http://dx.doi.org/10.5012/bkcs.2014.35.12.3609

Microwave Assisted Synthesis of 1,3,4-Oxadiazole/Thiohydantoin Hybrid Derivatives *via* Dehydrative Cycliztion of Semicarbazide

Seung-Ju Yang,[a] Jae-Min Lee,[a] Gee-Hyung Lee, NaYeon Kim, Yong-Sang Kim, and Young-Dae Gong[*]

Innovative Drug Library Research Center, Department of Chemistry, College of Science, Dongguk University, Seoul 100-715, Korea. [*]E-mail: ydgong@dongguk.edu
Received July 29, 2014, Accepted September 16, 2014

A series of compounds containing both 1,3,4-oxadiazole and thiohydantoin were synthesized as a promising scaffold for application in medicinal chemistry. The key step of the synthesis is a microwave-assisted cyclization of semicarbazides possessing a thiohydantoin moiety at one of the acyl termini using $POCl_3$ as a dehydrating reagent. A wide range of semicarbazides were prepared through the substitution of hydrazides with an *N*-acylated thiohydantoin derived from the cyclization of the corresponding isothiocyanate with an amino acid and subsequent *N*-acylation of the resultant thiohydrantion. Consequently, the 58 number of 1,3,4-oxadiazole derivatives having a thiohydantoin substituent were prepared in good overall yields.

Key Words : Thiohydantoin, 1,3,4-Oxadiazole, Semicarbazide, Microwave, Amino acid

Introduction

Heterocyclic compounds serve as ideal scaffolds to which pharmacophores can be appended to yield potent and selective drugs.[1] This is particullarly true for five-membered heterocyclic compounds, which are core components of a large number of substances that possess interesting biological activities. Among this family, 1,3,4-oxadiazoles and thiohydantoins have been used as "privileged" scaffolds to produce intriguing substances in numerous therapeutic areas including anti-inflamatories,[2] antimicrobial,[3] anti-diabetes,[4] and anti-cancer.[5] In this context, we previously reported that 1,3,4-oxadiazole derivatives show potent biological activity in a canonical Wnt signaling pathway.[6] Moreover, there have been reports that 1,3,4-oxadiazoles substituted with other heterocyclic unit such as pyrazole,[7a] 1,2,3-triazole,[7b] and pyridine[7c] also show potent biological activity. Along these lines, we became interested in the synthesis of 1,3,4-oxadiazole derivatives equipped with a thiohydrantoin moiety as a heterocyclic unit. While synthetic methods for both thiohydantoin[8] and 1,3,4-oxadiazole[9] derivatives have been studied well, synthetic routes for the preparation of 1,3,4-oxadiazoles possessing a 2-thiohydantoin moiety are unprecedented in the literature. To this end, we developed a reliable and expedient synthetic route for the preparation of 1,3,4-oxadiazole derivatives possessing a thiohydantoin moiety.

Microwave irradiation in chemical synthesis has been well recognized both for increasing reaction rates and for reducing side reaction. It can generate the desired compound in a relatively short time, compared to conventional thermal heating conditions, and with low cost. Thus a broad range of applications of microwave irradiation have been reported in combinatorial chemistry,[10] peptide synthesis,[11] polymer chemistry,[12] green chemistry,[13] and carbohydrate chemistry.[14]

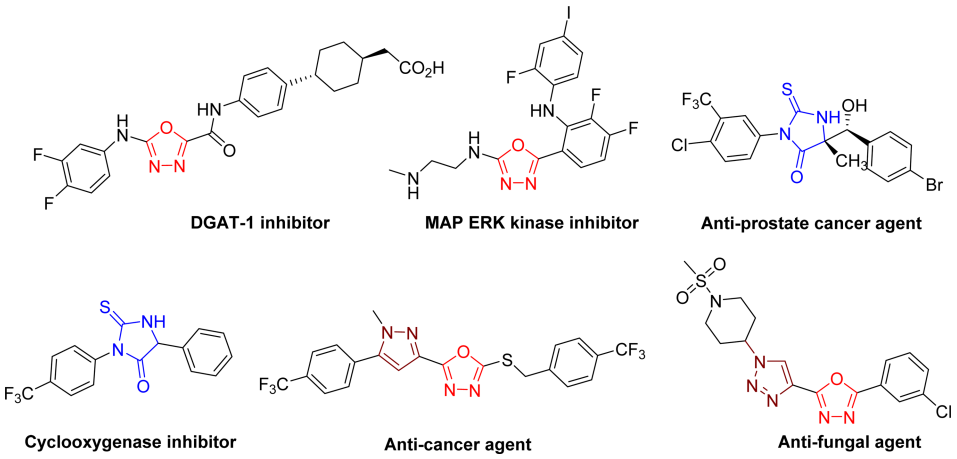
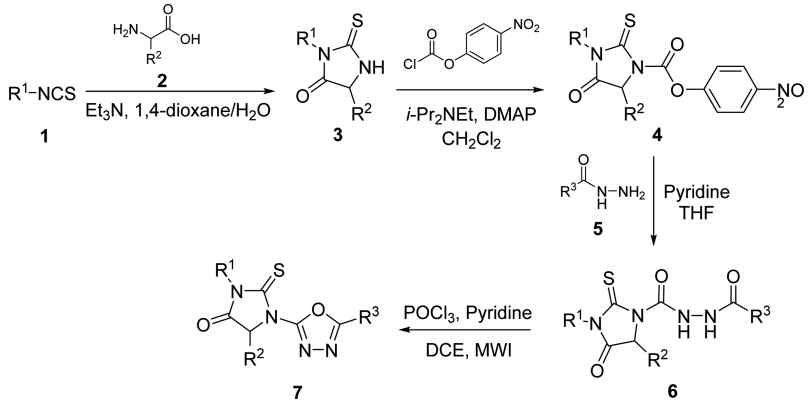


Figure 1. Biologically active compounds containing 1,3,4-oxadiazole, thiohydantoin, and 1,3,4-oxadiazole equipped with heterocyclic unit.

[a]These authors contributed equally to this work.



Scheme 1. Synthetic route for the synthesis of 1,3,4-oxadiazoles equipped with a thiohydantoin moiety.

We sought to develop an efficient synthetic method for the preparation of various drug-like 1,3,4-oxadiazole derivatives equipped with a thiohydrantoin substituent employing microwave irradiation. Herein, we report our recent progress on this project, which includes a microwave-assisted dehydrative cyclization process for the 1,3,4-oxadiazole derivatives **7**.

Results

The sequence used to prepare the thiohydantoin **3** employs the isothiocyanate **1** as the first diversity element. Treatment of isothiocyanates **1** with various amino acids **2**, which are second diversity element, in the presence of triethylamine at room temperature leads to production of the corresponding cyclized thiohydantoin **3** under a thermodynamic condition. However when R^1 is benzyl, 2,4-dimethoxy benzyl, and ethyl, reaction time was long (10-12 h) for converting to thiohydantoin despite heating to 100 °C (data not shown). We therefore modified reaction condition by using microwave irradiation. Before we conducted microwave assisted cyclization, we prepared thiourea intermediate under thermodynamic condition (Table 1). Et_3N was added slowly to the mixture of isothiocyanates **1** and amino acids **2** in 1,4-dioxane-H_2O (1:1, v/v) and then the reaction mixture was stirred for 1 h at room temperature. We checked formation of thiourea intermediate by thin layer chromatography (TLC). Next, concentrated HCl was added to the reaction mixture until the pH became ~2[15] and then it was irradiated with microwave radiation. The cyclization was concluded within 2 min. The results are summarized in Table 1.

As the strategy for preparation of semicarbazide **6**, thiohydantoin **3** was acylated with 4-nitrophenyl chloroformate in the presence of *i*-Pr_2NEt/cat DMAP in CH_2Cl_2 at room temperature. It generated the corresponding acylated thiohydantoin **4** in a good yield. The results of *N*-acylation of thiohydantoin are summarized in Table 2.

For the synthesis of semicarbazide **6**, we used various hydrazides **5** as the third diversity element. The substitution reaction was smoothly going well with a pyridine in a tetrahydrofuran (THF) at 60 °C for 8 h. The results of the substitution reactions of compounds **4** are summarized in Table 3.

To investigate suitable methods for effective synthesis of 1,3,4-oxadiazoles **7**, dehydrative cyclization of semicarbazide **6a** was investigated by using various dehydrating reagents such as trimethylsillyl chloride (TMSCl),[16] *p*-

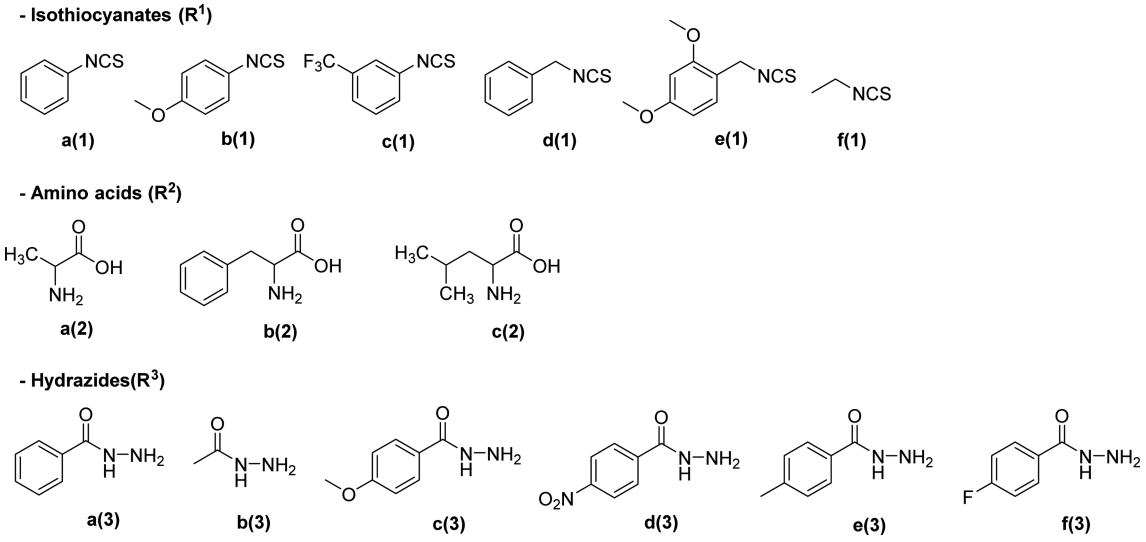
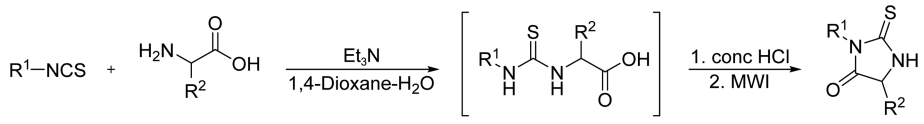


Figure 2. Building blocks.

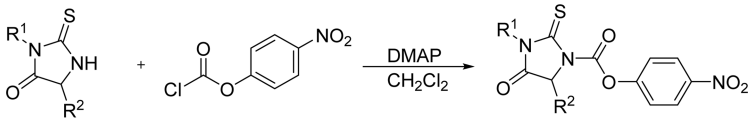
Table 1. Yields of the cyclization reaction of isothiocyanates **1** with amino acids **2**[a]



No	R^1	R^2	Yield[b] (%)	No	R^1	R^2	Yield[b] (%)
3a	Ph	Me	93	**3h**	Bn	Me	80
3b	Ph	Bn	84	**3i**	Bn	Bn	82
3c	Ph	*i*-Bu	84	**3j**	2,4-DiMeO-Ph	Me	77
3d	4-MeO-Ph	Me	91	**3k**	2,4-DiMeO-Ph	Bn	69
3e	4-MeO-Ph	Bn	85	**3l**	Ethyl	Me	71
3f	3-CF_3-Ph	Me	94	**3m**	Ethyl	Bn	78
3g	3-CF_3-Ph	Bn	81				

[a]Reaction condition : Amino acid **2** (1.0 equiv) was added to a solution of isothiocyanate (1.0 equiv) in the 1,4-dioxane–H_2O (1:1, v/v) and cooled to 0 °C. Et_3N (2.0 equiv) was added slowly to the reaction mixture and the solution was stirred for 1 h, followed by the addition of conc. HCl (3.0 equiv) at 0 °C until the pH reached ~2. The reaction mixture was transferred into a sealed vessel and microwave radiated at 160 °C for 2 min. [b]Isolated yield. MWI : Microwave irradiation.

Table 2. Yields of the *N*-acylation of thiohydantoins **3**[a]



No	R^1	R^2	Yield[b] (%)	No	R^1	R^2	Yield[b] (%)
4a	Ph	Me	82	**4h**	Bn	Me	76
4b	Ph	Bn	90	**4i**	Bn	Bn	86
4c	Ph	*i*-Bu	83	**4j**	2,4-DiMeO-Ph	Me	83
4d	4-MeO-Ph	Me	67	**4k**	2,4-DiMeO-Ph	Bn	84
4e	4-MeO-Ph	Bn	84	**4l**	Ethyl	Me	69
4f	3-CF_3-Ph	Me	83	**4m**	Ethyl	Bn	77
4g	3-CF_3-Ph	Bn	88				

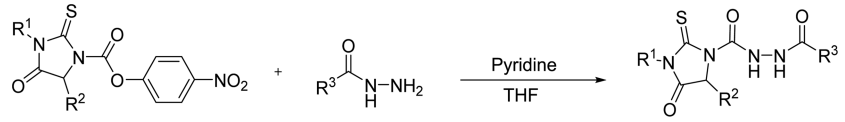
[a]Reaction condition : Thiohydantoin (1.0 equiv) was added to the solution of 4-nitrophenyl chloroformate (1.3 equiv) and DMAP (0.01 equiv) in CH_2Cl_2. After 30 min, *i*-Pr_2Net (1.0 equiv) was added slowly to the reaction mixture and the solution was stirred for 2 h. [b]Isolated yield.

toluenesulfonyl chloride (*p*-TsCl),[17] and phosphorus oxychloride ($POCl_3$)[18] in various conditions. The results of the dehydrative cyclization of **6a** are summarized in Table 4. First, we used TMSCl as a dehydrating agent in various condition (Table 4, Entries 1-3), but we could not obtain the desired product **7a**. On the other hand, the side product **8a** was obtained with Et_3N (Table 4, entry 3). We checked the ^1H and ^{13}C NMR spectrum of side product **8a** (Figure 1 in the supporting information) and proposed the reaction mechanism (Scheme 2). In this side reaction, thiohydantoin act as a leaving group instead of trimethyl silanol.

Next, we used *p*-TsCl for the dehydrative cyclization with various base (Table 4, Entries 4-7). In the case of pyridine, there was a no reaction (Table 4, Entry 4) and side product **8b** was obtained with *i*-Pr_2Net or Et_3N (Table 4, Entries 6, 7). Only with DMAP (Table 4, Entry 5), we could obtain desired product **7a** in a low yield with the side product **8b**. $^1H/^{13}C$ NMR, and LC/MS spectrum of **8b** are showed in Figure 2 of supporting information and proposed mechanism is described in Scheme 3. In the case of *p*-TsCl, side product **8b** was also obtained in the similar manner of TMSCl.

We therefore searched another dehydrating reagent which only afford desired product **7a** without side product **8**. In various organic synthesis, $POCl_3$ has been used as a dehydrating reagent.[18] We therefore used $POCl_3$ as both a dehydrative reagent and a solvent. In our study $POCl_3$ generated only desired product **7a** without side product **8** in a moderate yield (Table 4, Entries 8). However, $POCl_3$ has a high toxicity and difficult to quench. Accordingly, we used stoichiometric amounts of $POCl_3$ with pyridine as a scavenger in dichlroethane (DCE) (Table 4, Entry 9). However, there was a long reaction time and low yield. To overcome these problems, we used microwave irradiation for the efficient dehydrative cyclization. As a result, semicarbazide **6a** was converted to the 1,3,4-oxadiazole **7a** with a microwave irradiation in a short time and high yield (Table 4, Entry 10). To compare reaction time and conversion between thermodynamic condition (Table 4, Entry 9) and microwave irradiation (Table 4, Entry 10), we used HPLC analysis. In the result of HPLC analysis, we confirmed that semicarbazide

Table 3. Yields of substitution reaction of *N*-acylated thiohydantoin **4** with hydrazide **5**[a]



4 **5** **6**

No	R^1	R^2	R^3	Yield[b] (%)	No	R^1	R^2	R^3	Yield[b] (%)
6a	Ph	Me	Ph	80	**6ad**	3-CF_3-Ph	Me	4-NO_2-Ph	34
6b	Ph	Me	Me	76	**6ae**	3-CF_3-Ph	Bn	Ph	48
6c	Ph	Me	4-MeO-Ph	70	**6af**	3-CF_3-Ph	Bn	Me	47
6d	Ph	Me	4-NO_2-Ph	48	**6ag**	3-CF_3-Ph	Bn	4-MeO-Ph	55
6e	Ph	Me	4-Me-Ph	63	**6ah**	3-CF_3-Ph	Bn	4-NO_2-Ph	59
6f	Ph	Me	4-F-Ph	76	**6ai**	Bn	Me	Ph	76
6g	Ph	Bn	Ph	69	**6aj**	Bn	Me	Me	75
6h	Ph	Bn	Me	76	**6ak**	Bn	Me	4-MeO-Ph	73
6i	Ph	Bn	4-MeO-Ph	86	**6al**	Bn	Me	4-NO_2-Ph	73
6j	Ph	Bn	4-NO_2-Ph	61	**6am**	Bn	Bn	Ph	69
6k	Ph	Bn	4-Me-Ph	91	**6an**	Bn	Bn	Me	59
6l	Ph	Bn	4-F-Ph	69	**6ao**	Bn	Bn	4-MeO-Ph	67
6m	Ph	*i*-Bu	Ph	81	**6ap**	Bn	Bn	4-NO_2-Ph	65
6n	Ph	*i*-Bu	Me	71	**6aq**	2,4-DiMeO-Bn	Me	Ph	81
6o	Ph	*i*-Bu	4-MeO-Ph	73	**6ar**	2,4-DiMeO-Bn	Me	Me	83
6p	Ph	*i*-Bu	4-NO_2-Ph	65	**6as**	2,4-DiMeO-Bn	Me	4-MeO-Ph	83
6q	Ph	*i*-Bu	4-Me-Ph	77	**6at**	2,4-DiMeO-Bn	Me	4-NO_2-Ph	70
6r	Ph	*i*-Bu	4-F-Ph	61	**6au**	2,4-DiMeO-Bn	Bn	Ph	75
6s	4-MeO-Ph	Me	Ph	78	**6av**	2,4-DiMeO-Bn	Bn	Me	79
6t	4-MeO-Ph	Me	Me	69	**6aw**	2,4-DiMeO-Bn	Bn	4-MeO-Ph	78
6u	4-MeO-Ph	Me	4-MeO-Ph	70	**6ax**	2,4-DiMeO-Bn	Bn	4-NO_2-Ph	72
6v	4-MeO-Ph	Me	4-NO_2-Ph	77	**6ay**	Ethyl	Me	Ph	72
6w	4-MeO-Ph	Bn	Ph	77	**6az**	Ethyl	Me	Me	84
6x	4-MeO-Ph	Bn	Me	84	**6ba**	Ethyl	Me	4-MeO-Ph	93
6y	4-MeO-Ph	Bn	4-MeO-Ph	86	**6bb**	Ethyl	Me	4-NO_2-Ph	86
6z	4-MeO-Ph	Bn	4-NO_2-Ph	62	**6bc**	Ethyl	Bn	Ph	84
6aa	3-CF_3-Ph	Me	Ph	84	**6bd**	Ethyl	Bn	Me	88
6ab	3-CF_3-Ph	Me	Me	42	**6be**	Ethyl	Bn	4-MeO-Ph	85
6ac	3-CF_3-Ph	Me	4-MeO-Ph	62	**6bf**	Ethyl	Bn	4-NO_2-Ph	74

[a]Reaction condition: *N*-acylated thiohydantoin **4** (1.0 equiv) was added to the mixture of hydrazide (1.05 equiv) and pyridine (1.05 equiv) in THF at room temperature. The reaction mixture was heated to 60 °C and then stirred for 8 h. [b]Isolated yield.

6a was smoothly converted to the 1,3,4-oxadiazole **7a** with microwave irradiation within 30 min, while under thermodynamic conditions a large amount of starting material still remained after 24 h (Figure 3).

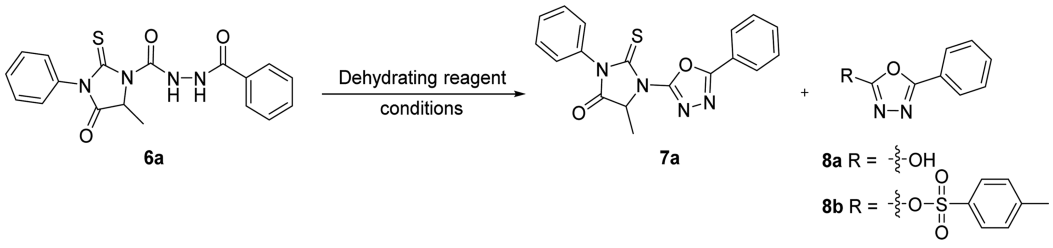
Next, several representative semicarbazides **6** were used to compare reaction time and conversion with both microwave irradiation and thermodynamic conditions (Table 1 in Supporting Information). Most of results show that microwave irradiation reduced the reaction time and increased the yield. Consequently, we utilized $POCl_3$/pyridine with microwave irradiation for the dehydrative cyclization of semicarbazide **6**. Next, we explored the various substrate to afford various 1,3,4-oxadiazole derivatives **7** and obtained our desired compounds **7** in a good yield. The results are summarized in a Table 5.

Finally, we turned our attention to the evaluation of the potential drug properties of 1,3,4-oxadiazole derivatives **7**. In the drug discovery process, the ultimate goal is synthesis of orally available drug. To this end, Lipinski's Rule[19] and similar formulations serve as guideline to an estimation of the physicochemical properties of the 1,3,4-oxadiazole derivatives **7**. The key bioavailability parameters including molecular weight, lipophilicity, number of hydrogen bond donors and acceptors, number of rotatable bonds, and the polar surface area are displayed in the Figure 4. As can be seen by viewing the data, even though lipophilicity (ALogP) is slightly high, most of the key parameters of 1,3,4-oxadiazole derivatives **7** fall within the range of those predicted for reasonable oral bioavailable drugs by using the commonly known guidelines.

Conclusions

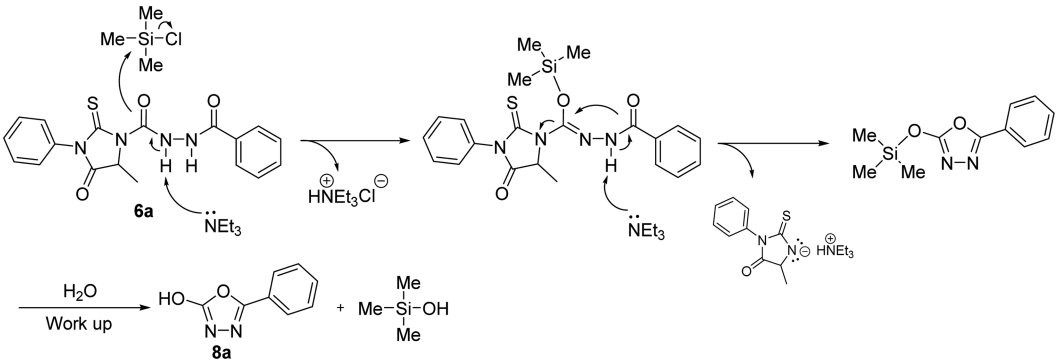
In conclusion, we developed efficient synthetic route for

Table 4. Optimization of reaction condition for the dehydrative cyclization[a]

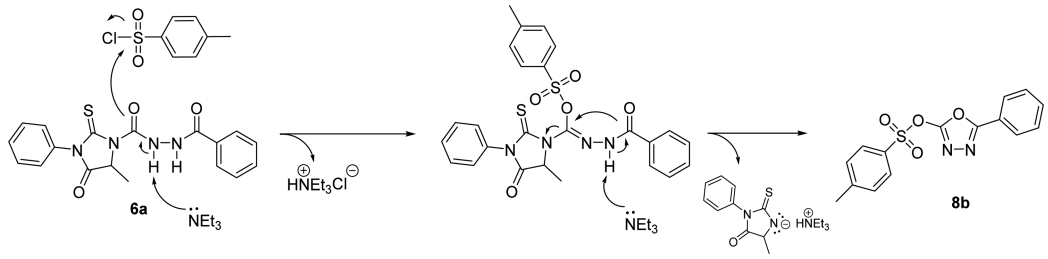


Entry	Dehyrdrating reagent	Solvent	Temp.	Time	Yield[b]	
					7a	**8**
1	TMSCl	DCE	60 °C	4 h	N.R.	
2	TMSCl/pyridine	DCE	60 °C	4 h	N.R.	
3	TMSCl/Et_3N	DCE	60 °C	2 h	–	54%(**8a**)
4	*p*-TsCl/pyridine	DCE	60 °C	8 h	N.R.	
5	*p*-TsCl/DMAP	DCE	rt	8 h	39%	20%(**8b**)
6	*p*-TsCl/*i*-Pr_2NEt	DCE	rt	8 h	–	37%(**8b**)
7	*p*-TsCl/Et_3N	DCE	rt	6 h	–	36%(**8b**)
8	$POCl_3$	neat	80 °C	8 h	64%	–
9[c]	$POCl_3$/pyridine	DCE	80 °C	24 h	58%	–
10	$POCl_3$/pyridine	DCE	MWI, 160 °C	0.5 h	88%	–

[a]A mixture of semicarbazide **6** (1.0 equiv), $POCl_3$ (1.2 equiv), and pyridine (2.2 equiv) in DCE in a vessel was loaded into a microwave. The vessel was sealed and irradiated with stirring at a 160 °C at 4 bar for 30 min. [b]Isolated yield. [c]$POCl_3$ (1.2 equiv) was added to the reaction mixture of semicarbazide **6** (1.0 equiv) and pyridine (2.2 equiv) in DCE at room temperature. The reaction mixture was heated to 80 °C and then stirred for 24 h. N.R: No reaction. MWI: Microwave irradiation.



Scheme 2. Proposed mechanism of side reaction by TMSCl/Et_3N in DCE.



Scheme 3. Proposed mechanism of side reaction by *p*-TsCl/Et_3N in DCE.

synthesis of 1,3,4-oxadiazole derivatives having thiohydantoin moiety with a three diversity point *via* microwave assisted organic synthesis. Various isothiocyanates, aminoacids, and hydrazideds were used as building block. Consequently, 58 1,3,4-oxadiazole derivatives equipped with thiohydantoin moiety were synthesized and fully characterized. Finally the calculated physicochemical properties of our synthesized library are well distributed within reasonable oral acceptable drug-like ranges. We believe that these molecules will serve valuable library for medicinal chemistry.

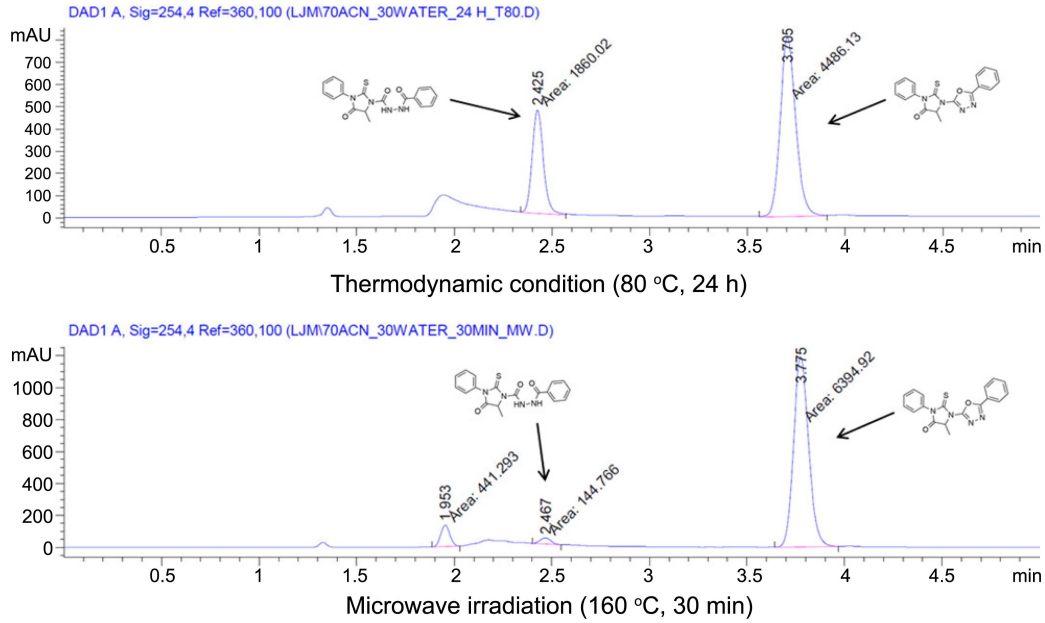
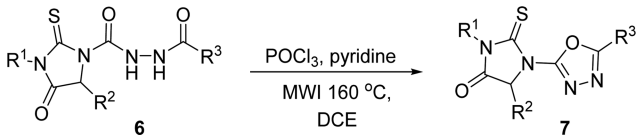


Figure 3. Comparison of reaction time and conversion between thermodynamic and microwave irradiation condition.

Table 5. Results of the dehydrative cyclization of semicarbazide **6**[a]



No	R^1	R^2	R^3	Yield[b] (%)	No	R^1	R^2	R^3	Yield[b] (%)
7a	Ph	Me	Ph	88	**7ad**	3-CF_3-Ph	Me	4-NO_2-Ph	53
7b	Ph	Me	Me	84	**7ae**	3-CF_3-Ph	Bn	Ph	54
7c	Ph	Me	4-MeO-Ph	78	**7af**	3-CF_3-Ph	Bn	Me	75
7d	Ph	Me	4-NO_2-Ph	64	**7ag**	3-CF_3-Ph	Bn	4-MeO-Ph	68
7e	Ph	Me	4-Me-Ph	66	**7ah**	3-CF_3-Ph	Bn	4-NO_2-Ph	44
7f	Ph	Me	4-F-Ph	67	**7ai**	Bn	Me	Ph	77
7g	Ph	Bn	Ph	70	**7aj**	Bn	Me	Me	65
7h	Ph	Bn	Me	90	**7ak**	Bn	Me	4-MeO-Ph	85
7i	Ph	Bn	4-MeO-Ph	84	**7al**	Bn	Me	4-NO_2-Ph	72
7j	Ph	Bn	4-NO_2-Ph	71	**7am**	Bn	Bn	Ph	74
7k	Ph	Bn	4-Me-Ph	80	**7an**	Bn	Bn	Me	85
7l	Ph	Bn	4-F-Ph	75	**7ao**	Bn	Bn	4-MeO-Ph	88
7m	Ph	*i*-Bu	Ph	85	**7ap**	Bn	Bn	4-NO_2-Ph	60
7n	Ph	*i*-Bu	Me	86	**7aq**	2,4-DiMeO-Bn	Me	Ph	86
7o	Ph	*i*-Bu	4-MeO-Ph	97	**7ar**	2,4-DiMeO-Bn	Me	Me	79
7p	Ph	*i*-Bu	4-NO_2-Ph	65	**7as**	2,4-DiMeO-Bn	Me	4-MeO-Ph	85
7q	Ph	*i*-Bu	4-Me-Ph	71	**7at**	2,4-DiMeO-Bn	Me	4-NO_2-Ph	71
7r	Ph	*i*-Bu	4-F-Ph	62	**7au**	2,4-DiMeO-Bn	Bn	Ph	80
7s	4-MeO-Ph	Me	Ph	91	**7av**	2,4-DiMeO-Bn	Bn	Me	88
7t	4-MeO-Ph	Me	Me	94	**7aw**	2,4-DiMeO-Bn	Bn	4-MeO-Ph	84
7u	4-MeO-Ph	Me	4-MeO-Ph	83	**7ax**	2,4-DiMeO-Bn	Bn	4-NO_2-Ph	75
7v	4-MeO-Ph	Me	4-NO_2-Ph	64	**7ay**	Ethyl	Me	Ph	73
7w	4-MeO-Ph	Bn	Ph	76	**7az**	Ethyl	Me	Me	85
7x	4-MeO-Ph	Bn	Me	91	**7ba**	Ethyl	Me	4-MeO-Ph	74
7y	4-MeO-Ph	Bn	4-MeO-Ph	97	**7bb**	Ethyl	Me	4-NO_2-Ph	69
7z	4-MeO-Ph	Bn	4-NO_2-Ph	68	**7bc**	Ethyl	Bn	Ph	84
7aa	3-CF_3-Ph	Me	Ph	62	**7bd**	Ethyl	Bn	Me	83
7ab	3-CF_3-Ph	Me	Me	78	**7be**	Ethyl	Bn	4-MeO-Ph	94
7ac	3-CF_3-Ph	Me	4-MeO-Ph	65	**7bf**	Ethyl	Bn	4-NO_2-Ph	74

[a]Reaction condition: A mixture of semicarbazide 6 (1.0 equiv), $POCl_3$ (1.2 equiv), and pyridine (2.2 equiv) in DCE in a vessel was loaded into a microwave. The vessel was sealed and irradiated with stirring at a 160 °C at 4 bar for 30 min. [b]Isolated yield.

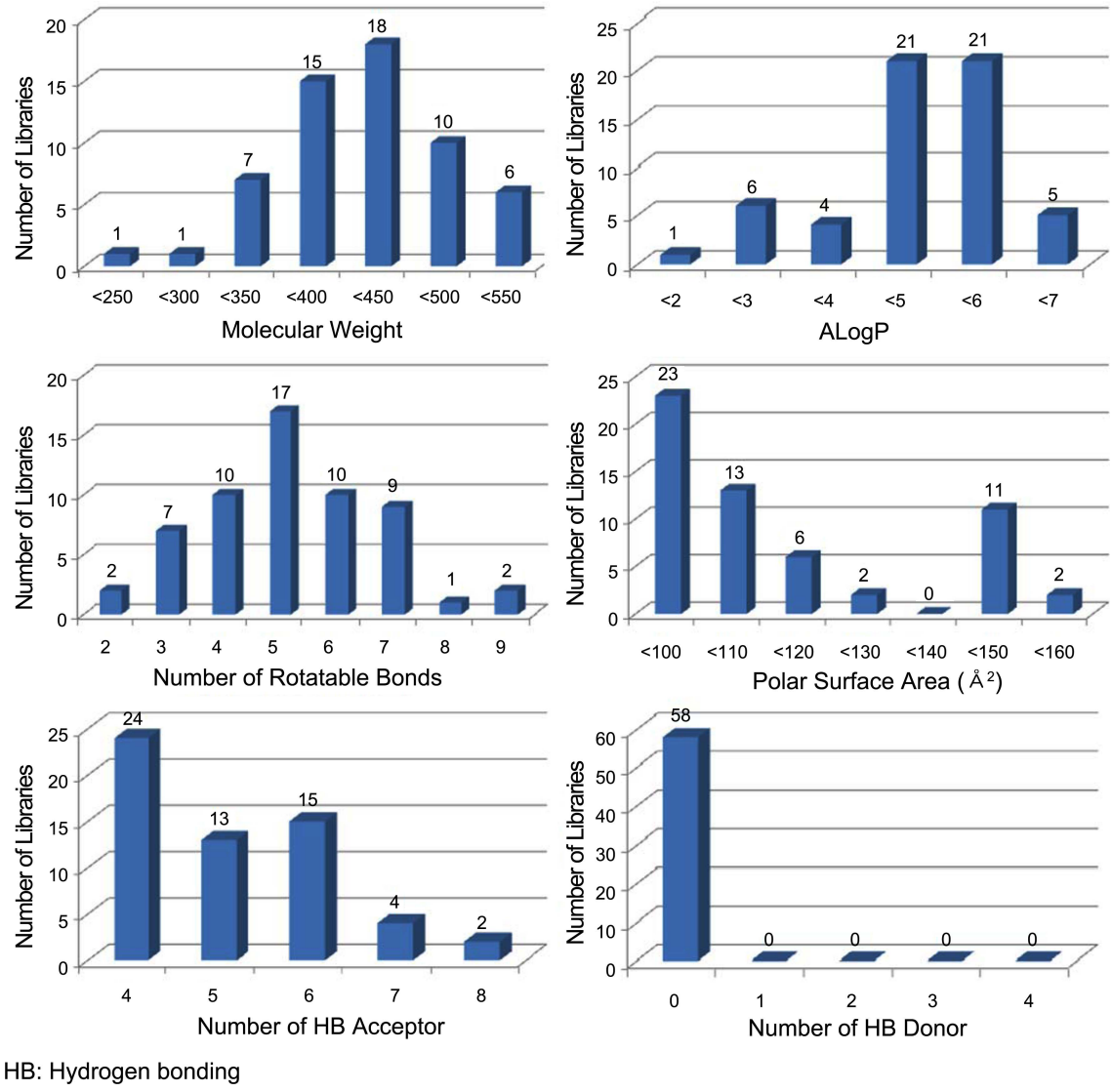


Figure 4. Calculated Physicochemical Properties of the 1,3,4-oxadiazole Derivatives **7**.

Experimental Section

General Procedure for Synthesis. All chemicals were reagent grade and used as purchased. Reactions were monitored by TLC. Flash column chromatography was carried out on silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded in d units relative to deuterated solvent as an internal reference using a 500 MHz NMR instrument. Liquid chromatography tandem mass spectrometry analysis was performed on an electrospray ionization (ESI) mass spectrometer with photodiode-array detector (PDA) detection. High-resolution mass spectrometry spectra were obtained using TOF LC/MS system.

Representative Procedure for the Preparation of 5-Methyl-3-phenyl-2-thioxo imidazolidin-4-one (3a). DL-Alanine **2a** (623.6 mg, 7.0 mmol, 1.0 equiv) was added to a solution of phenyl isothiocyanate **1a** (936.3 mg , 7.0 mmol, 1.0 equiv) in 1,4-dioxane–H_2O (15 mL; 1:1, v/v) at 0 °C. Et_3N (1.42 g, 14.0 mmol, 2.0 equiv) was added slowly to the reaction mixture and the solution was stirred for 1 h at room temperature, followed by the addition of concentrated HCl (2.13 mL, 21.0 mmol, 3.0 equiv) at 0 °C until the pH reached ~2. The reaction mixture was transferred into a 20 mL sealed reactor vessel and irradiated with stirring at 160 °C for 2 min. After cooling to room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$ until the pH became ~6. The precipitate formed was filtered and dried to yield the desired compound **3a** (1.34 g, 93%); white solid. ^{1}H NMR (500 MHz, DMSO) δ 10.55 (br s, 1H), 7.62–7.38 (m, 3H), 7.29 (dd, J = 5.3, 3.3 Hz, 2H), 4.46 (q, J = 7.1 Hz, 1H), 1.39 (d, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, DMSO) δ 182.0, 175.0, 133.5, 128.9, 128.7, 128.6, 55.1, 16.2. HRMS (ESI): *m/z* $[M+1]^+$ calcd for $C_{10}H_{10}N_2OS$: 207.0587, found: 207.0584.

Representative Procedure for the Preparation of 4-Nitrophenyl 5-Methyl-4-oxo-3-phenyl-2-thioxoimidazolidine-1-carboxylate (4a). A 2-thiohydantoin **3a** (1.03 g, 5.0 mmol, 1.0 equiv) was added to the solution of 4-nitrophenyl chloroformate (1.31 g, 6.5 mmol, 1.3 equiv) and DMAP (6.1

mg, 0.05 mmol, 0.01 equiv) in CH_2Cl_2 (15 mL). After stirring 30 minutes, *i*-Pr_2NEt (646.2 mg, 5.00 mmol, 1.0 equiv) was slowly added and the solution was stirred at room temperature for 2 h. The reaction mixture was washed with H_2O (10 mL), after which the aqueous layer was removed. The aqueous layer was back-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$. The organic layers were evaporated to afford crude product mixture and then triturated by *n*-hexane/diethyl ether to yield compound **4a** (1.52 g, 82%); white solid. ^{1}H NMR (500 MHz, DMSO) δ 8.38 (d, *J* = 9.1 Hz, 2H), 7.64 (d, *J* = 9.1 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 2H), 5.11 (q, *J* = 6.9 Hz, 1H), 1.77 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO) δ 179.7, 172.2, 154.3, 147.7, 145.5, 133.2, 129.4, 129.2, 128.9, 125.6, 123.0, 58.6, 16.7. mp 195−197 °C. LC/MS (ESI): *m/z* = 372.1 $[M+1]^+$. HRMS (ESI): *m/z* $[M+1]^+$ calcd for $C_{17}H_{13}N_3O_5S$: 372.0649, found: 372.0646.

Representative Procedure for the Preparation of *N′*-Benzoyl-5-methyl-4-oxo-3-phenyl-2-thioxoimidazolidine-1-carbohy-drazide (6a). Benzoic hydrazide (143.0 mg, 1.05 mmol, 1.05 equiv) and pyridine (83.1 mg, 1.05 mmol, 1.05 equiv) in THF(1.5 mL) was stirred for 30 minutes and then compound **4a** (371.4 mg 1.0 mmol, 1.0 equiv) was added to the reaction mixture at room temperature. The reaction mixture was heated to 60 °C and then stirred for 8 h. The mixture was cooled to room temperature and extracted with EtOAc (4.0 mL) and H_2O (2 mL), after which the aqueous layer was removed. The aqueous layer was back-extracted with EtOAc (3 × 4 mL). The combined organic layers were dried over $MgSO_4$. The organic layers were evaporated to afford crude product mixture and then triturated by n-hexane/diethyl ether to yield semicarbazide **6a** (294.7 mg, 80%); white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.73 (s, 1H), 8.30 (s, 1H), 7.85 (d, *J* = 7.3 Hz, 2H), 7.59–7.41 (m, 6H), 7.28 (dd, *J* = 8.1, 1.3 Hz, 2H), 4.95 (q, *J* = 6.9 Hz, 1H), 1.81 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.9, 171.9, 165.6, 151.1, 132.7, 132.2, 131.5, 130.1, 129.7, 129.0, 128.5, 127.5, 58.5, 17.5. mp 176−179 °C. LC/MS (ESI): *m/z* = 369.1 $[M+1]^+$.

Representative Procedure for the Preparation of 5-Methyl-3-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-2-thioxoimidazolidin-4-one (7a). A mixture of semicarbazide **6a** (184.2 mg, 0.5 mmol, 1.0 equiv) and Pyridine (87.0 mg, 1.1 mmol, 2.2 equiv) in DCE (3.0 mL) was stirred for 30 min. $POCl_3$ (92.0 mg, 0.6 mmol, 1.2 equiv) was slowly added to the reaction mixture at room temperature. The reaction mixture was transferred into a 5 mL sealed reactor vessel and irradiated with stirring at 160 °C for 30 min. After cooling to room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ until the pH became 6-7. The mixture was extracted with DCM (5.0 mL) and H_2O (3 mL), after which the aqueous layer was removed. The aqueous layer was back-extracted with DCM (3 × 4 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica gel (eluent: EtOAc–hexane, 2:5) and then triturated by *n*-hexane/diethyl ether to yield the 1,3,4-oxadiazole **7a** (154.2 mg, 88%); white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 6.7 Hz, 2H), 7.63–7.47 (m, 6H), 7.35 (d, *J* = 7.3 Hz, 2H), 5.09 (q, *J* = 6.9 Hz, 1H), 1.86 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 171.7, 163.4, 156.5, 132.6, 132.2, 130.0, 129.7, 129.3, 128.5, 127.0, 123.4, 60.1, 16.3. mp 124−126 °C. LC/MS (ESI): *m/z* = 351.1 $[M+1]^+$. HRMS (ESI): *m/z* $[M+1]^+$ calcd for $C_{18}H_{14}N_4O_2S$: 351.0910, found: 351.0909.

Acknowledgments. This research was conducted under the Industrial Infrastructure Program for Fundamental Technologies and Institute for Advancement of Technology through the Inter-ER Cooperation Projects (R0002016) which are funded by the Ministry of Trade, Industry & Energy, Korea to YDG and Open Translational Research Center for Innovative Drug (2012M3A9C1053532) which are funded by National Research Foundation of Korea.

Supporting Information Available. Full analytical data of compounds, along with copies of ^{1}H NMR, ^{13}C NMR, LC/MS, and HRMS spectra of synthesized compounds. Copies of ^{1}H NMR, and ^{13}C NMR spectra of side product **8a**. Copies of ^{1}H NMR, ^{13}C NMR, and LC/MS spectra of side product **8b**. Comparison data between microwave irradiation and thermodynamic condition.

References

1. (a) Matin, A.; Gavande, N.; Kim, M. S.; Yang, N. X.; Salam, N. K.; Hanrahan, J. R.; Roubin, R. H.; Hibbs, D. E. *J. Med. Chem.* **2009**, *52*, 6835. (b) Priego, E. M.; Kuenzel, J. V. F. D.; IJzerman, A. P.; Camarasa, M. J.; Perez-Perez, M. J. *J. Med. Chem.* **2002**, *45*, 3337. (c) Galal, S. A.; El-All, A. S. A.; Abdallah, M. M.; El-Diwani, H. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2420. (d) Lahm, G. P.; Stevenson, T. M.; Selby, T. P.; Freudenberger, D. C.; Flexner, L.; Bellin, C. A.; Dubas, C. M.; Smith, B. K.; Hughes, K. A.; Hollingshaus, J. G.; Clark, C. E.; Benner, E. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6274.
2. (a) Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, *36*, 1090. (b) 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. (c) Gauthier, M. P.; Michaux, C.; Rolin, S.; Vastersaegher, C.; Leval, X. D.; Julemont, F.; Pochet, L.; Masereel, B. *Bioorg. Med. Chem.* **2006**, *14*, 918.
3. (a) El-Emam, A. A.; Al-Deeb, O. A.; Al-Omar, M.; Lehmann, J. *Bioorg. Med. Chem.* **2004**, *12*, 5107. (b) Hollar, B. S.; Gonsalves, R.; Shenoy, S. *Eur. J. Med. Chem.* **2000**, *35*, 267.
4. McCoull, W.; Addie, M. S.; Birch, A. M.; Birtles, S.; Buckett, L. K.; Butlin, R. J.; Bowker, S. S.; Boyd, S.; Chapman, S.; Davies, R. D. M.; Donald, C. S.; Green, C. P.; Jenner, C.; Kemmitt, P. D.; Leach, A. G.; Moody, G. C.; Gutierrez, P. M.; Nicholas, J. N.; Nowak, T.; Packer, M. J.; Plowright, A. T.; Revill, J.; Schofield, P.; Sheldon, C.; Stokes, S.; Turnbull, A. V.; Wang, S. J. Y.; Whalley, D. P.; Wood. J. M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3873.
5. (a) Warmus, J. S.; Flamme, C.; Zhang, L. Y.; Barrett, S.; Bridges, A.; Chen, H.; Gowan, R.; Kaufman, M.; Sebolt-Leopold, J.; Leopold, W.; Merriman, R.; Ohren, J.; Pavlovsky, A.; Przybranowski, S.; Tecle, H.; Valik, H.; Whitehead, C.; Zhang E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6171. (b) Khatik, G. L.; Kaur, J.; Kumar, V.; Tikoo, K.; Venugopalan, P.; Nair, V. A. *Eur. J. Med. Chem.* **2011**,

46, 3291.
6. Gong, Y. D.; Yang, S. J.; Kim, S. H. 2-Amino-substituted oxadiazole derivatives and pharmaceutical composition comprising the same. KR 10-2013-013059, October 10, 2013.
7. (a) Puthiyapurayil, P.; Poojary, B.; Chikkanna, C.; Buridipad, S. K. *Eur. J. Med. Chem*. **2012**, *53*, 203. (b) Sangshetti, J. N.; Chabukswar, A. R.; Shinde, D. B. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 444. (c) Zhang, L. R.; Liu, Z. J.; Zhang, H.; Sun, J.; Luo, Y.; Zhao, T. T.; Gong, H. B. *Bioorg. Med. Chem.* **2012**, *20*, 3615.
8. (a) Zhang, W.; Lu, Y. *Org. Lett.* **2003**, *14*, 2555. (b) Elokdah, H.; Sulkowski, T. S.; Abou-Gharbia, M.; Butera, J. A.; Chai, S. Y.; McFarlane, G. R.; McKean, M. L.; Babiak, J. L.; Adelman, S. J.; Quinet, E. M. *J. Med. Chem.* **2004**, *47*, 681. (c) Muccioli, G. G.; Wouters, J.; Charlier, C.; Scriba, G. K. E.; Pizza, T.; Pace, P. D.; Martino, P. D.; Poppitz, W.; Poupaert, J. H.; Lambert, D. M. *J. Med. Chem.* **2006**, *49*, 872. (d) Bouzroura, S.; Hammal, L.; Nedjar-Kolli, B.; Balegroune, F.; Hamadene, M.; Poulain, S. *Synthetic Communications* **2007**, *38*, 448.
9. (a) Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett*. **1999**, *40*, 3275. (b) Rostamizadeh, S.; Housaini, S. A. G. *Tetrahedron Lett.* **2004**, *45*, 8753. (c) Dolman, S. J.; Gosselin, F.; O`Shea, P. D.; Davies, I. *E. J. Org. Chem*. **2006**, *71*, 9548. (d) Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett*. **2001**, *42*, 2583. (e) Fulop, F.; Semega, E.; Dombi, G.; Bernath, G. *J. Heterocycl. Chem.* **1990**, *27*, 951-955. (f) Kucukguzel, G.; Kocatepe, A.; Clercq, E. D.; Sahin, F.; Gulluce, M. *Eur. J. Med. Chem.* **2006**, *41*, 353. (g) Omar, A. M. E.; Aboulwafa, O. *J. Heterocycl. Chem.* **1984**, *21*, 1415.
10. (a) Lahred, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406. (b) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem*. **2002**, *4*, 95. (c) Kappe, C. O. *Curr. Opin. Chem. Biol*. **2002**, *6*, 314. (d) Wathey, B.; Tierney, J.; Lidström, P.; Westman, J. *Drug Discovery Today.* **2002**, *7*, 373. (e) Blackwell, H. E. *Org. Biomol. Chem.* **2003**, *1*, 1251.
11. (a) Collins, J. M.; Leadbeater, N. E. *Org. Biomol. Chem*. **2007**, *5*, 1141. (b) Rizzolo, F.; Sabatino, G.; Chelli, M.; Rovero, P.; Papini, A. M. *Int. J. Pept. Res. Ther.* **2007**, *13*, 203. (c) Coantic, S.; Subra, G.; Martinez, J. *Int. J. Pept. Res. Ther.* **2008**, *14*, 143. (d) Bacsa, B.; Bosze, S.; Kappe, C. O. *J. Org. Chem.* **2010**, *75*, 2103. (e) Hjørringgaard, C. U.; Pedersen, J. M.; Vosegaard, T.; Nielsen, N. C.; Skrydsturp, T. *J. Org. Chem.* **2009**, *74*, 1329.
12. (a) Bogdal, D.; Prociak, A. *Microwave-Enhanced Polymer Chemistry and Technology,* Blackwell Publishing: Oxford, 2007. (b) Hoogenboom, R.; Schubert, U. S. *Macromol. Rapid Commun*. **2007**, *28*, 368. (c) Bardts, M.; Gonsior, N.; Ritter, H. *Macromol. Chem. Phys.* **2008**, *209*, 25. (d) Holtze, C.; Antonietti, M.; Tauer, K. *Macromolecule* **2006**, *39*, 5720.
13. (a) Varma, R. S. *Clean Products and Processes* **1999**, 132. (b) Varma, R. S. In *Advances in Green Chemistry: Chemical Syntheses Using Microwave Irradiation*; Astra Zeneca Research Foundation, Kavitha Printers, Bangalore, India, 2002. (c) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578. (d) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem*. **2004**, *6*, 128.
14. (a) Das, S. K. *Synlett.* **2004**, 915. (b) Corsaro, A.; Chiacchio, U.; Pistara, V.; Romeo, G. *Curr. Org. Chem*. **2004**, *8*, 511.
15. (a) Khatik, G. L.; Kaur, J.; Kumar, V.; Tikoo, K.; Venugopalan, P.; Nair, V. A. *Eur. J. Med. Chem.* **2011**, *46*, 3291. (b) Lin, M. J.; Sun, C. M. *Tetrahedron Lett*. **2003**, *44*, 8739.
16. Hwang, J. Y.; Choi, H. S.; Lee, D. H.; Gong, Y. D. *J. Comb. Chem.* **2005**, *7*, 816.
17. (a) Yang, S. J.; Lee, S. H.; Kwak, H. J.; Gong, Y. D. *J. Org. Chem.* **2013**, *78*, 438. (b) Baxendale, I. R.; Ley, S. V.; Martinelli, M. *Tetrahedron* **2005**, 5323.
18. (a) Conole, D.; Beck, T. M.; Jay-Smith, M.; Tingle, M. D.; Eason, C. T.; Brimble, M. A.; Rennison, D. *Bioorg. Med. Chem*. **2014**, *22*, 2220. (b) Balsells, J.; DiMichele, L.; Liu, J.; Kubryk, M.; Hansen, K.; Armstrong, iii, J. D. *Org. Lett.* **2005**, *7*, 1039. (c) Wang, C.; Palsson, L.; Batsanov, A. S.; Bryce, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 3789.
19. Lipinski, C. A.; Lombardo, F.; Doming, B. W.; Feeney, P. J. *Adv. Drug Delivery Rew.* **1997**, *23*, 3.