Concise Syntheses of the Novel 1*H*-Pyrrolo[3,2-*g*]quinazoline Ring System and its [2,3-*f*] Angular Isomer

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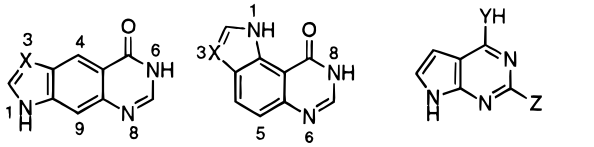
Introduction

Several years ago, Leonard and co-workers reported on the synthesis of a series of linear benzo-substituted purines, agents that act as purine mimics in many enzymatic reactions.[1] These are chemically designated as imidazo[4,5-*g*]quinazolines and are exemplified by *lin*-benzohypoxanthine (**1**). There soon followed the synthesis of a number of angular analogues[2] including the imidazo[4,5-*f*] series of compounds exemplified by *prox*-benzohypoxanthine (**2**). More recently, others have extended this work to the synthesis of isomeric forms of these tricycles including linear[3] and angular[4] pyrazoloquinazoline systems. However, reports describing the synthesis of corresponding benzo-substituted deazapurines (*i.e.*, pyrroloquinazolines) are sparse. Apart from the synthesis of a single angular isomer (pyrrolo[3,2-*f*]-quinazoline)[5] of this heterocyclic system, these ring systems have never been made. We report in this paper approaches toward the first synthesis of a linear pyrroloquinazoline and one of its angular isomers, exemplified by compounds **3** and **4**, respectively. Heterocycle **3** can be viewed as a linear extension of the deazapurine **5**[6] (*i.e.*, pyrrolo[2,3-*d*]pyrimidine ring system), which is an important precursor of the 4-amino analogue **6**.[7] Heterocycle **6** and its 2-amino derivative **7** are structural elements of the important antitumor nucleoside tubercidin,[8] which is highly stable toward acid hydrolysis, and a series of novel antifolate inhibitors of dihydrofolate reductases,[9] respectively.



1: X = N
3: X = C

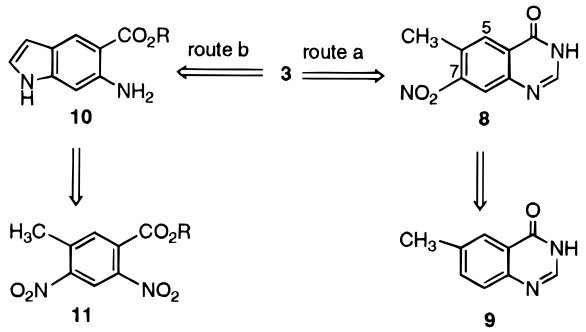
2: X = N
4: X = C

5: Y = O; Z = H
6: Y = N; Z = H
7: Y = N; Z = NH_2

Results and Discussion

To construct our targeted 1*H*-pyrrolo[3,2-*g*]quinazoline ring system, exemplified by **3**, we initially adopted a strategy whereby the indole ring would be annulated via Batcho−Leimgruber indole synthesis[10] onto a 7-nitroquinazolinone precursor **8** (Scheme 1, route a). Accordingly, nitration of 6-methylquinazolin-4-one[11] (**9**) was evaluated under a number of conditions. However, this provided predominately the 5-nitro isomer[3c,4d,e] instead of the desired 7-isomer **8**. Thus, we pursued the construction of **3** by a reverse sequence in which pyrimidine ring annulation was carried out on a suitably functionalized indole precursor **10** (Scheme 1, route b).

Scheme 1



The synthesis of linear target **3** is shown in Scheme 2. Fischer esterification of commercially available 3-methyl-4-nitrobenzoic acid (**12**) gave ethyl ester **13**[12] in 92% yield, which was then nitrated regioselectively with cold fuming nitric acid to afford an 86:14 mixture of desired product **14**[13] and its isomer **15** in 98% yield. Ester **14** was purified to >97% isomeric purity in an overall yield of 70% by crystallization from 2-propanol. At this juncture, **14** could be parlayed into target compound **3** by one of two routes. In the first, Batcho−Leimgruber indole synthesis was performed by condensation of **14** with DMF dimethyl acetal in refluxing *p*-dioxane to cleanly give the enamino ester **16**, which was not isolated but was directly reductively cyclized via catalytic hydrogenation to the indolic anthranilate **17** in 96% yield. Indole **17** was contaminated with 4−10% of the corresponding 1-hy-

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(4) Pyrazolo[3,4−*h*]quinazolines: (a) ref 3a; Pyrazolo[4,3-*f*]-quinazolines: (b) ref 3d; Pyrazolo[3,4-*f*]quinazolines: (c) ref 3c. (d) Foster, R. H.; Leonard, N. J. *J. Org. Chem.* **1980**, *45*, 3072−3077. (e) Lichtenthaler, F. W.; Cuny, E. *Heterocycles* **1981**, *15*, 1053−1059.

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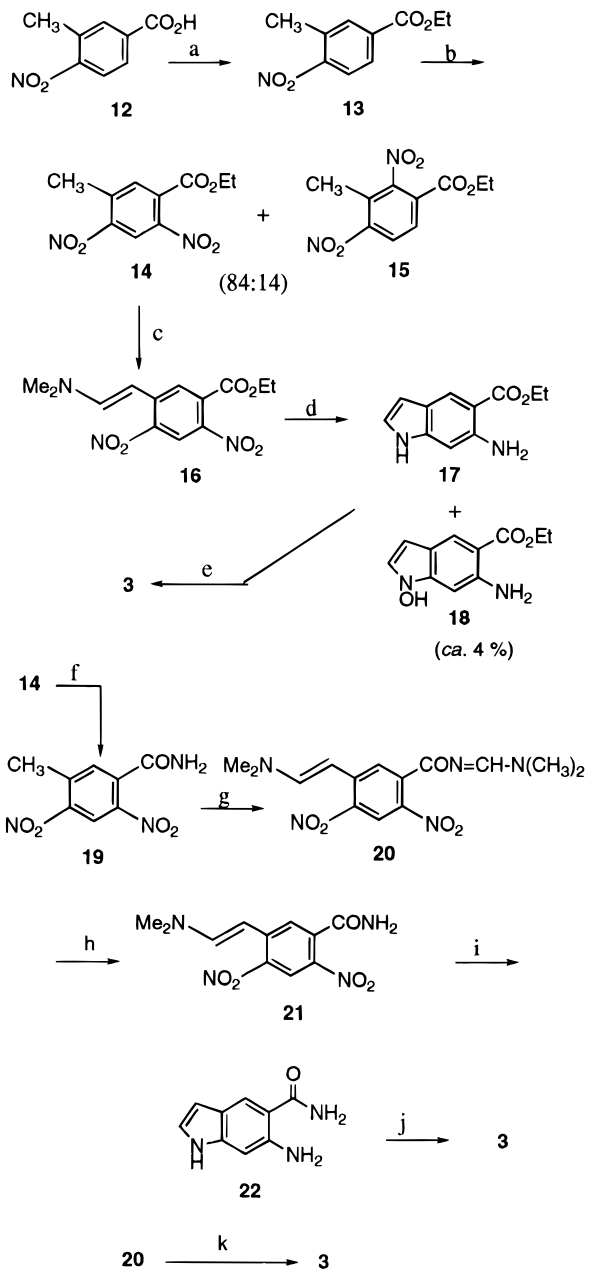
Scheme 2[a]



[a] Key: (a) EtOH, H_2SO_4, reflux, 24 h, 92%; (b) fuming HNO_3, H_2SO_4, −20 °C, 5.75 d, 70%; (c) DMFDMA, *p*-dioxane, reflux, 1.5 h; (d) 5% Pd/C, H_2 (60 psi), MeOH, 1 h, 96% two steps; (e) formamidine acetate, 2-methoxyethanol, reflux, 2 h, 64%; (f) anhyd NH_3/MeOH, 80 °C, 12 h, 90%; (g) BBDM, DMF, 25 °C, 1 h, 84%; (h) MeOH, glacial HOAc, reflux, 2 d, 80%; (i) 10% Pd/C, H_2, THF, 12 h, 72%; (j) $(EtO)_3CH$, 100 °C, 1 h, 50%; (k) RaNi, H_2 (1500 psi), 1:1 THF:MeOH, 25 °C, 57%.

droxyindole **18** that displayed the same R_f by TLC.[14] Annulation of the pyrimidinone ring onto **17** proceeded smoothly in 64% yield with formamidine acetate[15] in refluxing 2-methoxyethanol to provide target compound **3** without any *N*-hydroxy impurity. More classical methods of ring closure including the Niementowski reaction (hot formamide)[16] and s-triazine in refluxing alcohol[17] failed.

In a second route to **3**, shown in Scheme 2, aminolysis of dinitro ester **14** to amide **19**[18] followed by condensation with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) in DMF at room temperature afforded the enamino amidine **20** as a brick red solid in 76% yield over two steps.[19] Similar reaction with DMF dimethyl acetal proceeded much less cleanly. Since **20** contains the necessary framework for further elaboration to target **3** via tandem ring closure, we subjected it to various conditions of reductive cyclization, including numerous conditions of catalytic hydrogenation over 10% Pd/C, and selected dissolving metal reductions.[20] Amongst these, the best condition developed involved high pressure Raney nickel hydrogenation in 1:1 THF:MeOH[21] at high dilution to afford compound **3** in 57% yield on a small scale. However, larger scale reactions were highly irreproducible, with 10−15% yields the norm. Thus, we found it more convenient to selectively hydrolyze the amidine side chain of **20** with mildly acidic methanol to give the enamino amide **21** in 80% yield. Reductive ring closure similar to that described above for **16** gave the indole amide **22** in 72% yield.[22] Compound **22** as well as **17** are quite air sensitive and darken while in solution. Ring closure of **22** to target **3** proceeded uneventfully in hot triethyl orthoformate. Solutions of **3** in common organic solvents are also unstable, but it can be stored as a solid without significant decomposition.

The synthesis of angular target compound **4**, shown in Scheme 3, proceeded in a much more straightforward fashion. Thus, Fischer esterification of 3-methyl-6-nitrobenzoic acid **23** provided ester **24** in 91% yield. Nitration of **24** with fuming nitric acid in triflic acid[23] proceeded to give a 1:1 mixture of compound **25**[13] and its regioisomer **14** in 61% yield. Following separation by careful column chromatography, bis-nitro ester **25** was condensed with DMF dimethyl acetal in DMF at 100 °C

(14) Although **18** is not observed in the EIMS of the mixture, it is evident by high-field NMR. Thus, in the Me_2SO-d_6 ^1H NMR spectrum of the mixture of **17** and **18**, H-2 and H-3 of the indole ring of **17** resonate at δ 7.09 and 6.29, respectively, and display couplings to the indolic NH proton as well as to each other. Impurity **18** is evidenced by the presence of the additional resonances at δ 7.30 and 6.23, which are coupled only to each other, and another exchangeable resonance at δ 5.87. In the $CDCl_3$ ^{13}C NMR spectrum, there are additional resonances at δ 132.96, 122.93, 100.02, 59.64 and 16.26. The 132.96 and 100.02 signals are the most prominent, and correspond to CH carbons from the DEPT spectrum. Therefore, they most likely correspond to C-2 and C-3, respectively, of **18**.

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(19) It is imperative to use pure (*tert*-butyloxy)bis(dimethylamino)-methane in this reaction. In one run utilizing old reagent, the reaction did not proceed cleanly. Attempted purification of crude **20** by column chromatography resulted in significant decomposition, in part to amide **21**.

(20) (a) Aqueous $TiCl_3$: Lloyd, D. H.; Nichols, D. E. *Tetrahedron Lett.* **1983**, *24*, 4561−4562. (b) Fe/HOAc/EtOH: Ponticello, G. S.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 4003−4005. (c) Zn/HOAc: Glushkov, R. G.; Volskova, V. A.; Magidson, O. Y. *Khim.-Farm. Zh.* **1967**, *1*, 25−32; *Chem. Abstr.* **1968**, *68*, 105143f.

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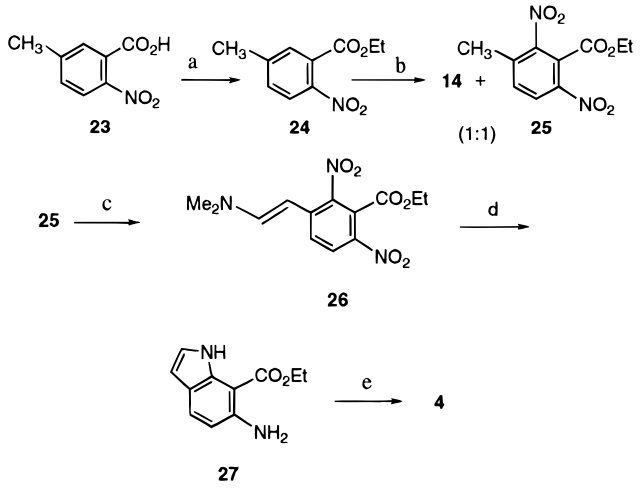
(22) In a separate run in which the reaction was worked up before there was theoretical uptake of H_2, we isolated a component, mp 171 °C dec, *ca.* 87% pure by ^1H NMR, that displayed the same R_f by TLC as desired product **22**. Its ^1H NMR and CIMS suggest that it is the intermediate 1-hydroxy analogue of **22**, corresponding to **18** observed in the reduction **16** to **17**;[14] ^1H NMR (Me_2SO-d_6) δ 10.92 (s, exchanges with D_2O, 1H), 7.74 (s, 1H), 7.65 (br s, exchanges with D_2O, 1H), 7.15 (d, J = 3.4 Hz, 1H), 6.94 (br s, exchanges with D_2O, 1H), 6.55 (s, 1H), 6.22 (s, exchanges with D_2O, 2H), 6.11 (d, J = 3.4 Hz, 1H); CIMS m/z (relative intensity) 192 (14), 191(M^+, 40), 175 (100), 174 (43).

(23) Coon, C. L.; Hill, M. E. U.S. Patent 3714272; *Chem. Abstr.* **1973**, *78*, 97303x.

Scheme 3[a]



[a] Key: (a) EtOH, H_2SO_4, reflux, 2 d, 91%; (b) fuming HNO_3, CF_3SO_3H, CH_2Cl_2, 25 °C, 20 h, 31%; (c) DMFDMA, DMF, 100 °C, 4 h, 70%; (d) 10% Pd/C, H_2 (50 psi), MeOH, 4 h, 48% (e) formamide, 150−180 °C, 3 h, 44%.

to afford compound **26** in 70% yield. Reductive cyclization of **26** via catalytic hydrogenation to indole **27** followed by condensation with formamide at 100 °C gave target pyrrolo[2,3-*f*]quinazolinone **4** in 21% yield over two steps. Yields for the synthesis of angular target **4** were not optimized.

In summary, we have developed synthetic pathways to two novel pyrroloquinazoline heterocycles, benzo-substituted variants of the biologically important pyrrolo-[2,3-*d*]pyrimidine ring system. We expect these heterocycles to find broad application as novel templates in organic synthesis and drug design.

Experimental Section

Melting points are uncorrected. Column chromatography was carried out in the flash mode utilizing E. Merck 230−400-mesh silica gel. Analytical TLC was carried out on E. Merck silica gel 60 F_{254} plates with detection by UV light. Palladium on activated carbon utilized in catalytic hydrogenations was purchased from Aldrich Chemical Co. All reaction solvents were reagent grade or distilled-in-glass and were stored over activated 3A (for lower alcohols) or 4A molecular sieves. Following normal workup procedures, organic extracts were dried over anhyd Na_2SO_4 or $MgSO_4$ prior to concentration.

3-Methyl-4-nitrobenzoic Acid, Ethyl Ester (13). A solution of 102.1 g (564 mmol) of 3-methyl-4-nitrobenzoic acid (**12**) dissolved in 1 L of absolute EtOH was carefully treated with 10 mL of concd H_2SO_4. The solution was heated at reflux for 24 h then concentrated to 300 mL by allowing the EtOH to distill off. Upon cooling solids precipitated. The suspension was further cooled to about −10 °C, and then the solids were collected, washed with a small amount of cold EtOH, and recrystallized from 450 mL of boiling hexanes to afford 108 g (92%) of **13** as a pale yellow solid: mp 52.5−53.5 °C (lit.[12] mp 55 °C); ^{1}H NMR ($CDCl_3$) δ 11.53 (s, 1H), 7.98−7.93 (m, 3H), 4.38 (q, J = 7.0 Hz, 2H), 2.58 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.23; H, 5.25; N, 6.65.

4,6-Dinitro-*m*-toluic Acid, Ethyl Ester (14). A solution of 112 g (535 mmol) of ester **13** in 460 mL of concd H_2SO_4 was cooled to −10 °C and then treated dropwise over a 45 min period with 106 mL of fuming HNO_3 so as to maintain the internal temperature at −10 °C. The solution was stored at −20 °C for 5.75 d. The resulting golden yellow syrup was carefully poured into about 3.2 L of crushed ice precipitating out a waxlike solid. The suspension was extracted into EtOAc (3 × 600 mL), and the combined extracts were washed with 5% aq NaOH until the aqueous phase remained neutral and then dried. Concentration gave 133 g of an oil that solidified as an 86:14 mixture of isomers (monitored by ^{1}H NMR or TLC utilizing 4:1 hexanes:EtOAc). The crude solid was triturated in 150 mL of *i*-PrOH and then filtered to leave a pale white solid. The solid was dissolved in 400 mL of hot *i*-PrOH, and the solution was allowed to slowly cool to 25 °C. After storage the solid was collected, washed with *i*-PrOH, and dried to leave 95 g (70%) of **14**, 98% by ^{1}H NMR, as a white solid: mp 60.5−62.5 °C (lit.[13] mp 47−48 °C): ^{1}H NMR (Me_2SO-d_6) δ 8.61 (s, 1H), 8.00 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 2.63 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 164.1, 149.8, 145.4, 140.2, 134.4, 130.7, 121.3, 63.2, 19.8, 14.0; CIMS m/z (relative intensity) 255 (MH^+, 36). Anal. Calcd for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.53; H, 4.05; N, 11.00.

The filtrate was concentrated to a *ca.* 1:1 mixture of isomers. Dissolution of the solid in dilute 2:1 hexanes:*i*-PrOH followed by storage at 25 °C for several weeks resulted in the crystallization of >90% pure material. An additional crystallization from *i*-PrOH gave pure **15**: mp 75.5−76 °C: ^{1}H NMR ($CDCl_3$) δ 8.04 (d, J = 8.7 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 4.41 (q, J = 7.0 Hz, 2H), 2.45 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); CIMS m/z (relative intensity) 255 (MH^+, 36), 209 (100). Anal. Calcd for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.31; H, 3.97; N, 11.03.

6-Amino-1*H*-indole-5-carboxylic Acid, Ethyl Ester (17). A solution of 15.0 g (59 mmol) of ester **14** and 9.4 mL (71 mmol) of DMF dimethyl acetal in 250 mL of *p*-dioxane was heated at reflux for 1.5 h. The resulting deep red solution, containing (*E*)-5-[2-(dimethylamino)ethenyl]-2,4-dinitrobenzoic acid, ethyl ester (**16**) as the sole product, was cooled to 25 °C, diluted with 100 mL of MeOH and then hydrogenated at 60 psi over 8.0 g of 5% Pd/C. After 1 h, when H_2 uptake had ceased, the mixture was filtered and concentrated to give a solid that was purified by column chromatography. Elution with EtOAc/petroleum ether (1:1) afforded 11.6 g (96%) of **17**, contaminated with *ca.* 4% of the corresponding 1-hydroxyindole **18**.[14] Crystallization from aq MeOH provided pure **17**: mp 139 °C; ^{1}H NMR (Me_2SO-d_6) δ 10.68 (br s, exchanges with D_2O, 1H), 8.02 (s, 1H), 7.09 (dd, J = 3.1, 2.4 Hz, 1H), 6.64 (s, 1H), 6.29 (m, 1H), 6.18 (br s, exchanges with D_2O, 2H), 4.24 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.8, 146.4, 140.5, 124.8, 123.9, 120.6, 107.9, 103.5, 96.0, 60.1, 14.5; EIMS m/z (relative intensity) 204 (M^+, 92), 158 (100), 130 (59), 104 (19). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.39; H, 6.04; N, 13.44.

5-Methyl-2,4-dinitrobenzamide (19). A solution of 5.0 g (24 mmol) of ester **14** in 50 mL of saturated anhydrous NH_3 in MeOH was stirred in a pressure reactor at 80 °C for 12 h. The mixture was concentrated, and the resulting black residue was purified by column chromatography eluting with EtOAc:hexanes (1:1) to give 4.0 g (90%) of **19**: mp 173−174 °C: ^{1}H NMR (Me_2SO-d_6) δ 8.63 (s, 1H), 8.25 (s, exchanges D_2O, 1H), 7.93 (s, exchanges D_2O, 1H), 7.81 (s, 1H), and 2.63 (s, 3H); ^{13}C NMR (Me_2SO-d_6) δ 165.7, 148.1, 144.3, 139.1, 136.0, 133.2, 120.6, 19.3; CIMS m/z (relative intensity) 226 (MH^+, 38), 209 (100). Anal. Calcd for $C_8H_7N_3O_5$: C, 42.68; H, 3.13; N, 18.66. Found: C, 42.74 H, 3.15; N, 18.43.

***N*-[(Dimethylamino)methylene]- (*E*)-5-[2-(dimethylamino)ethenyl]-2,4-dinitrobenzamide (20).** A solution of 2.25 g (10 mmol) of benzamide **19** in 10 mL of DMF was treated with 6.2 mL (30 mmol) of (*tert*-butyloxy)bis(dimethylamino)methane. The reaction mixture was stirred at 25 °C for 1 h. The solvent was evaporated *in vacuo*, and the residue was suspended in H_2O. The precipitate was collected then washed successively with H_2O and Et_2O to afford 2.76 g (84%) of **20** as a red solid: mp 218−219 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.55 (s, 1H), 8.47 (s, 1H), 8.04 (d, J = 13.0 Hz, 1H), 7.76 (1H, s), 5.95 (d, J =13.0 Hz, 1H), 3.21 (s, 3H), 3.00 (m, 9H); ^{13}C NMR (Me_2SO-d_6) 176.0, 160.5, 151.5, 141.6, 139.0, 138.9, 137.1, 123.3, 122.1, 88.9, 40.9, 35.0; CIMS m/z (relative intensity) 336 (MH^+, 43), 335 (12). Anal. Calcd for $C_{14}H_{17}N_5O_5$: C, 50.15; H, 5.11; N, 20.89. Found: C, 50.16; H, 4.94; N 20.59.

(*E*)-5-[2-(Dimethylamino)ethenyl]-2,4-dinitrobenzamide (21). A suspension of 13.0 g (38.8 mmol) of benzamide **20**, 500 mL of MeOH, and 2.5 mL of glacial HOAc was heated at reflux for 2 d. The hot mixture was filtered, the filtrate was cooled slowly to 25 °C, and then the precipitated solid was collected. Two additional crops were collected by concentrating

each respective mother liquor to a solid followed by crystallization from MeOH. A total of 8.7 g (80%) of **21**: mp 254−255 °C, was collected: ^{1}H NMR (Me_2SO-d_6) δ 8.54 (s, 1H), 8.14 (d, J = 12.8 Hz, 1H), 7.99 (br s, exchanges with D_2O, 1H), 7.76 (s, 1H), 7.71 (br s, exchanges with D_2O, 1H), 5.93 (d, J = 13.0 Hz, 1H); ^{13}C NMR (Me_2SO-d_6) δ 167.7, 152.6, 142.4, 139.6, 137.0, 136.5, 124.1, 122.8, 89.4; CIMS m/z (relative intensity) 281 (MH^+, 34), 280 (20), 264 (100). Anal. Calcd for $C_{11}H_{12}N_4O_5$: C, 47.15; H, 4.32; N 19.99. Found: C, 47.11; H, 4.25; N, 19.62.

6-Amino-1*H*-indole-5-carboxamide (22). A mixture of 1.9 g (6.8 mmol) of enamine **21**, 0.96 g of 10% Pd/C, and 190 mL of THF was hydrogenated at 1 atm for 12 h. The mixture was filtered, and the filtrate was concentrated to a solid that was triturated in acetone/ether to afford 0.86 g (72%) of **22**, mp 234−235 °C dec, as an off-white solid. An analytical sample gave mp 239−240 °C dec: ^{1}H NMR (Me_2SO-d_6) δ 10.57 (s, exchanges with D_2O, 1H), 7.76 (s, 1H), 7.67 (br s, exchanges with D_2O, 1H), 7.06−7.03 (m, 1H; collapses to d, J = 3.1 Hz with D_2O), 6.88 (br s, exchanges with D_2O, 1H), 6.56 (s, 1H), 6.22 (d, J = 3.2 Hz, 1H), 6.07 (s, exchanges with D_2O, 2H); CIMS m/z (relative intensity) 175 (M^+, 58), 159 (100), 158 (71). Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.52; H, 5.35; N 23.59.

1,6-Dihydro-5*H*-pyrrolo[3,2-*g*]quinazolin-5-one (3). Method A. A solution of 10.3 g (50 mmol) of the aminoindole **17** and 6.3 g (60 mmol) of formamidine acetate in 200 mL of 2-methoxyethanol was heated at reflux for 2 h and then concentrated to dryness. The residue was slurried in H_2O and filtered to afford crude **3**. The solid was dissolved in excess 1 N aq NaOH, and the solution was filtered and then brought to neutrality with 3 N aq HCl. The solid was collected and dried to give 6.0 g (64%) of **3**: mp 347 °C dec: ^{1}H NMR (Me_2SO-d_6) δ 11.75 (br s, exchanges with D_2O, 1H), 11.49 (br s, exchanges with D_2O, 1H), 8.40 (s, 1H), 7.93 (s, 1H), 7.63 (s, 1H), 7.62 (dd, J = 3.0, 2.4 Hz), 6.68 (dd, J = 3.0, 0.9 Hz); ^{13}C NMR δ 161.7, 143.0, 142.2, 140.0, 129.4, 127.8, 117.6, 115.5, 107.2, 102.1; CIMS m/z (relative intensity) 186 (MH^+, 100), 185 (61). Anal. Calcd for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.57; H, 3.64; N, 22.66.

Method B. A suspension of 0.25 g (1.4 mmol) of indole amide **22** and 7 mL of triethyl orthoformate was heated at 100 °C for 1 h. The mixture was cooled to 25 °C and filtered, and the filtrate was concentrated to a solid that was triturated in hot EtOAc. The solids were collected and dried to leave 0.13 g (50%) of pure **3**, mp > 280 °C, identical with material obtained by method A.

Method C. A mixture of 0.6 g (1.8 mmol) of **20** and 0.2 g of Raney nickel in 50 mL of 1:1 THF:MeOH was hydrogenated in a rocking autoclave at 1500 psi at 25 °C for 22 h. The catalyst was filtered, and the filtrate was concentrated. The crude solid was triturated in *i*-PrOH, collected, washed with *i*-PrOH and Et_2O, and then dried to leave 0.19 g (57%) of **3**, mp > 280 °C, shown to contain minor impurities by ^{1}H NMR.

5-Methyl-2-nitrobenzoic Acid, Ethyl Ester (24). A solution of 99 g (0.54 mol) of acid **23**, 1 L of EtOH, and 70 g of concd H_2SO_4 was heated at reflux for 2 d. The solution was concentrated, and the resultant oil was diluted with 300 mL of EtOAc. The organic phase was washed with 1% aq NaOH until the aqueous phase remained basic, dried, and concentrated *in vacuo* at 40 °C overnight to afford 103 g (91%) of **24** as a yellow oil: ^{1}H NMR (Me_2SO-d_6) δ 7.89 (d, J = 8.2 Hz, 1H), 7.64 (s, 1H), 7.60 (d, J = 8.2 Hz, 1H), 4.31 (q, J = 7.0 Hz, 2H), 2.45 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 165.1, 145.0, 132.6, 129.8, 127.2, 124.2, 62.0, 20.7, 13.7; CIMS m/z (relative intensity) 210 (MH^+, 3), 164 (100). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.46; H, 5.34; N, 6.55.

2,6-Dinitro-*m*-toluic Acid, Ethyl Ester (25). To a solution of 9.7 g (64 mmol) of CF_3SO_3H in 20 mL of CH_2Cl_2 was added over 10 min 2.3 g (34 mmol) of fuming HNO_3. The resulting suspension was stirred at 25 °C for 10 min, and then 7.1 g (34 mmol) of ester **24** was added portionwise. The mixture was stirred at 25 °C for 20 h and then poured carefully into stirring ice cold H_2O. The aqueous phase was separated and further extracted with CH_2Cl_2. The combined organic extracts were washed with 1% aq NaOH until the aqueous phase remained basic and then with H_2O, dried, and concentrated to a yellow oil. Column chromatography eluting with hexanes:EtOAc (8:1) afforded 2.7 g (31%) of **25** as a solid, mp 58−59 °C (lit.[13] mp 58−59 °C): ^{1}H NMR (Me_2SO-d_6) δ 8.30 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 162.4, 148.2, 145.1, 138.7, 135.6, 127.9, 123.2, 63.8, 18.4, 13.8; CIMS m/z (relative intensity) 254 (M^+, 4.6), 209 (100). Anal. Calcd for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.31; H, 3.98; N, 11.00. Further workup afforded 2.6 g (30%) of isomeric compound **14**.

(*E*)-3-[2-(Dimethylamino)ethenyl]-2,6-dinitrobenzoic Acid, Ethyl Ester (26). A mixture of 1.1 g (4.9 mmol) of ester **25**, 1.3 mL (9.7 mmol) of DMF dimethyl acetal, and 5 mL of DMF was heated at 100 °C for 4 h. The solution was cooled and poured into H_2O, and the precipitated red solid was collected. The solid was washed with H_2O and dried to afford 1.2 g (70%) of **26**: mp 174−175 °C: ^{1}H NMR (Me_2SO-d_6) δ 7.95 (d, J = 9.3 Hz, 1H), 7.87 (d, J = 12.7 Hz, 1H), 7.78 (d, J = 9.3 Hz, 1H), 4.92 (d, J = 12.7 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.90 (br s, 6H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 163.4, 151.4, 141.4, 141.3, 136.7, 126.7, 125.7, 123.2, 86.3, 63.1, 13.8; CIMS m/z (relative intensity) 310 (MH^+, 81), 309 (32). Anal. Calcd for $C_{13}H_{15}N_3O_6$: C, 50.49; H, 4.89; N, 13.59. Found: C, 50.94; H, 4.93; N, 13.51.

6-Amino-1*H*-indole-7-carboxylic Acid, Ethyl Ester (27). A mixture of 1.1 g (3.5 mmol) of enamine **26**, 0.5 g of 10% Pd/C, and 100 mL of MeOH was hydrogenated at 50 psi for 4 h. The mixture was filtered, concentrated, and then purified by column chromatography eluting with 4:1 hexanes:EtOAc. The product fractions were concentrated to a solid that was triturated from hexanes to afford 0.35 g (48%) of **27**: mp 81−82 °C: ^{1}H NMR (Me_2SO-d_6) δ 10.3 (br s, exchanges with D_2O, 1H), 7.39 (d, J = 8.6 Hz, 1H), 6.95 (m, 1H), 6.63 (s, exchanges with D_2O, 2H), 6.45 (dd, J = 8.7, 2.4 Hz, 1H), 6.23 (m, 1H), 4.36 (q, J = 7.3 Hz, 2H), 1.31 (t, J = 7.3 Hz, 3H); ^{13}C NMR (Me_2SO-d_6) δ 168.1, 149.9, 135.0, 127.8, 122.2, 119.0, 110.7, 102.4, 94.0, 60.0, 15.1; CIMS m/z (relative intensity) 204 (M^+, 100). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.66; H, 5.98; N, 13.64.

1,6-Dihydro-9*H*-pyrrolo[2,3-*f*]quinazolin-9-one (4). A solution of 0.10 g (0.49 mmol) of indole **27** in 2 mL of formamide was heated for 1 h each at 130 °C, 150 °C, and 180 °C. The mixture was cooled and poured into ice-cold H_2O. The aqueous suspension was extracted with EtOAc, and the organic layer was washed with brine, dried, and concentrated. Purification of the oily residue by column chromatography eluting with 9:1 CH_2Cl_2:MeOH gave a solid that was crystallized from *ca.* 2:1 EtOAc:hexanes to provide 0.042 g (44%) of **4**: mp 297−298 °C; ^{1}H NMR (Me_2SO-d_6) δ 12.3 (br s, exchanges with D_2O, 1H), 11.5 (br s, exchanges with D_2O, 1H), 8.03 (s, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.38 (dd, J = 3.0, 2.6 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 6.59 (dd, J = 3.0, 2.2 Hz, 1H); ^{13}C NMR (Me_2SO-d_6) δ 160.8, 145.5, 142.9, 130.8, 127.3, 126.7, 125.6, 118.0, 107.9, 102.1; CIMS m/z (relative intensity) 186 (MH^+, 96), 185 (100). Anal. Calcd for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.59; H, 3.79; N, 22.59.

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