

Novel Solution- and Solid-Phase Syntheses of Heterocyclic Systems

Gaëlle Cabon, Berangere Gaucher, Aline Gegout, Sophie Heulle, and Thierry Masquelin*

Abstract: Heterocyclic compounds are an attractive source of screening library structures because they possess varied structural diversity and can exhibit potent biological activity. In this context, we present some of our new and versatile approaches to rapid and efficient syntheses of pharmacologically relevant core structures. These include: combination of both solution- and solid-phase processes in the synthesis of pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-ones and pyrazolo[1,5-*a*]-[1,3,5]-triazines; parallel, multi-generation synthesis of highly functionalized heterocyclic compounds in solution; a multi-step synthesis of 2,5-diketopiperazine on solid support taking advantage of a bicyclic β -lactam scaffold, and a combined solid- and solution-phase synthesis of a new class of 2,4-diaminothiazoles.

Keywords: Bicyclic β -lactam · Combined solution- and solid-phase processes · Heterocycles · Parallel multi-generation synthesis

1. Introduction

The dramatic developments in molecular biology and high-throughput screening over the past 30 years have intensified the demand for highly diverse libraries of low-molecular weight organic molecules. One way to meet this demand is through appropriate application of combinatorial chemistry. The term combinatorial chemistry implies: generation of a chemical library, a deconvolution strategy, and a linked high-throughput screening system. Four general approaches have been developed for the purpose of synthesis and evaluation of chemical libraries: (a) libraries derived from biological sources [1–3]; (b) a parallel synthetic approach using solution-phase or solid-phase methodologies or a combination of the two; (c) ‘split and mix’

synthesis; (d) affinity binding selection approach [1–3]. The original idea of combinatorial chemistry randomly synthesizing a plethora of compounds, often as mixtures, with the associated belief that solely high numbers could speed up the drug development process was a dream-like concept for many chemists. It took several years before scientists realized that it was not only the number of compounds but also their quality and diversity that was essential for proper progress in medicinal chemistry. The prevailing approach today is based on both solution- and solid-phase chemistry directed towards the synthesis of discrete, high-purity compounds. Combinatorial chemistry became a standard tool in medicinal chemistry. Nowadays, medicinal chemists recognize its power in delivering the targeted compounds in a much faster way, and in acceptable quantities and purities.

Initial-phase combinatorial chemistry is applied to discover lead compounds rapidly, which are then subjected to lead validation, followed by lead optimization to produce drug candidates. Since heterocyclic products are pharmacologically rich, possess varied structural diversity, and exhibit potent biological activity, they are an attractive source of library structures. In this context, one major focus of our activities is the development of new solution- and solid-phase access to a diverse array of low-molecular weight heterocyclic compounds.

We present below some of our new approaches to rapid and efficient syntheses of pharmacologically relevant core structures; combination of solution- and solid-phase processes in the synthesis of pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-ones and pyrazolo[1,5-*a*]-[1,3,5]-triazines; parallel multi-generation synthesis of highly functionalized heterocycles in solution; a multi-step synthesis of 2,5-diketopiperazine on a solid support taking advantage of a bicyclic β -lactam scaffold, and finally a combined solid- and solution-phase synthesis of a new class of 2,4-diaminothiazoles.

2. Pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-ones and Pyrazolo[1,5-*a*]-[1,3,5]-triazines

Pyrazoles and fused pyrazolo-heterocycles are common components of a large number of natural products and pharmacologically active molecules. Despite intense synthetic interest in these heterocyclic classes, and a number of unique approaches to satisfy the ever-growing need for new chemical entities with inherent pharmacological activity, there is still a need for new general procedures. Thus, in an extension of our studies towards the synthesis of versatile heterocycles on solid-supports, we have established a new general access to pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-ones and

*Correspondence: Dr. T. Masquelin
Combinatorial & Parallel Chemistry
Basilea Pharmaceutica Ltd
PO Box 3255
B75/052
Grenzacherstrasse 487
CH-4002 Basel
Tel.: +41 61 606 12 79
E-Mail: thierry.masquelin@basileapharma.com

pyrazolo[1,5-*a*]-[1,3,5]-triazines of types **8** and **11** (Scheme 1). The production of our libraries starts with key polymer-bound 3H-pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-one intermediates **4** synthesized as outlined in Scheme 1. Thus, condensation of pyrazoles **1** with ethoxycarbonyl isothiocyanate **2** in dry acetone at 65 °C, followed by treatment with sodium ethanolate (1N EtONa/EtOH) in EtOH at 65 °C gave 3H-pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-ones **4**, easily attached onto support, using commercially available Merrifield resin **3** (1.8 mmol/g) [5–7], in the presence of *N*-ethyl-diisopropylamine (DIPEA; 3 equiv.) in dry *N,N*-dimethylformamide (DMF) at 65 °C (the formation of the resin-bound compounds of type **4** was followed by ATR/FT-IR [8]). In this context, the solid-phase attachment is used to both purify the diverse 3H-pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-ones using a scavenging process, and introduce new points of diversity taking advantages of the sulfur-based safety catch linkage.

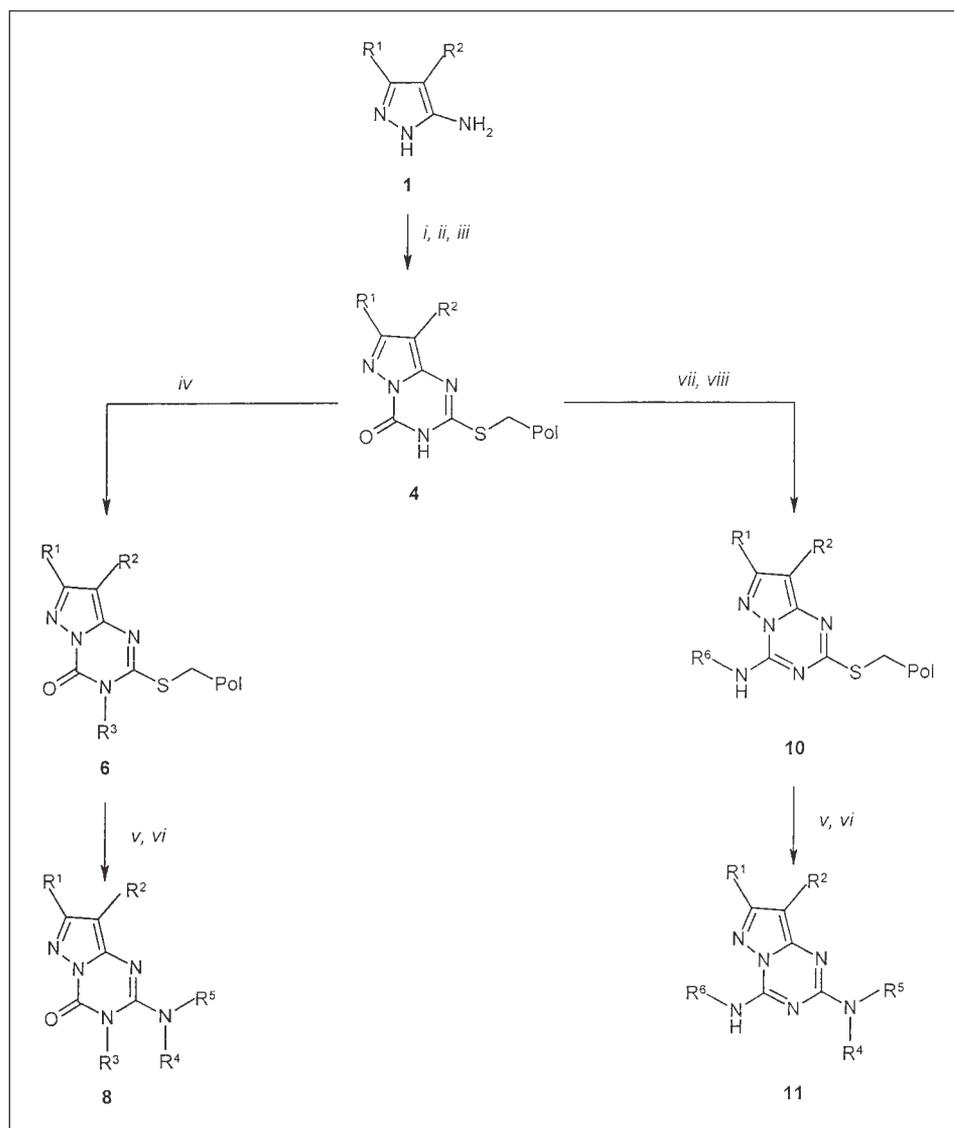
At this stage, we first investigated the reaction of the polymer-bound 3H-pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-ones **4** with alkyl-halides **5** in DMF at 85 °C, in the presence of 1-*tert*-butyl-4,4,4-tris-(dimethylamino)-2,2-bis-[tris-(dimethylamino)phosphoranylideneamino]-2λ⁵,4λ⁵-catenadi-(phosphazene) (phosphazene; 3.2 equiv.), followed by oxidation with 1.3 equiv. of *N*-(phenylsulfonyl)-3-phenyloxaziridine [9] and subsequent cleavage with various amines **7** in dioxane at 65 °C, leading to 2-amino-3-substituted-pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-ones of type **8** in good yields and high purities (Table 1).

Additionally, treatment of the polymer-bound 3H-pyrazolo[1,5-*a*]-[1,3,5]-triazin-4-ones **4** with phosphorous oxychloride (POCl₃) in toluene in the presence of DIPEA at 110 °C, afforded the corresponding 4-chloro intermediates, which underwent nucleophilic substitution with amines **9** to furnish 4-amino polymer-bound pyrazolo[1,5-*a*]-[1,3,5]-triazines **10**.

Finally, oxidation of **10** with 1.3 equiv. of *N*-(phenylsulfonyl)-3-phenyloxaziridine, followed by cleavage from the support with amines **7**, allow us to generate 2,4-diamino-pyrazolo[1,5-*a*]-[1,3,5]-triazines of type **11** in good yields and high purities (Table 2). The developed strategy appeared ideally suited for the parallel synthesis of a diverse array of low-molecular weight heterocyclic compounds on solid-phase.

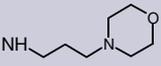
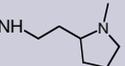
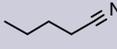
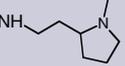
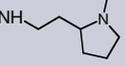
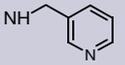
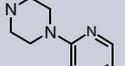
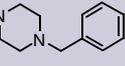
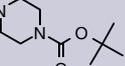
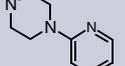
3. Parallel, Multi-generation Synthesis of Highly Functionalized Heterocycles in Solution

Among the several possible approaches to carry out successfully combinatorial organic synthesis, we also focused our attention on multi-component and multi-generation solution-phase approaches towards five-membered heterocycles and their conversion into fused heterocycles. The success of every combinatorial chemistry approach



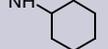
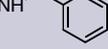
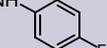
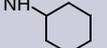
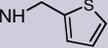
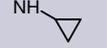
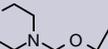
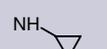
Scheme 1. Reagents and conditions: *i*) EtO₂C-NCS (**2**), acetone, rt-65 °C; *ii*) EtONa, EtOH, rt-65 °C; *iii*) Merrifield resin (**3**), DIPEA, DMF, rt-65 °C; *iv*) R³-X (**5**), phosphazene, DMF, rt-85 °C; *v*) CHCl₃, oxaziridine, rt; *vi*) R⁴R⁵-NH (**7**), diox., rt-65 °C; *vii*) POCl₃, DIPEA, tol., 110 °C; *viii*) R⁶-NH₂ (**9**), diox., rt-65 °C

Table 1. Preparation of pyrazolo[1,5a]-[1,3,5]-triazin-4-ones **8**.

R ¹	R ²	R ³	R ⁴ R ⁵ N-	Products	Yield ^a /Purity ^b [%]
	H	H		8a	45/76
	H			8b	53/95
	H			8c	66/82
	H			8d	84/96
	H	H		8e	80/97
	H	H		8f	72/99
H	Br	H		8g	67/99
H	Br	H		8h	81/92
H	CO ₂ Et	H		8i	87/94

^aYields in % are based on weight of crude material and are relative to the initial loading. ^bHPLC Purity of the purified material (confirmed by ¹H-NMR), measured on YMC-Pack Pro C18 column (75×4.6 mm) with a gradient 12% AcCN/H₂O → 95% AcCN within 5.4 min; flow rate, 2.64 ml/min; UV detection at 200–300 nm.

Table 2. Preparation of pyrazolo[1,5a]-[1,3,5]-triazines **11**.

R ¹	R ²	R ⁴ R ⁵ N-	R ⁶ NH-	Products	Yield ^a /Purity ^b [%]
	H		NH ₂	11a	75/96
	H		NH ₂	11b	80/99.5
Me-S	CN	NH ₂		11c	77/95
Me-S	CN	NH ₂		11d	83/99
Me	H			11e	67/92
Me	H			11f	67/94

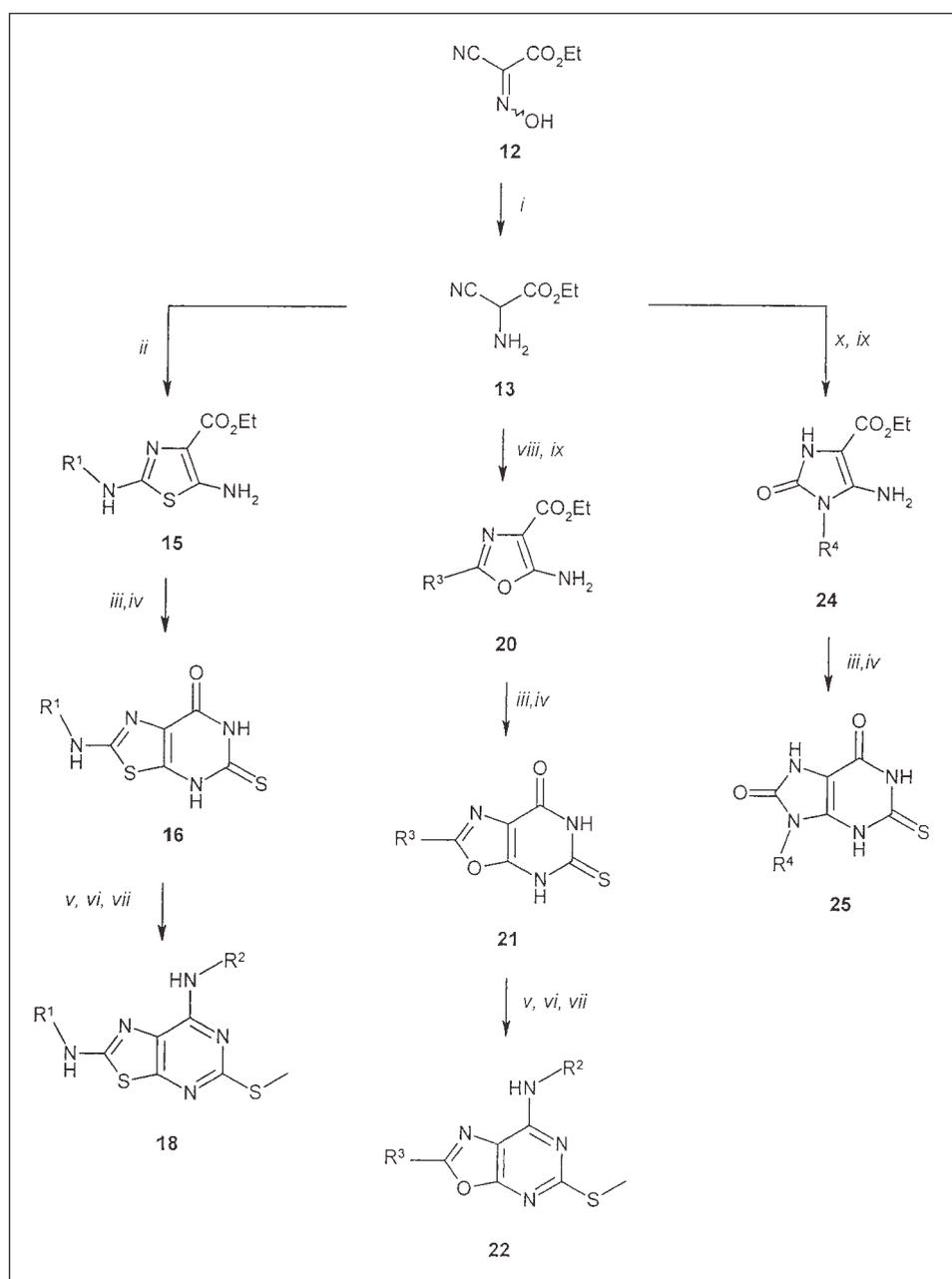
^aYields in % are based on weight of crude material and are relative to the initial loading. ^bHPLC Purity of the purified material (confirmed by ¹H-NMR), measured on YMC-Pack Pro C18 column (75×4.6 mm) with a gradient 12% AcCN/H₂O → 95% AcCN within 5.4 min; flow rate, 2.64 ml/min; UV detection at 200–300 nm.

is critically dependent on the availability of the necessary building blocks. As shown in Scheme 2, we selected ethyl-2-amino cyano acetate **13**, a multifunctional central building block, easily accessible by the reduction of ethyl cyano-(hydroxyimino) acetate **12** [10–12], to generate a palette of pharmacologically relevant core structures, such as thiazoles **15**, oxazoles **20** and imidazolones **24**, with additional elements of structural diversity.

Thus, we describe in Scheme 2 a rapid entry into a series of polyfunctionalized thiazoles **15**, easily obtained in pure form by simple precipitation, in good yields and purities (Table 3) starting from ethyl-2-amino cyano acetate **13** and isothiocyanates **14**. Subsequent condensation with ethoxycarbonyl-isothiocyanate **2** and treatment with sodium ethanolate in EtOH at 75 °C, led to the corresponding fused heterocycles of type **16** in pure form after acidification, precipitation and filtration of the suspension (Table 3). S-alkylation of **16** with MeI performed in acetone with Cs₂CO₃, followed by chlorination with POCl₃ in toluene in the presence of DIPEA at 110 °C, afforded the corresponding 4-chloro intermediates, which underwent nucleophilic substitution with amines **17** to furnish compounds of type **18** in pure form (Table 4). At this stage removal of solution-phase excess reactants, reagents, and byproducts is accomplished by incubation with CMR/R resins (Complementary Molecular Reactivity and Recognition resins: [13]) and filtration of the reaction mixture. The CMR/R library purification strategy is general and highly amenable to automation.

In order to explore in depth the potential of our building block **13** to generate highly functionalized heterocycles libraries, we studied the reaction of **13** with acyl chlorides of type **19** under standard conditions and subjected the corresponding amide to acid-catalyzed cyclization (Scheme 2), affording amino-oxazoles **20** in good overall yields and purities (Table 5). At this stage, applying the previously described process: condensation with ethoxycarbonyl-isothiocyanate **2**, and treatment with sodium ethanolate led to the corresponding fused heterocycles of type **21** (Table 5). Finally S-alkylation of **21**, followed by chlorination and nucleophilic substitution yielded compounds of type **22** in pure form, using the CMR/R library purification strategy (Table 4).

Additionally to demonstrate the versatility of our building block **13**, we condensed **13** with isocyanates **23**, and submitted the corresponding intermediates to an acid-catalyzed cyclization, allowing us to generate imidazolones of type **24**. Fused



Scheme 2. Reagents and conditions: *i*) $\text{Na}_2\text{S}_2\text{O}_4$, H_2O , rt; *ii*) $\text{R}^1\text{-NCS}$ (**14**) diox.; *iii*) $\text{EtO}_2\text{C-NCS}$ (**2**), acetone, rt–85 °C; *iv*) EtONa , EtOH , rt–75 °C; *v*) MeI , Cs_2CO_3 , acetone, rt; *vi*) POCl_3 , DIPEA, tol. , 110 °C; *vii*) $\text{R}^2\text{-NH}_2$ (**17**), diox., rt–95 °C; *viii*) $\text{R}^3\text{-COCl}$ (**19**), TEA, CH_2Cl_2 , rt; *ix*) HCl g, diox., rt; *x*) $\text{R}^4\text{-NCO}$ (**23**), diox., rt–65 °C

with amino acids **30** in DMF to yield the polymer-bound di-substituted pyrrolidines **31**. At this stage, deprotection of the pyrrolidine nitrogen carried out using tetrakis-(triphenylphosphine) palladium ($\text{Pd}(\text{PPh}_3)_4$) together with a borane dimethylamine complex ($\text{Me}_2\text{NH}\cdot\text{BH}_3$) [17] furnished the free amine intermediate, which underwent a base-catalyzed cyclization using tetramethyl guanidine (TMG) in DMF at 60 °C to afford the corresponding polymer-bound diketopiperazines of type **32**. The compounds could be easily cleaved off the resin under standard conditions to yield the final products **33** in good yields and high purities (Table 7).

Additionally a third vector of diversity was introduced onto **32**, by alkylation with alkyl halides **34** in the presence of phosphazene. The resulting diketopiperazines of type **35** are easily cleaved off the resin. This strategy allows for a rapid synthesis of libraries of diketopiperazines on solid-support and demonstrates the potential of the bicyclic β -lactam building block, which can also be used in many different ways for the construction of pyrrolidine libraries.

5. Combined Solid- and Solution-phase Synthesis of a New Class of 2,4-Diaminothiazoles and Fused Heterocycles

Solid-phase synthesis of small organic molecules has emerged as an important tool in drug discovery. Another example of a successful application of solid-phase chemistry constitutes the highly versatile synthesis of 2,4-diaminothiazoles, which is an important heterocyclic nucleus in medicinal chemistry. Our multigeneration strategy combines the cyclocondensation reaction

heterocycles **25** were generated applying the previously described modifications to **24** (Table 6). The described parallel solution multigeneration strategies combined with the CMR/R library purification method could be fully automated and performed on a robotic system.

4. A Multistep Synthesis of 2,5-Diketopiperazine on Solid-Support Taking Advantage of a Bicyclic β -Lactam Scaffold

Among the broad range of heterocyclic scaffolds representing lead structures for discovery of potential pharmacophores, we next focused our attention on a new solid-phase synthesis of diketopiperazine deriv-

atives. Present in the core of many natural products, diketopiperazine contributes interesting therapeutic properties [14]. Our solid-phase strategy is based on the use of the bicyclic β -lactam **27** as starting material, which allows the introduction of a large variety of building blocks, and contains different potential attachment points for solid-phase. In our approach the scaffold **27** was attached *via* the alcohol function to a Wang resin activated as trichloroacetamide **26** [15][16] to finally obtain the resin-bound bicyclic β -lactam **28** (Scheme 3). Therefore, the β -lactam nitrogen was acylated with acid-chlorides **29** in DMF in the presence of DIPEA (5 equiv.) and dimethylamino-pyridine (DMAP; 2 equiv.) allowing the introduction of the first diversity vector, followed by the opening of the intermediates

Table 3. Preparation of 2,5-diaminothiazole **15** and fused heterocycles **16**.

R ¹ -NCS	Products	Yield/Purity [%]	Products	Yield ^a /Purity ^b [%]
	15a	36/96	16a	56/99
	15b	63/92	16b	28/99
	15c	99/98	16c	53/99
	15d	85/97	16d	62/99
	15e	84/97	16e	55/99
	15f	70/97	16f	66/99

Table 4. Preparation of fused heterocycles **18** and **22**.

R ¹	R ³	R ² -NH ₂	Products	Yield ^a /Purity ^b [%]
			18a	44/98.5
			18b	52/99
			22a	47/93
			22b	58/98

Table 5. Preparation of 5-amino-oxazoles **20** and fused heterocycles **21**.

R ³ -COCl	Products	Yield/Purity [%]	Products	Yield ^a /Purity ^b [%]
	20a	76/99	21a	22/99
	20b	51/98	21b	38/99
	20c	71/80	21c	35/99
	20d	74/93	21d	42/99
	20e	36/96	21e	27/99

of a polymer-bound thiuronium salt **36** with isothiocyanates **37**, α -bromoketones **38** using a polymer-supported auto-scavenging (PSAS) purification strategy and a solution-phase intramolecular cyclization. Thus, when resin-bound thiuronium salt **36**, easily prepared by reaction of thiourea with commercially available Merrifield resin, was allowed to react with isothiocyanates **37** in DMF in the presence of DIPEA as well as N,N-diethylaminomethyl polystyrene resin, and followed by condensation with α -bromoketones **38**, the corresponding 2,4-diaminothiazoles **39** were formed in high yields and purities (Scheme 4; Table 8). At this stage to be able to perform the desired intramolecular annelation, deprotection of the Boc group was carried out efficiently by the use of Amberlyst A-15 resin. With the free amines **40** in hand, the intramolecular cyclization was performed with carbonyl diimidazole (CDI) in DMF in the presence of triethyl amine (Et₃N) to generate the final products **41** in moderate yields and high purities (Table 8). The synthesis of a small library of fused heterocycles as outlined in Scheme 4 was carried out successfully.

6. Conclusion

In conclusion, we have demonstrated the capability of combinatorial chemistry to produce rapidly and efficiently a diverse array of low-molecular weight heterocycle compounds using solution- and solid-phase strategies. The payoff of combinatorial chemistry to drug discovery is already becoming obvious in terms of significant increase in the number of lead candidates and time savings from lead candidate identification to validation.

For all Tables:

^aYields in % are based on weight of crude material and are relative to the initial loading.
^bHPLC Purity of the purified material (confirmed by ¹H-NMR), measured on YMC-Pack Pro C18 column (75×4.6 mm) with a gradient 12% AcCN/H₂O → 95% AcCN within 5.4 min; flow rate, 2.64 ml/min; UV detection at 200–300 nm.

Table 6. Preparation of imidazolones **24** and fused heterocycles **25**.

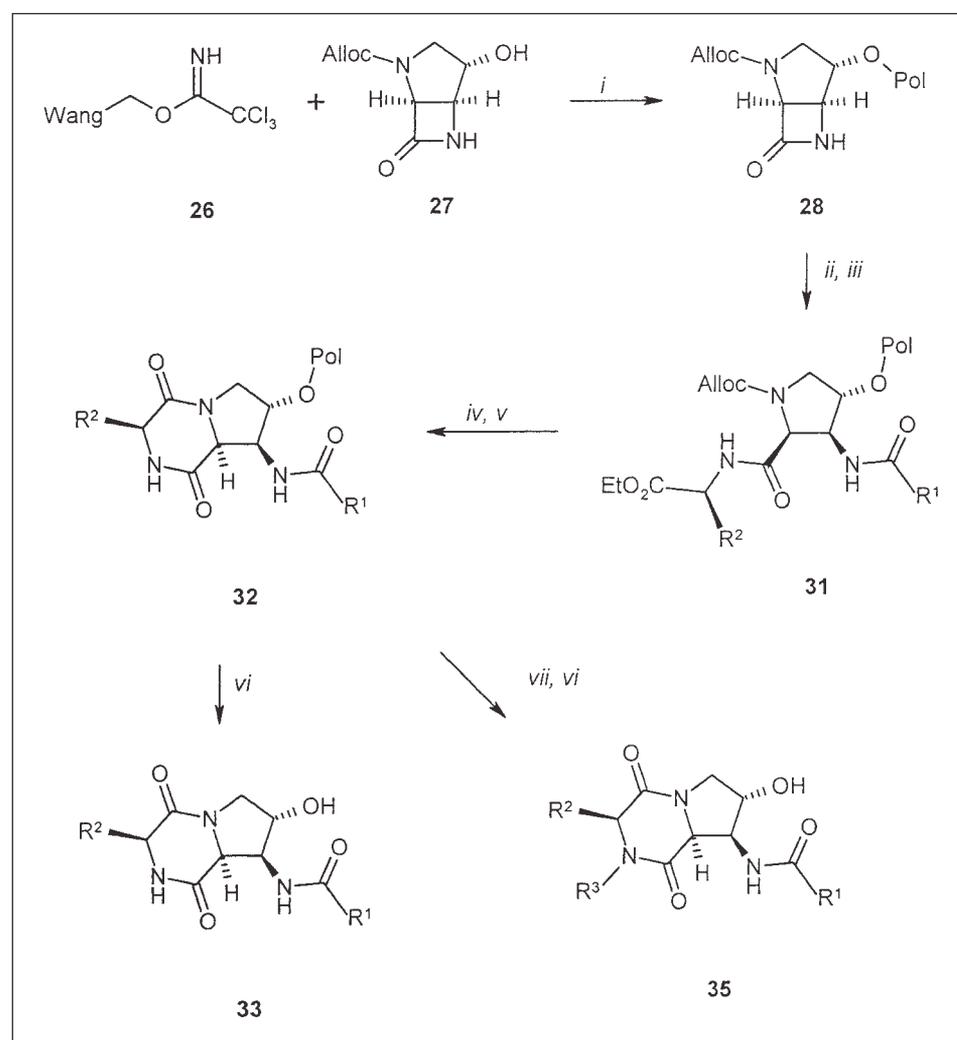
R ⁴ -NCO	Products	Yield/Purity [%]	Products	Yield ^a /Purity ^b [%]
	24a	97/99	25a	60/99
	24b	21/92	25b	48/99

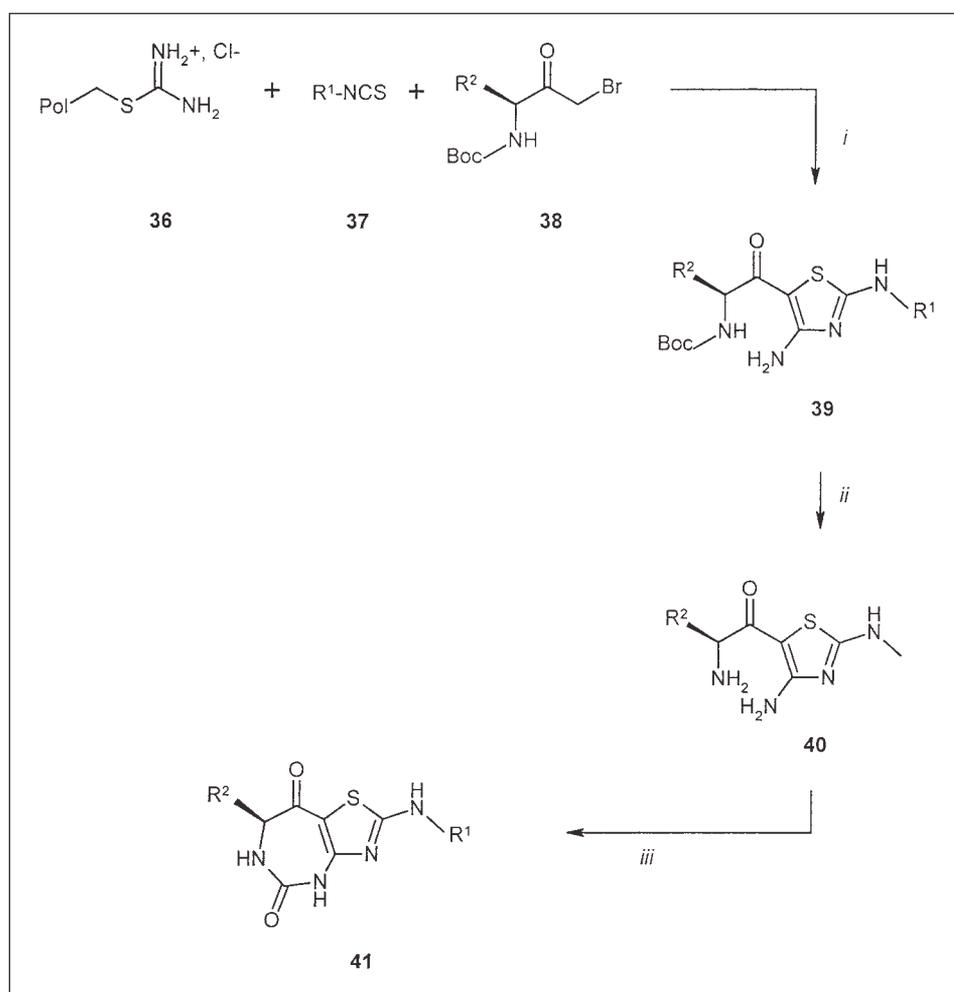
^aYields in % are based on weight of crude material and are relative to the initial loading. ^bHPLC Purity of the purified material (confirmed by ¹H-NMR), measured on YMC-Pack Pro C18 column (75×4.6 mm) with a gradient 12% AcCN/H₂O → 95% AcCN within 5.4 min; flow rate, 2.64 ml/min; UV detection at 200–300 nm.

Table 7. Preparation of diketopiperazines **33** and **35**.

R ¹	R ²	R ³	Products	Yield ^a /Purity ^b [%]
	H		33a	33/99
			33b	40/99.5
			33c	39/83
			33d	39/99
			35a	24/99.5
			35b	25/99
			35c	25/99.5
			35e	25/99.5

^aYields in % are based on weight of crude material and are relative to the initial loading. ^bHPLC Purity of the purified material (confirmed by ¹H-NMR), measured on YMC-Pack Pro C18 column (75×4.6 mm) with a gradient 12% AcCN/H₂O → 95% AcCN within 5.4 min; flow rate, 2.64 ml/min; UV detection at 200–300 nm.





Scheme 4. Reagents and conditions: *i*) a) **37**, DIPEA, DEAMP-resin, DMF, rt; b) **38**, DMF, rt; *ii*) Amberlyst A-15, CH₂Cl₂, rt; *iii*) CDI, Et₃N, DMF

Table 8. Preparation of 2,4-diaminothiazoles **39** and fused heterocycles **41**.

R ¹	R ²	Products	Yield ^a /Purity ^b [%]
		39a	94/96
		39b	98/93
	Me	39c	84/97
		39d	87/97
		41a	70/93
	Me	41b	58/77
		41c	44/99.5

^aYields in % are based on weight of crude material and are relative to the initial loading. ^bHPLC Purity of the purified material (confirmed by ¹H-NMR), measured on YMC-Pack Pro C18 column (75×4.6 mm) with a gradient 12% AcCN/H₂O → 95% AcCN within 5.4 min; flow rate, 2.64 ml/min; UV detection at 200–300 nm.

Acknowledgements

The authors would like to thank L. Bury and A. Gruschwitz for the purification of the libraries, Roche colleagues for analytical results, as well as Prof. M. Page, Dr. G. Schmid, and Dr. M. Roger-Evans for helpful discussions and proof-reading.

Received: March 25, 2003

- [1] J.K. Scott, G.P. Smith, *Science* **1990**, *249*, 386.
- [2] S.E. Cwirla, E.A. Peters, R.W. Barrett, W.J. Dower, *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 6378.
- [3] J.J. Devlin, L.C. Panganiban, P.E. Devlin, *Science* **1990**, *249*, 404.
- [4] Z. Xin, Z. Pei, T. von Geldem, M. Jirousek, *Tetrahedron Lett.* **2000**, *41*, 1147.
- [5] A. Chucholowski, T. Masquelin, D. Obrecht, J. Stadlwieser, J.M. Villalgorido, *Chimia* **1996**, *50*, 525.
- [6] T. Masquelin, D. Sprenger, R. Baer, F. Gerber, Y. Mercadal, *Helv. Chim. Acta* **1998**, *81*, 646.
- [7] D. Obrecht, C. Abrecht, F. Grieder, J.-M. Villalgorido, *Helv. Chim. Acta* **1997**, *80*, 65.
- [8] P. Griffiths, 'Chemical Analysis', John Wiley & Sons, New York, **1974**, Vol. 43.
- [9] F.A. Davis, O.D. Stringer, *J. Org. Chem.* **1982**, *47*, 1774.
- [10] H.-S. Ahn, A. Bercovici, G. Boykow, A. Bronnenkant, S. Chackalamannil, J. Chow, R. Cleven, J. Cook, M. Czarniecki, C. Domalski, A. Fawzi, M. Green, A. Gundes, G. Ho, M. Laudicina, N. Lindo, K. Ma, M. Manna, B. McKittrick, B. Mirzai, T. Nechuta, B. Neustadt, C. Puchalski, K. Pula, L. Silverman, E. Smith, A. Stamford, R.P. Tedesco, H. Tsai, D. Tulshian, H. Vaccaro, R.W. Watkins, X. Weng, J.T. Witkowski, Y. Xia, H. Zhang, *J. Med. Chem.* **1997**, *40*, 2196.
- [11] J.C. Caille, S. Didierlaurent, D. Lefrancois, M.H. Lelievre, C. Sury, J. Aszodi, *Synthesis* **1995**, *6*, 635.
- [12] H.R. Snyder, L. Katz, *J. Am. Chem. Soc.* **1947**, *69*, 3140.
- [13] D.L. Flynn, J.Z. Crich, R.V. Devraj, S.L. Hockerman, J.J. Parlow, M.S. South, S. Woodard, *J. Am. Chem. Soc.* **1997**, *119*, 4874.
- [14] A. Bianco, J. Furrer, D. Limal, G. Guichard, K. Elbayed, J. Raya, M. Piotta, J.-P. Briand, *J. Comb. Chem.* **2000**, *2*, 681.
- [15] S. Hanessian, F. Xie, *Tetrahedron. Lett.* **1998**, *39*, 736; S. Hanessian, F. Xie, *Tetrahedron. Lett.* **1998**, *39*, 737.
- [16] M. Steger, C. Hubschwerlen, G. Schmid, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2537.
- [17] P. Gomez-Martinez, M. Dessolin, F. Guibé, F. Albericio, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2871.