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SYNTHESIS OF 7-ARYLMETHYL-SUBSTITUTED DERIVATIVES OF 2-AMINO-2-PYRROLYDIN-1-YL-5,6,7,8-TETRAHYDROPYRIDO-[3,4-*d*]PYRIMIDINE

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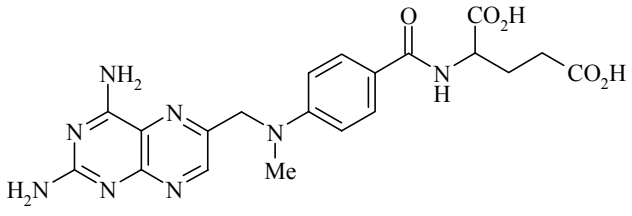
7-Benzyl-2-pyrrolidin-1-yl-5,6,7,8-tetrahydro-3H-pyrido[3,4-d]pyrimidin-4-one was prepared by condensation of 1-benzyl-4-ethoxycarbonyl-3-oxopiperidine with pyrrolidine-1-carboxamidine. Subsequent treatment of the product with trifluoromethansulfonyl anhydride, aqueous ammonia, and hydrogen in the presence of palladium on carbon gave 4-amino-2-pyrrolidin-1-yl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine in 80% yield. The given compound was used in the reductive amination of aldehydes in the synthesis of various 7-arylmethyl-substituted derivatives of 4-amino-2-pyrrolidin-1-yl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine.

Keywords: 1-benzyl-4-ethoxycarbonyl-3-oxopiperidine, pyrido[3,4-*d*]pyrimidines, pyrrolidine-1-carboxamidine, sodium triacetoxyborohydride, reductive amination, condensation.

Amino-substituted derivatives of pyrido[*d*]pyrimidines have high biological activity, in particular they inhibit dehydrofolatereductase, leading to the death of many pathogenic microorganisms [1, 2]. Various structural analogs of *methotrexate* (**1**), for example pyrido[*d*]pyrimidines **2** and **3** (*piritrexim*), are among such compounds with especially high reactivity [3, 4].



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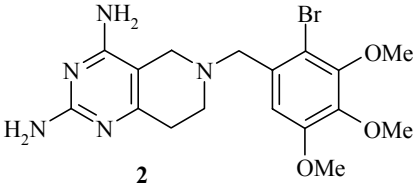

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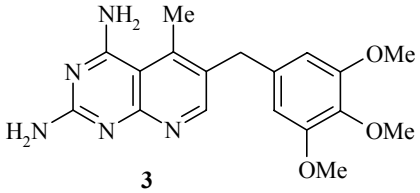

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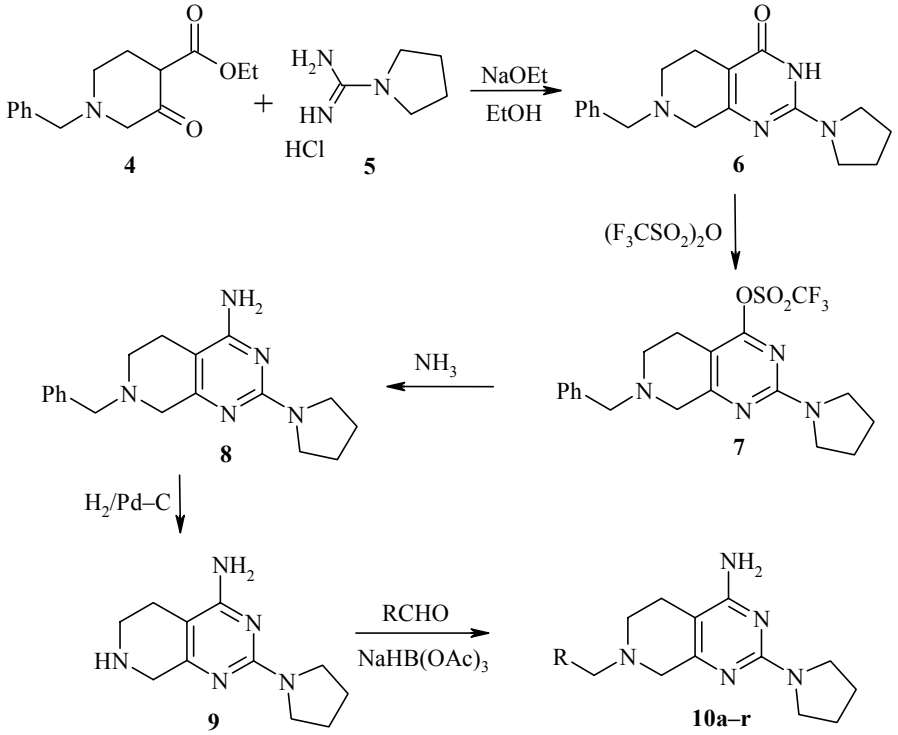
In previous work we showed that a suitable method for the synthesis of derivatives of pyrido-[3,4-*d*]pyrimidine is the condensation of 1-benzyl-4-ethoxycarbonyl-3-oxopiperidine (**4**) with morpholine-4-carboxamidine, which gave 7-benzyl-2-morpholin-4-yl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-one [5] in high yield. In the present work we have studied the condensation of the keto ester **4** with pyrrolidine-1-carboxamidine (**5**) and developed a method for the preparation of pyrido[3,,4-*d*]pyrimidines **10a-d**, which are structural analogs of compounds **2** and **3**.



4 **5** **6** **7** **8** **9** **10a–r**

10 a R = 4-EtC_6H_4, **b** R = 4-MeOC_6H_4, **c** R = 4-EtOC_6H_4, **d** R = 2-FC_6H_4, **e** R = 2-HOC_6H_4, **f** R = 2-MeOC_6H_4, **g** R = 2-EtOC_6H_4, **h** R = 2,4-$(MeO)_2C_6H_3$, **i** R = 2-OH-4-MeOC_6H_3, **j** R = 3,4-$(MeO)_2C_6H_3$, **k** R = 3-MeO-4-HOC_6H_3, **l** R = 3-OH-4-MeOC_6H_3, **m** R = 3-MeO-4-EtOC_6H_3, **n** R = 3-HOCH_2-4-MeOC_6H_3, **o** R = 3-EtO-4-HOC_6H_3, **p** R = 3,5-$(MeO)_2C_6H_3$, **q** R = 2,4,5-$(MeO)_3C_6H_2$, **r** R = 2-thienyl

Boiling an alcoholic solution of the keto ester **4** with an equimolar amount of amidine **5** in the presence of three equivalents of EtONa for 3 h led to a new compound. According to elemental analysis, IR and ^{1}H NMR spectroscopy and mass spectrometry (Tables 1-4), the new compound is 7-benzyl-2-pyrrolidin-1-yl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-one (**6**), the yield of which was 73%.

Reaction of compound **6** with trifluoromethanesulfonic anhydride in pyridine at -20°C gave the triflate derivative **7** in 55% yield. Prolonged heating (12 h, 100°C) of the triflate **7** in a mixture of DMF and aqueous ammonia gave the amine **8** in 67% yield. Hydrogenation of the amine **8** in methanol solution in the presence of a suspension of palladium on carbon removed the benzyl substituent and gave the diamine **9** in 80% yield. The latter readily underwent reductive amination with aldehydes in the presence of sodium triacetoxyborohydride to give compounds **10a-r** with yields of 71-79%.

Table 1. Characteristics of Compounds **6, 8, 9** and **10a-r**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
6	$C_{18}H_{22}N_4O$	69.91 / 69.65	7.29 / 7.14	17.79 / 18.05	228-230	73
8	$C_{18}H_{23}N_5$	70.05 / 69.87	7.37 / 7.49	22.58 / 22.63	164-165	67
9	$C_{11}H_{17}N_5$	60.46 / 60.25	7.68 / 7.77	31.86 / 31.93	148-150	80
10a	$C_{20}H_{27}N_5$	71.34 / 71.18	8.14 / 8.06	20.52 / 20.75	175-176	78
10b	$C_{19}H_{25}N_5O$	67.48 / 67.23	7.64 / 7.42	20.41 / 20.63	198-200	75
10c	$C_{20}H_{27}N_5O$	68.21 / 67.96	7.91 / 7.70	19.59 / 19.81	147-148	71
10d	$C_{18}H_{22}FN_5$	66.28 / 66.03	6.82 / 6.77	21.04 / 21.39	190-191	74
10e	$C_{18}H_{23}N_5O$	66.71 / 66.44	7.22 / 7.12	21.25 / 21.52	165-166	73
10f	$C_{19}H_{25}N_5O$	67.48 / 67.23	7.56 / 7.42	20.48 / 20.63	157-158	76
10g	$C_{20}H_{27}N_5O$	68.18 / 67.96	7.82 / 7.70	19.62 / 19.81	155-156	72
10h	$C_{20}H_{27}N_5O_2$	65.26 / 65.02	7.48 / 7.36	18.86 / 19.03	153-154	78
10i	$C_{19}H_{25}N_5O_2$	64.46 / 64.20	7.30 / 7.09	19.54 / 19.70	199-200	76
10j	$C_{20}H_{27}N_5O_2$	65.27 / 65.02	7.51 / 7.36	18.86 / 19.03	163-164	79
10k	$C_{19}H_{25}N_5O_2$	64.36 / 64.20	7.32 / 7.09	19.48 / 19.70	189-190	73
10l	$C_{19}H_{25}N_5O_2$	64.47 / 64.20	7.30 / 7.09	19.45 / 18.70	192-193	75
10m	$C_{21}H_{29}N_5O_2$	65.94 / 65.77	7.83 / 7.62	17.96 / 18.26	159-160	74
10n	$C_{20}H_{27}N_5O_2$	65.28 / 65.02	7.52 / 7.36	18.78 / 19.03	116-117	77
10o	$C_{20}H_{27}N_5O_2$	65.24 / 65.02	7.58 / 7.36	18.81 / 19.03	205-207	75
10p	$C_{20}H_{27}N_5O_2$	65.30 / 65.02	7.54 / 7.36	18.78 / 19.03	140-141	76
10q	$C_{21}H_{29}N_5O_3$	63.38 / 63.14	7.48 / 7.32	17.26 / 17.53	170-171	78
10r	$C_{16}H_{21}N_5S$	61.18 / 60.92	6.92 / 6.71	21.96 / 22.20	168-169	71

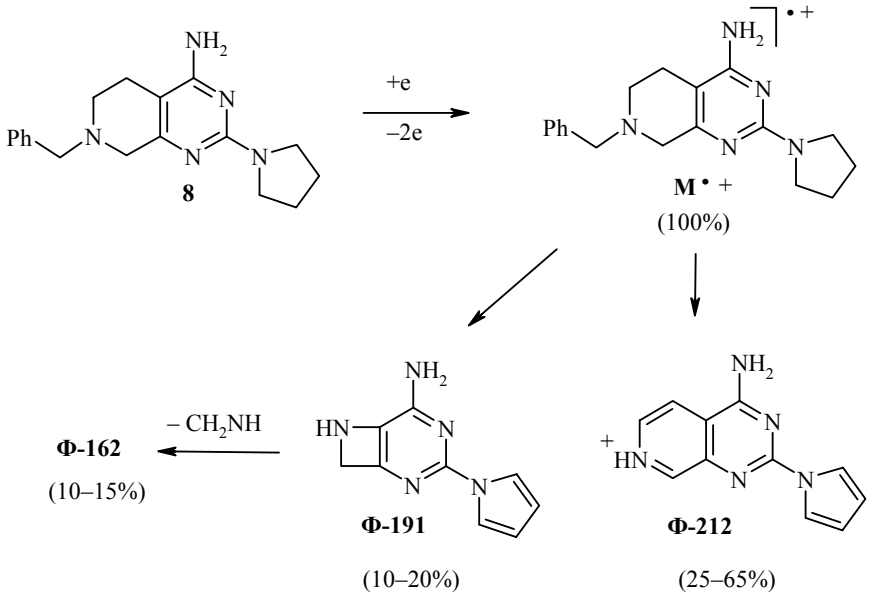
Signals of the amino group at 5.90 ppm and methylene protons of the piperidine and pyrrolidine rings at 1.8, 2.5, 2.6, 3.4, and 3.7 ppm are common to the ^{1}H NMR spectra of compounds **8** and **10a-r**. The ^{1}H NMR spectra of compounds **6**, **8**, and **10a-r** contain common signals of the methylene protons of the 7-arylmethyl substituents at 3.2 ppm (Table 5).

Mass spectrometric data provide interesting information on the properties of compounds **6**, **8**, **9**, and **10a-r.** Intense peaks of the molecular ions (100%) on a background of a small number of fragment ions shows that compounds **6**, **8**, and **10a-r** have high stability in an electron impact (Table 3). The presence in the mass spectra of compounds **6**, **8**, and **10a-r** of peaks of ions with masses 212, 191, 162 indicates a common fragmentation scheme for these compounds, including the initial loss of the 7-arylmethyl substituent of the

Table 2. IR Spectra of Compounds **6, 8, 9,** and **10a-r**

Com-pound	ν, cm^{-1}			
	OH	NH	CH	C=C, C=N
6		3230	3010, 2960, 2850	1610, 1580, 1575, 1545
8		3350, 3220, 1675	3010, 2960, 2850	1590, 1575, 1540
9		3350, 3240, 3230, 1675	3005, 2965, 2850	1595, 1580, 1545
10a		3355, 3220, 1670	3010, 2965, 2850	1585, 1570, 1540
10b		3355, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10c		3355, 3220, 1675	3010, 2960, 2850	1600, 1580, 1560, 1540
10d		3355, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10e	3470	3350, 3220, 1670	3010, 2960, 2850	1600, 1580, 1560, 1540
10f		3350, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10g		3350, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10h		3350, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10i	3470	3350, 3220, 1675	3010, 2960, 2850	1600, 1580, 1555, 1540
10j		3350, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10k	3485	3350, 3220, 1670	3010, 2960, 2850	1590, 1565, 1545
10l	3470	3350, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10m		3350, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10n	3495	3350, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10o	3485	3350, 3220, 1675	3010, 2960, 2850	1590, 1565, 1545
10p		3350, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10q		3350, 3220, 1675	3010, 2960, 2850	1600, 1585, 1560, 1540
10r		3350, 3220, 1675	3005, 2965, 2850	1590, 1580, 1560, 1540

various derivatives of 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine with subsequent decomposition of the piperidine ring. The fragmentation scheme differs principally from that of the decomposition of 7-benzyl-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidines, with a bulky substituent at position 4, which we studied previously [5]. As a rule, the



basic direction of fragmentation of the latter included primary decomposition of the pyrimidine ring with elimination of R–CN units. Apparently the strong electron-donor pyrrolidine substituent in position 2 of compounds **6**, **8**, and **10a-r** strongly increases the binding electron density in their pyrimidine rings, directing fragmentation into the primary decomposition of the piperidine ring.

This work shows that condensation of 1-benzyl-4-ethoxycarbonyl-3-oxopiperidine with pyrrolidine-1-carboxamidine permits the preparation in high yield of 7-benzyl-2-pyrrolidin-4-yl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]pyrimidin-4-one, which may be used as the key starting material in the synthesis of a variety of derivatives of 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine.

Table 3. Mass Spectra of Compounds **6**, **8**, **9**, and **10a-r**

Com-pound	*m/z* (I_{rel}, %)
6	310 $[M]^+$ (100), 192 (30)
8	309 $[M]^+$ (100), 212 (25), 191 (10), 162 (10)
9	219 $[M]^+$ (25), 191 (15), 156 (100), 79 (50)
10a	337 $[M]^+$ (100), 212 (35), 162 (10), 83 (25)
10b	339 $[M]^+$ (100), 212 (55), 162 (5)
10c	353 $[M]^+$ (100), 212 (35), 151 (5), 107 (5)
10d	327 $[M]^+$ (100), 212 (40), 191 (30), 162 (15)
10e	325 $[M]^+$ (100), 212 (65), 191 (15), 162 (5), 107 (5)
10f	339 $[M]^+$ (100), 212 (30), 191 (15)
10g	353 $[M]^+$ (100), 212 (40), 191 (15), 162 (5)
10h	369 $[M]^+$ (100), 212 (25), 167 (20), 151 (15), 137 (5)
10i	355 $[M]^+$ (50), 221 (65), 212 (100), 191 (20), 162 (15), 151 (5), 137 (25)
10j	369 $[M]^+$ (100), 212 (20), 191 (5), 162 (5), 151 (5)
10k	355 $[M]^+$ (100), 212 (35), 162 (5), 137 (20)
10l	355 $[M]^+$ (100), 212 (35), 162 (5)
10m	383 $[M]^+$ (100), 212 (15), 181 (5), 137 (5), 79 (5)
10n	369 $[M]^+$ (100), 212 (20), 167 (10)
10o	369 $[M]^+$ (100), 212 (15), 151 (10), 79 (5)
10p	369 $[M]^+$ (100), 212 (20), 151 (10)
10q	399 $[M]^+$ (100), 212 (20), 198 (5), 181 (20), 167 (40)
10r	316 $[M]^+$ (100), 212 (55), 191 (15), 162 (5)

Table 4. ^{1}H NMR Spectra of Compounds **6**, **8-10**

Com-pound	Chemical shifts, δ, ppm						
	5-CH_2	6-CH_2	8-CH_2	Ar–CH_2*	2-$N(CH_2)_4$, 4H, br. s	NH_2	NH
6	2.45	2.60	3.65	3.20	1.83, 3.38		10.2
8	2.45	2.60	3.65	3.20	1.83, 3.38	5.90	
9	2.30	2.60	3.65		1.83, 3.38	6.10	5.6
10	2.45	2.60	3.65	3.20	1.83, 3.38	5.90	

* See Table 5.

Table 5. ^{1}H NMR Spectra of Compounds **6**, **8-10** (Signals of the Protons of the Ar Fragment)

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
6	7.25 (3H, m, H-3',4',5'); 7.32 (2H, d, *J* = 8.5, H-2',6')
8	7.25 (3H, m, H-3',4',5'); 7.32 (2H, d, *J* = 8.5, H-2',6')
10a	1.10 (3H, t, *J* = 6.5, CH_3); 2.60 (2H, m, CH_2); 7.17 (2H, d, *J* = 8.5, H-3',5'); 7.26 (2H, d, *J* = 8.5, H-2',6')
10b	3.75 (3H, s, OCH_3); 6.88 (2H, d, *J* = 8.5, H-3',5'); 7.26 (2H, d, *J* = 8.5, H-2',6')
10c	1.35 (3H, t, *J* = 6.5, CH_3); 4.00 (2H, q, *J* = 6.5, OCH_2); 6.87 (2H, d, *J* = 8.5, H-3',5'); 7.24 (2H, d, *J* = 8.5, H-2',6')
10d	7.15 (2H, m, H-6',4'); 7.30 (1H, dd, J_{H-H} = 8.5, J_{F-H} = 6.0, H-3'); 7.46 (1H, t, *J* = 8.5, H-5')
10e	6.76 (2H, m, H-3',5'); 7.13 (2H, m, H-4',6'); 10.0 (1H, br. s, OH)
10f	3.80 (3H, s, OCH_3); 6.91 (1H, t, *J* = 8.5, H-5'); 6.97 (1H, d, *J* = 8.5, H-3'); 7.22 (1H, t, *J* = 8.5, H-4'); 7.35 (1H, d, *J* = 8.5, H-6')
10g	1.34 (3H, t, *J* = 6.5, CH_3); 4.05 (2H, q, *J* = 6.5, OCH_2); 6.90 (1H, t, *J* = 8.5, H-5'); 6.95 (1H, d, *J* = 8.5, H-3'); 7.19 (1H, t, *J* = 8.5, H-4'); 7.35 (1H, d, *J* = 8.5, H-6')
10h	3.75 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 6.50 (1H, dd, *J* = 8.5, *J* = 1.5, H-5'); 6.57 (1H, d, *J* = 1.5, H-3'); 7.25 (1H, d, *J* = 8.5, H-6')
10i	3.70 (3H, s, OCH_3); 6.33 (2H, m, H-3',5'); 7.00 (1H, d, *J* = 8.5, H-6'); 10.0 (1H, br. s, OH)
10j	3.75 (6H, s, $2OCH_3$); 6.33 (3H, m, H-2',5',6')
10k	3.80 (3H, s, OCH_3); 6.80 (2H, s, H-5',6'); 6.90 (1H, s, H-2'); 8.70 (1H, s, OH)
10l	3.75 (3H, s, OCH_3); 6.71 (1H, d, *J* = 8.5, H-6'); 6.80 (1H, s, H-2'); 6.85 (1H, d, *J* = 8.5, H-5'); 8.70 (1H, s, OH)
10m	1.30 (3H, t, *J* = 6.5, CH_3); 3.75 (3H, s, OCH_3); 4.00 (2H, q, *J* = 6.5, OCH_2); 6.84 (1H, d, *J* = 8.5 , H-5'); 6.87 (1H, d, *J* = 8.5, H-6'); 6.90 (1H, s, H-2')
10n	3.75 (3H, s, OCH_3); 4.50 (2H, d, *J* = 5.5, CH_2); 4.85 (1H, t, *J* = 5.5, OH); 6.80 (1H, d, *J* = 8.5, H-5'); 7.18 (1H, d, *J* = 8.5, H-6'); 7.38 (1H, s, H-2')
10o	1.30 (3H, t, *J* = 6.5, CH_3); 4.00 (2H, q, *J* = 6.5, OCH_2); 6.71 (2H, s, H-5',6'); 6.89 (1H, s, H-2'); 8.55 (1H, s, OH)
10p	3.75 (6H, s, $2OCH_3$); 6.38 (1H, s, H-4'); 6.54 (2H, s, H-2',6')
10q	3.75 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 6.68 (1H, s, H-3'); 6.96 (1H, s, H-6')
10r	6.98 (1H, dd, *J* = 5.4, *J* = 4.0, H-4'); 7.03 (1H, d, *J* = 4.0, H-3'); 7.41 (1H, d, *J* = 5.5, H-5')

EXPERIMENTAL

IR spectra of KBr disks were recorded on a Specord M-80 machine, ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker AMX-400 machine (400 MHz). Mass spectra were recorded with a Finnigan MAT-90 machine with an ionization energy of 70 eV. Silicagel, type L 40/100, was used for column chromatography. Reactions were monitored by TLC on Silufol UV-254 platess.

The keto ester **4** was obtained from the Acros company. The preparation of amidine **5** was described elsewhere [6].

7-Benzyl-2-pyrrolidin-1-yl-5,6,7,8-tetrahydro-3H-pyrido[3,4-*d*]-pyrimidin-4-one (6). Amidine hydrochloride **5** (22.4 g, 150 mmol) was added in small portions to a stirred solution of NaOEt, prepared from Na (7.0 g, 300 mmol) and absolute ethanol (300 ml). The keto ester **4** (35.5 g, 148 mmol) was then added dropwise, the mixture was boiled for 3 h, the solvent was removed in vacuum, and the residue was added to saturated aqueous solution of ammonium chloride. The residue which did not dissolve in water was filtered off, washed with water, methanol, and then ether, and dried in the air.

4-Amino-7-benzyl-2-pyrrolidin-1-yl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine [8]. Trifluromethane-sulfonic anhydride (4.92 g, 12 mmol) was added dropwise to a stirred suspension of compound **6** (5.58 g, 18 mmol) in pyridine (50 ml) cooled to -20°C, after which the reaction temperature was allowed to rise slowly to room temperature. The mixture was stirred for 20 min at room temperature and poured into water (500 ml). The precipitate was filtered off, washed with water, and dried in the air. The yield of triflate **7** was 4 g (53%). The triflate was dissolved in DMF (20 ml), potassium carbonate (6.7 g, 50 mmol) and 25% aqueous ammonia (5 ml) were added to the solution, which was then stirred at 100°C for 12 h, then cooled and diluted with water (200 ml). The product was extracted with dichloromethane (2 x 200 ml), the extract was dried over Na_2SO_4, and the solvent was removed in vacuum. The residue was recrystallized from ethyl acetate.

4-Amino-2-pyrrolidin-1-yl-5,6,7,8-tetrahydro[3,4-*d*]pyrimidine (9). A solution of compound **8** (15.45 g, 50 mmol) in methanol (300 ml) was hydrogenated under a pressure of 3 atm at 50°C in the presence of 10% palladium on charcoal (0.7 g). After absorption of the calculated amount of hydrogen (50 mmol), the catalyst was filtered from the solution which was then reduced to 80% in vacuum. The precipitate was filtered off, washed with ether and dried in the air.

4-Amino-7-arylmethyl-2-pyrrolidin-1-yl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidines 10a-r. To a solution of compound **9** in dry dichloromethane (10 ml), an aldehyde (2.6 mmol), triethylamine (1 ml, 8 mmol), and three drops of acetic acid were added, and the mixture was stirred at room temperature for 3 h. $NaHB(OAc)_3$ (1.25 g, 6 mmol) was added in small portions and the mixture was stirred at room temperature for 48 h. After the reaction was completed a saturated aqueous solution of Na_2CO_3 (20 ml) was added. The reaction product was extracted with dichloromethane (2×20 ml), the extract was washed with a saturated aqueous solution of $CaCl_2$ and dried over Na_2SO_4. The solvent was removed in vacuum, and the residue was chromatographed on a column of silica gel with 1:3 ethyl acetate–hexane as eluent.

The properties of compounds **6**, **8**, **9**, and **10a-r** are cited in Tables 1-5.

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