ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

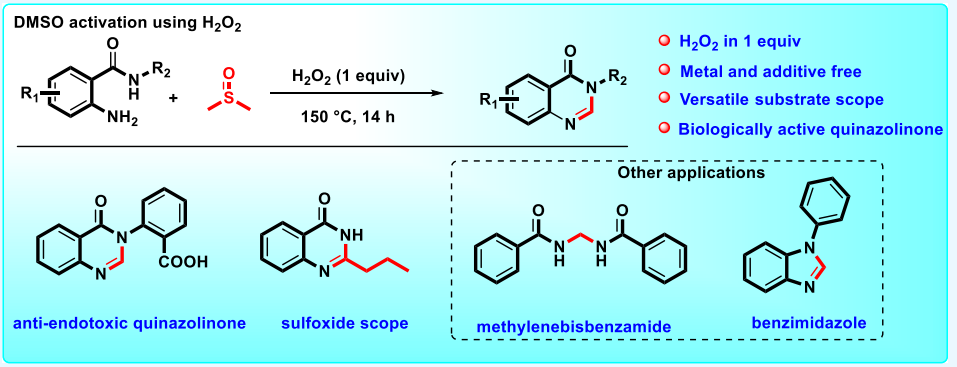
H_2O_2-Mediated Synthesis of a Quinazolin-4(3*H*)-one Scaffold: A Sustainable Approach

Sumit Kumar, Kishor Padala,* and Barnali Maiti*

Cite This: *ACS Omega* 2023, 8, 33058−33068

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A quinazolin-4(3*H*)-one ring system is a privileged heterocyclic moiety with distinctive biological properties. From this perspective, the development of an efficient strategy for the synthesis of quinazolin-4(3*H*)-one has always been in demand for the synthetic chemistry community. In this report, we envisaged an efficient protocol for the synthesis of quinazolin-4(3*H*)-one using substituted 2-amino benzamide with dimethyl sulfoxide (DMSO) as a carbon source and H_2O_2 as an effective oxidant. Mechanistically, the reaction proceeds through the radical approach with DMSO as one carbon source. To further substantiate the synthetic claim, the synthetic protocol has been extended to the synthesis of the anti-endotoxic active compound 3-(2-carboxyphenyl)-4-(3*H*)-quinazolinone.

INTRODUCTION

The advancement of strong and step-economic approaches to access architecturally varied drug-like compound assemblies remains a challenge. Quinazolin-4(3*H*)-one heterocycles are important subunits of a broad variety of synthetic pharmaceuticals, natural products, and biologically active drug molecules.[1] Quinazolin-4(3*H*)-one exhibits various biological activities such as anticancer, antihypertensive, anticancer, anti-inflammatory, anti-depression, anti-lipid accumulation, anti-cerebral palsy, etc.[2] Synthetic chemists have focused heavily on developing quinazolin-4(3*H*)-one-based compounds using a variety of environmentally friendly techniques because of their wide range of applications in natural products, medicines, and medicinal chemistry.[3] Figure 1 depicts some of the marketed drugs based on quinazolin-4(3*H*)-one.[4]

Numerous starting materials have been used in the previously reported literature for the synthesis of quinazolinones, among which 2-amino benzamide serves as one prominent substrate.[5] Additionally, many different techniques have been developed to produce annulation products from the common substrate 2-amino benzamide.[6,3c] A transition metal-assisted and metal-free synthesis technique has been devised in response to the need for a specific derivative with a certain functional group.[7,8] Besides this, some of the developed synthetic routes are restricted to a metal approach which is a major problem for pharmaceutical preparations due to the presence of its impurities in the final desired product.[9] A transitional metal-free approach is more desirable in terms of yield and reaction conditions, but there are still some limitations in the previous reports to use an extra additive in a stoichiometric amount or limited substrate scope. Therefore, simple, green, and affordable metal-free approaches are more desirable due to their sustainability in real life.[10,11] Some of the usual substrates used for the annulation of 2-amino benzamides are benzaldehyde,[12] acetophenone,[13] benzyl alcohol,[14] methanol,[15] methyl arene,[16] CO_2,[17] isocyanides,[18] etc. (Figure 2). To achieve this synthesis, various approaches have been made, and out of that, there is a competition and challenging task to develop a greener, cost-effective, and environmentally benign approach.

Received: July 18, 2023
Accepted: August 9, 2023
Published: August 30, 2023

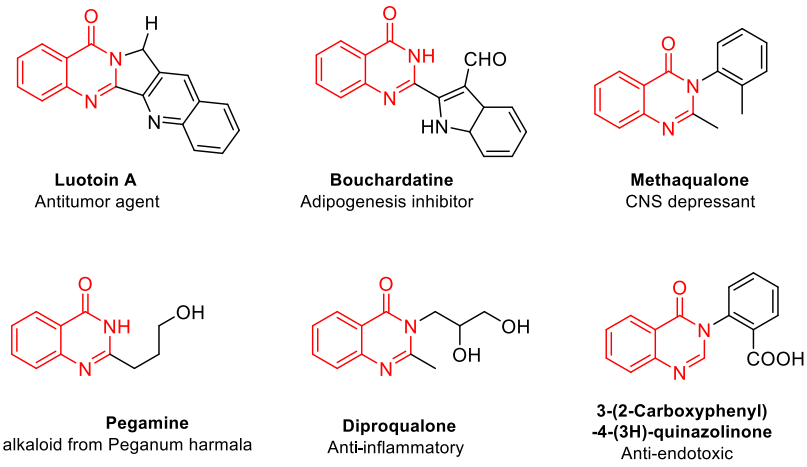


Figure 1. Typical structure exhibiting quinazolinones in various drug scaffolds and natural products.

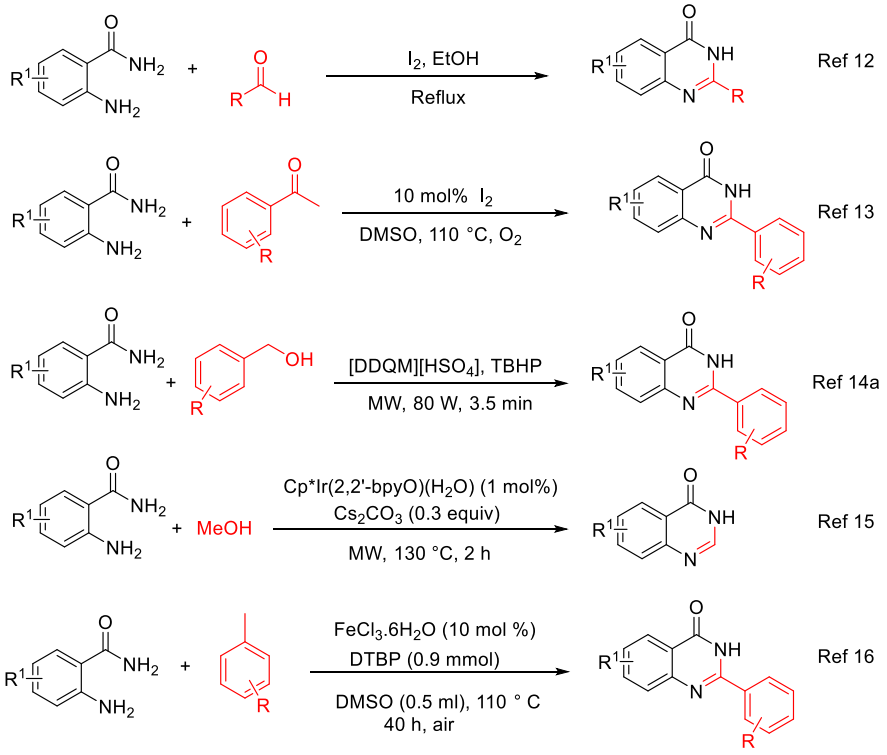


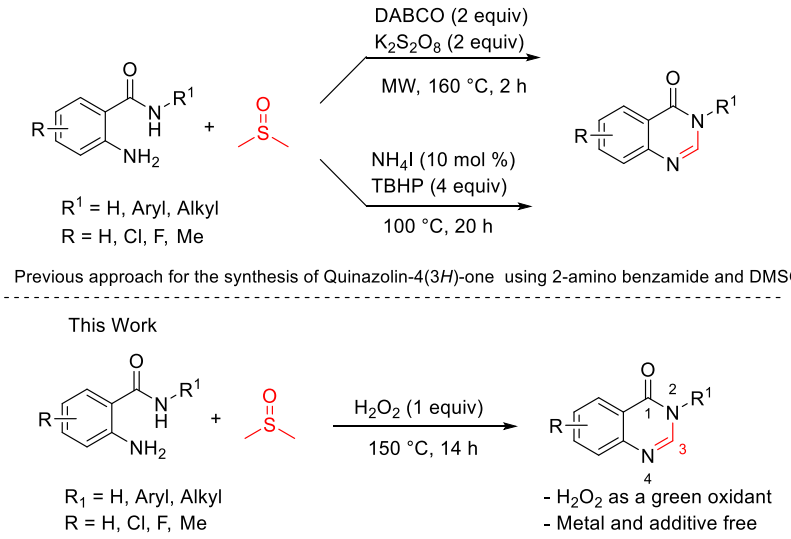
Figure 2. Various approaches for the synthesis of quinazolinones by annulation of 2-amino benzamide.

Using 2-amino benzamide as one of the starting materials and choosing another partner for its annulation have its own importance and substitution pattern at various positions of quinazolinones (Figures 1 and 2). Benzaldehyde, acetophenone, and toluene provide a phenyl ring at the 3rd position to form an annulated product, while ethylene glycol,[19] methanol,[15] and dimethyl sulfoxide (DMSO) provide unsubstitution for the annulation product at the 3rd position (Figure 2 and Scheme 1). Selecting DMSO as one carbon source has various importance to achieve the targeted structure. DMSO provides the methine source while working as an effective solvent. Every substitution has a purpose and function, and the usage of DMSO in annulation provides unsubstitution at the 3rd position, which can be used for other targeted synthesis, such as the creation of the biologically active compound bouchardatine (Figure 1).[20] Because of its great solubilizing power, low toxicity, and affordable availability, it is also one of the most commonly used solvents for organic synthesis.[21] DMSO is used in many transformations as a reaction precursor to generate different synthons and various functionalization such as methylation, methylenation, annulation, cyanation, formylation, etc.[22,4a] Continuous research is ongoing in this field, with its application extended in the pharmaceutical industry, functional materials, and agrochemicals.[23,8a]

Considering the various approaches for the synthesis of quinazolinones using 2-amino benzamide and DMSO, very few approaches have been taken using the oxidants, such as persulfate salt and *tert*-butyl hydroperoxide (TBHP) along with the required additive (Scheme 1). Jung and Manjunatha's group disclosed the synthesis of quinazolinones using 2-amino benzamide and DMSO using $K_2S_2O_8$ as an oxidant and 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in microwave

https://doi.org/10.1021/acsomega.3c05162
ACS Omega 2023, 8, 33058−33068

Scheme 1. Synthesis of Quinazolin-4(3*H*)-one Using 2-Amino Benzamide and DMSO as a Methine Source



conditions.[10b] Later on, Wu's group reported the synthesis of quinazolinones using 2-amino benzamide and DMSO using NH_4I as a catalyst and TBHP as an effective oxidant.[4a] However, these methods require either microwave heating or a catalyst with an oxidant. Herein, we report a transition metal-free approach using H_2O_2 as a green oxidant in 1 equiv and without the use of any additives to synthesize quinazolinone scaffolds in good yields.[24] The scope of the substrate and the reaction conditions have expanded to include certain additional biologically significant components.

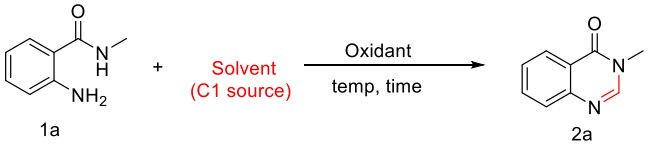
RESULTS AND DISCUSSION

Initially, 2-amino-*N*-methylbenzamide was selected as the benchmark substrate to optimize the reaction condition for the synthesis of *N*-methyl quinazolin-4(3*H*)-one (Scheme 1). At first, the reaction between 2-amino-*N*-methylbenzamide **1a** (0.33 mmol) and DMSO was performed at room temperature (Table 1, entry 1). However, *N*-methyl quinazolin-4(3*H*)-one **2a** was not obtained at room temperature for 20 h. Next, the reaction mixture of 2-amino-*N*-methylbenzamide **1a** and DMSO was heated at 140 °C, which yielded 23% desired *N*-methyl quinazolin-4(3*H*)-one **2a** after 20 h (Table 1, entry 2). Next, we planned to improve the yield of the reaction by adding H_2O_2, a better effective sustainable oxidant. Upon performing the reaction between **1a** and DMSO at 130 °C for 20 h in the presence of H_2O_2 (1.65 mmol, 5 equiv), an isolated yield of 44% was observed (Table 1, entry 3). However, when an extra additive $FeCl_3$ was used along with H_2O_2, the yield increased to 48% at 130 °C for 20 h (Table 1, entry 4).

From the optimization study, we have understood that the reaction is highly temperature- and oxidant-dependent. It is significant to note that while using the reaction with H_2O_2, a trace amount of product was observed below the temperature of 120 °C. DMSO as a synthon has been tested at higher temperatures in some of the reported reactions and found to be more efficient. In Jung and Manjunatha's group (Scheme 1), significant yields were observed at 160 °C for 8 h under thermal conditions. Considering the fact about DMSO degradation, it can undergo a runaway reaction near its boiling point, while other external factors or reactants can influence its rate of degradation.[25,10b] Next, we plan to improve the reaction yield by increasing the reaction temperature. To our delight, by adding H_2O_2 (1.65 mmol, 5 equiv) at 140 °C, the reaction yield improved significantly (Table 1, entry 5). However, the optimum yield of 73% of *N*-methyl quinazolin-4(3*H*)-one **2a** was achieved at 150 °C for 20 h (Table 1, entry 6). Also, we observed the product formation at a higher temperature in lower yield without any external catalyst (Table 1, entry 2). Introducing only 1 equiv of peroxide increased the catalytic and degradation process of DMSO. At higher temperatures, DMSO itself acts as an autocatalytic decomposition process. Adding an external catalyst will speed up this process. The detailed and complete mechanistic pathway for DMSO degradation is still unknown.[25c,d]

Next, we investigated the role of other solvents such as dimethyl formamide (DMF), dimethylacetamide (DMA), and

Table 1. Optimization of Reaction Conditions for the Synthesis of Quinazolin-4(3*H*)-one[a]

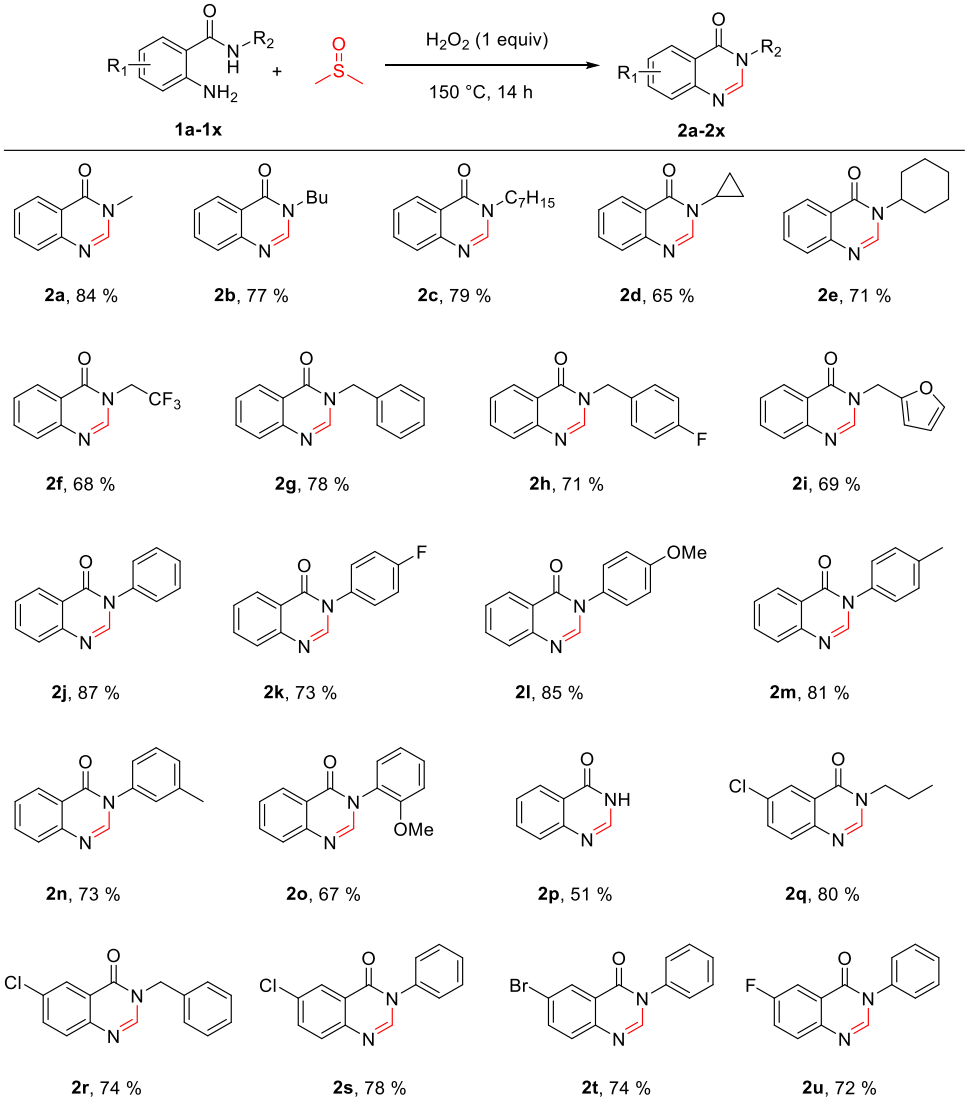


entry	solvent	oxidant (equiv)	temperature (°C)	time (h)	yield (%)[b]
1	DMSO		rt	20	0
2	DMSO		140	20	23
3	DMSO	H_2O_2 (5)	130	20	44
4	DMSO	H_2O_2 (5)	130	20	48[c]
5	DMSO	H_2O_2 (5)	140	20	60
6	DMSO	H_2O_2 (5)	150	20	73
7	DMA	H_2O_2 (5)	150	20	40
8	DMF	H_2O_2 (5)	150	20	22
9	NMP	H_2O_2 (5)	150	20	18
10	DMSO	H_2O_2 (3)	150	14	77
11	DMSO	H_2O_2 (2)	150	14	82
12	**DMSO**	**H_2O_2 (1)**	**150**	**14**	**84**
13	DMSO	H_2O_2 (0.5)	150	14	72
14	DMSO	H_2O_2 (1)	150	14	84[d]

[a]Reaction conditions: 1a (50 mg, 0.33 mmol, 1 equiv), solvent (2 mL), H_2O_2 (5 equiv, 1.65 mmol, 30% in water). [b]Isolated yield. [c]20 mol % $FeCl_3$ and 5 equiv of H_2O_2 used. [d]Reaction under N_2 (DMSO, NMP, and DMF).

https://doi.org/10.1021/acsomega.3c05162
ACS Omega 2023, 8, 33058−33068

Scheme 2. Substrate Scope of the Quinazolin-4(3*H*)-one Derivative[a]



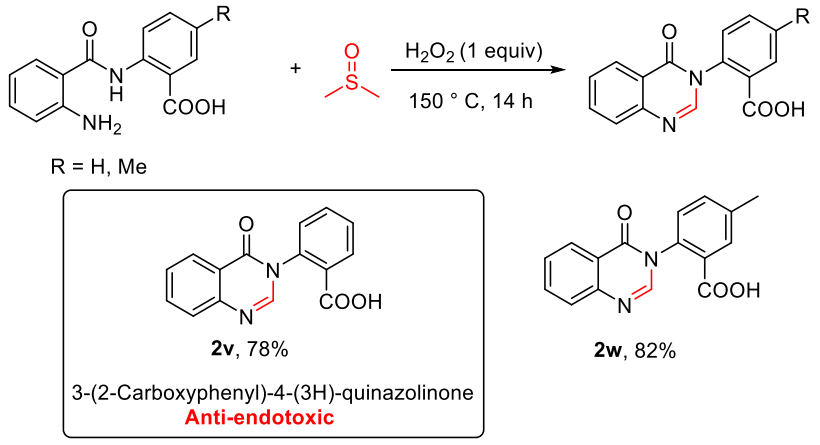
[a]Reaction Conditions: **1a** (1 mmol), DMSO (2 mL), H_2O_2 (1 equiv, 30% in water). 150 °C, 14 h, and mentioned yields indicate isolated yields.

N-methyl-2 pyrrolidone (NMP) to check their participation as a methine synthon in the model reaction. However, a moderate reaction yield of 40% was obtained by employing DMA as one carbon source as well as a solvent (Table 1, entry 7). Using DMF and NMP as synthons, we failed to obtain a satisfactory yield (Table 1, entries 8 and 9). The optimum reaction temperature of 150 °C was found after a brief investigation (Table 1, entry 6). However, considering the atom economy and green sustainable synthesis, we reduced the amount of H_2O_2 to 3.0, 2.0, and 1.0 equiv and observed the actual time requirement. Next, the yields of the reaction slightly increased by decreasing the amount of H_2O_2 to 1 equiv. Later on, when the amount of H_2O_2 decreased to 0.5, the yield of the reaction was affected, and the product was obtained in an isolated yield of 72% only (Table 1, entries 10−13). When the reaction was performed under a nitrogen atmosphere, the product formation was observed with the same yield. On the other hand, it is well known that DMSO itself acts as an oxidizer under air or peroxide (Table 1, entry 14).[25b] Thus, the 1.0 equiv of H_2O_2as the oxidant at 150 °C, was observed as the optimum condition for the model reactions as described in entry (Table 1, entry 12).

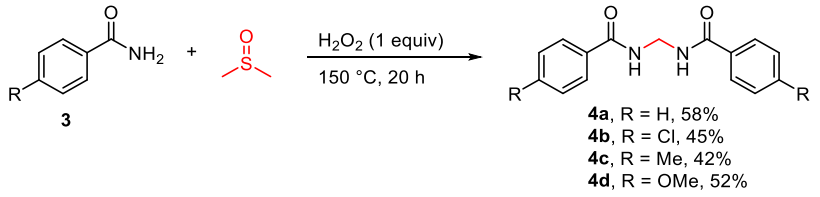
After determining the ideal reaction conditions, the reactions of several 2-amino-*N*-substituted benzamides (**1a-x**) in combination with DMSO were investigated. The results are shown in Scheme 2. First, the substrate with aliphatic substitution on amides was checked, which afforded the corresponding quinazolinones in moderate to good yields (65−84%). The amide-containing cyclopropyl ring and cyclohexyl ring were well tolerated under these conditions, which afforded the desired product in 65 and 71% yields (**2d-2e**). Further, upon changing the functionality from aliphatic to trifluoroethyl, benzyl, 2-methyl furan (**2f-2i**) tolerated well and furnished the corresponding quinazolinones in an isolated yield of 68−78%. Electron-withdrawing substituents such as trifluoroethyl-substituted amide (**1f**) and *N*-phenyl-substituted amide-containing 4-F group (**1h**) smoothly participated in this reaction in a slightly lower yield of 68 and 71% as compared to *N*-phenyl-substituted amide (**2g**, 78%). Later on, we explored our substrate scope to amide-containing aromatic substitution (**2j-2o**), and various substituents such as Me, OMe, and F were

https://doi.org/10.1021/acsomega.3c05162
ACS Omega 2023, 8, 33058−33068

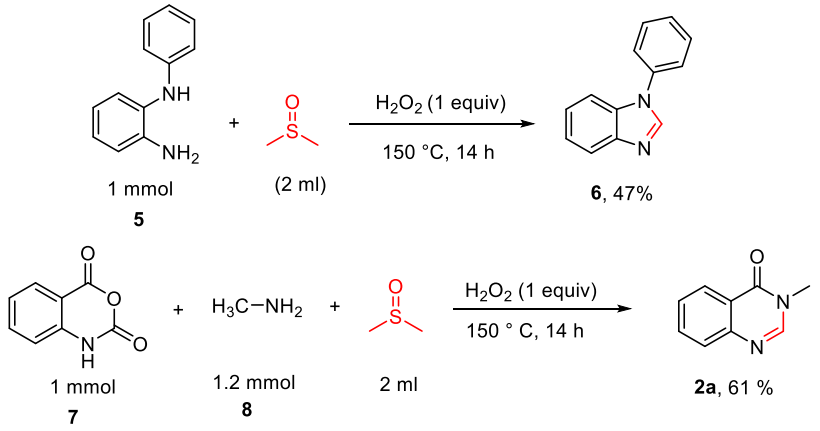
Scheme 3. Synthesis of a Biologically Active Quinazolin-4(3*H*)-one Derivative



Scheme 4. Synthesis of *N,N′*-Methylenedibenzamide Derivatives from 2-Amino Benzamide and DMSO



Scheme 5. Various Synthetic Applications of the Developed Methodology with a Different Starting Material



well tolerated, which afforded the desired product in isolated yields of 67 to 87%. The substrate 2-amino-*N*-phenyl benzamide (**1j**) was well tolerated, which furnished the corresponding 3-phenylquinazolin-4(3*H*)-one (**2j**) in an isolated yield of 87% due to the electron-releasing group. Further, 2-amino-*N*-phenyl benzamide containing electron-donating groups such as *p*-OMe (**2l**) and *p*-Me (**2m**) gave the desired product in isolated yields of 85 and 81%. The 2-amino-*N*-phenyl benzamides containing *m*-Me (**2n**) and *o*-OMe (**2o**) furnished the desired product in a slightly lower yield of 73 and 67%. After that, when we tested the 2-amino benzamide (**2p**) with any alteration, we achieved the corresponding quinazolinones in an isolated yield of 51%. Next, we examined the substrate scope of the aromatic ring of 2-amino-*N*-substituted benzamide with various *N*-substitution (**1q-1u**). We investigated the substrate scope of 2-amino-5-chloro-*N*-substituted benzamide with aliphatic, benzylic, and aromatic substitution at *N*-substitution (**1q-1s**).

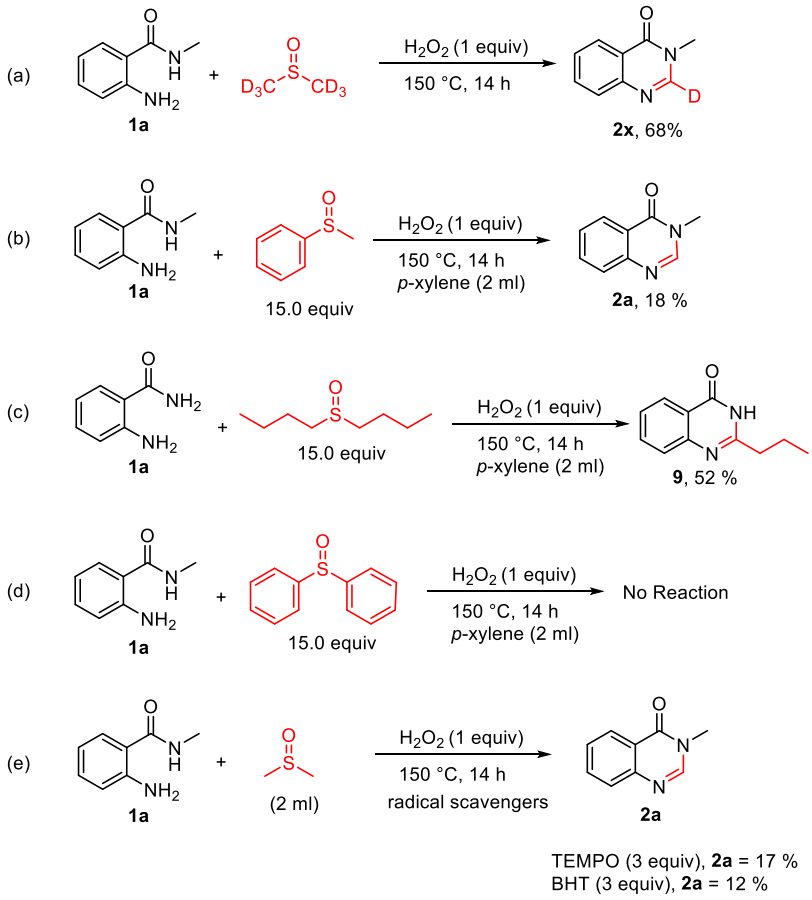
Interestingly, all the substitution patterns were well tolerated, which gave the corresponding product in good yields (74−80%). Further changing the aromatic substitution to bromine (**1 t**) and fluorine (**1u**) afforded the desired product in the isolated yield of 74 and 72%. After synthesizing various substitution patterns of the quinazolinone moiety, we focused our attention to synthesize the biologically important compound and related molecule.

We checked our optimized reaction conditions with 2-(2-aminobenzamido)benzoic acid (**1v**) which contains carboxylic group (−COOH) in its structural unit. Delightfully, we observed the expected product 3-(2-carboxyphenyl)-4-(3*H*)-quinazolinone (**2v**) in a 78% isolated yield. This derivative of quinazolinones is well known for its anti-endotoxic property and of pharmaceutical importance.[26] Similarly, another related derivative (**2w**) was synthesized using the same conditions in an isolated yield of 82% (Scheme 3).

Based on the above results, we tried our conditions with benzamide instead of 2-amino benzamide.

https://doi.org/10.1021/acsomega.3c05162
ACS Omega 2023, 8, 33058−33068

Scheme 6. Various Scopes of Sulfoxide and Controlled Experiments



Interestingly, under the reaction conditions, corresponding benzamide (**3**) with DMSO in the presence of H_2O_2 (1 equiv) at 150 °C for 20 h afforded a methylene-bridged coupling product in a moderate yield of 42−58% (Scheme 4).

Further, the scope of this reaction was extended with different starting materials like *N*1-phenylbenzene-1,2-diamine (**5**) under the optimized reaction conditions, which yielded 1-phenyl-1*H*-benzo[*d*]imidazole (**6**) in an isolated yield of 47% (Scheme 5). It is worth noting that we have prepared the starting material 2-amino-*N*-substituted benzamide (**1a**) from isatoic anhydride (**7**) and corresponding amine (Supporting Information). We have tried the reaction in a one-pot three-component, with isatoic anhydride (**7**), methyl amine (**8**), and DMSO under our optimized reaction condition. Most interestingly, we isolated the corresponding 3-methylquinazolin-4(3*H*)-one (**2a**) with a yield of 61% (Scheme 5).

To examine the actual participation of DMSO, we have tested the scope of various sulfoxides such as DMSO-d_6, methyl phenyl sulfoxide, dibutyl sulfoxide (DBSO), and diphenyl sulfoxide. When we conducted the reaction of **1a** with DMSO-d_6, we observed the corresponding product **2x** in which hydrogen is replaced by deuterium (Scheme 6a). When the same reaction is conducted with methyl phenyl sulfoxide instead of DMSO under the mentioned reaction condition, we obtained the product in an isolated yield of 18% (Scheme 6b). Similarly, we ensured the reaction of DBSO with **1a** (Scheme 6c), and we observed 2-propylquinazolin-4(3*H*)-one (**9**) in an isolated yield of 52%. When we checked the scope of diphenyl sulfoxide (Scheme 6d), we did not observe any product formation, showing that α-hydrogen is compulsory to proceed with the reaction. Finally, to predict the reaction pathway, we performed the reaction (Scheme 6e) with radical scavengers such as TEMPO or BHT. In the presence of radical scavengers, the product yield is decreased, and this result shows that the reaction follows a radical pathway.

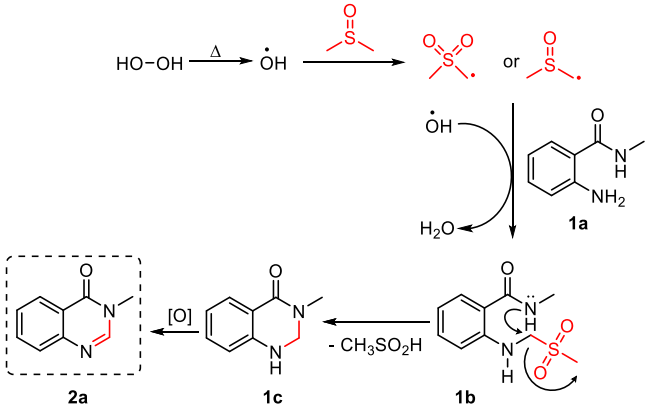
The detailed and complete mechanistic pathway for DMSO degradation at higher temperatures is still unknown.[25c] Based on our control experiments and previous literature reports, we proposed the reaction through a free radical mechanism. The above control experiments confirm that the methine source originated from DMSO.[27] Initially, at high temperature, hydrogen peroxide is homolytically cleaved to a hydroxide radical, which subsequently reacts with DMSO to form a DMSO-based radical. The generated radical reacts with **1a** to form the intermediate **1b** by the elimination of water. The intermediate **1b** was subsequently converted to **1c** with the removal of methanesulfinic acid (Me_3SO_2H). Finally, the intermediate **1c** underwent oxidation to form the final desired product **2a** (Scheme 7).[27,28]

CONCLUSIONS

In conclusion, we have developed an efficient and sustainable method for the synthesis of quinazolin-4(3*H*)-one by using 2-amino benzamide with DMSO as a carbon source and H_2O_2 as a green oxidant. This methodology worked well with different substrates and gave the desired product with moderate to good yield. The scope of this methodology has been successfully extended to prepare a biologically active molecule which shows anti-endotoxic nature. The scope of different sulfoxides and controlled experiments with radical scavengers have been

https://doi.org/10.1021/acsomega.3c05162
ACS Omega 2023, 8, 33058−33068

Scheme 7. Plausible Reaction Mechanism



performed to explain the mechanistic pathway. Numerous control experiments have been performed to prove the mechanism. Further, this developed method has been used for the coupling of two benzamides and the synthesis of other heterocycles.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, commercially available solvents and reagents were used. The reaction was carried out in a 30 mL reaction tube. To perform thin layer chromatography (TLC), 0.25 mm silica gel-coated plates were used. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and DEPT-135 NMR spectra were recorded on a Bruker DRX400 spectrometer using trimethylsilane (TMS) as an internal standard. The peak multiplicities are assigned as s (singlet), d (doublet), dd (doublet of doublet), and m (multiplet). FT-IR spectra were recorded for some selected compounds using an IRAffinity (SHIMADZU) and Nicolet iS50 (Thermo Scientific) spectrometer on a KBr disc or ATR mode. Some selected compounds and all new compounds were analyzed by HRMS analysis. All chemical shifts (δ) are reported in ppm from TMS and *d*-solvent as the internal standard reference. The coupling constants (J) are reported in Hz. 100−200 mesh silica gel was used for column chromatography and separated by using the mixture of ethyl acetate and hexane solvent. The column elution is mentioned in percentage concerning the volume ratio of ethyl acetate/hexane ratios. All of the spectroscopic data for the products matched the reported literature listed in the reference in every way.

General Procedure for the Synthesis of Compounds (2a-2x). In a 30 mL reaction tube, we added 2-amino-*N*-substituted benzamide **1a** (1 mmol), DMSO (2 mL), and H_2O_2 (1 equiv, 30% in water), and the mixture was stirred with a magnetic stirrer bar. H_2O_2 was injected into the reaction tube using a micro syringe and heated for 14 h at 150 °C with continuous stirring. The completion of the reaction mixture was monitored using TLC. Once the reaction was completed as seen by TLC, the reaction mixture was cooled to room temperature and washed with water, and the organic layer was extracted using ethyl acetate (10 mL × 3). The extracted organic layer was dried using Na_2SO_4 and concentrated using rotavapor. The crude product was purified using column chromatography on silica gel.

General Procedure for the Synthesis of 4a-4d. In a 30 mL reaction tube, we added substituted benzamide **3a-3d** (1 mmol), DMSO (2 mL), and H_2O_2 (1 equiv, 30% in water), and the mixture was stirred with a magnetic stirrer bar. H_2O_2 was injected into the reaction tube using a micro syringe and heated for 20 h at 150 °C with continuous stirring. The progress of the reaction mixture was monitored using TLC. Once the reaction was completed as seen by TLC, the reaction mixture was cooled to room temperature and washed with water, and the organic layer was extracted using ethyl acetate (10 mL × 3). The extracted organic layer was dried using Na_2SO_4 and concentrated using rotavapor. The crude product was purified using column chromatography on silica gel.

Compound **6** was prepared using the above procedure by using *N*1-phenylbenzene-1,2-diamine **5** (1 mmol, 184.24 mg) instead of benzamide **3a**.

Compound **2a**, Scheme 5, was synthesized using the above procedure using isatoic anhydride (1 mmol, 163.13 mg), methyl amine (1.2 equiv, 30% in water), DMSO (2 mL), and H_2O_2 (1 equiv, 30% in water) and heated for 14 h at 150 °C with continuous stirring.

Compound **9** was synthesized using the corresponding substituted benzamide (1 mmol), dibutyl sulfoxide (15 equiv), *p*-xylene (2 mL), and H_2O_2 (1 equiv, 30% in water). Once the reaction was completed as seen by TLC, the reaction mixture was washed with 10% aqueous HCl solution and ethyl acetate (15 mL). The aqueous layer was separated and quenched with a 10% NaOH solution until it neutralized completely, as seen using litmus paper. The resulted aqueous solution was added with ethyl acetate (15 mL × 2), and the organic layer was separated. The organic layer was distilled using a rota evaporator, which resulted in a white pure solid.

Substrate Synthesis (1a-1x). The starting material 2-amino-*N*-substituted benzamide **1a-1x** was synthesized using the previously reported literature by refluxing isatoic anhydride (1 equiv) and substituted amine (1 equiv) in water at 80 °C overnight. The reaction completion was monitored using TLC. After completion of the reaction, the reaction mixture was washed with water, extracted using ethyl acetate, and dried over Na_2SO_4. The pure product was isolated using column chromatography over silica gel using hexane and ethyl acetate.[4a,10c]

Spectral Data of All Compounds. *3-Methylquinazolin-4(3H)-one (**2a**).*[10b] Light yellow solid; 84% yield (134.5 mg); eluent (16% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3467.38, 1650.76, 1612.19, 1474.31, 1336.42, 1062.58, 775.24, 696.17, 544.79. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.21 (dd, J = 7.9, 2.0 Hz, 1H), 7.87 (m, J = 8.4, 7.1, 1.6 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.65−7.55 (m, 1H), 3.55 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ 161.89, 149.66, 149.36, 135.35, 128.37, 128.16, 127.07, 122.68, 34.76. HRMS (ESI): calc. for [$C_9H_8N_2O$] (M + H) 162.0748, measured 162.0736.

*3-Butylquinazolin-4(3H)-one (**2b**).*[4a] Light yellow solid; 77% yield (155.7 mg); eluent (22% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3063.37, 2957.30, 1664.26, 1610.27, 1371.14, 766.56, 691.35. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.9 Hz, 1H), 7.96 (s, 1H), 7.71−7.60 (m, 2H), 7.46−7.38 (m, 1H), 3.93 (t, J = 7.3 Hz, 2H), 1.77−1.65 (m, 2H), 1.40−1.28 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.15, 148.21, 146.70, 134.21, 127.47, 127.30, 126.78, 122.28, 46.89, 31.51, 19.98, 13.72. HRMS (ESI): calc. for [$C_{12}H_{14}N_2O$] (M + H) 203.1140, measured 203.1215.

*3-Heptylquinazolin-4(3H)-one (**2c**).* Light yellow solid; 79% yield (193 mg); eluent (16% ethyl acetate in hexanes).

https://doi.org/10.1021/acsomega.3c05162
ACS Omega 2023, 8, 33058−33068

FT-IR (KBr, cm^{-1}): 3046.01, 2930.30, 1657.51, 1611.23, 1472.38, 1108.86, 765.60, 693.28. ^1H NMR (400 MHz, CDCl3) δ 8.29 (d, J = 8.1 Hz, 1H), 8.01 (s, 1H), 7.76−7.66 (m, 2H), 7.48 (m, J = 8.2, 6.8, 1.5 Hz, 1H), 4.00−3.93 (m, 2H), 1.77 (m, J = 7.4 Hz, 2H), 1.36−1.23 (m, 8H), 0.89−0.81 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 161.15, 148.22, 146.71, 134.20, 127.48, 127.29, 126.79, 122.29, 47.19, 31.73, 29.49, 28.93, 26.73, 22.63, 14.11. HRMS (ESI): calc. for $[C_{15}H_{20}N_2O]$ (M + H) 245.1649, measured 245.1685.

3-Cyclopropylquinazolin-4(3H)-one (**2d**).[4a] Light yellow solid; 65% yield (121 mg); eluent (16% ethyl acetate in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 9.8 Hz, 1H), 8.11 (s, 1H), 7.78−7.66 (m, 2H), 7.50 (t, J = 7.5 Hz, 1H), 3.25 (m, J = 7.3, 4.1 Hz, 1H), 1.22 (d, J = 6.7 Hz, 2H), 0.97−0.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.46, 147.71, 146.93, 134.38, 127.49, 127.46, 126.75, 121.99, 29.46, 6.63.

3-Cyclohexylquinazolin-4(3H)-one (**2e**).[4a] White solid; 71% yield (162 mg); eluent (16% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3071.08, 2928.37, 1664.26, 1597.73, 1477.20, 1273.75, 733.31. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 9.7 Hz, 1H), 8.11 (s, 1H), 7.77−7.66 (m, 2H), 7.48 (t, J = 8.2 Hz, 1H), 4.81 (m, J = 12.3, 3.7 Hz, 1H), 1.97 (dd, J = 24.8, 12.7 Hz, 4H), 1.78 (d, J = 13.1 Hz, 1H), 1.70−1.59 (m, 2H), 1.52 (m, J = 13.1, 3.2 Hz, 2H), 1.32−1.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.85, 147.65, 144.05, 134.23, 127.38, 127.23, 127.10, 122.09, 53.52, 32.74, 26.04, 25.42.

3-(2,2,2-Trifluoroethyl)quinazolin-4(3H)-one (**2f**).[10b] Yellow solid; 68% yield (155.2 mg); eluent (16% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3557.05, 3028.65, 1679.69, 1616.05, 1476.24, 1374.03, 1166.72, 776.20. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 7.9 Hz, 1H), 8.03 (s, 1H), 7.80 (t, J = 8.5 Hz, 1H), 7.73 (d, J = 7.1 Hz, 1H), 7.55 (t, J = 6.9 Hz, 1H), 4.68 (q, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.58, 147.73, 145.40, 135.17, 128.15, 127.96, 127.29, 124.75, 121.87 (d, J = 19 Hz), 45.62 (q, J = 35.6 Hz).

3-Benzylquinazolin-4(3H)-one (**2g**).[4a] White solid; 78% yield (184.2 mg); eluent (22% ethyl acetate in hexanes). FT-IR (ATR, cm^{-1}): 3073.97, 1674.87, 1606.41, 1475.27, 1316.17, 940.12, 691.35. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.1 Hz, 1H), 8.10 (s, 1H), 7.78−7.67 (m, 2H), 7.54−7.47 (m, 1H), 7.37−7.29 (m, 5H), 5.20 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.09, 148.06, 146.36, 135.76, 134.33, 129.05, 128.33, 127.97, 127.54, 127.40, 126.90, 122.23, 49.62. HRMS (ESI): calc. for $[C_{15}H_{12}N_2O]$ (M + H) 237.1028, measured 237.1066.

3-(4-Fluorobenzyl)quinazolin-4(3H)-one (**2h**). White solid; 71% yield (180.5 mg); eluent (20% ethyl acetate in hexanes). FT-IR (ATR, cm^{-1}): 3071.08, 1675.83, 1608.34, 1512.28, 1473.34, 1366.31, 1221.68, 776.20. ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.1 Hz, 1H), 8.10 (s, 1H), 7.77−7.67 (m, 2H), 7.49 (t, J = 8.1 Hz, 1H), 7.39−7.31 (m, 2H), 7.05−6.97 (m, 2H), 5.14 (s, 2H). ^{13}C NMR (100 MHz, CDCl3) δ 163.83, 161.37, 161.02, 148.03, 146.14, 134.37, 131.64 (d, J = 3 Hz), 129.92 (d, J = 8 Hz), 127.49 (d, J = 9 Hz), 126.83, 122.17, 115.94 (d, J = 22 Hz), 49.04. HRMS (ESI): calc. for $[C_{15}H_{11}FN_2O]$ (M + H) 256.0927, measured 256.0971.

3-(Furan-2-ylmethyl)quinazolin-4(3H)-one (**2i**).[4a] Yellow solid; 69% yield (156.1 mg); eluent (18% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3109.65, 2926.44, 1668.12, 1612.19, 1473.34, 1354.74, 1015.33, 744.27. ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.1 Hz, 1H), 8.16 (s, 1H), 7.76−7.67 (m, 2H), 7.50−7.45 (m, 1H), 7.36 (d, J = 2.0 Hz, 1H), 6.45 (d, J = 3.3 Hz, 1H), 6.35−6.30 (m, 1H), 5.17 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.78, 148.53, 148.07, 146.13, 143.28, 134.44, 127.61, 127.46, 126.91, 122.23, 110.88, 110.07, 42.21.

3-Phenylquinazolin-4(3H)-one (**2j**).[10b] Yellow solid; 87% yield (193.3 mg); eluent (14% ethyl acetate in hexanes). FT-IR (ATR, cm^{-1}): 3062.40, 1669.08, 1609.30, 1473.34, 1261.21, 765.60, 690.39. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31−8.27 (m, 1H), 8.05 (s, 1H), 7.76−7.67 (m, 2H), 7.51−7.45 (m, 3H), 7.44−7.39 (m, 1H), 7.38−7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.80, 147.90, 146.12, 137.51, 134.62, 129.68, 129.15, 127.69, 127.61, 127.21, 127.03, 122.41. HRMS (ESI): calc. for $[C_{14}H_{10}N_2O]$ (M + H) 224.0905, measured 224.0910.

3-(4-Fluorophenyl)quinazolin-4(3H)-one (**2k**).[8c] White solid; 73% yield (175.3 mg); eluent (16% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3073.97, 1662.33, 1592.91, 1505.16, 1260.25, 836.95, 774.27. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 9.8 Hz, 1H), 8.09 (s, 1H), 7.83−7.73 (m, 2H), 7.57−7.52 (m, 1H), 7.45−7.38 (m, 2H), 7.26−7.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.84, 160.07 (d, J = 58 Hz), 146.80, 144.83, 133.69, 132.38, 127.90 (d, J = 8 Hz), 126.77, 126.62, 126.14, 121.23, 115.66 (d, J = 24 Hz). HRMS (ESI): calc. for $[C_{14}H_9FN_2O]$ (M + H) 242.0811, measured 242.0811.

3-(4-Methoxyphenyl)quinazolin-4(3H)-one (**2l**).[4a] Yellow solid; 85% yield (214.4 mg); eluent (18% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3300, 2920, 1680, 1520, 1260, 769. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 7.9 Hz, 1H), 8.11 (s, 1H), 7.82−7.72 (m, 2H), 7.54 (m, J = 8.2, 6.7, 1.7 Hz, 1H), 7.33 (d, J = 8.9 Hz, 2H), 7.07−7.01 (m, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.16, 160.04, 148.04, 146.56, 134.61, 130.30, 128.26, 127.69, 127.66, 127.27, 126.70, 122.50, 114.95. HRMS (ESI): calc. for $[C_{15}H_{12}N_2O_2]$ (M + H) 254.1011, measured 254.1020.

3-(p-Tolyl)quinazolin-4(3H)-one (**2m**).[4a] White solid; 81% yield (191.3 mg); eluent (12% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3316.96, 2925.48, 1683.55, 1600.62, 1259.28, 772.35. ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, J = 7.9, 2.2 Hz, 1H), 8.11 (s, 1H), 7.83−7.73 (m, 2H), 7.54 (m, J = 8.2, 6.7, 1.7 Hz, 1H), 7.37−7.28 (m, 4H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.03, 148.06, 146.43, 139.37, 135.06, 134.64, 130.37, 127.71, 127.31, 126.87, 125.10, 122.54, 21.33. HRMS (ESI): calc. For $[C_{15}H_{12}N_2O]$ (M + H) 238.1061, measured 238.1069.

3-(m-Tolyl)quinazolin-4(3H)-one (**2n**).[4a] White solid; 73% yield, (172.4 mg); eluent (10% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 2919.69, 2855.50, 1669.08, 1463.70, 1259.289, 776.20. ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 9.5 Hz, 1H), 8.12 (s, 1H), 7.83−7.75 (m, 2H), 7.58−7.52 (m, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.25−7.18 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.00, 148.05, 146.36, 139.99, 137.57, 134.69, 130.09, 129.62, 127.80, 127.77, 127.71, 127.34, 124.13, 122.57, 21.49.

3-(2-Methoxyphenyl)quinazolin-4(3H)-one (**2o**).[4a] Light yellow solid; 67% yield (169 mg); eluent (13% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 2924.52, 2849.31, 1680.65, 1611.23, 1504.20, 1455.02, 1273.75, 749.20. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (m, J = 8.0, 1.5, 0.7 Hz, 1H), 7.97 (s, 1H), 7.81−7.73 (m, 2H), 7.52 (m, J = 8.3, 6.5, 2.0 Hz, 1H), 7.46 (m, J = 8.1, 1.7 Hz, 1H), 7.33 (dd, J = 7.7, 1.7 Hz, 1H), 7.13−7.06 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.78, 154.80, 148.16, 147.30, 134.49, 131.04,

https://doi.org/10.1021/acsomega.3c05162
ACS Omega 2023, 8, 33058−33068

129.25, 127.60, 127.41, 127.27, 126.10, 122.80, 121.10, 112.38, 55.94.

Quinazolin-4(3H)-one (**2p**).[4a] White solid; 51% yield (74.5 mg); eluent (46% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 2921.62, 1698.97, 1613.16, 1259.28, 1026.90, 769.45, 696.17. ^{1}H NMR (400 MHz, DMSO) δ 12.30 (s, 1H), 8.25−8.13 (m, 2H), 7.87 (t, J = 7.6 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 161.21, 149.21, 145.85, 134.78, 127.67, 127.20, 126.30, 123.09. HRMS (ESI): calc. for [$C_8H_6N_2O$] (M + H) 148.0592, measured 148.0575.

6-Chloro-3-propylquinazolin-4(3H)-one (**2q**). White solid; 80% yield (178.1 mg); eluent (18% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3071.08, 2961.16, 1670, 1605.05, 1463.70, 1367.28, 836.95, 793.56. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 2.3 Hz, 1H), 8.00 (s, 1H), 7.69−7.60 (m, 2H), 3.98−3.92 (m, 2H), 1.82 (h, J = 7.4 Hz, 2H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.17, 146.88, 146.75, 134.68, 133.19, 129.20, 126.22, 123.36, 48.84, 22.71, 11.21. HRMS (ESI): calc. for [$C_{11}H_{12}ClN_2O$] (M + H) 223.0638, measured 223.0603.

3-Benzyl-6-chloroquinazolin-4(3H)-one (**2r**). White solid; 74% yield (200.4 mg); eluent (12% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3063.37, 2918.73, 1668.12, 1600.62, 1469.49, 1324.85, 1262.18, 833.09. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 2.3 Hz, 1H), 8.08 (s, 1H), 7.69−7.61 (m, 2H), 7.38−7.29 (m, 5H), 5.18 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.17, 146.63, 146.58, 135.54, 134.84, 133.37, 129.29, 129.20, 128.57, 128.16, 126.40, 123.36, 49.85. HRMS (ESI): calc. for [$C_{15}H_{12}ClN_2O$] (M + H) 271.0638, measured 271.0606.

6-Chloro-3-phenylquinazolin-4(3H)-one (**2s**).[4a] White solid; 78% yield (200.2 mg); eluent (16% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3044.08, 1671.98, 1607.37, 1467.56, 1251.57, 919.87, 834.06, 695.21. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 2.2 Hz, 1H), 8.11 (s, 1H), 7.77−7.69 (m, 2H), 7.59−7.48 (m, 3H), 7.44−7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.88, 146.53, 146.41, 137.35, 135.14, 133.72, 129.88, 129.45, 129.40, 127.06, 126.69, 123.62.

6-Bromo-3-phenylquinazolin-4(3H)-one (**2t**).[4a] White solid; 74% yield (222.8 mg); eluent (10% ethyl acetate in hexanes). FT-IR (ATR, cm^{-1}): 3067.22, 2919.69, 1462.74, 1270.86, 923.73, 684.60. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 2.3 Hz, 1H), 8.12 (s, 1H), 7.89 (d, J = 2.3 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.59−7.47 (m, 3H), 7.41 (d, J = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.73, 146.85, 146.55, 137.91, 137.32, 129.88, 129.85, 129.54, 129.46, 127.04, 123.91, 121.46.

6-Fluoro-3-phenylquinazolin-4(3H)-one (**2u**).[8c] White solid; 72% yield (172.9 mg); eluent (5% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.99 (dd, J = 8.4, 3.1 Hz, 1H), 7.78 (dd, J = 8.9, 4.9 Hz, 1H), 7.59−7.48 (m, 4H), 7.44−7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.78, 160.23 (d, J = 14 Hz), 145.56 (d, J = 2 Hz), 144.68 (d, J = 2 Hz), 137.39, 130.17 (d, J = 8 Hz), 129.85, 129.40, 127.07, 123.90 (d, J = 9 Hz), 123.23 (d, J = 24 Hz), 112.30 (d, J = 25 Hz).

2-(4-Oxoquinazolin-3(4H)-yl)benzoic Acid (**2v**).[27b] Light yellow solid; 78% yield (207.6 mg); eluent (42% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, DMSO) δ 13.14 (s, 1H), 8.37 (s, 1H), 8.23 (d, J = 7.9 Hz, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.98−7.92 (m, 1H), 7.86 (m, J = 7.6, 1.7 Hz, 1H), 7.81 (d, J = 7.1 Hz, 1H), 7.73 (t, J = 8.4 Hz, 1H), 7.65 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 167.09, 161.53, 149.20, 148.39, 146.70, 138.39, 135.85, 134.60, 132.32, 131.02, 130.78, 128.54, 128.47, 127.58, 123.13.

5-Methyl-2-(4-oxoquinazolin-3(4H)-yl)benzoic Acid (**2w**). White solid; 82% yield (229.8 mg); eluent (40% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 2923.55, 1694.15, 1615.09, 1479.13, 1265.07, 1213.97, 744.27. ^{1}H NMR (400 MHz, DMSO) δ 8.33 (s, 1H), 8.22 (d, J = 6.6 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 8.1 Hz, 1H), 7.64 (t, J = 7.4 Hz, 2H), 7.52 (d, J = 7.9 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 166.34, 160.76, 148.37, 147.72, 139.74, 135.08, 134.96, 134.12, 131.86, 129.96, 129.23, 127.68, 127.59, 126.73, 122.31, 20.93. HRMS (ESI): calc. for [$C_{16}H_{13}N_2O_3$] (M + H) 281.0926, measured 281.0905.

3-Methylquinazolin-4(3H)-one (**2x**). White solid; 68% yield (109.6 mg); eluent (16% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3470.27, 2912.94, 1654.62, 1611.23, 1476.24, 779.10. ^{1}H NMR (400 MHz, DMSO) δ 8.22 (dd, J = 7.9, 1.7 Hz, 1H), 7.88 (m, J = 8.6, 7.1, 1.6 Hz, 1H), 7.73 (d, J = 6.8 Hz, 1H), 7.63−7.57 (m, 1H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 160.65, 148.42, 148.11, 134.10, 127.12, 126.92, 125.83, 121.44, 33.46.

N,N′-Methylenedibenzamide (**4a**).[27a] White solid; 58% yield (73.7 mg); eluent (30% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3310.21, 2967.91, 1636.30, 1524.45, 1487.81, 1286.28, 1110.79, 808.02. ^{1}H NMR (400 MHz, DMSO) δ 9.10 (t, J = 5.7 Hz, 2H), 7.97 (d, J = 7.0 Hz, 4H), 7.59 (t, J = 7.3 Hz, 2H), 7.52 (t, J = 7.4 Hz, 4H), 4.93 (t, J = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 167.70, 135.19, 132.63, 129.49, 128.65, 46.41.

N,N′-Methylenebis(4-chlorobenzamide) (**4b**).[27a] Light yellow solid; 45% yield (72.7 mg); eluent (24% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, DMSO) δ 9.19 (t, J = 5.6 Hz, 2H), 7.96 (d, J = 8.7 Hz, 4H), 7.57 (d, J = 8.6 Hz, 4H), 4.88 (t, J = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 166.71, 137.50, 133.91, 130.62, 129.60, 46.43.

N,N′-Methylenebis(4-methylbenzamide) (**4c**).[27a] White solid; 42% yield (59.2 mg); eluent (30% ethyl acetate in hexanes). FT-IR (KBr, cm^{-1}): 3334.32, 1633.41, 1279.53, 1108.88, 754.99, 612.28. ^{1}H NMR (400 MHz, DMSO) δ 7.70 (d, J = 8.2 Hz, 4H), 7.60 (s, 2H), 7.21 (d, J = 8.2 Hz, 4H), 5.02 (t, J = 6.4 Hz, 2H), 2.38 (s, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 168.59, 142.64, 130.77, 129.39, 127.38, 45.72, 21.61.

N,N′-Methylenebis(4-methoxybenzamide) (**4d**).[27a] White solid; 52% yield (81.7 mg); eluent (40% ethyl acetate in hexanes). FT-IR (ATR, cm^{-1}): 3323.71, 2919.69, 1624.734, 1233.25, 1027.87, 661.46. ^{1}H NMR (400 MHz, DMSO) δ 8.92 (t, J = 5.6 Hz, 2H), 7.95 (d, J = 8.9 Hz, 4H), 7.04 (d, J = 8.9 Hz, 4H), 4.89 (t, J = 5.7 Hz, 2H), 3.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 167.16, 162.92, 130.51, 127.42, 114.67, 56.56, 46.31.

1-Phenyl-1H-benzo[d]imidazole (**6**).[4a] Brown solid; 47% yield (90.3 mg); eluent (5% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.91−7.85 (m, 1H), 7.61−7.44 (m, 6H), 7.37−7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.14, 142.41, 136.48, 133.83, 130.18, 128.17, 124.19, 123.83, 122.93, 120.72, 110.59.

2-Propylquinazolin-4(3H)-one (**9**).[10b] White solid; 52% yield (97.8 mg); FT-IR (ATR, cm^{-1}): 3049.87, 1675.83, 1621.84, 1471.42, 899.62, 770.422. ^{1}H NMR (400 MHz, DMSO) δ 12.19 (s, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H),

https://doi.org/10.1021/acsomega.3c05162
ACS Omega 2023, 8, 33058−33068

2.60 (t, J = 7.5 Hz, 2H), 1.77 (q, J = 7.5 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 161.92, 157.40, 148.91, 134.30, 126.77, 125.95, 125.72, 120.80, 36.38, 20.26, 13.52.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c05162.

Copies of ^{1}H and ^{13}C NMR, DEPT-135 NMR, IR, and HRMS spectral data of unknown compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Kishor Padala − *Department of Chemistry, Central Tribal University of Andhra Pradesh, Vizianagaram, Andhra Pradesh 535003, India*; Email: kishor.padala@gmail.com, kishor.padala@ctuap.ac.in

Barnali Maiti − *Department of Chemistry, School of Advanced Science, Vellore Institute of Technology, Vellore, Tamil Nadu 632014, India*; orcid.org/0000-0001-8338-0720; Email: barnalimaiti.m@gmail.com, barnali.m@vit.ac.in

Author

Sumit Kumar − *Department of Chemistry, School of Advanced Science, Vellore Institute of Technology, Vellore, Tamil Nadu 632014, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c05162

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

K.P. gratefully acknowledges the financial support from the CSIR-HRDG, India, Project File No. 02(0454)/21/EMR-II and DST SERB, India, Project File No. CRG/2021/003497, and B.M. gratefully acknowledges the Chancellor of VIT for providing an opportunity to carry out this study and VIT for providing the "VIT SEED Grant-RGEMS Fund (SG20220031)" for carrying out this research work. We sincerely acknowledge the VIT-SIF for providing the instrumental facilities.

■ REFERENCES

(1) (a) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M.; Luotonin, A. A naturally occurring human DNA topoisomerase I poison. *J. Am. Chem. Soc.* **2003**, *125*, 13628−13629. (b) Michael, J. P. Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep.* **2008**, *25*, 166−187. (c) Kshirsagar, U. A. Recent developments in the chemistry of quinazolinone alkaloids. *Org. Biomol. Chem.* **2015**, *13*, 9336−9352.

(2) (a) Asif, M. Chemical characteristics, synthetic methods, and biological potential of quinazoline and quinazolinone derivatives. *Int. J. Med. Chem.* **2014**, *2014*, No. 395637. (b) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. Recent advances in the structural library of functionalized quinazoline and quinazolinone scaffolds: Synthetic approaches and multifarious applications. *Eur. J. Med. Chem.* **2014**, *76*, 193−244. (c) Gatadi, S.; Lakshmi, T. V.; Nanduri, S. 4 (3*H*)-Quinazolinone derivatives: Promising antibacterial drug leads. *Eur. J. Med. Chem.* **2019**, *170*, 157−172. (d) Rajput, R.; Mishra, A. P. A review on biological activity of quinazolinones. *Int. J. Pharm. Pharm. Sci.* **2012**, *4*, 66−70. (e) Xie, Z.; Lan, J.; Zhu, H.; Lei, G.; Jiang, G.; Le, Z. Visible light induced tandem reactions: An efficient one pot strategy for constructing quinazolinones using in-situ formed aldehydes under photocatalyst-free and room-temperature conditions. *Chin. Chem. Lett.* **2021**, *32*, 1427−1431. (f) Xu, W.; Fu, H. Amino acids as the nitrogen-containing motifs in copper-catalyzed domino synthesis of *N*-heterocycles. *J. Org. Chem.* **2011**, *76*, 3846−3852.

(3) (a) Jafari, E.; Khajouei, M. R.; Hassanzadeh, F.; Hakimelahi, G. H.; Khodarahmi, G. A. Quinazolinone and quinazoline derivatives: recent structures with potent antimicrobial and cytotoxic activities. *Res. Pharm. Sci.* **2016**, *11*, 1−14. (b) Rohokale, R. S.; Kshirsagar, U. A. Advanced synthetic strategies for constructing quinazolinone scaffolds. *Synthesis* **2016**, *48*, 1253−1268. (c) Zhang, Z.; Wang, M.; Zhang, C.; Zhang, Z.; Lu, J.; Wang, F. The cascade synthesis of quinazolinones and quinazolines using an α-MnO_2 catalyst and tert-butyl hydroperoxide (TBHP) as an oxidant. *Chem. Commun.* **2015**, *51*, 9205−9207. (d) Xie, Z.; Lan, J.; Yan, L.; Chen, X.; Li, Q.; Meng, J.; Le, Z. Photocatalyst-free visible-light-promoted quinazolinone synthesis at room temperature utilizing aldehydes generated in situ via C-C bond cleavage. *Org. Biomol. Chem.* **2021**, *19*, 2436−2441.

(4) (a) Wu, J.; Yu, X.; Zhong, L.; Jin, K.; Zhao, G.; Zhu, J.; Shi, H.; Wei, Y. Dimethyl Sulfoxide as Methyl Source for the Synthesis of Quinazolinones under Metal-Free Conditions. *Asian J. Org. Chem.* **2022**, *11*, No. e202200278. (b) Yadav, P.; Yadav, S.; Awasthi, A.; Phanindrudu, M.; Bhowmick, S.; Tiwari, D. K. DMSO as a dual carbon synthon in one-pot tandem synthesis of *N*-alkylated quinazolinones from anthranilamides and acetophenones. *New J. Chem.* **2022**, *46*, 16289−16296.

(5) (a) Viji, M.; Vishwanath, M.; Sim, J.; Park, Y.; Jung, C.; Lee, S.; Lee, H.; Lee, K.; Jung, J. K. α-Hydroxy acid as an aldehyde surrogate: metal-free synthesis of pyrrolo [1, 2-a] quinoxalines, quinazolinones, and other *N*-heterocycles via decarboxylative oxidative annulation reaction. *RSC Adv.* **2020**, *10*, 37202−37208. (b) Ambethkar, S.; Kalaiselvi, M.; Padmini, V.; Bhuvanesh, N. Synthesis of 3-Substituted Quinazolinones via C-N and C−C bond Cleavage of Enaminone. *ChemistrySelect* **2017**, *2*, 5329−5332.

(6) Zhaleh, S.; Hazeri, N.; Maghsoodlou, M. T. Green protocol for synthesis of 2, 3-dihydroquinazolin-4 (1 *H*)-ones: Lactic acid as catalyst under solvent-free condition. *Res. Chem. Intermed.* **2016**, *42*, 6381−6390.

(7) Witt, A.; Bergman, J. Recent developments in the field of quinazoline chemistry. *Curr. Org. Chem.* **2003**, *7*, 659−677.

(8) (a) Xie, C.; Zhang, Z.; Li, D.; Gong, J.; Han, X.; Liu, X.; Ma, C. Dimethyl sulfoxide involved one-pot synthesis of quinoxaline derivatives. *J. Org. Chem.* **2017**, *82*, 3491−3499. (b) Hikawa, H.; Ino, Y.; Suzuki, H.; Yokoyama, Y. Pd-catalyzed benzylic C−H amidation with benzyl alcohols in water: A strategy to construct quinazolinones. *J. Org. Chem.* **2012**, *77*, 7046−7051. (c) Natte, K.; Neumann, H.; Wu, X. F. Pd/C as an efficient heterogeneous catalyst for carbonylative four-component synthesis of 4 (3 *H*)-quinazolinones. *Catal. Sci. Technol.* **2015**, *5*, 4474−4480.

(9) (a) Zhou, J.; Fang, J. One-pot synthesis of quinazolinones via iridium-catalyzed hydrogen transfers. *J. Org. Chem.* **2011**, *76*, 7730−7736. (b) Zhang, W.; Meng, C.; Liu, Y.; Tang, Y.; Li, F. Auto-Tandem Catalysis with Ruthenium: From o-Aminobenzamides and Allylic Alcohols to Quinazolinones via Redox Isomerization/Acceptorless Dehydrogenation. *Adv. Synth. Catal.* **2018**, *360*, 3751−3759. (c) Li, Z.; Dong, J.; Chen, X.; Li, Q.; Zhou, Y.; Yin, S. F. Metal-and oxidant-free synthesis of quinazolinones from β-ketoesters with o-amino-benzamides via phosphorous acid-catalyzed cyclocondensation and selective C−C bond cleavage. *J. Org. Chem.* **2015**, *80*, 9392−9400.

(10) (a) Kumar, S.; Padala, K. The recent advances in $K_2S_2O_8$-mediated cyclization/coupling reactions via an oxidative trans-formation. *Chem. Commun.* **2020**, *56*, 15101−15117. (b) Lee, S.; Sim, J.; Jo, H.; Viji, M.; Srinu, L.; Lee, K.; Lee, H.; Manjunatha, V.; Jung, J. K. Transition metal-free synthesis of quinazolinones using dimethyl sulfoxide as a synthon. *Org. Biomol. Chem.* **2019**, *17*, 8067−8070. (c) Zhao, D.; Wang, T.; Li, J. X. Metal-free oxidative synthesis of quinazolinones via dual amination of sp^3 C−H bonds. *Chem. Commun.* **2014**, *50*, 6471−6474.

(11) (a) Wu, X. F.; He, L.; Neumann, H.; Beller, M. Palladium-catalyzed carbonylative synthesis of quinazolinones from 2-amino-benzamide and aryl bromides. *Chem. − Eur. J.* **2013**, *19*, 12635−12638. (b) Li, C. J. Cross-dehydrogenative coupling (CDC): exploring C− C bond formations beyond functional group transformations. *Acc. Chem. Res.* **2009**, *42*, 335−344.
(12) Tian, X.; Song, L.; Li, E.; Wang, Q.; Yu, W.; Chang, J. Metal-free one-pot synthesis of 1, 3-diazaheterocyclic compounds via I_2-mediated oxidative C−N bond formation. *RSC Adv.* **2015**, *5*, 62194−62201.
(13) Mohammed, S.; Vishwakarma, R. A.; Bharate, S. B. Iodine Catalyzed Oxidative Synthesis of Quinazolin-4 (3 *H*)-ones and Pyrazolo [4, 3-d] pyrimidin-7 (6 *H*)-ones via Amination of sp^3 C−H Bond. *J. Org. Chem.* **2015**, *80*, 6915−6921.
(14) (a) Dutta, B.; Dutta, N.; Dutta, A.; Gogoi, M.; Mehra, S.; Kumar, A.; Deori, K.; Sarma, D. [DDQM][HSO4]/TBHP as a Multifunctional Catalyst for the Metal Free Tandem Oxidative Synthesis of 2-Phenylquinazolin-4 (3*H*)-ones. *J. Org. Chem.* **2022**, DOI: 10.1021/acs.joc.2c00908. (b) Sarma, D.; Majumdar, B.; Deori, B.; Jain, S.; Sarma, T. K. Photoinduced enhanced decomposition of TBHP: a convenient and greener pathway for aqueous domino synthesis of quinazolinones and quinoxalines. *ACS Omega* **2021**, *6*, 11902−11910.
(15) Li, F.; Lu, L.; Liu, P. Acceptorless Dehydrogenative Coupling of o-Aminobenzamides with the Activation of Methanol as a C1 Source for the Construction of Quinazolinones. *Org. Lett.* **2016**, *18*, 2580−2583.
(16) (a) Jang, Y.; Lee, S. B.; Hong, J.; Chun, S.; Lee, J.; Hong, S. Synthesis of 2-aryl quinazolinones via iron-catalyzed cross-dehydrogenative coupling (CDC) between N−H and C−H bonds. *Org. Biomol. Chem.* **2020**, *28*, 5435−5441. (b) Xiaoxiao, Y.; Wangheng, B.; Jianye, Z.; Yuting, Z.; Mengru, Z.; Jiwei, W. Synthesis of Quinazolin-4 (3H)-ones via Ammonium Iodide-Catalyzed Dual Amination of sp3 C—H Bonds. *Chin. J. Org. Chem.* **2022**, *42*, 2449. (c) Xu, N.; Zhang, Y.; Chen, W.; Li, P.; Wang, L. Photoinduced N-Methylation and N-Sulfonylation of Azobenzenes with DMSO Under Mild Reaction Conditions. *Adv. Synth. Catal.* **2018**, *360*, 1199−1208.
(17) Jacquet, O.; Das Neves Gomes, C.; Ephritikhine, M.; Cantat, T. Complete catalytic deoxygenation of CO_2 into formamidine derivatives. *ChemCatChem* **2013**, *5*, 117−120.
(18) Jiang, X.; Tang, T.; Wang, J. M.; Chen, Z.; Zhu, Y. M.; Ji, S. J. Palladium-catalyzed one-pot synthesis of quinazolinones via tert-butyl isocyanide insertion. *J. Org. Chem.* **2014**, *79*, 5082−5087.
(19) Chandrua Senadi, G.; Suresha Kudale, V. Sustainable methine sources for the synthesis of heterocycles under metal-and peroxide-free conditions. *Green Chem.* **2019**, *21*, 979−985.
(20) Ghosh, P.; Ganguly, B.; Das, S. C−H functionalization of quinazolinones by transition metal catalysis. *Org. Biomol. Chem.* **2020**, *18*, 4497−4518.
(21) Yan, M.; Zhou, D.; Gao, Y.; Ma, Y. Metal-Free Synthesis of Methylene-Bridged Bisamide via Selectfluor-Mediated Oxidative Methylenation. *ChemistrySelect* **2018**, *3*, 13006−13009.
(22) (a) Cui, H. L. Recent Advances in DMSO-Based Direct Synthesis of Heterocycles. *Molecules* **2022**, *27*, 8480. (b) Russell, G. A.; Weiner, S. A. Methylation of Aromatic Hydrocarbons by Dimethyl Sulfoxide in the Presence of Base1. *J. Org. Chem.* **1966**, *31*, 248−251. (c) Yadav, P.; Awasthi, A.; Gokulnath, S.; Tiwari, D. K. DMSO as a Methine Source in TFA-Mediated One-Pot Tandem Regioselective Synthesis of 3-Substituted-1-Aryl-1 H-Pyrazolo-[3, 4-b] quinolines from Anilines and Pyrazolones. *J. Org. Chem.* **2021**, *86*, 2658−2666. (d) Phanindrudu, M.; Wakade, S. B.; Tiwari, D. K.; Likhar, P. R.; Tiwari, D. K. Transition-metal-free approach for the synthesis of 4-aryl-quinolines from alkynes and anilines. *J. Org. Chem.* **2018**, *83*, 9137−9143. (e) Wakade, S. B.; Tiwari, D. K.; Ganesh, P. S.; Phanindrudu, M.; Likhar, P. R.; Tiwari, D. K. Transition-metal-free quinoline synthesis from acetophenones and anthranils via sequential one-carbon homologation/conjugate addition/annulation cascade. *Org. Lett.* **2017**, *19*, 4948−4951.
(23) (a) Zhu, X.; Zhang, F.; Kuang, D.; Deng, G.; Yang, Y.; Yu, J.; Liang, Y. K_2S as sulfur source and DMSO as carbon source for the synthesis of 2-unsubstituted benzothiazoles. *Org. Lett.* **2020**, *22*, 3789−3793.
(24) Burek, B. O.; Bormann, S.; Hollmann, F.; Bloh, J. Z.; Holtmann, D. Hydrogen peroxide driven biocatalysis. *Green Chem.* **2019**, *21*, 3232−3249.
(25) (a) Duan, T.; Zhai, T.; Liu, H.; Yan, Z.; Zhao, Y.; Feng, L.; Ma, C. One-pot three-component synthesis of quinazolines via a copper-catalysed oxidative amination reaction. *Org. Biomol. Chem.* **2016**, *14*, 6561−6567. (b) Gao, X.; Pan, X.; Gao, J.; Huang, H.; Yuan, G.; Li, Y. Ammonium iodide-induced sulfonylation of alkenes with DMSO and water toward the synthesis of vinyl methyl sulfones. *Chem. Commun.* **2015**, *51*, 210−212. (c) Deguchi, Y.; Kono, M.; Koizumi, Y.; Izato, Y. I.; Miyake, A. Study on autocatalytic decomposition of dimethyl sulfoxide (DMSO). *Org. Process Res. Dev.* **2020**, *24*, 1614−1620. (d) Wang, Z.; Richter, S. M.; Gates, B. D.; Grieme, T. A. Safety concerns in a pharmaceutical manufacturing process using dimethyl sulfoxide (DMSO) as a solvent. *Org. Process Res. Dev.* **2012**, *16*, 1994−2000.
(26) He, L.; Li, H.; Chen, J.; Wu, X. F. Recent advances in 4 (3H)-quinazolinone syntheses. *RSC Adv.* **2014**, *4*, 12065−12077.
(27) (a) Pankaj, S. Ammonium persulfate activated DMSO as a one-carbon synthon for the synthesis of methylenebisamides and other applications. *RSC Adv.* **2015**, *5*, 101641−101646. (b) Bowman, W. R.; Elsegood, M. R.; Stein, T.; Weaver, G. W. Radical reactions with 3*H*-quinazolin-4-ones: synthesis of deoxyvasicinone, mackinazolinone, luotonin A, rutaecarpine and tryptanthrin. *Org. Biomol. Chem.* **2007**, *5*, 103−113.
(28) (a) Patel, O. P.; Anand, D.; Maurya, R. K.; Yadav, P. P. H_2O_2/DMSO-promoted regioselective synthesis of 3, 3′-bisimidazopyridinylmethanes via intermolecular oxidative C (sp2)−H bond activation of imidazoheterocycles. *J. Org. Chem.* **2016**, *81*, 7626−7634. (b) Jiang, Y.; Loh, T. P. Catalytic and direct methyl sulfonylation of alkenes and alkynes using a methyl sulfonyl radical generated from a DMSO, dioxygen and copper system. *Chem. Sci.* **2014**, *5*, 4939−4943. (c) Sanchez-Cruz, P.; Santos, A.; Diaz, S.; Alegría, A. E. Metal-independent reduction of hydrogen peroxide by semiquinones. *Chem. Res. Toxicol.* **2014**, *27*, 1380−1386.

https://doi.org/10.1021/acsomega.3c05162
ACS Omega 2023, 8, 33058−33068