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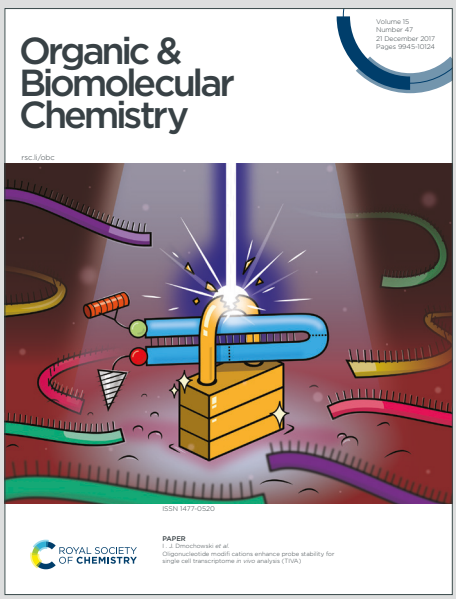

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COMMUNICATION

Visible-Light Induced Copper(I)-Catalyzed Oxidative Cyclization of *o*-Aminobenzamides with Methanol and Ethanol *via* HAT

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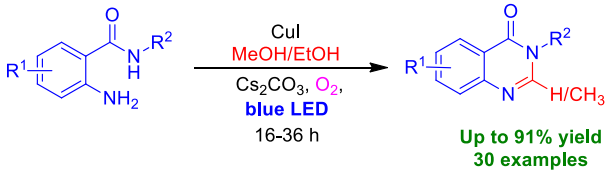
The *in-situ* generated Ligand-Copper superoxo complex absorbing light energy that activate the alpha C(sp^3)–H of MeOH and EtOH *via* hydrogen atom transfer (HAT) process for the synthesis of quinazolinones from oxidative cyclization of alcohol with *o*-aminobenzamide has been investigated. The synthetic utility of this protocol offers an efficient synthesis of quinazolinone intermediate for Erlotinb (Anti-cancer agent) and 30 examples were reported.

Quinazolinones are one of the important scaffolds and frequently occur in various natural products and biologically active molecules including anti-inflammatory, anitimicrobial, antitubercular, antiviral activities, and anticancer etc.[1-4] Due to their broad range of bioactive molecules, various synthetic strategies have been employed.[5-9] Among the various synthetic efforts, the direct oxidative condensation of alcohols with *o*-aminobenzamides to quinazolinones by the molecular oxygen has received significant attention because O_2 is inexpensive and green oxidant, and produces water as the only by-product.[10-12] So far, Many transition metals including vanadium[13], Iron[14], Copper complexes[15] and organic dye as photosensitizer[16] has been employed for oxidative condensation of alcohols to quinazolinones, although the scope of aliphatic alcohol was respectively limited. Therefore, the development of green, atom-economic functionalization of aliphatic alcohol for oxidative condensation is highly desirable.

With growing environmental awareness in aliphatic alcohols, MeOH is a renewable feedstock from value-added chemicals, cost-effective reagent and environmental friendliness, and is frequently used in pharmaceuticals, and materials.[17,18] So far, the synthetic utilization of MeOH have used as a C1 source in methylation, methoxylation, formylation, methoxycarbonylation, and oxidative methyl ester formation reactions.[19,20] Recent years, the oxidative condensation of MeOH has attracted significant interest in organic synthesis. The use of methanol as a C1 Source for the oxidative condensation have been reported by Ir-complexes[21] under microwave at higher temperature and Cu(II) catalyst[22] with TBHP as oxidants at higher temperature. In 2020, S. Kerdphon *et al*[23] investigated methanol as a C1 Source for the oxidative condensation by Cu(II) catalyst with molecular oxygen as oxidants at higher temperature. However, these methods require costly metal complexes, stoichiometric amount of oxidants and harsh reaction conditions. To overcome that, the activation of C(sp^3)-H of MeOH under ambient conditions are on high demand.

The use of visible light-promoted photoredox catalysis has been attracted significantly towards the development of alpha C(sp^3)-H of alcohols *via* the HAT process.[24-26] Macmillan *et al*.[27] and Hwang *et al*.[28] have reported the activation of C(sp^3)-H methanol to α-oxy radical by visible light induced photoredox catalyst. Recently, our group established a visible-light-driven Cu(I)-catalysed aerobic oxidative C(sp)-S coupling reaction and the resulting alkynyl sulfides were converted to 2-phenylbenzothiazole via "thia-Wolff rearrangement".[29] To continue our research interest in visible light mediated Cu-catalyst, we wish to report herein the visible-light induced Ligand-copper superoxo catalyzed oxidative cyclization of MeOH with *o*-aminobenzamides *via* HAT process for the synthesis of quinazolinones.



Scheme 1. Visible light induced synthesis of quinazolinones using ethanol and methanol *via* HAT

The initial studies were carried out using the reaction of anthranilamide **1a** (0.36 mmol) and MeOH (0.18 M) in the presence of CuCl (5 mol %), K_2CO_3 (0.36 mmol) with molecular oxygen under blue LED afforded quinazolinone **2a** in 65% isolated yield for enabling the optimization of the reaction condition. Among the other bases, Cs_2CO_3 offered upto 70% yield (Table 1, entry 2). However, the reaction was failed to provide **2a** with NaH and Et_3N. The different mole amount of Cs_2CO_3 improved the formation of **2a** upto 80% (Table 1, entry

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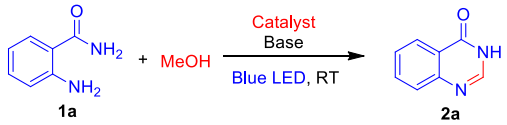
5). When CuCl was replaced by other CuX (X=Br, I) catalysts, CuI significantly improved the yield to 88% (Table 1, entry 8). Increasing the amount of CuI (10 mol%) had no obvious effect on the yield of **2a**. However, $Cu(OTf)_2$ resulted in lower yields (Table 1, entry 10). In control experiments, there was no reaction occurred in the absence of catalyst, light and Base, indicates their crucial roles in the current protocol (Table 1, entries 12 and 14).

Table 1: Optimization table for quinazolinone **2a** from *o*-Amino benzamide**1a** and methanol[a]



Entry	Catalyst	Base (equiv.)	Time (h)	Yield (%)[b]
1	CuCl	K_2CO_3 (1)	24	65
2	CuCl	Cs_2CO_3 (1)	24	70
3	CuCl	NaH (1)	24	n.r.
4	CuCl	Et_3N (1)	24	n.r.
5	CuCl	Cs_2CO_3 (2)	24	80
6	CuCl	Cs_2CO_3 (2.5)	24	80
7	CuBr	Cs_2CO_3 (2)	24	82
8	CuI	CS_2CO_3 (2)	16	88
9[c]	CuI	CS_2CO_3 (2)	16	88
10	$Cu(OTf)_2$	Cs_2CO_3 (2)	24	20
11[d]	CuI	Cs_2CO_3 (2)	16	55
12	CuI	-	16	n.r.
13	-	Cs_2CO_3 (2)	16	n.r.
14[e]	CuI	Cs_2CO_3 (2)	16	n.r.

[a]Reaction conditions: 0.36 mmol (**1a**), MeOH (2 mL), and 5 mol% of CuI. The solution was irradiated with blue light in presence of O_2 atmosphere. [b]Yields were determined after purification of the compound. [C]10 mol % of CuI used. [d]Reaction performed in open air. [e]Reaction performed in dark. n.r. = no reaction.

Encouraged by these promising results, a diverse array of anthranilamide derivatives were explored by using methanol under optimized conditions shown in Table 2. Methyl substituted anthranilamide **1b** and **1c** afforded corresponding quinazolinone **2b** and **2c** with 85% and 80% yield respectively. Halogen (F, Cl and Br) substituted anthranilamide **1d-1f** reacts smoothly with methanol resulted in the best yield of 80-88%. The nitro substituted anthranilamide **1g** also afforded corresponding quinazolinone **2g** with 77% yield. Phenyl and napthyl bearing anthranilamide **1h-j** also effectively coupled with methanol afforded the corresponding product **2h-j** in good yields. Next, the phenylethynyl, 2-etynyl pyridine and 1-octyne substituted anthranilamide **1k-n** also well suited for this new catalytic protocol leads to the corresponding products **2k-n** in 65-75% yields.

Table 2: Substrate scope of *o*-aminobenzamides with methanol[a]

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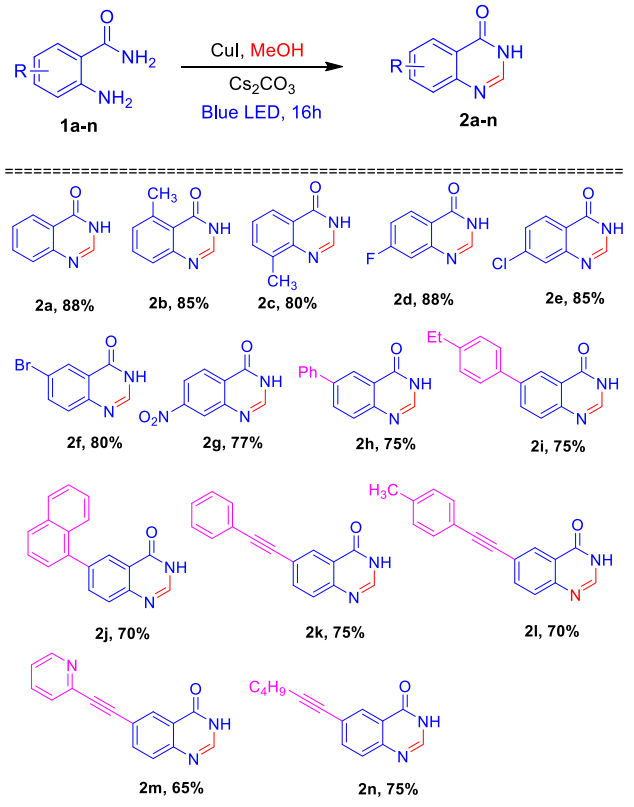
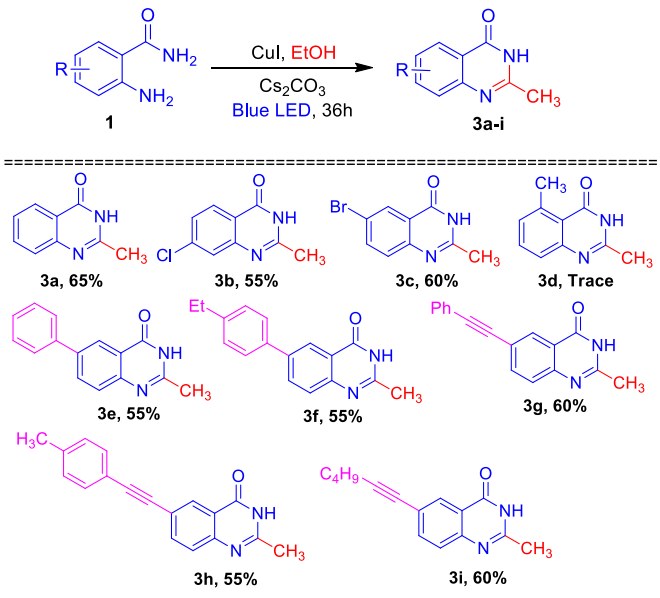


[a]Standard condition. Yields were determined after purification of the compound.

Next, we investigate the scope of the *o*-aminobenzamide with ethanol and results are shown in Table 3. All the substituted *o*-aminobenzamides derivatives were effecitively coupled with ethanol under this protocol.

Table 3: Substrate scope of *o*-amino benzamides with ethanol[a]



[a]Standard condition. Yields were determined after purification of the compound.

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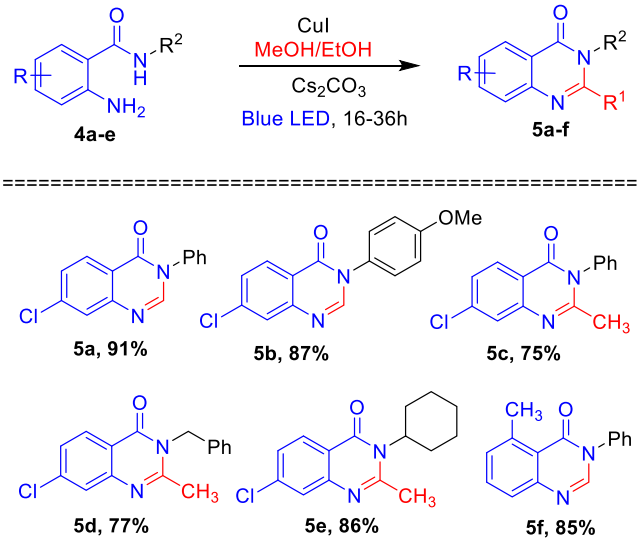
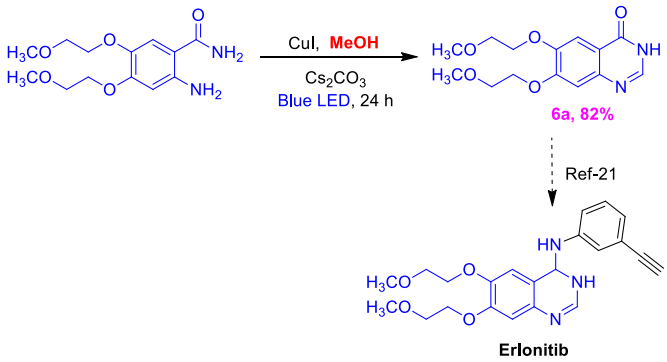
All the derivatives resulted to the corresponding quinazolinones **3a-i** in 55-65% yield, respectively. In contrast, 2-amino-6-methylbenzamide **1d** afforded the trace amount of **3d**. Notably, ethanol shows less reactivity and takes longer times up to 36 h towards this new catalytic protocol and also produces slightly lower yields than methanol.

Further, we screened the reactivity of *o*-amino-*N*-substituted benzamides with methanol and ethanol for the protocol and results are shown in Table 4. All the 2-amino-*N*-substiturtedbenzamide derivatives were reacted smoothly with methanol and ethanol afforded corresponding products **5a-f** in 75-91% yield. Interestingly, *o*-amino-*N*-substituted benzamides shows higher reactivity towards the coupling with methanol and ethanol, than *o*-aminobenzamide.

Table 4: Substrate scope of *o*-amino-*N*-substituted benzamides with methanol and ethanol[a]



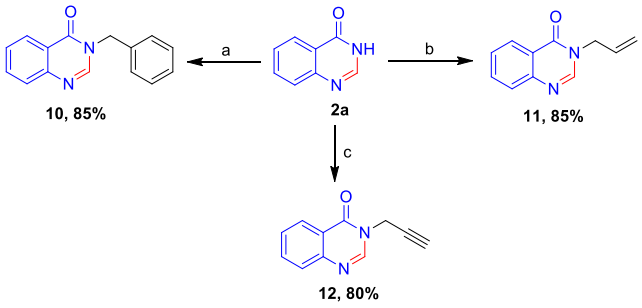
[a]Standard condition. Yields were determined after purification of the compound.



Scheme 2: Synthesis of Erlotinib (Anti-cancer agent) intermediate

To show the practical utility of this new protocol, we synthesized the quinazolinones intermediate **6a** of Erlotinib (Anti-cancer agent) and depicted in scheme 2. The reaction of 2-amino-4,5-bis(3-methoxypropyl)benzamide **1n** with methanol under optimized reaction conditions afforded the quinazolinones intermediate **6a** in 82% yield. According to the literature, further chlorination reaction followed by amination with 3-ethynylaniline could afforded the Erlotinib.

Scheme 3: Synthetic transformations of quinazoline **2a**.



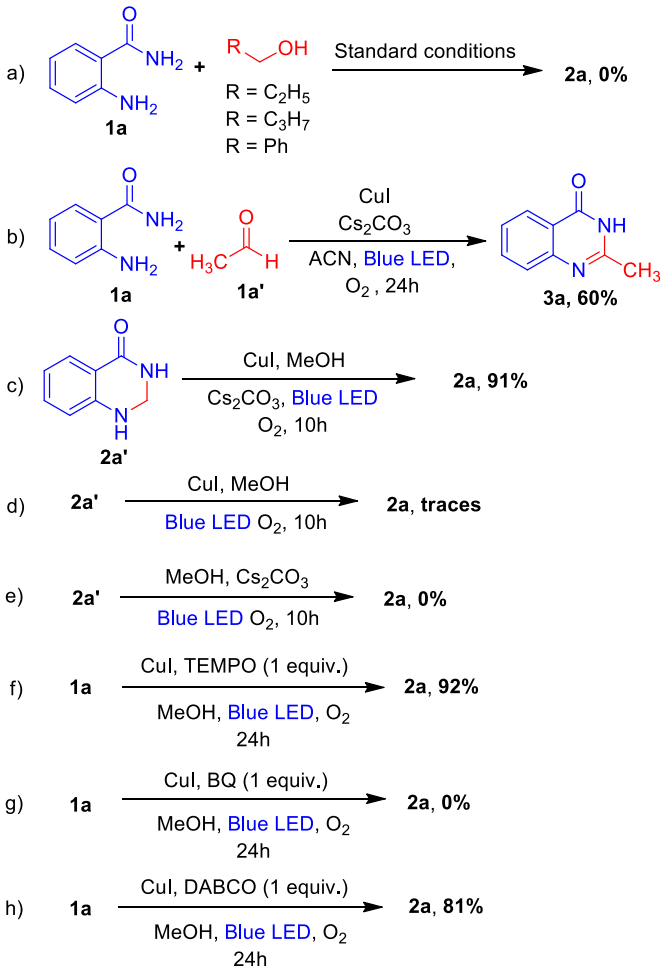
Reagents and condition: (a) BnBr, **7** (1.1 equiv.), K_2CO_3 (2.1 equiv.), THF, 12 h, rt; (b) allyl bromide, **8** (1.1 equiv.), K_2CO_3 (2.1 equiv.), THF, 12 h, rt; (c) propargyl bromide, **9** (1.1 equiv.), K_2CO_3 (2.1 equiv.), THF, 12 h, rt.

Due to biological importance of *N*-alkylated quinazolinones, the synthetic utility of *N*-alkylation reactions on quinazolinone **2a** were shown in scheme 3. Quinazolinone **2a** was treated with various alkyl bromides **7-9** in presence of K_2CO_3, afforded corresponding *N*-alkylated compounds **10-12** with 80-85% yields.

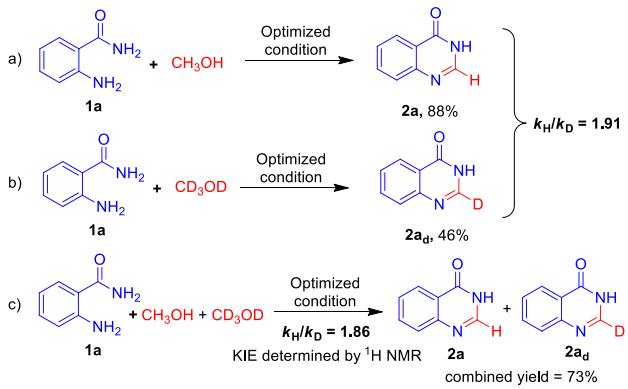
Several control experiments were carried out to investigate the reaction mechanism as shown in Scheme 4. The other higher alkyl alcohols (e.g. propayl alcohol, butyl alcohol and benzyl alcohols) instead of methanol/ethanol were used to react with *o*-aminobenzamide **1a** (Scheme 4a), but no reaction was observed. However, the reaction of acetaldehyde **1a'** with *o*-aminobenzamide **1a** afforded **2a** in 60% yield (Scheme 4b). The results indicate that higher order alcohols were failed to give desired product and aldehyde may be one of the reaction intermediate. 2,3-dihydroquinazolin-4(1H)-one **2a'** was treated under the standard reaction conditions afforded the desired product **2a** in 91% yield within 10 hours (Scheme 4c), it reveals that 2,3-dihydroquinazolin-4(1H)-one **2a'** is one of the intermediate in oxidative cyclization. Furthermore, the reaction with **2a'** was carried out in the absence of base and CuI resulted in trace and 0% yield of **2a**, respectively (Scheme 4d and 4e). These experiments clearly showed the needs of base and catalyst in the dehydrogenation of quinazolinone **2a**. In trapping and quenching experiments, the reaction was performed with addition of TEMPO afforded 92% yield of **2a** (Scheme 4f). Based on ttheoretical study of H-atom abstraction by TEMPO in alcohol oxidation, [30] It clearly reveals that the presence of TEMPO radical does not affect the yield of benzaldehyde in the catalytic oxidation, suggesting the

involvement of an intramolecular H-atom abstraction. Further quenching experiments for superoxo radical and singlet oxygen,[31] the reaction were performed with addition of benzoquinone (BQ) and 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded **2a** in 0% and 81% yield, respectively (Scheme 4g and 4h), implies that the involvement of superoxo radical in reaction.

Scheme 4: Control experiments



Scheme 5: Kinetic Isotope Effect (KIE)



The reaction of **1a** with methanol-d_4 under the optimized conditions, afforded corresponding deuterated product **2a$_d$** with 46% yield (Scheme 5b). This experiment has confirmed that C-2 carbon source of **2a** was methanol. A KIE value of 1.91 was determined from two parallel reactions (Scheme 5a and 5b), and KIE value of 1.86 was also determined from competition reaction of **1a** with 1:1 ratio of methanol and methanol-d_4 (Scheme 5c). The moderate KIE value implies that the activation of methanol is one of the kinetically important steps in the oxidative cyclization of *o*-aminobenzamides.[32]

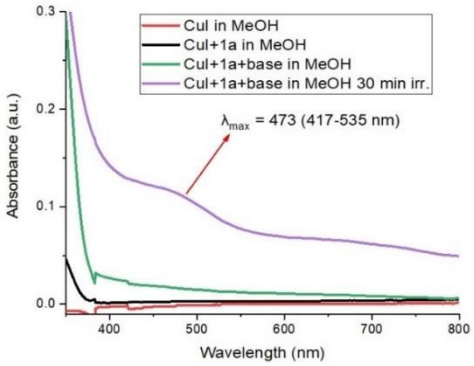
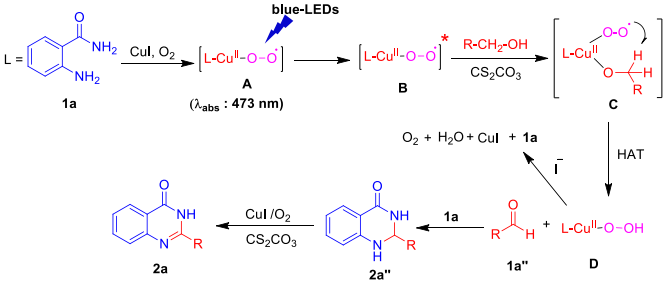


Figure 1. UV-visible absorption spectra of CuI in MeOH (red); CuI and substrate **1a** (black); CuI, substrate **1a** and base (green) and after irradiation MeOH solvent (purple).

Based on the experimental studies, UV-vis absorption spectra and literature report,[33] a possible reaction mechanism is proposed in Scheme 6. In this scenario, the Cu(I)I coordinated with **1a** and molecular oxygen to form Ligand-Cu(II) superoxo complexes **A**. These Ligand-Cu(II) superoxo complexes **A** has absorbed Visible light (λ_{max} = 473 nm) and produces excited state of Cu(II) superoxo complexes **B** as shown in figure 1.[34] The excited state of **B** undergoes coordination with alcohol to form a complex **C**. The resulted complex **C** is implicated to initiate the oxidation reaction *via* hydrogen atom transferred from alpha C(sp^3)-H of alcohol to furnish Cu(II)hydroperoxo complex **D** and aldehyde **1a''**. The theoretical study of H-atom abstraction by TEMPO in alcohol oxidation suggest a pathway where the overlap of HOMO of alkoxide to π* LUMO of TEMPO.[30] Similarly, a copper(II)-superoxide orbital is proposed to interact with an accessible HOMO of alkoxide in the abstraction of α-H atom. Further, EPR measurements showed signals for the formation of Cu(II)hydroperoxo complex (L-Cu(II)OOH) **D** (Fig. S1, ESI†).[35] Next, complex **D** can undergo reductive elimination to form a recycle Cu(I) system and **1a**. The resulted **1a''** undergoes condensation reaction with *o*-aminobenzamide **1a** to produce quinazolinone **2a''**, followed by reaction of CuI and Cs_2CO_3 under molecular oxygen afforded the desired quinazolinone **2a**.



Scheme 6: Plausible Mechanism.

Conclusions

In conclusion, we have investigated the visible light-mediated Cu(I) catalysed oxidative cyclization of aliphatic alcohols with cyclization partner of *o*-aminobenzamides to synthesize quinazolinones in the presence of molecular oxygen. This method is only limited to MeOH and EtOH. The *in-situ* formation of Ligand-Copper superoxo complex with visible light (λmax=473 nm) has activated the aliphatic alpha C(sp^3)–H alcohol to aldehyde *via* hydrogen atom transfer (HAT). The synthetic utility of this method offers an efficient synthesis of quinazolinone intermediate for Erlotinb (Anti-cancer agent).

Acknowledgments

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Conflicts of interest

There are no conflicts to declare.

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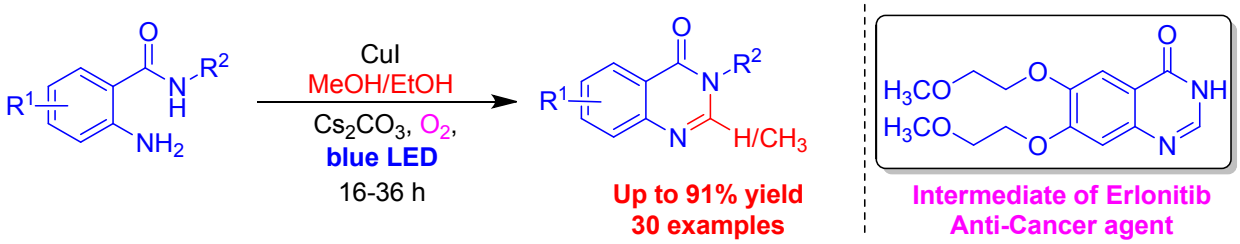

- Oxidant free
- Green Approach
- Good functional group tolerance
- No chemical wastage

The activation the C(SP^3)-H of MeOH via HAT for synthesis of quinazolinones has been achieved by *in-situ* generated Ligand-copper-superoxo complex under visible-light.