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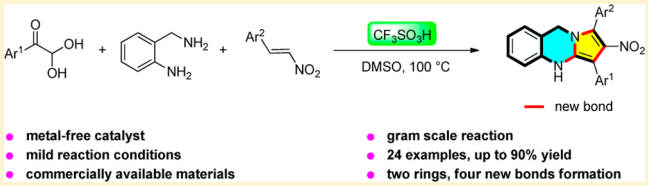
Acid-Catalyzed Multicomponent Tandem Double Cyclization: A One-pot, Metal-free Route to Synthesize Polyfunctional 4,9-Dihydropyrrolo[2,1-*b*]quinazolines

Qun Cai, Deng-Kui Li, Rong-Rong Zhou, Shi-Yi Zhuang, Jin-Tian Ma, Yan-Dong Wu,* and An-Xin Wu*

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, P. R. China

Supporting Information

ABSTRACT: An acid-catalyzed multicomponent tandem double cyclization protocol has been developed for the synthesis of polyfunctional 4,9-dihydropyrrolo[2,1-*b*]-quinazolines from simple and readily available arylglyoxal monohydrates, 2-aminobenzylamine, and *trans*-*β*-nitrostyrenes. This practical and metal-free reaction proceeds through an imine formation/cyclization/Michael addition/Henry cyclization protocol, resulting in the construction of four new bonds and two ring moieties directly in one pot.



The straightforward construction of fused N-heterocyclic scaffolds is an important and ongoing research area in organic synthesis due to their presence in drugs and functional materials.[1] Among them, 4,9-dihydropyrrolo[2,1-*b*]quinazoline is one of the privileged structural motifs in heteropolycyclic systems, and its derivatives can be found in numerous natural products and biologically active molecules such as vasicoline (**I**),[2] vasicine (**II**),[3] batracylin (**III**),[4] and antimicrobial molecule (**IV**)[5] (Figure 1).

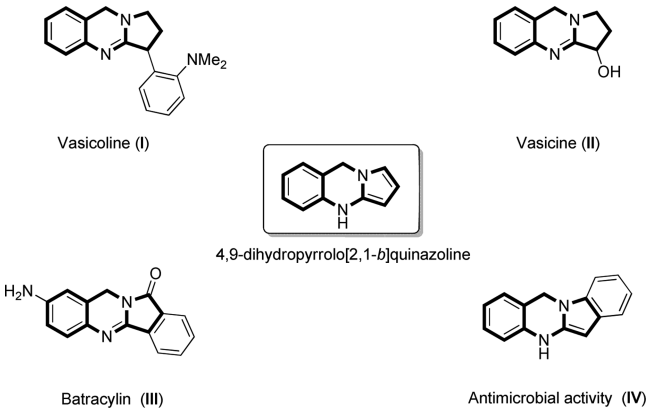
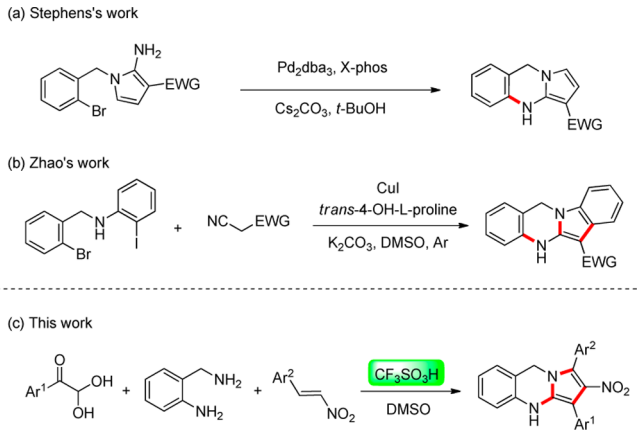


Figure 1. Selected natural products and biologically active compounds with a 4,9-dihydropyrrolo[2,1-*b*]quinazoline moiety.

Due to the importance and utility of 4,9-dihydropyrrolo[2,1-*b*]quinazoline derivatives, a simplified synthesis of this heteropolycyclic system offers great value. To the best of our knowledge, however, only a few approaches have been reported thus far to construct this novel structure. In 2011, Stephens and co-workers exploited a Pd-catalyzed intramolecular C−N coupling reaction for the synthesis of 4,9-dihydropyrrolo[2,1-*b*]quinazolines from prefabricated 2-aminopyrroles having a 2-bromobenzyl group at the N-1 position (Scheme 1a).[6] In addition, the Zhao group reported a Cu-catalyzed Ullmann-type coupling reaction for the synthesis of 5,12-dihydroindolo-[2,1-*b*]quinazolines through a sequential C−C and C−N bond formation from *N*-(2-bromobenzyl)-2-iodoanilines and aceto-nitriles substituted with electron-withdrawing groups under an argon condition (Scheme 1b).[7] Despite these limited examples, the development of new and practical synthetic strategies, especially metal-free pathways, to access polyfunctional 4,9-dihydropyrrolo[2,1-*b*]quinazolines is highly desirable.

Scheme 1. Strategies for the Synthesis of 4,9-Dihydropyrrolo[2,1-*b*]quinazoline Derivatives



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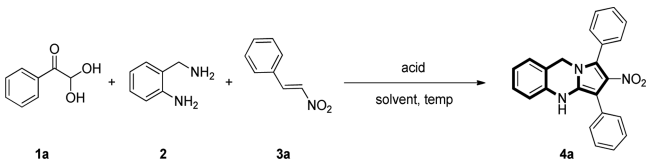
In recent years, tandem cyclization has emerged as a versatile and economical strategy for the synthesis of highly functionalized polycyclic ring systems, which has attracted substantial interest from chemists.[8−14] In particular, tandem double cyclization has found wide applications in total synthesis of natural products because of its advantages in unparalleled efficiencies, reducing the reaction steps and waste production.[15,16] In continuation of our efforts to synthesize heterocycles using tandem cyclization methods,[17] we herein report a new acid-catalyzed multicomponent reaction to construct polysubstituted 4,9-dihydropyrrolo[2,1-*b*]quinazolines from readily available arylglyoxal monohydrates, 2-aminobenzylamine, and *trans*-*β*-nitrostyrenes in a single operation (Scheme 1c). Notably, this work represents a fascinating approach for the direct construction of three C−N bonds and one C−C bond via tandem double cyclization in a single step without any metal additives.

Our initial investigations of the tandem double cyclization reaction focused on optimizing the reaction conditions of phenylglyoxal monohydrate **1a**, 2-aminobenzylamine **2**, and *trans*-*β*-nitrostyrene **3a** in the presence of different Brønsted acids and solvents. To our delight, the reaction proceeded to give the desired product **4a** in 30% yield when it was conducted in methanol with 30 mol % of CF_3SO_3H (Table 1, entry 1). Thus, we screened a series of solvents, including *i*-PrOH, $CHCl_3$, CH_3CN, 1,4-dioxane, THF, DMF, and DMSO (Table 1, entries 2−8), and DMSO was shown to be the most effective for this reaction. Based on this encouraging result, we then evaluated several other acids, but none of these performed any better than CF_3SO_3H (Table 1, entries 9−13). After screening several different amounts of CF_3SO_3H, we found that 30 mol% of CF_3SO_3H was still the most suitable for the reaction (Table 1, entries 14−18 vs entry 8). Moreover, the yield decreased slightly when the reaction was performed at a lower or higher temperature (Table 1, entries 19−22).

Table 1. Optimization of the Reaction Conditions[a]



1a 2 3a 4a

entry	solvent	acid (mol%)	temp (°C)	yield[b] (%)
1	MeOH	CF_3SO_3H(30)	65	30
2	*i*-PrOH	CF_3SO_3H(30)	80	48
3	$CHCl_3$	CF_3SO_3H(30)	40	10
4	CH_3CN	CF_3SO_3H(30)	80	28
5	1,4-dioxane	CF_3SO_3H(30)	100	16
6	THF	CF_3SO_3H(30)	66	12
7	DMF	CF_3SO_3H(30)	100	76
8	**DMSO**	**CF_3SO_3H(30)**	**100**	**88**
9	DMSO	CH_3SO_3H(30)	100	70
10	DMSO	CH_3CO_2H(30)	100	82
11	DMSO	CF_3CO_2H(30)	100	68
12	DMSO	TsOH(30)	100	74
13	DMSO	HCl(30)	100	62
14	DMSO		100	trace
15	DMSO	CF_3SO_3H(10)	100	35
16	DMSO	CF_3SO_3H(60)	100	75
17	DMSO	CF_3SO_3H(120)	100	trace
18	DMSO	CF_3SO_3H(150)	100	trace
19	DMSO	CF_3SO_3H(30)	r.t.	50
20	DMSO	CF_3SO_3H(30)	60	56
21	DMSO	CF_3SO_3H(30)	80	70
22	DMSO	CF_3SO_3H(30)	120	73

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (0.24 mmol, 1.2 equiv), **3a** (0.2 mmol, 1.0 equiv), and acid (*x* mol%) were heated in 2 mL of solvent in a sealed tube for 3 h. [b]Isolated yields.

With the optimized conditions in hand, the substrate scope of arylglyoxal monohydrate (**1**) was explored. It is noteworthy that the reaction demonstrated a wide tolerance for diverse substituents of arylglyoxal monohydrates. As shown in Scheme 2, arylglyoxals bearing electron-neutral (4-H, 4-Me), electron-rich (4-OMe, 3-OMe), and electron-deficient (3-NO_2) substituents were smoothly converted to the corresponding products in moderate to excellent yields (76−90%; **4a**−**4e**). Gratifyingly, halo-substituted (4-Cl, 4-Br, 3-Br) arylglyoxals were also found to furnish the corresponding products in excellent yields (82−87%; **4f**−**4h**), which provided the possibility for further functionalization. Additionally, heterocyclic (2-thiophenyl and 3-thiophenyl) and sterically hindered (1-naphthyl and 2-naphthyl) arylglyoxals were found to be suitable for this transformation (70−80%; **4i**−**4l**). Furthermore, the structure of **4b** was unambiguously confirmed by X-ray diffraction analysis (see the Supporting Information).

Encouraged by the results described above, the scope of aryl-substituted nitroolefins (**3**) was subsequently examined (Scheme 3). Much to our satisfaction, the electronic properties of the aryl-substituents on the nitroolefins were shown to have little influence on the efficiency of this reaction. In general, electron-neutral (4-Me), electron-rich (4-OMe, 4-OH), and halogenated (4-F; 2-Cl; 2,4-Cl_2; 2-Br) groups were all found compatible under the optimal reaction conditions with excellent yields (72−85%; **4m**−**4s**). Sterically hindered (1-naphthyl) nitroolefin was also tolerated in this reaction to afford the desired product **4t** in 74% yield. Furthermore, methyl-, bromo-, 3-thiophenyl-, and 2-naphthyl-substituted arylglyoxal monohydrates reacted smoothly with 2-aminobenzylamine and methyl- or methoxyl-substituted nitrostyrene to obtain the corresponding products in moderate yields (68−87%; **4u**−**4x**).

To gain some insight into the mechanism of this reaction, a series of control experiments were performed as shown in Scheme 4. When phenylglyoxal monohydrate **1a** reacted with 2-aminobenzylamine **2** under the standard conditions for 0.5 h, 1,2,3,4-tetrahydroquinazoline **B** was obtained in 15% yield together with large amounts of quinazoline **5** (Scheme 4a). Then, the treatment of **B** and *trans*-*β*-nitrostyrene **3a** under the standard conditions directly generated the target product **4a** in 85% yield (Scheme 4b). These results implied that **B** was the key intermediate for this reaction. To further demonstrate the reaction order of three substrates, **2** and **3a** were first subjected to the reaction under the standard conditions for 2 h, then **1a** was added into the mixture; however, the target product **4a** was not obtained, which excluded the reaction order of (**2** + **3a**) + **1a** (Scheme 4c). Furthermore, when this reaction was conducted under an argon condition, the desired product **4a** was isolated in 13% yield along with a possible unstable intermediate **D** detected by MS (Scheme 4d). In contrast, when this reaction was conducted under an oxygen condition, **4a** was still isolated in a low yield accompanying the byproduct **5** in 41% yield (Scheme 4e), which indicated that a large amount of oxygen is unfavorable to the smooth transformation of the reaction.

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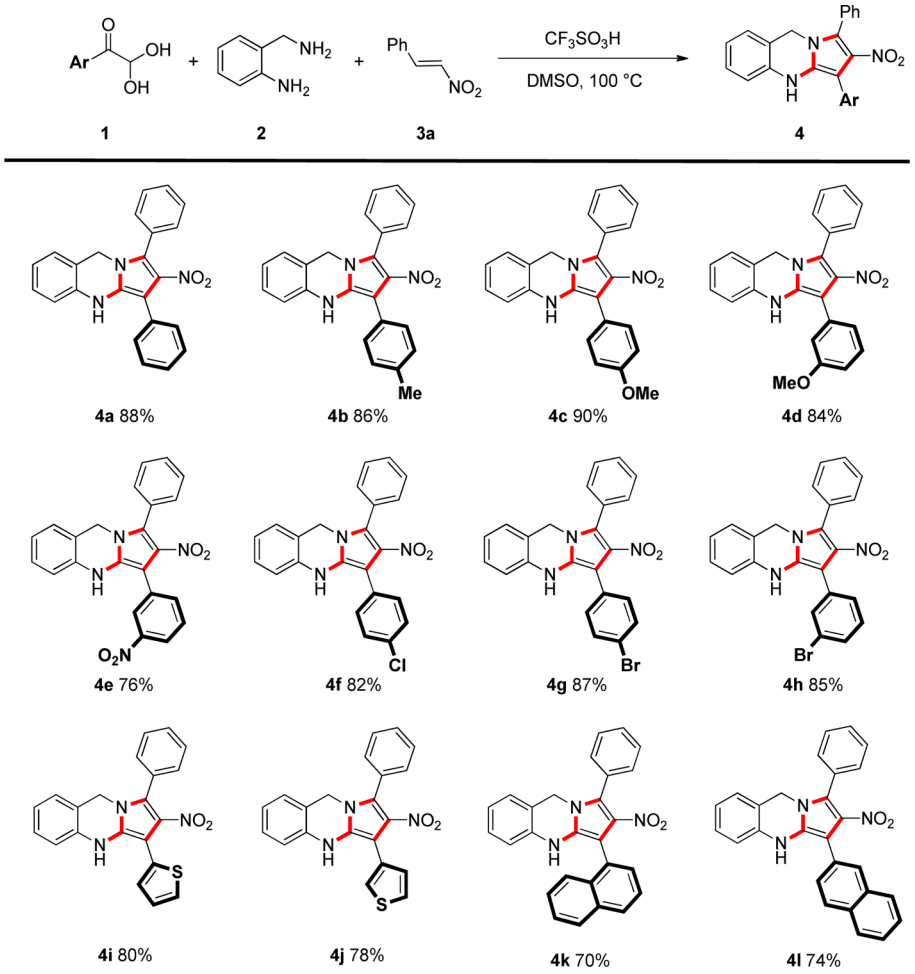
Scheme 2. Scope of Arylglyoxal Monohydrates[a,b]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), **3a** (0.3 mmol), and CF_3SO_3H (0.09 mmol) were heated in 3 mL of DMSO in a sealed tube for 3 h. [b]Isolated yields.

Based on the above results and previous reports,[17−19] a possible mechanism for the formation of polyfunctional 4,9-dihydropyrrolo[2,1-*b*]quinazolines **4** was presented in Scheme 5 (**4a** as an example). Initially, phenylglyoxal monohydrate **1a** transformed to the corresponding dehydrated species **1a′**, which was protonated to form **1a″** in acid condition. Subsequently, **1a″** reacted with 2-aminobenzylamine **2** to afford imine intermediate **A**. Then, intramolecular cyclization of intermediate **A** led to the formation of intermediate **B**. Afterward, Michael addition of intermediate **B** to *trans*-*β*-nitrostyrene **3a** furnished intermediate **C**, which straightly underwent intramolecular Henry cyclization to form intermediate **D**. Finally, **D** went through oxidative aromatization to give the desired product **4a**.

To further make this reaction more attractive in terms of synthetic practicality, a gram-scale synthesis of 4,9-dihydropyrrolo[2,1-*b*]quinazolines (**4a**) was carried out. To our great pleasure, the reaction proceeded well and the desired product **4a** was isolated in 80% yield (Scheme 6).

In conclusion, we have developed a highly efficient multicomponent tandem double cyclization protocol for the synthesis of polyfunctional 4,9-dihydropyrrolo[2,1-*b*]-quinazolines from simple and readily available starting materials in one pot. This method features in the consecutive construction of four new bonds and two rings under metal-free conditions. This reaction represents a highly efficient and convenient methodology for the synthesis of diversely substituted heteropolycyclic scaffolds under mild conditions.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all starting materials and catalysts were obtained from commercial suppliers and used without further purification. All new compounds were fully characterized. TLC analysis was performed using precoated glass plates. Column chromatography was performed using silica gel (200−300 mesh). IR spectra were recorded as KBr pellets with absorption in cm^{-1}. ^1H spectra were recorded with 600/400 MHz spectrometers and resonances (δ) are given in ppm relative to TMS (internal standard). ^{13}C spectra were recorded with 150/100 MHz NMR spectrometers. HRMS were obtained on a 7.0T FTMS equipped with ESI or APCI. Melting points were determined using an electrothermal capillary melting point apparatus and not corrected.

General Procedures for the Synthesis of the Products 4 (4a as an Example). A mixture of phenylglyoxal monohydrate **1a** (46 mg, 0.3 mmol), 2-aminobenzylamine **2** (44 mg, 0.36 mmol), *trans*-*β*-nitrostyrene **3a** (45 mg, 0.3 mmol), and CF_3SO_3H (14 mg, 0.09 mmol) was heated at 100 °C in 3 mL of DMSO in a sealed tube for 3 h until almost completed conversion of the substrates by TLC analysis, then it was extracted with EtOAc three times (3 × 50 mL). The extract was dried over anhydrous Na_2SO_4 and was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc = 5/1) to afford the product **4a**.

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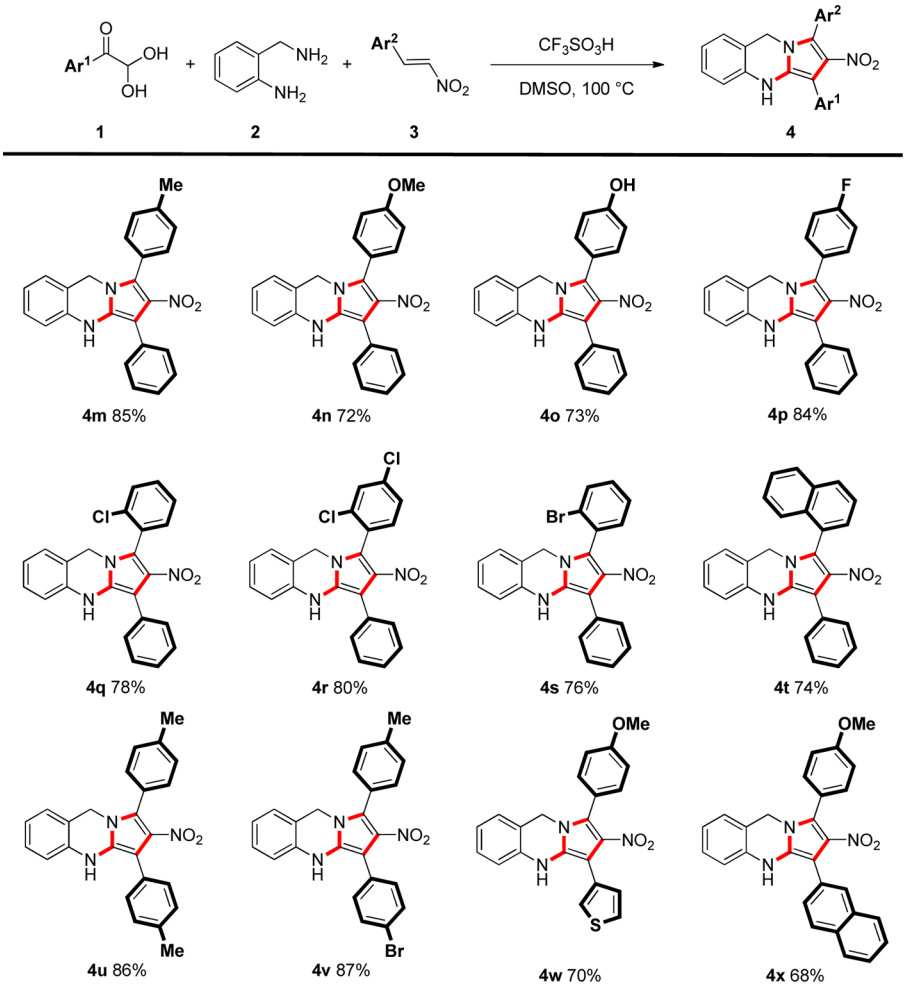
Scheme 3. Scope of Nitroolefins and Arylglyoxal Monohydrates[a,b]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), **3** (0.3 mmol), and CF_3SO_3H (0.09 mmol) were heated in 3 mL of DMSO in a sealed tube for 3 h. [b]Isolated yields.

Experimental Procedure for Preparation of B and 5. A mixture of phenylglyoxal monohydrate **1a** (76 mg, 0.5 mmol), 2-aminobenzylamine **2** (73 mg, 0.6 mmol), and CF_3SO_3H (23 mg, 0.15 mmol) was heated at 100 °C in 3 mL of DMSO in a sealed tube for 0.5 h until almost completed conversion of the substrates by TLC analysis, then it was extracted with EtOAc three times (3 × 50 mL). The extract was dried over anhydrous Na_2SO_4 and was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc = 10/1) to afford **B** and **5**.

Gram Scale Reaction for Product 4a. A mixture of phenylglyoxal monohydrate **1a** (760 mg, 5 mmol), 2-aminobenzylamine **2** (732 mg, 6 mmol), *trans*-β-nitrostyrene **3a** (745 mg, 5 mmol), and CF_3SO_3H (225 mg, 1.5 mmol) was heated at 100 °C in 50 mL of DMSO in a sealed tube for 5 h until almost completed conversion of the substrates by TLC analysis, then it was extracted with EtOAc three times (3 × 100 mL). The extract was dried over anhydrous Na_2SO_4 and was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc = 5/1) to afford the product **4a**.

Analytical Data for Products 4, B, and 5. *2-Nitro-1,3-diphenyl-4,9-dihydropyrrolo[2,1-b]quinazoline (**4a**).* Yield: 88% (97 mg); Yellow solid; mp 98−100 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.93 (s, 1H), 7.58 (d, *J* = 6.0 Hz, 2H), 7.52 (d, *J* = 6.6 Hz, 3H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.40−7.28 (m, 3H), 7.19−6.99 (m, 3H), 6.79 (t, *J* = 7.2 Hz, 1H), 4.89 (s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 136.6, 131.7, 131.4, 130.9, 130.2, 129.5, 129.0, 128.8, 128.32, 128.28, 128.1, 127.4, 126.9, 126.4, 119.9, 114.8, 114.2, 96.3, 44.1; IR (KBr):, 3410, 3056, 2924, 2858, 1621, 1587, 1547, 1492, 1345, 1250, 844, 763, 700 cm^{-1}; HRMS (APCI): *m*/*z* [M+H]$^+$ calcd for $C_{23}H_{18}N_3O_2$: 368.1394; found: 368.1398.

*2-Nitro-1-phenyl-3-(p-tolyl)-4,9-dihydropyrrolo[2,1-b]quinazoline (**4b**).* Yield: 86% (98 mg); Yellow solid; mp 203−205 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.54−7.46 (m, 5H), 7.34−7.26 (m, 4H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.36 (s, 1H), 4.84 (s, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 136.7, 136.3, 131.8, 130.7, 129.6, 129.1, 129.0, 128.9, 128.7, 128.6, 128.4, 127.3, 126.9, 120.9, 114.6, 114.3, 110.0, 97.4, 44.6, 21.3; IR (KBr): 3415, 3020, 2919, 2853, 1620, 1588, 1548, 1492, 1344, 1255, 848, 755, 696 cm^{-1}; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{24}H_{20}N_3O_2$: 382.1550; found: 382.1556.

*3-(4-Methoxyphenyl)-2-nitro-1-phenyl-4,9-dihydropyrrolo[2,1-b]quinazoline (**4c**).* Yield: 90% (107 mg); Yellow solid; mp 152−154 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.85 (s, 1H), 7.60−7.45 (m, 5H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.13−7.05 (m, 3H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.77 (t, *J* = 6.6 Hz, 1H), 4.88 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.0, 136.7, 131.6, 131.5, 130.8, 129.4, 129.0, 128.9, 128.3, 128.1, 127.0, 126.9, 123.7, 119.8, 114.7, 114.2, 113.8, 96.1, 55.1, 44.1; IR (KBr): 3405, 3057, 2836, 1624, 1590, 1492, 1468, 1341, 1248, 1178, 1030, 836, 750, 699 cm^{-1}; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{24}H_{20}N_3O_3$: 398.1499; found: 398.1497.

*3-(3-Methoxyphenyl)-2-nitro-1-phenyl-4,9-dihydropyrrolo[2,1-b]quinazoline (**4d**).* Yield: 84% (100 mg); Yellow solid; mp 183−185 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.94 (s, 1H), 7.60−7.49 (m, 5H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.14−7.09 (m, 2H), 7.08 (d, *J* = 7.2 Hz,

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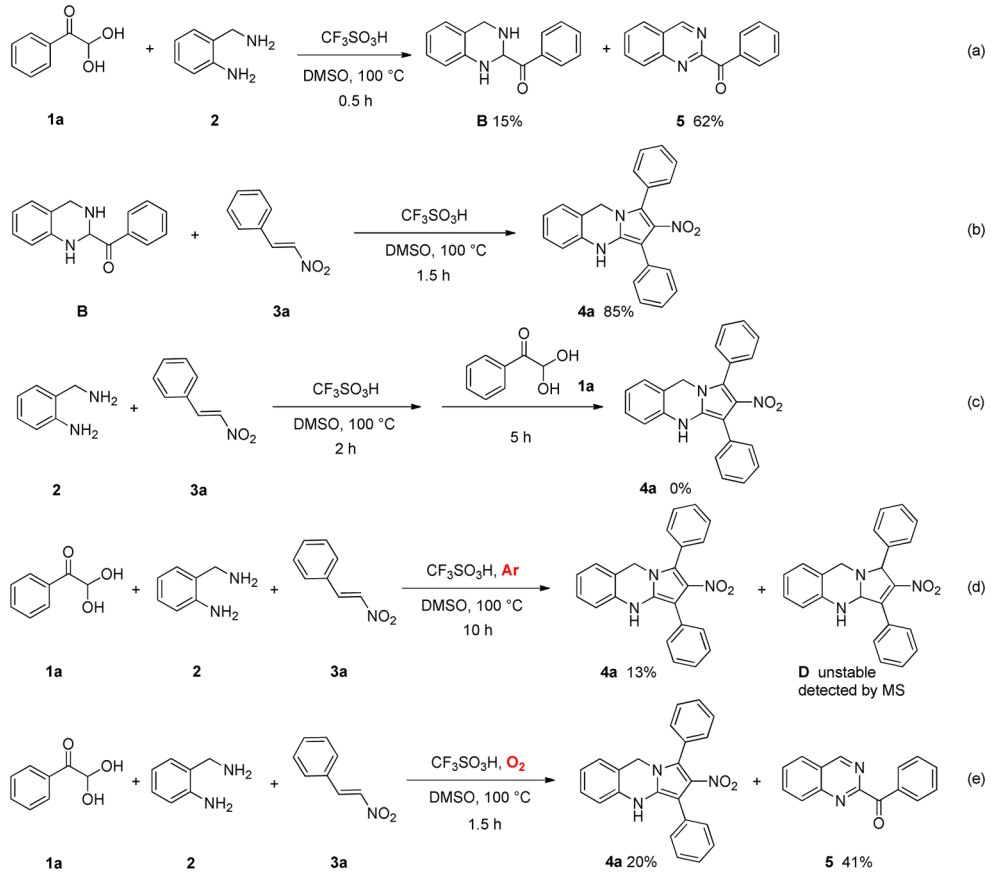
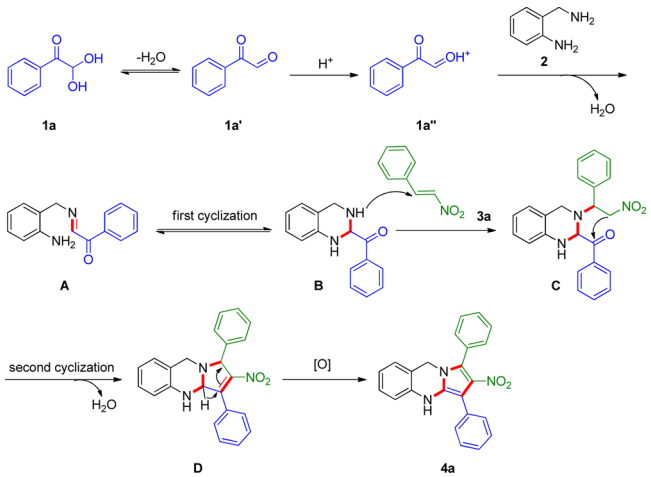
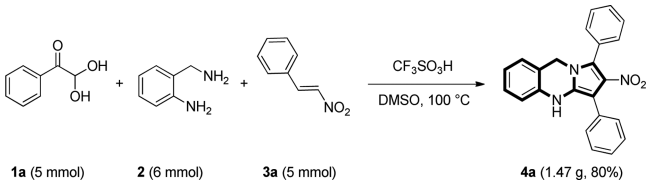
Scheme 4. Control Experiments



Scheme 5. Possible Mechanism



Scheme 6. Gram-scale Experiment of Product 4a



1H), 6.94−6.87 (m, 3H), 6.78 (t, J = 7.8 Hz, 1H), 4.88 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 159.1, 136.6, 132.9, 131.5, 130.8, 129.5, 129.2, 129.0, 128.8, 128.3, 128.1, 127.2, 126.9, 122.6, 119.9, 115.6, 114.8, 114.2, 112.2, 96.2, 54.9, 44.1; IR (KBr): 3362, 3040, 2830, 1618, 1590, 1544, 1485, 1464, 1334, 1256, 757, 702 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{24}H_{20}N_3O_3$: 398.1499; found: 398.1497.

*2-Nitro-3-(3-nitrophenyl)-1-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4e**).* Yield: 76% (94 mg); Yellow solid; mp 150−152 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 9.14 (s, 1H), 8.23−8.14 (m, 2H), 7.82 (d, J = 7.2 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.62−7.51 (m, 5H), 7.17−7.09 (m, 2H), 7.01 (d, J = 7.8 Hz, 1H), 6.82 (t, J = 7.8 Hz, 1H), 4.91 (s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 147.8, 137.4, 136.2, 133.6, 130.9, 130.8, 130.3, 129.6, 129.2, 128.6, 128.40, 128.35, 128.2, 127.1, 125.0, 121.3, 120.3, 114.6, 114.2, 94.1, 44.2; IR (KBr): 3379, 2842, 1625, 1589, 1530, 1495, 1345, 1259, 1036, 832, 753, 700 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{23}H_{17}N_4O_4$: 413.1244; found: 413.1244.

*3-(4-Chlorophenyl)-2-nitro-1-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4f**).* Yield: 82% (99 mg); Yellow solid; mp 133−135 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.99 (s, 1H), 7.57 (d, J = 6.6 Hz, 2H), 7.52 (d, J = 6.0 Hz, 3H), 7.48 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 7.12 (t, J = 7.8 Hz, 1H), 7.09−7.00 (m, 2H), 6.79 (t, J = 7.2 Hz, 1H), 4.88 (s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 136.4, 132.2, 131.1, 130.8, 130.7, 129.8, 129.0, 128.7, 128.3, 128.2, 128.1, 127.7, 127.0, 120.0, 114.7, 114.2, 95.0, 44.1; IR (KBr): 3415, 2922, 1624, 1588, 1547, 1491, 1341, 1257, 1194, 1091, 838, 749, 700 cm^{-1}; HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{23}H_{16}ClN_3NaO_2$: 424.0823; found: 424.0823.

*3-(4-Bromophenyl)-2-nitro-1-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4g**).* Yield: 87% (116 mg); Yellow solid; mp 134−136 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.99 (s, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.57 (d, J = 6.6 Hz, 2H), 7.54−7.45 (m, 3H), 7.31 (d, J = 7.8 Hz, 2H), 7.12 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.79 (t, J = 7.8 Hz, 1H), 4.88 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 136.4, 132.4, 131.1, 131.00, 130.97, 130.7, 129.6, 128.9, 128.6, 128.2, 128.0, 127.6, 126.8, 119.9, 119.6, 114.6,

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114.1, 95.0, 44.0; IR (KBr): 3404, 3059, 2925, 2856, 1680, 1623, 1587, 1490, 1258, 1195, 833, 749, 698 cm^{-1}; HRMS (ESI): m/z $[M + K]^+$ calcd for $C_{23}H_{16}BrN_3KO_2$: 484.0058; found: 484.0050.

*3-(3-Bromophenyl)-2-nitro-1-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4h**).* Yield: 85% (114 mg); Yellow solid; mp 157−159 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 9.07 (s, 1H), 7.57 (d, J = 6.0 Hz, 2H), 7.55−7.49 (m, 5H), 7.41−7.35 (m, 2H), 7.13 (t, J = 7.8 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 6.80 (t, J = 7.2 Hz, 1H), 4.89 (s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 136.4, 134.3, 132.9, 131.1, 130.8, 130.2, 129.9, 129.5, 129.3, 129.1, 128.7, 128.3, 128.1, 127.8, 127.0, 121.5, 120.1, 114.7, 114.2, 94.9, 44.2; IR (KBr): 3377, 2921, 1622, 1589, 1546, 1494, 1471, 1334, 1260, 854, 753, 703 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{17}BrN_3O_2$: 446.0499; found: 446.0499.

*2-Nitro-1-phenyl-3-(thiophen-2-yl)-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4i**).* Yield: 80% (89 mg); Yellow solid; mp 220−222 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 9.03 (s, 1H), 7.62−7.56 (m, 3H), 7.55−7.49 (m, 3H), 7.20−7.11 (m, 4H), 7.04 (d, J = 7.2 Hz, 1H), 6.79 (t, J = 6.6 Hz, 1H), 4.88 (s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 136.3, 132.1, 131.6, 131.0, 130.8, 129.1, 128.7, 128.5, 128.4, 128.2, 127.6, 127.2, 126.9, 126.5, 120.2, 114.9, 114.1, 88.5, 44.2; IR (KBr): 3408, 3101, 1622, 1588, 1549, 1494, 1471, 1357, 1250, 1178, 851, 759 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{15}N_3NaO_2S$: 396.0777; found: 396.0778.

*2-Nitro-1-phenyl-3-(thiophen-3-yl)-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4j**).* Yield: 78% (87 mg); Yellow solid; mp 264−266 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 8.86 (s, 1H), 7.60−7.47 (m, 7H), 7.12 (d, J = 3.6 Hz, 3H), 7.07 (d, J = 7.8 Hz, 1H), 6.82−6.75 (m,, 1H), 4.87 (s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 136.5, 131.4, 130.9, 130.8, 129.84, 129.82, 129.0, 128.9, 128.3, 128.1, 127.2, 126.9, 124.9, 123.7, 120.0, 114.8, 114.2, 91.5, 44.1.; IR (KBr): 3411, 3103, 1623, 1590, 1546, 1493, 1471, 1355, 1333, 1250, 757, 699 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{16}N_3O_2S$: 374.0958; found: 374.0957.

*3-(Naphthalen-1-yl)-2-nitro-1-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4k**).* Yield: 70% (87 mg); Yellow solid; mp 163−165 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 8.81 (s, 1H), 8.03−7.93 (m, 2H), 7.80 (d, J = 8.4 Hz, 1H), 7.71−7.65 (m, 2H), 7.64−7.45 (m, 7H), 7.12−7.04 (m, 2H), 6.92 (d, J = 7.2 Hz, 1H), 6.81−6.73 (m, 1H), 4.98 (s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 136.6, 133.5, 133.2, 132.3, 131.0, 130.1, 129.8, 129.1, 129.04, 129.00, 128.3, 128.1, 127.6, 127.5, 127.0, 126.1, 125.9, 125.7, 125.5, 119.8, 114.4, 114.0, 109.6, 93.7, 44.3; IR (KBr): 3404, 3052, 1624, 1588, 1546, 1493, 1254, 1208, 792, 864, 750, 698 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{20}N_3O_2$: 418.1550; found: 418.1552.

*3-(Naphthalen-2-yl)-2-nitro-1-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4l**).* Yield: 74% (93 mg); Yellow solid; mp 137−139 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.88−7.80 (m, 4H), 7.51−7.43 (m, 8H), 7.09 (t, J = 7.2 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 6.83 (t, J = 7.8 Hz, 1H), 6.59 (d, J = 7.8 Hz, 1H), 6.49 (s, 1H), 4.80 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 136.1, 133.5, 132.2, 131.7, 130.7, 129.5, 129.4, 129.2, 128.8, 128.6, 128.44, 128.37, 128.2, 127.7, 127.6, 127.5, 126.8, 126.1, 125.9, 120.9, 114.5, 114.3, 97.4, 44.6; IR (KBr): 3412, 3053, 1623, 1588, 1493, 1469, 1343, 1250, 1203, 823, 751, 699 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{20}N_3O_2$: 418.1550; found: 418.1551.

*2-Nitro-3-phenyl-1-(p-tolyl)-4,9-dihydropyrrolo[2,1-b]quinazoline (**4m**).* Yield: 85% (97 mg); Yellow solid; mp 201−203 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.46−7.42 (m, 2H), 7.39 (d, J = 7.2 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.33−7.28 (m, 3H), 7.12 (t, J = 7.2 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.85 (t, J = 7.8 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.41 (s, 1H), 4.82 (s, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 139.2, 136.2, 131.7, 131.6, 130.5, 129.7, 129.1, 129.0, 128.7, 128.6, 127.7, 126.82, 126.79, 125.7, 120.8, 114.5, 114.3, 97.4, 44.6, 21.4; IR (KBr): 3416, 3018, 1620, 1591, 1553, 1502, 1473, 1344, 1256, 1198, 849, 753, 703 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{20}N_3O_2$: 382.1550; found: 382.1559.

*1-(4-Methoxyphenyl)-2-nitro-3-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4n**).* Yield: 72% (86 mg); Yellow solid; mp 129−131 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 8.90 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.35 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.15−7.09 (m, 2H), 7.07 (d, J = 8.4 Hz, 3H), 6.82−6.74 (m, 1H), 4.88 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 159.7, 136.7, 132.4, 131.8, 131.4, 130.2, 129.3, 128.3, 128.1, 127.6, 126.9, 126.3, 120.6, 119.9, 114.8, 114.3, 113.7, 96.3, 55.2, 44.1; IR (KBr): 3354, 3052, 2838, 1620, 1588, 1550, 1498, 1468, 1339, 1251, 1030, 848, 760, 701 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{20}N_3O_3$: 398.1499; found: 398.1507.

*4-(2-Nitro-3-phenyl-4,9-dihydropyrrolo[2,1-b]quinazolin-1-yl)-phenol (**4o**).* Yield: 73% (84 mg); Yellow solid; mp 252−254 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 9.87 (s, 1H), 8.85 (s, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.35−7.23 (m, 3H), 7.16−7.03 (m, 3H), 6.89 (d, J = 8.4 Hz, 2H), 6.79 (t, J = 7.2 Hz, 1H), 4.87 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.1, 136.7, 132.2, 131.8, 131.3, 130.0, 129.1, 128.1, 128.0, 127.9, 126.8, 126.2, 119.8, 118.8, 115.1, 114.7, 114.4, 96.2, 44.0; IR (KBr): 3409, 2843, 1620, 1589, 1551, 1497, 1467, 1342, 1275, 1251, 852, 756, 702 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{18}N_3O_3$: 384.1343; found: 384.1348.

*1-(4-Fluorophenyl)-2-nitro-3-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4p**).* Yield: 84% (97 mg); Yellow solid; mp 190−192 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 8.92 (s, 1H), 7.68−7.62 (m, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.40−7.31 (m, 5H), 7.16−7.05 (m, 3H), 6.79 (t, J = 7.2 Hz, 1H), 4.89 (s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 162.5 (d, 1JC−F = 244.5 Hz), 136.6, 133.31, 133.25, 131.6, 131.5, 130.2, 129.5, 128.3, 128.1, 126.9, 126.4, 126.3, 125.2, 119.9, 115.4, 115.2, 114.8, 114.2, 96.4, 44.1; IR (KBr): 3408, 1622, 1589, 1551, 1499, 1472, 1345, 1235, 853, 759, 702 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{17}FN_3O_2$: 386.1299; found: 386.1305.

*1-(2-Chlorophenyl)-2-nitro-3-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4q**).* Yield: 78% (94 mg); Yellow solid; mp 115−117 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.55 (d, J = 7.8 Hz, 1H), 7.52−7.36 (m, 7H), 7.34 (t, J = 6.6 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.86 (t, J = 7.8 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 6.39 (s, 1H), 4.87−4.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 135.9, 135.3, 132.6, 132.0, 131.5, 130.9, 129.9, 129.7, 129.3, 128.7, 128.64, 128.61, 127.0, 126.9, 126.8, 124.3, 120.9, 114.3, 114.0, 97.3, 44.2; IR (KBr): 3405, 3057, 1621, 1587, 1547, 1489, 1344, 1255, 1198, 846, 757, 701 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{23}H_{16}ClN_3NaO_2$: 424.0823; found: 424.0832.

*1-(2,4-Dichlorophenyl)-2-nitro-3-phenyl-4,9-dihydropyrrolo[2,1-b]quinazoline (**4r**).* Yield: 80% (105 mg); Yellow solid; mp 144−146 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.61−7.57 (m, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.45−7.38 (m, 4H), 7.36 (t, J = 7.2 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.90 (t, J = 7.8 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.38 (s, 1H), 4.89−4.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 136.4, 136.2, 135.9, 133.5, 132.2, 131.3, 130.0, 129.7, 129.6, 128.8, 128.3, 127.4, 127.3, 127.2, 126.9, 122.8, 121.1, 114.4, 113.9, 97.6, 44.3; IR (KBr): 3416, 3052, 2849, 1668, 1622, 1585, 1493, 1338, 1273, 842, 749, 696 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{23}H_{15}Cl_2N_3NaO_2$: 458.0434; found: 458.0435.

*1-(2-Bromophenyl)-2-nitro-3-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4s**).* Yield: 76% (102 mg); Yellow solid; mp 142−144 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.72 (d, J = 7.8 Hz, 1H), 7.55−7.38 (m, 6H), 7.38−7.30 (m, 2H), 7.13 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.86 (t, J = 7.8 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 6.38 (s, 1H), 4.86−4.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 135.9, 132.7, 132.6, 131.7, 131.5, 131.0, 130.8, 129.9, 129.1, 128.7, 128.6, 127.5, 127.0, 126.9, 126.0, 125.4, 120.9, 114.3, 113.9, 97.2, 44.2; IR (KBr): 3424, 1624, 1586, 1548, 1486, 1343, 1255, 1198, 1029, 846, 752, 701 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{17}BrN_3O_2$: 446.0499; found: 446.0502.

*1-(Naphthalen-1-yl)-2-nitro-3-phenyl-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4t**).* Yield: 74% (93 mg); Yellow solid; mp 161−163 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.04−7.84 (m, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.60−7.53 (m 2H), 7.53−7.35 (m, 6H), 7.35−7.28 (m, 1H), 7.05 (t, J = 6.6 Hz, 1H), 6.84−6.64 (m, 2H), 6.58 (d, J = 7.8 Hz, 1H), 6.46 (s, 1H), 4.74−4.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 135.9, 133.4, 132.7, 131.7, 129.9, 129.8, 129.30, 129.25, 128.7, 128.6, 128.5, 127.1, 126.9, 126.8, 126.7, 126.3, 125.7, 125.2, 124.8, 120.8,

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114.2, 114.1, 97.2, 44.1; IR (KBr): 3402, 3053, 1621, 1587, 1541, 1479, 1340, 1256, 860, 787, 750, 700 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{20}N_3O_2$: 418.1550; found: 418.1551.

*2-Nitro-1,3-di-p-tolyl-4,9-dihydropyrrolo[2,1-b]quinazoline (**4u**).* Yield: 86% (102 mg); Yellow solid; mp 146−148 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.37 (d, J = 7.8 Hz, 2H), 7.32−7.28 (m, 4H), 7.27 (d, J = 7.8 Hz, 2H), 7.14 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.2 Hz, 1H), 6.85 (t, J = 7.8 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 6.36 (s, 1H), 4.83 (s, 2H), 2.44 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 139.2, 136.6, 136.3, 131.7, 130.6, 129.5, 129.1, 128.9, 128.7, 128.6, 127.5, 126.9, 125.8, 120.8, 114.6, 114.2, 109.9, 97.3, 44.6, 21.5, 21.3; IR (KBr): 3425, 2918, 1623, 1591, 1549, 1498, 1463, 1337, 1255, 916, 814, 751, 730 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{25}H_{21}N_3NaO_2$: 418.1526; found: 418.1534.

*3-(4-Bromophenyl)-2-nitro-1-(p-tolyl)-4,9-dihydropyrrolo[2,1-b]-quinazoline (**4v**).* Yield: 87% (120 mg); Yellow solid; mp 280−282 °C; ^1H NMR (DMSO-d_6, 600 MHz): δ 8.94 (s, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.37−7.21 (m, 4H), 7.17−6.98 (m, 3H), 6.78 (t, J = 7.2 Hz, 1H), 4.86 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 138.5, 136.4, 132.5, 131.1, 131.0, 130.6, 129.6, 128.9, 128.0, 127.8, 126.9, 125.7, 119.9, 119.6, 114.6, 114.1, 95.0, 44.1, 21.0; IR (KBr): 3417, 2918, 1621, 1589, 1551, 1499, 1471, 1339, 1257, 843, 819, 752 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{19}BrN_3O_2$: 460.0655; found: 460.0655.

*1-(4-Methoxyphenyl)-2-nitro-3-(thiophen-3-yl)-4,9-dihydropyrrolo[2,1-b]quinazoline (**4w**).* Yield: 70% (85 mg); Yellow solid; mp 147−149 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.39 (d, J = 8.4 Hz, 3H), 7.29 (s, 1H), 7.20−7.12 (m, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 7.8 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 6.43 (s, 1H), 4.83 (s, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.2, 136.3, 132.0, 131.6, 129.5, 129.3, 128.7, 127.5, 126.9, 125.7, 122.4, 120.9, 120.7, 115.1, 114.6, 114.3, 113.9, 92.5, 55.3, 44.6; IR (KBr): 3377, 1620, 1591, 1546, 1502, 1473, 1331, 1251, 1108, 867, 803, 765 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{18}N_3O_3S$: 404.1063; found: 404.1067.

*1-(4-Methoxyphenyl)-3-(naphthalen-2-yl)-2-nitro-4,9-dihydropyrrolo[2,1-b]quinazoline (**4x**).* Yield: 68% (91 mg); Yellow solid; mp 142−144 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.88−7.80 (m, 4H), 7.46 (d, J = 6.6 Hz, 3H), 7.39 (d, J = 7.8 Hz, 2H), 7.09 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 7.8 Hz, 2H), 6.95 (d, J = 7.2 Hz, 1H), 6.83 (t, J = 7.2 Hz, 1H), 6.61 (d, J = 7.8 Hz, 1H), 6.48 (s, 1H), 4.81 (s, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.2, 136.3, 133.5, 132.2, 132.1, 131.7, 129.6, 129.2, 128.6, 128.4, 128.2, 127.8, 127.67, 127.65, 127.5, 126.8, 126.1, 125.9, 120.9, 120.6, 114.6, 114.3, 113.9, 97.4, 55.3, 44.6; IR (KBr): 3402, 3050, 2931, 2836, 1622, 1589, 1550, 1467, 1334, 1250, 1177, 821, 747 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{22}N_3O_3$: 448.1656; found: 448.1661.

*Phenyl(1,2,3,4-tetrahydroquinazolin-2-yl)methanone (**B**).* Yield: 15% (18 mg); White solid; mp 161−163 °C; ^1H NMR (CD_3OD, 600 MHz): δ 7.94 (d, J = 7.2 Hz, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.48−7.28 (m, 4H), 7.20 (t, J = 7.8 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.03 (t, J = 8.4 Hz, 2H), 5.45 (s, 1H), 4.73 (s, 2H); ^{13}C NMR (CD_3OD, 150 MHz): δ 164.4, 131.3, 130.2, 130.0, 129.9, 129.8, 128.7, 128.0, 127.5, 127.4, 119.1, 73.0, 43.8; IR (KBr): 3513, 3370, 3052, 2939, 2844, 1733, 1599, 1482, 1447, 1255, 1137, 1089, 943, 909, 807, 750, 705 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{15}N_2O$: 239.1179; found: 239.1178.

*Phenyl(quinazolin-2-yl)methanone (**5**).* Yield: 62% (73 mg); Yellow solid; mp 106−108 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.55 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.14−8.07 (m, 2H), 8.04−7.96 (m, 2H), 7.77 (t, J = 7.6 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.7, 160.8, 158.7, 149.5, 135.4, 134.9, 133.4, 131.0, 129.4, 129.2, 128.3, 127.2, 124.7; IR (KBr): 3060, 2350, 1743, 1700, 1644, 1519, 1397, 1317, 807, 770, 734, 697 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{11}N_2O$: 235.0866; found: 235.0869.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01660.

Crystallographic data and copies of the ^1H and ^{13}C NMR spectra (PDF)

Crystallographic data of **4b** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chwuyd@mail.ccnu.edu.cn.

*E-mail: chwuax@mail.ccnu.edu.cn.

Notes

The authors declare no competing financial interest.

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