Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 2304–2312
Tetrahedron

An efficient solid-phase synthesis of 2-alkyl-4,6-diaminopyrimidines and 2,4,6-triaminopyrimidines

Csaba Wéber,* Ádám Demeter and István Greiner

Chemical and Biotechnological Research and Development, Gedeon Richter Ltd, PO Box 27, H-1475 Budapest, Hungary

Received 26 September 2005; revised 11 November 2005; accepted 1 December 2005

Available online 20 December 2005

Abstract—An efficient and simple approach for the solid-phase synthesis of 2,4,6-triaminopyrimidines and 2-alkyl-4,6-diaminopyrimidines is described. Primary amines were immobilized on 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene resin via reductive amination. Attachment of two different 4,6-dichloropyrimidines led to the corresponding 4-chloro-6-aminopyrimidine intermediates. Aromatic nucleophilic substitution with various aliphatic amines or the corresponding lithium amides afforded the desired aminopyrimidines in high yield and excellent purity after acidic cleavage from the resin. The products were characterized by LC–MS, ^{1}H and ^{13}C NMR spectroscopy. Deuterium exchange experiments revealed that the investigated aminopyrimidines have a general tendency toward C-5 protonation.

1. Introduction

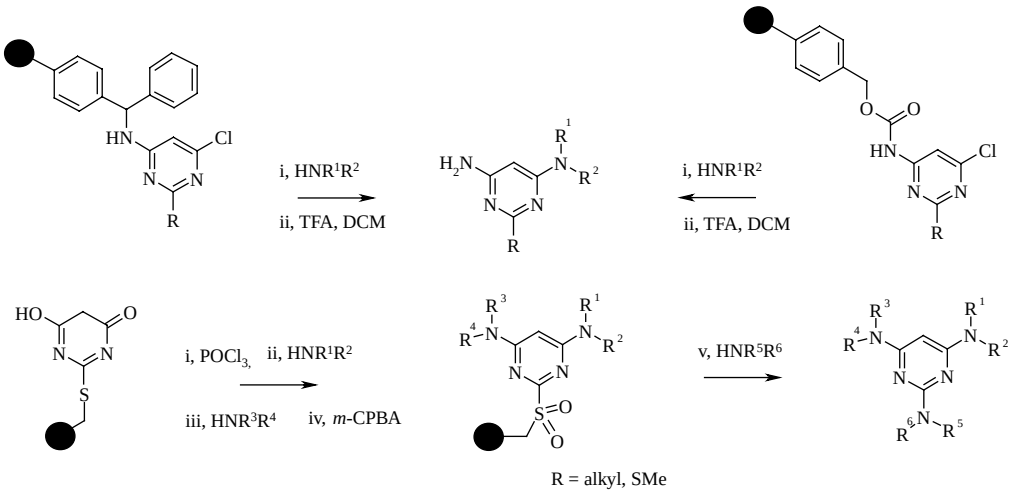
Di- and triaminopyrimidines are reported to exhibit diverse biological and pharmacological activities including acting as tyrosine kinase[1] and dihydrofolate reductase[2] inhibitors, as well as antibacterial,[3] antiallergenic[4] and antimalarial[5] agents. Antiviral,[6] antidepressant[7] and antiprotozoan[8] activities of diaminopyrimidines have been disclosed as well. With the potent biological and pharmacological activities of aminopyrimidines in mind, the development of an efficient solid-phase strategy for the synthesis of these compounds was explored.

In addition to a number of reports describing the solution-phase syntheses of aminopyrimidines[9] examples of solid-phase syntheses of these compounds can be found in the literature. Thus, various aminopyrimidines have been prepared on solid support starting either by de novo synthesis of the pyrimidine core onto the resin,[10,11] or by initial attachment of the pyrimidine to the resin and subsequent modification.[12–18] Most of the known methods couple the pyrimidine core to the resin either via an alkylsulfinyl group[10,11,15] or via the amino group of a Rink amide linker (Scheme 1).[12,13] Attachment to the solid support via an amino group using a carbamate bond has been reported as well.[14,17,18] There are two disadvantages of using an alkylsulfenyl group as a linker. Firstly, for substitution by amines the sulfide has to be oxidized to sulfone or sulfoxide, which can result in formation of undesired by-products (*N*-oxides). Secondly, removing of the excess of amine used in the last step requires an extra chemical step. The drawback of using methods based on a Rink amide linker is that they afford aminopyrimidines that are not substituted at one of the amino groups. Moreover, a general problem originates from the introduction of the third amino group, which requires very harsh conditions limiting the field of amines that can be used in this step. Although trimethyl aluminium catalyzed substitution of the sulfone group at the C-2-position by aromatic amines under mild conditions has been published recently, the method was used only for the synthesis of 2,4-diaminopyrimidines.[16]

Our aim was to develop a simple, efficient and robust synthetic strategy for the synthesis of 2-alkyl-4,6-diamino-pyrimidines and 2,4,6-triaminopyrimidines that would not only allow the use of a wide range of primary and secondary aliphatic amines but would easily be automated and would also be amenable to either large or small focused library synthesis. Our approach differs from previous ones by using solid-phase supported amines instead of the Rink linker and by using strongly nucleophilic lithium amides, generated from the amines, for the introduction of the third amino group.

Keywords: Solid-phase; Aliphatic amines; 4,6-Dichloropyrimidines.
Abbreviations: DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; DMAC, *N*,*N*-dimethylacetamide; THF, tetrahydrofuran; TFA, trifluoroacetic acid; TEA, triethylamine; DIEA, *N*,*N*-diisopropylethylamine; *m*-CPBA, 3-chloroperbenzoic acid; Pip, piperidine; Pyr, pyrrolidine; Pip-C(2,6), carbon atoms of piperidine at 2- and 6-positions; Pip-H(2,6), hydrogen atoms connected to Pip-C(2,6); eq, equatorial; ax, axial; ^{x}H and ^{y}H, chemically nonequivalent hydrogen atoms.
* Corresponding author. Tel.: +36 1 431 5144; fax: +36 1 432 6002; e-mail: cs.weber@richter.hu

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.12.004



Scheme 1. Linkage strategies for aminopyrimidines.

2. Results and discussion

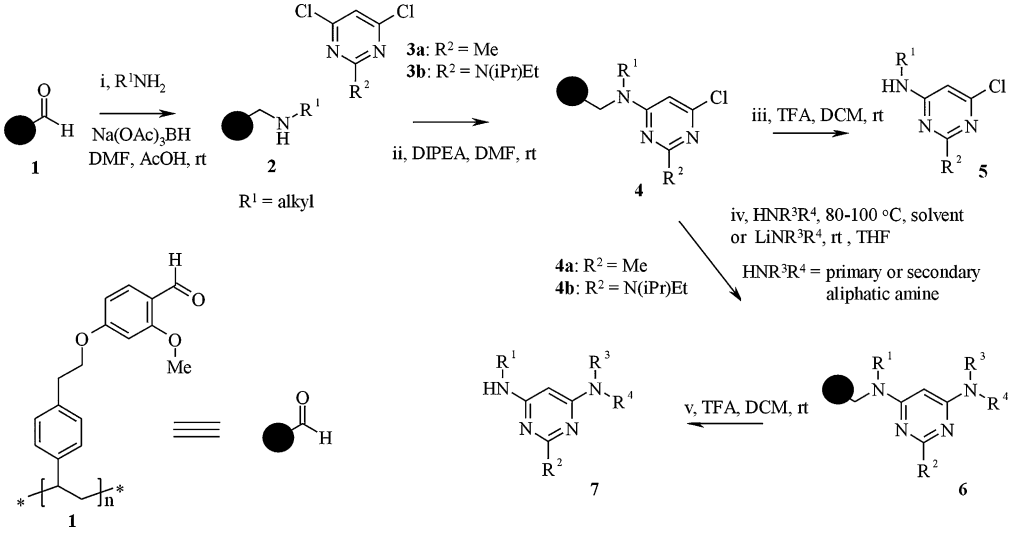
Herein, we report an efficient solid-phase synthesis of 2,4,6-triaminopyrimidines and 2-alkyl-4,6-diaminopyrimidines from acid labile 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene **1** in which sequential aromatic nucleophilic substitutions of the chlorines of 4,6-dichloropyrimidines are employed as key steps (Scheme 2).

Although the use of 2-(4-formyl-3-methoxyphenoxy)ethyl linker for the synthesis of aminopyrimidines had not been demonstrated before, it was successfully employed for solid-phase synthesis of diaminoquinazolines.[19] For the synthesis of aminopyrimidines the more acid sensitive 4-formyl-3,5-dimethoxyphenoxy linker was employed by Arvanitis et al.[16]

In the first step, 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene resin **1** was loaded with various primary aliphatic amines by reductive amination (Scheme 2).[20] The conversion proved to be quantitative, as checked by elemental analysis (N content). Primary amines branched at the α-position were also applied successfully in this step.

We chose to make use of two different 4,6-dichloropyrimidines (**3a**, **3b**) in order to explore the chemistry outlined in Scheme 2. Both 2-alkyl- and 2-aminopyrimidines can easily be synthesized: **3a** was prepared in one step from 2-methyl-4,6-pyrimidinedione,[21] **3b** from 2,4,6-trichloropyrimidine.[22]

Attachment of the two pyrimidines (**3a**, **3b**) to a supported secondary amine **2** was achieved in the presence of *N*,*N*-diisopropylethylamine (DIEA) in *N*,*N*-dimethylformamide (DMF) at room temperature. Quantitative attachment was obtained for a pyrimidine concentration of 1.5 M for 100 h at room temperature. Resin loadings were verified by the N content of the resin. At this point, it was checked whether the *o*-methoxybenzyl group of aminopyrimidine intermediate **4** can be cleaved by TFA/DCM mixture. Treatment of **4** with 10% TFA in DCM resulted in the formation of the expected 4-chloro-6-amino derivatives **5** in nearly



Scheme 2. Solid-phase synthesis of aminopyrimidines.

Table 1. Purities and yields of 6-amino-4-chloropyrimidines (**5**)

	Product	R^1	R^2	Yield (%)[a]	Purity (%)[b]
1	**5/1**	*n*-Hexyl	*N*-Isopropylethylamino	96	98
2	**5/2**	2-Methylbutyl	*N*-Isopropylethylamino	91	99
3	**5/3**	2-Heptyl	*N*-Isopropylethylamino	92	98
4	**5/4**	*n*-Hexyl	Methyl	94	99
5	**5/5**	2-Methylbutyl	Methyl	96	97
6	**5/6**	2-Heptyl	Methyl	98	98

[a] The yields were determined by weight based on the loading of **4**.
[b] The purities were determined by HPLC–MS at 254 nm.

quantitative yields and excellent purities (Table 1). The structures of these products was confirmed by NMR and mass spectrometry as well. Yields obtained from the N content of **4** are equal, within experimental error, to those calculated from the weight of **5**.

In the next step, aromatic nucleophilic substitution reaction of solid-phase bound 4-chloro-6-aminopyrimidine derivatives **4** with various aliphatic amines was studied. Release from the resin was achieved by treating **6** with 10% TFA in DCM to yield the desired product **7**. Formation of **7** in high purity was proven by HPLC, ^{1}H and ^{13}C NMR analysis of the unpurified material.

Reactions of 2-methyl- and 2-(*N*-isopropylethylamino)pyrimidine derivatives **4** with primary and secondary aliphatic amines, branched and unbranched four to six-membered cyclic amines were investigated in different solvents (*N*,*N*-dimethylacetamide (DMAC), *n*-BuOH, $MeNO_2$) using 20 fold excess of amines. Because in the course of our former experiments DMAC was found to be the best solvent of amines, it was tried first. While in the case of using unbranched four to six-membered cyclic amines the reaction was complete in 140 h in DMAC at 100 °C (Table 2, entries 1–11), primary and acyclic secondary aliphatic amines did not give pure products under these conditions. In the latter cases, in addition to the desired aminopyrimidines, 6-amino-4-dimethylaminopyrimidine side products were observed up to 15–45% of the product.

Formation of this type of side product in reaction of chloropyrimidines and amines in DMF was reported by Load[23] previously. Cyclic amines branched at α-position did not give pure product with **4a**, probably because of steric effects (Table 2, entries 12 and 13). While reactions of 2-methyl derivatives **4a** with primary and secondary aliphatic amines in *n*-BuOH or $MeNO_2$ afforded the desired products in high yield and purity (Table 2, entries 14–19), 2-amino derivatives **4b** did not give pure products under the same conditions. This is probably due to the fact that the chlorine in **4b** is less reactive than it is in **4a** because of the stronger electron donating effect of the *N*-isopropylethylamino group compared to the methyl group.

To replace the chlorine of **4b** by aliphatic amines under mild conditions a new approach was examined. Since we could not achieve high conversion neither by prolonged reaction times nor by higher concentrations of the amines we tried to increase the nucleophilic character of the reagent. Amines were deprotonated by *n*-BuLi, forming lithium amides, before adding resin to the solution. The reaction conducted at room temperature afforded the desired triaminopyrimidines in moderate yield and high purity after acidic cleavage from the resin (Table 2, entries 20 and 21).

Table 2. Purities and yields of 4,6-diaminopyrimidines (**7**)

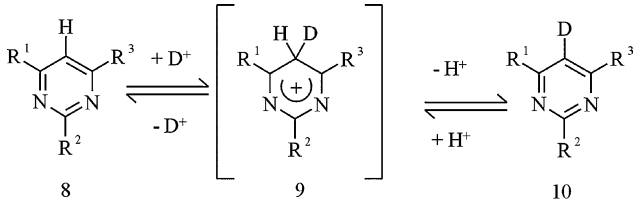
	Product	R^1	R^2	HNR^3R^4	Solvent	Yield (%)[a]	Purity (%)[b]
1	**7/1**	*n*-Hexyl	*N*-Isopropylethylamino	4-Methylpiperidin-1-yl	DMAC	89	95
2	**7/2**	2-Methylbutyl	*N*-Isopropylethylamino	4-Methylpiperidin-1-yl	DMAC	84	98
3	**7/3**	2-Methylbutyl	*N*-Isopropylethylamino	Pyrrolidin-1-yl	DMAC	89	99
4	**7/4**	2-Methylbutyl	*N*-Isopropylethylamino	Azetidin-1-yl	DMAC	87	81
5	**7/5**	*n*-Hexyl	Methyl	4-Methylpiperidin-1-yl	DMAC	95	99
6	**7/6**	2-Methylbutyl	Methyl	4-Methylpiperidin-1-yl	DMAC	94	99
7	**7/7**	2-Heptyl	Methyl	4-Methylpiperidin-1-yl	DMAC	93	99
8	**7/8**	2-Methylbutyl	Methyl	4-Phenylpiperazin-1-yl	DMAC	86	99
9	**7/9**	2-Methylbutyl	Methyl	Pyrrolidin-1-yl	DMAC	77	99
10	**7/10**	2-Heptyl	Methyl	Pyrrolidin-1-yl	DMAC	96	99
11	**7/11**	2-Methylbutyl	Methyl	Azetidin-1-yl	DMAC	84	99
12	**7/12**	2-Methylbutyl	Methyl	2-Ethylpiperidin-1-yl	DMAC	—	28
13	**7/13**	2-Methylbutyl	Methyl	2,6-Dimethylpiperidin-1-yl	DMAC	—	0
14	**7/14**	2-Methylbutyl	Methyl	Bis(*n*-butyl)amino	*n*-BuOH	82	95
15	**7/14**	2-Methylbutyl	Methyl	Bis(*n*-butyl)amino	$MeNO_2$	79	91
16	**7/15**	*n*-Hexyl	Methyl	*n*-Hexylamino	*n*-BuOH	87	98
17	**7/15**	*n*-Hexyl	Methyl	*n*-Hexylamino	$MeNO_2$	85	80
18	**7/16**	2-Methylbutyl	Methyl	*n*-Hexylamino	*n*-BuOH	85	98
19	**7/17**	2-Heptyl	Methyl	*n*-Hexylamino	*n*-BuOH	87	98
20	**7/18**	*n*-Hexyl	*N*-Isopropylethylamino	Bis(*n*-butyl)amino	THF	61	91
21	**7/19**	*n*-Hexyl	*N*-Isopropylethylamino	*n*-Hexylamino	THF	57	93

[a] The yields were determined by weight based on the loading of **4**.
[b] The purities were determined by HPLC–MS at 254 nm.

In summary, the next conditions were found to be optimal for the synthesis of **7**:

1. DMAC, 100 °C, 140 h, $c_{amine}=1.8$ mmol/1 mL solvent, for the introduction of four to six-membered unbranched cyclic aliphatic amines.
2. *n*-BuOH, 100 °C, 140 h, $c_{amine}=1.8$ mmol/1 mL solvent, for the introduction of unbranched primary and secondary aliphatic amines into 2-alkylpyrimidines.
3. Lithium amide salt of the amine, room temperature, THF, 24 h, $c_{Li-amide}=0.5$ M for the introduction of unbranched primary and secondary aliphatic amines into 2-aminopyrimidines.

We have recently showed that *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethyl-2,4,6-pyrimidinetriamine (**8**, $R^1=R^2=R^3=NMe_2$, Fig. 1) could be carbon-protonated at the C(5) position in addition to the expected N(1) protonation.[22] We also described the synthesis of the first stable cationic sigma complex in the pyrimidine series.[24] In a forthcoming paper, we gave detailed account of the structure determination aspect of that work.[25] In the case of compound **8** ($R^1=R^2=R^3=NMe_2$) the C(5) and N(1) protonated forms could be detected simultaneously, showing that the exchange between the two protonated forms is slow on the NMR chemical shift timescale. Keeping on this track, in this paper we investigated the generality of carbon protonation of aminopyrimidines on aminopyrimidine derivatives (**5** and **7**). The C(5) protonated forms of the investigated compounds could not be detected directly due to their small population. An indirect proof, however, was observed via deuterium exchange NMR experiments (Fig. 1).



R^1: primary aliphatic amino group
R^2 : Me or -N(iPr)Et
R^3: Cl, primary or secondary aliphatic amino group

Figure 1. Deuterium exchange via the C(5) protonated sigma complex.

D_2O (5%) was added to the DMSO-d_6 solutions of selected derivatives prepared as TFA salts, and their ^1H NMR spectra were recorded at 30 °C immediately after addition of D_2O and again several hours later.

We observed nearly complete deuterium exchange of the H(5) proton for **7/1**, **7/2**, **7/3** within 1–3 h. Deuterium exchange of H(5) proceeded on a somewhat slower timescale (3–24 h) for **7/6–10**. After 2 days 70, 50 and 80% deuterium exchange was observed on the H(5) signal of **7/14**, **7/16** and **7/17**, respectively. It is interesting to note that **7/11** did not show considerable deuterium exchange, which is attributed to the presence of the strained azetidine ring. For the 4-chloro derivatives, deuterium exchange at H(5) was nearly complete for **5/2**, while **5/5** and **5/6** did not show exchange after 2 days.

The observed deuterium exchange proves the ongoing C(5) protonation indirectly, since the exchange process involves the presence of the C(5) protonated sigma complex form (**9**). The observed deuterium exchange characteristic of the investigated compounds, that is, the rate of exchange, qualitatively seems to show correlation with the electron donating effect of amino substituents. However, further investigations (precise exchange rate measurements) are required to prove this correlation.

3. Conclusion

A simple and efficient four-step strategy has been described for the solid-phase synthesis of 2,4,6-triaminopyrimidines and 2-alkyl-4,6-diaminopyrimidines. The synthetic approach provides convenient access to pharmacologically interesting aminopyrimidine derivatives in good yields and excellent purities. To the best of our knowledge, this is the first example of using 2-(4-formyl-3-methoxyphenoxy)ethyl linker for the synthesis of aminopyrimidines and the first solid-phase method applying lithium amide as nucleophile for displacing the chlorine of chloropyrimidines. Deuterium exchange experiments proved that 2,4,6-triaminopyrimidines and 2-alkyl-4,6-diaminopyrimidines have a general tendency toward C(5) protonation.

Further investigation to assess the applicability of the synthetic strategy to the automated synthesis of large aminopyrimidine libraries as well as a detailed study of C-5 protonation of aminopyrimidines are in progress.

4. Experimental

4.1. General

Reagents were obtained from Sigma-Aldrich. 2-(4-Formyl-3-methoxyphenoxy)ethyl polystyrene resin was purchased from Novabiochem (cat number: 01-64-0399, batch number: A26869, 100–200 mesh, 1% cross-linked, 1.2 mmol/g). Solvents were obtained from Merck and were used as received. Small scale parallel solid-phase reactions were performed using an Advanced ChemTech PLS 4×6 system in 8 mL glass reaction vials (1.5×5 cm) with Teflon-lined screw-cap. Cleavage and washing of the resin were performed in 8 mL Teflon vials (1.5×5 cm) equipped with a filter at the bottom.

Purity was determined by HPLC (Hewlett-Packard HP 1100) using an acetonitrile/water gradient (100% water to 95% acetonitrile v/v, with 0.1% TFA with a run time of 20 min) on a Discovery RP C_{16}–amide column (5 cm× 4.6 mm, 5 μm) operating at a flow rate of 1 mL/min; analysis was conducted at 254 nm wavelength, and retention times were recorded. The sample concentration was 1.0 mg/mL. Molecular parent ion identity was confirmed via mass spectrometry using electrospray ionization and a probe voltage of 4.0 kV.

The structures of compounds having at least 80% purity were confirmed by nuclear magnetic resonance (NMR)

spectroscopy. NMR spectra were recorded either at 300 or 500 MHz for ^{1}H and 125 or 75 MHz for ^{13}C on a Varian INOVA spectrometer. The chemical shifts are reported in ppm relative to TMS in $CDCl_3$ or in DMSO-d_6 at 30 °C. HRMS were performed on a FinninganMAT 95XP apparatus (EI, 70 eV, resolution: 10,000).

Melting points are uncorrected.

4.1.1. Resin-bound amines (2). Resin (3.0 g, 3.6 mmol) was added to a mixture of DMF (30 mL) and DCM (20 mL). Aliphatic primary amine (36 mmol) and acetic acid (36 mmol, 2.2 mL) were added dropwise. The resulting mixture was shaken for 2 h and then $NaBH(OAc)_3$ (3.68 g, 17 mmol) was added in 4 portions. After 24 h reaction at room temperature the resin was washed [3×30 mL DMF, 3×30 mL MeOH, 3×30 mL DCM, 3×30 mL DMF (5% TEA), 3×30 mL DCM (5% TEA), 3×30 mL MeOH (5% TEA), 4×30 mL MeOH, 4×30 mL DCM] and dried under vacuo for 48 h. The loading of the resin was determined by N content: **2a** (*N*-hexyl): 1.06 mmol/g (conversion=97%); **2b** (*N*-2-methylbutyl): 1.08 mmol/g (conversion=98%); **2c** (*N*-2-heptyl): 1.04 mmol/g (conversion=95%).

4.1.2. 4,6-Dichloro-2-methylpyrimidine (3a).[21] 4,6-Dihydroxy-2-methylpyrimidine (5.0 g, 0.04 mol) was stirred in $POCl_3$ (30 mL) at 140 °C for 3 h. The excess of $POCl_3$ was distilled off and the residue was poured onto crushed ice (50 g). The precipitate was filtered off and purified by silica gel column chromatography (50 g silica gel, $CHCl_3$) to give 5.4 g product (colourless crystal). Yield: 84%. Mp 46–47 °C. Mp published:[21] 49 °C. HPLC–MS: $M^+=162$ (EI); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.64 (s, 3H, CH_3), 7.18 [s, 1H, H(5)]. ^{13}C NMR ($CDCl_3$, 125 MHz, 30 °C): δ 25.7 CH_3, 118.4 C(5), 161.6, 169.8 C(4, 6), C(2).

4.1.3. 4,6-Dichloro-2-(*N*-isopropylethylamino)-pyrimidine (3b). A solution of 2,4,6-trichloropyrimidine (6.6 g, 0.036 mol) in DCM (100 mL) was cooled to −40 °C under a N_2 atmosphere. A solution of *N*,*N*-diisopropylethylamine (7.26 mL, 0.04 mol) and *N*-isopropylethylamine (4.84 mL, 0.04 mol) in DCM (100 mL) was added dropwise to the solution of trichloropyrimidine over 30 min. The reaction was allowed to warm up to room temperature over 2 h and was refluxed for 6 h. The solution was washed with water (2×200 mL), dried over Na_2SO_4, following which solvent removal was performed at reduced pressure and at temperature less than 40 °C. The 2-amino isomer was separated from its regioisomer by column chromatography (450 g silica gel, hexane/ethyl acetate=98:2). $m=3.0$ g (colourless oil). Yield=38%. HPLC–MS: $M^+=233$ (EI); ^{1}H NMR (DMSO-d_6, 500 MHz, 30 °C): δ 1.13 (t, 3H, $J=7$ Hz, CH_3CH_2N–), 1.14 (d, 6H, $J=6.5$ Hz, $(CH_3)_2CHN$–), 3.39 (q, 2H, $J=7$ Hz, CH_3CH_2N–), 4.79–4.88 [m, 1H, $(CH_3)_2CHN$–], 6.40 [s, 1H, H(5)]. ^{13}C NMR (DMSO-d_6, 125 MHz, 50 °C): δ 14.3, 20.3 [$(CH_3)_2CHN$–, CH_3CH_2N–], 37.4 CH_3CH_2N–, 47.1 $(CH_3)_2CHN$–, 107.0 C(5), 160.3, 161.2 C(2, 4, 6). Anal. Calcd for: $C_9H_{13}Cl_2N_3$; C, 46.17%; H, 5.60%; Cl, 30.28%; N, 17.95%. Found: C, 46.25%; H, 5.58%; Cl, 30.35%; N, 18.01%.

4.2. General procedure for the preparation of polymer-bound 4-chloropyrimidines (4)

To a suspension of polymer-bound amine (1.3 g, ≅1.4 mmol) **2** in DMF (4 mL) was added 4,6-dichloropyrimidine derivative **3** (20.7 mmol) and DIEA (1.25 mL, 7 mmol). The mixture was shaken for 120 h at room temperature. The polymer was filtered off, washed (3×20 mL DMF, 3×20 mL MeOH, 3×20 mL DCM, 3×20 mL MeOH, 3×20 mL DCM, 3×20 mL MeOH, 3×20 mL DCM), and dried in vacuo for 48 h to give resin **4**. Capacities of the resins ranged from 0.85 to 0.94 mmol/g based on a N content ranging from 2.7 to 3.5 mmol/g. Conversions calculated from the N content were 95–98%.

4.3. Cleavage of 4 from the resin: preparation of 6-amino-4-chloropyrimidines 5

Resin **4** (50 mg, 0.042–0.048 mmol) was shaken in DCM–TFA (9/1) (2 mL) for 2 h, then it was filtered off. The filtrate was combined with washes of DCM (2×1 mL) and MeOH (2×1 mL), the solvent was evaporated then the residue was dried under vacuo overnight to give **5**. The products as trifluoroacetate salts were obtained as glassy colourless or yellowish oils or semisolids. The weight of the products ranged from 14 to 17 mg. The yields were calculated from weight of **5** based on the loading of **4**, and ranged from 91 to 99%.

4.3.1. 6-(*n*-Hexylamino)-2-(*N*-isopropylethylamino)-4-chloropyrimidine (5/1). Yield: 96%. Glassy yellowish oil. ^{1}H NMR (DMSO-d_6, 500 MHz, 30 °C): δ 0.86 (t, 3H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH$–), 1.11 (t, 3H, $J=7$ Hz, CH_3CH_2N–), 1.12 [d, 6H, $J=7$ Hz, $(CH_3)_2CHN$–], 1.22–1.34 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.44–1.53 [m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.15–3.45 [br m, 4H, $CH_3(CH_2)_3CH_2CH_2NH$–, CH_3CH_2N–], 4.78 [m, 1H, $J=7$ Hz, –N$CH(CH_3)_2$], 5.70 [s, 1H, H(5)], 7.13 [br s, 1H, $CH_3(CH_2)_3CH_2CH_2NH$–]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8 $CH_3(CH_2)_5NH$–, 14.9 CH_3CH_2N–, 20.1 $(CH_3)_2CHN$–, 22.0 $CH_3CH_2(CH_2)_3CH_2NH$–, 26.1 $CH_3(CH_2)_2CH_2(CH_2)_2NH$–, 28.9 $CH_3(CH_2)_3CH_2CH_2NH$–, 30.9 $CH_3CH_2CH_2(CH_2)_3NH$–, 36.1 CH_3CH_2N–, 40.4 $CH_3(CH_2)_5CH_2NH$–, 45.4 $(CH_3)_2CHN$–, 91.8 C(5), 156.7 C(6), 160.0 C(2), 163.4 C(4); HPLC–MS: $M^+=298$ (EI); Purity: 98%. HRMS: (EI), *m*/*z* [M^+] found: 298.1931, calcd for $C_{15}H_{27}^{35}ClN_4$: 298.1924.

4.3.2. 4-Chloro-2-(*N*-isopropylethylamino)-6-(2-methyl-*n*-butylamino)pyrimidine (5/2). Yield: 91%. Glassy yellowish oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.85 [d, 3H, $J=7$ Hz, $CH_3CH_2(CH_3)CHCH_2NH$–], 0.87 [t, 3H, $J=7$ Hz, $CH_3CH_2(CH_3)CHCH_2NH$–], 1.11 (t, $J=7$ Hz, 3H, CH_3CH_2N–), 1.12 [d, 6H, $J=7$ Hz, $(CH_3)_2CHN$–], 1.14–1.25 [m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH$–], 1.25–1.50 [m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH$–] 1.50–1.70 [m, 1H, $CH_3CH_2(CH_3)CHCH_2NH$–], 2.9–3.1 [m, 1H, $CH_3CH_2(CH_3)CHCH^xH^yNH$–], 3.15–3.35 [br m, 1H, $CH_3CH_2(CH_3)$- $CHCH^xH^yNH$–], 3.36 [q, 2H, $J=7$ Hz, CH_3CH_2N–], 4.78 [heptett, 1H, $J=7$ Hz, $CH_3CH_2(N$–$)CH(CH_3)_2$], 5.73 [s, 1H, H(5)], 7.21 [br s, 1H, $CH_3(CH_2)_3CH_2CH_2NH$–]. HPLC–MS: $M^+=284$ (EI); Purity: 99%. HRMS: (EI), *m*/*z* [M^+] found: 284.1774, calcd for $C_{14}H_{25}^{35}ClN_4$: 284.1768.

4.3.3. 4-Chloro-6-(2-heptylamino)-2-(*N*-isopropylethylamino)pyrimidine (5/3). Yield: 92%. Glassy yellowish oil. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.82 [t, 3H, $CH_3CH(NH–)(CH_2)_4CH_3$], 1.05–1.20 [m, 12H, $CH_3CH_2N–$, $(CH_3)_2CHN–$, $CH_3CH(NH–)(CH_2)_4CH_3$], 1.20–1.35 [m, 6H, $CH_3CH(NH–)CH_2(CH_2)_3CH_3$], 1.35–1.40 [m, 1H, $CH_3CH(NH–)CH^xH^y(CH_2)_3CH_3$], 1.40–1.55 [m, 1H, $CH_3CH(NH–)CH^xH^y(CH_2)_3CH_3$], 3.35–3.50 [q, 2H, $CH_3CH_2N–$], 4.00–4.15 [m, 1H, $CH_3CH(NH)(CH_2)_4CH_3$], 4.65–4.85 [m, 1H, $–NCH(CH_3)_2$], 5.69 [s, 1H, H(5)], 6.95 [br m, 1H, $CH_3CH(NH)(CH_2)_4CH_3$], 8.9–9.0 [br s, 1H, CF_3COOH]. HPLC–MS: $M^+=312$ (EI); Purity: 98%. HRMS: (EI), *m/z* [M^+] found: 312.2092, calcd for $C_{16}H_{29}^{35}ClN_4$: 312.2081.

4.3.4. 6-(*n*-Hexylamino)-4-chloro-2-methylpyrimidine (5/4). Yield: 94%. Glassy colourless oil. NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 3H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH–$], 1.22–1.34 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH–$], 1.50 [p, 2H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH–$], 2.32 [s, 3H, Me(C2)], 3.0–3.4 [br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH–$], 6.35 [s, 1H, H(5)], 7.4–8.1 [br m, 1H, $CH_3(CH_2)_3CH_2CH_2NH–$], ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8 $CH_3(CH_2)_4CH_2NH–$, 22.0 $CH_3CH_2(CH_2)_3CH_2NH–$, 25.2 $CH_3C(2)$, 25.9 $CH_3(CH_2)_2CH_2CH_2CH_2NH–$, 28.51 $CH_3(CH_2)_3CH_2CH_2NH–$, 30.9 $CH_3CH_2CH_2(CH_2)_3NH–$, 40.9 $CH_3(CH_2)_3CH_2CH_2NH–$, 100.6 C(5), 163.2 C(4), 167.4 C(2), The C(6) signal is broadened to the extent that it escapes detection. HPLC–MS: $M^+=227$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 227.1178, calcd for $C_{11}H_{18}^{35}ClN_3$: 227.1189.

4.3.5. 4-Chloro-2-methyl-6-(2-methyl-*n*-butylamino)pyrimidine (5/5). Yield: 96%. Glassy colourless oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86 (d, 3H, $J=6.9$ Hz, $CH_3CH_2(CH_3)CHCH_2NH–$), 0.87 (t, 3H, $CH_3CH_2(CH_3)CHCH_2NH–$), 1.05–1.20 (m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH–$), 1.25–1.50 (m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH–$), 1.50–1.68 (m, 1H, $CH_3CH_2(CH_3)CHCH_2NH–$), 2.31 [s, 3H, $CH_3(C2)$], 2.80–3.35 [m, 2×1H, $CH_3CH_2(CH_3)CHCH^xH^yNH–$], 6.37 [s, 1H, H(5)], 7.60 (br s, 1H, $CH_3CH_2(CH_3)CHCH_2NH–$). HPLC–MS: $M^+=213$ (EI); Purity: 97%. HRMS: (EI), *m/z* [M^+] found: 213.1039, calcd for $C_{10}H_{16}^{35}ClN_3$: 213.1033.

4.3.6. 4-Chloro-6-(2-heptylamino)-2-methylpyrimidine (5/6). Yield: 98%. Glassy colourless oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.85 [t, 3H, $J=6.6$ Hz, $CH_3CH(NH–)(CH_2)_4CH_3$], 1.09 [d, 3H, $J=6.6$ Hz, $CH_3CH(NH–)(CH_2)_4CH_3$], 1.18–1.35 [m, 6H, $CH_3CH(NH–)CH_2(CH_2)_3CH_3$], 1.35–1.55 [m, 2H, $CH_3CH(NH–)CH_2(CH_2)_3CH_3$], 2.31 [s, 3H, $CH_3(2)$], 4.0–4.3 [br m, 1H, $CH_3CH(NH)(CH_2)_4CH_3$], 6.2–6.4 [br s, 1H, H(5)], 7.5–7.7 [br m, 1H, $CH_3CH(NH)(CH_2)_4CH_3$]. HPLC–MS: $M^+=241$ (EI); Purity: 98%. HRMS: (EI), *m/z* [M^+] found: 241.1360, calcd for $C_{12}H_{20}^{35}ClN_3$: 241.1346.

4.4. Preparation of resin-bound 4,6-diamino- and 2,4,6-triaminopyrimidines (6)

Method A. Resin **4** (100 mg, ≅0.085–0.094 mmol) was swollen in DMAC (for reaction with four to six member cyclic amines) or in *n*-BuOH (for reaction of acyclic primary and secondary amines with 2-alkylpyrimidines) (1.0 mL), and the amine (1.7–1.84 mmol) was added. The mixture was shaken for 140 h at 100 °C. The resin was filtered off and washed (3×2 mL DMF, 3×2 mL MeOH, 3×2 mL DCM, 3×2 mL DMF, 3×2 mL MeOH, 3×2 mL DCM) to give **6**. *Method B*. (For reaction of 2,6-diamino-4-chloropyrimidines with acyclic aliphatic amines): to a solution of amine (0.85–0.94 mmol) in THF (4 mL, water content <0.01% v/v) *n*-BuLi (0.76 mmol, 0.48 mL 15% solution m/m in *n*-hexane) was added dropwise. (The vials had been dried and purged with argon previously). The reaction mixture was shaken for 20 min at room temperature. Resin **4** (0.085–0.094 mmol, 100 mg) was washed with dry THF (3×3 mL), then it was added to the solution of lithium amide. The mixture was shaken for 24 h at room temperature, and then the resin was filtered off and washed (3×4 mL MeOH, 3×4 mL THF, 3×4 mL DCM, 3×4 mL MeOH, 3×4 mL DCM).

4.5. Cleavage of 6 from the resin: preparation of 2-alkyl-4,6-diaminopyrimidines and 2,4,6-triaminopyrimidines (7)

The same procedure was followed as in the case of 6-amino-4-chloropyrimidines (**5**).

4.5.1. 6-(*n*-Hexylamino)-2-(*N*-isopropylethylamino)-4-(4-methylpiperidin-1-yl)pyrimidine (7/1). Yield: 89%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.88 (t, 3H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH–$), 0.92 (d, 3H, $J=6$ Hz, Pip-CH_3), 0.98–1.1 [m, 2H, Pip-H_{ax}(3, 5)], 1.15 (t, 3H, $J=7$ Hz, $CH_3CH_2N–$), 1.20 [d, 6H, $J=7$ Hz, $(CH_3)_2CHN–$], 1.22–1.40 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH–$], 1.49–1.60 [m, 2H, $CH_3(CH_2)_3CH_2CH_2NH–$], 1.64–1.74 [m, 3H, Pip-H_{eq}(3, 5), Pip-H(4)], 2.82–3.0 [m, 2H, Pip-H_{ax}(2,6)], 3.15–3.25 (br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH–$), 3.35–3.42 [q, 2H, $CH_3CH_2(N–)CH(CH_3)_2$,], 4.0–4.2 [br m, 2H, Pip-H_{eq}(2,6)], 4.51 [m, 1H, $CH_3CH_2(N–)CH(CH_3)_2$], 5.35 [s, 1H, H(5)], 7.14 (br t, 1H, $CH_3(CH_2)_3CH_2CH_2NH–$), 10.54 (br s, 1H, CF_3COOH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6, $CH_3(CH_2)_3CH_2CH_2NH–$, 14.0 $CH_3CH_2N–$, 19.6 $(CH_3)_2CHN–$, 21.2 Pip-CH_3, 21.7 $CH_3CH_2(CH_2)_4NH–$, 25.7 $CH_3(CH_2)_2CH_2(CH_2)_2NH–$, 27.6 $CH_3(CH_2)_3CH_2CH_2NH–$, 30.2 Pip-C(4), 30.7 $CH_3CH_2CH_2(CH_2)_3NH–$, 33.2 Pip-C(3, 5) 36.3 $CH_3CH_2N–$, 41.0 $CH_3(CH_2)_3CH_2CH_2NH–$, 44.3 Pip-C(2,6), 47.1 $(CH_3)_2CHN–$, 69.0 C(5), 150.4 C(2), 154.4 160.1 C(4). HPLC–MS: $M^+=361$ (EI); Purity: 95%. HRMS: (EI), *m/z* [M^+] found: 361.3211, calcd for $C_{21}H_{39}N_5$ 361.3205.

4.5.2. 6-(2-Methyl-*n*-butylamino)-4-(4-methylpiperidin-1-yl)-2-(*N*-isopropylethylamino)pyrimidine (7/2). Yield: 84%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.89 [t, 3H, $J=6.3$ Hz, $CH_3CH_2CH(CH_3)CH_2NH–$], 0.91 (d, 3H, $J=5.1$ Hz, Pip-*Me*), 0.92 (d, 3H, $J=6.6$ Hz, $CH_3CH_2CH(CH_3)CH_2NH–$), 0.98–1.1 [m, 2H, Pip-H_{ax}(3, 5)], 1.1–1.3 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH–$], 1.15 (t, 3H, $J=6.9$ Hz, $CH_3CH_2N–$), 1.20 [d, 6H, $J=6.9$ Hz, $(CH_3)_2CHN–$], 1.34–1.52 (br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH–$), 1.55–1.78 [m, 4H, Pip-H_{eq}(3, 5), Pip-H(4), $CH_3CH_2CH(CH_3)CH_2NH–$], 2.8–3.0 [br m, 2H, Pip-H_{ax}(2,6)], 3.0–3.2 [br m, 2H $CH_3CH_2CH(CH_3)CH_2NH–$], 3.37 (q, 2H, $CH_3CH_2N–$), 4.0–4.3 [br m, 2H, Pip-H_{eq}(2,6)], 4.3–4.5 [br m, 1H, $(CH_3)_2CHN–$], 5.37 [s, 1H, H(5)],

7.0–7.4 (br s, 1H, NH), 10.4–10.7 [br s, 1H, CF_3COOH]. HPLC–MS: $M^+=347$ (EI); Purity: 98%. HRMS: (EI), *m/z* [M^+] found: 347.3040, calcd for $C_{20}H_{37}N_5$: 347.3049.

4.5.3. 2-(*N*-Isopropylethylamino)-6-(2-methyl-*n*-butylamino)-4-(pyrrolidin-1-yl)pyrimidine (7/3). Yield: 89%. Yellowish foam. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.90 [t, 3H, $J=7.5$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.92 [d, 3H, $J=6.6$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.15 [t, 3H, $J=6.9$ Hz, CH_3CH_2N–], 1.10–1.18 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.20 [d, 6H, $J=6.6$ Hz, $(CH_3)_2CHN$–], 1.30–1.50 [br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.50–1.75 [br m, 1H, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.75–2.0 [m, 4H, Pyr-H(3, 4)], 2.90–3.20 [m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 3.30–3.70 [m, 6H, CH_3CH_2N–, Pyr-H(2, 5)], 4.4–4.8 [br m, 1H, $(CH_3)_2CHN$–], 5.04 [s, 1H, H(5)], 7.1–7.3 [br s, 1H, $CH_3CH_2CH(CH_3)CH_2NH$–], 10.4–10.7 (br s, 1H, CF_3COOH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 10.7 $CH_3CH_2CH(CH_3)CH_2NH$–, 14.1 CH_3CH_2N–, 16.9 $CH_3CH_2CH(CH_3)CH_2NH$, 19.8 $(CH_3)_2CHN$–, 22.0 Pyr-C(3, 4), 27.0 $CH_3CH_2CH(CH_3)CH_2NH$–, 33.8 $CH_3CH_2CH(CH_3)CH_2NH$–, 36.1 CH_3CH_2N–, 46.5 Pyr-C(1, 5), 46.9 $CH_3CH_2CH(CH_3)CH_2NH$–, 47.5 $(CH_3)_2CHN$–, 69.9 C(5), 150.0 C(2), 153.5 C(6), 153.7 C(4). HPLC–MS: $M^+=319$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 319.2742, calcd for $C_{18}H_{33}N_5$: 319.2736.

4.5.4. 4-(Azetidin-1-yl)-2-(*N*-isopropylethylamino)-6-(2-methyl-*n*-butylamino)pyrimidine (7/4). Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.89 [t, 3H, $J=7.5$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.92 [d, 3H, $J=7.0$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.10–1.22 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.14 [t, 3H, $J=7$ Hz, CH_3CH_2N–], 1.19 [d, 6H, $J=7$ Hz, $(CH_3)_2CHN$–], 1.38–1.48 [br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.58–1.68 [br m, 1H, $CH_3CH_2CH(CH_3)CH_2NH$–], 2.28–2.38 [m, 2H, azetidine–H(3)], 2.90–3.20 [m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 3.35–3.50 [m, 2H, CH_3CH_2N–], 4.00–4.15 [m, 4H, azetidine–H(2, 4)], 4.50–4.70 [br m, 1H, $(CH_3)_2CHN$–], 4.90 [s, 1H, H(5)], 7.34 [br s, 1H, $CH_3CH_2CH(CH_3)CH_2NH$–], 10.4–10.9 (br s, 1H, CF_3COOH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 10.9 $CH_3CH_2CH(CH_3)CH_2NH$–, 14.2 CH_3CH_2N–, 15.5 azetidine–C(3), 16.9 $CH_3CH_2CH(CH_3)CH_2NH$–, 19.7 $(CH_3)_2CHN$–, 26.2 $CH_3CH_2CH(CH_3)CH_2NH$–, 33.5 $CH_3CH_2CH(CH_3)CH_2NH$–, 36.3 CH_3CH_2N–, 47.0 $(CH_3)_2CHN$–, 47.3 $CH_3CH_2CH(CH_3)CH_2NH$–, 49.7 azetidine–C(2, 4), 67.9 C(5), 150.6 C(2), 153.6 C(6), 161.6 C(4). HPLC–MS: $M^+=305$ (EI); Purity: 81%. HRMS: (EI), *m/z* [M^+] found: 305.2567, calcd for $C_{17}H_{31}N_5$: 305.2579.

4.5.5. 6-(*n*-Hexylamino)-4-(4-methylpiperidin-1-yl)-2-methylpyrimidine (7/5). Yield: 95%. Colourless semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 3H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH$–], 0.92 [d, 3H, $J=6$ Hz, *Me*-Pip], 0.98–1.12 [m, 2H, Pip-H_{ax}(3, 5)], 1.24–1.38 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.54 [p, 2H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.64–1.76 [m, 3H, Pip-H_{eq}(3, 5), Pip-H(4)], 2.36 [s, 3H, Me(C2)], 2.90–3.10 [m, 2H, Pip-H_{ax}(2,6)], 3.20–3.30 [m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.90–4.80 [br m, 2H, Pip-H_{eq}(2,6)], 5.74 [s, 1H, H(5)], 8.31 [m, 1H, $CH_3(CH_2)_3CH_2CH_2NH$–]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.7 $CH_3(CH_2)_3CH_2CH_2NH$–, 21.3 Pip-CH_3, Me(C2), 21.9 $CH_3CH_2(CH_2)_3CH_2NH$–, 25.8 $CH_3(CH_2)_2CH_2(CH_2)_2NH$–, 27.9 $CH_3(CH_2)_3CH_2CH_2NH$–, 30.1 Pip-C(4), 30.8 $CH_3CH_2CH_2(CH_2)_3NH$–, 33.3 Pip-C(3, 5), 41.2 $CH_3(CH_2)_3CH_2CH_2NH$–, 44.7 Pip-C(2,6), 75.6 C(5), 154.7 C(6), 158.5 C(2), 159.7 C(4). HPLC–MS: $M^+=290$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 290.2479, calcd for $C_{17}H_{30}N_4$: 290.2470.

4.5.6. 2-Methyl-6-(2-methyl-*n*-butylamino)-4-(4-methylpiperidin-1-yl)pyrimidine (7/6). Yield: 94%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 3H, $J=7.5$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.90 [d, 3H, $J=7.5$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.92 [d, 3H, $J=7$ Hz, Pyp-CH_3], 0.98–1.12 [br m, 2H, Pip-H_{ax}(3, 5)], 1.12–1.22 [m, 1H $CH_3CH_xH_yCH(CH_3)CH_2NH$–], 1.38–1.48 [m, 1H, CH_3CH_x-$H_y$$CH(CH_3)CH_2NH$–], 1.60–1.76 [br m, 4H, Pip-H_{eq}(3, 5), Pip-H(4), $CH_3CH_2CH(CH_3)CH_2NH$–], 2.36 [s, 3H, Me-C(2)], 2.8–3.04 [m, 2H, Pip-H_{ax}(2,6)], 3.05–3.13 [m, 1H, $CH_3CH_2CH(CH_3)CH_xH_yNH$–], 3.14–3.22 [m, 1H, CH_3CH_2-$CH(CH_3)CH_xH_yNH$–], 3.9–4.6 [br m, 2H, Pip-H_{eq}(2,6)], 5.75 [s, 1H, H(5)], 8.15 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 10.9 $CH_3CH_2CH(CH_3)CH_2NH$–, 16.8 CH_3-$CH_2CH(CH_3)CH_2NH$–, 21.3 Me-C(2), Pip-CH_3, 26.2 CH_3-$CH_2CH(CH_3)CH_2NH$–, 30.1 Pip-C(4), 33.3 Pip-C(3, 5), 33.7 $CH_3CH_2CH(CH_3)CH_2NH$–, 44.7 Pip-C(2,6), 46.8 CH_3CH_2-$CH(CH_3)CH_2NH$–, 75.6 C(5), 154.6 C(6), 158.4, 158.8 C(2, 4). HPLC–MS: $M^+=276$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 276.2325, calcd for $C_{16}H_{28}N_4$: 276.2309.

4.5.7. 6-(2-Heptylamino)-2-methyl-4-(4-methylpiperidin-1-yl)pyrimidine (7/7). Yield: 93%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86 [t, 3H, $J=6.9$ Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 0.92 (d, 3H, $J=6.3$ Hz, Pip-*Me*), 0.98–1.10 [m, 2H, Pip-H_{ax}(3, 5)], 1.13 [d, 3H, $J=6.3$ Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.18–1.40 [m, 6H, CH_3-$CH(NH$–$)CH_2(CH_2)_3CH_3$], 1.40–1.58 [m, 2H, $CH_3CH(NH$–$)$ $CH_2(CH_2)_3CH_3$], 1.60–1.78 [m, 3H, Pip-H_{eq}(3, 5), Pip-H(4)], 2.36 [s, 3H, Me-C(2)], 2.85–3.20 [m, 2H, Pip-H_{ax}(2,6)], 3.70–3.90 [m, 2H, Pip-H_{eq}(2,6)], 4.0–4.60 [br m, 1H, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 5.76 [s, 1H, H(5)], 8.01 (d, 1H, $J=8.4$ Hz, NH). HPLC–MS: $M^+=304$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 304.2622, calcd for $C_{18}H_{32}N_4$: 304.2627.

4.5.8. 2-Methyl-4-(4-phenylpiperazin-1-yl)-6-(2-methyl-*n*-butylamino)pyrimidine (7/8). Yield: 86%. Red glassy oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.89 [t, 3H, $J=7.2$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.91 [d, 3H, $J=6.9$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.10–1.30 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.36–1.54 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.59–1.75 [m, 1H, CH_3-$CH_2CH(CH_3)CH_2NH$–], 2.39 [s, 3H, Me-C(2)], 3.0–3.30 [m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 3.70–4.0 [m, 8H, piperazine,], 5.85 [s, 1H, H(pyrimidin–C5)], 6.78–6.86 (m, 1H), 6.95–7.04 (m, 2H), 7.20–7.30 (m, 2H) (phenyl-H), 8.0–8.20 (br s, 1H, NH). HPLC–MS: $M^+=339$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 339.2410, calcd for $C_{20}H_{29}N_5$: 339.2423.

4.5.9. 2-Methyl-6-(2-methyl-*n*-butylamino)-4-(pyrrolidin-1-yl)pyrimidine (7/9). Yield: 77%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.88 (t, 3H, $J=7.5$ Hz, $CH_3CH_2(CH_3)CHCH_2NH$–), 0.90 (d, 3H,

J=6.5 Hz, $CH_3CH_2(CH_3)CHCH_2NH$–), 1.11–1.21 [m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH$–], 1.37–1.47 [m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH$–], 1.60–1.70 [m, 1H, $CH_3CH_2(CH_3)CHCH_2NH$–], 1.84–2.06 [m, 4H, Pyr-H(3, 4)], 2.38 [s, 3H, Me-C(2)], 3.0–3.3 [br m, 2H, $CH_3CH_2(CH_3)CHCH^xH^yNH$–], 3.30–3.65 [br m, 4H, Pyr-H(2, 5)], 5.41 [s, 1H, H(5)], 7.99 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 10.9 $CH_3CH_2(CH_3)CHCH_2NH$–, 16.8 $CH_3CH_2(CH_3)CHCH_2NH$–, 21.3 CH_3(2), 24.5 Pyr-C(3, 4), 26.2 $CH_3CH_2(CH_3)CHCH_2NH$–, 33.7 $CH_3CH_2(CH_3)CHCH_2NH$–, 46.9 $CH_3CH_2(CH_3)CHCH_2NH$–, 47.2 Pyr-C(2, 4), 76.0 C(5), 158.4, 158.7, 159.0 C(2, 4, 6). HPLC–MS: M^+ = 248 (EI); Purity: 99%. HRMS: (EI), m/z [M^+] found: 248.2011, calcd for $C_{14}H_{24}N_4$: 248.2001.

4.5.10. 6-(2-Heptylamino)-2-methyl-4-(pyrrolidin-1-yl)pyrimidine (7/10). Yield: 96%. Yellowish foam. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86 [t, 3H, J=6.6 Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.13 [d, 3H, J=6.6 Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.20–1.58 [br m, 8H, $CH_3CH(NH$–$)CH_2(CH_2)_3CH_3$], 1.84–2.08 [br m, 4H, Pyr-H(3, 4)], 2.38 [s, 3H, Me-C(2)], 3.20–3.60 [br m, 4H, Pyr-H(2, 5)], 4.20–5.20 [br m, 1H, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 5.41 [s, 1H, H(5)], 8.05 (d, 1H, J=8.4 Hz, NH). HPLC–MS: M^+=276 (EI); Purity: 99%. HRMS: (EI), m/z [M^+] found: 276.2324, calcd for $C_{16}H_{28}N_4$: 276.2314.

4.5.11. 4-(Azetidin-1-yl)-2-methyl-6-(2-methyl-*n*-butylamino)pyrimidine (7/11). Yield: 84%. Yellowish glassy oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86 [t, 3H, J=6.6 Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.88 [d, 3H, J=6.6 Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.08–1.24 [br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.32–1.50 [br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.54–1.74 [br m, 1H, $CH_3CH_2\ CH(CH_3)CH_2NH$–], 2.36 [s, 3H, Me-C(2)], 2.90–3.30 [br m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 4.0–4.30 (m, 6H, azetidine–H), 5.26 [s, 1H, H(5)], 8.05–8.25 (br s, 1H, NH). HPLC–MS: M^+=234 (EI); Purity: 99%. HRMS: (EI), m/z [M^+] found: 234.1857, calcd for $C_{13}H_{22}N_4$: 234.1844.

4.5.12. 4-(2-Ethylpiperidin-1-yl)-2-methyl-6-(2-methyl-*n*-butylamino)pyrimidine (7/12). Yellowish oil. HPLC–MS: M^+=290 (EI); Purity: 28%. HRMS: (EI), m/z [M^+] found: 290.2478, calcd for $C_{17}H_{30}N_4$: 290.2470.

4.5.13. 4-Bis(*n*-butyl)amino-2-methyl-6-(2-methyl-*n*-butylamino)pyrimidine (7/14). Yield: 82% Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.84–0.98 [m, 12H, $CH_3CH_2CH(CH_3)CH_2NH$–, $(CH_3(CH_2)_2CH_2)_2N$–], 1.08–1.72 [m, 11H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–, $(CH_3(CH_2)_2CH_2)_2N$–], 2.35 [s, 3H, Me-C(2)], 2.90–3.20 [m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 3.20–3.70 [br m, 4H, $(CH_3(CH_2)_2CH_2)_2N$–], 5.50 [s, 1H, H(5)], 7.86 (br s, 1H, NH). HPLC–MS: M^+=306 (EI); Purity: 95%. HRMS: (EI), m/z [M^+] found: 306.2771, calcd for $C_{18}H_{34}N_4$: 306.2783.

4.5.14. 4,6-Bis(*n*-hexylamino)-2-methylpyrimidine (7/15). Yield: 87%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 6H, J=7 Hz, $CH_3(CH_2)_4CH_2NH$–], 1.22–1.36 [m, 12H, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.52 [p, 4H, J=7 Hz, $CH_3(CH_2)_3CH_2CH_2NH$–], 2.31 [s, 3H, Me(C2)], 3.10–3.30 [br m, 4H, $CH_3(CH_2)_3CH_2CH_2NH$–], 5.39 [s, 1H, H(5)], 7.82 [br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8 $CH_3(CH_2)_4CH_2NH$–, 21.8 br, MeC(2), 22.0 $CH_3CH_2(CH_2)_3CH_2NH$–, 25.9 $CH_3(CH_2)_2CH_2CH_2CH_2NH$–, 28.1 $CH_3(CH_2)_3CH_2CH_2NH$–, 30.8 $CH_3CH_2CH_2(CH_2)_3NH$–, 40.9 $CH_3(CH_2)_3CH_2CH_2NH$–, 75.5 C(5), 156.0–162.0 br, C(2, 4, 6). HPLC–MS: M^+= 292 (EI); Purity: 98%. HRMS: (EI), m/z [M^+] found: 292.2622, calcd for $C_{17}H_{32}N_4$: 292.2627.

4.5.15. 6-(*n*-Hexylamino)-2-methyl-4-(2-methyl-*n*-butylamino)pyrimidine (7/16). Yield: 85%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.80–0.96 [m, 9H, $CH_3(CH_2)_4CH_2NH$–, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.08–1.70 [m, 11H, $CH_3(CH_2)_4CH_2NH$–, $CH_3CH_2CH(CH_3)CH_2NH$–], 2.36 [s, 3H, Me-C(2)], 2.80–3.40 [br m, 4H, $CH_3(CH_2)_4CH_2NH$–,$CH_3CH_2CH(CH_3)CH_2NH$–], 5.47 [s, 1H, H(5)], 7.7–8.4 (br s, 2H, NH). HPLC–MS: M^+=278 (EI); Purity: 98%. HRMS: (EI), m/z [M^+] found: 278.2461, calcd for $C_{16}H_{30}N_4$: 278.2470.

4.5.16. 4-(2-Heptylamino)-6-(*n*-hexylamino)-2-methylpyrimidine (7/17). Yield: 87%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [q, 6H, J=7 Hz, $CH_3(CH_2)_4CH_2NH$–, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.13 [d, 3H, J=6.5 Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.18–1.35 [m, 12H, $CH_3(CH_2)_3CH_2CH_2NH$–, $CH_3CH(NH$–$)CH_2(CH_2)_3CH_3$], 1.40–1.65 [m, 4H, $(CH_2)_3CH_2CH_2NH$–, $CH_3CH(NH$–$)CH_2(CH_2)_3CH_3$], 2.34 [s, 3H, Me-C(2)], 3.0–3.40 [br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.50–4.00 [br m, 1H, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 5.46 [s, 1H, H(5)], 8.14 (br m, 2H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.7 $CH_3(CH_2)_4CH_2NH$–, $CH_3CH(NH$–$)(CH_2)_4CH_3$, 19.9 $CH_3CH(NH$–$)(CH_2)_4CH_3$, 21.1 Me(C2), 21.9 $CH_3CH_2(CH_2)_4NH$–, $CH_3CH(NH$–$)(CH_2)_3CH_2CH_3$, 25.0 $CH_3CH(NH$–$)CH_2CH_2(CH_2)_2CH_3$, 25.9 $CH_3(CH_2)_2CH_2(CH_2)_2NH$–, 27.9 $CH_3(CH_2)_3CH_2CH_2NH$–, 30.8 $CH_3CH_2CH_2(CH_2)_3NH$–, 31.0 $CH_3CH(NH$–$)(CH_2)_2CH_2CH_2CH_3$, 35.6 $CH_3CH(NH$–$)CH_2(CH_2)_3CH_3$, 41.1 $CH_3(CH_2)_3CH_2CH_2NH$–, 47.0 $CH_3CH(NH$–$)(CH_2)_4CH_3$, 73.5–76.8 br, C(5), 156–163 br, C(2, 4, 6). HPLC–MS: M^+=306 (EI); Purity: 98%. HRMS: (EI), m/z [M^+] found: 306.2795, calcd for $C_{18}H_{34}N_4$: 306.2783.

4.5.17. 4-Bis(*n*-butyl)amino-6-(*n*-hexylamino)-2-(*N*-isopropylethylamino)pyrimidine (7/18). Yield: 61%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.88 [t, 3H, J=7 Hz, $CH_3(CH_2)_4CH_2NH$–], 0.90 [m, 6H, (CH_3 $(CH_2)_2CH_2)_2N$–], 1.14 (t, 3H, J=7 Hz, CH_3CH_2N–), 1.19 [d, 6H, J=7 Hz, $(CH_3)_2CHN$–], 1.22–1.37 [m, 10H, $CH_3(CH_2)_3CH_2CH_2NH$–, $(CH_3CH_2CH_2CH_2)_2N$–], 1.48–1.60 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH$–, $(CH_3CH_2CH_2CH_2)_2N$–], 3.18 [m, 2H, $CH_3(CH_2)_4CH_2NH$–], 3.36 [m, 2H, $CH_3(CH_2)_2CH_2^xN(-)CH_2^y(CH_2)_2CH_3$], 3.42 [q, 2H, J=7 Hz, CH_3CH_2N–], 3.51 [m, 2H, $CH_3(CH_2)_2CH_2^xN(-)CH_2^y(CH_2)_2CH_3$], 4.55 [br m, 1H, $(CH_3)_2CHN$–], 5.08 [s, 1H, H(5)], 7.28 (s, 1H, NH), 10.70 (br s, 1H, CF_3COOH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6 ($CH_3(CH_2)_2CH_2)_2N$–, 13.8 $CH_3(CH_2)_4CH_2NH$–, 14.4 CH_3CH_2N–, 19.4 $(CH_3CH_2CH_2CH_2)_2N$–, 19.8 $(CH_3)_2CHN$–, 21.9 $CH_3CH_2(CH_2)_3CH_2N$–, 25.9 $CH_3(CH_2)_2CH_2CH_2CH_2N$–, 27.9 $CH_3(CH_2)_3CH_2CH_2N$–, 29.2 $CH_3CH_2CH_2^XCH_2N(-)CH_2CH_2^yCH_2CH_3$, 29.7 $CH_3CH_2CH_2^xCH_2N(-)CH_2CH_2^yCH_2CH_3$, 30.8 $CH_3CH_2CH_2(CH_2)_3N$–, 36.2 CH_3CH_2N–, 41.2

$CH_3(CH_2)_4CH_2N$–, 47.2 $(CH_3)_2CHN$–, 47.8 $(CH_3CH_2CH_2$-$CH_2)_2N$–, 69.1 C(5), 150.15 C(2), 153.8 C(6), 158.20 br, C(4). HPLC–MS: $M^+=391$ (EI); Purity: 91%. HRMS: (EI), *m/z* [M^+] found: 391.3668, calcd for $C_{23}H_{45}N_5$: 391.3675.

4.5.18. 4,6-Bis(*n*-hexylamino)-2-(*N*-isopropylethylamino)pyrimidine (7/19). Yield: 57%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 6H, $J=7$ Hz, $CH_3(CH_2)_4CH_2NH$–], 1.14 [t, 3H, $J=7$ Hz, CH_3CH_2N–], 1.19 [d, 6H, $J=6.5$ Hz, $(CH_3)_2CHN$–], 1.22–1.40 [br m, 12H, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.44–1.62 [br m, 4H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.0–3.30 [br m, 4H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.30–3.50 [br m, 2H, CH_3CH_2N–], 4.45–4.70 [br m, 1H, $(CH_3)_2CHN$–], 5.03 [s, 1H, H(5)], 7.60–8.20 [br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–], 10.72 [br m, 1H, CF_3COOH]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8 $CH_3(CH_2)_4CH_2NH$–, 14.4 CH_3CH_2N–, 19.8 $(CH_3)_2CHN$–, 221.0 $CH_3CH_2(CH_2)_3CH_2NH$–, 26.0 $CH_3(CH_2)_2CH_2CH_2CH_2NH$–, 26.9 $CH_3(CH_2)_3CH_2CH_2$-NH–, 30.9 $CH_3CH_2CH_2(CH_2)_3NH$–, 38.8.CH_3CH_2N–, 41.3 $CH_3(CH_2)_3$ CH_2CH_2NH–, 47.4 $(CH_3)_2CHN$–, 70.8 C(5), Signals due to the C(2, 4, 6) carbons could not be detected. HPLC–MS: $M^+=363$ (EI); Purity: 93%. HRMS: (EI), *m/z* [M^+] found: 363.3369, calcd for $C_{21}H_{41}N_5$: 363.3362.

Acknowledgements

The authors wish to thank Györgyi I. Szendrei for HPLC–MS and Gábor Czira for HRMS measurements.

References and notes

1. Thomas, A. P. WO 9515952, 1995; *Chem. Abstr.*, *123*, 286077.
2. Ayer, D. E. WO 9106542, 1991; *Chem. Abstr.*, *115*, 114546.
3. Roth, B.; Strelitz, J. Z.; Rauckman, B. S. *J. Med. Chem.* **1980**, *23*, 379–384.
4. Mulin, R. J.; Keith, B. R.; Bigham, E. C.; Duch, D. S.; Ferone, R.; Heath, L. S.; Singer, S.; Waters, K. A.; Wilson, H. R. *Biochem. Pharmacol.* **1992**, *43*, 1627–1634.
5. Russel, P. B.; Hitchings, G. H. *J. Am. Chem. Soc.* **1951**, *73*, 3763–3770.
6. Arvanitis, A. G.; Gilligan, P. J.; Chorvat, R. J.; Cheeseman, R. S.; Christos, T. E.; Bakthavatchalam, R.; Beck, J. P.; Cocuzza, J. P.; Hobbs, F. W.; Wilde, R. G.; Arnold, C.; Chidester, D.; Curry, M.; He, L.; Hollis, A.; Klaczkiewicz, J.; Krenitsky, P. J.; Rescinito, J. P.; Scholfield, E.; Culp, S.; De Souza, E. B.; Fitzgerald, L.; Grigoriadis, D.; Tam, S. W.; Wong, Y. N.; Huang, S.-M.; Shen, H. L. *J. Med. Chem.* **1999**, *42*, 805–818.
7. Franchetti, P.; Capellacci, L.; Abu Sheikha, G.; Grifantini, M.; Loi, A. G.; De Montis, A.; Spiga, M. G.; La Colla, P. *Nucleosides Nucleotides* **1995**, *14*, 607–610.
8. Kinnamon, K. E.; Engle, R. R.; Poon, B. T.; Ellis, W. Y.; Mc Call, J. W.; Dzimianski, M. T. *Ann. Trop. Med. Parasitol.* **1999**, *93*, 851–858.
9. Vorbrueggen, H. *Adv. Heterocycl. Chem.* **1990**, *49*, 117–192 and references there in.
10. Obrecht, D.; Abrecht, C.; Gieder, A.; Villalgordo, J. M. *Helv. Chim. Acta* **1997**, *80*, 65–72.
11. Masquelin, T.; Sprenger, D.; Baer, R.; Gerber, F.; Mercadal, Y. *Helv. Chim. Acta* **1998**, *81*, 646–660.
12. Guillier, F.; Roussel, P.; Moser, H.; Kane, P.; Bradley, M. *Chem. Eur. J.* **1999**, *5*, 3450–3458.
13. Di Lucrezia, R.; Gilbert, I. H.; Floyd, C. D. *J. Comb. Chem.* **2000**, *2*, 249–253.
14. Barillari, C.; Barlocco, D.; Raveglia, L. F. *Eur. J. Org. Chem.* **2001**, 4737–4741.
15. Yoo, K. H.; Kim, S. E.; Shin, K. J.; Kim, D. C.; Park, S. W.; Kim, D. J. *Synth. Commun.* **2001**, *31*, 835–840.
16. Arvanitis, E. A.; Chadha, N.; Pottorf, R. S.; Player, M. R. *J. Comb. Chem.* **2004**, *6*, 414–419.
17. Zucca, C.; Bravo, P.; Volonterio, A.; Zanda, M.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2001**, *42*, 1033–1035.
18. Montebugnoli, D.; Bravo, P.; Brenna, E.; Mioskowski, C.; Panzeri, W.; Viani, F.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2003**, *59*, 7147–7156.
19. Dener, J. F.; Lease, T. G.; Novack, A. R.; Plunkezz, M. J.; Hocker, M. D.; Fantauzzi, P. P. *J. Comb. Chem.* **2001**, *3*, 590–597.
20. Wéber, C.; Bielik, A.; Szendrei, G. I.; Keserű, G. M.; Greiner, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1279–1281.
21. Hanan, G. S.; Schubert, U. S.; Volkmer, D.; Riviere, E.; Lehn, J. M. *Can. J. Chem.* **1997**, *75*, 169–182.
22. Delia, T. J.; Stark, D.; Glenn, S. K. *J. Heterocycl. Chem.* **1995**, *32*, 1177–1180.
23. Ladd, D. L. *Heterocycl. Chem.* **1982**, *19*, 917–922.
24. Demeter, Á.; Wéber, C.; Brlik, J. *J. Am. Chem. Soc.* **2003**, *125*, 2535–2540.
25. Demeter, Á.; Wéber, C. *Concepts Magn. Reson.* **2004**, *22A*, 12–24.