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# Synthesis of Cu-catalysed quinazolinones using a $C_{sp3}$–H functionalisation/cyclisation strategy†

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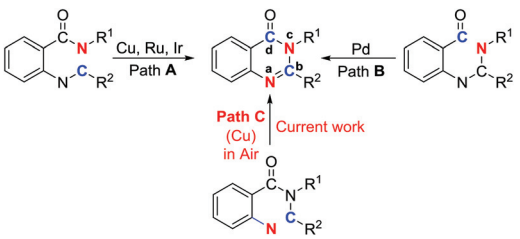
A series of 2,3-disubstituted-4(3*H*)-quinazolinones were synthesised *via* a copper-catalysed $C_{sp3}$–H functionalisation/cyclisation of 2-amino-*N*,*N*-dialkylbenzamides. In comparison to the reported methods this strategy allows an easy access to diversely substituted quinazolinones under mild conditions in air. The reaction also exhibits good functional group tolerance and would be of value to heterocyclic researchers as well as pharmaceutical process chemists. The reaction is proposed to proceed through a double SET type radical mechanism.



## 1. Introduction

The structural motif of quinazolinone (also known as 4(3*H*)-quinazolinone) has attracted considerable attention in the past few decades due to the promising bio-activity of its derivatives ranging from antimalarial, antimicrobial, anti-inflammatory, anticonvulsant, antihypertensive, and antidiabetic, to antitumor activities.[1] Its occurrence as a major building block of a large number of alkaloids[2] further elevates its case for synthetic evaluation. 2,3-Disubstituted-4(3*H*)-quinazolinones amongst other derivatives of quinazolinones have gained commercial relevance in the form of drugs such as rutaecarpine, (+)-febrifugine, afloqualone and raltitrexed. Due to this inherent importance, there is considerable interest and need to investigate and optimise the synthesis of quinazolinones and their derivatives.

General synthetic strategies for obtaining substituted quinazolinones are well-known[3] and the introduction of transition-metal catalysed[4–7] processes has contributed immensely in making the procedures synthetically attractive. Recent studies have focussed on the employment of two types of metal-catalysed cyclisation processes for an efficient and economical construction of the quinazolinone structural motif (Scheme 1). Following path **A**, the C–N bond forming ring closure between **b** and **c** positions could be achieved using Ru, Cu and Ir based catalytic systems,[8] while path **B** constitutes an efficient palladium catalysed cyclocarbonylation connecting positions **c** and **d**.[9] A third pathway (path **C**) has also been reported which includes an intra-molecular aza-Wittig reaction linking **a** and **b**,[3c–e] although a metal-mediated protocol is yet to be explored. We report herein, our investigations into the synthesis of 2,3-disubstituted-4(3*H*)-quinazolinone through pathway **C** *via* a copper-catalysed $C_{sp3}$–H functionalisation/cyclisation of 2-amino-*N*,*N*-dialkylbenzamides.




**Scheme 1** Cyclisation strategies for the construction of the quinazolinone structural motif.

## 2. Results and discussion

C–H bond functionalisation[10] in recent years has emerged as a powerful synthetic strategy for the direct functionalisation of substrates without the requirement of pre-functionalization (a pre-requisite for cross-coupling reactions). Amongst the various C–H bonds available for functionalisation, $C_{sp3}$–H bond functionalisation remained a major synthetic challenge. In this regard, dehydrogenative or oxidative functionalisation strategies for the $C_{sp3}$–H bond[11] are known and have proved useful towards the construction of various structural motifs. The

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utilisation of mild and green oxidants coupled with the application of labile reagents contributes largely to the synthetic appeal of this strategy. We therefore envisaged a commercially available tetrakis(pyridine)copper(II) triflate-catalysed dehydrogenative $C_{sp3}$–H bond functionalisation/cyclisation strategy under aerobic conditions as a practical and efficient approach for the construction of the quinazolinone moiety. A recent report by Maiti and co-workers[12] in 2014 involving the cyclization of *o*-hydroxy-*N*,*N*-dialkylbenzamides was envisaged as the possible starting point. Although, in comparison to phenols, aniline derivatives would provide an interesting challenge in terms of reactivity while their biological significance is immense.

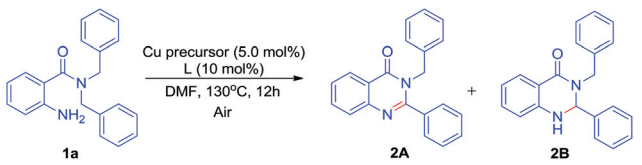
In the first attempt, 2-amino-*N*,*N*-dibenzylbenzamide under the dehydrogenative coupling conditions with $CuCl_2{\cdot}2H_2O$ (no ligand added) in air as an oxidant and *m*-xylene as the solvent at 130 °C provided a mixture of 3-benzyl-2-phenylquinazolin-4(3*H*)-one (**2A**) and 3-benzyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**2B**) in poor yields (entry 1, Table 1).

Adding pyridine as a ligand helped improve the yield as well as the selectivity of the dehydrogenative coupling reaction (entry 2, Table 1). On further screening of different copper catalyst precursors, $Cu(OTf)_2$ in combination with pyridine was found to provide the best selectivity (entry 8, Table 1). The choice of solvent greatly impacts the selectivity with the exclusive formation of quinazolin-4(3*H*)-one (**2A**) observed in DMF (entry 11, Table 1). Other nitrogen based ligands that have shown promising results in copper-catalysed couplings such as L-proline, 1,10-phenanthroline, and DMAP failed to further improve either yield or selectivity. Interestingly, the employment of an easily synthesised[13] and commercially available $Cu(Py)_4(OTf)_2$ provided the desired quinazolinone in competitive yield (entry 20, Table 1).

With an active catalytic system identified, the substrate scope of the dehydrogenative coupling reaction was further explored. Variation in the alkyl groups $R^1$ and $R^2$ on the backbone of 2-amino-*N*,*N*-dialkylbenzamides would allow the synthesis of a diverse range of 2,3-disubstituted quinazolinones (Scheme 2). Initial observations revealed the more efficient functionalisation of *N*-benzyl $C_{sp3}$–H compared to *N*-alkyl $C_{sp3}$–H bonds.

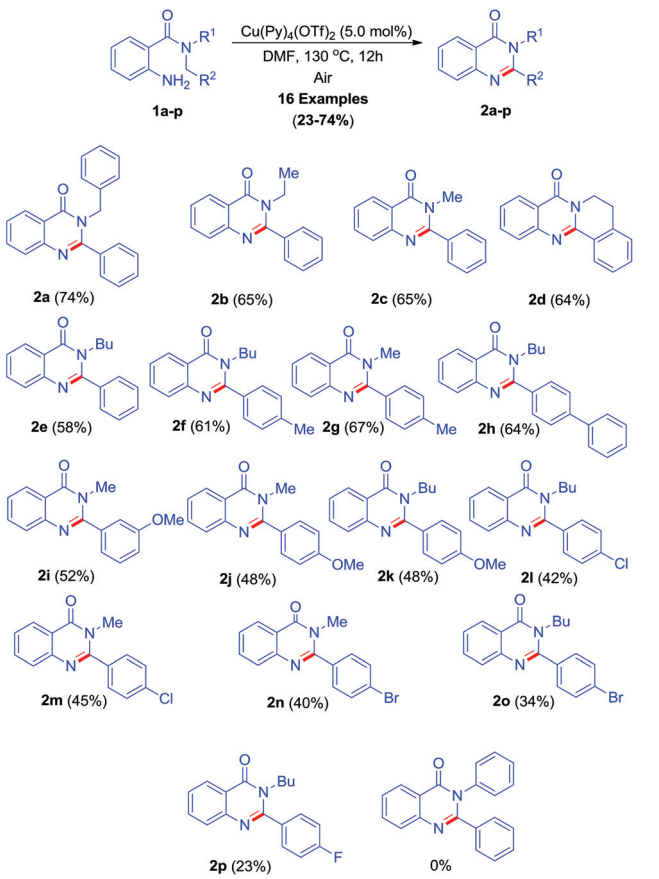
The selectivity obtained was nearly exclusive providing 2-arylsubstituted quinazolinones in good yields. Next, substituent effects were explored providing an insight into the reaction mechanism. An electronic influence on the aryl substituent $R^2$ affects the catalytic efficiency adversely with the unsubstituted benzamides furnishing the cyclised product in competitive yields as do those with only mildly electron-releasing 4-Me substituents. The introduction of strongly electron-releasing substituents (3- or 4-MeO) brought about a slight reduction in

**Table 1** Optimization study for copper-catalysed $C_{sp3}$–H functionalisation/cyclisation strategy for quinazolinone synthesis




| No | Copper precursor | Ligand | Solvent | % Yield (**2A**/**2B**) |
|---|---|---|---|---|
| **Copper precursor screening** | | | | |
| 1 | $CuCl_2{\cdot}2H_2O$ | — | *m*-Xylene | 20/16 |
| 2 | $CuCl_2{\cdot}2H_2O$ | Pyridine | *m*-Xylene | 46/11 |
| 3 | $Cu(OAc)_2{\cdot}H_2O$ | Pyridine | *m*-Xylene | 65/18 |
| 4 | $Cu(OAc)_2$ | Pyridine | *m*-Xylene | 75/11 |
| 5 | CuOAc | Pyridine | *m*-Xylene | 67/22 |
| 6 | $CuCl_2$ (anhyd) | Pyridine | *m*-Xylene | 57/13 |
| 7 | $Cu(acac)_2$ | Pyridine | *m*-Xylene | 47/18 |
| 8 | $Cu(OTf)_2$ | Pyridine | *m*-Xylene | 58/2 |
| **Solvent screening** | | | | |
| 9 | $Cu(OTf)_2$ | Pyridine | PhMe | 45/0 |
| 10 | $Cu(OTf)_2$ | Pyridine | MeCN | 8/0 |
| 11 | $Cu(OTf)_2$ | Pyridine | DMF | 62/0 |
| 12 | $Cu(OTf)_2$ | Pyridine | THF | 9/0 |
| 13 | $Cu(OTf)_2$ | Pyridine | DCE | — |
| 14 | $Cu(OTf)_2$ | Pyridine | MeOH | — |
| 15 | $Cu(OTf)_2$ | Pyridine | $H_2O$ | — |
| **Ligand screening** | | | | |
| 16 | $Cu(OTf)_2$ | L-Proline | DMF | 32/0 |
| 17 | $Cu(OTf)_2$ | 1,10-Phenanthroline | DMF | 20/0 |
| 18 | $Cu(OTf)_2$ | DMAP | DMF | 60/0 |
| 19 | $Cu(OTf)_2$ | 2-$NH_2$-pyridine | DMF | 32/0 |
| 20 | $Cu(Py)_4(OTf)_2$ | — | DMF | 74/0 |
| 21[a] | $Cu(Py)_4(OTf)_2$ | — | DMF | 30/0 |
| 22 | $Cu(DMF)_4(OTf)_2$ | — | DMF | 42/0 |

[a] Pyridine is replaced by 4-*N*,*N*-dimethylamino pyridine.




**Scheme 2** Synthesis of 2,3-disubstituted-4(3*H*)-quinazolinones.

yield whereas electron-withdrawing substituents (Cl, Br, and F) provided poorer results. These studies point strongly towards the involvement of a radical mechanism that is significantly influenced by electronic effects of the substituents.

Of the synthesised quinazolinones, compound **2a** was crystallized from dichloromethane in the monoclinic space group $P2_1/n$ with eight molecules in the unit cell and two molecules in the asymmetric unit (Fig. 1).[14] These two independent molecules can be distinguished by the torsion angle between their backbones and the phenyl substituents which is 79.7° for molecule 1 and 69.4° for molecule 2, clearly verifying that the presence of two independent molecules is not due to overlooked symmetry. The orientation of the benzyl substituent is further slightly different in the two molecules although this difference is not as much pronounced.

We next turned our attention to the possibility of synthesising 2,3-dihydroquinazolin-4(1*H*)-ones using the developed protocol with *N*,*N*-dibenzyl-2-(propylamino)benzamide as a starting material. To test the feasibility of the catalytic procedure, *N*,*N*-dibenzyl-2-(propylamino)benzamide (**3a**) was subjected to dehydrogenative coupling which provided the corresponding dihydroquinazolin-4(1*H*)-one (**4a**) in good yield (Scheme 3). Other alkyl substituents (such as butyl) when employed unfortunately did not furnish the desired dihydroquinazolinones as the preferential cyclisation failed to occur.

## 3. Mechanistic studies

The dehydrogenative coupling reaction giving access to 2,3-disubstituted-4(3*H*)-quinazolinones is most likely going through a SET (single electron transfer) mechanism[15] with an iminium-type intermediate involved in the rate-limiting step. To test this hypothesis, we first performed the catalytic dehydrogenative coupling reaction with a radical scavenger (TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxyl) added at the initial stage of the reaction (Scheme 4). As expected the catalytic reaction failed to furnish the cyclised product supporting the envisaged intermediacy of radical species.

The role of molecular oxygen (previously present in the form of air or pure $O_2$ supplied *via* a balloon) in promoting the cyclisation reaction was next investigated with the catalytic reaction performed under a nitrogen atmosphere. The reaction proceeded sluggishly with a poor yield of the product, confirming the requirement of molecular oxygen for an effective cyclisation (Scheme 5).

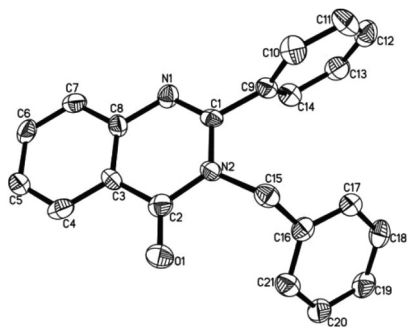
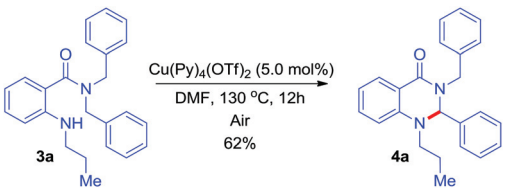
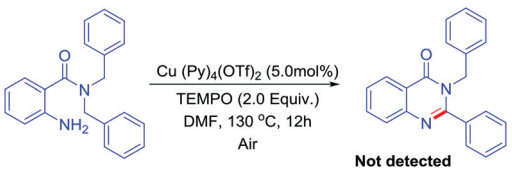


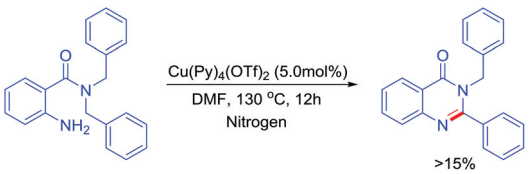

**Fig. 1** Single crystal X-ray structure of molecule 1 of compound **2a**. Ellipsoids are shown with 50% probability. H atoms are omitted for clarity reasons.




**Scheme 3** Synthesis of dihydroquinazolinones *via* copper-catalysed C–H functionalisation/cyclisation.




**Scheme 4** Dehydrogenative coupling with TEMPO as a radical scavenger.




**Scheme 5** Catalytic reaction performed under an inert $N_2$ atmosphere.

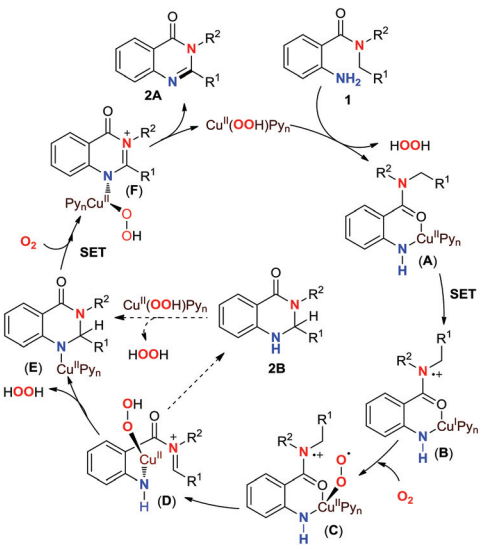



**Fig. 2** Plausible SET-type mechanism for the synthesis of quinazolinones.

Based on these observations a plausible mechanistic proposal involving a SET mechanism[11a,15] is being put forth (Fig. 2). The reaction initiates through a loss of proton from the disubstituted benzamide resulting in a substrate bound Cu(II) center (**A**). This further undergoes a single electron transfer to oxidise the amide-nitrogen resulting in the formation of intermediate **B**.[16] The generation of a Cu(II)-superoxo species could then be envisaged *via* Cu(I) (**B**) functionalisation of a molecule of $O_2$.[17] The abstraction of the H atom from the *N*-benzylic C–H bond by intermediate **C** would then lead to the formation of a Cu(II)hydroperoxo complex **D** as well as an active iminium ion intermediate. In the final step, a nucleophilic attack of the iminium carbon atom by the anilide ion and loss of the H atom leads to the formation of the cyclised **2B** product which would then undergo a second SET mechanism leading to the formation of 2,3-disubstituted-4(3*H*)-quinazolinones.

# 4. Conclusion

We have reported herein a simple and highly practical protocol for the synthesis of 2,3-disubstituted-4(3*H*)-quinazolinones *via* copper-catalysed dehydrogenative $C_{sp3}$–H functionalisation/cyclisation of 2-amino-*N*,*N*-dialkylbenzamides. The catalytic conditions were also found to be useful towards the synthesis of dihydroquinazolinones. A SET-type mechanism involving an iminium radical cation as the possible intermediate has been found to be operational in the catalytic reaction.

# 6. Experimental section

## 6.1 General remark

All the catalytic reactions were conducted in open air in Schlenk tubes. TLC analysis was performed on a Merck 5554 aluminium backed silica gel plate and the compound was visualized by ultraviolet light (254 nm). All yields refer to isolated yields obtained by column chromatography. NMR spectroscopic data of compounds ($^1$H, $^{13}$C) were recorded on an Agilent 400 MHz spectrometer in $CDCl_3$ and DMSO-d$^6$. Chemical shifts are reported in parts per million downfield from an internal standard tetramethylsilane. Coupling constant *J* values are reported in hertz (Hz). Elemental analysis was performed using an Elementar Vario Micro cube. All the chemicals were obtained from commercial sources.

**X-ray structural analysis.** A suitable single crystal of **2a** was mounted on a thin glass fibre coated with paraffin oil. X-ray single-crystal structural data were collected at low temperature (170 K) using a STOE-IPDS 2T diffractometer equipped with a normal-focus, 2.4 kW, sealed-tube X-ray source with graphite-monochromated MoKα radiation ($\lambda$ = 0.71073 Å). The program XArea was used for the integration of diffraction profiles; numerical absorption correction was made with the programs X-shape and X-red32; all from STOE© 2010. The structure was solved by SHELXT-2014[18] and refined by full-matrix least-squares methods using SHELXL-2013.[19] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically on calculated positions using a riding model with their $U_{iso}$ values constrained to $1.2U_{eq}$ of their pivot atoms. All calculations were carried out using SHELX-2013[19] and WinGX GUI, Ver2013.2.[20,21] Crystallographic data are summarized in Table 2.

Table 2 Crystal data and structure refinement for 3-benzyl-2-phenylquinazolin-4(3*H*)-one (**2a**)

| | |
|---|---|
| Empirical formula | $C_{21}H_{16}N_2O$ |
| Formula weight | 312.36 |
| Temperature | 170(2) K |
| Wavelength | 0.71073 Å |
| Crystal system, space group | Monoclinic, *P*21/*n* |
| Unit cell dimensions | *a* = 9.933(2) Å, alpha = 90 deg<br>*b* = 29.454(6) Å, beta = 112.40(3) deg<br>*c* = 11.470(2) Å, gamma = 90 deg |
| Volume | 3102.5(12) Å$^3$ |
| *Z*, calculated density | 8, 1.337 Mg m$^{-3}$ |
| Absorption coefficient | 0.083 mm$^{-1}$ |
| *F*(000) | 1312 |
| Crystal size | 0.292 × 0.081 × 0.060 mm |
| Theta range for data collection | 3.109 to 20.818 deg |
| Limiting indices | $-9 \le h \le 9$, $-29 \le k \le 29$, $-11 \le l \le 11$ |
| Reflections collected/unique | 10 622/3231 [*R*(int) = 0.1280] |
| Completeness to theta | = 25.242, 57.6% |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 3231/0/433 |
| Goodness-of-fit on $F^2$ | 0.794 |
| Final *R* indices [$I > 2\sigma(I)$] | *R*1 = 0.0448, w*R*2 = 0.0723 |
| *R* indices (all data) | *R*1 = 0.1464, w*R*2 = 0.0960 |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.159 and −0.202 e Å$^{-3}$ |

## 6.2 Synthesis of $Cu(Py)_4(OTf)_2$

Tetrakis(pyridine)bis(trifluoromethanesulfonato-*O*)copper(II) was synthesized by a reported method.[22] The commercially available chemicals were purchased from Aldrich Chemical Co. or Alfa Aesar and were used without further purification. All the reaction solvents were dried by standard methods before use.

## 6.3 General procedure for synthesis of quinazolinone

In a dry Schlenk tube, 2-amino-*N*-benzylbenzamide (0.5 mmol), 2 ml of DMF, and tetrakis(pyridine)copper(II) triflate (5 mol%) were added. The resulting solution was stirred at 130 °C in open air for 12 h. After 12 h, the reaction was monitored by TLC for completion and on cooling the reaction mixture the solvent was removed by using a rotary evaporator under reduced pressure. The residue thus obtained was further purified by column chromatography (15% ethyl acetate in petroleum ether) to provide the cyclised quinazolinone as a white solid.

**3-Benzyl-2-phenylquinazolin-4(3*H*)-one (2a).**[23] $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.19 (d, *J* = 7.9 Hz, 1H), 7.86 (t, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.51–7.37 (m, 5H), 7.18 (t, *J* = 6.1 Hz, 3H), 6.89 (d, *J* = 6.5 Hz, 2H), 5.16 (s, 2H). $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 161.9, 156.6, 147.3, 137.0, 135.4, 135.3, 130.2, 128.9, 128.7, 128.4, 127.8, 127.7, 127.6, 126.8, 126.6, 120.7, 48.6. Anal. calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.19. Found: C, 80.68; H, 5.11; N, 8.14.

**3-Ethyl-2-phenylquinazolin-4(3*H*)-one (2b).**[23] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.34 (d, $J$ = 8.2 Hz, 1H), 7.79–7.71 (m, 2H), 7.55–7.48 (m, 6H), 4.04 (q, $J$ = 7.0 Hz, 2H), 1.21 (t, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.0, 156.1, 147.1, 135.5, 134.3, 129.7, 128.8, 127.6, 127.4, 126.9, 126.6, 120.9, 41.1, 14.1. Anal. calcd for $C_{16}H_{14}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.24; H, 5.06; N, 11.33.

**3-Methyl-2-phenylquinazolin-4(3*H*)-one (2c).**[23] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.36–8.32 (m, 1H), 7.80–7.73 (m, 2H), 7.54 (dtt, $J$ = 9.6, 7.3, 2.1 Hz, 6H), 3.50 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.7, 156.1, 147.2, 135.3, 134.3, 130.0, 128.8, 127.9, 127.4, 126.9, 126.6, 120.4, 34.2. Anal. calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.39; H, 5.18; N, 11.60.

**5*H*-Isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2d).**[26] $^1$H NMR (400 MHz, DMSO $d_6$) $\delta$ 8.34 (d, $J$ = 7.8 Hz, 1H), 8.14 (d, $J$ = 7.9 Hz, 1H), 7.80 (t, $J$ = 7.6 Hz, 1H), 7.71 (d, $J$ = 8.0 Hz, 1H), 7.55–7.35 (m, 4H), 4.27 (t, $J$ = 6.3 Hz, 2H), 3.08 (t, $J$ = 6.1 Hz, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 161.0, 149.7, 147.7, 138.1, 134.8, 132.1, 129.4, 128.2, 127.8, 127.7, 127.6, 126.9, 126.7, 120.8, 39.6, 26.8. Anal. calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.27; H, 4.72; N, 11.41.

**3-Butyl-2-phenylquinazolin-4(3*H*)-one (2e).**[25] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.31 (dd, $J$ = 7.8, 0.8 Hz, 1H), 7.76–7.69 (m, 2H), 7.52–7.45 (m, 6H), 3.98–3.92 (m, 2H), 1.56 (dt, $J$ = 15.3, 7.6 Hz, 2H), 1.20–1.09 (m, 2H), 0.73 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.1, 156.2, 147.1, 135.5, 134.2, 129.7, 128.7, 127.7, 127.3, 126.9, 126.7, 120.8, 45.6, 30.6, 19.8, 13.3. Anal. calcd for $C_{18}H_{18}N_2O$: C, 77.06; H, 6.52; N, 10.06. Found: C, 77.14; H, 6.51; N, 9.79.

**3-Butyl-2-(*p*-tolyl)quinazolin-4(3*H*)-one (2f).**[25] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.30 (d, $J$ = 7.6 Hz, 1H), 7.75–7.68 (m, 2H), 7.46 (ddd, $J$ = 8.1, 6.3, 2.0 Hz, 1H), 7.39 (d, $J$ = 8.0 Hz, 2H), 7.29 (d, $J$ = 8.0 Hz, 2H), 4.00–3.94 (m, 2H), 2.41 (s, 3H), 1.57 (dt, $J$ = 15.4, 7.6 Hz, 2H), 1.16 (dq, $J$ = 14.8, 7.4 Hz, 2H), 0.75 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.2, 156.4, 147.1, 139.8, 134.2, 132.6, 129.3, 127.6, 127.3, 126.8, 126.6, 120.8, 45.7, 30.7, 21.4, 19.9, 13.4. Anal. calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.11; H, 6.68; N, 9.41.

**3-Methyl-2-(*p*-tolyl)quinazolin-4(3*H*)-one (2g).**[23] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.30 (d, $J$ = 8.5 Hz, 1H), 7.75–7.69 (m, 2H), 7.49–7.42 (m, 3H), 7.30 (d, $J$ = 7.9 Hz, 2H), 3.48 (s, 3H), 2.41 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.8, 156.2, 147.3, 140.2, 134.2, 132.4, 129.4, 127.9, 127.4, 126.8, 126.6, 120.4, 34.3, 21.4. Anal. calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.85; H, 5.78; N, 11.36.

**2-([1,1′-Biphenyl]-4-yl)-3-methylquinazolin-4(3*H*)-one (2h).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.32 (d, $J$ = 7.9 Hz, 1H), 7.76–7.70 (m, 4H), 7.62 (dd, $J$ = 8.9, 7.8 Hz, 4H), 7.48 (ddd, $J$ = 9.4, 5.2 Hz, 3H), 7.41–7.35 (m, 1H), 3.55 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.7, 155.9, 147.3, 143.0, 140.0, 134.3, 134.1, 128.9, 128.5, 127.9, 127.5, 127.5, 127.1, 127.0, 126.6, 120.4, 34.3. Anal. calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.62; H, 5.12; N, 8.71.

**2-(3-Methoxyphenyl)-3-methylquinazolin-4(3*H*)-one (2i).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.32–8.27 (m, 1H), 7.76–7.69 (m, 2H), 7.47 (ddd, $J$ = 8.2, 5.9, 2.3 Hz, 1H), 7.40 (t, $J$ = 7.9 Hz, 1H), 7.05 (ddd, $J$ = 10.7, 10.0, 5.2 Hz, 3H), 3.84 (s, 3H), 3.47 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.6, 159.8, 155.9, 147.2, 136.4, 134.3, 130.0, 127.4, 127.0, 126.6, 120.5, 120.0, 115.8, 113.4, 55.4, 34.1. Anal. calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.18; H, 5.35; N, 10.43.

**2-(4-Methoxyphenyl)-3-methylquinazolin-4(3*H*)-one (2j).**[24] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.30 (d, $J$ = 8.5 Hz, 1H), 7.76–7.69 (m, 2H), 7.54–7.44 (m, 3H), 7.01 (d, $J$ = 8.7 Hz, 2H), 3.86 (s, 3H), 3.51 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.9, 160.9, 156.0, 147.3, 134.2, 129.7, 127.7, 127.3, 126.7, 126.6, 120.3, 114.1, 55.4, 34.4. Anal. calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.31; H, 5.36; N, 10.40.

**3-Butyl-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one (2k).**[25] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.29 (ddd, $J$ = 8.0, 1.2, 0.6 Hz, 1H), 7.73–7.67 (m, 2H), 7.46 (dt, $J$ = 4.1, 2.0 Hz, 2H), 7.44 (d, $J$ = 2.0 Hz, 1H), 7.02–6.97 (m, 2H), 4.02–3.96 (m, 2H), 3.85 (s, 3H), 1.61–1.52 (m, 2H), 1.17 (dt, $J$ = 14.9, 7.5 Hz, 2H), 0.76 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.3, 160.5, 156.1, 147.1, 134.1, 129.4, 127.9, 127.3, 126.7, 126.6, 120.7, 114.0, 55.4, 45.7, 30.7, 19.9, 13.4. Anal. calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.03; H, 6.50; N, 9.02.

**3-Butyl-2-(4-chlorophenyl)quinazolin-4(3*H*)-one (2l).**[25] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.17 (d, $J$ = 8.0 Hz, 1H), 7.64–7.53 (m, 2H), 7.39–7.31 (m, 5H), 3.85–3.78 (m, 2H), 1.43 (dt, $J$ = 15.3, 7.7 Hz, 2H), 1.09–0.99 (m, 2H), 0.64 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.0, 155.1, 146.9, 136.0, 134.3, 133.9, 129.2, 129.0, 127.3, 127.1, 126.7, 120.8, 45.7, 30.7, 19.8, 13.4. Anal. calcd for $C_{18}H_{17}ClN_2O$: C, 69.12; H, 5.48; N, 8.96. Found: C, 69.24; H, 5.57; N, 8.78.

**2-(4-Chlorophenyl)-3-methylquinazolin-4(3*H*)-one (2m).**[24] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 8.2 Hz, 1H), 7.70 (ddd, $J$ = 15.6, 11.3, 4.2 Hz, 2H), 7.50–7.43 (m, 5H), 3.44 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.5, 154.9, 147.1, 136.3, 134.4, 133.7, 129.5, 129.1, 127.4, 127.2, 126.7, 120.4, 34.2. Anal. calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.13; N, 10.38. Found: C, 66.64; H, 4.17; N, 10.24.

**2-(4-Bromophenyl)-3-methylquinazolin-4(3*H*)-one (2n).**[24] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.30 (dd, $J$ = 8.0, 0.9 Hz, 1H), 7.79–7.63 (m, 4H), 7.47 (ddt, $J$ = 8.8, 4.0, 1.8 Hz, 3H), 3.48 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.6, 155.0, 147.1, 134.4, 134.1, 132.1, 129.7, 127.4, 127.2, 126.7, 124.6, 120.4, 34.2. Anal. calcd for $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; N, 8.89. Found: C, 57.03; H, 3.36; N, 8.95.

**2-(4-Bromophenyl)-3-butylquinazolin-4(3*H*)-one (2o).**[25] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.29 (d, $J$ = 7.9 Hz, 1H), 7.76–7.62 (m, 4H), 7.49 (t, $J$ = 7.0 Hz, 1H), 7.40 (d, $J$ = 8.3 Hz, 2H), 3.98–3.91 (m, 2H), 1.55 (dt, $J$ = 15.3, 7.7 Hz, 2H), 1.16 (dt, $J$ = 14.8, 7.4 Hz, 2H), 0.77 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.0, 155.1, 146.9, 134.4, 134.3, 131.9, 129.5, 127.3, 127.1, 126.7, 124.2, 120.8, 45.7, 30.7, 19.9, 13.4. Anal. calcd for $C_{18}H_{17}BrN_2O$: C, 60.52; H, 4.80; N, 7.84. Found: C, 60.29; H, 4.65; N, 7.75.

**3-Butyl-2-(4-fluorophenyl)quinazolin-4(3*H*)-one (2p).** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.32–8.28 (m, 1H), 7.77–7.67 (m, 2H), 7.55–7.46 (m, 3H), 7.20 (t, $J$ = 8.6 Hz, 2H), 3.99–3.91 (m, 2H), 1.55 (dt, $J$ = 15.3, 7.6 Hz, 2H), 1.16 (dt, $J$ = 14.8, 7.4 Hz, 2H),

0.76 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 164.5, 162.0, 155.2, 146.9, 134.3, 131.6, 130.0, 129.9, 127.3, 127.1, 126.7, 120.8, 116.0, 115.8, 45.7, 30.7, 19.8, 13.4. Anal. calcd for $C_{18}H_{17}FN_2O$: C, 72.95; H, 5.78; N, 9.45. Found: C, 72.75; H, 5.90; N, 9.41.

**3-Benzyl-2-phenyl-1-propyl-2,3-dihydroquinazolin-4(1*H*)-one (4a).**[26] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (dd, $J$ = 7.7, 1.5 Hz, 1H), 7.49–7.05 (m, 11H), 6.87–6.78 (m, 1H), 6.57 (d, $J$ = 8.3 Hz, 1H), 5.76 (d, $J$ = 15.2 Hz, 1H), 5.31 (s, 1H), 3.58 (d, $J$ = 15.2 Hz, 1H), 3.18 (ddd, $J$ = 13.9, 8.2, 5.3 Hz, 1H), 2.90–2.79 (m, 1H), 1.37 (m, 2H), 0.73 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 162.5, 145.9, 138.4, 136.5, 133.7, 129.0, 128.9, 128.7, 128.7, 128.1, 127.64, 126.4, 117.9, 116.6, 112.7, 75.0, 50.8, 46.6, 20.3, 11.1. Anal. calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.59; H, 6.89; N, 7.64.

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