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Traceless solid-phase synthesis of 2,4,6-chlorodiamino and triaminopyrimidines

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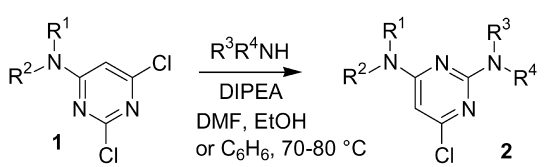
Abstract—An effective traceless solid-phase synthesis of chloro-diaminopyrimidines via an amino-de-chlorination reaction of polymer-bound 4-alkoxycarbonylamino-2,6-dichloropyrimidines has been developed. After release from the polymer the target molecules were obtained in good to excellent purity, although with modest regiocontrol. Further reaction of solid-supported *N*-alkoxycarbonyl-chloro-diaminopyrimidines with secondary amines afforded triaminopyrimidines in good purity under mild conditions, whereas less nucleophilic primary amines did not perform well under the conditions explored so far.

Polyamino-pyrimidines are very important in biology and in the pharmaceutical chemistry, and have a number of applications as therapeutic agents.[1] In order to make available large arrays of polyamino-pyrimidines for high throughput biological screening, solid-phase combinatorial chemistry is the method of choice. The sequential S_NAr chloride/amine displacement (amino-de-chlorination) of chloro-pyrimidine scaffolds anchored on solid-support is potentially more versatile and attractive than the de novo solid-phase construction of the pyrimidine core. Although some solid-phase syntheses of polyamino-pyrimidines based on the former strategy are already available,[2] they are affected by several drawbacks, such as limited structural diversity of the generated libraries (for example use of Rink resin, therefore one of the amino residues after release from the polymer must be a $-NH_2$),[2c] indirect multi-step introduction of the amino-groups, and low product purity due to the production of many different regioisomers and/or pyrimidines with different degree of amino-substitution on the same resin bead.

Recently, we described the highly regioselective solution- and solid-phase 4-amino-de-chlorination of 2,4,6-trichloro-pyrimidine by, respectively, *N*-sodium and *N*-potassium carbamates.[3] We now report the accomplishment of our final goal, namely an effective solid-phase synthesis of 2,4,6-chlorodiamino- and triamino-pyrimidines.

We first investigated both viability and regioselectivity of the amino-de-chlorination of 4-alkoxycarbonylamino-2,6-dichloropyrimidines in solution, since to our knowledge such a reaction has not been described previously. What we already knew from the literature,[4] as well as from our own experience,[5] was that unprotected 4-amino-2,6-dichloro-pyrimidines **1** (Scheme 1) undergo highly regioselective 2-amino-de-chlorination affording 2,4-diamino-pyrimidines **2**.

To our surprise, and rather disappointingly, the amino-de-chlorination of 4-amino-2,6-dichloropyrimidines *N*-protected as carbamates (such as the *N*-Boc compound **3**, Scheme 2) was found to be not regioselective, affording mixtures of 2,4- and 4,6-diaminopyrimidines **4** and **5**, respectively.[6] However, this drawback was counterbalanced by several attractive features, such as high yields, very mild



Scheme 1. 2-Amino-de-chlorination of 4-amino-2,6-dichloropyrimidines.

Keywords: triaminopyrimidines; regioisomers; de-chlorination.
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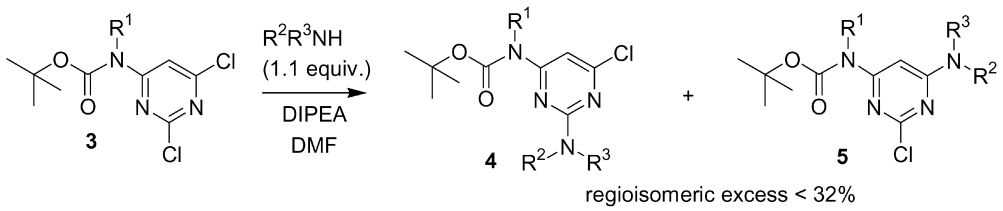
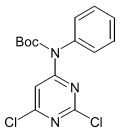
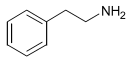
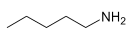
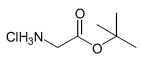
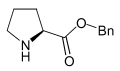
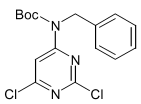
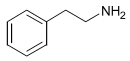
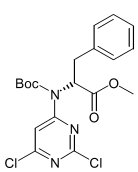


Scheme 2. Solution-phase amino-de-chlorination of **3**.

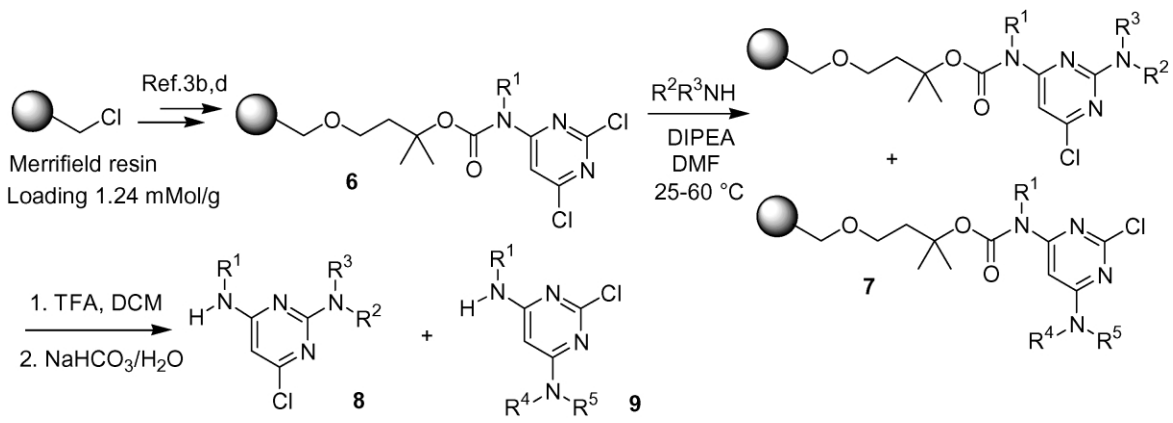
conditions and general scope (Table 1). In fact, secondary amines and amino-esters like piperidine and proline reacted at rt a primary amines and amino-esters required heating at 60°C, while only aniline reacted quite sluggishly at 60°C. DMF was found to be an excellent solvent for these reactions,[7] and DIPEA was used as base. As a qualitative trend, carbamates **3** were found to be more reactive than the corresponding aminopyrimidines **1**.

Satisfactorily, the optimized conditions for sequential amino-de-chlorination developed in solution worked well also in the solid-phase version. Different polymer supported *N*-Boc-like 4-amino-2,6-dichloropyrimidines **6** (Scheme 3) were reacted in DMF with a set of amines (Table 2) affording the resins **7a**–**p**. Traceless release from the resins by TFA afforded a library of regioisomeric chloro-diaminopyrimidines **8** and **9a**–**p**, generally in good to excellent purities and slight predominance of the 2,4-diamino-derivatives **8**, as determined by GC–MS (see Fig. 1). Only for the reactions of phenylalanine polymer **6c**

Table 1. Solution-phase amino-de-chlorination of **3**

Entry	Substrate	R^2R^3NH	Conditions	Regioisomeric ratio (**4**:**5**)[a]	Products	Yield (%)[b]
1			1 h, 25°C	43:57	**4**,**5a**	84
2	 **3a**		3 h, 60°C	49:51	**4**,**5b**	88
3			4 h, 60°C	41:59	**4**,**5c**	69
4[c]			2 h, 60°C	53:47	**4**,**5d**	98
5			3 h, 25°C	36:64	**4**,**5e**	98
6	 **3b**		0.5 h, 25°C	56:44	**4**,**5f**	88
7			4 h, 60°C	52:48	**4**,**5g**	87
8			12 h, 60°C	34:66	**4**,**5h**	47
9	 **3c**		2 h, 25°C	47:53	**4**,**5i**	85

[a] Determined by GC.
[b] Isolated overall yields.
[c] 2.2 Equiv. of both H-Gly-O*t*Bu·HCl and DIPEA were used.



Scheme 3. Solid-phase amino-de-chlorination of **6**.

with dibenzylamine and phenethylamine we could detect just traces of the desired products.

Besides the regioisomers **8** and **9**, the other products observed after release from the resin (usually <5% of the whole mixture) were, as already observed in solution (see note 7), *N*,*N*-dimethylamino-pyrimidines[8] and the 4-chloro-2,6-diaminopyrimidines having the NHR^1 residue in 2-position, arising from amino-de-chlorination of the minor 2-amino-4,6-dichloropyrimidine regioisomers on the starting resin **6**, which are usually present in very low amount.[9]

We finally explored the amino-de-chlorination of resin-bound chloro-aminopyrimidines **6** and **7** to give triamino-pyrimidines **10** (Scheme 4). This third amino-de-chlorination reaction required higher temperatures than the second, because the pyrimidine nucleus is progressively deactivated toward S_NAr reaction. Secondary amines, such as piperidine, reacted smoothly with **6a** (DMF, 80°C, 4 h) affording, after release by TFA, the triamine **10a** in very good purity (82%). The only by-products observed by GC–MS (Fig. 2) were the intermediate regioisomeric chloro-diaminopyrimidines (16% overall). In contrast, reaction of primary amines, such as *n*-pentylamine, with **6a** in DMF (70°C, 24 h) produced the triaminopyrimidine **10b** (81%),[10] arising by double amino-de-chlorination, first with *n*-pentylamine and then with dimethylamine formed from DMF (see note 7). The dipentylamino derivative **10c** was formed as a minor product (4%). Other solvents were therefore explored in order to achieve better results with primary amines, such as THF, which has good resin swelling properties.

Thus, a THF suspension of the chlorodiaminopyrimidine resin **7d** was heated in a sealed tube with benzylamine (100°C, 4 h), but after release from the resin negligible amount of the target triamines was detected.

For the sake of comparison, several diamino-chloropyrimidines **8** and **9** were prepared in solution from pure **4** and **5**, respectively, by TFA cleavage of the *N*-Boc function (Scheme 5). The samples were analyzed by GC–MS and found to be identical to those prepared in solid-phase.

Ongoing studies are directed toward the investigation of the structural and conformational properties of 4-*N*-alkoxy-carbonyl-diaminopyrimidines **4** and **5**.

1. Experimental

1.1. General

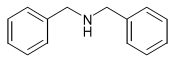
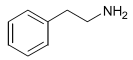
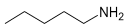
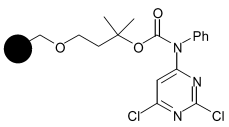
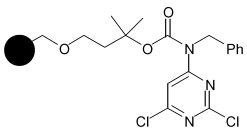
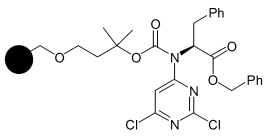
Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Coupling constants (J) are reported in Hertz. Me_4Si was used as internal standard (δ_H and δ_C=0.00) for ^1H and ^{13}C nuclei, while C_6F_6 was used as external standard (δ_F=−162.90) for ^{19}F nuclei. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m; etc. Commercially available reagent-grade solvents were employed without purification. Grignard reagents were purchased from Sigma/Aldrich/Fluka Company. Reactions performed in dry solvents were carried out under nitrogen atmosphere. Melting points are uncorrected and were obtained on a capillary apparatus. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Merck silica gel 60 (230–400 ASTM mesh) was employed for flash chromatography (FC). Merrifield resin was purchased from Novabiochem. For the preparation of compounds **3** see Ref. 3c.

1.2. Solution-phase amino-de-chlorination of 3: synthesis of 4 and 5. General procedure

A mixture of **3** (1 mMol), amine R_2R_3NH (1.1 equiv.) and DIPEA (1.1 equiv.) in dry DMF (5 mL) was heated at the appropriate temperature, for the time indicated in Table 1. The reaction mixture was extracted with diethyl ether (3 times), the collected organic phases washed once with water and then with brine. The solvent was removed at reduced pressure, and the residue purified by flash chromatography to provide pure regioisomers **4** and **5**.

1.2.1. (6-Chloro-2-piperidin-1-yl-pyrimidin-4-yl)-phenyl-carbamic acid *tert*-butyl ester (4a). Solid, mp 119–120°C (*n*-Hex); R_f 0.45 (hexane/diethyl ether=9:1); ^1H NMR (250 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.36–1.46 (m, 4H), 1.50–1.59 (m, 2H), 3.41 (brs, 4H), 7.09–7.13 (m, 3H), 7.24–7.39 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.7 (s),

Table 2. Solid-phase amino-de-chlorination of **6**

Substrate		Amine (Key: temperature/time, equiv. amine; equiv. DIPEA, resin product; loading (mMol/g),[a] ratio of released **8/9**;[b] purity (%) of **8/9**[b])				
						
6°		25°C/3 h, 4.0; 2.0, **7a**; 0.556, 2.67/1.00; 99.7	25°C/3 h, 4.0; 2.0, **7b**; 0.686, 1.00/1.14; 94.5	60°C/4 h, 1.1; 1.0, **7c**; 0.629, 2.06/1.00; 96.1	60°C/4 h, 1.1; 1.0, **7d**; 0.536, 5.25/1.00; 93.8	60 °C/4 h, 1.1; 1.0, **7e**; 0.601, 1.96/1.00; 87.8
6b		25°C/3 h, 4.0; 2.0, **7f**; 0.719, 2.07/1.00; 87.2[c]	25°C/3 h, 4.0; 2.0, **7g**; 0.834, 1.64/1.00; 90.5	60°C/4 h, 1.1; 1.0, **7h**; 0.587, 2.11/1.00; 88.9	60°C/4 h, 1.1; 1.0, **7i**; 0.622, 2.83/1.00; 95.8	60 °C/4 h, 1.1; 1.0, **7j**; 0.786, 2.43/1.00; 84.5
6c		25 °C/3 h, 4.0; 2.0, **7k**; n.d.[d,e], 2.22/1.00; 51.9	25°C/3 h, 4.0; 2.0, **7l**; 0.420, 1.37/1.00; 48.8	60°C/4 h, 1.1; 1.0, **7m**; n.d.[d,e], n.d.[d,e]; <5	60°C/4 h, 1.1; 1.0, **7n**; n.d.[d,e], n.d.[d,e]; <5	60 °C/4 h, 1.1; 1.0, **7p**; 0.380, 5.78/1.00; 44.1

[a] Determined by elemental analysis (chlorine content) of the resin.
[b] Determined by GC–MS analysis after treatment with aq. $NaHCO_3$.
[c] The third regioisomer, namely the (4-chloro)diaminopyrimidine with NHR^1 in 2-position, was present as the ca. 7%.
[d] Not determined.
[e] Not determined in light of the low purity of the released product.

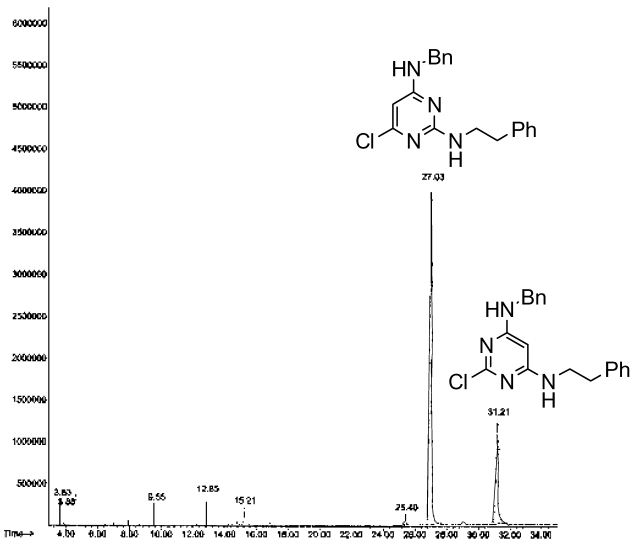


Figure 1. GC analysis of **8** and **9i**.

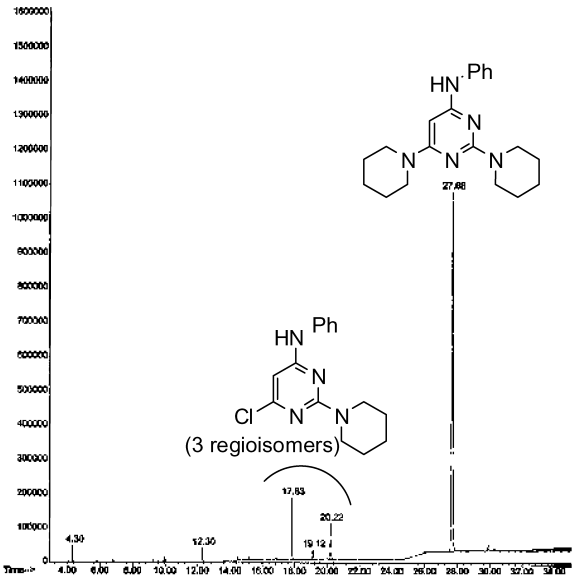
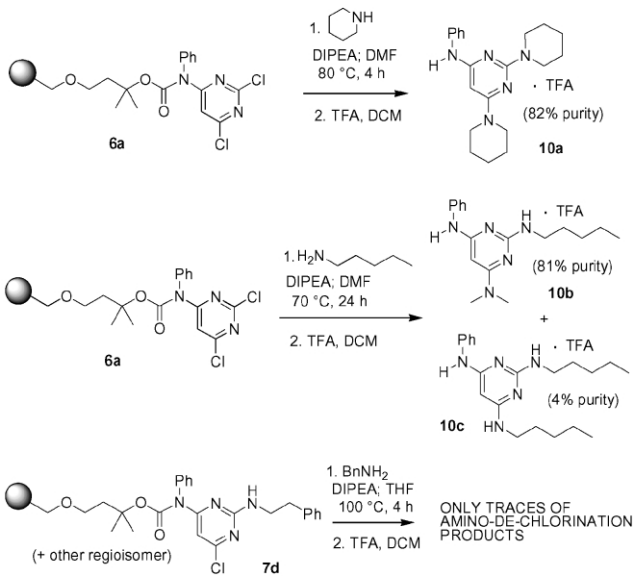
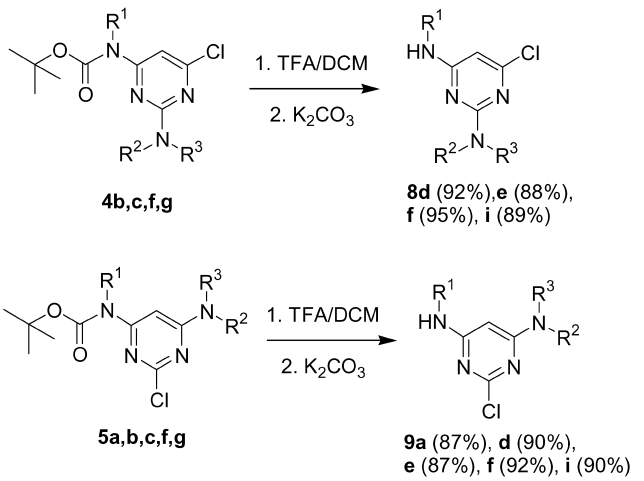


Figure 2. GC analysis of **10a**.



Scheme 4. Solid-phase de-chloro-amination to triaminopyrimidines.



Scheme 5. Solution-phase *N*-Boc cleavage.

25.5 (s), 28.0 (p), 44.7 (s), 82.5 (q), 99.5 (t), 127.0 (t), 128.5 (t), 128.6 (t), 140.55 (q), 153.0 (q), 159.9 (q) 161.3 (q), 162.3 (q); IR (Microscope, cm^{-1}) 2942, 1720, 1600, 1585, 1518, 1314, 1275, 1254, 1151; MS (PCI, isobutane, 70 eV) *m/z* (%) 388 (M^+, 95), 332 (63), 288 (100), 205 (16), 196 (8). Anal. calcd for $C_{20}H_{25}ClN_4O_2$: C, 61.77; H, 6.48; N, 14.41. Found: C, 61.73; H, 6.70; N, 14.44.

1.2.2. (2-Chloro-6-piperidin-1-yl-pyrimidin-4-yl)-phenyl-carbamic acid *tert*-butyl ester (5a). Solid, mp 142–143°C (*n*-Hex); R_f 0.15 (hexane/diethyl ether=9:1); ^1H NMR (250 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.50–1.73 (m, 6H), 3.59 (brt, 4H, *J*=5.2 Hz), 6.83 (s, 1H), 7.12–7.20 (m, 2H), 7.23–7.39 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.4 (s), 25.5 (s), 28.05 (p), 45.5 (s), 82.2 (q), 93.0 (t), 127.0 (t), 128.2 (t), 128.7 (t), 140.5 (q), 153.1 (q), 159.4 (q) 162.2 (q), 163.8 (q); IR (Microscope, cm^{-1}) 2942, 1727, 1600, 1394, 1123, 1089; MS (PCI, isobutane, 70 eV) *m/z* (%) 389 (M^++1, 100), 388 (M^+, 10), 333 (20), 288 (60), 205 (20).

1.2.3. (6-Chloro-2-phenethylamino-pyrimidin-4-yl)-phenyl-carbamic acid *tert*-butyl ester (4b). Solid, mp 140–142°C (diisopropyl ether/$CHCl_3$); R_f 0.41 (hexane/diethyl ether=7:3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.50 (bs, 2H), 3.14 (bs, 2H), 5.50 (bs, 1H), 6.94 (bs, 2H), 7.08–7.42 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.9 (p), 35.4 (s), 42.7 (s), 83.1 (q), 100.9 (t), 126.3 (t), 127.4 (t), 128.4 (t), 128.6 (t), 128.8 (t), 138.8 (q) 140.1 (q), 152.7 (q), the three pyrimidine carbons were obscured due to low intensity; IR (KBr, cm^{-1}) 3440, 3273, 1729, 1600, 1575, 1287, 1151, 749; MS (PCI, isobutane, 70 eV) *m/z* (%) 425 (M^++1, 100), 369 (20). Anal. calcd for $C_{23}H_{25}ClN_4O_2$: C, 65.01; H, 5.93; N, 13.19. Found: C, 64.91; H, 6.00; N, 13.19.

1.2.4. (2-Chloro-6-phenethylamino-pyrimidin-4-yl)-phenyl-carbamic acid *tert*-butyl ester (5b). Solid, mp 178.6–179.8°C (dec.) (*n*-Hex/$CHCl_3$); R_f 0.18 (hexane/diethyl ether=7:3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.92 (t, 2H, *J*=7 Hz), 3.58 (bs, 2H), 5.05–5.95 (bs, 1H, NH), 6.78 (s, 1H), 7.08–7.45 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.0 (p), 35.2 (s), 42.5 (s), 82.7 (q), 126.8 (t),

127.3 (t), 128.4 (t), 128.8 (t), the three pyrimidine carbons and the CH_2N were obscured due to low intensity; IR (Microscope, cm^{-1}) 3261, 3115, 2972, 1731, 1600, 1461, 1417, 1290, 1160, 1089; MS (PCI, isobutane, 70 eV) *m/z* (%) 425 (M^++1, 100), 369 (10).

1.2.5. (6-Chloro-2-pentylamino-pyrimidin-4-yl)-phenyl-carbamic acid *tert*-butyl ester (4c). Solid, mp 145–147°C (*n*-Hex); R_f 0.48 (hexane/diethyl ether=4:1); ^1H NMR (250 MHz, $CDCl_3$) δ 0.84 (t, 3H, J=7 Hz), 0.95–1.32 (bm, 6H), 1.40 (s, 9H), 2.82 (bs, 2H), 4.75–5.40 (bs, 1H), 7.04–7.42 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.0 (p), 22.3 (s), 28.0 (p), 28.8 (s), 28.9 (s) 41.4 (s), 82.8 (q), 100.3 (t), 127.2 (t), 128.6 (t), 140.3 (q), 152.8 (q), 160.5 (q) 162.7 (q); IR (KBr, cm^{-1}) 3446, 3272, 1732, 1607, 1579, 1298, 1298, 1148, 1147; MS (PCI, isobutane, 70 eV) *m/z* (%) 391 (M^++1, 100), 335 (10), 291 (5). Anal. calcd for $C_{20}H_{27}ClN_4O_2$: C, 61.45; H, 6.96; N, 14.33. Found: C, 61.66; H, 6.99; N, 14.55.

1.2.6. (2-Chloro-6-pentylamino-pyrimidin-4-yl)-phenyl-carbamic acid *tert*-butyl ester (5c). Solid, mp 115–117°C (*n*-Hex); R_f 0.20 (hexane/diethyl ether=4:1); ^1H NMR (250 MHz, $CDCl_3$) δ 0.91 (bm, 3H), 1.28–1.48 (bm, 13H), 1.61 (bm, 2H), 3.27 (bs, 2H), 4.75–5.40 (bs, 1H), 6.75 (s, 1H), 7.09–7.43 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.0 (p), 22.3 (s), 28.0 (p), 28.8 (s), 28.9 (s) 41.8 (s), 82.6 (q), 90.8 (t), 127.2 (t), 128.4 (t), 128.8 (t), 140.0 (q), 152.9 (q); IR (KBr, cm^{-1}) 3432.0, 1702.1, 1584.2, 1152.0, 757.0; MS (PCI, isobutane, 70 eV) *m/z* (%) 391 (M^++1, 100), 335 (10), 291 (5).

1.2.7. [4-(*tert*-Butoxycarbonyl-phenyl-amino)-6-chloro-pyrimidin-2-ylamino]-acetic acid *tert*-butyl ester (4d). Solid; mp 114–116°C (*n*-Hex); R_f 0.33 (hexane/diethyl ether=3:2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.39 (s, 9H), 3.40–4.00 (br m, 2H), 5.88 (br s, 1H), 7.04–7.10 (m, 2H), 7.25–7.39 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.9 (p), 28.0 (p), 43.7 (s), 81.5 (q), 82.7 (q), 101.5 (t), 127.2 (t), 128.6 (t), 128.7 (t), 140.2 (q), 152.8 (q), 160.6 (q), 161.3 (q), 162.6 (q), 169.3 (q); IR (KBr, cm^{-1}); 3271, 3143, 2980, 1752, 1725, 1606, 1578, 1301, 1161, 1122, 1104, 852, 690; MS (PCI, isobutane, 70 eV) *m/z* (%) 435 (M^++1, 100), 379 (10). Anal. calcd for $C_{21}H_{27}ClN_4O_4$: C, 57.99; H, 6.26; N, 12.88. Found: C, 58.31; H, 6.20; N, 13.01.

1.2.8. [6-(*tert*-Butoxycarbonyl-phenyl-amino)-2-chloro-pyrimidin-4-ylamino]-acetic acid *tert*-butyl ester (5d). Oil; R_f 0.19 (*n*-Hex/diethyl ether=3:2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.47 (s, 9H), 3.99 (d, 2H, J=4.65 Hz), 5.77 (brs, 1H), 6.76 (s, 1H), 7.08–7.13 (d, 2H), 7.23–7.37 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.0 (2×p), 43.8 (s), 82.3 (2xq), 94.2 (broad, t), 127.1 (t), 128.3 (t), 128.7 (t), 140.05 (q), 152.9 (q), 159.1 (q), 161.5 (q), 164.2 (q), 168.9 (q). IR (KBr, cm^{-1}) 3339, 2982, 1714, 1605, 1591, 1569, 1292, 1271, 1252, 1155; MS (PCI, isobutane, 70 eV) *m/z* (%) 435 (M^++1, 100), 379 (20).

1.2.9. L-1-[4-(*tert*-Butoxycarbonyl-phenyl-amino)-6-chloro-pyrimidin-2-yl]-pyrrolidine-2-carboxylic acid benzyl ester (4e). Oil, $[\alpha]_D^{20}=-72.0$ (*c* 0.5, $CHCl_3$); R_f 0.40 (*n*-Hex/diethyl ether=7:3); ^1H NMR (250 MHz, DMSO/333 K) δ 1.39 (s, 9H), 1.76–2.00 (m, 3H), 2.16–2.30 (m, 1H), 3.35 (m, 2H), 4.25 (m, 1H), 4.85–5.15 (m,2H), 7.11 (br signal, 1H), 7.24–7.42 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.7 (s), 28.0 (p), 30.2 and 30.4 (s), 46.7 and 46.9 (s), 59.2 (t), 66.2 and 66.5 (s), 82.5 (q), 100.7 and 100.8 (t), 127.0 (t), 127.7 and 127.8 (t), 128.1 (t), 128.4 and 128.5 (t), 128.8 (t), 136.0 (q), 140.1 and 140.4 (q), 152.8 and 152.9 (q), 158.5 and 158.6 (q), 160.9 and 161.3 (q), 161.9 and 162.3 (q), 172.0 and 173.2 (q, CO); IR (KBr, cm^{-1}) IR (film, cm^{-1}); 2979, 1729, 1574, 1531, 1414, 1295, 1155, 1066, 1024, 854; MS (PCI, isobutane, 70 eV) *m/z* (%) 508 (M^+, 37), 409 (21), 373 (100), 317 (4), 273 (98), 91 (78).

1.2.10. L-1-[6-(*tert*-Butoxycarbonyl-phenyl-amino)-2-chloro-pyrimidin-4-yl]-pyrrolidine-2-carboxylic acid benzyl ester (5e). Oil, $[\alpha]_D^{20}=-43.7$ (*c* 2.0, $CHCl_3$); R_f 0.25 (*n*-Hex/diethyl ether=7:3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.95–2.34 (m, 4H), 3.35–3.68 (m, 2H), 4.73 (br signal, 1H), 5.13 (d, J=12.4 Hz, 1H), 5.23 (d, J=12.4 Hz, 1H), 6.77 (br signal, 1H), 6.12–7.18 (brd, 2H), 7.24–7.40 (m, 8H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.9 (s), 28.0 (p), 29.6 (s), 47.0 (s), 59.6 (t), 66.7 (s), 82.3 (q), 93.3 (t), 127.0 (t), 127.9 (t), 128.1 (t), 128.3 (t), 128.5 (t), 128.7 (t), 135.7 (q), 140.3 (q), 152.9 (q), 158.7 (q), 161.6 (q), 162.0 (q), 172.5 (q); IR (film, cm^{-1}); 2980, 1724, 1576, 1532, 1495, 1282, 1152, 973, 864; MS (PCI, isobutane, 70 eV) *m/z* (%) 509 (M^++1, 37), 410 (80), 408 (100), 373 (33), 317 (4), 273 (98), 91 (48).

1.2.11. Benzyl-(6-chloro-2-piperidin-1-yl-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (4f). Solid, mp 104.2–106.2°C (*n*-Hex); R_f 0.57 (*n*-Hex/diethyl ether=9:1); ^1H NMR (250 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.46–1.65 (m, 6H), 3.66 (t, 4H, J=5 Hz), 5.17 (s, 2H), 7.12–7.34 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.7 (s), 25.6 (s), 28.0 (p), 45.0 (s), 48.8 (s), 82.6 (q), 99.9 (t), 126.8 (t), 126.9 (t), 128.2 (t), 139.1 (q), 153.4 (q), 160.0 (q) 161.3 (q), 161.5 (q); IR (KBr, cm^{-1}) 3418.2, 2940.2, 1720.4, 1575.0, 1527.2, 1383.4, 1360.1, 1280.7, 1236.7, 1147.2, 982.3, 707.9; MS (PCI, isobutane, 70 eV) *m/z* (%) 403 (M^++1, 100), 347 (10). Anal. calcd for $C_{27}H_{29}ClN_4O_4$: C, 63.71; H, 5.74; N, 11.01. Found: C, 63.83; H, 5.88; N, 11.00.

1.2.12. Benzyl-(2-chloro-6-piperidin-1-yl-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (5f). Solid, mp 107.7–108.7°C (*n*-Hex); R_f 0.32 (*n*-Hex/diethyl ether=9:1); ^1H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.64 (bs, 6H), 3.60 (bs, 4H), 5.19 (s, 2H), 7.15 (s, 1H), 7.24–7.28 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.5 (s), 25.6 (s), 28.1 (p), 45.6 (s), 48.6 (s), 82.3 (q), 91.3 (t), 126.8 (t), 127.5 (t), 128.2 (t), 139.2 (q), 153.6 (q), 159.0 (q) 160.9 (q), 164.0 (q); IR (KBr, cm^{-1}) 3408.1, 2938.8, 2853.8, 1715.6, 1560.3, 1494.6, 1467.2, 1449.0, 1420.0, 1365.8, 1313.8, 1270.5, 1209.2, 1151.2, 983.3, 874.1, 851.0, 825.2, 741.9, 714.8.

1.2.13. Benzyl-(6-chloro-2-phenetylamino-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (4g). Solid, mp 162–163°C (*n*-Hex); R_f 0.38 (*n*-Hex/diethyl ether=7:3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.70–2.89 (m, 2H), 3.48–3.66 (m, 2H), 5.19–5.30 (m, 2H), 5.30–5.56 (bs, 1H), 7.01–7.35 (m, 10H), 7.42 (bs, 1H);^{13}C NMR (63 MHz, $CDCl_3$) δ 28.0 (p), 35.6 (s), 42.8 (s), 48.8 (s), 83.0 (q), 101.2 (t) 126.4 (t), 126.7 (t), 126.9 (t), 128.3 (t), 128.6 (t), 128.8 (t), 138.8 (q), 153.2 (q), 160.8 (q), 162.0 (q); IR (KBr,

cm^{-1}) 3263, 3137, 2974, 1728, 1607, 1577, 1391, 1369, 1352, 1236, 1144, 957; MS (PCI, isobutane, 70 eV) *m/z* (%) 440 (M^++1, 15), 439 (M^+, 30), 383 (40), 247 (100), 91 (95). Anal. calcd for $C_{24}H_{27}ClN_4O_2$: C, 65.67; H, 6.20; N, 12.76. Found: C, 65.77; H, 6.19; N, 12.49.

1.2.14. Benzyl-(2-chloro-6-phenetylamino-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (5g). Solid, mp 157–158°C (*n*-Hex); R_f 0.25 (*n*-Hex/diethyl ether=7:3); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.91 (t, *J*=6.7 Hz, 2H), 3.52–3.68 (m, 2H), 5.09–5.27 (br signal, 1H), 5.21 (brs, 2H), 7.0 (brs, 1H), 7.18–7.42 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.1 (p), 35.3 (s), 42.8 (s), 48.5 (s), 82.5 (q), 91.3 (t) 126.7 (t), 126.9 (t), 127.5 (t), 128.2 (t), 128.5 (t), 128.8 (t), 138.3 (q), 139.0 (q), 153.5 (q), 160.0 (q), 164.1 (q), 164.9 (q); IR (KBr, cm^{-1}) 3427.4, 3254.4, 1720.1, 1591.3, 1583.0, 1415.9, 1370.0, 1245.4, 1149.5, 964.8; MS (PCI, isobutane, 70 eV) *m/z* (%) 440 (M^++1, 16), 439 (M^+, 31), 382 (84), 247 (100), 91 (80).

1.2.15. Benzyl-(6-chloro-2-phenylamino-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (4h). Solid, mp 142–144°C (*n*-Hex), R_f 0.40 (*n*-Hex/diethyl ether=8:2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44 (s, 9H), 5.24 (bs, 2H), 6.95–7.01 (bt, 1H), 7.03 (brs, 1H), 7.13–7.38 (bm, 9H), 7.60 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.9 (p), 48.9 (s), 83.1 (q), 103.2 (t), 119.5 (t), 122.9 (t), 126.3 (t), 126.8 (t), 128.3 (t), 128.8 (t), 138.2 (q), 138.6 (q), 153.2 (q), 158.5 (q), 161.3 (q), 161.9 (q); IR (KBr, cm^{-1}); 3353.8, 1701.7, 1580.3, 1560.0, 1530.2, 1478.8, 1447.0, 1373.4, 1251.5, 1152.0, 1149.3; MS (PCI, isobutane, 70 eV) *m/z* (%) 410 (M^+, 75), 354 (70), 311 (100). Anal. calcd for $C_{22}H_{23}ClN_4O_2$: C, 64.31; H, 5.64; N, 13.64. Found: C, 63.99; H, 5.72; N, 13.73.

1.2.16. Benzyl-(2-chloro-6-phenylamino-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (5h). Solid, mp 125–126°C (*n*-Hex), R_f 0.30 (*n*-Hex/diethyl ether=8:2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 9H), 5.21 (bs, 2H), 6.92 (brs, 1H), 7.10–7.42 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.9 (p), 48.6 (s), 82.7 (q), 92.4 (t), 122.2 (t), 125.0 (t), 126.9 (t), 127.5 (t), 128.2 (t), 129.5 (t), 137.7 (q), 138.7 (q), 153.2 (q), 161.4 (q), 163.0 (q), 164.9 (q); IR (KBr, cm^{-1}) 3340.7, 1694.5, 1625.2, 1578.1, 1496.9, 1453.6, 1377.8, 1268.2, 1148.9; MS (PCI, isobutane, 70 eV) *m/z* (%) 411 (M^++1, 87), 355 (95), 311 (100).

1.2.17. L-2-[*tert*-Butoxycarbonyl-(6-chloro-2-piperidin-1-yl-pyrimidin-4-yl)-amino]-3-phenyl-propionic acid benzyl ester (4i). Oil; $[\alpha]_D^{20}$=+70.2 (*c* 1.5, $CHCl_3$); R_f 0.38 (*n*-Hex/diethyl ether=4:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.51–1.78 (bm, 6H), 3.23 (dd, 1H, *J*=14 Hz), 3.52 (dd, 1H, *J*=14 Hz), 3.64 (s, 4H), 3.68 (s, 3H), 5.59 (dd, 1H, *J*=10 Hz), 7.04–7.28 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.7 (s), 25.8 (s), 27.8 (p), 35.7 (s), 45.0 (s), 52.2 (p), 58.9 (t), 83.3 (q), 99.8 (t), 126.5 (t), 128.3 (t), 129.4 (t), 138.0 (q), 152.3 (q), 159.6 (q) 160.1 (q), 161.5 (q), 171.4 (q); IR (film, cm^{-1}) 2936.5, 2855.5, 1732.1, 1575.2, 1533.0, 1449.6, 1423.1, 1369.8, 1304.6, 1282.1, 1256.0, 1148.6, 1040.8, 753.3; MS (PCI, isobutane, 70 eV) *m/z* (%) 475 (M^++1, 100), 419 (20), 375 (20).

1.2.18. L-2-[*tert*-Butoxycarbonyl-(2-chloro-6-piperidin-1-yl-pyrimidin-4-yl)-amino]-3-phenyl-propionic acid benzyl ester (5i). Oil; $[\alpha]_D^{20}$=+96.2 (*c* 1.0, $CHCl_3$); R_f 0.23 (*n*-Hex/diethyl ether=4:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.50–1.74 (bm, 6H), 3.23 (dd, 1H, *J*=14 Hz), 3.44–3.58 (bm, 5H), 3.73 (s, 3H), 5.77 (dd, 1H, *J*=9 Hz), 6.91 (s, 1H), 7.08–7.26 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.5 (s), 25.5 (s), 28.0 (p), 36.5 (s), 45.6 (s), 52.2 (p), 58.8 (t), 83.0 (q), 90.8 (t), 126.4 (t), 128.1 (t), 129.7 (t), 138.0 (q), 152.4 (q), 158.2 (q) 159.8 (q), 164.0 (q), 171.4 (q); IR (film, cm^{-1}). 2938.5, 2856.5, 1724.8, 1583.0, 1527.7, 1449.0, 1393.8, 1369.6, 1253.6, 1219.9, 1150.4, 978.3, 863.0, 752.0; MS (PCI, isobutane, 70 eV) *m/z* (%) 475 (M^++1, 100) and 419 (10).

1.3. Solid-phase amino-de-chlorination of resins 6

To a suspension of resin **6** (100 mol%) in dry DMF (20 mL/mmol) the amine and DIPEA were added in the amount reported in Table 1. The mixture was shaken under nitrogen atmosphere at the temperatures and times reported in Table 1 or Scheme 4. The resin was filtered away and sequentially washed with DCM (×1), 1:1 DMF/H_2O (×2), DMF (×2), 1:1 DMF/H_2O (×2), DMF (×2), DCM (×2), THF (×2), DCM (×2), MeOH (×4), DCM (×2), then the solvent was removed under reduced pressure.

1.3.1. Resin 7a. IR (Microscope, cm^{-1}): 3518.9, 3026.9, 2929.7, 2853.9, 1943.0, 1869.2, 1802.0, 1724.9, 1600.2, 1578.2, 1529.2, 1492.6, 1452.1, 1369.6, 1315.4, 1268.7, 1216.4, 1145.4, 1093.9, 1027.7, 973.2, 818.9, 760.2, 705.4.

1.3.2. Resin 7b. IR (Microscope, cm^{-1}): 3517.6, 3425.0, 3026.2, 3001.8, 2969.0, 2924.0, 2851.2, 1944.6, 1872.3, 1803.5, 1713.7, 1601.3, 1493.2, 1452.1, 1365.9, 1265.4, 1217.8, 1152.1, 1095.5, 1028.8, 758.3, 704.9.

1.3.3. Resin 7c. IR (Microscope, cm^{-1}): 3026.1, 2970.2, 1944.4, 1871.9, 1803.7, 1727.8, 1600.0, 1573.9, 1531.4, 1493.8, 1452.5, 1326.6, 1264.9, 1219.1, 1144.1, 1095.9, 820.3, 756.9, 704.4.

1.3.4. Resin 7d. IR (Microscope, cm^{-1}): 3415.6, 3027.0, 2930.0, 2852.6, 1944.5, 1873.2, 1803.0, 1731.5, 1582.7, 1495.5, 1455.5, 1369.2, 1278.3, 1145.5, 1098.5, 820.3, 763.9, 705.9.

1.3.5. Resin 7e. IR (Microscope, cm^{-1}): 3426.6, 3026.9, 2925.9, 2854.3, 1944.7, 1875.6, 1802.8, 1721.9, 1575.2, 1494.4, 1452.3, 1318.9, 1181.4, 1146.1, 1095.4, 820.3, 757.9, 705.0.

1.3.6. Resin 7f. IR (Microscope, cm^{-1}): 3432.3, 3025.7, 2968.9, 2923.0, 2852.6, 1944.8, 1872.0, 1803.8, 1718.1, 1601.3, 1577.1, 1537.4, 1492.6, 1452.1, 1492.6, 1452.1, 1364.4, 1147.0, 1094.0, 820.1, 753.4, 697.8.

1.3.7. Resin 7g. IR (Microscope, cm^{-1}): 3025.7, 2924.5, 2851.5, 1941.6, 1872.3, 1803.2, 1719.6, 1578.2, 1534.3, 1491.9, 1450.0, 1261.7, 1120.4, 1027.8, 819.1, 760.8, 701.2.

1.3.8. Resin 7h. IR (Microscope, cm^{-1}): 3524.0, 3060.6, 3026.6, 2921.1, 2852.1, 1944.8, 1871.8, 1803.7, 1722.2, 1601.4, 1574.1, 1538.8, 1494.7, 1455.4, 1367.4, 1212.2, 1142.0, 1029.0, 758.6, 695.1.

1.3.9. Resin 7j. IR (Microscope, cm^{-1}): 3425.1, 3060.4, 3026.8, 2926.1, 2854.1, 1942.4, 1801.7, 1718.9, 1578.6, 1492.7, 1453.3, 1369.5, 1211.9, 1141.1, 819.6, 760.6, 704.8.

1.3.10. Resin 7k. IR (Microscope, cm^{-1}): 3524.9, 3060.5, 3026.3, 2926.8, 2853.7, 1944.0, 1870.4, 1802.7, 1732.0, 1584.1, 1495.3, 1455.5, 1369.4, 1269.7, 1141.6, 762.5, 705.8.

1.3.11. Resin 7l. IR (Microscope, cm^{-1}): 3435.9, 3083.1, 3060.4, 3027.5, 3002.3, 2926.4, 2851.9, 1944.8, 1871.7, 1802.3, 1716.8, 1601.6, 1582.0, 1494.8, 1455.8, 1368.1, 1247.2, 1151.7, 760.8, 706.1.

1.3.12. Resin 7m. IR (Microscope, cm^{-1}): 3672.9, 3082.4, 3060.1, 3026.0, 2924.8, 2850.8, 1944.2, 1871.9, 1802.6, 1731.9, 1573.9, 1494.5, 1454.6, 1265.9, 1143.7, 962.8, 758.6, 696.1.

1.3.13. Resin 7n. IR (Microscope, cm^{-1}): 3424.9, 3082.2, 3059.4, 3025.5, 2926.2, 2853.0, 1942.4, 1872.1, 1803.6, 1719.0, 1585.0, 1491.6, 1454.9, 1265.4, 907.6, 761.4, 695.5.

1.3.14. Resin 7p. IR (Microscope, cm^{-1}): 3419.9, 3083.1, 3060.4, 3026.0, 2923.7, 1944.6, 1871.8, 1802.9, 1731.8, 1579.9, 1453.4, 1268.6, 1142.0, 752.4, 697.4.

1.4. Release of aminopyrimidines 8, 9 and 10 from the resins. General procedure

The resin **7** was suspended in a 8:2 DCM/TFA solution (1 mL/70 mg of resin) for 24 h at 25°C. The resin was filtered away and washed with DCM (×2), and MeOH (×3). The solvents were removed at reduced pressure providing the regioisomeric pyrimidines **8** and **9** as trifluoroacetic acid salts in variable degrees of purity (see Table 2). Before GC–MS analysis the samples were washed with aqueous $NaHCO_3$, in order to remove TFA and obtain the free aminopyrimidines. Analogous procedure afforded triaminopyrimidines **10a** and **10b**.

1.4.1. (6-Chloro-2-piperidin-1-yl-pyrimidin-4-yl)-phenyl-amine (8a). GC–MS; t_1, *m/z* (%): 17.07 min, 288 (72.5) [M^+, **8a**]; MS, *m/z* (%): 288 (M^+, 100), 273 (40), 259 (65), 245 (30), 233 (32), 219 (10), 204 (25), 84 (43).

1.4.2. (2-Chloro-6-piperidin-1-yl-pyrimidin-4-yl)-phenyl-amine (9a). GC–MS; t_1, *m/z* (%): 19.17 min, 288 (27.2) [M^+, **9a**]; MS, *m/z* (%): 288 (M^+, 100), 273 (5), 259 (80), 245 (20), 233 (40), 219 (10), 205 (35), 84 (50).

1.4.3. (6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl-amine (8b). GC–MS; t_1, *m/z* (%): 17.05 min, 290 (44.2) [M^+, **8b**]; MS, *m/z* (%): 290 (M^+, 70), 275 (15), 259 (100), 245 (60), 233 (80), 219 (5), 204 (35), 143 (30), 77 (35).

1.4.4. (2-Chloro-6-morpholin-4-yl-pyrimidin-4-yl)-phenyl-amine (9b). GC–MS; t_1, *m/z* (%): 18.90 min, 290 (50.3) [M^+, **9b**]; MS, *m/z* (%): 290 (M^+, 90), 259 (95), 245 (60), 233 (100), 219 (5), 204 (35), 143 (45), 77 (30).

1.4.5. 6-Chloro-2-*N*,*N*-dibenzylamino-4-*N*-phenylamino pyrimidine (8c). GC–MS; t_1, *m/z* (%): 21.54 min, 400 (64.7) [M^+, **8c**]; MS, *m/z* (%): 400 (M^+, 8), 309 (100), 91 (15).

1.4.6. 2-Chloro-6-*N*,*N*-dibenzylamino-4-*N*-phenylamino pyrimidine (9c). GC–MS; t_1, *m/z* (%): 25.20 min, 400 (31.4) [M^+, **9c**]; MS, *m/z* (%): 400 (M^+, 5), 309 (100), 91 (15).

1.4.7. 6-Chloro-2-*N*-phenethylamino-4-*N*-phenylamino pyrimidine (8d). GC–MS; t_1, *m/z* (%): 23.26 min, 324 (78.8) [M^+, **8d**]; MS, *m/z* (%): 324 (M^+, 15), 233 (100), 220 (10), 91 (8), 77 (13).

1.4.8. 2-Chloro-6-*N*-phenethylamino-4-*N*-phenylamino pyrimidine (9d). GC–MS; t_1, *m/z* (%): 26.24 min, 324 (15.1) [M^+, **9d**]; MS, *m/z* (%): 324 (M^+, 15), 233 (100), 220 (70), 91 (30), 77 (23).

1.4.9. 6-Chloro-2-*N*-pentylamino-4-*N*-phenylamino pyrimidine (8e). GC–MS; t_1, *m/z* (%): 16.51 min, 290 (58.2) [M^+, **8e**]; MS, *m/z* (%): 290 (M^+, 35), 275 (10), 261 (20), 247 (40), 233 (100), 219 (50), 204 (10), 143 (30), 116 (25), 77 (20).

1.4.10. 2-Chloro-6-*N*-phenethylamino-4-*N*-phenylamino pyrimidine (9e). GC–MS; t_1, *m/z* (%): 18.44 min, 290 (29.7) [M^+, **9e**]; MS, *m/z* (%): 290 (M^+, 70), 275 (10), 261 (15), 247 (85), 233 (100), 220 (98), 204 (10), 143 (83), 116 (26), 91 (22), 77 (25).

1.4.11. Benzyl-(6-chloro-2-piperidin-1-yl-pyrimidin-4-yl)-amine (8f). GC–MS; t_1, *m/z* (%): 18.08 min, 302 (58.8) [M^+, **8f**]; MS, *m/z* (%): 302 (M^+, 100), 287 (30), 273 (45), 259 (20), 246 (22), 233 (5), 219 (18), 106 (16), 91 (55).

1.4.12. Benzyl-(2-chloro-6-piperidin-1-yl-pyrimidin-4-yl)-amine (9f). GC–MS; t_1, *m/z* (%): 21.21 min, 302 (28.4) [M^+, **9f**]; MS, *m/z* (%): 302 (M^+, 100), 287 (5), 273 (50), 259 (10), 246 (18), 233 (5), 219 (20), 106 (30), 91 (60).

1.4.13. Benzyl-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-amine (8g). GC–MS; t_1, *m/z* (%): 18.12 min, 304 (56.2) [M^+, **8g**]; MS, *m/z* (%): 304 (M^+, 75), 289 (20), 273 (100), 259 (50), 247 (52), 106 (30), 91 (30).

1.4.14. Benzyl-(2-chloro-6-morpholin-4-yl-pyrimidin-4-yl)-amine (9g). GC–MS; t_1, *m/z* (%): 20.93 min, 304 (34.3) [M^+, **9g**]; MS, *m/z* (%): 304 (M^+, 100), 273 (45), 259 (30), 247 (60), 106 (60), 91 (70).

1.4.15. 4-*N*-Benzylamino-6-chloro-2-*N*,*N*-dibenzyl-amino-pyrimidine (8h). GC–MS; t_1, *m/z* (%): 23.31 min, 414 (65.52) [M^+, **8h**]; MS, *m/z* (%): 414 (M^+, 15), 379 (3), 323 (100), 233 (3), 218 (2), 91 (60).

1.4.16. 4-*N*-Benzylamino-2-chloro-6-*N*,*N*-dibenzyl-amino-pyrimidine (9h). GC–MS; t_1, *m/z* (%): 29.33 min, 414 (32.61) [M^+, **9h**]; MS, *m/z* (%): 414 (M^+, 8), 379 (2), 323 (100), 233 (4), 218 (2), 91 (50).

1.4.17. 4-*N*-Benzylamino-6-chloro-2-*N*-phenethylamino-pyrimidine (8i). GC–MS; t_1, *m/z* (%): 27.03 min, 338

(52.0) [M^+, **8i**]; MS, *m/z* (%): 338 (M^+, 25), 247 (100), 234 (18), 91 (80).

1.4.18. 4-*N*-Benzylamino-2-chloro-6-*N*-phenethylamino-pyrimidine (9i). GC–MS; t_1, *m/z* (%): 31.21 min, 338 (16.9) [M^+, **9i**]; MS, *m/z* (%): 338 (M^+, 25), 247 (100), 234 (55), 91 (90).

1.4.19. 4-*N*-Benzylamino-6-chloro-2-*N*-pentylamino pyrimidine (8j). GC–MS; t_1, *m/z* (%): 18.76 min, 304 (59.8) [M^+, **8j**]; MS, *m/z* (%): 304 (M^+, 50), 289 (7), 275 (15), 261 (30), 247 (70), 234 (50), 106 (35), 91 (100).

1.4.20. 4-*N*-Benzylamino-2-chloro-6-*N*-pentylamino pyrimidine (9j). GC–MS; t_1, *m/z* (%): 22.13 min, 304 (24.7) [M^+, **9j**]; MS, *m/z* (%): 304 (M^+, 75), 289 (5), 275 (8), 261 (45), 247 (40), 234 (38), 106 (70), 91 (100).

1.4.21. L-2-(6-Chloro-2-piperidin-1-yl-pyrimidin-4-ylamino)-3-phenyl-propionic acid benzyl ester (8k). GC–MS; t_1, *m/z* (%): 31.23 min, 450 (63.47) [M^+, **8k**]; MS, *m/z* (%): 450 (M^+, 20), 359 (25), 315 (70), 212 (80), 91 (100).

1.4.22. L-2-(2-Chloro-6-piperidin-1-yl-pyrimidin-4-ylamino)-3-phenyl-propionic acid benzyl ester (9k). GC–MS; t_1, *m/z* (%): 41.56 min, 450 (32.26) [M^+, **9k**]; MS, *m/z* (%): 450 (M^+, 5), 359 (30), 315 (50), 212 (100), 91 (80).

1.4.23. L-2-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-3-phenyl-propionic acid benzyl ester (8l). GC–MS; t_1, *m/z* (%): 31.25 min, 452 (61.06) [M^+, **8l**]; MS, *m/z* (%): 452 (M^+, 15), 361 (18), 317 (45), 214 (55), 91 (100).

1.4.24. L-2-(2-Chloro-6-morpholin-4-yl-pyrimidin-4-ylamino)-3-phenyl-propionic acid benzyl ester (9l). GC–MS; t_1, *m/z* (%): 40.56 min, 452 (38.49) [M^+, **9l**]; MS, *m/z* (%): 452 (M^+, 8), 361 (20), 317 (50), 214 (100), 91 (95).

1.4.25. L-2-(6-Chloro-2-pentylamino-pyrimidin-4-ylamino)-3-phenyl-propionic acid benzyl ester (8p). GC–MS; t_1, *m/z* (%): 28.94 min, 452 (74.99) [M^+, **8p**]; MS, *m/z* (%): 452 (M^+, 15), 361 (30), 317 (45), 214 (35), 91 (100).

1.4.26. L-2-(2-Chloro-6-pentylamino-pyrimidin-4-ylamino)-3-phenyl-propionic acid benzyl ester 9p. GC–MS; t_1, *m/z* (%): 37.53 min, 452 (19.36) [M^+, **9p**]; MS, *m/z* (%): 452 (M^+, 7), 361 (40), 317 (55), 214 (65), 91 (100).

1.4.27. (2,6-Di-piperidin-1-yl-pyrimidin-4-yl)-phenyl amine (10a). GC–MS; t_1, *m/z* (%): 27.68 min, 337 (81.3) [M^+, **10a**]; MS, *m/z* (%): 337 (M^+, 100), 322 (10), 308 (80), 294 (15), 282 (20), 268 (13), 254 (50), 84 (15).

1.4.28. 6-*N*,*N*-Dimethylamino-2-*N*-pentylamino-4-*N*-phenylamino pyrimidine (10b). GC–MS; t_1, *m/z* (%): 18.14 min, 299 (81.1%) [M^+, **10b**]; MS, *m/z* (%): 299 (M^+, 100), 284 (20), 270 (22), 256 (90), 242 (70), 214 (40), 200 (30), 186 (16), 171 (10).

1.4.29. 2,6-Bis-*N*,*N*-dipentylamino-4-*N*-phenylamino pyrimidine (10c). GC–MS; t_1, *m/z* (%): 23.95 min, 341 (4.2%) [M^+, **10c**]; MS, *m/z* (%): 341 (M^+, 85), 326 (15), 312 (30), 298 (100), 284 (90), 271 (32), 256 (16), 242 (30), 228 (40), 215 (42), 201 (26).

1.5. Removal of the Boc-protecting group in solution. General procedure

To a solution of **4** or **5** (1.0 mmol) in CH_2Cl_2 (5 mL) stirred at rt under nitrogen atmosphere, a 20% $_{vol.}$ solution of TFA in DCM (2 mL) was added by syringe. The reaction mixture was stirred for an additional hour at the same temperature, then monitored by TLC and quenched by portion-wise addition of solid K_2CO_3 up to pH 7. Then the mixture was diluted with water (10 mL) and the organics were separated, washed with water (2×5 mL), dried over anhydrous sodium sulphate, filtered and evaporated to dryness under reduced pressure to give a residue that was purified by flash chromatography, providing pure **8** or **9**. GC–MS analysis confirmed that compounds **8** and **9** prepared in solution are identical to those obtained through solid-phase synthesis (see above).

1.5.1. Compound 9a. 87% yield; solid, mp 118–120°C (diisopropylether); R_f 0.35 (*n*-Hex/EtOAc=9:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50–1.75 (m, 6H), 3.49 (m, 4H), 5.76 (s, 1H), 6.71 (br s, 1H, NH), 7.12–7.45 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.4 (s), 25.4 (s), 45.4 (s), 99.4 (t), 122.6 (t), 124.7 (t), 129.5 (t), 138.5 (q), 160.0 (q), 162.4 (q), 163.7 (q); IR (microscope, cm^{-1}): 3271, 3030, 2924, 1674, 1630, 1569, 1525, 1498, 1196, 1139. Anal. calcd for $C_{15}H_{17}ClN_4$: C, 62.39; H, 5.93; N, 19.40. Found: C, 62.67; H, 6.02; N, 18.99.

1.5.2. Compound 8d. 92% yield; solid, mp 140–142°C (diisopropylether); R_f 0.42 (*n*-Hex/EtOAc=6:4); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.03 (t, 2H, J=7.3 Hz), 3.80 (dt, 2H, J=11.2, 4.2 Hz), 6.12 (br s, 1H), 7.02 (br s, 1H, NH), 7.25–7.60 (m, 11H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 35.3 (s), 42.8 (s), 92.1 (t), 124.5 (t), 126.7 (t), 128.7 (t), 128.8 (t), 129.8 (t), 163.5 (q), 164.0 (q), 164.5 (q), IR (microscope, cm^{-1}): 3254, 2934, 2853, 1718, 1595, 1219, 1151, 976. Anal. calcd for $C_{18}H_{17}ClN_4$: C, 66.56; H, 5.28; N, 17.25. Found: C, 66.44; H, 5.08; N, 17.48.

1.5.3. Compound 9d. 90% yield; oil, R_f 0.35 (*n*-Hex/EtOAc=6:4); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.86 (t, 2H, J=7.3 Hz), 3.42 (br signal, 2H), 4.11 (br s, 1H, NH), 5.33 (s, 1H), 5.60 (br s, 1H, NH), 7.10–7.55 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 35.1 (s), 43.1 (s), 93.0 (t), 123.3 (t), 125.6 (t), 126.8 (t), 128.7 (t), 128.8 (t), 129.6 (t), 137.6 (q), 137.9 (q), 158.2 (q), 161.6 (q), 163.6 (q); IR (KBr, cm^{-1}) 3242, 2857, 2568, 1879, 1617, 1414, 1272, 996.

1.5.4. Compound 8e. 88% yield; oil, R_f 0.45 (*n*-Hex/EtOAc=6:4); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.11 (br t, 3H, J=6.6 Hz), 1.41–1.50 (m, 4H), 1.73 (dt, 2H, J=14.3, 7.3 Hz), 3.54 (br signal, 2H), 6.12 (s, 1H), 7.04 (br s, 1H, NH), 7.32–7.58 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.9 (p), 21.2 (s), 27.7 (s), 27.8 (s), 40.7 (s), 123.7 (t), 128.9 (t).

1.5.5. Compound 9e. 87% yield; solid, mp 153–155°C (diisopropylether); R_f 0.42 (*n*-Hex/EtOAc=6:4); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J=6.9 Hz), 1.20–1.40 (m, 4H), 1.56 (m, 4H), 3.12 (m, 2H), 5.2 (br s, 1H, NH), 5.56 (s, 1H), 7.03 (br s, 1H, NH), 7.10–7.43 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.9 (p), 22.3 (s), 28.9 (s), 29.7 (s), 41.8 (s), 82.4 (t), 123.1 (t), 125.1 (t), 129.5 (t), 138.2 (q), 159.6q), 162.4 (q), 164.4 (q); IR (microscope, cm^{-1}): 3691, 3271, 2692, 2905, 1671, 1625, 1412, 1254, 1113. Anal. calcd for $C_{15}H_{19}ClN_4$: C, 61.96; H, 6.59; N, 19.27. Found: C, 62.09; H, 6.28; N, 18.97.

1.5.6. Compound 8f. 95% yield; oil, R_f 0.45 (*n*-Hex/EtOAc=6:4); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.55–1.80 (m, 6H), 3.80 (m, 4H), 4.59 (d, 2H, J=5.5 Hz), 5.13 (br s, 1H, NH), 5.74 (s, 1H), 7.32–7.48 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.8 (s), 24.9 (s), 44.9 (s), 45.5 (s), 100.0 (t), 127.5 (t), 127.6 (t), 128.7 (t), 138.5 (q), 160.0 (q), 161.0 (q), 163.7 (q); IR (microscope, cm^{-1}): 3415, 2315, 2932, 2853, 1591, 1518, 1484, 1245, 1127, 972.

1.5.7. Compound 9f. 92% yield; oil, R_f 0.40 (*n*-Hex/EtOAc=6:4); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.58–1.83 (m, 6H), 3.56 (m, 4H), 4.51 (d, 2H, J=5.4 Hz), 5.31 (s, 1H), 5.64 (br s, 1H, NH), 7.25–7.50 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.4 (s), 28.1 (s), 45.6 (s), 48.6 (s), 91.3 (t), 126.8 (t), 127.2 (t), 127.5 (t), 137.7 (q), 153.6 (q), 159.2 (q), 163.8 (q).

1.5.8. Compound 8i. 89% yield; solid, mp 88–90°C (diisopropylether); R_f 0.36 (*n*-Hex/EtOAc=6:4); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.85 (t, 2H, J=6.9 Hz), 3.64 (dt, 2H, J=13.1, 6.9 Hz), 4.51 (br s, 2H), 5.13 (br s, 1H, NH), 5.73 (s, 1H), 7.15–7.40 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 35.9 (s), 42.7 (s), 45.5 (s), 92.1 (t), 126.4 (t), 127.4 (t), 127.6 (t), 128.5 (t), 128.8 (t), 138.1 (q), 139.2 (q), 159.8 (q), 161.4 (q), 164.0 (q); IR (microscope, cm^{-1}): 3419, 3269, 2927, 1595, 1527, 1453, 1349, 1094, 786, 748, 698. Anal. calcd for $C_{19}H_{19}ClN_4$: C, 67.35; H, 5.65; N, 16.54. Found: C, 67.06; H, 5.66; N, 16.59.

1.5.9. Compound 9i. 90% yield; solid, mp 88–90°C (diisopropylether); R_f 0.30 (*n*-Hex/EtOAc=6:4); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.75 (t, 2H, J=7.3 Hz), 3.32 (br m, 2H), 3.97 (s, 2H), 4.36 (br s, 1H, NH), 5.04 (s, 1H), 7.05–7.35 (m, 11H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 35.3 (s), 42.8 (s), 48.5 (s), 91.2 (t), 126.7 (t), 126.9 (t), 127.5 (t), 128.2 (t), 128.8 (t), 128.5 (t), 138.3 (q), 139.0 (q), 153.5 (q), 159.0 (q), 164.9 (q); IR (KBr, cm^{-1}) 3256, 2392, 1611, 1504, 1358, 1151, 982, 880.

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4. See for example: D'Atri, G.; Gomarasca, P.; Resnati, G.; Tronconi, G.; Scolastico, C.; Sirtori, C. R. *J. Med. Chem.* **1984**, *27*, 1621–1629.
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6. The regioisomers **4** and **5** could be easily separated by flash chromatography. The structure of regioisomers **4** and **5** has been assigned making extensive use of X-ray diffraction (full data will be reported elsewhere) and chemical correlation with known pyrimidines (such as those described in Ref. 3). The regioisomers **4**, **5** and **8**, **9** are difficult to distinguish by means of spectroscopic methods, due to their close similarities. A useful empirical method to distinguish **4** from **5**, and **8** from **9** is based on TLC and GC analyses: in all cases **4** and **8** had higher R_f and lower t_r than, respectively, **5** and **9**.
7. When DMF is used as solvent, primary amines RNH_2 (such as benzylamine, phenethylamine or *n*-pentylamine) in excess, unnecessarily long reaction time or excessive warming should be all avoided, because highly reactive dimethylamine is produced from the reaction: $RNH_2+Me_2N-CHO\rightarrow RNH-CHO+Me_2NH$. Dimethylamine competes with RNH_2 in the amino-de-chlorination affording *N*,*N*-dimethylamino-pyrimidine by-products. The same side-reaction was observed in the solid-phase version. Obviously, this undesired event could be avoided by using other solvents such as benzene, ethanol or THF, but we qualitatively observed slower and less efficient reactions. Direct formylation of amines by DMF has been previously described: (a) Birkofer, L.; Hartwig, I. *Chem. Ber.* **1956**, *89*, 1608–1614. (b) Pettit, G. R.; Thomas, E. G. *J. Org. Chem.* **1959**, *24*, 895–896, We are currently investigating the use of *N*,*N*-dimethylacetamide (DMA) and *N*-methyl-pyrrolidone (NMP).
8. Formation of *N*,*N*-dimethylamino-pyrimidines in the solid-phase was observed mainly with primary amines, when longer reaction times or higher temperatures than those reported in Table 2 were used.
9. See Ref. 3c for further details.
10. Surprisingly, a single regioisomer of **10b** was detected by GC–MS. The regiochemistry portrayed in Scheme 4 was not assessed spectroscopically.