Efficient Synthesis of Flupirtine Analogues Derived from Pyrimidine

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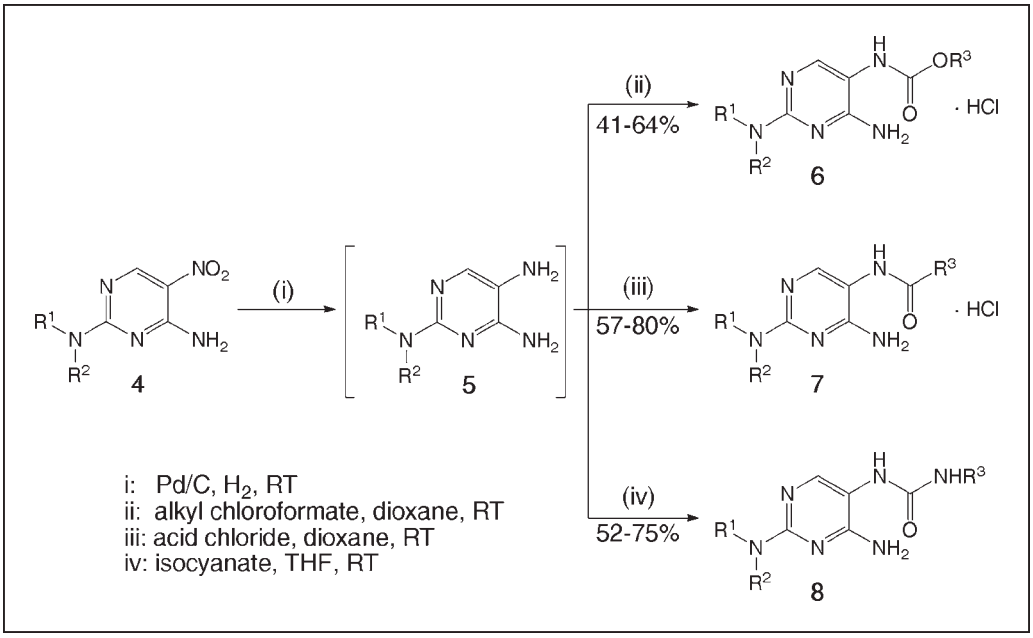

The synthesis of novel N^2-substituted 5-alkoxycarbonylamino-2,4-diaminopyrimidines, 5-acylamino-2,4-diaminopyrimidines, and 2,4-diamino-5-ureidopyrimidines as analogues of the analgesic flupirtine is described.

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INTRODUCTION

Flupirtine, a centrally acting nonopiate 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 N^5-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-

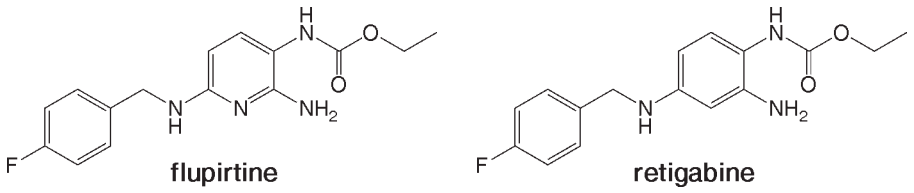
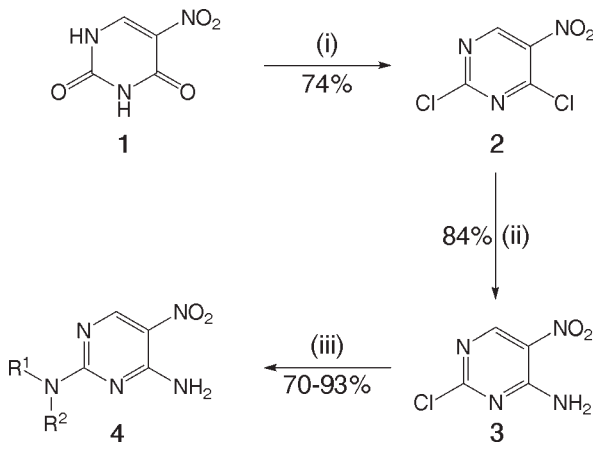


Figure 1. Chemical structure of flupirtine and retigabine.

Scheme 1. Synthesis of N^2-substituted 5-nitropyrimidine-2,4-diamines (**4a–g**). Reagents and conditions: (i) $POCl_3$, *N*,*N*-dimethylaniline, reflux; (ii) NH_3, ethanol, 0°C; (iii) R^1R^2NH, ethanol, reflux.



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

Table 1

N^2-Substituted 5-nitropyrimidine-2,4-diamines (**4a–g**) prepared.

Compound	R^1	R^2	Yield (%)
4a	4-$FC_6H_4CH_2$	H	81
4b	—$(CH_2)_2O(CH_2)_2$—		84
4c	4-$MeC_6H_4CH_2$	H	93
4d	$PhCH_2CH_2$	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 chlorofomates to produce the desired **6a–g** as stable, amorphous hydrochlorides in 41–64% overall yield (Scheme 2, Table 2). The N^2-substituted 5-alkoxycarbonylamino-2,4-diaminopyrimidines (**6a–g**) are characterized by a strong (C=O)-absorption band at

Scheme 2. Synthesis of N^2-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, H_2, RT; (ii) alkyl chloroformate, dioxane, RT; (iii) acid chloride, dioxane, RT; (iv) isocyanate, THF, RT.

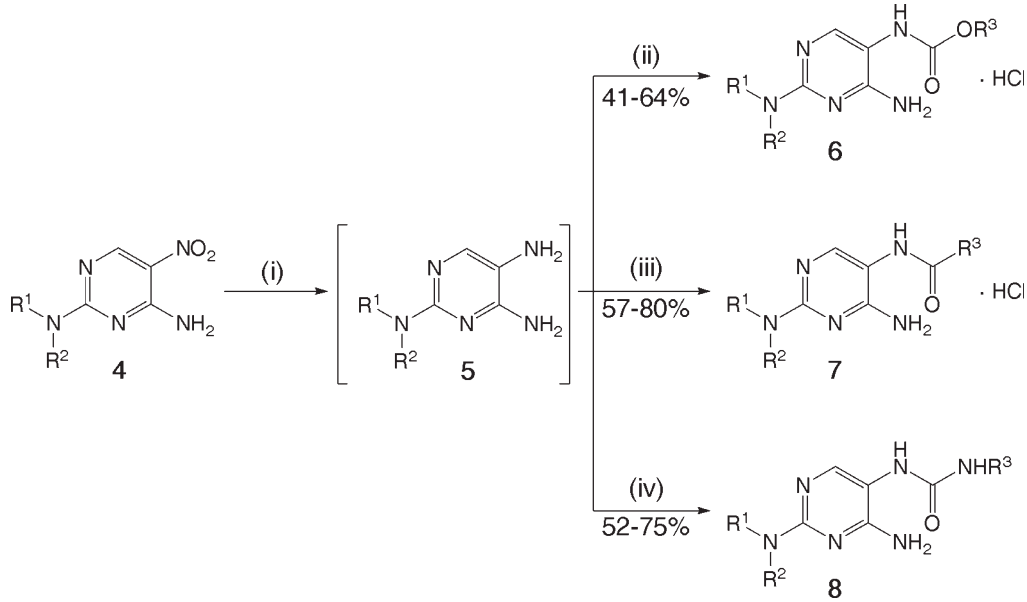


Table 2

N^2-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-$FC_6H_4CH_2$	H	Et	59
6b	4-$FC_6H_4CH_2$	H	^{n}Pr	53
6c	4-$FC_6H_4CH_2$	H	^{n}Bu	64
6d	4-$FC_6H_4CH_2$	H	^{i}Bu	47
6e	4-$MeC_6H_4CH_2$	H	Et	51
6f	4-$MeC_6H_4CH_2$	H	^{n}Pr	41
6g	4-$MeC_6H_4CH_2$	H	^{i}Bu	49
6h	—$(CH_2)_2O(CH_2)_2$—		Et	35[a]
7a	4-$FC_6H_4CH_2$	H	Me	64
7b	4-$FC_6H_4CH_2$	H	Et	69
7c	4-$FC_6H_4CH_2$	H	^{n}Bu	70
7d	4-$FC_6H_4CH_2$	H	c-(Pentyl)CH_2	80
7e	4-$FC_6H_4CH_2$	H	3-(MeO)Ph	58
7f	4-$FC_6H_4CH_2$	H	3-Me-Ph	59
7g	Bn	H	Me	59
7h	Bn	Me	Et	62
7i	4-$MeC_6H_4CH_2$	H	Me	61
7j	4-$MeC_6H_4CH_2$	H	Et	63
7k	Ph	H	Et	57
7l	$PhCH_2CH_2$	H	Et	63
8a	4-$FC_6H_4CH_2$	H	Et	56
8b	4-$FC_6H_4CH_2$	H	^{n}Pr	59
8c	4-$FC_6H_4CH_2$	H	*c*-Hexyl	75
8d	4-$FC_6H_4CH_2$	H	Ph	52
8e	4-$FC_6H_4CH_2$	H	3-Cl-Ph	54
8f	—$(CH_2)_2O(CH_2)_2$—		Et	72
8g	—$(CH_2)_2O(CH_2)_2$—		^{n}Pr	71
8h	—$(CH_2)_2O(CH_2)_2$—		*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 N^5-acylation 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 N^2-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 N^2-substituted 2,4-diamino-5-ureidopyrimidines (**8a–h**) in 52–75% yield.

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

In summary, we have synthesized a variety of novel N^2-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. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and [D_6]DMSO as solvent. X-ray crystal analysis was performed on a Bruker Smart APEX CCD diffractometer with Mo Kα-radiation at 100 K.

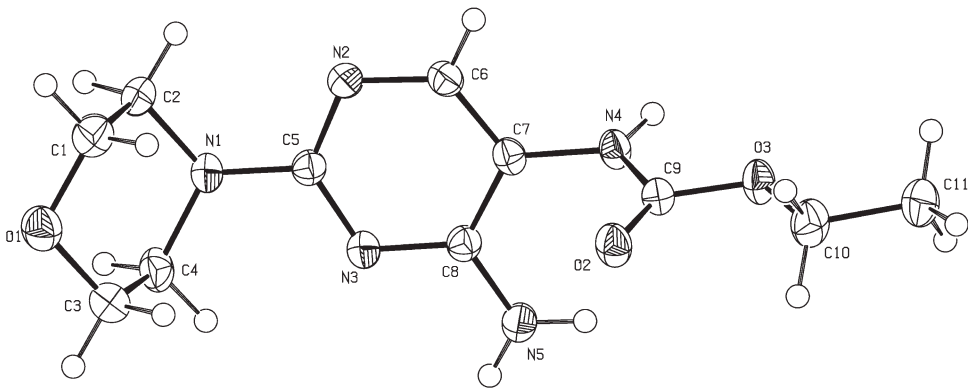


Figure 2. X-ray crystal structure of compound **6h**.

General procedure for the preparation of N^2-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.

N^2-(4-Fluorobenzyl)-5-nitropyrimidine-2,4-diamine (4a). This compound was obtained as yellow crystals in 81% yield, mp 195°C. ν_{max} (KBr)/cm^{-1} 3469, 3282, 1560. δ_H (400 MHz, [D6]DMSO): 4.49 (1.5H, d, J = 6.4 Hz, $ArCH_2$), 4.55 (0.5H, d, J = 6.4 Hz, $ArCH_2$), 7.09–7.42 (4H, m, ArH), 7.91–8.25 (2H, m, NH_2), 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, $^2J_{C-F}$ = 21.4 Hz), 119.5, 120.5, 129.0 (d, $^3J_{C-F}$ = 8.4 Hz), 129.5 (d, $^3J_{C-F}$ = 7.6 Hz), 135.2 (d, $^4J_{C-F}$ = 3.1 Hz), 135.8 (d, $^4J_{C-F}$ = 3.1 Hz), 157.1, 157.4, 157.7, 157.9, 161.2 (d, $^1J_{C-F}$ = 241.9 Hz), 161.3 (d, $^1J_{C-F}$ =242.6 Hz), 161.8, 162.0; due to existence of rotamers some signals appear twice. HRMS-FAB: m/z [M + H]$^+$ calcd. for $C_{11}H_{10}FN_5O_2$: 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). ν_{max} (KBr)/cm^{-1} 3469, 3280, 1560. δ_H (400 MHz, [D6]DMSO): 3.58–3.95 (8H, m, CH_2), 8.03 + 8.19 (2H, 2s, NH_2), 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 $C_8H_{11}N_5O_3$: 226.0940; found: 226.0942.

N^2-(4-Methylbenzyl)-5-nitropyrimidine-2,4-diamine (4c). This compound was obtained as yellow crystals in 93% yield, mp 221°C. ν_{max} (KBr)/cm^{-1} 3471, 3352, 1618, 1543. δ_H (400 MHz, [D6]DMSO): 2.27 (3H, s, CH_3), 4.48 (1.5H, d, J = 6.4 Hz, $ArCH_2$), 4.53 (0.5H, d, J = 6.6 Hz, $ArCH_2$), 7.06–7.26 (4H, m, ArH), 7.91–8.24 (2H, m, NH_2), 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 $C_{12}H_{13}N_5O_2$: 260.1148; found: 260.1148.

5-Nitro-N^2-(2-phenylethyl)pyrimidine-2,4-diamine (4d). This compound was obtained as yellow powder in 80% yield, mp 176°C. ν_{max} (KBr)/cm^{-1} 3485, 3356, 1542. δ_H (400 MHz, [D6]DMSO): 2.79–2.91 (2H, m, CH_2CH_2Ph), 3.46–3.63 (2H, m, CH_2CH_2Ph), 7.14–7.38 (5H, m, ArH), 7.81–8.32 (3H, complex m, NH, and NH_2), 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 $C_{12}H_{13}N_5O_2$; 260.1148; found: 260.1150.

5-Nitro-N^2-phenylpyrimidine-2,4-diamine (4e). This compound was obtained as yellow powder in 92% yield, mp 239°C. ν_{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, NH_2), 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 $C_{10}H_9N_5O_2$: 232.0835; found: 232.0835.

N^2-Benzyl-5-nitropyrimidine-2,4-diamine (4f). This compound was obtained as yellow crystals in 84% yield, mp 194°C. ν_{max} (KBr)/cm^{-1} 3469, 3354, 1620, 1543. δ_H (400 MHz, [D6]DMSO): 4.54 (1.5H, d, J = 6.6 Hz, $ArCH_2$), 4.59 (0.5H, d, J = 6.6 Hz, $ArCH_2$), 7.19–7.38 (5H, m, ArH), 7.91–8.24 (2H, complex m, NH_2), 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 $C_{11}H_{11}N_5O_2$: 246.0991; found: 246.0995.

N^2-Benzyl-N^2-methyl-5-nitropyrimidine-2,4-diamine (4g). This compound was obtained as yellow powder in 70% yield, mp 84°C. ν_{max} (KBr)/cm^{-1} 3433, 3280. δ_H (400 MHz, [D6]DMSO): 3.10 (1.5H, s, CH_3), 3.16 (1.5H, s, CH_3), 4.89 (1H, s, $ArCH_2$), 4.95 (1H, s, $ArCH_2$), 7.18–7.42 (5H, m, ArH), 7.97–8.32 (2H, m, NH_2), 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 $C_{12}H_{13}N_5O_2$: 260.1148; found: 260.1150.

General procedure for the preparation of N^2-substituted 5-alkoxycarbonylamino-2,4-diaminopyrimidines (6a–g). A suspension of the respective N^2-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. ν_{max} (KBr)/cm^{-1} 3349, 3192, 3104, 1744. δ_H (400 MHz, [D6]DMSO): 1.36 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.43 (2H, q, J = 7.0 Hz, CH_2CH_3), 4.65 (2H, d, J = 5.9 Hz, $ArCH_2$), 5.15 (2H, s, NH_2), 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, $^2J_{C-F}$ = 21.3 Hz), 115.1, 121.6, 130.1 (d, $^3J_{C-F}$ = 8.1 Hz), 134.1 (d, $^4J_{C-F}$ = 2.9 Hz), 149.0, 150.4, 158.0, 161.3 (d, $^1J_{C-F}$ = 242.8 Hz). Calc. for $C_{14}H_{17}ClFN_5O_2$: 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. ν_{max} (KBr)/cm^{-1} 3319, 3168, 3035, 1748. δ_H (400 MHz, [D6]DMSO): 0.99 (3H, t, J = 7.4 Hz, $CH_2CH_2CH_3$), 1.71–1.80 (2H, m, $CH_2CH_2CH_3$), 4.34 (2H, t, J = 6.4 Hz, $CH_2CH_2CH_3$), 4.65 (2H, d, J = 5.8 Hz, $ArCH_2$), 5.27 (2H, s, NH_2), 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, $ArCH_2$), 5.37 (2H, s, NH_2), 7.12–7.53 (4H, m, ArH), 7.54 (1H, s, ArH), 9.23 (1H, s, NH), 9.33 (1H, s, NH), 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, $ArCH_2$), 5.47 (2H, s, NH_2), 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, CH_3), 4.42 (2H, q, J = 7.1 Hz, CH_2CH_3), 4.63 (2H, d, J = 5.9 Hz, $ArCH_2$), 5.27 (2H, s, NH_2), 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, CH_3), 4.33 (2H, t, J = 6.5 Hz, $CH_2CH_2CH_3$), 4.63 (2H, d, J = 5.8 Hz, $ArCH_2$), 5.36 (2H, s, NH_2), 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, CH_3), 4.16 (2H, d, J = 6.0 Hz, $CH_2CH(CH_3)_2$), 4.63 (2H, d, J = 4.4 Hz, $ArCH_2$), 5.42 (2H, s, NH_2), 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, NH_2), 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 N^2-substituted 5-acylamino-2,4-diaminopyrimidines (7a–l).. A suspension of the respective N^2-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, CH_3), 4.53 (2H, d, J = 5.9 Hz, $ArCH_2$), 7.10–7.49 (4H, m, ArH), 8.00 (1H, s, ArH), 8.38 (1H, s, NH), 8.57 (2H, s, NH_2), 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. ν_{max} (KBr)/cm^{-1} 3293, 3171, 1676. δ_H (400 MHz, [D6]DMSO): 1.05 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.38 (2H, q, J = 7.5 Hz, CH_2CH_3), 4.53 (2H, d, J = 5.9 Hz, $ArCH_2$), 7.14–7.46 (4H, m, ArH), 8.00 (1H, s, ArH), 8.33 (1H, s, NH), 8.53 (2H, s, NH_2), 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, $^2J_{C-F}$ = 21.3 Hz), 129.5 (d, $^3J_{C-F}$ = 8.1 Hz), 134.3, 136.1, 151.6, 160.8, 161.3 (d, $^1J_{C-F}$ = 242.8 Hz), 173.3. Calc. for $C_{14}H_{17}ClFN_5O$: 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. ν_{max} (KBr)/cm^{-1} 3312, 3150, 1671. δ_H (400 MHz, [D6]DMSO): 0.89 (3H, t, J = 7.3 Hz $CH_2CH_2CH_2CH_3$), 1.26–1.37 (2H, m, $CH_2CH_2CH_2CH_3$), 1.49–1.60 (2H, m, $CH_2CH_2CH_2CH_3$), 2.40 (2H, t, J = 7.6 Hz, $CH_2CH_2CH_2CH_3$), 4.53 (2H, d, J = 6.1 Hz, $ArCH_2$), 7.12–7.49 (4H, m, ArH), 8.07 (1H, s, ArH), 8.46 (1H, s, NH), 8.57 (2H, s, NH_2), 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, $^2J_{C-F}$ = 21.4 Hz), 129.5 (d, $^3J_{C-F}$ = 7.6 Hz), 134.3, 135.7, 151.5, 160.6, 161.3 (d, $^1J_{C-F}$ = 242.6 Hz), 172.5. Calc. for $C_{16}H_{21}ClFN_5O$: 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. ν_{max} (KBr)/cm^{-1} 3296, 3188, 3122, 1684. δ_H (400 MHz, [D6]DMSO): 1.07–1.79 (8H, m, CH_2), 2.12–2.28 (1H, m, CH), 2.40 (2H, d, J = 7.4 Hz, CH_2), 4.53 (2H, d, J = 5.9 Hz, $ArCH_2$), 7.12–7.48 (4H, m, ArH), 8.09 (1H, s, ArH), 8.45–8.53 (3H, m, NH and NH_2), 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, $^2J_{C-F}$ = 20.6 Hz), 129.5 (d, $^3J_{C-F}$ = 7.6 Hz), 134.3, 135.5, 151.5, 160.5, 161.3 (d, $^1J_{C-F}$ = 242.6 Hz), 172.1. Calc. for $C_{18}H_{23}ClFN_5O$: 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. ν_{max} (KBr)/cm^{-1} 3355, 3288, 3156, 1668. δ_H (400 MHz, [D6]DMSO): 3.84 (3H, s, CH_3), 4.56 (2H, d, J = 5.9 Hz, $ArCH_2$), 7.13–7.62 (8H, m, ArH), 7.96 (1H, s, ArH), 8.24 + 8.57 (2H, 2s, NH_2), 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, $^2J_{C-F}$ = 21.3 Hz), 117.6, 120.4, 129.3, 129.6 (d, $^3J_{C-F}$ = 8.1 Hz), 134.3, 134.9, 139.3, 152.3, 159.0, 161.4 (d, $^1J_{C-F}$ = 242.8 Hz), 162.0, 166.3. Calc. for $C_{19}H_{19}ClFN_5O_2$: 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. ν_{max} (KBr)/cm^{-1} 3262, 1686. δ_H (400 MHz, [D6]DMSO): 2.39 (3H, s, CH_3), 4.56 (2H, d, J = 6.1 Hz, $ArCH_2$), 7.13–7.90 (8H, m, ArH), 7.95 (1H, s, ArH), 8.21 + 8.55 (2H, 2s, NH_2), 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, $^2J_{C-F}$ = 21.4 Hz), 125.2, 128.0, 128.5, 129.5 (d, $^3J_{C-F}$ = 8.4 Hz), 132.3, 133.4, 134.2, 137.3, 139.2, 152.2, 161.3 (d, $^1J_{C-F}$ = 242.6 Hz), 162.0, 166.6. Calc. for $C_{19}H_{19}ClFN_5O$: 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. ν_{max} (KBr)/cm^{-1} 3388, 3155, 1697. δ_H (400 MHz, [D6]DMSO): 2.06 (3H, s, CH_3), 4.56 (2H, d, J = 6.0 Hz, $ArCH_2$), 7.24–7.40 (5H, m, ArH), 8.03 (1H, s, ArH), 8.42 (1H, s, NH), 8.49–8.68 (2H, m, NH_2), 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 $C_{13}H_{16}ClN_5O$: 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. ν_{max} (KBr)/cm^{-1} 3346, 3266, 3185, 1685. δ_H (400 MHz, [D6]DMSO): 1.06 (3H, t, J = 7.6 Hz, CH_2CH_3), 2.40 (2H, q, J = 7.4 Hz, CH_2CH_3), 3.10 (3H, s, CH_3), 4.84 (2H, s, $ArCH_2$), 7.26–7.46 (5H, m, ArH), 8.00 (1H, s, ArH), 8.34 + 8.50 (2H, 2s, NH_2), 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 $C_{15}H_{20}ClN_5O$: C, 55.99; H, 6.26; N, 21.76. Found: C, 55.76; H, 21.70; N, 6.36.

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. ν_{max} (KBr)/cm^{-1} 3399, 3142, 1695. δ_H (400 MHz, [D6]DMSO): 2.05 (3H, s, CH_3), 2.28 (3H, s, CH_3), 4.50 (2H, d, J = 6.1 Hz, $ArCH_2$), 7.12–7.28 (4H, m, ArH), 7.99 (1H, s, ArH), 8.36 (1H, s, NH), 8.54 (2H, s, NH_2), 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 $C_{14}H_{18}ClN_5O$: 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. ν_{max} (KBr)/cm^{-1} 3394, 3261, 3129, 1694. δ_H (400 MHz, [D6]DMSO): 1.04 (3H, t, J = 7.6 Hz, CH_2CH_3), 2.28 (3H, s, CH_3), 2.38 (2H, q, J = 7.5 Hz, CH_2CH_3), 4.50 (2H, d, J = 5.9 Hz, $ArCH_2$), 7.12–7.28 (4H, m, ArH), 7.99 (1H, s, ArH), 8.31 (1H, s, NH), 8.49 (2H, s, NH_2), 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 $C_{15}H_{20}ClN_5O$: 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. ν_{max} (KBr)/cm^{-1} 3314, 3162, 1676. δ_H (400 MHz, [D6]DMSO): 1.07 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.43 (2H, q, J = 7.4 Hz, CH_2CH_3), 7.10–7.69 (5H, m, ArH), 8.22 (1H, s, ArH), 8.68 (2H, s, NH_2), 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 $C_{13}H_{16}ClN_5O$: 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. ν_{max} (KBr)/cm^{-1} 3387, 3314, 3118, 1696. δ_H (400 MHz, [D6]DMSO): 1.05 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.40 (2H, q, J = 7.6 Hz, CH_2CH_3), 2.85

(2H, t, J = 7.5 Hz, CH_2CH_2Ph), 3.49–3.59 (2H, m, CH_2CH_2Ph), 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, [D6]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 $C_{15}H_{20}ClN_5O$: 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, [D6]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, [D6]DMSO): 15.5, 34.3, 43.4, 108.3, 114.7 (d, $^2J_{C-F}$ = 21.4 Hz), 128.9 (d, $^3J_{C-F}$ = 7.6 Hz), 137.4 (d, $^4J_{C-F}$ = 3.1 Hz), 153.4, 156.8, 160.0, 160.6, 160.9 (d, $^1J_{C-F}$ = 241.1 Hz). Calc. for $C_{14}H_{17}FN_6O$: 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, [D6]DMSO): 0.84 (3H, t, J = 7.4 Hz, $CH_2CH_2CH_3$), 1.34–1.47 (2H, m, $CH_2CH_2CH_3$), 2.92–3.03 (2H, m, $CH_2CH_2CH_3$), 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, [D6]DMSO): 11.2, 23.0, 41.2, 43.3, 108.3, 114.6 (d, $^2J_{C-F}$ = 21.3 Hz), 128.8 (d, $^3J_{C-F}$ = 8.1 Hz), 137.3 (d, $^4J_{C-F}$ = 2.9 Hz), 153.2, 156.8, 159.9, 160.4, 160.8 (d, $^1J_{C-F}$ = 241.4 Hz). Calc. for $C_{15}H_{19}FN_6O$: 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, [D6]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, [D6]DMSO): 24.5, 25.3, 33.1, 43.3, 48.1, 108.4, 114.7 (d, $^2J_{C-F}$ = 21.4 Hz), 128.8 (d, $^3J_{C-F}$ = 7.6 Hz), 137.4 (d, $^4J_{C-F}$ = 3.1 Hz), 153.0, 156.0, 159.8, 160.3, 160.9 (d, $^1J_{C-F}$ = 241.1 Hz). Calc. for $C_{18}H_{23}FN_6O$: 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, [D6]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, [D6]DMSO): 43.3, 107.3, 114.7 (d, $^2J_{C-F}$ = 21.1 Hz), 117.9, 121.3, 128.6, 128.9 (d, $^3J_{C-F}$ = 7.3 Hz), 137.4 (d, $^4J_{C-F}$ = 2.8 Hz), 140.2, 154.1, 154.2, 160.3, 160.8, 160.9 (d, $^1J_{C-F}$ = 241.9 Hz). Calc. for $C_{18}H_{17}FN_6O$: 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, [D6]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, [D6]DMSO): 43.2, 106.8, 114.6 (d, $^2J_{C-F}$ = 20.6 Hz), 116.3, 117.3, 120.8, 130.1, 128.8 (d, $^3J_{C-F}$ = 8.4 Hz), 132.9, 137.3 (d, $^4J_{C-F}$ = 3.1 Hz), 141.8, 154.0, 154.2, 160.3, 160.8, 160.8 (d, $^1J_{C-F}$ = 241.1 Hz). Calc. for $C_{18}H_{16}ClFN_6O$: 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, [D6]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, [D6]DMSO): 15.4, 34.2, 44.2, 66.0, 108.5, 152.8, 156.6, 159.1, 160.1. Calc. for $C_{11}H_{18}N_6O_2$: 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, [D6]DMSO): 0.84 (3H, t, J = 7.4 Hz, $CH_2CH_2CH_3$), 1.32–1.48 (2H, m, $CH_2CH_2CH_3$), 2.93–3.05 (2H, m, $CH_2CH_2CH_3$), 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, [D6]DMSO): 11.4, 23.1, 41.3, 44.3, 66.1, 108.7, 152.8, 156.8, 159.2, 160.2. Calc. for $C_{12}H_{20}N_6O_2$: 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, [D6]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, [D6]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 $C_{15}H_{24}N_6O_2$: C, 56.23; H, 7.55; N, 26.23. Found: C, 56.04; H, 7.67; N, 25.95.

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[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) Å^3, $T = 153$ 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; $R[F^2 > 2\sigma(F^2)] = 0.051$, $wR(F^2) = 0.114$, $S = 1.21$.

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