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Domino Reaction of Arylglyoxals with Pyrazol-5-amines: Selective Access to Pyrazolo-Fused 1,7-Naphthyridines, 1,3-Diazocanes, and Pyrroles

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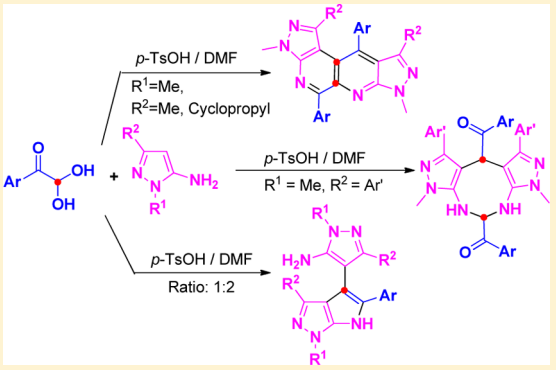
Supporting Information

ABSTRACT: New multicomponent domino reactions of arylglyoxals with pyrazol-5-amines have been established, providing selective access to unprecedented pyrazolo-fused 1,7-naphthyridines, 1,3-diazocanes, and pyrroles (up to 52 examples). The unreported dipyrazolo-fused 1,7-naphthyridines were regioselectively synthesized through a special double [3 + 2 + 1] heteroannulation accompanied by direct C−C formation between two electrophilic sites of arylglyoxals. The unusual [3 + 3 + 1 + 1] cyclization resulted in 20 examples of novel dipyrazolo-fused 1,3-diazocanes, whereas pyrrolo[2,3-*c*]pyrazoles were obtained in good yields by varying arylglyoxals **1** and pyrazol-5-amines **2** in the ratio 1:2. Mechanisms of formation of these three new types of heterocycles are also proposed.



INTRODUCTION

The structural range and biological importance of functional 1,7-naphthyridines have made them attractive targets of research for many years.[1] Their derivatives are found in various natural alkaloids such as eburnamonine,[2] anisopusine,[3] and tacamonine[4] (Figure 1), which have appreciable chemical and biological importance. In addition, a variety of synthetic 1,7-naphthyridine derivatives have possessed widespread biological activities, including hypotensive activity,[5] neurokinin NK1-receptor antagonists,[6] antimalarial agents,[7] selective Tpl2 kinase inhibitors,[8] anti-inflammatory activity,[9] and antagonistic agents.[10] The synthesis of functional 1,7-naphthyridines and their derivatives has played an important role in organic and medical chemistry due to their therapeutic and pharmacological properties. However, only a few references exist concerning 1,7-naphthyridine syntheses,[11] and these synthetic procedures still have several limitations involving poor yields, multiple steps, and even metal catalysts. These alarming situations have encouraged us to develop new methodologies for their syntheses.

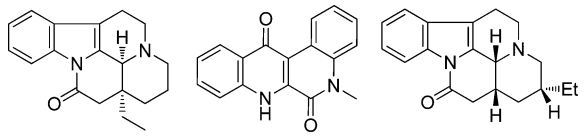


Figure 1. Several representative natural products.

Multicomponent domino reactions (MDRs) are some of the most effective methods to improve synthetic efficiency, which can realize reaction cascades, generating natural products or natural-like analogues.[12,13] Recently, we established a new four-component reaction of arylglyoxals[14] and electron-rich pyrazol-5-amines in *n*-butyric acid, providing highly substituted dipyrazolo-fused 2,6-naphthyridine derivatives (Scheme 1).[14a] In this reaction, when the Brønsted acid promoter was changed from *n*-butyric acid to *p*-TsOH, dipyrazolo-fused 1,7-naphthyridines were unexpectedly obtained through different [3 + 2 + 1] bis-cyclizations, whereas dipyrazolo-fused 2,6-naphthyridines were not observed (Scheme 1). It can be inferred that the acidity of the Brønsted acid promoter may control the direction of the reaction. Further investigations illustrated that the variation of substituents at pyrazole N1 or C3 positions can lead to different products (Scheme 1). Herein, we report this interesting discovery.

RESULTS AND DISCUSSION

To develop metal-free conditions for selective [3 + 2 + 1] bis-cyclizations, we began our study with the reaction of 2,2-dihydroxy-1-phenylethanone (**1a**) with 1,3-dimethyl pyrazol-5-

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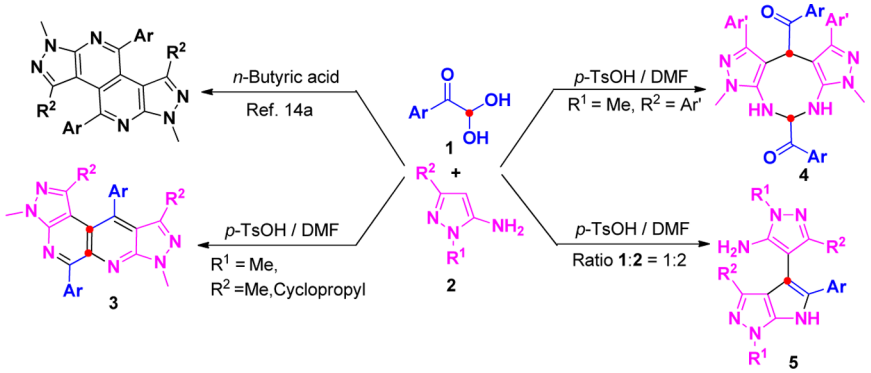
Scheme 1. Synthesis of Pyrazolo-Fused 1,7-Naphthyridines, 1,3-Diazocanes, and Pyrroles



amines **2** in DMF solvent. In our previous report, this reaction promoted by *n*-butyric acid gave tetracyclic dipyrazolo-fused 2,6-naphthyridines. To continue our efforts in this project, *p*-toluenesulfonic acid (*p*-TsOH) was chosen as a Brønsted acid promoter in this reaction system, due to its strong acidity, easy availability, and wide utilization in heterocyclic synthesis.[15] Delightedly, this bis-cyclization reaction proceeded smoothly to generate unprecedented tetracyclic dipyrazolo-fused 1,7-naphthyridines in 63% yield. The relative structure of compound **3c** was determined by spectroscopic analysis and X-ray crystallographic study (see the Supporting Information).

Encouraged by the interesting results reported above, we next optimized the reaction conditions for this protocol. We screened different Brønsted acid and Lewis acid promoters for the domino reaction using DMF as a solvent. As shown in Table 1, the reaction did not proceed in the presence of

Table 1. Optimization of Reaction Conditions

entry	promoter (amt (equiv))	solvent	temp (°C)	yield (%)
1	CF_3SO_3H (1.0)	DMF	100	trace
2	CF_3COOH (1.0)	DMF	100	trace
3	$ZnCl_2$ (1.0)	DMF	100	trace
4	$InCl_3$ (1.0)	DMF	100	trace
5	*p*-TsOH (1.0)	DMF	100	63
6	*p*-TsOH (1.0)	toluene	100	12
7	*p*-TsOH (1.0)	CH_3CN	100	29
8	*p*-TsOH (1.0)	EtOH	100	45
9	*p*-TsOH (1.0)	DMF	120	70
10	*p*-TsOH (1.0)	DMF	130	62
11	*p*-TsOH (0.2)	DMF	120	39
12	*p*-TsOH (1.5)	DMF	120	41

CF_3SO_3H or CF_3COOH or with Lewis acids such as $InCl_3$ and $ZnCl_2$. Subsequently, different solvents were optimized. The desired product **3a** was isolated in low yield (12%) in toluene solvent. Other polar solvents such as acetonitrile and EtOH were inferior to DMF in terms of yield. Taking DMF as the optimized solvent, we varied other parameters. To verify whether the role of *p*-TsOH was catalytic or stoichiometric, we carried out two reactions, where *p*-TsOH was used in amounts of 1.5 equiv (entry 10; see the Supporting Information) and 20 mol % (entry 11; see the Supporting Information). The use of a catalytic amount of *p*-TsOH decreased the yield of the product **3a**, whereas a higher loading of *p*-TsOH also failed to improve the yield of **3a**. When the reaction temperature was elevated to 120 °C, the use of 1.0 equiv of *p*-TsOH in DMF was more effective in pushing this reaction forward, resulting in product **3a** in 70% yield (entry 9).

Various structurally diverse arylglyoxals **1** and 1-methyl pyrazol-5-amines **2** were explored to establish the applicability of this protocol. The results are summarized in Table 2. A variety of functional groups in substituted arylglyoxal monohydrates were well tolerated to give moderate to good yields of dipyrazolo-fused 1,7-naphthyridines (**3a**–**l**). When the substituents on arylglyoxal monohydrates **1** were electron-withdrawing groups such as F, Cl, and Br, they showed weaker reactivity in comparison to those containing electron-neutral or electron-donating groups. Moreover, a cyclopropyl group at the 3-position of pyrazol-5-amines **2b** participated successfully in this reaction. Surprisingly, when an aryl group was placed at C3 of pyrazol-5-amines **2c**, the reaction did not provide the expected 1,7-naphthyridine but went in another direction to form the multifunctionalized 1,3-diazocane derivatives **4** (Table 3). These experimental facts indicated that the steric hindrance of substituents on the pyrazole ring may control the reaction pathway.

Functional 1,3-diazocanes belong to another family of species with an important framework, which have a nonplanar eight-membered ring with two nitrogen atoms. These diazocine units are expected to exhibit a boat (neutral state) to planar (dianion) conformational change via a two-electron-transfer process.[16] Therefore, the derivatives of diazocines are a significant class of synthons for biomimetic molecular recognition and supramolecular compunds.[17] Furthermore, 1,3-diazocane units commonly exist in natural products, represented by N^3,5′-cycloxanthosine[18] and cottoquinazolines A and D.[19] In view of their importance, we then explored the feasibility of this *p*-TsOH-promoted reaction for the formation of fused 1,3-diazocanes. Various functional groups in arylglyoxals **1** did not hamper the reaction process. Reactions of Me-, MeO-, Cl-, F-, and Br-substituted arylglyoxals **1** with **2** all proceeded efficiently to give fused tricyclic 1,3-diazocanes in 65–79% yields. This reaction also tolerated the 4-nitrophenylglyoxal **1f**, which was smoothly transformed into the targeted 1,3-diazocane **4f** in 74% yield. Moreover, 3-phenyl-, 3-(4-chlorophenyl)-, and 3-(2-thienyl)-substituted pyrazol-5-amines **2c**–**e** all successfully participated in this reaction as well, leading to the corresponding pyrazolo[3,4-*b*]pyridines **5** with good results (Table 4). It is noteworthy that the protocols provide unusual pathways for the formation of unreported dipyrazolo-fused 1,7-naphthyridine and 1,3-diazocane derivatives, which are normally difficult to synthesize by other methods.

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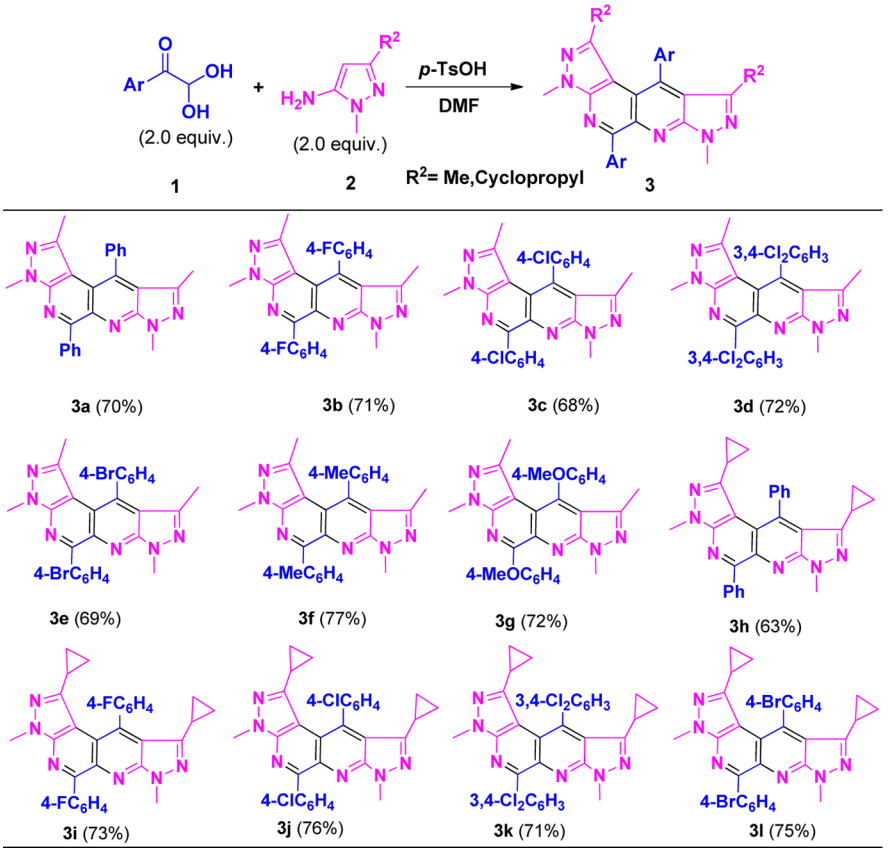
Table 2. Domino Synthesis of 1,7-Naphthyridines 3



Furthermore, we were eager to see the outcome of the reaction when pyrazol-5-amines **2** with an aryl group residing at the N1 position were employed as a multicomponent partners with arylglyoxals. Hence, we reacted 2,2-dihydroxy-1-phenylethanone (**1a**) with 1-phenyl-3-methylpyrazol-5-amine (**2f**) in DMF using *p*-TsOH as a promoter; after 20 min the unexpected pyrrolo[2,3-*c*]pyrazole **5a** was formed in 34% yield. In this reaction, **1a** and 1-phenyl-3-methylpyrazol-5-amine (**2f**) in a molar ratio of 1:2 were introduced to give the pyrrolo[2,3-*c*]pyrazole **5a**. Subsequently, the ratio of **1a** and **2f** was changed to 1:2, and the corresponding product **5a** was generated in a chemical yield of 78% under the same microwave irradiation conditions. The variation of substituents at pyrazole N1 and C3 positions, including phenyl, methyl, and cyclopropyl groups, afforded good yields of pyrazolo[3,4-*b*]pyridines **5** within short times. It should be noted that arylglyoxals **1** and the 3-(2-thienyl)-substituted pyrazol-5-amine **2e** in the ratio 1:2 also resulted in pyrrolo[2,3-*c*]pyrazole products **5q**−**t** in 70−74% yields. However, in the present system, the domino reaction between **1** and **2c**,**d** in a 1:2 ratio still gave dipyrazolo-fused 1,3-diazocanes predominantly, and pyrrolo[2,3-*c*]-pyrazoles were not observed, owing to their stronger steric hindrance. In general, these MDRs give new examples for synthesizing three types of heterocycles in an efficient and atom-economical strategy to discover new bioactive compounds.

The structural elucidation and attribution of regioselectivity of three types of heterocycles were unambiguously determined by their NMR spectroscopic analysis. The structures of 1,7-naphthyridines **3c** and 1,3-diazocanes **4a** and **5b** were further confirmed by X-ray diffraction analysis (see the Supporting Information). The regioselective formation of new dipyrazolo-fused 1,7-naphthyridines was easily achieved through a special [3 + 2 + 1] bis-cyclization with concomitant formation of five new σ bonds and direct C−C coupling between two electrophilic sites of arylglyoxals under metal-free or carbine-free conditions. The last two reactions readily resulted in an eight-membered macrocyclic motif and a five-membered ring, respectively, through a change of substituents on the pyrazole ring in a one-pot operation. This observation illustrates the high efficiency of bond formation, excellent selectivity, and remarkable increase in complexity starting from simple substrates.

We believe that this [3 + 2 + 1] bis-cyclization process is unique and different from that in our previous report.[14a] Electron-rich pyrazol-5-amines possessing strong 1,3-bis-nucleophilic centers showed high reactivity in heterocyclic synthesis, and both nucleophilic sites easily take part simultaneously in the cyclization. Thus, it is difficult to capture its uncyclized intermediate. We reasoned that a similar uncyclized intermediate may be captured when the nucleophilicity of the 1,3-bis-nucleophile is softer. To understand this domino process, we attempted to treat *p*-toluidine with soft nucleophilicity to replace one molecule of pyrazol-5-amines. Then, the four-component reaction of **1e** with **2a** and *p*-toluidine **6** was performed in the presence of 1.0 equiv of *p*-TsOH in DMF solvent at 120 °C under microwave irradiation conditions. Fortunately, the pyrazolo[3,4-*b*]pyridine **7** was generated in 62% yield (Scheme 2). It is indicated that the mechanism for the synthesis of pyrazolo-fused 1,7-naphthyridines **3** may undergo this similar process of formation of a pyrazolo[3,4-*b*]pyridine intermediate.

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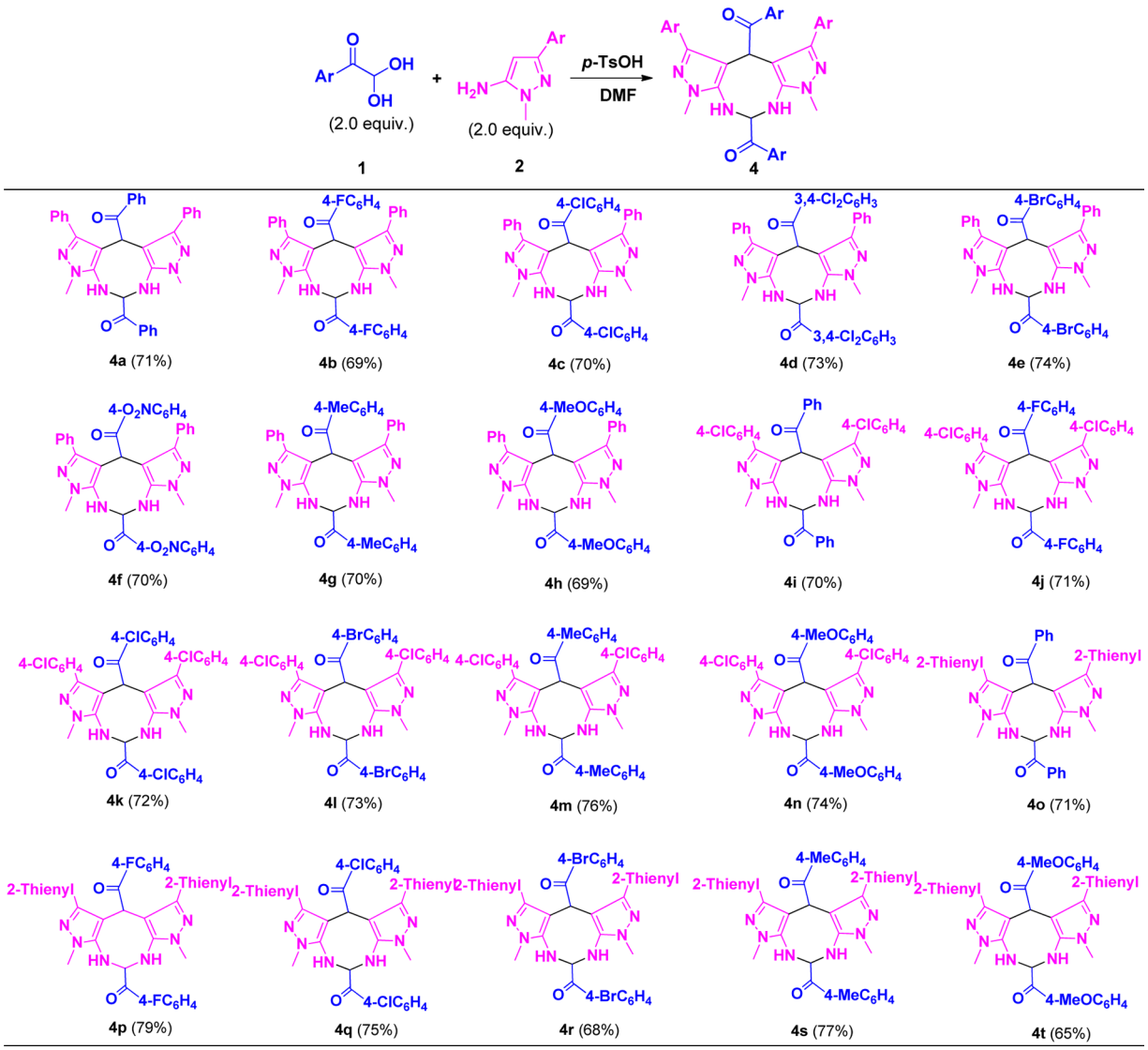
Table 3. Domino Synthesis of 1,3-Diazocanes 4



On the basis of experimental results, reasonable mechanisms for three different domino reactions are postulated in Schemes 3 and 4. In the former, arylglyoxals **1** protonated by *p*-TsOH underwent dehydration and subsequent addition with pyrazol-5-amines **2** to intermediate **A**, followed by intermolecular C═O addition of intermediate **B** and dehydration to yield active allenes **E**. Next, intramolecular 6π electrocyclization of allenes **E** occurred, providing pyrazolo[3,4-*b*]pyridines **G**, similar to product **7** above. The pyrazolo[3,4-*b*]pyridine intermediate **G** was transformed into the final dipyrazolo-fused 1,7-naphthyridines **3** through intramolecular second C═O addition and third dehydration. Similar to the former reaction, the second reaction initially gave the imines **B**, which were involved in the C═N addition with intermediate **C** to generate adducts **I**. The 1,3-diazocanes were obtained through intramolecular Michael addition and tautomerization. In both reactions, the key steps of MDRs involve tandem formation of two different condensation intermediates **B** and **C** that are trapped by two different C═O and C═N additions, although the reason for these selective additions is not clear to us. The third reaction involved initial condensation, intermolecular Michael addition, and cyclization.

In conclusion, we have discovered novel multicomponent domino reactions (arylglyoxals and pyrazol-5-amines) for the selective synthesis of fused 1,7-naphthyridines, 1,3-diazocanes, and pyrazoles by varying the substituents on the pyrazol-5-amine ring. The [3 + 2 + 1] bis-cyclization reaction simultaneously installs two C−N and three C−C bonds through a key 6π electrocyclization process, showing that the procedure allows the efficient synthesis of diverse 1,7-naphthyridine derivatives selectively. The latter [3 + 3 + 1 + 1] heteroannulation represents the first example for the formation of this special fused 1,3-diazocane skeleton, which provides a new insight into multicomponent reactions. The last [3 + 2] heterocyclization reaction worked well with a broad range of highly compatible substrates to afford pyrrolo[2,3-*c*]pyrazoles with biological relevance in good yields. Further investigations are in progress to probe the mechanism of these transformations and to synthesize more complex products and evaluate their biological activity.

EXPERIMENTAL SECTION

General Methods. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden.

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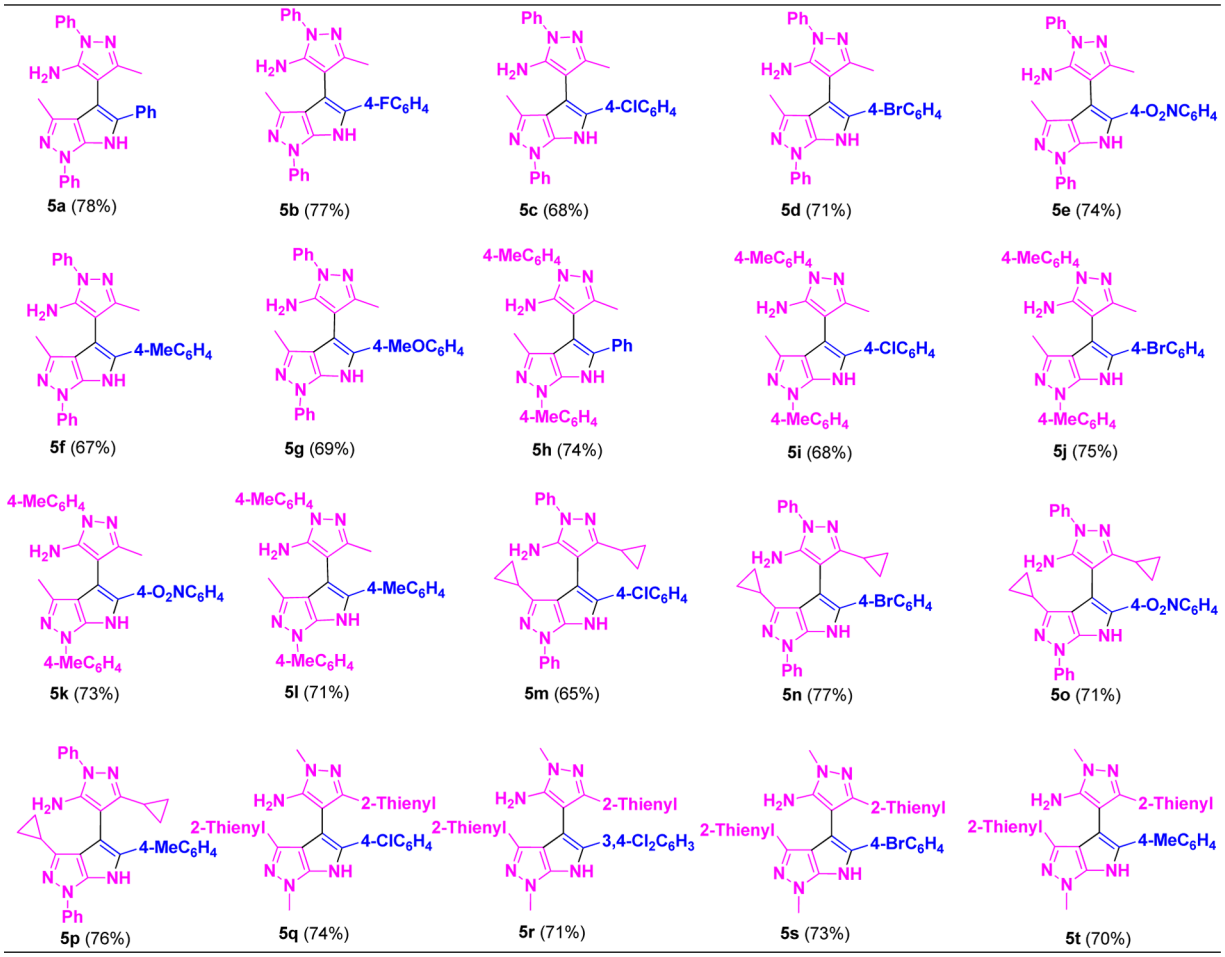
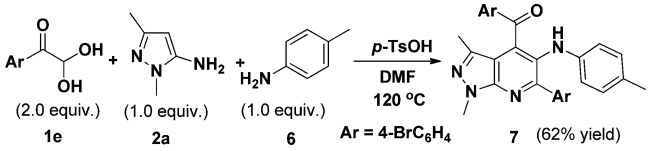
Table 4. Domino Synthesis of 1,3-Diazocanes 5



Scheme 2. Control Experiment



The reaction temperatures were measured by infrared detector during microwave heating.

Representative Synthesis of 3: 1,3,7,9-Tetramethyl-5,10-diphenyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-*f*][1,7]-naphthyridine (3a). Typically, 2,2-dihydroxy-1-phenylethanone (**1a**; 2.2 mmol, 0.334 g, 1.1 equiv) and 1,3-dimethyl-1*H*-pyrazol-5-amine (**2a**; 2.0 mmol, 0.222 g, 1.0 equiv) were introduced into a 10 mL Initiator reaction vial, and *p*-TsOH (1.0 equiv), and DMF (1.5 mL) were then added successively. Subsequently, the reaction vial was closed and then prestirred for 10 s. The mixture was irradiated (time, 20 min; temperature, 120 °C; absorption level, high; fixed hold time) until TLC (petroleum ether/acetone 3/1) revealed that conversion of the starting material **2a** was complete. After it was cooled to room temperature, the reaction mixture was diluted with cold water (20 mL) and neutralized with 10% NaOH solution. The solid product was collected by Büchner filtration and was purified by flash column chromatography (silica gel, petroleum ether/acetone mixtures, 7/1, v/v) to afford the desired pure **3a** as a yellow solid (0.146 g, yield 70%, mp 279−280 °C): ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.25 (d, J = 7.2 Hz, 2H), 7.60−7.51 (m, 8H), 4.19 (s, 3H), 4.11 (s, 3H), 1.94 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 160.2, 148.3, 146.8, 141.7, 141.1, 141.0, 140.2, 139.3, 138.1, 131.6, 131.1, 129.3, 129.0, 128.3, 127.6, 121.9, 116.4, 105.9, 34.0, 33.5, 15.4, 14.9; IR (KBr, ν, cm^{-1}) 3046, 1586, 1544, 1501, 1483, 1446, 1406, 1384, 1344; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{23}N_6$ 419.1984 [M + H]$^+$, found 419.1963.

*5,10-Bis(4-fluorophenyl)-1,3,7,9-tetramethyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3b**).* Yellow solid: 0.322 g, yield 71%; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.29−8.26 (m, 2H), 7.53−7.49 (m, 2H), 7.32−7.27 (m, 4H), 4.20 (s, 3H), 4.12 (s, 3H), 1.98 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 163.5 ($^1J_{CF}$ = 247.6 Hz), 163.4 ($^{1'}J_{CF}$ = 248.3 Hz), 159.1, 148.2, 146.7, 141.4, 140.9, 140.1, 139.9, 135.2 ($^4J_{CF}$ = 3.5 Hz), 134.0 ($^{4'}J_{CF}$ = 3.7 Hz), 133.5 ($^3J_{CF}$ = 8.2 Hz), 132.8 ($^{3'}J_{CF}$ = 8.1 Hz), 122.1, 115.6 ($^2J_{CF}$ = 21.3 Hz), 114.6 ($^{2'}J_{CF}$ = 21.3 Hz), 105.8, 100.0, 34.0, 33.6, 15.8, 15.0; IR (KBr, ν, cm^{-1}) 2936, 1598, 1548, 1450, 1407, 1346; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{21}F_2N_6$ 455.1796 [M + H]$^+$, found 455.1783.

*5,10-Bis(4-chlorophenyl)-1,3,7,9-tetramethyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3c**).* Yellow solid: 0.330 g, yield 68%; mp 288−289 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.21 (d, J = 8.4 Hz, 2H), 7.59−7.54 (m, 4H), 7.47 (d, J = 8.0 Hz, 2H), 4.19 (s, 3H), 4.11 (s, 3H), 1.99 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 159.0, 148.2, 146.7, 141.3, 140.8, 140.0, 139.6, 137.6, 136.4, 135.6, 135.3, 132.9, 132.4, 128.7, 127.8, 121.8, 116.3, 105.8, 34.0, 33.6, 15.9, 15.1; IR (KBr, ν, cm^{-1}) 2937, 1586, 1543, 1484, 1449, 1377, 1342; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{21}Cl_2N_6$ 487.1205 [M + H]$^+$, found 487.1198.

*5,10-Bis(3,4-dichlorophenyl)-1,3,7,9-tetramethyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3d**).* Yellow solid: 0.399 g, yield 72%; mp 268−270 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.49 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.73−7.67 (m, 3H), 7.42 (d, J = 8.0 Hz, 1H), 4.24 (s, 3H), 4.17 (s, 3H), 2.07 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 148.1, 146.5,

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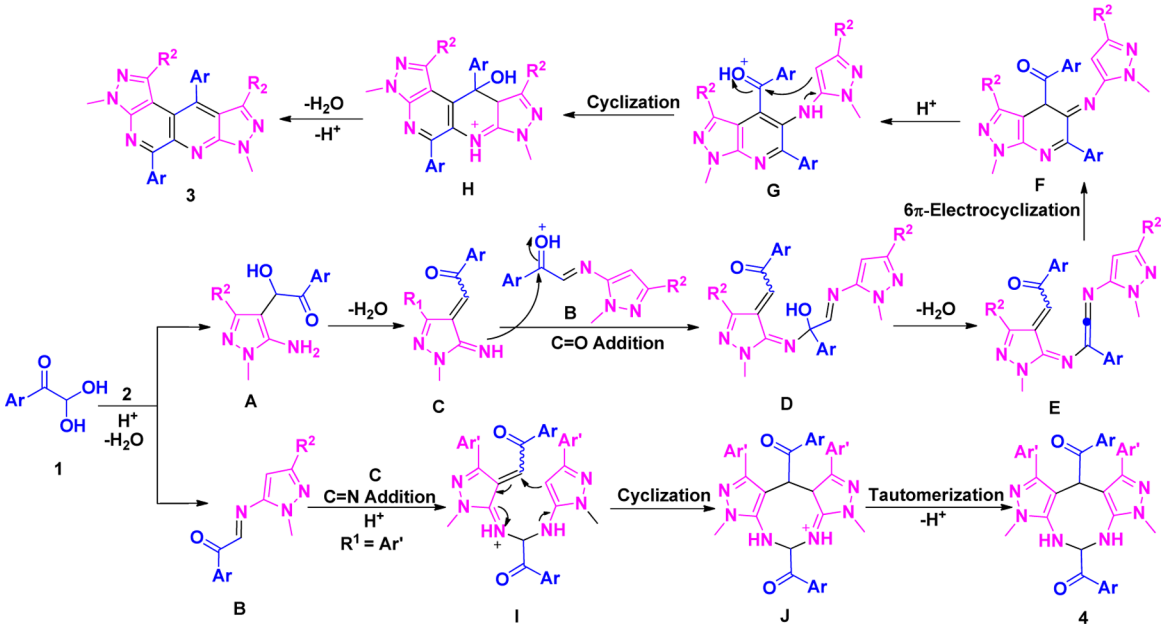
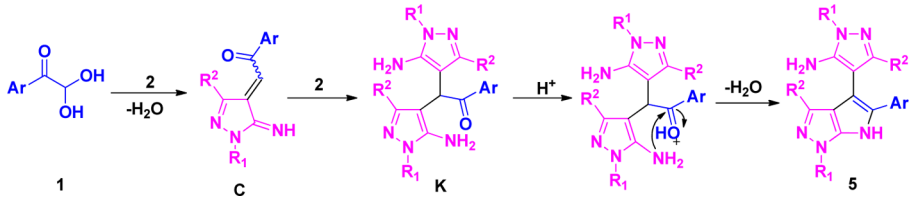
Scheme 3. Proposed Mechanisms for the Synthesis of Products 3 and 4



Scheme 4. Proposed Mechanism for the Synthesis of Products 5



146.2, 143.0, 141.1, 140.5, 139.8, 138.8, 138.0, 134.0, 133.6, 133.4, 133.0, 132.8, 131.8, 130.8, 130.5, 130.4, 129.6, 121.6, 116.2, 100.0, 34.1, 33.6, 16.1, 15.3; IR (KBr, ν, cm^{-1}): 2939, 1586, 1540, 1501, 1473, 1446, 1406, 1380, 1342; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{19}Cl_4N_6$ 555.0425 $[M + H]^+$, found 555.0405.

*5,10-Bis(4-bromophenyl)-1,3,7,9-tetramethyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3e**).* Yellow solid: 0.397 g, yield 69%; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.14 (d, J = 8.0 Hz, 2H), 7.75−7.70 (m, 4H), 7.41 (d, J = 8.0 Hz, 2H), 4.19 (s, 3H), 4.12 (s, 3H), 2.00 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 160.8, 148.2, 146.7, 141.3, 140.8, 140.0, 139.6, 138.0, 136.8, 133.2, 132.7, 132.2, 131.7, 131.6, 130.8, 121.7, 116.3, 105.8, 34.0, 33.6, 15.8, 15.1; IR (KBr, ν, cm^{-1}) 2937, 1585, 1543, 1483, 1406, 1344; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{21}Br_2N_6$ 577.0174 $[M + H]^+$, found 577.0152.

*1,3,7,9-Tetramethyl-5,10-di-p-tolyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3f**).* Yellow solid: 0.343 g, yield 77%; mp 298−299 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.19 (d, J = 7.6 Hz, 2H), 7.41−7.36 (m, 6H), 4.21 (s, 3H), 4.12 (s, 3H), 2.53 (s, 3H), 2.51 (s, 3H), 1.97 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 148.4, 146.8, 141.7, 141.4, 141.3, 140.4, 140.0, 139.3, 139.2, 136.4, 135.0, 131.6, 131.0, 128.9, 128.4, 122.0, 116.5, 105.9, 33.9, 33.6, 21.5(2), 21.5(1), 15.4, 15.0; IR (KBr, ν, cm^{-1}) 2932, 1585, 1543, 1505, 1449, 1341; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{27}N_6$ 447.2297 $[M + H]^+$, found 447.2286.

*5,10-Bis(4-methoxyphenyl)-1,3,7,9-tetramethyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3g**).* Yellow solid: 0.344 g, yield 72%; mp 281−282 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.31 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.10 (t, J = 9.2 Hz, 4H), 4.20 (s, 3H), 4.13 (s, 3H), 3.95 (s, 6H), 2.01 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 160.5, 160.4, 159.5, 148.3, 146.9, 141.7, 141.2, 141.0, 140.4, 133.2, 132.3, 131.9, 130.4, 122.4, 116.8, 113.7, 113.1, 105.7, 55.5, 55.4, 33.9, 33.5, 15.8, 15.1; IR (KBr, ν, cm^{-1}) 2933, 1605, 1590, 1544, 1518, 1487, 1383; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{27}N_6O_2$, 479.2195 $[M + H]^+$, found 479.2183.

*1,9-Dicyclopropyl-3,7-dimethyl-5,10-diphenyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3h**).* Yellow solid: 0.296 g, yield 63%; mp 209−210 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.25 (d, J = 7.2 Hz, 2H), 7.66−7.64 (m, 2H), 7.58−7.54 (m, 3H), 7.52−7.49 (m, 3H), 4.16 (s, 3H), 4.08 (s, 3H), 1.22−1.16 (m, 1H), 0.90−0.86 (m, 2H), 0.70−0.66 (m, 2H), 0.63−0.58 (m, 2H), 0.34−0.30 (m, 2H), 0.17−0.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 159.8, 148.6, 146.6, 146.4, 145.9, 141.4, 140.3, 139.4, 138.7, 131.6, 130.8, 128.9, 128.8, 128.2, 127.5, 121.9, 116.6, 106.3, 34.1, 33.6, 10.2, 10.0, 9.3, 7.7; IR (KBr, ν, cm^{-1}) 3056, 1543, 1487, 1443, 1387, 1354; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{27}N_6$ 471.2297 $[M + H]^+$, found 471.2283.

*1,9-Dicyclopropyl-5,10-bis(4-fluorophenyl)-3,7-dimethyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3i**).* Yellow solid: 0.369 g, yield 73%; mp 231−232 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.28−8.25 (m, 2H), 7.66−7.62 (m, 2H), 7.26−7.23 (m, 4H), 4.16 (s, 3H), 4.09 (s, 3H), 1.24−1.19 (m, 1H), 0.93−0.90 (m, 2H), 0.74−0.70 (m, 2H), 0.68−0.64 (m, 2H), 0.42−0.38 (m, 2H), 0.28−0.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 163.5 ($^1J_{CF}$ = 247.2 Hz), 163.2 ($^{1'}J_{CF}$ = 247.8 Hz), 158.7, 148.5, 146.5, 146.2, 145.6, 140.2, 140.1(6), 135.3 ($^4J_{CF}$ = 3.3 Hz), 134.6 ($^{4'}J_{CF}$ = 3.4 Hz), 133.5 ($^3J_{CF}$ = 8.1 Hz), 132.6 ($^{3'}J_{CF}$ = 8.0 Hz), 122.0, 116.8, 115.4 ($^2J_{CF}$ = 21.3 Hz), 114.5 ($^{2'}J_{CF}$ = 21.3 Hz), 106.2, 34.2, 33.6, 10.4, 10.1, 9.2, 7.7; IR (KBr, ν, cm^{-1}) 3008, 1605, 1583, 1543, 1514, 1456, 1354; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{25}F_2N_6$ 507.2109 $[M + H]^+$, found 507.2101.

*5,10-Bis(4-chlorophenyl)-1,9-dicyclopropyl-3,7-dimethyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3j**).* Yellow solid: 0.409 g, yield 76%; mp 243−246 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.20 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H),

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7.52 (t, J = 10.0 Hz, 4H), 4.16 (s, 3H), 4.08 (s, 3H), 1.28−1.23 (m, 1H), 0.94−0.90 (m, 2H), 0.75−0.72 (m, 2H), 0.70−0.65 (m, 2H), 0.42−0.39 (m, 2H), 0.34−0.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 158.6, 148.5, 146.5, 146.2, 145.5, 140.1, 139.9, 137.6, 136.9, 132.9, 132.3, 131.3, 129.1, 128.6, 127.8, 121.8, 116.5, 106.2, 34.2, 33.6, 10.4, 10.2, 9.5, 7.7; IR (KBr, ν, cm^{-1}) 3004, 1587, 1541, 1487, 1396, 1354; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{25}Cl_2N_6$ 539.1518 $[M + H]^+$, found 539.1503.

*1,9-Dicyclopropyl-5,10-bis(3,4-dichlorophenyl)-3,7-dimethyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3k**).* Yellow solid: 0.430 g, yield 71%; mp 240−242 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.45 (d, J = 2.0 Hz, 1H), 8.13−8.11 (m, 1H), 7.86 (d, J = 1.6 Hz, 1H), 7.62 (t, J = 8.8 Hz, 2H), 7.47−7.45 (m, 1H), 4.16 (s, 3H), 4.11 (s, 3H), 1.29−1.23 (m, 1H), 1.02 (s, 1H), 0.90 (s, 2H), 0.79−0.66 (m, 3H), 0.45−0.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 156.9, 148.5, 146.3, 146.1, 145.2, 139.8, 138.9, 138.4, 138.1, 133.5, 133.3, 133.2, 133.1, 132.8, 131.7, 130.7, 130.3, 130.2, 129.5, 121.5, 116.4, 106.2, 34.3, 33.7, 10.7, 10.3, 9.6, 8.7, 7.9, 7.2; IR (KBr, ν, cm^{-1}) 3003, 1584, 1537, 1475, 1391; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{23}Cl_4N_6$ 607.0738 $[M + H]^+$, found 607.0722.

*5,10-Bis(4-bromophenyl)-1,9-dicyclopropyl-3,7-dimethyl-3,7-dihydrodipyrazolo[3,4-b:4′,3′-f][1,7]naphthyridine (**3l**).* Yellow solid: 0.471 g, yield 75%; mp 266−268 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.14 (d, J = 8.0 Hz, 2H), 7.71−7.66 (m, 4H), 7.55 (d, J = 8.0 Hz, 2H), 4.16 (s, 3H), 4.09 (s, 3H), 1.30−1.24 (m, 1H), 0.93−0.90 (m, 2H), 0.76−0.66 (m, 4H), 0.44−0.40 (m, 2H), 0.34−0.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 158.6, 148.5, 146.5, 146.3, 145.5, 140.0, 139.9, 138.1, 137.4, 133.2, 132.5, 131.5, 130.8, 123.6, 123.2, 121.7, 116.4, 106.2, 34.2, 33.7, 10.5, 10.2, 9.5, 7.7; IR (KBr, ν, cm^{-1}) 3087, 3009, 1590, 1543, 1485, 1392,1353; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{25}Br_2N_6$ 629.0487 $[M + H]^+$, found 629.0466.

Representative Synthesis of 4: (3,7-Dimethyl-1,9-diphenyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-*d*:4′,3′-*g*][1,3]diazocine-5,10-diyl)bis(phenylmethanone) (4a). Typically, 2,2-dihydroxy-1-phenylethanone (**1a**; 2.2 mmol, 0.334 g, 1.1 equiv) and 1-methyl-3-phenyl-1*H*-pyrazol-5-amine (**2c**; 2.0 mmol, 0.346 g, 1.0 equiv) were introduced into a 10 mL Initiator reaction vial, and *p*-TsOH (1.0 equiv) and DMF (1.5 mL) were then added successively. Subsequently, the reaction vial was closed and then prestirred for 10 s. The mixture was irradiated (time, 25 min; temperature, 120 °C; absorption level, high; fixed hold time) until TLC (petroleum ether/acetone 3/1) revealed that conversion of the starting material **2c** was complete. After it was cooled to room temperature, the reaction mixture was diluted with cold water (20 mL) and neutralized with 10% NaOH solution. The solid product was collected by Büchner filtration and was purified by flash column chromatography (silica gel, petroleum ether/acetone mixtures, 8/1, v/v) to afford the desired pure **4a**. Yellow solid: 0.410 g, yield 71%; mp 269−270 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.11 (d, J = 7.6 Hz, 2H), 7.77 (t, J = 7.2 Hz, 1H), 7.69 (t, J = 7.6 Hz, 2H), 7.48 (t, J = 7.2 Hz), 7.35 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 7.19 (t, J = 7.6 Hz, 6H), 7.13 (d, J = 7.2 Hz, 4H), 6.76 (t, J = 8.0 Hz, 1H), 6.19 (d, J = 8.4 Hz, 2H), 5.83 (s, 1H), 3.53 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 202.7, 193.1, 148.4, 145.7, 135.9, 134.7, 134.3, 134.0, 133.8, 129.6, 129.2, 129.0, 128.9, 128.5, 128.1, 127.9, 100.5, 67.7, 41.6, 35.3; IR (KBr, ν, cm^{-1}) 3374, 3191, 1695, 1674, 1567, 1529, 1446, 1370; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{29}N_6O_2$ 577.2347 $[M - H]^-$, found 577.2346.

*(3,7-Dimethyl-1,9-diphenyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-fluorophenyl)methanone) (**4b**).* Yellow solid: 0.424 g, yield 69%; mp 283−285 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.18−8.14 (m, 2H), 7.56 (t, J = 8.8 Hz, 2H), 7.42−7.39 (m, 2H), 7.32−7.28 (m, 2H), 7.19 (t, J = 8.0 Hz, 4H), 7.13−7.11 (m, 4H), 7.03 (t, J = 8.8 Hz, 2H), 6.72 (t, J = 8.4 Hz, 1H), 6.18 (d, J = 8.4 Hz, 2H), 5.76 (s, 1H), 3.54 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 201.2, 191.7, 165.9 ($^1J_{CF}$ = 252.1 Hz), 165.3 ($^{1'}J_{CF}$ = 251.4 Hz), 148.4, 145.6, 133.9, 132.5 ($^4J_{CF}$ = 2.9 Hz), 132.2 ($^3J_{CF}$ = 9.6 Hz), 131.4 ($^{3'}J_{CF}$ = 9.4 Hz), 131.0 ($^{4'}J_{CF}$ = 2.8 Hz), 128.9, 128.1, 127.9, 116.8 ($^2J_{CF}$ = 22.2 Hz), 116.1 ($^{2'}J_{CF}$ = 21.7 Hz), 100.4, 67.7, 41.6, 35.3; IR (KBr, ν, cm^{-1}) 3347, 3175, 1699, 1584, 1570, 1531, 1489, 1447, 1393; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{27}F_2N_6O_2$ 613.2164 $[M - H]^-$, found 613.2143.

*(3,7-Dimethyl-1,9-diphenyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-chlorophenyl)methanone) (**4c**).* Yellow solid: 0.452 g, yield 70%; mp 288−289 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.07 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.33−7.26 (m, 6H), 7.19 (t, J = 7.6 Hz, 4H), 7.11 (d, J = 7.2 Hz, 4H), 6.66 (t, J = 8.0 Hz, 1H), 6.20 (d, J = 8.0 Hz, 2H), 5.74 (s, 1H), 3.54 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 201.7, 192.0, 148.4, 145.6, 139.5, 138.7, 134.5, 133.8, 133.1, 131.0, 130.3, 129.8, 129.1, 129.0, 128.1, 127.9, 100.2, 67.9, 41.7, 35.4; IR (KBr, ν, cm^{-1}) 3344, 3173, 1696, 1587, 1570, 1533, 1489, 1447, 1399; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{27}Cl_2N_6O_2$ 645.1567 $[M - H]^-$, found 645.1574.

*(3,7-Dimethyl-1,9-diphenyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((3,4-dichlorophenyl)methanone) (**4d**).* Yellow solid: 0.521 g, yield 73%; mp 274−276 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.17 (s, 1H), 8.03−7.97 (m, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.36−7.29 (m, 3H), 7.20 (t, J = 7.6 Hz, 4H), 7.12 (d, J = 7.6 Hz, 4H), 6.57 (t, J = 8.4 Hz, 1H), 6.24 (d, J = 8.0 Hz, 2H), 5.71 (s, 1H), 3.56 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 200.8, 191.2, 148.4, 145.6, 137.3, 136.8, 136.0, 134.7, 133.6, 132.5, 132.1, 132.0, 131.4, 131.0, 130.1, 129.6, 129.0, 128.4, 128.2, 127.9, 99.9, 68.4, 41.9, 35.4; IR (KBr, ν, cm^{-1}) 3369, 3155, 1698, 1655, 1583, 1571, 1498, 1448, 1377; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{25}Cl_4N_6O_2$ 713.0788 $[M - H]^-$, found 713.0789.

*(3,7-Dimethyl-1,9-diphenyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-bromophenyl)methanone) (**4e**).* Yellow solid: 0.545 g, yield 74%; mp 290−292 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.07 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.33−7.24 (m, 6H), 7.19 (t, J = 7.6 Hz, 4H), 7.11 (d, J = 7.6 Hz, 4H), 6.66 (t, J = 8.4 Hz, 1H), 6.21 (d, J = 8.0 Hz, 2H), 5.74 (s, 1H), 3.55 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 201.2, 191.6, 147.9, 145.1, 139.1, 138.2, 134.0, 133.4, 132.6, 130.5, 129.8, 129.3, 128.6, 128.5, 127.6, 127.4, 99.7, 67.4, 41.2, 34.9; IR (KBr, ν, cm^{-1}) 3342, 3182, 1697, 1587, 1490, 1448, 1399; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{27}Br_2N_6O_2$ 735.0542 $[M - H]^-$, found 735.0529.

*(3,7-Dimethyl-1,9-diphenyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-nitrophenyl)methanone) (**4f**).* Yellow solid: 0.468 g, yield 70%; mp 290−291 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.54 (d, J = 9.2 Hz, 2H), 8.26 (d, J = 9.2 Hz, 2H), 8.00 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.21 (t, J = 8.0 Hz, 4H), 7.12 (t, J = 7.2 Hz, 4H), 6.61 (t, J = 8.0 Hz, 1H), 6.25 (d, J = 8.0 Hz, 2H), 5.77 (s, 1H), 3.53 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 201.5, 191.5, 150.2, 149.7, 147.9, 145.0, 140.6, 138.9, 133.2, 129.9, 128.9, 128.5, 127.6, 127.4, 124.1, 123.4, 99.3, 68.1, 41.8, 34.8; IR (KBr, ν, cm^{-1}) 3366, 3178, 1697, 1603, 1568, 1520, 1444, 1378; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{27}N_8O_6$, 667.2052 $[M - H]^-$, found 667.2031.

*(3,7-Dimethyl-1,9-diphenyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis(p-tolylmethanone) (**4g**).* Yellow solid: 0.424 g, yield 70%; mp 271−273 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.00 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.31−7.25 (m, 4H), 7.18 (t, J = 7.2 Hz, 4H), 7.12 (d, J = 7.2 Hz, 4H), 7.00 (d, J = 8.0 Hz, 2H), 6.75 (t, J = 8.4 Hz, 1H), 6.14 (d, J = 8.4 Hz, 2H), 5.80 (s, 1H), 3.53 (s, 6H), 2.44 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 201.6, 192.1, 147.9, 145.2, 144.9, 143.9, 133.5, 132.6, 131.2, 129.6, 129.0, 128.9, 128.4, 128.2, 127.5, 127.4, 100.1, 67.0, 40.9, 34.8, 21.3, 20.9; IR (KBr, ν, cm^{-1}) 3368, 3187, 1694, 1606, 1568, 1528, 1446, 1378; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{33}N_6O_2$ 605.2665 $[M - H]^-$, found 605.2653.

*(3,7-Dimethyl-1,9-diphenyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-methoxyphenyl)methanone) (**4h**).* Yellow solid: 0.440 g, yield 69%; mp 263−265 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.09 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.2 Hz, 2H), 7.22 (t, J = 8.8 Hz, 3H), 7.18−7.13 (m, 7H), 6.78 (t, J = 8.4 Hz, 1H), 6.70 (d, J = 8.8 Hz,

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2H), 6.13 (d, J = 8.4 Hz, 2H), 5.76 (s, 1H), 3.90 (s, 3H), 3.75 (s, 3H), 3.55 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 200.7, 191.5, 164.4, 163.6, 148.3, 145.7, 134.1, 131.7, 131.0, 128.9, 128.3, 128.0, 127.9, 126.9, 114.9, 114.2, 100.8, 67.2, 56.2, 56.0, 41.3, 35.3; IR (KBr, ν, cm^{-1}) 3374, 1684, 1655, 1601, 1570, 1528, 1443, 1377; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{33}N_6O_4$, 637.2558 [M − H]$^-$, found 637.2528.

(1,9-Bis(4-chlorophenyl)-3,7-dimethyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis-(phenylmethanone) ***(4i)***. Yellow solid: 0.452 g, yield 70%; mp 283−285 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.08 (d, J = 8.8 Hz, 2H), 7.78 (t, J = 7.2 Hz, 1H), 7.70 (t, J = 7.6 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.36−7.34 (m, 2H), 7.30−7.25 (m, 6H), 7.12 (d, J = 8.4 Hz, 4H), 6.66 (t, J = 8.4 Hz, 1H), 6.23 (d, J = 8.4 Hz, 2H), 5.61 (s, 1H), 3.53 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 202.8, 192.9, 147.2, 145.8, 135.9, 134.7, 134.2, 133.8, 132.9, 132.8, 129.6, 129.5(7), 129.2, 129.1, 129.0, 128.4, 100.6, 67.6, 41.8, 35.4; IR (KBr, ν, cm^{-1}) 3354, 3187, 1696, 1634, 1595, 1580, 1564, 1446, 1373; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{27}Cl_2N_6O_2$ 645.1573 [M − H]$^-$, found 645.1558.

(1,9-Bis(4-chlorophenyl)-3,7-dimethyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-fluorophenyl)methanone) ***(4j)***. Yellow solid: 0.484 g, yield 71%; mp 280−282 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.16−8.12 (m, 2H), 7.56 (t, J = 8.8 Hz, 2H), 7.45−7.41 (m, 2H), 7.29 (t, J = 8.4 Hz, 4H), 7.15−7.10 (m, 6H), 6.62 (t, J = 8.0 Hz, 1H), 6.24 (d, J = 8.4 Hz, 2H), 5.55 (s, 1H), 3.54 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 201.3, 191.5, 166.0 ($^1J_{CF}$ = 251.9 Hz), 165.4 ($^{1'}J_{CF}$ = 251.4 Hz), 147.1, 145.7, 133.0, 132.7, 132.4 ($^4J_{CF}$ = 2.8 Hz), 132.2 ($^3J_{CF}$ = 9.8 Hz), 131.3 ($^{3'}J_{CF}$ = 9.6 Hz), 131.0 ($^{4'}J_{CF}$ = 2.8 Hz), 129.6, 129.1, 116.8 ($^2J_{CF}$ = 22.1 Hz), 116.2 ($^{2'}J_{CF}$ = 21.9 Hz), 100.6, 67.7, 41.9, 35.4; IR (KBr, ν, cm^{-1}) 3353, 3180, 1692, 1631, 1592, 1581, 1562, 1446, 1371; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{25}Cl_2F_2N_6O_2$ 681.1382 [M − H]$^-$, found 681.1356.

(1,9-Bis(4-chlorophenyl)-3,7-dimethyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-chlorophenyl)methanone) ***(4k)***. Yellow solid: 0.514 g, yield 72%; mp 294−296 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.05 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.38−7.33 (m, 4H), 7.29 (d, J = 8.4 Hz, 4H), 7.11 (d, J = 8.4 Hz, 4H), 6.55 (t, J = 8.0 Hz, 1H), 6.25 (d, J = 8.4 Hz, 2H), 5.53 (s, 1H), 3.54 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 201.8, 191.9, 147.2, 145.7, 139.6, 138.8, 134.5, 133.0, 132.9(7), 132.7, 131.0, 130.2, 129.8, 129.6, 129.2, 129.1, 100.4, 67.9, 41.9, 35.4; IR (KBr, ν, cm^{-1}) 3347, 3183, 1693, 1633, 1587, 1567, 1446, 1399, 1374; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{25}Cl_4N_6O_2$ 713.0764 [M − H]$^-$, found 713.0761.

(1,9-Bis(4-chlorophenyl)-3,7-dimethyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-bromophenyl)methanone) ***(4l)***. Yellow solid: 0.587 g, yield 73%; mp 288−290 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.98−7.93 (m, 4H), 7.51 (d, J = 8.8 Hz, 2H), 7.28 (t, J = 8.4 Hz, 6H), 7.12 (d, J = 8.4 Hz, 4H), 6.55 (t, J = 8.0 Hz, 1H), 6.25 (d, J = 8.0 Hz, 2H), 5.52 (s, 1H), 3.54 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 202.0, 192.1, 147.1, 145.7, 134.8, 133.3, 133.0, 132.7, 132.6, 132.2, 131.0, 130.3, 129.6, 129.1, 128.9, 128.0, 100.4, 67.8, 41.9, 35.4; IR (KBr, ν, cm^{-1}) 3342, 3106, 1676, 1650, 1600, 1520, 1406, 1347; HRMS (ESI-TOF) m/z calcd for $C_{36}H_{25}Br_2Cl_2N_6O_2$ 802.9757 [M − H]$^-$, found 802.9781.

(1,9-Bis(4-chlorophenyl)-3,7-dimethyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis(p-tolylmethanone) ***(4m)***. Yellow solid: 0.512 g, yield 76%; mp 298−300 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.98 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 8.0 Hz, 6H), 7.12−7.06 (m, 6H), 6.66 (t, J = 8.4 Hz, 1H), 6.19 (d, J = 8.4 Hz, 2H), 5.58 (s, 1H), 3.53 (s, 6H), 2.44 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 202.0, 192.4, 147.1, 145.8, 145.4, 144.5, 133.1, 132.9, 132.8(5), 131.7, 130.1, 129.6, 129.5(9), 129.3, 129.0, 128.6, 100.7, 67.4, 41.6, 35.4, 21.8, 21.4; IR (KBr, ν, cm^{-1}) 3349, 3201, 1687, 1605, 1580, 1561, 1509, 1447, 1374; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{31}Cl_2N_6O_2$ 673.1880 [M − H]$^-$, found 673.1882.

(1,9-Bis(4-chlorophenyl)-3,7-dimethyl-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-methoxyphenyl)methanone) ***(4n)***. Yellow solid: 0.522 g, yield 74%; mp 298−299 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.07 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 4H), 7.23 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 4H), 6.78 (d, J = 8.8 Hz, 2H), 6.69 (t, J = 8.4 Hz, 1H), 6.17 (d, J = 8.4 Hz, 2H), 5.55 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.54 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 200.2, 190.9, 164.0, 163.2, 146.6, 145.3, 132.4, 132.3(6), 131.2, 130.4, 129.1, 128.5, 127.7, 126.3, 114.4, 113.8, 100.5, 66.7, 55.7, 55.5, 41.0, 34.9; IR (KBr, ν, cm^{-1}) 3351, 3188, 1688, 1601, 1575, 1510, 1444, 1420, 1373; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{31}Cl_2N_6O_4$, 705.1778 [M − H]$^-$, found 705.1751.

(3,7-Dimethyl-1,9-bis(thiophen-2-yl)-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis-(phenylmethanone) ***(4o)***. Yellow solid: 0.419 g, yield 71%; mp 268−270 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.14 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.6 Hz, 1H), 7.64−7.56 (m, 4H), 7.43 (t, J = 7.2 Hz, 1H), 7.30 (d, J = 5.2 Hz, 2H), 7.22 (t, J = 7.6 Hz, 2H), 6.95−6.93 (m, 2H), 6.84−6.78 (m, 3H), 6.34 (s, 1H), 4.68 (d, J = 8.4 Hz, 2H), 3.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 200.1, 193.1, 144.5, 143.4, 135.3, 134.8, 134.4, 133.3, 133.2, 129.4, 129.1, 128.8, 128.5, 127.6, 125.7, 125.3, 102.3, 67.8, 40.8, 34.7; IR (KBr, ν, cm^{-1}) 3354, 3187, 1685, 1596, 1574, 1526, 1447, 1324; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{25}N_6O_2S_2$, 589.1481 [M − H]$^-$, found 589.1475.

(3,7-Dimethyl-1,9-bis(thiophen-2-yl)-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-fluorophenyl)methanone) ***(4p)***. Yellow solid: 0.495 g, yield 79%; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.21−8.18 (m, 2H), 7.66−7.62 (m, 2H), 7.32−7.30 (m, 2H), 7.29−7.26 (m, 2H), 6.96−6.93 (m, 2H), 6.91−6.87 (m, 2H), 6.82−6.78 (m, 3H), 6.29 (s, 1H), 4.60 (d, J = 8.8 Hz, 2H), 3.53 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 199.6, 191.0, 165.4 ($^1J_{CF}$ = 251.9 Hz), 164.9 ($^{1'}J_{CF}$ = 251.7 Hz), 145.3, 141.9, 135.2, 131.7 ($^4J_{CF}$ = 2.7 Hz), 131.6 ($^3J_{CF}$ = 9.6 Hz), 130.9 ($^{3'}J_{CF}$ = 9.4 Hz), 130.4 ($^{4'}J_{CF}$ = 2.7 Hz), 127.5, 126.2, 124.0, 116.3 ($^2J_{CF}$ = 22.1 Hz), 115.7 ($^{2'}J_{CF}$ = 21.7 Hz), 99.8, 67.6, 40.9, 34.8; IR (KBr, ν, cm^{-1}) 3356, 3176, 1688, 1599, 1574, 1526, 1444, 1334; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{23}F_2N_6O_2S_2$, 625.1292 [M − H]$^-$, found 625.1278.

(3,7-Dimethyl-1,9-bis(thiophen-2-yl)-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-chlorophenyl)methanone) ***(4q)***. Yellow solid: 0.494 g, yield 75%; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.02 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.56−7.53 (m, 4H), 7.37 (d, J = 8.4 Hz, 2H), 6.97−6.95 (m, 2H), 6.68 (d, J = 3.2 Hz, 2H), 6.54 (t, J = 8.0 Hz, 1H), 6.22 (d, J = 8.0 Hz, 2H), 6.13 (s, 1H), 3.51 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 200.6, 191.9, 145.8, 142.5, 139.6, 138.9, 135.7, 134.4, 133.0, 130.9, 130.3, 129.8, 129.3, 128.1, 126.7, 124.6, 100.2, 68.3, 41.5, 35.4; IR (KBr, ν, cm^{-1}) 3340, 3179, 1684, 1589, 1572, 1526, 1489, 1399, 1318; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{23}Cl_2N_6O_2S_2$, 657.0701 [M − H]$^-$, found 657.0684.

(3,7-Dimethyl-1,9-bis(thiophen-2-yl)-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-bromophenyl)methanone) ***(4r)***. Yellow solid: 0.509 g, yield 68%; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.04−8.02 (m, 2H), 7.75−7.30 (m, 2H), 7.48−7.46 (m, 2H), 7.38−7.36 (m, 2H), 7.32−7.31 (m, 2H), 6.95−6.93 (m, 2H), 6.82−6.81 (m, 2H), 6.78−6.76 (m, 1H), 6.29 (s, 1H), 4.51 (d, J = 8.8 Hz, 2H), 3.57 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 200.8, 192.1, 145.8, 142.5, 135.7, 134.7, 133.4, 132.7, 132.2, 131.0, 130.4, 128.8, 128.1, 128.0, 126.7, 124.7, 100.2, 68.3, 41.5, 35.4; IR (KBr, ν, cm^{-1}) 3328, 1688, 1604, 1574, 1527, 1513, 1459, 1422; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{23}Br_2N_6O_2S_2$, 746.9670 [M − H]$^-$, found 746.9653.

(3,7-Dimethyl-1,9-bis(thiophen-2-yl)-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis(p-tolylmethanone) ***(4s)***. Yellow solid: 0.476 g, yield 77%; mp 279−280 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.06 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 7.30 (d, J = 4.8 Hz, 2H), 7.03 (d, J = 7.6 Hz, 2H), 6.94−6.92 (m, 2H), 6.84−6.81 (m, 3H), 6.32 (s, 1H), 4.64 (d, J = 8.8 Hz, 2H), 3.55 (s, 6H), 2.47 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 199.7, 192.8,

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145.7, 144.5, 144.1, 143.4, 134.8, 132.7, 130.8, 129.8, 129.6, 129.3, 128.9, 127.6, 125.7, 125.4, 102.3, 67.6, 40.7, 34.8, 21.9, 21.6; IR (KBr, ν, cm^{-1}) 3339, 1683, 1601, 1574, 1527, 1510, 1459, 1420; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{29}N_6O_2S_2$ 617.1794 $[M - H]^-$, found 617.1787.

*(3,7-Dimethyl-1,9-bis(thiophen-2-yl)-3,4,5,6,7,10-hexahydrodipyrazolo[3,4-d:4′,3′-g][1,3]diazocine-5,10-diyl)bis((4-methoxyphenyl)methanone) (**4t**).* Yellow solid: 0.423 g, yield 65%; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.16 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.30−7.28 (m, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.93−6.91 (m, 2H), 6.90−6.86 (m, 1H), 6.83−6.82 (m, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.30 (s, 1H), 4.55 (d, J = 8.8 Hz, 2H), 3.92 (s, 3H), 3.79 (s, 3H), 3.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 198.7, 191.8, 164.7, 163.6, 144.4, 143.5, 135.1, 132.0, 131.2, 128.1, 127.6, 126.1, 125.6, 125.3, 114.4, 113.7, 102.4, 67.3, 55.7, 55.4, 40.5, 34.9; IR (KBr, ν, cm^{-1}) 3326, 1675, 1610, 1578, 1525, 1510, 1459, 1428; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{29}N_6O_4S_2$ 649.1692 $[M - H]^-$, found 649.1678.

Representative Synthesis of 5: 3-Methyl-4-(3-methyl-1,5-diphenyl-1,6-dihydropyrrolo[2,3-*c*]pyrazol-4-yl)-1-phenyl-1*H*-pyrazol-5-amine (5a). Typically, 2,2-dihydroxy-1-phenylethanone (**1a**; 1.0 mmol, 0.152 g, 1.0 equiv) and 1-phenyl-3-methylpyrazol-5-amine (**2f**; 2.0 mmol, 0.346 g, 2.0 equiv) were introduced in a 10 mL Initiator reaction vial, and *p*-TsOH (1.0 equiv) and DMF (1.5 mL) were then added successively. Subsequently, the reaction vial was closed and then prestirred for 10 s. The mixture was irradiated (time, 30 min; temperature, 120 °C; absorption level, high; fixed hold time) until TLC (petroleum ether/acetone 3/1) revealed that conversion of the starting material **2f** was complete. After room temperature, the reaction mixture was diluted with cold water (20 mL) and neutralized with 10% NaOH solution. The solid product was collected by Büchner filtration and was purified by recrystallization from 95% EtOH to afford the desired pure **5a**. White solid: 0.346 g, yield 78%; mp 251−254 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.35 (s, 1H), 7.68−7.62 (m, 4H), 7.51−7.45 (m, 6H), 7.37−7.30 (m, 3H), 7.25−7.21 (m, 2H), 3.72 (s, 2H), 2.45 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 148.5, 142.9, 141.0, 140.8, 139.5, 133.2, 132.4, 130.0, 129.7, 129.5, 129.0, 128.5, 127.1, 126.0, 124.9, 123.3, 118.7, 117.7, 105.6, 97.5, 13.3, 12.8; IR (KBr, ν, cm^{-1}) 3287, 3059, 1624, 1596, 1499, 1387, 1268; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{23}N_6$ 443.1984 $[M - H]^-$, found 443.2009.

*4-(5-(4-Fluorophenyl)-3-methyl-1-phenyl-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**5b**).* White solid: 0.356 g, yield 77%; mp 270−271 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.73 (s, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 7.6 Hz, 2H), 7.46−7.38(m, 6H), 7.30 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.01 (t, J = 8.4 Hz, 2H), 3.71 (s, 2H), 2.42 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 161.7 ($^1J_{CF}$ = 246.0 Hz), 148.4, 142.9, 140.9 ($^4J_{CF}$ = 2.1 Hz), 139.4, 131.7, 129.9, 129.6, 129.5, 128.0 ($^3J_{CF}$ = 7.9 Hz), 126.9, 124.9, 123.9, 123.8, 123.2, 120.5, 118.6, 117.7, 115.9 ($^2J_{CF}$ = 21.5 Hz), 97.2, 13.2, 12.8; IR (KBr, ν, cm^{-1}) 3286, 1629, 1598, 1509, 1454, 1353, 1225; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{22}FN_6$ 461.1890 $[M - H]^-$, found 461.1914.

*4-(5-(4-Chlorophenyl)-3-methyl-1-phenyl-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**5c**).* White solid: 0.325 g, yield 68%; mp 297−300 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 11.52 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.53−7.42 (m, 6H), 7.29 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 4.99 (s, 2H), 2.30 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 147.4, 145.1, 141.0, 140.2, 140.0, 139.5, 133.0, 132.3, 131.2, 129.8, 129.5, 128.8, 128.7, 126.1, 124.4, 122.6, 119.0, 117.5, 101.9, 96.9, 13.4, 13.2; IR (KBr, ν, cm^{-1}) 3437, 2923, 1596, 1573, 1522, 1458, 1350, 1284; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{22}ClN_6$ 477.1595 $[M - H]^-$, found 477.1614.

*4-(5-(4-Bromophenyl)-3-methyl-1-phenyl-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**5d**).* White solid: 0.371 g, yield 71%; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.30 (s, 1H), 7.67−7.61 (m, 4H), 7.51−7.45 (m, 6H), 7.34−7.32 (m, 3H), 7.24−7.22 (m, 1H), 3.74 (s, 2H), 2.44 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 148.4, 141.0, 140.9, 139.4, 132.2, 132.1, 130.1, 129.9, 129.7, 129.5, 129.3, 129.1, 127.4, 125.0, 123.3, 120.8, 118.8, 117.8, 103.3, 97.0, 13.2, 12.8; IR (KBr, ν, cm^{-1}) 3437, 2923, 1596, 1573, 1522, 1458, 1350, 1284; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{22}BrN_6$ 521.1090 $[M - H]^-$, found 521.1078.

*3-Methyl-4-(3-methyl-5-(4-nitrophenyl)-1-phenyl-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-1-phenyl-1H-pyrazol-5-amine (**5e**).* An red solid: 0.362 g, yield 74%; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 11.69 (s, 1H), 8.23 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.56−7.48 (m, 4H), 7.31 (t, J = 7.6 Hz), 7.25 (t, J = 7.2 Hz), 5.11 (s, 2H), 2.31 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 147.2, 145.2, 145.1, 141.8, 140.9, 140.7, 139.9, 139.3, 131.3, 129.9, 129.6, 127.0, 126.3, 124.8, 124.1, 122.8, 119.7, 117.8, 105.4, 96.4, 13.4, 13.2; IR (KBr, ν, cm^{-1}) 3378, 3062, 1594, 1570, 1499, 1375, 1320, 1272; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{22}N_7O_2$ 488.1835 $[M - H]^-$, found 488.1860.

*3-Methyl-4-(3-methyl-1-phenyl-5-(p-tolyl)-1,6-dihydropyrrolo-[2,3-c]pyrazol-4-yl)-1-phenyl-1H-pyrazol-5-amine (**5f**).* White solid: 0.307 g, yield 67%; mp 296−298 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.37 (s, 1H), 7.67−7.61 (m, 4H), 7.48−7.44 (m, 4H), 7.36−7.29 (m, 3H), 7.22 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 7.2 Hz, 2H), 3.70 (s, 2H), 2.44 (s, 3H), 2.35 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 147.5, 145.0, 140.7, 140.1, 140.0, 139.6, 136.0, 133.7, 131.3, 129.8, 129.5, 129.3, 127.2, 126.0, 124.3, 122.4, 118.9, 117.4, 100.6, 97.5, 21.3, 13.5, 13.2; IR (KBr, ν, cm^{-1}) 3355, 3071, 2917, 1620, 1579, 1509, 1079; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{25}N_6$ 457.2141 $[M - H]^-$, found 457.2157.

*4-(5-(4-Methoxyphenyl)-3-methyl-1-phenyl-1,6-dihydropyrrolo-[2,3-c]pyrazol-4-yl)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**5g**).* White solid: 0.327 g, yield 69%; mp 270−273 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.81 (s, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.6 Hz, 4H), 7.39 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 3.70 (s, 2H), 2.43 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 148.7, 142.8, 140.7, 139.5, 134.8, 132.6, 129.6, 129.4, 128.8, 127.7, 126.7, 125.9, 124.6, 123.9, 123.2, 122.3, 118.5, 117.7, 100.4, 97.7, 55.3, 13.3, 12.9; IR (KBr, ν, cm^{-1}) 3332, 2920, 1676, 1570, 1520, 1409, 1289, 1248; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{25}N_6O$ 473.2090 $[M - H]^-$, found 473.2107.

*3-Methyl-4-(3-methyl-5-phenyl-1-(p-tolyl)-1,6-dihydropyrrolo-[2,3-c]pyrazol-4-yl)-1-(p-tolyl)-1H-pyrazol-5-amine (**5h**).* White solid: 0.349 g, yield 74%; mp 272−273 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.16 (s, 1H), 7.54 (d, J = 7.6 Hz, 2H), 7.50−7.45 (m, 4H), 7.37−7.28 (m, 5H), 7.25−7.23 (m, 2H), 3.67 (s, 2H), 2.45 (s, 3H), 2.40 (s, 3H) 2.39 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 147.1, 145.0, 141.2, 139.5, 137.1, 134.2, 133.7, 133.5, 132.4, 131.9, 130.2, 129.8, 128.5, 127.3, 126.9, 123.9, 118.0, 117.7, 101.4, 98.0, 21.2, 20.9, 13.3, 11.9; IR (KBr, ν, cm^{-1}) 3364, 3079, 2917, 1659, 1567, 1509; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{27}N_6$ 471.2297 $[M - H]^-$, found 471.2332.

*4-(5-(4-Chlorophenyl)-3-methyl-1-(p-tolyl)-1,6-dihydropyrrolo-[2,3-c]pyrazol-4-yl)-3-methyl-1-(p-tolyl)-1H-pyrazol-5-amine (**5i**).* White solid: 0.344 g, yield 68%; mp 286−289 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 11.45 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 7.2 Hz, 4H), 7.42 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 9.2 Hz, 4H), 4.90 (s, 2H), 2.35 (s, 6H), 2.28 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 147.0, 144.9, 140.9, 139.7, 137.6, 137.3, 135.4, 133.5, 133.1, 132.1, 131.1, 130.2, 129.9, 128.8, 128.7, 122.7, 118.9, 117.5, 101.9, 96.7, 21.0, 20.9, 13.4, 13.2; IR (KBr, ν, cm^{-1}) 3339, 3079, 2919, 1614, 1562, 1521, 1348; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{26}ClN_6$ 505.1908 $[M - H]^-$, found 505.1935.

*4-(5-(4-Bromophenyl)-3-methyl-1-(p-tolyl)-1,6-dihydropyrrolo-[2,3-c]pyrazol-4-yl)-3-methyl-1-(p-tolyl)-1H-pyrazol-5-amine (**5j**).* White solid: 0.413 g, yield 75%; mp 296−298 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.61 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 9.2 Hz, 4H), 7.30 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 4H), 3.69 (s, 2H), 2.42 (s, 3H), 2.38 (s, 6H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 148.0, 142.1, 141.0, 140.6, 137.0, 134.7, 132.3, 132.0, 131.3, 131.1, 131.0, 130.2, 130.0, 127.5, 123.4, 120.7, 118.6, 117.9,

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102.5, 96.8, 21.1, 21.0, 13.2, 12.8; IR (KBr, ν, cm^{-1}) 3356, 3036, 1611, 1574, 1522, 1466, 1381, 1285; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{26}BrN_6$ 549.1403 $[M - H]^-$, found 549.1391.

3-Methyl-4-(3-methyl-5-(4-nitrophenyl)-1-(p-tolyl)-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-1-(p-tolyl)-1H-pyrazol-5-amine (**5k**). An red solid: 0.377 g, yield 73%; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 11.62 (s, 1H), 8.22 (s, 2H), 7.83−7.78 (m, 4H), 7.55 (s, 2H), 7.33−7.30 (m, 4H), 5.02 (s, 2H), 2.37 (s, 6H), 2.31 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 146.9, 145.0, 141.8, 141.0, 140.2, 137.5, 137.1, 135.6, 133.9, 131.2, 130.2, 130.0, 126.9, 124.1, 122.9, 119.6, 117.8, 105.5, 96.2, 21.0, 20.9, 13.4, 13.1; IR (KBr, ν, cm^{-1}) 3335, 2921, 1592, 1522, 1461, 1338, 1269; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{26}N_7O_2$ 516.2148 $[M - H]^-$, found 516.2174.

3-Methyl-4-(3-methyl-1,5-di-p-tolyl-1,6-dihydropyrrolo[2,3-c]-pyrazol-4-yl)-1-(p-tolyl)-1H-pyrazol-5-amine (**5l**). White solid: 0.345 g, yield 71%; mp 275−277 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.47 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.26−7.24 (m, 4H), 7.12 (d, J = 8.0 Hz), 3.65 (s, 2H), 2.43 (s, 3H), 2.38 (s, 6H), 2.34 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 148.3, 142.7, 140.8, 140.4, 137.2, 136.7, 136.4, 134.5, 132.4, 130.5, 130.3, 130.1, 129.9, 129.6, 125.9, 123.3, 118.5, 117.8, 101.3, 97.4, 21.2, 21.1, 20.9, 13.2, 12.9; IR (KBr, ν, cm^{-1}) 3334, 3025, 1614, 1595, 1521, 1381, 1348; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{29}N_6$ 485.2454 $[M - H]^-$, found 485.2483.

4-(5-(4-Chlorophenyl)-3-cyclopropyl-1-phenyl-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-3-cyclopropyl-1-phenyl-1H-pyrazol-5-amine (**5m**). White solid: 0.345 g, yield 65%; mp 289−291 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.65 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.46−7.38 (m, 6H), 7.30−7.26 (m, 3H), 7.19 (t, J = 7.2 Hz, 1H), 3.66 (s, 2H), 2.10−2.03 (m, 1H), 1.75−1.70 (m, 1H), 0.98−0.92 (m, 3H), 0.90−0.86 (m, 2H), 0.78−0.71 (m, 2H), 0.65−0.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 153.5, 147.3, 143.0, 141.0, 139.4, 132.5, 132.0, 131.7, 129.6, 129.4, 128.9, 127.5, 126.9, 124.7, 123.5, 118.2, 117.8, 97.4, 9.3, 8.6, 8.3, 8.2, 7.9, 7.3; IR (KBr, ν, cm^{-1}) 3412, 1597, 1574, 1516, 1454, 1403, 1382; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{26}ClN_6$ 529.1908 $[M - H]^-$, found 529.1915.

4-(5-(4-Bromophenyl)-3-cyclopropyl-1-phenyl-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-3-cyclopropyl-1-phenyl-1H-pyrazol-5-amine (**5n**). White solid: 0.442 g, yield 77%; mp 296−298 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.65 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.46−7.42 (m, 6H), 7.35−7.29 (m, 3H), 7.19 (t, J = 7.6 Hz, 1H), 3.67 (s, 2H), 2.09−2.04 (m, 1H), 1.75−1.71 (m, 1H), 0.99−0.93 (m, 3H), 0.90−0.87 (m, 2H), 0.81−0.71 (m, 2H), 0.65−0.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 153.5, 147.3, 142.9, 141.0, 139.5, 132.2, 131.9, 131.8, 129.5, 129.4, 127.7, 126.8, 124.7, 123.4, 120.6, 118.3, 117.8, 97.4, 9.3, 8.6, 8.3, 8.2, 7.9, 7.2; IR (KBr, ν, cm^{-1}) 3423, 1598, 1518, 1454, 1407, 1380, 1352; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{26}BrN_6$ 573.1403 $[M - H]^-$, found 573.1385.

3-Cyclopropyl-4-(3-cyclopropyl-5-(4-nitrophenyl)-1-phenyl-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-1-phenyl-1H-pyrazol-5-amine (**5o**). White solid: 0.384 g, yield 71%; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.57 (s, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.68−7.59 (m, 6H), 7.51−7.46 (m, 4H), 7.36−7.31 (m, 1H), 7.26−7.22 (m, 1H), 3.78 (s, 2H), 2.09−2.04 (m, 1H), 1.72−1.68 (m, 1H), 1.03−0.99 (m, 3H), 0.94−0.90 (m, 2H), 0.80−0.74 (m, 2H), 0.65−0.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 142.4, 140.4, 139.9, 137.0, 136.5, 134.5, 134.0, 132.4, 128.9, 124.4, 124.3, 121.85, 120.6, 119.8, 119.0, 118.2, 112.8, 96.6, 3.9, 3.2(3), 3.2(0), 3.1, 2.9, 2.1; IR (KBr, ν, cm^{-1}) 3423, 1596, 1502, 1454, 1407, 1330; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{26}N_7O_2$ 540.2148 $[M - H]^-$, found 540.2165.

3-Cyclopropyl-4-(3-cyclopropyl-1-phenyl-5-(p-tolyl)-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-1-phenyl-1H-pyrazol-5-amine (**5p**). White solid: 0.388 g, yield 76%; mp 286−288 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.39 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.48−7.42 (m, 4H), 7.37 (d, J = 7.6 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 3.64 (s, 2H), 2.34 (s, 3H), 2.12−2.05 (m, 1H), 1.82−1.77 (m, 1H), 1.00−0.93 (m, 3H), 0.92−0.87 (m, 2H), 0.83−0.73 (m, 2H), 0.68−0.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 153.7, 147.2, 140.7, 139.6, 136.7, 133.2, 130.3, 129.5(5), 129.4(8), 129.4, 128.3, 126.7, 126.1, 124.5, 123.4, 118.1, 117.7, 98.0, 21.2, 9.3, 8.6, 8.2, 7.9, 7.3, 6.7; IR (KBr, ν, cm^{-1}) 3419, 1595, 1567, 1455, 1359, 1336; HRMS (ESI-TOF) m/z calcd for $C_{33}H_{29}N_6$ 509.2454 $[M - H]^-$, found 509.2475.

4-(5-(4-Chlorophenyl)-1-methyl-3-(thiophen-2-yl)-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-1-methyl-3-(thiophen-2-yl)-1H-pyrazol-5-amine (**5q**). White solid: 0.363 g, yield 74%; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 11.46 (s, 1H), 7.49−7.46 (m, 2H), 7.36−7.34 (m, 2H), 7.23−7.22 (m, 1H), 7.16−7.15 (m, 1H), 6.82−6.80 (m, 1H), 6.75−6.73 (m, 2H), 6.61−6.60 (m, 1H), 4.97 (s, 2H), 3.92 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 147.2, 145.1, 143.1, 138.0, 137.8, 135.4, 133.5, 133.0, 131.1, 128.8, 127.8, 127.7, 127.4, 124.3, 124.2(5), 124.2, 122.9, 114.9, 101.5, 93.8, 36.1, 35.2; IR (KBr, ν, cm^{-1}) 3372, 3068, 1699, 1632, 1582, 1540, 1498, 1381; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{18}ClN_6S_2$ 489.0723 $[M - H]^-$, found 489.0711.

4-(5-(3,4-Dichlorophenyl)-1-methyl-3-(thiophen-2-yl)-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-1-methyl-3-(thiophen-2-yl)-1H-pyrazol-5-amine (**5r**). White solid: 0.372 g, yield 71%; mp 251−252 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 11.57 (s, 1H), 7.70 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 4.8 Hz, 1H), 7.17 (d, J = 4.8 Hz, 1H), 6.82 (t, J = 4.4 Hz, 1H), 6.77−6.75 (m, 2H), 6.62 (d, J = 3.6 Hz, 1H), 5.05 (s, 2H), 3.93 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 147.2, 145.2, 143.0, 137.8, 137.6, 135.6, 134.7, 132.0, 131.5, 131.0, 128.6, 127.8, 127.5, 127.4, 125.8, 124.5, 124.4, 124.3, 122.9, 115.0, 102.7, 93.2, 36.1, 35.2; IR (KBr, ν, cm^{-1}) 3369, 3078, 1695, 1622, 1583, 1541, 1498, 1385; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{17}Cl_2N_6S_2$ 523.0333 $[M - H]^-$, found 523.0321.

4-(5-(4-Bromophenyl)-1-methyl-3-(thiophen-2-yl)-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-1-methyl-3-(thiophen-2-yl)-1H-pyrazol-5-amine (**5s**). White solid: 0.391 g, yield 73%; mp 258−260 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 11.47 (s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 5.2 Hz, 1H), 7.16 (t, J = 2.8 Hz, 1H), 6.81 (s, 1H), 6.75−6.74 (m, 2H), 6.60 (s, 1H), 4.98 (s, 2H), 3.92 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 147.2, 145.1, 143.0, 137.9, 137.8, 135.4, 133.5, 133.3, 131.7, 128.0, 127.8, 127.4, 124.3, 124.2(5), 124.2(0), 122.9, 119.6, 115.0, 101.5, 93.8, 36.1, 35.2; IR (KBr, ν, cm^{-1}) 3372, 1664, 1613, 1544, 1505, 1487, 1397, 1328; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{18}BrN_6S_2$ 535.0198 $[M - H]^-$, found 535.0174.

Methyl-4-(1-methyl-3-(thiophen-2-yl)-5-(p-tolyl)-1,6-dihydropyrrolo[2,3-c]pyrazol-4-yl)-3-(thiophen-2-yl)-1H-pyrazol-5-amine (**5t**). White solid: 0.375 g, yield 70%; mp 265−267 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 11.31 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.22−7.20 (m, 1H), 7.15−7.14 (m, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.81−6.79 (m, 1H), 6.75−6.73 (m, 2H), 6.59−6.58 (m, 1H), 4.88 (s, 2H), 3.91 (s, 3H), 3.65 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 147.2, 144.9, 143.2, 138.1, 138.0, 135.9, 135.2, 135.0, 131.3, 129.4, 127.7, 127.4, 126.2, 124.1, 124.0, 122.9, 114.8, 100.1, 94.4, 36.1, 35.2, 21.1; IR (KBr, ν, cm^{-1}) 3367, 1625, 1533, 1486, 1454, 1421, 1380; HRMS (ESI-TOF) m/z calcd for $C_{25}H_{21}N_6S_2$ 469.1269 $[M - H]^-$, found 469.1285.

Synthesis of (4-Bromophenyl)(6-(4-bromophenyl)-1,3-dimethyl-5-(*p*-tolylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)-methanone (7). Typically, 1-(4-bromophenyl)-2,2-dihydroxyethanone (**1e**; 2.0 mmol, 0.462 g, 2.0 equiv) was introduced into a 10 mL Initiator reaction vial, and then 1,3-dimethyl-1*H*-pyrazol-5-amine (**2a**; 1.0 mmol, 0.111 g), *p*-toluidine (**3a**; 1.0 mmol, 0.107 g), *p*-TsOH (1.0 mmol, 0.172 g), and 1.5 mL of DMF were then added successively. Subsequently, the reaction vial was capped and then prestirred for 20 s. The mixture was irradiated (time, 20 min; temperature, 115 °C; absorption level, high; fixed hold time) until TLC (petroleum ether/ethyl acetate 3/1) revealed that conversion of the starting materials **1a** and **3a** was complete. After room temperature, the reaction mixture was diluted with cold water (20 mL) and neutralized with 10% NaOH solution. The solid product was collected by Büchner filtration and was purified by flash column chromatography (silica gel, petroleum ether (bp 60−90 °C)/ethyl acetate mixtures) to afford the desired pure pyrazolo[3,4-*b*]pyridine 7.

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Yellow solid: 0.366 g, yield 62%; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.61 (d, J = 8.0 Hz, 2H), 7.49 (s, 5H), 7.47 (s, 1H), 6.79 (d, J = 8.0 Hz, 2H), 6.27 (d, J = 8.0 Hz, 2H), 5.14 (s, 1H), 4.15 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.8, 159.5, 155.1, 149.2, 144.6, 143.2, 141.0, 139.4, 137.1, 132.0, 131.5, 130.7, 130.7, 129.6, 129.4, 126.3, 123.6, 117.8, 115.4, 33.8, 20.5, 13.8. IR (KBr, ν, cm^{-1}) 3374, 1666, 1583, 1513, 1347, 1258, 1205, 1070, 1009, 812, 798. HRMS (ESI-TOF) m/z calcd for $C_{28}H_{21}Br_2N_4O$ 589.0062 $[M - H]^-$, found: 589.0044.

■ ASSOCIATED CONTENT

Supporting Information

Figures and CIF files giving ^{1}H and ^{13}C NMR spectra of all pure products and X-ray crystal data for **3c**, **4a**, **5b**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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