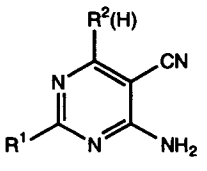
A Novel Solution- and Solid-Phase Approach to 2,4,5-Tri- and 2,4,5,6-Tetrasubstituted Pyrimidines and Their Conversion into Condensed Heterocycles

by **Thierry Masquelin***, **Daniel Sprenger**, **Roman Baer**, **Fernand Gerber**, and **Yves Mercadal**

F. Hoffmann-La Roche AG, Pharma Research, CH-4070 Basel

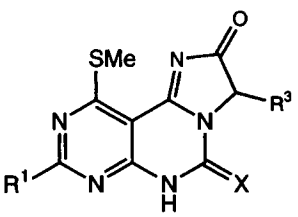
A novel general synthesis of 2,4,5-tri- and 2,4,5,6-tetrasubstituted pyrimidines **5a–d** and **7a, e, f, g** by condensation of thiouronium salts of type **3** with (ethoxymethylidene)malononitrile (**4**) and [bis(methylthio)methylidene]malononitrile (**6**), respectively, was first established in solution (*Scheme 1*) and successfully transferred onto solid support by using the polymer-bound thiouronium salt **11** (*Scheme 3*). Further investigations were directed toward a multidirectional cleavage procedure of the 2-(alkylsulfinyl) intermediates, obtained from the 2-(alkylthio)pyrimidines **7a** (*Scheme 2*) or **12** and **14** (*Schemes 3* and *4*), with different nucleophiles to form highly substituted pyrimidines. In addition, fused-heterocycle derivatives **22a–h**, **24a–c**, and **26a–e** were generated in good-to-excellent yields by condensation of **7a, e, h** with versatile isocyanates and isothiocyanates, with subsequent alkylation (*Scheme 5*).

1. Introduction. – Solid-phase synthesis was first introduced in 1963 by *Merrifield* [1] in an effort to overcome many of the problems associated with solution peptide synthesis. Nowadays, this approach is no longer limited to the peptide, oligonucleotide, and biopolymer area. Recent studies have exploited the advantages of solid-phase synthesis [2][3], and a large number of synthetic approaches have evolved to generate libraries of small organic molecules on a solid-phase manifold [4–8]. In an extension of our recent studies [9] towards combinatorial and parallel synthesis of versatile heterocycles on a solid support, we report herein a novel solution- and solid-phase approach to 2,4,5-tri- and 2,4,5,6-tetrasubstituted pyrimidines **A** and their subsequent conversion into fused heterocycles **B** and **C**.



A

B

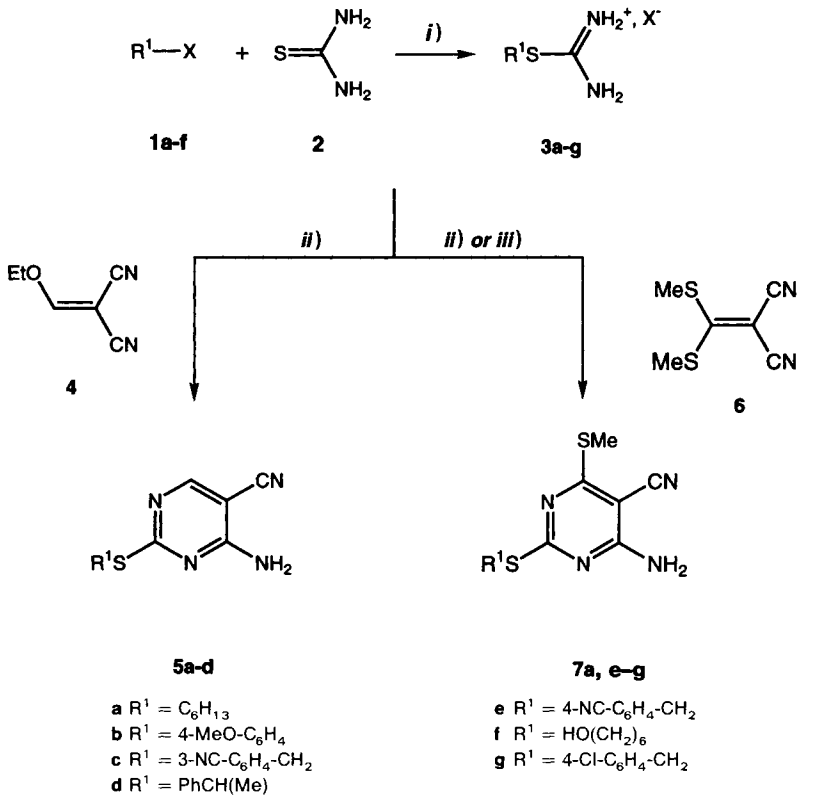


C

Our strategy efficiently combines the reaction of both (ethoxymethylidene)-malononitrile (**4**) and [bis(methylthio)methylidene]malononitrile (**6**) with thiouronium salts of type **3** and **11** to form the pyrimidine skeleton, bearing versatile functional groups for the iterative construction of annelated rings with the known nucleophilic displacement of the 2-alkylsulfinyl group of pyrimidine [10][11] with various nucleophiles [12][13].

2. Results and Discussion. – In recent years, ketene-dithioacetal derivatives have found wide spread use in the synthesis of polyfunctionalized heterocycles [14–18]. We found that the reaction of the ketene derivatives **4** and **6** with thiouronium salts **3a–g** in the presence of *N*-ethyldiisopropylamine ((i-Pr)$_2$EtN) in DMF at room temperature or in EtOH at 75° gave the corresponding 2,4,5-tri- and 2,4,5,6-tetrasubstituted pyrimidines **5a–d** and **7a, e–g** in good yields (*Scheme 1*, *Table 1*). The required bis-nucleophilic thiouronium salts of type **3** were easily accessible from thiourea (**2**) and a large variety of alkyl halides **1** in excellent yields (*Table 2*) [19].

Scheme 1



i) EtOH, 65°, *ii*) DMF, (i-Pr)$_2$EtN, 0° to r.t., *iii*) EtOH, (i-Pr)$_2$EtN, 75°.

Table 1. *Synthesis of 2,4,5-Tri- and 2,4,5,6-Tetrasubstituted Pyrimidines* **5** *and* **7**

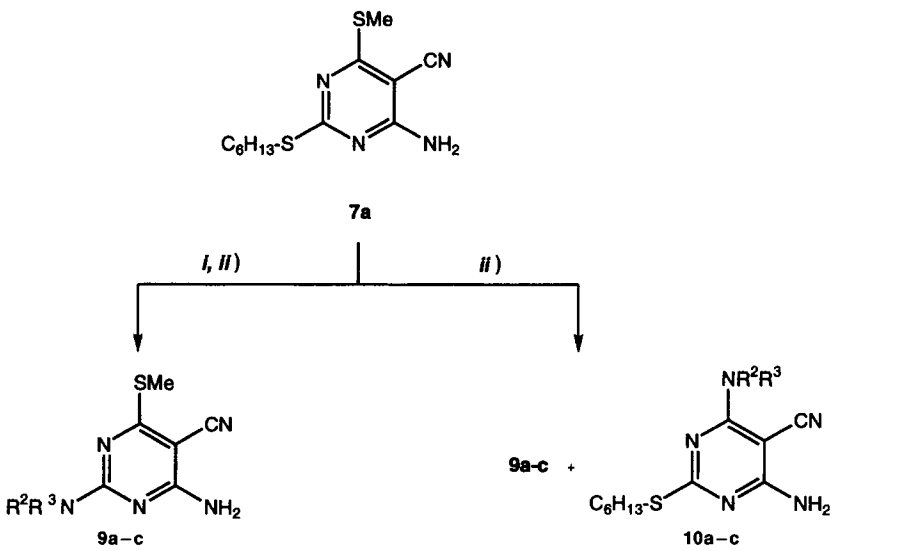
Starting materials	**4/3a**	**4/3b**	**4/3c**	**4/3d**	**6/3a**	**6/3e**	**6/3f**	**6/3a**
R^1	C_6H_{13}	4-MeOC_6H_4	3-CN-C_6H_4-Cl_2	PhCH(Me)	C_6H_{13}	4-CN-$C_6H_4CH_2$	HO$(CH_2)_6$	4-Cl-C_6H_4-CH_2
Product	**5a**	**5b**	**5c**	**5d**	**7a**	**7e**	**7f**	**7g**
Yield [%]	77	72	78	71	77	76	42	78

Table 2. *Synthesis of Thiouronium Salts* **3a-f**

Starting material	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**
R^1	C_6H_{13}	4-MeO-C_6H_4	3-NC-C_6H_4-CH_2	PhCH(Me)	4-NC-$C_6H_4CH_2$	$HO(CH_2)_5$
Product	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**
Yield [%]	95	52	98	99	98	99

As already reported [11], compounds of type **7** reacted directly with amines in dioxane at 80° to afford mixtures of the corresponding 2-amino and 4-amino analogues **9** and **10**, respectively (*Method C*; *Scheme 2*, *Table 3*). At this stage, purification by flash chromatography (FC) on silica gel led to the pure compounds. Moreover, we observed that previous oxidation of the (alkylthio)pyrimidines **7a** with 1.2 equiv. of 3-chloroperbenzoic acid (*m*-CPBA) gave the corresponding 2-(alkylsulfinyl)-substituted pyrimidine (and traces of 2,4-disulfinyl-substituted pyrimidine), which, upon treatment with various amines, afforded, after FC, products **9a–c** in good yields (*Method D*) (*Table 3*).

Scheme 2



9a R^2R^3N = pyrrolidin-1-yl
b R^2R^3N = MeNH
c R^2R^3N = [2-(morpholin-4-yl)ethyl]amino

10a R^2R^3N = pyrrolidin-1-yl
b R^2R^3N = MeNH
c R^2R^3N = [2-(morpholin-4-yl)ethyl]amino

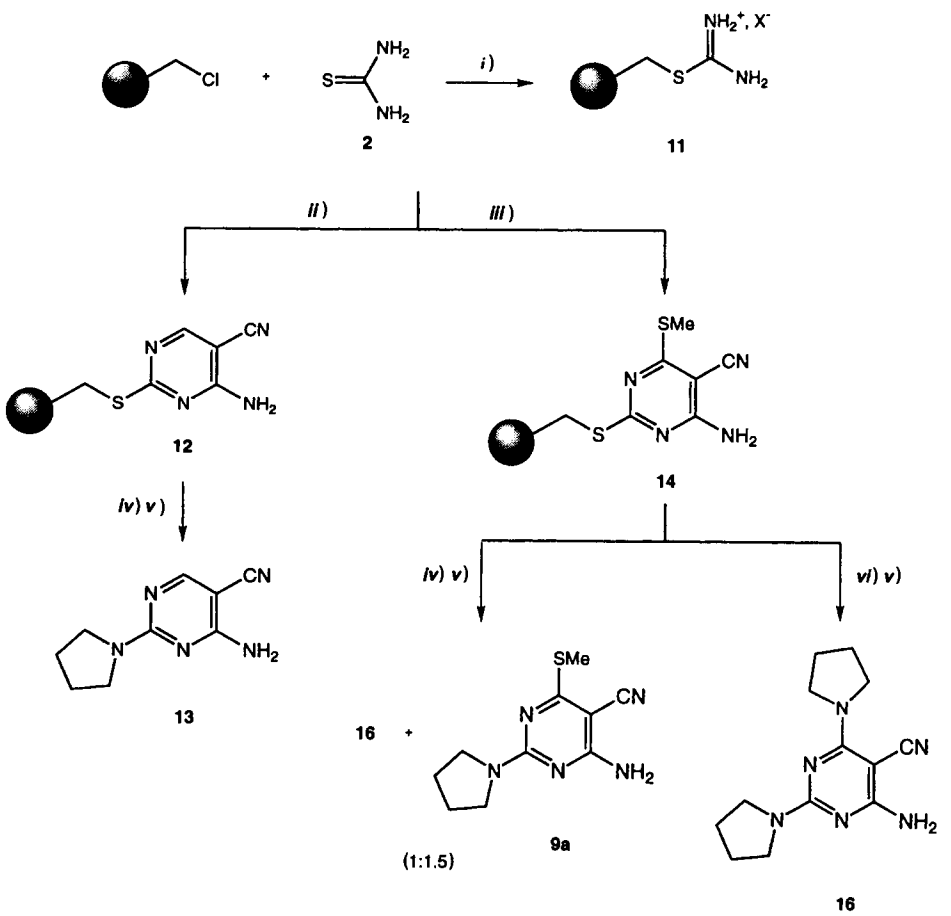
i) *m*-CPBA (1.2 equiv.), CH_2Cl_2. *ii*) R^2R^3NH, dioxane, r.t. to 80°.

Table 3. *Synthesis of Substituted Pyrimidines* **9a-c** *and* **10a-c** *from* **7a**

Base R^2R^3NH	Pyrrolidine	Pyrrolidine	$MeNH_2$	$MeNH_2$	$(Morph)CH_2CH_2NH_2$	$(Morph)CH_2CH_2NH_2$
Method	*D*	*C*	*D*	*C*	*D*	*C*
Product	**9a**	**9a/10a**	**9b**	**9b/10b**	**9c**	**9c/10c**
Yield [%]	66	32, 63	85	40, 58	96	33, 55

As part of our ongoing project, devoted towards the development of efficient methodologies for the combinatorial and parallel syntheses of heterocyclic systems on a solid support, the aforementioned reaction sequence appeared ideally suited for a solid-phase process. Thus, when resin-bound thiouronium salt **11**, prepared by reaction of thiourea with commercially available high-loaded *Merrifield* resin (3.4 mmol/g) [9], was allowed to react with (ethoxymethylidene)malononitrile (**4**) and [bis(methylthio)methylidene]malononitrile (**6**) in DMF in the presence of $(i\text{-Pr})_2EtN$, the corresponding polymer-bound (alkylthio)pyrimidines of type **12** and **14** were formed (*Scheme 3*).

Scheme 3



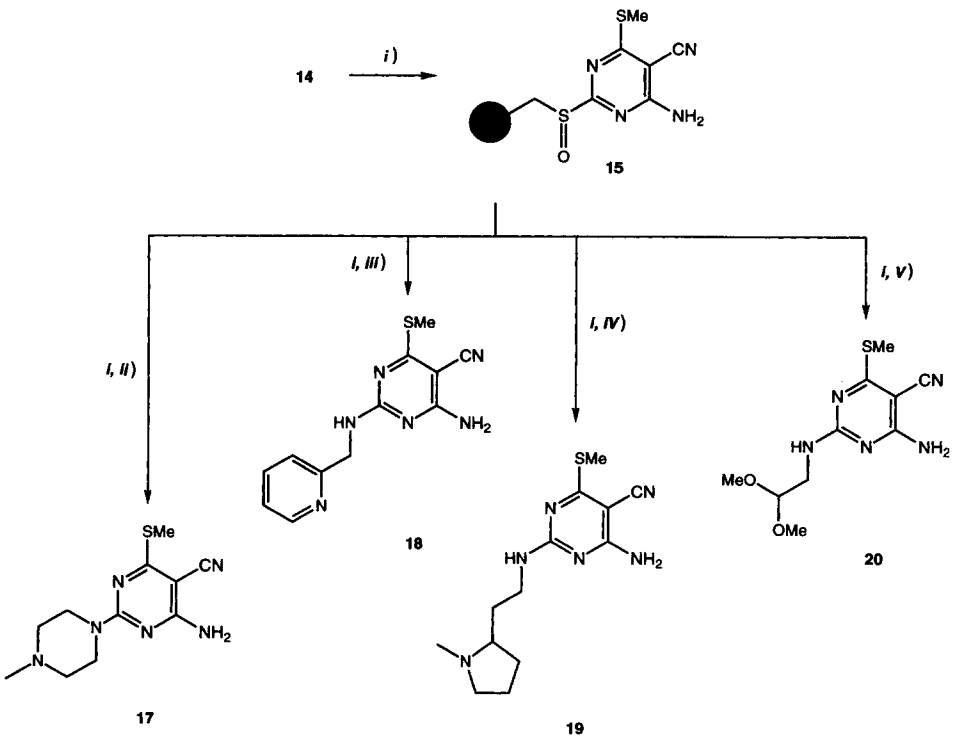
i) EtOH/dioxane 1:4, 85°. *ii*) DMF, $(i\text{-Pr})_2EtN$, **4**, 0° to r.t. *iii*) DMF, $(i\text{-Pr})_2EtN$, **6**, 0° to r.t. *iv*) *m*-CPBA (1.2 equiv.) CH_2Cl_2, 0° to r.t. *v*) Pyrrolidine, dioxane, r.t. *vi*) *m*-CPBA (6 equiv.), CH_2Cl_2, 0° to r.t.

The formation of the polymer-bound compounds was easily followed by ATR/FT-IR (attenuated total reflexion method) [20]. As a key step in the sequence, compound **12** was oxidized with 1.2 equiv. of *m*-CPBA in CH_2Cl_2 to form the intermediate alkylsulfinyl derivative, which was subjected to cleavage with pyrrolidine in dioxane at room temper-

ature leading to the final product **13** in high yield and purity. Following the same procedure (1.2 equiv. of *m*-CPBA), oxidation of the 2,4-bis(alkylthio)pyrimidine **14** and subsequent cleavage with pyrrolidine afforded a 1:1.5 mixture of 2,6-dipyrrolidylpyrimidine **16** and 2-pyrrolidylpyrimidine **9a**, easily separated by FC. Using 6 equiv. of *m*-CPBA in the oxidation of **14** gave the 2,4-bis(alkylsulfonyl) intermediate which, on treatment with pyrrolidine, gave **16** in 78% overall yield and 99.5% purity (HPLC).

To demonstrate the utility of our approach towards an easy and versatile access to 2,4,5-tri- and 2,4,5,6-tetrasubstituted pyrimidines, we studied the reaction conditions of the crucial cleavage step and subjected the polymer-bound sulfoxide **15** (obtained after oxidation of **14**) to a multidirectional cleavage with different nucleophiles in dioxane (*Scheme 4*). Thus, compounds **17**–**20** were obtained in good yields and high purities (*Table 4*).

Scheme 4



i) *m*-CPBA (1.2 equiv.), CH_2Cl_2. *ii*) 1-Methylpiperazine (1 equiv.), dioxane, r.t. to 65°. *iii*) [(Pyridin-2-yl)methyl]amine (1 equiv.), dioxane, r.t. to 65°. *iv*) 2-(1-Methylpyrrolidin-2-yl)ethylamine (1 equiv.), dioxane, r.t. to 65°. *v*) 2,2-Dimethoxy(ethyl)amine (1.5 equiv.), dioxane, r.t.

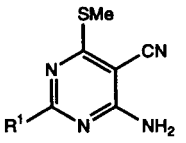
Table 4. *Synthesis of Pyrimidines* **17**–**20**

Product	**17**	**18**	**19**	**20**
Yield [%]	30	26	35	93.5
Purity [%][a])	99.5	95.5	97	94

[a]) HPLC Purity of the isolated product, measured on a *Superspher® 60 RP-select* column with a gradient 55% $MeCN/H_2O$ → 100% MeCN within 12 min.

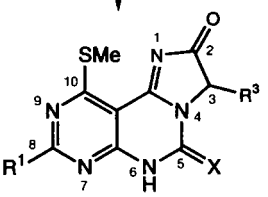
To further extend the scope of our method and examine the range of functionalization and hence the reactivity of the building blocks that are employed, we performed transformations as depicted in *Scheme 5*. Thus, treatment of pyrimidines **7a, e, h** with

Scheme 5



7a $R^1 = C_6H_{13}S$
e R^1 = 4-NC–C_6H_4–CH_2S
h R^1 = Me

i) *ii)*

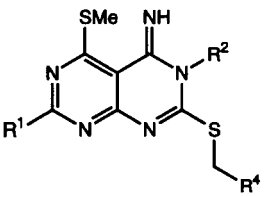


22a X = S, R^1 = Me, R^2 = 3-F–C_6H_4–CH_2 (89%)
b X = S, R^1 = Me, R^2 = Ph (98%)
c X = O, R^1 = Me, R^2 = 3,5-$F_2C_6H_3$ (50%)
d X = S, $R^1 = C_6H_{13}S$, R^2 = 3-MeO_2C–C_6H_4 (63%)

24a X = O, R^1 = Me, $R^3 = Me_2CHCH_2$ (72%)
b X = S, R^1 = Me, $R^3 = Me_2CH$ (75%)
c X = S, R^1 = Me, R^3 = Et (75%)

22e X = S, $R^1 = C_6H_{13}S$, R^2 = 3-F–C_6H_4–CH_2 (82%)
f X = S, $R^1 = C_6H_{13}S$, R^2 = 3-Cl–C_6H_4–CH_2 (89%)
g X = S, R^1 = 4-NC–C_6H_4–CH_2S, R^2 = 3,4-$Cl_2C_6H_3$–CH_2 (80%)
h X = S, R^1 = 4-NC–C_6H_4–CH_2S, R^2 = Ph (56%)

iii)



26a R^1 = Me, R^2 = 3-F–C_6H_4–CH_2, R^4 = 4-MeO_2C–C_6H_4 (53%)
b $R^1 = C_6H_{13}S$, R^2 = 3-F–C_6H_4–CH_2, R^4 = H (55%)
c $R^1 = C_6H_{13}S$, R^2 = 3-Cl–C_6H_4–CH_2, $R^4 = CO_2{}^tBu$ (84%)
d R^1 = 4-NC–C_6H_4–CH_2, R^2 = Ph, R^4 = 4-NC–C_6H_4 (90%)
e R^1 = 4-NC–C_6H_4–CH_2, R^2 = Ph, R^4 = 4-MeO_2C–C_6H_4 (77%)

i) R^2-NCX (**21**), DMF, DBU, 0° to r.t. *ii)* Alkyl-O_2C-CH(R^3)-NCX (**23**), DMF, DBU or Cs_2CO_3, 0° to r.t. *iii)* R^4CH_2X (**25**), DMF, base, 0° to r.t.

isocyanates and isothiocyanates of types **21** and **23** in DMF at room temperature in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) furnished the corresponding condensed systems of types **22** and **24** in good yields (*Method E*).

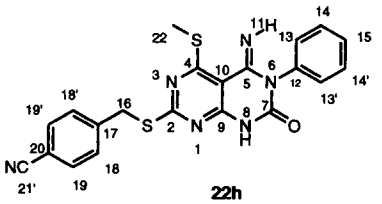
Mechanistic arguments [21][22], spectral data (*Tables 5* and *6*), and 2D-NMR experiments established the structures of type **22** and **24** and showed that, under our experimental conditions, no *Dimroth*-type rearrangement was observed [23].

Thus, the HMBC (heteronuclear multiple-bond connectivity) [24] experiments accomplished on **22** confirmed the absence of long-range coupling H–N(6)/C(13) and H–N(6)/C(13′) which would be expected in a similar compound resulting from *Dimroth*-type rearrangement. Moreover, the HMBC experiment of compound **24**

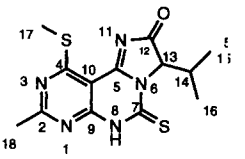
Table 5. *Selected ^{1}H-NMR Data for Fused Bicyclic Derivatives* **22h**, **24b**, *and* **26h**. δ in ppm, J in Hz. Arbitrary numbering.

	22h[a])	**24b**[a])	**26h**[a])
NH(8)	11.80	13.64	
H–C(13)		4.40 (*d*, *J* = 3.6)	
NH(11)	7.30 (*s*)		6.95
H–C(14)		3.27	
H–C(13), H–C(13′)	7.35		7.50
Me(15)		1.18 (*d*, *J* = 6.8)	
H–C(14), H–C(14′)	7.59		7.65
Me(16)		0.64 (*d*, *J* = 6.8)	
H–C(15)	7.53		7.65
CH_2(16)-S	4.56 (*s*)		4.61 (*s*)
Me(18)		2.62 (*s*)	
H–C(18), H–C(18′)	7.80		7.80
H–C(19), H–C(19′)	7.71		7.67
MeS	2.31 (*s*)	2.55 (*s*)	2.33
CH_2(23)-S			4.45 (*s*)
H–C(25), H–C(25′)			7.75
H–C(26), H–C(26′)			7.62

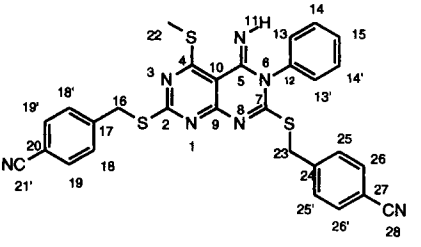
[a])



22h



24b



26h

Table 6. *Selected ^{13}C-NMR Data for Fused Bicyclic Derivatives* **22h**, **24b**, *and* **26h**. δ in ppm. Arbitrary numbering.

	22h[a])	**24b**[a])	**26h**[a])
C(2)	169.6	170.6	170.8
C(4)	171.1	173.6	172.2
C(5)	148.8	170.9	150.6
C(7)	155.0	166.3	165.0
C(19)	151.4	155.7	159.3
C(10)	102.1	100.4	107.2
C(12)	133.7	186.1	133.3
C(13)		66.9	
C(13), C(13′)	129.7		129.9
C(14), C(14′)	130.1		130.9
C(14)		25.9	
C(15)	129.2	17.1	131.2
C(16), C(23)	33.7	15.1	35.3, 33.9
C(17), C(24)	109.7	13.5	109.8, 110.2
C(18)		26.6	
C(18),(18), C(25), C(25′)	132.2		132.3, 132.2
C(19), C(19′), C(26), C(26′)	129.8		130.2, 129.7
C(20), C(27)	144.0		144.2, 142.9
C(21), C(28)	118.7		118.7, 118.6
C(22)	14.3		14.6

[a]) See *Footnote a* in *Table 5*.

showed characteristic long-range couplings between *H*–C(13)/C(5), *H*–(13)/C(7), and *H*–C(13)/C(12) supporting the established structure **24** for this fused system. Additional strong support comes from the significant low δ(C) of the pyrazolone carbonyl group (C(12)) at 186.1 ppm. On the one hand, estimation from increments results in 190 ppm, whereas the C=O group in a *Dimroth*-type rearrangement product would appear at *ca.* 170 ppm, and on the other hand, ^{13}C-NMR data bank [25] retrieval led to hits with R′(RHN)C=N–COMe moieties exhibiting C=O shifts ranging from 185.1 to 187.5 ppm.

Having achieved a practical route to highly functionalized fused pyrimidines, we studied the alkylation of these compounds. Derivatives of type **22** were reacted with alkyl bromides of type **25** in DMF at room temperature in the presence of base (*Method F; Scheme 5*). The expected *S*-alkylated derivatives **26a–e** were obtained in moderate-to-good yields.

3. Conclusion. – Starting from commercially available ketene derivatives of types **4** and **6**, we have demonstrated that thiouronium salts **3a–g** and **11** are highly versatile and useful building blocks for the synthesis of novel 2,4,5-tri- and 2,4,5,6-tetrasubstituted pyrimidines **5a–d**, **7a, e, f**, **9a–c**, **13**, and **16–20** in solution and on solid support. Furthermore, we have demonstrated that the oxidation and cleavage steps constitute an efficient type of safety-catch linker strategy [9][12][13][26]. These highly functionalized molecules are interesting building blocks, allowing us to further extend the scope of (alkylthio)pyrimidine chemistry to the production of multigeneration fused-heterocycle libraries with additional elements of diversity. Application of this strategy towards new fused heterocyclic compounds are under investigation and will be published in due course.

We wish to thank our colleagues from Physical Methods, *F. Hoffmann-La Roche AG*, for IR (Mr. *A. Bubendorf*), NMR (Dr. *W. Arnold*), and mass spectra (Dr. *W. Vetter* and Mr. *W. Meister*) and elemental analysis (Dr. *St. Müller*). We thank Prof. Sir *J. Baldwin*, Oxford, and Profs. Drs. *A. Vasella* and *F. Diederich* for their valuable advice and stimulating discussions.

Experimental Part

General. All reactions which require air- or moisture-sensitive reactants and solvents were carried out in oven- or flame-dried glassware under a positive pressure of dry Ar. Reaction solvents and liquid reagents were purified before use. All other reactants were 'reagent-grade' unless described otherwise. Anal. TLC: 2.5 × 10 cm precoated TLC plates, SiO_2 *60F-254*, layer thickness 0.25 mm (*E. Merck & Co.*, Darmstadt, Germany). Flash chromatography (FC) [27]: *E. Merck* SiO_2 *60* (70–230 mesh ASTM). HPLC: *Superspher* ®*-60-RP-select* column, gradient 55% MeCN/H_2O (with 1% CF_3COOH) until 100% MeCN within 12 min. M.p.: *Büchi-Smp-20* apparatus; uncorrected. IR: *Nicolet-7199-FT-IR* spectrometer; solids in KBr pellets, liquids as thin films; in cm^{-1}. ^1H-NMR Spectra: *Bruker-AC-250* apparatus, at 250 MHz, in DMSO or $CDCl_3$; $SiMe_4$ as internal standard; chemical shifts δ in ppm, J in Hz. MS: *Finnigan-MS9-AEI* or *-Mat90*; *m/z* (rel.%).

Method A. A mixture of thiourea **2** (1 mmol) and alkyl halide **1** (1.2 mmol) in EtOH (1 ml) was stirred for several hours at 65°. After consumption of **1**, the mixture was cooled to r.t. and evaporated. The residue was suspended in Et_2O and filtered: **3**, pure enough without further purification.

Method B. Procedure 1. To a stirred mixture of thiouronium salt **3** (1.1 mmol) and ketene derivative **4** or **6** (1 mmol) in DMF (2 ml) under Ar at 0°, $(i\text{-}Pr)_2EtN$ (1.1 mmol) was added. The mixture was stirred at r.t. for several hours and poured onto ice, 1N aq. HCl, and AcOEt. The org. layer was washed with brine, dried, and evaporated and the residue chromatographed (SiO_2, toluene/AcOEt 4:1).

Method B. Procedure 2. To a stirred mixture of thiouronium salt **3** (1.1 mmol) and ketene derivative **4** or **6** (1 mmol) in EtOH (5 ml) under Ar at r.t., $(i\text{-}Pr)_2EtN$ (2.75 mmol) was added. The mixture was stirred at r.t., warmed to 75° for several hours, cooled to r.t., and filtered, affording **5** or **7** which were purified by FC (SiO_2) as indicated below.

Method C. A mixture of **7** (1 mmol) and excess of amine R^2R^3NH in dioxane (3 ml) was stirred for several hours at 80°. After consumption of **7**, the mixture was cooled to r.t., poured onto H_2O, and extracted with $CHCl_3$. The org. phase was washed with brine, dried, and evaporated. The residue was chromatographed (SiO_2) as indicated below.

Method D. To a stirred soln. of pyrimidine **7** (1 mmol) in CH_2Cl_2 (3 ml) under Ar at 0°, 1.2 mmol of 3-chloroperbenzoic acid (*m*-CPBA) was added. After stirring at r.t. for 2 h, the mixture was poured onto sat. aq. $NaHCO_3$ soln. and extracted with AcOEt. The org. phase was washed with brine, dried, and evaporated. To a soln. of the residue in dioxane (3 ml), amine R^2R^3NH (1.2 mmol) was added. The mixture was stirred at r.t. or warmed at 80° for several hours and poured onto ice, 1N aq. HCl, and AcOEt. The org. layer was washed with brine, dried, and evaporated. The residue was chromatographed (SiO_2) as indicated below.

Method E. To a stirred soln. of pyrimidines **7** (1 mmol) in DMF (3 ml) under Ar at 0°, isocyanate or isothiocyanate of type **21** or **23** (1.1 mmol) was added, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or Cs_2CO_3 (1.1 mmol). After stirring at r.t. for 2 h, the mixture was warmed up at 45° for several hours and poured onto ice, 1N aq. HCl, and AcOEt. The org. layer was washed with brine, dried, and evaporated. The residue was chromatographed (SiO_2) as indicated below.

Method F. To a stirred soln. of fused pyrimidine **22** (1 mmol) in DMF (3 ml) under Ar at 0°, an alkyl bromide **25** (1.1 mmol) was added, followed by base 1.1 mmol, DBU, $(i\text{-}Pr)_2EtN$, or Cs_2CO_3). After stirring at r.t. for several hours, the mixture was poured onto ice, 1N aq. HCl, and AcOEt. The org. layer was washed with brine, dried, and evaporated. The residue was chromatographed (SiO_2) as indicated below.

Polymer-Bound Thiouronium Salt **11**. A mixture of high-loaded *Merrifield* resin (50 g, 170 mmol) thiourea (**2**) (64.70 g, 850 mmol), and dioxane/EtOH 4:1 (350 ml) was shaken at 85° for 15 h and then washed successively with EtOH (600 ml) at 70° dioxane (300 ml) at r.t., and pentane (300 ml) at r.t. The polymer-bound thiouronium salt **11** was then dried at 60°/high vacuum for 24 h: 96% of conversion based on elemental analysis. IR: 3040*s*, 2940*s*, 1643*s*, 1520*m*, 1500*m*, 1420*s*, 1325*w*, 1260*m*, 1215*w*, 1190*m*, 1050*m*, 1030*m*, 880*w*, 830*m*.

Polymer-Bound 2-(Alkylthio)-4-aminopyrimidine-5-carbonitrile **12**. Resin **11** (10 g, 27 mmol) was swollen with dry DMF (250 ml) and cooled to 0°. Then, (ethoxymethylidene)propanedinitrile (**4**; 5.93 g, 48.6 mmol) followed by $(i\text{-}Pr)_2EtN$ (12.53 ml, 135 mmol) were added. After stirring for 96 h, the mixture was washed successively with DMF, THF, Et_2O, and pentane. The resin was dried at 50°/high vacuum for 12 h: 13.7 g of **12**, 75% of conversion

based on elemental analysis. IR: 3280*w*, 2940*m*, 2220*s*, 1630*m*, 1580*s*, 1540*s*, 1400*s*, 1385*s*, 1299*s*, 1252*s*, 1117*s*, 870*s*, 700*s*.

Polymer-Bound 3-(Alkylthio)-4-amino-6-(methylthio)pyrimidine-5-carbonitrile **14**. Resin **11** (9.25 g, 25 mmol) was swollen with dry DMF (280 ml) and cooled to 0°. Then, [bis(methylthio)methylidene]propanedinitrile (**6**, 8.5 g, 50 mmol), followed by $(i\text{-Pr})_2$EtN (16.15 ml, 125 mmol), was added. After stirring for 96 h, the mixture was washed successively with DMF, dioxane, Et_2O, and pentane. The resin was dried at 50°/high vacuum for 12 h: 74% of conversion based on elemental analysis. IR: 3340*w*, 3210*w*, 2930*m*, 2210*s*, 1640*m*, 1620*s*, 1337*m*, 1253*m*, 1117*s*, 870*s*, 701*m*.

Polymer-Bound 2-(Alkylsulfinyl)-4-amino-6-(methylthio)pyrimidine-5-carbonitrile **15**. Resin **14** was washed with CH_2Cl_2. Then, dry CH_2Cl_2 (10 ml per mmol) and *m*-CPBA (1.2 equiv.) were added at r.t. The mixture was stirred at r.t. for 18 h, washed successively with CH_2Cl_2 at r.t., i-PrOH at 60°, dioxane at 60°, dioxane at 60°, Et_2O at r.t., and pentane. The resin was dried at 50° high vacuum for 12 h. 100% of conversion based on elemental analysis. IR: 3340*w*, 3210*w*, 2920*w*, 2210*w*, 1630*m*, 1554*m*, 1510*m*, 1400*s*, 1385*s*, 1299*s*, 1252*s*, 1117*s*, 1069*m*, 870*s*, 700*s*.

Hexyl Carbamimidothioate Hydrobromide (**3a**). According to *Method* A, with **1a** (18.56 g, 0.112 mol), **2** (5.71 g, 0.075 mol), and EtOH (50 ml): 17.1 g (95%) of **3a**. White solid. M.p. 75–76°. IR: 3259*s*, 3082*s*, 1643*s*, 1540*w*, 666*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 9.0 (br. *s*, NH_2); 7.78 (br. *s*, NH_2); 7.78 (br. *s*, NH_2); 3.4–3.25 (*t*, J = 7.2, 2 aliph. H); 1.85–1.65 (*m*, 2 aliph. H); 1.55–1.2 (*m*, 6 aliph. H); 1.0–0.8 (*t*, J = 6.2, 3 aliph. H). MS: 161 (100, $[M + H]^+$).

4-Methoxyphenyl Carbamimidothioate Hydroiodide (**3b**). A soln. of **1b** (2.81 g, 12 mmol) in DMF (5 ml) was treated with **2** (0.76 g, 10 mmol), $[NiCl_2(PEt_3)_2]$ (0.087 g, 0.24 mmol), and $NaBH_3CN$ (0.023 g, 0.36 mmol). The mixture was stirred at 60° for 3 h and then allowed to come to −10°. The suspension was filtered and the solid triturated with EtOH, filtered, and washed with Et_2O: 1.62 g (52%) of **3b**. White solid. IR: 3387*m*, 3075*m*, 1640*s*, 1587*s*, 1492*m*, 1250*s*, 1176*m*, 1021*m*, 831*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.86 (br. *s*, 2 NH_2); 7.65–7.55 (*m*, 2 arom. H); 7.2–7.05 (*m*, 2 arom. H); 3.84 (*s*, 3 aliph. H). MS: 182 (10, M^+), 140 (100), 128 (25), 125 (35), 97 (15). Anal. calc. for $C_8H_{11}IN_2OS$: C 30.98, H 3.58, N 9.03; found: C 31.04, H 3.66, N 9.05.

3-Cyanobenzyl Carbamimidothioate Hydrobromide (**3c**). According to *Method A*, with **1c** (4.7 g, 24 mmol), **2** (1.52 g, 20 mmol), and EtOH (20 ml): 5.35 g (98%) of **3c**. White solid. Mp. 155–156° IR: 3446*m*, 3075*s*, 2232*m*, 1655*s*, 1617*w*, 900*w*, 805*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 9.14 (br. *s*, 2 NH_2); 7.9 (*m*, 1 arom. H); 7.85–7.75 (*m*, 2 arom. H); 7.7–7.6 (*m*, 1 arom. H); 4.56 (*s*, 2 aliph. H). MS: 272 (25, M^+). Anal. calc. for $C_{11}H_{16}N_4S$: C 55.9, H 6.82, N 23.71, S 13.57; found: C 55.94, H 6.64, N 23.69, S 13.64.

1-Phenylethyl Carbamimidothioate Hydrobromide (**3d**). According to *Method A*, with **1d** (4.44 g, 24 mmol), **2** (1.52 g, 20 mmol), and EtOH (20 ml): 5.16 g (99%) of **3d**. Pale-brown solid. IR: 3254*s*, 3066*s*, 1645*s*, 1493*m*, 763*m*, 700*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 9.26 (br. *s*, NH_2); 9.03 (br. *s*, NH_2); 7.55–7.25 (*m*, 5 arom. H); 5.3–5.15 (*q*, J = 7.0, 1 aliph. H); 1.7–1.6 (*d*, J = 7.0, 3 aliph. H). MS: 115, (M^+), 105 (100), 79 (15), 76 (25), 43 (20). Anal. calc. for $C_{11}H_{16}N_4S$: C 66.9, H 6.82, N 23.71, S 13.57; found: C 55.94, H 6.64, N 23.69, S 13.64.

4-Cyanobenzyl Carbamimidothioate Hydrobromide (**3e**). According to *Method A*, with **1e** (20 g, 0.102 mol), **2** (6.47 g, 0.085 mol), and EtOH (85 ml): 27.2 g (98%) of **3e**. White solid. IR: 3446*m*, 3075*s*, 2232*m*, 1655*s*, 1617*w*, 900*w*, 805*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 9.14 (br. *s*, 2 NH_2); 7.9 (*s*, 1 arom. H); 7.85–7.75 (*m*, 2 arom. H); 7.7–7.6 (*m*, 1 arom. H); 4.56 (*s*, 2 aliph. H). MS: 191 (100, M^+), 149 (60), 116 (80), 89 (20), 44 (35), 43 (75). Anal. calc. for $C_9H_{10}BrN_3S$: C 39.72, H 3.7, N 15.44; found: C 39.65, H 3.63, N 15.37.

6-Hydroxyhexyl Carbamimidothioate Hydrobromide (**3f**): According to *Method A*, with **1f** (2.71 g, 15 mmol), **2** (0.76 g, 10 mmol), and EtOH (10 ml): 2.55 g (99%) of **3f**. White solid. M.p. 130–132°. IR: 3345*s*, 2936*m*, 1646*s*, 1540*w*, 1055*m*, 692*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.98 (br. *s*, 2 NH_2); 4.4–4.3 (*m*, OH); 3.45–3.3 (*m*, 2 aliph. H); 3.2–3.05 (*t*, J = 7.2, 2 aliph. H); 1.6–1.25 (*m*, 9 aliph. H). MS: 177 (100, $[M + H]^+$). Anal. calc. for $C_7H_{17}BrN_2OS$: C 33.41, H 6.82, N 10.65, S 12.18; found: C 33.38, H 6.76, N 10.41, S 12.05.

4-Amino-2-(hexylthio)pyrimidine-5-carbonitrile (**5a**). According to *Method B* (*Procedure 1*), with **3a** (0.435 g, 1.8 mmol), **4** (0.20 g, 1.64 mmol), and $(i\text{-Pr})_2$EtN (0.337 ml, 1.97 mmol): 0.298 g (77%) of **5a**. Pale-yellow solid after FC. M.p. 123.5–124°. IR: 3420*s*, 3338*m*, 2927*m*, 2228*m*, 1642*s*, 1584*s*, 1531*s*, 777*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.32 (*s*, 1 arom. H); 5.5 (*s*, NH_2); 3.12–3.05 (*t*, J = 7.25, 2 aliph. H); 1.8–1.6 (*m*, 2 aliph. H); 1.5–1.25 (*m*, 4 aliph. H); 1.0–0.8 (*t*, J = 6.25, 3 aliph. H). MS: 236 (25, M^+), 203 (10), 189 (40), 179 (55), 166 (80), 152 (100), 147 (20), 120 (20), 94 (25). Anal. calc. for $C_{11}H_{16}N_4S$: C 55.9, H 6.82, N 23.71, S 13.57; found: C 55.94, H 6.64, N 23.69, S 13.64.

4-Amino-2-[(2-methoxyphenylthio]pyrimidine-5-carbonitrile (**5b**). According to *Method B* (*Procedure 1*), with **3b** (0.559 g, 1.8 mmol), **4** (0.20 g, 1.64 mmol), and $(i\text{-Pr})_2$EtN (0.337 ml, 1.97 mmol): 0.304 g (72%) of **5b**. Pale yellow solid after FC. IR: 3445*w*, 2230*w*, 1668*s*, 1590*s*, 1253*s*, 1160*m*, 1040*m*, 840*s*. ^{1}H-NMR ((D_6)DMSO,

250 MHz): 8.36 (*s*, 1 arom. H); 7.85 (br. *s*, NH_2); 7.5–7.4 (*m*, 2 arom. H); 7.05–6.95 (*m*, 2 arom. H); 3.79 (*s*, 3 aliph. H). MS: 259 (100, $[M + H]^+$). Anal. calc. for $C_{12}H_{10}N_4OS$: C 55.6, H 3.89, N 21.58, S 12.35; found: C 55.58, H 3.77, N 21.67, S 12.21.

4-Amino-2-[(3-cyanobenzyl)thio]pyrimidine-5-carbonitrile (**5c**). According to *Method B* (*Procedure 1*), with **3c** (0.490 g, 1.8 mmol), **4** (0.20 g, 1.64 mmol), and (i-Pr)$_2$EtN (0.337 ml, 1.97 mmol): 0.368 g (78%) of **5c**. Pale-yellow solid after FC. IR: 3420*w*, 2230*w*, 2215*w*, 1655*w*, 1655*s*, 1590*m*, 1540*s*, 900*w*, 810*m*, 780*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.45 (*s*, 1 arom. H); 8.2 (br. *s*, NH_2); 7.95 (*s*, 1 arom. H); 7.8–7.7 (*d*, J = 7.5, 1 arom. H); 7.65–7.55 (*d*, J = 7.5, 1 arom. H); 7.6–7.45 (*t*, J = 7.5, 1 arom. H); 4.36 (*s*, 2 aliph. H). MS: 268 (100, $[M + H]^+$). Anal. calc. for $C_{13}H_9N_5S$: C 58.22, H 3.39, N 26.09, S 11.99; found: C 55.58, H 3.39, N 25.87, S 11.98.

4-Amino-2-[(1-phenylethylthio]pyrimidine-5-carbonitrile (**5d**). According to *Method B* (*Procedure 1*), with **3d** (0.471 g, 1.8 mmol), **4** (0.20 g, 1.64 mmol), and (i-Pr)$_2$EtN (0.337 ml, 1.97 mmol): 0.298 g (71%) of **5d**. Pale-yellow solid after FC. IR: 3389*w*, 2220*w*, 1665*m*, 1585*m*, 1545*m*, 785*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.45 (*s*, 1 arom. H); 8.05 (br. *s*, NH_2); 7.5–7.2 (*m*, 5 arom. H); 5.0–4.9 (*q*, J = 7.1, 1 aliph. H); 1.7–1.65 (*d*, J = 7.1, 3 aliph. H). MS: 257 (100, $[M + H]^+$), 153 (60). Anal. calc. for $C_{13}H_{12}N_4S$: C 60.88, H 4.72, N 21.84, S 12.50; found: C 60.98, H 4.59, N 22.0, S 12.45.

4-Amino-2-(hexylthio)-6-(methylthio)pyrimidine-5-carbonitrile (**7a**). According to *Method B* (*Procedure 2*), with **3a** (27.15 g, 0.112 mol), **6** (17.4 g, 0.1 mmol), and (i-Pr)$_2$EtN (19.3 ml, 0.112 mmol): 21.3 g (78%) of **7a**. Pale-yellow solid after FC (CH_2Cl_2/AcOEt/hexane (1:1:3). IR: 3362*s*, 3168*s*, 2959*m*, 2216*m*, 1655*s*, 1527*s*, 1170*mn*, 1007*m*, 862*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.25 (*s*, NH_2); 3.0–2.85 (*t*, J = 7.25, 2 aliph. H); 2.40 (*s*, 3 aliph. H); 1.65–1.5 (*m*, 2 aliph. H); 1.4–1.15 (*m*, 4 aliph. H); 0.8–0.65 (*t*, J = 6.25, 3 aliph. H). MS: 282 (65, M^+), 249 (20), 235 (50), 225 (70), 212 (100), 166 (30), 151 (35), 139 (30), 92 (10), 41 (20).

4-Amino-2-[(4-cyanobenzyl)thio]-6-(methylthio)pyrimidine-5-carbonitrile (**7e**). According to *Method B* (*Procedure 2*) with **3e** (0.490 g, 1.8 mmol), **6** (0.20 g, 1.64 mmol), and (i-Pr)$_2$EtN (0.337 ml, 1.97 mmol): 0.368 g (78%) of **7e**. Pale-yellow solid after FC (AcOEt/hexane 1:1). IR: 3361*s*, 2219*m*, 1661*m*, 1634*s*, 1528*s*, 859*m*. ^{1}H-NMR ((D$_6$)DMS, 250 MHz): 7.8 (br. *s*, NH_2); 7.85–7.75 (*m*, 2 arom. H); 7.7–7.6 (*m*, 2 arom. H); 4.45 (*s*, 2 aliph. H); 2.47 (*s*, 3 aliph. H). MS: 314 (20, $[M + H]^+$).

4-Amino-2-[(6-hydroxyhexyl)thio]-6-(methylthio)pyrimidine-5-carbonitrile (**7f**). According to *Method B* (*Procedure 2*), with **3f** (0.497 g, 1.94 mmol), **6** (0.30 g, 1.76 mmol), and (i-Pr)$_2$EtN (0.75 ml, 4.45 mmol): 0.22 g (42%) of **7f**. Pale-yellow solid after FC (AcOEt/hexane 1:1). IR: 3371*s*, 3204*s*, 2928*s*, 2213*s*, 1649*s*, 1528*s*, 1071*m*, 863*m*, 776*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.75 (br. *s*, NH_2); 4.4–4.3 (*t*, J = 5.2, OH); 3.4–3.3 (*m*, 2 aliph. H); 3.1–3.0 (*t*, J = 7.4, 2 aliph. H); 2.53 (*s*, 3 aliph. H); 1.7–1.55 (*m*, 2 aliph. H); 1.5–1.25 (*m*, 6 aliph. H). MS: 298 (40, M^+), 267 (20), 251 (70), 225 (70), 212 (90), 198 (100), 193 (25), 181 (20), 166 (35), 151 (40), 139 (30), 92 (20), 61 (15), 55 (20), 41 (30), 31 (20).

4-Amino-[(4-chlorobenzyl)thio]-6-(methylthio)pyrimidine-5-carbonitrile (**7g**). According to *Method B* (*Procedure 2*), with **3g** (0.306 g, 1.29 mmol), **6** (0.20 g, 1.17 mmol), and (i-Pr)$_2$EtN (0.5 ml, 2.92 mmol): 0.29 g (78%) of **7g**. White solid after FC (AcOEt/hexane 1:1). IR: 3440*m*, 2215*w*, 1664*m*, 1528*m*, 875*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.85 (br. *s*, NH_2); 7.5–7.35 (*m*, 4 arom. H); 4.38 (*s*, 2 aliph. H); 2.55 (*s*, 3 aliph. H). MS: 322 (100, M^+), 289 (35), 254 (40), 210 (20), 166 (30), 125 (100), 119 (15), 89 (20).

4-Amino-6-(methylthio)-2-(pyrrolidin-1-yl)pyrimidine-5-carbonitrile (**9a**). According to *Method D*, with **7a** (0.10 g, 0.36 mmol): 0.055 g (66%) of **9a**. White solid after FC (AcOEt/hexane 1:1). IR: 3414*s*, 2982*m*, 2193*s*, 1645, 1509*s*, 963*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.07 (br. *s*, NH_2); 3.65–3.5 (*m*, 2 aliph. H); 3.45–3.35 (*m*, 2 aliph. H); 2.47 (*s*, 3 aliph. H); 1.95–1.8 (*m*, 4 aliph. H). MS: 235 (100, M^+), 206 (60), 70 (25).

4-Amino-2-(methylamino)-6-(methylthio)pyrimidine-5-carbonitrile (**9b**). According to *Method D*, with **7a** (0.2 g, 0.7 mmol): 0.116 g (85%) of **9b**. White solid after FC (AcOEt/hexane 1:1). IR: 3438*s*, 3146*m*, 2197*s*, 1668*s*, 1561*s*, 903*m*, 701*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.45–7.30 (*m*, NH); 7.15–7.0 (*m*, NH_2); 2.8–2.7 (*m*, 3 aliph. H); 2.44 (*s*, 3 aliph. H). MS: 196 (100, $[M + H]^+$).

4-Amino-6-(methylthio)-2-{[2-(morpholin-4-yl)ethyl]amino}pyrimidine-5-carbonitrile (**9c**). According to *Method D*, with **7a** (0.27 g, 0.9 mmol): 0.255 g (96%) of **9c**. White solid after FC (AcOEt/EtOH 1:9). IR: 3434*s*, 2810*w*, 2198*m*, 1660*m*, 1548*s*, 1118*m*, 780*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.45–7.3 (*m*, NH); 7.15–7.0 (*m*, NH_2); 3.65–3.55 (*m*, 4 aliph. H); 3.45–3.35 (*m*, 2 aliph. H); 2.46 (*s*, 3 aliph. H); 2.45–2.3 (*m*, 6 aliph. H). MS: 294 (15, M^+), 113 (25), 100 (100).

4-Amino-2-(hexylthio)-6-(pyrrolidin-1-yl)pyrimidine-5-carbonitrile (**10a**): According to *Method C*, with **7a** (0.5 g, 1.77 mmol) and pyrrolidine (0.585 ml, 7.08 mmol) at r.t. for 18 h: 0.132 g (32%) of **9a** and 0.342 g (63%) of **10a**. **10a**: White solid after FC (AcOEt/hexane 1:3). IR: 3469*s*, 3229*m*, 2198*s*, 1640*s*, 1589*s*, 1462*w*, 960*m*, 780*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.3–7.2 (*m*, NH); 7.09 (br. *s*, NH_2); 3.05–2.9 (*t*, J = 7.2, 2 aliph. H); 2.85–

2.76 (*d*, *J* = 4.5, 3 aliph. H); 1.65–1.55 (*m*, 2 aliph. H); 1.4–1.25 (*m*, 6 aliph. H); 0.9–0.75 (*t*, *J* = 6.2, 3 aliph. H). MS: 305 (100, $[M + H]^+$).

4-Amino-2-(hexylthio)-6-(methylamino)pyrimidine-5-carbonitrile (**10b**). According to *Method C*, with **7a** (0.2 g, 0.7 mmol) and excess of *N*-methylamine (gas) at 60° for 18 h: 0.06 g (40%) of **9b** and 0.110 g (58%) of **10b**. **10b**: White solid after FC AcOEt/hexane (1:3). IR: 3370*m*, 3358*m*, 2198*m*, 1638*m*, 1585*s*, 1552*s*, 953*w*, 700*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 7.4–7.3 (*m*, NH); 7.13 (br. *s*, NH_2); 3.05–2.9 (*t*, *J* = 7.2, 2 aliph. H); 2.85–2.75 (*d*, *J* = 4.5, 3 aliph. H); 1.65–1.55 (*m*, 2 aliph. H); 1.4–1.25 (*m*, 6 aliph. H); 0.9–0.75 (*t*, *J* = 6.2, 3 aliph. H). MS: 266 (100, $[M + H]^+$).

4-Amino-2-(hexylthio)-6-{[2-(morpholin-4-yl)ethyl]amino}pyrimidine-5-carbonitrile (**10c**). According to *Method C*, **7a** (0.2 g, 0.7 mmol) and excess of [2-(morpholin-4-yl)ethyl]amine at 80° for 72 h: 0.07 g (33%) of **9c** and 0.135 g (55%) of **10c**. **10c**: White solid after FC (AcOEt/EtOH 1:9). IR 3370*s*, 2205*m*, 1670*m*, 1580*s*, 1548*s*, 1118*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 7.3–7.2 (*t*, *J* = 5.9, NH); 7.17 (br. *s*, NH_2); 3.65–3.55 (*t*, *J* = 4.4, 4 aliph. H); 3.5–3.45 (*m*, 2 aliph. H); 3.0–2.9 (*t*, *J* = 7.2, 2 aliph. H); 2.5–2.35 (*m*, 6 aliph. H); 1.65–1.55 (*m*, 2 aliph. H); 1.4–1.25 (*m*, 6 aliph. H); 0.9–0.75 (*t*, *J* = 6.2, 3 aliph. H). MS: 365 (10, $[M + H]^+$), 252 (20), 194 (15), 113 (95), 100 (100), 70 (15).

4-Amino-2-(pyrrolidin-1-yl)pyrimidine-5-carbonitrile (**13**). Resin **12** (0.5 g, 1 mmol) was washed with CH_2Cl_2, and dry CH_2Cl_2 (10 ml) and 1.2 equiv. of *m*-CPBA were added at 0°. The mixture was stirred at r.t. for 18 h, washed successively with CH_2Cl_2 at r.t., i-PrOH at 60°, dioxane at 60°, and Et_2O at r.t. Then, dry dioxane (15 ml) and pyrrolidine (0.415 ml, 5 mmol) were added at r.t. The mixture was stirred at r.t. for 3 h and then filtered. The filtrate was evaporated and the residue (0.11 g) filtered through SiO_2 with AcOEt/hexane 1:2: 0.06 g (32%) of **13**. Pale-yellow solid. M.p. 215°. IR: 3480*w*, 3370*w*, 3120*w*, 2990*w*, 2210*m*, 1660*s*, 1610*s*, 1530*s*, 790*s*, 745*s*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.23 (*s*, 1 arom. H); 7.25 (*s*, NH_2); 3.55–3.35 (*m*, 4 aliph. H); 1.9–1.8 (*m*, 4 aliph. H). MS: 189 (50, M^+), 161 (40), 160 (100), 70 (25).

4-Amino-2,6-di(pyrrolidin-1-yl)pyrimidine-5-carbonitrile (**16**). Resin **14** (1.09 g, 0.5 mmol) was washed with CH_2Cl_2, and dry CH_2Cl_2 (5 ml) and *m*-CPBA (0.518 g, 3 mmol) were added at r.t. The mixture was stirred at r.t. for 15 h, washed successively with CH_2Cl_2 at r.t., i-PrOH at 60°, dioxane at 60°, and Et_2O at r.t., followed by addition of dry dioxane (8 ml) and pyrrolidine (1.5 ml) at r.t., and the mixture was stirred at 60° for 4 h and then filtered. The filtrate was evaporated and the residue filtered through SiO_2 with AcOEt/CH_2Cl_2 5:95: 0.06 g (78%) of **16**. White solid. IR: 3410*s*, 2969*m*, 2184*s*, 1642*s*, 1560*s*, 1522*s*, 783*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 6.46 (br. *s*, NH_2); 3.65–3.5 (*m*, 4 aliph. H); 3.45–3.3 (*m*, 4 aliph. H); 1.9–1.8 (*m*, 8 aliph. H). MS: 259 (100 $[M + H]^+$).

4-Amino-6-(methylthio)-2-(pyrrolidin-1-yl)pyrimidine-5-carbonitrile (**9a**). As described for **13**, with resin **14** (0.5 g, 0.75 mmol) CH_2Cl_2 (7.5 ml), and *m*-CPBA (0.235 g, 0.95 mmol). Then, dry dioxane (4 ml) and pyrrolidine (0.054 g, 0.75 mmol) were added at r.t. The mixture was stirred at 65° for 4 h and the product collected after filtration and evaporation. The procedure was repeated with dry dioxane (4 ml) and pyrrolidine (0.054 g, 0.75 mmol), stirring at 65° for 4 h, and filtration. The filtrate was evaporated and the crude product analyzed by HPLC (87%). The residue (0.154 g) was filtered through SiO_2 with AcOEt/CH_2Cl_2 1:4: 0.043 g (22%) of **16** and 0.065 g (37%) of **9a**, both white solids. IR, ^{1}H-NMR, MS of **9a**: identical to those obtained using *Method D*.

4-Amino-2-(4-methylpiperazin-1-yl)-6-(methylthio)pyrimidine-5-carbonitrile **17**. As described for **13**, with resin **14** (0.5 g, 0.75 mmol), dry CH_2Cl_2 (7.5 ml); and *m*-CPBA (0.95 mmol). Then, dry dioxane (4 ml) and 1-methylpiperazine (0.075 g 0.75 mmol) were added at r.t. The mixture was stirred at 65° for 4 h and the product collected after filtration and evaporation. The procedure was repeated with dry dioxane (4 ml) and 1-methylpiperazine (0.075 g, 0.75 mmol), stirring at 65° for 4 h and filtration. The filtrate was evaporated and the crude product analyzed by HPLC (87%). The residue (0.140 g) was filtered through SiO_2 with AcOEt/EtOH 1:1:0.06 g (30%) of **17**. White solid. IR: 3405*w*, 2820*w*, 2215*m*, 1670*m*, 1555*s*, 1495*s*, 1150*m*, 795*s*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 7.16 (br. *s*, NH_2); 3.76 (br. *s*, 4 aliph. H); 2.46 (*s*, 3 aliph. H); 2.4–2.3 (*m*, 4 aliph. H); 2.19 (*s*, 3 aliph. H). MS: 265 (100, $[M + H]^+$).

4-Amino-6-(methylthio)-2-{[(pyridin-2-yl)methyl]amino}pyrimidine-5-carbonitrile (**18**). As described for **13**, with resin **14** (0.5 g, 0.75 mmol), dry CH_2Cl_2 (7.5 ml), and *m*-CPBA (0.235 g, 0.95 mmol). Then, as described for **17**, with twice dry dioxane (4 ml) and 0.081 g (0.75 mmol) of [(pyridin-2-yl)methyl]amine. HPLC of the crude product: 86%. The residue (0.150 g) was filtered through SiO_2 with AcOEt/EtOH 1:20: 0.054 g (26%) of **18**. White solid. IR: 3398*m*, 3108*m*, 2190*m*, 1661*m*, 1662*s*, 1523*s*, 1029*m*, 891*m*, 779*m*, 714*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.6–8.4 (*m*, 2 arom. H); 8.15–8.0 (*m*, NH); 7.75–7.65 (*m*, 1 arom. H); 7.4–7.3 (*m*, 1 arom. H); 7.1–7.0 (*m*, NH_2); 4.65–4.45 (*m*, 2 aliph. H); 2.46 (*s*, 3 aliph. H). MS: 273 (100, $[M + H]^+$).

4-Amino-2-{[2-(1-methylpyrrolidin-2-yl)ethyl]amino}-5-(methylthio)pyrimidine-5-carbonitrile (**19**). As described for **13**, with resin **14** (0.5 g, 0.75 mmol) dry CH_2Cl_2 (7.5 ml), and *m*-CPBA (0.235 g, 0.95 mmol). Then, as

described for **17**, with twice dry dioxane (4 ml) and of 2-(1-methylpyrrolidin-2-yl)ethylamine (0.096 g, 0.75 mmol). HPLC of the crude product: 70%. The residue (0.142 g) was filtered through SiO_2 with MeOH: 0.077 g (35%) of **19**. White solid: IR: 3405*m*, 2795*m*, 2196*m*, 1667*m*, 1549*s*, 1532*s*, 1114*m*, 777*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 7.5–7.4 (*m*, NH); 7.08 (br. *s*, NH_2); 3.4–3.3 (*m*, 2 aliph. H); 2.95–2.85 (*m*, 1 aliph. H); 2.45 (*s*, 3 aliph. H); 2.17 (*s*, 3 aliph. H); 2.05–1.3 (*m*, 8 aliph. H). MS: 293 (100, $[M + H]^+$).

4-Amino-2-(2,2-dimethoxyethylamino)-6-(methylthio)pyrimidine-5-carbonitrile (**20**). As described for **13**, with resin **14** (0.5 g, 0.75 mmol), dry CH_2Cl_2 (7.5 ml), and *m*-CPBA 0.155 g (0.90 mmol) (final washing with pentane). Then, as described for **17**, with twice dry dioxane (4 ml) and 2,2-dimethoxyethylamine (0.118 g, 1.12 mmol) at r.t. for 4 h. HPLC of the crude product: 93.8%. Crude product: 0.189 g (93.5%) of **20**. White solid. IR: 3434*s*, 2194*s*, 1663*s*, 1549*s*, 1460*m*, 1091*m*, 800*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 7.55–7.45 (*m*, NH); 7.05 (br. *s*, NH_2); 4.55–4.45 (*m*, 1 aliph. H); 3.4–3.25 (*m*, 2 aliph. H); 3.26 (*s*, 2 MeO); 2.46 (*s*, 3 aliph. H). MS: 270 (100, $[M + H]^+$), 238 (80).

3-(3-Fluorobenzyl)-3,4-dihydro-4-imino-7-methyl-5-(methylthio)pyrimido[4,5-d]pyrimidine-2(1H)-thione (**22a**). According to *Method E*, with **7a**, (0.18 g, 1 mmol), 3-fluorobenzyl isothiocyanate (**21a**); (0.184 g, 1.1 mmol), and DBU (0.164 ml, 1.1 mmol) at 45° for 3 h: 0.3 g (89%) of **22a**. White solid after FC with $MeCN/CH_2Cl_2$ 1:20. IR: 3460*m*, 1616*s*, 1589*s*, 1490*w*, 893*w*, 785*w*, 714*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.86 (br. *s*, NH); 8.63 (br. *s*, NH); 7.5–7.0 (*m*, 4 arom. H); 5.78 (*s*, 2 aliph. H); 2.54 (*s*, 3 aliph. H); 2.37 (*s*, 3 aliph. H). MS: 347 (100, M^+), 314 (15), 207 (30), 192 (20), 109 (35).

3,4-Dihydro-4-imino-7-methyl-5-(methylthio)-3-phenylpyrimido[4,5-d]pyrimidine-2(1H)-thione (**22b**). According to *Method E*, with **7h**, (10 g, 55 mmol), phenyl isothiocyanate (**21b**) (8.25 g, 61.03 mmol), and DBU (9.12 ml, 61.03 mmol) at r.t. for 18 h: 17.1 g (98%) of **22b**. Yellow solid after trituration with hexane. IR: 3428*s*, 1642*s*, 1535*s*, 1492*s*, 783*w*, 699*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.9 (br. *s*, NH); 7.65–7.25 (*m*, 5 arom. H); 7.04 (br. *s*, NH); 2.57 (*s*, 3 aliph. H); 2.4 (*s*, 3 aliph. H). MS: 316 (100 $[M + H]^+$).

3-(3,5-Difluorophenyl)-3,4-dihydro-4-imino-7-methyl-5-(methylthio)pyrimido[4,5-d]pyrimidine-2(1H)-one (**22c**). According to *Method E*, with 3,5-difluorophenyl isocyanate (**21c**); (0.171 g, 1.1 mmol), and DBU (0.164 ml, 1.1 mmol) at 45° for 3 h: 0.13 g (50%) of **22c**. White solid after FC (Me_3CN/CH_2Cl_2 1:20). IR: 3436*s*, 1718*s*, 1635*s*, 1546*s*, 1511*s*, 794*m*, 751*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 11.82 (br. *s*, NH); 7.72 (br. *s*, NH); 7.6–7.5 (*m*, 2 arom. H); 7.35–7.25 (*m*, 1 arom. H); 2.54 (*s*, 3 aliph. H); 2.40 (*s*, 3 aliph. H). MS: 335 (30, M^+), 320 (45), 316 (100).

Methyl 3-[7-(Hexylthio)-3,4-dihydro-4-imino-5-(methylthio)-2-thioxopyrimido[4,5-d]pyrimidine-3(1H)-yl]benzoate (**22d**). According to *Method E*, with **7a** (0.282 g, 1 mmol), methyl 3-isothiocyanatobenzoate (**21d**; 0.212 g, 1.1 mmol), and DBU (0.164 ml, 1.1 mmol) at r.t. for 1 h: 0.30 g (63%) of **22d**. White solid after FC ($AcOEt/CH_2Cl_2$ 1:40) and crystallization from $MeCN/H_2O$. IR: 3417*s*, 1726*s*, 1639*s*, 1523*s*, 1249*s*, 880*m*, 780*m*, 713*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.95 (br. *s*, NH); 7.4–7.05 (*m*, 3 arom. H); 8.1–7.5 (*m*, 4 arom. H); 7.16 (br. *s*, NH); 3.87 (*s*, 3 aliph. H); 3.2–3.1 (*t*, $J = 7.2$, 2 aliph. H); 2.41 (*s*, 3 aliph. H); 1.75–1.65 (*m*, 2 aliph. H); 1.5–1.25 (*m*, 6 aliph. H); 0.9–0.75 (*t*, $J = 6.2$, 3 aliph. H). MS: 476 (100, $[M + H]^+$).

3-(3-Fluorobenzyl)-7-(hexylthio)-3,4-dihydro-4-imino-5-(methylthio)pyrimido[4,5-d]pyrimidine-2(1H)-thione (**22e**). According to *Method E*, with **7a** (0.282 g, 1 mmol), 3-fluorobenzyl isothiocyanate (**21e**; 0.184 g, 1.1 mmol), and DBU (0.164 ml, 1.1 mmol) at r.t. for 3 h: 0.37 g (82%) of **22e**. White solid after FC (CH_2Cl_2/AcOEt 40:1). IR: 3437*s*, 1614*m*, 1585*m*, 1526*s*, 880*w*, 786*w*, 690*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.85 (br. *s*, NH); 8.5 (br. *s*, NH); 7.4–7.0 (*m*, 4 arom. H); 5.77 (*s*, 2 aliph. H); 3.2–3.1 (*t*, $J = 7.2$, 2 aliph. H); 2.38 (*s*, 3 aliph. H); 1.75–1.65 (*m*, 2 aliph. H); 1.5–1.25 (*m*, 6 aliph. H); 0.9–0.75 (*t*, $J = 6.2$, 3 aliph. H). MS: 450 (100, $[M + H]^+$).

3-(3-Chlorobenzyl)-7-(hexylthio)-3,4-dihydro-4-imino-5-(methylthio)pyrimido[4,5-d]pyrimidine-2(1H)-thione (**22f**). According to *Method E*, with **7a** (0.282 g, 1 mmol), 3-chlorobenzyl isothiocyanate (**21f**; 0.202 g, 1.1 mmol), and DBU (0.164 ml, 1.1 mmol) at r.t. for 18 h: 0.414 g (89%) of **22f**. White solid after FC (CH_2Cl_2/AcOEt 40:1). IR: 3433*s*, 1613*m*, 1582*m*, 1525*s*, 880*w*, 780*w*, 710*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.85 (br. *s*, NH); 8.55 (br. *s*, NH); 7.5–7.2 (*m*, 4 arom. H); 5.75 (*s*, 2 aliph. H); 3.2–3.1 (*t*, $J = 7.2$, 2 aliph. H); 2.38 (*s*, 3 aliph. H); 1.75–1.65 (*m*, 2 aliph. H); 1.5–1.25 (*m*, 6 aliph. H); 0.9–0.75 (*t*, $J = 6.2$, 3 aliph. H). MS: 466 (100, $[M + H]^+$).

4-{{[6-(3,4-Dichlorobenzyl)-5,6,7,8-tetrahydro-5-imino-4-(methylthio)-7-thioxopyrimido[4,5-d]pyrimidin-2-yl]thio}methyl}benzonitrile (**22g**, X = S). According to *Method E*, with **7e** (0.1 g, 0.319 mmol), 3,4-dichlorobenzyl isothiocyanate (**21g**; 0.76 g, 0.35 mmol), and 0.053 ml, DBU (0.35 mmol) at 45° for 3 h: 0.136 g (80%) of **22g**. White solid after FC ($MeCN/CH_2Cl_2$ 1:20). IR: 3439*m*, 2215*w*, 1614*m*, 1577*m*, 1485*w*, 820*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.98 (br. *s*, NH); 8.67 (br. *s*, NH); 7.7–7.5 (*m*, 6 arom. H); 7.35–7.25 (*m*, 1 arom. H); 5.72 (*s*, 2 aliph. H); 4.55 (*s*, 2 aliph. H); 2.29 (*s*, 3 aliph. H). MS: 530 (100, $[M + H]^+$), 437 (80), 413 (30), 391 (50), 351 (30), 345 (20), 329 (25).

4-{{[5,6,7,8-Tetrahydro-5-imino-4-(methylthio)-6-phenyl-7-thioxopyrimido[4,5-d]pyrimidin-2-yl]thio}methyl}benzonitrile (**21h**). According to *Method E*, with **7e** (0.1 g, 0.319 mmol), phenyl isothiocyanate (**21h**, 0.042 ml, 0.35 mmol), and DBU (0.053 ml, 0.35 mmol) at 45° for 3 h: 0.08 g (56%) of **22h**. White solid after FC (MeCN/CH_2Cl_2 1:20). IR: 3431*m*, 2210*w*, 1634*m*, 1584*m*, 1528*s*, 765*w*, 705*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 13.0 (br. *s*, NH); 7.8–7.3 (*m*, 9 arom. H); 7.0 (br. *s*, NH); 4.57 (*s*, 2 aliph. H); 2.32 (*s*, 3 aliph. H). MS: 449 (100, $[M + H]^+$).

3-Isobutyl-8-methyl-10-(methylthio)imidazo[1,2-c]pyrimido[5,4-e]pyrimidine-2,5(3H,6H)-dione (**24a**). According to *Method E*, with **7a** (0.18 g, 1 mmol), ethyl 2-isocyanato-4-methylpentanoate (**23a**; 0.204 g, 1.1 mmol), and DBU (0.164 ml, 1.1 mmol) at r.t. for 72 h: 0.23 g (72%) of **24a**. Pale-yellow solid after trituration with MeCN. IR: 3429*s*, 1711*m*, 1646*s*, 1559*s*, 1472*s*, 1205*m*, 1163*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.48 (br. *s*, NH); 4.4–4.3 (*m*, 1 aliph. H); 2.59 (*s*, 3 aliph. H); 2.53 (*s*, 3 aliph. H); 1.9–1.75 (*m*, 3 aliph. H); 0.9–0.75 (*m*, 6 aliph. H). MS: 320 (30, $[M + H]^+$).

3-Isopropyl-8-methyl-10-(methylthio)-5-thioxoimidazo[1,2-c]pyrimido[5,4-e]pyrimidin-2(3H)-one (**24b**). According to *Method E*, with **7h** (0.18 g, 1 mmol), ethyl 2-isothiocyanato-3-methylbutanoate (**23b**, 0.191 g, 1.1 mmol), and Cs_2CO_3 (0.358 mg, 1.1 mmol) at r.t. for 18 h: 0.24 g (72%) of **24b**. White solid after FC (MeCN/CH_2Cl_2 1:20). IR: 3437*s*, 1754*m*, 1599*s*, 1537*s*, 1508*s*, 1195*s*, 1195*s*, 802*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 13.64 (br. *s*, NH); 4.4-4.35 (*d*, J = 3.6, 1 aliph. H); 3.35–3.2 (*m*, 1 aliph. H); 2.61 (*s*, 3 aliph. H); 2.54 (*s*, 3 aliph. H); 1.25–1.16 (*d*, J = 6.8, 3 aliph. H); 0.7–0.6 (*d*, J = 6.8, 3 aliph. H). MS: 321 (100, M^+), 306 (20), 278 (20), 223 (20).

3-Ethyl-5,6-dihydro-8-methyl-10-(methylthio)-5-thioxoimidazo[1,2-c]pyrimido[5,4-e]pyrimidin-2(3H)-one (**24c**). According to *Method E*, with **7h** (0.18 g, 1 mmol), methyl 2-isothiocyanatobutanoate (**23c**; 0.175 g, 1.1 mmol), and Cs_2CO_3 (0.65 mg, 2 mmol) at r.t. for 18 h: 0.25 g (75%) of **24c**. Pale-yellow solid after FC (AcOEt/CH_2Cl_2 1:20). IR: 3436*s*, 1751*m*, 1599*s*, 1537*s*, 1195*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 13.68 (br. *s*, NH); 4.6–4.5 (*m*, 1 aliph. H); 2.62 (*s*, 3 aliph. H); 2.55 (*s*, 3 aliph. H); 2.5–2.4 (*m*, 1 aliph. H); 2.3–2.0 (*m*, 1 aliph. H); 0.75–0.6 (*m*, 3 aliph. H). MS: 308 (100, $[M + H]^+$).

Methyl 4-{{[3-(3-Fluorobenzyl)-3,4-dihydro-4-imino-7-methyl-5-(methylthio)pyrimido[4,5-d]pyrimidin-2-yl]thio}methyl}benzoate (**26a**). According to *Method F*, with **22a** (0.2 g, 0.576 mmol) methyl 4-(bromomethyl)benzoate (**25a**, 0.145 g, 0.634 mmol), and (i-Pr)$_2$EtN (0.082 ml, 0.634 mmol) at 60° for 3 h: 0.15 g (53%) of **26a**. Pale-brown solid after trituration with Et_2O. IR: 3431*m*, 1721*s*, 1613*s*, 1531*s*, 1503*m*, 1280*m*, 820*w*, 780*w*, 710*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.5 (br. *s*, NH); 7.75–7.6 (*m*, 3 arom. H); 7.55–7.45 (*m*, 2 arom. H); 6.9 (*s*, NH); 2.68 (*s*, 3 aliph. H); 2.43 (*s*, 3 aliph. H); 2.4 (*s*, 3 aliph. H). MS: 496 (100, $[M + H]^+$).

3-(3-Fluorobenzyl)-7-(hexylthio)-2,5-bis(methylthio)pyrimido[4,5-d]pyrimidin-(3H)-imine (**26b**). According to *Method F*, with **22e** (0.2 g, 0.634 mmol), methyl iodide (**25b**; 0.099 g, 0.697 mmol), and K_2CO_3 (0.096 mg, 0.697 mmol) at r.t. for 18 h: 0.115 g (55%) of **26b**. Pale brown solid after FC (CH_2Cl_2/AcOEt 10:1). IR: 3436*m*, 1637*s*, 1509*s*, 801*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.57 (br. *s*, NH); 7.5–7.15 (*m*, 4 arom. H); 5.35 (*s*, 2 aliph. H); 3.97 (*s*, 2 aliph. H); 3.25–3.1 (*t*, J = 7.2, 2 aliph. H); 2.97 (*s*, 3 aliph. H); 2.37 (*s*, 3 aliph. H); 1.75–1.25 (*m*, 8 aliph. H); 0.9–0.75 (*t*, J = 6.2, 3 aliph. H). MS: 329 (100, M^+), 314 (90), 296 (40), 282 (35), 242 (25), 123 (15), 77 (20).

tert-*Butyl {[3-(3-Chlorobenzyl)-7-(hexylthio)-3,4-dihydro-4-imino-5-(methylthio)pyrimido[4,5-d]pyrimidin-2-yl]thio}acetate* (**26c**). According to *Method F*, with **22f** (0.2 g, 0.429 mmol), 0.085 g (0.436 mmol) of *tert*-butyl bromoacetate (0.085 g, 0.436 mmol), **25c**, and (i-Pr)$_2$EtN (0.061 ml, 0.472 mmol) at 60° for 2 h: 0.208 g (84%) of **26c**. Pale-brown solid after trituration with Et_2O. IR: 3433*m*, 1733*s*, 1612*s*, 1495*s*, 1149*s*, 853*m*. ^{1}H-NMR ((D)$_6$DMSO, 250 MHz): 8.57 (br. *s*, NH); 7.5–7.15 (*m*, 4 arom. H); 5.35 (*s*, 2 aliph. H); 3.97 (*s*, 2 aliph. H); 3.25–3.1 (*t*, J = 7.2, 2 aliph. H); 2.37 (*s*, 3 aliph. H); 1.75–1.25 (*m*, 17 aliph. H); 0.9–0.75 (*t*, J = 6.2, 3 aliph. H). MS: 580 (100, $[M + H]^+$).

4-{{[7-[(4-Cyanobenzyl)thio]-3,4-dihydro-4-imino-5-(methylthio)-3-phenylpyrimido[4,5-d]pyrimidin-2-yl]-thio}methyl}benzonitrile (**26d**). According to *Method F*, with **22h** (0.05 g, 0.11 mmol), 4-(bromomethyl)-benzonitrile (**25d**; 0.026 g, 0.123 mmol), and DBU (0.02 ml, 0.123 mmol) at r.t. for 18 h: 0.056 g (90%) of **26d**. White solid after FC (AcOEt/CH_2Cl_2 1:20). IR: 3438*m*, 2226*m*, 1641*m*, 1615*w*, 1502*s*, 845*w*, 770*w*, 705*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.95–7.5 (*m*, 13 arom. H); 6.98 (br. *s*, NH); 4.62 (*s*, 2 aliph. H); 4.48 (*s*, 2 aliph. H); 2.33 (*s*, 3 aliph. H). MS: 564 (100, $[M + H]^+$).

Methyl 4-{{[7-[(4-Cyanobenzyl)thio]-3,4-dihydro-4-imino-5-(methylthio)-3-phenylpyrimido[4,5-d]pyrimidin-2-yl]thio}methyl}benzoate (**26e**). According to *Method F*, with **22h** (0.132 g, 0.294 mmol), methyl (4-bromomethyl)benzoate (**25a**; 0.074 g, 0.324 mmol), and DBU (0.048 ml, 0.324 mmol) at r.t. for 18 h: 0.135 g (77%) of **26e**. Pale-brown solid after FC (toluene/AcOEt 4:1). IR: 3436*m*, 3304*w*, 2220*w*, 1719*s*, 1637*s*, 1523*s*, 1499*s*, 1297*s*, 799*w*, 765*w*, 700*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.95–7.5 (*m*, 13 arom. H); 6.95 (br. *s*, NH); 4.61 (*s*, 2 aliph. H); 4.45 (*s*, 2 aliph. H); 3.83 (*s*, 3 aliph. H); 2.33 (*s*, 3 aliph. H). MS: 597 (100, $[M + H]^+$).

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