ^{n}BuLi (1.6 M in hexanes, 6.3 mL, 10 mmol, 1.0 equiv.) and 2-methoxybenzoyl chloride (1.64 mL, 11.0 mmol, 1.1 equiv.) were used. *N*-(2-Methoxybenzoyl)-3-methyl-1*H*-indole (**7c**, 2.26 g, 8.50 mmol, 85 %) was obtained as a yellowish powder. **Molecular formula:** $C_{17}H_{15}NO_2$. **Molecular mass:** 265.306 g/mol. R_f (DCM): 0.65. **Mp:** 112 – 114 °C. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.46 – 8.41 (*br*, 1 H, CH), 7.54 – 7.47 (*m*, 2 H, CH), 7.44 – 7.30 (*m*, 3 H, CH), 7.08 (*pt*, J = 7.5 Hz, 1 H, CH), 7.03 (*d*, J = 8.4 Hz, 1 H, CH), 6.86 – 6.79 (*br*, 1 H, CH), 3.79 (*s*, 3 H, OCH_3), 2.21 (*d*, J = 1.4 Hz, 3 H, CH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 166.9 (CO), 156.4 (C), 136.0 (C), 132.2 (C), 132.0 (CH), 128.9 (CH), 125.3 (C), 125.1 (CH), 124.2 (CH), 123.8 (CH), 120.8 (CH), 118.9 (CH), 118.0 (C), 116.7 (CH), 111.6 (CH), 55.9 (OCH_3), 9.8 (CH_3). **MS** (EI^+, 70 eV) *m/z* (%): 266.1 (22), 265.1 (87) M^+, 136.0 (11), 135.0 (100) $[M–C_9H_8N]^+ = [C_8H_7O_2]^+$. **IR** (ATR): ν = 3021 (*w*), 2935 (*m*), 2836 (*w*), 1739 (*s*), 1682 (*vs*), 1598 (*s*), 1449 (*vs*), 1362 (*vs*), 1245 (*s*), 1216 (*s*), 1166 (*w*), 1111 (*m*), 1024 (*s*), 938 (*w*), 873 (*s*), 746 (*vs*), 662 cm^{-1} (*m*). **CHN analysis** calcd. for $C_{17}H_{15}NO_2$: C 76.96 %, H 5.70 %, N 5.28 %; found: C 76.92 %, H 5.62 %, N 5.15 %.

***N*-(2,3-Dimethoxybenzoyl)-3-methyl-1*H*-indole (7d).** 3-Methylindole (0.66 g, 5.0 mmol), ^{n}BuLi (1.6 M in hexanes, 3.2 mL, 5.1 mmol, 1.0 equiv.) and 2,3-dimethoxybenzoyl chloride (1.1 g, 5.5 mmol, 1.1 equiv.) were used. *N*-(2,3-Dimethoxybenzoyl)-3-methyl-1*H*-indole (**7d**, 1.14 g, 3.85 mmol, 70 %) was obtained as a tan powder. **Molecular formula:** $C_{18}H_{17}NO_3$. **Molecular mass:** 295.332 g/mol. R_f (DCM): 0.59. **Mp:** 95 – 97 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.64 – 8.26 (*br*, 1 H, CH), 7.51 (*d*, J = 7.6 Hz, 1 H, CH), 7.42 – 7.28 (*m*, 2 H, CH), 7.17 (*dd*, J = 8.3 Hz, 7.6 Hz, 1 H, CH), 7.08 (*dd*, J = 8.3 Hz, 1.5 Hz, 1 H, CH), 6.99 (*dd*, J = 7.6 Hz, 1.5 Hz, 1 H, CH), 6.82 (*s*, 1 H, CH), 3.94 (*s*, 3 H, OCH_3), 3.83 (*s*, 3 H, OCH_3), 2.19 (*s*, 3 H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.5 (CO), 153.0 (C), 146.2 (C), 136.0 (C), 132.3 (C), 130.7 (C), 125.1 (CH), 124.6 (CH), 124.3 (CH), 123.9 (CH), 119.9 (CH), 119.0 (CH), 118.2 (C), 116.7 (CH), 114.4 (CH), 61.9 (OCH_3), 56.1 (OCH_3), 9.8 (CH_3). **MS** (EI^+, 70 eV) *m/z* (%): 296.0 (26), 295.0 (78) M^+, 166.0 (16), 165.0 (100) $[M–C_9H_8N]^+ = [C_9H_9O_3]^+$. **HRMS** ($ESI^+$) *m/z:* calcd. for $[M+Na]^+ = [C_{18}H_{17}NO_3Na]^+$: 318.1101, found: 318.1096. **IR** (ATR): ν = 2940 (*m*), 1684 (*s*), 1582 (*m*), 1452 (*s*), 1351 (*s*), 1260 (*m*), 1219 (*m*), 1165 (*w*), 1085 (*w*), 1033 (*m*), 996 (*s*), 927 (*m*), 878 (*w*), 739 cm^{-1} (*s*). **CHN analysis** calcd. for $C_{18}H_{17}NO_3$: C 73.20 %, H 5.80 %, N 4.74 %; found: C 72.98 %, H 5.76 %, N 4.60 %.

***N*-(2,3-Dimethoxybenzoyl)-2-methyl-1*H*-indole (7e).** 2-Methylindole (1.27 g, 9.72 mmol), ^{n}BuLi (1.6 M in hexanes, 6.1 mL, 9.7 mmol, 1.0 equiv.) and 2,3-dimethoxybenzoyl chloride (2.14 g, 10.7 mmol, 1.1 equiv.) were used. *N*-(2,3-Dimethoxybenzoyl)-2-methyl-1*H*-indole (**7e**, 0.497 g, 1.68 mmol, 17 %) was obtained as a red powder. **Molecular formula:** $C_{18}H_{17}NO_3$. **Molecular mass:** 295.332 g/mol. R_f (DCM): 0.37. **Mp:** 83 – 84 °C. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.42 (*d*, J = 7.6 Hz, 1 H, CH), 7.38 (*d*, J = 8.3 Hz, 1 H, CH), 7.20 – 7.12 (*m*, 2 H, CH), 7.12 – 7.04 (*m*, 2 H, CH), 6.95 (*dd*, J = 7.6 Hz, 1.6 Hz, 1 H, CH), 6.36 (*s*, 1 H, CH), 3.92 (*s*, 3 H, OCH_3), 3.77 (*s*, 3 H, OCH_3), 2.28 (*s*, 3 H, CH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 167.7 (CO), 153.2 (C), 146.7 (C), 137.9 (C), 137.2 (C), 132.1 (C), 129.9 (C), 124.7 (CH), 123.5 (CH), 123.3 (CH), 120.2 (CH), 119.7 (CH), 115.1 (CH), 115.1 (CH), 109.7 (CH), 61.8 (OCH_3), 56.1 (OCH_3), 16.3 (CH_3). **MS** (EI^+, 70 eV) *m/z* (%): 295.5 (19) M^+, 165.4 (100) $[M–C_9H_8N]^+ = [C_9H_9O_3]^+$, 122.3 (13) $[M–CH_3–C_{10}H_8NO]^+ = [C_7H_6O_2]^+$. **HRMS** ($ESI^+$) *m/z:* calcd. for $[M+H]^+ = [C_{18}H_{18}NO_3]^+$: 296.1287, found: 296.1279. **IR** (ATR): ν = 3356 (*br w*), 2929 (s), 2328 (*br w*), 2096 (*w*), 1922 (*br w*), 1682 (*vs*), 1584 (*s*), 1447 (*vs*), 1330 (*vs*), 1259 (*m*), 1226 (*m*), 1159 (*m*), 1073 (*vs*), 983 (*vs*), 818 (*vs*), 746 (*vs*), 665 cm^{-1} (*m*).

***rac*-*N*-(3-Hydroxybutyryl)-1*H*-indole (7f).** To a solution of indole (1.17 g, 10.0 mmol) in anhydrous Et_2O (50 mL) under nitrogen was added ^{n}BuLi (1.6 M in hexanes, 6.30 mL, 10.0 mmol, 1.00 equiv.). The reaction mixture was stirred for 5 min. *rac*-β-Butyrolactone (0.90 mL, 11 mmol, 1.1 equiv.) was added, resulting in a voluminous precipitate. The reaction mixture was stirred for 24 h and washed with water (50 mL). The organic phase was separated off and the aqueous phase extracted with Et_2O (3 × 50 mL). The combined organic phases were dried with sodium sulfate and the solvent was removed under reduced pressure. Chromatographic purification of the residue (silica, DCM/EtOAc 95:5) yielded *rac*-*N*-(3-hydroxybutyryl)-1*H*-indole (**7f**, 408 mg, 2.00 mmol, 20 %) as a light brown oil. **Molecular formula:** $C_{12}H_{13}NO_2$. **Molecular mass:** 203.237 g/mol. R_f (chloroform): 0.12. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.45 (*d*, J = 8.0 Hz, 1 H, CH), 7.57 (*d*, J = 7.7 Hz, 1 H, CH), 7.40 (*d*, J = 3.8 Hz, 1 H, CH), 7.36 (*ddd*, J = 8.5 Hz, 7.2 Hz, J = 1.3 Hz, 1 H, CH), 7.29 (*pt*, J = 7.5 Hz, 1 H, CH), 6.65 (*d*, J = 3.8 Hz, 1 H, CH), 4.47 (*dqd*, J = 8.6 Hz, 6.4 Hz, 3.2 Hz, 1 H, CH), 3.20 – 2.95 (*br*, 1 H, OH), 3.04 (*dd*, J = 16.8 Hz, 3.2 Hz, 1 H, CH_2), 2.99 (*dd*, J = 16.8 Hz, 8.6 Hz, 1 H, CH_2), 1.35 (*d*, J = 6.4 Hz, 3 H, CH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 171.2 (CO), 135.6 (C), 130.5 (C), 125.4 (CH), 124.4 (CH), 124.1 (CH), 121.1 (CH), 116.7 (CH), 109.9 (CH), 64.0 (CH), 44.1 (CH_2), 22.4 (CH_3). **MS** (EI^+, 70 eV) *m/z* (%): 204.1 (24), 203.1 (69) M^+, 118.1 (15), 117.1 (100) $[M–C_4H_6O_2]^+ = [C_8H_7N]^+$. **HRMS** ($ESI^+$) *m/z:* calcd. for $[M+Na]^+ = [C_{12}H_{13}NO_2Na]^+$: 226.0839, found: 226.0834. **IR** (ATR): ν = 3417 (*br w*), 2973 (*w*), 2928 (*w*), 1693 (*vs*), 1584 (*w*), 1538 (*m*), 1449 (*vs*), 1393 (*s*), 1340 (*vs*), 1283 (*m*), 1202 (*vs*), 1153 (*m*), 1110 (*s*), 1079 (*s*), 1018 (*w*), 956 (*m*), 926 (*m*), 879 (*m*), 853 (*m*), 748 (*vs*), 717 cm^{-1} (*vs*).

General Procedure 2 – Synthesis of *N*-(Hydroxyacyl)-1*H*-indoles and 2*H*-[1,3]Oxazino[3,2-*a*]indolin-4(3*H*)-ones. To a solution of the *N*-acylindole **7** in anhydrous DCM (3.0 mL) was added boron tribromide solution (1.0 M in DCM) and the reaction mixture was stirred for 24 h. MeOH (2.0 mL) was added carefully (vigorous reaction!) and the solvent was removed under reduced pressure. To the dry residue, MeOH (2.0 mL) was again added and evaporated, repeating this process 20 times to volatilize residual boron compounds. The residue was filtered through a

short pad of silica using chloroform, yielding the *N*-(hydroxyacyl)-1*H*-indole **8** or 2*H*-[1,3]oxazino[3,2-*a*]indolin-4(3*H*)-one **4**.

5a*H*-Benzo[5,6][1,3]oxazino[3,2-*a*]indol-12(6*H*)one (4a). *N*-(2-Methoxybenzoyl)-1*H*-indole (**7a**, 251 mg, 1.00 mmol) and boron tribromide solution (1.0 M in DCM, 3.0 mL, 3.0 mmol, 3.0 equiv.) were used. 5a*H*-Benzo[5,6][1,3]oxazino[3,2-*a*]indol-12(6*H*)one (**4a**, 213 mg, 898 µmol, 90 %) was obtained as a colorless powder. **Molecular formula:** $C_{15}H_{11}NO_2$. **Molecular mass:** 237.253 g/mol. **R_f** (chloroform): 0.78. **Mp:** 130 – 131 °C. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.14 (*d*, J = 7.9 Hz, 1 H, CH), 8.08 (*dd*, J = 7.7 Hz, 1.7 Hz, 1 H, CH), 7.53 – 7.49 (*m*, 1 H, CH), 7.33 – 7.24 (*m*, 2 H, CH), 7.20 (*pt*, J = 7.5 Hz, 1 H, CH), 7.12 – 7.05 (*m*, 2 H, CH), 6.06 (*dd*, J = 8.2 Hz, 6.9 Hz, 1 H, CH), 3.60 (*dd*, J = 16.5 Hz, 8.2 Hz, 1 H, CH_2), 3.49 (*dd*, J = 16.5 Hz, 6.9 Hz, 1 H, CH_2). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 159.3 (CO), 156.8 (C), 140.5 (C), 134.5 (CH), 128.5 (2 × CH), 127.2 (C), 124.9 (CH), 124.3 (CH), 123.4 (CH), 119.9 (C), 116.9 (CH), 115.5 (CH), 89.6 (CH), 35.3 (CH_2). **MS** (EI^+, 70 eV) *m/z* (%): 238.2 (38), 237.2 (100) M^+, 121.1 (12) $[M–C_8H_6N]^+$ = $[C_7H_5O_2]^+$, 120.1 (21) $[M–C_8H_7N]^+$ = $[C_7H_4O_2]^+$, 117.2 (68) $[M–C_7H_4O_2]^+$ = $[C_8H_7N]^+$, 92.2 (16) $[M–C_8H_4NO_2]^+$ = $[C_6H_5CH_3]^+$. **IR** (ATR): ν = 3326 (*br w*), 3048 (*w*), 2324 (*br w*), 2096 (*w*), 1931 (*br w*), 1741 (*w*), 1659 (*vs*), 1600 (*m*), 1476 (*vs*), 1427 (*vs*), 1314 (*m*), 1220 (*m*), 1151 (*m*), 1079 (*s*), 1023 (*m*), 938 (*w*), 857 (*s*), 746 cm^{-1} (*vs*). **CHN analysis** calcd. for $C_{15}H_{11}NO_2$: C 75.94 %, H 4.67 %, N 5.90 %; found: C 75.60 %, H 4.60 %, N 5.84 %.

4-Hydroxy-5a*H*-benzo[5,6][1,3]oxazino[3,2-*a*]indol-12(6*H*)one (4b). *N*-(2,3-Dimethoxybenzoyl)-1*H*-indole (**7b**, 200 mg, 711 µmol) and boron tribromide solution (1.0 M in DCM, 4.3 mL, 4.3 mmol, 6.0 equiv.) were used. 4-Hydroxy-5a*H*-benzo[5,6][1,3]oxazino[3,2-*a*]indol-12(6*H*)one (**4b**, 140 mg, 553 µmol, 78 %) was obtained as a greyish powder. **Molecular formula:** $C_{15}H_{11}NO_3$. **Molecular mass:** 253.253 g/mol. **R_f** (chloroform): 0.17. **Mp:** 232 – 233 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.15 (*d*, J = 8.0 Hz, 1 H, CH), 7.62 (*dd*, J = 7.7 Hz, 1.7 Hz, 1 H, CH), 7.37 – 7.21 (*m*, 2 H, CH), 7.20 – 7.03 (*m*, 3 H, CH), 6.11 (*dd*, J = 8.1 Hz, 6.8 Hz, 1 H, CH), 5.45 (*s*, 1 H, OH), 3.63 (*dd*, J = 16.7 Hz, 8.1 Hz, 1 H, CH_2), 3.53 (*dd*, J = 16.7 Hz, 6.8 Hz, 1 H, CH_2). **^{13}C NMR** (151 MHz, DMSO-d_6): δ = 158.6 (CO), 146.0 (C), 145.0 (C), 140.0 (C), 128.0 (CH), 127.9 (C), 125.3 (CH), 124.1 (CH), 123.0 (CH), 120.9 (CH), 120.5 (C), 117.5 (CH), 114.1 (CH), 89.5 (CH), 34.3 (CH_2). **MS** (EI^+, 70 eV) *m/z* (%): 254.1 (35), 253.1 (94) M^+, 137.1 (10) $[M–C_8H_6N]^+$ = $[C_7H_5O_3]^+$, 136.0 (63) $[M–C_8H_7N]^+$ = $[C_7H_4O_3]^+$, 118.1 (85) $[M–C_7H_3O_3]^+$ = $[C_8H_8N]^+$, 117.1 (100) $[M–C_7H_4O_3]^+$ = $[C_8H_7N]^+$, 108.1 (16), 90.1 (15), 89.1 (19), 80.1 (13), 52.2 (18), 51.2 (11). **IR** (ATR): ν = 3213 (*br m*), 2329 (*br w*), 2096 (*w*), 1871 (*w*), 1646 (*vs*), 1589 (*vs*), 1441 (*vs*), 1329 (*s*), 1179 (*vs*), 1070 (*s*), 977 (*w*), 843 (*m*), 811 (*m*), 735 cm^{-1} (*vs*). **CHN analysis** calcd. for $C_{15}H_{11}NO_3$: C 71.14 %, H 4.38 %, N 5.53 %; found: C 70.72 %, H 4.32 %, N 5.43 %.

***N*-(2-Hydroxybenzoyl)-3-methyl-1*H*-indole (8c).** *N*-(2-Methoxybenzoyl)-3-methyl-1*H*-indole (**7c**, 133 mg, 500 µmol) and boron tribromide solution (1.0 M in DCM, 1.5 mL, 1.5 mmol, 3.0 equiv.) were used. *N*-(2-Hydroxybenzoyl)-3-methyl-1*H*-indole (**8c**, 110 mg, 464 µmol, 93 %) was obtained as a yellowish powder. **Molecular formula:** $C_{16}H_{13}NO_2$. **Molecular mass:** 251.280 g/mol. **R_f** (chloroform): 0.54. **Mp:** 157 – 160 °C. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 9.97 (*s*, 1 H, OH), 8.30 (*d*, J = 8.0 Hz, 1 H, CH), 7.66 – 7.27 (*m*, 6 H, CH), 7.13 (*d*, J = 7.9 Hz, 1 H, CH), 7.03 – 6.97 (*m*, 1 H, CH), 2.31 (*s*, 3 H, CH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 170.2 (CO), 161.2 (C), 136.4 (C), 135.0 (CH), 131.9 (C), 131.2 (CH), 125.2 (CH), 124.7 (CH), 124.1 (CH), 119.2 (2 × CH), 118.6 (C), 118.5 (CH), 116.5 (CH), 116.4 (C), 9.8 (CH_3). **MS** (EI^+, 70 eV) *m/z* (%): 252.3 (11), 251.3 (55) M^+, 132.3 (10), 131.2 (100) $[M–C_7H_4O_2]^+$ = $[C_9H_9N]^+$, 130.2 (51) $[M–C_7H_5O_2]^+$ = $[C_9H_8N]^+$, 121.2 (26) $[M–C_9H_8N]^+$ = $[C_7H_5O_2]^+$, 65.4 (10) $[C_5H_5]^+$. **IR** (ATR): ν = 3230 (*br s*), 2966 (*w*), 2293 (*w*), 2082 (*w*), 1928 (*br w*), 1740 (*m*), 1649 (*vs*), 1597 (*vs*), 1449 (*vs*), 1357 (*vs*), 1212 (*s*), 1100 (*m*), 1038 (*w*), 934 (*w*), 873 (*s*), 741 cm^{-1} (*vs*). **CHN analysis** calcd. for $C_{16}H_{13}NO_2$: C 76.48 %, H 5.21 %, N 5.57 %; found: C 76.33 %, H 5.12 %, N 5.53 %.

***N*-(2,3-Dihydroxybenzoyl)-3-methyl-1*H*-indole (8d).** *N*-(2,3-Dimethoxybenzoyl)-3-methyl-1*H*-indole (**7d**, 89 mg, 0.30 mmol) and boron tribromide solution (1.0 M in DCM, 1.8 mL, 1.8 mmol, 6.0 equiv.) were used. *N*-(2,3-Dihydroxybenzoyl)-3-methyl-1*H*-indole (**8d**, 45 mg, 0.15 mmol, 51 %) was obtained as a light pink powder. **Molecular formula:** $C_{16}H_{13}NO_3$. **Molecular mass:** 267.279 g/mol. **R_f** (chloroform): 0.17. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 10.11 (*s*, 1 H, OH), 8.29 (*d*, J = 8.4 Hz, 1 H, CH), 7.55 (*d*, J = 8.0 Hz, 1 H, CH), 7.47 – 7.11 (*m*, 5 H, CH), 6.91 (*pt*, J = 7.0 Hz, 1 H, CH), 5.77 (*s*, 1 H, OH), 2.29 (*s*, 3 H, CH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 170.1 (CO), 148.3 (C), 146.0 (C), 136.4 (C), 132.0 (C), 125.3 (CH), 124.7 (CH), 124.2 (CH), 122.1 (CH), 119.6 (CH), 119.5 (CH), 119.2 (CH), 118.8 (C), 116.6 (C), 116.5 (CH), 9.9 (CH_3). **MS** (EI^+, 70 eV) *m/z* (%): 268.0 (33), 267.0 (100) M^+, 137.0 (16) $[M–C_9H_8N]^+$ = $[C_7H_5O_3]^+$, 132.1 (13), 131.1 (87) $[M–C_7H_4O_3]^+$ = $[C_9H_9N]^+$, 130.0 (39) $[M–C_7H_5O_3]^+$ = $[C_9H_8N]^+$. **HRMS** (ESI^+) *m/z:* calcd. for $[M+Na]^+$ = $[C_{16}H_{13}NO_3Na]^+$: 290.0788, found: 290.0781. **IR** (ATR): ν = 3361 (*br w*), 2923 (*w*), 1647 (*s*), 1592 (*s*), 1450 (*vs*), 1391 (*vs*), 1347 (*vs*), 1264 (*vs*), 1210 (*vs*), 1182 (*vs*), 1123 (*s*), 1062 (*s*), 1018 (*w*), 961 (*m*), 907 (*m*), 848 (*s*), 788 (*m*), 741 cm^{-1} (*vs*).

4-Hydroxy-5a-methyl-5a*H*-benzo[5,6][1,3]oxazino[3,2-a]indol-12(6*H*)one (4e). *N*-(2,3-Dimethoxybenzoyl)-2-methyl-1*H*-indole (**7e**, 70 mg, 0.30 mmol) and boron tribromide solution (1.0 M in DCM, 1.8 mL, 1.8 mmol, 6.0 equiv.) were used. 4-Hydroxy-5a-methyl-5a*H*-benzo[5,6][1,3]oxazino[3,2-a]indol-12(6*H*)one (**4e**, 60 mg, 0.22 mmol, 75 %) was obtained as tan crystals. **Molecular formula:** $C_{16}H_{13}NO_3$. **Molecular mass:** 267.279 g/mol. **R_f** (chloroform): 0.22. **Mp:** 196 – 197 °C. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.19 (*d*, J = 8.0 Hz, 1 H, CH), 7.61 (*dd*, J = 7.8 Hz, 1.5 Hz, 1 H, CH), 7.30 (*t*, J = 7.8 Hz, 1 H, CH), 7.28 – 7.24 (*m*, 1 H, CH), 7.15 (*dd*, J = 8.0 Hz, 1.5 Hz, 1 H, CH), 7.11 (*t*, J = 7.5 Hz, 1 H, CH), 7.05 (*t*, J = 8.0 Hz, 1 H, CH), 5.42 (*s*, 1 H, OH), 3.67 (*d*, J = 15.7 Hz, 1 H, CH_2), 3.34 (*d*, J = 15.7 Hz, 1 H, CH_2), 1.61 (*s*, 3 H, CH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 158.3 (CO), 145.0 (C), 142.2 (C), 140.3 (C), 128.6 (CH), 126.5 (C), 125.0 (CH), 124.5 (CH), 123.1 (CH), 120.2 (CH), 119.5 (CH), 119.1 (C), 116.3 (CH), 97.7 (C), 43.3 (CH_2), 24.1 (CH_3). **MS** (EI^+, 70 eV) *m/z* (%): 268.1 (22), 267.1 (78) M^+, 136.0 (45) $[M–C_9H_9N]^+$ = $[C_7H_4O_3]^+$, 132.1 (100) $[M–C_7H_3O_3]^+$ = $[C_9H_{10}N]^+$, 131.1 (68) $[M–C_7H_4O_3]^+$ = $[C_9H_9N]^+$, 130.1 (27) $[M–C_7H_5O_3]^+$ = $[C_9H_8N]^+$, 89.1 (12). **HRMS** (ESI^+) *m/z:* calcd. for $[M+Na]^+$ = $[C_{16}H_{13}NO_3Na]^+$: 290.0793, found: 290.0790. **IR** (ATR): ν = 3277 (*br s*), 2104 (*w*), 1740 (*w*), 1637 (*vs*), 1590 (*vs*), 1475 (*vs*), 1421 (*vs*), 1268 (*s*), 1208 (*vs*), 1129 (*w*), 1070 (*m*), 967 (*m*), 842 (*m*), 744 cm^{-1} (*vs*).

Single crystal X-ray data for **4e** were collected with Agilent Super-Nova dual source wavelength diffractometer with an Atlas CCD detector using multilayer optics monochromatized Mo-*K*α (λ = 0.71073 Å) radiation at 120 K The data collection and reduction was done using the program *CrysAlisPro*[17], the intensities are corrected for absorption with "Analytical" method[18]. The structure were solved with direct methods (*SHELXT*[19]) and refined by full-matrix least squares on F^2 using the *OLEX2*[20], which utilizes the *SHELXL*-2015 module[21]. Anisotropic displacement parameters were assigned to non-H atoms. All the hydrogen atoms were refined using riding models with U_{eq}(H) of 1.5U_{eq}(parent) for hydroxyl and terminal methyl groups, and 1.2 U_{eq}(parent) for other groups. $C_{16}H_{13}NO_3$, *Mr* = 267.27 g/mol, Crystal dimensions: 0.19 x 0.34 x 0.44 mm, monoclinic, space group $P2_1/c$, *a* = 8.9929(5) Å, *b* = 12.9009(8) Å, *c* = 11.3316(7) Å, β = 100.242(6)°, *V* = 1293.7(1) Å^3, *Z* = 4, D_c = 1.372 Mg/m^3, µ= 0.096 mm^{-1}, *F*000 = 560, *T* = 120.0(1) K, θ range for cell measurement: 3.55 - 26°, R_1 = 0.0465 (0.0634), *wR*2 = 0.1025 (0.1149), R_{int} = 0.0321, 2522 independent reflections of which 1995 are I_o>2σ(I_o),

183 parameters, 0 restraints, *GooF* = 1.055, -0.227<Δρ<0.208 e/Å^3. CCDC 1575105 contains the supplementary data for this structure.

General Procedure 3 – Synthesis of 2*H*-[1,3]Oxazino[3,2-*a*]indolin-4(3*H*)-ones. To a solution of the *N*-(hydroxyacyl)-1*H*-indole (100 µmol) in anhydrous DCM (3.0 mL) was added triflic acid and the reaction mixture was stirred for 24 h. Saturated aqueous sodium hydrogen carbonate solution (3.0 mL) was added and the mixture was vigorously shaken. The organic phase was separated and the aqueous phase was extracted with chloroform (2.0 mL). The combined organic phases were dried with sodium sulfate and the solvent was removed under reduced pressure. The residue was filtered through a short pad of silica using chloroform, yielding the 2*H*-[1,3]oxazino[3,2-*a*]indolin-4(3*H*)-one.

6-Methyl-5a*H*-benzo[5,6][1,3]oxazino[3,2-*a*]indol-12(6*H*)one (4c). *N*-(2-Hydroxybenzoyl)-3-methyl-1*H*-indole (**8c**, 25 mg) and triflic acid (26 µL, 0.30 mmol, 3.0 equiv.) were used. 6-Methyl-5a*H*-benzo[5,6][1,3]oxazino[3,2-*a*]indol-12(6*H*)one (**4c**, 24 mg, 96 µmol, 96 %, *dr* = 3.8 : 1 *trans* : *cis*) was obtained as a yellowish powder. **Molecular formula:** $C_{16}H_{13}NO_2$. **Molecular mass:** 251.280 g/mol. **R_f** (chloroform): 0.50. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.15 (*d*, J = 7.6 Hz, 1 H, CH *cis* / *trans*), 8.08 (*d*, J = 7.8 Hz, 1 H, CH *cis* / *trans*), 7.53 – 7.48 (*m*, 1 H, CH *cis* / *trans*), 7.36 – 7.28 (*m*, 1 H, CH *cis* / *trans*), 7.28 – 7.22 (*m*, 1 H, CH *cis* / *trans*), 7.21 – 7.16 (*m*, 1 H, CH *cis* / *trans*), 7.15 – 7.06 (*m*, 2 H, CH *cis* / *trans*), 6.00 (*d*, J = 7.8 Hz, 1 H, CH *cis*), 5.57 (*d*, J = 7.1 Hz, 1 H, CH *trans*), 3.79 – 3.66 (*m*, 1 H, CH *cis* / *trans*), 1.57 (*d*, J = 7.0 Hz, 3 H, CH_3 *trans*), 1.42 (*d*, J = 7.3 Hz, 3 H, CH_3 *cis*). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 159.6 (CO *cis*), 159.1 (CO *trans*), 157.0 (C *cis*), 156.9 (C *trans*), 139.8 (C *trans*), 139.1 (C *cis*), 134.4 (CH *trans*), 134.4 (CH *cis*), 134.0 (C *cis*), 132.2 (C *trans*), 128.6 (CH *cis* / *trans*), 128.4 (CH *trans*), 128.4 (CH *cis*), 124.5 (CH *cis*), 124.5 (CH *trans*), 124.3 (CH *cis*), 123.6 (CH *trans*), 123.3 (CH *trans*), 123.2 (CH *cis*), 119.7 (C *trans*), 119.5 (C *cis*), 117.1 (CH *cis*), 117.0 (CH *trans*), 115.6 (CH *cis*), 115.4 (CH *trans*), 96.3 (CH *trans*), 90.6 (CH *cis*), 42.1 (CH *trans*), 39.1 (CH *cis*), 16.5 (CH_3 *trans*), 15.4 (CH_3 *cis*). **MS** (EI$^+$, 70 eV) *m/z* (%): 252.1 (39), 251.1 (100) M^+, 131.1 (85) $[M–C_7H_4O_2]^+ = [C_9H_9N]^+$, 130.1 (35) $[M–C_7H_5O_2]^+ = [C_9H_8N]^+$, 121.0 (10) $[M–C_9H_8N]^+ = [C_7H_5O_2]^+$. **IR** (ATR): ν = 2970 (*w*), 2880 (*w*), 1665 (*vs*), 1606 (*s*), 1470 (*vs*), 1419 (*vs*), 1362 (*m*), 1314 (*s*), 1225 (*m*), 1152 (*m*), 1105 (*s*), 1058 (*m*), 1019 (*m*), 917 (*m*), 868 (*m*), 743 (*vs*), 691 cm^{-1} (*m*). **CHN analysis** calcd. for $C_{16}H_{13}NO_2$: C 76.48 %, H 5.21 %, N 5.57 %; found: C 76.02 %, H 5.07 %, N 5.56 %.

4-Hydroxy-6-methyl-5a*H*-benzo[5,6][1,3]oxazino[3,2-*a*]indol-12(6*H*)one (4d). *N*-(2,3-Dihydroxybenzoyl)-3-methyl-1*H*-indole (**8d**, 27 mg) and triflic acid (52 µL, 0.60 mmol, 6.0 equiv.) were used. 4-Hydroxy-6-methyl-5a*H*-benzo[5,6][1,3]oxazino[3,2-*a*]indol-12(6*H*)one (**4d**, 20 mg, 74 µmol, 74 %, *dr* = 5.9 : 1 *trans* : *cis*) was obtained as a colorless powder. **Molecular formula:** $C_{16}H_{13}NO_3$. **Molecular mass:** 267.279 g/mol. **R_f** (chloroform): 0.14. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.15 (*d*, J = 8.0 Hz, 1 H, CH *cis* / *trans*), 7.62 (*dd*, J = 7.7 Hz, 1.5 Hz, 1 H, CH *cis* / *trans*), 7.35 – 7.24 (*m*, 1 H, CH *cis* / *trans*), 7.18 – 7.07 (*m*, 4 H, CH *cis* / *trans*), 6.05 (*d*, J = 7.9 Hz, 1 H, CH *cis*), 5.62 (*d*, J = 6.8 Hz, 1 H, CH *trans*), 5.46 (*s*, 1 H, OH *trans*), 5.40 (*s*, 1 H, OH *cis*) 3.82 – 3.68 (*m*, 1 H, CH *cis* / *trans*), 1.59 (*d*, J = 7.1 Hz, 3 H, CH_3 *trans*), 1.45 (*d*, J = 7.3 Hz, 3 H, CH_3 *cis*). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 159.0 (CO *cis* / *trans*), 144.4 (C *cis* / *trans*), 144.0 (C *cis* / *trans*), 139.8 (C *cis* / *trans*), 131.9 (C *cis* / *trans*), 128.8 (CH *cis* / *trans*), 124.7 (CH *cis*), 124.6 (CH *cis* / *trans*), 124.3 (C *cis* / *trans*), 123.6 (CH *trans*), 123.6 (CH *cis* / *trans*), 120.2 (CH *trans*), 120.2 (CH *cis*), 119.7 (CH *cis* / *trans*), 115.7 (CH *cis*), 115.5 (CH *trans*), 97.1 (CH *trans*), 91.4 (CH *cis*), 42.0 (CH *trans*), 39.1 (CH *cis*), 16.7 (CH_3 *trans*), 15.4 (CH_3 *cis*). **MS** (EI$^+$, 70 eV) *m/z* (%): 268.1 (12), 267.1 (40) M^+, 136.0 (21) $[M–C_9H_9N]^+ = [C_7H_4O_3]^+$, 132.1 (37) $[M–C_7H_3O_3]^+ = [C_9H_{10}N]^+$, 131.1 (100) $[M–C_7H_4O_3]^+ = [C_9H_9N]^+$, 130.1 (28) $[M–C_7H_5O_3]^+ = [C_9H_8N]^+$. **HRMS** (ESI$^+$) *m/z:* calcd. for $[M+Na]^+ = [C_{16}H_{13}NO_3Na]^+$: 290.0788, found: 290.0784. **IR** (ATR): ν = 3016 (*m*), 2970 (*m*), 2146 (*w*), 1986 (*w*), 1739 (*vs*), 1638 (*w*), 1587 (*w*), 1435 (*m*), 1366 (*vs*), 1216 (*vs*), 1098 (*w*), 1059 (*w*), 739 cm^{-1} (*m*).

2-Methyl-10,10a-dihydro-2*H*-[1,3]oxazino[3,2-*a*]indol-4(3*H*)-one (5a). *rac*-*N*-(3-Hydroxybutyryl)-1*H*-indole (**7f**, 20 mg) and triflic acid (26 µL, 0.30 mmol, 3.0 equiv.) were used. 2-Methyl-10,10a-dihydro-2*H*-[1,3]oxazino[3,2-*a*]indol-4(3*H*)-one (**5a**, 14 mg, 70 µmol, 70 %, *dr* > 10 : 1 (*R**,*S**) : (*R**,*R**)) was obtained as reddish crystals. **Molecular formula:** $C_{12}H_{13}NO_2$. **Molecular mass:** 203.237 g/mol. **R_f** (chloroform): 0.17. **Mp:** 103 – 106 °C. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.96 (*d*, J = 8.0 Hz, 1 H, CH), 7.31 – 7.14 (*m*, 2 H, CH), 7.05 (*pt*, J = 7.5 Hz, 1 H, CH), 5.65 (*dd*, J = 8.5 Hz, 7.5 Hz, 1 H, CH), 4.19 – 4.03 (*m*, 1 H, CH), 3.29 (*dd*, J = 15.7 Hz, 7.5 Hz, 1 H, CH_2), 3.18 (*dd*, J = 15.7 Hz, 8.5 Hz, 1 H, CH_2), 2.64 (*dd*, J = 17.6 Hz, 4.8 Hz, 1 H, CH_2), 2.40 (*dd*, J = 17.5 Hz, 10.5 Hz, 1 H, CH_2), 1.39 (*d*, J = 6.2 Hz, 3 H, CH_3). **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 165.0 (CO), 140.3 (C), 128.1 (CH), 127.5 (C), 124.8 (CH), 124.5 (CH), 116.7 (CH), 90.8 (CH), 72.3 (CH), 39.3 (CH_2), 35.7 (CH_2), 21.6 (CH_3). **MS** (EI$^+$, 70 eV) *m/z* (%): 204.1 (49), 203.0 (100) M^+, 117.1 (39) $[M–C_4H_6O_2]^+ = [C_8H_7N]^+$. **IR** (ATR): ν = 2973 (*m*), 2913 (*w*), 2329 (*w*), 2038 (*w*), 1918 (*w*), 1736 (*m*), 1656 (*vs*), 1479 (*vs*), 1434 (*vs*), 1380 (*vs*), 1307 (*s*), 1236 (*m*), 1126 (*s*), 1056 (*m*), 977 (*w*), 928 (*w*), 864 (*m*), 812 (*w*), 757 (*vs*), 692 cm^{-1} (*s*). **CHN analysis** calcd. for $C_{12}H_{13}NO_2$: C 70.92 %, H 6.45 %, N 6.89 %; found: C 70.42 %, H 6.24 %, N 6.60 %.

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Keywords: Indole • Acid catalysis • Cyclization • Cascade reaction • Oxazin

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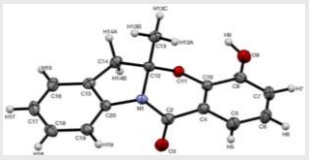

2*H*-[1,3]Oxazino[3,2-α]indolin-4(3*H*)-ones are easily prepared starting from indole and readily available 2-methoxybenzoylchlorides by formation of the indole acyl followed by BBr_3 deprotection/cyclization cascade.

Heterocycle

*J. M. Hartmann, M. de Groot, K. Schäringer, K. Henke, K. Rissanen and M. Albrecht**

Page No. – Page No.

2*H*-[1,3]Oxazino[3,2-α]indolin-4(3*H*)-ones: A New Class Of Polyheterocyclic Indole-based Compounds