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Cu-Catalyzed Direct Diversification of 2-(2-Bromophenyl)quinazolin-4(3*H*)-ones through Orthogonal Reactivity Modulation

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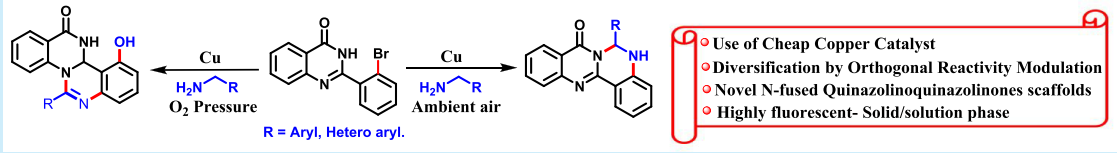
Supporting Information



ABSTRACT: A modular strategy to obtain three different products from a single substrate was developed. The present methodology unveils new step-economical and cost-efficient routes to access diverse fused quinazolinoquinazolinone derivatives which are not prevalent in literature. Owing to the importance of quinazolinones in therapeutics, quick access to the arena of these scaffolds could be a valuable addition to the scientific domain of heterocyclic chemistry.

Quinazolinones belong to a privileged class of N-heterocycles due to their great abundance in several natural products and pharmaceuticals which exhibit a wide range of biological activities, including anti-inflammatory, antitubercular, antiviral, and anticancer activities, etc. (Figure 1).[1] Due to the extensive biological significance of the

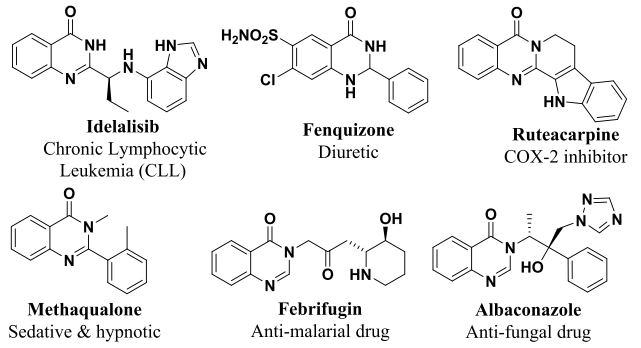


Figure 1. Some quinazolinone-based drugs and natural products.

quinazolinone moiety, the development of new synthetic methods for the construction of quinazolinone based molecular scaffolds draws considerable attention. Furthermore, synthesis of a new molecular scaffold containing a quinazolinone nucleus by a short and efficient synthetic route is in high demand for various kinds of interests, especially for the therapeutic targets in the pharmaceutical sectors worldwide.

In the past few decades, transition metal catalyzed direct C−H bond functionalization has emerged as a powerful tool to construct new carbon−carbon (C−C) and C−heteroatom (C−X) bonds for the synthesis of structurally complex natural or unnatural compounds.[2] This C−H functionalization strategy provides direct access and delivers more atom-economical routes in the synthesis of complex structures as compared to the traditional synthetic protocols, and this technique also opens up the scope for the late stage derivatization of bioactive molecules.[3] Hence, use of different transition metal catalysts in C−H functionalization reactions received the spotlight over the past few years. However, the majority of the C−H bond functionalization strategies depend on the use of different noble metals, for example, palladium,[4] rhodium,[5] etc. However, the scope is still limited due to the expensive scale-up procedure of these techniques. In contrast to these highly expensive metal catalysts, cheap copper catalysts may be widely utilized to functionalize specific C−H bonds in large scale and thus copper catalyzed C−H functionalization reactions have gained much focus with critical progression.[6]

In spite of the fact that a number of methodologies involving synthesis of quinazoline fused structures have been accomplished,[7] most of these methods suffer from the major drawback of using expensive metal catalysts. Thus, a straightforward, efficient strategy for the synthesis of quinazolinone fused polyheterocycles is still a challenging

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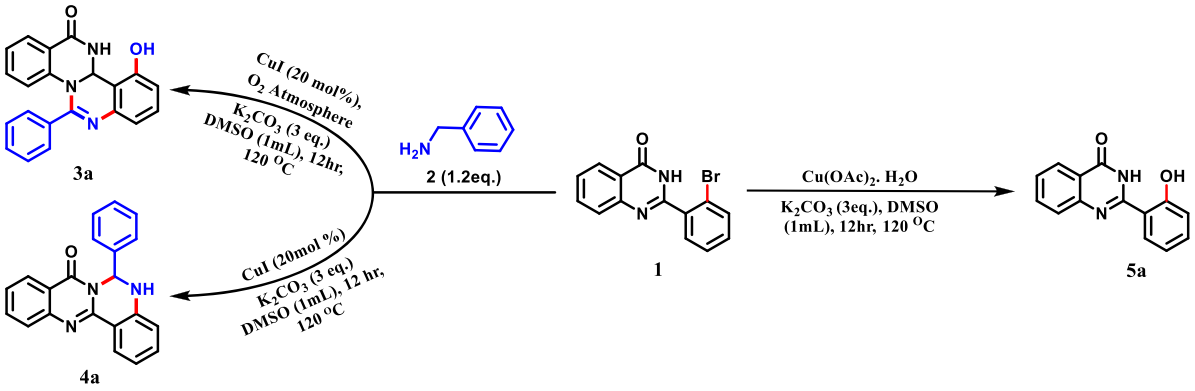
Table 1. Optimization of Reaction Conditions[a,b,c]



entry	catalyst	ligand	base	oxidant/inert atm.	solvent	compound/yield[d] (%)
1	CuI	1,10-Phen	K_2CO_3	N_2	DMSO	–
2	CuI	Bipy	K_2CO_3	N_2	DMSO	–
3	CuI	L-HP	K_2CO_3	N_2	DMSO	–
4	CuI	L-HP	K_2CO_3	$AgNO_3$	DMSO	–
5	CuI	L-HP	K_2CO_3	O_2	DMSO	–
6	CuI	1,10-Phen	K_2CO_3	O_2	DMSO	**3a**/60%
7	**CuI**	–	K_2CO_3	**O_2**	**DMSO**	**3a**[a]/88%
8	**CuI**	–	K_2CO_3	–	**DMSO**	**4a**[b]/89%
9	CuI	–	K_2CO_3	–	DMF	**4a**/40%
10	CuI	–	Cs_2CO_3	–	DMSO	**4a**/60%
11	CuI	–	K_2CO_3	N_2	DMSO	**4a**/0%
12	$Cu(OAc)_2{\cdot}H_2O$	–	K_2CO_3	O_2	DMSO	**5a**/92%
13	$Cu(OAc)_2{\cdot}H_2O$	1,10-Phen	K_2CO_3	–	DMSO	**5a**/90%
14	**$Cu(OAc)_2{\cdot}H_2O$**	–	K_2CO_3	–	**DMSO**	**5a**[c]/ **92%**

[a]Optimized reaction conditions: **1** (0.1 mmol), benzylamine (0.15 mmol), CuI (20 mol %), K_2CO_3(0.3 mmol), O_2 atmosphere, DMSO (1 mL),120 °C, 12 h. [b]**1** (0.1 mmol), benzylamine (0.15 mmol), CuI (20 mol %), K_2CO_3 (0.3 mmol), DMSO (1 mL), 120 °C, 12 h. [c]**1** (0.1 mmol), $Cu(OAc)_2$. H_2O (20 mol %), K_2CO_3 (0.3 mmol), DMSO (1 mL), 120 °C, 12 h. [d]Yields of isolated products.

task in the synthetic community. These facts inspired us to develop an efficient synthetic route for the construction of quinazolinone fused polyheterocycles through copper catalyzed C−H functionalization. In an ongoing project in our laboratory toward the synthesis of quinazolinonefused N-heterocycles and the study of their photophysical properties,[7f] we were interested in constructing quinazolinoquinazolines via C−H functionalization. We expected these new heterocycles to be highly fluorescent active because of their extended conjugation. Interestingly during the course of study, we observed a single substrate of this reaction produced diverse quinazolinone fused scaffolds depending on the presence of an oxygen atmosphere. To the best of our knowledge, we are the first group to report copper catalysis in such a diversity oriented synthesis of the quinazolinone moiety using a single substrate, 2-(2-bromophenyl)quinazolin-4(3*H*)-one.

Initially, 2- (2-bromophenyl)quinazolin-4(3*H*)-one and benzylamine were used as model substrates to optimize reaction conditions including catalysts, ligands, bases, solvents, and oxidants. As shown in the Table 1, it was found that, under the catalysis of CuI (20 mol %) with different ligands such as 1,10-phenanthroline (1,10-Phen), 2,2′-bipyridine (2,2′-bipy), and L-hydroxyproline (L-HP) in DMSO under N_2 at 120 °C after 12 h, no product formation was observed (entries 1−3). By keeping the ligand same, i.e., L-HP, and using oxidants such as silver nitrate ($AgNO_3$) or oxygen, no product formation was observed (entries 4−5). After changing the ligand from L-HP to 1,10-Phen under the positive pressure of oxygen under the same condition delivered the product (**3a**) in 60% yield (entry 6). However, the product yield improved further without any ligand to about 88% (**3a**) (entry 7). The same reaction conditions were utilized without the use of oxygen. Surprisingly, it afforded a new product (**4a**) with a better yield of about 89% (entry 8). Changing the solvent from DMSO to DMF decreased the reaction yields (entry 9). Changing the base from K_2CO_3 to Cs_2CO_3 slightly decreased the product formation (entry 10). Under the nitrogen atmosphere the same reaction conditions yield 0% product (entry 11). Afterward, we changed the catalyst from CuI to Cu $(OAc)_2{\cdot}H_2O$, which was found to produce compound **5a** with 92% yield. It was surprising to observe benzylamine served no role under these reaction conditions. Moreover, the presence or absence of oxygen/ligand did not affect the yield of compound **5a** (entries 12−14).

After obtaining the optimized conditions, we next studied the substrate scope in the presence of oxygen (Scheme 1).We synthesized a small set of these compounds to show the generality and scope of the above conditions. Different types of benzylamines were found to be well tolerated and provided the desired products in moderate to good yields (**3a**−**3i**). The structural ambiguity is confirmed by ROESY spectra (see SI, p S29). Benzylamines with an electron-donating group (−Me, −OMe, etc.) on the benzene ring produced a slightly lesser yield than in the case of an electron-withdrawing group ($-CF_3$, $-OCF_3$, etc.). Interestingly, compounds in this series showed solid state fluorescence in the green-orange region (Scheme 1). Next, we explored the substrate scope for the products formed in absence of oxygen (Scheme 2). Under the optimized

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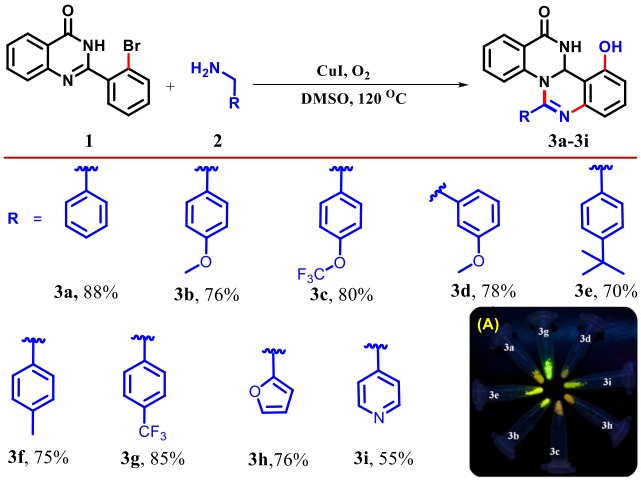
Scheme 1. Synthesis of 11-Hydroxy-6-phenyl-11b,12-dihydro-13*H* Quinazolino[3,4-*a*]quinazolin-13-ones[a,b]



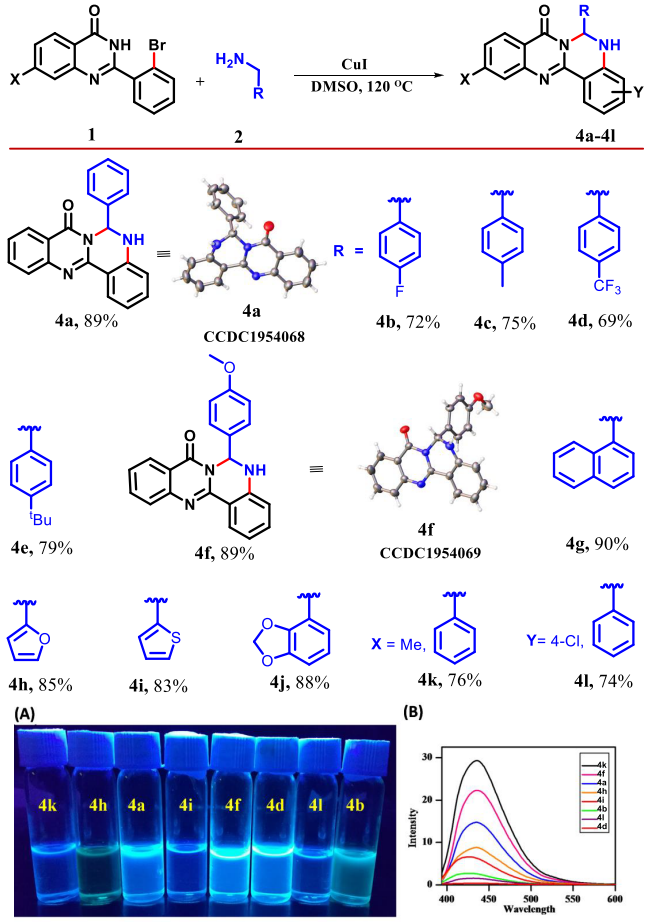
[a]Conditions: 1 (0.1 mmol, 1 equiv), benzyl amine (0.15 mmol, 1.2 equiv), CuI (20 mol %), K_2CO_3 (3 equiv), DMSO (1 mL), 120 °C, O_2, 18 h. [b]Isolated yields. (A) Solid state fluorescence of compound **3** series (under long UV, 365 nm).

condition, this catalytic system with different types of benzylamines yielded the desired products from moderate to good yields (**4a**−**4l**). Benzylamines with electron-donating groups (−Me, −OMe, etc.) produced better yields than in the case of electron-withdrawing groups (like $-CF_3$, OCF_3, etc.). The structures of compounds **4a** and **4f** were established by single crystal X-ray diffraction studies (see SI, pp S17−S19). Surprisingly, all the compounds of this series showed bright blue fluorescence in solution state (Scheme 2).

Further, we studied the substrate scope for copper catalyzed hydroxylation[8] (Scheme 3) and synthesized three different derivatives by varying the substituent on 2-aminobenzamide and 2-bromobenzaldehyde moieties. Various electron-donating as well as electron-withdrawing substituents on the benzene ring were found to be equally compatible in this case, smoothly giving the desired products with good yields (**5a**−**5c**). Interestingly, all the compounds in the **5** series showed bright green fluorescence in the solid state which may be due to the Excited State Internal Proton Transfer (ESIPT) process operating inside the molecule.[8c] The structure of compound **5a** was further confirmed by single crystal X-ray diffraction analysis (see SI, p S20).

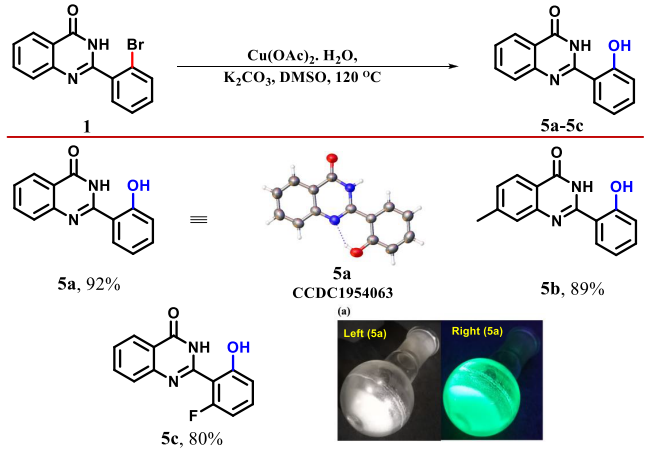
The unexpected and unprecedented results found in the present study encouraged us to perform a control set of experiments (Scheme 4). These studies were focused toward determining the reaction mechanism behind hydroxylation as well as cyclization under variable conditions. A few test reactions were performed to establish the mechanistic pathway. Herein, we found that the reaction failed to produce the desired product **5a** under an O_2 environment in the absence of $Cu(OAc)_2{\cdot}H_2O$ (reaction 1). The same was also observed in the case of reaction 2, where the substrate was changed from 2-(2-bromophenyl)quinazolin-4(3*H*)-one to 2-phenylquinazolin-4(3*H*)-one, to establish the necessity of the −Br group for hydroxylation for series **5**. In the case of reaction 3, where *N*-methyl quinazolinone was used as a substrate, 0% conversion of the product resulted hence proving the directed hydroxylation of the quinazolinone moiety. The same reaction conditions in the presence of TEMPO almost gave a

Scheme 2. Synthesis of 6-Phenyl-5,6-dihydro-8*H*-quinazolino[4,3*b*]quinazolin-8-ones[a,b]



[a]Conditions: **1** (0.1 mmol, 1 equiv), Amine (0.15 mmol, 1.2 equiv), CuI (20 mol %), K_2CO_3 (3 equiv), DMSO, 120 °C, 12 h. [b]Isolated yields. (A) Solution Phase fluorescence of a few selected compound **4** series in CH_2Cl_2. (B) Spectra of compound **4** series (10 mM in CH_2Cl_2, λ_{Ex} = 340−384 nm, λ_{Em} = 420−450 nm).

Scheme 3. Synthesis of 2-(2-Hydroxyphenyl)quinazolin-4(3*H*)-ones[a,b]



[a]Conditions: **1** (0.1 mmol, 1 equiv), $Cu(OAc)_2.H_2O$ (20 mol %), K_2CO_3 (3 equiv), DMSO, 120 °C, 12 h. [b]Isolated yields. (a) Normal light (left) and solid state fluorescence of compound **5a** captured by irradiation at 365 nm (right)

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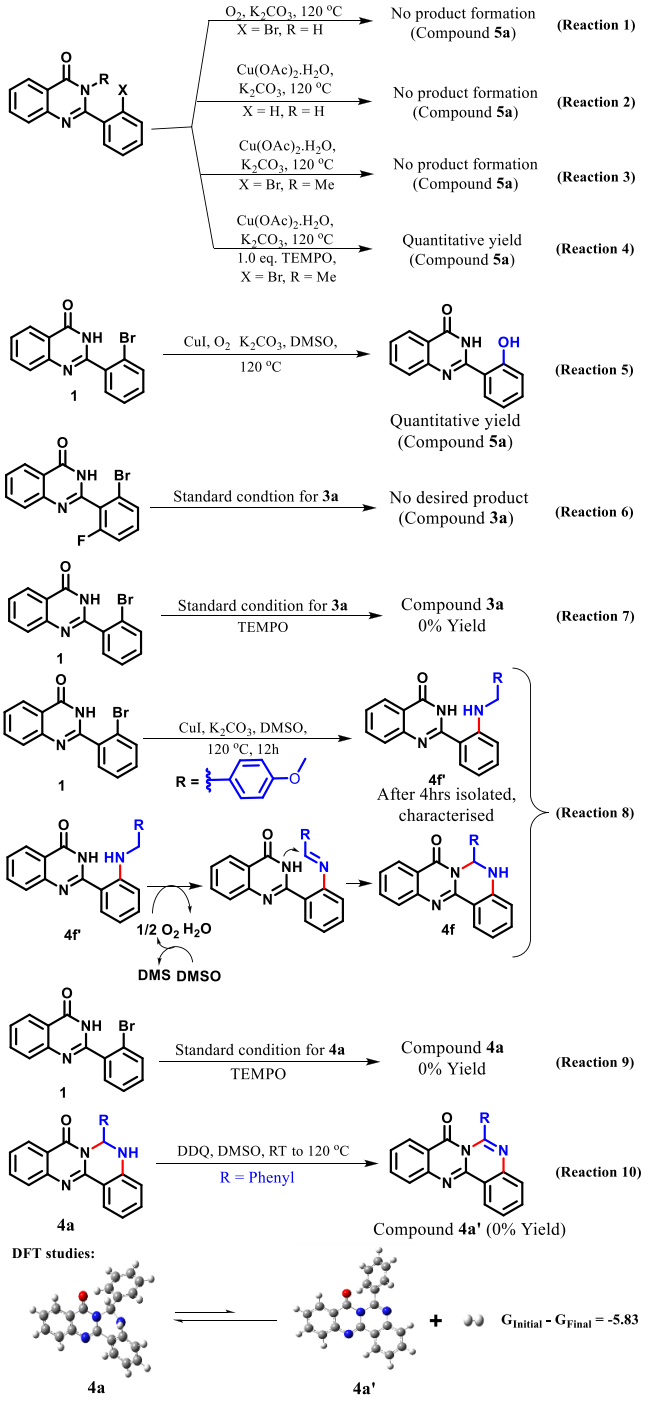
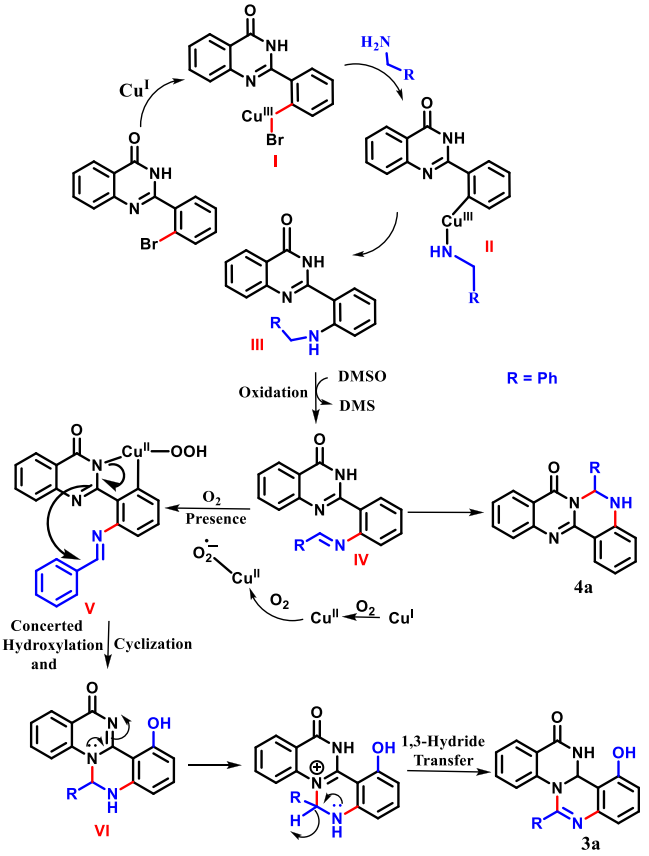
Scheme 4. Control Experiments



quantitative yield (reaction 4). Substrate **1** without benzylamine in the presence of O_2 under CuI catalysis forms the compound **5a** in quantitative yield (reaction 5). While testing with a 2,6-disubstituted substrate, however compound **3a** was not formed under the reported conditions (reaction 6). This study hereby concludes that the cyclization and hydroxylation in the case of formation of compound **3a** follows a concerted pathway and also C−H hydroxylation occurs only when the *ortho*-position is unsubstituted. In the next reaction, presence of a radical quencher, TEMPO, yielded 0% of product **3a**, indicating that it involves the free radical mechanism (reaction 7). In reaction 8, we confirmed that the formation the compound **4** series first involves N-arylation (**4f′** isolated and characterized (see SI, pp S11−S12, S54−S55)) followed by imine formation in the presence DMSO, finally producing the cyclized compound, **4f**. In the next reaction, the presence the radical quencher TEMPO yielded 0% of product **4a**, indicating that it involves the free radical mechanism (reaction 9). Next, we performed a reaction where DDQ was introduced with compound **4a** to check whether any aromatization takes place. However, no reaction of compound **4a** occurred in the presence of DDQ, therefore indicating that compound **4a** is −5.83 kcal/mol more stable than the aromatized compound **4a′** which was further studied by DFT (see SI, p S21).

Based on the control experiments, a plausible reaction mechanism has been proposed and depicted in Scheme 5.

Scheme 5. Plausible Mechanism



Initially, under copper catalysis[9] substrate **1** and benzylamine **3** becomes converted to intermediate **III**. Intermediate **III** oxidized to imine intermediate **IV** in the presence of DMSO.[10] Next, intermediate **IV** follows two distinct pathways regarding the presence and absence of O_2. In the presence of O_2, the *in situ* superoxide radical[11] is generated by the redox couple Cu^I/Cu^{II} and this forms the metallocomplex **V** which then undergoes concerted hydroxylation and cyclization to form the intermediate **VI**. Now, intermediate **VI** goes through tautomerization and 1,3-hydride transfer to deliver the final product **3**.[12] On the other hand, in the absence of O_2 compound **4** was formed from intermediate **IV** through simple cyclization.

In conclusion, from a single quinazolinone substrate, three diverse quinazolinone derivatives were synthesized in high yields by efficient copper catalyzed modular methodology. Twenty four such different quinazolinone derivatives were

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synthesized and reported in this paper. The most astonishing aspect of this work is C−H hydroxylation (compound **3** series) which is highly important from a therapeutic point of view, as a hydroxyl functional group is very much abundant in bioactive molecules. Another very important feature of these molecules is solid state fluorescence (**3** series) and solution state as well (**4** series). In future, the photophysical properties of these derivatives will be explored to make "Biomolecular probes". Our laboratory is currently investigating this kind of probes which will be highly useful in the field of medical diagnostics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03428.

General information, General procedures, X-ray crystallography data, DFT studies, and ^{1}H and ^{13}C NMR spectra for all synthesized compounds (PDF)

Accession Codes

CCDC 1954063 and 1954068−1954069 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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