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Efficient and selective microwave-assisted copper-catalyzed synthesis of quinazolinone derivatives in aqueous

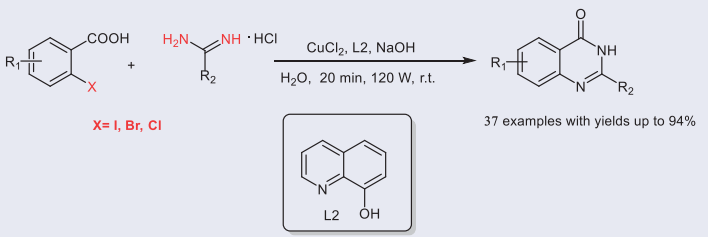
Fang Ke, Caiqin Liu, Peng Zhang, Jianhua Xu, and Xiaole Chen

College of Pharmacy, Fujian Medical University, Fuzhou, China

ABSTRACT

Microwave-assisted copper-catalyzed cascade reactions between 2-halobenzoic acids and amidines to synthesize quinazolinone derivatives in water are reported. A variety of target products were obtained in good to excellent yields up to 94%. Its application was performed by the synthesis of 4-(1H-benzo[d]imidazol-2-ylthio)-6-methoxypteridine, which displayed significant anti-proliferation effect.

GRAPHICAL ABSTRACT



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KEYWORDS
Catalysis; copper; microwave; quinazolinone; water

Introduction

Quinazolinone derivatives are an important class of heterocyclic compounds found in many natural and synthetic products,[1] which exhibit biological or medicinal activities, and can be used as hypnotic, sedative, analgesic, antifungal, antibacterial, anticancer, and antitumor reagents.[2] For example, raltitrexed and icotinib, which contain quinazoline fragment, have already appeared in market or in clinical trials as therapeutic agents for the treatment of cancer (Figure 1).[3]

Generally, quinazolinones are obtained by using ortho-amino or halogen benzoic acid derivatives as starting materials.[4] For example, Li and coworkers synthesized quinazolinones scaffold from anthranilic acid and cyanogens (Scheme 1, path 1).[5] Wang and coworkers developed a convenient microwave-assisted synthesis of 2-substituted quinazolinones from anthranilic acid analogs and amides in the presence of acetic acid (Scheme 1, path 2).[6] However, the majority of these reported procedures usually

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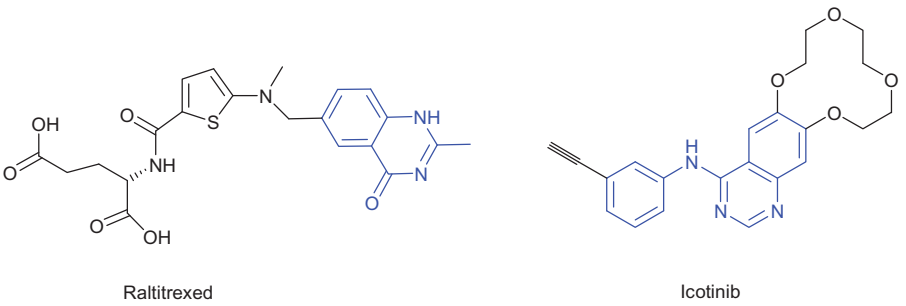
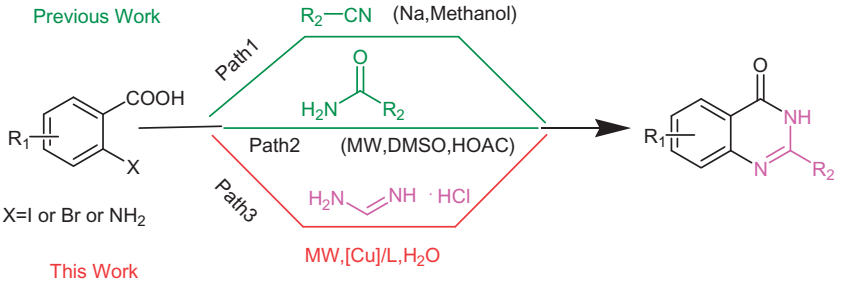


Figure 1. Selected examples of quinazolinone derivatives.



Scheme 1. Different pathways for the synthesis of quinazolinones.

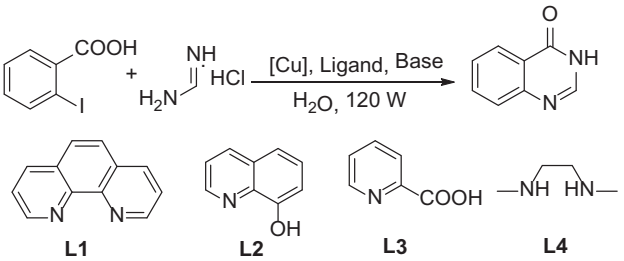
required harsh conditions, and the yields were not very satisfactory and the use of expensive, air-sensitive, or toxic reagents.[7] The development of novel, effective and practical quinazolinone synthetic method remains an unmet challenge for organic chemists. Over the past few decades, progress has been made in the copper-catalyzed N-arylations,[8] and a series of N-heterocycles have been obtained by this method, some of the reported procedures to synthesize quinazolinones rely on the reaction of ortho-halobenzoic acid derivatives.[9] For example, Fu and coworkers reported some novel and useful domino methods to construct quinazolinones using readily available α-amino acids as the nitrogen-containing motifs.[10]

On the other hand, the development of environmentally benign catalytic systems, in particular, the use of water as a reaction medium, has attracted attention in recent years.[11] Meanwhile, microwave (MW)-assisted transition metal catalyzed reactions is advantageous for enabling rapid, reproducible, and scalable chemistry development in research laboratories as well as industrial processes.[12]

Results and discussion

In continuation of our endeavors to develop simple and environmentally friendly protocols,[13] herein is reported an efficient copper-catalyzed cascade reaction of amidines with substituted 2-halobenzoic acids to synthesize quinazolinone derivatives by using water as solvent under microwave irradiation. Compared with the reported protocols, this method has the following advantages: water is used as solvent instead of normal organic solvents; the mild reaction conditions such as low temperature and without inert atmosphere; the microwave-assisted catalysis shows high efficiency with good to

Table 1. Optimization of the catalytic conditions[a].



Entry	[Cu] source	Ligand	Base	t /min	Yield (%)[b]
1	CuI	**L1**	KOH	20	35
2	CuI	**L2**	KOH	20	80
3	CuI	**L3**	KOH	20	20
4	CuI	**L4**	KOH	20	45
5	$CuCl_2$	**L2**	KOH	20	83
6	$Cu(OAc)_2$	**L2**	KOH	20	72
7	$CuSO_4$	**L2**	KOH	20	75
8	CuO	**L2**	KOH	20	45
9	$CuCl_2$	–	KOH	20	10
10	–	**L2**	KOH	20	trace
11	$CuCl_2$	**L2**	K_2CO_3	20	67
12	$CuCl_2$	**L2**	NaOH	20	90
13[c]	$CuCl_2$	**L2**	NaOH	20	90
14	$CuCl_2$	**L2**	Cs_2CO_3	20	85
15	$CuCl_2$	**L2**	–	20	13
16	$CuCl_2$	**L2**	NaOH	15	81
17	$CuCl_2$	**L2**	NaOH	25	88

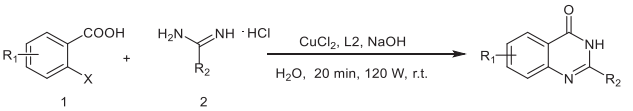
[a]Reaction conditions: 2-iodobenzoic acid (1.0 mmol), acetamidine hydrochloride (1.2 mmol), Cu source (10 mol%), ligand (10 mol%), and base (4.0 mmol) in water (3 mL) under air.
[b]Determined by GC with 1,4-dichlrobenzene as internal standard.
[c]With addition of $(n\text{-}Bu)_4NBr$.

high yields and only 20 min reaction time; the application is performed by the synthesis of 4-(1H-benzo[d]imidazol-2-ylthio)-6-methoxypteridine, which displays significant anti-proliferation effect.

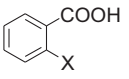
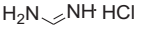
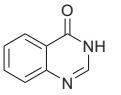
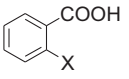
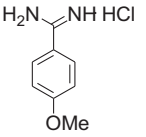
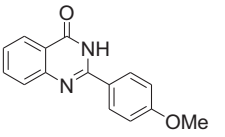
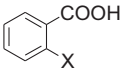
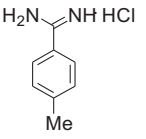
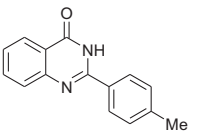
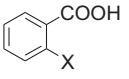
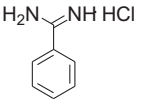
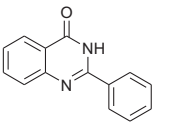
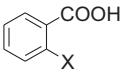
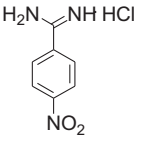
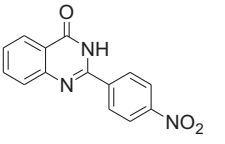
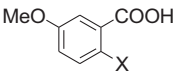
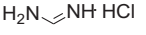
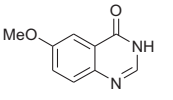
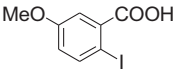
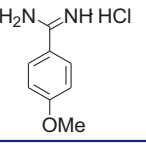
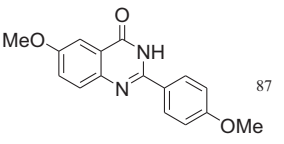
To establish the proper catalytic conditions, several factors were screened by using 2-iodobenzoic acid and acetamidine hydrochloride as model substrates. As shown in Table 1, four different ligands were examined, and 8-hydroxyquinoline gave the best result of 80% yield (Table 1, entries 1–4). Next, several copper salts such as CuI, $CuCl_2$, Cu $(OAc)_2$, $CuSO_4$, and CuO were screened for this reaction, and $CuCl_2$ was found to be superior to others (Table 1, entries 5–8). Meanwhile, control experiments confirmed the necessity of catalyst, and only 10% yield or trace of product was obtained in the absence of ligand or metal salts (Table 1, entries 9 and 10). Investigation of a variety of bases revealed that NaOH was better than the others including KOH, K_2CO_3, and Cs_2CO_3 (Table 1, entries 10–15). Meanwhile, similar yield was obtained in the presence of phase-transfer catalysts (PTCs) (Table 1, entry 12). Further studies revealed the optimal reaction time to be 20 min under microwave irradiation at 120 W in water at room temperature (Table 1, entries 16–17). Thus, the optimal catalytic conditions consist of $CuCl_2$ (10 mol%), **L2** (10 mol%), and NaOH (4 equiv) in water at room temperature for 20 min under 120 W microwave in the air.

With the optimized reaction conditions in hand, we investigated the substrate scope of this methodology by using a variety of 2-halobenzoic acids and amidines, and the

Table 2. Copper-catalyzed synthesis of quinazolinone derivatives[a].



1 2

Entry	1	2	Product	Yield(%)[b]
1				90(X=I) 81 (X=Br) 56(X=Cl)
2				88 (X=I) 80 (X=Br) 50(X=Cl)
3				88(X=I) 76 (X=Br)
4				88 (X=I) 74 (X=Br)
5				94 (X=I) 78 (X=Br) 52(X=Cl)
6				89 (X=I) 55 (X=Br)
7				87

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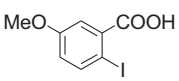
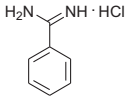
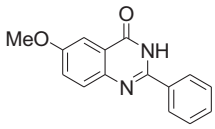
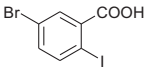
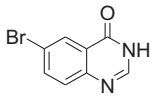
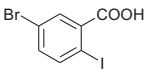
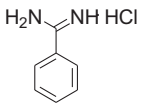
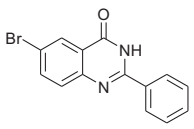
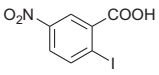
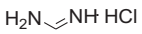
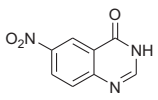
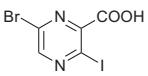
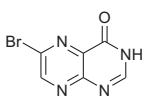
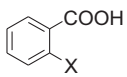
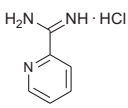
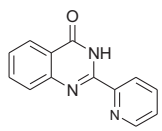
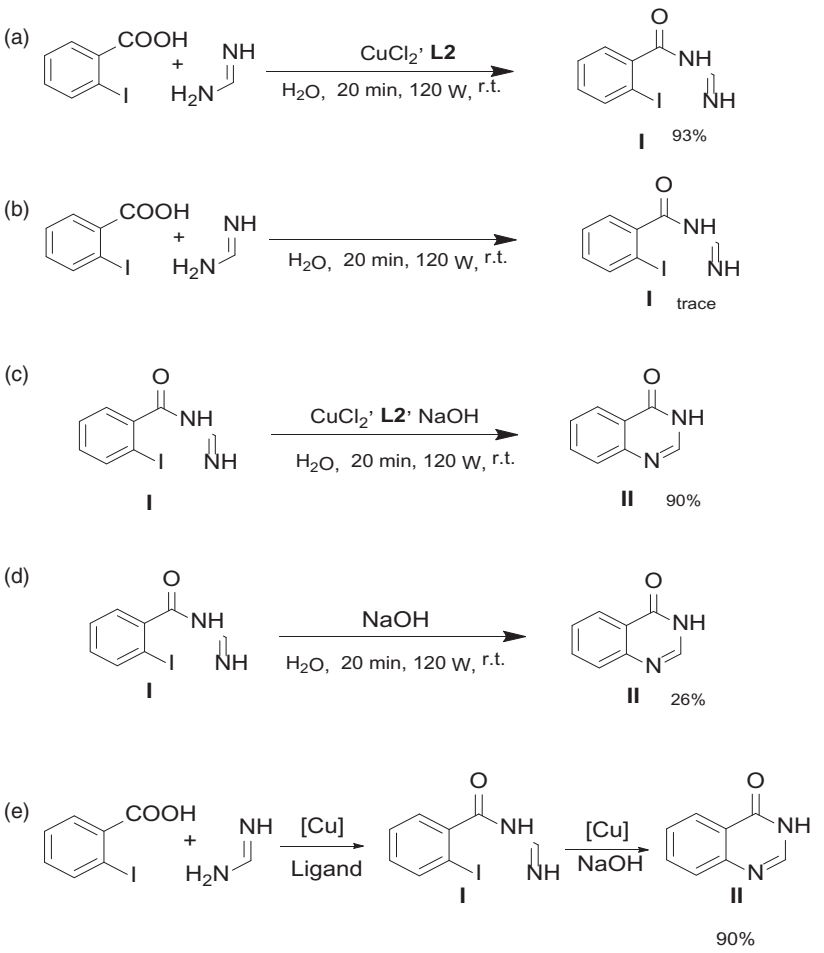
8				91
9				91
10				92
11				93
12				84
13				88 (X=I) 83 (X=Br)

[a]Reaction conditions: 2-halobenzoic acids (1.0 mmol), amidines (1.2 mmol), $CuCl_2$ (10 mol%), 8-hydroxyquinoline (10 mol%), NaOH (4.0 mmol), water (3 mL) at room temperature, under air.
[b]Isolated yields.

results were listed in Table 2. In general, the catalytic reactions were performed smoothly with a variety of substrates bearing different functional groups including methoxyl, methyl, nitro and bromo groups, resulting in moderate to excellent yields ranging from 55% to 94%. As expectedly, aryl iodides were more reactive than aryl bromides and aryl chlorides. For example, 2-iodobenzoic acid, 2-bromobenzoic acid and 2-chlorobenzoic acid gave the target products in yields 90%, 81%, and 56%, respectively (Table 2, entry 1). Meanwhile, the reactivity of the substituted 2-halobenzoic acids and amidines containing electron-withdrawing groups was slightly higher than those containing electron-donating groups (Table 2, entries 5–7). And the highest yield 94% was obtained in the case of 4-nitrobenzamidine (Table 2, entry 5).

Furthermore, the cascade reactions of aryl halides bearing three different halogen atoms were also tested, and the reaction occurred at iodo position with high selectivity to form a monosubstituted product, which indicated the potential further functionalization (Table 2, entries 9 and 10). On the other hand, it is noteworthy that the catalytic



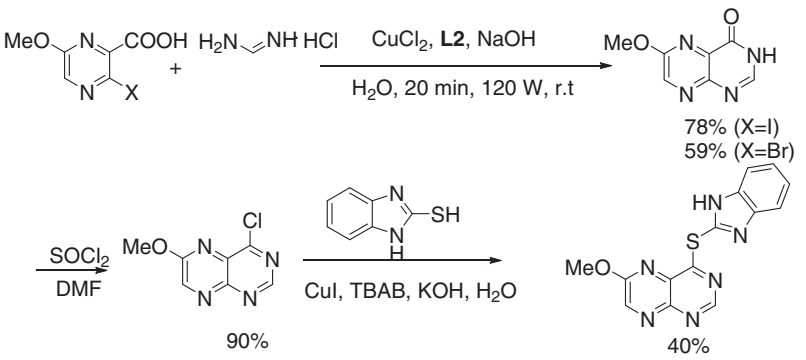
Scheme 2. Proposed catalytic pathway for the reaction.

system was also proved to be efficient in the reactions between more challenging heterocyclic halides or amidines, allowing easy access to heterocyclic quinazolinone derivatives, which are found in numerous appealing compounds (Table 2, entries 12 and 13).

To study the possible reaction pathway, the mixture was measured during the reaction, and *N*-(iminomethyl)-2-iodobenzamide **I** was detected by LC/MS, indicating that the reaction might have undergone two reactions to give the product during the catalysis. Indeed, control experiments afforded the cascade product in 90% yield from the isolated substrate **I** under the optimal catalytic conditions.

To explore the catalytic mechanism, the following experiments were performed as shown in Scheme 2, 2-halobenzoic acid reacted well with amidine to provide amide **I** in 93% under Cu source and ligand without NaOH (Scheme 2(a)). When copper source and ligand are not present, the yield is reduced to trace (Scheme 2(b)), which suggested copper source and ligand are essential for reaction. Furthermore, When the amide **I** is converted to the target product **II**, the copper source and the ligand are also important (Scheme 2(c,d)).

Based on our studies as well as literature, the reaction pathway is assumed as shown in Scheme 2(e). Firstly, the reaction between 2-halobenzoic acid and amidine yields



Scheme 3. Synthesis of 4-(1H-benzo[d]imidazol-2-ylthio)-6-methoxypteridine in water.

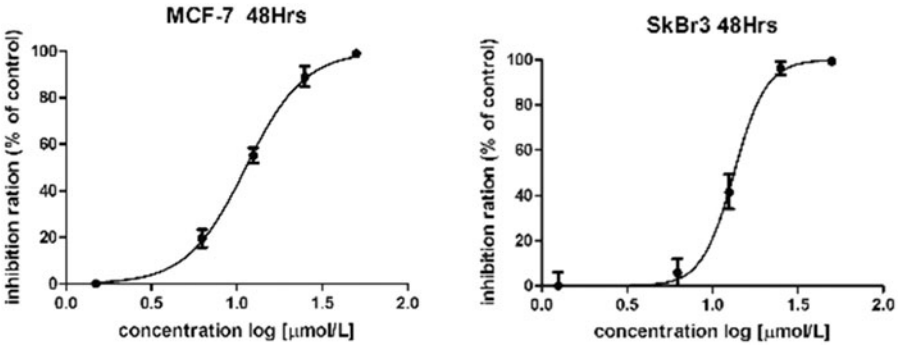


Figure 2. Relationship between inhibition rate for MCF-7 and SkBr3 cells and initial concentration.

amide **I**. Then the intramolecular C–N reactions of the halide and amino groups could successfully provide the target product **II** under the reaction conditions.[9a,10c]

Furthermore, it was reported that quinazolinones could be easily transformed into the corresponding quinazolines, which have various biological and medicinal activities.[14] The present method provides a novel strategy for the synthesis of a diverse array of quinazoline derivatives. For example, 4-(1H-benzo[d]imidazol-2-ylthio)-6-methoxypteridine was prepared by this method starting from 3-iodo-6-methoxypyrazine-2-carboxylic acid and acetamidine hydrochloride in a total yield of 28% (Scheme 3).

The obtained compound was then used in the MTT assay, and the results were graphically represented in Figure 2. They displayed significant anti-proliferation effects on both tested human breast cancer cell lines MCF-7 and SkBr3, and the IC_{50} values obtained against MCF-7 cells and SkBr3 cells were 11.30 μM and 13.39 μM, respectively.

Conclusion

In conclusion, an efficient protocol for the synthesis of quinazolinone derivatives through copper-catalyzed cascade couplings of substituted 2-iodobenzoic acids and amidines in water under microwave heating has been disclosed. The reactions can be carried out in the air without an inert atmosphere, and water as a reaction medium instead of the usually used organic solvents. Further studies into the reaction

mechanism, and to expand the potential applications are currently in progress in our laboratories.

Experimental

In a 10 mL glass tube 2-iodobenzoic acid (1.0 mmol), acetamidine hydrochloride (1.2 mmol), $CuCl_2$ (0.1 mmol), L2 (0.1 mmol), and NaOH (4.0 equiv.) and 3.0 mL water were placed. The vessel was then sealed with a septum and placed into the microwave cavity. Initial microwave irradiation of 120 W by using a CEM Discover microwave synthesizer was used at the room temperature for 20 min. The reaction mixture was stirred continuously during the reaction. After completion of the reaction, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography to afford the corresponding product. All the products were confirmed by NMR and MS spectroscopic analysis.

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References

[1] (a) Jafari, E.; Khajouei, M. R.; Hassanzadeh, F.; Hakimelahi, G. H.; Khodarahmi, G. *A. Res. Pharm. Sci*. **2016**, *11*, 1–14. (b) Abdel-Aziz, A. A.-M.; Abou-Zeid, L. A.; Eltahir, K. E. H.; Mohamed, M. A.; Abu Ei-Enin, M. A.; Ei-Azab, A.,S. Design, Synthesis of 2,3-Disubstitued 4(3H)-Quinazolinone Derivatives as anti-Inflammatory and Analgesic Agents: COX-1/2 Inhibitory Activities and Molecular Docking Studies. *Bioorgan. Med. Chem*. **2016**, *24*, 3818–3828 (c) Xu, G.; Wang, L.; Li, M. M.; Tao, M. L.; Zhang, W. Q. Phosphorous Acid Functionalized Polyacrylonitrile Fibers with a Polarity Tunable Surface Micro-Environment for One-Pot C–C and C–N Bond Formation Reactions. *Green Chem*. **2017**, *19*, 5818–5830 (d) Kondo, T.; Yoshimura, T.; Yuanjun, D.; Kimura, Y.; Yamada, H.; Toshimitsu, A. Simple, Selective, and Practical Synthesis of 2-Substituted 4(3H)-Quinazolinones by Yb(OTf)3-Catalyzed Condensation of 2-Aminobenzamide with Carboxamides. *Heterocycles* **2015**, *90*, 857–865 (e) Ge, W.; Zhu, X.; Wei, Y. Iodine-Catalyzed Oxidative System for Cyclization of Primary Alcohols with o-Aminobenzamides to Quinazolinones Using DMSO as the Oxidant in Dimethyl Carbonate. *RSC Adv*. **2013**, *3*, 10817–10822 (f) Feng, Y. D.; Tian, N.; Li, Y. D.; Jia, C. Q.; Li, X. N.; Wang, L. H.; Cui, X. L. Construction of Fused Polyheterocycles through Sequential [4 + 2] and [3 + 2] Cycloadditions. *Org. Lett*. **2017**, *19*, 1658–1661. (g) Gao, X.; Yu, B.; Mei, Q.; Yang, Z.; Zhao, Y.; Zhang, H.; Hao, L.; Liu, Z. Atmospheric CO_2 Promoted Synthesis of N-Containing Heterocycles over B(C 6 F 5) 3 Catalyst. *New J. Chem*. **2016**, *40*, 8282–8287. (h) Hung, M. U.; Liao, B. S.; Liu, Y. H.; Peng, S. M.; Liu, S. T. Dicopper Complexes Catalyzed Coupling/Cyclization of 2-Bromobenzoic Acids with Amidines Leading to Quinazolinones. *Appl. Organometal. Chem*. **2014**, *28*, 661–665.

[2] (a) Wang, Z.; Wu, X.; Wang, L.; Zhang, J.; Liu, J.; Song, Z.; Tang, Z. Facile and Efficient Synthesis and Biological Evaluation of 4-Anilinoquinazoline Derivatives as EGFR Inhibitors. *Bioorg. Med. Chem. Lett*. **2016**, *26*, 2589–2593. (b) Mhaske, S. B.; Argade, N. P. The Chemistry of Recently Isolated Naturally Occurring Quinazolinone Alkaloids. *Tetrahedron*. **2006**, *62*, 9787–9826. (c) Mabkhot, Y. N.; Al-Har, M. S.; Barakat, A.; Aldawsari, F. D.; Aldalbahi, A.; Ul-Haq, Z. Synthesis, anti-Microbial and Molecular

Docking Studies of Quinazolin-4(3H)-One Derivatives. *Molecules* **2014**, *19*, 8725–8739. (d) Abbas, S. Y.; El-Bayouki, K. A. M.; Basyouni, W. M.; Mostafa, E. S. New Series of 4(3H)-Quinazolinone Derivatives: Syntheses and Evaluation of Antitumor and Antiviral Activities. *Med. Chem. Res*. **2018**, *27*, 571–582. (e) Liu, S.; Wang, W.; Jiang, L.; Wan, S. B.; Zhang, L. J.; Yu, R.; Jiang, T. 2-Pyridinyl-4(3H)-Quinazolinone: A Scaffold for anti-Influenza a Virus Compounds. *Chem. Biol. Drug Des*. **2015**, *86*, 1221–1225. doi:10.1016/j.bmcl.2016.04.032

[3] (a) Xia, X.; Wang, L.; Zhang, X.; Wang, S.; Lei, L.; Cheng, L.; Xu, Y.; Sun, Y.; Hang, B.; Zhang, G.; et al. Halofuginone-Induced Autophagy Suppresses the Migration and Invasion of MCF-7 Cells via Regulation of STMN1 and p53. *J. Cell. Biochem*. **2018**, *119*, 4009–4020. (b) Eguchi, S. *Top. Heterocycl. Chem*. **2006**, *6*, 113–156. (c) Zhao, P.; Ding, Z.; Tang, L.; Zhou, X.; World, J. Preliminary Investigation of Intraperitoneal Raltitrexed in Patients with Gastric Cancer. *World J. Surg. Oncol*. **2014**, *12*, 403. (d) Liu, Y.; Wu, W.; Hong, W.; Sun, X.; Wu, J.; Huang, Q. Raltitrexed-Based Chemotherapy for Advanced Colorectal Cancer. *Clin. Res. Hepatol. Gas*. **2014**, *38*, 219–225. doi:10.1002/jcb.26559

[4] (a) Sharma, S.; Bhattacherjee, D.; Das, P. Oxalic/malonic acids as carbon building blocks for benzazole, quinazoline and quinazolinone synthesis . *Org. Biomol. Chem*. **2018**, 16, 1337–1342. (b) Xu, G.; Tong, C.; Cui, S. L.; Dai, L. Y. A Silver Catalyzed Domino Reaction of N -Cyanamide Alkenes and 1,3-Dicarbonyls for the Synthesis of Quinazolinones. *Org. Biomol. Chem*. **2018**, *16*, 5899–5902. (c) Rostamizadeh, S.; Nojavan, M.; Aryan, R.; Isapoor, E.; Azad, M. J. Amino Acid-Based Ionic Liquid Immobilized on α-Fe2O3-MCM-41: An Efficient Magnetic Nanocatalyst and Recyclable Reaction Media for the Synthesis of Quinazolin-4(3H)-One Derivatives. *Mol. Catal. A: Chem*. **2013**, *374–375*, 102–110. (d) Zhu, K.; Hao, J.-H.; Zhang, C.-P.; Zhang, J.; Feng, Y.; Qin, H.-L. Diversified Facile Synthesis of Benzimidazoles, Quinazolin-4(3H)-Ones and 1,4-Benzodiazepine-2,5-Diones via Palladium-Catalyzed Transfer Hydrogenation/Condensation Cascade of Nitro Arenes under Microwave Irradiation. *RSC Adv*. **2015**, *5*, 11132–11135. doi:10.1039/C7OB03064A

[5] Li, H.-Z.; He, H.-Y.; Han, Y.-Y.; Gu, X.; He, L.; Qi, Q.-R.; Zhao, Y.-L.; Yang, L. A General Synthetic Procedure for 2-Chloromethyl-4(3H)-Quinazolinone Derivatives and Their Utilization in the Preparation of Novel Anticancer Agents with 4-Anilinoquinazoline Scaffolds. *Molecules* **2010**, *15*, 9473–9485. doi:10.3390/molecules15129473

[6] Li, M.; Wang, L.; Li, J.; Liu, C.; Li, T.; Gan, L.; Duan, Y. Evaporation Characteristics of Micropores in Biomimetic Micropump. *Arkivoc* **2014**, *9*, 41–50.

[7] (a) Banerji, B.; Bera, S.; Chatterjee, S.; Killi, S. K.; Adhikary, S. Regioselective Synthesis of Quinazolinone-/Phenanthridine-Fused Heteropolycycles by Pd-Catalyzed Direct Intramolecular Aerobic Oxidative C–H Amination from Aromatic Strained Amides. *Chemistry* **2016**, *22*, 3506–3512. (b) Roy, A. D.; Subramanian, A.; Roy, R. Auto-Redox Reaction: tin(II) Chloride-Mediated One-Step Reductive Cyclization Leading to the Synthesis of Novel Biheterocyclic 5,6-Dihydro-Quinazolino[4,3-b]Quinazolin-8-Ones with Three-Point Diversity. *J. Org. Chem*. **2006**, *71*, 382–385. doi:10.1002/chem.201504186

[8] (a) He, W.; Zhao, H.; Yao, R.; Cai, M. A Highly Efficient Heterogeneous Copper-Catalyzed Cascade Reaction of 2-Halobenzoic Acids and Amidines Leading to Quinazolinones. *RSC Adv*. **2014**, *4*, 50285–50294. (b) Liu, M. L.; Shu, M. M.; Yao, C. C.; Yin, G. D.; Wang, D. J.; Huang, J. K. Synthesis of Pyrido-Fused Quinazolinone Derivatives via Copper-Catalyzed Domino Reaction. *Org. Lett*. **2016**, *18*, 824–827. (c) Li, T.; Chen, M. L.; Yang, L.; Xiong, Z. X.; Wang, Y. W.; Li, F.; Chen, D. Y. Copper-Catalyzed Consecutive Reaction to Construct Quinazolin-4(3H)-Ones and Pyrido[2,3-d]Pyrimidin-4(3H)-Ones. *Tetrahedron*. **2016**, *72*, 868–874. (d) Chen, J.-N.; Wang, X.-F.; Li, T.; Wu, D.-W.; Fu, X.-B.; Zhang, G.-J.; Shen, X.-C.; Wang, H.-S. Design, Synthesis, and Biological Evaluation of Novel Quinazolinyl-Diaryl Urea Derivatives as Potential Anticancer Agents. *Eur. J. Med. Chem*. **2016**, *107*, 12–25. (e) Rao, K. R.; Raghunadh, A.; Mekala, R.; Meruva, S. B.; Pratap, T. V.; Krishna, T.; Kalita, D.; Laxminarayana, E.; Prasad, B.; Pal, M. Glyoxylic Acid in the Reaction of Isatoic Anhydride with Amines: A

Rapid Synthesis of 3-(un)Substituted Quinazolin-4(3H)-Ones Leading to Rutaecarpine and Evodiamine. *Tetrahedron Lett*. **2014**, *55*, 6004–6006. (f) Chen, X.; Chen, T.; Zhou, Y.; Han, D.; Han, L.; Yin, S. Metal-Free Aerobic Oxidative C–N Bond Cleavage of Tertiary Amines for the Synthesis of N-Heterocycles with High Atom Efficiency. *Org. Biomol. Chem*. **2014**, *12*, 3802–3807. (g) Xu, Y.; Xie, Q.; Li, W.; Sun, H.; Wang, Y.; Shao, L. A Convenient Aqueous Copper-Catalyzed Synthesis of Quinazolinones. *Tetrahedron*. **2015**, *71*, 4853–4858. doi:10.1039/C4RA09379H

[9] (a) Tiwari, A. R.; Bhanage, B. M. Transition-Metal Free Synthesis of Quinazolinones via Tandem Cyclization of 2-Halobenzoic Acids with Amidines. *Rsc Adv*. **2015**, *5*, 57235–57239. (b) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. Copper-Catalyzed Domino Synthesis of Quinazolinones via Ullmann-Type Coupling and Aerobic Oxidative C-H Amidation. *Org. Lett*. **2011**, *13*, 1274–1277. (c) Lu, J.; Gong, X.; Yang, H.; Fu, H. Concise Copper-Catalyzed One-Pot Tandem Synthesis of Benzimidazo[1,2-b]Isoquinolin-11-One Derivatives. *Chem. Commun. (Camb.)* **2010**, *46*, 4172–4174. (d)Xu, L.; Jiang, Y.; Ma, D. Synthesis of 3-Substituted and 2,3-Disubstituted Quinazolinones via Cu-Catalyzed Aryl Amidation. *Org. Lett*. **2012**, *14*, 1150–1153. (e) Upadhyaya, K.; Thakur, R. K.; Shukla, S. K.; Tripathi, R. P. *J. Org. Chem*. **2016**, *81*, 5046–5055. (f) Yu, L.; Wang, M.; Li, P. H.; Wang, L. *Appl. Organomet. Chem*. **2012**, *26*, 576–582. doi:10.1039/C5RA11159E

[10] (a) Xu, W.; Fu, H. J. Amino Acids as the Nitrogen-Containing Motifs in Copper-Catalyzed Domino Synthesis of N-Heterocycles. *J. Org. Chem*. **2011**, *76*, 3846–3852. (b) Huang, X.; Yang, H.; Fu, H.; Qiao, R.; Zhao, Y. Efficient Copper-Catalyzed Synthesisof 2-Amino-4(3H)-Quinazolinone and 2-AminoquinazolineDerivatives. *Synthesis* **2009**, *2009*, 2679–2688. (c) Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhao, Y. Highly Efficient Copper-Catalyzed Cascade Synthesis of Quinazoline and Quinazolinone Derivatives. *Chem. Commun*. **2008**, *0*, 6333–6335. doi:10.1021/jo2002227

[11] (a) Lin, J. J.; Luo, Z. Z.; Liu, J. J.; Li, P. Photocatalytic Degradation of Methylene Blue in Aqueous Solution by Using ZnO-SnO 2 Nanocomposites. *Mat. Sci. Semicon. Proc*. **2018**, *87*, 24–31. (b) Fattahi, N.; Ayubi, M.; Ramazani, A. Amidation and Esterification of Carboxylic Acids with Amines and Phenols by N,N′-Diisopropylcarbodiimide: A New Approach for Amide and Ester Bond Formation in Water. *Tetrahedron*. **2018**, *74*, 4351–4356. (c) Ramesh, K.; Satyanarayana, G. An Approach to One-Pot Regioselective Synthesis of Indenones through Palladium-Catalyzed Annulation in Water. *Eur. J. Org. Chem*. **2018**, *2018*, 4135–4146. doi:10.1016/j.mssp.2018.07.003

[12] (a) Rahaman, R.; Barman, P. Iodine-Catalyzed Mono- and Disulfenylation of Indoles in PEG 400 through a Facile Microwave-Assisted Process. *Eur. J. Org. Chem*. **2017**, *2017*, 6327–6334. (b) Zhang, X.; Ye, D.; Sun, H.; Guo, D.; Wang, J.; Huang, H.; Zhang, X.; Jiang, H.; Liu, H. Microwave-Assisted Synthesis of Quinazolinone Derivatives by Efficient and Rapid Iron-Catalyzed Cyclization in Water. *Green Chem*. **2009**, *11*, 1881. doi:10.1002/ejoc.201701293

[13] (a) Ke, F.; Chen, X.; Li, Z.; Xiang, H.; Zhou, X. Microwave-Assisted Copper-Catalyzed Hydroxylation of Aryl Halides in Water. *RSC Adv*. **2013**, *3*, 22837–22840. (b) Deng, H.; Li, Z.-K.; Ke, F.; Zhou, X. Cu-Catalyzed Three-Component Synthesis of Substituted Benzothiazoles in Water. *Chemistry*. **2012**, *18*, 4840–4843. (c) Ke, F.; Qu, Y.; Jiang, Z.; Li, Z.; Wu, D.; Zhou, X. An Efficient Copper-Catalyzed Carbon − Sulfur Bond Formation Protocol in Water. *Org. Lett*. **2011**, *13*, 454–457. doi:10.1039/c3ra44613a

[14] (a) Shuck-Lee, D.; Chen, F. F.; Willard, R.; Raman, S.; Ptak, R.; Hammarskjold, M.-L.; Rekosh, D. Heterocyclic Compounds That Inhibit Rev-RRE Function and Human Immunodeficiency Virus Type 1 Replication. *Antimicrob. Agents Chemother*. **2008**, *52*, 3169–3179. (b) Juvale, K.; Wiese, M. 4-Substituted-2-Phenylquinazolines as Inhibitors of BCRP. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 6766–6769. (c) Juvale, K.; Gallus, J.; Wiese, M. Investigation of Quinazolines as Inhibitors of Breast Cancer Resistance Protein (ABCG2). *Bioorg. Med. Chem*. **2013**, *21*, 7858–7873. doi:10.1128/AAC.00274-08