5. A Novel and Efficient Approach for the Combinatorial Synthesis of Structurally Diverse Pyrimidines on Solid Support[1])

by **Daniel Obrecht**[2])*, **Christine Abrecht, Alfred Grieder**, and **José M. Villalgordo**[3])

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

(22.X.96)

We describe a versatile novel approach for the synthesis of 2,4,6-trisubstituted pyrimidines on solid support. Thus, polymer-bound thiouronium salt **2** reacted in high yield in a cyclocondensation reaction with the acetylenic ketones **3** to form, after *tert*-butyl-ester cleavage, the polymer-bound carboxylic acids **4**, which were cleaved by oxidation with 3-chloroperbenzoic acid and pyrrolidine to form the 2-pyrrolidinylpyrimidine-4-carboxylic acids **6a–c** in high yields and purities without further purification (*Scheme 1*). Alternatively, acid **4a** was subjected to an *Ugi* four-component condensation which gave the polymer-bound *Ugi* products **9a–e** in good yields (*Scheme 2*). Multidirectional cleavage reaction of sulfone **8a** with different nucleophiles resulted in the clean formation of pyrimidine-4-carboxamides **10–13** (*Scheme 3*). This strategy combines efficiently solid-phase chemistry with a multicomponent reaction and a multidirectional cleavage step to form highly diverse pyrimidines in a parallel array.

1. Introduction. – In recent years, multiple synthesis technologies on solid support directed toward the generation of diverse, small organic molecules has generated considerable interest as it relates to efficient lead-structure identification [1–4]. Thus, a number of protocols based on adaptations of known solution-phase syntheses have been developed for construction of compound libraries on solid support of benzodiazepines [5–7], hydantoins [8] [9], 1*H*-imidazoles [10] [11], 1*H*-pyrroles [12], pyrrolidines [13], 1*H*-pyrazoles and isoxazoles [14], dihydropyridines [15], β-lactams [16], and dihydropyrimidines [17] among other compound classes [18–21].

As a part of an ongoing project, devoted toward the development of efficient methodologies for a parallel version of the combinatorial synthesis of different molecularily diverse heterocyclic systems on solid support, we have focused our attention on pyrimidine derivatives, due to the broad range of useful properties they display [22] [23], and developed a new and general synthetic route on solid support toward these potentially interesting compounds. Our strategy efficiently combines a versatile cyclocondensation reaction of acetylenic ketones with a polymer-bound isothiourea, to form polymer-bound 2-(alkylthio)-4,6-disubstituted pyrimidines, with the nucleophilic displacement reaction of the 2-sulfonyl group of pyrimidines [24] [25] by various nucleophiles as the key cleavage reaction.

2. Results and Discussions. – Acetylenic ketones are versatile building blocks which have been widely used as synthons in a variety of reaction types and for the synthesis of different heterocyclic systems, such as 3-halofurans, flavones, and styrylchromones [26],

[1]) Presented in part at the 'Random & Rational Conference' in Princeton on September 16, 1996.

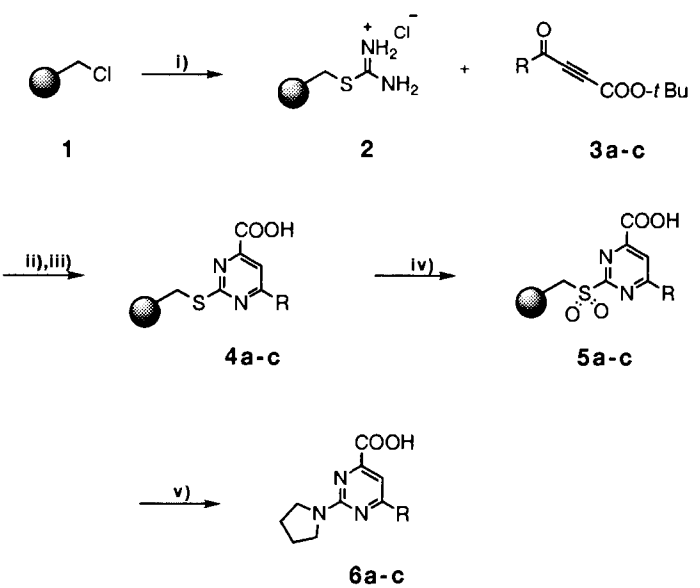
[2]) Present address: *POLYPHOR Ltd.*, Winterthurerstrasse 190, CH-8057 Zürich.

[3]) Present address: Departament de Quimica, Universitat de Girona, Plaça del Hospital 6, E-17071 Girona.

4*H*-thiopyran-4-ones [27], 1,5-benzodiazepines [28], 3-halo-1*H*-pyrroles and 1*H*-pyrrole derivatives [29], and others [30] [31]. Herein, we report a novel cyclocondensation reaction of acetylenic ketones with resin-bound thiouronium salt **2** which was obtained quantitatively after 15 h by reaction of thiourea in dioxane/EtOH 4:1 with commercially available high-loaded *Merrifield* resin (3.5 mmol/g). Condensation with 1.2 equiv. of acetylenic ketones **3a–c** in DMF in the presence of 1.5 equiv. of diisopropylethylamine ((i-Pr)$_2$EtN) at room temperature led to the corresponding pyrimidine-carboxylic acids **4a–c** after cleavage of the intermediate *tert*-butyl esters with 50% CF_3COOH in CH_2Cl_2 at room temperature. The formation of the polymer-bound compounds was followed by FT-IR spectroscopy (see *Exper. Part*).

The next issue to be addressed was the cleavage of the pyrimidine derivatives from the polymeric support. As already stated, the ammonolysis and alcoholysis of alkylthio groups [25] of pyrimidines have been described in solution; but the reaction conditions needed to achieve these transformations with the corresponding polymer-bound pyrimidinecarboxylic acids turned out to be impracticable in our case, due to the harsh reaction conditions needed, leading in the best cases to the desired compounds with low levels of purity. However, oxidation of the 2-alkylthio group to the corresponding sulfones **5a–c** with 3 equiv. of 3-chloroperbenzoic acid (3-$ClC_6H_4CO_3H$) in CH_2Cl_2 proved to be the key step for the successful cleavage reactions yielding, *e.g.*, with pyrrolidine in dioxane at room temperature after 6 h, the corresponding pyrimidine derivatives **6a–c** in excellent yields and with high levels of purity (typically, ≥ 96–99%) (*Scheme 1*, *Table 1*).

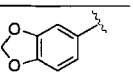
Scheme 1[a])



[a]) See *Table 1* for **a–c**.

i) Thiourea, dioxane/EtOH 4:1, 85°, 15 h. ii) (i-Pr)$_2$EtN (1.5 equiv.; slow addition), DMF, r.t., 24 h. iii) 50% CF_3COOH, CH_2Cl_2, r.t., 15 h. iv) 3-$ClC_6H_4CO_3H$ (3 equiv.), CH_2Cl_2, 15 h. v) Pyrrolidine, dioxane, r.t., 6 h.

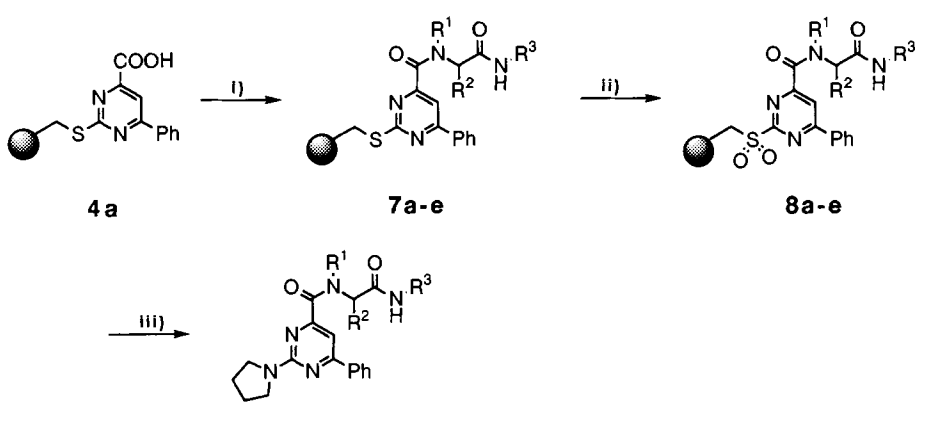
Table 1. *Synthesis of Pyrimidine-carboxylic Acids* **6a–c**

	R		
			
Compound	**6a**	**6b**	**6c**
Yield[a])	90%	87%	85%
Purity[b])	98%	96%	99%
t_R[c])	7.2	4.8	5.9
MS	269 ($[M-1]^-$)	259 ($[M-1]^-$)	313 ($[M-1]^-$)

[a]) Isolated yields. [b]) HPLC purity of the crude reaction mixture. [c]) Retention time in min, measured on a *Superspher®-60-RP-Select* column with a gradient 50% MeCN/H_2O (with 1% CF_3COOH) until 100% MeCN within 20 min.

In view of achieving the highest possible degree of molecular diversity, we aimed at combining our solid-phase pyrimidine-assembly strategy with the attractive features of multicomponent reactions [32]. One of the most useful multicomponent condensations with respect of easy availability of commercial building blocks is the *Ugi* four-component reaction [33] [34], where a carboxylic acid, an amine, an aldehyde, and an isocyanide form an α-(acylamino)amide in usually good yield. We have initiated our studies toward the preparation of highly molecularly diverse pyrimidines by studying the *Ugi* reaction using the polymer-bound pyrimidine-carboxylic acids of type **4** as the acid component. Thus, when **4a** and a five-fold excess of different amines R^1NH_2, aldehydes R^2CHO, and isonitriles R^3NC were vortexed in dioxane/MeOH 4:1 at 55° for 48 h in the presence of molecular sieves (4 Å), the corresponding α-(acylamino)amides **7a–e** (*Scheme 2*) were efficiently formed. Oxidation to the corresponding sulfones **8a–e** and cleavage with pyrrolidine, led to the corresponding *Ugi* products **9a–e** in good yields and excellent levels of puritiy (see *Table 2*).

Scheme 2[a])



[a]) See *Table 2* for **a–e**.

i) R^1NH_2, R^2CHO, R^3NC (5 equiv.), dioxane/MeOH 4:1, 55°, 48 h. ii) 3-$ClC_6H_4CO_3H$ (3 equiv.), CH_2Cl_2, r.t., 15 h. iii) Pyrrolidine (1 equiv.), dioxane, r.t., **6** h.

Table 2. *Pyrimidine Derivatives* **9** (*Scheme 2*)

Entry	R^1	R^2	R^3	Yield[a])	Purity[b])	t_R[c])	MS
9a	4-(MeO)C_6H_4	Me_2CHCH_2	c-C_6H_{11}	86	95	19.3	570.5
9b	c-C_6H_{11}	Me_2CH	c-C_6H_{11}	72	98	23.0	532.7
9c	$MeCH_2CH_2$	Me_2CH	c-C_6H_{11}	65	90	19.5	492.5
9d	$PhCH_2$	Me_2CH	Bu	77	91	17.9	514.5
9e	4-(MeO)C_6H_4	Me_2CH	c-C_6H_{11}	87	94	17.7	556.5

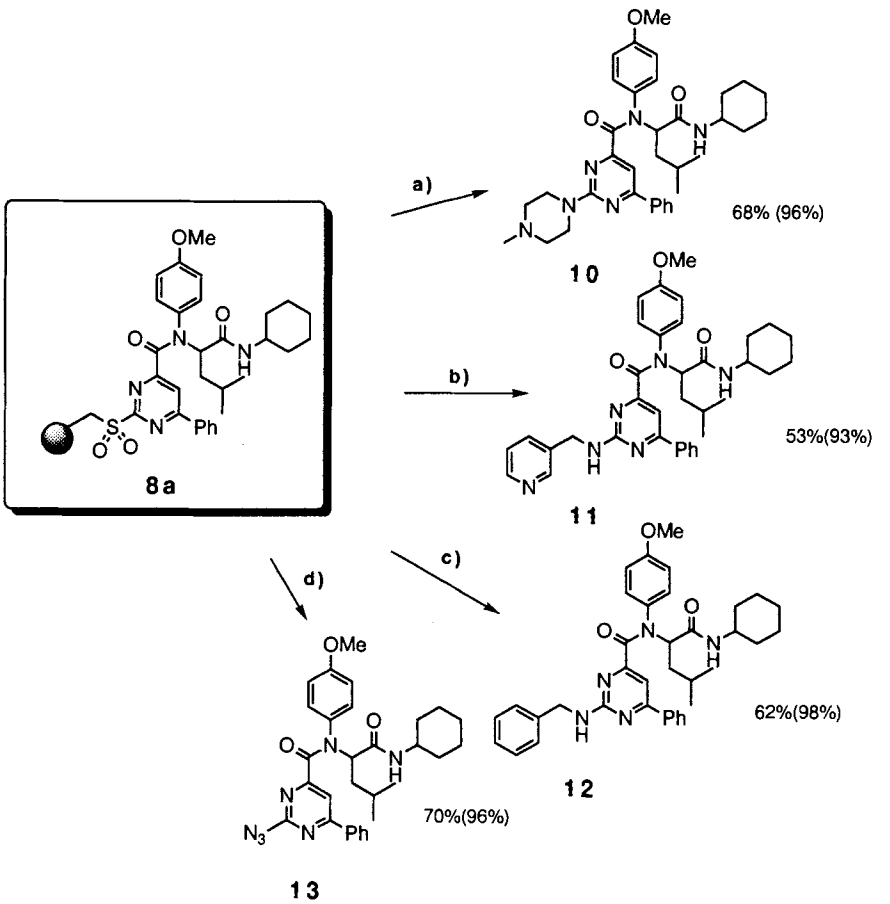
[a]) Isolated yields. [b]) HPLC purity of the crude reaction mixture. [c]) Retention time in min, measured on a *Superspher®-60-RP-Select* column with a gradient 50% MeCN/H_2O (with 1% CF_3COOH) until 100% MeCN within 20 min.

One limitation so far encountered was the well known lack of reactivity of aromatic aldehydes and isonitriles under the *Ugi*-reaction conditions. To extend the scope of our method by introduction of a third substituent at the 2-position of the pyrimidines, we studied the reaction conditions of the crucial cleavage step. By treatment of polymer-bound sulfone **8a** under various conditions, we found that only 1 equiv. of the corresponding nucleophiles, such as primary and secondary amines and azide anion, were necessary to perform the cleavage reactions in high yields. Thus, compounds **10–13** were obtained in good yields and high purities from sulfone **8a** and 1 equiv. of *N*-methylpyrazine, pyridine-3-methanamine, benzylamine, and sodium azide, respectively, in dioxane or DMF at 65° (*Scheme 3*).

In summary, we have developed a novel and highly versatile synthesis of 2,4,6-trisubstituted pyrimidines on solid support featuring the condensation reaction of polymer-bound thiouronium salt **2** with acetylenic ketones **3** to form the pyrimidine-carboxylic acids **4** after acidic cleavage of the *tert*-butyl-ester groups. The polymer-bound acids **4** were then cleaved by oxidation with 3-$ClC_6H_4CO_3H$ in CH_2Cl_2 and treatment with pyrrolidine to give the 2-pyrrolidinylpyrimidine-4-carboxylic acids **6a–c** in high yields and purities, or were subjected to an *Ugi* four-component condensation to form carboxamides **9a–e**. In addition, we were able to demonstrate a multidirectional cleavage of sulfone **8a** with different nucleophiles to form the highly diverse pyrimidine-carboxamides **10–13**, thus efficiently combining our solid-phase strategy with a multiple-component condensation and a multidirectional cleavage reaction. Using high-loaded *Merrifield* resin (3.5 mmol per g), we routinely used 150 mg of resin per compound and ended up with 75–120 mg of products in purities typically greater than 90% (by HPLC analysis). Furthermore, we have demonstrated a novel concept of polymer-bound safety catch resin [35] using the oxidation of the 2-alkylthio group to the corresponding sulfone to activate and facilitate the cleavage reaction. We have used the present strategy for the synthesis of twelf highly diverse, structurally and pharmacologically interesting pyrimidines in a very efficient manner. Further applications of this strategy toward different functionalized pyrimidines, as well as the extension for the final cleavage with different types of nucleophiles are in progress and will be published on due course.

We thank Mr. *D. Sprenger* for technical assistance and Dr. *W. Huber* for assistance with FT-IR. We wish to thank also Profs. *J. Baldwin* (Oxford), *H.-J. Hansen* (Zürich), *F. Diederich* (Zürich), *A. Vasella* (Zürich), *H. Heimgartner* (Zürich), and *K. Müller* (*F. Hoffmann-La Roche AG*, Basel) for fruitful discussions.

Scheme 3. *Multidirectional Cleavage Mode with Different Nucleophiles.* Yields of isolated products from **4a**. In parenthesis, the HPLC purity of crude reaction mixture is given.



a) *N*-Methylpyrazine (1 equiv.), dioxane, 65°, 5 h. b) Pyridine-3-methanamine (1 equiv.), dioxane, 65°, 5 h. c) Benzylamine (1 equiv.), dioxane, 65°, 5 h. d) Sodium azide (3 equiv.), DMF, 65°, 5 h.

Experimental Part

General. See [36]. ATR(attenuated total reflexion)-IR Spectra (cm^{-1}): on beads [37]; *Nicolet-550* or *-850* spectrometer coupled to a *Niplan* microscope equiped with a *Spectratech* ATR objective using 4 cm^{-1} resolution with 200–500 scans co-added and a MCT detector.

Polymer-Bound Thiouronium Salt **2**. A mixture of 50 g (170 mmol) of the high-loaded *Merrifield* resin (*Senn Chemicals AG*), 64.70 g (850 mmol) of thiourea, and 350 ml of dioxane/EtOH 4:1 was shaken at 85° for 15 h, washed successively with 4 × 150 ml of EtOH at 70°, 2 × 150 ml of dioxane at r.t., and 2 × 150 ml of pentane at r.t. The polymer-bound thiouronium salt **2** was then collected and dried at 60°/high vacuum for 24 h. IR: 3040*s*, 2940*s*, 1643*s*, 1520*m*, 1500*m*, 1420*s*, 1325*w*, 1260*m*, 1215*w*, 1190*w*, 1125*w*, 1090*m*, 1050*m*, 1030*m*, 880*w*, 830*m*, 700*s*.

Polymer-Bound Pyrimidine-carboxylic Acids **4a–c**: *General Procedure.* During 5 min, 4.0 g (10.56 mmol) of resin **2** were swollen with 20 ml of dry DMF, and the solvent was removed. Then, 1.2 equiv. of the corresponding acetylenic ketone **3a–c** and 30 ml of dry DMF were added. To this suspension, a dry soln. of 1.5 equiv. of $(i\text{-Pr})_2$EtN

in dioxane (up to 10 ml) was added dropwise within 24 h *via* a syringe pump at r.t. with constant shaking. After additional vortexing for 24 h, the mixture was washed successively with DMF (3 × 50 ml), i-PrOH (3 × 50 ml), dioxane (3 × 50 ml), i-PrOH (3 × 50 ml), CH_2Cl_2 (3 × 50 ml), and pentane (3 × 50 ml). The resin was collected and dried at 40°/high vacuum for 12 h. The polymer-bound *tert*-butyl pyrimidinecarboxylate was then swollen in CH_2Cl_2 (20 ml) for 5 min, the solvent flushed, 50% CF_3COOH/CH_2Cl_2 (30 ml) slowly added at r.t., and the mixture shaken for 15 h. After removal of the reagents, the resin was washed successively with 50-ml portions of CH_2Cl_2 (4 ×), CH_2Cl_2/Et_3N 4:1 (3 ×), DMF (2 ×), i-PrOH (2 ×), and dioxane/2N HCl until pH 2 was reached, followed by washings with DMF (2 ×), i-PrOH (2 ×), and pentane (2 ×) and drying. IR (on bead; **4a**): 3030*w*, 2920*m*, 2860*m*, 1730*s* (C=O), 1570*s*, 1530*s*, 1500*m*, 1450*s*, 1425*w*, 1385*s*, 1290*w*, 1260*s*, 1240*s*, 1180*s*, 1120*s*, 1080*m*, 870*s*, 830*m*, 750*s*, 690*s*. IR (on bead; **4b**): 3040*w*, 2940*m*, 2870*m*, 1730*s* (C=O), 1605*s*, 1570*s*, 1535*s*, 1490*s*, 1385*m*, 1280*s*, 1200*m*, 1130*m*, 1020*s*, 940*m*, 895*m*, 880*m*, 800*m*, 750*s*, 700*s*, 685*s*. IR (on bead; **4c**): 3040*w*, 2930*m*, 2860*m*, 1725*s* (C=O), 1570*s*, 1525*s*, 1500*s*, 1445*s*, 1375*s*, 1280*m*, 1235*s*, 1185*m*, 1160*w*, 1120*s*, 1105*m*, 1080*w*, 1035*s*, 935*m*, 920*m*, 870*s*, 810*s*, 795*s*, 760*s*, 700*s*.

6-Aryl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxylic Acids **6a–c**: *General Procedure*. Polymer-bound pyrimidinecarboxylic acid **4a–c** was washed with CH_2Cl_2 (5 ml/mmol) and dry CH_2Cl_2 (3 ml/mmol), and 3-$ClC_6H_4CO_3H$ (3 equiv.) was added at r.t. The mixture was vortexed at r.t. for 15 h, washed successively with CH_2Cl_2 (3 ×), i-PrOH (3 ×), pentane (3 ×), CH_2Cl_2 (3 ×), and dioxane (2 ×) (10 ml/mmol of resin). Then dry dioxane (3 ml/mmol of resin) and 1.5 equiv. of pyrrolidine were added at r.t. The mixture was vortexed at r.t. for 6 h and then evaporated and the crude product analyzed by HPLC.

6-Phenyl-2-(pyrrolidin-2-yl)pyrimidine-4-carboxylic Acid (**6a**): ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.15–8.05 (*m*, 2 arom. H); 7.55–7.4 (*m*, 4 arom. H); 3.6–3.55 (*m*, 4 H); 2-0–1.85 (*m*, 4 aliph. H). MS: 268.2 ($[M - H]^-$).

6-(2-Furyl)-2-(pyrrolidin-1-yl)pyrimidine-4-carboxylic Acid (**6b**): ^{1}H-NMR (250 MHz, (D_6)DMSO): 7.88 (*s*, 1 arom. H); 7.25 (*s*, 1 arom. H); 7.25–7.2 (*m*, 1 arom. H); 6.75–6.65 (*m*, 1 arom. H); 3.55–3.5 (*m*, 4 H); 1.95–1.9 (*m*, 4 aliph. H). MS: 258.1 ($[M - H]^-$).

6-(Benzo[1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pyrimidine-4-carboxylic Acid (**6c**): ^{1}H-NMR (250 MHz, (D_6)DMSO): 13.4 (br. *s*, 1 H); 7.8–7.7 (*m*, 2 arom. H); 7.50 (*s*, 1 arom. H); 7.1–7.0 (*m*, 1 arom. H); 6.11 (*s*, 2 H); 3.7–3.5 (*m*, 4 H); 2.0–1.9 (*m*, 4 aliph. H). MS: 312.1 ($[M - H]^-$).

N-*(Carbamoylalkyl)-2-(pyrrolidin-1-yl)pyrimidine-3-carboxamides* **9a–e**: *General Procedure*. A mixture of 5 equiv. of primary amine R^1NH_2 and 5 equiv. of aldehyde R^2CHO in dry dioxane/MeOH 4:1 in the presence of molecular sieves (4 Å) was shaken at r.t. for 3 h. Then 5 equiv. of isonitrile R^3NC and 1 equiv. of the polymer-bound carboxylic acid **4a** were added. The mixture was vortexed at 55° for 48 h to give the polymer-bound pyrimidine **7a–e**. After removal of excess of reagents, the resin was successively washed (5 ml/mmol of resin) with dioxane (3 ×), DMF (3 ×), CH_2Cl_2 (3 ×), i-PrOH (3 ×), CH_2Cl_2 (3 ×), i-PrOH (3 ×), CH_2Cl_2 (3 ×), and pentane (2 ×) and dried. Resin-bound compound **7a–e** was swollen with CH_2Cl_2 (5 ml/mmol of resin) during 5 min and the solvent flushed, and CH_2Cl_2 (3 ml/mmol of resin) and 3 equiv. of 3-$ClC_6H_4CO_3H$ were added. The mixture was vortexed at r.t. for 15 h, then excess of reagents were flushed, and the resulting polymer-bound sulfone **8a–e** was successively washed with three cycles of CH_2Cl_2 (3 ×), i-PrOH (3 ×) (5 ml/mmol of resin), and pentane (2 ×) and dried. Resin-bound compound **8a–e** was then swollen in CH_2Cl_2 (5 ml/mmol of resin) during 5 min and the solvent flushed. Then, dioxane (3 ml/mmol of resin) and pyrrolidine (1 equiv.) were added. The mixture was vortexed at r.t. for 6 h and the crude mixture analyzed by HPLC. The solvent was evaporated, CH_2Cl_2 added, the soln. containing **9a–e** filtered through a small silica-gel cartridge, the filtrate evaporated, and the residue dried under high vacuum.

N-{*1-[(Cyclohexylamino)carbonyl]-3-methylbutyl*}-N-*(4-methoxyphenyl)-6-phenyl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxamide* (**9a**): ^{1}H-NMR (250 MHz, $CDCl_3$): 8.05–7.9 (*m*, 2 arom. H); 7.5–7.4 (*m*, 3 arom. H); 7.15–7.0 (*m*, 2 H); 6.88 (*s*, 1 H); 6.8–6.65 (*m*, 3 arom. H); 5.3–5.2 (*m*, 1 H); 3.95–3.8 (br. *m*, 1 H); 3.71 (*s*, 3 H); 3.6–3.35 (*m*, 4 H); 2.1–1.85 (*m*, 6 aliph. H); 1.85–1.5 (*m*, 6 H); 1.5–1.1 (*m*, 6 aliph. H); 1.0–0.8 (*m*, 6 H). MS: 570.5 ($[M - H]^+$).

N-*Cyclohexyl*-N-{*1-[(cyclohexylamino)carbonyl]-2-methylpropyl*}*-6-phenyl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxamide* (**9b**): ^{1}H-NMR (250 MHz, $CDCl_3$): 8.55–8.45 (br. *s*, NH); 8.25–8.15 (*m*, 2 arom. H); 7.5–7.3 (*m*, 3 arom. H); 7.05 (*s*, 1 H); 4.1–4.0 (*m*, 1 H); 3.8–3.7 (*m*, 6 H); 3.35–3.3 (*m*, 1 H); 3.25–3.15 (*m*, 1 H); 2.1–2.0 (*m*, 29 H). MS: 532.7 ($[M + 1]^+$)..

N-{*1-[(Cyclohexylamino)carbonyl]-2-methylpropyl*}*-6-phenyl-*N-*propyl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxamide* (**9c**): ^{1}H-NMR (250 MHz, $CDCl_3$; rotamer mixture; only data of major rotamer): 8.15–8.05 (*m*, 2 arom. H); 7.55–7.45 (*m*, 3 H); 7.2 (br. *s*, 1 H); 7.05 (*s*, 1 H); 4.1–4.0 (*m*, 1 H); 3.7–3.65 (*m*, 4 H); 2.45–2.3 (*m*, 1 H); 2.1–0.6 (*m*, 28 H). MS: 492.5 ($[M + 1]^+$).

N-*Benzyl*-N-{*1-[(butylamino)carbonyl]-2-methylpropyl*}-*6-phenyl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxamide* (**9d**): ^{1}H-NMR (250 MHz, $CDCl_3$; rotamer mixture; only data of major rotamer): 8.2–7.9 (*m*, 2 arom. H); 7.6–7.45 (*m*, 4 arom. H, NH); 7.3–7.15 (*m*, 5 arom. H); 4.9–4.85 (*m*, 1 H); 4.5–4.45 (*m*, 1 H); 4.2–4.1 (*m*, 1 H); 3.8–3.6 (*m*, 4 H); 3.05–2.95 (*m*, 2 H); 2.55–2.5 (*m*, 1 H); 2.1–1.95 (*m*, 4 aliph. H); 1.3–1.2 (*m*, 4 aliph. H); 0.9–0.65 (*m*, 9 aliph. H). MS: 514.5 ($[M + 1]^+$).

N-{*1-[(Cyclohexylamino)carbonyl]-2-methylpropyl*}-N-*(4-methoxyphenyl)-6-phenyl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxamide* (**9e**): ^{1}H-NMR (250 MHz, $CDCl_3$): 8.0–7.9 (*m*, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 7.2–7.1 (*m*, 2 arom. H); 6.9 (br. *d*, NH); 6.84 (*s*, 1 arom. H); 6.75–6.6 (*m*, 2 H); 4.5–4.4 (*m*, 1 H); 3.9–3.7 (*m*, 1 H); 3.69 (*s*, 3 H); 3.55–2.9 (*m*, 4 H); 2.6–2.4 (*m*, 1 H); 2.0–1.85 (*m*, 4 H); 1.85–1.5 (*m*, 4 aliph. H); 1.5–1.1 (*m*, 6 aliph. H); 1.1–0.9 (*m*, 6 H). MS: 556.5 ($[M + 1]^+$).

Cleavage of Polymer-Bound Sulfone **8a** *with Different Nucleophiles.* Resin-bound compound **8a** was suspended in CH_2Cl_2 (5 ml/mmol of resin) during 5 min and the solvent flushed. Dioxane or DMF (3 ml/mmol of resin) and the corresponding nucleophile were added. The mixture was vortexed at 65° for 5 h and then analyzed by HPLC. The solvent was evaporated, CH_2Cl_2 added, the soln. containing product **10–13** filtered through a small silica-gel cartridge, the soln. evaporated and the residue dried under high vacuum.

N-{*1-[(Cyclohexylamino)carbonyl]-3-methylbutyl*}-N-*(4-methoxyphenyl)-2-(4-methylpiperazin-1-yl)-6-phenylpyrimidine-4-carboxamide* (**10**): ^{1}H-NMR (250 MHz, $CDCl_3$): 8.0–7.9 (*m*, 2 arom. H); 7.5–7.4 (*m*, 3 H); 7.1–6.95 (*m*, 3 H); 6,75–6.6 (*m*, 2 arom. H, NH); 5.35–5.25 (*m*, 1 H); 3.95–3.75 (*m*, 1 H); 3.71 (*s*, 6 H); 2.45–2.25 (*m*, 8 H); 2.0–1.85 (*m*, 2 H); 1.8–1.55 (*m*, 5 H); 1.5–1.1 (*m*, 6 aliph. H); 1.0–0.8 (*m*, 6 aliph. H). MS: 556.5 ($[M + 1]^+$).

N-{*1-[(Cyclohexylamino)carbonyl]-3-methylbutyl*}-N-*(4-methoxyphenyl)-6-phenyl-2-[(pyridin-3-ylmethyl)-amino]pyrimidine-4-carboxamide* (**11**): ^{1}H-NMR (250 MHz, $CDCl_3$): 8.6–8.5 (*m*, 2 arom. H); 7.85–7.75 (*m*, 2 H); 7.5–7.45 (*m*, 1 H); 7.45–7.35 (*m*, 3 H); 7.3–7.25 (*m*, 1 H); 7.05–6.9 (*m*, 3 H); 6.7–6.6 (*m*, 3 H); 5.5–5.4 (*m*, 1 H); 5.3–5.2 (*m*, 1 H); 3.95–3.75 (*m*, 1 H); 3.70 (*s*, 3 H); 2.0–1.85 (*m*, 2 H); 1.8–1.5 (*m*, 4 H); 1.5–1.1 (*m*, 6 aliph. H); 1.0–0.8 (*m*, 6 H). MS: 607.4 ($[M + 1]^+$).

2-(Benzylamino)-N-{*1-[(cyclohexylamino)carbonyl]-3-methylbutyl*}-N-*(4-methoxyphenyl)-6-phenylpyrimidine-4-carboxamide* (**12**): ^{1}H-NMR (250 MHz, $CDCl_3$): 7.9–7.8 (*m*, 2 H); 7.5–7.35 (*m*, 3 H); 7.35–7.15 (*m*, 5 H); 7.05–6.9 (*m*, 3 H); 6.7–6.6 (*m*, 3 H); 5.45–5.35 (*m*, 1 H); 5.25 (*t*, 1 H); 4.55 (*s*, 2 H); 3.8–3.7 (*m*, 1 H); 3.69 (*s*, 3 H); 2.0–1.85 (*m*, 2 H); 1.8–1.5 (*m*, 4 H); 1.5–1.1 (*m*, 6 aliph. H); 1.0–0.8 (*m*, 6 aliph. H). MS: 606.4 ($[M + 1]^+$).

2-Azido-N-{*1-[(cyclohexylamino)carbonyl]-3-methylbutyl*}-N-*(4-methoxyphenyl)-6-phenylpyrimidine-4-carboxamide* (**13**): ^{1}H-NMR (250 MHz, $CDCl_3$): 8.05–7.95 (*m*, 2 H); 7.6–7.45 (*m*, 3 H); 7.41 (*s*, 1 H); 7.15–7.0 (*m*, 2 H); 6.75–6.65 (*m*, 2 H); 6.5–6.45 (*m*, 1 H); 5.25–5.15 (*m*, 1 H); 3.95–3.75 (*m*, 1 H); 3.72 (*s*, 3 H); 2.05–1.85 (*m*, 2 H); 1.85–1.55 (*m*, 5 aliph. H); 1.55–1.15 (*m*, 6 aliph. H); 1.0–0.8 (*m*, 6 aliph. H). MS: 542.4 ($[M + 1]^+$).

REFERENCES

[1] M. A. Gallop, R. W. Barret, W. J. Dower, S. P. A. Fodor, E. M. Gordon, *J. Med. Chem.* **1994,** *37,* 1233.
[2] E. M. Gordon, R. W. Barret, W. J. Dower, S. P. A. Fodor, M. A. Gallop, *J. Med. Chem.* **1994,** *37,* 1385.
[3] J. S. Früchtel, G. Jung, *Angew. Chem.* **1996,** *108,* 19.
[4] S. H. DeWitt, A. W. Czarnik, *Acc. Chem. Res.* **1996,** *29,* 114.
[5] C. G. Boojamra, K. M. Burow, J. A. Ellman, *J. Org. Chem.* **1995,** *60,* 5742.
[6] J. A. Ellman, *Acc. Chem. Res.* **1996,** *29,* 132.
[7] D. A. Goof, R. N. Zuckermann, *J. Org. Chem.* **1995,** *60,* 5744.
[8] S. H. DeWitt, J. S. Kiely, C. J. Stankovic, M. C. Schroeder, D. M. R. Cody, M. R. Pavia, *Proc. Natl. Acad. Sci. U.S.A.* **1993,** *90,* 6909.
[9] B. A. Dressman, L. A. Spangle, S. W. Kaldor, *Tetrahedron Lett.* **1996,** *37,* 937.
[10] C. Zhang, E. J. Moran, T. F. Woiwode, K. M. Short, A. M. M. Mjali, *Tetrahedron Lett.* **1996,** *37,* 751.
[11] S. Sarshar, D. Siev, A. M. M. Mjali, *Tetrahedron Lett.* **1996,** *37,* 835.
[12] A. M. Strocker, T. A. Keating, P. A. Tempest, R. W. Armstrong, *Tetrahedron Lett.* **1996,** *37,* 1149.
[13] M. M. Murphy, J. R. Schullek, E. M. Gordon, M. A. Gallop, *J. Am. Chem. Soc.* **1995,** *117,* 7029.
[14] A. L. Marzinik, E. R. Felder, *Tetrahedron Lett.* **1996,** *37,* 1003.
[15] M. F. Gordeev, D. Y. Patel, E. M. Gordon, *J. Org. Chem.* **1996,** *61,* 924.
[16] B. Ruhland, A. Bhandari, E. M. Gordon, M. A. Gallop, *J. Am. Chem. Soc.* **1996,** *118,* 253.
[17] P. Wipf, A. Cunningham, *Tetrahedron Lett.* **1995,** *36,* 7819.
[18] P. H. H. Hermkens, H. C. J. Ottenheijm, D. Rees, *Tetrahedron* **1996,** *52,* 4527.
[19] C. P. Holmes, J. P. Chinn, G. C. Look, E. M. Gordon, M. A. Gallop, *J. Org. Chem.* **1995,** *60,* 7328.

[20] D. W. Gordon, J. Steele, *Bioorg. Med. Chem. Lett.* **1995,** *5,* 47.
[21] R. Mohan, Y.-L. Chou, M. M. Morrisey, *Tetrahedron Lett.* **1996,** *37,* 3963.
[22] In 'Comprehensive Heterocyclic Chemistry', Eds. A. R. Katritzky and C. W. Rees, Pergamon Press, New York, 1984, Vol. 1, pp. 143–221.
[23] In 'Comprehensive Heterocyclic Chemistry', Eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, Vol. 3, pp. 57–155.
[24] D. Strekowski, R. A. Harden, R. A. Watson, *Synthesis* **1988,** 70.
[25] C. J. Shishoo, K. S. Jain, *J. Heterocycl. Chem.* **1992,** *29,* 883.
[26] D. Obrecht, *Helv. Chim. Acta* **1989,** *72,* 447.
[27] W.-D. Rudorf, R. Schwarz, *Tetrahedron Lett.* **1987,** *28,* 4267.
[28] W. Ried, E. König, *Liebigs Ann. Chem.* **1972,** *755,* 24.
[29] T. Masquelin, D. Obrecht, *Synthesis* **1995,** 276.
[30] B. Santiago, C. R. Dalton, E. W. Huber, J. M. Kane, *J. Org. Chem.* **1995,** *60,* 4947.
[31] A. Guzmán, M. Romero, F. Talamás, R. Villena, R. Greenhouse, J. M. Muchowski, *J. Org. Chem.* **1996,** *61,* 2470.
[32] R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996,** *29,* 123.
[33] I. Ugi, S. Lohberger, R. Karl, in 'Comprehensive Organic Synthesis', Eds. B. M. Trost and I. Fleming, Pergamon, New York, 1991, Vol. 2, pp. 1083–1109.
[34] I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994,** *18,* 115.
[35] G. W. Kenner, J. R. McDermott, R. C. Sheppard, *J. Chem. Soc., Chem. Commun.* **1971,** 636.
[36] D. Obrecht, U. Bohdal, C. Broger, D. Bur, P. Schönholzer, C. Spiegler, K. Müller, *Helv. Chim. Acta* **1995,** *78,* 563.
[37] B. Yan, *J. Org. Chem.* **1995,** *60,* 5736.