Solid-Phase Synthesis of Novel 7,8-Functionalized Pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine Derivatives via Cyclization Reactions of Dithiocarboxy Resin Bound Pyrazoles

Young-Dae Gong* and In Ae Ryu

Center for High Throughput Synthesis Platform Technology, Korea Research Institute of Chemical Technology, P.O. Box 107, Yuseong, Daejon 305-600, Korea

Received February 7, 2009

A general method is described for the solid-phase synthesis of novel 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives. The sequence developed for this purpose is based on cyclization reactions of resin-bound 3,4-functionalized-5-amino-1-dithiocarboxypyrazoles **4** and **5**, promoted by reaction with various isocyanates. The resin-bound pyrazoles produced by cyclization reactions of cyanocarboimidates **8** or 3-ethoxyacrylonitriles **9** with Merrifield resin linked hydrazine dithiocarbazate **3**, serve as key intermediates for subsequent bicyclic heterocycle diversification. Reactions of the resin-bound 5-amino-1-dithiocarboxy pyrazoles **4** and **5** with various aryl isocyanates produce the novel 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives **6** and **7** in good yields and high purities.

Introduction

Heterocyclic skeletons serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs.[1] This is especially true for five-member ring heterocyclic compounds, which are core components of a large number of substances that possess a wide range of interesting biological activities. In this respect, the potential of the pyrazole scaffold to serve as a privileged structure for the generation of drug-like libraries in drug-discovery programs has been amply demonstrated. The recent success of a pyrazole COX-II (cyclooxygenase) inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry.[2] In addition, the pyrimidinedione and pyrimidinonethione ring systems found in quinazolinediones and quinazolinonethiones have been used as drug pharmacophores.[3] By using the bioisostere concept, we have designed scaffolds that combine the pyrimidinonethione moiety found in quinazolinonethiones with the pyrazole ring system. The pyrazolo[1,5-*a*][1,3,5]thioxotriazine bicyclic system, coming from this formulation, is present in substances that are known inhibitors of protein kinase CK2 (casein kinase),[4] phosphodiesterase (PDE4),[5] and DNA gyrase.[6] Another driving force for this combined drug discovery and high-throughput organic synthesis program, focusing on drug-like small heterocyclic molecules,[7] is the development of novel modulators of protein kinase CK2 and PDE4 that participate in the control of inflammatory diseases. Since these types of modulators possess pyrazolo[1,5-*a*][1,3,5]triazine functionality, one of the purposes of this effort was the development of a new types of scaffolds, such as the pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine, that might be found in protein kinase inhibitors.

* To whom correspondence should be addressed. E-mail: ydgong@krict.re.kr.

Several reports exist describing the efficient solution-phase synthesis of pyrazolo[1,5-*a*][1,3,5]triazine derivatives that possess drug-like properties.[8] However, methods to readily generate pyrazolo[1,5-*a*][1,3,5]thioxotriazines by employing solid-phase synthesis have not been reported. As a result, we undertook an investigation aimed at developing efficient and simple parallel solid-phase synthetic methods to produce various drug-like pyrazolo[1,5-*a*][1,3,5]thioxotriazine derivatives.

Below, we describe studies that have led to the development of an efficient procedure for the synthesis of a novel 7,8-functionalized-pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives **6** and **7** (Scheme 1) that involves solid phase cyclization reactions of resin-bound 3,4-functionalized-5-amino-1-dithiocarboxy-pyrazoles **4** and **5** with various isocyanates. These key intermediates then serve as precursors for the target 7,8-functionalized-pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazines **6** and **7**.

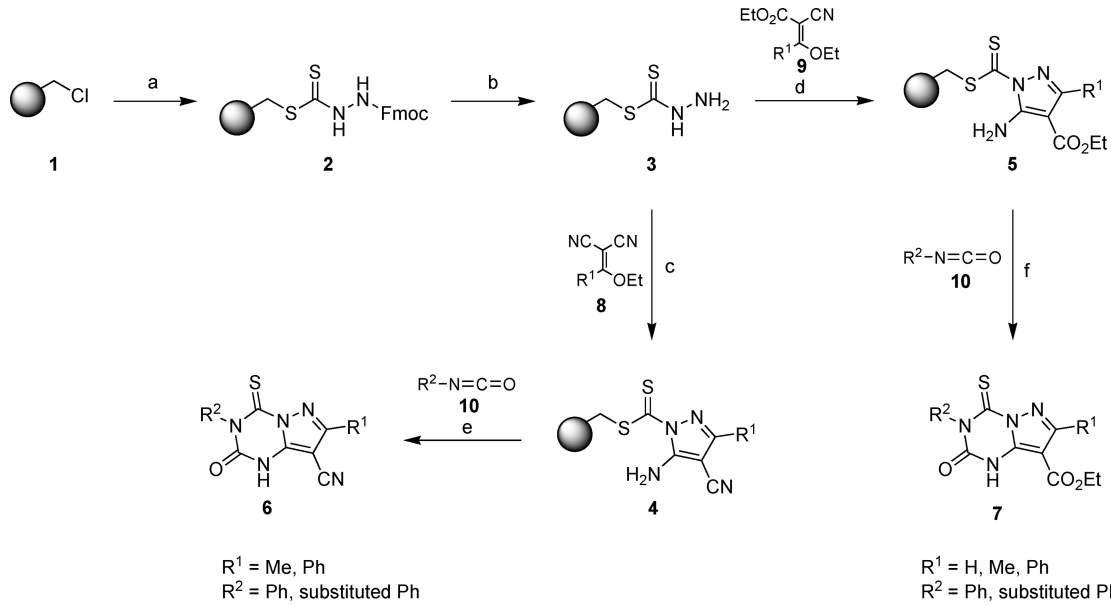
Results and Discussion

The Merrifield resin **1** was selected as the polymer support used in this investigation, since its benzyl chloride moieties would serve as a suitable site for introduction of a dithiocarbazate linker. Indeed, reaction of this resin with carbon disulfide followed by treatment with Fmoc protected hydrazine (NaH, DMF, room temperature) leads to formation of the resin bound dithiocarbazate **3**. Reactions of **3** with cyanocarboimidates **8** and 3-ethoxyacrylonitriles **9** produce the respective polymer-bound 5-amino-1-dithiocarboxy pyrazole resins **4** and **5**.[7c] Finally, the target 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives **6** and **7** were liberated from the respective 5-aminopyrazole resins **4** and **5** by reaction with various aryl isocyanates.

The progress of all of the solid phase reactions employed in these sequences was monitored by using ATR-FTIR

10.1021/cc900020j CCC: $40.75
Published on Web 04/30/2009

Scheme 1[a]



[a] Reagents and conditions: (a) CS_2, Fmoc-hydrazine, NaH, DMF, rt, 24 h; (b) 5% piperidine, DMF, rt, 2 h; (c) cyanocarboimidates **8**, Et_3N, MeCN, rt, 17 h; (d) substituted-3-ethoxyacrylonitriles **9**, Et_3N, dioxane, 80 °C, 17 h; (e) isocyanate **10**, Et_3N, THF, 40 °C, 12 h; (f) isocyanate **10**, NaH, THF, 40 °C, 12 h.

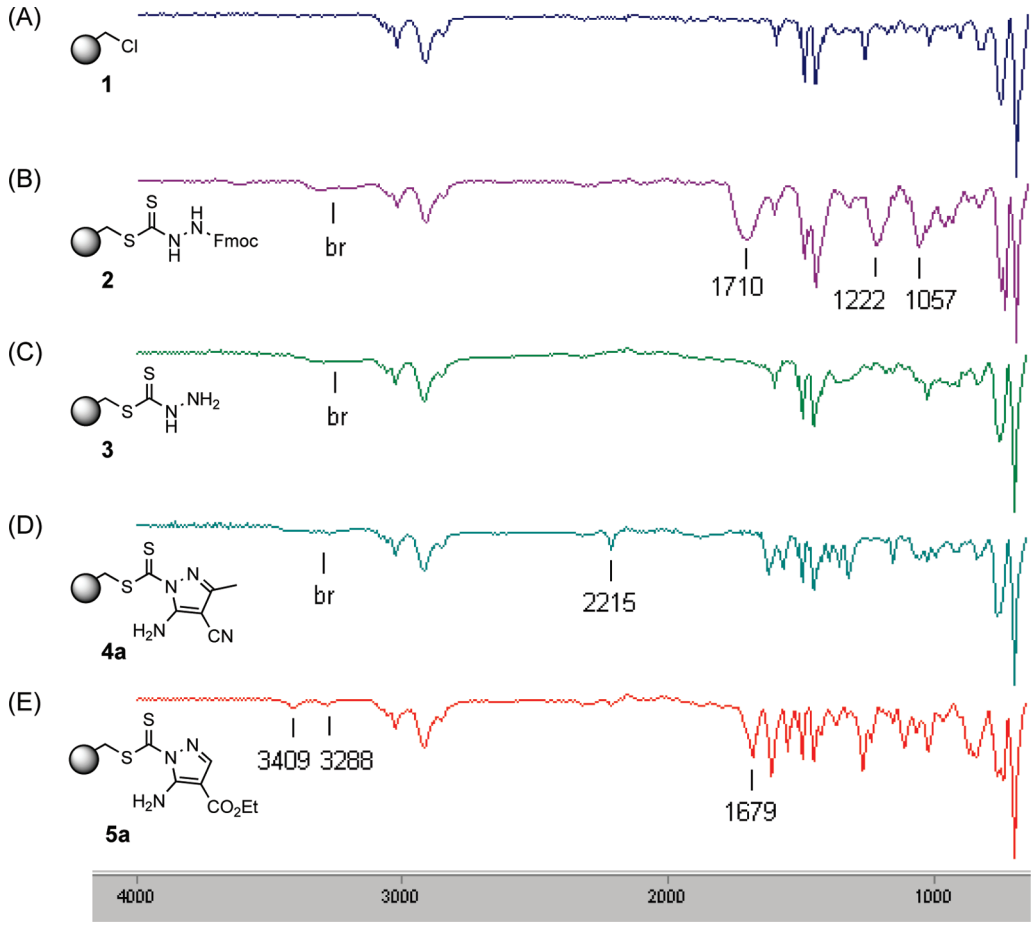


Figure 1. ATR-FTIR spectra of single-beads of the resins **1** (A), **2** (B), **3** (C), **4a** (D), and **5a** (E).

spectroscopy on single beads (Figure 1). For example, the formation of the Fmoc-dithiocarbazate resin **2** was demonstrated by the generation of prominent Fmoc-carbamate bands at 1710 and 1222 cm^{-1} and a dithiocarbazate band at 1057 cm^{-1} by ATR-FTIR (Figure 1B). Deprotection of Fmoc group of the resin **2** with 5% piperidine produces the free dithiocarbazate resin **3**, which is identified by disappearing of Fmoc-carbazate stretching band at 1710 cm^{-1} (Figure 1C). In this step, the use of 5% piperidine was essential, because higher concentration causes loss of desired substrate from

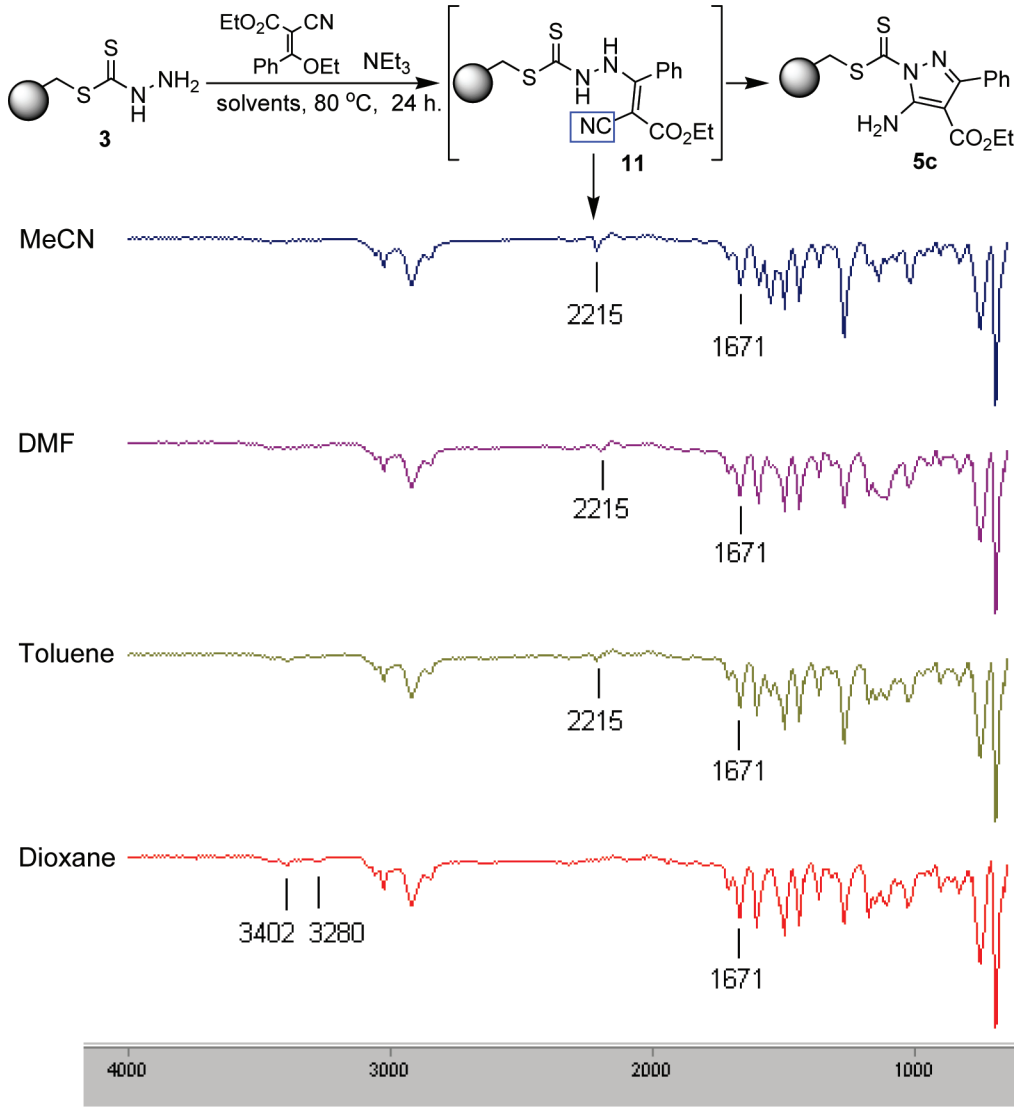


Figure 2. Monitoring of the 5-aminopyrazole intermediate resin **5c** on single-beads by using ATR-FTIR spectroscopy.

the resin **2**. Formation of the pyrazole resin **4**, the dithiocarbazate resin **3** is treated with cyanocarboimidates **8** in acetonitrile. The progress of this reaction was monitored by the appearance of the cyanonitrile stretching band at 2215 cm^{-1} (Figure 1D). In contrast, cyclization reactions of hydrazine dithiocarbazate resin **3** with substituted-3-ethoxy-acrylonitriles **9** do not take place smoothly in acetonitrile. Instead, the processes leading to **5** proceed well in 1,4-dioxane, as indicated by the disappearance of the cyano stretching band of intermediate **11** at 2215 cm^{-1} (Figure 2).

The concurrent cyclization-resin cleavage reactions of 5-amino pyrazole resins **4** and **5** were explored in more detail to find optimal conditions. The results show that reactions of the 4-cyano-5-amino pyrazole resins **4** with isocyanates take place in the presence of Et_3N (THF, 40 °C, 12 h). On the other hand, in the case of reactions of the 4-ethylcarboxy-5-amino pyrazole resins **5**, the strong base NaH is required (THF, 40 °C, 12 h). As shown in Table 1, variously substituted aryl isocyanates react to generate the target 7,8-functionalized-pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives **6** and **7** in good five step overall yields by starting from the Merrifield resin and in high purities (Tables 1 and 2). The LC/MS spectrum of the representative crude

Table 1. Products, Yields, and Purities of 7-Substituted-8-cyanonitrile-1,2,3,4-tetrahydro pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine Derivatives **6**

product	R^1	R^2	yield[a] (%)	purity[b] (%)
6a	Me	Ph	32	99
6b	Me	4-Me-Ph	28	99
6c	Me	4-Et-Ph	29	99
6d	Me	4-*t*-Bu-Ph	20	99
6e	Me	3,5-di-Me-Ph	30	99
6f	Me	4-MeO-Ph	29	99
6g	Me	4-NO_2-Ph	32	99
6h	Me	4-F-Ph	34	99
6i	Me	3-CF_3−Ph	33	99
6j	Me	2-Cl-Ph	33	99
6k	Me	benzyl	25	99
6l	Ph	Ph	30	99
6m	Ph	4-Me-Ph	37	99
6n	Ph	4-Et-Ph	37	99
6o	Ph	4-*t*-Bu-Ph	31	99
6p	Ph	3,5-di-Me-Ph	38	99
6q	Ph	4-MeO-Ph	38	99
6r	Ph	4-NO_2-Ph	16	99
6s	Ph	4-F-Ph	38	99
6t	Ph	3-CF_3-Ph	31	99
6u	Ph	2-Cl-Ph	34	99
6v	Ph	benzyl	33	99

[a] Five-step overall yields from Merrifield resin **1** (2.0 mmol/g). [b] All of the purified products were checked by LC/MS.

Table 2. Products, Yields, and Purities of 7-Substituted-8-ethylcarboxy-1,2,3,4-tetrahydropyrazolo [1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine Derivatives **7**

product	R^1	R^2	yield[a] (%)	purity[b] (%)
7a	H	Ph	27	99
7b	H	4-Me-Ph	20	99
7c	H	4-Et-Ph	23	99
7d	H	4-*t*-Bu-Ph	22	99
7e	H	4-MeO-Ph	28	99
7f	H	4-NO_2-Ph	20	99
7g	H	4-F-Ph	11	99
7h	H	3-CF_3-Ph	23	99
7i	Me	Ph	25	99
7j	Me	4-Me-Ph	23	99
7k	Me	4-Et-Ph	29	97
7l	Me	4-*t*-Bu-Ph	27	98
7m	Me	4-MeO-Ph	26	99
7n	Me	4-NO_2-Ph	27	99
7o	Me	4-F-Ph	22	99
7p	Me	3-CF_3-Ph	18	99
7q	Me	benzyl	25	99
7r	Ph	Ph	25	99
7s	Ph	4-Me-Ph	26	99
7t	Ph	4-Et-Ph	30	99
7u	Ph	4-*t*-Bu-Ph	29	97
7v	Ph	4-MeO-Ph	25	99
7w	Ph	4-NO_2-Ph	28	99
7x	Ph	4-F-Ph	28	99
7y	Ph	3-CF_3-Ph	26	99
7z	Ph	benzyl	24	99

[a] Five-step overall yields from Merrifield resin **1** (2.0 mmol/g). [b] All of the purified products were checked by LC/MS.

product mixture containing the thioxotriazine derivatives **6a** and **7a** are shown in Figure 3. The crude product of 7-methyl-8-cyanonitrile-1,2,3,4-tetrahydro pyrazolo [1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine **6a** was produced in high purity by phenylisocyanate addition and cyclization reaction of **4a** with Et_3N in THF at 40 °C (entry 1 in Table 1, see Figure 3, LC/MS spectrum of the crude product **6a**). Similarly, cyclization reaction of **5a** with phenylisocyanate also gives **7a** in good purity crude product (entry 1 in Table 2, see Figure 3, LC/MS spectrum of the crude product **7a**).

Having established a flexible method for solid phase synthesis of 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives **6** and **7**, our attention next turned to the evaluation of the potential drug properties of members of this family. In general, the goal of a drug discovery process is to synthesize chemical entities which are orally bioavailable, that is, they possess physicochemical properties that allow them to be absorbed into the gastrointestinal system. Lipinski's Rule[9] and similar formulations served as guidelines for an estimation of the physicochemical properties of the 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives calculated using Accord for Excel functions.[10] Of particular interest were the key bioavailability parameters molecular weight, lipophilicity, number of hydrogen bond donors and acceptors, number of rotatable bonds, and polar surface area. The results of these physicochemical property data were indicated in the Supporting Information. As can be seen by viewing the data, most of the key parameters for members of the constructed library fall within the range of those predicted to be reasonable oral availability drug-like libraries based on commonly known rule.

In conclusion, the results of the investigation described above demonstrate that 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives **6** and **7** can be efficiently prepared by using a concise solid phase synthetic sequence involving the intermediacy of the 5-amino-1-dithiocarboxypyrazole resins **4** and **5**. Cyclization reactions

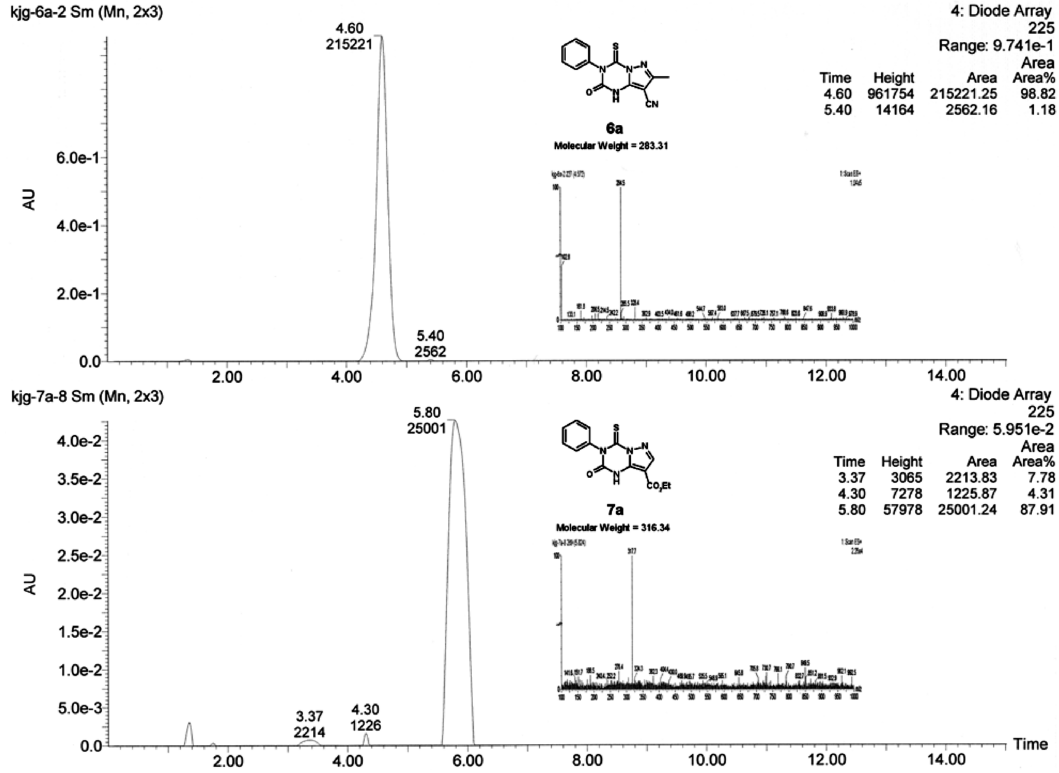


Figure 3. LC/MS spectra of the crude products **6a** and **7a**, cleaved from resins **4a** and **5a**, respectively, after cyclization reaction with phenylisocyanate. The crude product was treated with syringe filter(Whatman) before LC/MS injection.

of pyrazole resins **4** and **5**, promoted by treatment with various substituted aryl isocyanates results in liberation from the resins of the respective target 7,8-functionalized-pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazines derivatives **6** and **7** in high overall yields and purities. Finally, the calculated physicochemical properties of members of the constructed library fall within orally available drug-like ranges.

Acknowledgment. This research was supported by a grant (2008-05681) from R&D Program, Ministry of Education, Science and Technology, Korea, and a grant from the Basic Research Program of Korea Research Institute of Chemical Technology.

Supporting Information Available. Full experimental procedures, analytical data of compounds, copies of ^{1}H NMR, ^{13}C NMR, and LC-MS spectra of compounds **6a**−**6v** and **7a**−**7z**, and ATR-FTIR spectra of resins **1**−**5** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Krchňák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (c) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135.

(2) (a) Labanauskas, L.; Kalcas, V.; Udrenaite, E.; Gaidelis, P.; Brukstus, A.; Dauksas, A. *Pharmazie* **2001**, *56*, 617. (b) Song, Y.; Connor, D. T.; Sercel, A. D.; Sorenson, R. J.; Doubleday, R.; Unangst, P. C.; Roth, B. D.; Beylin, V. G.; Beylin, V. G.; Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D. *J. Med. Chem.* **1999**, *42*, 1161. (c) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–3. (d) Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, *36*, 1090. (e) Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J.; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D. *J. Med. Chem.* **1993**, *36*, 1802.

(3) (a) Buckley, G. M.; Davies, N.; Dyke, H. J.; Gilbert, P. J.; Hannah, D. R.; Haughan, A. F.; Hunt, C. A.; Pitt, W. R.; Profit, R. H.; Ray, N. C.; Richard, M. D.; Sharpe, A.; Taylor, A. J.; Whitworth, J. M.; Williams, S. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 751. (b) Langlois, M.; Soulier, J. L.; Rampillon, V.; Gallais, C.; Bremont, B.; Shen, S.; Yang, D.; Giudice, A.; Sureau, F. *Eur. J. Med. Chem.* **1994**, *29*, 925.

(4) (a) Nie, Z.; Perretta, E.; Erickson, P.; Margosiak, S.; Lu, J.; Averill, A.; Almassy, R.; Chu, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 619.

(5) (a) Rabossion, P.; Schultz, D.; Muller, C.; Reimund, J.-M.; Pinna, G.; Mathieu, R.; Bernard, P.; Do, Q.-T.; Desjarlais, R. L.; Justiano, H.; Lugnier, C.; Bourguinon, J.-J. *Eur. J. Med. Chem.* **2008**, *43*, 816.

(6) (a) Lubbers, T.; Angehrn, P.; Gmunder, H.; Herzig, S.; Kulhanek, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 821.

(7) (a) Jeon, M.-K.; Kim, M.-S.; Kwon, J.-J.; Gong, Y.-D.; Lee, D.-H. *Tetrahedron* **2008**, *64*, 9060–9072. (b) Hwang, J. Y.; Gong, Y.-D. *J. Comb. Chem.* **2006**, *8*, 297. (c) Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Yoo, S.-e.; Gong, Y.-D. *J. Comb. Chem.* **2005**, *7*, 136. (d) Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Yoo, S.-e.; Gong, Y.-D. *J. Comb. Chem.* **2005**, *7*, 816. (e) Lee, I. Y.; Lee, J. Y.; Lee, H. J.; Gong, Y.-D. *Synlett.* **2005**, 2483–2485. (f) Lee, I. Y.; Kim, S. Y.; Lee, J. Y.; Yu, C.-M.; Lee, D. H.; Gong, Y.-D. *Tetrahedron Lett.* **2004**, *45*, 9319. (g) Gong, Y.-D.; Seo, J.-s.; Chon, Y.-S.; Hwang, J.-Y.; Park, J.-Y.; Yoo, S.-e. *J. Comb. Chem.* **2003**, *5*, 577.

(8) (a) Fisher, E.; Kreutmann, J.; Rembarz, G.; Rosenthal, S. *Pharmazie* **1976**, *31*, 546. (b) Popowycz, F.; Bernard, P.; Raboisson, P.; Joseph, B. *Synthesis* **2007**, 367. (c) Mathieu, R.; Schmitt, M.; Bourguignon, J.-J. *Tetrahedron Lett.* **2006**, *47*, 5099.

(9) Lipinski, C. A.; Lombardo, F.; Doming, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3.

(10) *Accord for Excel*, version 6.1; Synopsys Scientific Systems, Ltd.: Headingley, Leeds, U.K.

CC900020J