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Unified Approach to Pyrazole-Fused Heterocyclic and Carbocyclic Motifs through One-Pot Condensation and Intramolecular Dipolar Cycloaddition Reaction

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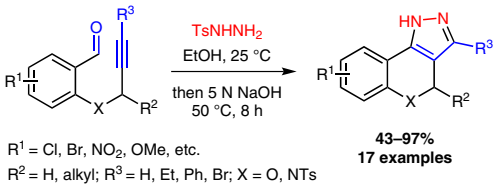

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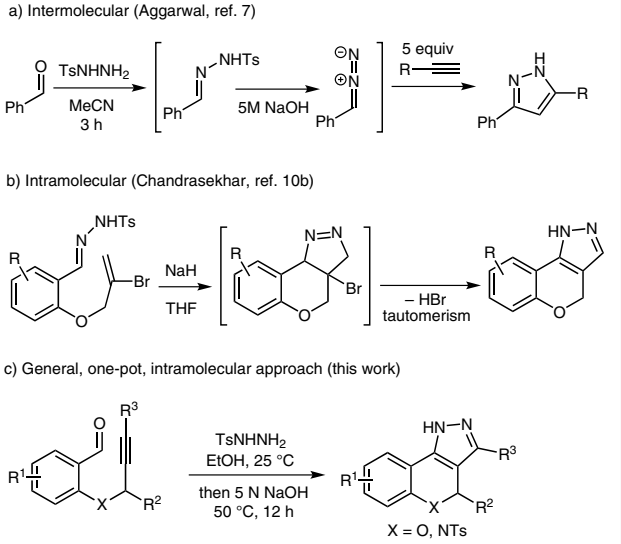
Abstract A one-pot synthesis of highly substituted pyrazoles that are fused to dihydrochromenes, dihydroquinolines and cyclopentane motifs, from readily available precursors is reported. The reaction involves conversion of alkyne-tethered aldehydes into the corresponding tosylhydrazones, base-mediated generation of diazo compounds, and subsequent intramolecular dipolar cycloaddition reaction. A range of internal and terminal alkynes as well as bromoalkyne compounds can be employed as the tethered dipolarophile to afford the corresponding cycloadducts.

Key words intramolecular dipolar cycloaddition, pyrazoles, tosyl hydrazones, diazo compounds, alkynes

The pyrazole nucleus is widespread in a number of pharmaceutical agents and agrochemicals,[2] and the synthesis of pyrazoles and their annulated derivatives has become increasingly important. Cyclocondensation of hydrazine derivatives and 1,3-dicarbonyl compounds (Knorr pyrazole synthesis) is one of the most widely used methods for pyrazole construction.[3] Although the simplicity and efficiency of this approach is remarkable, the control of regiochemistry is challenging in the reaction of unsymmetrical substrates.[4] The reaction between alkynes and diazo compounds through 1,3-dipolar cycloaddition is another useful method for the generation of pyrazole derivatives.[5] However, the hazardous nature of diazo compounds is a serious limitation of this method. The availability of new methods for the generation of diazo compounds from stable tosylhydrazones has addressed this issue to a large extent.[6] In 2003, Aggarwal reported that 3-substituted pyrazoles can be conveniently prepared through intermolecular 1,3-dipolar cycloaddition of terminal alkynes and aryldiazomethanes generated in situ (Scheme 1, a).[7] The regioselectivity is very high for this intermolecular process; however, a five-fold excess of the dipolarophile is required. Additionally, the use of internal alkynes to generate trisubstituted pyrazoles was not explored.

Intramolecular dipolar cycloaddition (IDC) reactions constitute a powerful and versatile synthetic strategy for the construction of fused and spiro-polycyclic systems from readily available precursors.[8] The inherent regio- and stereochemical preferences of dipolar cycloaddition reactions are often amplified in IDC reactions because of the geometrical demands imposed by the tethering of dipole and dipolarophile. Therefore, IDC reactions have featured significantly as key bond-forming events in numerous natural product syntheses.[9] The intramolecular variant of dipolar cycloaddition reactions of alkynes and diazo compounds generated from tosyl hydrazones are, however, less investigated.[10] A report by Chandrasekhar describes the use of preformed tosylhydrazones that incorporate a bromoalkene dipolarophile (Scheme 1, b).[10b] The initially formed cycloadduct undergoes aromatization through dehydrobromination to afford pyrazoles. The bromovinyl group acts as a synthetic equivalent of a terminal alkyne and this method affords 3-unsubstituted pyrazoles.

We surmised that the experimentally simple approach of the IDC reaction of terminal and internal alkynes and diazo compounds would lead to the generation of fused pyrazole derivatives. A detailed investigation on the feasibility of this approach for the construction of oxygen and nitrogen heterocycles as well as carbocycles fused to pyrazoles was undertaken. In addition to the generation of such polycyclic systems, we also aimed to study the effects of additional substituents R^2 and R^3 on the alkynyl moiety on the outcome of the IDC reaction. Our efforts in this direction culminated in the development of a unified, convenient, one-pot approach to the synthesis of highly substituted

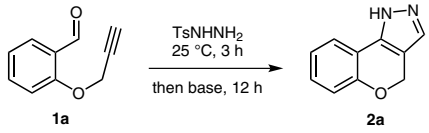


Scheme 1 Pyrazole construction through 1,3-dipolar cycloaddition reactions of alkynes and diazo compounds

fused pyrazole derivatives (Scheme 1, c). Our findings are described in detail in the following sections.

The investigations began by subjecting *O*-propargyl salicylaldehyde (**1a**) to reaction conditions for hydrazone synthesis, generation of the corresponding diazo compound and subsequent IDC reaction in one-pot. The method described by Aggarwal was deemed as a suitable starting point for this purpose.[7] The reaction conditions that were tested are listed in Table 1. The formation of tosyl hydrazone from **1a** proceeded to near completion (as indicated by TLC analysis) in acetonitrile, tetrahydrofuran (THF), and ethanol. Exposure of the tosylhydrazone to various bases was then attempted to generate the diazo compound. The use of 5 N NaOH and acetonitrile as solvent resulted in the formation of the expected cycloadduct **2a** in 47% yield at room temperature (entry 1). The yield of the product rose to 87% when the reaction temperature was increased to 50 °C (entry 2). A slightly diminished yield of **2a** (75%) was obtained when the strength of base was reduced to 2 N (entry 3). Other bases such as potassium carbonate, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), sodium hydride, and potassium *tert*-butoxide mediated the formation of the diazo compound and IDC reaction, albeit in significantly lower yields (entries 4–7). Reaction in THF at 50 °C using 5 N NaOH furnished **2a** in 83% yield. The best yield of **2a** (96%) was obtained when the reaction was carried out in ethanol using 5 N NaOH at 50 °C (entry 9).

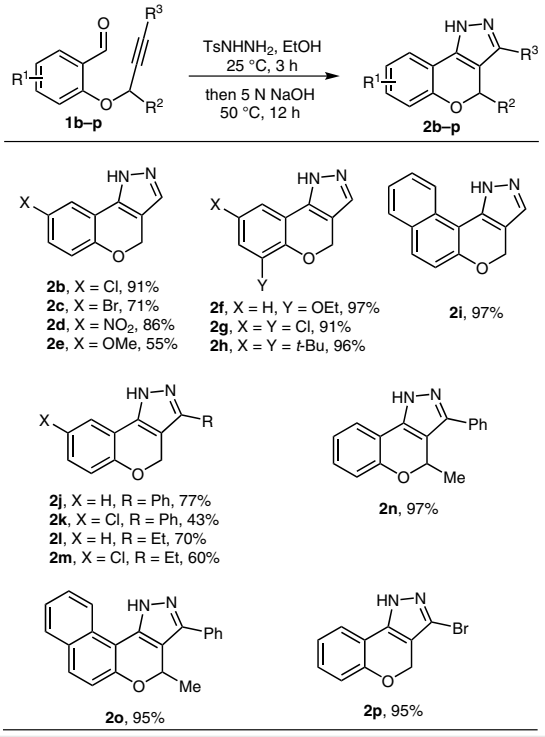
Table 1 Optimization of Reaction Conditions[a]



Entry	Base	Temp (°C)	Solvent	Yield (%)[b]
1	5 N NaOH	25	MeCN	47
2	5 N NaOH	50	MeCN	87
3	2 N NaOH	50	MeCN	75
4	K_2CO_3	50	MeCN	56
5	DBU	50	MeCN	46
6	NaH	50	MeCN	55
7	*t*-BuOK	0	MeCN	47
8	5 N NaOH	50	THF	83
9	5 N NaOH	50	EtOH	96

[a] Reaction conditions: **1a** (0.5 mmol), $TsNHNH_2$ (0.5 mmol), solvent (3 mL), 3 h; then base, 8 h.
[b] Isolated yield.

The generality and scope of this one-pot protocol for accessing dihydrochromenopyrazoles such as **2a** was then investigated. Variously substituted *O*-propargyl salicylaldehydes **1b–p** were subjected to the optimized reaction conditions and the corresponding cycloadducts **2b–p** were obtained. The results are listed in Scheme 2.

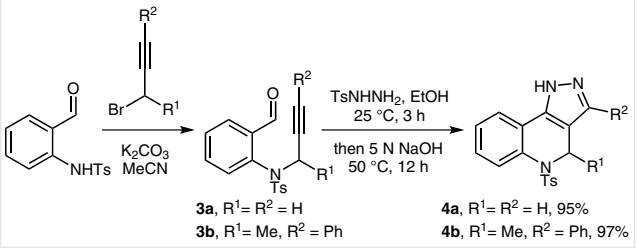


Scheme 2 Scope of the dihydrochromenopyrazole synthesis (isolated yields given)

As evident from the results presented in Scheme 2, substitutions at various positions on the dihydrochromenopyrazole may be achieved by using this one-pot approach. Alkyl and aryl groups are well-tolerated on the propargylic

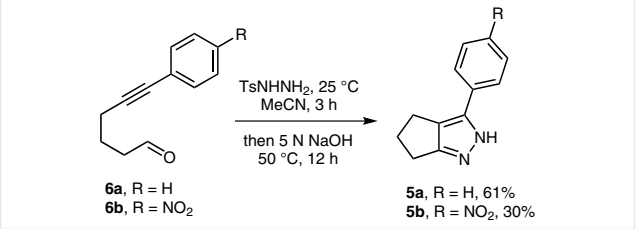
and terminal alkynyl carbons (**2n–o**). Additionally, salicylaldehydes bearing halo and nitro functionalities afforded the corresponding products **2b–d**, **2g**, and **2m** in high yields. Importantly, bromopyrazole derivative **2p** was obtained in 95% yield from the corresponding bromoalkyne. It may be noted that 3-bromopyrazoles are valuable medicinal agents and very few methods are available for their synthesis.[11] The formation of **2p** also demonstrates the compatibility of a bromoalkyne in the IDC reaction. In short, this one-pot method allows convenient access to valuable functionalized dihydrochromenopyrazole derivatives from readily available starting materials.

This synthetic approach was also successfully applied for the generation of analogous nitrogen heterocycles. Alkynyl aldehydes **3a** and **3b**,[12] derived from 2-aminobenzaldehyde, underwent the condensation–IDC reaction sequence efficiently to afford dihydropyrazoloquinolines **4a** and **4b** in excellent yields (Scheme 3).



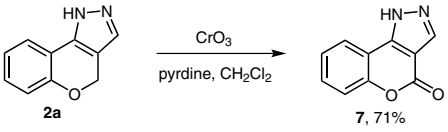
Scheme 3 One-pot synthesis of dihydropyrazoloquinoline derivatives **4a** and **4b**

The versatility of the IDC reaction is further illustrated in the synthesis of cyclopentane-fused pyrazoles **5a** and **5b**. The methylene-tethered alkynyl aldehydes **6a** and **6b**[13] were smoothly converted into the cycloadducts **5a** and **5b** under slightly modified conditions of the one-pot IDC reaction (Scheme 4). Here, acetonitrile was found to be a better solvent than ethanol as the use of the former gave cleaner products in slightly improved yields.



Scheme 4 Synthesis of cyclopentane-fused pyrazoles through the one-pot IDC reaction

The synthetic utility of the cycloadducts generated in the present study is illustrated by the conversion of dihydrochromenopyrazole **2a** into pyrazolocoumarin **7**.[14] This oxidation was carried out in a straightforward manner by using chromium trioxide (Scheme 5).[15] It may be noted that structural scaffolds generated by the fusion of coumarin to various heterocyclic rings are valuable targets in medicinal chemistry.[16]



Scheme 5 Oxidative conversion of dihydrochromenopyrazole **2a** into pyrazolocoumarin **7**

In summary, a convenient one-pot protocol for accessing pyrazole-fused polycyclic scaffolds was developed. The method relies of the base-mediated generation of diazo compounds in situ from *N*-tosyl hydrazones of aldehydes tethered to alkynes. Formation of the tosyl hydrazones and subsequent diazo compound-alkyne intramolecular dipolar cycloaddition reactions were conveniently carried out in one pot under environmentally benign reaction conditions (ethanol and aqueous NaOH). The protocol allows the synthesis of pyrazolo-dihydrochromenes endowed with various substituents at defined positions. The method is also applicable for the synthesis of pyrazolo-dihydroquinoline derivatives as well as cyclopentane-fused pyrazoles, and a representative pyrazolo-coumarin was synthesized through oxidation of a cycloadduct. This method delivers valuable products from readily available starting materials and nonhazardous reagents in a simple one-pot operation.

All the reactions were carried out in flame-dried glassware. All reagents were purchased and used without prior purification. Technical grade EtOAc and hexanes were used for column chromatography and distilled prior to use. Analytical thin-layer chromatography was performed using aluminum backed UVF254 precoated silica gel plates. Visualization of the spots was achieved by exposure to UV light and/or iodine vapor. Column chromatography was carried out with silica gel (60–120 mesh and 100–200 mesh). Melting points were recorded with an electrothermal apparatus and are uncorrected. IR spectra were obtained with a Perkin Elmer 881 or FTIR 820/PC instrument and values are expressed in cm^{-1}. All ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 as solvents with a Varian Bruker 300 MHz, a Varian Unity 400 MHz, or an Avance 500 MHz spectrometer at ambient temperature; chemical shifts (δ) are given in ppm on a scale downfield from TMS, and coupling constants (*J*) are in Hz. The signal patterns are indicated as: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet. Mass spectra were obtained with a Finnegan Mat1020B, a micromass VG 70–70H or an Agilent technologies LC/MSD treapSL spectrometer operating at 70 eV by using the direct inlet system. High-resolution mass spectra (HRMS) were recorded with a QSTAR XL Hybrid MS/MS mass spectrometer. Propargyl ethers **1a–p** and sulfonamides **3a** and **3b** were prepared according to reported procedures.[17] Oxidative conversion of **2a** into coumarin derivative **7** was carried out as described for a similar system.[15]

Synthesis of Dihydrochromenopyrazoles; Typical Procedure

To a solution of **1a** (0.5 mmol) in EtOH (3 mL), $TsNHNH_2$ (0.5 mmol) was added and the solution was stirred for 3 h at r.t. under nitrogen atmosphere. NaOH (5 N, 100 µL, 0.5 mmol) was added and the solution was stirred at r.t. for 20 min. The temperature was then increased to 50 °C and stirring was continued until complete consumption of hydrazone was observed by TLC. The solvent was evaporated and the residue was diluted with distilled water (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and the product was purified by column chromatography (hexane–EtOAc, 70:30) to furnish fused pyrazoles as the pure product.

1,4-Dihydrochromeno[4,3-*c*]pyrazole (2a)

Yield: 83 mg (96%); white solid; mp 173–175 °C.

IR (KBr): 3113, 2909, 1612, 1590, 1464, 1346, 1214, 1027, 815, 741 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 2, 7.5 Hz, 1 H), 7.39 (s, 1 H), 7.24–7.20 (m, 1 H), 7.01 (td, *J* = 1, 7.5 Hz, 1 H), 6.97 (dd, *J* = 1, 8 Hz, 1 H), 5.32 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.0, 142.0, 129.5, 125.5, 122.1, 121.8, 117.7, 117.2, 116.6, 63.7.

HRMS: *m*/*z* [M + H] calcd for$C_{10}H_9N_2O$: 173.0715; found: 173.0708.

8-Chloro-2,4-dihydrochromeno[4,3-*c*]pyrazole (2b)

Yield: 94 mg (91%); white solid; mp 160–162 °C.

IR (KBr): 3425, 2928, 1655, 1471, 1027, 1001, 822, 766 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 2.4 Hz, 1 H), 7.39 (s, 1 H), 7.15 (dd, *J* = 2.4, 8.8 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 1 H), 5.31 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 151.7, 127.9, 125.8, 125.0, 121.4, 117.8, 113.9, 110.5, 63.6.

HRMS: *m*/*z* [M + H] calcd for $C_{10}H_8ClN_2O$: 207.0325; found: 207.0321.

8-Bromo-1,4-dihydrochromeno[4,3-*c*]pyrazole (2c)

Yield: 89 mg (71%); white solid; mp 146–148 °C.

IR (KBr): 3162, 2923, 1581, 1467, 1384, 1216, 1057, 761 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 2.4 Hz, 1 H), 7.39 (s, 1 H), 7.30 (dd, *J* = 2.4, 8.8 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 5.32 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2, 139.4, 130.7, 125.0, 124.2, 119.6, 118.2, 113.1, 110.4, 63.6.

HRMS: *m*/*z* [M + H] calcd for $C_{10}H_8BrN_2O$: 250.982; found: 250.9818.

1,4-Dihydro-8-nitrochromeno[4,3-*c*]pyrazole (2d)

Yield: 93 mg (86%); pale-yellow solid; mp 152–154 °C.

IR (KBr): 3369, 2973, 2870, 1589, 1331, 1286, 1096, 788 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.85 (d, *J* = 3.0 Hz, 1 H), 8.16 (dd, *J* = 2.5, 9.0 Hz, 1 H), 7.73 (s, 1 H), 7.09 (d, *J* = 8.5 Hz, 1 H), 4.59 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ = 161.5, 139.8, 130.3, 130.2, 124.1, 124.0, 116.9, 116.5, 114.9, 65.5.

HRMS: *m*/*z* [M + H] calcd for $C_{10}H_8N_3O_3$: 218.0566; found: 218.0559.

1,4-Dihydro-7-methoxychromeno[4,3-*c*]pyrazole (2e)

Yield: 55 mg (55%); white solid; mp 170–172 °C.

IR (KBr): 3421, 3140, 2922, 1626, 1588, 1461, 1276, 1155, 1118, 1018, 784 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.8 Hz, 1 H), 7.36 (s, 1 H), 6.59 (dd, *J* = 2.4, 8.4 Hz, 1 H), 6.55 (d, *J* = 2.1 Hz, 1 H), 5.31 (d, *J* = 0.8 Hz, 2 H), 3.81 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ = 159.8, 154.3, 122.3, 110.5, 109.0, 107.0, 101.9, 63.6, 54.6.

HRMS: *m*/*z* [M + H] calcd for $C_{11}H_{11}N_2O_2$: 203.0821; found: 203.0815.

6-Ethoxy-1,4-dihydrochromeno[4,3-*c*]pyrazole (2f)

Yield: 105 mg (97%); white solid; mp 178–180 °C.

IR (KBr): 3334, 3115, 2920, 1566, 1470, 1445, 1264, 1111, 1040, 997, 728 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.39 (s, 1 H), 7.33 (dd, *J* = 1.5, 7.5 Hz, 1 H), 6.95 (t, *J* = 8 Hz, 1 H), 6.87 (dd, *J* = 1.5, 8.5 Hz, 1 H), 5.39 (d, *J* = 0.5 Hz, 2 H), 4.14 (q, *J* = 7 Hz, 2 H), 1.47 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 142.9, 140.7, 125.5, 121.0, 118.5, 114.2, 113.0, 110.7, 64.2, 63.9, 14.5.

HRMS: *m*/*z* [M + H] calcd for $C_{12}H_{13}N_2O_2$: 217.0977; found: 217.0970.

6,8-Dichloro-1,4-dihydrochromeno[4,3-*c*]pyrazole (2g)

Yield: 109 mg (91%); white solid; mp 164–166 °C.

IR (KBr): 3326, 2925, 1611, 1443, 1378, 1257, 1161, 1102, 978, 757, 674 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 2.5 Hz, 1 H), 7.71 (s, 1 H), 7.34 (d, *J* = 2.5 Hz, 1 H), 4.52 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ = 147.4, 127.7, 125.3, 121.8, 119.7, 110.1, 64.2.

HRMS: *m*/*z* [M + H] calcd for $C_{10}H_7Cl_2N_2O$: 240.9935; found: 240.9929.

6,8-Di-*tert*-butyl-1,4-dihydrochromeno[4,3-*c*]pyrazole (2h)

Yield: 136 mg (96%); white solid; mp 188–190 °C.

IR (KBr): 3136, 2957, 2862, 1632, 1466, 1440, 1208, 1081, 1000 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 2.0 Hz, 1 H), 7.39 (s, 1 H), 7.29 (d, *J* = 2.0 Hz, 1 H), 5.23 (s, 2 H), 1.41 (s, 9 H), 1.32 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.2, 143.8, 138.2, 125.3, 125.2, 124.1, 117.9, 117.0, 112.0, 62.6, 35.0, 34.5, 31.5, 29.9.

HRMS: *m*/*z* [M + H] calcd for $C_{18}H_{25}N_2O$: 285.1967; found: 285.1969.

1,4-Dihydrobenzo[5,6]chromeno[4,3-*c*]pyrazole (2i)

Yield: 108 mg (97%); white solid; mp 158–160.

IR (KBr): 3346, 3106, 2917, 2856, 1620, 1517, 1462, 1371, 1213, 1009, 812, 741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.21 (d, *J* = 8.4 Hz, 1 H), 7.79 (d, *J* = 8 Hz, 1 H), 7.73 (d, *J* = 8.8 Hz, 1 H), 7.60–7.57 (m, 1 H), 7.45 (s, 1 H), 7.43–7.38 (m, 1 H), 7.20 (d, *J* = 8.8 Hz, 1 H), 5.37 (d, *J* = 0.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 144.3, 129.9, 129.8, 128.2, 127.3, 125.8, 124.1, 122.9, 118.6, 112.5, 111.7, 63.4.

HRMS: *m*/*z* [M + H] calcd for $C_{14}H_{11}N_2O$: 223.0871; found: 223.0868.

1,4-Dihydro-3-phenylchromeno[4,3-*c*]pyrazole (2j)

Yield: 96 mg (77%); white solid; mp 268–230 °C.

IR (KBr): 3421, 3121, 2922, 2853, 1613, 1469, 1216, 748, 687 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 0.9, 4.5 Hz, 1 H), 7.50–7.40 (m, 5 H), 7.23 (d, *J* = 0.9, 4.5 Hz, 1 H), 7.04–6.98 (m, 2 H), 5.49 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 127.2, 126.1, 124.4, 120.2, 119.7, 115.0, 106.4, 62.4.

HRMS: *m*/*z* [M + H] calcd for $C_{16}H_{13}N_2O$: 249.1028; found: 249.1024.

8-Chloro-1,4-dihydro-3-phenylchromeno[4,3-*c*]pyrazole (2k)

Yield: 61 mg (43%); white solid; mp 294–296 °C.

IR (KBr): 3423, 2923, 2854, 1628, 1466, 1218, 1110, 799 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 7.74 (d, *J* = 2.4 Hz, 1 H), 7.50–7.44 (m, 4 H), 7.38 (d, *J* = 6.9 Hz, 1 H), 7.12 (dd, *J* = 2.4, 8.7 Hz, 1 H), 6.90 (d, *J* = 8.7 Hz, 1 H), 5.51 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 127.2, 126.8, 126.3, 124.4, 124.0, 119.6, 116.7, 106.5, 63.9.

HRMS: *m*/*z* [M + H] calcd for $C_{16}H_{12}ClN_2O$: 283.0638; found: 280.0636.

3-Ethyl-1,4-dihydrochromeno[4,3-*c*]pyrazole (2l)

Yield: 70 mg (70%); white solid; mp 255–256 °C.

IR (KBr): 3062, 2924, 2853, 1605, 1511, 1470, 1213, 1085, 746 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.21–7.17 (m, 1 H), 6.99–6.95 (m, 2 H), 5.26 (s, 2 H), 2.66 (q, *J* = 7.5 Hz, 2 H), 1.26 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 141.9, 141.5, 129.2, 122.1, 121.6, 117.8, 117.0, 108.4, 63.6, 18.5, 12.9.

HRMS: *m*/*z* [M + H] calcd for $C_{12}H_{13}N_2O$: 201.1028; found: 201.1030.

8-Chloro-3-ethyl-1,4-dihydrochromeno[4,3-*c*]pyrazole (2m)

Yield: 69 mg (59%); white solid; mp 138–140 °C.

IR (KBr): 3358, 3125, 2924, 1602, 1510, 1462, 1216, 807 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 2.5 Hz, 1 H), 7.13 (dd, *J* = 2.5, 8.5 Hz, 1 H), 6.88 (d, *J* = 8.5 Hz, 1 H), 5.25 (s, 2 H), 2.68 (q, *J* = 7.5 Hz, 2 H), 1.28 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 142.3, 140.6, 128.9, 121.9, 119.6, 118.4, 108.6, 63.7, 18.4, 12.9.

HRMS: *m*/*z* [M + H] calcd for $C_{12}H_{12}ClN_2O$: 235.0638; found: 235.0636.

1,4-Dihydro-4-methyl-3-phenylchromeno[4,3-*c*]pyrazole (2n)

Yield: 126 mg (96%); white solid; mp 290–291 °C.

IR (KBr): 3061, 2922, 1614, 1464, 1214, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.50–7.46 (m, 4 H), 7.43–7.41 (m, 1 H), 7.24–7.22 (m, 1 H), 7.03–6.98 (m, 2 H), 5.83 (q, *J* = 6.8 Hz, 1 H), 1.51 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.2, 141.4, 140.0, 130.1, 129.5, 128.9, 128.3, 126.6, 122.0, 121.4, 117.6, 116.8, 113.7, 71.1, 22.0.

HRMS: *m*/*z* [M + H] calcd for $C_{17}H_{15}N_2O$: 263.1184; found: 263.1182.

4-Methyl-3-phenyl-1,4-dihydrobenzo[5,6]chromeno[4,3-*c*]pyrazole (2o)

Yield: 148 mg (95%); white solid; mp 153–155 °C.

IR (KBr): 3250, 2923, 2854, 1616, 1457, 1379, 1212, 813, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.25 (d, *J* = 8.5 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.5 Hz, 1 H), 7.61–7.58 (m, 1 H), 7.52–7.51 (m, 4 H), 7.50–7.39 (m, 2 H), 7.21 (d, *J* = 8.5 Hz, 1 H), 5.84 (q, *J* = 6.5 Hz, 1 H), 1.57 (d, *J* = 6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 129.2, 129.1, 129.0, 128.8, 128.4, 127.6, 127.5, 126.3, 126.1, 125.7, 123.2, 118.7, 113.7, 110.9, 70.0, 21.3.

HRMS: *m*/*z* [M + H] calcd for $C_{21}H_{17}N_2O$: 313.1341; found: 313.1339.

3-Bromo-1,4-dihydrochromeno[4,3-*c*]pyrazole (2p)

Yield: 119 mg (95%); white solid; mp 214–216 °C.

IR (KBr): 3149, 2925, 2854, 1728, 1626, 1453, 1348, 1206, 993, 917, 819, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.39 (m, 1 H), 7.23–7.21 (m, 1 H), 7.02–6.98 (m, 2 H), 5.24 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.8, 129.5, 121.6, 121.2, 116.6, 114.6, 110.1, 63.3.

HRMS: *m*/*z* [M + H] calcd for $C_{10}H_8BrN_2O$: 250.982; found: 250.9816.

4,5-Dihydro-5-tosyl-1*H*-pyrazolo[4,3-*c*]quinolone (4a)

Yield: 156 mg (96%); white solid; mp 154–156 °C.

IR (KBr): 3139, 2923, 1595, 1464, 1344, 1164, 1040, 673, 570 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.60 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.41–7.37 (m, 1 H), 7.34–7.30 (m, 1 H), 7.21 (s, 1 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 6.86 (d, *J* = 8.0 Hz, 2 H), 4.93 (s, 2 H), 2.19 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.3, 134.2, 133.9, 127.9, 127.4, 126.8, 126.5, 126.2, 125.1, 121.7, 110.9, 42.7, 20.6.

HRMS: *m*/*z* [M + H] calcd for $C_{17}H_{16}N_3O_2S$: 326.0963; found: 326.0961.

4,5-Dihydro-4-methyl-3-phenyl-5-tosyl-1*H*-pyrazolo[4,3-*c*]quinolone (4b)

Yield: 199 mg (96%); white solid; mp 238–240 °C.

IR (KBr): 3143, 2924, 2854, 1735, 1466, 1220, 806 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 1.2, 8.4 Hz, 1 H), 7.65 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.55–7.53 (m, 2 H), 7.53–7.38 (m, 5 H), 7.36 (d, *J* = 6 Hz, 2 H), 7.35 (d, *J* = 6.4 Hz, 2 H), 5.73 (q, *J* = 6.8 Hz, 1 H), 2.20 (s, 3 H), 1.39 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.8, 133.4, 131.1, 128.3, 127.9, 127.4, 126.9, 126.6, 126.2, 125.5, 124.9, 121.0, 113.3, 48.8, 21.0, 20.2.

HRMS: *m*/*z* [M + H] calcd for $C_{24}H_{22}N_3O_2S$: 416.1433; found: 416.1427.

3-Phenyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazole (5a)

Yield: 43 mg (47%); viscous oil.

IR (KBr): 3419, 2924, 2855, 1633, 1462, 1023, 801, 693 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 2 H), 7.41 (t, *J* = 7.0 Hz, 2 H), 7.32–7.28 (m, 1 H), 2.85 (t, *J* = 7.5 Hz, 2 H), 2.76 (t, *J* = 7.5 Hz, 2 H), 2.54 (quin, *J* = 7.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 143.7, 139.4, 138.2, 125.8, 124.3, 123.5, 30.8, 24.3, 24.0.

HRMS: *m*/*z* [M + H] calcd for $C_{12}H_{13}N_2$: 185.1079; found: 185.1077.

3-(4-Nitrophenyl)-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazole (5b)

Yield: 33 mg (30%); pale-yellow solid; mp 190–192 °C.

IR (KBr): 3337, 3134, 2924, 2853, 1598, 1515, 1343, 1159, 1106, 853, 693 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.5 Hz, 2 H), 7.83 (d, *J* = 8.5 Hz, 2 H), 2.92–2.90 (m, 2 H), 2.80 (br s, 2 H), 2.65 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.7, 144.1, 138.5, 129.6, 125.8, 125.3, 124.3, 30.9, 24.4, 24.0.

HRMS: *m*/*z* [M + H] calcd for $C_{12}H_{12}N_3O_2$: 230.0930; found: 230.0926.

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Supporting Information

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