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An Aldehyde-Driven, Fe(0)-Mediated, One-Pot Reductive Cyclization: Direct Access to 5,6-Dihydro-quinazolino[4,3-*b*]quinazolin-8-ones and Photophysical Study

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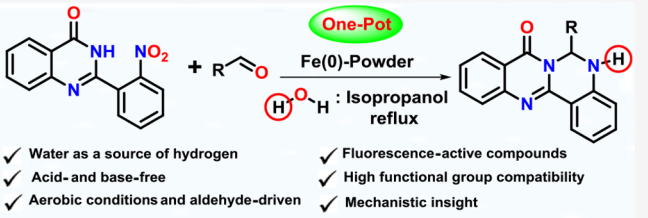
ABSTRACT: A short, proficient, and regioselective synthesis of biheterocyclic 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones has been revealed via an Fe(0)-powder-mediated, one-pot reductive cyclization protocol. Mechanistic investigation proved that water acts as a source of hydrogen for the reduction of the nitro group and the reaction rate was accelerated by an aldehyde. The designed transformation works under aerobic conditions, providing a series of bio-inspired molecular scaffolds. In addition, the photophysical study showed blue fluorescence emission with a good fluorescence quantum yield.



INTRODUCTION

Fused N-heteropolycycles are an important class of organic compounds which have gained sufficient attention due to their wide range of medicinal and pharmacological applications.[1] Specifically, quinazolinone and quinazolinone-fused compounds are reported to have a broad range of pharmacological roles, such as anti-inflammatory, anticancer, diuretic, anticonvulsant, and antihypertensive agents.[2] Some examples of natural products and bioactive molecules having a quinazolinone-fused tetracyclic framework, such as luotonin A, tryptanthrin, auranthine, and rutecarpine, have been depicted in Figure 1.[3−5]

Due to the extensive biological significance of quinazolinone-fused compounds (Figure 1), numerous synthetic methods have been established for the synthesis of such fused N-heterocycles. Among them, transition-metal-catalyzed reactions have gotten attention for the past few years.[6]

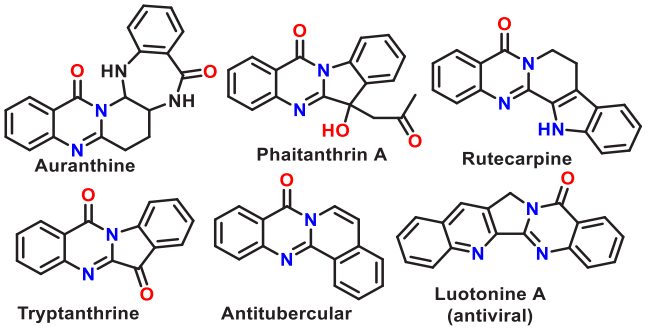


Figure 1. Bioactive quinazolinone-fused compounds.

Although sufficient progress has been made in this direction, the synthesis of those molecules using C−N-bond-forming reactions remains a challenge because C−N-bond-forming reactions require the use of expensive catalysts, harsh reaction conditions, and toxic reagents.[7−9] Thus, an efficient and straightforward strategy to synthesize quinazolinone-fused N-heterocycles is a challenging task for the synthetic organic chemist. It motivated us to develop an efficient protocol for the synthesis of those heteropolycyclic compounds via a cost-effective method.

In 2017, Feng and co-workers reported a Pd−Cu-catalyzed oxidative cyclization reaction for the synthesis of fused, polycyclic compounds through C−N and C−C bond formation starting from 2-phenyl-4(3H)-quinazolinone (Scheme 1).[10] Recently, in 2021, Malasala and co-workers reported a microwave-assisted, copper-mediated approach for the synthesis of fused quinazoline derivatives starting from 2-(2-bromophenyl)quinazolin-4(3H)-ones.[11] In the same year, Wang and co-workers unveiled a Ru(II)-catalyzed C−C/C−N annulation reaction for the synthesis of fused quinazolinones from 2-arylquinazolinones with vinylene (Scheme 1).[12] There are few approaches for the synthesis of those fused heteropolycyclic compounds starting from either 2-phenyl-quinazolin-4(3H)-ones or 2-(2-bromophenyl)quinazolin-4(3H)-ones; however, there is one report where 2-(2-

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Scheme 1. Previously Reported Approaches and Present Approach

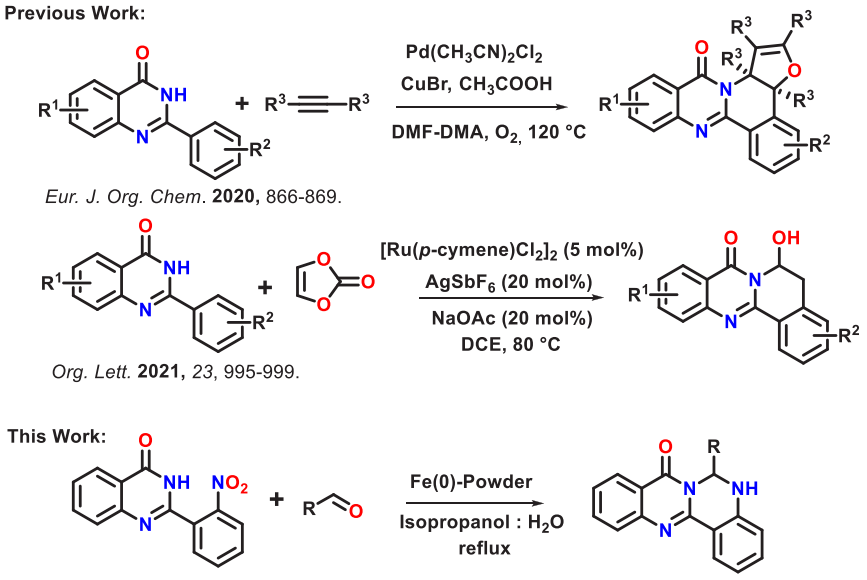
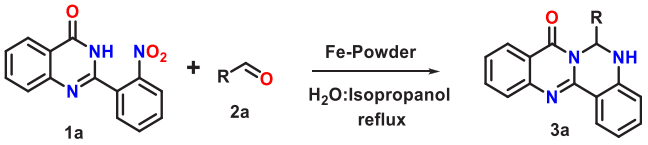


Table 1. Optimization of the Reaction Conditions[a]



entry	reagent	additives (equiv)	solvent	temp. (°C)	yield[b] (%)
1	$Cu(OAc)_2$ (20%)	$N_2H_4{\cdot}_2O$ (3)	DMSO	110	0
2	$Cu(OAc)_2$ (20%)	$N_2H_4{\cdot}_2O$ (3)	iPrOH	110	0
3	$Cu(OAc)_2$ (20%)	$NaBH_4$ (2)	iPrOH	110	25
4	$Cu(OAc)_2$ (20%)	$NaBH_4$ (4)	iPrOH	110	40
5	$Cu(OAc)_2$ (20%)	KOtBu (1.2)	iPrOH	110	30
6	$Cu(OAc)_2$ (20%)	KOtBu (3)	iPrOH	110	37
7	$Cu(OAc)_2$ (50%)	KOtBu (3)	iPrOH	110	35
8	$Pd(OAc)_2$ (10%)	KOtBu (1.2)	iPrOH	110	20
9	$Pd(OAc)_2$ (10%)	KOtBu (3)	iPrOH	110	23
10	$Pd(OAc)_2$ (20%)	KOtBu (3)	iPrOH	110	25
11	$Cu(OAc)_2$ (20%)	-	iPrOH	110	0
12	$Cu(OAc)_2$ (20%)	KOtBu (1.2)	DMSO	110	trace
13	$Cu(OAc)_2$ (20%)	KOtBu (1.2)	DMA	110	trace
14	$Cu(OAc)_2$ (20%)	NH_4Cl (1.5)	iPrOH	110	trace
15	Fe (20%)	NH_4Cl (3)	iPrOH	110	30
16	Fe (1 equiv)	NH_4Cl (3)	iPrOH	110	35
17	Fe (3 equiv)	NH_4Cl (3)	iPrOH	110	71
18	Fe (20%)	-	iPrOH:H_2O (4:1)	110	32
19	Fe (1 equiv)	-	iPrOH:H_2O (4:1)	110	52
20	Fe (3 equiv)	-	iPrOH:H_2O(4:1)	110	83
21	-	-	iPrOH:H_2O (4:1)	110	0

[a]**1a** (1.0 mmol), Fe powder (3 equiv), aldehydes (1.5 equiv), 2 mL of isopropanol, 0.5 mL of H_2O, 110 °C, 12−24 h. [b]Isolated yield.

nitrophenyl)quinazolin-4(3H)-one was used as a starting material for the synthesis of 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones.[13] This reaction's limitations were that it was applied to only primary alcohols, required a large excess of $SnCl_2$, and had a limited substrate scope. Therefore, the development of an efficient and convenient method for the synthesis of fused, heteropolycyclic compounds is desirable.

Iron is the least expensive and nearly the least hazardous element compared to other metals on the periodic table; however, it has not been used much in organic synthesis as a reaction mediator. This is probably because iron is not very reactive and there are not any good ways to make it more reactive.[14] Among the iron-based reagents, mostly Fe/HCl and Fe/NH_4Cl are used for the reduction of nitro groups.[15] From a modern perspective, those reagents are certainly not environmentally friendly.

Herein, we disclose an efficient and regioselective one-pot protocol for the synthesis of novel biheterocyclic 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones starting from 2-(2-nitrophenyl)quinazolin-4(3H)-one. The reaction proceeded

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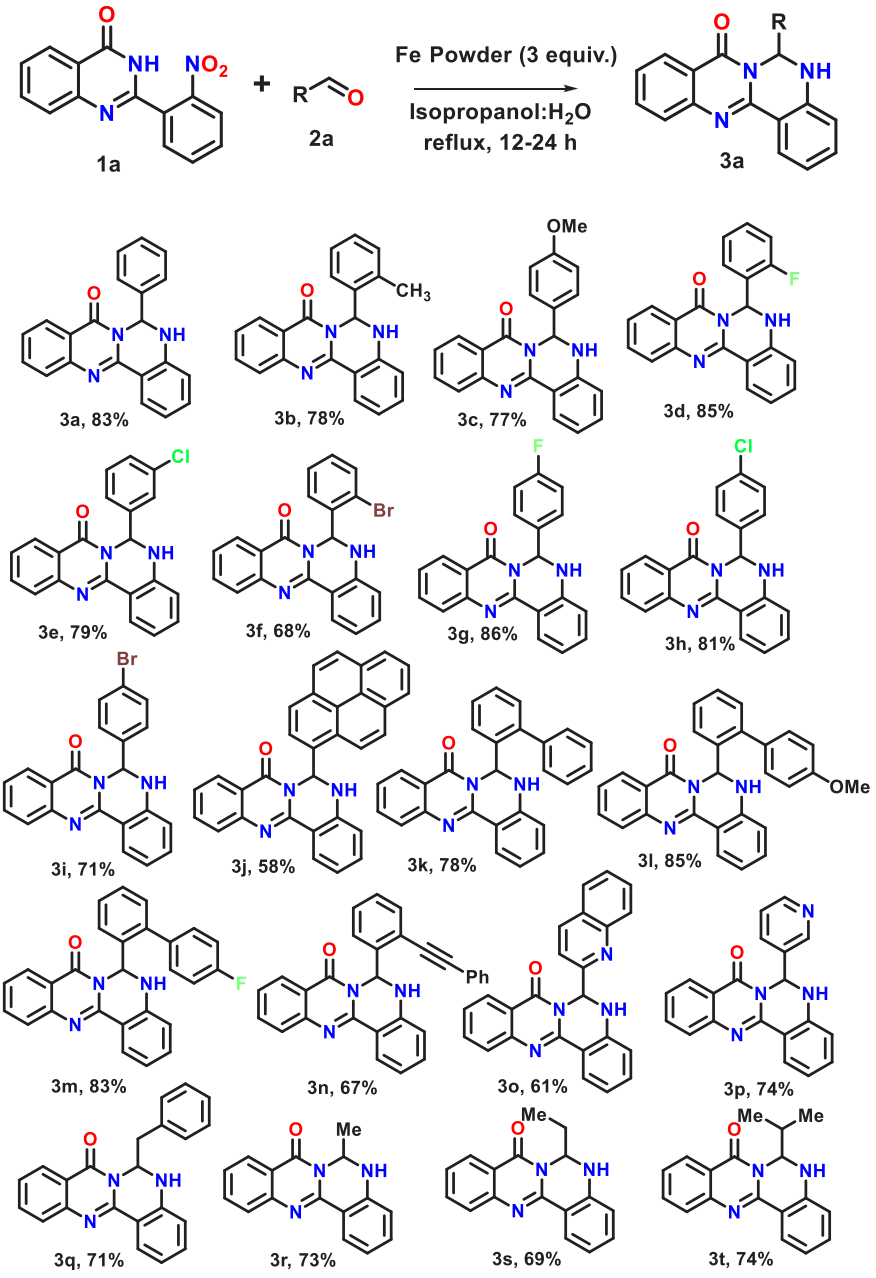
Scheme 2. Substrate Scope of the Reaction



through an iron-mediated, one-pot reductive cyclization process. Mechanistic studies indicate that water was acting as a source of hydrogen for the reduction of the nitro group, which was proven by the deuterium-labeling experiment. In this reaction, aldehyde had a crucial role, which accelerated the conversion of the starting material to the product. The substrate scope of the reaction, functional group tolerance, and photophysical studies of the synthesized, novel compounds are unveiled in this study.

RESULTS AND DISCUSSION

As a continuation of our ongoing efforts toward the synthesis of fused N-heterocycles[16] and their photophysical studies,[16a] we developed a one-pot synthesis of quinazolinone starting from 2-nitrobenzaldehyde with an aldehyde.[16b] We were interested in constructing quinazolinone-fused N-heterocycles. Toward this, our work was initiated with 2-(2-nitrophenyl)-quinazolin-4(3H)-one (**1a**)[16c] as a starting material. At the beginning, compound **1a** was subjected to various reaction conditions to obtain the desired product. Based on previous studies, compound **1a** was reacted with $Cu(OAc)_2$ (20 mol %), $N_2H_4{\cdot}H_2O$ (3 equiv), and benzaldehyde (1.2 equiv) in a DMSO solvent at 110 °C to get the desired product (Table 1, entry 1). However, the reaction did not result in the formation of the product; instead, a complex TLC was observed. Changing the solvent to isopropyl alcohol also did not result in product formation (Table 1, entry 2). When $N_2H_4{\cdot}H_2O$ was replaced with $NaBH_4$ in an isopropyl alcohol solvent, the desired product was formed with a 25% conversion of the starting material to the product. Doubling the number of equivalents of $NaBH_4$ resulted in a slight increase in the yield of the reaction (Table 1, entry 4). The reaction was also performed with a stoichiometric and excess amount of $Cu(OAc)_2$, but the yield was not improved. Under the basic

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medium, in the presence of KOtBu, the reaction gave only 30% conversion to the product (Table 1, entry 5). Changes in the number of equivalents of KOtBu or $Cu(OAc)_2$ or the addition of other metal catalysts did not improve the results (Table 1, entries 6−10). In the presence of only a copper catalyst, the reaction did not yield the product (Table 1, entry 11). Changing the solvent to DMSO or DMA and adding NH_4Cl instead of KOtBu led to the formation of a small amount of the product (Table 1, entries 12−14). In the presence of Fe powder and NH_4Cl in an isopropanol solvent, the reaction produced a higher yield (Table 1, entries 15−17). A solvent system of isopropyl alcohol and water (4:1) gave a good yield in the absence of NH_4Cl (Table 1, entries 18−20). The reaction did not give rise to product formation in the absence of Fe powder (Table 1, entry 21). The best yield was observed in the presence of 3 equiv of Fe powder in an isopropanol:-water (4:1) solvent system (Table 1, entry 20). Finally, the reaction was performed with only an isopropanol:water (4:1) solvent system, but a better yield was not observed.

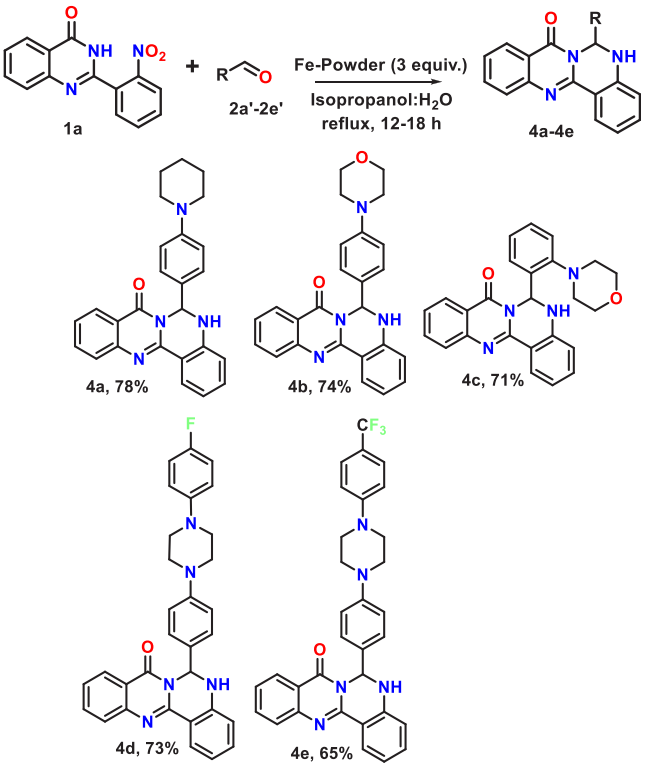
Various other solvents (such as MeOH, EtOH, tBuOH, HFIP, 1,4-dioxane, THF, DMF, DCE, DMAc, acetonitrile, toluene, and xylene) were also screened; however, those solvents did not give rise to a better yield. After having optimized the reaction conditions (Fe powder (3 equiv), aldehydes (1.5 equiv), 2.5 mL of isopropanol, 0.5 mL of H_2O, 110 °C), various electronically and sterically varied aldehydes (**2a**) were reacted with 2-(2-nitrophenyl)quinazolin-4(3H)-one (**1a**) to see the substrate diversity of the reaction. A series of quinazolinone-fused heterocycles (**3**) were obtained smoothly with yields of 58−86% (Scheme 2). Substrates containing electron-donating groups afforded the corresponding products (**3b** and **3c**) in 78% and 77% yields, respectively. Substrates containing halogen atoms produced the corresponding products (**3d**−**3i**) in 68−86% yields.

A highly conjugated polycyclic-ring-containing substrate (**3j**) was also synthesized; however, the yield of the reaction was much lower (58%). This low yield could be explained by the lower reactivity of the polycyclic, conjugated starting aldehyde (**2j**). The reaction was further explored for the synthesis of novel bi-aryl electron-donating and electron-withdrawing-group-containing compounds (**3k**−**3m**) with yields of 78−85%. Heterocyclic aldehydes (**2o** and **2p**) also reacted smoothly to give the corresponding products (**3o** and **3p**) in 61% and 74% yields, respectively. The reaction was also well-suited for the aliphatic aldehydes and gave the corresponding products (**3q** and **3t**) with 69−74% yields.

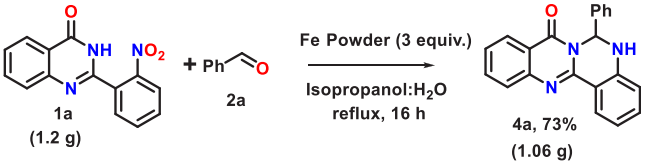
Synthesis of Bio-Inspired Molecular Scaffolds. Compounds containing derivatives of piperidine,[17] morpholine,[18] or piperazine[19] are prone to show antitubercular activities.[19,20] Considering their biological importance, we attempted to synthesize dihydro-quinazolino[4,3-*b*]quinazolin-8-one derivatives containing a piperidine, morpholine, or piperazine motif to study their fluorescence properties. Toward this, a series of aldehydes (**2a′**−**2e′**) were synthesized and subjected to a reaction with compound **1a**. It was found that those aldehydes (**2a′**−**2e′**) reacted smoothly with compound **1a**, giving the corresponding products (**4a**−**4e**) in 65−78% yields (Scheme 3).

To see the applicability of the reaction in gram-scale synthesis, the reaction was carried out with 1.2 g of the starting material under standardized conditions (Scheme 4). It was observed that the reaction went smoothly to give the corresponding product in a 73% yield, which suggests that

Scheme 3. Synthesis of Bio-Inspired Molecular Scaffolds



Scheme 4. Gram-Scale Synthesis



this is a scalable method for the synthesis of dihydro-quinazolino[4,3-*b*]quinazolin-8-ones.

To understand the mechanism of the reaction, control experiments were conducted, as shown in Scheme 5. The reaction was conducted in the absence of aldehyde, and it was observed that only the nitro group was reduced to give product **5** (Scheme 5, (i)). This experiment indicates that intermediate **5** is formed during the reaction. However, conversion of the starting material **1a** to the intermediate **5** was only 30% after 24 h. The addition of the aldehyde to the reaction mixture resulted in its complete conversion into the product, indicating that the aldehyde is accelerating the reaction rate by reacting with an amine (**5**), formed in situ, in the reaction medium. Further, the reaction did not give rise to product formation in the absence of H_2O, indicating the essential role of water in the reaction medium (Scheme 5, (ii)). When the reaction was performed in the absence of an aldehyde and in the presence of a D_2O:isopropanol solvent system, deuterated product **5D** was formed (Scheme 5, (iii)), which clearly indicates that, during the reduction process, hydrogen came from water. From that, it can be stated that H_2O is used as a source of hydrogen in the reduction process to form intermediate **5** from the starting material **1a**. The reaction produced the desired product in good yield in the presence of BTH, proving that it does not proceed via a radical pathway (Scheme 5, (iv)). Therefore, it can be stated that the reaction is going through an electron

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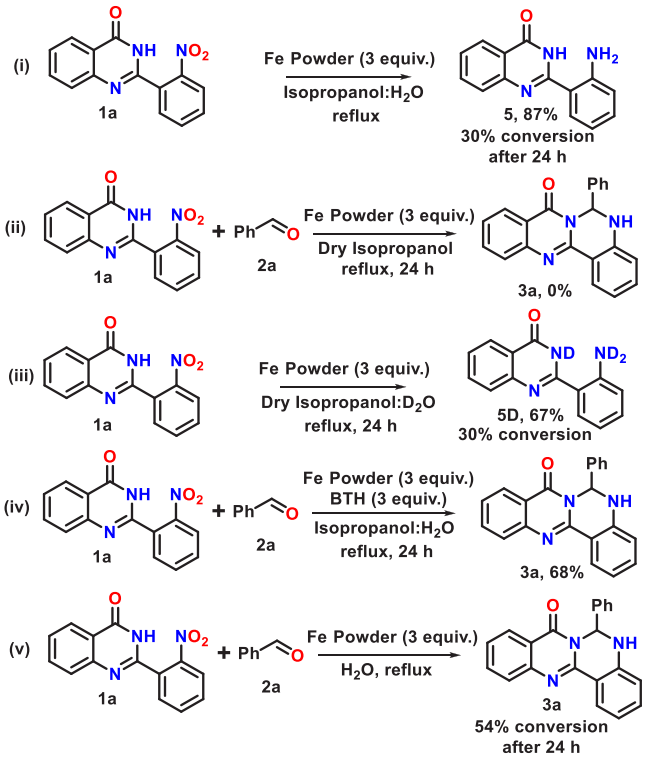
Scheme 5. Control Experiments



transfer mechanism. The reaction resulted in 54% conversion to the product when it was conducted only in water in the absence of 2-propanol (Scheme 5, (v)). This could be explained by the lower solubility of the starting material in water.

Based on the control experiments and earlier literature reports, a mechanism is proposed in Scheme 6. In the first step, the nitro group present in compound **1a** is reduced to form an amine intermediate (**I**) in the presence of Fe powder and water via an electron transfer mechanism. Then this amine intermediate (**I**) reacts with aldehydes (**2a**) to form an imine intermediate (**II**), which undergoes intramolecular cyclization to form the desired product (**3a**).

Photophysical Studies. With the diverse 5,6-dihydroquinazolino[4,3-*b*]quinazolin-8-ones in hand, we turned our attention to the study of the photophysical properties of those synthesized compounds (**3j**−**4e**) as shown in Table 2.

Table 2. Photophysical Properties of the Products

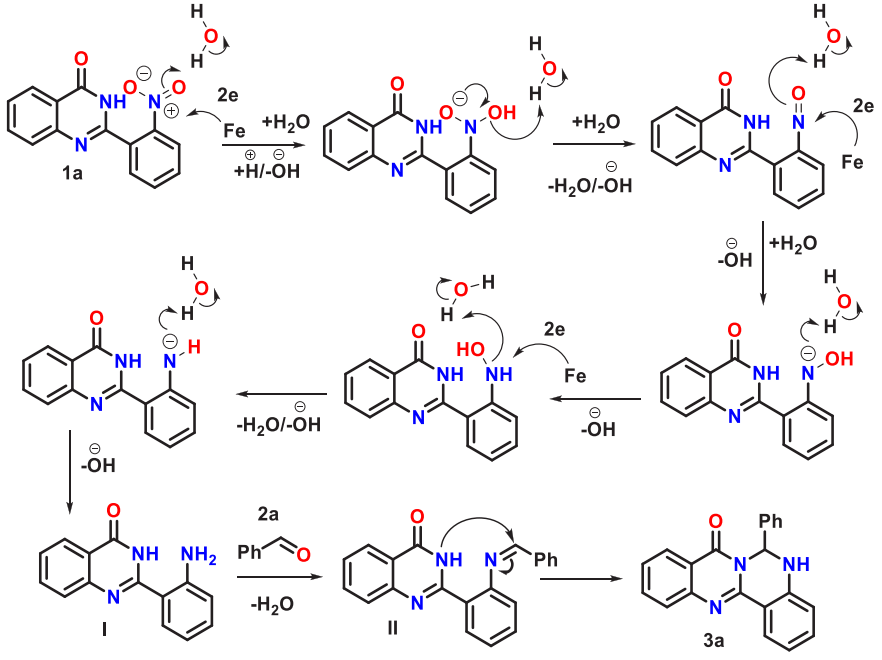
compounds	λ_{absmax} [a] (nm)	λ_{emmax} [b] (nm)	log ε	Φ_F [c]
3j	279	438	4.44	0.28
3k	305	438	4.51	0.39
3l	305	439	4.45	0.72
3m	279	434	4.28	0.22
3n	286	435	4.80	0.27
3o	303	438	4.35	0.06
3p	295	432	4.86	0.15
3q	306	432	4.89	0.17
4a	307	493	4.57	0.14
4b	271	442	4.54	0.20
4c	305	440	4.81	0.12
4d	297	443	4.45	0.13
4e	266	442	4.96	0.45

[a]Absorption maxima in DCM (5×10^{-6} mol/L). [b]Emission maxima in DCM (5×10^{-6} mol/L). [c]Fluorescence quantum yield, determined by quinine sulfate (Φ_F = 0.546 in H_2SO_4).

Fluorescence emission spectra and UV−vis spectra of the synthesized novel compounds (**3j**−**4e**) were measured in DCM at a 5×10^{-6} mol/L concentration. The fluorescence emission spectra of the compounds are presented in Figure 2.

The UV−vis study showed that the absorption band of compounds **3j**−**4e** covers 250−430 nm and consists of two to three absorption peaks, which are ascribed to $\pi-\pi^*$ and $n-\pi^*$ charge transfer transitions. The compounds (**3j**−**4e**) have

Scheme 6. Proposed Mechanism



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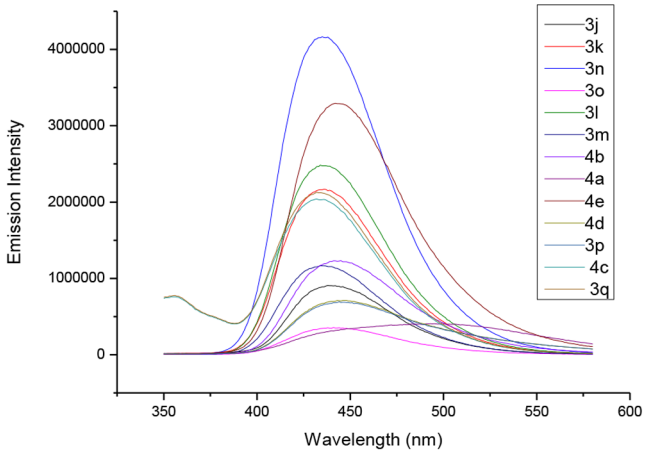

Figure 2. Emission spectra of compounds **3j**–**4e** in DCM (5×10^{-6} mol/L).

shown a blue fluorescence emission with a quantum yield (Φ_F) up to 0.72. A bathochromic shift in absorption wavelength was observed for compound **4a**. Exceptionally high emission maxima (493 nm) were observed for compound **4a** compared to others with a quantum yield (Φ_F) of 0.14. Compound **4e** has shown the minimum absorption wavelength with a quantum yield (Φ_F) of 0.45. The maximum quantum yield ($\Phi_F = 0.72$) was observed for compound **3l** with an absorption wavelength of 305 nm.

CONCLUSIONS

In conclusion, we have developed an efficient and regioselective one-pot protocol for the synthesis of novel biheterocyclic 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones starting from 2-(2-nitrophenyl)quinazolin-4(3H)-one. The reaction proceeded through an iron-powder-mediated, one-pot reductive cyclization process. Mechanistic studies revealed that water was acting as a source of hydrogen for the reduction of the nitro group, which was proven by the deuterium-labeling experiment. In this reaction, the aldehyde had played a significant role, accelerating the reduction process by converting an amine, formed in situ, to the product. The reaction has shown a wide substrate scope with a high yield and a high functional group tolerance. In addition, several bio-inspired molecular scaffolds have also been synthesized. The photophysical properties of the synthesized fused compounds were studied and found to show blue fluorescence emission with a moderate to good fluorescence quantum yield. The outcomes provided here might be of great relevance in the fields of medicinal chemistry and materials science.

EXPERIMENTAL SECTION

General Information. All chemicals, unless otherwise stated, were purchased from commercial suppliers and utilized without additional purification. Silica gel with a mesh size of 100–200 was used for column chromatography purifications. Without additional purification, commercial-grade chemicals and solvents were used. Experiments involving moisture- or air-sensitive chemicals were carried out in oven-dried glassware under positive nitrogen or argon pressure and using freshly distilled solvents. Merck 60 F254 precoated silica gel plates of 0.2 mm thickness were used for analytical thin-layer chromatography (TLC). During elution of the column, TLC plates were viewed using UV radiation (254 nm) on a Spectroline model ENF-24061/F 254 nm instrument. Flash chromatography was carried out with the specified solvent system and 60–120 mesh silica gel. Typically, columns were packed as slurry and pre-equilibrated with the appropriate solvent system before use. High-resolution mass spectral analysis (HRMS) was carried out on a Bruker Daltonics MicroTOF-Q-II mass spectrometer using MeOH as a solvent, and an electrospray ionization (ESI) positive method was used. A Bruker 400 NMR spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) was used to record the ^{1}H NMR and ^{13}C{^{1}H} NMR spectra of the synthesized compounds. For ^{1}H NMR spectra, chemical shifts are reported as δ in units of parts per million (ppm) relative to the signal of chloroform-*d* (δ 7.26, singlet). Multiplicities were given as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), or m (multiplet). For a given resonance, the number of protons (*n*) is indicated by *n*H. Coupling constants (*J* value) are reported in hertz (Hz). For ^{13}C{^{1}H} NMR spectra, chemical shifts are reported as δ in units of parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.0, triplet).

Synthesis of Compound 1a.[16c] Anthranilamide (1 mmol), substituted benzaldehydes (1.1 mmol), and $CuCl_2 \cdot 2H_2O$ (2 mmol) in ethanol (15 mL) were added to an oven-dried, round-bottom flask. The reaction mixture was then refluxed for 16 h in an oil bath, and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and distilled water was added until precipitates formed. The precipitates were filtered and washed with distilled water. The product **1a** was obtained as a pale yellow solid: yield 88% (231 mg); R_f = 0.3 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (1 H, s), 8.20 (2 H, t, *J* = 9.0), 8.00–7.77 (4 H, m), 7.66 (1 H, d, *J* = 8.1), 7.57 (1 H, t, *J* = 7.5); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 161.9, 152.1, 149.0, 147.9, 135.1, 134.4, 132.0, 131.9, 129.6, 127.8, 127.6, 126.3, 125.0, 121.6.

General Procedure for the Synthesis of 5,6-Dihydro-8H-quinazolino[4,3-*b*]quinazolin-8-ones. One millimole of compound **1a**, 2 mL of isopropanol, 0.5 mL of H_2O, Fe powder (3 equiv), and substituted aldehydes of type **2** (1.5 equiv) were added to an oven-dried, round-bottom flask and allowed to reflux in an oil bath until completion (12–24 h, confirmed by TLC). After completion, the reaction mixture was extracted with ethyl acetate (10 mL) and water (10 mL). After separation of the aqueous and organic layers, the aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The combined organic layer was collected and washed with a brine solution (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude reaction mixture was purified by silica gel (100–200) column chromatography to obtain the desired product of type **3**.

Characterization Data for Products 3a–tand4a–e. *6-Phenyl-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**3a**).*[11] The compound **3a** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow solid: yield 83% (269 mg); R_f = 0.5 (20% EtOAc + pet ether); mp 167–169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (1 H, dd, *J* = 8.0, 1.2), 8.11 (1 H, dd, *J* = 7.9, 1.2), 7.99 (1 H, d, *J* = 3.7), 7.85 (1 H, ddd, *J* = 8.5, 7.2, 1.5), 7.73 (1 H, d, *J* = 7.7), 7.54–7.47 (1 H, m), 7.35–7.29 (1 H, m), 7.28–7.14 (6 H, m), 6.95–6.89 (1 H, m), 6.85–6.77 (1 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 148.2, 147.7, 145.6, 139.9, 135.5, 134.2, 129.0, 128.6, 127.7, 127.3, 127.1, 126.7, 126.1, 120.3, 119.2, 116.3, 116.0, 62.9; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{15}N_3ONa$ 348.1107, found 348.1113.

*6-(o-Tolyl)-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**3b**).* The compound **3b** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow solid: yield 78% (264 mg); R_f = 0.4 (20% EtOAc + pet ether); mp 229–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (1 H, dd, *J* = 8.0, 1.3), 8.06 (1 H, dd, *J* = 8.0, 1.2), 7.87–7.80 (1 H, ddd, *J* = 8.4, 7.1, 1.5), 7.76 (1 H, d, *J* = 7.7), 7.55 (1 H, d, *J* = 3.7), 7.49–7.43 (1 H, m), 7.31–7.24 (2 H, m), 7.22 (1 H, d, *J* = 7.4), 7.12 (1 H, td, *J* = 7.4, 1.0), 6.91 (1 H, t, *J* = 7.4), 6.87–6.80 (1 H, m), 6.75 (2 H, t, *J* = 7.9), 2.62 (3 H, s); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.8, 148.2, 148.1, 144.5, 138.6, 135.6, 135.4, 134.2, 131.5, 128.7, 127.7, 127.3, 126.8, 126.7, 126.5, 124.2, 120.3, 119.2,

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116.4, 115.7, 61.3, 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{17}N_3ONa$ 362.1264, found 362.1269.

*6-(4-Methoxyphenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**3c**).*[21] The compound **3c** was synthesized by the above-described method. The reaction took 14 h to complete, and the product was obtained as a yellowish solid: yield 77% (273 mg); R_f = 0.3 (20% EtOAc + pet ether); mp 231−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (1 H, dd, J = 8.0, 1.2), 8.11 (1 H, dd, J = 7.9, 1.2), 7.92 (1 H, d, J = 3.6), 7.88−7.81 (1 H, m), 7.72 (1 H, d, J = 7.9), 7.54−7.46 (1 H, m), 7.36−7.28 (1 H, m), 7.18 (1 H, d, J = 3.5), 7.07 (2 H, d, J = 8.7), 6.90 (1 H, d, J = 7.8), 6.85−6.76 (3 H, m), 3.62 (3 H, s); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 159.5, 148.1, 147.7, 145.6, 135.4, 134.1, 131.8, 127.7, 127.4, 127.3, 127.1, 126.7, 120.3, 119.2, 116.3, 116.0, 114.3, 62.6, 55.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{18}N_3O_2$ 356.1394, found 356.1399.

*6-(2-Fluorophenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**3d**).*[22] The compound **3d** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow solid: yield 85% (291 mg); R_f = 0.5 (20% EtOAc + pet ether); mp 201−203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (1 H, dd, J = 7.9, 1.2), 8.09 (1 H, dd, J = 8.0, 1.2), 7.85 (1 H, m), 7.75 (2 H, d, J = 7.6), 7.52−7.45 (1 H, m), 7.36 (1 H, d, J = 3.6), 7.34−7.27 (2 H, m), 7.26−7.18 (1 H, ddd, J = 10.7, 8.2, 0.9), 7.03−6.96 (1 H, m), 6.93−6.80 (3 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.8 (d, J = 245), 159.7, 148.1, 147.9, 144.7, 135.5, 134.2, 131.1 (d, J = 9), 127.7, 127.3, 127.1 (d, J = 9), 127.0, 126.9, 126.8, 125.0 (d, J = 3), 120.3, 119.4, 116.5 (d, J = 21), 116.3, 115.5, 59.1 (d, J = 4); ^{19}F NMR (377 MHz, DMSO-d_6) δ −117.7; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{14}N_3OFNa$ 366.1013, found 366.1019.

*6-(3-Chlorophenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**3e**).*[23] The compound **3e** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a white solid: yield 79% (283 mg); R_f = 0.6 (20% EtOAc + pet ether); mp 173−175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (1 H, dd, J = 7.9, 1.1), 8.15−8.09 (1 H, m), 7.98 (1 H, d, J = 3.6), 7.92−7.83 (1 H, m), 7.74 (1 H, d, J = 8.1), 7.52 (1 H, t, J = 7.5), 7.39−7.22 (5 H, m), 7.01 (1 H, d, J = 7.4), 6.94 (1 H, d, J = 8.1), 6.84 (1 H, t, J = 7.6); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 148.1, 147.4, 145.3, 142.5, 135.6, 134.3, 133.8, 131.0, 128.7, 127.8, 127.4, 127.1, 126.8, 126.3, 124.7, 120.3, 119.5, 116.4, 116.0, 62.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{15}ClN_3O$ 360.0898, found 360.0904.

*6-(2-Bromophenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**3f**).* The compound **3f** was synthesized by the above-described method. The reaction took 13 h to complete, and the product was obtained as a yellowish solid: yield 68% (274 mg); R_f = 0.6 (60% EtOAc + pet ether); mp 198−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (1 H, dd, J = 8.2, 1.3), 8.07 (1 H, dd, J = 8.0, 1.1), 7.89−7.81 (1 H, m), 7.77 (1 H, d, J = 7.7), 7.68 (1 H, dd, J = 7.8, 1.2), 7.62 (1 H, d, J = 3.9), 7.50−7.44 (1 H, m), 7.37 (1 H, d, J = 3.9), 7.32−7.26 (1 H, m), 7.24−7.10 (2 H, m), 6.90−6.82 (3 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.7, 148.1, 147.9, 144.0, 138.7, 135.5, 134.2, 133.9, 130.9, 128.5, 127.7, 127.3, 126.9, 126.8, 126.2, 122.0, 120.3, 119.5, 116.8, 115.7, 63.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{15}BrN_3O$ 404.0393, found 404.0399.

*6-(4-Fluorophenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**3g**).*[11] The compound **3g** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow solid: yield 86% (249 mg); R_f = 0.5 (20% EtOAc + pet ether); mp 161−163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (1 H, dd, J = 8.0, 1.2), 8.11 (1 H, dd, J = 7.9, 1.2), 7.97 (1 H, d, J = 3.7), 7.85 (1 H, ddd, J = 8.5, 7.2, 1.5), 7.73 (1 H, d, J = 7.8), 7.54−7.47 (1 H, m), 7.36−7.30 (1 H, m), 7.26−7.17 (3 H, m), 7.13−7.04 (2 H, m), 6.92 (1 H, d, J = 7.9), 6.86−6.78 (1 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 162.2 (d, J = 243), 160.1, 148.1, 147.5, 145.4, 136.17 (d, J = 3), 135.5, 134.2, 128.34 (d, J = 8), 127.7, 127.4, 127.1, 126.8, 120.3, 119.4, 116.4, 115.9 (d, J = 22), 115.8, 62.4; ^{19}F NMR (377 MHz, DMSO-d_6) δ −113.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{15}FN_3ONa$ 366.1013, found 366.1019.

*6-(4-Chlorophenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**3h**).*[24] The compound **3h** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a yellowish solid: yield 81% (290 mg); R_f = 0.5 (60% EtOAc + pet ether); mp 247−249 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (1 H, dd, J = 8.0, 1.2), 8.11 (1 H, dd, J = 8.0, 1.3), 7.98 (1 H, d, J = 3.7), 7.86 (1 H, ddd, J = 8.5, 7.2, 1.5), 7.74 (1 H, d, J = 7.7), 7.55−7.48 (1 H, m), 7.37−7.29 (3 H, m), 7.24 (1 H, d, J = 3.7), 7.18 (2 H, d, J = 8.5), 6.92 (1 H, d, J = 7.7), 6.87−6.79 (1 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 148.1, 147.5, 145.3, 138.9, 135.5, 134.2, 133.3, 129.1, 128.1, 127.7, 127.4, 127.1, 126.8, 120.3, 119.5, 116.4, 116.0, 62.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{15}ClN_3O$ 360.0898, found 360.0903.

*6-(4-Bromophenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**3i**).*[11] The compound **3i** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow solid: yield 71% (286 mg); R_f = 0.6 (20% EtOAc + pet ether); mp 162−165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (1 H, dd, J = 8.0, 1.2), 8.10 (1 H, dd, J = 7.9, 1.2), 7.97 (1 H, d, J = 3.7), 7.86 (1 H, ddd, J = 8.5, 7.2, 1.5), 7.73 (1 H, d, J = 7.9), 7.55−7.49 (1 H, m), 7.48−7.43 (2 H, m), 7.37−7.30 (1 H, m), 7.21 (1 H, d, J = 3.7), 7.11 (2 H, d, J = 8.4), 6.91 (1 H, d, J = 7.8), 6.87−6.79 (1 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 148.1, 147.5, 145.3, 139.3, 135.6, 134.3, 132.0, 128.4, 127.7, 127.4, 127.1, 126.8, 121.9, 120.3, 119.5, 116.4, 116.0, 62.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{15}BrN_3O$ 404.0393, found 404.0398.

*6-(Pyren-1-yl)-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**3j**).* The compound **3j** was synthesized by the above-described method. The reaction took 22 h to complete, and the product was obtained as a yellow solid: yield 58% (260 mg); R_f = 0.4 (20% EtOAc + pet ether); mp 191−193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (1 H, d, J = 9.4), 8.42 (2 H, dd, J = 11.2, 8.5), 8.36−8.27 (3 H, m), 8.18−8.10 (2 H, m), 8.08−8.00 (3 H, m), 7.92−7.81 (3 H, m), 7.53−7.44 (2 H, m), 7.26−7.17 (1 H, m), 6.85 (1 H, t, J = 7.5), 6.70 (1 H, d, J = 8.1); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.0, 148.5, 148.3, 144.5, 135.5, 134.1, 133.7, 131.28, 131.23, 130.6, 128.7, 128.2, 127.8, 127.6, 127.5, 127.4, 127.0, 126.9, 126.7, 126.2, 126.0, 125.1, 124.7, 124.2, 123.4, 122.3, 120.5, 119.3, 116.6, 115.8, 61.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{31}H_{20}N_3O$ 450.1601, found 450.1607.

*6-([1,1′-Biphenyl]-2-yl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**3k**).* The compound **3k** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as an off-white solid: yield 78% (312 mg); R_f = 0.7 (20% EtOAc + pet ether); mp 224−226 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29−8.22 (1 H, m), 8.02 (1 H, dd, J = 7.9, 1.1), 7.85−7.79 (1 H, m), 7.73 (1 H, d, J = 8.0), 7.65 (2 H, d, J = 7.1), 7.56 (2 H, t, J = 7.5), 7.51−7.40 (2 H, m), 7.35−7.27 (2 H, m), 7.21 (1 H, d, J = 7.1), 7.18−7.09 (3 H, m), 6.94 (1 H, d, J = 3.4), 6.87 (1 H, t, J = 7.2), 6.81 (1 H, d, J = 8.1); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.8, 148.0, 147.9, 144.2, 140.9, 140.4, 138.4, 135.4, 134.1, 131.3, 129.9, 128.9, 128.8, 128.4, 127.9, 127.6, 127.2, 126.8, 126.7, 124.6, 120.5, 119.3, 116.8, 115.5, 62.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{20}N_3O$ 402.1601, found 402.1606.

*6-(4′-Methoxy-[1,1′-biphenyl]-2-yl)-5,6-dihydro-8H-quinazolino-[4,3-b]quinazolin-8-one (**3l**).* The compound **3l** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a yellow liquid: yield 85% (366 mg); R_f = 0.7 (30% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (1 H, dd, J = 7.9, 1.2), 8.02 (1 H, dd, J = 8.0, 1.2), 7.85−7.78 (1 H, m), 7.73 (1 H, d, J = 7.9), 7.57 (2 H, d, J = 8.7), 7.47−7.40 (1 H, m), 7.33−7.24 (2 H, m), 7.17 (2 H, dd, J = 9.8, 5.4), 7.14−7.05 (4 H, m), 6.93 (1 H, d, J = 3.5), 6.89−6.83 (1 H, m), 6.80 (1 H, d, J = 8.1), 3.85 (1 H, s); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.8, 159.1, 148.09, 148.02, 144.3, 140.7, 138.5, 135.4, 134.1, 132.6, 131.5, 131.0, 128.8, 128.0, 127.6, 127.2, 126.8, 126.6, 124.5, 120.5, 119.3, 116.7,

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115.5, 114.3, 62.0, 55.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{22}N_3O_2$ 432.1707, found 432.1712.

*6-(4′-Fluoro-[1,1′-biphenyl]-2-yl)-5,6-dihydro-8H-quinazolino-[4,3-b]quinazolin-8-one (**3m**).* The compound **3m** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow solid: yield 83% (347 mg); R_f = 0.7 (30% EtOAc + pet ether); mp 171−173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (1 H, dd, J = 7.9, 1.2), 8.02 (1 H, dd, J = 8.0, 1.2), 7.85−7.79 (1 H, m), 7.73 (1 H, d, J = 7.9), 7.70−7.64 (2 H, m), 7.48−7.35 (3 H, m), 7.34−7.28 (2 H, m), 7.20 (1 H, d, J = 6.8), 7.18−7.07 (3 H, m), 7.03 (1 H, d, J = 3.6), 6.90−6.84 (1 H, m), 6.78 (1 H, d, J = 8.1); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 162.23 (d, J = 243), 159.8, 148.0, 147.9, 144.2, 139.8, 138.5, 136.74 (d, J = 4), 135.4, 134.1, 131.91 (d, J = 8), 131.4, 128.9, 128.6, 127.6, 127.2, 126.8, 126.7, 124.6, 120.4, 119.3, 116.7, 115.6 (d, J = 21), 115.56, 61.9; ^{19}F NMR (377 MHz, DMSO-d_6) δ −115.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{19}FN_3O$ 420.1507, found 420.1512.

*6-(2-(Phenylethynyl)phenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**3n**).* The compound **3n** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as an off-white solid: yield 67% (284 mg); R_f = 0.7 (20% EtOAc + pet ether); mp 173−175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (1 H, dd, J = 7.9, 1.0), 8.07 (1 H, dd, J = 7.9, 1.1), 7.88−7.80 (1 H, m), 7.76 (1 H, d, J = 7.8), 7.73−7.67 (2 H, m), 7.65−7.59 (2 H, m), 7.57 (1 H, d, J = 3.5), 7.52−7.43 (4 H, m), 7.34−7.26 (2 H, m), 7.17 (1 H, td, J = 7.7, 1.1), 6.97 (1 H, d, J = 7.7), 6.91−6.83 (2 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.8, 148.1, 148.0, 144.5, 141.9, 135.4, 134.1, 133.3, 132.1, 129.5, 129.2, 129.1, 127.7, 127.3, 126.8, 126.7, 124.6, 122.7, 121.1, 120.4, 119.4, 116.7, 116.1, 115.8, 95.3, 87.0, 62.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{29}H_{20}N_3O$ 426.1601, found 426.1606.

*6-(Quinolin-2-yl)-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**3o**).* The compound **3o** was synthesized by the above-described method. The reaction took 18 h to complete, and the product was obtained as a yellowish solid: yield 61% (229 mg); R_f = 0.4 (30% EtOAc + pet ether); mp 242−245 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (1 H, d, J = 8.6), 8.17 (1 H, dd, J = 7.9, 1.2), 8.13−8.06 (2 H, m), 7.92−7.84 (2 H, m), 7.77 (1 H, d, J = 7.8), 7.72 (1 H, d, J = 8.6), 7.63−7.57 (1 H, m), 7.56−7.47 (3 H, m), 7.36 (1 H, d, J = 3.9), 7.28−7.20 (1 H, m), 6.87 (1 H, d, J = 7.8), 6.81−6.72 (1 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.5, 157.9, 148.5, 148.4, 146.4, 144.9, 137.9, 135.3, 133.7, 130.4, 129.2, 128.2, 127.7, 127.3, 127.2, 127.0, 126.5, 120.5, 119.3, 119.1, 116.7, 116.3, 64.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{17}N_4O$ 377.1397, found 377.1399.

*6-(Pyridin-2-yl)-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**3p**).* The compound **3p** was synthesized by the above-described method. The reaction took 14 h to complete, and the product was obtained as a yellowish liquid: yield 74% (241 mg); R_f = 0.3 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (2 H, dd, J = 12.2, 2.8), 8.19 (1 H, dd, J = 7.9, 1.1), 8.16−8.09 (1 H, m), 8.00 (1 H, d, J = 3.6), 7.91−7.82 (1 H, m), 7.74 (1 H, d, J = 7.9), 7.56−7.48 (2 H, m), 7.40−7.31 (2 H, m), 7.28 (1 H, dd, J = 8.0, 4.8), 6.95 (1 H, d, J = 8.0), 6.89−6.81 (1 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 149.9, 148.1, 147.6, 147.4, 145.2, 135.6, 135.4, 134.3, 134.0, 127.8, 127.4, 127.1, 126.9, 124.1, 120.3, 119.6, 116.5, 116.0, 61.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{15}N_4O$ 327.1240, found 327.1246.

*6-Benzyl-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**3q**).* The compound **3q** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a white solid: yield 71% (240 mg); R_f = 0.4 (20% EtOAc + pet ether); mp 229−231 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (1 H, d, J = 8.2), 8.11 (1 H, d, J = 7.9), 7.86−7.77 (1 H, m), 7.69 (1 H, d, J = 8.2), 7.46 (1 H, t, J = 7.5), 7.42−7.36 (1 H, m), 7.31−7.16 (4 H, m), 7.04 (2 H, d, J = 6.8), 6.86 (2 H, dd, J = 7.6, 5.1), 6.27−6.17 (1 H, m), 3.05 (1 H, dd, J = 13.2, 8.9), 2.81 (1 H, dd, J = 13.2, 3.9); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.5, 148.1, 147.3, 145.1, 136.4, 135.1, 134.1, 129.9, 128.8, 127.5, 127.4, 127.1, 126.8, 126.4, 120.5, 119.0, 116.5, 115.7, 63.4, 39.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{18}N_3O$ 340.1444, found 340.1450.

*6-Methyl-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**3r**).*[13] The compound **3r** was synthesized by the above-described method. The reaction took 12 h to complete and was obtained as a pale yellow liquid: yield 73% (191 mg); R_f = 0.6 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19−8.10 (2 H, m), 7.84−7.77 (1 H, m), 7.67 (1 H, d, J = 7.8), 7.50−7.42 (1 H, m), 7.40−7.31 (1 H, m), 7.11 (1 H, d, J = 2.9), 6.90−6.82 (2 H, m), 6.27−6.17 (1 H, m), 1.33 (3 H, d, J = 6.1); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.5, 148.2, 147.2, 145.6, 135.1, 134.0, 127.5, 127.4, 126.4, 126.8, 126.4, 120.5, 118.9, 116.4, 115.1, 59.3, 19.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3O$ 264.1131, found 264.1137.

*6-Ethyl-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**3s**).*[13] The compound **3s** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow liquid: yield 69% (191 mg); R_f = 0.5 (20% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19−8.10 (2 H, m), 7.85−7.76 (1 H, m), 7.68 (1 H, d, J = 8.0), 7.52−7.43 (1 H, m), 7.41−7.30 (2 H, m), 6.90 (1 H, d, J = 8.0), 6.85 (1 H, t, J = 7.5), 6.03−5.59 (1 H, m), 1.86−1.70 (1 H, m), 1.62−1.47 (1 H, m), 0.84 (3 H, t, J = 7.4); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.7, 148.1, 147.4, 145.4, 135.1, 134.0, 127.5, 127.4, 126.9, 126.4, 120.5, 118.8, 116.2, 115.7, 63.5, 26.1, 9.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{16}N_3O$ 278.1288, found 278.1293.

*6-Isopropyl-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**3t**).* The compound **3t** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow liquid: yield 74% (215 mg); R_f = 0.5 (20% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (2 H, dd, J = 7.9, 0.9), 7.85−7.76 (1 H, m), 7.68 (1 H, d, J = 8.0), 7.52−7.41 (2 H, m), 7.38−7.30 (1 H, m), 6.90 (1 H, d, J = 8.0), 6.85−6.78 (1 H, m), 5.84 (1 H, dd, J = 8.4, 3.7), 2.15−2.01 (1 H, m), 0.88 (3 H, d, J = 6.7), 0.70 (3 H, d, J = 6.8); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.2, 148.0, 147.6, 145.6, 135.1, 134.0, 127.5, 127.3, 127.1, 126.3, 120.5, 118.5, 115.9, 115.8, 66.7, 32.0, 18.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{18}N_3O$ 292.1444, found 292.1449.

*6-(4-(Piperidin-1-yl)phenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**4a**).* The compound **4a** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow liquid: yield 78% (318 mg); R_f = 0.4 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (1 H, dd, J = 8.0, 1.1), 8.14−8.09 (1 H, m), 7.88 (1 H, d, J = 3.5), 7.87−7.81 (1 H, m), 7.72 (1 H, d, J = 7.9), 7.53−7.45 (1 H, m), 7.36−7.28 (1 H, m), 7.14 (1 H, d, J = 3.5), 6.97 (2 H, d, J = 8.7), 6.89 (1 H, d, J = 8.0), 6.83−6.77 (1 H, m), 6.75 (2 H, d, J = 8.9), 3.06−2.96 (4 H, m), 1.54−1.39 (6 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 151.6, 148.2, 147.87, 145.8, 135.4, 134.1, 129.1, 127.6, 127.3, 127.1, 126.9, 126.6, 120.4, 119.0, 116.2, 115.9, 115.6, 62.7, 49.4, 25.4, 24.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{25}N_4O$ 409.2023, found 409.2029.

*6-(4-Morpholinophenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**4b**).* The compound **4b** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a pale yellow solid: yield 74% (303 mg); R_f = 0.5 (40% EtOAc + pet ether); mp 215−217 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (1 H, dd, J = 8.0, 1.2), 8.14−8.08 (1 H, m), 7.90 (1 H, d, J = 3.6), 7.88−7.82 (1 H, m), 7.72 (1 H, d, J = 8.0), 7.49 (1 H, dd, J = 11.0, 4.0), 7.36−7.27 (1 H, m), 7.16 (1 H, d, J = 3.5), 7.00 (2 H, d, J = 8.8), 6.90 (1 H, d, J = 7.9), 6.85−6.74 (3 H, m), 3.68−3.59 (4 H, m), 3.03−2.93 (4 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 151.2, 148.2, 147.8, 145.8, 135.4, 134.1, 130.1, 127.7, 127.3, 127.1, 126.9, 126.6, 120.4, 119.0, 116.3, 116.0, 115.1, 66.4, 62.7, 48.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{23}N_4O_2$ 411.1816, found 411.1821.

*6-(2-Morpholinophenyl)-5,6-dihydro-8H-quinazolino[4,3-b]-quinazolin-8-one (**4c**).* The compound **4c** was synthesized by the above-described method. The reaction took 14 h to complete, and the

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product was obtained as yellow solid: yield 71% (291 mg); R_f = 0.4 (20% EtOAc + pet ether); mp 228−230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (1 H, d, J = 7.3), 8.07 (1 H, dd, J = 7.9, 1.1), 7.89−7.82 (1 H, m), 7.76 (1 H, d, J = 7.9), 7.62 (1 H, d, J = 3.1), 7.51−7.44 (1 H, m), 7.39 (1 H, d, J = 7.5), 7.31−7.19 (2 H, m), 7.04 (1 H, d, J = 3.1), 6.91 (1 H, t, J = 7.3), 6.82 (2 H, t, J = 7.5), 6.74 (1 H, dd, J = 7.8, 1.2), 3.98−3.78 (4 H, m), 3.27−3.13 (2 H, m), 2.86−2.73 (2 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.9, 151.0, 148.4, 148.2, 144.9, 136.3, 135.4, 134.0, 130.0, 127.7, 127.2, 126.8, 126.7, 125.7, 125.0, 123.5, 120.4, 119.1, 116.5, 115.5, 67.3, 60.7, 53.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{23}N_4O_2$ 411.1816, found 411.1823.

*6-(4-(4-(4-Fluorophenyl)piperazin-1-yl)phenyl)-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**4d**).* The compound **4d** was synthesized by the above-described method. The reaction took 18 h to complete, and the product was obtained as an off-white solid: yield 73% (367 mg); R_f = 0.4 (30% EtOAc + pet ether); mp 269−271 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (1 H, dd, J = 7.9, 1.1), 8.12 (1 H, d, J = 7.9), 7.91 (1 H, d, J = 3.5), 7.89−7.82 (1 H, m), 7.73 (1 H, d, J = 8.1), 7.50 (1 H, t, J = 7.5), 7.37−7.29 (1 H, m), 7.16 (1 H, d, J = 3.5), 7.07−6.99 (4 H, m), 6.98−6.93 (2 H, m), 6.90 (1 H, d, J = 8.0), 6.88−6.77 (3 H, m), 3.22−3.15 (4 H, m), 3.14−3.06 (4 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 156.6 (d, J = 235), 151.0, 148.23 (d, J = 3), 148.22, 147.8, 145.8, 135.4, 134.1, 130.1, 127.7, 127.3, 127.1, 126.9, 126.6, 120.4, 119.0, 117.94 (d, J = 8), 116.3, 116.0, 115.75 (d, J = 22), 115.70, 62.7, 49.4, 48.3; ^{19}F NMR (377 MHz, DMSO-d_6) δ −124.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{31}H_{27}FN_5O$ 504.2194, found 504.2200.

*6-(4-(4-(4-(Trifluoromethyl)phenyl)piperazin-1-yl)phenyl)-5,6-dihydro-8H-quinazolino[4,3-b]quinazolin-8-one (**4e**).* The compound **4e** was synthesized by the above-described method. The reaction took 12 h to complete, and the product was obtained as a white solid: yield 65% (334 mg); R_f = 0.3 (30% EtOAc + pet ether); mp 231−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (1 H, d, J = 6.9), 8.11 (1 H, d, J = 7.1), 7.93 (1 H, d, J = 3.6), 7.89−7.82 (1 H, m), 7.73 (1 H, d, J = 8.1), 7.55−7.45 (3 H, m), 7.37−7.27 (1 H, m), 7.16 (1 H, d, J = 3.4), 7.11−6.98 (4 H, m), 6.94−6.77 (4 H, m), 3.36−3.29 (4 H, m), 3.23−3.12 (4 H, m); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.1, 153.5, 150.8, 148.1, 147.8, 145.8, 135.4, 134.1, 130.1, 127.7, 127.3, 127.1, 126.9, 126.7, 126.66, 126.62, 124.0, 120.4, 119.1, 118.6, 118.3, 116.3, 115.9, 115.6, 114.7, 114.4, 113.6, 62.7, 47.9, 47.2; ^{19}F NMR (377 MHz, DMSO-d_6) δ −59.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{32}H_{27}F_3N_5O$ 554.2162, found 554.2162.

Synthesis of Compound 5. One-half millimole of compound **1**, 2 mL of isopropanol, 0.5 mL of H_2O, and Fe powder (3 equiv) were added to an oven-dried, round-bottom flask, and the mixture was allowed to reflux in an oil bath for 12 h (monitored by TLC). After that, the reaction mixture was extracted with ethyl acetate (10 mL) and water (10 mL). After separation of the two layers, the aqueous layer was collected and extracted with ethyl acetate (3 × 10 mL). Then the combined organic layer was washed with a brine solution (10 mL) and concentrated in vacuo. The crude product was purified by silica gel (100−200) column chromatography to obtain the pure product of type **5**.

2-(2-Aminophenyl)quinazolin-4(3H)-one (5). The compound **5** was synthesized by the above-described method and obtained as a pale yellow solid: yield 87% (103 mg); R_f = 0.3 (30% EtOAc + pet ether); mp 201−203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (1 H, s), 8.12 (1 H, dd, J = 7.9, 1.0), 7.83−7.77 (1 H, m), 7.76−7.69 (2 H, m), 7.51−7.44 (1 H, m), 7.22−7.15 (1 H, m), 7.04 (2 H, s), 6.82 (1 H, dd, J = 8.2, 0.8), 6.59 (1 H, t, J = 7.5); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 162.5, 154.0, 149.8, 148.5, 135.0, 132.2, 129.3, 127.3, 126.7, 126.2, 120.9, 117.0, 115.4, 112.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{12}N_3O$ 238.0975, found 238.0980.

2-(2-(Amino-d_2)phenyl)quinazolin-4(3H)-one-3-*d* (5D). One-half millimole of compound **1** in 2.5 mL of isopropanol:D_2O (4:1) and Fe powder (3 equiv) were added to an oven-dried, round-bottom flask and allowed to reflux in an oil bath for 12 h (monitored by TLC). After that, the reaction mixture was concentrated in vacuo and purified by column chromatography using 100−200 silica gel to get the desired product of type **5D**; obtained as a pale yellow solid: yield 67% (80 mg); R_f = 0.3 (30% EtOAc + pet ether); mp 195−197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (1 H, d, J = 7.9), 7.81 (1 H, t, J = 7.6), 7.70 (1 H, d, J = 8.0), 7.64 (1 H, d, J = 8.0), 7.49 (1 H, t, J = 7.5), 7.20 (1 H, t, J = 7.0), 6.80 (1 H, d, J = 8.3), 6.63 (1 H, t, J = 7.5).

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00766.

^{1}H and ^{13}C NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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