Traceless Solid-Phase Synthesis of 2,4,6-Trisubstituted Thiazolo[4,5-*d*]pyrimidine-5,7-dione Derivatives

Taeho Lee,[†] Ji-Hoon Park,[†,‡] Duck-Hyung Lee,[‡] and Young-Dae Gong*[,†]

Center for High Throughput Synthesis Platform Technology, Korea Research Institute of Chemical Technology, P.O. Box 107, Singseongno, Yuseong-gu, Daejeon 305-600, Korea and Department of Chemistry, Sogang University, Shinsoo-Dong 1, Mapo-gu, Seoul 121-742, Korea

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An expedient, traceless, solid-phase synthesis of 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives has been developed. The solid-phase synthetic route utilizes urea formation by a microwave irradiation promoted reaction of a thiazole amino ester resin with an isocyanate. The resulting urea resin is converted to a thiazolopyrimidinedione resin, containing two diversity elements at N-4 and N-6, by using a one-pot cyclization/N-alkylation process. After oxidation to form a sulfone, nucleophilic C-2 substitution with amines, the third diversity element, gives the target 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimide-5,7-dione derivatives. This highly efficient solid-phase synthetic sequence enables the incorporation of three points of diversity into the preparation of the thiazolo[4,5-*d*]pyrimidine-5,7-dione ring system.

Introduction

The combinatorial synthesis of small organic molecules in either the solution-phase or on solid support has had a significant impact in the area of drug discovery.[1,2] Among small molecule families, heterocyclic compounds have received particular attention in this regard, since they are often important structural components of bioactive molecules.[2] Thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives (**1**, Figure 1), congeners of xanthine and uracil (pyrimidinedione), exhibit a wide range of important biological properties[3] and, as a result, they serve as attractive targets for combinatorial library construction via solid-phase synthesis. For examples, thiazolo[4,5-*d*]pyrimidinedione have demonstrated activities as TNF-α inhibitors for rheumatoid arthritis, multiple sclerosis, and ashma,[3a] as antidepressant agents acting on the central nervous system, [3b] as hepatitis C virus (HCV) polymerase inhibitors, [3c] and as antihuman cytomegalovirus (HCMV) agents.[3d] In view of these diverse properties, methods for efficient synthesis of thiazolo[4,5-*d*]pyrimidine-5,7-diones have attracted much attention and led to the development of a number of preparative routes.[4] However, we have not been able to uncover reports which describe the synthesis of thiazolo[4,5-*d*]pyrimidine-5,7-diones on solid supports or concise approaches for solution-phase synthesis of 2,4,6-trisubstituted analogs. Related to this, several solid-phase syntheses of xanthine[5] and pyrrolo-[3,2-*d*]pyrimidinedione[6] have recently been described.

In an early effort, we developed a facile, rapid, traceless linker based solid-phase strategy for the preparation of a small molecule library based on the thiazole and fused-thiazole scaffolds.[7] As part of an ongoing drug discovery project, we required concise solid- or solution-phase routes for the construction of a fused-thiazolo heterocycle library. Below are described recent results from this investigation that has led to the first solid-phase synthetic protocol for preparation of 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives **1** (see Figure 1), which we believe is

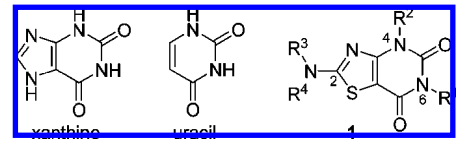
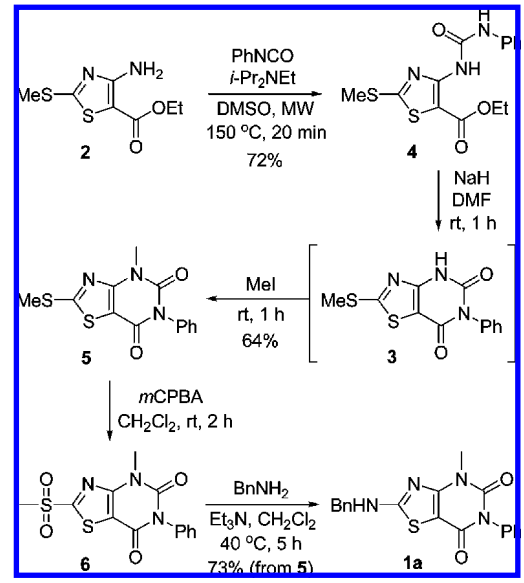


Figure 1. Structures of xanthine, uracil, and thiazolo[4,5-*d*]pyrimidine-5,7-dione **1**.

Scheme 1. Solution-Phase Synthesis of Thiazolo[4,5-*d*]pyrimidine-5,7-dione **1a**



* To whom correspondence should be addressed. Phone: 82-42-860-7149. Fax: 82-42-860-7698.
[†] Korea Research Institute of Chemical Technology.
[‡] Sogang University.

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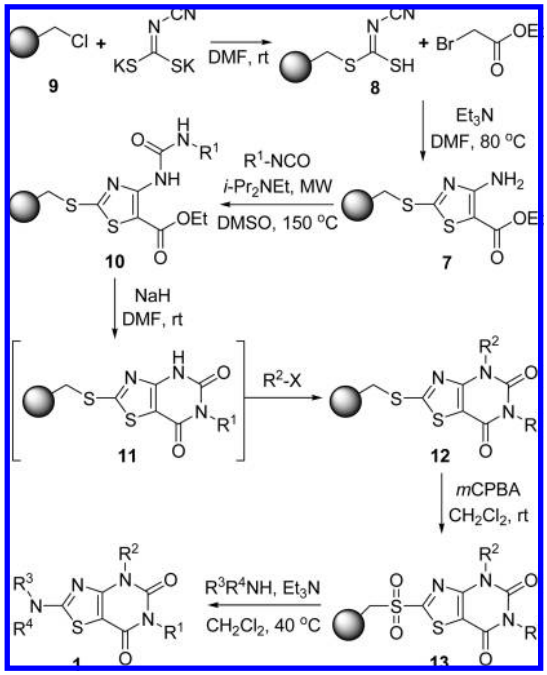
Scheme 2. Solid-Phase Synthesis of Thiazolo[4,5-*d*]pyrimidine-5,7-dione Derivatives **1**



applicable to high-throughput construction of drug-like compound libraries.

Results and Discussion

In preliminary studies, the development of reactions and conditions for the solution-phase synthesis of thiazolo-[4,5-*d*]pyrimidine-5,7-dione derivatives **1** was explored (Scheme 1). The route begins with conversion of the known thiazole amino ester **2**[7a,8] to the thiazolo[4,5-*d*]pyrimidine-5,7-dione **3** via reaction with isocyanates that serve as one diversity element. This is exemplified by the reaction of amino ester **2** with phenyl isocyanate in the presence of pyridine, *t*-BuOLi, or diisopropylethylamine. This process did not lead to high yielding formation of thiazolourea **4**, even in refluxing THF, toluene, or DMSO. Recently, microwave (MW) irradiation has been shown to be a powerful tool for various solution- or solid-phase chemical reactions.[9] Interestingly, reaction of **2** with phenyl isocyanate under MW irradiation conditions (*i*-Pr_2NEt, DMSO, 150 °C, 20 min), led to thiazolourea **4** in a 72% yield. Although MW-assisted reaction of amino ester compound with isocyanate in DMSO/H_2O is known to generate pyrimidinediones (e.g., **3**),[10] only urea **4** was obtained in our case.

Attempts to promote cyclization of thiazolourea **4** to form the thiazolo[4,5-*d*]pyrimidinedione ring by using various reaction conditions (NaOH, THF/H_2O,[4g,11] NaOEt, EtOH,[5b,12] and *t*-BuOK, toluene, or THF[13]) were unsuccessful. In contrast, the desired thiazolo[4,5-*d*]pyrimidine-5,7-dione **5** is obtained by employing a one-pot cyclization/N-alkylation procedure in a 64% yield. Accordingly, treatment of thiazolourea **4** with NaH in DMF[14] for 1 h at room temperature to generate cyclization product **3** is followed by in situ N-alkylation with methyl iodide for 1 h to generate **5**.

The thiazolo[4,5-*d*]pyrimidine-5,7-dione **5** was oxidized to form sulfone **6** by reaction with *m*CPBA in CH_2Cl_2. The sulfone group in **6** (crude) was displaced by reaction with benzylamine in CH_2Cl_2 to produce the target thiazolo [4,5-*d*]pyrimidine-5,7-dione derivative **1a** (73% yield from **5**). This product was characterized by using ESI-LC-MS, as well as ^{1}H and ^{13}C NMR spectroscopy. Overall, this solution-phase synthetic route is efficient and practical.

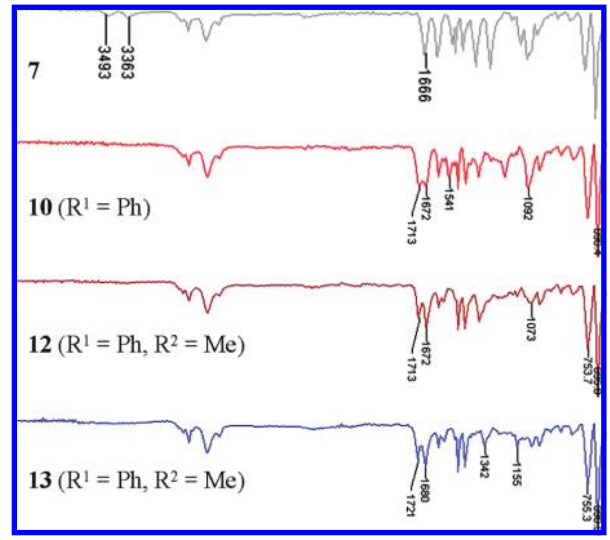


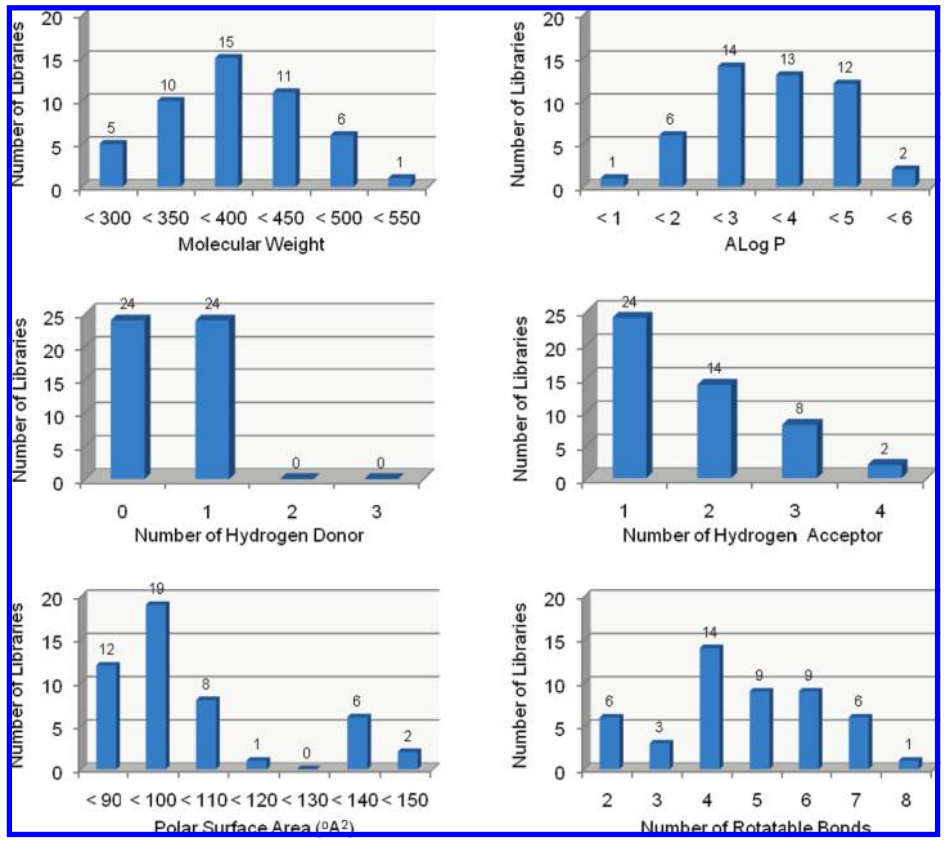
Figure 2. ATR-FTIR spectra of resins **7**, **10**, **12**, and **13** (R^1 = Ph, R^2 = Me).

On the basis of successful solution-phase reaction conditions, the solid-phase synthetic route for preparation of thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives utilizes appropriate isocyanates, alkyl halides, and amines as key building blocks and diversity elements. The sequence begins with formation of thiazole amino ester resin **7** through reaction of the solid supported cyanocarbonimidodithioate **8** with ethyl 2-bromoacetate (Scheme 2). The known resin **8** is derived from the Merrifield resin **9** by reaction with dipotassium cyanodithioimidocarbonate.[7]

The amino ester resin **7** is first swollen in DMSO and then treated under MW irradiation conditions with isocyanate (the first diversity element) to give the corresponding thiazolourea resin **10**. The progress of this reaction (R^1 = Ph) was monitored by using ATR-FTIR, which showed that the NH_2 stretching bands at 3493 and 3363 cm^{-1} disappeared in concert with the shift of an ester stretching band from 1666 cm^{-1} to 1672 cm^{-1} and the appearance of a urea carbonyl stretching band at 1713 cm^{-1} (Figure 2). The one-pot cyclization/N-alkylation of thiazolourea resin **10**, using NaH/alkyl halide (the second diversity element), was carried out in DMF at room temperature. Accordingly, treatment of resin **10** with NaH in DMF provided the intermediate **11**, which undergoes in situ N-alkylation with methyl iodide to provide the desired thiazolo[4,5-*d*]pyrimidine-5,7-dione resin **12** (R^1 = Ph, R^2 = Me). The progress of this process was monitored by using ATR-FTIR, which displayed the disappearance of the characteristic CNH band at 1541 cm^{-1}. Treatment of resin **13** with *m*CPBA in CH_2Cl_2 provides the resin-bound sulfone intermediate resin **13**. Although this reaction is not amenable to ATR-FTIR monitoring, it models well-known solution-phase thiazole forming reactions.[7,15]

Finally, the sulfone group in resin **13** is displaced by desulfonative substitution reaction with the corresponding

Chart 1. Calculated Physicochemical Properties of the 2,4,6-Trisubstituted Thizaolo[4,5-*d*]pyrimidine-5,7-dione Derivatives 1



amines (benzylamine for **1a**), serving as a third diversity element in CH_2Cl_2. This process, which is accompanied by concurrent cleavage from the resin, furnished the final thiazolo[4,5-*d*]pyrimidine-5,7-dione derivative **1a** (34% over six steps, from Merrifield resin **9**) which was purified by column chromatography. The ^{1}H NMR spectrum of thiazolo[4,5-*d*]pyrimidine-5,7-dione **1a** matched that of material produced by using the solution-phase synthetic route.

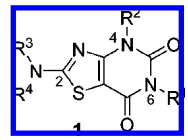
By using the new solid-phase synthetic route, we were able to prepare the thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives displayed in Table 1 starting from Merrifield resin **9** and appropriate isocyanates (R^1NCO), alkyl halides (R^2X), and amines (R^3R^4NH).

The results summarized in Table 1 show that when R^1 is phenyl or 4-methoxyphenyl, the corresponding thiazolo[4,5-*d*]pyrimidine-5,7-diones are produced in good yields (Table 1, entries 1−32, 21−34%). However, when R^1 is ethyl, the overall yields are lower (entries 33−48, 10−21%). Also, in contrast to cases in which the R^2 substituent is a benzyl or methyl where the yields of the thiazolo[4,5-*d*]pyrimidine-5,7-diones are high (entries 1−16, 25−34%), routes in which R^2 is the electron-withdrawing benzyl (4-nitrobenzyl) proceed inefficiently (entries 17−24, 21−28%). Among the R^3R^4NH series, desulfonative nucleophilic substitution takes place smoothly with benzyl, primary aliphatic, and secondary amines (entries 1−8). The isolated overall yields for thiazolo[4,5-*d*]pyrimidine-5,7-diones ranged from 10 to 34% for the six step linear pathway (average yield for each step was 69 to 84%) from the Merrifield resin **9**. Moreover, the target compounds are furnished in high purities [>95% as judged from LC-MS traces (integration of diode array 200−400 nm traces)] and characterized by using MS as well as ^{1}H and ^{13}C NMR spectroscopy.

Having established a flexible procedure for solid-phase synthesis of 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives **1**, our attention next turned to the evaluation of the potential drug properties of members of this heterocycle family. In general, the ultimate goal of a drug discovery programs is the synthesis of chemical entities that are orally bioavailable; that is, they possess physiological properties that allow them to be absorbed into the gastrointestinal system. Lipinski's Rule[16] and similar formulations serve as guides to an estimation of the physicochemical properties of the 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives calculated using Accord for Excel functions.[17] Of particular interest are the key bioavailability parameters including molecular weight, lipophilicity, number of hydrogen bond donors and acceptors, number of rotatable bonds, and the polar surface area. Chart 1 displays the results of these physicochemical property calculations, performed on the library we have constructed (see Table 1). As can be seen by viewing the data, most of the key parameters for members of the library fall within the range of those predicted for reasonable oral bioavailable drugs by using the commonly known guidelines.

In summary, this investigation has led to the development of the first traceless solid-phase synthetic route that efficiently generates 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives, which are congeners of xanthine and uracil. The sequence contains three diversity sites that are introduced in reactions involving isocyanates (R^1), alkyl halides (R^2), and amines (R^3). The strategy, based on an efficient solution-

Table 1. Prepared Thiazolo[4,5-*d*]pyrimidine-5,7-dione Derivatives **1** Using Solid-Phase Synthetic Route[a]



entry	products	R^1	R^2	R^3R^4N	Yield (%)[b]	entry	products	R^1	R^2	R^3R^4N	Yield (%)[b]
1	**1a**	Ph	Me	BnNH	34	25	**1y**	4-MeO-Ph	Me	BnNH	29
2	**1b**	Ph	Me	4-MeO-BnNH	31	26	**1z**	4-MeO-Ph	Me	4-MeO-BnNH	30
3	**1c**	Ph	Me	n-PrNH	30	27	**1aa**	4-MeO-Ph	Me	n-PrNH	29
4	**1d**	Ph	Me	$C_6H_{11}CH_2NH$	31	28	**1ab**	4-MeO-Ph	Me	$C_6H_{11}CH_2NH$	31
5	**1e**	Ph	Me	Et_2N	29	29	**1ac**	4-MeO-Ph	Me	Et_2N	23
6	**1f**	Ph	Me		25	30	**1ad**	4-MeO-Ph	Me		21
7	**1g**	Ph	Me		30	31	**1ae**	4-MeO-Ph	Me		26
8	**1h**	Ph	Me		31	32	**1af**	4-MeO-Ph	Me		23
9	**1i**	Ph	Bn	BnNH	32	33	**1ag**	Et	Me	BnNH	13
10	**1j**	Ph	Bn	4-MeO-BnNH	32	34	**1ah**	Et	Me	4-MeO-BnNH	12
11	**1k**	Ph	Bn	n-PrNH	33	35	**1ai**	Et	Me	n-PrNH	15
12	**1l**	Ph	Bn	$C_6H_{11}CH_2NH$	29	36	**1aj**	Et	Me	$C_6H_{11}CH_2NH$	14
13	**1m**	Ph	Bn	Et_2N	31	37	**1ak**	Et	Me	Et_2N	12
14	**1n**	Ph	Bn		27	38	**1al**	Et	Me		15
15	**1o**	Ph	Bn		26	39	**1am**	Et	Me		15
16	**1p**	Ph	Bn		30	40	**1an**	Et	Me		19
17	**1q**	Ph	4-NO_2-Bn	BnNH	27	41	**1ao**	Et	Bn	BnNH	18
18	**1r**	Ph	4-NO_2-Bn	4-MeO-BnNH	24	42	**1ap**	Et	Bn	4-MeO-BnNH	17
19	**1s**	Ph	4-NO_2-Bn	n-PrNH	28	43	**1aq**	Et	Bn	n-PrNH	20
20	**1t**	Ph	4-NO_2-Bn	$C_6H_{11}CH_2NH$	23	44	**1ar**	Et	Bn	$C_6H_{11}CH_2NH$	16
21	**1u**	Ph	4-NO_2-Bn	Et_2N	22	45	**1as**	Et	Bn	Et_2N	19
22	**1v**	Ph	4-NO_2-Bn		21	46	**1at**	Et	Bn		10
23	**1w**	Ph	4-NO_2-Bn		24	47	**1au**	Et	Bn		21
24	**1x**	Ph	4-NO_2-Bn		22	48	**1av**	Et	Bn		18

[a] All reactions were performed on 150−200 mg scale of resin **13** and R^2X (MeI, BnBr, and 4-NO_2−BnBr) were used. [b] Six-step overall isolated yield from Merrifield resin **9** (loading capacity = 0.94 mmol/g).

phase sequence, enables the construction of a large library and is potentially applicable for the preparation of other drug-like thiazolo-fused ring systems. Finally, the calculated physicochemical properties of members of the library constructed by using this approach are well distributed within reasonable oral acceptable drug-like ranges. Further studies in this area are underway, the results of which will be reported in due course.

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Supporting Information Available. Full experimental procedures, analytical data of compounds, copies of ^1H NMR, ^{13}C NMR, and LC-MS spectra of compounds **1a**−**1av**, **4**, and **5**, and ATR-FTIR spectra of resins **7**−**10** and **12**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Nicolaou, K. C.; Hanko, R.; Hatwig, W. *Handbook of Combinatorial Chemistry*; Wiley-VCH: Washington, DC,

2002. (b) Wilson, S. R.; Czarnik, A. W. *Combinatorial Chemistry, Synthesis and Application*; Wiley: New York, 1997.

(2) (a) Kennedy, J. P.; Williams, L.; Bridges, T. M.; Daniels, R. N.; Weaver, D.; Lindsley, C. W. *J. Comb. Chem.* **2008**, *10*, 345–354. (b) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Salvino, J. M.; Zhang, W. *J. Comb. Chem.* **2007**, *9*, 855–902. (c) Dolle, R. E.; Le Bourdonnec, B.; Morales, G. A.; Moriarty, K. J.; Salvino, J. M. *J. Comb. Chem.* **2006**, *8*, 597–635.

(3) For biological activities of thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives, see(a) Carson, D. A.; Cottam, H. B.; Deng, L. PCT Int. Appl. WO2000069861, 2000. (b) Berger, A.; Borgeas, E. E.;Ger. Offen. DE2038922, 1971. (c) Abe, H.; Tanaka, M.; Sugimoto, K.; Suma, A.; Yokota, M.; Shiozaki, M.; Ito, K.; Ueyama, K.; Motoda, D.; Noguchi, T.; Adachi, T.; Tsuruha, J.; Doi, S. PCT Int. Appl. WO2007119889, 2007. (d) Lewis, A. F.; Revankar, G. R.; Fennewald, S. M.; Susan, M.; Huffman, J. H.; Rando, R. F. *J. Heterocycl. Chem.* **1995**, *32*, 547–556.

(4) For syntheses of thiazolo[4,5-*d*]pyrimidine-5,7-dione derivatives, see(a) Iaroshenko, V. O.; Volochnyuk, D. M.; Yan, W.; Vovk, M. V.; Boiko, V. J.; Rusanov, E. B.; Groth, U. M.; Tolmachev, A. A. *Synthesis* **2007**, 3309–3318. (b) Chande, M. S.; Bhandari, J. D.; Karyekar, A. S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1995**, *34B*, 985–989. (c) Ahluwalia, V. K.; Shashibala; Aggarwal, R.; Chandra, R. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1989**, *28*, 964–965. (d) Ichiba, M.; Senga, K. *J. Heterocycl. Chem.* **1985**, *22*, 381–384. (e) Walek, W.; Manfred, G.; Kurt, K. W.; Werner, R. D. Ger. (East) DD208355, 1984. (f) Walek, W. *Z. Chem.* **1983**, *23*, 179–180. (g) Gompper, R.; Gäng, M.; Saygin, F. *Tetrahedron Lett.* **1966**, *17*, 1885–1889.

(5) For solid-phase syntheses of xanthine, see(a) He, R.; Ching, S. M.; Lam, Y. *J. Comb. Chem.* **2006**, *8*, 923–928. (b) He, R.; Lam, Y. *J. Comb. Chem.* **2005**, *7*, 916–920. (c) Beer, D.; Bhalay, G.; Dunstan, A.; Glen, A.; Haberthuer, S.; Moser, H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1973–1976. (d) Heizmann, G.; Eberle, A. N. *Mol. Diversity* **1997**, *2*, 171–174.

(6) For solid-phase syntheses of pyrrolo[3,2-*d*]pyrimidinedione, see(a) Fridkin, G.; Lubell, W. D. *J. Comb. Chem.* **2005**, *7*, 977–986. (b) Rombouts, F. J. R.; Frederik, J. R.; Fridkin, G.; Lubell, W. D. *J. Comb. Chem.* **2005**, *7*, 589–598.

(7) (a) Lee. T.; Park, J.-H.; Jeon, M.-K.; Gong, Y.-D. *J. Comb. Chem.* **2009**, *11*, 288–293. (b) Lee, I. Y.; Lee, J. Y.; Lee, H. J.; Gong, Y.-D. *Synlett* **2005**, 2483–2485.

(8) (a) Wamhoff, H.; Berressem, R.; Herrmann, S. *Synthesis* **1993**, 107–111. (b) Leysen, D. C.; Haemers, A.; Bollaet, W. *J. Heterocycl. Chem* **1984**, *21*, 1361–1366. (c) Walek, W.; Pallas, M.; Augcstin, M. *Tetrahedron* **1976**, *32*, 623–627.

(9) For recent reviews, see(a) Tierney, J. P., Lidström, P. *Microwave Assisted Organic Synthesis*; Blackwell: Oxford, U.K., 2005. (b) Molteni, V.; Ellis, D. A. *Curr. Org. Synth* **2005**, *2*, 333–375. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberin, R. *J. Comb. Chem.* **2002**, *4*, 95–105.

(10) Li, Z.; Huang, H.; Sun, H.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2008**, *10*, 484–486.

(11) (a) Xin, Z.; Pei, Z.; Geldem, T.; Jirousek, M. *Tetrahedron Lett.* **2000**, *41*, 1147–1150. (b) Baraldi, P. G.; Cacciari, B.; Manfredini, S.; Pollini, G. P.; Simoni, D.; Spalluto, G.; Zanirato, V. *J. Org. Chem.* **1995**, *60*, 1461–1463.

(12) (a) Chowdhury, A. Z.; M, S.; Shibata, Y. *Chem. Pharm. Bull* **2001**, *49*, 391–395. (b) Ogawva, K.; Yamawaki, I.; Matsusita, Y. I.; Nomura, N.; Kador, P. F.; Kinoshita, J. H. *Eur. J. Med. Chem.* **1993**, *28*, 769–782.

(13) (a) Meyer, M. D.; Altenbach, R. J.; Bai, H.; Basha, F. Z.; Carroll, W. A.; Kerwin, J. F.; Lebold, S. A.; Lee, E.; Pratt, J. K.; Sippy, K. B.; Tietje, K.; Wendt, M. D.; Brune, M. E.; Buckner, S. A.; Hancock, A. A.; Drizin, I. *J. Med. Chem.* **2001**, *44*, 1971–1985. (b) Romine, J. L.; Martin, S. W.; Meanwell, N. A.; Epperson, J. R. *Synthesis* **1994**, 846–850.

(14) Danswan, G.; Kennewell, P. D.; Tully, W. R. *J. Heterocycl. Chem.* **1989**, *26*, 293–299.

(15) (a) Johnson, S. G.; Connolly, P. J.; Murray, W. V. *Tetrahedron Lett.* **2006**, 4853–4856. (b) Alvarez-Ibarra, C.; Fernández-Granda, R.; Quiroga, M. L.; Carbonell, A.; Cárdenas, F.; Giralt, E. *J. Med. Chem.* **1997**, *40*, 668–676. (c) Yamanaka, H.; Ohba, S.; Sakamoto, T. *Heterocycles* **1990**, *31*, 1115–1127.

(16) Lipinski, C. A.; Lombardo, F.; Doming, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25.

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

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