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Knoevenagel Reactions of Indole-3-carbaldehyde. Synthesis of 3-Substituted Indole Derivatives

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Abstract—The Knoevenagel condensations of 1*H*-indole-3-carbaldehyde with various CH acids gave a number of substituted 3-(1*H*-indol-3-yl)acrylonitriles and acrylamides which were alkylated to afford the corresponding *N*-alkyl derivatives. The latter were used as Michael acceptors in the synthesis of 4*H*-pyran, pyridine, 5,6,7,8-tetrahydroquinoline, and [1,3]thiazolo[3,2-*a*]pyridine derivatives containing an indole fragment.

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Many physiologically active natural compounds contain an indole fragment [1, 2], which stimulates researchers' interest in indole derivatives. We previously reported an unusual transformation of piperidinium 3-cyano-5-ethoxycarbonyl-4-(1*H*-indol-3-yl)-6-methyl-1,4-dihydropyridine-2-thiolate in boiling acetic acid, which involved cleavage of the C–C bond between the indole and dihydropyridine fragments [3]. In this work we studied the condensation of 1*H*-indole-3-carbaldehyde (**1**) with CH acids **2a**–**2f** and **3**, alkylation of the condensation products, and behavior of the alkyl derivatives as Michael acceptors.

1*H*-Indole-3-carbaldehyde (**1**) reacted with CH acids **2a**–**2f** and **3** in ethanol at room temperature in the presence of a catalytic amount of morpholine to give the corresponding Knoevenagel condensation products, 3-(1*H*-indol-3-yl)prop-2-enamides **4a**–**4f** and 4-(1*H*-indol-3-ylmethylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**5**) (Scheme 1). Compounds like **4** and **5** were synthesized previously by reactions of 3-aminomethylideneindoles with CH acids in a mixture of ethanol and acetic acid [4], on heating in ethanol in the presence of potassium hydroxide [5] or L-proline [6], under solvent-free conditions in the presence of piperidine under microwave irradiation at 160°C [7], or at 85°C in the presence of 4-dimethylaminopyridine [8].

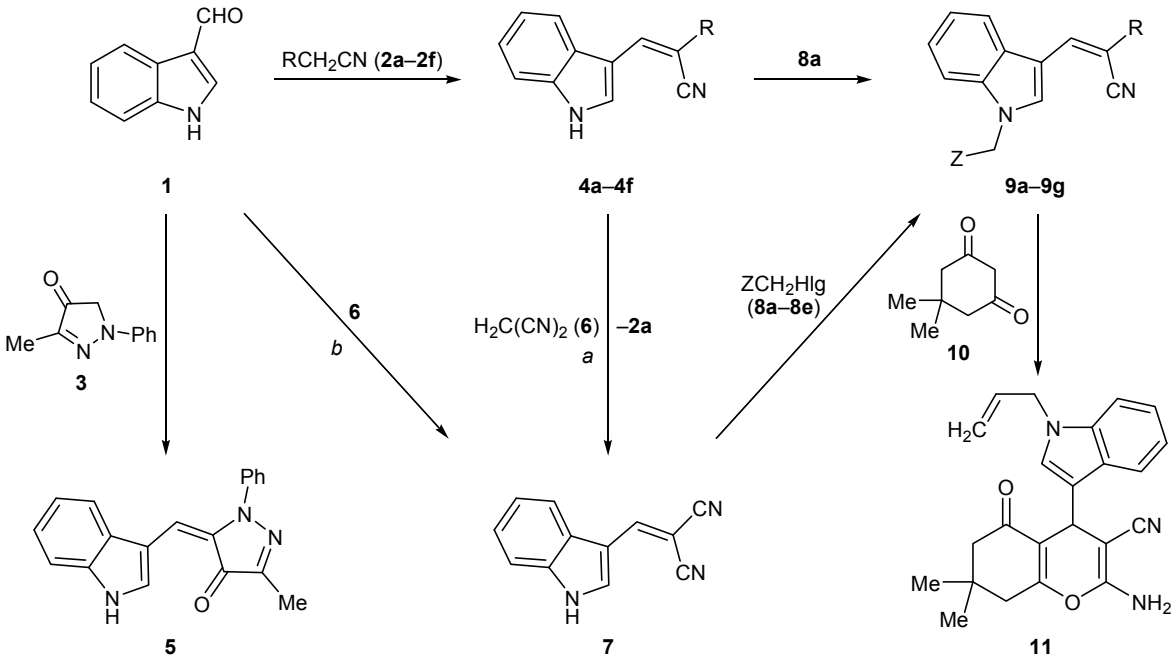
Compounds **4** and **5** can be regarded as Michael acceptors. However, the reaction of **4a** with malononitrile (**6**) in DMF in the presence of morpholine at 20°C led to the formation of 2-(1*H*-indol-3-ylmethylidene)malononitrile (**7**) as a result of exchange of methylene components [9, 10] (Scheme 1, *a*). Substituted acrylonitrile **7** was also synthesized independently, by directly reacting 1*H*-indole-3-carbaldehyde (**1**) with malononitrile (**6**) in ethanol at 20°C in the presence of morpholine (Scheme 1, *b*).

The alkylation of 1*H*-indoles **4a**–**4f** and **7** with alkyl halides **8a**–**8e** in DMF in the presence of an equimolar amount of potassium hydroxide at 20°C regioselectively afforded the corresponding *N*-alkyl derivatives, 3-(1-alkyl-1*H*-indol-3-yl)prop-2-enenitriles **9a**–**9g**, despite the presence of two other more nucleophilic centers in their molecules, C^2 of malononitrile [11] and amide nitrogen atom [12].

The Michael reaction of substituted acrylonitrile **9a** with dimedone **10** in DMF at 20°C in the presence of a catalytic amount of morpholine produced the expected [13–15] 5,6,7,8-tetrahydro-4*H*-chromene derivative **11** (Scheme 1).

Taking into account ambiguous behavior of 3-alkenylindoles **4** in the Michael reaction, we synthesized 2-cyano-3-(1*H*-indol-3-yl)prop-2-enethioamide (**12**) by condensation of 1*H*-indole-3-carbaldehyde (**1**) with cyanothioacetamide (**13**) in ethanol in the presence of morpholine at 20°C and studied its behavior as Michael acceptor toward carbon-centered nucleophiles

Scheme 1.



2, **4**, R = *cyclo*-$C_3H_5NHC(O)$ (**a**), $Me(CH_2)_6OC(O)$ (**b**), 1,3-thiazol-2-ylcarbamoyl (**c**), $PhCH_2NHC(O)$ (**d**), Furan-2-ylmethylcarbamoyl (**e**), $(CN)_2C{=}C(NH_2)$ (**f**); **8**, Hlg = Br, Z = $CH_2{=}CH$ (**a**); Hlg = Cl, Z = H_2NCO (**b**); Hlg = I, Z = H (**c**); Hlg = Cl, Z = EtOC(O) (**d**), Ph (**e**); **9**, R = CN, Z = $CH_2{=}CH$ (**a**), Ph (**b**), EtOC(O) (**c**), H (**d**), H_2NCO (**e**); Z = $CH_2{=}CH$, R = $Me(CH_2)_6OC(O)$ (**f**); *cyclo*-$C_3H_5NHC(O)$ (**g**).

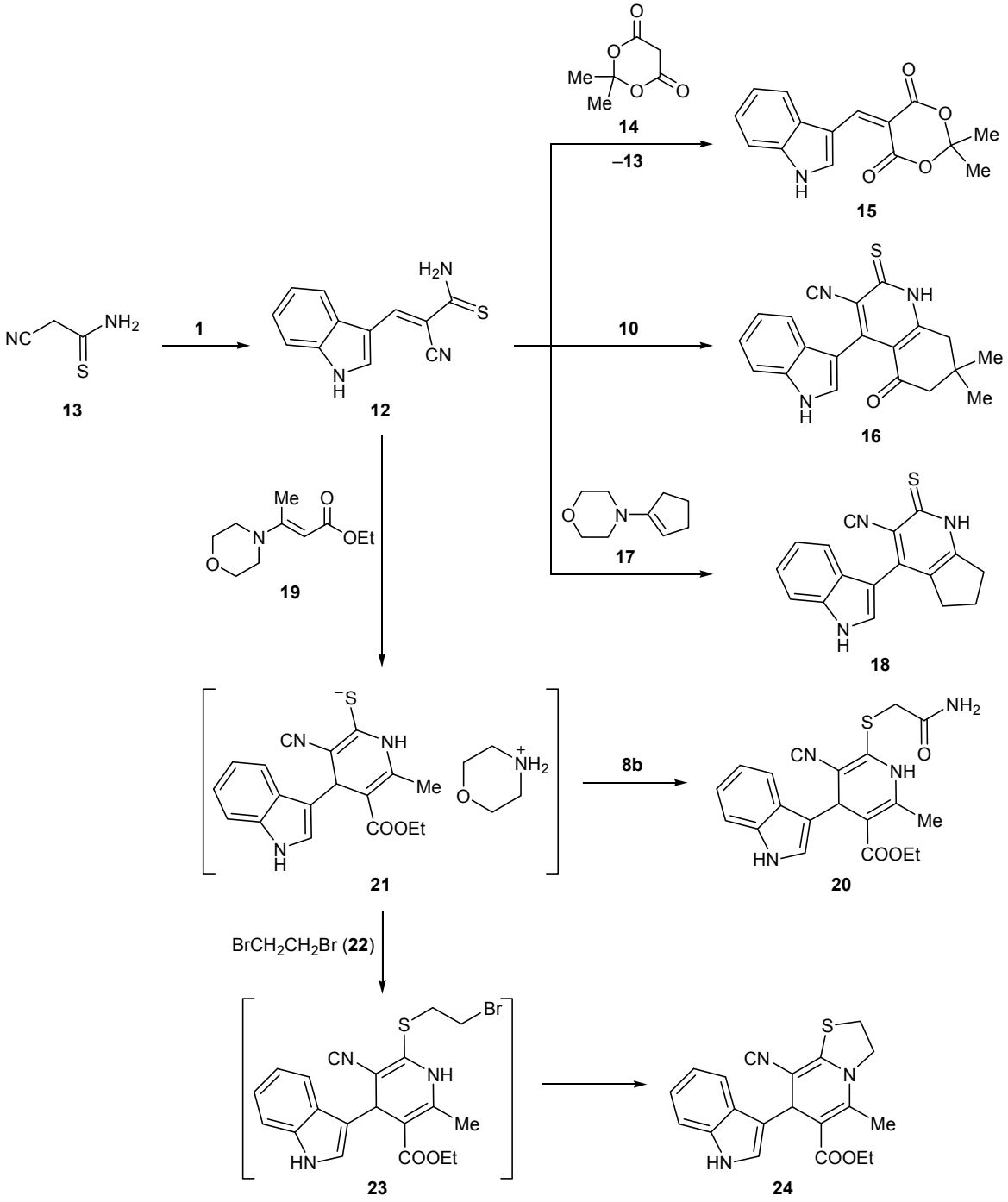
(Scheme 2). Thioamide **12** was synthesized previously from the same initial compounds in anhydrous ethanol at room temperature using piperidine or triethylamine as catalyst [16]; however, neither spectral nor physicochemical characteristics of the product were given in [16].

The reaction of **12** with Meldrum's acid (**14**) in boiling ethanol in the presence of *N*-methylmorpholine involved exchange of methylene components to give compound **15**. In contrast, the condensation of **12** with dimedone **10** under similar conditions followed the path typical of (arylmethylidene)cyanothioacetamides [17–19], leading to hexahydroquinoline derivative **16** (Scheme 2).

We also studied reactions of 3-(1*H*-indol-3-yl)-2-cyanoprop-2-enethioamide (**12**) with enamines. The reaction of **12** with 4-(cyclopent-1-en-1-yl)morpholine (**17**) afforded compound **18** as a result of the Stork reaction [20] (alkylation of enamines with alkenes). The three-component condensation of thioamide **12** with ethyl 3-(morpholin-4-yl)but-2-enoate (**19**) and 2-chloroacetamide (**8b**) in ethanol at 20°C led to the formation of dihydropyridine derivative **20** through intermediate morpholinium salt **21** which was isolated by us previously [3]. Analogous reaction with 1,2-dibromoethane (**22**) instead of **8b** followed essentially the same path, but sulfide **23** underwent *in situ* intramolecular alkylation to produce thiazolopyridine **24** which is promising as intermediate products for the synthesis of medicines and ensembles of heterocycles [21–26] (Scheme 2).

The structure of all isolated compounds was unambiguously proved by a set of physicochemical methods (see Experimental). The IR spectra of substituted acrylamides **4a**–**4f** characteristically showed absorption bands due to stretching vibrations of the N–H, C≡N, and C=O groups at 3310–3408, 2195–2202, and 1665–1708 cm^{-1}, respectively. In the ^1H NMR spectra of *N*-alkylindoles **9a**–**9g** we observed signals from aromatic protons and NCH_2 and CH= groups at δ 5.03–5.66 and 8.59–8.66 ppm, respectively. In the ^1H NMR spectrum of substituted 1,4-dihydropyridine **20**, signals of protons of the SCH_2 group appeared as two doublets at δ 3.62 and 3.77 ppm with a geminal coupling constant ^2J of 14.9 Hz. Analogous pattern was observed by us previously in the spectra of partially hydrogenated 2-(alkylsulfanyl)pyridines [27–29]; presumably, the SCH_2 protons become nonequivalent due to restricted rotation of the $SCH_2C(O)NH_2$ fragment.

Scheme 2.



EXPERIMENTAL

The IR spectra were recorded in mineral oil on an IKS-40 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Varian VXR-400 spectrometer at 399.97 and 100 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were obtained using an Agilent 1100 Series LC/MSD instrument (electron impact, 70 eV; samples were introduced as solutions in acetic acid). The elemental compositions were determined with a Perkin Elmer CHN analyzer. The melting points were measured on a Kofler hot stage. The progress of reactions and the purity of the isolated compounds were monitored by TLC on Silufol UV-254 plates using acetone–hexane (3 : 5) as eluent; spots were

visualized by treatment with iodine vapor and under UV light.

Compounds 4a–4f (*general procedure*). A mixture of 1.5 g (10 mmol) 1*H*-indole-3-carbaldehyde (**1**) and 10 mmol of CH acid **4a**–**4f** in 20 mL of ethanol containing 3 drops of morpholine was stirred for 4 h at 20°C. The mixture was left to stand for 24 h, and the precipitate was filtered off and washed with ethanol and hexane.

2-Cyano-*N*-cyclopropyl-3-(1*H*-indol-3-yl)prop-2-enamide (4a). Yield 2.1 g (82%), light yellow cotton-like solid, mp 205–207°C (from BuOH). IR spectrum, ν, cm^{-1}: 3300 (NH), 2195 (C≡N), 1668 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.60 br.s (2H, CH_2), 0.69 br.s (2H, CH_2), and 2.77 br.s (1H, CH) (C_3H_5); 7.21–7.28 m (2H, H_{arom}), 7.54 d (1H, H_{arom}, J = 7.1 Hz), 7.92 d (1H, H_{arom}, J = 6.8 Hz), 8.31 br.s (1H, CONH), 8.40 s (1H, 2-H), 8.44 s (1H, CH=), 12.31 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 6.3 (2C), 23.7, 98.3, 110.0, 113.2, 118.9, 119.1, 121.9, 123.7, 127.6, 130.5, 136.4, 142.2, 164.0. Mass spectrum: *m*/*z* 252.0 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 71.58; H 5.14; N 16.66. $C_{15}H_{13}N_3O$. Calculated, %: C 71.70; H 5.21; N 16.72. *M* 251.3.

Heptyl 2-cyano-3-(1*H*-indol-3-yl)prop-2-enoate (4b). Yield 2.1 g (68%), yellow plates fluorescing under UV light, mp 107–109°C (from EtOH). IR spectrum, ν, cm^{-1}: 3310 (NH), 2200 (C≡N), 1708 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.85 t (3H, Me, J = 6.7 Hz), 1.13–1.43 m (8H, CH_2), 1.66 t (2H, CH_2, J = 7.1 Hz), 4.22 t (2H, OCH_2, J = 6.5 Hz), 7.23–7.32 m (2H, H_{arom}), 7.56 d (1H, H_{arom}, J = 7.7 Hz), 7.94 d (1H, H_{arom}, J = 7.5 Hz), 8.55 s (1H, 2-H), 8.57 s (1H, CH=), 12.57 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.0, 22.1, 25.4, 28.2, 28.4, 31.2, 65.4, 92.4, 110.0, 113.1, 118.1, 118.6, 122.2, 123.7, 127.0, 132.8, 136.4, 146.7, 163.4. Mass spectrum: *m*/*z* 311.2 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 73.40; H 7.05; N 8.95. $C_{19}H_{22}N_2O_2$. Calculated, %: C 73.52; H 7.14; N 9.02. *M* 310.4.

2-Cyano-3-(1*H*-indol-3-yl)-*N*-(1,3-thiazol-2-yl)-prop-2-enamide (4c). Yield 2.1 g (72%), yellow powder, mp 225–227°C (from BuOH). IR spectrum, ν, cm^{-1}: 3312 (NH), 2202 (C≡N), 1669 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.12–7.32 m (4H, H_{arom}), 7.34–7.61 m (2H, H_{arom}), 8.04 br.s (1H, CONH), 8.57 s (1H, 2-H), 8.85 s (1H, CH=), 12.53 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 91.3, 97.8, 110.4, 113.3, 113.7, 119.0, 119.1, 122.3, 123.9, 128.0, 131.6, 135.1, 136.5, 143.9, 163.7. Mass spectrum: *m*/*z* 295.0 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 61.12; H 3.33; N 18.89. $C_{15}H_{10}N_4OS$. Calculated, %: C 61.21; H 3.42; N 19.04. *M* 294.3.

***N*-Benzyl-2-cyano-3-(1*H*-indol-3-yl)prop-2-enamide (4d).** Yield 2.4 g (79%), yellow powder, mp 212–214°C (from BuOH). IR spectrum, ν, cm^{-1}: 3305 (NH), 2200 (C≡N), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.47 s (2H, CH_2), 7.02–7.49 m (7H, H_{arom}), 7.53 d (1H, H_{arom}, J = 8.1 Hz), 7.93 d (1H, H_{arom}, J = 7.8 Hz), 8.51 s (1H, 2-H), 8.55 s (1H, CH=), 8.85 br.s (1H, CONH), 12.36 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 43.5, 97.7, 110.1, 113.2, 118.9, 119.2, 122.0, 123.7, 127.3, 127.7, 127.8 (2C), 128.8 (2C), 130.8, 136.5, 139.9, 142.8, 162.7. Mass spectrum: *m*/*z* 302.2 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 75.66; H 4.91; N 13.80. $C_{19}H_{15}N_3O$. Calculated, %: C 75.73; H 5.02; N 13.94. *M* 301.4.

2-Cyano-*N*-(furan-2-ylmethyl)-3-(1*H*-indol-3-yl)-prop-2-enamide (4e). Yield 2.3 g (80%), yellow powder, mp 221–223°C (from dioxane). IR spectrum, ν, cm^{-1}: 3313 (NH), 2196 (C≡N), 1666 (CONH). ^{1}H NMR spectrum, δ, ppm: 4.42 d (2H, NCH_2, J = 5.5 Hz), 6.30 s (1H, 3′-H), 6.41 s (1H, 4′-H), 7.22–7.28 m (2H, H_{arom}), 7.55 d (1H, H_{arom}, J = 7.7 Hz), 7.59 s (1H, CH=), 7.92 d (1H, H_{arom}, J = 8.1 Hz), 8.45 s (1H, 5′-H), 8.49 s (1H, 2-H), 8.77 t (1H, NHCO, J = 5.5 Hz), 12.34 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 36.8, 97.6, 107.6, 110.0, 111.0, 113.2, 118.9, 119.1, 122.0, 123.7, 127.7, 130.8, 136.5, 142.5, 142.8, 152.6, 162.6. Mass spectrum, *m*/*z* 292.0 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 69.92; H 4.38; N 14.29. $C_{17}H_{13}N_3O_2$. Calculated, %: C 70.09; H 4.50; N 14.43. *M* 291.9.

2-Amino-4-(1*H*-indol-3-yl)buta-1,3-diene-1,1,3-tricarbonitrile (4f). Yield 1.8 g (70%), yellow crystals, mp 242–244°C (from dioxane). IR spectrum, ν, cm^{-1}: 3408, 3396, 3311 (NH, NH_2), 2196 (C≡N), 1638 (δNH_2). ^{1}H NMR spectrum, δ, ppm: 7.19–7.33 m (2H, H_{arom}), 7.57 d (1H, H_{arom}, J = 7.5 Hz), 7.97 d (1H, H_{arom}, J = 7.2 Hz), 8.40 s (1H, 2-H), 8.56 s (1H, CH=), 8.74 br.s and 8.85 br.s (1H each, NH_2), 12.52 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 48.6, 92.8, 110.6, 113.4, 116.2, 116.7, 117.7, 119.2, 122.4, 124.1, 127.7, 132.0, 136.5, 146.3, 166.6. Mass spectrum: *m*/*z* 260.1 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 69.36; H 3.60; N 27.04. $C_{15}H_9N_5$. Calculated, %: C 69.50; H 3.50; N 27.00. *M* 259.3.

4-(1*H*-Indol-3-ylmethylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5-(4*H*)-one (5) was synthesized in a similar way from aldehyde **1** and 1.74 g (10 mmol)

of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**3**). Yield 2.3 g (77%), bright red crystals, mp 225–227°C (from BuOH); published data [4]: mp 235–236°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1665 (C=O). ^1H NMR spectrum, δ, ppm: 2.41 s (3H, Me), 7.16 t (1H, H_{arom}, J = 7.0 Hz), 7.31 d (2H, H_{arom}, J = 7.8 Hz), 7.43 t (2H, H_{arom}, J = 7.5 Hz), 7.59 d (1H, H_{arom}, J = 7.0 Hz), 8.01 d (2H, H_{arom}, J = 7.8 Hz), 8.10 s (1H, 2-H), 8.16 d (1H, H_{arom}, J = 6.8 Hz), 9.82 s (1H, CH=), 12.66 br.s (1H, NH). Mass spectrum: m/z 302.1 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 75.65; H 4.88; N 13.80. $C_{19}H_{15}N_3O$. Calculated, %: C 75.73; H 5.02; N 13.94. M 301.4.

2-(1*H*-Indol-3-ylmethylidene)malononitrile (7). *a*. A mixture of 2.1 g (10 mmol) of compound **4a**, 0.66 g (10 mmol) of malononitrile (**6**), and 0.87 mL (10 mmol) of morpholine in 25 mL of DMF was stirred for 2 h at 20°C. The mixture was left to stand for 24 h and was then diluted with an equal volume of water. The precipitate was filtered off and washed with water, ethanol, and hexane. Yield 1.3 g (69%), yellow crystals, mp 218–220°C (from EtOH); published data [6]: mp 223°C.

b. A mixture of 1.5 g (10 mmol) of aldehyde **1**, 0.66 g (10 mmol) of malononitrile (**6**), and 3 drops of morpholine in 25 mL of ethanol was stirred for 2 h at 20°C. The mixture was left to stand for 24 h, and the precipitate was filtered off and washed with ethanol and hexane. Yield 1.5 g (80%); the melting point and spectral parameters of the product were identical to those of a sample of **7** prepared as described in *a*.

Compounds 9a–9g (*general procedure*). Alkyl halide **8a**–**8e**, 10 mmol, and 10% aqueous potassium hydroxide, 5.6 mL (10 mmol), were added in succession with stirring at 20°C to a mixture of 10 mmol of substituted indole **4a**–**4f** or **7** and 30 mL of DMF. The mixture was stirred for 4 h and left to stand for 24 h. The mixture was diluted with an equal volume of water, and the precipitate was filtered off and washed with water, ethanol, and hexane.

2-[1-(Prop-2-en-1-yl)-1*H*-indol-3-ylmethylidene]-malononitrile (9a). Yield 1.75 g (75%), light green needles, mp 111–113°C (from AcOH). IR spectrum: ν 2208 cm^{-1}, sh (C≡N). ^1H NMR spectrum, δ, ppm: 5.05 d (2H, CH_2, J = 4.5 Hz), 5.18 d (1H, =CH_2, J_{trans} = 17.1 Hz), 5.26 d (1H, =CH_2, J_{cis} = 10.2 Hz), 5.83–6.16 m (1H, CH_2=C**H**), 7.24–7.31 m (2H, H_{arom}), 7.55 d (1H, H_{arom}, J = 7.2 Hz), 8.00 d (1H, H_{arom}, J = 7.5 Hz), 8.51 s (1H, 2-H), 8.60 s (1H, CH=). Mass spectrum, m/z 234.1 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 77.10; H 4.82; N 18.08. $C_{15}H_{11}N_3$. Calculated, %: C 77.23; H 4.75; N 18.01. M 233.3.

2-(1-Benzyl-1*H*-indol-3-ylmethylidene)malononitrile (9b). Yield 2.2 g (79%), yellow cotton-like material, mp 186–188°C (from AcOH). IR spectrum: ν 2218 cm^{-1}, sh (C≡N). ^1H NMR spectrum, δ, ppm: 5.66 s (2H, CH_2), 7.21–7.38 m (7H, H_{arom}), 7.62 d (1H, H_{arom}, J = 5.5 Hz), 8.06 d (1H, H_{arom}, J = 5.5 Hz), 8.66 s (1H, 2-H), 8.69 s (1H, CH=). ^{13}C NMR spectrum, δ_C, ppm: 50.8, 70.5, 110.9, 112.4, 116.1, 116.3, 119.9, 123.5, 124.6, 127.9, 128.0 (2C), 128.4, 129.3 (2C), 135.8, 136.7, 136.7, 152.4. Mass spectrum: m/z 284.2 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 80.41; H 4.75; N 14.84. $C_{19}H_{13}N_3$. Calculated, %: C 80.54; H 4.62; N 14.83. M 283.4.

Ethyl 2-[3-(2,2-dicyanoethenyl)-1*H*-indol-1-yl]-acetate (9c). Yield 2.1 g (76%), light yellow cotton-like material, mp 199–200°C (from dioxane); sublimes at 170°C. IR spectrum, ν, cm^{-1}: 2212 sh (C≡N), 1714 (C=O). ^1H NMR spectrum, δ, ppm: 1.28 t (3H, Me, J = 7.0 Hz), 4.19 q (2H, OCH_2, J = 7.0 Hz), 5.36 s (2H, NCH_2), 7.19–7.32 m (2H, H_{arom}), 7.50 d (1H, H_{arom}, J = 7.5 Hz), 7.98 d (1H, H_{arom}, J = 7.8 Hz), 8.59 s (1H, 2-H), 8.64 s (1H, CH=). Mass spectrum: m/z 280.1 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 68.72; H 4.55; N 14.93. $C_{16}H_{13}N_3O_2$. Calculated, %: C 68.81; H 4.69; N 15.05. M 279.3.

2-(1-Methyl-1*H*-indol-3-ylmethylidene)malononitrile (9d). Yield 1.7 g (82%), yellow crystals fluorescing under UV light, mp 174–176°C (from dioxane). IR spectrum: ν 2206 cm^{-1}, sh (C≡N). ^1H NMR spectrum, δ, ppm: 3.97 s (3H, Me), 7.22–7.34 m (2H, H_{arom}), 7.53 d (1H, H_{arom}, J = 7.7 Hz), 7.97 d (1H, H_{arom}, J = 8.0 Hz), 8.46 s (1H, 2-H), 8.51 s (1H, CH=). Mass spectrum: m/z 208.0 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 75.27; H 4.33; N 20.40. $C_{13}H_9N_3$. Calculated, %: C 75.35; H 4.38; N 20.27. M 207.2.

2-[3-(2,2-Dicyanoethenyl)-1*H*-indol-1-yl]acetamide (9e). Yield 2.0 g (79%), light yellow cotton-like material fluorescing under UV light, mp 275–277°C (from dioxane). IR spectrum, ν, cm^{-1}: 3411, 3382, 3305 (NH_2), 2202 sh (C≡N), 1667 ($CONH_2$). ^1H NMR spectrum, δ, ppm: 5.03 s (2H, CH_2), 7.23–7.31 m (3H, H_{arom}, NH_2), 7.47 d (1H, H_{arom}, J = 7.6 Hz), 7.73 br.s (1H, NH_2), 7.80 d (1H, H_{arom}, J = 7.3 Hz), 8.52 s (1H, 2-H), 8.59 s (1H, CH=). Mass spectrum: m/z 251.1 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 67.04; H 3.89; N 22.44. $C_{14}H_{10}N_4O$. Calculated, %: C 67.19; H 4.03; N 22.39. M 250.3.

Heptyl 2-cyano-3-[1-(prop-2-en-1-yl)-1*H*-indol-3-yl)prop-2-enoate (9f). Yield 2.4 g (67%), light yellow needles fluorescing under UV light, mp 64–65°C (from AcOH). IR spectrum, ν, cm^{-1}: 2205 (C≡N), 1711 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, Me, J = 6.7 Hz), 1.25–1.49 m (8H, CH_2), 1.72 t (2H, CH_2, J = 7.1 Hz), 4.27 t (2H, OCH_2, J = 6.6 Hz), 5.04 d (2H, NCH_2, J = 5.5 Hz), 5.18 d (1H, =CH_2, J_{trans} = 17.0 Hz), 5.27 d (1H, =CH_2, J_{cis} = 11.4 Hz), 6.00–6.18 m (1H, CH=), 7.25–7.31 m (2H, H_{arom}), 7.55 d (1H, H_{arom}, J = 7.1 Hz), 7.87 d (1H, H_{arom}, J = 7.8 Hz), 8.48 s (1H, 2-H), 8.54 s (1H, CH=). Mass spectrum: m/z 351.2 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 75.31; H 7.35; N 8.07. $C_{22}H_{26}N_2O_2$. Calculated, %: C 75.40; H 7.48; N 7.99. M 350.5.

2-Cyano-*N*-cyclopropyl-3-[1-(prop-2-en-1-yl)-1*H*-indol-3-yl]prop-2-enamide (9g). Yield 2.1 g (71%), yellow cotton-like material fluorescing under UV light, mp 235–237°C (from BuOH). IR spectrum, ν, cm^{-1}: 3300 (NH), 2212 (C≡N), 1667 (CONH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.65 br.s (2H, CH_2), 0.89 br.s (2H, CH_2), and 2.89 br.s (1H, CH) (C_3H_5); 4.84 s (2H, NCH_2), 5.18 d (1H, =CH_2, J_{trans} = 17.3 Hz), 5.32 d (1H, =CH_2, J_{cis} = 9.8 Hz), 5.94–6.11 m (1H, C**H**=CH_2), 6.26 br.s (1H, NH), 7.11–7.23 m (3H, H_{arom}), 7.88 m (1H, H_{arom}), 8.36 s (1H, 2-H), 8.66 s (1H, CH=). ^{13}C NMR spectrum, δ_C, ppm: 6.8 (2C), 23.4, 49.9, 95.2, 110.7, 118.6, 119.0, 119.3, 122.3, 122.5, 123.8, 128.5, 131.6, 132.5, 136.2, 144.0, 163.2. Mass spectrum: m/z 292.1 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 74.05; H 5.90; N 14.32. $C_{18}H_{17}N_3O$. Calculated, %: C 74.21; H 5.88; N 14.42. M 291.4.

2-Amino-7,7-dimethyl-5-oxo-4-[1-(prop-2-en-1-yl)-1*H*-indol-3-yl]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (11). A mixture of 2.3 g (10 mmol) of acrylonitrile **9a**, 1.4 g (10 mmol) of dimedone **10**, and 3 drops of morpholine in 30 mL of DMF was stirred for 2 h at 20°C. The mixture was left to stand for 24 h, diluted with an equal volume of water, and left to stand for 24 h more. The precipitate was filtered off and washed with water, ethanol, and hexane. Yield 2.9 g (77%), light yellow crystals, mp 180–182°C (from BuOH). IR spectrum, ν, cm^{-1}: 3411, 3382, 3310 (NH_2), 2195 (C≡N), 1714 (C=O), 1633 (δNH_2). ^{1}H NMR spectrum, δ, ppm: 0.92 s (3H, Me), 1.08 s (3H, Me), 2.06 d and 2.18 d (1H each, CH_2, ^2J = 16.1 Hz), 3.11 s (2H, CH_2), 4.49 s (1H, 4-H), 4.74 d (2H, NCH_2, J = 5.2 Hz), 5.01 d (1H, =CH_2, J_{trans} = 17.1 Hz), 5.14 d (1H, =CH_2, J_{cis} = 10.2 Hz), 5.84–6.13 m (1H, CH=), 6.66 br.s (2H, NH_2), 6.97 t (1H, H_{arom}, J = 7.9 Hz), 7.07 br.s (2H, 2′-H, H_{arom}), 7.29 d (1H, H_{arom}, J = 8.2 Hz), 7.37 t (1H, H_{arom}, J = 7.9 Hz). Mass spectrum: m/z 374.2 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 73.80; H 6.18; N 11.34. $C_{23}H_{23}N_3O_2$. Calculated, %: C 73.97; H 6.21; N 11.25. M 373.5.

2-Cyano-3-(1*H*-indol-3-yl)prop-2-enethioamide (12). A mixture of 1.5 g (10 mmol) of aldehyde **1**, 1.0 g (10 mmol) of cyanothioacetamide (**13**), and 3 drops of morpholine in 30 mL of ethanol was stirred for 5 h at 20°C. The precipitate was filtered off and washed with ethanol and hexane. Yield 2.0 g (85%), yellow crystals, mp 174–176°C (from EtOH) [3].

5-(1*H*-Indol-3-ylmethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (15). A mixture of 2.3 g (10 mmol) of thioacrylamide **12**, 1.4 g (10 mmol) of Meldrum's acid (**14**), and 1.1 mL (10 mmol) of *N*-methylmorpholine was refluxed for 2 h. After cooling, a solid crystallized from the mixture and was filtered off and washed with ethanol and hexane. Yield 1.8 g (68%), light yellow crystals, mp 234–235°C (from EtOH). IR spectrum, ν, cm^{-1}: 3314 (NH), 1718 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.72 s (6H, Me), 7.33–7.41 m (2H, H_{arom}), 7.62 d (1H, H_{arom}, J = 8.1 Hz), 7.91 d (1H, H_{arom}, J = 7.8 Hz), 8.75 s (1H, 2-H), 9.34 s (1H, CH=), 12.90 br.s (1H, NH). Mass spectrum: m/z 270.0 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 66.31; H 4.79; N 5.22. $C_{15}H_{13}NO_4$. Calculated, %: C 66.42; H 4.83; N 5.16. M 271.3.

4-(1*H*-Indol-3-yl)-7,7-dimethyl-5-oxo-2-sulfanylidene-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (16). A mixture of 2.3 g (10 mmol) of amide **12**, 1.4 g (10 mmol) of dimedone **10**, and 1.1 mL (10 mmol) of *N*-methylmorpholine in 25 mL of DMF was stirred for 4 h at 20°C and was left to stand for 24 h. The mixture was diluted with an equal volume of water and left to stand for 48 h, and the precipitate was filtered off and washed with water, ethanol, and hexane. Yield 2.4 g (69%), yellow crystals, mp 310°C (decomp., from AcOH). IR spectrum, ν, cm^{-1}: 3315, 3164 (NH), 2229 (C≡N), 1690 (C=O), 1208 (C=S). ^{1}H NMR spectrum, δ, ppm: 0.98 s (3H, Me), 1.12 s (3H, Me), 2.23 d and 2.55 d (1H each, CH_2, ^2J = 16.0 Hz), 2.96 d and 3.05 d (1H each, CH_2, ^2J = 16.2 Hz), 6.89–6.93 m (1H, H_{arom}), 7.11–7.19 m (2H, H_{arom}), 7.44 d (1H, H_{arom}, J = 7.9 Hz), 7.74 s (1H, 2′-H), 11.62 br.s (1H, N$^{1'}$H), 14.14 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 27.3, 28.3, 32.1, 40.1, 51.9, 110.6, 112.2, 115.9, 117.0, 117.3, 119.1, 119.9, 121.7, 126.1, 127.3, 136.2, 149.4, 159.0, 180.1, 192.3. Mass spectrum: m/z 348.0 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 69.01; H 5.14; N 11.95. $C_{20}H_{17}N_3OS$. Calculated, %: C 69.14; H 4.93; N 12.09. M 347.4.

4-(1*H*-Indol-3-yl)-2-sulfanylidene-2,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carbonitrile (18) was synthesized in a similar way from thioamide **12** and 1.5 g (10 mmol) of 4-(cyclopent-1-en-1-yl)morpholine (**17**). Yield 2.3 g (78%), yellow powder, mp 287–289°C. IR spectrum, ν, cm^{-1}: 3162 (NH), 2212 (C≡N), 1210 (C=S). ^{1}H NMR spectrum, δ, ppm: 2.01 t (2H, CH_2, J = 7.6 Hz), 2.55–2.68 m (2H, CH_2), 2.96 t (2H, CH_2, J = 8.0 Hz), 7.13 t (1H, H_{arom}, J = 7.4 Hz), 7.21 t (1H, H_{arom}, J = 8.0 Hz), 7.39 d (1H, H_{arom}, J = 8.0 Hz), 7.51 t (1H, H_{arom}, J = 7.4 Hz), 7.84 s (1H, 2′-H), 12.02 br.s (1H, N^1′H); no pyridine NH signal was observed, presumably because of fast H–D exchange. Mass spectrum, m/z 292.0 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 69.94; H 4.46; N 14.53. $C_{17}H_{13}N_3S$. Calculated, %: C 70.08; H 4.50; N 14.42. M 291.4.

Ethyl 6-(2-amino-2-oxoethylsulfanyl)-5-cyano-4-(1*H*-indol-3-yl)-2-methyl-1,4-dihydropyridine-3-carboxylate (20). A mixture of 2.3 g (10 mmol) of amide **12** and 2 g (10 mmol) of enamine **19** in 30 mL of ethanol was stirred for 5 h at 20°C. 2-Chloroacetamide (**8b**), 0.94 g (10 mmol), was then added, and the mixture was stirred for 2 h and left to stand for 24 h. The mixture was diluted with an equal volume of water, and the precipitate was filtered off. Yield 2.8 g (71%), colorless plates, mp 218–220°C (from BuOH). IR spectrum, ν, cm^{-1}: 3372, 3330, 3205 (NH, NH_2), 2196 (C≡N), 1681 (C=O, ester), 1669 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.09 t (3H, Me, J = 7.1 Hz), 2.25 s (3H, Me), 3.62 d and 3.77 d (1H each, SCH_2, ^2J = 14.9 Hz), 3.98 q (2H, OCH_2, J = 7.1 Hz), 4.81 s (1H, 4-H), 6.98 t (1H, H_{arom}, J = 7.9 Hz), 7.01–7.15 m (2H, H_{arom}, 2′-H), 7.34 d (1H, H_{arom}, J = 8.0 Hz), 7.45 d (1H, H_{arom}, J = 7.9 Hz), 7.58 br.s and 7.90 br.s (1H each, NH_2), 10.40 br.s (1H, N^{1}H), 10.92 br.s (1H, N^1′H). ^{13}C NMR spectrum, δ_C, ppm: 14.6, 18.9, 34.3, 59.8, 87.8, 101.1, 109.2, 114.2, 115.4, 115.9, 117.4, 119.2, 121.4, 123.7, 125.6, 136.6, 143.3, 144.7, 165.6, 172.0. Mass spectrum: m/z 395.0 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 60.41; H 4.93; N 14.19. $C_{20}H_{20}N_4O_3S$. Calculated, %: C 60.59; H 5.08; N 14.13. M 396.5.

Ethyl 8-cyano-(1*H*-indol-3-yl)-5-methyl-3,7-dihydro-2*H*-[1,3]thiazolo[3,2-*a*]pyridine-6-carboxylate (24). A mixture of 2.3 g (10 mmol) of amide **12** and 2 g (10 mmol) of enamine **19** in 30 mL of ethanol was stirred for 5 h at 20°C, 0.9 mL (10 mmol) of 1,2-dibromoethane (**22**) was added. and the mixture was stirred for 2 h. The mixture was then diluted with 20 mL of DMF, 5.6 mL (10 mmol) of 10% aqueous potassium hydroxide was added, and the mixture was stirred for 1 h and left to stand for 24 h. The mixture was diluted with an equal volume of water, and the precipitate was filtered off and washed with water, ethanol, and hexane. Yield 2.6 g (72%), yellow crystals, mp 174–176°C (from BuOH). IR spectrum, ν, cm^{-1}: 3328 (NH), 2197 (C≡N), 1716 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.05 t (3H, Me, J = 6.5 Hz), 2.43 s (3H, Me), 3.95 t (2H, OCH_2, J = 6.5 Hz), 4.17 t (2H, NCH_2, J = 7.7 Hz), 4.25 t (2H, SCH_2, J = 7.7 Hz), 4.92 s (1H, 7-H), 7.00 t (1H, H_{arom}, J = 7.8 Hz), 7.04–7.16 m (2H, H_{arom}, 2′-H), 7.37 d (1H, H_{arom}, J = 7.8 Hz), 7.44 d (1H, H_{arom}, J = 7.5 Hz), 10.95 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.4, 17.0, 28.5, 33.9, 52.5, 60.0, 78.6, 104.5, 112.2, 119.1, 119.3, 119.6, 120.7, 121.4, 123.8, 126.0, 137.1, 144.2, 152.0, 167.6. Mass spectrum: m/z 364.2 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 65.66; H 5.20; N 11.62. $C_{20}H_{19}N_3O_2S$. Calculated, %: C 65.73; H 5.24; N 11.50. M 365.5.

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