Synthesis of Novel Oxazolyl-indoles

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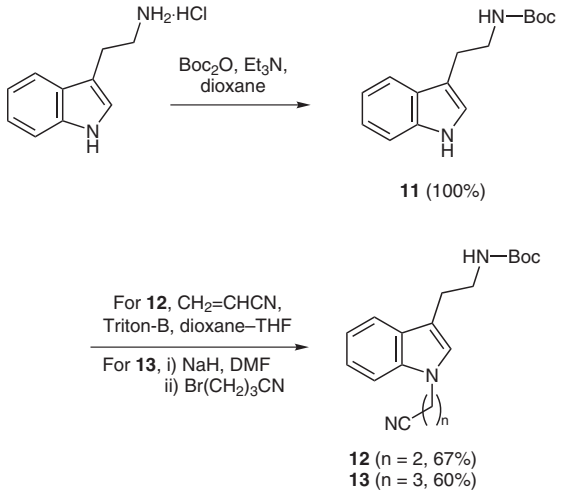
Abstract: We describe the synthesis of oxazolyl-indoles that are structurally related to pimprinaphine. The effect of the indole *N*-cyanoalkyl substituents on the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated oxidation was evaluated.

Key words: oxazolyl-indoles, Yonemitsu reaction, DDQ-mediated oxidation, cyclizations, coupling

Pimprinaphine (**1**) is a 2,5-disubstituted (3-indolyl)oxazole that was isolated from *Streptoverticillium olivoreticuli* (Figure 1).[1,2] The related (3-indolyl)oxazole pimprinine (**2**) was isolated from *Streptomyces pimprina*, pimprinethine (**3**) was isolated from *Streptomyces cinnamoneus*, and WS-30581A (**4**) and WS-30581B (**5**) were isolated from *Streptoverticillium wasksmanni*.[3,4] All of these compounds **1**–**5** show interesting biological activities. For example, pimprinine (**2**) inhibits monoamine oxidase (MAO) and has an anti-epileptic effect, while compounds **4** and **5** have potent inhibitory effects on platelet aggregation. Recently, Pettit and co-workers isolated the new oxazolyl-indoles in this series, labradorin 1 (**6**) and labradorin 2 (**7**), from *Pseudomonas syringae*, which were found to be potent inhibitors against human cancer cells.[5] Oxazole subunits are also found in other biologically active natural products.[6] Although the syntheses of **1**–**7** have been reported,[7] bis(indolyl)oxazoles related to pimprinaphine (**1**) are unknown in the literature.

We herein describe the synthesis of novel bis(indolyl)oxazoles **8**, **9**[8] and the parent compound **10**.

For the synthesis of **8** and **9**, tryptamine hydrochloride was first protected using di-*tert*-butyl dicarbonate in the presence of triethylamine to furnish **11** in quantitative yield.[9] Cyanoalkyl groups were then attached to the indole nitrogen of **11** to furnish **12** and **13** in 67% and 60% yields, respectively (Scheme 1).



Scheme 1

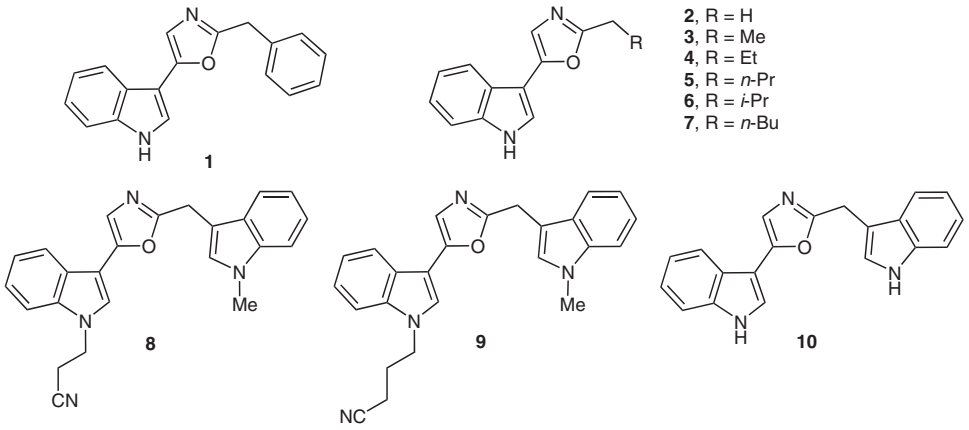


Figure 1

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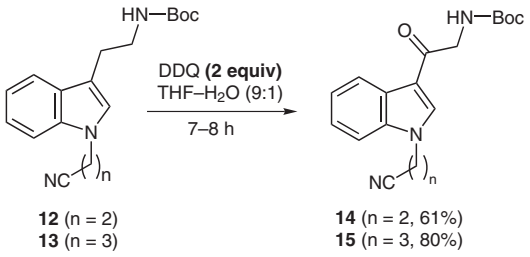
Compounds **12** and **13** were then subjected to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated oxidation[2] to give the desired products **14** and **15**, respectively (Scheme 2). A small difference in yields was observed in this DDQ-mediated oxidation.

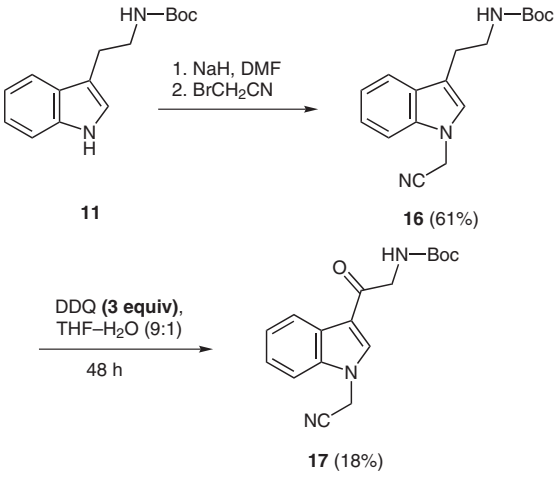
To study the DDQ-mediated oxidation more carefully, we subjected compound **16**, prepared from **11**, to the same reaction conditions (Scheme 3). A striking reduction in yield and rate of reaction was observed in the preparation of **17**. The DDQ-mediated oxidation was found to be very difficult for **16**, which we believe could be due to the electron-withdrawing effect of the cyanomethyl substituent. A longer reaction time was required even in the presence of three equivalents of DDQ. We have previously observed a similar effect in the Pd(II)-catalyzed oxidative cyclization of a bisindolylmaleimide bearing a cyanomethyl functionality.[8a]



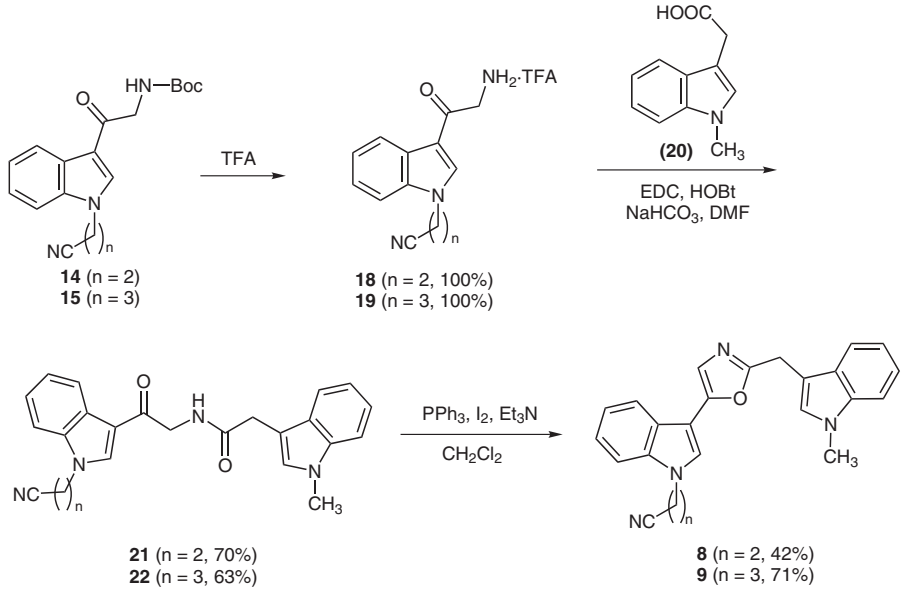
Scheme 2

The Boc groups of **14** and **15** were deprotected using trifluoroacetic acid to furnish the free amine as a trifluoroacetic acid salt in quantitative yield (Scheme 4).[10] The crude products **18** and **19**, which were reasonably pure by proton-NMR, were used in the next step without further purification. Coupling of **18** and **19** with *N*-methylindole-3-acetic acid (**20**)[11] in the presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide and *N*-hydroxybenzotriazole gave the ketoamides **21** and **22** in 70% and 63% yields, respectively. Finally, compounds **21** and **22** were treated with triphenylphosphine and iodine in the presence of triethylamine[12] to furnish the target oxazoles **8** and **9**. A higher yield was obtained for oxazole **9** whereas a lower yield was registered for **8**, perhaps due to the decomposition of the starting material **21** via a retro-Michael reaction and loss of acrylonitrile in the presence of triethylamine.

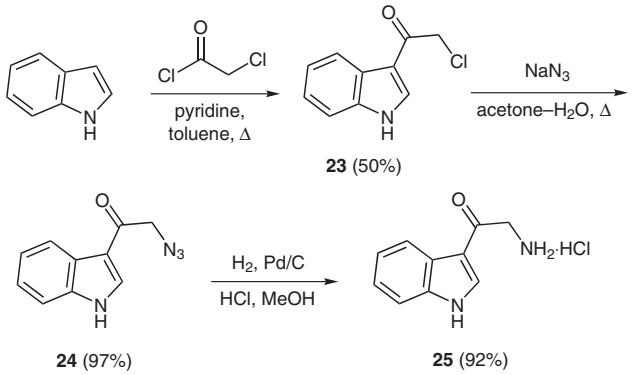
In an initial biological study, an in vitro proliferation assay of the new oxazolyl-indole **9** was performed. A dose-dependent proliferative response of murine T cells was apparent when cells were stimulated with oxazole **9** at a concentration range of 2–8 nM.[13,14] Further biological evaluation of these compounds is in progress.



Scheme 3



Scheme 4



Scheme 5

In order to synthesize **10**, we acylated indole with chloroacetyl chloride in pyridine to furnish **23** (Scheme 5).[15] The chloride **23** was subsequently converted to the azide **24** by treatment with sodium azide in acetone–water in 97% yield.[16] The azide **24** was easily converted to the amine hydrochloride **25** in excellent yield by hydrogenation over palladium-on-carbon in the presence of hydrochloric acid in methanol.[17] No column chromatography was necessary for the preparation of the hydrochloride salt **25** from indole via this three-step sequence.

The amine hydrochloride **25** could be coupled with indole-3-acetic acid (**26**) in the previous manner to produce the corresponding ketoamide, but we decided on a different method. In the event, coupling of the azide **24** with indole-3-acetic acid (**26**) in the presence of trimethylphosphine in tetrahydrofuran–toluene furnished ketoamide **27** in high yield (Scheme 6).[18] This N-unsubstituted ketoamide **27** did not furnish the oxazole **10** upon treatment with triphenylphosphine and iodine even in the presence of excess triethylamine. Ketoamide **27** was finally treated with phosphorus oxychloride in pyridine to furnish the target molecule **10** in good yield.[19]

In summary, we have synthesized novel bis(indolyl)oxazoles **8**, **9** and **10**. A strong deactivating effect was observed for the DDQ-mediated oxidation of indole **16** bearing an *N*-cyanomethyl group, indicating that an electron-withdrawing group in simple indoles would generally disfavor the Yonemitsu oxidation.[20]

Melting points were determined with a Mel-Temp Laboratory Device apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 600 series FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian XL-300 or 500 Fourier transform NMR spectrometer. Both low- and high-resolution mass spectra were carried out at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana Champaign. Anhydrous THF and CH_2Cl_2 were prepared by a solvent purification system. All other solvents (analytical grade) including anhydrous solvents and reagents were used as received. All experiments were performed under a nitrogen atmosphere.

1,1-Dimethylethyl[2-(1*H*-indol-3-yl)ethyl]carbamate (11)

To a stirred solution of tryptamine hydrochloride (5.90 g, 30 mmol) and Et_3N (12.7 mL, 90 mmol) in dioxane (25 mL) at r.t. was added dropwise a solution of Boc_2O (7.20 g, 33 mmol) in dioxane (25 mL). The mixture was stirred at r.t. for 24 h. EtOAc (150 mL) was added and the mixture was washed with H_2O (3 × 100 mL), brine (100 mL) and then dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 2:1) to yield the desired product (7.81 g, 100%) as a white solid.

Mp 88–90 °C (Lit.[9] 94–95 °C).

IR (thin film): 3411, 3327, 2976, 1692, 1512, 1457, 1366, 1250, 1169, 742 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (br s, 1 H), 7.62 (d, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.21–7.24 (m, 1 H), 7.13–7.16 (m, 1 H), 7.02 (s, 1 H), 4.67 (br s, 1 H), 3.48 (m, 2 H), 2.97 (t, *J* = 6.7 Hz, 2 H), 1.47 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.3, 136.6, 127.5, 122.3, 122.2, 119.5, 118.9, 113.1, 111.4, 79.4, 41.1, 28.6, 26.0.

1,1-Dimethylethyl{2-[1-(2-cyanoethyl)-1*H*-indol-3-yl]ethyl}carbamate (12)

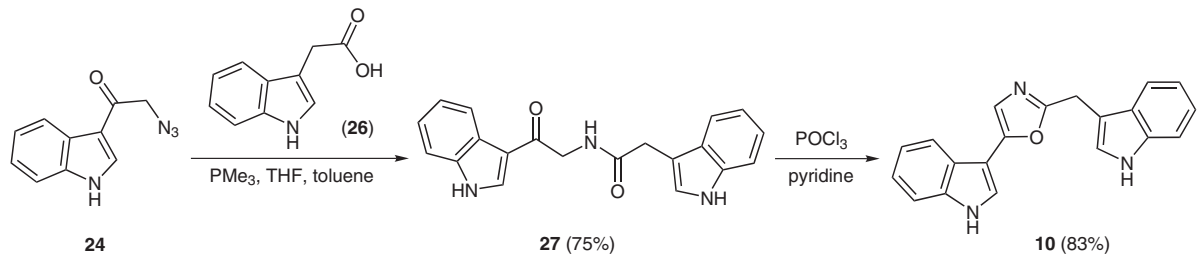
To a stirred solution of **11** (2.60 g, 10 mmol) and acrylonitrile (1.4 mL, 20 mmol) in dioxane–THF (60 mL, 1:1) at 0 °C was added dropwise a catalytic amount (0.5 mL) of Triton-B (40% benzyltrimethylammonium hydroxide solution in MeOH). The reaction mixture was stirred for 4 h allowing it to warm to r.t. It was then heated at 70 °C for 2 h. The mixture was cooled to r.t. and poured into H_2O (50 mL). It was acidified with HCl (0.5 N, 25 mL) and the aq phase was extracted with EtOAc (2 × 75 mL). The combined organic layer was washed with H_2O (50 mL), brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 1:1) to yield the desired product (2.09 g, 67%) as a white solid.

Mp 85–87 °C.

IR (thin film): 3415, 2975, 2932, 2251, 1700, 1512, 1467, 1366, 1250, 1172, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.9 Hz, 1 H), 7.24–7.30 (m, 2 H), 7.14–7.17 (m, 1 H), 6.98 (s, 1 H), 4.36 (t, *J* = 6.71 Hz, 2 H), 3.43 (m, 2 H), 2.93 (t, *J* = 6.7 Hz, 2 H), 2.75 (t, *J* = 6.7 Hz, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 135.8, 128.4, 125.3, 122.3, 119.7, 119.5, 117.5, 113.4, 108.8, 67.0, 58.9, 41.9, 28.4, 25.8, 19.1.



Scheme 6

MS (EI): *m*/*z* (%) = 313 [M$^+$], 257, 240, 212, 183 (100), 156, 143, 106, 91.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{23}N_3O_2$: 313.1790; found: 313.1795.

1,1-Dimethylethyl[2-[1-(3-cyanopropyl)-1*H*-indol-3-yl]ethyl]carbamate (13)

To a stirred suspension of NaH (60% dispersion in mineral oil, 0.84 g, 21 mmol) in DMF (10 mL) at 0 °C was added dropwise a solution of **11** (3.65 g, 14 mmol) dissolved in DMF (15 mL). The mixture was stirred 0 °C for 30 min and then a solution of bromobutyronitrile (2.61 g, 17.5 mmol) in DMF (10 mL) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 40 h. It was then cooled to 0 °C and cold H_2O (100 mL) was added very slowly. The aq phase was extracted with EtOAc (2 × 50 mL). The combined organic phase was washed with H_2O (3 × 50 mL), brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 1:1) to yield the desired product (2.74 g, 60%) as a yellowish oil.

IR (thin film): 3365, 2974, 2932, 2246, 1699, 1511, 1468, 1365, 1249, 1170, 742 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 7.9 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.25–7.28 (m, 1 H), 6.96 (s, 1 H), 4.68 (br s, 1 H), 4.28 (t, *J* = 6.4 Hz, 2 H), 3.46 (m, 2 H), 2.96 (t, *J* = 7.0 Hz, 2 H), 2.25–2.28 (m, 2 H), 2.19 (quin, *J* = 6.7 Hz, 2 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1, 136.4, 128.3, 125.7, 122.3, 119.5, 118.9, 112.9, 109.3, 44.3, 41.1, 28.6, 26.2, 25.9, 14.8.

MS (EI): *m*/*z* (%) = 327 [M$^+$], 271, 254, 210, 197 (100), 143, 130.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{25}N_3O_2$: 327.1947; found: 327.1945.

1,1-Dimethylethyl[2-[1-(2-cyanoethyl)-1*H*-indol-3-yl]-2-oxoethyl]carbamate (14)

To a stirred solution of **12** (0.94 mg, 3 mmol) in THF–H_2O (50 mL, 9:1) at 0 °C was added DDQ (1.37 g, 6 mmol). The mixture was stirred for 3 h at 0 °C, then slowly allowed to warm to r.t. and continued to stir for 4 h. It was then poured into EtOAc (100 mL), washed with 5% NaOH solution (100 mL), sat. aq $NaHCO_3$ solution (2 × 100 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 1:2) to yield the desired product (0.60 g, 61%) as a white solid.

Mp 126–128 °C.

IR (thin film): 3418, 2977, 2252, 1705, 1657, 1529, 1392, 1166, 749 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.52 (s, 1 H), 8.17 (d, *J* = 7.6 Hz, 1 H), 7.71 (d, *J* = 8.2 Hz, 1 H), 7.24–7.32 (m, 2 H), 7.02 (t, *J* = 5.8 Hz, 2 H), 4.58 (t, *J* = 6.6 Hz, 2 H), 4.28 (d, *J* = 6.1 Hz, 2 H), 3.15 (d, *J* = 6.6 Hz, 2 H), 1.41 (s, 9 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 190.4, 156.0, 136.2, 135.9, 125.8, 123.2, 122.4, 121.4, 118.5, 113.6, 110.9, 77.9, 46.8, 28.2, 18.4.

MS (EI): *m*/*z* (%) = 327 [M$^+$], 271, 254, 213, 197 (100), 129.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{21}N_3O_3$: 327.1583; found: 327.1580.

A small amount of unreacted starting material (0.22 g, 23%) was recovered after column chromatography.

1,1-Dimethylethyl[2-[1-(3-cyanopropyl)-1*H*-indol-3-yl]-2-oxoethyl]carbamate (15)

To a stirred solution of **13** (1.34 g, 4.09 mmol) in THF–H_2O (50 mL, 9:1) at 0 °C was added DDQ (1.86 g, 8.18 mmol). The mixture was stirred for 8 h at 0 °C. It was then poured into EtOAc (100 mL), washed with 5% NaOH solution (100 mL), sat. aq $NaHCO_3$ solution (2 × 100 mL), brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 1:2) to yield the desired product (1.12 g, 80%) as a yellowish oil.

IR (thin film): 3416, 2976, 2931, 2360, 2247, 1705, 1652, 1527, 1393, 1163, 748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30–8.32 (m, 1 H), 7.85 (s, 1 H), 7.38–7.40 (m, 1 H), 7.30–7.36 (m, 2 H), 5.65 (br s, 1 H), 4.52 (s, 2 H), 4.34 (t, *J* = 6.7 Hz, 2 H), 2.32 (t, *J* = 6.1 Hz, 2 H), 2.23 (quin, *J* = 6.7 Hz, 2 H), 1.48 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.5, 156.1, 136.5, 133.9, 126.3, 124.2, 123.3, 122.7, 118.4, 114.8, 109.9, 79.8, 47.8, 45.3, 28.5, 25.8, 14.8.

MS (EI): *m*/*z* (%) = 341 [M$^+$], 268, 211 (100), 144.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}N_3O_3$: 341.1740; found: 341.1745.

A trace amount of unreacted starting material (0.08 g, 6%) was recovered after column chromatography.

1,1-Dimethylethyl[2-(1-cyanomethyl-1*H*-indol-3-yl)ethyl]carbamate (16)

To a stirred suspension of NaH (60% dispersion in mineral oil, 0.84 g, 21 mmol) in DMF (10 mL) at 0 °C was added dropwise a solution of **11** (3.65 g, 14 mmol) dissolved in DMF (15 mL). The mixture was stirred at 0 °C for 30 min and then a solution of bromoacetonitrile (2.11 g, 17.5 mmol) in DMF (10 mL) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 24 h. Then another portion of bromoacetonitrile (0.42 g) was added and the reaction was stirred for a further 12 h. It was then cooled to 0 °C and diluted with Et_2O (10 mL). H_2O (100 mL) was added very slowly. The aq phase was extracted with Et_2O (2 × 50 mL) and then EtOAc (2 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL), brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 2:1) to yield the desired product (2.55 g, 61%) as a white solid.

Mp 99–101 °C.

IR (thin film): 3417, 3354, 2976, 2931, 1694, 1614, 1513, 1465, 1366, 1250, 1171, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 7.9 Hz, 1 H), 7.31–7.36 (m, 2 H), 7.20–7.24 (m, 1 H), 6.92 (s, 1 H), 4.94 (s, 2 H), 4.69 (br s, 1 H), 3.46 (s, 2 H), 2.94 (t, *J* = 7.0 Hz, 2 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1, 136.4, 128.7, 125.0, 123.2, 120.6, 119.8, 115.1, 114.7, 109.0, 40.8, 34.2, 28.6, 25.9.

MS (EI): *m*/*z* (%) = 299 [M$^+$], 276, 260, 243, 220, 182, 169 (100), 143, 130, 104.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{21}N_3O_2$: 299.1634; found: 299.1633.

1,1-Dimethylethyl[2-(1-cyanomethyl-1*H*-indol-3-yl)-2-oxoethyl]carbamate (17)

To a stirred solution of **16** (1.33 g, 4.44 mmol) in THF–H_2O (50 mL, 9:1) at 0 °C was added DDQ (2.02 g, 8.88 mmol). The mixture was stirred for 3 h at 0 °C, then slowly allowed to warm to r.t. and continued to stir for 3 h. An additional amount of DDQ (1.01 g, 4.44 mmol) was added and the mixture was stirred at r.t. for 48 h. It was then poured into EtOAc (100 mL), washed with 5% NaOH solution (100 mL), sat. aq $NaHCO_3$ solution (2 × 100 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 1:2) to yield the desired product (0.24 g, 18%) as a white solid.

Mp 139–141 °C.

IR (thin film): 3415, 2978, 1702, 1659, 1531, 1391, 1166, 1047, 748 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.51 (s, 1 H), 8.21 (d, *J* = 7.6 Hz, 1 H), 7.71 (d, *J* = 8.2 Hz, 1 H), 7.39 (t, *J* = 8.2 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.08 (t, *J* = 5.8 Hz, 1 H), 5.65 (s, 2 H), 4.29 (d, *J* = 5.8 Hz, 2 H), 1.41 (s, 9 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 190.9, 156.0, 135.9, 135.8, 125.8, 123.8, 123.0, 121.7, 115.9, 114.5, 110.6, 78.0, 46.9, 34.5, 28.2;

MS (EI): *m*/*z* (%) = 313 [M$^+$], 257, 240, 213, 183 (100), 169, 143, 91.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{19}N_3O_3$: 313.1427; found: 313.1423.

A large amount of unreacted starting material (0.89 g, 67%) was recovered from the reaction mixture after column chromatography.

3-[3-(2-Aminoacetyl)indol-1-yl]propionitrile Trifluoroacetate (18)

Compound **14** (0.17 g, 0.5 mmol) was dissolved in neat TFA (8 mL) at r.t. and stirred for 15 min. The solvent was evaporated by rotary evaporation. The residual TFA was removed by co-evaporation with benzene (3 × 10 mL). It was then extensively dried in vacuo and the white solid (0.17 g, 100%) was used in the next reaction without any further purification.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.63 (s, 1 H), 8.26 (br s, 3 H), 8.19 (d, *J* = 7.9 Hz, 1 H), 7.77 (d, *J* = 7.9 Hz, 1 H), 7.30–7.37 (m, 2 H), 4.62 (t, *J* = 6.4 Hz, 2 H), 4.36 (s, 2 H), 3.17 (t, *J* = 6.4 Hz, 2 H).

4-[3-(2-Aminoacetyl)indol-1-yl]butyronitrile Trifluoroacetate (19)

Compound **15** (0.84 g, 2.45 mmol) was dissolved in neat TFA (30 mL) at r.t. and stirred for 25 min. The solvent was evaporated by rotary evaporation. The residual TFA was removed by co-evaporation with benzene (4 × 10 mL). The residue was then extensively dried in vacuo to yield the desired product (0.87 g, 100%) as a white solid which was used in the next reaction without any further purification.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.58 (s, 1 H), 8.27 (br s, 2 H), 8.18–8.20 (m, 1 H), 7.68 (d, *J* = 7.3 Hz, 1 H), 7.28–7.36 (m, 2 H), 4.33–4.38 (m, 4 H), 2.58 (t, *J* = 7.3 Hz, 2 H), 2.16 (quin, *J* = 6.96 Hz, 2 H).

***N*-[2-[1-(2-Cyanoethyl)-1*H*-indol-3-yl]-2-oxoethyl]-1-methyl-1*H*-indole-3-acetamide (21)**

To a mixture of amine trifluoroacetate **18** (0.17 g, 0.5 mmol), 1-methylindole-3-acetic acid (0.11 g, 0.6 mmol), EDC·H_2O (0.29 g, 1.5 mmol), HOBt·H_2O (0.20 g, 1.5 mmol) and $NaHCO_3$ (0.63 g, 7.5 mmol) at r.t. was added DMF (5 mL). The mixture was stirred at r.t. for 20 h. It was then poured into sat. aq $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with HCl (1 N, 50 mL), H_2O (50 mL), brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 9:1) to yield the desired product (0.14 g, 70%) as a yellowish solid.

Mp 155–157 °C.

IR (thin film): 3392, 3053, 2928, 2251, 1644, 1527, 1392, 1185, 1064, 746 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.53 (s, 1 H), 8.17–8.22 (m, 2 H), 7.70–7.33(m, 1 H), 7.62 (d, *J* = 7.7 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 1 H), 7.25–7.33 (m, 3 H), 7.15 (t, *J* = 7.2 Hz, 1 H), 7.00–7.05 (m, 1 H), 4.56 (t, *J* = 6.6 Hz, 2 H), 4.47 (d, *J* = 5.5 Hz, 2 H), 3.76 (s, 3 H), 3.65 (s, 2 H), 3.13 (t, *J* = 6.6 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 189.9, 170.9, 136.5, 136.2, 136.1, 128.2, 127.6, 125.8, 123.2, 122.5, 121.4, 121.1, 119.0, 118.5, 118.4, 113.7, 110.9, 109.5, 108.1, 45.9, 41.8, 32.3, 18.3.

MS (EI): *m*/*z* (%) = 398 [M$^+$], 323, 271, 197 (100), 144, 129, 102.

HRMS (EI): *m*/*z* calcd for $C_{24}H_{22}N_4O_2$: 398.1743; found: 398.1745.

***N*-{2-[1-(3-Cyanopropyl)-1*H*-indol-3-yl]-2-oxoethyl}-1-methyl-1*H*-indole-3-acetamide (22)**

To a mixture of amine trifluoroacetate **19** (0.87 g, 2.45 mmol), 1-methylindole-3-acetic acid (1.40 g, 7.35 mmol), EDC·H_2O (1.41 g, 7.35 mmol), HOBt·H_2O (0.99 g, 7.35 mmol) and $NaHCO_3$ (3.09 g, 36.75 mmol) at r.t. was added DMF (25 mL). The mixture was stirred at r.t. for 24 h. It was then poured into sat. aq $NaHCO_3$ solution (100 mL) and extracted with EtOAc (2 × 100 mL). The organic phase was washed with HCl (1N, 100 mL), H_2O (100 mL), brine (100 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to yield the desired product (0.64 g, 63%) as a yellowish-white solid.

Mp 73–75 °C.

IR (thin film): 3392, 3053, 2935, 2247, 1646, 1527, 1467, 1394, 1215, 1161, 1073, 919, 744 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.48 (s, 1 H), 8.18–8.21 (m, 2 H), 7.62 (d, *J* = 8.2 Hz, 2 H), 7.39 (d, *J* = 8.2 Hz, 1 H), 7.24–7.31 (m, 3 H), 7.15 (t, *J* = 8.2 Hz, 1 H), 7.02 (t, *J* = 7.0 Hz, 1 H), 4.48 (d, *J* = 5.5 Hz, 2 H), 4.29 (t, *J* = 7.0 Hz, 2 H), 3.76 (s, 3 H), 3.65 (s, 2 H), 2.51 (t, *J* = 7.0 Hz, 2 H), 2.12 (quin, *J* = 7.0 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 189.9, 170.9, 136.5, 136.3, 128.3, 127.6, 125.9, 123.1, 122.3, 121.5, 121.1, 120.0, 119.0, 118.4, 113.3, 110.6, 109.5, 108.1, 45.9, 44.9, 32.3, 25.3, 13.9.

MS (EI): *m*/*z* (%) = 412 [M$^+$], 394, 285, 228, 211 (100), 197, 171, 144, 129, 77.

HRMS (EI): *m*/*z* calcd for $C_{25}H_{24}N_4O_2$: 412.1899; found: 412.1892.

3-{3-[2-(1-Methyl-1*H*-indol-3-ylmethyl)oxazol-5-yl]indol-1-yl}propionitrile (8)

To a stirred solution of PPh_3 (53 mg, 0.2 mmol), I_2 (52 mg, 0.2 mmol) and Et_3N (41 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) at r.t. was added a solution of ketoamide **21** (40 mg, 0.1 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 24 h and then diluted with CH_2Cl_2 (15 mL). The organic phase was treated with 5% aq $Na_2S_2O_3$ solution (25 mL). Et_2O (100 mL) was added and the combined organic phase was washed with sat. aq $NaHCO_3$ (25 mL). The bicarbonate solution was extracted with CH_2Cl_2 (15 mL). The combined organic phases were dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to yield the desired product (16 mg, 42%) as a yellowish-brown oil.

IR (thin film): 1690, 1611, 1467, 990, 745 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.80 (d, *J* = 7.9 Hz, 1 H), 7.74 (d, *J* = 7.9 Hz, 1 H), 7.43 (s, 1 H), 7.32–7.34 (m, 3 H), 7.25–7.28 (m, 2 H), 7.17–7.20 (m, 2 H), 7.12 (s, 1 H), 4.47 (t, *J* = 6.7 Hz, 2 H), 4.37 (s, 2 H), 3.79 (s, 3 H), 2.85 (t, *J* = 6.7 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.8, 146.7, 135.9, 127.9, 127.2, 125.8, 123.9, 122.5, 121.3, 120.6, 119.9, 119.7, 118.8, 118.7, 118.6, 110.6, 109.7, 107.9, 104.0, 41.3, 32.3, 24.2, 18.5.

MS (EI): *m*/*z* (%) = 380 (100) [M$^+$], 214, 197, 174, 144, 129.

HRMS (EI): *m*/*z* calcd for $C_{24}H_{20}N_4O$: 380.1641; found: 380.1637.

4-{3-[2-(1-Methyl-1*H*-indol-3-ylmethyl)oxazol-5-yl]indol-1-yl}butyronitrile (9)

To a stirred solution of PPh_3 (106 mg, 0.4 mmol), I_2 (103 mg, 0.4 mmol), Et_3N (0.12 mL, 0.8 mmol) in CH_2Cl_2 (3 mL) at r.t. was added a solution of **22** (83 mg, 0.2 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at r.t. for 22 h and then diluted with CH_2Cl_2 (10 mL) and washed with 5% aq $Na_2S_2O_3$ (25 mL). Et_2O (100 mL) was added and the combined organic phase was washed with sat. aq $NaHCO_3$ solution (25 mL) and then dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column

chromatography on silica gel (CH_2Cl_2–hexanes, 95:5) to yield the desired product (56 mg, 71%) as a yellowish oil.

IR (thin film): 1693, 1635, 1613, 1467, 1373, 1172, 742 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.82 (d, *J* = 7.9 Hz, 1 H), 7.76 (s, 1 H), 7.63 (d, *J* = 7.9 Hz, 1 H), 7.56 (d, *J* = 8.5 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H), 7.34 (s, 1 H), 7.31 (s, 1 H), 7.25 (t, *J* = 7.0 Hz, 1 H), 7.14–7.17 (m, 2 H), 7.05 (t, *J* = 7.0 Hz, 1 H), 4.28 (t, *J* = 7.3 Hz, 4 H), 3.76 (s, 3 H), 2.46 (t, *J* = 7.0Hz, 2 H), 2.09 (quin, *J* = 7.0 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.7, 146.9, 136.7, 136.1, 127.9, 127.2, 125.9, 123.9, 122.4, 121.3, 120.4, 120.0, 119.9, 119.5, 118.8, 118.7, 110.3, 109.7, 108.0, 103.6, 44.4, 32.3, 25.6, 24.2, 13.9.

MS (EI): *m*/*z* (%) = 394 (100) [M^+], 319, 293, 277, 265, 201, 171, 158, 144, 84.

HRMS (EI): *m*/*z* calcd for $C_{25}H_{22}N_4O$: 394.1794; found: 394.1786.

A small amount of starting material (12 mg, 15%) was recovered after column chromatography.

2-Chloro-1-(1*H*-indol-3-yl)ethanone (23)

To a stirred solution of indole (11.72 g, 100 mmol) and pyridine (8.2 mL, 100 mmol) in toluene (250 mL) at 60 °C was added dropwise chloroacetyl chloride (1.13 g, 100 mmol) over 1.5 h. After the addition was complete, the reaction mixture was stirred at the same temperature for a further 1 h. After cooling to r.t., H_2O (300 mL) and MeOH (50 mL) were added. The mixture was stirred at r.t. for an additional 1 h. The solid precipitate was filtered through a sintered glass funnel and washed with H_2O. The crude solid was purified by recrystallization from EtOH to yield the desired product (9.68 g, 50%) as a brownish solid.[21]

Mp 231–233 °C (Lit.[15] 230–232 °C).

^1H NMR (DMSO-d_6): δ = 12.15 (br s, 1 H), 8.44 (d, *J* = 2.7 Hz, 1 H), 8.17 (d, *J* = 7.6 Hz, 1 H), 7.50 (d, *J* = 8.1 Hz, 1 H), 7.23 (quin, *J* = 7.1 Hz, 2 H), 4.89 (s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 186.2, 136.6, 134.8, 125.4, 123.2, 122.2, 121.2, 113.6, 112.3, 46.4.

2-Azido-1-(1*H*-indol-3-yl)ethanone (24)

A mixture of **23** (0.90 g, 4.65 mmol) and sodium azide (0.61 g, 9.3 mmol) in acetone (120 mL) and H_2O (60 mL) was heated at reflux for 20 h. After cooling to r.t., H_2O (50 mL) was added and the product was extracted into CH_2Cl_2 (50 mL, 2 × 25 mL) and dried over Na_2SO_4. The solvent was evaporated and the crude solid was purified by recrystallization from CH_2Cl_2–MeOH to yield the desired product (0.90 g, 97%) as a light brown solid.

Mp 182–184 °C (Lit.[16] 181–183 °C).

^1H NMR (500 MHz, DMSO-d_6): δ = 12.12 (br s, 1 H), 8.37 (s, 1 H), 8.16–8.18 (m, 1 H), 7.49–7.51 (m, 1 H), 7.21–7.26 (m, 2 H), 4.62 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 189.0, 136.5, 134.4, 125.2, 123.2, 122.2, 121.1, 113.6, 112.4, 53.9.

2-Amino-1-(1*H*-indol-3-yl)ethanone Hydrochloride (25)

To a mixture of **24** (200 mg, 1 mmol) in MeOH (10 mL) was carefully added Pd/C (50 mg) followed by HCl (0.5 mL). The flask was fitted with a three-way stop-cock connected to a H_2-filled balloon and the air inside the flask was removed. The reaction mixture was stirred under this H_2 atmosphere for 3 h. The Pd/C was removed by filtration through Hyflo. The solvent was evaporated from the filtrate and the crude residue was purified by recrystallization from CH_2Cl_2–MeOH to yield the desired product (193 mg, 92%) as a pale brown solid.

Mp > 250 °C (Lit.[22] 267–269 °C).

^1H NMR (500 MHz, DMSO-d_6): δ = 12.51 (br s, 1 H), 8.52 (d, *J* = 3.4 Hz, 1 H), 8.41 (br s, 3 H), 8.15–8.17 (m, 1 H), 7.52–7.54 (m, 1 H), 7.22–7.27 (m, 2 H), 4.36 (d, *J* = 5.5 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.7, 136.6, 135.2, 125.1, 123.2, 122.3, 120.9, 113.1, 112.5, 43.9.

***N*-[2-(1*H*-Indol-3-yl)-2-oxoethyl]-1*H*-indole-3-acetamide (27)**

To a stirred solution of **24** (1.00 g, 5 mmol) and indole-3-acetic acid (1.05 g, 6 mmol) in THF (50 mL) was added PMe_3 (1 M solution in toluene, 5 mL, 5 mmol). The reaction mixture was stirred at r.t. for 15 h and then heated at reflux for 90 min. After cooling, EtOAc (30 mL) was added. The mixture was washed with 5% aq NaOH solution (20 mL). The organic phase was dried ($MgSO_4$) and concentrated. The solid residue was slurried with Et_2O (30 mL) and filtered through a sintered glass funnel to yield the desired product (1.24 g, 75%) as a yellowish solid.

Mp 220–222 °C (dec).

^1H NMR (500 MHz, DMSO-d_6): δ = 12.03 (br s, 1 H), 10.92 (s, 1 H), 8.42 (s, 1 H), 8.16–8.18 (d, 2 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 7.9 Hz, 1 H), 7.29 (s, 1 H), 7.18–7.24 (m, 2 H), 7.08 (t, *J* = 7.5 Hz, 1 H), 6.99 (t, *J* = 7.3 Hz, 1 H), 4.50 (d, *J* = 4.9 Hz, 2 H), 3.66 (s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 190.3, 171.1, 136.4, 136.1, 133.7, 127.3, 125.4, 124.0, 122.9, 121.9, 121.2, 121.0, 118.8, 118.4, 114.0, 112.2, 111.3, 108.8, 45.9, 32.6.

ESI-MS: *m*/*z* = 332 [M + H^+].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1399; found: 332.1397.

3-[2-[(3-Indolyl)methyl]-5-oxazolyl]-1*H*-indole (10)

To a stirred solution of **27** (33 mg, 0.1 mmol) in pyridine (2.5 mL) at r.t. was added dropwise $POCl_3$ (0.5 mL, 5.5 mmol). The mixture was stirred at r.t. for 3 h. It was then diluted with EtOAc (25 mL) and poured into an ice-cold sat. $NaHCO_3$ solution (50 mL). The aq phase was extracted with EtOAc (3 × 50 mL). The combined organic extract was then washed with H_2O (50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 9:1) to yield the desired product (26 mg, 83%) as a light yellow solid.

Mp 200–202 °C (dec).

^1H NMR (500 MHz, acetone-d_6): δ = 10.64 (br s, 1 H), 10.18 (br s, 1 H), 7.83–7.85 (m, 1 H), 7.73–7.74 (m, 1 H), 7.66 (s, 1 H), 7.47 (d, *J* = 7.9 Hz, 1 H), 7.39–7.41 (m, 1 H), 7.36 (s, 1 H), 7.24–7.25 (m, 1 H), 7.18–7.21 (m, 1 H), 7.10–7.15 (m, 2 H), 7.04–7.07 (m, 1 H), 4.32 (s, 2 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 162.0, 148.9, 137.7, 128.4, 125.1, 124.3, 124.1, 123.4, 123.2, 122.4, 121.1, 120.6, 120.4, 119.7, 112.7, 112.2, 110.6, 106.0, 25.5.

ESI-MS: *m*/*z* = 314 [M + H^+].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}N_3O$: 314.1293; found: 314.1285.

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