Synthesis of 3-indolylazoles and meridianin derivatives from indolyl enaminonitriles

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Abstract

The reaction of indole derivatives with cyanoacetic acid followed by treatment with DMFDMA gave the intermediate indolyl enaminonitriles **3**. Further reaction with aminoguanidine yielded 5'-cyanomeridianin analogues **4**. The same intermediate reacted with *p*-methoxyphenylhydrazine to give the pyrazolyl derivative **8**.

Treatment of (2*E*)-3-dimethylamino-2-(1*H*-indol-3-yl)-propenoate **3a** with hydroxylamine hydrochloride in basic medium afforded (5-amino-isoxazol-4-yl)-(1*H*-indol-3-yl)-methanone **5** and the acrylic acid derivative **6** after a short or a long heating, respectively. Unequivocal structural elucidation of the latter compound was achieved from single-crystal X-ray diffraction studies.

Keywords: Indole, alkaloids, enaminonitrile, meridianins, 3-indolylazoles

Introduction

Enaminonitriles are versatile reagents which have been efficiently utilized for the synthesis of heteroaromatics.¹ Meridianin alkaloids, isolated from the south atlantic tunicate *Aplidium meridianum*,² are indole derivatives substituted at the C-3 position by a 2-aminopyrimidine ring. Since abnormal protein phosphorylation is related to many human diseases interest on the search for inhibitors of kinases has increased. A vast number of inhibitors of CDKs have been discovered, however, only very few GSK-3 inhibitors have been described. Meridianins²⁻⁴ (Figure 1) were described as potent kinase inhibitors,⁴ inhibiting CDKs, GSK-3, PKA and other protein kinases in the low micromolar range. Some derivatives displayed also antitumor activity.⁵

There are three reported approaches for the synthesis of meridianins from indole derivatives based on a Suzuki cross-coupling with indole-3-boronic acid derivatives.⁶ A Bredereck synthesis was also described from β -enaminones, which were, in turn, obtained from 3-acetylindole derivatives.^{5,7,8} More recently, meridianins were also obtained from trimethylsilylindole indole derivatives.⁹

Figure 1. General representation of meridianin alkaloids.

Results and discussion

Following our interest in the chemistry of β -enaminonitriles,¹⁰⁻¹³ in this manuscript we describe our most recent results that explore the potential of 3(2*E*)-3-dimethylamino-2-(1*H*-indol-3-yl)-propenoate in the synthesis of 5'-cyanomeridianin C, G and 3-heteroarylindoles. Commercially available indole and indole-3-carboxaldehyde were employed as the starting materials giving access to the meridianin analogs **4a-c** in a straightforward three-step synthesis following the Bredereck approach⁷ (Scheme 1), and to **14** from one-pot synthesis as shown in Scheme 3.

Recently, a facile procedure for the cyanoacetylation of indoles leading to compounds **2a-c** has been reported.¹⁴ This one-step approach, applying cyanoacetic acid in acetic anhydride for the inclusion of the cyanoacetyl functionality, provides an easy access to cyanoacetylated indoles **2a-c**. The Bredereck protocol⁷ was used for the formation of the 2-aminopyrimidine ring. When compounds **2a-c** were treated with dimethylformamide dimethylacetal (DMFDMA),¹⁵ without solvent at room temperature, the corresponding enaminonitriles **3a-c** were obtained in yields ranging from 78 to 88%.

Direct conversion of **3a-c** into 5'-cyano meridianin C and meridianin G derivatives **4a-c**, involving the formation of the 2-aminopyrimidine ring, was achieved in 70-78% by treatment with guanidine hydrochloride in the presence of anhydrous potassium carbonate (Scheme 1). The structure of compounds **4a-c** was established on the basis of elemental analysis, IR, mass, ¹H and ¹³C NMR spectral data studies (*cf.* Experimental Section).

Heating compound **3a** for 7 hours, with hydroxylamine hydrochloride in the presence of base, did not produce the isoxazole **5**, but led instead to the formation of the indole derivative **6**.

Scheme 1

The alternative structure **5** was excluded based on FT-IR and NMR data. The ¹H NMR spectrum of **6** showed two signals that are D₂O exchangeable at 7.90 and 12.20 and a singlet for H-2 at 8.48 ppm, while ¹³C NMR showed a carbonyl signal at 181.55 ppm (C-3). Unequivocal structural elucidation was achieved from single-crystal X-ray diffraction studies. Compound **6** crystallises in the centrosymmetric monoclinic C2/c space group, with the asymmetric unit being composed of a whole molecular unit (Figure 2) with typical geometrical features for the bond lengths and angles (see caption of Figure 2).

Figure 2. Schematic representation of the molecular unit of compound **6**. Non-hydrogen atoms are represented as thermal ellipsoids (drawn at the 50% probability level) and hydrogen atoms as small spheres with arbitrary radii. The atomic labelling scheme is also provided for all non-hydrogen atoms. Selected bond lengths (in Å): O1–C1 1.262(2); O2–C1 1.337(3); O3–C4

1.316(2); N1–C3 1.140(2); N2–C5 1.349(2); N2–C8 1.373(2); C1–C2 1.459(2); C2–C4 1.392(3); C2–C3 1.417(2); C4–C6 1.442(2); C5–C6 1.387(2); C6–C7 1.446(2); C7–C12 1.406(2); C7–C8 1.413(2); C8–C9 1.392(3); C9–C10 1.371(3); C10–C11 1.411(3); C11–C12 1.364(3). Selected bond angles (in degrees): C5–N2–C8 109.70(15); O1–C1–O2 120.18(16); O1–C1–C2 120.15(17); O2–C1–C2 119.66(16); C4–C2–C3 122.47(15); C4–C2–C1 120.52(15); C3–C2–C1 116.99(16); N1–C3–C2 176.64(19); O3–C4–C2 119.06(16); O3–C4–C6 113.99(16); C2–C4–C6 126.95(15); N2–C5–C6 110.16(17); C5–C6–C4 128.31(17); C5–C6–C7 105.91(15); C4–C6–C7 125.78(15); C12–C7–C8 118.12(17); C12–C7–C6 135.45(16); C8–C7–C6 106.43(15); N2–C8–C9 129.18(17); N2–C8–C7 107.79(16); C9–C8–C7 123.03(17); C10–C9–C8 117.23(18); C9–C10–C11 120.8(2); C12–C11–C10 121.9(2); C11–C12–C7 118.86(18).

When the reaction proceeded under mild heating conditions, for 30 minutes at 60°C, the product isolated (26%) was the oxazole derivative **5**. The singlet due to H-3 may be seen at 8.97 and the NH₂ signal is located at 8.18 ppm and readily exchanges with D₂O. It is assumed that **5** may be formed initially and with prolonged heating, in basic medium, yields **6**. Removal of the proton 3 from **5**, which is known to happen in basic medium, would open the isoxazole ring to an amide whose hydrolysis would give the corresponding carboxylic acid derivative **6**. Ring opening always occurs in the same fashion leading to the stereoisomer *E* depicted in Figure 2.

This configuration has important consequences in the crystal packing as it permits the existence of a vast network composed of strong and highly directional hydrogen bonding interactions (Figure 3a): (i) the carboxylic acid groups of two neighbouring units are engaged in a typical $R^2_2(8)$ graph set motif¹⁶ [O2–H2...O1ⁱ: $d_{D...A}$ of 2.933(2) Å with $\angle(\text{DAH})$ of *ca.* 165°; symmetry code (i) $-x, 2-y, -z$], which are reinforced by (ii) two very strong $S^1_1(6)$ intramolecular motifs [O3–H3...O1: $d_{D...A}$ of 2.470(2) Å with $\angle(\text{DAH})$ of *ca.* 151°]. The two aforementioned graph set motifs promote the existence of molecular dimers within the structure (Figure 3a) which are, in turn, interconnected by way of two N2–H2A...N1ⁱⁱ interactions [$d_{D...A}$ of 2.932(2) Å with $\angle(\text{DAH})$ of *ca.* 164°; symmetry code (i) $1/2-x, 2.5-y, 1-z$] involving the heterocyclic NH moiety and the pendant C≡N moiety. These interactions promote the existence of a third graph set motif, $R^2_2(16)$, which is in the genesis of the one-dimensional zigzag supramolecular tape depicted in Figure 3a. Individual tapes close pack in a typical alternate ABAB... fashion along the [100] direction of the unit cell mediated by the need to effectively fill the available space (Figure 3b).

Figure 3. (a) Schematic representation of the one-dimensional zigzag supramolecular tape assembled by adjacent molecules of compound **6** engaged in strong and highly directional (N,O)–H... (N,O) hydrogen bonding interactions (dashed green lines – see main text for geometrical details on the represented interactions). (b) Close packing of adjacent supramolecular tapes (represented in different colour) along the [100] direction of the unit cell depicting the actual crystal structure of compound **6**.

As anticipated, the treatment of compound **3a** with *p*-methoxyphenylhydrazine, in refluxing ethanol, in a basic medium, afforded as single product only pyrazole **7** (Scheme 1). The structure of the pyrazole **9** was excluded due to the absence of the typical signals of cyano groups in both the FT-IR and ^{13}C NMR spectra. The ^1H NMR of compound **7** showed all the expected signals which was not sufficient to differentiate between structures **7** and **8**. For this reason, we collected the HMQC and HMBC NMR spectra and performed an unambiguous assignment in the ^1H and ^{13}C NMR spectra (*cf.* Experimental Section). In the HMBC spectrum, no correlation peak between the pyrazole H-3 at 8.13 ppm and carbon signals at 130.67 (C-1'') was observed. This occurrence is characteristic only for structure **7** but not for **8**.¹⁷

Compound **3a** reacted with malononitrile in the presence of piperidine as a catalyst to give **10** in 75% yield. The structure of compound **10** was readily established from ^1H NMR data, which revealed all the expected protons of the indole moiety alongside with a singlet at 8.59 ppm for the H-4 of the pyridinone ring and a NH broad signal at 13.10 ppm. Two signals due to CN groups were found in the ^{13}C NMR spectrum at 115.44 and 116.96 ppm. The formation of the pyridine-3,5-dicarbonitrile **10** from the reaction of **3a** with malononitrile is assumed to take place through the sequence depicted in Scheme 2.

Scheme 2

The reactivity of the methylene group in compound **2** was exploited by reacting this compound with trichloroacetonitrile in ethanol in the presence of sodium acetate to obtain the new enamine **11** (Scheme 1). The structure of compound **11** was established by ^1H NMR data which revealed the absence of a signal for the methylene group and the emergence of another at 11.98 ppm corresponding to two protons of the amino group.

Recently Stanovnik *et al.* reported the synthesis of condensed indolylpyrimidones as meridianin analogs¹⁸ and polycyclic meridianin analogs with the uracil structural unit.¹⁹ Treatment of ethyl 2-cyano-3-(1*H*-indol-3-yl)acrylate **13** with guanidine hydrochloride in the presence of anhydrous potassium carbonate in ethanol at reflux temperature affords the corresponding 2-amino-6-(1*H*-indol-3-yl)-4-oxo-1,4-dihydropyrimidine-5-carbonitrile **14** (Scheme 3).

Scheme 3

Conclusion

Two novel indolyl enamionitriles (**3b** and **3c**) were prepared and reacted with guanidine hydrochloride yielding two new meridianin derivatives (**4b** and **4c**).

The reactivity of the enaminonitrile **3a** was tested with *p*-methoxyphenylhydrazine and malononitrile giving a pyrazole derivative **7** and a pyridone derivative **10**, respectively.

The reaction of **3a** with hydroxylamine hydrochloride in basic medium produced, as expected, the oxazole derivative **5**. When the heating period was extended a different product, whose structure, **6**, was elucidated from single-crystal X-ray diffraction.

Experimental Section

General. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. FT-IR spectra were registered on a Perkin Elmer FT-IR 1600 using Nujol emulsions between NaCl plates. ^1H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity Plus Spectrometer at 298 K. Chemical shifts are reported in ppm relative to solvent peak or TMS; coupling constants (J) are given in Hz. Double resonance, HMQC (heteronuclear multiple quantum coherence) and HMBC (heteronuclear multiple bond correlation) experiments were carried out for complete assignment of ^1H and ^{13}C signals in the NMR spectra. ESI mass spectrum was obtained on a LC-MS Finnigan LXQ spectrometer. High-resolution mass spectra were obtained on a Bruker FTMS APEXIII (ESI-TOF). Elemental analyses were obtained on a Leco CHNS-932 instrument.

General procedure for the preparation of compounds (2a-c)

To a solution of cyanoacetic acid (5.0 g, 50 mmol) in Ac_2O (50 mL) at 50 °C, indole (5.85 g, 50 mmol) was added. The resulting solution was heated at 85 °C for 5 min. During that period 3-cyanoacetylindole started to crystallize. The mixture was allowed to cool and the solid was collected, washed with MeOH, and dried. The same procedure was applied with 2-methylindole to give **2b** and with 5-bromoindole to produce **2c**. Compounds **2a**, **b** were found to be identical to those described in the literature.¹⁴

3-(5-Bromo-1H-indol-3-yl)-3-oxopropanenitrile (2c). Pale yellow solid, Yield 85%, mp 296-298 °C, FT-IR (Nujol; in cm^{-1}): ν = 3205 (NH), 2252 (CN), 1634 (CO); ^1H NMR ($\text{DMSO}-d_6$): δ = 4.50 (s, 2H, CH_2), 7.38 (dd, 1H, J = 8.7, 1.8 Hz, H-6), 7.49 (d, 1H, J = 9.0, Hz, H-7), 8.24 (d, 1H, J = 2.1 Hz, H-4), 8.41 (s, 1H, H-2), 12.35 (bs, 1H, NH). ^{13}C NMR ($\text{DMSO}-d_6$): δ = 29.48 (CH_2), 113.87 (C-3), 114.57 (C-7), 115.07 (C-Br), 116.21 (CN), 123.11 (C-2), 125.94 (C-6), 126.88 (C-3a), 135.38 (C-7a), 136.55 (C-4), 183.10 (CO). Anal. Calcd. (in %) for $\text{C}_{11}\text{H}_7\text{BrN}_2\text{O}$ (263.09): C, 50.22; H, 2.68; N, 10.65. Found: C, 50.10; H, 2.78; N, 10.65.

General procedure to prepare compounds (3a-c)

A mixture of **2a-c** (10 mmol) and DMFDMA (11 mmol) was stirred for 5 min. at room temperature, and the yellow solid that formed was filtered off and crystallized from EtOH to afford **3a-c** in 78-88% yield. Compound **3a** was found to be identical to that previously described in the literature.⁵

3-(Dimethylamino)-2-(1*H*-indole-3-carbonyl)acrylonitrile (3a). Yellow crystals, yield 78%, mp 170-171 °C (lit.⁵ mp 160-163 °C); δ = 3.26 (s, 3H, CH₃), 3.35 (s, 3H, CH₃), 7.13 (td, 1H, J = 1.2, 6.9 Hz, H-5), 7.18 (td, 1H, J = 6.9 Hz, H-6), 7.46 (dd, 1H, J = 7.8, 2.1 Hz, H-7), 7.99 (s, 1H, =CH), 8.13 (dd, 1H, J = 7.5, 2.1 Hz, H-4), 8.27 (d, 1H, J = 3 Hz, H-2), 11.75 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ = 38.51 (CH₃), 47.39 (CH₃), 77.62 (C-CN), 111.70 (C-7), 114.70 (C-3), 121.12 (C-5), 121.75 (C-4 or CN), 121.78 (C-4 or CN), 122.49 (C-6), 126.77 (C-3a), 131.14 (C-2), 135.83 (C-7a), 158.67 (=CH), 181.74 (CO).

3-(Dimethylamino)-2-(2-methyl-1*H*-indole-3-carbonyl)acrylonitrile (3b). Yellow crystals, yield 85%, mp 192-193 °C, FT-IR (Nujol; in cm⁻¹): ν = 3274 (NH), 2225 (CN), 1689 (CO); ¹H NMR (DMSO-*d*₆): δ = 2.48 (s, 3H, CH₃), 3.19 (s, 3H, N-CH₃), 3.35 (s, 3H, N-CH₃), 7.00-7.11 (m, 2H, H-5, 6), 7.32 (dd, 1H, J = 6.9, 2.1 Hz, H-7), 7.56 (dd, 1H, J = 6.9, 2.1 Hz, H-4), 7.74 (s, 1H, =CH), 11.54 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ = 13.51 (CH₃), 38.44 and 47.09 (2 x N-CH₃), 81.38 (C-CN), 110.88 (C-7), 112.90 (C-2), 119.68 (C-4), 120.03 (CN and C-5 or C6), 121.19 (C-5 or C-6), 126.91 (C-3a), 134.77 (C-7a), 139.69 (C-3), 158.53 (=CH), 185.49 (CO). Anal. Calcd. (in %) for C₁₅H₁₅N₃O (253.30); C, 71.13; H, 5.97; N, 16.59. Found: C, 70.93; H, 6.00; N, 16.66.

2-(5-Bromo-1*H*-indole-3-carbonyl)-3-(dimethylamino)acrylonitrile (3c). Yellow crystals, Yield 88%, mp 252-254 °C, FT-IR (Nujol; in cm⁻¹): ν = 3285 (NH), 2227 (CN), 1664 (CO); ¹H NMR (DMSO-*d*₆): δ = 3.27 (s, 3H, CH₃), 3.31 (s, 3H, CH₃), 7.30 (dd, 1H, J = 8.7, 1.8 Hz, H-6), 7.45 (d, 1H, J = 9.0 Hz, H-7), 7.99 (s, 1H, =CH), 8.28 (d, 1H, J = 1.8 Hz, H-4), 8.32 (s, 1H, H-2), 11.92 (bs, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ = 47.49 and 38.57 (2 x CH₃), 77.36 (C-CN), 113.94 (C-3 or C-5), 114.02 (C-5 or C-3), 114.22 (C-7), 121.64 (CN), 123.95 (C-4), 125.06 (C-6), 128.59 (C-3a), 132.33 (C-2), 134.57 (C-7a), 158.75 (C-2), 181.42 (CO). Anal. Calcd. (in %) for C₁₄H₁₂BrN₃O (318.17): C, 52.85; H, 3.80; N, 13.21. Found: C, 52.86; H, 3.98; N, 13.21.

General procedure to prepare meridianin derivatives (4a-c)

A mixture of enamionitrile **3a-c** (10 mmol), guanidine hydrochloride (12.0 mmol), anhydrous K₂CO₃ (2.0 g, 15.0 mmol), and absolute ethanol (20 mL) was heated at reflux for 7 h. After cooling, the mixture was poured into ice-water and the solid formed was filtered off to afford 5'-cyano-meridianin derivatives **4a-c** as yellow solids. Recrystallization from EtOH led to overall yields of 70-78%. Spectral data for compound **4a** are in good agreement with those reported in the literature.⁵

2-Amino-4-(1*H*-indol-3-yl)pyrimidine-5-carbonitrile (4a). Off white solid powder (70%), mp 257-258 °C (lit.⁵ mp 258-259 °C). ¹H NMR (DMSO-*d*₆): δ = 7.12-7.27 (m, 2H, H-5', 6'), 7.50 (d, 1H, J = 7.5 Hz, H-7'), 7.54 and 7.64 (2 bs, 2H, NH₂), 8.47 (s, 1H, H-6), 8.57 (s, 1H, H-2'), 8.65 (d, 1H, J = 7.2 Hz, H-4'), 11.95 (bs, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ = 89.23 (C-5), 111.56 (C-3'), 112.04 (C-7'), 119.82 (CN), 121.09 (C-5'), 122.80 (C-6'), 123.27 (C-4'), 125.73 (C-3'a), 130.04 (C-2'), 136.36 (C-7'a), 163.14 (C-4 or C-2), 163.17 (C-2 or C-4), 165.35 (C-6).

2-Amino-4-(2-methyl-1*H*-indol-3-yl)pyrimidine-5-carbonitrile (4b). Yellow powder (74%), mp 280-282 °C, FT-IR (Nujol; in cm⁻¹): ν = 3295 (NH), 3150 (NH₂), 2215 (CN); ¹H NMR

(DMSO- d_6): δ = 2.51 (s, 3H, CH₃), 7.02-7.14 (m, 2H, H-5', 6'), 7.34-7.36 (m, 1H, H-7'), 7.59-7.61 (m, 1H, H-4'), 7.64 (s, 2H, NH₂), 8.65 (s, 1H, H-6), 11.64 (s, 1H, NH). ¹³C NMR (DMSO- d_6): δ = 13.82 (CH₃), 94.40 (C-5), 109.72 (C-3'), 110.94 (C-7'), 118.40 (CN), 119.51 (C-4'), 119.78 (C-5'), 121.47 (C-6'), 126.35 (C-3'a), 135.15 (C-7'a), 137.95 (C-2'), 163.17 (C-4 or C-2), 163.28 (C-2 or C-4), 165.37 (C-6). Anal. Calcd. (in %) for C₁₄H₁₁N₅ (249.27): C, 67.46; H, 4.45; N, 28.10. Found: C, 67.38; H, 4.52; N, 28.15.

2-Amino-4-(5-bromo-1H-indol-3-yl)pyrimidine-5-carbonitrile (4c). Yellow crystals (78%), mp 325-327 °C, FT-IR (Nujol; in cm⁻¹): ν = 3428 (NH), 3290, 3148 (NH₂), 2211 (CN); ¹H NMR (DMSO- d_6): δ = 7.34-7.36 (m, 1H, H-6'), 7.47-7.49 (m, 1H, H-7'), 7.57, 7.81 (bs, 2H, NH₂), 8.49 (s, 1H, H-2'), 8.57 (s, 1H, H-6), 8.75 (d, 1H, H-4'), 12.10 (bs, 1H, NH). ¹³C NMR (DMSO- d_6): δ = 89.31 (C-5), 111.12 (C-3'), 114.06 (CN), 114.15 (C-7'), 119.60 (C-5'), 125.01 (C-4'), 125.51 (C-6'), 127.30 (C-3'a), 131.18 (C-2'), 135.12 (C-7'a), 162.74 (C-4 or C-2), 163.11 (C-2 or C-4), 163.41 (C-6). Anal. Calcd. (in %) for C₁₃H₈BrN₅ (314.14): C, 49.70; H, 2.57; N, 22.29. Found: C, 49.35; H, 2.68; N, 22.10.

(5-Amino-isoxazol-4-yl)-(1H-indol-3-yl)-methanone (5). A mixture of enaminonitrile **3a** (100.5 mg, 0.42 mmol) and anhydrous K₂CO₃ (84 mg, 0.61 mmol) in absolute ethanol (20 mL) was stirred for 10 min. at room temperature. Hydroxylamine hydrochloride (0.5 mmol) was added and the mixture was warmed at 60 °C for 30 min, cooled, poured into ice-water, and extracted with diethyl ether (3x50 mL). The combined extracts were dried (MgSO₄) and the solvent was evaporated to give compound **5** as an off-white solid (25 mg, 29%) mp 217.0-219.5 °C; ¹H NMR (DMSO- d_6): 7.10-7.24 (m, 2H, H-5' and 6'), 7.46 (d, J =7.0 Hz, 1H, H-7'), 8.16-8.20 (s, 2H, NH₂, exchangeable with D₂O), 8.24 (d, 1H, J = 7.0 Hz, H-4'), 8.31 (1H, d, J =3Hz, H-2'), 8.97 (1H, s, H-3), 11.95 (bs, 1H, NH, exchangeable with D₂O). ¹³C NMR (DMSO- d_6): δ = 94.30 (C-4), 115.38 (C-3'), 111.99 (C-7'), 121.32 (C-5'), 121.54 (C-4'), 122.70 (C-6'), 126.28 (C-3'a), 131.40 (C-2'), 136.26 (C-7'a), 149.82 (C-3), 171.49 (C-5), 180.89 (CO). ESI-TOF, C₁₂H₁₀N₃O₂ (M⁺+1) Calc: 228.07675; Found: 228.07675.

General procedure to prepare compounds **6** and **7**.

A mixture of enaminonitrile **3a** (10 mmol), hydroxylamine hydrochloride **6** or *p*-methoxyphenyl hydrazine hydrochloride **7** (12.0 mmol), anhydrous K₂CO₃ (2.0 g, 15.0 mmol), and absolute ethanol (20 mL) was heated at reflux for 7 h. After cooling, the mixture was poured into ice-water and the resulting solid was filtered off and recrystallized from EtOH.

2-Cyano-3-hydroxy-3-(1H-indol-3-yl)-acrylic acid (6). Brown crystals (81%), mp 235-237 °C, FT-IR (Nujol): ν = 3399, 3256 (NH), 2208 (CN), 1641 (CO) cm⁻¹; ¹H NMR (DMSO- d_6): δ = 7.19 (dt, 1H, H-5'), 7.24 (dt, 1H, J = 7.2 and 1.2 Hz, H-6'), 7.53 (d, 1H, J = 7.5 Hz, H-7'), 7.60-8.40 (br s, 1H, OH, D₂O exchangeable), 8.10 (d, 1H, J = 7.5 Hz, H-4'), 8.48 (d, 1H, J = 3.2 Hz, H-2'), 12.20 (s, 1H, NH, D₂O exchangeable). ¹³C NMR (DMSO- d_6): δ = 69.53 (C-2), 109.30 (C-3'), 112.55 (C-7'), 119.19 (CN), 121.91 (C-5') 121.96 (C-4'), 123.10 (C-6'), 125.59 (C-3'a), 132.28 (C-2'), 135.98 (C-7'a), 173.96 (C-1), 181.55 (C-3). ESI-MS: 208.17 ([M-1]⁺). Anal.

Calcd. (in %) for $C_{12}H_7N_3O$ (209.20): C, 68.89; H, 3.37; N, 20.09. Found: C, 68.45; H, 3.27; N, 20.39.

(5-Amino-1-(4-methoxyphenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methanone (7). Brown crystals (81%), mp 230-232°C, FT-IR (Nujol): $\nu = 3278$ (NH), 1650 (CO), cm^{-1} ; 1H NMR (DMSO- d_6): $\delta = 3.82$ (s, 3H, OCH₃), 6.81 (s, 2H, NH₂), 7.10 (d, 2H, $J = 9.0$ Hz, (H-3'',5''), 7.14-7.22 (m, 2H, H-5', 6'), 7.45-7.47 (m, 1H, H-7'), 7.49 (d, 2H, $J = 9.0$ Hz, (H-2'',6''), 8.13 (s, 1H, H-3), 8.23-8.25 (m, 1H, H-4'), 8.29 (d, 1H, $J = 2.7$ Hz, H-2'), 11.86 (s, 1H, NH). ^{13}C NMR (DMSO- d_6): $\delta = 55.47$ (OCH₃), 104.09 (C-4), 111.88 (C-7'), 114.58 (C-3'',5''), 115.97 (C-3'), 121.05 (C-5'), 121.56 (C-4'), 122.51 (C-6'), 125.52 (C-2'',6''), 126.40 (C-3'a), 130.67 (C-1'), 131.03 (C-2'), 136.22 (C-7'a), 139.96 (C-3), 150.40 (C-5), 158.47 (C-4'), 182.94 (CO). ESI⁺-MS: 333.33 ([M+1]⁺). Anal. Calcd. (in %) for $C_{19}H_{16}N_4O_2$ (332.36): C, 68.66; H, 4.85; N, 16.86. Found: C, 68.49; H, 5.00; N, 16.86.

6-(1H-Indol-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (10). To a mixture of enaminonitrile **3a** (10 mmol) and malononitrile (0.66 g; 10 mmol) in ethanol (15 mL) piperidine (0.2 mL) was added. The reaction mixture was refluxed for 3 h and was then left to cool to room temperature. The precipitated product was collected by filtration and crystallized from ethanol to afford **10** as brown crystals in 75 % yield. mp 198-200 °C, FT-IR (Nujol): $\nu = 3266$ (NH), 22211 (CN), 1634 (CO), cm^{-1} ; 1H NMR (DMSO- d_6): $\delta = 7.18$ -7.29 (m, 2H, H-5', 6'), 7.52-7.55 (m, 1H, H-7'), 7.72 (d, 1H, $J = 7.2$ Hz, H-4'), 8.14 (d, 1H, $J = 3.0$ Hz, H-2'), 8.59 (s, 1H, H-4), 12.24 (s, 1H, NH indole), 13.10 (bs, 1H, NH). ^{13}C NMR (DMSO- d_6): $\delta = 88.71$ (C-5), 99.55 (C-3), 106.14 (C-3'), 122.58 (C-7'), 115.44 (CN), 116.96 (CN), 120.46 (C-4'), 121.0 (C-5'), 122.97 (C-6'), 124.16 (C-3'a), 131.11 (C-2'), 136.31 (C-7'a), 150.53 (C-4), 155.05 (C-6), 160.17 (CO). ESI-MS: 259.10 ([M-1]⁺). Anal. Calcd. (in %) for $C_{15}H_8N_4O$ (260.25): C, 69.23; H, 3.10; N, 21.53. Found: C, 69.09; H, 3.41; N, 21.68.

3-Amino-4,4,4-trichloro-2-(1H-indole-3-carbonyl)but-2-enenitrile (11). To a solution of **2a** (10 mmol) in ethanol (25 mL) and sodium acetate (4.1 g, 50 mmol), trichloroacetonitrile (4.33 g, 30 mmol) was added. The reaction mixture was stirred for 48 h and then poured into water, and the solid product was filtered off and crystallized from dimethylformamide to give **9** as a brown powder (74%), mp 212-214 °C, FT-IR (Nujol): $\nu = 3279$ (NH), 2215 (CN), 1620 (CO), cm^{-1} ; 1H NMR (DMSO- d_6): $\delta = 7.18$ -7.24 (m, 2H, H-5', 6'), 7.48-7.51 (m, 1H, H-7'), 8.16-8.18 (m, 1H, H-4'), 8.47 (d, 1H, $J = 3.2$ Hz, H-2'), 9.42 (bs, 1H, NH), 11.98 (s, 2H, NH₂). ^{13}C NMR (DMSO- d_6): $\delta = 76.10$ (C-2) 91.61 (C-4, CCl₃), 112.22 (C-7'), 114.52 (C-3'), 119.80 (CN), 121.76 (C-5'), 121.78 (C-4'), 122.92 (C-6'), 126.54 (C-3'a), 132.28 (C-2'), 135.77 (C-7'a), 167.41 (C-3), 185.45 (CO). ESI-MS: 326.17 (^{35}Cl , [M-1]⁺), 328.08 (^{35}Cl (2), ^{37}Cl , [M-1]⁺), 330.00 (^{35}Cl , ^{37}Cl (2) [M-1]⁺). Anal. Calcd. (in %) for $C_{13}H_8Cl_3N_3O$ (328.58): C, 47.52; H, 2.45; N, 12.79. Found: C, 47.26; H, 2.85; N, 12.81.

Ethyl 2-cyano-3-(1H-indol-3-yl)acrylate (13). To a solution of 3-formylindole (10 mmol) in ethanol (25 mL) and ethylcyanoacetate (10 mmol), and piperidine (0.2 mL) was added. The reaction mixture was refluxed for 2 h and then left to cool to room temperature. The solid that precipitated was filtered off and recrystallized from ethanol to give **13** as yellow crystals in 92%

yield. mp 170-171 °C, FT-IR (Nujol): ν = 3278 (NH), 2224 (CN), 1680 (CO), cm^{-1} ; ^1H NMR (CDCl_3): δ = 1.41 (t, 3H, J = 7.2 Hz, CH_3), 4.38 (q, 2H, J = 7.2 Hz, CH_2), 7.32-7.36 (m, 2H, H-5',6'), 7.48-7.51 (m, 1H, H-7'), 7.84-7.86 (m, 1H, H-4'), 8.64 (s, 1H, =CH), 8.67 (d, 1H, J = 3.3 Hz, H-2'), 9.24 (bs, 1H, NH). ^{13}C NMR (CDCl_3): δ = 14.30 (CH_3), 62.04 (CH_2), 94.93 (C-2), 111.23 (C-3'), 112.20 (C-7'), 118.13 (CN), 118.33 (C-4'), 122.65 (C-5'), 124.23 (C-6'), 127.39 (C-3'a), 130.68 (C-2'), 135.60 (C-7'a), 146.55 (C-3'), 163.76 (C-1). Anal. Calcd. (in %) for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$ (240.26): C, 69.99; H, 5.03; N, 11.66. Found: C, 69.97; H, 5.16; N, 11.86.

2-Amino-6-(1H-indol-3-yl)-4-oxo-1,4-dihydropyrimidine-5-carbonitrile (14). A mixture of **13** (10 mmol), guanidine hydrochloride (12.0 mmol), anhydrous K_2CO_3 (2.0 g, 15.0 mmol), and absolute ethanol (20 mL) was heated at reflux temperature for 7 h. After cooling, the mixture was poured into ice-water and neutralized with acetic acid. A solid product formed which was filtered off and recrystallized from EtOH to afford **14** as a yellow solid in 77 % yield. mp 252-253 °C, FT-IR (Nujol): ν = 3327 (NH), 2211 (CN), 1659 (CO), cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ = 7.10-7.22 (m, 4H, H-5', 6', NH_2), 7.47 (d, 1H, J = 8.4 Hz, H-7'), 8.44 (d, 1H, J = 3.0 Hz, H-2'), 8.57 (d, 1H, J = 7.5 Hz, H-4'), 11.31 (s, 1H, NH indole), 11.92 (s, 1H, NH). ^{13}C NMR ($\text{DMSO}-d_6$): δ = 79.40 (C-5) 111.77 (C-3'), 111.96 (C-7'), 119.28 (CN), 120.88 (C-5'), 122.54 (C-6'), 123.51 (C-4'), 126.13 (C-3'a), 130.51 (C-2'), 136.25 (C-7'a), 155.98 (C-2), 162.21 (CO), 166.67 (C-6). ESI-MS: 250.08 ($[\text{M}-1]^+$). Anal. Calcd. (in %) for $\text{C}_{13}\text{H}_9\text{N}_5\text{O}$ (251.24): C, 62.15; H, 3.61; N, 27.87. Found: C, 62.40; H, 3.26; N, 27.77.

Single-crystal X-ray Diffraction

A single-crystal of compound **6** was manually harvested from the crystallization vial and mounted on a Hampton Research CryoLoop using FOMBLIN Y perfluoropolyether vacuum oil (LVAC 25/6) purchased from Aldrich²⁰ with the help of a Stemi 2000 stereomicroscope equipped with Carl Zeiss lenses. Data were collected at 150(2) K on a Bruker X8 Kappa APEX II charge-coupled device (CCD) area-detector diffractometer (Mo K_α graphite-monochromated radiation, λ = 0.71073 Å) controlled by the APEX2 software package,²¹ and equipped with an Oxford Cryosystems Series 700 cryostream monitored remotely using the software interface Cryopad.²² Images were processed using the software package SAINT+,²³ and data were corrected for absorption by the multi-scan semi-empirical method implemented in SADABS.²⁴ The crystal structure was solved by employing the direct methods implemented in SHELXS-97.^{25,26} This strategy allowed the immediate location of the vast majority of the atoms. All the remaining non-hydrogen atoms were directly located from difference Fourier maps calculated from successive full-matrix least squares refinement cycles on F^2 using SHELXL-97.^{26,27} All non-hydrogen atoms have been successfully refined using anisotropic displacement parameters.

Hydrogen atoms bound to carbon/nitrogen and oxygen were placed at their idealized positions using the *HFIX 43* or *147* instructions in SHELXL and included in subsequent refinement cycles in riding-motion approximation with isotropic thermal displacements parameters (U_{iso}) fixed at 1.2 or $1.5 \times U_{\text{eq}}$ of the carbon/nitrogen or oxygen atom to which they are attached, respectively.

The last difference Fourier map synthesis showed the highest peak (0.494 eÅ^{-3}) and deepest hole (-0.635 eÅ^{-3}) located at 0.40 Å and 0.51 Å from O1 and O2, respectively.

Crystal data: $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_3$, $M = 228.20$, monoclinic, space group $C2/c$, $Z = 8$, $a = 27.964(6) \text{ Å}$, $b = 5.3241(11) \text{ Å}$, $c = 17.278(4) \text{ Å}$, $\beta = 124.186(19)^\circ$, $V = 2127.9(8) \text{ Å}^3$, $\mu(\text{MoK}\alpha) = 0.105 \text{ mm}^{-1}$, $D_c = 1.425 \text{ g cm}^{-3}$, brown prism with crystal size of *ca.* $0.25 \times 0.20 \times 0.20 \text{ mm}^3$. Of a total of 39590 reflections collected, 2856 were independent ($R_{\text{int}} = 0.0308$). Final $R1 = 0.0602$ [$I > 2\sigma(I)$] and $wR2 = 0.2172$ (all data). Data completeness to $\theta = 29.13^\circ$, 99.6%.

Crystallographic data (excluding structure factors) for compound **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-816317. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 2EZ, U.K. Fax: (+44) 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.

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