ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

One-Pot Syntheses of Isoquinolin-3-ones and Benzo-1,4-diazepin-2,5-diones Utilizing Ugi-4CR Post-Transformation Strategy†

Chao Che,*[,‡,§,∥] Song Li,[‡,∥] Zhixiong Yu,[§] Fangfang Li,[‡] Shengchang Xin,[‡] Liyan Zhou,[‡] Shuo Lin,*[,‡,⊥] and Zhen Yang*[,‡,⊗]

[‡]Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China

[§]South China Center of Innovative Pharmaceuticals (SCCIP), Guangzhou 510663, China

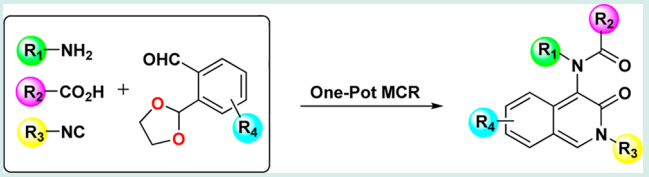
[∥]Shenzhen Shengjie Biotech Co., Ltd., Shenzhen 518055, China

[⊥]Department of Molecular, Cell, and Developmental Biology, University of California, Los Angeles, United States

[⊗]Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), College of Chemistry, Peking University, Beijing 100871, China

Supporting Information

ABSTRACT: One-pot and efficient syntheses of structurally diverse isoquinolin-3-ones and isoquinolin-3-one-based benzo-1,4-diazepin-2,5-diones have been developed. The notable features of the process include the Ugi condensation of monomasked phthalaldehydes with amines, carboxylic acids, and isonitriles, followed by $HClO_4$-mediated intramolecular condensation of the carbonyl with amide.



KEYWORDS: *isoquinolin-3-ones, benzo-1,4-diazepin-2,5-diones, multicomponent reaction, Ugi-4CR, one-pot synthesis, diversity-oriented synthesis*

INTRODUCTION

Multicomponent reactions (MCRs)[1] serve as a powerful tool for the rapid and efficient assembly of complex structures from simple starting materials and with minimized production of wastes. These highly step-economic reactions are appealing in both combinatorial and diversity-oriented synthesis, and are particularly useful for the construction of diverse chemical libraries of "drug-like" molecules.[2]

The isoquinolinones constitute the scaffolds of great biological and pharmacological interest in medicinal chemistry and exhibit an array of promising biological properties, including antitumor,[3] anti-inflammatory,[4] antimalarial,[5] antiarrhythmic,[6] antithrombotics activities,[7] and inhibition to NS5B polymerase of HCV,[8] PDE5,[9] and PARP.[10] These scaffolds are also widely found in many biologically active alkaloids, such as 2-hydroxyaccuminatine (**I**)[11] and oxyavicine (**II**) (Figure 1).[12] On the other hand, benzodiazepines and its analogues are recognized as privileged scaffolds in medicinal chemistry and exhibit a wide scope of biological activity, known as anxiolytic drugs,[13] antitumor agents (**III**),[14] antitubercular agents,[15] and anti-HIV agents.[16] Recently, these classes of compounds were found to hit various pharmacologically relevant targets, such as $GABA_A$ receptor,[17] histone deacetylases (HDAC),[18] apoptotic protease-activating factor 1 (Apaf-1),[19] and Hdm2 protein (**IV**).[20]

For many years our laboratories have been involved in developing a chemical genetic approach to analyze biological systems by way of interfacing libraries of small molecules with creative biological assays.[21] As part of this research objective, we became interested in establishing a novel synthetic strategy to construct diverse isoquinolinone and benzodiazepine-based heterocycles. In a previous paper, we have reported a diversity-

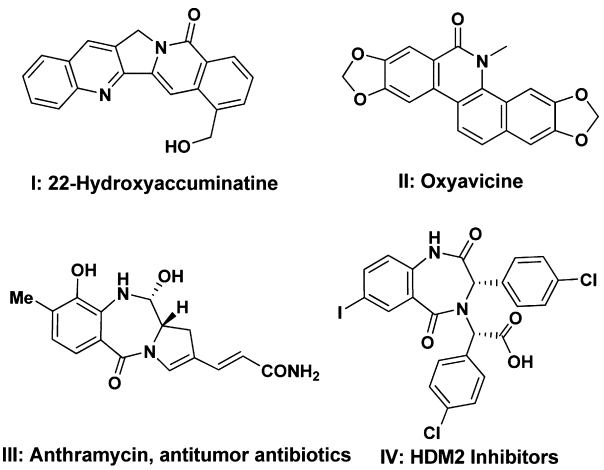


Figure 1. Medicinally important isoquinolinones and benzodiazepanones.

Received: January 2, 2013
Revised: February 25, 2013

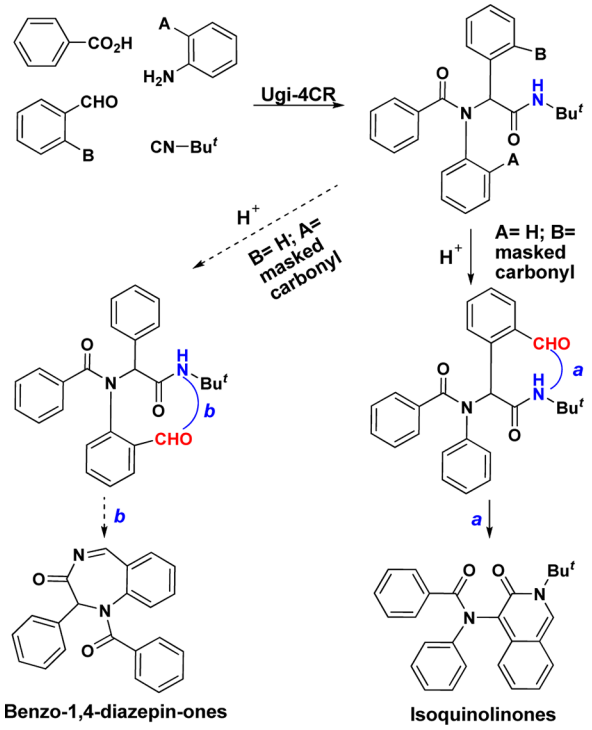
   dx.doi.org/10.1021/co400001h | *ACS Comb. Sci.* XXXX, XXX, XXX−XXX

based approach for the construction of isoquinoline scaffolds via Ugi-Heck reaction sequence.[22,23] As a continuing effort, we herein report an alternative Ugi-based MCR approach to one-pot syntheses of diverse isoquinolinones and isoquinolinones-based benzo-1,4-diazepin-2,5-diones.

RESULTS AND DISCUSSION

The Ugi reaction, offering a large number of potential inputs, has gained popularity as a powerful tool for generating diverse compound libraries, and its union with other transformations can further expand the structural type of compound libraries. From a design perspective, it was envisioned that the isoquinolinones could be assembled through an intramolecular condensation of a carbonyl with the amide group in the α-acylaminoamide which was in turn produced by the Ugi-4CR of carboxylic acid, amine, isonitrile, and monomasked phthalaldehyde (Scheme 1, Path a), and the benzo-1,4-diazepinone could

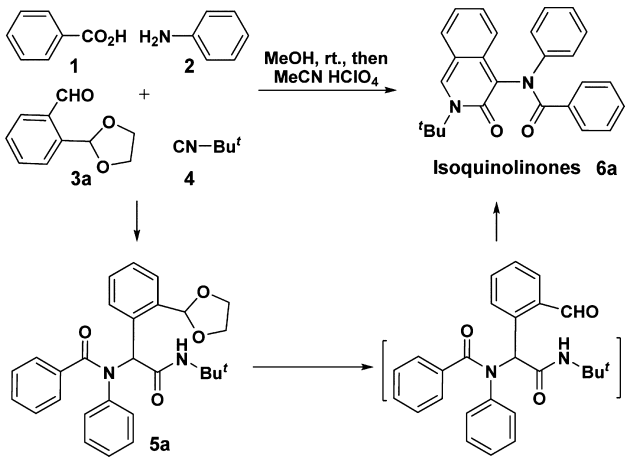
Scheme 1. Synthetic Analysis for Isoquinolinones and Benzo-1,4-diazepinones



be built up in a similar manner using the aniline bearing a masked carbonyl in *ortho* position (Scheme 1, Path b). The proposed strategy could provide rapid access to a variety of isoquinolones and benzo-1,4-diazepinones from simple starting materials.

The proposed strategy was examined by the Ugi reaction of aldehyde **3a** with benzoic acid, aniline, and *tert*-butyl isonitrile in MeOH at room temperature (Scheme 2), which was followed by the treatment with various Brønsted acids. We were pleased to find that a number of Brønsted acids including PTSA, H_2SO_4, HCl, and $HClO_4$ were able to facilitate the desired transformation. After a preliminary survey of reaction parameters, the use of $HClO_4$ in acetonitrile was found to be most effective to provide isoquinolinone **6a** in 82% yield. During our further study of benzo-1,4-diazepinone construction, we encountered difficulties in the Ugi reaction, and the

Scheme 2. One-Pot Synthesis of Isoquinolinones



products were messy and often the Passerini product was obtained as the major product.

To profile the scope and potential of the present reaction, we next examined a series of commercially available carboxylic acids, amines, isonitriles with aldehyde **3a** to form the structurally diversified isoquinolinones under the optimal reaction conditions, and their derived products are listed in Table 1. Pleasingly, all the selected substrates underwent Ugi-4CR/hydrolysis/intramolecular condensation transformations smoothly to give the corresponding isoquinolinones (**6b**–**k**) in good to excellent yields. With regard to carboxylic acid input, the performances of aromatic acids were slightly better than those of aliphatic acids, and aromatic or aliphatic amines appear to be comparable in this transformation. In addition, substituents on the amide nitrogen originating from isonitriles did not affect the annulations, since *ter*-butyl, cyclohexyl, and propyl isonitriles provided the similar results.

To further extend the reaction scope, four additional substituted 2-(1,3-dioxolan-2-yl)benzaldehyde **3b**, **3c**, **3d**, and **3e** were made (see Supporting Information for detail), and their annulated results are listed in Table 2. With regard to the substituent effect on the phenyl ring of 2-(1,3-dioxolan-2-yl)benzaldehyde, neither electron-donating groups (Table 2, entries 1 to 6) nor electron-withdrawing groups (Table 2, entries 7 to 10) on the phenyl ring affected the efficiency of the reaction. Once again, all the expected products were obtained in good to excellent yields.

As an expansion of this study, we decided to develop the post-transformation strategy for the developed Ugi-condensation synthetic protocol to further expand the compound library of biological interest. We envisioned that quinolin-3-one-based benzo-1,4-diazepin-2,5-diones **7a** could be synthesized starting from nitro-substituted benzoic acid, glycine methyl ester, aldehyde, and isonitrile, as shown in the Scheme 3. The reaction sequence for the formation of **7a** involved the Ugi-condensation reaction followed by the intramolecular lactamization which was achieved through the reduction of the nitro group under acidic conditions. In addition, this sequence could be achieved in one-pot fashion, which makes this process more practical and efficient. By varying of acid, aldehyde, and isonitrile components, a series of benzo-1,4-diazepin-2,5-diones were generated in moderate to good yields, as listed in the Table 3.

In summary, we have developed an efficient and one-pot synthesis of structurally diverse isoquinolinones and isoquino-

dx.doi.org/10.1021/co400001h | ACS Comb. Sci. XXXX, XXX, XXX–XXX

Table 1. Synthesis of Compounds 6b−6k

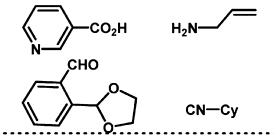
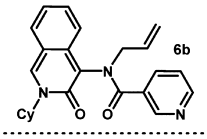
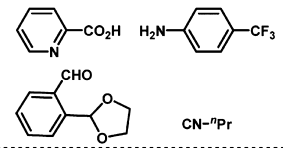
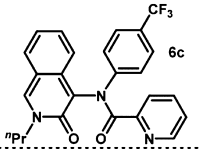
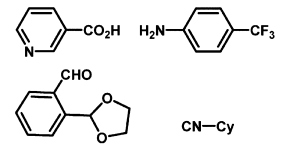
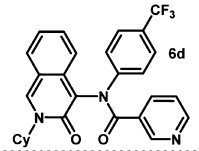
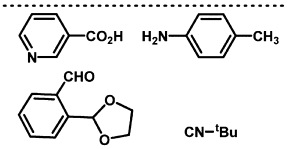
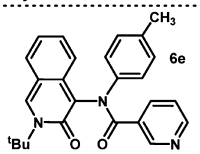
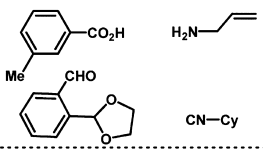
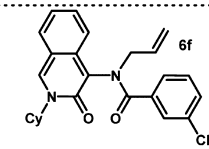
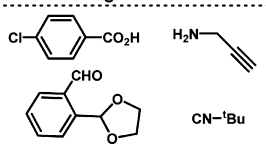
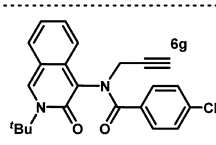
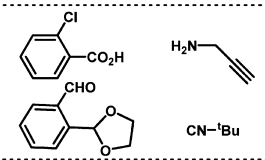
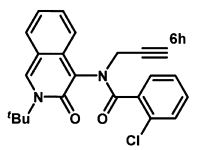
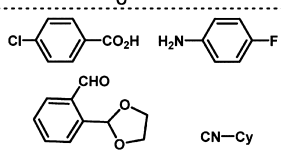
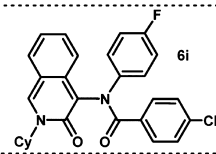
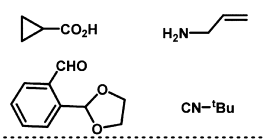
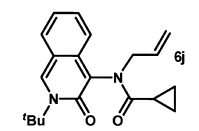
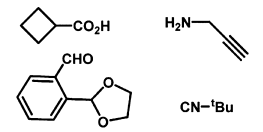
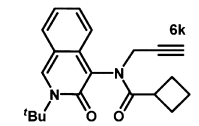
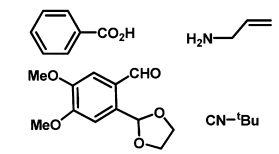
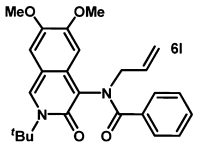
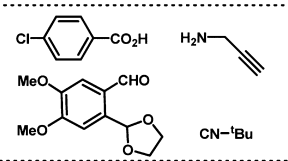
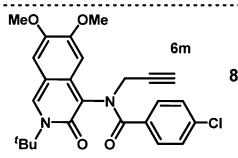
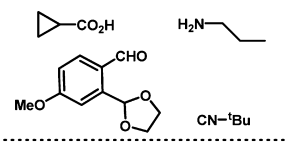
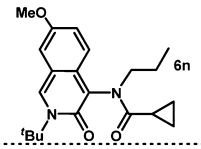
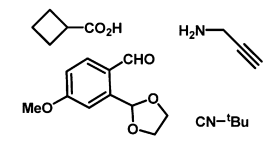
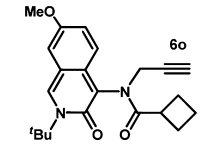
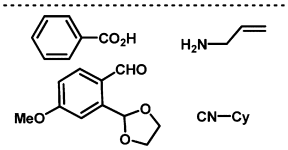
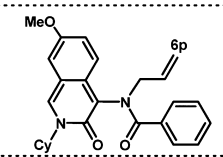
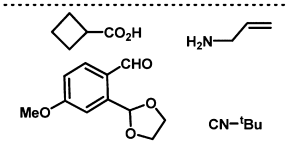
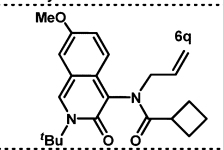
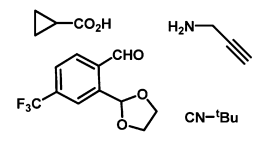
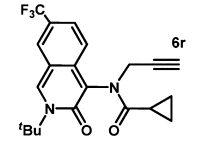
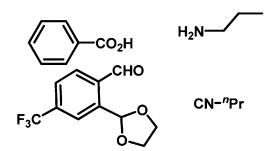
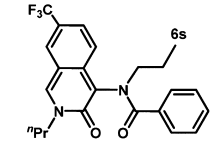
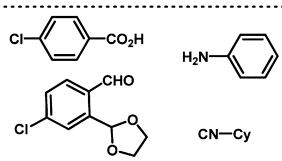
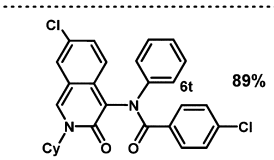
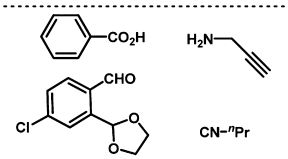
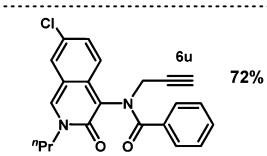
entry	Starting Materials	Product	Yield
1			76%
2			83%
3			80%
4			68%
5			70%
6			77%
7			89%
8			72%
9			62%
10			64%

Table 2. Synthesis of Compounds 6l−6u

entry	Starting Materials	Product	Yield
1			72%
2			86%
3			72%
4			69%
5			75%
6			74%
7			66%
8			54%
9			89%
10			72%

linone-based benzo-1,4-diazepin-2,5-diones involving Ugi-4CR/condensation and Ugi-4CR/condensation/reduction/lactamization sequence. This developed synthetic protocol was anticipated to be applicable in the fields of combinatorial chemistry, diversity-oriented synthesis, and drug discovery. The biological evaluation of the synthesized compounds is currently underway in our lab, and the results will be reported in due course.

EXPERIMENTAL PROCEDURES

General Experimental Details. Unless noted otherwise, all reactions were performed under a nitrogen atmosphere, and materials obtained from commercial suppliers were used without further purification. Purification of products was

dx.doi.org/10.1021/co400001h | ACS Comb. Sci. XXXX, XXX, XXX−XXX

Scheme 3. One-Pot Synthesis of Isoquinolinone-Based Benzo-1,4-diazepin-2,5-diones

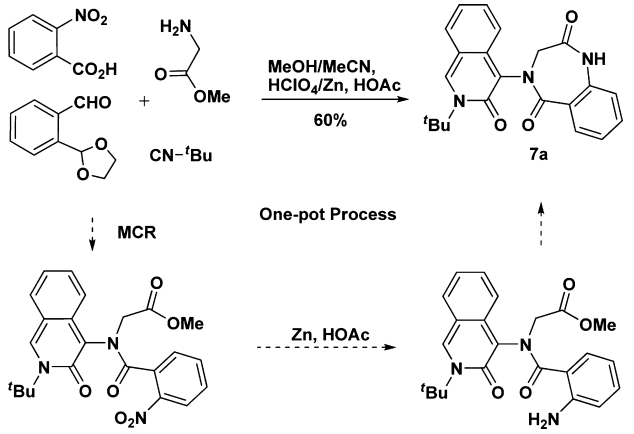
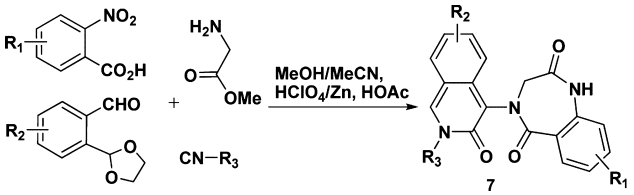


Table 3. Synthesis of Compounds 7b−7u



entry	R_1	R_2	R_3	product	yield
1	H	H	Cy	**7b**	67%
2	H	H	*n*-Py	**7c**	62%
3	5-F	H	*n*-Py	**7d**	78%
4	4-Cl	H	*t*-Bu	**7e**	80%
5	4-Cl	H	Cy	**7f**	68%
6	5-MeO	H	*n*-Py	**7g**	54%
7	5-MeO	H	Cy	**7h**	50%
8	5-Cl	4,5-2MeO	Cy	**7i**	53%
9	4-Cl	4,5-2MeO	Cy	**7j**	63%
10	H	4,5-2MeO	*n*-Py	**7k**	56%
11	5-MeO	4,5-2MeO	Cy	**7l**	46%
12	H	5-MeO	*t*-Bu	**7m**	53%
13	5-F	5-MeO	Cy	**7n**	47%
14	4-Cl	5-MeO	*t*-Bu	**7o**	45%
15	5-MeO	5-CF_3	*t*-Bu	**7p**	40%
16	5-F	5-CF_3	*t*-Bu	**7q**	35%
17	H	5-CF_3	Cy	**7r**	56%
18	H	5-Cl	*t*-Bu	**7s**	54%
19	5-Cl	5-Cl	*t*-Bu	**7t**	48%
20	5-MeO	5-Cl	Cy	**7u**	48%

conducted by flash column chromatography on silica gel (200−300 mesh) purchased from Qing Dao Hai Yang Chemical Industry Co. ^{1}H NMR spectra were recorded on a Bruker 300 or 500 MHz spectrometer using residual solvent (δ ($CDCl_3$) = 7.26) as internal standard. All the coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were recorded on the same instruments, and chemical shifts were measured relative to solvent resonances (δ ($CDCl_3$) = 77.0). High-resolution mass spectra were obtained on a quadrupole time-of-flight (QqTOF) mass spectrometer.

Typical Procedure for Four Component Reaction to Isoquinolinones 6. To a solution of 2-(1,3-dioxolan-2-yl)benzaldehyde (0.5 mmol) in MeOH (3 mL) were added amine (0.5 mmol), carboxylic acid (0.5 mmol), and isocyanide (0.5 mmol). The reaction mixture was stirred at room temperature for 12 h, and the solvent was removed under vacuum. To the resulting residue in CH_3CN (4 mL) was added $HClO_4$ (70%, 6.1 μL, 0.075 mmol), and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was worked up by the addition of $NH_3{\cdot}H_2O$ to pH = 8 and then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (CH_2Cl_2/CH_3OH = 50:1) to give the desired product. **6a**, yellow solid; Mp 190 °C; IR ν 3063, 2976, 2898, 1664, 1637, 1564, 1531, 1483, 1396, 1371, 1319, 1286, 856, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (*s*, 1H), 7.54−7.49 (*m*, 3H), 7.41−7.26 (*m*, 6H), 7.18−7.08 (*m*, 4H), 6.92−6.87 (*m*, 1H), 1.71 (*s*, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 142.7, 138.0, 137.9, 137.0, 133.2, 129.6, 129.2, 128.7, 127.1, 125.6, 125.5, 123.6, 121.5, 119.3, 115.8, 64.3, 28.2; HRMS (*m*/*z*) calc. for $C_{26}H_{25}N_2O_2$ (+) 397.1916, found 397.1907.

Typical Procedure for MCR to Benzo-1,4-diazepin-2,5-diones 7. To a mixture of glycine methyl ester hydrochloride (0.56 mmol) and Na_2CO_3 (0.28 mmol) in MeOH (3 mL) prestirring for 15 min were added 2-(1,3-dioxolan-2-yl)-benzaldehyde (0.56 mmol), 2-nitrobenzoic acid (0.56 mmol), and *tert*-butyl isocynide (0.56 mmol). The reaction mixture was stirred at room temperature for 12 h, and the solvent was removed under vacuum. To the resulting residue in CH_3CN (4 mL) was added $HClO_4$ (70%, 6.1 μL, 0.075 mmol), and the reaction mixture was stirred at room temperature for 8 h. The solvent was then removed under vacuum to give the yellow solid, to which was added AcOH (4 mL) and Zinc powder (364 mg), and the reaction mixture was stirred at 60 °C for 8 h. The reaction mixture was worked up by the addition of $NH_3{\cdot}H_2O$ to pH = 8 and then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (CH_2Cl_2/CH_3OH = 50:1) to give the desired product. **7a**, yellow solid; Mp 165 °C; IR ν 3219, 3068, 2974, 2924, 1693, 1641, 1533, 1481, 1448, 1408, 1190, 758, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (*s*, 1H), 8.46 (*s*, 1H), 8.09 (*dd*, *J* = 0.9, 6.9 Hz, 1H), 7.51 (*m*, 2H), 7.32 (*m*, 3H), 7.18 (*d*, *J* = 8.1 Hz, 1H), 7.06 (*d*, *J* = 6.9 Hz, 1H), 6.96 (*m*, 1H), 4.51 (*d*, *J* = 15.3 Hz, 1H), 4.14 (*d*, *J* = 15.3 Hz, 1H), 1.86 (*s*, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 167.3, 158.0, 138.0, 137.8, 136.3, 133.4, 132.7, 132.2, 129.1, 126.1, 125.0, 122.2, 122.0, 120.9, 120.0, 116.4, 64.9, 52.3, 28.6; HRMS (*m*/*z*) calc. for $C_{22}H_{22}N_3O_3$ (+) 376.1661, found 376.1660.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, compound characterization data, and ^{1}H, ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: 86-755-26032530 (C.C.), 310-267-4970 (S.L.), 86-755-26032971 (Z.Y). Fax: 86-755-26033180 (C.C.), 310-267-4971 (S.L.), 86-755-26032163 (Z.Y.). E-mail: chec@pkusz.edu.cn (C.C.), shuolin@ucla.edu (S.L.), zyang@pku.edu.cn (Z.Y.).

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 21102006), the Natural Science Foundation of Guangdong Province (Grant No. S2011010000185), Guangdong Innovative Research Team Program (Grant No. 201001Y0104701332), and Shenzhen Science and Technology Plan Projects (Grant No. JSA201005310118A, and GJHS20120628101219318).

Notes

The authors declare no competing financial interest.

DEDICATION

[†]This paper is dedicated to Professor Zhongning Zhang on the occasion of his 70th birthday.

REFERENCES

(1) (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. *Acc. Chem. Res.* **1996**, *29*, 123−131. (b) Dömling, A.; Ugi, I. Multicomponent Reactions with Isocynides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (c) Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev.* **2006**, *106*, 17−89. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186. (e) Enders, D.; Grondal, C.; Hüttl, M. R. M. Asymmetric Organocatalytic Domino Reactions. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570−1581. (f) Toure, B. B.; Hall, D. G. Natural Product Synthesis Using Multicomponent Reaction Strategies. *Chem. Rev.* **2009**, *109*, 4439−4486.

(2) (a) Blackwell, H. E. Hitting the SPOT: Small-molecule Macroarrays Advance Combinatorial Synthesis. *Curr. Opin. Chem. Biol.* **2006**, *10*, 203−212. (b) Akritopoulou-Zanze, I. Isocyanide-based Multicomponent Reactions in Drug Discovery. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324−331. (c) Bräuer, S.; Almstetter, M.; Antuch, W.; Behnke, D.; Taube, R.; Furer, P.; Hess, S. Evolutionary Chemistry Approach toward Finding Novel Inhibitors of the Type 2 Diabetes Target Glucose-6-phosphate Translocase. *J. Comb. Chem.* **2005**, *7*, 218−226. (d) Weber, L. The Application of Multi-component Reactions in Drug Discovery. *Curr. Med. Chem.* **2002**, *9*, 205−2093. (e) Hulme, C.; Gore, V. Multi-component Reactions: Emerging Chemistry in Drug Discovery 'From Xylocain to Crixivan'. *Curr. Med. Chem.* **2003**, *10*, 51−80. (f) Dömling, A. The Discovery of New Isocyanide-based Multi-component Reactions. *Curr. Opin. Chem. Biol.* **2000**, *4*, 318−323.

(3) Roth, J.; Madoux, F.; Hodder, P.; Roush, W. R. Synthesis of Small Molecule Inhibitors of the Orphan Nuclear Receptor Steroidogenic Factor-1 (NR5A1) Based on Isoquinolinone Scaffolds. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2628−2632.

(4) Hu, J.; Zhang, W. D.; Liu, R. H.; Zhang, C.; Shen, Y. H.; Li, H. L.; Liang, M. J.; Xu, X. K. Benzophenanthridine Alkaloids from *Zanthoxylum nitidum* (Roxb.) DC, and Their Analgesic and Anti-Inflammatory Activities. *Chem. Biodiversity* **2006**, *3*, 990−995.

(5) Micale, N.; Ettari, R.; Schirmeister, T.; Evers, A.; Gelhaus, C.; Leippe, M.; Zappalà, M.; Grasso, S. Novel 2*H*-Isoquinolin-3-ones as Antiplasmodial Falcipain-2 Inhibitors. *Bioorg. Med. Chem.* **2009**, *17*, 6505−6511.

(6) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.; Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G. D.; Dinsmore, C. J. Design and Synthesis of Novel Isoquinoline-3-nitriles as Orally Bioavailable Kv1.5 Antagonists for the Treatment of Atrial Fibrillation. *J. Med. Chem.* **2006**, *49*, 6954−6957.

(7) Hutchinson, J. H.; Cook, J. J.; Brashear, K. M.; Breslin, M. J.; Glass, J. D.; Gould, R. J.; Halczenko, W.; Holahan, M. A.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Hartman, G. D. Non-Peptide Glycoprotein IIb/IIIa Antagonists. 11. Design and *in Vivo* Evaluation of 3,4-Dihydro-1(1*H*)-isoquinolinone-Based Antagonists and Ethyl Ester Prodrugs. *J. Med. Chem.* **1996**, *39*, 4583−4591.

(8) (a) Ontoria, J. M.; Rydberg, E. H.; Di Marco, S.; Tomei, L.; Attenni, B.; Malancona, S.; Martin Hernando, J. I.; Gennari, N.; Koch, U.; Narjes, F.; Rowley, M.; Summa, V.; Olsen, D. B.; De Francesco, R.; Altamura, S.; Migliaccio, G.; Carfi, A. Identification and Biological Evaluation of a Series of 1*H*-Benzo[*de*]isoquinoline-1,3(2*H*)-diones as Hepatitis C Virus NS5B Polymerase Inhibitors. *J. Med. Chem.* **2009**, *52*, 5217−5227. (b) Malancona, S.; Donghi, M.; Ferrara, M.; Hernando, J. I. M.; Pompei, M.; Pesci, S.; Ontoria, J. M.; Koch, U.; Rowley, M.; Summa, V. Allosteric Inhibitors of Hepatitis C Virus NS5B Polymerase Thumb Domain Site II: Structure-Based Design and Synthesis of New Templates. *Bioorg. Med. Chem.* **2010**, *18*, 2836−2848.

(9) (a) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Takagi, M.; Kikkawa, K.; Omori, K. Novel, Potent, and Selective Phosphodiesterase 5 Inhibitors: Synthesis and Biological Activities of a Series of 4-Aryl-1-isoquinolinone Derivatives. *J. Med. Chem.* **2001**, *44*, 2204−2218. (b) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Fujishigeb, K.; Takagi, M.; Kikkawa, K.; Omori, K. 1,7- and 2,7-Naphthyridine Derivatives as Potent and Highly Specific PDE5 Inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2341−2345.

(10) (a) Rhee, H. K.; Lim, S. Y.; Jung, M. J.; Kwon, Y.; Kim, M. H.; Choo, H. Y. Synthesis of Isoquinolinone-Based Tetracycles as Poly (ADP-Ribose) Polymerase-1 (PARP-1) Inhibitors. *Bioorg. Med. Chem.* **2009**, *17*, 7537−7541. (b) Jagtap, P. G.; Baloglu, E.; Southan, G. J.; Mabley, J. G.; Li, H.; Zhou, J.; Duzer, J.; Salzman, A. L.; Szabo, C. Discovery of Potent Poly(ADP-ribose) Polymerase-1 Inhibitors from the Modification of Indeno[1,2-*c*]isoquinolinone. *J. Med. Chem.* **2005**, *48*, 5100−5103.

(11) Lin, L. Z.; Cordell, G. A. Quinoline alkaloids from Camptotheca acuminata. *Phytochemistry* **1989**, *28*, 1295−1297.

(12) Wang, S. Q.; Wang, G. Q.; Huang, B. K.; Zhang, Q. Y.; Qin, L. P. Isoquinoline Alkaloids from *Broussonetia Papyrifera* Fruits. *Chem. Nat. Compd.* **2007**, *43*, 100−102.

(13) (a) Wright, W. B.; Brabander, H. J.; Greenblatt, E. N.; Day, I. P.; Hardy, R. A. Derivatives of 1,2,3,11a-Tetrahydro-5H-Pyrrolo[2,1-C][1,4]Benzodiazepine-5,11(10H)-Dione as Anxiolytic Agents. *J. Med. Chem.* **1978**, *21*, 1087−1089. (b) Li, X.; Yu, J.; Atack, J. R.; Cook, J. M. Development of Selective Ligands for Benzodiazepine Receptor Subtypes by Manipulating the Substituents at Positions 3- and 7- of Optically Active BzR Ligands. *Med. Chem. Res.* **2004**, *13*, 259−281.

(14) (a) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. Isolation and Characterization of Anthramycin, a New Antitumor Antibiotic. *J. Am. Chem. Soc.* **1965**, *87*, 5791−5793. (b) Leimgruber, W.; Batcho, A. D.; Schenker, F. The Structure of Anthramycin. *J. Am. Chem. Soc.* **1965**, *87*, 5793−5795. (c) Cooper, N.; Hagan, D. R.; Tiberghien, A.; Ademefun, T.; Mattews, C. S.; Howard, P. W.; Thurston, D. E. Synthesis of Novel C2-Aryl Pyrrolobenzodiazepines (Pbds) as Potential Antitumour Agents. *Chem. Commun.* **2002**, 1764−1765.

(15) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Reddy, G.; Raghavan, S. Solid-Phase Synthesis of a Library of Pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones with Potential Antitubercular Activity. *J. Comb. Chem.* **2007**, *9*, 29−42.

(16) Hsu, M. C.; Schutt, A. D.; Holly, M.; Slice, L. W.; Sherman, M. L.; Richman, D. D.; Potash, M. J.; Volsky, D. J. Inhibition of HIV Replication in Acute and Chronic Infections in Vitro by A Tat Antagonist. *Science* **1991**, *254*, 1799−1802.

(17) (a) Araújo, A. C.; Nicotra, F.; Airoldi, C.; Costa, B.; Giagnoni, G.; Fumagalli, P.; Cipolla, L. Synthesis and Biological Evaluation of Novel Rigid 1,4-Benzodiazepine-2,5-dione Chimeric Scaffolds. *Eur. J. Org. Chem.* **2008**, 635−639. (b) Li, X.; Yu, J.; Atack, J. R.; Cook, J. M. Development of Selective Ligands for Benzodiazepine Receptor Subtypes by Manipulating the Substituents at Positions 3- and 7- of Optically Active BzR Ligands. *Med. Chem. Res.* **2004**, *13*, 259−281.

(18) Loudni, L.; Roche, J.; Potiron, V.; Clarhaut, J.; Bachmann, C.; Gesson, J.; Tranoy-Opalinski, I. Design, synthesis and biological evaluation of 1,4-benzodiazepine-2,5-dione-based HDAC inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4819−4823.
(19) Mondragón, L.; Orzáez, M.; Sanclimens, G.; Moure, A.; Armiñán, A.; Sepúlveda, P.; Messeguer, A.; Vicent, M. J.; Pérez-Payá, E. Modulation of Cellular Apoptosis with Apoptotic Protease-Activating Factor 1 (Apaf-1) Inhibitors. *J. Med. Chem.* **2008**, *51*, 521−529.
(20) (a) Marugan, J. J.; Leonard, K.; Raboisson, P.; Gushue, J. M.; Calvo, R.; Koblish, H. K.; Lattanze, J.; Zhao, S. Y.; Cummings, M. D.; Player, M. R.; Schubert, C.; Maroney, A. C.; Lu, T. Enantiomerically Pure 1,4-Benzodiazepine-2,5-diones as Hdm2 Antagonists. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3115−3120. (b) Leonard, K.; Marugan, J. J.; Raboisson, P.; Calvo, R.; Gushue, J. M.; Koblish, H. K.; Lattanze, J.; Zhao, S. Y.; Cummings, M. D.; Player, M. R.; Maroney, A. C.; Lu, T. Novel 1,4-benzodiazepine-2,5-diones as Hdm2 antagonists with improved cellular activity. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3463−3468.
(21) (a) Che, C.; Xiang, J.; Wang, G. X.; Fathi, R.; Quan, J. M.; Yang, Z. One-Pot Synthesis of Functionalized Quinoline-based Poly-Heterocycles by a Tandem Three-Component Reaction. *J. Comb. Chem.* **2007**, *9*, 982−989. (b) Xiang, J.; Yang, H.; Che, C.; Zou, H.; Yang, H.; Wei, Y.; Quan, J.; Zhang, H.; Yang, Z.; Lin, S. Identifying Tumor Cell Growth Inhibitors by Combinatorial Chemistry and Zebrafish Assays. *PLoS One* **2009**, *4*, e4361. (c) Zhong, H.; Zou, H.; Semenov, M. V.; Moshinsky, D.; He, X.; Huang, H.; Li, S.; Quan, J.; Yang, Z.; Lin, S. Characterization and Development of Novel Small-Molecules Inhibiting GSK3 and Activating Wnt Signaling. *Mol. BioSyst.* **2009**, *5*, 1356−1360. (d) Zou, H.; Zhou, L.; Li, Y.; Cui, Y.; Zhong, H.; Pan, Z.; Yang, Z.; Quan, J. Benzo[*e*]isoindole-1,3-diones as Potential Inhibitors of Glycogen Synthase Kinase-3 (GSK-3). Synthesis, Kinase Inhibitory Activity, Zebrafish Phenotype, and Modeling of Binding Mode. *J. Med. Chem.* **2010**, *53*, 994−1003. (e) Che, C.; Liu, L.; Gong, J.; Yang, Y.; Wang, G.; Yang, Z. Construction of All Carbon Quarternary Center by AlR_2Cl-Mediated Ring-Opening Reaction of Oxacycles. *Org. Lett.* **2010**, *12*, 488−491. (f) Che, C.; Li, S.; Jiang, X. L.; Quan, J. M.; Lin, S.; Yang, Z. One-Pot Synthesis of Chromeno[3,4-c]pyrrole-3,4-diones via Ugi-4CR and Intramolecular Michael Addition. *Org. Lett.* **2010**, *12*, 4682−4685. (g) Che, C.; Li, S.; Yang, B.; Xin, S. C.; Yu, Z. X.; Shao, T. F.; Tao, C. Y.; Lin, S.; Yang, Z. Synthesis and Characterization of Sant-75 Derivatives as Hedgehog Pathway Inhibitors. *Beilstein J. Org. Chem.* **2012**, *8*, 841−849.
(22) Xiang, Z.; Luo, T. P.; Lu, K.; Cui, J. Y.; Shi, X. M.; Fathi, R.; Chen, J. H.; Yang, Z. Concise Synthesis of Isoquinoline via the Ugi and Heck Reactions. *Org. Lett.* **2004**, *6*, 3155−3158.
(23) Key references from other groups on the Ugi-4CR post-transformations. Ugi/Smiles sequence: (a) Kaüm, L. E.; Grimaud, L.; Oble, J. Phenol Ugi-Smiles Systems: Strategies for the Multi-component N-Arylation of Primary Amines with Isocyanides, Aldehydes, and Phenols. *Angew. Chem., Int. Ed.* **2005**, *44*, 7961−7964. Ugi/aza-Wittig sequence: (b) Ramazani, A.; Rezaei, A. Novel One-Pot, Four-Component Condensation Reaction: An Efficient Approach for the Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazole Derivatives by a Ugi-4CR/*aza*-Wittig Sequence. *Org. Lett.* **2009**, *11*, 995−997. Ugi/IMDA sequence: (c) Lee, D.; Sello, J. K.; Schreiber, S. L. Pairwise Use of Complexity-Generating Reactions in Diversity-Oriented Organic Synthesis. *Org. Lett.* **2000**, *2*, 709−712. Ugi/Pictet-Spengler Sequence: (d) Wang, W.; Ollio, S.; Herdtweck, E.; Dömling, A. Polycyclic Compounds by Ugi-Pictet-Spengler Sequence. *J. Org. Chem.* **2011**, *76*, 637−644. Ugi/S_N2'-Heck sequence: (e) Riva, R.; Banfi, L.; Basso, A.; Cerulli, V.; Guanti, G.; Pani, M. A Highly Convergent Synthesis of Tricyclic N-Heterocycles Coupling an Ugi Reaction with a Tandem S_N2'-Heck Double Cyclization. *J. Org. Chem.* **2010**, *75*, 5134−5143. Ugi/1,4-addition sequence: (f) Bienaymé, H.; Bouzi, K. Synthesis of Rigid Hydrophobic Tetrazoles Using an Ugi Multi-Component Heterocyclic Condensation. *Tetrahedron Lett.* **1998**, *39*, 2735−2738. Ugi/Buchwald-Hartwig sequence: (g) Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. P. Rapid Access to Oxindoles by the Combined Use of an Ugi Four-Component Reaction and a Microwave-Assisted Intramolecular Buchwald-Hartwig Amidation Reaction. *Org. Lett.* **2006**, *8*, 4351−4354.