Synthesis of Novel Acyclonucleosides Containing Pyridazine

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This paper presents the synthesis of some novel acyclonucleosides involving pyrrolo[2,3-*c*]pyridazine and 4-hydroxybutyl side chain.

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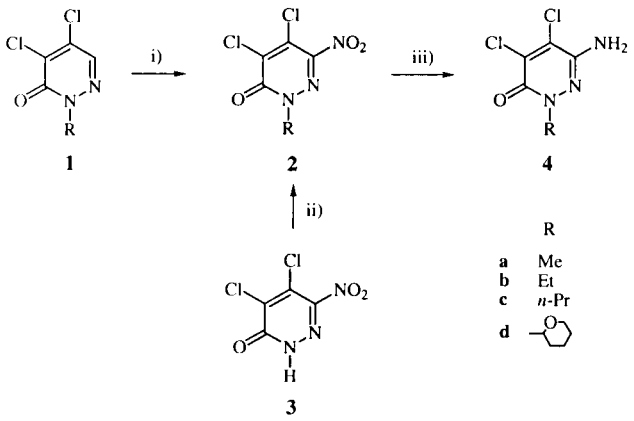
Nucleosides and acyclonucleosides involving pyrrolo-[2,3-*d*]pyrimidine or pyrrolo[2,3-*d*]pyridazine have shown antiproliferative activity and/or antiviral activity [1-6]. As a part of a study on novel diazine *N*-acyclonucleosides, we attempted to synthesize some bicyclic *N*-acyclonucleosides containing pyrrolo[2,3-*c*]pyridazine ring as an analog of pyrrolo[2,3-*d*]pyrimidine and pyrrolo[2,3-*d*]pyridazine.

In this paper, we report the results for the synthesis of some novel *N*-acyclonucleosides containing pyrrolo[2,3-*c*]-pyridazine as heterocyclic base and 4-hydroxybutyl group.

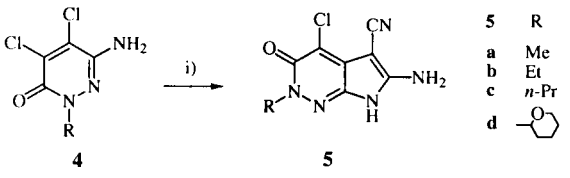
Our approach to the synthesis of pyrrolo[2,3-*c*]pyridazinone involved the use of a suitably substituted pyridazine that would contain an amino group in position-3 and a substituent in position-4 which was highly susceptible to nucleophilic displacement. Therefore, we chose to use 1-alkyl-3-amino-4,5-dichloropyridazin-6-ones **4** as the starting material for the synthesis of pyrrolo[2,3-*c*]pyridazine ring.

Scheme I



i) KNO_3, conc. H_2SO_4; ii) 3,4-dihydro-2H-pyran, $CH_3C_6H_4SO_3H.H_2O$, tetrahydrofuran; iii) Fe, NH_4Cl, $CHCl_3$, H_2O.

Scheme II



i) $CH_2(CN)_2$, NaH, tetrahydrofuran

Nitration of **1a-1c** with potassium nitrate and concentrated sulfuric acid gave the corresponding nitro compounds **2a-2c** in 71-82% yield [7]. Whereas, we could not obtain **2d** from **1d** because of the decomposition of **1d** under the same reaction condition. Therefore, tetrahydropyranyl derivative **2d** was synthesized by the reaction of **3** with 3,4-dihydro-2*H*-pyran and *p*-toluenesulfonic acid in refluxing tetrahydrofuran [8].

Reduction of **2** with iron/ammonium chloride/chloroform/water system [9] afforded the corresponding 3-amino derivatives **4** in good yield. The structures of **2** and **4** were established by ir, nmr and elemental analyses. In the infrared spectra of **4**, the absorption bands of NH_2 were detected in the 3540-3304 cm^{-1} range.

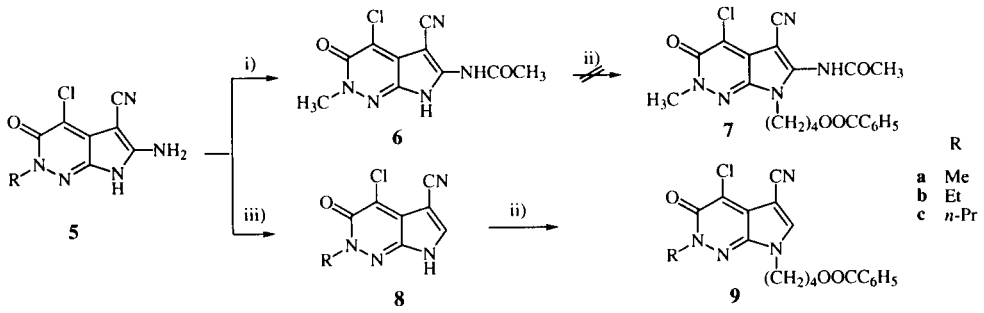
Reaction of **4** with malononitrile and sodium hydride in dry tetrahydrofuran gave selectively the corresponding **5** in 62-91% yield. The infrared spectra of **5** showed the absorption bands of NH (3450-3200 cm^{-1}), carbonyl (1720-1690 cm^{-1}) and cyano (2250-2218 cm^{-1}) groups. In proton magnetic resonance spectra of **5**, the proton signals were also detected for NH_2 (δ = 8.10-8.34 ppm as a broad singlet) and NH (δ = 11.54-11.65 ppm as a broad singlet). This cyclization is a very convenient and useful method for the pyrrolo[2,3-*c*]pyridazine ring.

Reaction of **5a** with acetic anhydride and potassium carbonate yielded **6** in 94% yield. The structure was established by ir, nmr and elemental analysis. Reaction of **6** with 4-iodobutyl benzoate [10] and potassium carbonate in dimethylformamide did not furnish the corresponding bicyclic compound **7**.

On the other hand, deamination of **5** with *tert*-butyl nitrite and hypophosphorous acid in dimethylformamide gave **8** in low yield. Alkylation of **8** with 4-iodobutyl benzoate and potassium carbonate in dimethylformamide yielded **9** in 56-74% yield. In the infrared spectra of **8**, the absorption bands of the NH_2 group for **5** were not detected. Whereas, the proton magnetic resonance spectra of **8** showed one aromatic proton signal as a singlet at δ 8.77-8.78 ppm. The infrared spectra of **9** showed the absorption bands of an ester group, whereas the absorption band of NH for **8** disappeared.

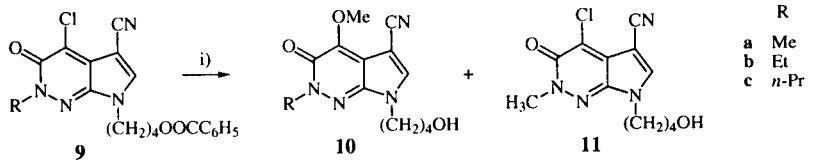
Debenzoylation of **9** with potassium carbonate/methanol system gave the corresponding acyclonucleosides **10** and

Scheme III



i) $(CH_3CO)_2O$, K_2CO_3; ii) $I(CH_2)_4OOCC_6H_5$, K_2CO_3, DMF; iii) *tert*-Butyl nitrite, H_3PO_2 (50%), DMF.

Scheme IV



i) 1. K_2CO_3, MeOH; 2. Amberlite IRC-50H$^+$.

Table 1
Yields, Melting Points and Infrared Spectral Data of **2, 4** and **5**

Compound No	Yield (%)	Mp(°C) (lit. mp)	IR (Potassium bromide) (cm^{-1})
2a	82	99-100 (98-99) [7]	2900, 2890, 1688, 1583, 1505, 1418, 1370, 1340, 1310, 1208
2b	77	88-89	1700, 1600, 1550, 1350, 1240, 1200, 1100, 1040, 990
2c	71	38-39	3000, 1680, 1590, 1350, 1330, 1200, 1110, 1090, 1000, 900
2d	87	112-113	2990, 1710, 1620, 1580, 1550, 1350, 1050, 800
4a	91	194-195 (193-195) [7]	3500, 3350, 2980, 1650, 1620, 1590, 1460, 1360, 1215, 1040, 900
4b	86	129-130	3540, 3350, 3000, 1660, 1620, 1590, 1530, 1470, 1220, 1140
4c	3	92-93	3500, 3450, 3350, 3290, 3200, 2950, 2890, 1640, 1620, 1580, 1460, 1220, 1060, 1010, 900
4d	85	173-174	3406, 3304, 3250, 3200, 2950, 2854, 1670, 1635, 1590, 1520, 1449, 1392, 1317, 1215, 1167, 1035, 939
5a	91	>300	3450, 3250, 3200, 3100, 2980, 2250, 1720, 1710, 1570, 1540, 1440, 1220, 1120
5b	80	>300	3370, 3200, 2980, 2250, 1700, 1620, 1550, 1440, 1240, 1200
5c	62	>300	3400, 3360, 3250, 3100, 2980, 2250, 1690, 1670, 1630, 1440, 1240, 1200
5d	72	>300	3400, 3300, 3298, 3040, 2980, 2218, 1693, 1620, 1575, 1413, 1218, 1167, 1067, 1029, 897

Table 2
Yields, Melting Points and Infrared Spectral Data of **6, 8 ~ 11**

Compound No	Yield (%)	Mp(°C)	IR (Potassium bromide) (cm^{-1}) [a]
6	94	>300	3450, 3250, 3200, 3090, 3000, 2236, 1740, 1720, 1660, 1620, 1580, 1540, 1340, 1210, 1140, 1000
8a	33	>280 dec.	3190, 3100, 2900, 2260, 1660, 1600, 1460, 1340, 1220, 1150, 1020, 800
8b	17	>300	3466, 3100, 2944, 2890, 2250, 1647, 1584, 1512, 1461, 1314, 1245, 1197, 1143, 948
8c	22	>280 dec.	3190, 3150, 3100, 3000, 2900, 2270, 1670, 1600, 1570, 1550, 1480, 1350, 1320, 1220, 1160, 970, 805
9a	74	178-179	3120, 3050, 3000, 2980, 2250, 1720, 1660, 1620, 1540, 1440, 1340, 1300, 1200, 1 140
9b	56	149-150	3130, 3080, 3000, 2900, 2250, 1740, 1660, 1650, 1550, 1420, 1340, 1300, 1200, 1140
9c	60	148-149	3130, 3080, 3000, 2900, 2250, 1740, 1660, 1650, 1550, 1420, 1340, 1300, 1200, 1140
10a	59	137-138	3490 (br), 2990, 2250, 1610, 1560, 1440, 1420, 1340, 1200, 1090, 940
10b	80	Liquid	3450 (br), 3150, 3080, 2950, 2890, 2240, 1615, 1440, 1320, 1200, 1060
10c	71	Liquid	3480 (br), 3100, 2990, 2240, 1600, 1560, 1440, 1330, 1200, 1090
11	13	165-166	3442, 2230, 1647, 1608, 1539, 1413, 1335, 1167, 1059, 672, 612

[a] Abbriviation used: br = broad.

Table 3

Nmr Spectral Data of **2, 4, 5, 7a** and **7b**

Compound No	Solvent [a]	^{1}H Nmr (δ, ppm) [b]	^{13}C Nmr (δ, ppm)
2a	C	3.66 (s, 3H)	40.0, 97.9, 128.3, 136.4, 154.2
2b	C	1.32 (t, 3H), 4.16 (q, 2H)	13.4, 49.4, 130.0, 138.3, 145.5, 155.7
2c	C	1.02 (t, 3H), 1.90 (q, 2H), 4.21 (t, 2H)	11.3, 21.8, 55.5, 129.8, 138.3, 155.9
2d	C	1.58 (m, 4H), 2.00 (m, 2H), 3.67 (t, 1H), 4.04 (m, 1H), 5.94 (dd, 1H, J = 2.5, 2.3)	21.1, 23.4, 27.0, 28.5, 67.6, 83.7, 124.7, 128.5, 137.4, 153.8
4a	C	3.59 (s, 3H), 4.42 (br s, NH_2)	40.5, 129.3, 136.2, 144.1, 155.2
4b	C	1.27 (t, 3H), 4.02 (q, 2H), 4.38 (br s, NH_2)	13.8, 47.8, 129.2, 136.4, 144.2, 154.8
4c	C	0.96 (t, 3H), 1.81 (q, 2H), 4.01 (t, 2H), 4.38 (br s, NH_2)	11.4, 21.8, 54.0, 129.1, 136.3, 144.0, 155.0
4d	C	1.64 (m, 4H), 2.08 (m, 2H), 3.73 (t, 1H), 4.14 (m, 1H), 4.60 (br s, NH_2), 5.98 (dd, 1H, J = 1.7, 2.1)	23.2, 25.3, 29.2, 69.3, 84.1, 130.1, 136.3, 144.1, 154.8
5a	D	3.57 (s, 3H), 8.10 (br s, NH_2), 11.54 (br s, NH)	57.3, 110.4, 113.1, 129.2, 138.2, 153.8, 159.0
5b	D	1.23 (t, 3H), 4.04 (q, 2H), 8.18 (br s, NH_2), 11.55 (br s, NH)	11.7, 44.5, 57.3, 113.3, 129.1, 138.6, 153.4, 159.0, 159.1
5c	D	0.85 (t, 3H), 1.68 (q, 2H), 3.97 (t, 2H), 8.21 (br s, NH_2), NH no detection	11.3, 21.8, 53.1, 59.5, 112.7, 115.6, 131.4, 140.9, 156.0, 161.4
5d	D	1.64 (m, 4H), 2,26 (m, 2H), 3.58 (t, 1H), 3.94 (d, 1H, J = 11.0), 5.90 (d, 1H, J = 9.7), 8.34 (s, NH_2), 11.65 (br s, NH)	22.8, 25.1, 28.8, 40.7, 67.8, 83.0, 111.8, 115.5, 131.8, 141.2, 155.8
6	D	2.23 (s, 3H), 3.71 (s, 3H), 12.19 (br s, NH_2)	24.0, 41.2, 65.8, 113.8, 117.6, 128.6, 139.5, 153.0, 156.1, 170.5

[a] Solvent: C = Deuteriochloroform, D = Dimethyl-d_6 sulfoxide, [b] Abbriviations used: s = singlet, t = triplet, br s = broad singlet, q = quartet, m = multiplet, Ar = aromatic. The proton signals of NH and OH were exchangeable with deuterium oxide.

Table 4

Nmr Spectral Data of **8-11**

Compound No	Solvent [a]	^{1}H Nmr (δ, ppm) [b]	^{13}C Nmr (δ, ppm)
8a	D	3.80 (s, 3H), 8.78 (s, 1H), 13.80 (br s, NH)	41.9, 100.4, 114.6, 128.6, 141.6, 150.2, 156.0
8b	D	1.32 (t, 3H), 4.24 (q, 2H), 8.78 (s, 1H), 12.95 (br s, NH)	13.8, 48.5, 80.6, 114.6, 121.2, 128.4, 141.9, 150.3, 155.5
8c	D	0.88 (t, 3H), 1.77 (m, 2H), 4.16 (t, 2H), 8.77 (s, 1H), 12.98 (br s, NH)	9.0, 19.4, 25.4, 78.3, 112.4, 119.0, 126.2, 139.6, 148.1, 153.5
9a	C	1.85 (t, 2H), 2.03 (m, 2H), 3.92 (s, 3H), 4.16 (t, 2H), 4.39 (t, 2H), 7.92 (s, 1H), 7.73 (m, Ar. 5H)	26.2, 26.3, 42.6, 46.2, 63.9, 82.6, 100.9, 113.5, 125.0, 128.7, 128.9, 129.0, 130.0, 133.7, 140.7, 147.3, 157.0, 166.9
9b	C	1.40 (t, 3H), 1.94 (m, 4H), 4.16 (t, 2H), 4.37 (m, 4H), 7.87 (s, 1H), 7.72 (m, Ar. 5H)	12.3, 24.6, 44.5, 47.8, 62.2, 80.8, 111.8, 123.5, 126.7, 127.2, 128.2, 131.9, 139.2, 145.6, 154.8, 165.1
9c	C	0.97 (t, 3H), 1.37 (m, 4H), 2.05 (t, 2H), 4.17 (t, 2H), 4.28 (t, 2H), 4.41 (t, 2H), 7.74 (m, Ar. 5H)	11.4, 22.2, 26.3, 46.2, 55.8, 64.0, 82.5, 99.7, 113.5, 125.1, 128.4, 128.9, 130.0, 133.6, 140.8, 147.4, 156.7, 166.9
10a	C	1.52 (q, 2H), 1.89 (m, 2H + OH), 3.65 (t, 2H), 3.81 (s, 3H), 4.01 (t, 2H), 4.33 (s, 3H), 7.64 (s, 1H)	26.3, 29.6, 41.7, 46.0, 61.2, 62.4, 81.1, 115.0, 117.7, 143.2, 144.6, 146.4, 156.6
10b	C	1.40 (t, 3H), 1.61 (m, 2H + OH), 1.96 (t, 2H), 3.72 (t, 2H), 4.08 (t, 2H), 4.31 (q, 2H), 4.41 (s, 3H), 7.66 (s, 1H)	13.8, 26.0, 29.2, 45.6, 47.9, 60.8, 62.1, 80.9, 114.6, 117.0, 143.0, 143.9, 146.3, 155.7
10c	C	0.98 (t, 3H), 1.58 (m, 2H + OH), 1.88 (m, 2H), 1.95 (m, 2H), 3.72 (q, 2H), 4.07 (t, 2H), 4.22 (t, 2H), 4.41 (s, 3H), 7.64 (s, 1H)	11.2, 21.9, 26.0, 29.2, 29.7, 45.6, 54.3, 60.8, 62.1, 97.3, 143.9
11	C	1.54 (m, 2H + OH), 1.92 (m, 2H), 3.67 (t, 2H), 3.89 (s, 3H), 4.06 (t, 2H), 7.84 (s, 1H)	26.4, 29.4, 42.7, 46.5, 62.4, 82.3, 113.6, 124.8, 128.8, 140.8, 147.8

[a] Solvent; C = Deuteriochloroform, D = Dimethyl-d_6 sulfoxide, [b] Abbriviations used: s = singlet, t = triplet, br s = broad singlet, q = quartet, m = multiplet, Ar = aromatic. The proton signals of NH and OH were exchangeable with deuterium oxide.

11. The structures of **10** and **11** were established by ir, nmr and elemental analyses. Potassium carbonate/methanol system is convenient and mild reagent for *O*-debenzoylation or methoxylation.

Further work including the chemical transformation and biological activity is under way in our laboratory.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Magnetic resonance spectra were obtained on a Varian Unity Plus 300 or a Bruker FTNMR-DRX 500 spectrometer with chemical shift values reported in δ units (part per

Table 5

Elemental Analytical Data of **2**, **4**, **5**, **6**, **8** and **9**

Compound No	Molecular Formula	Elemental Analyses(%) (Calcd./Found) C	H	N
2a	$C_5H_3N_3O_3Cl_2$	26.81	1.35	18.76
		26.65	1.43	18.82
2b	$C_6H_5N_3O_3Cl_2$	30.28	2.12	17.65
		30.48	2.23	17.79
2c	$C_7H_7N_3O_3Cl_2$	33.36	2.80	16.67
		33.57	2.96	16.86
2d	$C_9H_9N_3O_4Cl_2$	36.76	3.08	14.29
		36.50	3.03	14.18
4a	$C_5H_5N_3OCl_2$	30.95	2.60	21.66
		30.75	2.57	21.96
4b	$C_6H_7N_3OCl_2$	34.64	3.39	20.20
		34.74	3.31	20.30
4c	$C_7H_9N_3OCl_2$	37.86	4.08	18.92
		37.97	4.09	18.90
4d	$C_9H_{11}N_3O_2Cl_2$	40.93	4.20	15.91
		40.83	4.10	15.77
5a	$C_8H_6N_5OCl$	42.97	2.70	31.32
		42.89	2.68	31.20
5b	$C_9H_8N_5OCl$	45.49	3.39	29.47
		45.67	3.31	29.40
5c	$C_{10}H_{10}N_5OCl$	47.72	4.00	27.83
		47.89	4.05	27.97
5d	$C_{12}H_{12}N_5O_2Cl$	49.07	4.12	23.84
		49.16	4.32	23.96
6	$C_{10}H_8N_5O_2Cl$	45.21	3.04	26.36
		45.48	3.23	26.55
8a	$C_8H_5N_4OCl$	46.06	2.42	26.86
		46.14	2.53	26.91
8b	$C_9H_7N_4OCl$	48.55	3.17	25.17
		48.56	3.27	25.36
8c	$C_{10}H_9N_4OCl$	50.75	3.83	23.67
		50.98	3.99	23.95
9a	$C_{19}H_{17}N_4O_3Cl$	59.30	4.45	14.56
		59.49	4.64	14.76
9b	$C_{20}H_{19}N_4O_3Cl$	60.23	4.80	14.05
		60.34	4.94	14.14
9c	$C_{21}H_{21}N_4O_3Cl$	61.09	5.13	13.57
		61.22	5.30	13.73
10a	$C_{13}H_{16}N_4O_3$	56.51	5.84	20.28
		56.52	5.89	20.44
10b	$C_{14}H_{18}N_4O_3$	57.92	6.25	19.30
		57.99	6.35	19.46
10c	$C_{15}H_{20}N_4O_3$	59.20	6.62	18.41
		59.32	6.79	18.75
11	$C_{12}H_{13}N_4O_2Cl$	51.34	4.67	19.96
		51.23	4.54	19.95

million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. Open-bed chromatography was carried out on silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent. 1-Alkyl-4,5-dichloropyridazin-6-ones **1a-1c** were prepared by Cho's method [11].

4,5-Dichloro-1-methyl-3-nitropyridazin-6-one (**2a**).

A solution of **1a** (45.0 g, 0.25 mole), potassium nitrate (101.0 g, 1 mole) and concentrated sulfuric acid (150 ml) was stirred for 8 hours at 110°. After cooling to room temperature, the solution was poured into ice water (600 ml) with stirring. The resulting precipitate was filtered, washed with water (200 ml x 5) and dried in air to furnish **2a** in 82% (45.8 g) yield.

4,5-Dichloro-1-ethyl-3-nitropyridazin-6-one (**2b**).

A mixture of **1b** (6.43 g, 0.033 mole), potassium nitrate (13.35 g, 0.132 mole) and concentrated sulfuric acid (15 ml) was stirred for 8 hours at 110°. After cooling to room temperature, the solution was poured into ice water (100 ml) with stirring. The resulting precipitate was filtered, washed with water (100 ml x 5) and dried in air to give **2b** in 77% (6.1 g) yield.

4,5-Dichloro-3-nitro-1-propylpyridazin-6-one (**2c**).

A solution of **1c** (43.1 g, 0.208 mole), potassium nitrate (105.0 g, 1.038 moles) and concentrated sulfuric acid (150 ml) was stirred for 8 hours at 110°. After cooling to room temperature, the solution was poured into ice water (700 ml) with stirring. The resulting precipitate was filtered, washed with water (200 ml x 5) and dried in air to give **2c** in 71% (37.1 g) yield.

4,5-Dichloro-3-nitro-1-(tetrahydro-2*H*-pyran-2-yl)pyridazin-6-one (**2d**) [8].

A mixture of 3,4-dihydro-2*H*-pyran (1.5 g, 17.8 mmoles), **3** (0.92 g, 4.36 mmoles), [7], tetrahydrofuran (40 ml) and *p*-toluenesulfonic acid monohydrate (0.08 g, 0.42 mmole) was refluxed for 28 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure. The resulting residue was dried in air to afford **2d** in 87% (1.12 g) yield.

3-Amino-4,5-dichloro-1-methylpyridazin-6-one (**4a**) [7, 9].

A solution of **2a** (2.95 g, 0.013 mole), chloroform (30 ml), water (50 ml), ammonium chloride (4.8 g, 0.09 mole) and activated iron powder (5 g) was refluxed for 9 hours. After cooling to room temperature, the mixture was applied to the top of an open-bed silica gel column (3 x 4 cm). The column was eluted with chloroform. Fractions containing the product were combined, evaporated under reduced pressure and dried in air to yield **4a** in 91% (2.29 g) yield.

3-Amino-4,5-dichloro-1-ethylpyridazin-6-one (**4b**).

A mixture of **2b** (5.97 g, 0.025 mole), chloroform (50 ml), water (50 ml), ammonium chloride (8.01 g, 0.15 mole) and activated iron powder (5 g) was refluxed for 14 hours. After cooling to room temperature, the mixture was applied to the top of an open-bed silica gel column (3 x 5 cm). The column was eluted with chloroform. Fractions containing the product were combined, evaporated under reduced pressure and dried in air to give **4b** in 86% (4.47 g) yield.

3-Amino-4,5-dichloro-1-propylpyridazin-6-one (**4c**).

A solution of **2c** (20.1 g, 0.0794 mole), chloroform (150 ml), water (150 ml), ammonium chloride (46.45 g, 0.867 mole) and activated iron powder (15 g) was refluxed for 14 hours. After cooling to room temperature, the solution was applied to the top of an open-bed silica gel column (3 x 15 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to afford **4c** in 83% (14.6 g) yield.

3-Amino-4,5-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)pyridazin-6-one (**4d**).

A mixture of **2d** (1.12 g, 3.79 mmoles), chloroform (40 ml), water (30 ml), ammonium chloride (1.5 g, 0.029 mole) and activated iron powder (4 g) was refluxed for 2.5 hours. After cooling to room temperature, the solution was applied to the top of an open-bed silica gel column (2.5 x 5 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure. The resulting residue was recrystallized from chloroform/*n*-hexane (1:3, v/v) to afford **4d** in 85% (0.85 g) yield.

6-Amino-4-chloro-5-cyano-2-methyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**5a**).

After a mixture of malononitrile (1.29 g, 0.02 mole), dry tetrahydrofuran (30 ml) and sodium hydride (1.04 g, 0.026 mole, 60%) was stirred for 1 hour at room temperature, **4a** (3.01 g, 0.015 mole) was added to the mixture. The reaction mixture was stirred for 5 hours at 50-60°. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in water (300 ml), and the solution was then neutralized by acetic acid (15 ml). The resulting precipitate was filtered and dried in air. The crude product was recrystallized from methanol to furnish **5a** in 91% (3.1 g) yield.

6-Amino-4-chloro-5-cyano-2-ethyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**5b**).

After a mixture of malononitrile (0.21 g, 3 mmoles), dry tetrahydrofuran (20 ml) and sodium hydride (0.16 g, 3.9 mmoles, 60%) was stirred for 1 hour at room temperature, **4b** (0.5 g, 2.4 mmoles) was added to the mixture. The reaction mixture was stirred for 11 hours at 50-60°. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in water (100 ml), and the solution was then neutralized by acetic acid (8 ml). The resulting precipitate was filtered and dried in air. The crude product was recrystallized from methanol to furnish **5b** in 80% (0.46 g) yield.

6-Amino-4-chloro-5-cyano-2-propyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**5c**).

After a mixture of malononitrile (0.17 g, 2.6 mmoles), dry tetrahydrofuran (20 ml) and sodium hydride (0.14 g, 3.4 mmoles, 60%) was stirred for 1 hour at room temperature, **4c** (0.5 g, 2 mmoles) was added to the mixture. The reaction mixture was stirred for 11 hours at 50-60°. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in water (100 ml), and the solution was then neutralized by acetic acid (8 ml). The resulting precipitate was filtered and dried in air. The crude product was recrystallized from methanol to furnish **5c** in 62% (0.46 g) yield.

6-Amino-4-chloro-5-cyano-2-(tetrahydro-2*H*-pyran-2-yl)-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**5d**).

After a mixture of malononitrile (0.23 g, 3.48 mmoles), dry tetrahydrofuran (40 ml) and sodium hydride (0.18 g, 4.52 mmoles, 60%) was stirred for 1 hour at room temperature, **4d** (0.71 g, 2.68 mmoles) was added to the mixture. The reaction mixture was stirred for 4.5 hours at 50-60°. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in water (100 ml), and the solution was then neutralized by acetic acid (8 ml). The resulting precipitate was filtered and dried in air. The crude product was recrystallized from methanol to furnish **5d** in 72% (0.54 g) yield.

6-Acetamido-4-chloro-5-cyano-2-methyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**6**).

A mixture of **5a** (1.0 g, 4.47 mmoles), potassium carbonate (1.24 g, 8.94 mmoles) and acetic anhydride (30 ml) was refluxed for 25 minutes. After cooling to room temperature, the reaction mixture was poured into water (180 ml) with stirring. After leaving the mixture alone for 12 hours at room temperature, the resulting precipitate was filtered and dried in air to give **6** in 94% (1.07 g) yield.

4-Chloro-5-cyano-2-methyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**8a**).

A solution of **5a** (2.01 g, 8.99 mmoles), *tert*-butylnitrite (4.6 ml, 35.76 mmoles) and *N,N*-dimethylformamide (15 ml) was stirred for 1 hour at 50-60°. After cooling to room temperature and then adding hypophosphorous acid (6.8 ml, 65.6 mmoles, 50%), the reaction mixture was stirred for 1 hour at room temperature. The solution was coevaporated with silica gel (4 g) under reduced pressure. The product was extracted with chloroform from the resulting residue by a Soxhlet apparatus. The extract was evaporated under reduced pressure. The resulting residue was recrystallized from methanol to give **8a** in 33% (0.61 g) yield.

4-Chloro-5-cyano-2-ethyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**8b**).

A solution of **5b** (2.0 g, 8.41 mmoles), *tert*-butyl nitrite (2.84 ml, 23.84 mmoles) and *N,N*-dimethylformamide (10 ml) was stirred for 4 hours at 50-60°. After cooling to room temperature and then adding hypophosphorous acid (3 ml, 51.58 mmoles, 50%), the reaction mixture was stirred for 1 hour at room temperature. The solution was coevaporated with silica gel (4 g) under reduced pressure. The product was extracted with chloroform from the resulting residue by a Soxhlet apparatus. The extract was evaporated under reduced pressure. The resulting residue was recrystallized from methanol to give **8b** in 17% (0.33 g) yield.

4-Chloro-5-cyano-2-propyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**8c**).

A solution of **5c** (1.0 g, 3.97 mmoles), *tert*-butylnitrite (1.42 ml, 11.92 mmoles) and *N,N*-dimethylformamide (7 ml) was stirred for 2 hours at 50-60°. After cooling to room temperature and then adding hypophosphorous acid (1.9 ml, 17.86 mmoles, 50%), the reaction mixture was stirred for 2.5 hours at room temperature. The solution was coevaporated with silica gel (4 g) under reduced pressure. The product was extracted with chloroform from the resulting residue by a Soxhlet apparatus. The extract was evaporated under reduced pressure. The resulting residue was recrystallized from methanol to give **8c** in 22% (0.21 g) yield.

7-(4-Benzoyloxybutyl)-4-chloro-5-cyano-2-methyl-7*H*-pyrrolo-[2,3-*c*]pyridazin-3(2*H*)-one (**9a**).

A solution of 4-iodobutylbenzoate (1.01 g, 3.31 mmoles) [10], *N,N*-dimethylformamide (10 ml), **8a** (0.46 g, 2.20 mmoles) and potassium carbonate (0.36 g, 2.6 mmoles) was stirred for 21 hours and then refluxed for additional 1 hour. After cooling to room temperature, the solution was coevaporated with silica gel (1 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 7 cm). The column was eluted with chloroform. Fractions containing the product were

combined, evaporated under reduced pressure and dried in air to give **9a** in 74% (0.63 g) yield.

7-(4-Benzoyloxybutyl)-4-chloro-5-cyano-2-ethyl-7*H*-pyrrolo-[2,3-*c*]pyridazin-3(2*H*)-one (**9b**).

A solution of 4-iodobutylbenzoate [10] (0.39 g, 1.28 mmoles), *N*,*N*-dimethylformamide (5 ml), **8b** (0.19 g, 0.85 mmoles) and potassium carbonate (0.15 g, 1.11 mmoles) was stirred for 6 hours and then refluxed for additional 2 hours. After cooling to room temperature, the solution was coevaporated with silica gel (1 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with chloroform. Fractions containing the product were combined, evaporated under reduced pressure and dried in air. The crude product was recrystallized from ethyl acetate/*n*-hexane to give **9b** in 56% (0.19 g) yield.

7-(4-Benzoyloxybutyl)-4-chloro-5-cyano-2-methyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**9c**).

A solution of 4-iodobutylbenzoate [10] (0.29 g, 0.95 mmole), *N*,*N*-dimethylformamide (8 ml), **8c** (0.15 g, 0.63 mmole) and potassium carbonate (0.11 g, 0.82 mmole) was stirred for 8 hours and then refluxed for additional 1 hour. After cooling to room temperature, the solution was coevaporated with silica gel (2 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 7 cm). The column was eluted with chloroform. Fractions containing the product were combined, evaporated under reduced pressure and dried in air to give **9c** in 60% (0.16 g) yield.

5-Cyano-7-(4-hydroxybutyl)-4-methoxy-2-methyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**10a**) and 4-Chloro-5-cyano-7-(4-hydroxybutyl)-2-methyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3-(2*H*)-one (**11**).

A mixture of **9a** (0.55 g, 1.42 mmoles), potassium carbonate (1.97 g, 14.2 mmoles) and methanol (25 ml) was stirred for 3 hours at room temperature. After adding Amberlite IRC-50 resin (H^+ form, 2 g), the mixture was stirred for additional 11 hours at room temperature. The resin was filtered off and washed with hot methanol (50 ml x 3). The filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 9 cm). The column was eluted with chloroform. Fractions containing **10a** (R_f = 0.36; chloroform/methanol = 10:1, v/v) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from chloroform/*n*-hexanne = 1:2, v/v) to give **10a** in 59% (0.23 g) yield. Fractions containing **11** (R_f = 0.26; chloroform/methanol = 10:1, v/v) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from chloroform/*n*-hexane (1:2, v/v) to afford **11** in 13% (0.05 g) yield.

5-Cyano-7-(4-hydroxybutyl)-4-methoxy-2-ethyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3(2*H*)-one (**10b**).

A solution of **9b** (0.133 g, 0.33 mmole), potassium carbonate (0.06 g, 0.43 mmole) and methanol (10 ml) was stirred for 4 hours at room temperature. The mixture was filtered off, and the residue was then washed with methanol (50 ml). The combined filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with chloroform/methanol (10:1,v/v). Fractions containing the product were combined, evaporated under reduced pressure and dried in air to give **10b** in 80% (0.077 g) yield.

5-Cyano-7-(4-hydroxybutyl)-4-methoxy-2-propyl-7*H*-pyrrolo-[2,3-*c*]pyridazin-3(2*H*)-one (**10c**).

A solution of **9c** (0.1 g, 0.23 mmole), potassium carbonate (0.04 g, 0.3 mmole) and methanol (10 ml) was stirred for 4 hours. The mixture was filtered off and washed with methanol (50 ml). The combined filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with chloroform/methanol (10:1, v/v). Fractions containing the product were combined, evaporated under reduced pressure and dried in air to afford **10c** in 71% (0.05 g) yield.

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