Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Multisubstituted 2-Aminopyrroles/pyridines via Chemoselective Michael Addition/Intramolecular Cyclization Reaction

Xueyu Qi, Haoyue Xiang, Qian He, and Chunhao Yang*

State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai, 201203, China

Supporting Information

ABSTRACT: A facile and efficient synthetic strategy to construct polysubstituted 2-aminopyrroles/pyridines was developed via chemoselective Michael addition/intramolecular cyclization reaction under very mild conditions. It suggested that the chemoselectivity of the process could be controlled by the leaving ability of the halides.

Multisubstituted pyrroles and pyridines are important scaffolds in medicinal chemistry and organic chemistry due to their prevalence in numerous natural products and synthetic compounds. In particular, 2-aminopyrrole and its derivatives, recognized as core structures in medicinal chemistry, have shown a diverse range of bioactivities such as MEK inhibitory[1] and cytotoxicities.[2] Furthermore, aminopyrroles have been used as precursors for the synthesis of purine analogues including pyrrolopyrimidines, pyrrolotriazines, and pyrrolopyridines. These pyrrole-derived heterocycles exhibit remarkable biological activities such as antifolates,[3] anti-inflammatories,[4] microtubule inhibitors,[5] JAK3 kinase inhibitors,[6] glycogen synthase kinase-3β inhibitors,[7] and NAMPT inhibitors.[8] Additionally, as an important subset of pyridines, 2-aminopyridines are not only extremely useful building blocks for the construction of various significant nitrogen-containing heterocycles[9] but also highly attractive compounds themselves since they are key structural cores of natural products and medicinally important compounds that are identified as promising leads along with a variety of pharmacological and biological activity including antimalarial agents,[10] β-secretase (BACE1) inhibitors,[11] nitric oxide synthase (NOS) inhibitors,[12] and CHK2 inhibitors.[13]

Over recent decades, considerable efforts have been devoted to the synthesis of various substituted pyrroles and pyridines.[14] Nevertheless, there are a limited number of methods that have been developed for the preparation of 2-aminopyrroles that are not readily available through general pyrrole ring-formation methods. Most of these synthetic approaches to 2-aminopyrroles need a prolonged reaction time,[15] expensive transition metal additives,[16] or require multistep elaboration from commercially available materials.[17] At the same time, many methods have been developed for the synthesis of 2-aminopyridines. Classical access to 2-aminopyridines has relied on Chichibabin reaction,[18] but with a narrow scope, unsatisfactory yields, and poor functional group tolerance for the strong bases employed in this reaction. Recently, metal-catalyzed aminations of 2-halopyridines and pyridine-*N*-oxides have emerged as an alternative strategy to synthesize 2-aminopyridines.[19] However, these methods are established upon the modification of the preformed pyridine nucleus and need expensive transition metals, which are unsatisfactory from an economical and ecological point of view. Thus, it is still challenging and highly desirable to design facile, practical, and streamlined synthetic methods for 2-aminopyrroles and 2-aminopyridines under mild conditions, especially for those with flexible substitution groups. Toward this end, the multicomponent reaction has recently been used as a powerful tool to assemble multisubstituted 2-aminopyrroles[17c] and 2-aminopyridines[20] directly. Even so, there are still no simple and straightforward methods for the synthesis of substituted 2-aminopyrrole/pyridines simultaneously under the same reaction conditions using readily available and simple starting materials such as 3-halogenated chromones.

Chromones are greatly useful building blocks for constructing various heterocycles.[21] Recently, our group concentrates on developing novel strategies for the synthesis of heterocyclic scaffolds. Inspired by the success of the studies that reported 3-halogenated chromones can react with *N*,*N*-bis-nucleophiles, acetamidine hydrochloride,[21c,e] we used *C*,*N*-bis-nucleophiles, ethyl 2-amidinoacetate hydrochloride **2a** instead of the *N*,*N*-bis-nucleophiles to react with 3-halogenated chromones. As we expected, the 3-halogenated chromone **1** was first attacked by the carbon ion, but not the nitrogen atom with lone pair

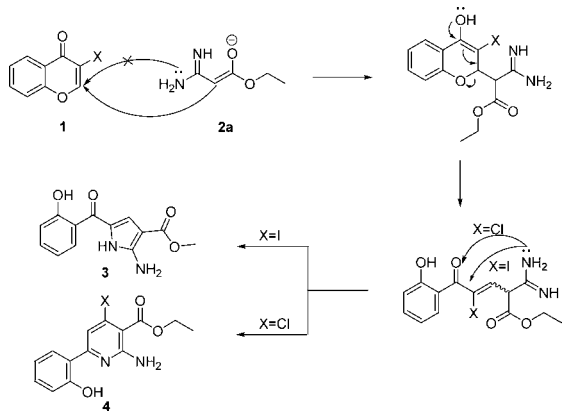
Received: June 30, 2014
Published: July 25, 2014

ACS Publications © 2014 American Chemical Society

dx.doi.org/10.1021/ol5018855 | *Org. Lett.* 2014, 16, 4186–4189

electrons. Afterward, 2-aminopyrrole/pyridines could be chemoselectively obtained respectively, which was controlled by using different halides with different leaving abilities (Scheme 1).

Scheme 1. Outline of the New Strategy for the Synthesis of 2-Aminopyrroles/pyridines Starting with Halogenated Chromones



It is worth noting that *ortho*-amino and carboxylate groups can be introduced to pyrrole/pyridine rings simultaneously in one step for this new strategy, and the desired products can be further exploited to construct a pyrrolo[2,3-*d*]pyrimidine and benzofuro[3,2-*b*]pyridine ring respectively which are found in natural products and medicinal compounds, such as folate antimetabolite Pemetrexed,[22] Akt inhibitor CCT128930,[23] marine alkaloids rigidins A–E,[24] topoisomerase inhibitors,[25] and endothelin receptor antagonist[26] (Figure 1). Moreover,

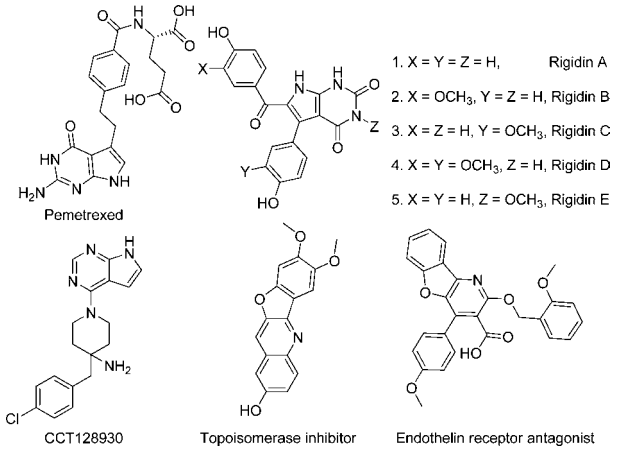
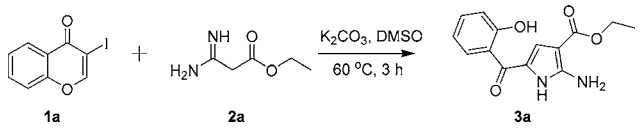


Figure 1. Structures of bioactive compounds with the pyrrolo[2,3-*d*]pyrimidine and benzofuro[3,2-*b*]pyridine ring system.

compared to many reported methods, the reaction for the synthesis of 2-amino-pyrroles/pyridines can be carried out under mild conditions without any metal catalysts, which was advantageous from the viewpoint of green chemistry and sustainability. Therefore, a very practical synthetic strategy to obtain polysubstituted 2-aminopyrroles/pyridines was developed here for their biological and chemical significance.

Initially, we screened parameters to find the optimal conditions (Table 1). We started our studies by treating 3-iodochromone **1a** with ethyl 2-amidinoacetate hydrochloride

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	solvent	base	tem	yield[b] (%)
1	NMP	DBU	100	36
2	DMSO	DBU	100	40
3	DMF	DBU	100	20
4	dioxane	DBU	100	16
5	toluene	DBU	100	16
6	MeCN	DBU	100	12
7	EtOH	DBU	100	trace
8	DMSO	DBU	80	42
9	DMSO	DBU	60	52
10	DMSO	DBU	40	45
11	DMSO	DBU	rt	28
12[c]	DMSO	DBU	60	52
13[d]	DMSO	DBU	60	38
14	DMSO	K_2CO_3	60	76
15	DMSO	Et_3N	60	trace
16	DMSO	Cs_2CO_3	60	71
17	DMSO	Na_2CO_3	60	72
18[d]	DMSO	K_2CO_3	60	73

[a]Reaction conditions: **1a** (0.5 mmol 1.0 equiv), **2a** (5.5 mmol 1.1 equiv), base (2.4 equiv), solvent (2.0 mL); all reagents were mixed and stirred under air at rt for 5 min and then were heated at 60 °C for 3 h. [b]Isolated yields. [c]1.5 equiv of **2a** was used. [d]3.0 equiv of base was used.

2a in the presence of DBU (2.4 equiv) in NMP at 100 °C for 3 h. To our delight, the desired product **3a** was obtained in a 36% yield (Table 1, entry1). Afterward, the solvent was shown to have a great influence on the yields, with DMSO providing the best result (Table 1, entries 1–7). The investigation of reaction temperature indicated that the optimal temperature was 60 °C (Table 1, entries 2, 8–11). Further studies showed that increasing the amount of ethyl 2-amidinoacetate hydrochloride (1.5 equiv) had no obvious effect on the yield (Table 1, entry 9 vs 12), while increasing the amount of base resulted in a reduced yield (Table 1, entry 9 vs 13, 14 vs 18). Finally, the effect of base was investigated. We found that the inorganic bases compared organic bases greatly improved the yield (Table 1, entries 9, 14–17). Thus, the optimal reaction conditions were determined to include K_2CO_3 (2.4 equiv), amidine (1.1 equiv) in DMSO (2.0 mL) at 60 °C for 3 h. The structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis (Figure 2).

With the optimal reaction conditions in hand, the scope of substrates for this new reaction was investigated (Scheme 2). It was found that the chromone rings with electron-donating groups gave the corresponding products in better yields than those with electron-withdrawing groups (Scheme 2, **3b**, **3c**, **3f** vs **3d**, **3e**, **3g**–**3o**). Whereas methoxy groups anywhere on the chromones provided lower yields than other electron-donating groups (Scheme 2, **3i** vs **3h**, **3m** vs **3k**). The steric factor also greatly influences the yield (Scheme 2, **3a** vs **3j**). The results of probing the effect of the different amidine reactants showed that the amidine containing the ethoxycarbonyl group has a higher yield than those with a carbamoyl group (Scheme 2, **3q**–**3v**).

After successfully synthesizing 2-aminopyrroles from 3-iodochromone, we turned our attention to 3-chlorochromone

dx.doi.org/10.1021/ol5018855 | *Org. Lett.* 2014, 16, 4186–4189

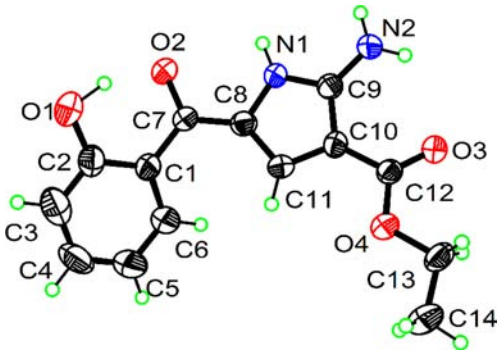
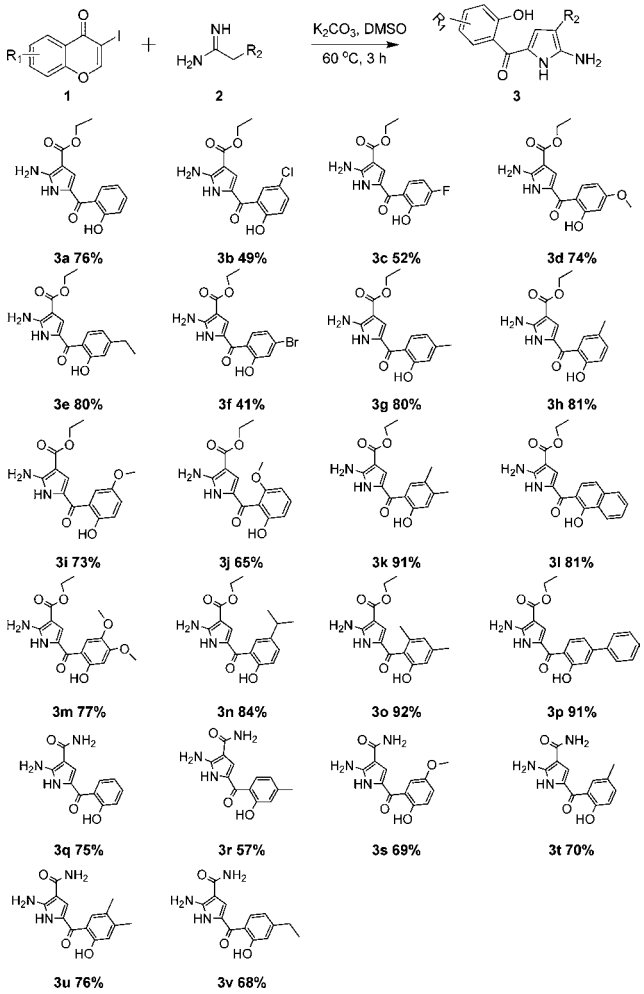


Figure 2. X-ray crystal structure of **3a**.

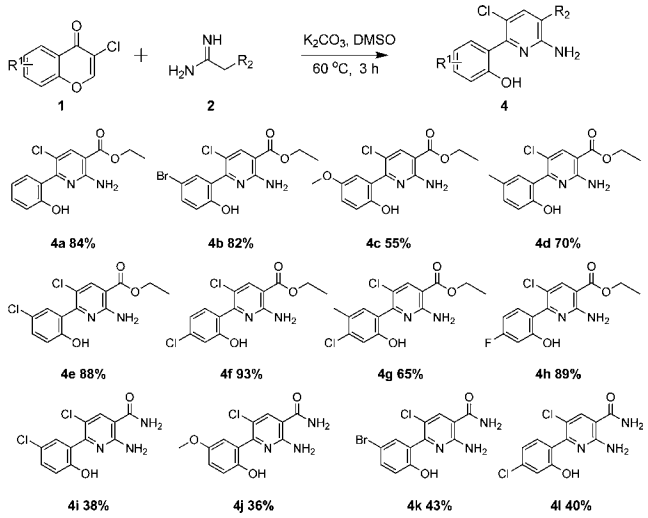
Scheme 2. Synthesis of 2-Aminopyrroles[a,b]



[a]Reagents and reaction conditions: 3-iodochromone derivatives **1** (0.5 mmol), amidine 5 (0.55 mmol), and K_2CO_3 (1.2 mmol) in DMSO (2 mL), heated to 60 °C for 3 h. [b] Isolated yield.

to obtain 2-aminopyridines. Because of the weak leaving ability of the chlorine atom, the yield of 2-aminopyridines **4a** was 84% under previous optimized conditions. We next examined the scope of substrates by using a variety of substituted 3-chlorochromones (Scheme 3). As we expected, the chromone rings bearing electron-withdrawing groups afforded better yields of the corresponding products than those with electron-donating groups (Scheme 3, **4c**, **4d** vs **4b**, **4e**, **4f**, **4h**), because electron-withdrawing groups can strengthen the

Scheme 3. Synthesis of 2-Aminopyridine[a,b]

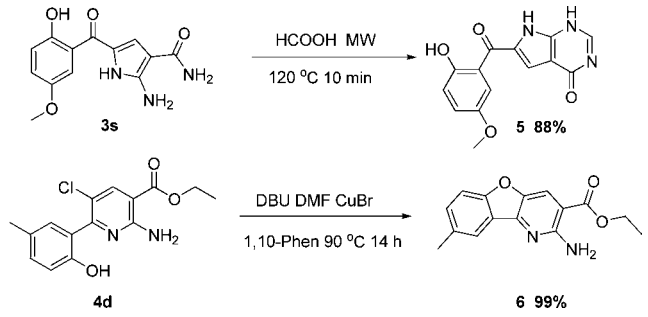


[a]Reagents and reaction conditions: 3-chlorochromone derivatives 1 (0.5 mmol), ethyl 2-amidinoacetate hydrochloride **5a** (0.55 mmol), and K_2CO_3 (1.2 mmol) in DMSO (2 mL), heated to 60 °C for 3 h. [b] Isolated yield.

electrophilicity of the carbonyl group. The amidine containing the carbamoyl group delivered the corresponding products in diminished yield (Scheme 3, **4i**–**4l**).

To demonstrate the synthetic utility of the reaction's products, 2-aminopyrrole-3-carboxamide **3s** was smoothly converted to pyrrolo[2,3-*d*]pyrimidine **5** in 88% yield under microwave irradiation at 120 °C for 10 min and compound **6** was obtained in 99% yield catalyzed by CuBr (Scheme 4).

Scheme 4. Synthetic Utility of 2-Aminopyrrole/pyridine



In conclusion, our investigation has successfully provided a direct and facile synthesis of 2-aminopyrrole/pyridines through a chemoselective Michael addition/intramolecular cyclization sequence. The synthetic ultility of the resulting 2-aminopyrroles/pyridines was demonstrated by converting compounds **3s** and **4d** to the corresponding pyrrolo[2,3-*d*]-pyrimidine **5** and benzofuro[3,2-*b*]pyridine **6** respectively. Although the utility of the final products is somewhat limited by the presence of a phenolic hydroxyl group in these structures, we believe that these products could be widely applied in constructing natural products and medicinal derivatives with the pyrrolo[2,3-*d*]pyrimidine or benzofuro-[3,2-*b*]pyridine ring system.

dx.doi.org/10.1021/ol5018855 | *Org. Lett.* 2014, 16, 4186–4189

■ ASSOCIATED CONTENT

Supporting Information

CCDC-1009838 contains the supplementary crystallographic data for compound **3a**. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk. General experimental information and copies of ^{1}H and ^{13}C NMR of new compounds are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chyang@simm.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Ministry of Science and Technology of China ("Key New Drug Creation and Manufacturing Program", 2012ZX09301001-001), the National Natural Science Foundation of China (81321092), and SKLDR/SIMM (SIMM1403ZZ-01).

■ REFERENCES

(1) Wallace, M. B.; Adams, M. E.; Kanouni, T.; Mol, C. D.; Dougan, D. R.; Feher, V. A.; O'Connell, S. M.; Shi, L.; Halkowycz, P.; Dong, Q. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4156.
(2) Cocco, M. T.; Congiu, C.; Lilliu, V.; Onnis, V. *Bioorg. Med. Chem.* **2006**, *14*, 366.
(3) Wang, Y.; Cherian, C.; Orr, S.; Mitchell-Ryan, S.; Hou, Z.; Raghavan, S.; Matherly, L. H.; Gangjee, A. *J. Med. Chem.* **2013**, *56*, 8684.
(4) Mohamed, M. S.; Kamel, R.; El-hameed, R. H. A. *Med. Chem. Res.* **2013**, *22*, 2244.
(5) Gangjee, A.; Kurup, S.; Smith, C. D. *Bioorg. Med. Chem.* **2013**, *21*, 1180.
(6) Norman, P. *Expert. Opin. Ther. Pat.* **2014**, *24*, 121.
(7) La Pietra, V.; La Regina, G.; Coluccia, A.; Famiglini, V.; Pelliccia, S.; Plotkin, B.; Eldar-Finkelman, H.; Brancale, A.; Ballatore, C.; Crowe, A. *J. Med. Chem.* **2013**, *56*, 10066.
(8) Dragovich, P. S.; Bair, K. W.; Baumeister, T.; Ho, Y.-C.; Liederer, B. M.; Liu, X.; Liu, Y.; O'Brien, T.; Oeh, J.; Sampath, D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4875.
(9) (a) Masurier, N.; Moreau, E.; Lartigue, C.; Gaumet, V.; Chezal, J.-M.; Heitz, A.; Teulade, J.-C.; Chavignon, O. *J. Org. Chem.* **2008**, *73*, 5989. (b) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217.
(10) Younis, Y.; Douelle, F.; Feng, T.-S.; Cabrera, D. G. l.; Manach, C. L.; Nchinda, A. T.; Duffy, S.; White, K. L.; Shackleford, D. M.; Morizzi, J. *J. Med. Chem.* **2012**, *55*, 3479.
(11) Malamas, M. S.; Barnes, K.; Hui, Y.; Johnson, M.; Lovering, F.; Condon, J.; Fobare, W.; Solvibile, W.; Turner, J.; Hu, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2068.
(12) Kumar, H.; Siddiqui, A. A.; Gupta, S. P. *Lett. Drug Des. Discovery* **2013**, *10*, 666.
(13) Hilton, S.; Naud, S.; Caldwell, J. J.; Boxall, K.; Burns, S.; Anderson, V. E.; Antoni, L.; Allen, C. E.; Pearl, L. H.; Oliver, A. W. *Bioorg. Med. Chem.* **2010**, *18*, 707.
(14) (a) Gao, M.; He, C.; Chen, H.; Bai, R.; Cheng, B.; Lei, A. *Angew. Chem., Int. Ed. Engl.* **2013**, *52*, 6958. (b) Zhao, M. N.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. *Chemistry* **2014**, *20*, 1839. (c) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (d) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325.
(15) (a) Nair, V.; Vinod, A.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427. (b) Fontaine, P.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 1555.
(16) Demir, A. S.; Emrullahoglu, M.; Buran, K. *Chem. Commun. (Camb)* **2010**, *46*, 8032.
(17) (a) Chien, T.-C.; Meade, E. A.; Hinkley, J. M.; Townsend, L. B. *Org. Lett.* **2004**, *6*, 2857. (b) Demir, A. S.; Emrullahoglu, M. *Tetrahedron* **2005**, *61*, 10482. (c) Frolova, L. V.; Evdokimov, N. M.; Hayden, K.; Malik, I.; Rogelj, S.; Kornienko, A.; Magedov, I. V. *Org. Lett.* **2011**, *13*, 1118.
(18) Chichibabin, A.; Zeide, O. *Zhurnal Russkago Fiziko-Khimicheskago Obshchestva* **1914**, *46*, 1216.
(19) (a) Thomas, S.; Roberts, S.; Pasumansky, L.; Gamsey, S.; Singaram, B. *Org. Lett.* **2003**, *5*, 3867. (b) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett.* **2010**, *12*, 5254. (c) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127.
(20) (a) Tu, S.; Jiang, B.; Zhang, Y.; Jia, R.; Zhang, J.; Yao, C.; Shi, F. *Org. Biomol. Chem.* **2007**, *5*, 355. (b) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899.
(21) (a) Han, X.; Yue, Z.; Zhang, X.; He, Q.; Yang, C. *J. Org. Chem.* **2013**, *78*, 4850. (b) Zhang, X.; He, Q.; Xiang, H.; Song, S.; Miao, Z.; Yang, C. *Org. Biomol. Chem.* **2014**, *12*, 355. (c) Sheng, J.; Chao, B.; Chen, H.; Hu, Y. *Org. Lett.* **2013**, *15*, 4508. (d) Cheng, M.; Yan, J.; Hu, F.; Chen, H.; Hu, Y. *Chem. Sci.* **2013**, *4*, 526. (e) Chao, B.; Lin, S.; Ma, Q.; Lu, D.; Hu, Y. *Org. Lett.* **2012**, *14*, 2398.
(22) Hanna, N.; Shepherd, F. A.; Fossella, F. V.; Pereira, J. R.; De Marinis, F.; von Pawel, J.; Gatzemeier, U.; Tsao, T. C. Y.; Pless, M.; Muller, T. *J. Clin. Oncol.* **2004**, *22*, 1589.
(23) Yap, T. A.; Walton, M. I.; Hunter, L.-J. K.; Valenti, M.; de Haven Brandon, A.; Eve, P. D.; Ruddle, R.; Heaton, S. P.; Henley, A.; Pickard, L. *Mol. Cancer Ther.* **2011**, *10*, 360.
(24) Cao, B.; Ding, H.; Yang, R.; Wang, X.; Xiao, Q. *Marine Drugs* **2012**, *10*, 1412.
(25) Luzzio, M. J.; Besterman, J. M.; Evans, M. G.; Johnson, M. R.; Dezube, M.; Profeta, S., Jr. 1992, WO9221661A1.
(26) Osswald, M.; Dorsch, D.; Mederski, W.; Wilm, C.; Schmitges, C.; Christadler, M. 1997, EP755934A1.