RESEARCH FRONT

Full Paper

CSIRO PUBLISHING

Aust. J. Chem. **2009**, *62*, 1000–1006

www.publish.csiro.au/journals/ajc

Novel Orthogonal Synthesis of a Tagged Combinatorial Triazine Library via Grignard Reaction

Jae Wook Lee,[A] *Jacqueline T. Bork*,[A] *Hyung-Ho Ha*,[B] *Animesh Samanta*,[B] *and Young-Tae Chang*[B,C]

[A]Department of Chemistry, New York University, New York, NY 10003, USA.

[B]Department of Chemistry, and NUS MedChem Program of Life Sciences Institute, National University of Singapore, 117543, Singapore.

[C]Corresponding author. Email: chmcyt@nus.edu.sg

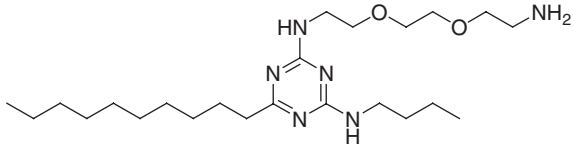
To expand the diversity of 1,3,5-triazine libraries to aryl and alkyl functionalities through the C–C bond, we employed a novel orthogonal synthesis via Grignard monoalkylation or monoarylation of cyanuric chloride in solution to prepare aryl- or alkyl-substituted triazine building blocks. These aryl- or alkyl-substituted triazine building blocks were captured by a resin-bound amine, followed by amination and acidic cleavage with high purity. Herein, we demonstrate a novel orthogonal synthesis of a tagged aryl- and alkyl-triazine library on solid support, utilizing building blocks prepared via Grignard reaction in solution. Through incorporation of a triethylene glycol linker at one of the alternate sites on the triazine scaffold we explored an intrinsic tagged library approach.

Manuscript received: 14 March 2009.
Manuscript accepted: 11 May 2009.

Introduction

Combinatorial chemistry on solid support is a promising methodology for the synthesis of a large number of molecules with a high degree of diversity. More importantly, in conjunction with high-throughput screening, this methodology has become a powerful tool for the generation and optimization of lead molecules in the drug discovery process.[1] The 1,3,5-triazine core, possessing three-fold symmetry, was chosen as the scaffold for our libraries because it allows for versatile modifications, uncomplicated by regiochemical concerns and has proven a useful biological target.[2] The structural modification of these heterocycles at the 2-, 4-, and 6- positions has led to the development of several derivatives with a broad range of biological properties; such as anticancer,[3] antitrypanosomal,[4] antiretroviral,[5] antimicrobial,[6] CDK inhibitors,[7] Erm methyltransferase inhibitors,[8] oestrogen receptor modulators,[9] glucocerebrosidase inhibitiors,[10] and p38MAPK inhibitors.[11] Moreover, we reported the triazine analogue Tubulyzine as an inhibitor of tubulin polymerization.[12,13] In addition, this class of triazines has been described as chiral auxiliaries for NMR spectroscopy[14] and as fluorescent molecules.[15] Recently, we carried out a high-throughput screen of a series of triazine molecules that inhibit β-amyloid aggregation.[16] One of the selected molecules, the alkyltriazine G12 (Fig. 1),[17] exhibited an inhibitory effect against Aβ42 peptide aggregation comparable to tannic acid and dopamine, known inhibitors of this process.

In continuation of our research on the development of novel inhibitors against Aβ42 peptide aggregation and the general development of molecular probes of biological function, we designed a tagged aryl- and alkyl-substituted triazine library (carba-analogues) on solid support utilizing building blocks prepared via Grignard reaction in solution. Furthermore, in comparison to conventional triazine derivatives and conventional carba-analogues of those compounds (Fig. 2), we will be able to evaluate the role of heteroatoms, such as N(H), O, and S, and thus provide valuable information for structure–activity relationship analysis.



G12

Fig. 1. The structure of G12 (Aβ42 peptide aggregation inhibitor).

An aryl substitution on the triazine scaffold was previously reported by our research group.[18c] However, this relied on palladium-catalyzed reactions via solid support as a final derivatization step, which did not support the synthesis of alkyl derivatives. Although this previous method is satisfactory, we have investigated other possibilities in order to expand the diversity to both aryl- and alkyl-functional groups and to provide an overall more efficient synthesis. Building on precedent for the Grignard alkylation and Grignard arylation to efficiently derivatize the triazine scaffold, we sought to expand compound diversity by incorporating this orthogonally into our library design.[18]

Herein, we report the use of Grignard reactions in the solid phase combinatorial synthesis of a library of aryl- and alkyl-triazine compounds.

10.1071/CH09153 0004-9425/09/091000

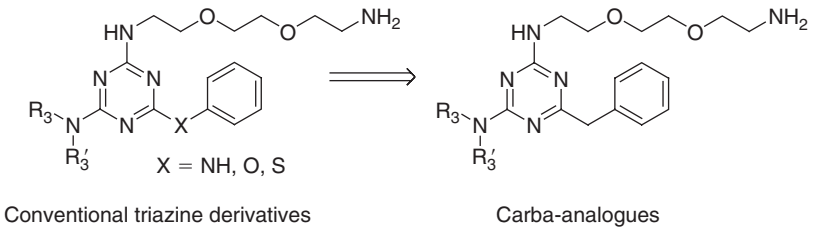


Fig. 2. Structure of conventional triazine derivatives and carba-analogues.

Results and Discussion

As described above, an orthogonal synthetic strategy was used in the synthesis of aryl and alkyl substituted-1,3,5-substituted triazine libraries. Scheme 1 illustrates the orthogonal strategy for the tagged triazine library, in which we constructed a library of 588 triazines using entries A–L as alternate functionality for building block I (Table 1). Resin-bound monosubstituted triazine with triethylene glycol (TG) was used as a representative linker. This was prepared according to conventional methods by coupling TG-amine to a 4-formyl-3-dimethoxyphenoxymethyl-functionalized polystyrene resin (PAL) by reductive amination in the presence of $NaBH(OAc)_3$ in DMF. To avoid a possible side reaction of the triazine scaffold with the amine group on the TG linker, one of the amine groups on the TG linker was Boc-protected before the reductive amination step. Building block I (**2**) was synthesized using the Grignard reaction, which involved the coupling of various aryl- and alkyl-magnesium halides with cyanuric chloride in THF/diethyl ether. Generalizing a previously described procedure from the literature,[19,20] we tested various commercially available Grignard reagents (Table 1, entries A–L) in the mono-alkylation and -arylation of cyanuric chloride (building block I). In general, the compounds containing alkyl functionalities (entries B, D, G), when compared to aryl functionalities (entries A, C, H), resulted in lower overall yields. All alkyl-functionalized triazines were purified by column chromatography, while aryl functionalized triazines were purified by recrystallization. The monoalkyl- and monoaryl-substituted triazines were captured by the resin-bound amine **1** through nucleophilic substitution, resulting in a resin-bound triazine **3**. The chloride of resin-bound triazine **3** was displaced with various amines **4** (building block II) by heating in a mixture of *n*-BuOH:1-methyl-2-pyrrolidinone (NMP) (1:1) with *N*,*N*-diisopropylethylamine (DIEA) at 120°C. The advantage of this approach over palladium-catalyzed coupling was that it allowed displacement of the resin-bound triazine with secondary amines, such as piperidine and di-(*n*-butyl)amine. Cleavage was accomplished by treatment of with 10% TFA/DCM, thus providing compound **5**. Analysis of products by LCMS showed that crude, off-resin purity was >90%. The purity of the crude cleavage products is summarized in Table 2. The purity of products was dependent on the nature of the substituted group of building blocks I and II. As we expected, decanyl triazine (Table 1, entry G) showed relatively lower purity due to bulkiness of building block I. The relationship between the purity of product and the reactivity of building block II was addressed in our previous report.[18a] From these results, the use of amino acid derivatives (building block II), gave lower crude purity and reduced reactivity, whereas higher yields were obtained with less bulky building block I groups.

Conclusions

These results demonstrate an improvement in the combinatorial synthesis of aryl- and alkyl-functionalized triazine derivatives relative to previous methods. In particular, the previous Suzuki method only allowed for aryl substituents; whereas, this improved method allows for both aryl and alkyl substitution. Alkyl- and aryl-diverivatives were efficiently achieved via a preparation of building block I in solution phase. Purification and isolation of aryl- and alkyl-triazine compounds (building block I) relied on considerably simple methods; either recrystallization or column chromatography was employed. Consequently, these aryl- and alkyl-triazine compounds can be synthesized on large scale, which allows for straight forward extension of chemical libraries by varying building block II with different amines.

In conclusion, we have developed an enhanced method for the synthesis of aryl/alkyl functionalized triazine libraries on solid support. The further development and expansion of triazine libraries to other functionalities, which includes the extension of the Grignard derivatization to various aryl- and alkyl-magnesium halides, is underway. Libraries prepared via these methods will provide a structurally diverse pool of compounds to probe biological function and identify potential leads for further pharmacological development.

Experimental

General

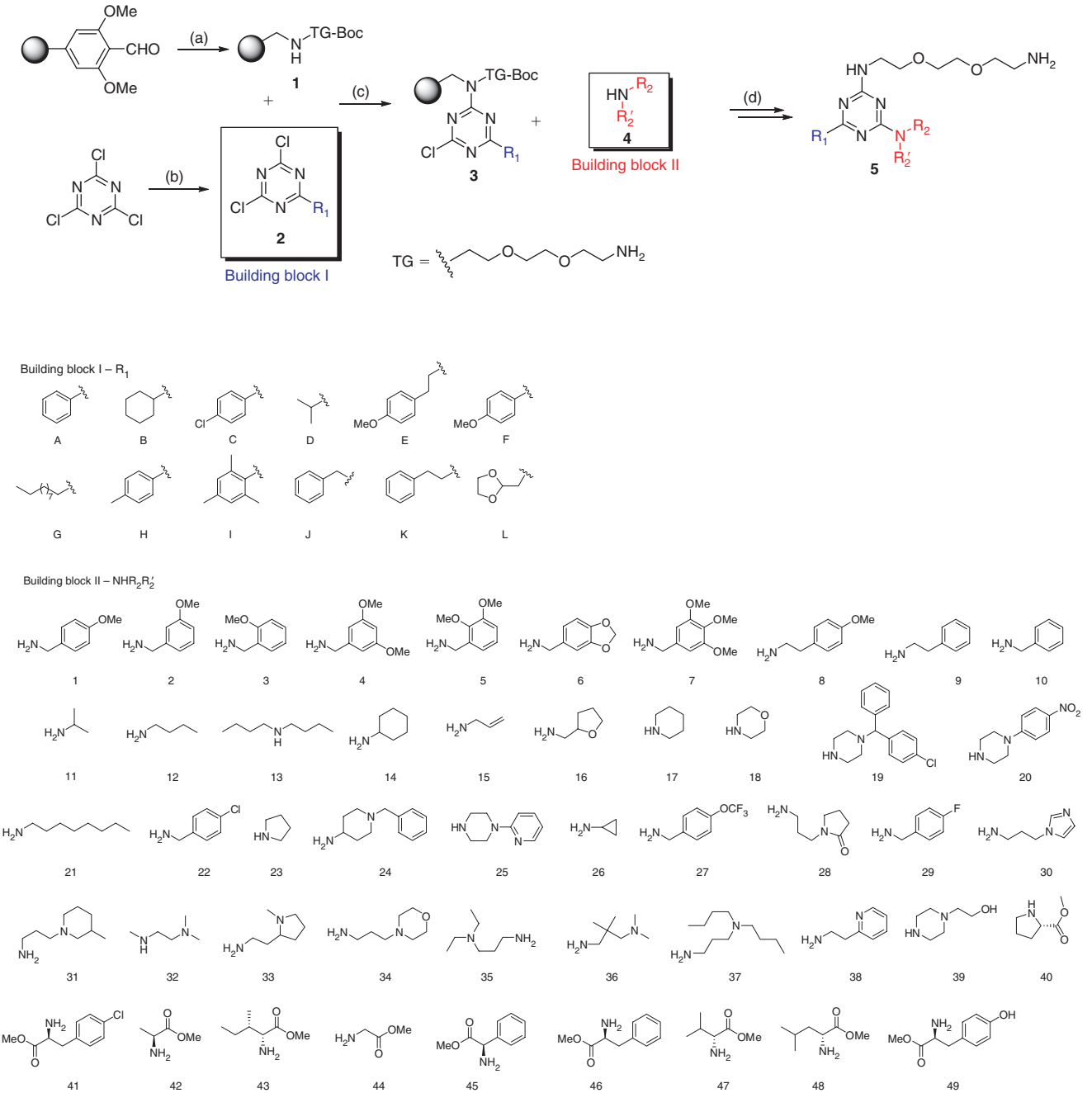
Materials and solvents were obtained from commercial suppliers and, unless otherwise noted, were used without further purification. Anhydrous tetrahydrofuran (THF) and NMP from Acros were used as reaction solvents without any previous purification. PAL–aldehyde resin from Midwest Bio-Tech was used as the solid support. For the synthesis of building block I, general coupling reactions were performed through solution phase chemistry and were purified by flash column chromatography on Merck silica gel 60-PF_{245}. All products were identified by LCMS from Agilent Technology using a C18 column (20×4.0 mm), with a gradient of 5–95% CH_3CN (containing 1% acetic acid)/H_2O (containing 1% acetic acid) as eluant.

Equipment

Thermal reactions were performed using a standard heat block from VWR scientific Products using 4 mL vials. Resin filtration procedures were carried out using 70 μ PE frit cartridge from Applied Separations.

Loading of Amine onto PAL Resin via Reductive Amination (1)

To a suspension of 4-formyl-3,5-dimethoxyphenoxymethyl-functionalized polystyrene resin (PAL) (1.0 g, 1.1 mmol) in



Scheme 1. Orthogonal strategy for the tagged triazine library: Reagents and conditions: (a) (i) NH_2-TG-Boc, 2% HOAc in THF, rt, 1 h. (ii) $NaBH(OAc)_3$, overnight. (b) R_1MgX, THF, 0°C to rt, 8 h. (c) DIEA, 60°C, 3 h. (d) (i) NMP:BuOH (1:1), DIEA, 120°C, 3 h. (ii) 10% TFA/DCM, rt, 0.5 h.

THF (40 mL) was added Boc-protected TG-amine (5.5 mmol), followed by the addition of HOAc (0.9 mL). After shaking at room temperature for 1 h, $NaBH(OAc)_3$ (1.63 g, 7.7 mmol) was added, and the reaction continued shaking at room temperature for 8 h. Using a PE frit cartridge, the solvents and excess reagents were filtered off and washed with DMF, dichloromethane (MC), and MeOH (20 mL × 3), and a final wash with DCM and dried under nitrogen gas.

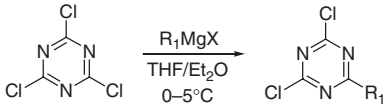
General Procedure for the Preparation of Building Block I (2) via Grignard Alkylation (Table 1)

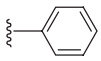
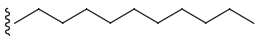
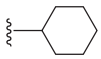
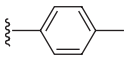
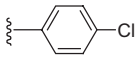
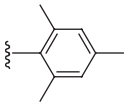
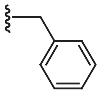
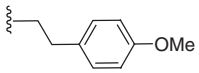
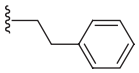
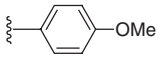
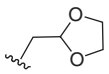
A solution with THF/ether (1:1) (125 mL) of alkylmagnesium halide (Br or Cl) (13.0 mmol) was slowly added to a cooled (0–5°C), mechanically stirred solution of cyanuric chloride (10.93 mmol, 2 g) in benzene (125 mL); the mixture was stirred at 0°C for 4 h, subsequently warmed to room temperature and stirred for a further 4 h. The reaction mixture was quenched with 1 N HCl (40 mL), extracted with ethyl acetate and washed with water. The organic layers were combined and dried over $MgSO_4$. The solvent was removed under vacuum.

2,4-Dichloro-6-phenyl-[1,3,5]triazine (A)

Phenyl magnesium bromide, recrystallization with acetone, pale yellow solid, 77%.

Table 1. Synthesis of mono-alkylated or arylated triazine intermediate (2) via Grignard reaction



Entry	R_1MgX	**2** (% yield)	Entry	R_1MgX	**2** (% yield)
A		77	G		47
B		36	H		83
C		78	I		48
D		34	J		88
E		75	K		80
F		70	L		65

2,4-Dichloro-6-cyclohexyl-[1,3,5]triazine (B)

Cyclohexyl magnesum chloride, methylenechloride/hexane (1/100 v/v), white crystals, 36%.

2,4-Dichloro-6-(4-chlorophenyl)-[1,3,5]triazine (C)

4-Chlorophenyl magnesium bromide, recrystallization with DCM, white solid, 78%.

2,4-Dichloro-6-isopropyl-[1,3,5]triazine (D)

Isopropyl magnesiumchloride, methylenechloride/hexane (1/100 v/v), yellow oil, 34%.

2,4-Dichloro-6-[2-(4-methoxy-phenyl)-ethyl]-[1,3,5]triazine (E)

4-Methoxyphenethyl magnesium chloride, recrystallization with acetone, orange solide, 75%.

2,4-Dichloro-6-[2-(4-methoxy-phenyl)]-[1,3,5]triazine (F)

4-Methoxyphenyl magnesium bromide, recrystallization with acetone, white crystals, 70%.

2,4-Dichloro-6-decyl-[1,3,5]triazine (G)

Decyl magnesium bromide, methylenechloride/hexane (1/100 v/v), yellow oil, 47%.

*2,4-Dichloro-6-(*p*-tolylphenyl)-[1,3,5]triazine (H)*

p-tolyl magnesium bromide, recrystallization with DCM, white crystals, 83%.

2,4-Dichloro-6-(2-mesityl)-[1,3,5]triazine (I)

2-Mesityl magnesium bromide, methylenechloride/hexane (1/100 v/v), white solid, 48%.

2,4-Dichloro-6-benzyl-[1,3,5]triazine (J)

Benzyl magnesium chloride, recrystallization with acetone, white solid, 88%.

2,4-Dichloro-6-phenethyl-[1,3,5]triazine (K)

Phenethyl magnesium chloride, recrystallization with acetone, white solid, 80%.

2,4-Dichloro-6-[1,3]dioxolan-2-ylmethyl-[1,3,5]triazine (L)

1,3-Dioxlan-2-ylmethyl-magnesium bromide, methylene chloride/hexane (1/9 v/v), 65%.

Resin Capture of Triazine Scaffold via Amine Substitution (3)

To a suspension of the PAL resin-bound amine (125 mg, 0.132 mmol) in THF (2.5 mL) was added 2,4-dichloro-alkyl/aryl-[1,3,5]triazines (125 mg), followed by addition of diisopropylethylamine (DIEA) (0.15 mL). The reaction was placed in a heating block set at 60°C for 2.5 h. Solvents and excess reagent were filtered through a PE frit cartridge and washed with DMF, DCM, MeOH (3 mL × 3) consecutively, with a final wash with DCM (3 mL), and dried under nitrogen gas.

Synthesis of Compound (5)

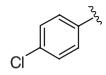
To a suspension of the resin (**3**, 10 mg, 11 μmol) in NMP (0.25 mL) was added an amine (0.2 mmol), followed by the addition of *n*-butanol (0.25 mL) and diisopropylethylamine (DIEA)

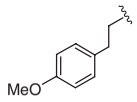
Table 2. Purity of the final products (LC-MS, 250 nm, purity [%])

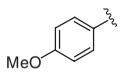
Purity was obtained by RP-HPLC/MS of the crude final products after cleavage from the solid support

>90%
80–89%
70–79%



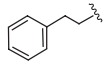











Building blocks I, II	2A	2B	2C	2D	2E	2F	2G	2H	2I	2J	2K	2L
1	96	96	94	88	90	95	86	86	95	96	95	87
2	95	96	95	87	85	95	84	90	96	97	95	90
3	97	94	92	90	90	92	90	91	95	95	94	91
4	94	93	90	85	87	97	80	84	98	98	94	73
5	95	95	95	93	88	98	80	88	98	94	96	85
6	94	95	94	95	93	95	92	92	98	94	95	92
7	94	95	95	92	92	96	92	85	95	95	95	90
8	94	94	93	96	90	95	95	90	92	95	95	88
9	97	94	93	95	92	95	98	84	97	93	99	90
10	91	95	95	89	95	95	97	88	94	97	98	93
11	96	88	93	82	96	94	78	86	90	95	99	95
12	95	93	97	94	94	97	97	92	95	98	99	97
13	97	89	99	85	95	94	71	83	94	92	97	94
14	98	90	77	90	100	96	96	88	97	94	97	95
15	99	88	93	88	89	95	76	86	92	95	96	94
16	100	89	93	87	91	96	74	85	90	95	96	92
17	100	73	100	94	95	97	97	93	95	98	97	88
18	100	91	93	94	98	96	76	86	92	98	97	96
19	94	73	92	84	89	95	81	85	89	91	95	90
20	100	89	100	88	90	94	88	91	90	85	99	95
21	90	99	97	99	96	100	93	98	95	97	97	95
22	99	98	99	100	94	100	96	90	91	96	97	95
23	100	99	100	99	99	100	100	<80	95	97	100	90
24	96	97	95	97	91	95	95	<80	90	95	93	91
25	100	96	100	99	95	99	99	<80	99	99	99	92
26	100	97	100	96	100	100	97	<80	90	96	99	95
27	100	97	99	99	97	99	99	<80	92	94	98	93
28	94	98	95	99	94	96	93	<80	91	91	93	96
29	99	98	99	99	99	99	99	<80	96	94	99	95
30	90	92	96	93	95	94	91	<80	92	92	95	90
31	96	94	92	97	90	95	70	80	90	95	99	85
32	95	90	94	90	90	95	80	85	85	90	95	95

(*Continued*)

Table 2. (Continued)

33	95	97	92	90	85	75	97	86	92	91	95	95	90	85	75	99
34	90	93	88	88	75	80	92	85	90	88	90	90	88	80	80	99
35	95	92	90	93	80	92	98	87	95	90	95	90	97	90	80	99
36	80	94	87	85	86	70	89	85	87	89	90	90	90	85	80	99
37	95	95	90	90	81	80	96	85	89	95	91	90	98	90	80	99
38	91	95	75	80	80	70	85	90	87	99	90	90	98	90	80	99
39	94	95	95	95	90	92	94	98	90	96	96	90	98	90	80	99
40	85	95	95	90	99	75	95	93	96	99	91	90	98	90	80	99
41	80	80	95	95	95	80	90	80	80	90	95	86	87	85	80	99
42	90	70	80	70	90	80	90	85	95	88	90	86	90	85	80	99
43	90	97	95	99	91	90	92	85	80	95	94	90	88	83	80	99
44	98	90	90	90	92	80	90	85	98	80	87	85	88	83	80	99
45	80	70	90	95	80	70	80	85	95	85	85	86	90	85	80	99
46	97	70	98	95	70	80	70	95	95	86	90	92	90	85	80	99
47	80	92	95	95	99	70	97	95	95	95	80	90	84	85	80	99
48	90	80	90	95	85	90	95	95	95	95	80	90	84	85	80	99
49	99	95	95	96	90	99	95	95	95	94	70	95	94	85	80	99

(30 μL, 0.22 mmol). The reaction was placed in a heating block set at 120°C for 3 h. The excess reagents were filtered through a PE frit cartridge and washed with DMF, DCM, MeOH (1 mL × 3) consecutively, with a final wash with DCM (1 mL). The resin was dried under vacuum. The product cleavage reaction was performed using 10% trifluoroacetic acid (TFA) in dichloromethane (1 mL) for 30 min at room temperature and washed with DCM (0.5 mL).

Accessory Publication

Representative tagged library compounds are available on the Journal's website.

Acknowledgements

This work was supported by a grant from National Institute of Health (CA-96912). We thank Dr. Matthew S. Tremblay for critical reading of the manuscript.

References

[1] (a) Combinatorial Chemistry and Molecular Diversity, in *Drug Discovery* **1998** (Eds E. M. Gordon, J. F. Kerwin Jr) (John Wiley & Sons Ltd.: New York, NY).
(b) R. E. Ziegert, J. Toräng, K. Knepper, S. Bräse, *J. Com. Chem.* **2005**, *7*, 147.
(c) K. S. Lam, M. Lebl, V. Krchňák, *Chem. Rev.* **1997**, *97*, 411.
(d) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288.

[2] (a) D. P. Walsh, Y. T. Chang, *Chem. Rev.* **2006**, *106*, 2476. doi:10.1021/CR0404141
(b) J. L. Silen, A. T. Lu, D. W. Solas, M. A. Gore, D. Maclean, N. H. Shah, J. M. Coffin, N. S. Bhinderwala, Y. W. Wang, K. T. Tsutsui, G. C. Look, D. A. Campbell, R. L. Hale, M. Navre, C. R. Deluca-Flaherty, *Antimicrob. Agents Chemother.* **1998**, *42*, 1447.

[3] (a) Z. Hu, T. Ma, Z. Chen, Z. Ye, G. Zhang, Y. Lou, Y. Yu, *J. Comb. Chem.* **2009**, *11*, 267. doi:10.1021/CC800157K
(b) R. Menicagli, S. Samaritani, G. Signore, F. Vaglini, L. D. Via, *J. Med. Chem.* **2004**, *47*, 4649. doi:10.1021/JM0495374

[4] B. Klenke, M. Stewart, M. P. Barrett, R. Brun, I. H. Gilbert, *J. Med. Chem.* **2001**, *44*, 3440. doi:10.1021/JM010854+

[5] D. W. Ludovici, R. W. Kavash, M. J. Kukla, C. Y. Ho, H. Ye, B. L. De Corte, K. Andries, M. P. Běthune, H. Azijn, R. Pauwels, H. E. L. Moereels, J. Heeres, L. M. H. Koymans, M. R. de Jonge, K. J. A. Van Aken, F. F. D. Daeyaert, P. J. Lewi, K. Das, E. Arnold, P. A. J. Janssen, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2229. doi:10.1016/S0960-894X(01)00411-5

[6] C. Zhou, J. Min, Z. Liu, A. Young, H. Deshazer, T. Gao, Y.-T. Chang, N. R. Kallenbach, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1308. doi:10.1016/J.BMCL.2008.01.031

[7] G.-H. Kuo, A. DeAngelis, S. Emanuel, A. Wang, Y. Zhang, P. J. Connolly, X. Chen, R. H. Gruninger, C. Rugg, A. Fuentes-Pesquera, S. A. Middleton, L. Jolliffe, W. V. Murray, *J. Med. Chem.* **2005**, *48*, 4535. doi:10.1021/JM040214H

[8] P. J. Hajduk, J. Dinges, J. M. Schkeryantz, D. Janowick, M. Kaminski, M. Tufano, D. J. Augeri, A. Petros, V. Nienaber, P. Zhong, R. Hammond, M. Coen, B. Beutel, L. Katz, S. W. Fesik, *J. Med. Chem.* **1999**, *42*, 3852. doi:10.1021/JM990293A

[9] B. R. Henke, T. G. Consler, N. Go, R. L. Hale, D. R. Hohman, S. A. Jones, A. T. Lu, L. B. Moore, J. T. Moore, L. A. Orband-Miller, R. G. Robinett, J. Shearin, P. K. Spearing, E. L. Stewart, P. S. Turnbull, S. L. Weaver, S. P. Williams, G. B. Wisely, M. H. Lambert, *J. Med. Chem.* **2002**, *45*, 5492. doi:10.1021/JM020291H

[10] W. Huang, W. Zheng, D. J. Urban, J. Inglese, E. Sidransky, C. P. Austin, C. J. Thomas, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5783. doi:10.1016/J.BMCL.2007.08.050

[11] K. Leftheris, G. Ahmed, R. Chan, A. J. Dyckman, Z. Hussain, K. Ho, J. Hynes, J. Letourneau, W. Li, S. Lin, A. Metzger, K. J. Moriarty, C. Riviello, Y. Shimshock, J. Wen, J. Wityak, S. T. Wrobleski,

H. Wu, J. Wu, M. Desai, K. M. Gillooly, T. H. Lin, D. Loo, K. W. McIntyre, S. Pitt, D. R. Shen, D. J. Shuster, R. Zhang, D. Diller, A. Doweyko, J. Sack, J. Baldwin, J. Barrish, J. Dodd, I. Henderson, S. Kanner, G. L. Schieven, M. Webb, *J. Med. Chem.* **2004**, *47*, 6283. doi:10.1021/JM049521D

[12] E. I. Fahime, M. Bouchentouf, B. F. Benabdallah, D. Skuk, J. F. Lafreniere, Y.-T. Chang, J. P. Tremblay, *Biochem. Cell Biol.* **2003**, *81*, 81. doi:10.1139/O03-054

[13] H. S. Moon, E. M. Jacobson, S. M. Khersonsky, M. R. Luzung, D. P. Walsh, W. Xiong, J. W. Lee, P. B. Parikh, J. C. Lam, T.-W. Kang, G. R. Rosania, A. F. Schier, Y.-T. Chang, *J. Am. Chem. Soc.* **2002**, *124*, 11608. doi:10.1021/JA026720I

[14] G. Uccello-Barretta, A. Iuliano, E. Franchi, F. Balzano, P. Salvadori, *J. Org. Chem.* **1998**, *63*, 9197. doi:10.1021/JO9806153

[15] T. Murase, M. Fujita, *J. Org. Chem.* **2005**, *70*, 9269. doi:10.1021/JO051268H

[16] W. Kim, Y. Kim, J. Min, D. J. Kim, Y.-T. Chang, M. H. Hecht, *ACS Chem. Biol.* **2006**, *1*, 461. doi:10.1021/CB600135W

[17] Data for G12: *m/z* (LCMS): Calc. for $C_{23}H_{46}N_6O_2$: 438.4, found: 439.4 $[M+H]^+$. δ_H [(D_4)methanol] 0.89 (t, $J = 7.0$ Hz, 3H), 0.95 (t, $J = 7.5$ Hz, 3H), 1.24–1.43 (m, 16H), 1.56 (m, 2H), 1.67 (m, 2H), 2.33–2.46 (m, 2H), 3.12 (t, $J = 5.0$ Hz, 2H), 3.37 (m, 2H), 3.59 (m, 2H), 3.63–3.72 (m, 8H).

[18] (a) J. T. Bork, J. W. Lee, S. M. Khersonsky, H. S. Moon, Y.-T. Chang, *Org. Lett.* **2003**, *5*, 117. doi:10.1021/OL027195V
(b) S. M. Khersonsky, Y.-T. Chang, *J. Comb. Chem.* **2004**, *6*, 474. doi:10.1021/CC049965V
(c) J. T. Bork, J. W. Lee, Y.-T. Chang, *Tetrahedron Lett.* **2003**, *44*, 6141. doi:10.1016/S0040-4039(03)01451-5

[19] R. Menicagli, S. Samaritani, V. Zucchelli, *Tetrahedron* **2000**, *56*, 9705. doi:10.1016/S0040-4020(00)00925-X

[20] (a) V. Meyer, F. J. Nabe, *J. Prakt. Chem.* **1910**, *82*, 537.
(b) A. Ostrogovitch, *Chem. Ztg.* **1912**, *36*, 738.
(c) W. Hentrich, W. Hardtmann, *US Patent 1,911,689* **1933**; *Chem. Abstr*. **1933**, *27*, 3952.
(d) R. Hirt, H. Nidecker, R. Berchtold, *Helv. Chim. Acta* **1950**, *33*, 1365. doi:10.1002/HLCA.19500330536
(e) C. Grundmann, H. Ulrick, A. Kreutzberger, *Chem. Ber.* **1953**, *86*, 181. doi:10.1002/CBER.19530860210
(f) H. Koopman, *Rec. Trav. Chim.* **1961**, *80*, 158.
(g) H. Bader, N. M. Smyth, *J. Org. Chem.* **1964**, *29*, 952. doi:10.1021/JO01027A512
(h) R. A. Shaw, B. C. Smith, R. C. Golesworth, *Chem. Abstr* **1964**, *60*, 14527a.
(i) A. D. Forbes, P. Gould, I. R. Hills, *J. Chem. Soc.* **1965**, 1113. doi:10.1039/JR9650001113
(j) H. Bader, E. R. Ruckel, F. X. Markley, C. G. Santangelo, P. Schickedantz, *J. Org. Chem.* **1965**, *30*, 702. doi:10.1021/JO01014A011
(k) G. N. Pazenko, T. N. Lebedeva, L. I. Chovnik, U. P. Getmanchuk, V. N. Skopenko, Sintez i Svoistva Monomerov, Akad. Nauk SSSR, Inst. Nefstekhim. Sinteza Sb. Rabot 12–0i [Dvenadtsatoi]Konf. Po Vysokomolekul. Soedin. **1962**, 287–291; *Chem. Abstr.* **1965**, *62*, 7759e.
(l) Upjohn Co., *Neth. Appl. 6,501,753* **1965**; *Chem. Abstr*. **1966**, *64*, 5117h.
(m) A. S. Estrin, E. G. Sochilin, I. M. Dolgopolskii, *Zh. Obshch. Khim.* **1965**, *35*, 2074.
(n) E. R. Ruckel, *US Patent 3268527* **1966**; *Chem. Abstr.* **1966**, *65*, 15403h.
(o) H. K. Bader, E. R. Ruckel, *US Patent 3268528* **1966**; *Chem. Abstr.* **1967**, *66*, 2597f.
(p) J. J. Ursprung (Upjohn Co.) *US Patent 3,270,015* **1966**; *Chem. Abstr.* **1967**, *66*, 65524f.
(q) T. Kauffmann, P. Baldi, W. Brinkwerth, B. Greving, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 848. doi:10.1002/ANIE.197208481
(r) C. P. Joshua, V. P. Rajan, *Aust. J. Chem.* **1974**, *27*, 2627.
(s) F. K. Chakrabarti, R. W. Goulding, A. Todd, *J. Chem. Soc., Perkin Trans. I* **1973**, *I*, 2499. doi:10.1039/P19730002499
(t) J. K. Chakrabarti, A. Todd, *Chem. Abstr.* **1974**, *80*, 63688y.
(u) T. W. Giants (Hughes Aircraft Co.), *US Patent 4,442,278* **1984**; *Chem. Abstr.* **1984**, *101*, 39310e.
(v) F. Lehr, M. Greve, A. R. Katritzky, *Dyes Pigments* **1986**, *7*, 419. doi:10.1016/0143-7208(86)80010-9
(w) M. J. Kukla, D. W. Ludovici, P. A. J. Janssen, J. Heeres, H. E. L. Moereels, *Chem. Abstr.* **1998**, *128*, 257449f.