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A New and Efficient Synthesis of Substituted 6-[(2′-Dialkylamino)ethyl] Pyrimidine and 4-*N*,*N*-Dialkyl-6-vinyl-cytosine Derivatives and Evaluation of their Anti-Rubella Activity

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Abstract—New 6-[(2′-dialkylamino)ethyl]-4(3*H*)-pyrimidinones were prepared by a multistep procedure starting from acetone dicarboxylic acid diethyl ester and urea derivatives. These compounds were used as starting materials to obtain 4-*N*,*N*-dialkyl-6-vinyl-pyrimidine derivatives by an unprecedented tandem C-6 side chain Hofmann-like elimination/C-4 pyrimidinone substitution. Among the new derivatives obtained, various compounds show anti-Rubella activity. The inhibition of HIV-1 Reverse Transcriptases (RT), from both wild type and modified viruses, is also reported.

Introduction

Rubella virus (RV) is a small plus-strand RNA virus classified in the *Rubivirus* genus of the family of the *Togaviridae*[1] and is the causative agent of the disease known as German measles, predominantly a childhood disease. The infection occurs only in humans and is generally mild, even if complications—polyarthralgia in adult women — can exist and occasionally more serious sequelae can occur.[2] Because RV causes serious birth defects in the newborn (congenital rubella syndrome, CRS), when infection occurs during the first trimester of pregnancy, the primary public health interest is its teratogenicity. The development of live and attenuated vaccines and the expansion of vaccination strategies, since 1970 in developed countries, have reduced the incidence of CSR disease.[3]

Even if natural and semisynthetic polysaccharides,[4] fungizone[5] and mopyridone[6] show inhibitory effects against RV, an efficient chemotherapy for this virus is not available.

5-Substitued pyrimidines and their nucleosides are of immense biological significance because they exhibit a wide range of antiviral and anticancer activity. In contrast to the extensive studies about these derivatives, less attention has been devoted to the 6-substituted isomers, probably because of their no easy synthetic availability and their supposed biological inactivity.[7] In the last few years, 6-substitued pyrimidines, as for example 1 - [(2 - hydroxyethyl)methyl] - 6 - (phenylthio)thymine (HEPT),[8–11] and 3,4-dihydro-2-alkoxy-6-benzyl-4-oxo-pyrimidines (DABOs),[12] showed a potent and selective activity against human immunodeficiency virus type-1 (HIV-1). For this reason new synthetic procedures to obtain 6-substitued pyrimidines are of great interest. In the course of our studies on the chemistry and biological evaluation of C-6 substitued uracil and pyrimidinone derivatives,[13,14] we have reported that 2-methoxy- and 2-methylthio-6-[(2-alkylamino)ethyl]-4(3H)-pyrimidinones showed a biological activity against positive strand (rubella virus and Sindbis virus) and negative strand (vescicular stomatitis virus) RNA viruses.[15] One of these compounds, the 2-methylthio-6-[(2′-diethylamino)ethan-1′-yl]-4(3*H*)-pyrimidinone **1,** is an efficient inhibitor of RV. Moreover, we have briefly communicated[16] that 2-methoxy- and 2-methylthio-4(3*H*)-pyrimidinones bearing a diethylamino moiety on the C-6

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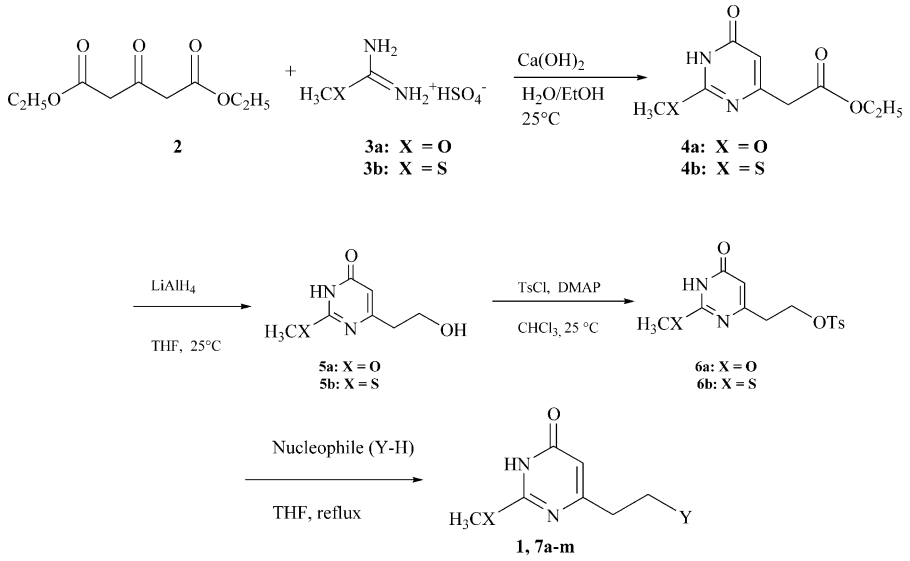
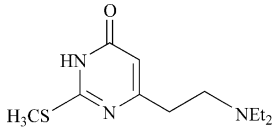


Scheme 1. **1**: X = S, Y = –N(Et)$_2$; **7a**: X = O, Y = –N(Et)$_2$; **7b**: X = O, Y = pyrrolidino; **7c**: X = O, Y = piperidino; **7d**: X = O, Y = morpholino; **7e**: X = O, Y = piperazino; **7f**: X = O, Y = 2-methylpiperidino; **7g**: X = O, Y = hexamethyleneimino; **7h**: X = O, Y = dihexylamino; **7i**: X = S, Y = piperidino; **7l**: X = S, Y = morpholino; **7m**: X = S, Y = piperazino.

side chain afford a direct nucleophilic C-4 hydroxy substitution when treated with a dry alcoholic solution of sodium alkoxides prepared from alcohols and Na. An unprecedented tandem C-6 side Hofmann-like elimination was also observed when sodium alkoxides, prepared from alcohols and NaH in dioxane, were used. This rearrangement is a new and selective entry to substituted *N,N*-dialkyl-6-vinyl pyrimidine and 6-vinyl cytosine derivatives whose synthesis, by classical procedures, is not easy to obtain. We are reporting here in detail these data and the application of these procedures to the synthesis of 2-methoxy-6-[(2′-alkylamino)ethyl]-4(3H)-pyrimidinones **7b–h**, 2-methoxy- and 2-methylthio-4-alkoxy-6-[(2′-diethylamino)ethyl]pyrimidines **8a–b**, **9a–b**, **10a–b**, **11a–b**, 2-methoxy- and 2-methylthio-4-*N,N*-dialkyl-6-vinyl-pyrimidine derivatives **12a–n**, and 4-morpholino-6-vinyl-cytosine derivative **13**. Their antiviral activity against RV and data of the inhibition of HIV-1 Reverse Transcriptases (RT), from both wild type and modified virus, are also described.



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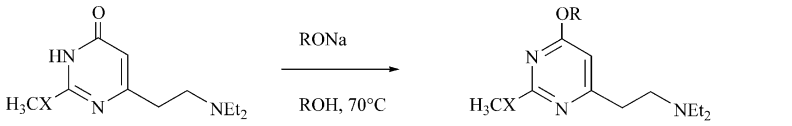
Chemistry

Starting materials, 2-methoxy- and 2-methylthio-6-[(2′-dialkylamino)ethyl]4(3*H*)-pyrimidinones **1**, **7a** and **7i–m,** were prepared using the procedure previously reported.[15] New derivatives **7b–h** were synthetized in a similar way (Scheme 1). Briefly, 4(3*H*)-pyrimidinone **4a** and **4b** were obtained by reaction of acetone dicarboxylic acid diethyl ester **2** and *O*-methylisourea hydrogen sulphate **3a** or *S*-methylisothiourea hydrogen sulphate **3b** with Ca(OH)$_2$ in ethanol–water mixture. After reduction with LiAlH$_4$, the alcohols **5a** and **5b** (67 and 65% yields, respectively) were treated with *p*-toluensulfonyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) in CHCl$_3$, to give **6a** and **6b** in 83 and 85% yields, respectively. Compounds **7b–h** were then obtained by reaction between **6a** and an excess of the appropriate dialkylamino nucleophile in refluxing THF (yields ranging from 60 to 89%) (Scheme 1).

Compounds **8a–b**, **9a–b**, **10a–b** and **11a–b** were obtained in acceptable yields when **7a** and **1** were treated with an excess of sodium alkoxide (prepared from dry alcohol, in the presence of Na) at 70 °C (Scheme 2). The reaction was selective, and products of C-2 *trans*-alkoxylation, usually observed under similar experimental conditions, were not recovered in the reaction mixture. To the best of our knowledge, this is the first example in the literature of a direct and selective C-4 hydroxy (oxo) substitution on pyrimidinones in the presence of leaving groups in the C-2 position.

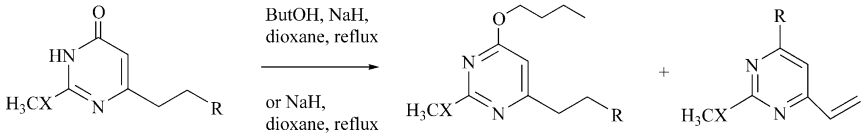
Liotta and coworkers reported that the selectivity in the nucleophilic substitution of chloro pyrimidines with alkoxides can depend on the use of alkoxides generated from Na or sodium hydride (NaH).[17] On the basis of these data, compounds **1** and **7a** were treated with sodium *n*-butoxide generated by *n*-butanol and NaH in dry dioxane at 100 °C. Under these experimental conditions, an unprecedented tandem C-6 side-chain Hofmann-like elimination followed by a direct C-4 hydroxy (oxo) substitution (by the diethylamino nucleophile) gave **12a** and **12b** as the main products, besides small amounts of **10a** and **10b** (Scheme 3, Table 1, entries 1 and 2). The reaction was operative also at room temperature although if lower yields of **12a–b** (11 and 9% yields, respectively) were obtained. Chemical evidences for a concerted intermolecular four centre mechanism[18] were obtained in the presence of 6-methyl-2-methoxy-4(3H)-pyrimidinone or methyl benzoate as scavengers of the diethyl amino nucleophile.[16] No traces of possible



7a: X = O
1 : X = S

8a: X = O, R = CH_3; 8b: X = S, R = CH_3;
9a: X = O, R = CH_2CH_3; 9b: X = S, R = CH_2CH_3;
10a: X = O, R = $CH_2CH_2CH_2CH_3$;
10b: X = S, R = $CH_2CH_2CH_2CH_3$;
11a: X = O, R = CH_2Ph; 11b: X = S, R = CH_2Ph.

Scheme 2.



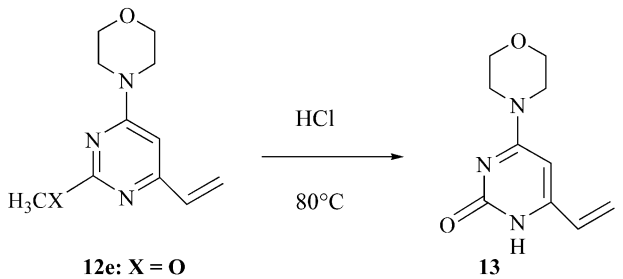
1-7a-m **10a-n** **12a-n**

Scheme 3. See Table 1 for the assignment of the R substituent.

Table 1. Reaction of 2-methoxy or 2-methylthio-6-[(2′-dialkylamino)]-4(3*H*)-pyrimidinones with NaH or *n*-ButOH/NaH systems

Entry	Substrate			Reaction condition	Product **10** (Yield%)[a]	Product **12** (Yield%)[a]
	Compound	X	R			
1	**7a**	O	—N(Et)Et	NaH/*n*-ButOH NaH	**10a** (13)	**12a** (87) **12a** (74)
2	**1**	S	—N(Et)Et	NaH/*n*-ButOH NaH	**10b** (28)	**12b** (72) **12b** (55)
3	**7b**	O	—N(pyrrolidine)	NaH/*n*-ButOH NaH	**10c** (10)	**12c** (90) **12c** (64)
4	**7c**	O	—N(piperidine)	NaH/*n*-ButOHNaH	**10d** (14)	**12d** (86) **12d** (63)
5	**7d**	O	—N(morpholine)	NaH/*n*-ButOH NaH	**10e** (20)	**12e** (80) **12e** (65)
6	**7e**	O	—N(piperazine)NH	NaH/*n*-ButOH NaH	**10f** (19)	**12f** (81) **12f** (55)
7	**7f**	O	—N(2-methylpiperidine)	NaH/*n*-ButOH NaH	**10g** (22)	**12g** (78) **12g** (66)
8	**7g**	O	—N(azepane)	NaH/*n*-ButOH NaH	**10h** (20)	**12h** (80) **12h** (70)
9	**7h**	O	$-N(C_6H_{13})_2$	NaH/*n*-ButOH NaH	**10i** (45)	**12i** (55) **12i** (60)
10	**7i**	S	—N(piperidine)	NaH/*n*-ButOH NaH	**10l** (18)	**12l** (82) **121** (65)
11	**7l**	S	—N(morpholine)	NaH/*n*-ButOH NaH	**10m** (18)	**12m** (82) **12m** (55)
12	**7m**	S	—N(piperazine)NH	NaH/*n*-ButOH NaH	**10n** (15)	**12n** (85) **12n** (60)

[a]Products isolated by flash chromatography and identified by ^1H and ^{13}C NMR spectra.



Scheme 4.

cross-reaction products were recovered. This hypothesis was further confirmed by some infrared and ultraviolet data.[16]

To test the generality of this procedure, we treated **7b–m** under similar experimental conditions. 2-Methoxy- and 2-methylthio-4-dialkylamino-6-vinyl-pyrimidines **12c–n** were obtained as the main products, besides small amounts of 4-alkoxy derivatives **10c–n** (Table 1, entries 3–12).

As shown in Table 1, the substituent on the C-2 position of the 4(3*H*)-pyrimidinone ring (that is oxygen vs sulphur atom) did not influence the Hofmann-like elimination/substitution process, and the corresponding 6-substituted derivatives were obtained in comparable yields (Table 1, entries 1 vs 2, 4 vs 10, 5 vs 11, 6 versus 12). On the other hand, the steric hindrance of the dialkylamino moiety appears to be a crucial factor in the selectivity between the C-4 hydroxy substitution and the Hofmann-like elimination. Thus, in the case of the bulky dihexylamino moiety the selectivity was low and the products were obtained in comparable amounts (Table 1, entry 9). These data are in accordance with the concerted intermolecular four-centre mechanism,[18] in which case only the hydroxy moiety in the C-4 position and the dialkylamino group in the C-6 side chain are hypothesized to be involved in a recognition process by formation of hydrogen bonding.

The introduction of alkenyl and alkynyl moieties into pyrimidines and pyrimidine nucleosides is of great interest in view of their biological activities.[19–23] Moreover, the simultaneous introduction of a vinyl moiety at C-6 and of an amino group at C-4 positions of the pyrimidine ring requires more than one synthetic step. For example, 6-vinyluracil derivatives have been obtained by the condensation between formaldehyde and the phosphonium salt of 6-chloromethyl uracil[24] or by reaction of orotaldehyde (6-formyl uracil) and the appropiate ylides,[20] following the classic Wittig procedure. Furthermore, the nucleophilic displacement of a leaving group, that is triazole,[25] or the sulphonic acid moiety,[26] at the C-4 position of the pyrimidinone ring, is a usual procedure for the synthesis of C-4 substituted pyrimidine derivatives. Thus, the one-pot conversion of 6-substituted 4(3*H*)-pyrimidinones into the corresponding *N,N*-dialkyl-6-vinyl pyrimidine derivatives appears an important tool for the synthesis of twice functionalized biologically active compounds. To avoid the presence of the C-4 hydroxy substitution as an undesiderable side process, compounds **1** and **7a–m** were treated with NaH (1.2 equiv/mol) in dioxane at 100 °C in the absence of alcohol as potential nucleophile. Under these experimental conditions, *N,N*-dialkyl-6-vinyl-pyrimidines **12a–n** were obtained in good yields as the only recovered products (Scheme 3, Table 1, entries 1–12).

Finally, it is well known that 2-alkoxy-pyrimidines[27] or 2-alkylthio-pyrimidines[28] are converted to the corresponding 2(1*H*)-pyrimidinones when treated with HCl at reflux. To test the use of this procedure for the conversion of **12a–n** into the corresponding cytosine derivatives, compounds **12e** and **12m** were selected as representative models, and treated with HCl (2 N water solution) at 80 °C for 12 h. Under this experimental conditions, the corresponding 4-morpholino-6-vinylcytosine derivative **13** was obtained in acceptable yields (65 and 68%, respectively) (Scheme 4).

Biology

The antiviral activity towards RV replication was evaluated in Vero cells. Confluent Vero cell monolayers were exposed to compounds **7b–h** and **12a–n** for 48 h at 37 °C. Cell morphology, viability, and yield were then examined. For antiviral assay, the compounds were tested starting from the highest non-cytotoxic concentration which did not affect any parameter considered in 100% of the cells. After virus adsorption, the viral inoculum was removed, cell monolayers were washed three times with PBS and incubated in the presence or absence of 2-fold dilutions of the compounds. Virus yield was evaluated by plaque assay after a single cycle of virus multiplication. The compounds were tested in two independent experiments conducted in duplicate. As showed by HEPT[8,9] and DABOs,[12] 6-substitued pyrimidine derivatives can inhibit the RT activity of HIV-1 virus. The HIV-1 polymerase-RT catalyses the multistep synthesis of a double-strand DNA copy of the viral RNA genome, for subsequent integration into the host cell DNA and represents an attractive target for the chemotherapy of HIV infection.[29] Several members of different classes of RT inhibitors are currently approved for the treatment of HIV. Among them, 2′,3′-dideoxynucleosides analogues — the nuclosides RT inhibitors (NRTIs) — have been widely used to treat AIDS patients.[30]

The possible anti HIV-1 activity, as RT inhibitors, of compounds **7a–m** and **12a–n** were investigated using nevirapine, a non-nucleoside RT inhibitor,[31] as reference compound.

Results

Data of activity of compound **1**, that was previously described,[15] are also reported in Table 2 as a reference. Among compounds **7b–h**, **7b** (at the concentration of 15 μg/mL) reduced the viral yield by 70%. For this

Table 2. Cytotoxicity and anti-RV activity of compounds[a] **7b–h** and **12a–n**

Entry	Compound	CC_{50}[b]	Viral yield (%)
1	**1**	250[c,d]	1.3[c,d]
2	**7b**	30	30
3	**7c**	125	84
4	**7d**	500	81
5	**7e**	500	78
6	**7f**	250	84
7	**7g**	125	n.a.[e]
8	**7h**	60	n.a.
9	**12a**	30	n.a.
10	**12b**	30	n.a.
11	**12c**	30	n.a.
12	**12d**	30	80
13	**12e**	115	n.a.
14	**12f**	125	n.a.
15	**12g**	30	81
16	**12h**	125	77
17	**12i**	125	n.a.
18	**12l**	115	n.a.
19	**12m**	115	n.a.
20	**12n**	125	n.a.

[a]Compounds at the highest non-cytotoxic concentration were added to Vero cells after viral adsorption (1 h, 37 °C) and maintained throughout the incubation. The values represent the% of plaque forming units relative to an untreated control. Data represent the mean of two independent experiments conducted in duplicate. The standard deviations were $<5\%$ for all values.
[b]The minimal concentration of compound (μg/mL) which affected one cytotoxicity parameter in 50% of cells.
[c]Inhibitory concentration of compound (μg/mL) required to inhibit virus yield by 50% (IC_{50}) for compound **1** = 3.9. Data from ref 15.
[d]Selectivity index (CC_{50}/IC_{50}) for compound **1** = 64. Data from ref 15.
[e]n.a., not active, viral yield (%) ≥ 90.

compound, the 50% inhibitory concentration of virus multiplication has been calculated on a dose–response curve obtained by plotting the percentage of plaque reduction, with respect to the control plaque count, versus the logarithm of compound dose. Triplicate wells were utilized for each concentration tested. The standard deviation was less than 5% of the mean value. The IC_{50} of **7b** was 4.8 μg/mL with a Selectivity Index of 6.2.

From data reported on Table 2 (see, for example, compound **1** vs **7b**) the presence of a sulphur atom in the C-2 position of the pyrimidinone ring is an important factor for the anti-Rubella activity. Among compounds **12a–h**, derivatives **12d**, **12g** and **12h** show an appreciable activity for a value of CC_{50} in the range of 30–125 μg/mL (Table 2, entries 12, 15 and 16). Thus, a large substituent on the C-4 position of the pyrimidine ring maintains a partial antiviral activity. On the basis of these data, it is possible to suggest that a methylthio group on the C-2 position, a side chain containing a pyrrolidino moiety on the 4(3*H*)-pyrimidinone scaffold, or a large substituent on the C-4 position of the pyrimidine ring, are the optimal candidates for the anti-Rubella activity. Only compounds **7h**, **12a**, **12b** and **12g** were found active in the RT biological assays. The activities were evaluated against recombinant HIV-1 RTs from both wild type (WT) and clinically relevant mutant viruses resistant to TIBO/nevirapine (K103N and V106A) or pyrimidinone derivatives (Y181I and Y188L). Nevirapine was used as reference drug (Table 3). Even if, these compounds exhibit values of K_i too high to be considered as drug candidates, the spectrum of activity requires some comments.

Table 3. Activities of compounds **7h** and **12a**, **b**, **g** against recombinant reverse transcriptases (RT)[a]

Entry	Compound	HIV-1 RT				
		WT	K103N	V106A	Y181I	Y188L
1	**7h**	639	423	457	412	n.a
2	**12a**	1615	n.a	n.a	n.a	n.a
3	**12b**	484	n.a	n.a	n.a	n.a
4	**12g**	n.a	n.a	863	n.a	n.a
5	Nevirapine	0.4	7	10.5	9	0.35

[a]The ability of the compounds **7h**, **12a**, **12b**, **12g** to inhibit the recombinant enzymes is reported in Table 3 as K_i (μM) values.
n.a., not active, $K_i \geq 2$ mM.

Compound **7h** shows an appreciable inhibitory activity both against the WT and recombinant HIV-1 RT. This pattern is similar, even if of different magnitude, to that showed by nevirapine. On the other hand, compounds **12a–b**, that are characterized by a diethylamino moiety in the C-4 position, are active only against the wild type form. Also in this case, the presence of a sulphur atom in the C-2 position appears to be an important factor for the biological activity (Table 3, entry 3). Noteworthy, the nature of the C-4 substituent can tune the selectivity, and in the case of **12g**, where a methylpiperidine is present as substituent, the inhibition against only one of the recombinant enzymes is observed (Table 3, entry 4).

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker (200 MHz) spectrometer and are reported in δ value. I.R. spectra were recorded on a Perkin-Elmer 298 spectrophotometer, using NaCl plates. Melting points were obtained on a Mettler FP-80 apparatus and are uncorrected. Microanalyses were performed with a C. Erba 1106 analyser. All solvents were ACS reagent grade, and when necessary, were redistilled and dried, prior to use, according to standard procedures: THF from K/benzophenone under argon atmosphere; dioxane from Na; $CHCl_3$ from P_2O_5; methanol from magnesium turnings; ethanol from Na; *n*-butanol from CaO.

TLC was carried out using Merck TLC plates Silica gel 60 F_{254}. Chromatographic purifications were performed on columns packed with Merck 60 silica gel, 230–400 mesh, for flash technique.

Starting material

Compounds **1**, **4a–b**, **5a–b**, **6a–b**, **7a**, **7i**, **7l**, **7m**, **7n** were synthesized as previously reported.[15]

2-Methoxy-6-[(2′-dialkylamino)ethan-1′-yl]-4(3*H*)-pyrimidinone (7b–h). General procedure. Substrate **6a** (1 mmol) was dissolved in anhydrous THF (15 mL). Then

were added 1.2 equiv/mol of the appropriate amine, and the reaction mixture was heated at 110 °C for 2 h. The cooled solution was diluted with $CHCl_3$ (50 mL), washed with NaCl (saturated solution), dried over anhydrous Na_2SO_4 and successively evaporated under reduced pressure. Purification of the crude product by flash chromatography gave products **7b–h** in good yields.

2-Methoxy-6-[(2′-pyrrolidino)ethan-1′-yl]-4(3*H*)-pyrimidinone (7b). 85%, yellow oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1150, 1600. ^1H NMR ($CDCl_3$): δ 2.0 (m, 4H, 2×CH_2) 2.75 (t, 2H, CH_2) 3.5 (m, 4H, 2×CH_2) 3.9 (s, 3H, OCH_3) 4.1 (t, 2H, CH_2) 5.8 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 38.38 (CH_2) 46.33 (CH_2) 50.06 (CH_2) 54.01(CH_2) 61.39 (OCH_3) 96.36 (CH) 162.44 (C) 164.11 (C) 169 (C). Anal. calcd for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.37; H, 7.67; N, 18.81.

2-Methoxy-6-[(2-piperidino)ethan-1-yl]-4(3*H*)-pyrimidinone (7c). 89%, brown oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1730, 1715, 1660. ^1H NMR (CDCl): δ 1.57 (m, 6H, 3×CH_2) 2.70 (t, 2H, CH_2) 3.56 (m, 4H, 2×CH_2) 3.85 (s, 3H, OCH_3) 3.90 (t, 2H, CH_2) 5.99 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 24.9 (CH_2) 26.13 (CH_2) 36.34 (CH_2) 55.06 (OCH_3) 55.32 (CH_2) 58.58 (CH_2) 100.86 (CH) 163.27 (C) 169.74 (C) 170.98 (C). Anal. calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.77; H, 8.05; N, 17.75.

2-Methoxy-6-[(2′-morpholino)ethan-1-yl]-4(3*H*)-pyrimidinone (7d). 78%, white solid. Mp 143–145 °C (ethyl acetate–methanol); I.R. ($CHCl_3$) (ν, cm^{-1}): 1050, 1545, 1605; ^1H NMR ($CDCl_3$): δ 2.8 (t, 2H, CH_2) 3.65 (m, 4H, 2×CH_2) 3.8 (m, 4H, 2×CH_2) 3.9 (s, 3H, OCH_3) 4.0 (t, 2H, CH_2) 6.02 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 29.66 (CH_2) 44.22 (CH_2) 54.25 (CH_2) 61.22 (CH_2) 66.44 (OCH_3) 98.47 (CH) 161.02 (C) 163.99 (C) 169.41 (C). Anal. calcd for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 55.24; H, 7.16; N, 17.55.

2-Methoxy-6-[(2′-piperazino)ethan-1′-yl]-4(3*H*)-pyrimidinone (7e). 78%, colourless oil. ^1H NMR ($CDCl_3$): δ 2.38 (m, 2H, CH_2) 2.57 (t, 2H, CH_2) 2.66 (t, 2H, CH_2) 2.74 (m, 2H, CH_2) 3.98 (s, 3H, OCH_3) 6.0 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) (δ, ppm): 34.62 (CH_2) 45.62 (CH_2) 53.75 (CH_2) 56.73 (OCH_3) 58.39 (CH_2) 100.14 (CH) 163.27 (C) 169.73 (C) 170.98 (C). Anal. calcd for $C_{11}H_{18}N_4O_2$: C, 55.44; H, 7.61; N, 23.51. Found: C, 55.24; H, 7.66; N, 23.55.

2-Methoxy-6-[2′-(2-methylpiperidino)ethan-1′-yl]-4(3*H*)-pyrimidinone (7f). 82%, brown oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1120, 1600; ^1H NMR ($CDCl_3$): δ 1.2 (d, 3H, CH_3) 1.7 (m, 6H, 3×CH_2) 2.7 (t, 2H, CH_2) 2.9 (m, 1H, CH) 3.85 (s, 3H, OCH_3) 3.95 (t, 2H, CH_2) 4.25 (m, 1H, CH) 4.65 (m, 1H, CH) 6.0 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 14.63 (CH_3) 25.11 (CH_2) 25.66 (CH_2) 35.09 (CH_2) 36.48 (CH_2) 52.12 (CH_2) 54.90 (CH_2) 55.01 (OCH_3) 57.01 (CH) 100.06 (CH) 163.27 (C) 169.07 (C) 170.98 (C). Anal. calcd for $C_{13}H_{21}N_3O_2$: C, 62.13; H, 8.42; N, 16.72. Found: C, 62.15; H, 8.47; N, 16.77.

2-Methoxy-6-[(2′-hexamethyleneimino)ethan-1′-yl]-4(3*H*)-pyrimidinone (7g). 70%, yellow oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1145, 1620; ^1H NMR ($CDCl_3$): δ 1.6 (m, 4H, 2×CH_2) 1.8 (m, 4H, 2×CH_2) 2.75 (t, 2H, CH_2) 3.5 (m, 4H, 2×CH_2) 3.9 (s, 3H, OCH_3) 4.0 (t, 2H, CH_2) 5.9 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 26.88 (CH_2) 28.41 (CH_2) 38.48 (CH_2) 53.97 (CH_2) 57.46 (OCH_3) 59.37 (CH_2) 99.10 (CH) 163.33 (C) 165 (C) 168.31 (C). Anal. calcd for $C_{13}H_{21}N_3O_2$: C, 62.13; H, 8.42; N, 16.72. Found: C, 62.15; H, 8.47; N, 16.77.

2-Methoxy-6-[(2′-dihexylamino)ethan-1′-yl]-4(3*H*)-pyrimidinone (7h). 60%, yellow oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1100, 1610. ^1H NMR ($CDCl_3$): δ 0.8 (m, 6H, 2×CH_3) 1.4 (m, 12H, 6×CH_2) 1.6 (m, 4H, 2×CH_2) 2.75 (t, 2H, CH_2) 3.4 (m, 4H, 2×CH_2) 3.85 (s, 3H, OCH_3) 4.0 (t, 2H, CH_2) 5.8 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 14.65 (CH_3) 23.14 (CH_2) 27.50 (CH_2) 27.65 (CH_2) 32.25 (CH_2) 36.34 (CH_2) 54.13 (CH_2) 56.31 (OCH_3) 59.37 (CH_2) 100.86 (CH) 163.27 (C) 169.73 (C) 170.73 (C). Anal. calcd for $C_{19}H_{35}N_3O_2$: C, 67.62; H, 10.45; N, 12.45. Found: C, 67.66; H, 10.47; N, 12.48.

2-Methoxy- and 2-methylthio-4-alkoxy-6-[(2′-diethylamino)ethyl]pyrimidines (8a–b, 9a–b, 10a–b, 11a–b). General procedure. Na metal (0.1 g-atoms, 2.29 g) in small pieces was carefully added to the appropriate dry alcohol (200 mmol). Dissolution of the metal was completed by heating the mixture at 70–80 °C, then compound **1** or **7a** (1 mmol) was added and the mixture was heated at 70 °C. After cooling, the mixture was diluted with H_2O (30 mL) and extracted with AcOEt (3×20 mL). The organic layer was dried over anhydrous Na_2SO_4, evaporated and purified by chromatography.

2,4-Dimethoxy-6-[(2′-diethylamino)ethyl]pyrimidine (8a). 85%, yellow oil. ^1H NMR ($CDCl_3$): δ 0.93 (t, 6H, 2×CH_3) 2.38 (q, 4H, 2×CH_2) 2.70 (t, 2H, CH_2) 2.91 (t, 2H, CH_2) 4.00 (s, 3H, OCH_3) 4.18 (s, 3H, OCH_3) 6.10 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.47 (CH_3) 36.10 (CH_2) 51.25 (CH_2) 54.13 (OCH_3) 55.05 (OCH_3) 58.95 (CH_2) 100.43 (CH) 167.04 (C) 169.35 (C) 169.74 (C). Anal. calcd for $C_{12}H_{21}N_3O_2$: C, 60.23; H, 8.84; N, 17.56. Found: C, 60.28; H, 8.18 ; N, 17.45.

2-Methylthio-4-methoxy-6-[(2′-diethylamino)ethyl]pyrimidine (8b). 65%, brown oil. ^1H NMR ($CDCl_3$): δ 0.95 (t, 6H, 2×CH_3) 2.35 (q, 4H, 2×CH_2) 2.43 (s, 3H, SCH_3) 2.70 (t, 2H, CH_2) 2.95 (t, 2H, CH_2) 4.18 (s, 3H, OCH_3) 6.17 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.47 (CH_3) 13.70 (SCH_3) 35.05 (CH_2) 51.25 (CH_2) 54.25 (OCH_3) 58.95 (CH_2) 104.71 (CH) 167.65 (C) 170.32 (C) 171.21 (C). Anal. calcd for $C_{12}H_{21}N_3OS$: C, 56.44; H, 8.29; N, 16.45. Found: C, 56.19; H, 8.39; N, 16.41.

2-Methoxy-4-ethoxy-6-[(2-diethylamino)ethyl]pyrimidine (9a). 72%, yellow oil. ^1H NMR ($CDCl_3$): δ 0.93 (t, 6H, 2CH_3) 1.40 (t, 3H, CH_3) 2.38 (q, 4H, 2×CH_2) 2.70 (t, 2H, CH_2) 2.93 (t, 2H, CH_2) 4.01 (s, 3H, OCH_3) 4.34 (q, 2H, OCH_2) 6.03 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.51 (CH_3) 14.40 (CH_3) 36.10 (CH_2) 51.25 (CH_2) 55.11 (OCH_3) 58.95 (CH_2) 62.60 (OCH_2) 100.71 (CH) 166.82 (C) 169.35 (C) 169.74 (C). Anal. calcd for $C_{13}H_{23}N_3O_2$:

C, 61.63; H, 9.15; N, 16.59. Found: C, 61.68; H, 9.21; N, 16.48.

2-Methylthio-4-ethoxy-6-[(2′-diethylamino)ethyl]pyrimidine (9b). 66%, brown oil. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 6H, 2×CH_3) 1.44 (t, 3H, CH_3) 2.38 (q, 4H, 2×CH_2) 2.43 (s, 3H, SCH_3) 2.70 (t, 2H, CH_2) 2.95 (t, 2H, CH_2) 4.34 (q, 2H, OCH_2) 6.15 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.45 (CH_3) 13.58 (SCH_3) 14.42 (CH_3) 35.05 (CH_2) 51.25 (CH_2) 58.78 (CH_2) 62.21 (OCH_2) 104.23 (CH) 167.43 (C) 170.32 (C) 171.21 (C). Anal. calcd for $C_{13}H_{23}N_3OS$: C, 57.96; H, 8.61; N, 15.60. Found: C, 57.90; H, 8.45; N, 15.48.

2-Methoxy-4-butoxy-6-[(2′-diethylamino)ethyl]pyrimidine (10a). 71%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 6H, 2×CH_3) 1.00 (t, 3H, CH_3) 1.73 (m, 4H, CH_2CH_2) 2.38 (q, 4H, 2×CH_2) 2.70 (t, 2H, CH_2) 2.95 (t, 2H, CH_2) 4.00 (s, 3H, OCH_3) 4.03 (t, 2H, OCH_2) 6.11 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.48 (CH_3) 13.65 (CH_3) 19.20 (CH_2) 30.90 (CH_2) 36.10 (CH_2) 51.25 (CH_2) 55.52 (OCH_3) 59.72 (CH_2) 66.31 (OCH_2) 100.23 (CH) 167.93 (C) 169.35 (C) 169.74 (C). Anal. calcd for $C_{15}H_{27}N_3O_2$: C, 64.02; H, 9.67; N, 14.93. Found: C, 64.08; H, 9.65; N, 14.98.

2-Methylthio-4-butoxy-6-[(2′-diethylamino)ethyl]pyrimidine (10b). 55%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 6H, 2×CH_3) 1.00 (t, 3H, CH_3) 1.73 (m, 4H, CH_2CH_2) 2.38 (q, 4H, 2×CH_2) 2.42 (s, 3H, SCH_3) 2.70 (t, 2H, CH_2) 2.95 (t, 2H, CH_2) 4.03 (t, 2H, OCH_2) 6.23 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.48 (CH_3) 13.70 (CH_3) 13.75 (SCH_3) 19.20 (CH_2) 30.90 (CH_2) 35.05 (CH_2) 51.25 (CH_2) 59.54 (CH_2) 66.30 (OCH_2) 103.85 (CH) 168.74 (C) 170.32 (C) 171.21 (C). Anal. calcd for $C_{15}H_{27}N_3OS$: C, 60.57; H, 9.15; N, 14.13. Found: C, 60.58; H, 9.19; N, 14.15.

2-Methoxy-4-benzyloxy-6-[(2′-diethylamino)ethyl]pyrimidine (11a). 70%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 6H, 2×CH_3) 2.35 (q, 4H, 2×CH_2) 2.70 (t, 2H, CH_2) 2.95 (t, 2H, CH_2) 4.03 (s, 3H, OCH_3) 4.99 (s, 2H, OCH_2) 6.07 (s, 1H, CH) 7.12 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 13.48 (CH_3) 35.05 (CH_2) 51.25 (CH_2) 55.48 (OCH_3) 58.95 (CH_2) 72.53 (OCH_2) 104.26 (CH) 128.65 (CH) 129.57 (CH) 130.41 (CH) 137.64 (C) 167.29 (C) 170.72 (C) 171.69 (C). Anal. calcd for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.44; H, 8.03; N, 13.35.

2-Methylthio-4-benzyloxy-6-[(2′-diethylamino)ethyl]pyrimidine (11b). 58%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 6H, 2×CH_3) 2.35 (q, 4H, 2×CH_2) 2.42 (s, 3H, SCH_3) 2.70 (t, 2H, CH_2) 2.95 (t, 2H, CH_2) 4.99 (s, 2H, OCH_2) 6.19 (s, 1H, CH) 7.12 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 13.48 (CH_3) 13.70 (SCH_3) 35.08 (CH_2) 52.22 (CH_2) 58.17 (CH_2) 74.16 (OCH_2) 103.77 (CH) 125.65 (CH) 128.81 (CH) 131.33 (CH) 138.26 (C) 168.11 (C) 170.74 (C) 172.31 (C). Anal. calcd for $C_{18}H_{25}N_3OS$: C, 65.22; H, 7.60; N, 12.68. Found: C, 65.32; H, 7.45; N, 12.66.

2-Methoxy- and 2-methylthio-4-butoxy-6-[(2′-dialkylamino)ethyl]pyrimidines (10a–n) and 2-methoxy and 2-methylthio-4-*N*,*N*-dialkylamino-6-vinyl-pyrimidines (12a–n).

General procedure. Compounds **1** or **7a**–**m** (1 mmol) were dissolved in 10 mL of anhydrous dioxane. To the resulting solution, were added 1.5 equiv/mol of NaH (60 wt% dispersion in mineral oil) and 1.5 equiv/mol of *n*-ButOH. The mixture was heated at reflux and the reaction was monitored by TLC (chloroform-methanol 95:5 as eluant) until complete conversion of **1** or **7a**–**m**. The mixture was allowed to cool, hydrochloric acid (2 N water solution) was carefully added to neutralize the solution and, after filtration of the inorganic residue, the filtrate was extracted with $CHCl_3$ (3×10 mL). The organic solutions were combined, dried over anhydrous Na_2SO_4 and the solvent removed by rotary evaporation. The crude was purified by flash chromatography to afford compounds **10a**–**n** and **12a**–**n** in good yields.

2-Methoxy-4-butoxy-6-[(2′-pyrrolidino)ethyl]pyrimidine (10c). 10%, brown oil. ^{1}H NMR ($CDCl_3$): δ 0.98 (t, 3H, CH_3) 1.69 (m, 4H, CH_2CH_2) 1.77 (m, 4H, 2×CH_2) 2.38 (m, 4H, 2×CH_2) 2.68 (t, 2H, CH_2) 2.87 (t, 2H, CH_2) 4.00 (s, 3H, OCH_3) 4.06 (t, 2H, OCH_2) 6.17 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.65 (CH_3) 19.29 (CH_2) 23.59 (CH_2) 31.90 (CH_2) 36.55 (CH_2) 53.64 (CH_2) 55.05 (OCH_3) 57.16 (CH_2) 66.29 (OCH_2) 100.11 (CH) 167.93 (C) 169.35 (C) 170.86 (C). Anal. calcd for $C_{15}H_{25}N_3O_2$: C, 64.49; H, 9.02; N, 15.04. Found: C, 64.44; H, 9.11; N, 14.94.

2-Methoxy-4-butoxy-6-[(2-piperidino)ethyl]pyrimidine (10d). 14%, brown oil. ^{1}H NMR ($CDCl_3$): δ 0.98 (t, 3H, CH_3) 1.41 (m, 2H, CH_2) 1.58 (m, 4H, 2×CH_2) 1.63 (m, 2H, CH_2) 1.71 (m, 4H, CH_2CH_2) 2.54 (m, 2H, CH_2) 2.70 (t, 2H, CH_2) 2.87 (t, 2H, CH_2) 4.00 (s, 3H, OCH_3) 4.02 (t, 2H, OCH_2) 6.20 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.65 (CH_3) 19.14 (CH_2) 24.64 (CH_2) 26.13 (CH_2) 31.78 (CH_2) 36.95 (CH_2) 55.05 (OCH_3) 55.64 (CH_2) 57.37 (CH_2) 66.30 (OCH_2) 100.16 (CH) 167.93 (C) 169.35 (C) 170.61 (C). Anal. calcd for $C_{16}H_{27}N_3O_2$: C, 65.50; H, 9.28; N, 14.32. Found: C, 65.24; H, 9.41; N, 14.51.

2-Methoxy-4-butoxy-6-[(2′-morpholino)ethyl]pyrimidine (10e). 20%, clear oil. ^{1}H NMR ($CDCl_3$): δ 0.98 (t, 3H, CH_3) 1.65 (m, 4H, CH_2CH_2) 2.36 (t, 4H, 2×CH_2) 2.73 (t, 2H, CH_2) 2.83 (t, 2H, CH_2) 3.87 (t, 4H, 2×CH_2) 4.00 (s, 3H, OCH_3) 4.02 (t, 2H, OCH_2) 6.19 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.70 (CH_3) 19.74 (CH_2) 30.90 (CH_2) 36.57 (CH_2) 53.34 (CH_2) 55.12 (OCH_3) 57.37 (CH_2) 65.85 (OCH_2) 67.04 (CH_2) 100.14 (CH) 167.93 (C) 169.35 (C) 172.61 (C). Anal. calcd for $C_{15}H_{25}N_3O_3$: C, 60.99; H, 8.53; N, 14.32. Found: C, 61.14; H, 8.57; N, 14.76.

2-Methoxy-4-butoxy-6-[(2′-piperazino)ethyl]pyrimidine (10f). 19%, brown oil. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, CH_3) 1.74 (m, 4H, CH_2CH_2) 2.38 (t, 4H, 2×CH_2) 2.73 (t, 2H, CH_2) 2.81 (t, 4H, 2×CH_2) 2.83 (t, 2H, CH_2) 4.00 (s, 3H, OCH_3) 4.03 (t, 2H, OCH_2) 6.11 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.74 (CH_3) 19.75 (CH_2) 30.81 (CH_2) 34.62 (CH_2) 45.62 (CH_2) 53.75 (CH_2) 55.16 (OCH_3) 58.71 (CH_2) 66.17 (OCH_2) 101.03 (CH) 165.33 (C) 167.05 (C) 170.65 (C). Anal. calcd for $C_{15}H_{26}N_4O_2$: C, 61.20; H, 8.90; N, 19.03. Found: C, 61.44; H, 8.44; N, 19.08.

2-Methoxy-4-butoxy-6-[2′-(2-methylpiperidino)ethyl]pyrimidine (10g). 22%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.90 (d, 3H, CH_3) 1.00 (t, 3H, CH_3) 1.73 (m, 4H, CH_2CH_2) 1.77 (m, 6H, 3×CH_2) 2.66 (m, 2H, CH_2) 2.76 (t, 2H, CH_2) 2.83 (t, 2H, CH_2) 2.90 (m, 1H, CH) 4.00 (s, 3H, OCH_3) 4.03 (t, 2H, OCH_2) 6.11 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.75 (CH_3) 19.32 (CH_2) 25.71 (CH_2) 26.46 (CH_2) 30.90 (CH_2) 35.10 (CH_2) 36.48 (CH_2) 52.01 (CH_2) 54.90 (CH_2) 55.17 (OCH_3) 57.01 (CH) 65.89 (OCH_2) 100.03 (CH) 166.93 (C) 169.35 (C) 170.61 (C). Anal. calcd for $C_{17}H_{29}N_3O_2$: C, 66.42; H, 9.51; N, 13.67. Found: C, 66.45; H, 9.23; N, 13.73.

2-Methoxy-4-butoxy-6-[(2′-hexamethyleneimino)ethyl]-pyrimidine (10h). 20%, brown oil. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, CH_3) 1.53 (m, 4H, 2×CH_2) 1.66 (m, 4H, 2CH_2) 1.71 (m, 4H, CH_2CH_2) 2.52 (m, 4H, 2×CH_2) 2.70 (t, 2H, CH_2) 2.91 (t, 2H, CH_2) 4.00 (s, 3H, OCH_3) 4.02 (t, 2H, OCH_2) 6.17 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.65 (CH_3) 19.34 (CH_2) 28.14 (CH_2) 28.60 (CH_2) 31.23 (CH_2) 32.16 (CH_2) 34.66 (CH_2) 35.77 (CH_2) 55.31 (OCH_3) 66.34 (OCH_2) 100.91 (CH) 168.33 (C) 169.85 (C) 171.58 (C). Anal. calcd for $C_{17}H_{29}N_3O_2$: C, 66.42; H, 9.18; N, 13.67. Found: C, 66.53; H, 9.17; N, 13.88.

2-Methoxy-4-butoxy-6-[(2′-dihexylamino)ethyl]pyrimidine (10i). 45%, brown oil. ^{1}H NMR ($CDCl_3$): δ 0.8 (t, 6H, 2×CH_3) 1.00 (t, 3H, CH_3) 1.31 (m, 8H, 4CH_2) 1.46 (m, 8H, 4CH_2) 1.73 (m, 4H, CH_2CH_2) 2.31 (t, 4H, 2×CH_2) 2.70 (t, 2H, CH_2) 2.87 (t, 2H, CH_2) 4.00 (s, 3H, OCH_3) 4.04 (t, 2H, OCH_2) 6.17 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.65 (CH_3) 13.70 (CH_3) 19.29 (CH_2) 27.19 (CH_2) 27.61 (CH_2) 29.59 (CH_2) 29.77 (CH_2) 30.90 (CH_2) 37.18 (CH_2) 54.07 (CH_2) 55.33 (OCH_3) 59.37 (CH_2) 66.34 (OCH_2) 100.11 (CH) 163.93 (C) 169.35 (C) 170.35 (C). Anal. calcd for $C_{23}H_{43}N_3O_2$: C, 70.18; H, 11.01; N, 10.68. Found: C, 70.21; H, 11.07; N, 10.65.

2-Methylthio-4-butoxy-6-[(2-piperidino)ethyl]pyrimidine (10l). 18%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, CH_3)$_t$ 1.56 (m, 4H, 2×CH_2) 1.71 (m, 4H, CH_2CH_2) 2.43 (s, 3H, SCH_3) 2.48 (m, 4H, 2×CH_2) 2.54 (m, 2H, CH_2) 2.70 (t, 2H, CH_2) 2.90 (t, 2H, CH_2) 4.03 (t, 2H, OCH_2) 6.29 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.70 (CH_3) 13.75 (SCH_3) 19.93 (CH_2) 24.94 (CH_2) 26.13 (CH_2) 30.90 (CH_2) 35.25 (CH_2) 55.32 (CH_2) 59.54 (CH_2) 66.34 (OCH_2) 103.85 (CH) 168.54 (C) 170.20 (C) 171.22 (C). Anal. calcd for $C_{16}H_{27}N_3OS$: C, 62.10; H, 8.79; N, 13.58. Found: C, 62.23; H, 8.75; N, 13.55.

2-Methylthio-4-butoxy-6-[(2′-morpholino)ethyl]pyrimidine (10m). 18%, clear oil. ^{1}H NMR ($CDCl_3$): δ 1.05 (t, 3H, CH_3) 1.71 (m, 4H, CH_2CH_2) 2.36 (t, 4H, 2×CH_2) 2.43 (s, 3H, SCH_3) 2.73 (t, 2H, CH_2) 2.91 (t, 2H, CH_2) 3.86 (t, 4H, 2×CH_2) 4.03 (t, 2H, OCH_2) 6.31 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.70 (CH_3) 13.75 (SCH_3) 19.24 (CH_2) 30.90 (CH_2) 35.52 (CH_2) 53.34 (CH_2) 58.54 (CH_2) 66.48 (OCH_2) 67.00 (CH_2) 103.85 (CH) 168.54 (C) 170.21 (C) 172.49 (C). Anal. calcd for $C_{15}H_{25}N_3O_2S$: C, 57.85; H, 8.09; N, 13.49. Found: C, 57.88; H, 8.32; N, 13.43.

2-Methylthio-4-butoxy-6-[(2′-piperazino)ethyl]pyrimidine (10n). 15%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.03 (t, 3H, CH_3) 1.70 (m, 4H, CH_2CH_2) 2.38 (t, 4H, 2×CH_2) 2.43 (s, 3H, SCH_3) 2.74 (t, 2H, CH_2) 2.81 (m, 4H, 2×CH_2) 2.89 (t, 2H, CH_2) 4.01 (t, 2H, OCH_2) 6.23 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.70 (CH_3) 13.77 (SCH_3) 19.74 (CH_2) 30.90 (CH_2) 35.58 (CH_2) 45.62 (CH_2) 53.74 (CH_2) 58.32 (CH_2) 66.32 (OCH_2) 103.46 (CH) 168.54 (C) 170.94 (C) 171.22 (C). Anal. calcd for $C_{15}H_{26}N_4OS$: C, 58.03; H, 8.44; N, 18.05. Found: C, 58.65; H, 8.45; N, 18.43.

2-Methoxy-4-*N*,*N*-dialkylamino-6-vinyl- and 2-Methylthio-4-*N*,*N*-dialkylamino-6-vinyl-pyrimidines (12a–n). General procedure. Compounds **1** or **7a**–**m** (1 mmol) were dissolved in 10 mL of anhydrous dioxane. To the resulting solution, NaH (1.2 equiv/mol, 60 wt% dispersion in mineral oil) was added. The mixture was refluxed and the progress of the reaction was monitored by TLC (chloroform–methanol 95:5 as eluant). After completion of the reaction, the mixture was cooled and HCl (2 N water solution) was carefully added to neutralize the solution. After filtration of the inorganic residue, the filtrate was extracted with $CHCl_3$ (3×10 mL). The organic solutions were combined, dried over anhydrous Na_2SO_4 and the solvent removed by evaporation. The crude product was purified by chromatography to afford compounds **12a**–**n** in good yields.

2-Methoxy-4-diethylamino-6-vinyl-pyrimidine (12a). 74%, colourless oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1150, 1560; ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 6H, 2×CH_3) 3.5 (m, 4H, 2×CH_2) 3.95 (s, 3H, OCH_3) 5.55 (dd, 1H, CH) 5.88 (s, 1H, CH) 6.5 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 12.69 (CH_3) 42.22 (CH_2) 53.81 (OCH_3) 94.91 (CH) 120.32 (CH_2) 135.97 (CH) 162.47 (C) 163.44 (C) 165.74 (C). Anal. calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.79; H, 8.27; N, 20.35.

2-Methylthio-4-diethylamino-6-vinyl-pyrimidine (12b). 55%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 6H, 2×CH_3) 2.9 (s, 3H, SCH_3) 3.5 (m, 4H, 2×CH_2) 5.55 (dd, 1H, CH) 6.3 (s, 1H, CH) 6.5 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 13.33 (SCH_3) 30.21 (CH_3) 42.22 (CH_2) 96.30 (CH) 120.93 (CH_2) 136.26 (CH) 162.47 (C) 163.44 (C) 165.74 (C). Anal. calcd for $C_{11}H_{17}N_3S$: C, 59.16; H, 7.67; N, 18.81. Found: C, 59.36; H, 7.67; N, 18.18.

2-Methoxy-4-pyrrolidin-6-vinyl-pyrimidine (12c). 64%, brown oil. IR. ($CHCl_3$) (ν, cm^{-1}): 1140, 1580; ^{1}H NMR ($CDCl_3$): δ 2.0 (m, 4H, 2×CH_2) 3.5 (m, 4H, 2×CH_2) 3.9 (s, 3H, OCH_3) 5.55 (dd, 1H, CH) 5.9 (s, 1H, CH) 6.55 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 25.65 (CH_2) 50.78 (CH_2) 53.71 (OCH_3) 98.19 (CH) 126.58 (CH_2) 133.99 (CH) 150.21 (C) 162.05 (C) 168.57 (C). Anal. calcd for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.47; H, 7.43; N, 20.35.

2-Methoxy-4-piperidin-6-vinyl-pyrimidine (12d). 63%, yellow oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1100, 1580; ^{1}H NMR ($CDCl_3$): δ 1.59–1.64 (m, 6H, 3×CH_2) 3.59–3.64 (m, 4H, 2×CH_2) 3.9 (s, 3H, OCH_3) 5.55 (dd, 1H, CH) 6.09

(s, 1H, CH) 6.44 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 24.56 (CH_2) 26.40 (CH_2) 46.20 (CH_2) 54.81 (OCH_3) 98.31 (CH) 126.70 (CH_2) 133.99 (CH) 152.66 (C) 161.80 (C) 168.32 (C). Anal. calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.78; H, 7.89; N, 19.35.

2-Methoxy-4-morpholin-6-vinyl-pyrimidine (12e). 65%, colourless oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1150, 1585; ^1H NMR ($CDCl_3$): δ 3.65 (m, 4H, 2×CH_2) 3.75 (m, 4H, 2×CH_2) 3.95 (s, 3H, OCH_3) 5.55 (dd, 1H, CH) 6.1 (s, 1H, CH) 6.5 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 48.20 (CH_2) 55.11 (OCH_3) 66.50 (CH_2) 96.60 (CH) 126.59 (CH_2) 133.99 (CH) 151.82 (C) 163.25 (C) 169.77 (C). Anal. calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.87; H, 6.99; N, 18.66.

2-Methoxy-4-piperazin-6-vinyl-pyrimidine (12f). 55%, colourless oil. ^1H NMR ($CDCl_3$): δ 2.38 (m, 4H, 2×CH_2) 3.33 (m, 4H, 2×CH_2) 4.02 (s, 3H, OCH_3) 5.65 (dd, 1H, CH) 6.07 (s, 1H, CH) 6.47 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 45.80 (CH_2) 46.20 (CH_2) 55.50 (OCH_3) 97.81 (CH) 126.59 (CH_2) 133.99 (CH) 151.87 (C) 161.80 (C) 168.32 (C). Anal. calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 59.87; H, 7.32; N, 25.66.

2-Methoxy-4-(2-methylpiperidin)-6-vinyl-pyrimidine (12g). 66%, brown oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1100, 1575; ^1H NMR ($CDCl_3$): δ 1.2 (d, 3H, CH_3) 1.7 (m, 6H, 3×CH_2) 2.95 (m, 1H, CH) 3.95 (s, 3H, OCH_3) 4.25 (m, 1H, CH) 4.7 (m, 1H, CH) 5.55 (dd, 1H, CH) 6.1 (s, 1H, CH) 6.5 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 17.29 (CH_3) 25.11 (CH_2) 25.66 (CH_2) 35.74 (CH_2) 46.49 (CH_2) 54.15 (CH) 56.85 (OCH_3) 97.37 (CH) 126.59 (CH_2) 132.87 (CH) 154.27 (C) 161.80 (C) 168.32 (C). Anal. calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.90; H, 8.32; N, 18.06.

2-Methoxy-4-hexamethyleneimin-6-vinyl-pyrimidine (12h). 70%, yellow oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1120, 1575; ^1H NMR ($CDCl_3$) (δ, ppm): 1.55 (m, 4H, 2×CH_2) 1.8 (m, 4H, 2×CH_2) 3.6 (m, 4H, 2×CH_2) 3.95 (s, 3H, OCH_3) 5.55 (dd, 1H, CH) 5.94 (s, 1H, CH) 6.5 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 26.69 (CH_2) 29.51 (CH_2) 47.67 (CH_2) 54.73 (OCH_3) 98.42 (CH) 126.59 (CH_2) 133.99 (CH) 155.07 (C) 161.74 (C) 168.07 (C). Anal. calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.90; H, 8.32; N, 18.06.

2-Methoxy-4-dihexylamin-6-vinyl-pyrimidine (12i). 60%, brown oil. I.R. ($CHCl_3$) (ν, cm^{-1}): 1150, 1585; ^1H NMR ($CDCl_3$): δ 0.8 (m, 6H, 2×CH_3) 1.4 (m, 12H, 6×CH_2) 1.6 (m, 4H, 2×CH_2) 3.4 (m, 4H, 2×CH_2) 3.9 (s, 3H, OCH_3) 5.55 (dd, 1H, CH) 5.9 (s, 1H, CH) 6.5 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 14.69 (CH_3) 23.51 (CH_2) 26.94 (CH_2) 29.57 (CH_2) 35.25 (CH_2) 49.32 (CH_2) 55.26 (OCH_3) 97.92 (CH) 126.59 (CH_2) 133.89 (CH) 155.03 (C) 161.55 (C) 168.07 (C). Anal. calcd for $C_{19}H_{33}N_3O$: C, 71.43; H, 10.41; N, .13.15. Found: C, 71.90; H, 10.45; N, 13.18.

2-Methylthio-4-piperidin-6-vinyl-pyrimidine (12l). 65%, colourless oil. ^1H NMR ($CDCl_3$): δ 1.59–1.64 (m, 6H, 3×CH_2) 2.84 (s, 3H, SCH_3) 3.59–3.4 (m, 4H, 2×CH_2) 5.55 (dd, 1H, CH) 6.09 (s, 1H, CH) 6.44 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 13.70 (SCH_3) 24.56 (CH_2) 26.40 (CH_2) 46.20 (CH_2) 103.27 (CH) 121.17 (CH_2) 133.47 (CH) 153.27 (C) 162.41 (C) 173.65 (C). Anal. calcd for $C_{12}H_{17}N_3S$: C, 61.24; H, 7.28; N, 17.85. Found: C, 61.34; H, 7.31; N, 17.18.

2-Methylthio-4-morpholin-6-vinyl-pyrimidine (12m). 55%, colourless oil. ^1H NMR ($CDCl_3$): δ 3.65 (m, 4H, 2×CH_2) 3.75 (m, 4H, 2×CH_2) 3.95 (s, 3H, SCH_3) 5.55 (dd, 1H, CH) 6.1 (s, 1H, CH) 6.5 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 13.78 (SCH_3) 29.67 (CH_2) 42.22 (CH_2) 66.48 (CH_3) 96.07 (CH) 121.17 (CH_2) 135.47 (CH) 161.26 (C) 162.36 (C) 171.18 (C). Anal. calcd for $C_{11}H_{15}N_3OS$: C, 55.67; H, 6.17; N, 17.71. Found: C, 55.80; H, 6.13; N, 17.40.

2-Methylthio-4-piperazin-6-vinyl-pyrimidine (12n). 60%, brown oil. ^1H NMR ($CDCl_3$): δ 2.38 (m, 4H, 2×CH_2) 2.95 (s, 3H, SCH_3) 3.33 (m, 4H, 2×CH_2) 5.65 (dd, 1H, CH) 6.07 (s, 1H, CH) 6.47 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) (δ,ppm): 13.88 (SCH_3) 45.80 (CH_2) 46.20 (CH_2) 102.78 (CH) 121.17 (CH_2) 133.92 (CH) 152.48 (C) 162.41 (C) 173.65 (C). Anal. calcd for $C_{11}H_{16}N_4S$: C, 55.90; H, 6.82; N, 23.71. Found: C, 55.80; H, 6.47; N, 23.89.

4-Morpholin-6-vinyl-cytosine (13). Compound **12e** (500 mg, 2.2 mmol) or **12m** (400 mg, 1.6 mmol) in 2 N hydrochloric acid (10 mL) were heated at 80 °C for 12 h. The solution was then cooled to room temperature, neutralized with $NaHCO_3$ (saturated solution) and extracted with $CHCl_3$ (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (chloroform–methanol: 98/2) to gave product **13** as a brown oil.

^1H NMR ($CDCl_3$): δ 3.65 (m, 4H, 2×CH_2) 3.75 (m, 4H, 2×CH_2) 5.70 (dd, 1H, CH) 5.8 (s, 1H, CH) 6.5 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 45.38 (CH_2) 65.81 (CH_2) 101.57 (CH) 131.61 (CH_2) 133.63 (CH) 142.48 (C) 163.83 (C) 168.03 (C). Anal. calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.85; H, 6.42; N, 20.88.

Cells

Vero cells were cultured at 37 °C in a 5% CO_2 atmosphere in Eagle's Minimum Essential Medium (MEM) containing 1.2 mg/mL $NaHCO_3$ and supplemented with 6% (v/v) foetal bovine serum (FBS), 2 mM glutamine, 100 IU/mL penicillin and 100 μg/mL streptomycin. For cell maintenance the serum concentration was lowered to 2% (v/v).

Virus

Rubella virus (Therien strain) was grown in Vero cells in maintenance medium. Semi confluent monolayers were inoculated with virus at a multiplicity of infection of 0.1 PFU/cell and incubated at 37 °C for 72 h. After infection, supernatant was collected, centrifuged at 1000*g* for

10 min to remove cellular debris, and then stored in small aliquots at −80 °C.

Cytotoxicity assays

The cytotoxicity of compounds was monitored by evaluting the effects on cell morphology, viability and growth. Vero cells in 24-well plates were cultured for 2 days at 37 °C in the presence or absence of 2-fold serially diluted compounds. After 48 h incubation, cytotoxicity was scored microscopically as morphological alterations (such as swelling, granularity, rounding up, shrinking and detachment). Cell morphology, viability and yield were examined. Cell viability was assessed on the basis of vital dye exclusion test, using Trypan Blue, and cell yield was determined by counting cells with an hemocytometer after trypsinization.

Antiviral assay

For antiviral assays, confluent monolayers of Vero cells grown in 24-well plates were inoculated with RV (3 PFU/cell). After virus adsorption (1 h, 37 °C), the viral inoculum was removed. Cell monolayers were washed three times with phosphate-buffered saline (PBS) and incubated with maintenance medium in the presence or absence of the compounds. Virus yield was evaluated by plaque assay after 48 h.

Plaque assay

Serial 10-fold dilutions of virus were inoculated on to confluent Vero cell monolayers. After a 1-h adsorption period at 37 °C, the inoculum was removed and cells were washed three times with PBS before being overlaid with MEM containing 0.4% (w/v) agar (Oxoid). After 5 days incubation at 37 °C, plaques were stained with 0.1% crystal violet solution.

HIV-1 RT RNA-dependent DNA polymerase activity assay. RNA-dependent DNA polymerase activity was assayed as follow: a final volume of 25 μL contained reaction buffer (50 mM di Tris–HCl pH 7.5, 1 mM DDT, 0.2 mg/mL BSA, 4% glycerol); 10 mM $MgCl_2$; 0.5 μg poly(rA)/oligo(dT)$_{10:1}$ (0.3 μM 3′-OH ends); 10 μM [^{3}H]-dTTP (1 Ci/mmol) and 2–4 nM RT. Reactions was incubated at 37 °C for the indicated time. 20 μL-aliquots were then spotted on glasses fiber filter GF/C which were immediately immersed in 5% ice-cold TCA. Filters were washed twice in 5% ice-cold TCA and once in EtOH for 5 min, dried and acid-precipitable radioactivity was quantitated by scintillation counting.

Inhibition assays. Reactions were performed under conditions described for the HIV-1 RT RNA-dependent DNA polymerase activity assay. Incorporation of radioactive dTTP into poly(rA)/oligo(dT) at different concentrations of substrate was monitorated in the presence of increasing fixed amounts of compounds. Data were then plotted according to Lineweaver–Burke and Dixon. For K_i determination, an interval of inhibitor concentrations between 0.2 and 5 K_i was used.

Kinetic parameters calculation. K_i values were calculated by non-least squares computer fitting of the experimental data to the equation for non-competitive inhibition.

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