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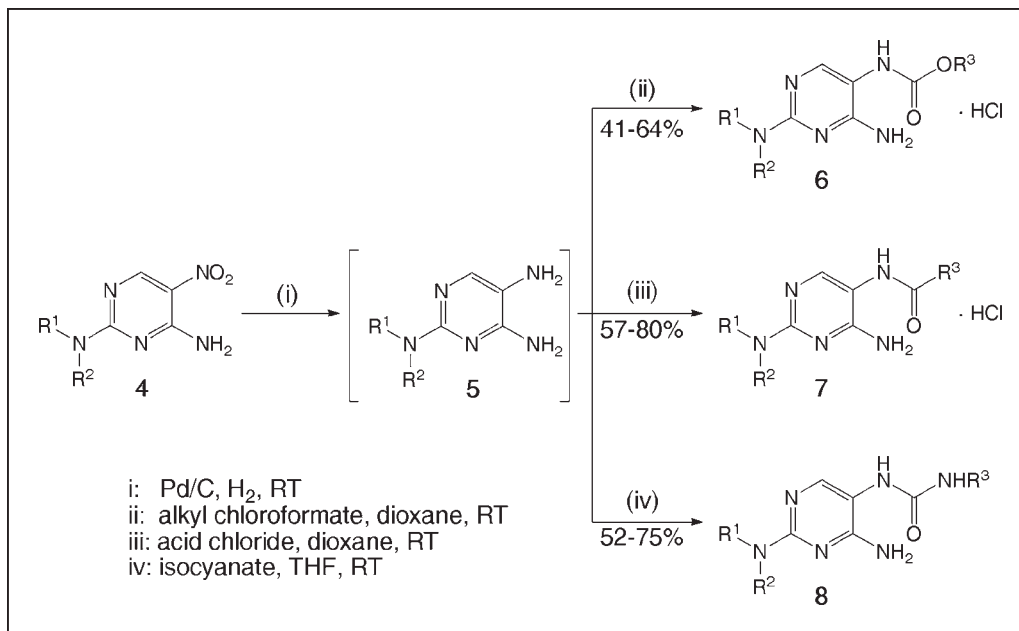
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The synthesis of novel N²-substituted 5-alkoxycarbonylamino-2,4-diaminopyrimidines, 5-acylamino-2,4-diaminopyrimidines, and 2,4-diamino-5-ureidopyrimidines as analogues of the analgesic flupirtine is described.

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INTRODUCTION

Flupirtine, a centrally acting nonopioid analgesic, has been effectively and safely used in therapy for over 20 years. From a subsequent drug design resulted retigabine (Fig. 1), the desaza analogue of flupirtine, as a highly active anticonvulsant, which is currently in late-stage development as a novel antiepileptic drug [1–3]. Both flupirtine and retigabine display their biological activity by activating neuronal KCNQ channels [4–10], which have been recently discovered as attractive targets for novel therapeutics against chronic and neuropathic pain, epilepsy, and other neuronal hyperexcitability disorders [11–14].

The development of simple and efficient methods for the preparation of new bioactive heterocyclic compounds represents an important challenge in organic and heterocyclic chemistry. As part of our research directed to novel polyaminosubstituted pyrimidine derivatives, we became interested in flupirtine/retigabine analogues with a pyrimidine core.

The synthesis of polysubstituted pyrimidine derivatives is usually achieved by (i) cyclization, (ii) ring transformation, (iii) aromatization, and (iv) substituent modification, and various efficient preparations have been published [15]. However, the synthesis of pyrimidine-2,4,5-triamine derivatives is still challenging because of the low stability of the latter. Pyrimidine-4,5-diamines with an enolizable group in the 2-position can easily form pyrimidopteridines by oxidative self-condensation [16,17]. Hence, there is a need for efficient synthetic procedures for the preparation of pyrimidine-2,4,5-triamine derivatives. We herein report on a facile and convenient synthesis of N⁵-acylated pyrimidine-2,4,5-triamines (6–8).

RESULTS AND DISCUSSION

Starting from commercially available 5-nitrouracil (1), chlorination [18], and subsequent ammonolysis [19] of 2 according to literature furnished 2-chloro-5-

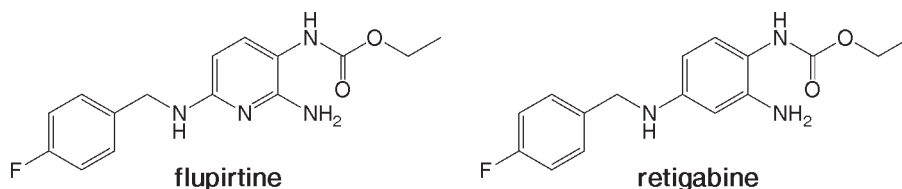
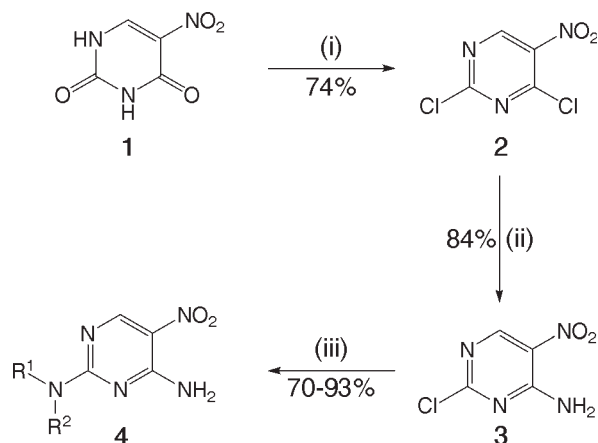


Figure 1. Chemical structure of flupirtine and retigabine.

Scheme 1. Synthesis of N²-substituted 5-nitropyrimidine-2,4-diamines (**4a–g**). Reagents and conditions: (i) POCl₃, *N,N*-dimethylaniline, reflux; (ii) NH₃, ethanol, 0°C; (iii) R¹R²NH, ethanol, reflux.



nitropyrimidin-4-amine (**3**). Treatment of **3** with 2 equiv. of primary or secondary amines in refluxing ethanol afforded the N²-substituted 5-nitropyrimidine-2,4-diamines **4a–g** in 70–93% yield (Scheme 1, Table 1).

Table 1
N²-Substituted 5-nitropyrimidine-2,4-diamines (**4a–g**) prepared.

Compound	R ¹	R ²	Yield (%)
4a	4-FC ₆ H ₄ CH ₂	H	81
4b	–(CH ₂) ₂ O(CH ₂) ₂ –	H	84
4c	4-MeC ₆ H ₄ CH ₂	H	93
4d	PhCH ₂ CH ₂	H	80
4e	Ph	H	92
4f	Bn	H	84
4g	Bn	Me	70

Catalytic hydrogenation of the key intermediates **4** delivered the corresponding pyrimidine-2,4,5-triamines **5** as labile compounds. All attempts to isolate the triaminopyrimidines **5** as free bases, hydrochlorides or sulfates failed. Consequently, the intermediates **5** were *in situ* reacted with alkyl chloroformates to produce the desired **6a–g** as stable, amorphous hydrochlorides in 41–64% overall yield (Scheme 2, Table 2). The N²-substituted 5-alkoxycarbonylamino-2,4-diaminopyrimidines (**6a–g**) are characterized by a strong (C=O)-absorption band at

Scheme 2. Synthesis of N²-substituted 5-alkoxycarbonylamino-2,4-diaminopyrimidines (**6a–h**), 5-acylamino-2,4-diaminopyrimidines (**7a–l**), and 2,4-diamino-5-ureidopyrimidines (**8a–h**). Reagents and conditions: (i) Pd/C, H₂, RT; (ii) alkyl chloroformate, dioxane, RT; (iii) acid chloride, dioxane, RT; (iv) isocyanate, THF, RT.

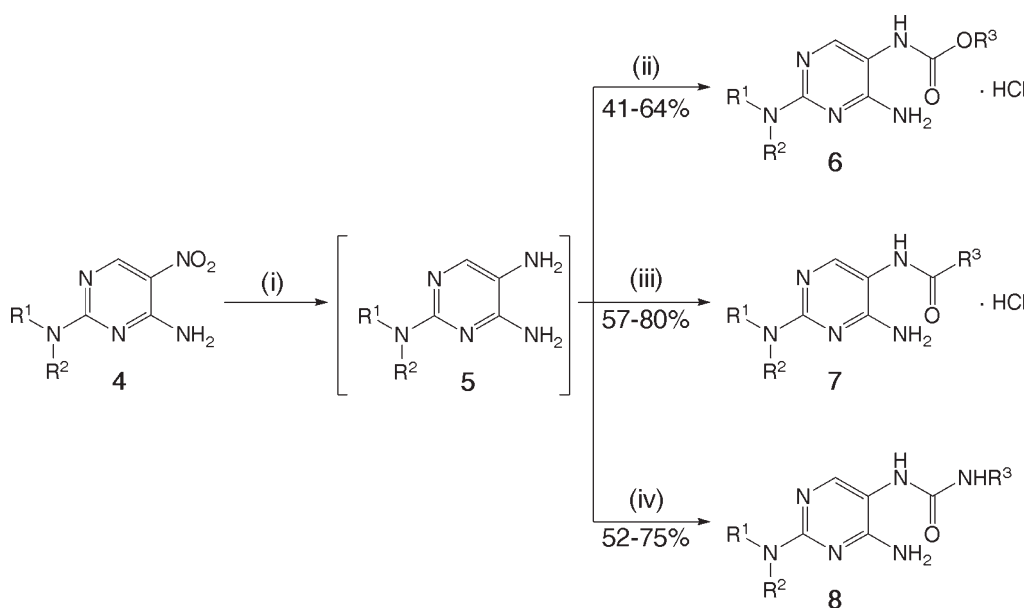


Table 2

N²-Substituted 5-alkoxycarbonylamino-2,4-diaminopyrimidines (**6a–h**), 5-acylamino-2,4-diamino-pyrimidines (**7a–l**), and 2,4-diamino-5-ureidopyrimidines (**8a–h**) prepared.

Compound	R ¹	R ²	R ³	Yield (%)
6a	4-FC ₆ H ₄ CH ₂	H	Et	59
6b	4-FC ₆ H ₄ CH ₂	H	ⁿ Pr	53
6c	4-FC ₆ H ₄ CH ₂	H	ⁿ Bu	64
6d	4-FC ₆ H ₄ CH ₂	H	ⁱ Bu	47
6e	4-MeC ₆ H ₄ CH ₂	H	Et	51
6f	4-MeC ₆ H ₄ CH ₂	H	ⁿ Pr	41
6g	4-MeC ₆ H ₄ CH ₂	H	ⁱ Bu	49
6h	—(CH ₂) ₂ O(CH ₂) ₂ —	—	Et	35 ^a
7a	4-FC ₆ H ₄ CH ₂	H	Me	64
7b	4-FC ₆ H ₄ CH ₂	H	Et	69
7c	4-FC ₆ H ₄ CH ₂	H	ⁿ Bu	70
7d	4-FC ₆ H ₄ CH ₂	H	c-(Pentyl)CH ₂	80
7e	4-FC ₆ H ₄ CH ₂	H	3-(MeO)Ph	58
7f	4-FC ₆ H ₄ CH ₂	H	3-Me-Ph	59
7g	Bn	H	Me	59
7h	Bn	Me	Et	62
7i	4-MeC ₆ H ₄ CH ₂	H	Me	61
7j	4-MeC ₆ H ₄ CH ₂	H	Et	63
7k	Ph	H	Et	57
7l	PhCH ₂ CH ₂	H	Et	63
8a	4-FC ₆ H ₄ CH ₂	H	Et	56
8b	4-FC ₆ H ₄ CH ₂	H	ⁿ Pr	59
8c	4-FC ₆ H ₄ CH ₂	H	c-Hexyl	75
8d	4-FC ₆ H ₄ CH ₂	H	Ph	52
8e	4-FC ₆ H ₄ CH ₂	H	3-Cl-Ph	54
8f	—(CH ₂) ₂ O(CH ₂) ₂ —	—	Et	72
8g	—(CH ₂) ₂ O(CH ₂) ₂ —	—	ⁿ Pr	71
8h	—(CH ₂) ₂ O(CH ₂) ₂ —	—	c-Hexyl	69

^a Isolated as free base.

1720–1750 cm^{−1} in the IR-spectrum. Instead of its hydrochloride, compound **6h** was isolated as free base. For this purpose, the alkoxyacylation was realized in the presence of triethylamine (see Experimental Section). After purification via column chromatography and subsequent crystallization from 1-propanol, **6h** was obtained in pure crystalline state, suitable for X-ray analysis. The X-ray crystal structure of **6h** proved the desired N⁵-acy-

lation unambiguously (Fig. 2) [20]. These findings are in accordance with the literature, which describes the 5-amino group as preferred position of (alkoxy)acylation for related polyaminosubstituted pyrimidine derivatives [15,21,22].

Analogously to the preparation of **6**, the reaction of the pyrimidine-2,4,5-triamines **5** with acid chlorides produced the desired N²-substituted 5-acylamino-2,4-diamino-pyrimidines **7a–l** as hydrochlorides in 57–80% yield (Scheme 2, Table 2). Compounds **7** display a sharp (C=O)-absorption band at 1670–1690 cm^{−1} in the IR-spectrum.

Similarly, several 5-ureidopyrimidine analogues were obtained according to Scheme 2 by *in situ* reaction of the intermediates **5** with isocyanates. A simple workup procedure followed by recrystallization from methanol provided the N²-substituted 2,4-diamino-5-ureidopyrimidines (**8a–h**) in 52–75% yield.

The structure of all synthesized compounds **6–8** were determined by IR-, ¹H-NMR, ¹³C-NMR-spectroscopy, and elemental analysis.

In summary, we have synthesized a variety of novel N²-substituted 5-alkoxycarbonylamino-2,4-diaminopyrimidines (**6**), 5-acylamino-2,4-diaminopyrimidines (**7**), and 2,4-diamino-5-ureidopyrimidines (**8**) as potentially bioactive pyrimidine analogues of flupirtine.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analysis were carried out with a Heraeus CHN-O-Rapid instrument. HRMS-FAB analysis were performed on a Micromass VG 70-250S spectrometer. IR spectra were recorded on a Varian 800 FT-IR. ¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and [D₆]DMSO as solvent. X-ray crystal analysis was performed on a Bruker Smart APEX CCD diffractometer with Mo K α -radiation at 100 K.

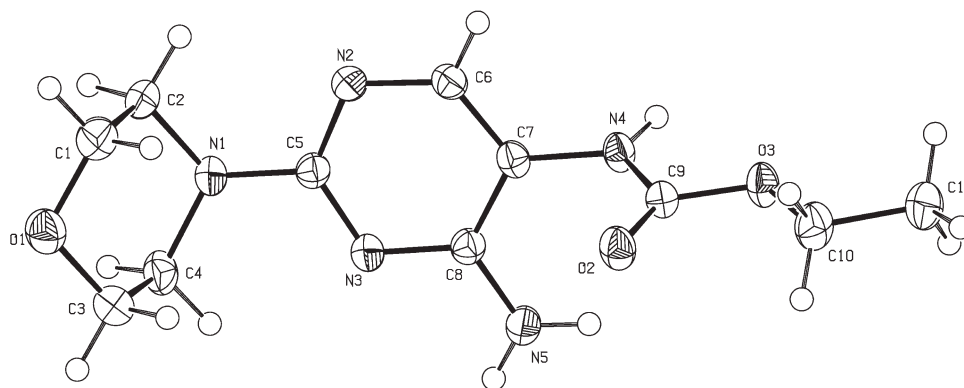


Figure 2. X-ray crystal structure of compound **6h**.

General procedure for the preparation of N²-substituted 5-nitropyrimidine-2,4-diamines (4a–g). The appropriate primary or secondary amine (20 mmol) was added to a suspension of 2-chloro-5-nitropyrimidin-4-amine (1.75 g, 10 mmol) in dry ethanol (40 mL). The mixture was refluxed for 2 h. The reaction was allowed to cool to room temperature; the separated solid was collected and recrystallized from methanol.

N²-(4-Fluorobenzyl)-5-nitropyrimidine-2,4-diamine (4a). This compound was obtained as yellow crystals in 81% yield, mp 195°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3469, 3282, 1560. δ_{H} (400 MHz, [D6]DMSO): 4.49 (1.5H, d, $J = 6.4$ Hz, ArCH₂), 4.55 (0.5H, d, $J = 6.4$ Hz, ArCH₂), 7.09–7.42 (4H, m, ArH), 7.91–8.25 (2H, m, NH₂), 8.37 (0.25H, t, $J = 6.9$ Hz, NH), 8.62 (0.75H, t, $J = 6.2$ Hz, NH), 8.86 (0.75H, s, ArH), 8.91 (0.25H, s, ArH); due to existence of rotamers some signals appear twice. δ_{C} (100 MHz, [D6]DMSO): 43.4, 43.5, 115.0 (d, $^2J_{\text{C-F}} = 21.4$ Hz), 119.5, 120.5, 129.0 (d, $^3J_{\text{C-F}} = 8.4$ Hz), 129.5 (d, $^3J_{\text{C-F}} = 7.6$ Hz), 135.2 (d, $^4J_{\text{C-F}} = 3.1$ Hz), 135.8 (d, $^4J_{\text{C-F}} = 3.1$ Hz), 157.1, 157.4, 157.7, 157.9, 161.2 (d, $^1J_{\text{C-F}} = 241.9$ Hz), 161.3 (d, $^1J_{\text{C-F}} = 242.6$ Hz), 161.8, 162.0; due to existence of rotamers some signals appear twice. HRMS-FAB: m/z [M + H]⁺ calcd. for C₁₁H₁₀FN₅O₂: 264.0897; found: 264.0893.

2-Morpholin-4-yl-5-nitropyrimidin-4-amine (4b). This compound was obtained as orange crystals in 84% yield, mp 215°C (lit. [23], 214°C). $\nu_{\max}$ (KBr)/cm⁻¹ 3469, 3280, 1560. δ_{H} (400 MHz, [D6]DMSO): 3.58–3.95 (8H, m, CH₂), 8.03 + 8.19 (2H, 2s, NH₂), 8.91 (1H, s, ArH). δ_{C} (100 MHz, [D6]DMSO): 44.1, 65.9, 119.5, 156.9, 157.3, 160.0. HRMS-FAB: m/z [M + H]⁺ calcd. for C₈H₁₁N₅O₃: 226.0940; found: 226.0942.

N²-(4-Methylbenzyl)-5-nitropyrimidine-2,4-diamine (4c). This compound was obtained as yellow crystals in 93% yield, mp 221°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3471, 3352, 1618, 1543. δ_{H} (400 MHz, [D6]DMSO): 2.27 (3H, s, CH₃), 4.48 (1.5H, d, $J = 6.4$ Hz, ArCH₂), 4.53 (0.5H, d, $J = 6.6$ Hz, ArCH₂), 7.06–7.26 (4H, m, ArH), 7.91–8.24 (2H, m, NH₂), 8.35 (0.25H, t, $J = 6.5$ Hz, NH), 8.60 (0.75H, t, $J = 6.2$ Hz, NH), 8.86 (0.75H, s, ArH), 8.91 (0.25H, s, ArH); due to existence of rotamers some signals appear twice. δ_{C} (100 MHz, [D6]DMSO): 20.6, 43.7, 43.9, 119.3, 120.3, 126.9, 127.4, 128.7, 135.7, 135.8, 135.9, 136.5, 157.0, 157.3, 157.6, 157.8, 161.8, 161.9; due to existence of rotamers some signals appear twice. HRMS-FAB: m/z [M + H]⁺ calcd. for C₁₂H₁₃N₅O₂: 260.1148; found: 260.1148.

5-Nitro-N²-(2-phenylethyl)pyrimidine-2,4-diamine (4d). This compound was obtained as yellow powder in 80% yield, mp 176°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3485, 3356, 1542. δ_{H} (400 MHz, [D6]DMSO): 2.79–2.91 (2H, m, CH₂CH₂Ph), 3.46–3.63 (2H, m, CH₂CH₂Ph), 7.14–7.38 (5H, m, ArH), 7.81–8.32 (3H, complex m, NH, and NH₂), 8.84 (0.75H, s, ArH), 8.92 (0.25H, s, ArH); due to existence of rotamers some signals appear twice. δ_{C} (100 MHz, [D6]DMSO): 34.5, 35.2, 42.3, 42.6, 119.2, 120.2, 126.0, 128.2, 128.6, 128.6, 139.2, 139.2, 156.9, 157.4, 157.4, 157.8, 161.6, 161.8; due to existence of rotamers some signals appear twice. HRMS-FAB: m/z [M + H]⁺ calcd. for C₁₂H₁₃N₅O₂: 260.1148; found: 260.1150.

5-Nitro-N²-phenylpyrimidine-2,4-diamine (4e). This compound was obtained as yellow powder in 92% yield, mp 239°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3467, 3344, 1560. δ_{H} (400 MHz, [D6]DMSO): 7.00–8.02 (5H, m, ArH), 8.21 + 8.53 (2H, 2s, NH₂), 8.99 (1H, s, ArH), 10.22 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 120.1, 123.0, 128.5, 139.1, 157.1, 157.2, 159.7.

HRMS-FAB: m/z [M + H]⁺ calcd. for C₁₀H₉N₅O₂: 232.0835; found: 232.0835.

N²-Benzyl-5-nitropyrimidine-2,4-diamine (4f). This compound was obtained as yellow crystals in 84% yield, mp 194°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3469, 3354, 1620, 1543. δ_{H} (400 MHz, [D6]DMSO): 4.54 (1.5H, d, $J = 6.6$ Hz, ArCH₂), 4.59 (0.5H, d, $J = 6.6$ Hz, ArCH₂), 7.19–7.38 (5H, m, ArH), 7.91–8.24 (2H, complex m, NH₂), 8.37 (0.25H, t, $J = 6.3$ Hz, NH), 8.62 (0.75H, t, $J = 6.2$ Hz, NH), 8.87 (0.75H, s, ArH), 8.91 (0.25H, s, ArH); due to existence of rotamers some signals appear twice. δ_{C} (100 MHz, [D6]DMSO): 44.0, 44.1, 119.4, 120.4, 126.7, 126.8, 126.9, 127.3, 128.2, 139.0, 139.5, 157.0, 157.4, 157.6, 157.9, 161.9, 162.0; due to existence of rotamers some signals appear twice. HRMS-FAB: m/z [M + H]⁺ calcd. for C₁₁H₁₁N₅O₂: 246.0991; found: 246.0995.

N²-Benzyl-N²-methyl-5-nitropyrimidine-2,4-diamine (4g). This compound was obtained as yellow powder in 70% yield, mp 84°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3433, 3280. δ_{H} (400 MHz, [D6]DMSO): 3.10 (1.5H, s, CH₃), 3.16 (1.5H, s, CH₃), 4.89 (1H, s, ArCH₂), 4.95 (1H, s, ArCH₂), 7.18–7.42 (5H, m, ArH), 7.97–8.32 (2H, m, NH₂), 8.94 (0.5H, s, ArH), 8.96 (0.5H, s, ArH); due to existence of rotamers some signals appear twice. δ_{C} (100 MHz, [D6]DMSO): 34.8, 35.1, 51.7, 51.8, 119.6, 119.7, 127.1, 127.2, 127.5, 128.5, 128.6, 128.8, 129.7, 137.1, 137.4, 156.8, 156.9, 157.3, 157.5, 161.0, 161.1; due to existence of rotamers some signals appear twice. HRMS-FAB: m/z [M + H]⁺ calcd. for C₁₂H₁₃N₅O₂: 260.1148; found: 260.1150.

General procedure for the preparation of N²-substituted 5-alkoxycarbonylamino-2,4-diaminopyrimidines (6a–g). A suspension of the respective N²-substituted 5-nitropyrimidine-2,4-diamine **4** (3 mmol) in dry dioxane (30 mL) was hydrogenated using a catalytic amount of 10% Pd/C (20 h/2 bar). Afterward, the suspension was filtered through a SPE tube RP-18 purchased from Supelco (Sigma-Aldrich, Munich, Germany) to remove the catalyst. A solution of the appropriate alkyl chloroformate (3.3 mmol) in dry dioxane (3 mL) was added to the filtrate dropwise over 5 min at room temperature. The reaction mixture was stirred for 30 min; the precipitate was collected and washed with diethyl ether (2 × 10 mL). Recrystallization from methanol/diethyl ether provided analytically pure products.

Ethyl {4-amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl} carbamate hydrochloride (6a). This compound was obtained as colorless solid in 59% yield, mp 140°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3349, 3192, 3104, 1744. δ_{H} (400 MHz, [D6]DMSO): 1.36 (3H, t, $J = 7.1$ Hz, CH₂CH₃), 4.43 (2H, q, $J = 7.0$ Hz, CH₂CH₃), 4.65 (2H, d, $J = 5.9$ Hz, ArCH₂), 5.15 (2H, s, NH₂), 7.11–7.53 (4H, m, ArH), 7.56 (1H, s, ArH), 8.91 (1H, s, NH), 9.28 (1H, s, NH), 9.45 (1H, t, $J = 6.0$ Hz, NH). δ_{C} (100 MHz, [D6]DMSO): 13.6, 44.0, 65.8, 114.9 (d, $^2J_{\text{C-F}} = 21.3$ Hz), 115.1, 121.6, 130.1 (d, $^3J_{\text{C-F}} = 8.1$ Hz), 134.1 (d, $^4J_{\text{C-F}} = 2.9$ Hz), 149.0, 150.4, 158.0, 161.3 (d, $^1J_{\text{C-F}} = 242.8$ Hz). Calc. for C₁₄H₁₇ClFN₅O₂: C, 49.20; H, 5.01; N, 20.49. Found: C, 49.13; H, 5.31; N, 20.44.

Propyl {4-amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl} carbamate hydrochloride (6b). This compound was obtained as colorless solid in 53% yield, mp 135°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3319, 3168, 3035, 1748. δ_{H} (400 MHz, [D6]DMSO): 0.99 (3H, t, $J = 7.4$ Hz, CH₂CH₂CH₃), 1.71–1.80 (2H, m, CH₂CH₂CH₃), 4.34 (2H, t, $J = 6.4$ Hz, CH₂CH₂CH₃), 4.65 (2H, d, $J = 5.8$ Hz, ArCH₂), 5.27 (2H, s, NH₂), 7.11–7.52

(4H, m, ArH), 7.56 (1H, s, ArH), 9.07 (1H, s, NH), 9.30 (1H, s, NH), 9.44 (1H, t, $J = 5.9$ Hz, NH). δ_C (100 MHz, [D6]DMSO): 10.1, 21.1, 44.0, 70.9, 114.9, 114.9 (d, $^2J_{C-F} = 21.4$ Hz), 121.1, 130.1 (d, $^3J_{C-F} = 8.4$ Hz), 134.1 (d, $^4J_{C-F} = 3.1$ Hz), 149.0, 150.8, 158.0, 161.3 (d, $^1J_{C-F} = 241.9$ Hz). Calc. for $C_{15}H_{19}ClFN_5O_2$: C, 50.64; H, 5.38; N, 19.68. Found: C, 50.24; H, 5.50; N, 19.67.

Butyl {4-amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl}carbamate hydrochloride (6c). This compound was obtained as colorless solid in 64% yield, mp 164°C. ν_{max} (KBr)/cm⁻¹ 3297, 3185, 3067, 1741. δ_H (400 MHz, [D6]DMSO): 0.93 (3H, t, $J = 7.4$ Hz, $CH_2CH_2CH_2CH_3$), 1.37–1.49 (2H, m, $CH_2CH_2CH_2CH_3$), 1.65–1.77 (2H, m, $CH_2CH_2CH_2CH_3$), 4.38 (2H, t, $J = 6.4$ Hz, $CH_2CH_2CH_2CH_3$), 4.65 (2H, d, $J = 5.9$ Hz, ArCH₂), 5.37 (2H, s, NH₂), 7.12–7.53 (4H, m, ArH), 9.43 (1H, t, $J = 5.9$ Hz, NH). δ_C (100 MHz, [D6]DMSO): 13.5, 18.4, 29.7, 44.0, 69.2, 114.9 (d, $^2J_{C-F} = 21.1$ Hz), 114.9, 121.7, 130.1 (d, $^3J_{C-F} = 8.3$ Hz), 134.2 (d, $^4J_{C-F} = 2.8$ Hz), 149.1, 150.5, 158.0, 161.4 (d, $^1J_{C-F} = 242.9$ Hz). Calc. for $C_{16}H_{21}ClFN_5O_2$: C, 51.96; H, 5.72; N, 18.94. Found: C, 51.82; H, 5.78; N, 19.07.

2-Methylpropyl {4-amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl}carbamate hydrochloride (6d). This compound was obtained as colorless solid in 47% yield, mp 149°C. ν_{max} (KBr)/cm⁻¹ 3295, 3183, 3063, 1742. δ_H (400 MHz, [D6]DMSO): 0.99 (6H, d, $J = 6.8$ Hz, $CH_2CH(CH_3)_2$), 1.99–2.15 (1H, m, $CH_2CH(CH_3)_2$), 4.17 (2H, d, $J = 6.5$ Hz, $CH_2CH(CH_3)_2$), 4.65 (2H, d, $J = 5.5$ Hz, ArCH₂), 5.47 (2H, s, NH₂), 7.10–7.55 (4H, m, ArH), 7.56 (1H, s, ArH), 9.33 (1H, s, NH), 9.36 (1H, s, NH), 9.44 (1H, t, $J = 5.5$ Hz, NH). δ_C (100 MHz, [D6]DMSO): 18.6, 27.0, 44.0, 74.9, 114.7, 114.9 (d, $^2J_{C-F} = 22.0$ Hz), 121.7, 130.1 (d, $^3J_{C-F} = 8.3$ Hz), 134.1 (d, $^4J_{C-F} = 2.8$ Hz), 149.1, 150.5, 158.0, 161.3 (d, $^1J_{C-F} = 242.9$ Hz). Calc. for $C_{16}H_{21}ClFN_5O_2$: C, 51.96; H, 5.72; N, 18.94. Found: C, 51.88; H, 5.90; N, 19.07.

Ethyl {4-amino-2-[(4-methylbenzyl)amino]pyrimidin-5-yl}carbamate hydrochloride (6e). This compound was obtained as colorless solid in 51% yield, mp 137°C. ν_{max} (KBr)/cm⁻¹ 3348, 3170, 3026, 1738. δ_H (400 MHz, [D6]DMSO): 1.36 (3H, t, $J = 7.1$ Hz, CH_2CH_3), 2.28 (3H, s, CH₃), 4.42 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 4.63 (2H, d, $J = 5.9$ Hz, ArCH₂), 5.27 (2H, s, NH₂), 7.05–7.39 (4H, m, ArH), 7.56 (1H, s, ArH), 9.07 (1H, s, NH), 9.27 (1H, s, NH), 9.36 (1H, t, $J = 5.6$ Hz, NH). δ_C (100 MHz, [D6]DMSO): 13.7, 20.7, 44.5, 65.8, 115.0, 121.6, 127.8, 128.8, 134.8, 136.3, 149.1, 150.5, 158.2. Calc. for $C_{15}H_{20}ClN_5O_2$: C, 53.33; H, 5.97; N, 20.73. Found: C, 53.20; H, 6.05; N, 20.60.

Propyl {4-amino-2-[(4-methylbenzyl)amino]pyrimidin-5-yl}carbamate hydrochloride (6f). This compound was obtained as colorless solid in 41% yield, mp 139°C. ν_{max} (KBr)/cm⁻¹ 3283, 3176, 3069, 1744. δ_H (400 MHz, [D6]DMSO): 0.98 (3H, t, $J = 7.4$ Hz, $CH_2CH_2CH_3$), 1.66–1.83 (2H, m, $CH_2CH_2CH_3$), 2.28 (3H, s, CH₃), 4.33 (2H, t, $J = 6.5$ Hz, $CH_2CH_2CH_3$), 4.63 (2H, d, $J = 5.8$ Hz, ArCH₂), 5.36 (2H, s, NH₂), 7.10–7.37 (4H, m, ArH), 7.56 (1H, s, ArH), 9.18 (1H, s, NH), 9.29 (1H, s, NH), 9.35 (1H, t, $J = 5.9$ Hz, NH). δ_C (100 MHz, [D6]DMSO): 10.1, 20.6, 21.1, 44.5, 71.0, 115.0, 121.5, 127.7, 128.8, 134.7, 136.3, 149.1, 150.6, 158.0. Calc. for $C_{16}H_{22}ClN_5O_2$: C, 54.62; H, 6.30; N, 19.90. Found: C, 54.28; H, 6.43; N, 19.92.

2-Methylpropyl {4-amino-2-[(4-methylbenzyl)amino]pyrimidin-5-yl}carbamate hydrochloride (6g). This compound was obtained as colorless solid in 49% yield, mp 150°C. ν_{max} (KBr)/cm⁻¹ 3286, 3179, 3061, 1745. δ_H (400 MHz, [D6]DMSO): 0.99 (6H, d, $J = 6.3$ Hz, $CH_2CH(CH_3)_2$), 1.98–2.14 (1H, m, $CH_2CH(CH_3)_2$), 2.28 (3H, s, CH₃), 4.16 (2H, d, $J = 6.0$ Hz, $CH_2CH(CH_3)_2$), 4.63 (2H, d, $J = 4.4$ Hz, ArCH₂), 5.42 (2H, s, NH₂), 7.05–7.41 (4H, m, ArH), 7.55 (1H, s, ArH), 9.24 (1H, s, NH), 9.31 (1H, s, NH), 9.36 (1H, t, $J = 5.7$ Hz, NH). δ_C (100 MHz, [D6]DMSO): 18.6, 20.6, 27.0, 44.5, 74.9, 114.8, 121.7, 127.8, 128.8, 134.7, 136.3, 149.1, 150.6, 158.0. Calc. for $C_{17}H_{24}ClN_5O_2$: C, 55.81; H, 6.61; N, 19.14. Found: C, 55.42; H, 6.68; N, 19.17.

Ethyl {4-amino-2-morpholin-4-ylpyrimidin-5-yl}carbamate (6h). A suspension of 2-morpholin-4-yl-5-nitropyrimidin-4-amine **4b** (0.676 g, 3 mmol) in dry dioxane (30 mL) was hydrogenated using a catalytic amount of 10% Pd/C (20 h/2 bar). Afterward, the suspension was filtered through a SPE tube RP-18 purchased from Supelco (Sigma-Aldrich, Munich, Germany) to remove the catalyst. To the filtrate was added triethylamine (0.4 g, 4 mmol). Next, a solution of ethyl chloroformate (0.358 g, 3.3 mmol) in dry dioxane (3 mL) was added dropwise over 5 min at room temperature. The reaction mixture was stirred for 30 min, and the triethylammonium chloride was separated by filtration and washed with THF. The combined organic layers were evaporated, and the crude product was purified by column chromatography using ethyl acetate/*n*-hexane (2:1) as eluent. The residue was recrystallized from dichloromethane/*n*-hexane. Crystals for X-ray analysis were obtained from 1-propanol.

Colorless solid, yield 35%, mp 161°C. ν_{max} (KBr)/cm⁻¹ 3487, 3296, 3202, 1716. δ_H (400 MHz, [D6]DMSO): 1.21 (3H, br. s, CH_2CH_3), 3.49–3.68 (8H, m, CH_2), 4.05 (2H, q, $J = 6.7$ Hz, CH_2CH_3), 6.34 (2H, s, NH₂), 7.72 (1H, s, ArH), 8.26 (1H, s, NH). δ_C (100 MHz, [D6]DMSO): 14.4, 44.1, 60.1, 66.0, 107.5, 152.6, 155.1, 159.3, 159.5. Calc. for $C_{11}H_{17}N_5O_3$: C, 49.43; H, 6.41; N, 26.20. Found: C, 49.37; H, 6.55; N, 25.87.

General procedure for the preparation of N²-substituted 5-acylamino-2,4-diaminopyrimidines (7a–l). A suspension of the respective N²-substituted 5-nitropyrimidine-2,4-diamine **4** (3 mmol) in dry dioxane (30 mL) was hydrogenated using a catalytic amount of 10% Pd/C (20 h/2 bar). Afterward, the suspension was filtered through a SPE tube RP-18 purchased from Supelco (Sigma-Aldrich, Munich, Germany) to remove the catalyst. A solution of the appropriate acid chloride (3.3 mmol) in dry dioxane (3 mL) was added to the filtrate dropwise over 5 min at room temperature. The reaction mixture was stirred for 30 min; the precipitate was collected and washed with diethyl ether (2 × 10 mL). Recrystallization from methanol/diethyl ether provided analytically pure products.

N-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]acetamide hydrochloride (7a). This compound was obtained as colorless solid in 64% yield, mp 239°C. ν_{max} (KBr)/cm⁻¹ 3294, 3174, 1654. δ_H (400 MHz, [D6]DMSO): 2.05 (3H, s, CH₃), 4.53 (2H, d, $J = 5.9$ Hz, ArCH₂), 7.10–7.49 (4H, m, ArH), 8.00 (1H, s, ArH), 8.38 (1H, s, NH), 8.57 (2H, s, NH₂), 9.65 (1H, s, NH), 12.39 (1H, s, NH). δ_C (100 MHz, [D6]DMSO): 23.0, 43.0, 109.1, 115.1 (d, $^2J_{C-F} = 21.4$ Hz), 129.4 (d, $^3J_{C-F} = 8.4$ Hz), 134.2, 136.4, 151.7, 160.9, 161.3 (d, $^1J_{C-F} = 242.6$ Hz), 169.6. Calc. for $C_{13}H_{15}ClFN_5O$: C, 50.09; H, 4.85; N, 22.46. Found: C, 50.00; H, 5.04; N, 22.43.

***N*-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]propanamide hydrochloride (7b).** This compound was obtained as colorless solid in 69% yield, mp 242°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3293, 3171, 1676. δ_{H} (400 MHz, [D6]DMSO): 1.05 (3H, t, J = 7.5 Hz, CH₂CH₃), 2.38 (2H, q, J = 7.5 Hz, CH₂CH₃), 4.53 (2H, d, J = 5.9 Hz, ArCH₂), 7.14–7.46 (4H, m, ArH), 8.00 (1H, s, ArH), 8.33 (1H, s, NH), 8.53 (2H, s, NH₂), 9.51 (1H, s, NH), 12.33 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 9.2, 28.5, 43.0, 109.2, 115.1 (d, $^2J_{\text{C-F}}$ = 21.3 Hz), 129.5 (d, $^3J_{\text{C-F}}$ = 8.1 Hz), 134.3, 136.1, 151.6, 160.8, 161.3 (d, $^1J_{\text{C-F}}$ = 242.8 Hz), 173.3. Calc. for C₁₄H₁₇ClFN₅O: C, 51.62; H, 5.26; N, 21.50. Found: C, 51.53; H, 5.42; N, 21.49.

***N*-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]pentanamide hydrochloride (7c).** This compound was obtained as colorless solid in 70% yield, mp 215°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3312, 3150, 1671. δ_{H} (400 MHz, [D6]DMSO): 0.89 (3H, t, J = 7.3 Hz, CH₂CH₂CH₂CH₃), 1.26–1.37 (2H, m, CH₂CH₂CH₂CH₃), 1.49–1.60 (2H, m, CH₂CH₂CH₂CH₃), 2.40 (2H, t, J = 7.6 Hz, CH₂CH₂CH₂CH₃), 4.53 (2H, d, J = 6.1 Hz, ArCH₂), 7.12–7.49 (4H, m, ArH), 8.07 (1H, s, ArH), 8.46 (1H, s, NH), 8.57 (2H, s, NH₂), 9.68 (1H, s, NH), 12.44 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 13.7, 21.7, 26.9, 35.1, 43.0, 109.3, 115.1 (d, $^2J_{\text{C-F}}$ = 21.4 Hz), 129.5 (d, $^3J_{\text{C-F}}$ = 7.6 Hz), 134.3, 135.7, 151.5, 160.6, 161.3 (d, $^1J_{\text{C-F}}$ = 242.6 Hz), 172.5. Calc. for C₁₆H₂₁ClFN₅O: C, 54.31; H, 5.98; N, 19.79. Found: C, 54.00; H, 6.27; N, 20.10.

***N*-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]-2-cyclopentylacetamide hydrochloride (7d).** This compound was obtained as colorless solid in 80% yield, mp 228°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3296, 3188, 3122, 1684. δ_{H} (400 MHz, [D6]DMSO): 1.07–1.79 (8H, m, CH₂), 2.12–2.28 (1H, m, CH), 2.40 (2H, d, J = 7.4 Hz, CH₂), 4.53 (2H, d, J = 5.9 Hz, ArCH₂), 7.12–7.48 (4H, m, ArH), 8.09 (1H, s, ArH), 8.45–8.53 (3H, m, NH and NH₂), 9.67 (1H, s, NH), 12.40 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 24.4, 31.8, 36.3, 41.4, 43.0, 109.3, 115.1 (d, $^2J_{\text{C-F}}$ = 20.6 Hz), 129.5 (d, $^3J_{\text{C-F}}$ = 7.6 Hz), 134.3, 135.5, 151.5, 160.5, 161.3 (d, $^1J_{\text{C-F}}$ = 242.6 Hz), 172.1. Calc. for C₁₈H₂₃ClFN₅O: C, 56.91; H, 6.10; N, 18.44. Found: C, 56.88; H, 6.28; N, 18.29.

***N*-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]-3-methoxybenzamide hydrochloride (7e).** This compound was obtained as colorless solid in 58% yield, mp 262°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3355, 3288, 3156, 1668. δ_{H} (400 MHz, [D6]DMSO): 3.84 (3H, s, CH₃), 4.56 (2H, d, J = 5.9 Hz, ArCH₂), 7.13–7.62 (8H, m, ArH), 7.96 (1H, s, ArH), 8.24 + 8.57 (2H, 2s, NH₂), 8.71 (1H, s, NH), 9.88 (1H, s, NH), 12.65 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 43.2, 55.4, 108.6, 113.3, 115.1 (d, $^2J_{\text{C-F}}$ = 21.3 Hz), 117.6, 120.4, 129.3, 129.6 (d, $^3J_{\text{C-F}}$ = 8.1 Hz), 134.3, 134.9, 139.3, 152.3, 159.0, 161.4 (d, $^1J_{\text{C-F}}$ = 242.8 Hz), 162.0, 166.3. Calc. for C₁₉H₁₉ClFN₅O₂: C, 56.51; H, 4.74; N, 17.34. Found: C, 56.38; H, 4.77; N, 17.29.

***N*-[4-amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]-3-methylbenzamide hydrochloride (7f).** This compound was obtained as colorless solid in 59% yield, mp 266°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3262, 1686. δ_{H} (400 MHz, [D6]DMSO): 2.39 (3H, s, CH₃), 4.56 (2H, d, J = 6.1 Hz, ArCH₂), 7.13–7.90 (8H, m, ArH), 7.95 (1H, s, ArH), 8.21 + 8.55 (2H, 2s, NH₂), 8.68 (1H, s, NH), 9.79 (1H, s, NH), 12.61 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 20.8, 43.1, 108.6, 115.1 (d, $^2J_{\text{C-F}}$ = 21.4 Hz), 125.2, 128.0, 128.5, 129.5 (d, $^3J_{\text{C-F}}$ = 8.4 Hz), 132.3, 133.4,

134.2, 137.3, 139.2, 152.2, 161.3 (d, $^1J_{\text{C-F}}$ = 242.6 Hz), 162.0, 166.6. Calc. for C₁₉H₁₉ClFN₅O: C, 58.84; H, 4.94; N, 18.06. Found: C, 58.70; H, 5.03; N, 18.19.

***N*-[4-Amino-2-(benzylamino)pyrimidin-5-yl]acetamide hydrochloride (7g).** This compound was obtained as colorless solid in 59% yield, mp 235°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3388, 3155, 1697. δ_{H} (400 MHz, [D6]DMSO): 2.06 (3H, s, CH₃), 4.56 (2H, d, J = 6.0 Hz, ArCH₂), 7.24–7.40 (5H, m, ArH), 8.03 (1H, s, ArH), 8.42 (1H, s, NH), 8.49–8.68 (2H, m, NH₂), 9.71 (1H, s, NH), 12.43 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 23.1, 43.8, 109.2, 127.2, 127.3, 128.4, 136.3, 138.1, 151.9, 160.9, 169.7. Calc. for C₁₃H₁₆ClN₅O: C, 53.15; H, 5.49; N, 23.84. Found: C, 52.88; H, 5.44; N, 23.93.

***N*-[4-Amino-2-(benzyl(methyl)amino)pyrimidin-5-yl]propanamide hydrochloride (7h).** This compound was obtained as colorless solid in 62% yield, mp 230°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3346, 3266, 3185, 1685. δ_{H} (400 MHz, [D6]DMSO): 1.06 (3H, t, J = 7.6 Hz, CH₂CH₃), 2.40 (2H, q, J = 7.4 Hz, CH₂CH₃), 3.10 (3H, s, CH₃), 4.84 (2H, s, ArCH₂), 7.26–7.46 (5H, m, ArH), 8.00 (1H, s, ArH), 8.34 + 8.50 (2H, 2s, NH₂), 9.55 (1H, s, NH), 12.42 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 9.2, 28.6, 35.5, 52.1, 109.8, 127.3, 127.4, 128.5, 134.9, 136.2, 150.9, 159.8, 173.2. Calc. for C₁₅H₂₀ClN₅O: C, 55.99; H, 6.26; N, 21.76. Found: C, 55.76; H, 6.36; N, 21.70.

***N*-[4-Amino-2-[(4-methylbenzyl)amino]pyrimidin-5-yl]acetamide hydrochloride (7i).** This compound was obtained as colorless solid in 61% yield, mp 238°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3399, 3142, 1695. δ_{H} (400 MHz, [D6]DMSO): 2.05 (3H, s, CH₃), 2.28 (3H, s, CH₃), 4.50 (2H, d, J = 6.1 Hz, ArCH₂), 7.12–7.28 (4H, m, ArH), 7.99 (1H, s, ArH), 8.36 (1H, s, NH), 8.54 (2H, s, NH₂), 9.65 (1H, s, NH), 12.32 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 20.6, 23.0, 43.5, 109.1, 127.3, 128.9, 134.9, 136.3, 151.8, 161.0, 169.6. Calc. for C₁₄H₁₈ClN₅O: C, 54.63; H, 5.89; N, 22.75. Found: C, 54.34; H, 6.03; N, 22.67.

***N*-[4-Amino-2-[(4-methylbenzyl)amino]pyrimidin-5-yl]propanamide hydrochloride (7j).** This compound was obtained as colorless solid in 63% yield, mp 241°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3394, 3261, 3129, 1694. δ_{H} (400 MHz, [D6]DMSO): 1.04 (3H, t, J = 7.6 Hz, CH₂CH₃), 2.28 (3H, s, CH₃), 2.38 (2H, q, J = 7.5 Hz, CH₂CH₃), 4.50 (2H, d, J = 5.9 Hz, ArCH₂), 7.12–7.28 (4H, m, ArH), 7.99 (1H, s, ArH), 8.31 (1H, s, NH), 8.49 (2H, s, NH₂), 9.50 (1H, s, NH), 12.26 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 9.2, 20.6, 28.5, 43.5, 109.2, 127.3, 128.9, 135.0, 136.0, 136.3, 151.7, 160.8, 173.2. Calc. for C₁₅H₂₀ClN₅O: C, 55.99; H, 6.26; N, 21.76. Found: C, 55.72; H, 6.42; N, 21.72.

***N*-[4-Amino-2-(phenylamino)pyrimidin-5-yl]propanamide hydrochloride (7k).** This compound was obtained as colorless solid in 57% yield, mp 257°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3314, 3162, 1676. δ_{H} (400 MHz, [D6]DMSO): 1.07 (3H, t, J = 7.5 Hz, CH₂CH₃), 2.43 (2H, q, J = 7.4 Hz, CH₂CH₃), 7.10–7.69 (5H, m, ArH), 8.22 (1H, s, ArH), 8.68 (2H, s, NH₂), 9.73 (1H, s, NH), 10.57 (1H, s, NH), 12.21 (1H, s, NH). δ_{C} (100 MHz, [D6]DMSO): 9.3, 28.6, 110.2, 121.4, 124.3, 129.0, 136.2, 137.3, 149.6, 160.5, 173.3. Calc. for C₁₃H₁₆ClN₅O: C, 53.15; H, 5.49; N, 23.84. Found: C, 53.28; H, 5.65; N, 24.13.

***N*-[4-Amino-2-[(2-phenylethyl)amino]pyrimidin-5-yl]propanamide hydrochloride (7l).** This compound was obtained as colorless solid in 63% yield, mp 249°C. $\nu_{\max}$ (KBr)/cm⁻¹ 3387, 3314, 3118, 1696. δ_{H} (400 MHz, [D6]DMSO): 1.05 (3H, t, J = 7.5 Hz, CH₂CH₃), 2.40 (2H, q, J = 7.6 Hz, CH₂CH₃), 2.85

(2H, t, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{Ph}$), 3.49–3.59 (2H, m, $\text{CH}_2\text{CH}_2\text{Ph}$), 7.19–7.35 (5H, m, ArH), 8.02 (1H, s, ArH), 8.40 (1H, s, NH), 8.54 + 8.12 (2H, 2s, NH_2), 9.63 (1H, s, NH), 12.24 (1H, s, NH). δ_{C} (100 MHz, $[\text{D}_6]\text{DMSO}$): 9.2, 28.5, 34.5, 42.0, 109.1, 126.2, 128.3, 128.7, 136.0, 138.7, 151.5, 160.7, 173.2. Calc. for $\text{C}_{15}\text{H}_{20}\text{ClN}_5\text{O}$: C, 55.99; H, 6.26; N, 21.76. Found: C, 55.66; H, 6.45; N, 21.73.

General procedure for the preparation of N^2 -substituted 2,4-diamino-5-ureidopyrimidines (8a–h). A suspension of the respective N^2 -substituted 5-nitropyrimidine-2,4-diamine **4** (3 mmol) in dry THF (30 mL) was hydrogenated using a catalytic amount of 10% Pd/C (15 h/2 bar). Afterward, the suspension was filtered through a SPE tube RP-18 purchased from Supelco (Sigma-Aldrich, Munich, Germany) to remove the catalyst. A solution of the appropriate isocyanate (3.3 mmol) in dry THF (3 mL) was added to the filtrate dropwise over 5 min at room temperature. The reaction mixture was stirred for 1 h and subsequently stored in a freezer for 5 h. The precipitate was collected and recrystallized from methanol to afford compounds **8a–h** as solid products.

1-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]-3-ethylurea (8a). This compound was obtained as colorless solid in 56% yield, mp 202°C. ν_{max} (KBr)/ cm^{-1} 3342, 2923, 2854, 1637, 1603. δ_{H} (400 MHz, $[\text{D}_6]\text{DMSO}$): 1.01 (3H, t, $J = 7.3$ Hz, CH_2CH_3), 2.94–3.18 (2H, m, CH_2CH_3), 4.39 (2H, d, $J = 6.4$ Hz, ArCH_2), 5.95 (1H, t, $J = 5.5$ Hz, NH), 6.07 (2H, s, NH_2), 6.88 (1H, t, $J = 6.4$ Hz, NH), 7.04 (1H, s, NH), 7.06–7.37 (4H, m, ArH), 7.55 (1H, s, ArH). δ_{C} (100 MHz, $[\text{D}_6]\text{DMSO}$): 15.5, 34.3, 43.4, 108.3, 114.7 (d, $^2J_{\text{C-F}} = 21.4$ Hz), 128.9 (d, $^3J_{\text{C-F}} = 7.6$ Hz), 137.4 (d, $^4J_{\text{C-F}} = 3.1$ Hz), 153.4, 156.8, 160.0, 160.6, 160.9 (d, $^1J_{\text{C-F}} = 241.1$ Hz). Calc. for $\text{C}_{14}\text{H}_{17}\text{FN}_6\text{O}$: C, 55.25; H, 5.63; N, 27.61. Found: C, 55.00; H, 5.80; N, 27.34.

1-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]-3-propylurea (8b). This compound was obtained as colorless solid in 59% yield, mp 201°C. ν_{max} (KBr)/ cm^{-1} 3448, 3344, 3232, 2964, 1637, 1604. δ_{H} (400 MHz, $[\text{D}_6]\text{DMSO}$): 0.84 (3H, t, $J = 7.4$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.34–1.47 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.92–3.03 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.39 (2H, d, $J = 6.4$ Hz, ArCH_2), 5.98 (1H, t, $J = 5.6$ Hz, NH), 6.05 (2H, s, NH_2), 6.88 (1H, t, $J = 6.0$ Hz, NH), 7.03 (1H, s, NH), 7.06–7.37 (4H, m, ArH), 7.55 (1H, s, ArH). δ_{C} (100 MHz, $[\text{D}_6]\text{DMSO}$): 11.2, 23.0, 41.2, 43.3, 108.3, 114.6 (d, $^2J_{\text{C-F}} = 21.3$ Hz), 128.8 (d, $^3J_{\text{C-F}} = 8.1$ Hz), 137.3 (d, $^4J_{\text{C-F}} = 2.9$ Hz), 153.2, 156.8, 159.9, 160.4, 160.8 (d, $^1J_{\text{C-F}} = 241.4$ Hz). Calc. for $\text{C}_{15}\text{H}_{19}\text{FN}_6\text{O}$: C, 56.59; H, 6.02; N, 26.40. Found: C, 56.35; H, 6.04; N, 26.41.

1-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]-3-cyclohexylurea (8c). This compound was obtained as colorless solid in 75% yield, mp 210°C. ν_{max} (KBr)/ cm^{-1} 3341, 3288, 2927, 2856, 1635, 1604. δ_{H} (400 MHz, $[\text{D}_6]\text{DMSO}$): 1.06–1.86 (10H, m, CH_2), 3.32–3.47 (1H, m, CH), 4.39 (2H, d, $J = 6.4$ Hz, ArCH_2), 5.86 (1H, d, $J = 7.6$ Hz, NH), 6.03 (2H, s, NH_2), 6.86 (1H, t, $J = 6.1$ Hz, NH), 6.97 (1H, s, NH), 7.04–7.36 (4H, m, ArH), 7.55 (1H, s, ArH). δ_{C} (100 MHz, $[\text{D}_6]\text{DMSO}$): 24.5, 25.3, 33.1, 43.3, 48.1, 108.4, 114.7 (d, $^2J_{\text{C-F}} = 21.4$ Hz), 128.8 (d, $^3J_{\text{C-F}} = 7.6$ Hz), 137.4 (d, $^4J_{\text{C-F}} = 3.1$ Hz), 153.0, 156.0, 159.8, 160.3, 160.9 (d, $^1J_{\text{C-F}} = 241.1$ Hz). Calc. for $\text{C}_{18}\text{H}_{23}\text{FN}_6\text{O}$: C, 60.32; H, 6.47; N, 23.45. Found: C, 60.04; H, 6.52; N, 23.45.

1-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]-3-phenylurea (8d). This compound was obtained as colorless solid in 52% yield, mp 198°C. ν_{max} (KBr)/ cm^{-1} 3345, 3291, 1646,

1610. δ_{H} (400 MHz, $[\text{D}_6]\text{DMSO}$): 4.41 (2H, d, $J = 6.4$ Hz, ArCH_2), 6.24 (2H, s, NH_2), 6.83–7.49 (11H, complex m, ArH and 2 NH), 7.61 (1H, s, ArH), 8.56 (1H, s, NH). δ_{C} (100 MHz, $[\text{D}_6]\text{DMSO}$): 43.3, 107.3, 114.7 (d, $^2J_{\text{C-F}} = 21.1$ Hz), 117.9, 121.3, 128.6, 128.9 (d, $^3J_{\text{C-F}} = 7.3$ Hz), 137.4 (d, $^4J_{\text{C-F}} = 2.8$ Hz), 140.2, 154.1, 154.2, 160.3, 160.8, 160.9 (d, $^1J_{\text{C-F}} = 241.9$ Hz). Calc. for $\text{C}_{18}\text{H}_{17}\text{FN}_6\text{O}$: C, 61.36; H, 4.86; N, 23.85. Found: C, 61.40; H, 5.22; N, 23.96.

1-[4-Amino-2-[(4-fluorobenzyl)amino]pyrimidin-5-yl]-3-(3-chlorophenyl)urea (8e). This compound was obtained as colorless solid in 54% yield, mp 183°C. ν_{max} (KBr)/ cm^{-1} 3296, 1654, 1596. δ_{H} (400 MHz, $[\text{D}_6]\text{DMSO}$): 4.41 (2H, d, $J = 6.1$ Hz, ArCH_2), 6.26 (2H, s, NH_2), 6.86–7.42 (9H, complex m, ArH and 2 NH), 7.60 (1H, s, ArH), 7.68 (1H, s, ArH), 8.80 (1H, s, NH). δ_{C} (100 MHz, $[\text{D}_6]\text{DMSO}$): 43.2, 106.8, 114.6 (d, $^2J_{\text{C-F}} = 20.6$ Hz), 116.3, 117.3, 120.8, 130.1, 128.8 (d, $^3J_{\text{C-F}} = 8.4$ Hz), 132.9, 137.3 (d, $^4J_{\text{C-F}} = 3.1$ Hz), 141.8, 154.0, 154.2, 160.3, 160.8, 160.8 (d, $^1J_{\text{C-F}} = 241.1$ Hz). Calc. for $\text{C}_{18}\text{H}_{16}\text{ClFN}_6\text{O}$: C, 55.89; H, 4.17; N, 21.73. Found: C, 55.49; H, 4.30; N, 21.41.

1-[4-Amino-2-morpholin-4-ylpyrimidin-5-yl]-3-ethylurea (8f). This compound was obtained as colorless solid in 72% yield, mp >300°C. ν_{max} (KBr)/ cm^{-1} 3469, 3319, 2971, 2857, 1629. δ_{H} (400 MHz, $[\text{D}_6]\text{DMSO}$): 1.01 (3H, t, $J = 7.1$ Hz, CH_2CH_3), 2.98–3.13 (2H, m, CH_2CH_3), 3.47–3.73 (8H, m, CH_2), 5.96 (1H, t, $J = 5.3$ Hz, NH), 6.19 (2H, s, NH_2), 7.12 (1H, s, NH), 7.66 (1H, s, ArH). δ_{C} (100 MHz, $[\text{D}_6]\text{DMSO}$): 15.4, 34.2, 44.2, 66.0, 108.5, 152.8, 156.6, 159.1, 160.1. Calc. for $\text{C}_{11}\text{H}_{18}\text{N}_6\text{O}_2$: C, 49.61; H, 6.81; N, 31.56. Found: C, 49.56; H, 6.92; N, 31.67.

1-[4-Amino-2-morpholin-4-ylpyrimidin-5-yl]-3-propylurea (8g). This compound was obtained as colorless solid in 71% yield, mp >300°C. ν_{max} (KBr)/ cm^{-1} 3448, 3302, 2965, 2863, 1631. δ_{H} (400 MHz, $[\text{D}_6]\text{DMSO}$): 0.84 (3H, t, $J = 7.4$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.32–1.48 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.93–3.05 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.46–3.72 (8H, m, CH_2), 5.99 (1H, t, $J = 5.6$ Hz, NH), 6.19 (2H, s, NH_2), 7.11 (1H, s, NH), 7.66 (1H, s, ArH). δ_{C} (100 MHz, $[\text{D}_6]\text{DMSO}$): 11.4, 23.1, 41.3, 44.3, 66.1, 108.7, 152.8, 156.8, 159.2, 160.2. Calc. for $\text{C}_{12}\text{H}_{20}\text{N}_6\text{O}_2$: C, 51.42; H, 7.19; N, 29.98. Found: C, 51.42; H, 7.28; N, 29.85.

1-[4-Amino-2-morpholin-4-ylpyrimidin-5-yl]-3-cyclohexylurea (8h). This compound was obtained as colorless solid in 69% yield, mp >300°C. ν_{max} (KBr)/ cm^{-1} 3447, 3345, 3277, 2948, 2924, 2853, 1605. δ_{H} (400 MHz, $[\text{D}_6]\text{DMSO}$): 1.04–1.88 (10H, m, CH_2), 3.32–3.47 (1H, m, CH), 3.48–3.71 (8H, m, CH_2), 5.87 (1H, d, $J = 7.9$ Hz, NH), 6.16 (2H, s, NH_2), 7.06 (1H, s, NH), 7.68 (1H, s, ArH). δ_{C} (100 MHz, $[\text{D}_6]\text{DMSO}$): 24.6, 25.3, 33.1, 44.3, 48.1, 66.1, 108.8, 152.3, 155.9, 159.1, 160.0. Calc. for $\text{C}_{15}\text{H}_{24}\text{N}_6\text{O}_2$: C, 56.23; H, 7.55; N, 26.23. Found: C, 56.04; H, 7.67; N, 25.95.

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REFERENCES AND NOTES

- [1] Porter, R. J.; Nohria, V.; Rundfeldt, C. *Neurotherapeutics* 2007, 4, 149.
- [2] Blackburn-Munro, G.; Dalby-Brown, W.; Mirza, N. R.; Mikkelsen, J. D.; Blackburn-Munro, R. E. *CNS Drug Rev* 2005, 11, 1.

- [3] Chung, S. S. *Curr Drug Ther* 2010, 5, 10.
- [4] Rundfeldt, C.; Netzer, R. *Neurosci Lett* 2000, 282, 73.
- [5] Main, M. J.; Cryan, J. E.; Dupere, J. R.; Cox, B.; Clare, J. J.; Burbidge, S. A. *Mol Pharmacol* 2000, 58, 253.
- [6] Wickenden, A. D.; Yu, W.; Zou, A.; Jegla, T.; Wagoner, P. K. *Mol Pharmacol* 2000, 58, 591.
- [7] Methling, K.; Reszka, P.; Lalk, M.; Vrana, O.; Scheuch, E.; Siegmund, W.; Terhaag, B.; Bednarski, P. *J. Drug Metab Dispos* 2009, 37, 479.
- [8] Rundfeldt, C. *Eur J Pharmacol* 1997, 336, 243.
- [9] Kornhuber, J.; Bleich, S.; Wiltfang, J.; Maler, M.; Parsons, C. G. *J Neural Transm* 1999, 106, 857.
- [10] Kornhuber, J.; Maler, M.; Wiltfang, J.; Bleich, S.; Degner, D.; Ruther, E. *Fortschr Neurol Psychiatr* 1999, 67, 466.
- [11] Gribkoff, V. K. *Expert Opin Ther Targets* 2003, 7, 737.
- [12] Gribkoff, V. K. *Expert Opin Ther Targets* 2008, 12, 565.
- [13] Wu, Y.-J.; Dworetzky, S. I. *Curr Med Chem* 2005, 12, 453.
- [14] Munro, G.; Dalby-Brown, W. *J Med Chem* 2007, 50, 2576.
- [15] For an excellent review see: von Angerer, S. In *Science of Synthesis*; Yamamoto, Y., Ed.; Thieme: Stuttgart, 2004; Vol. 16, pp 379–572.
- [16] Goldner, H.; Carstens, E. *J Prakt Chem (Leipzig)* 1961, 12, 242.
- [17] Taylor, E. C., Jr.; Loux, H. M.; Falco, E. A.; Hitchings, G. H. *J Am Chem Soc* 1955, 77, 2243.
- [18] Whittaker, N.; Jones, T. S. *G. J Chem Soc* 1951, 1565.
- [19] Isay, O. *Ber Dtsch Chem Ges* 1906, 39, 250.
- [20] Crystallographic data for compound **6h** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 751329. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Selected crystal data for compound **6h**: $C_{11}H_{17}N_5O_3$, $M_r = 267.30$, orthorhombic, $Pbca$, $a = 12.9475$ (10), $b = 7.4897$ (6), $c = 27.029$ (2) Å; $V = 2621.1$ (4) Å³, $T = 153$ K, $Z = 8$, $D_x = 1.334$ Mg m⁻³, $\mu = 0.10$ mm⁻¹, λ (Mo K_α) = 0.71073 Å, $F(000) = 1104$, 2950 independent reflections ($R_{int} = 0.045$), 2622 reflections with $I > 2\sigma(I)$; refinement method, full-matrix least-squares refinement on F^2 ; $R[F^2 > 2\sigma(F^2)] = 0.051$, $wR(F^2) = 0.114$, $S = 1.21$.
- [21] Wilson, W. *J Chem Soc* 1948, 10, 1157.
- [22] Leonard, N. J.; McDonald, J. J.; Henderson, R. E. L.; Reichmann, M. E. *Biochemistry* 1971, 10, 3335.
- [23] Wiley, R. H.; Lanet, J.; Hussung, K. H. *J Heterocycl Chem* 1964, 1, 175.