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SYNTHESIS OF 7-ALKYL-4-AMINO-7*H*-PYRROLO-[2,3-*d*]PYRIMIDINE-6-CARBOXYLIC ACIDS

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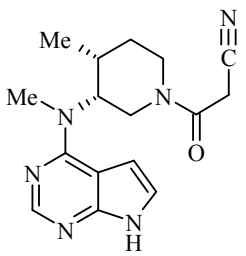
Two variants are discussed for the synthesis of ethyl N-alkyl-N-(6-amino-5-formylpyrimidin-4-yl)-glycinate derivatives, which are converted by intramolecular cyclization under the influence of sodium methoxide to give methyl 7H-pyrrolo[2,3-d]pyrimidine-6-carboxylates. New derivatives of pyrimido-[5',4':4,5]pyrrolo[2,1-c][1,4]oxazines containing 3-chloropropyl groups at position 8 have been prepared.

Keywords: ethyl *N*-alkylglycinate, pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine, 7*H*-pyrrolo[2,3-*d*]-pyrimidine, cyclization.

In recent years, pyrrolo[2,3-*d*]pyrimidine derivatives have been intensively studied and used successfully for the solution of real problems of medicinal chemistry and molecular biology. The increasing number of publications with the description of biological properties of compounds of this class indicates their considerable potential. Recently obtained derivatives of pyrrolo[2,3-*d*]pyrimidines have anticancer and antiproliferative activities, and are also antagonists of the CRF_1 receptor [1-3]. However the principal stimulus for the discovery of new substances in the 7*H*-pyrrolo[2,3-*d*]pyrimidine series has been the discovery of the strongly selective inhibitors of the kinases JAK3 (CP-690,550) and Akt (CCT128930), which are effective in therapy of autoimmune and oncological diseases [4-7].



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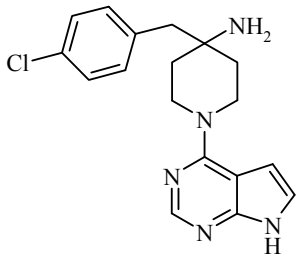

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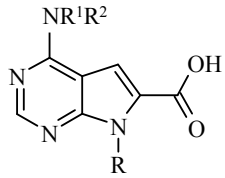

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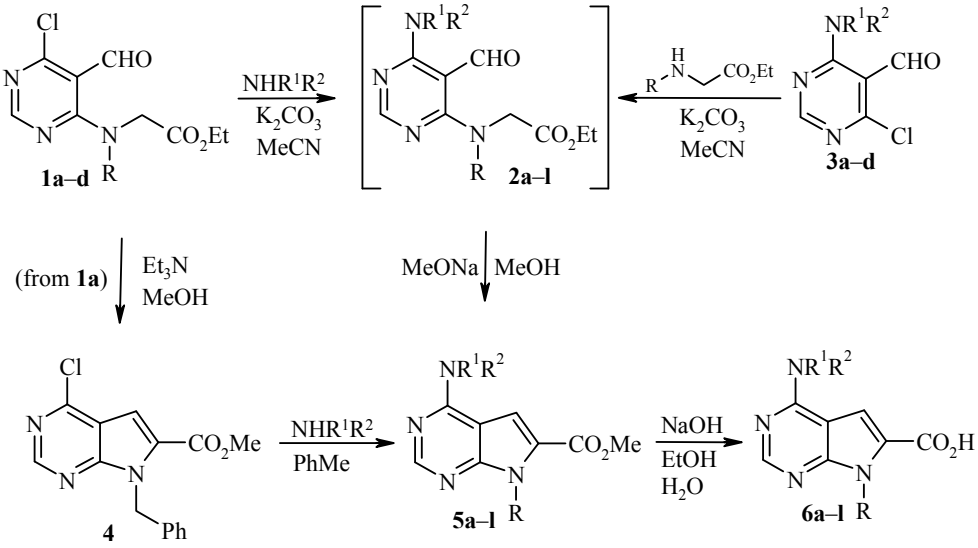
Despite the fact that the synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives has been well studied, some representatives could not be readily obtained. One example of this is the synthesis of compound **A**, which was not achieved using the previously described method [8, 9]. Starting from 4,6-dichloropyrimidine-5-carbaldehyde, we obtained compounds **1a-d**. Treatment of these with bases caused intramolecular cyclization with participation of the aldehyde and methylene groups, which was accompanied by pronounced resinification of the reaction mixture, apparently connected with nucleophilic attack at position 2 of the pyrimidine ring and the subsequent ring opening.



1a, **5a–d**, **6a–d** R = benzyl, **1b**, **5e**, **6e** R = allyl, **1c**, **5f**,**i**,**k**, **6f**,**i**,**k** R = 2-methoxyethyl, **1d**, **5g**,**h**,**j**,**l**, **6g**,**h**,**j**,**l** R = (tetrahydrofuran-2-yl)methyl; **3a**, **5a**,**e**,**f**,**g**, **6a**,**e**,**f**,**g** NR^1R^2 = NMe_2, **3b**, **5b**,**h**, **6b**,**h** NR^1R^2 = pyrrolidin-2-yl, **3c**, **5c**,**i**,**j**, **6c**,**i**,**j** NR^1R^2 = piperidin-1-yl, **3d**, **5d**,**k**,**l**, **6d**,**k**,**l** NR^1R^2 = morpholin-4-yl

Compound **4** was obtained in a sole example in 30% yield. Hence use of the sequence **1** → **4** → **5** for the synthesis of target compounds **6a-l** seemed unpromising. It should be noted that the chloroaldehydes **1a-d** were nevertheless successfully converted into the pyrrolo[2,3-*d*]pyrimidine derivatives **5a-l** in sufficiently high yields. This was facilitated by introduction of electron-donor substituents at position 4 of the pyrimidine ring, which decreased the electrophilicity of the carbon atom at position 2 of the heterocyclic ring. The most successful substitution of the labile chlorine atom by secondary amines in aldehydes **1a-d** was carried out in anhydrous acetonitrile in the presence of potassium carbonate. Compounds **2a-l** were also obtained by treatment of the aldehydes **3a-d** with *N*-acylglycinates. Monitoring of the conversions **1** → **2** and **3** → **2** was carried out by TLC. It should be noted that by-products were practically absent in these reactions. Aldehydes **2a-l** were oily substances which rapidly darkened in the air so they were used for further conversions without additional purification. Intramolecular cyclizations of aldehydes **2a-l** were carried out in absolute methanol with an equimolar quantity of sodium methoxide and were accompanied by transesterification. The required compounds – 7*H*-pyrrolo-[2,3-*d*]pyrimidine-6-carboxylic acids **6a-l** (Table 1) – were obtained by alkaline hydrolysis of the esters **5a-l**.

The introduction of the carboxylic group into the pyrrolo[2,3-*d*]pyrimidine nucleus opens the possibility for the creation of diverse chemical libraries, especially those of amides. Compounds with a (tetrahydrofuran-2-yl)methyl group at the nitrogen atom of the pyrrole ring are an exception. Treatment of compounds **6g**,**j**,**l** with thionyl chloride gave rise to opening of the tetrahydrofuran ring with subsequent transformation into tricyclic derivatives of pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazines **7a-c.** We had previously observed this recyclization in a similar example [10].

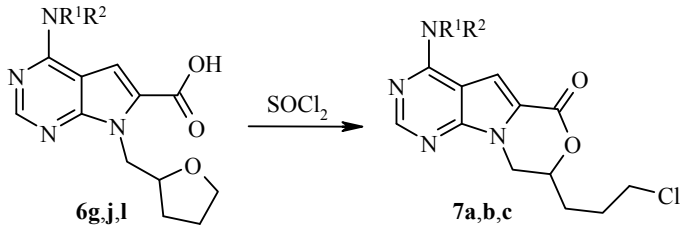
TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				Mp*, °C	Yield, % (Method)
		C	H	Cl	N		
1	2	3	4	5	6	7	8
1a	$C_{16}H_{16}ClN_3O$	57.62 57.58	4.80 4.83	10.65 10.62	12.56 12.59	121-122	59
1b	$C_{12}H_{14}ClN_3O$	50.81 50.80	4.95 4.97	12.59 12.50	14.85 14.81	81-82	58
1c	$C_{12}H_{16}ClN_3O$	47.85 47.77	5.39 5.34	11.79 11.75	13.95 13.93	75-76	55
1d	$C_{14}H_{18}ClN_3O$	51.34 51.30	5.59 5.54	10.85 10.82	12.79 12.82	73-74	50
4	$C_{15}H_{12}ClN_3O$	59.69 59.71	4.00 4.01	11.78 11.75	13.95 13.93	124-125	55
5a	$C_{17}H_{18}N_4O_2$	65.76 65.79	5.82 5.85	—	18.02 18.05	135-136	68 (A) 70 (B)
5b	$C_{19}H_{20}N_4O_2$	67.80 67.84	5.93 5.99	—	16.69 16.65	165-166	65 (A) 54 (B)
5c	$C_{20}H_{22}N_4O_2$	68.52 68.55	6.30 6.33	—	15.91 15.99	158-160	70 (A) 73 (B)
5d	$C_{19}H_{20}N_4O_3$	64.70 64.76	5.76 5.72	—	15.98 15.90	159-160	76 (A) 68 (B)
5e	$C_{13}H_{16}N_4O_2$	59.90 59.99	6.31 6.20	—	21.58 21.52	109-110	70
5f	$C_{13}H_{18}N_4O_3$	56.21 56.10	6.59 6.52	—	20.18 20.13	105-106	68
5g	$C_{15}H_{20}N_4O_3$	59.27 59.20	6.67 6.62	—	18.50 18.41	94-95	63
5h	$C_{17}H_{22}N_4O_3$	61.89 61.80	6.65 6.71	—	16.85 16.96	93-94	73
5i	$C_{16}H_{22}N_4O_3$	60.30 60.36	6.90 6.97	—	17.65 17.60	124-125	70
5j	$C_{18}H_{24}N_4O_3$	62.71 62.77	7.15 7.02	—	16.25 16.27	95-97	62
5k	$C_{15}H_{20}N_4O_4$	56.19 56.24	6.35 6.29	—	17.56 17.49	143-144	68
5l	$C_{17}H_{22}N_4O_4$	58.90 58.95	6.51 6.40	—	16.25 16.17	130-131	59
6a	$C_{16}H_{16}N_4O_2$	64.94 64.85	5.49 5.44	—	18.80 18.91	>270 (decomp.)	91
6b	$C_{18}H_{18}N_4O_2$	67.15 67.07	5.68 5.63	—	17.49 17.38	>300 (decomp.)	81
6c	$C_{19}H_{20}N_4O_2$	67.93 67.84	5.90 5.99	—	16.72 16.65	221-222	75
6d	$C_{18}H_{18}N_4O_3$	63.98 63.89	5.39 5.36	—	16.63 16.56	>280 (decomp.)	82
6e	$C_{12}H_{14}N_4O_2$	58.62 58.53	5.75 5.73	—	22.84 22.75	>240 (decomp.)	93
6f	$C_{12}H_{16}N_4O_3$	54.61 54.54	6.15 6.10	—	21.17 21.20	>260 (decomp.)	90
6g	$C_{14}H_{18}N_4O_3$	57.86 57.92	6.29 6.25	—	19.23 19.30	238-239	75
6h	$C_{16}H_{20}N_4O_3$	60.72 60.75	6.31 6.37	—	17.78 17.71	245-246	70
6i	$C_{15}H_{20}N_4O_3$	59.27 59.20	6.57 6.62	—	18.47 18.41	184-185	73
6j	$C_{17}H_{22}N_4O_3$	61.72 61.80	6.76 6.71	—	16.90 16.96	203-204	71

TABLE 1 (continued)

1	2	3	4	5	6	7	8
6k	$C_{14}H_{18}N_4O_4$	54.93 54.89	5.90 5.92	—	18.36 18.29	212-213	75
6l	$C_{16}H_{20}N_4O_4$	57.89 57.82	6.16 6.07	—	16.92 16.86	194-195	68
7a	$C_{14}H_{17}ClN_4O_2$	54.52 54.46	5.61 5.55	11.59 11.48	18.26 18.15	>255 (decomp.)	70
7b	$C_{17}H_{21}ClN_4O_2$	58.60 58.53	6.12 6.07	10.23 10.16	16.15 16.06	>256 (decomp.)	66
7c	$C_{16}H_{19}ClN_4O_3$	54.70 54.78	5.50 5.46	10.04 10.11	16.03 15.97	192-193	65

*Solvents for recrystallization: EtOH (compounds **5a-l**), 2-PrOH (compound **4**), DMF–EtOH (compounds **6a-l**), DMF (compounds **7a-c).**



6g,**j**,**l** **7a**,**b**,**c**

6g, **7a** NR^1R^2 = NMe_2, **6j**, **7b** NR^1R^2 = piperidin-1-yl, **6l**, **7c** NR^1R^2 = morpholin-4-yl

The composition and structures of the compounds synthesized were confirmed by elemental analysis and the data of IR spectra, chromato-mass spectroscopy, as well as ^{1}H and ^{13}C NMR spectra. The appearance of proton singlets in the region of 7.32-7.47 ppm in the ^{1}H NMR spectra of compounds **5a-l** indicates closure of the pyrrole ring. Characteristic of the pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazines **7a-c** is the presence of NCH_2 group signals in the form of two one-proton double doublets at 4.05-4.71 ppm. The ^{13}C NMR signal of the C-8 carbon in compounds **7a-c** was observed at 81.8-82.0 ppm (Tables 2-4).

So, in this work, we have found a method for the synthesis of 7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic acid derivatives, which are potential intermediates for the preparation of protein kinase inhibitors. It has been shown that some of the derivatives containing a (tetrahydrofuran-2-yl)methyl substituent at the nitrogen atom of the pyrrole ring on treatment with thionyl chloride underwent recyclization with the formation of pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine derivatives.

EXPERIMENTAL

IR spectra of KBr pellets were recorded with a Bruker Vertex 70 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury 400 spectrometer (400 MHz for ^{1}H nuclei, compounds **1b**, **5e**,**h**, **7a**), and a Bruker Avance DRX-500 spectrometer (500 and 125 MHz for ^{1}H and ^{13}C nuclei, respectively) in $CDCl_3$ (compounds **1a-d**, **4**, **5a-l**), DMSO-d_6 (compounds **6a-l**, **7a-c**), CF_3COOD (for ^{13}C spectra of compounds **6d**, **7a-c**) with TMS as internal standard. Chromato-mass spectrometry was performed on an Agilent 1100 Series HPLC, equipped with a diode matrix with an Agilent LC/MSD SL mass sensitive detector, chemical ionization at atmospheric pressure, and a scanning range of 80-1000 *m/z*. Elemental analysis was carried out by combustion using Pregl–Dumas method, analysis for chlorine content by chloride anion titration after combustion in oxygen.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized.

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
1a	1.29 (3H, t, ^3J = 7.0, $OCH_2C\underline{H}_3$); 4.19 (2H, s, CH_2Ph); 4.24 (2H, q, ^3J = 7.0, $OC\underline{H}_2CH_3$); 4.88 (2H, s, CH_2CO); 7.31-7.37 (5H, m, H Ph); 8.45 (1H, s, H-2); 10.27 (1H, s, CHO)
1b	1.28 (3H, t, ^3J = 7.0, $OCH_2C\underline{H}_3$); 4.08 (2H, d, ^3J = 5.5, NCH_2); 4.22-4.26 (4H, m, $C\underline{H}_2COOC\underline{H}_2CH_3$); 5.23 (1H, d, ^3J = 17.2) and 5.32 (1H, d, ^3J = 10.4, $NCH_2CH{=}C\underline{H}_2$); 5.82-5.91 (1H, m, $C\underline{H}{=}CH_2$); 8.37 (1H, s, H-2); 10.33 (1H, s, CHO)
1c	1.30 (3H, t, ^3J = 7.0, $OCH_2C\underline{H}_3$); 3.34 (3H, s, OCH_3); 3.76-3.78 (4H, m, $(C\underline{H}_2)_2OCH_3$); 4.24 (2H, q, ^3J = 7.0, $OC\underline{H}_2CH_3$); 4.41 (2H, s, CH_2CO); 8.37 (1H, s, H-2); 10.38 (1H, s, CHO)
1d	1.30 (3H, t, ^3J = 7.0, $OCH_2C\underline{H}_3$); 1.45-1.48 (1H, m) and 2.10-2.12 (1H, m, CH_2); 1.63-1.66 (2H, m, CH_2); 3.46-3.49 (1H, m) and 3.74-3.77 (1H, m, CH_2); 3.84-3.86 (2H, m, CH_2); 4.24 (2H, q, ^3J = 7.0, $OC\underline{H}_2CH_3$); 4.28-4.32 (1H, m, CH); 4.32-4.35 (1H, m) and 4.64-4.66 (1H, m, CH_2); 8.36 (1H, s, H-2); 10.38 (1H, s, CHO)
4	3.93 (3H, s, OCH_3); 5.97 (2H, s, CH_2Ph); 7.24-7.28 (5H, m, H Ph); 7.41 (1H, s, H-5); 8.81 (1H, s, H-2)
5a	3.44 (6H, s, $N(CH_3)_2$); 3.85 (3H, s, OCH_3); 5.89 (2H, s, CH_2Ph); 7.18-7.22 (3H, m, H Ph); 7.24-7.28 (2H, m, H Ph); 7.44 (1H, s, H-5); 8.44 (1H, s, H-2)
5b	2.05-2.14 (4H, m, $(CH_2)_2$ pyrrolidine); 3.82-3.85 (7H, m, $N(CH_2)_2$ pyrrolidine, OCH_3); 5.88 (2H, s, CH_2Ph); 7.18-7.28 (5H, m, H Ph); 7.41 (1H, s, H-5); 8.44 (1H, s, H-2)
5c	1.74-1.77 (6H, m, $(CH_2)_3$ piperidine); 3.86 (3H, s, OCH_3); 3.96-4.00 (4H, m, $N(CH_2)_2$ piperidine); 5.89 (2H, s, CH_2Ph); 7.19-7.22 (3H, m, H Ph); 7.25-7.28 (2H, m, H Ph); 7.38 (1H, s, H-5); 8.43 (1H, s, H-2)
5d	3.86-3.88 (7H, m, OCH_3, $N(CH_2)_2$ morpholine); 4.01-4.05 (4H, m, $O(CH_2)_2$ morpholine); 5.90 (2H, s, CH_2Ph); 7.19-7.22 (3H, m, H Ph); 7.25-7.28 (2H, m, H Ph); 7.37 (1H, s, H-5); 8.46 (1H, s, H-2)
5e	3.40 (6H, s, $N(CH_3)_2$); 3.87 (3H, s, OCH_3); 4.84 (1H, d, ^3J = 16.8) and 5.07 (1H, d, ^3J = 10.4, $NCH_2CH{=}C\underline{H}_2$); 5.22-5.25 (2H, m, NCH_2); 5.92-6.00 (1H, m, $C\underline{H}{=}CH_2$); 7.39 (1H, s, H-5); 8.38 (1H, s, H-2)
5f	3.31 (3H, s, $CH_2CH_2OC\underline{H}_3$); 3.42 (6H, s, $N(CH_3)_2$); 3.73 (2H, t, ^3J = 5.5, $C\underline{H}_2OCH_3$); 3.92 (3H, s, OCH_3); 4.86 (2H, t, ^3J = 5.5, NCH_2); 7.40 (1H, s, H-5); 8.41 (1H, s, H-2)
5g	1.68-1.72 (1H, m) and 1.84-1.86 (1H, m, CH_2); 1.95-1.98 (2H, m, CH_2); 3.42 (6H, s, $N(CH_3)_2$); 3.67-3.72 (1H, m) and 3.86-3.90 (1H, m, CH_2); 3.91 (3H, s, OCH_3); 4.30-4.34 (1H, m, CH); 4.63 (1H, dd, ^3J = 5.0, ^2J = 13.0) and 4.81 (1H, dd, ^3J = 8.5, ^2J = 13.0, NCH_2); 7.39 (1H, s, H-5); 8.40 (1H, s, H-2)
5h	1.67-1.72 (1H, m) and 1.82-1.86 (1H, m, CH_2); 1.94-1.98 (2H, m, CH_2); 2.05-2.20 (4H, m, $(CH_2)_2$ pyrrolidine); 3.67-3.72 (1H, m) and 3.76-3.79 (1H, m, CH_2); 3.88-3.91 (7H, m, OCH_3, $N(CH_2)_2$ pyrrolidine); 4.30-4.33 (1H, m, CH); 4.62 (1H, dd, ^3J = 3.5, ^2J = 13.0) and 4.81 (1H, dd, ^3J = 7.5, ^2J = 13.0, NCH_2); 7.36 (1H, s, H-5); 8.41 (1H, s, H-2)
5i	1.71-1.75 (6H, m, $(CH_2)_3$ piperidine); 3.32 (3H, s, $CH_2CH_2OC\underline{H}_3$); 3.73 (2H, t, ^3J = 5.5, $C\underline{H}_2OCH_3$); 3.92 (3H, s, OCH_3); 3.94-3.98 (4H, m, $N(CH_2)_2$ piperidine); 4.86 (2H, t, ^3J = 5.5, NCH_2); 7.34 (1H, s, H-5); 8.41 (1H, s, H-2)
5j	1.72-1.76 (6H, m, $(CH_2)_3$ piperidine); 1.72-1.76 (1H, m) and 1.84-1.88 (1H, m, CH_2); 1.94-1.99 (2H, m, CH_2); 3.69-3.72 (1H, m) and 3.84-3.89 (1H, m, CH_2); 3.91-3.95 (7H, m, $N(CH_2)_2$ piperidine, OCH_3); 4.30-4.35 (1H, m) and 4.60-4.65 (1H, m, CH_2); 4.78-4.83 (1H, m, CH); 7.32 (1H, s, H-5); 8.39 (1H, s, H-2)
5k	3.32 (3H, s, $CH_2CH_2OC\underline{H}_3$); 3.73 (2H, t, ^3J = 5.5, $C\underline{H}_2OCH_3$); 3.84-3.88 (4H, m, $N(CH_2)_2$ morpholine); 3.93 (3H, s, OCH_3); 3.98-4.04 (4H, m, $O(CH_2)_2$ morpholine); 4.88 (2H, t, ^3J = 5.5, NCH_2); 7.33 (1H, s, H-5); 8.44 (1H, s, H-2)
5l	1.59-1.63 (1H, m) and 1.74-1.77 (1H, m, CH_2); 1.80-1.85 (2H, m, CH_2); 3.55-3.58 (1H, m) and 3.60-3.65 (1H, m, CH_2); 3.71-3.75 (4H, m, $N(CH_2)_2$ morpholine); 3.85 (3H, s, OCH_3); 3.88-3.93 (4H, m, $O(CH_2)_2$ morpholine); 4.13-4.17 (1H, m, CH); 4.51 (1H, dd, ^3J = 7.0, ^2J = 13.5) and 4.80 (1H, dd, ^3J = 10.0, ^2J = 13.5, NCH_2); 7.47 (1H, s, H-5); 8.30 (1H, s, H-2)
6a	3.41 (6H, s, $N(CH_3)_2$); 5.82 (2H, s, CH_2Ph); 7.06-7.07 (2H, m, H Ph); 7.20-7.29 (3H, m, H Ph); 7.54 (1H, s, H-5); 8.32 (1H, s, H-2); 13.14 (1H, br. s, OH)

TABLE 2 (continued)

1	2
6b	1.95-2.06 (4H, m, $(CH_2)_2$ pyrrolidine); 3.65-3.69 (2H, m, NCH_2 pyrrolidine); 3.86-3.90 (2H, m, NCH_2 pyrrolidine); 5.78-5.82 (2H, m, CH_2Ph); 7.04-7.05 (2H, m, H Ph); 7.20-7.26 (3H, m, H Ph); 7.43 (1H, s, H-5); 8.27 (1H, s, H-2)
6c	1.70-1.74 (6H, m, $(CH_2)_3$ piperidine); 3.96-3.99 (4H, m, $N(CH_2)_2$ piperidine); 5.84 (2H, s, CH_2Ph); 7.09-7.10 (2H, m, H Ph); 7.22-7.30 (3H, m, H Ph); 7.63 (1H, s, H-5); 8.39 (1H, s, H-2)
6d	3.72-3.75 (4H, m, $N(CH_2)_2$ morpholine); 3.90-3.93 (4H, m, $O(CH_2)_2$ morpholine); 5.81 (2H, s, CH_2Ph); 7.04-7.06 (2H, m, H Ph); 7.22-7.26 (3H, m, H Ph); 7.52 (1H, s, H-5); 8.31 (1H, s, H-2); 13.05 (1H, br. s, OH)
6e	3.33 (6H, s, $N(CH_3)_2$); 4.70 (1H, d, ^3J = 17.2) and 5.01 (1H, d, ^3J = 10.0, $NCH_2CH{=}C\underline{H}_2$); 5.13-5.16 (2H, m, NCH_2); 5.93-5.97 (1H, m, $NCH_2C\underline{H}{=}CH_2$); 7.40 (1H, s, H-5); 8.22 (1H, s, H-2); 12.93 (1H, br. s, OH)
6f	3.21 (3H, s, $CH_2CH_2OC\underline{H}_3$); 3.34 (6H, s, $N(CH_3)_2$); 3.60 (2H, t, ^3J = 5.5, $C\underline{H}_2OCH_3$); 4.72 (2H, t, ^3J = 5.5, NCH_2); 7.40 (1H, s, H-5); 8.25 (1H, s, H-2); 12.97 (1H, br. s, OH)
6g	1.61-1.64 (1H, m) and 1.75-1.79 (1H, m, CH_2); 1.85-1.87 (2H, m, CH_2); 3.35 (6H, s, $N(CH_3)_2$); 3.56-3.59 (1H, m) and 3.74-3.78 (1H, m, CH_2); 4.17-4.21 (1H, m, CH); 4.49 (1H, dd, ^3J = 5.0, ^2J = 13.5) and 4.66 (1H, dd, ^3J = 8.5, ^2J = 13.5, NCH_2); 7.38 (1H, s, H-5); 8.24 (1H, s, H-2); 12.92 (1H, br. s, OH)
6h	1.61-1.64 (1H, m) and 1.77-1.81 (1H, m, CH_2); 1.86-1.89 (2H, m, CH_2); 2.05-2.09 (4H, m, $(CH_2)_2$ pyrrolidine); 3.56-3.59 (1H, m) and 3.70-3.75 (1H, m, CH_2); 3.76-3.79 (2H, m, NCH_2 pyrrolidine); 3.97-4.01 (2H, m, NCH_2 pyrrolidine); 4.14-4.17 (1H, m, CH); 4.57 (1H, dd, ^3J = 4.5, ^2J = 13.5) and 4.69 (1H, dd, ^3J = 8.5, ^2J = 13.5, NCH_2); 7.56 (1H, s, H-5); 8.38 (1H, s, H-2); 13.48 (1H, br. s, OH)
6i	1.59-1.63 (4H, m, $(CH_2)_2$ piperidine); 1.67-1.72 (2H, m, CH_2 piperidine); 3.21 (3H, s, $CH_2CH_2OC\underline{H}_3$); 3.60 (2H, t, ^3J = 5.5, $C\underline{H}_2OCH_3$); 3.89-3.92 (4H, m, $N(CH_2)_2$ piperidine); 4.72 (2H, t, ^3J = 5.5, NCH_2); 7.35 (1H, s, H-5); 8.25 (1H, s, H-2); 13.03 (1H, br. s, OH)
6j	1.58-1.61 (6H, m, $(CH_2)_3$ piperidine); 1.68-1.78 (4H, m, CH_2CH_2); 3.54-3.56 (1H, m) and 3.71-3.75 (1H, m, CH_2); 3.89 (4H, m, $N(CH_2)_2$ piperidine); 4.15-4.21 (1H, m, CH); 4.48 (1H, dd, ^3J = 5.5, ^2J = 13.5) and 4.65 (1H, dd, ^3J = 7.5, ^2J = 13.5, NCH_2); 7.33 (1H, s, H-5); 8.24 (1H, s, H-2); 12.98 (1H, br. s, OH)
6k	3.19 (3H, s, $CH_2CH_2OC\underline{H}_3$); 3.60 (2H, t, ^3J = 5.5, $C\underline{H}_2OCH_3$); 3.70-3.76 (4H, m, $N(CH_2)_2$ morpholine); 3.87-3.93 (4H, m, $O(CH_2)_2$ morpholine); 4.73 (2H, t, ^3J = 5.5, NCH_2); 7.44 (1H, s, H-5); 8.29 (1H, s, H-2); 13.07 (1H, br. s, OH)
6l	1.58-1.63 (1H, m) and 1.75-1.81 (3H, m, $2CH_2$); 3.53-3.59 (1H, m) and 3.57-3.62 (1H, m, CH_2); 3.70-3.74 (4H, m, $N(CH_2)_2$ morpholine); 3.87-3.93 (4H, m, $O(CH_2)_2$ morpholine); 4.15-4.18 (1H, m, CH); 4.51 (1H, dd, ^3J = 6.0, ^2J = 13.5) and 4.67 (1H, dd, ^3J = 8.0, ^2J = 13.5, NCH_2); 7.42 (1H, s, H-5); 8.29 (1H, s, H-2); 13.03 (1H, br. s, OH)
7a	1.90-1.95 (4H, m, $(C\underline{H}_2)_2CH_2Cl$); 3.48 (6H, s, $N(CH_3)_2$); 3.70-3.76 (2H, m, CH_2Cl); 4.14 (1H, dd, ^3J = 11.2, ^2J = 14.5) and 4.71 (1H, dd, ^3J = 2.0, ^2J = 14.5, NCH_2); 4.95 (1H, m, CH); 7.75 (1H, s, H-5); 8.42 (1H, s, H-2)
7b	1.68-1.73 (6H, m, $(CH_2)_3$ piperidine); 1.90-1.95 (4H, m, $(C\underline{H}_2)_2CH_2Cl$); 3.36-3.41 (2H, m, CH_2Cl); 4.00 (4H, s, $N(CH_2)_2$ piperidine); 4.13 (1H, dd, ^3J = 11.2, ^2J = 14.5) and 4.71 (1H, dd, ^3J = 2.0, ^2J = 14.5, NCH_2); 4.94 (1H, m, CH); 7.76 (1H, s, H-5); 8.42 (1H, s, H-2)
7c	1.90-1.95 (4H, m, $(C\underline{H}_2)_2CH_2Cl$); 3.70-3.76 (6H, m, $N(CH_2)_2$ morpholine, CH_2Cl); 3.91-3.96 (4H, m, $O(CH_2)_2$ morpholine); 4.05 (1H, dd, ^3J = 11.2, ^2J = 14.5) and 4.59 (1H, dd, ^3J = 2.0, ^2J = 14.5, NCH_2); 4.87-4.90 (1H, m, CH); 7.63 (1H, s, H-5); 8.33 (1H, s, H-2)

Melting points were determined on a Boetius hot stage apparatus. Reaction progress and the purity of obtained compounds were controlled by TLC on Silufol UV-254 plates with 19:1 $CHCl_3$–MeOH eluent.

Ethyl *N*-Alkyl-*N*-(6-chloro-5-formylpyrimidin-4-yl)glycinates 1a-d (General Method). A solution of $NaHCO_3$ (0.57 g, 6.7 mmol) in H_2O (20 ml) was added to a solution of 4,6-dichloropyrimidine-5-carbaldehyde [11] (1.00 g, 5.6 mmol) in CH_2Cl_2 (10 ml). The mixture was cooled to 0°C, and the corresponding

TABLE 3. ^{13}C NMR Spectra of Compounds **6a-l, 7a-c**

Compound	Chemical shifts, δ, ppm
6a	38.7 ($N(CH_3)_2$); 45.8 ($\underline{C}H_2Ph$); 101.3 (C-4a); 112.3 (C-5); 125.2, 126.8, 127.4, 128.6, 138.2 (6C Ph and C-6); 150.1, 151.0, 154.8 (C-2,4,7a); 161.9 (C=O)
6b	25.2, 26.5 ($(CH_2)_2$ pyrrolidine); 49.4 ($\underline{C}H_2Ph$); 51.2, 53.1 ($N(CH_2)_2$ pyrrolidine); 103.8 (C-4a); 117.5 (C-5); 128.1, 128.4, 129.8, 130.8, 137.2 (6C Ph and C-6); 146.7, 149.9, 150.6 (C-2,4,7a); 166.8 (C=O)
6c	23.0, 25.2 ($(CH_2)_3$ piperidine); 46.5, 48.7 ($N(CH_2)_2$ piperidine and $\underline{C}H_2Ph$); 101.5 (C-4a); 112.6 (C-5); 126.7, 127.4, 128.1, 129.2, 138.2 (6C Ph and C-6); 148.3, 151.0, 152.2 (C-2,4,7a); 162.3 (C=O)
6d	45.3, 45.6 ($N(CH_2)_2$ morpholine and $\underline{C}H_2Ph$); 66.1 ($O(CH_2)_2$ morpholine); 101.8 (C-4a); 110.9 (C-5); 124.9, 126.9, 127.3, 128.6, 139.0 (6C Ph and C-6); 153.8, 154.1, 158.0 (C-2,4,7a); 162.7 (C=O)
6e	38.8 ($N(CH_3)_2$); 44.6 ($N\underline{C}H_2CH=CH_2$); 101.9 (C-4a); 111.4 (C-5); 115.8 ($NCH_2CH=\underline{C}H_2$); 124.3 (C-6); 135.3 ($NCH_2\underline{C}H=CH_2$); 153.1, 154.2, 158.3 (C-2,4,7a); 162.7 (C=O)
6f	38.8 ($N(CH_3)_2$); 41.6 (NCH_2); 57.8 (OCH_3); 70.8 ($\underline{C}H_2OCH_3$); 101.9 (C-4a); 111.2 (C-5); 124.5 (C-6); 153.3, 153.6, 158.1 (C-2, C-4, C-7a); 162.8 (C=O)
6g	24.7, 28.2 ($(CH_2)_2$ tetrahydrofuran); 38.6 ($N(CH_3)_2$); 45.8 (NCH_2); 67.1 (CH_2 tetrahydrofuran); 77.0 (CH tetrahydrofuran); 101.9 (C-4a); 110.8 (C-5); 124.9 (C-6); 153.4, 153.8, 158.2 (C-2, C-4, C-7a); 163.0 (C=O)
6h	24.0 ($(CH_2)_2$ pyrrolidine); 24.8, 28.2 ($(CH_2)_2$ tetrahydrofuran); 46.7 (NCH_2); 50.4 ($N(CH_2)_2$ pyrrolidine); 67.2 (CH_2 tetrahydrofuran); 77.1 (CH tetrahydrofuran); 101.1 (C-4a); 112.0 (C-5); 127.6 (C-6); 145.7, 145.8, 149.2 (C-2,4,7a); 162.2 (C=O)
6i	23.9, 25.3 ($(CH_2)_3$ piperidine); 41.7 (NCH_2); 46.3 ($N(CH_2)_2$ piperidine); 57.9 (OCH_3); 70.8 ($\underline{C}H_2OCH_3$); 101.1 (C-4a); 110.2 (C-5); 124.8 (C-6); 153.7, 153.8, 157.5 (C-2,4,7a); 162.8 (C=O)
6j	23.9 (CH_2 piperidine); 24.7 (CH_2 tetrahydrofuran); 25.4 ($(CH_2)_2$ piperidine); 28.2 (CH_2 tetrahydrofuran), 45.9 (NCH_2); 46.3 ($N(CH_2)_2$ piperidine); 67.1 (CH_2 tetrahydrofuran); 77.1 (CH tetrahydrofuran); 101.4 (C-4a); 110.0 (C-5); 125.1 (C-6); 153.8, 153.9, 157.5 (C-2,4,7a); 163.0 (C=O)
6k	41.7 (NCH_2); 45.3 ($N(CH_2)_2$ morpholine); 58.1 ($O\underline{C}H_3$); 66.1 ($O(CH_2)_2$ morpholine); 70.8 ($\underline{C}H_2OCH_3$); 101.7 (C-4a); 110.1 (C-5); 125.2 (C-6); 153.7, 153.8, 158.0 (C-2,4,7a); 162.8 (C=O)
6l	24.7, 28.2 (CH_2 tetrahydrofuran); 45.3 (NCH_2); 45.8 ($N(CH_2)_2$ morpholine); 66.1 ($O(CH_2)_2$ morpholine); 67.1 (CH_2 tetrahydrofuran); 77.1 (CH tetrahydrofuran); 101.6 (C-4a); 109.8 (C-5); 125.6 (C-6); 153.6, 153.8, 157.9 (C-2,4,7a); 163.0 (C=O)
7a	29.1, 30.9 ($\underline{C}H_2CH_2CH_2Cl$); 42.4, 44.0 ($N(CH_3)_2$); 44.9 ($NCH_2$); 45.8 ($CH_2Cl$); 82.0 (C-8); 105.5 (C-4a); 116.5 (C-5); 124.7 (C-5a); 148.2, 148.5, 153.9 (C-2,4,10a); 164.2 (C-6)
7b	23.7, 26.4 ($(CH_2)_3$ piperidine); 28.7, 30.6 ($(\underline{C}H_2)_2CH_2Cl$); 44.6 ($NCH_2$); 45.5 ($CH_2Cl$); 50.5 ($N(CH_2)_2$ piperidine); 81.8 (C-8); 105.0 (C-4a); 115.7 (C-5); 124.2 (C-5a); 148.1, 148.8, 151.9 (C-2,4,10a); 164.2 (C-6)
7c	29.0, 30.9 ($(\underline{C}H_2)_2CH_2Cl$); 44.9 ($NCH_2$); 45.9 ($CH_2Cl$); 49.6 ($N(CH_2)_2$ morpholine); 67.5 ($O(CH_2)_2$ morpholine); 82.0 (C-8); 105.2 (C-4a); 115.5 (C-5); 125.0 (C-5a); 147.8, 148.3, 154.9 (C-2,4,10a); 164.2 (C-6)

ethyl *N*-alkyl glycinate (6.7 mmol) in CH_2Cl_2 (10 ml) was added dropwise with vigorous stirring. The reaction mixture was stirred for 10 h at 20-25°C. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×10 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuum. The residue was chromatographed on a column with $CHCl_3$ as eluent. Compounds **1a-d** were used for further reactions without recrystallization.

The constants of **4-amino-6-chloropyrimidine-5-carbaldehydes 3a-d** are cited elsewhere [12, 13].

Methyl 7-Benzyl-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (4). Et_3N (0.42 ml, 3.0 mmol) was added to a solution of compound **1a** (0.50 g, 1.5 mmol) in MeOH (15 ml). The mixture was refluxed for 20 h. The reaction mixture was evaporated in vacuum, and the residue was recrystallized from 2-PrOH.

Methyl 7-Alkyl-4-amino-7*H*-pyrrolo-[2,3-*d*]pyrimidine-6-carboxylates 5a-l (General Method). A. (Compounds **5a-d**). A mixture of compound **4** (0.50 g, 1.6 mmol) and secondary amine (4.8 mmol) was refluxed in toluene for 12 h. The precipitate was cooled and filtered off. The filtrate was evaporated in vacuum, and the residue was recrystallized from EtOH.

TABLE 4. IR and Mass Spectra of Compounds **5a-l**, **7a-c**

Com-pound	IR spectrum, ν (C=O), cm^{-1}	Mass spectrum, *m/z* $[M+1]^+$	Com-pound	IR spectrum, ν (C=O), cm^{-1}	Mass spectrum, *m/z* $[M+1]^+$
5a	1706	311	**5i**	1708	319
5b	1700	337	**5j**	1711	345
5c	1719	351	**5k**	1714	321
5d	1704	353	**5l**	1704	347
5e	1714	261	**7a**	1720	309
5f	1697	279	**7b**	1727	349
5g	1705	305	**7c**	1718	351
5h	1697	331			

B. (Compounds **5a-l**). A mixture of chloroaldehyde **1a-d** or **3a-d** (5.0 mmol), secondary amine (7.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in absolute MeCN was refluxed with stirring for 15-20 h. The mixture was cooled, the precipitate was filtered off and washed with absolute MeCN. The filtrate was evaporated in vacuum. The residue was dissolved in MeOH (5 ml), and a solution of MeONa (0.33 g, 6.0 mmol) in MeOH (3 ml) was added. The reaction mixture was heated to reflux, cooled and kept at 0°C for 12 h. The precipitate was filtered off, washed with H_2O, and recrystallized from EtOH.

7-Alkyl-4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic acids (6a-l) (General Method). NaOH (0.072 g, 1.8 mmol) was added to a suspension of compound **5a-l** (1.5 mmol) in 40% aqueous EtOH (10 ml), and the mixture was refluxed for 2-3 h. The mixture was cooled and acidified with dilute HCl (1:1) to pH 5-6. The reaction mixture was kept at 0°C for 12 h. The precipitate was filtered off, washed with water, and recrystallized from DMF-EtOH.

8-(3-Chloropropyl)-4-dimethylamino-8,9-dihydro-6*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-6-one (7a). A suspension of acid **6g** (0.50 g, 1.7 mmol) in $SOCl_2$ (1 ml) was refluxed for 3 h. The reaction mixture was cooled, the precipitate was filtered off, washed with PhH (10 ml) and EtOH (10 ml). The product was recrystallized from DMF.

8-(3-Chloropropyl)-4-(piperidin-1-yl)-8,9-dihydro-6*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-6-one (7b) was obtained analogously from acid **6j**.

8-(3-Chloropropyl)-4-(morpholin-4-yl)-8,9-dihydro-6*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-6-one (7c) was obtained analogously from acid **6l**.

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