Efficient Synthesis Of Arrays Of Amino Acid Derived Ugi Products With Subsequent Amidation

Wei Wang and Alexander Dömling*

University of Pittsburgh, Drug Discovery Institute, Pittsburgh, PA 15261

Several amino acid derived iminodicarboxylicacid monomethylesters have been converted into a small array of amide derivatives. Sequentially, we were using an Ugi reaction of α-amino acids, followed by a mild and efficient amidation. Thus we added to this well-known Ugi scaffold another dimension of diversity, thereby enhancing it is potentially use in the combinatorial and medicinal chemistry of multi component reactions (MCRs) and drug discovery. Synthesis of an exemplary array and pharmacophore features are discussed.

Introduction

Isocyanide-based multicomponent reactions (IMCRs) are among the most proliferative reaction classes of use in combinatorial chemistry.[1] This can be attributed to the commercial availability of many different starting materials thus leading to a potentially very large chemical space; in addition many basic IMCRs are known based on different reaction type, for example, Ugi,[2] Passerini,[3] van Leusen,[4] and Orru,[5] or based on different variation. For example, in the Ugi reaction the primary scaffold is mostly dictated by the type of acid component: for example, carboxylic acid, carbonic acid, thiocarboxylic acids,[6] HN_3, H_2O, H_2S, HNCO, HNCS, and phenol,[7] leading to α-aminoacylcarbonamides, carbamates, α-aminoacylthiocarbonamides tetrazoles, α-aminoamides, α-aminothioamides, hydantoines, thiohydantoines, and α-aminoarylamides, respectively.[8] On a second level, the scaffold diversity can be greatly enhanced by the introduction of orthogonal functional groups into the primary IMCR product and reacting it in subsequent transformations, for example, ring forming reactions. This two layered strategy has been extremely fruitful leading to a great manifold of scaffold now routinely used in combinatorial and medicinal chemistry for drug discovery proposes (Chart 1). Among recent scaffolds obtained by this two layered strategies are 3,4-dihydroquinoxalin-2-amines,[9] hexahydro-1*H*-isoindolones,[10] 1,4-substituted 1,2,3-triazoles,[11] tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide,[12] 4*H*-furo[3,4-b]pyrans,[13] 2-aminospiro(3′,4-(4*H*)-pyrans,[14] 5-aminothiazoles,[15] spiroquinolines,[16] cyanophenylamino-acetamide derivatives,[17] indolobenzazepinones,[18] pyrido[2,1-*a*]isoindoles,[19] 3-substituted isoindolinones,[20] or diketopiperazines leading to a potent, selective, and orally bioavailable oxytocin antagonist currently undergoing advanced clinical trial.[21]

Ugi very early recognized the use of bifunctional starting materials containing two of the four required functional groups undergoing intramolecular U-MCR and leading to cyclic products; for example, unprotected β-amino acids lead to β-lactams and ketocarboxylic acids result in cyclic lactams of different ring size.[18,22] α-Amino acids however react differently.[23] A key hallmark of Ugi MCRs is the formation of the α-adduct, comprising the addition of the acid anion onto the intermediate nitrilium ion. In the case of α-aminoacids, this leads to a 6-membered cyclic α-adduct intermediate. Transannular acylation is thermodynamically not possible because this would lead to a very strained α-lactam. Therefore other nucleophiles present will be acylated. If nucleophiles are presented in a side chain of a starting material this can lead to cyclic products. If however no nucleophilic side chain is available the usual solvent for Ugi reactions methanol acts as nucleophile and the product is an iminodicarboxylic acid monomethylester. If both reaction pathways are possible because of the presence of nucleophilic side chains and a nucleophilic solvent the reaction can be performed selectively by choosing appropriate non-nucleophilic, however protic solvents, for example, trifluoroethanol.[25,26,28–30] This reaction has been also termed U-5C-4CR for Ugi five-center (five participating functional groups) four-component reaction.[24] Several different useful scaffold types

Chart 1. Scaffold Diversity in Multicomponent Reactions Can Be Derived from Primary MCRs (Upper Layer) or from Secondary Transformations Based on Bifunctional Starting Materials (Bottom Layer)
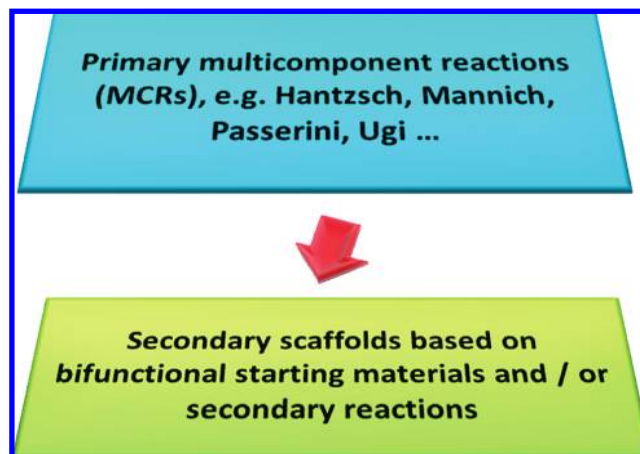

* To whom correspondence should be addressed. E-mail: asd30@pitt.edu.

Scheme 1. Scaffold Diversity of the IMCR of α-Aminoacids, Oxo-Components and Isocyanides
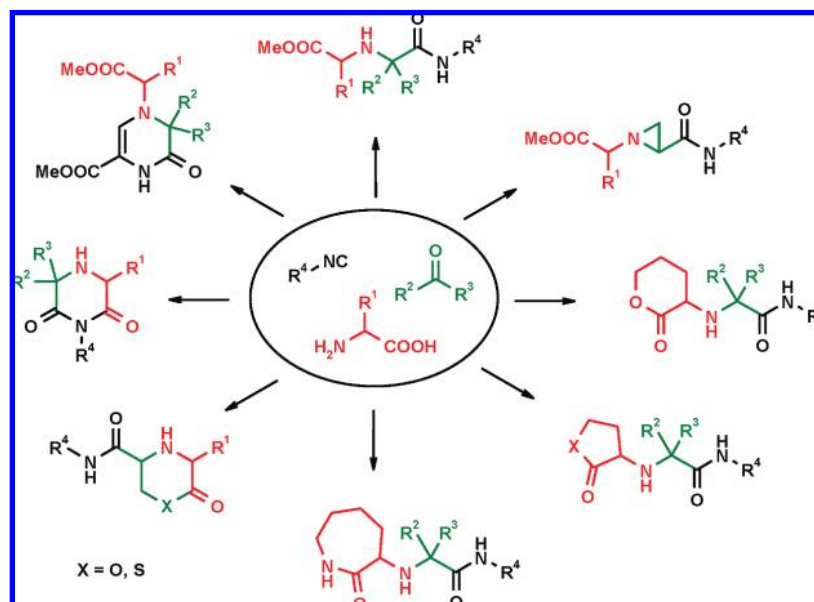
Scheme 2
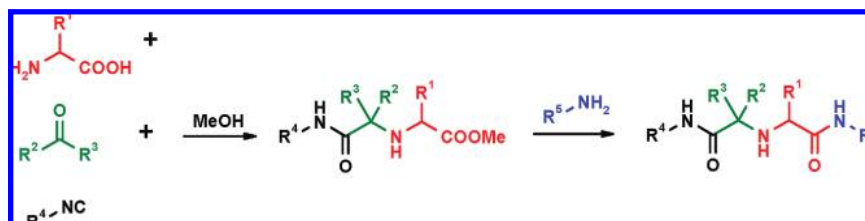
are thus amenable by the U-5C-4CR, including aziridines,[22] δ-lactames,[25] γ-lactames,[26] diketopiperazines,[27] 2-ketomorpholines,[28] γ-thiolactones,[29] 2-ketothiomorpholines,[30] and piperazineones (Scheme 1).[31]

The formation of a methylester during the U-5C-4CR is common and often inevitable because it is part of the starting material. Methylesters might serve as prodrugs for the corresponding carboxylic acid, however, often are not wanted in the specific molecular context. Therefore, and as a continuation of our search for new dimensions for IMCRs, we present here the one-pot postmodification of the methylester of U-5C-4CR scaffolds to form amides.[32]
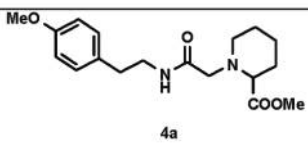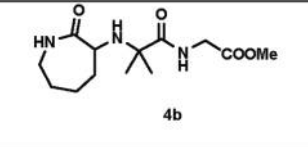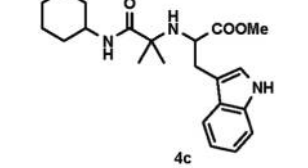
The amidation of an ester bond normally constitutes a several step sequence, involving esterfication, activation, and amidation, which is not particular suitable for automated chemistry. Several step functional group transformations should be avoided in liquid phase combinatorial chemistry because of the often different reaction conditions and the need to change solvent/reagents. Moreover, often several purification steps are involved. In addition, they often result in reduced overall yields. Alternatively, several one-pot procedures converting an ester directly in one step into their amide have been described. Recent methods include use of lipases,[33] AlMe₃,[34] Hünig's base,[35] refluxing conditions,[36] sulfuric acid,[37] Zn(CF₃CO₂)₂,[38] and Mg(ClO₄)₂.[39] Many of this methods have drastic conditions (Brønsted or Lewis acids, high dilution, high temperature) in common, which are often not compatible with labile compounds and with many functional groups. In addition one-pot amidations only yield products at mild temperatures and conditions, if one

Scheme 3
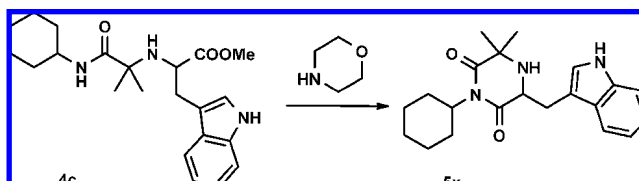
of the reactants is volatile and can be used in excess, for example, MeNH₂ or AcOEt.[40] In continuation of our search for reactions compatible with parallel chemistry that leads to high diversity of given scaffolds, we investigated conditions for the one-pot conversion of the methylester in the U-5C-4CR scaffold. For exampyl, recently, we described a one-pot amidation of amino acid derived isocyanoaceticacid methylesters under solventless conditions and ambient temperature.[41] Instrumental in our search for mild and efficient amidations was a recent paper of Mioskowski et al. who used the organocatalyst 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), together with primary and secondary amines, under solvent-free conditions.[42] To test if these conditions will work for our transformation, we synthesized **4a** from homoproline, formaldehyde and 4-methoxyphenyl ethylisocyanide in 20% yield (Scheme 3). For the U-5C-4CR, the influence of the bulkiness for the diastereoselectivity has been investigated in detail.[43] Not surprisingly, very high diastereoselectivities can be obtained in this IMCR while using bulky aldehydes. Therefore to avoid the formation of generally separable diastereomeric mixture we choose in this study symmetrical

Table 1
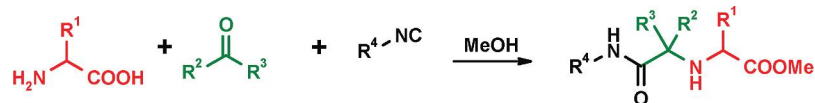
entry	α-amino acid	oxo component	isocyanide	product	yield
1	Pipecolinic acid	formaldehyde	4-methoxyphenyl ethylisocyanide	**4a**	20%
2	Lys	acetone	Isocyanoaceticacid methylester	**4b**	77%
3	Tyr	acetone	Cyclohexyl isocyanide	**4c**	20% (80% based on conversion)

aldehyde or ketone components. The methylester of **4a** was used to find optimal conditions for the direct amidation.

We found, that the original conditions of Mioskowsky et al. could not in all cases be transferred to our reactions. In fact, optimization with many different types of primary amines resulted in two general reaction conditions that were suitable

to convert several amines and U-5C-4CR products into their amidation products: solventless conditions (original protocol, A) or THF as a solvent (condition B). Thus we prepared three representative chiral U-5C-4CR on a 5 mmol scale (Table 1). These compounds served as staring materials for the diversification via amidation and an array of 3 × 8 = 24 compounds was

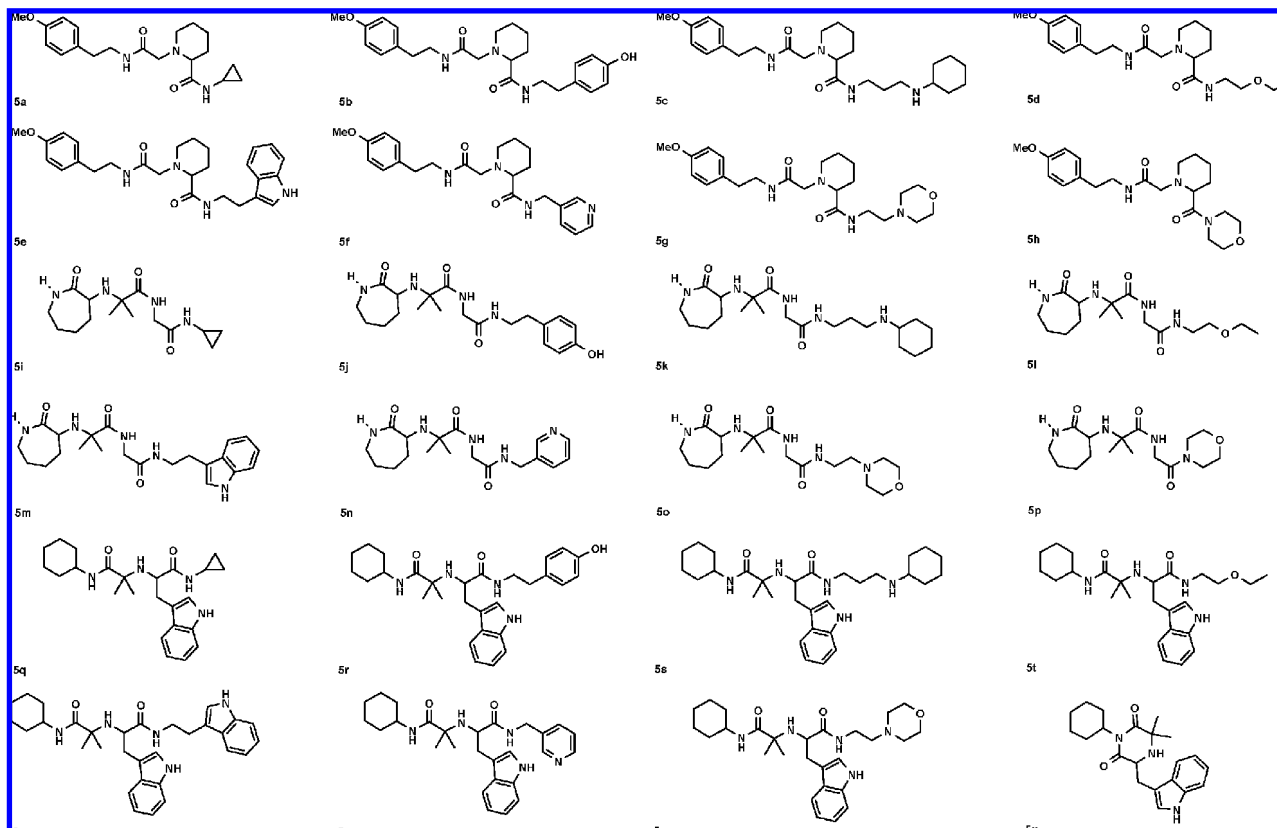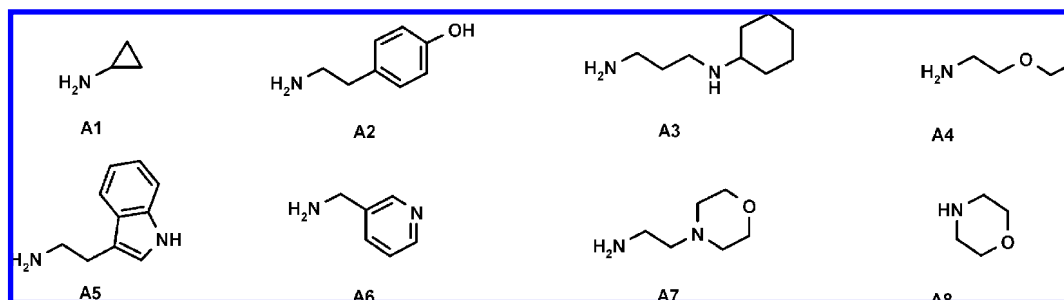**Figure 1.** Structures of products **5a−x**.

Table 2

entry	educt	amine	product	yield	condition
1	**4a**	**A1**	**5a**	54%	A
2		**A2**	**5b**	82%	A
3		**A3**	**5c**	20%	A
4		**A4**	**5d**	72%	A
5		**A5**	**5e**	66%	B
6		**A6**	**5f**	71%	A
7		**A7**	**5g**	52%	A
8		**A8**	**5h**	15%	A
9	**4b**	**A1**	**5i**	20%	A
10		**A2**	**5j**	53%	A
11		**A3**	**5k**	24%	A
12		**A4**	**5l**	35%	A
13		**A5**	**5m**	80%	B
14		**A6**	**5n**	33%	A
15		**A7**	**5o**	45%	A
16		**A8**	**5p**	36%	A
17	**4c**	**A1**	**5q**	30%	B
18		**A2**	**5r**	20%	B
19		**A3**	**5s**	20%	B
20		**A4**	**5t**	54%	B
21		**A5**	**5u**	56%	B
22		**A6**	**5v**	24%	B
23		**A7**	**5w**	20%	B
24		**A8**	**5x**	23%	B

prepared (Table 2, Figure 1). To scope the reaction, we choose several very different amines, including aliphatic, heterocyclic, aromatic, and functionalized **A1**−**A8**.

The yields under these conditions are low to moderate to high, ranging from 15 to 82%; however, all amines reacted under the selected two standard conditions and the desired product could be isolated by preparative TLC. All compounds were isolated and characterized by NMR HPLC-MS and HRMS (see Supporting Information). We made several noteworthy observations. A major side product of the reaction was the hydrolysis of the methylester due to traces of water in THF. For example, running model reaction **5v** under dry conditions could enhance the yields from 17.5% to 56%. When using a secondary amine (morpholine) together with **4a** and **4b**, we could isolate the expected morpholino amide. However, morpholine reaction with **4c**, proceeded into the formation of the 1,6-diketopiperazine (DKP) product without amide product formation (Scheme 3).

In addition, we observed the appearance of different conformers as seen in CDCl₃ in NMR in the case of the tryptophane derivatives **5q**−**5w**. We reasoned that these conformers are due to different isomeric intramolecular hydrogen bonds. Indeed changing the NMR solvent to MeOH-d_6, which has a high propensity to destroy intramolecular hydrogen bonds showed only one conformer.

This finding is of interest because it implies preferred conformation for this substance class, which is of importance for receptor binding. The cyclic Ugi products derived from pipecolinic acid and lysine; however because of steric reasons, they cannot form intramolecular hydrogen bonds. To support our hypothesis, we performed modeling studies and found two low-energy conformers characterized by two isomeric hydrogen bond induced rings (Figure 2).

The U-5C-4CR is a very versatile reaction allowing for the synthesis of large arrays of interesting compounds in a stereoselective manner. The variations that can be introduced are the oxo component, the isocyanide and the α-aminoacid. The general pharmacophore of the above-described backbone is presented in Table 3. It is composed of two secondary amide groups and a secondary amine if primary α-amino acids are used; for cyclic α-amino acids, for example, proline or homoproline, it comprises two secondary amide groups and a tertiary amine. Solubility is one of the most important properties in drug discovery, and accounts for oral bioavailabilty, absorption, concentration at the target site, excretion, and many more. We presumed the amine functionality in the above scaffold should render the compounds quite water soluble. To exemplify this, we measured the water solubility at pH 7.4 of one compound, and we were pleased to find very good solubility. The measured water solubility of **5j** at 37 °C are 14 and 56
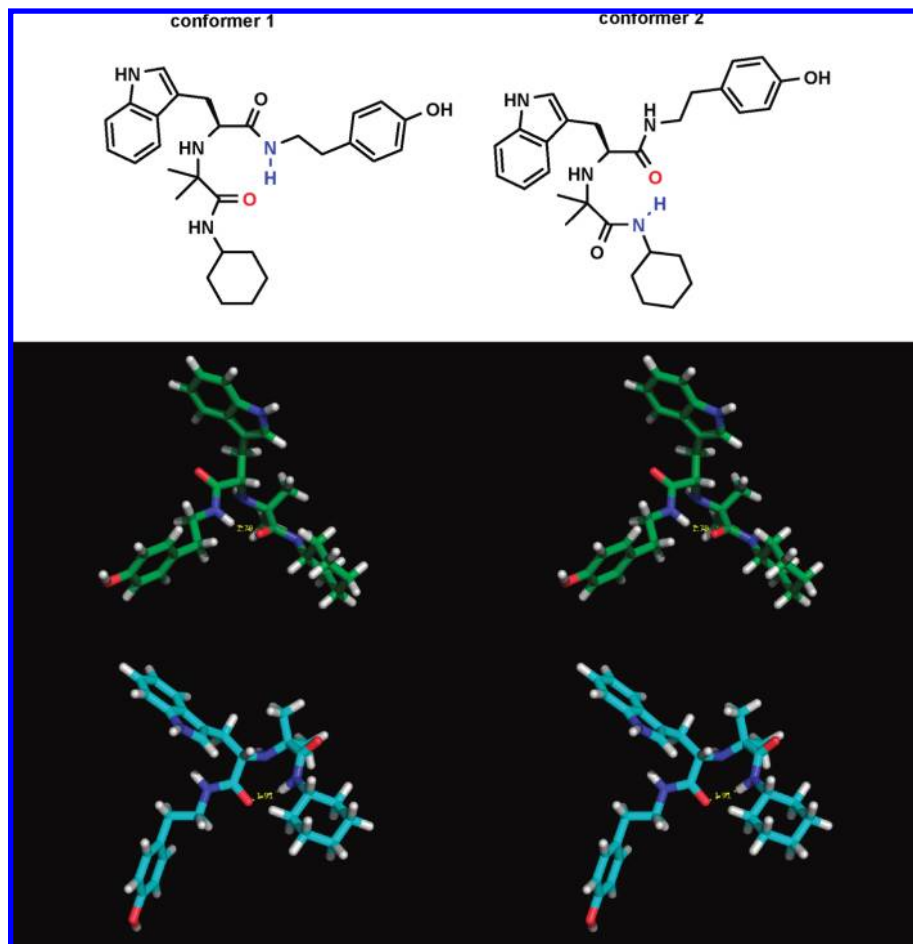
Figure 2. Two low-energy conformers for **5r** have been calculated using MOLOC.[44] Top left: 2D representation of the two proposed conformers with hydrogen bond donors (NH, OH) and acceptors (O) marked in red and blue. Bottom: Stereo picture of the two conformers. Both conformers exhibit an 8-membered ring including short intramolecular hydrogen bond contacts, 1.8 and 1.9 Å, respectively. The picture was rendered using PyMol.

Table 3. Several Calculated (ChemAxon* and Molinspiration** Software) and Measured Properties of **5j**

N-{[2-(4-Hydroxy-phenyl)-ethylcarbamoyl]-methyl}-2-methyl-2-(2-oxo-azepan-3-ylamino)- propionamide **5j** O=C1NCCCCC1NC(C)(C)C(NCC(NCCC2=CC=C(O)C=C2)=O)=O		
	M_W $C_{20}H_{30}N_4O_4$ 390.48	logP: 0.68*; miLogP: 0.947**
	Pfizer rules √*	rotbond 8[2]
	TPSA 119.5**[1]	volume 371.8*
	HBD 5	
	HBA 5	
	Measured solubility (pH 7.4; g/L): 14 and 56 (HCl salt)	
	ALOGpS -3.72 (75.03 mg/l)[45]	

[1] PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and blood-brain barrier penetration. [2] It has been shown to be a very good descriptor of oral bioavailability of drugs.

mg/mL for the free base and the HCl salt, respectively. Based on commonly accepted descriptors the majority of compounds based on this scaffold is "drug-like" (Table 3).

In conclusion, we described a one-pot amidation post-modification of the U-5C-4CR backbone. The reaction is generally displaying moderate to high yields and several

different types of amines react smoothly, including, aromatic, heterocyclic, aliphatic and functionalized. Twenty-four examples have been explicitly described. The resulting products display drug-like properties and will be of use in combinatorial and medicinal chemistry.

Supporting Information Available. Experimental methods; solubility measurements, LC-MS of the products, and NMR data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Weber, L. *Curr. Opin. Chem. Biol.* **2000**, *4*, 295–302. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467–473. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (d) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (e) Mihovilovic; Marko, D.; Stanetty, P. *Angew. Chem. Int. Ed* **2007**, *46*, 3612–3615. (f) Mironov, M. A. *QSAR Comb. Sci.* **2006**, *25*, 423–431. (g) Diego, J.; Ramón, M. Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634. (h) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, *495*, 7–4980. (i) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499. (j) Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630–645. (k) Zhu, J. *Eur. J. Org. Chem.* **2003**, *113*, 3–1144. (l) Hulme, C.; Lee, Y.-S. *Mol. Divers.* **2008**, *12*, 1–15.

(2) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.

(3) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.

(4) Van Leusen, D.; Van Leusen, A. M. *Org. React. (N.Y.)* **2003**, *57*, 419.

(5) (a) Bon, R. S.; Sprenkels, N. E.; Koningstein, M. M.; Schmitz, R. F.; de Kanter, F. J. J.; Domling, A.; Groen, M. B.; Orru, R. V. A. *Org. Biomol. Chem.* **2008**, *6*, 130–137. (b) Bon, R. S.; van Vliet, B.; Sprenkels, N. E.; Schmitz, R. F.; de Kanter, F. J. J.; Stevens, C. V.; Swart, M.; Bickelhaupt, F. M.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2005**, *70*, 3542–3553. (c) Elders, N.; Schmitz, R. F.; de Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 6135–6142. (d) Bon, R. S.; Sprenkels, N. E.; Koningstein, M. M.; Schmitz, R. F.; de Kanter, F. J. J.; Domling, A.; Groen, M. B.; Orru, R. V. A. *Org. Biomol. Chem.* **2008**, *6*, 130–137.

(6) Heck, S.; Dömling, A. *Synlett* **2000**, 424–426.

(7) EI Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7961–7964.

(8) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267–268.

(9) Shaabani, A.; Maleki, A.; Mofakham, H.; Khavasi, H. R. *J. Comb. Chem.* **2008**, *10*, 323–326.

(10) Zhang, L.; Lushington, G. H.; Neuenswander, B.; Hershberger, J. C.; Malinakova, H. C. *J. Comb. Chem.* **2008**, *10*, 285–302.

(11) Rodriìguez-Borges, J. E.; Goncalves, S.; do Vale, M. L.; Garciìa-Mera, X.; Coelho, A.; Sotelo, E. *J. Comb. Chem.* **2008**, *10*, 372–375.

(12) Shaabani, A.; Maleki, A.; Mofakham, H. *J. Comb. Chem.* **2008**, *10*, 595–598.

(13) Shaabani, A.; Soleimani, E.; Sarvary, A.; Rezayan, A. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3968–3970.

(14) Litvinov, Y. M.; Mortikov, V. Y.; Shestopalov, A. M. *J. Comb. Chem.* **2008**, *10*, 741–745.

(15) Thompson, M. J.; Chen, B. *Tetrahedron Lett.* **2008**, *49*, 5324–5327.

(16) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7044–7047.

(17) Shaabani, A.; Maleki, A.; Mofakham, H.; Khavasi, H. R. *J. Comb. Chem.* **2008**, *10*, 883–885.

(18) Beaumont, S.; Retailleau, P.; Dauban, P.; Dodd, R. H. *Eur. J. Org. Chem.* **2008**, *2008*, 5162–5175.

(19) Huang, X.; Zhang, T. *Tetrahedron Lett.* **2009**, *50*, 208–211.

(20) Wan, J.-P.; Zhou, J.; Mao, H.; Pan, Y.-J.; Wu, A.-X. *Tetrahedron* **2008**, *64*, 11115–11123.

(21) Borthwick, A. D.; Davies, D. E.; Exall, A. M.; Hatley, R. J. D.; Hughes, J. A.; Irving, W. R.; Livermore, D. G.; Sollis, S. L.; Nerozzi, F.; Valko, K. L.; Allen, M. J.; Perren, M.; Shabbir, S. S.; Woollard, P. M.; Price, M. A. *J. Med. Chem.* **2006**, *49*, 4159–4170.

(22) (a) Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1997**, *38*, 359–362. (b) Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591–5594. (c) Zhang, J.; Jacobson, A.; Rusche, J. R.; Herlihy, W. *J. Org. Chem.* **1999**, *64*, 1074–1076. (d) Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725–2728. (e) Pirrung, M. C.; Sarma, K. D. *Synlett* **2004**, 1425–1427.

(23) Demharter, A.; Hörl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 173–175.

(24) Ugi, I.; Demharter, A.; Hörl, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657–11664.

(25) Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Kim, Y.; Lee, D. H. *Tetrahedron Lett.* **1998**, *39*, 7109–7112.

(26) Kim, Y. B.; Park, S. J.; Keum, G.; Jang, M. S.; Kang, S. B.; Lee, D. H.; Kim, Y. *Bull. Korean Chem. Soc.* **2002**, *23*, 1277–1284.

(27) Sollis, S. L. *J. Org. Chem.* **2005**, *70*, 4735–4740.

(28) (a) Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. *Org. Lett.* **2001**, *3*, 4149–4152. (b) Ku, I. W.; Cho, S.; Doddareddy, M. R.; Jang, M. S.; Keum, G.; Lee, J.-H.; Chung, B. Y.; Kim, Y.; Rhim, H.; Kang, S. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5244–5248.

(29) (a) Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. *Org. Lett.* **2001**, *3*, 4149–4152. (b) Ku, I. W.; Cho, S.; Doddareddy, M. R.; Jang, M. S.; Keum, G.; Lee, J.-H.; Chung, B. Y.; Kim, Y.; Rhim, H.; Kang, S. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5244–5248.

(30) Srivastava, S.; Beck, B.; Herdtweck, E.; Khoury, K.; Dömling, A. *Heterocycles* **2009**, *77*, 731–738.

(31) Illgen, K.; Nerdinger, S.; Fuchs, T.; Friedrich, C.; Weber, L.; Herdtweck, E. *Synlett* **2004**, 53–56.

(32) (a) Dömling, A.; Achatz, S.; Beck, B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5483–5486. (b) Dömling, A.; Beck, B.; Baumbach, W.; Larbig, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 379–384. (c) Beck, B.; Leppert, C. A.; Mueller, B. K.; Dömling, A. *QSAR Comb. Sci.* **2006**, *25*, 527–535. (d) Dömling, A.; Beck, B.; Magnin-Lachaux, M. *Tetrahedron Lett.* **2006**, *47*, 4289–4291. (e) Dömling, A.; Herdtweck, E.; Heck, S. *Tetrahedron Lett.* **2006**, *47*, 1745–1747. (f) Dömling, A.; Beck, B.; Herdtweck, E.; Antuch, W.; Oefner, C.; Yehia, N.; Gracia-Marques, A. *Arkivoc* **2007**, *99*, 109. (g) Dömling, A.; Antuch, W.; Beck, B.; Schauer-Vukasinovic, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4115–4117. (h) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 916–916.

(33) Salinas, Y.; Oliart, R.; Ramírez-Lepe, M.; Navarro-Ocaña, A.; Valerio-Alfaro, G. *Appl. Microbiol. Biotechnol.* **2007**, *75*, 297–302.

(34) Arimitsu, S.; Fernandez, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656–2661.

(35) Lu, C.; DesMarteau, D. D. *Chem. Commun.* **2008**, *208*, 210.

(36) (a) Riggs, R. M.; Jennings, R. K.; Derstine, E. R.; Nguyen, T. M.; Trinh, T.; Riordan, J. M. *Lett. Drug Des. Discov.* **2008**, *5*, 25–28. (b) El-Azab, A. S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 333–348.

(37) Cosimelli, B.; Greco, G.; Ehlardo, M.; Novellino, E.; Da Settimo, F.; Taliani, S.; La Motta, C.; Bellandi, M.; Tuccinardi, T.; Martinelli, A.; Ciampi, O.; Trincavelli, M. L.; Martini, C. *J. Med. Chem.* **2008**, *51*, 1764–1770.

(38) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944–2945.

(39) Ohshima Petitjean, A.; Cuccia, L. A.; Schmutz, M.; Lehn, J.-M. *J. Org. Chem.* **2008**, *73*, 2481–2495.

(40) (a) Sherman, D.; Kawakami, J.; He, H.-Y.; Dhun, F.; Rios, R.; Liu, H.; Pan, W.; Xu, Y.-J.; Hong, S.-p.; Arbour, M.; Labelle, M.; Duncton, M. A. J. *Tetrahedron Lett.* **2007**, *48*, 8943–8946. (b) Devine, S. M.; Scammells, P. J. *Tetrahedron* **2008**, *64*, 1772–1777.

(41) Dömling, A.; Beck, B.; Fuchs, T.; Yazbak, A. *J. Comb. Chem.* **2006**, *8*, 872–880.

(42) Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 3863–3866.

(43) Sung, K.; Chen, F.-L.; Chung, M.-J. *Mol. Divers.* **2003**, *6*, 213–221.

(44) Gerber, P. R.; Müller, K. *J. Comput.-Aided Mol. Des.* **1995**, *9*, 251–268.

(45) Tetko, I. V.; Yu, V.; Kasheva, T. N.; Villa, A. E. P. *J. Chem. Inf. Comp. Sci.* **2001**, *41*, 1488−93.