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Paper

Intramolecular Cycloaddition Approach to Fused Pyrazoles: Access to 4,5-Dihydro-2*H*-pyrazolo[4,3-c]quinolines, 2,8-Dihydroinde-no[2,1-c]pyrazoles, and 4,5-Dihydro-2*H*-benzo[*e*]indazoles

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Abstract A straightforward and efficient method for the synthesis of pyrazoles fused with 1,2,3,4-tetrahydroquinoline, 2,3-dihydro-1*H*-indene, or 1,2,3,4-tetrahydronaphthalene involves the formation of the tosylhydrazone from an aromatic substrate carrying aldehyde and acetylenic functionalities at appropriate positions, followed by base-pro-moted generation of the diazo compound and subsequent intramolecular 1,3-dipolar cycloaddition. A number of functional groups were found to be compatible for this reaction sequence and yields were moderate to very good (44–95%). A plausible reaction mechanism supported by DFT calculations has been provided to explain the formation of products.

Key words cycloaddition, pyrazole, indazole, dihydroquinoline, quino-line

Pyrazoles, considered as privileged structural motif in medicinal chemistry,¹ are prevalent in core structures of natural products² and in a variety of commercial drugs.³ More specifically, fused pyrazoles like pyrazolo[4,3-*c*]quinolines are associated with a broad range of biological effects.⁴ Mention may be made of compound **1** (Figure 1), a well-known anti-inflammatory agent and interleukin 1 inhibitor,^{5a} and compounds **2a,b** (ELND006 and ELND007) that are potent metabolically stable γ-secretase inhibitors that selectively inhibit the production of amyloid-β over Notch.^{5b}

In addition, pyrazoles fused with carbocycles are also used as attractive building blocks for many pharmacologically active compounds.⁶ For example, indenopyrazole compound **3** (Figure 1) acts as a hypoxia inducible factor (HIF)-1 inhibitor,^{6b} displaying the highest activity at IC₅₀ of 0.014 μ M, while PF-3882845 (compound **4**, Figure 1) is reported as an orally efficacious mineralocorticoid receptor (MR) antagonist for hypertension and nephropathy.^{6e} In view of the immense biological activities of fused pyrazoles, convenient syntheses of novel scaffolds of this class are of interest. Thus, in continuation of our studies in heterocycles synthesis,⁷ we became interested in the construction of novel fused pyrazoles **5–7** (Figure 2).

Among the fused pyrazoles, those attached to different heterocycles, particularly quinoline frameworks,^{4e,8} have been studied to a larger extent; but pyrazoles fused with saturated quinolines (like those in Figure 2), particularly







pyrazolo[4,3-c]dihydroquinolines (i.e., **5**), are less known.^{4f,9} While the syntheses of 2,8-dihydroindeno[2,1-c]pyrazoles **6** and 4,5-dihydrobenzo[*e*]indazoles **7** are not yet reported, though few methods exist for their structural isomers^{10,11a} and related molecules.^{11b,c} Therefore, development of alternative, efficient, and straightforward procedures for the generation of fused pyrazoles 5–7 appeared relevant. We therefore took up the synthesis of dihydro-2H-pyrazolo-[4,3-c]quinolines 5 (Scheme 1, a), 2,8-dihydroindeno[2,1-c]pyrazoles **6** and 4.5-dihydro-2*H*-benzol*e*lindazoles **7** (Scheme 1, b) adopting a straightforward method, in which intramolecular [3+2] cycloaddition of alkyne-tethered tosylhydrazones was conceived to be the key step. Incidentally, during the course of this study, Suja et al.⁹ (Scheme 1, c) published the synthesis of two tautomers of 5 by performing the reaction for prolonged periods (12 h) and using a strong base (i.e., NaOH). In another publication,^{10a} Xu et al. (Scheme 1, d) carried out the synthesis of 6,5,5-tricyclic fused pyrazoles, structural isomers of 6 by executing the reaction at 60 °C for 12 hours using the costly reagent t-BuO-Li. Importantly, both of these reactions require a strong base, which may affect sensitive functional groups. Besides these, Valdés and co-workers^{11a} developed a cascade protocol comprising intermolecular [3+2]-cycloaddition/[1,5]sigmatropic rearrangement for the synthesis of tautomers of 7. The limitations are poor yields (42-57%) and long reaction time (12 h).

We commenced our investigation with the substrate N-(2-formylphenyl)-4-methyl-N-[3-(naphthalen-1-yl)prop-2vn-1-vl]benzenesulfonamide (8a), which can easily be obtained through N-tosylation of 2-aminobenzaldehyde followed by N-propargylation and Sonogashira coupling with naphthyl iodide (see Supporting Information). To check the prospect of cycloaddition reaction in the synthesis, the requisite tosylhydrazone 11a was smoothly prepared from aldehyde 8a through reaction with *p*-toluenesulfonyl hydrazide (NH₂NHTs) in acetonitrile at room temperature. Thereafter, an optimization study was carried out on hydrazone 11a by performing a series of experiments with variation of the reaction parameters such as base, solvent, temperature, etc. for the model conversion into 5a. Selected results are summarized in Table 1. Initial exposure of 11a to DBU in acetonitrile at room temperature for 24 hours afforded the desired fused pyrazole 5a in only 38% yield (Table 1, entry

1). This disappointing result prompted us to carry out the reaction at higher temperature. To our delight, when the reaction was performed in refluxing acetonitrile, considerable improvement in the yield (68%, entry 2) along with significant reduction of reaction time (2.5 h) was achieved. Replacing DBU by an inorganic base (i.e., K_2CO_3/Cs_2CO_3) caused a reduction in the yield of **5a** (entries 3, 4). We therefore pursued with DBU as a base but chose the higherboiling solvent 1,4-dioxane instead of acetonitrile. To our disappointment, the yield of the product **5a** was still not encouraging (entry 5). Pleasingly, employment of Cs_2CO_3 as base and 1,4-dioxane as solvent afforded product **5a** within 1 hour in excellent yield (88%, entry 6). However, the use of CsOAc lowered the yield to 64% (entry 7), suggesting the necessity of Cs_2CO_3 in this reaction. The use of Cs_2CO_3 in either





a less polar solvent (i.e., THF) or a more polar solvent (i.e., DMF) was not found to encouraging (entries 8, 9). Besides, a couple of reactions were conducted in 1,4-dioxane using stronger base (NaH/t-BuOK) but yields were found to be within the range of 52–67% (entries 10, 11). Thus, the reaction conditions of entry 6 of Table 1 were considered as optimal for further exploration.

Having established the optimized reaction conditions, we next sought to extend the scope and generality of the procedure employing a variety of substituents R at the alkyne moiety of substrate 8 as shown in Scheme 2. Indeed, a series of products **5a-i** could easily be synthesized within 1-2 hours and in good to excellent yields (64-95%). Introduction of the phenyl ring as substituent (R = Ph) as in substrate 8. vielded 76% of the desired product 5b (Scheme 2). Thereafter, the reactions also proceeded smoothly when electron-donating or -withdrawing group at the para position of the phenyl ring was present and the results are presented in Scheme 2. Electron-donating groups (viz., Me, OMe) afforded 5c,d in 64-70% yields, while electron-withdrawing groups (viz., CF₃, NO₂, CO₂Me) furnished products 5e,f,g in somewhat higher yields (72-90%). Furthermore, the reaction times were found to be shorter (1.2-1.5 h) in the case of electron-withdrawing groups compared to electron-donating groups (2 h). The substituents (R = pyridyl, thiophenyl) in substrate 8 and afforded the corresponding products 5h,i in good yields (68-78%). Notably, the subBased on previous reports^{9,12} and our own observations, a plausible reaction mechanism is outlined in Scheme 3 to explain the formation of products **5**. Initially, the reaction between 4-methylbenzenesulfonohydrazide and aldehyde **8** forms hydrazone **11**, which is then converted into the diazo species **A** in presence of the base.^{10a,11a,12b,c} Intramolecular 1,3-dipolar cycloaddition of the diazo compound forms a transient intermediate **B**, which in the presence of base undergoes deprotonation–reprotonation leading to pyrazole **5**. The possibility of 1,5-hydrogen shift, which is thermally allowed but would lead to the formation of **5'** is ruled out in this case. Incidentally, DFT calculations reveal that structure **5d** is stabler than **5d'** by about 4.22 kJ/mol (see Supporting Information).

The structures of products **5**¹³ were determined by spectroscopic (¹H and ¹³C NMR, and HRMS) and analytical data. In addition, single crystal X-ray¹⁴ analysis of **5d** and **5e** gave further support (Figure 3).

After successfully establishing an expedient strategy for synthesizing pyrazolo[4,3-c]dihydroquinolines **5**, we focused our attention to investigate the synthesis of products **6** and **7** under the optimized reaction conditions using the substrates **9** and **10** (Scheme 4). Accordingly, the alkyne





Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%) ^b
1	DBU	MeCN	r.t.	24	38
2	DBU	MeCN	reflux	2.5	68
3	K ₂ CO ₃	MeCN	reflux	3.0	38
4	Cs ₂ CO ₃	MeCN	reflux	2.0	55
5	DBU	1,4-dioxane	100	1.5	60
6	Cs ₂ CO ₃	1,4-dioxane	100	1.0	88
7	CsOAc	1,4-dioxane	100	1.5	64
8	Cs ₂ CO ₃	THF	reflux	2.0	75
9	Cs ₂ CO ₃	DMF	100	1.5	48
10	<i>t</i> -BuOK	1,4-dioxane	100	1.5	67
11	NaH	1,4-dioxane	100	2.0	52

^a Reaction conditions: **8a** (0.25 mmol), NH₂NHTs (0.5 mmol, 2 equiv) in MeCN (2 mL) at r.t. for 2 h; the resulting crude intermediate obtained (upon removal of MeCN) was then heated in the presence of base (1.5 equiv) in solvent (2 mL) under an atmosphere of argon at indicated temperature.

^b Isolated yield of pure product after chromatography.





tethered aldehydes 9 (n = 1) were treated with *p*-toluene-

sulfonyl hydrazide for 3 hours and thereafter, the resulting

crude hydrazones were exposed to the optimized reaction

conditions to obtain 2,8-dihydroindeno[2,1-c]pyrazoles 6.

In the case of substrate **9a** (R = naphthyl), the correspond-

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Figure 3 ORTEP diagram of compound 5d and 5e (drawn at 50% probability level)







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Scheme 2 One-pot synthesis of pyrazolo[4,3-c]dihydroquinolines **5**. *Reagents and conditions*: **8** (0.25 mmol), NH₂NHTs (0.5 mmol, 2 equiv) in MeCN (2 mL) at r.t. for 2 h; the resulting crude intermediate obtained (upon removal of MeCN) was then heated in 1,4-dioxane (2 mL) at 100 °C for 1–2 h in the presence of Cs_2CO_3 (0.38 mmol, 1.5 equiv). Yields of isolated pure products are shown.

cessitated longer reaction time period (3 h), yet diminished the yield of the product **6c** to 62%. Interestingly, incorporation of an electron-donating group (e.g., OMe) in the heteroaryl moiety as in substrate **9d** (R = 2,4-dimethoxypyrimidine) proved beneficial for product **6d** formation (82%). Electron-withdrawing substituents (F, CO₂Me) at the *para*position of the phenyl ring facilitated this reaction by reducing the reaction time to 2 hours, though the desired products **6e,f** were isolated in somewhat lower (60–75%) yields. To our disappointment, when an alkyl chain (R = Bu) was employed at the terminal position of the acetylene moiety as in substrate **9g**, the reaction required longer time period (3.5 h) and yield of the product **6g** dropped significantly to 44%.

We also anticipated that 6,6,5-tricyclic-fused pyrazoles **7**, a higher homologue of products **6**, could also be easily accessed utilizing the substrate **10** (Scheme 4). Indeed, when the hydrazones derived from the substrates **10** (n = 2, R = Ph, Bu) were exposed to our optimized conditions, the results were in tune with the previous reactions, providing the 4,5-dihydrobenzo[*e*]indazoles **7a,b** in 46–87% yields.

The structures of products **6** and **7** were concluded from ¹H and ¹³C NMR supported by mass spectral analysis. Although two tautomeric forms are possible, we prefer the structures shown based on X-ray crystallographic analysis of products **6b** and **6d** (Figure 4).



Figure 4 ORTEP diagram of 6b and 6d (drawn at 50% probability level)

In order to extend the synthetic utility of the products prepared, we decided to check the viability of a simple and straightforward transformation of products **5** into pyrazolo-[4,3-*c*]quinolines **12** through a base-promoted tosyl elimination as shown in Scheme 5. Towards this objective, **5b**



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Scheme 4 Synthesis of carbocycle fused pyarazoles **6**, **7**. *Reagents and conditions*: **9**/**10** (0.25 mmol), NH₂NHTs (0.5 mmol, 2 equiv) in MeCN (2 mL) for 3 h; the resulting crude intermediate was heated at 100 °C for 2–3.5 h in the presence of Cs_2CO_3 (0.38 mmol, 1.5 equiv) and 1,4-dioxane (2 mL). Yields of isolated pure products are shown.

was treated with different bases (i.e., Cs₂CO₃, K₂CO₃, Na₂CO₃, NaH, NaHDMS, or *t*-BuOK) in DMSO; to our disappointment, no reaction took place even after heating these reactions for several hours at 100–120 °C. Surprisingly, when potassium hydroxide was used as a base, the reaction was found to be complete within 3 hours, furnishing the expected product **12b** in 90% yield (Scheme 5). This transformation was then extended to the synthesis of **12a** (92%) and **12c** (95%) using the compounds **5a** and **5d**, respectively (Scheme 5).



The structures of the products **12** were established from spectroscopic (¹H and ¹³C NMR) and analytical data. Notably, pyrazolo[4,3-*c*]quinolines are well known for their biological relevance;⁴ consequently, several synthetic procedures have been reported using either multistep and/or costly reagents/starting materials.⁸ Therefore, our present approach may serve as an alternative for an easy access of pyrazolo[4,3-*c*]quinolines.

In conclusion, we have developed a facile method for accessing pyrazole-fused polycyclic scaffolds **5–7** starting from low cost and easily available starting materials. The method relies on a base-promoted generation of diazo compounds which underwent intramolecular 1,3-dipolar cycloaddition with a tethered alkyne moiety. The reactions were complete within few hours and a range of functional groups were compatible. The pyrazolo[4,3-c]quinolines **12** could also be easily prepared through a simple base (KOH) treatment of products **5**. We believe that this method will find applications in organic and medicinal chemistry as well.

All solvents were distilled prior to use. Petroleum ether (PE) refers to the fraction boiling in the range 60–80 °C. CH_2CI_2 was dried over P_2O_5 , distilled, and stored over 3Å molecular sieves in a sealed container. 1,4-Dioxane and THF were distilled over sodium and benzophenone. MeCN was dried over P_2O_5 , distilled, and stored under 4Å molecular sieves in a sealed container. Commercial grade anhyd DMF was used as such. All the reactions were carried out under argon atmosphere and anhydrous conditions unless otherwise noted. Analytical TLC was performed on silica gel 60 F_{254} aluminum TLC sheets. Visualization of the developed chromatogram was performed by UV absorbance or I_2 exposure. For purification, column chromatography was performed using 60–120 or 100–200 mesh silica gel. ¹H and ¹³C NMR spectra

were recorded on 300 or 600 MHz spectrometer using TMS as internal standard. Chemical shifts (δ) are given from TMS (δ = 0.00) in parts per million (ppm) with reference to the residual nuclei of the deuterated solvent used [CDCl₃: ¹H NMR 7.26 ppm (s); ¹³C NMR 77.0 ppm; DMSO-*d*₆: ¹H NMR 2.54 ppm (s); ¹³C NMR 39.5 ppm]. Coupling constants (*J*) are expressed in hertz (Hz) and standard abbreviations are used to denote spin multiplicities. All ¹³C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF, EI, or FAB ionization mode.

3-Aryl-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolines 5; General Procedure

To a well stirred solution of **8** (0.25 mmol, 1 equiv) in anhyd MeCN (2 mL) was added *p*-toluenesulfonyl hydrazide (95 mg, 0.5 mmol, 2.0 equiv) and the mixture was stirred at r.t. for 2 h. After completion of the reaction (monitored by TLC), MeCN was removed under reduced pressure to obtain a crude material that was then dissolved in 1,4-dioxane (2 mL), and Cs₂CO₃ (123 mg, 0.38 mmol, 1.5 equiv) was added. The mixture was allowed to stir at 100 °C for a few hours (see Scheme 2 in text) until the completion of reaction (TLC). Next, the solvent was evaporated under reduced pressure and the crude mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (25 mL), dried (anhyd Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel (100–200 mesh) column chromatography using EtOAc–PE to furnish **5**.

3-(Naphthalen-1-yl)-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (5a)

Yield: 99.2 mg (88%); pale yellow solid; mp 160-162 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 8.02–7.98 (m, 2 H), 7.87–7.85 (m, 1 H), 7.77–7.74 (m, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.63–7.55 (m, 3 H), 7.45–7.37 (m, 4 H), 7.02 (d, J = 8.1 Hz, 2 H), 6.92 (d, J = 8.1 Hz, 2 H), 4.87 (s, 2 H), 2.33 (s, 3 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 143.2, 135.3, 135.1, 133.9, 131.2, 129.9, 128.8, 128.5, 127.6, 127.2, 127.0, 126.9, 126.5, 126.3, 125.6, 125.3, 124.6, 122.5, 111.8, 43.4, 21.5.

HRMS (EI): m/z calcd for $C_{27}H_{21}N_3O_2S$ [M]⁺: 451.1354; found: 451.1345.

3-Phenyl-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (5b)

Yield: 76 mg (75%); white solid; mp 146-148 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 7.85 (d, *J* = 7.8 Hz, 1 H), 7.65 (d, *J* = 7.2 Hz, 1 H), 7.57–7.50 (m, 3 H), 7.48–7.43 (m, 3 H), 7.38–7.33 (m, 1 H), 7.01 (d, *J* = 8.1 Hz, 2 H), 6.83 (d, *J* = 8.1 Hz, 2 H), 5.07 (s, 2 H), 2.21 (s, 3 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 144.3, 143.2, 139.9, 135.2, 134.7, 129.4, 129.3, 128.8, 128.6, 128.5, 127.6, 126.9, 126.3, 125.3, 122.4, 109.6, 43.4, 21.3.

HRMS (EI): m/z calcd for $C_{23}H_{19}N_3O_2S$ [M]⁺: 401.1198; found: 401.1199.

3-(p-Tolyl)-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (5c) Yield: 66.4 mg (64%); pale yellow gum.

¹H NMR (CDCl₃, 300 MHz): δ = 7.84 (d, *J* = 8.1 Hz, 1 H), 7.64 (d, *J* = 7.2 Hz, 1 H), 7.45–7.40 (m, 1 H), 7.37–7.35 (m, 1 H), 7.33 (s, 4 H), 6.99 (d, *J* = 8.1 Hz, 2 H), 6.82 (d, *J* = 8.1 Hz, 2 H), 5.05 (s, 2 H), 2.46 (s, 3 H), 2.21 (s, 3 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 143.2, 139.1, 135.3, 134.7, 130.1, 128.8, 128.6, 128.5, 127.6, 126.9, 126.2, 122.5, 109.4, 43.4, 21.4, 21.3.

HRMS (EI): m/z calcd for $C_{24}H_{21}N_3O_2S$ [M]⁺: 415.1354; found: 415.1364.

3-(4-Methoxyphenyl)-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3c]quinoline (5d)

Yield: 75.4 mg (70%); pale white solid; mp 180–182 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 7.82 (d, *J* = 7.8 Hz, 1 H), 7.64–7.61 (m, 1 H), 7.41 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.36–7.32 (m, 3 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 6.98 (d, *J* = 8.1 Hz, 2 H), 6.81 (d, *J* = 8.1 Hz, 2 H), 5.02 (s, 2 H), 3.90 (s, 3 H), 2.21 (s, 3 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 160.0, 144.3, 143.2, 139.6, 135.2, 134.8, 128.8, 128.6, 128.4, 127.6, 127.5, 126.9, 125.5, 122.4, 121.8, 114.8, 109.0, 55.4, 43.4, 21.3.

HRMS (ESI): m/z calcd for $C_{24}H_{21}N_3O_3SNa$ [M + Na]⁺: 454.1201; found: 454.1202.

5-Tosyl-3-[4-(trifluoromethyl)phenyl]-4,5-dihydro-2*H*-pyrazo-lo[4,3-c]quinoline (5e)

Yield: 86.7 mg (74%); white solid; mp 244-246 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 7.84 (d, J = 7.8 Hz, 1 H), 7.76 (d, J = 8.1 Hz, 2 H), 7.59–7.52 (m, 3 H), 7.43 (td, J = 7.8, 1.1 Hz, 1 H), 7.35–7.31 (m, 1 H), 6.98 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.1 Hz, 2 H), 5.07 (s, 2 H), 2.21 (s, 3 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 143.4, 135.1, 134.7, 128.9, 128.7, 127.7, 126.9, 126.6, 126.4, 126.3, 124.3, 122.2, 110.6, 43.4, 21.4.

HRMS (EI): m/z calcd for $C_{24}H_{18}F_3N_3O_2S\ [M]^+:$ 469.1072; found: 469.1081.

3-(4-Nitrophenyl)-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (5f)

Yield: 80.2 mg (72%); brown solid; mp 268-270 °C.

¹H NMR (CDCl₃ + DMSO- d_6 , 600 MHz): δ = 8.25 (d, J = 8.4 Hz, 2 H), 7.69 (dd, J = 8.1, 0.9 Hz, 1 H), 7.66 (d, J = 9.0 Hz, 2 H), 7.56 (d, J = 6.6 Hz, 1 H), 7.31–7.28 (m, 1 H), 7.26–7.25 (m, 1 H), 6.85 (d, J = 8.4 Hz, 2 H), 6.71 (d, J = 7.8 Hz, 2 H), 4.99 (s, 2 H), 2.14 (s, 3 H).

¹³C NMR (CDCl₃ + DMSO-*d*₆, 150 MHz): δ = 146.9, 143.3, 134.7, 134.5, 128.6, 128.5, 128.4, 127.6, 126.8, 126.7, 124.3, 122.5, 110.5, 43.7, 21.4 HRMS (EI): *m/z* calcd for $C_{23}H_{18}N_4O_4S$ [M]⁺: 446.1049; found: 446.1051.

Methyl 4-(5-Tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-3-yl)benzoate (5g)

Yield: 103.2 mg (90%); white solid; mp 198-200 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 8.20 (d, J = 8.1 Hz, 2 H), 7.87–7.85 (m, 1 H), 7.61 (d, J = 7.5 Hz, 1 H), 7.53 (d, J = 8.4 Hz, 2 H), 7.45 (td, J = 7.7, 1.6 Hz, 1 H), 7.35–7.00 (m, 1 H), 6.99 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 8.1 Hz, 2 H), 5.09 (s, 2 H), 4.01 (s, 3 H), 2.24 (s, 3 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 166.5, 143.4, 135.1, 134.7, 134.0, 130.5, 129.9, 128.7, 128.6, 127.6, 126.9, 126.1, 124.4, 122.3, 110.5, 52.4, 43.4, 21.3.

HRMS (EI+): m/z calcd for $C_{25}H_{21}N_3O_4S$ [M]⁺: 459.1253; found: 459.1255.

3-(Pyridin-3-yl)-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (5h)

Yield: 68.3 mg (68%); pale yellow solid; mp 244-246 °C.

¹H NMR (CDCl₃ + DMSO- d_6 , 600 MHz): δ = 8.80 (s, 1 H), 8.54 (s, 1 H), 7.90 (s, 1 H), 7.67 (d, J = 7.8 Hz, 1 H), 7.53–7.48 (m, 2 H), 7.29–7.22 (m, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 6.71 (d, J = 8.4 Hz, 2 H), 4.96 (s, 2 H), 2.14 (s, 3 H).

¹³C NMR (CDCl₃ + DMSO-*d*₆, 150 MHz): δ = 143.3, 134.7, 128.6, 128.5, 128.3, 127.6, 126.7, 122.4, 110.1, 43.5, 21.4.

HRMS (EI+): m/z calcd for $C_{22}H_{18}N_4O_2S$ [M]⁺: 402.1150; found: 402.1147.

3-(Thiophen-2-yl)-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (5i)

Yield: 79.4 mg (78%); white solid; mp 134-136 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 7.87–7.84 (m, 1 H), 7.59–7.56 (m, 1 H), 7.48–7.42 (m, 2 H), 7.36 (td, *J* = 7.4, 1.0 Hz, 1 H), 7.24–7.18 (m, 2 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.1 Hz, 2 H), 5.06 (s, 2 H), 2.23 (s, 3 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 143.4, 135.0, 134.8, 132.0, 128.9, 128.7, 128.0, 127.4, 126.8, 125.8, 124.9, 123.9, 122.2, 109.4, 43.2, 21.3.

HRMS (EI+): m/z calcd for $C_{21}H_{17}N_3O_2S_2$ [M]⁺: 407.0762; found: 407.0763.

5-Tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (5j)

Yield: 77.2 mg (95%); white solid; mp 136-138 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 7.86–7.83 (m, 1 H), 7.63 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.41 (td, *J* = 7.7, 1.6 Hz, 1 H), 7.34 (td, *J* = 7.4, 1.2 Hz, 1 H), 7.23 (s, 1 H), 7.11 (d, *J* = 8.1 Hz, 2 H), 6.88 (d, *J* = 7.8 Hz, 2 H), 4.96 (s, 2 H), 2.21 (s, 3 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 143.3, 135.3, 134.9, 128.7, 128.6, 128.4, 127.5, 127.1, 125.3, 122.3, 112.5, 43.2, 21.3.

HRMS (EI+): m/z calcd for $C_{17}H_{15}N_3O_2S$ [M]⁺: 325.0885; found: 325.0878.

2,8-Dihydroindeno[2,1-c]pyrazoles 6 and 4,5-Dihydro-2*H*-benzo[*e*]indazoles 7; General Procedure

To a well stirred solution of substrate **9/10** (0.25 mmol, 1 equiv) in anhyd MeCN (2 mL) was added *p*-toluenesulfonyl hydrazide (95 mg, 0.5 mmol, 2.0 equiv) and the mixture was stirred at r.t. for 3 h. After complete consumption of the starting material (monitored by TLC), MeCN was removed under reduced pressure. The crude product was then dissolved in anhyd 1,4-dioxane (2 mL), and Cs₂CO₃ (123 mg, 0.38 mmol, 1.5 equiv) was added. The mixture was allowed to stir at 100 °C for a few hours (see Scheme 2) until completion of the reaction (TLC). The solvent was evaporated under reduced pressure and the crude mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (25 mL), dried (anhyd Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified through silica gel (100–200 mesh) column chromatography using EtOAc–PE to give **6/7**.

3-(Naphthalen-1-yl)-2,8-dihydroindeno[2,1-c]pyrazole (6a)

Yield: 42.3 mg (60%); yellow solid; mp 184–186 °C.

 ^1H NMR (CDCl₃, 300 MHz): δ = 8.06–7.98 (m, 3 H), 7.69 (s, 1 H), 7.60–7.51 (m, 4 H), 7.16–7.13 (m, 2 H), 6.97–6.95 (m, 1 H), 3.89 (s, 2 H).

¹³C NMR (CDCl₃, 75 MHz): δ = 146.5, 136.0, 133.8, 130.8, 129.4, 128.5, 127.9, 127.2, 127.0, 126.7, 126.5, 125.7, 125.4, 125.3, 124.9, 121.3, 30.1.

HRMS (EI): *m*/*z* calcd for C₂₀H₁₄N₂ [M]⁺: 282.1157; found: 282.1148.

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Phenyl-2,8-dihydroindeno[2,1-c]pyrazole (6b)

Yield: 49.3 mg (85%); yellow solid; mp 188-190 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 7.77–7.74 (m, 2 H), 7.70 (d, *J* = 7.5 Hz, 1 H), 7.57–7.55 (m, 1 H), 7.52–7.50 (m, 1 H), 7.48–7.42 (m, 2 H), 7.34–7.27 (m, 1 H), 7.24–7.19 (m, 1 H), 3.81 (s, 2 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 145.5, 136.1, 130.5, 129.1, 128.5, 126.9, 125.7, 125.1, 120.1, 30.2.

HRMS (EI): *m*/*z* calcd for C₁₆H₁₂N₂ [M]⁺: 232.1000; found: 232.0992.

3-(Pyridin-3-yl)-2,8-dihydroindeno[2,1-c]pyrazole (6c)

Yield: 36.1 mg (62%); pale yellow solid; mp 192–194 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 9.09 (s, 1 H), 8.67 (d, J = 3.9 Hz, 1 H), 8.08 (d, J = 7.8 Hz, 1 H), 7.66 (d, J = 7.5 Hz, 1 H), 7.51–7.45 (m, 2 H), 7.34–7.21 (m, 3 H), 3.80 (s, 2 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 159.9, 149.1, 147.8, 145.4, 135.5, 134.0, 127.3, 127.0, 125.9, 125.5, 124.7, 123.9, 120.0, 30.9.

HRMS (EI): *m*/*z* calcd for C₁₅H₁₁N₃ [M]⁺: 233.0953; found: 233.0954.

3-(2,4-Dimethoxypyrimidin-5-yl)-2,8-dihydroindeno[2,1-c]pyrazole (6d)

Yield: 60.3 mg (82%); brown solid; mp 212-216 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 8.89 (s, 1 H), 7.65 (d, *J* = 7.5 Hz, 1 H), 7.51 (d, *J* = 7.5 Hz, 1 H), 7.32 (t, *J* = 7.4 Hz, 1 H), 7.23–7.21 (m, 1 H), 4.19 (s, 3 H), 4.10 (s, 3 H), 3.81 (s, 2 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 166.9, 164.5, 157.4, 145.6, 135.6, 128.1, 126.9, 125.8, 125.4, 120.4, 106.1, 55.2, 54.6, 30.2.

HRMS (EI): m/z calcd for $C_{16}H_{14}N_4O_2$ [M]⁺: 294.1117; found: 294.1114.

3-(4-Fluorophenyl)-2,8-dihydroindeno[2,1-c]pyrazole (6e)

Yield: 37.5 mg (60%); yellow solid; mp 180-182 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 7.70–7.65 (m, 2 H), 7.56 (d, *J* = 7.2 Hz, 1 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.25–7.14 (m, 4 H), 3.72 (s, 2 H).

¹³C NMR (CDCl₃, 150 MHz): δ = 162.8 (d, J = 247.6 Hz), 145.4, 135.9, 128.7 (d, J = 7.7 Hz), 127.0, 126.8, 125.8, 125.3, 123.7, 119.9, 116.3 (d, J = 21.7 Hz), 30.2.

HRMS (EI): *m*/*z* calcd for C₁₆H₁₁FN₂ [M]⁺: 250.0906; found: 250.0901.

Methyl 4-(2,8-Dihydroindeno[2,1-c]pyrazol-3-yl)benzoate (6f)

Yield: 54.4 mg (75%); pale yellow solid; mp 226–228 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 8.21 (d, J = 8.1 Hz, 2 H), 7.84 (d, J = 8.1 Hz, 2 H), 7.70 (d, J = 7.5 Hz, 1 H), 7.51 (d, J = 7.2 Hz, 1 H), 7.35–7.30 (m, 1 H), 7.24–7.22 (m, 1 H), 3.97 (s, 3 H), 3.82 (s, 2 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 166.5, 160.3, 145.6, 135.9, 135.6, 134.9, 130.4, 129.8, 127.0, 126.5, 125.8, 125.5, 124.6, 120.3, 52.3, 30.2.

HRMS (EI): m/z calcd for $C_{18}H_{14}N_2O_2$ [M]⁺: 290.1055; found: 290.1055.

3-Butyl-2,8-dihydroindeno[2,1-c]pyrazole (6g)

Yield: 23.3 mg (44%); yellow solid; mp 96-98 °C.

¹H NMR (CDCl₃, 300 MHz): δ = 7.45 (d, *J* = 7.8 Hz, 2 H), 7.31 (d, *J* = 7.5 Hz, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 3.73 (s, 2 H), 2.90 (t, *J* = 7.7 Hz, 2 H), 1.82–1.71 (m, 2 H), 1.49–1.37 (m, 2 H), 0.96 (t, *J* = 7.4 Hz, 3 H).

 ^{13}C NMR (CDCl₃, 75 MHz): δ = 160.5, 145.0, 136.6, 126.9, 125.7, 124.5, 120.0, 31.2, 30.3, 25.7, 22.3, 13.8.

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HRMS (EI): m/z calcd for $C_{14}H_{16}N_2$ [M]⁺: 212.1313; found: 212.1301.

1-Phenyl-4,5-dihydro-2H-benzo[e]indazole (7a)

Yield: 53.5 mg (87%); pale yellow solid; mp 168–170 °C.

¹H NMR (CDCl₃, 600 MHz): δ = 7.63–7.61 (m, 2 H), 7.48–7.44 (m, 3 H), 7.30 (dd, J = 7.8, 1.2 Hz, 1 H), 7.25–7.23 (m, 1 H), 7.09 (td, J = 7.4, 1.4 Hz, 1 H), 7.04 (td, J = 7.5, 1.6 Hz, 1 H), 3.01 (t, J = 7.2 Hz, 2 H), 2.83 (t, J = 7.2 Hz, 2 H).

 ^{13}C NMR (CDCl₃, 150 MHz): δ = 135.3, 131.3, 130.6, 128.9, 128.8, 128.5, 128.4, 126.5, 125.8, 123.0, 113.8, 30.2, 21.9.

HRMS (EI): *m*/*z* calcd for C₁₇H₁₄N₂ [M]⁺: 246.1157; found: 246.1142.

1-Butyl-4,5-dihydro-2H-benzo[e]indazole (7b)

Yield: 24.8 mg (46%); pale yellow gum.

¹H NMR (CDCl₃, 600 MHz): δ = 7.43 (d, *J* = 7.2 Hz, 1 H), 7.27–7.24 (m, 2 H), 7.14–7.12 (m, 1 H), 2.99 (t, *J* = 6.9 Hz, 2 H), 2.96 (t, *J* = 7.8 Hz, 2 H), 2.88 (t, *J* = 6.9 Hz, 2 H), 1.77–1.74 (m, 2 H), 1.49–1.45 (m, 2 H), 0.97 (t, *J* = 7.5 Hz, 3 H).

 ^{13}C NMR (CDCl_3, 75 MHz): δ = 134.9, 128.6, 126.9, 125.6, 122.8, 30.5, 30.1, 29.6, 22.6, 21.7, 13.8.

HRMS (EI): *m*/*z* calcd for C₁₅H₁₈N₂ [M]⁺: 226.1470; found: 226.1472.

Pyrazolo[4,3-c]quinolines 12; General Procedure

To a well stirred solution of **5** (0.15 mmol, 1 equiv) in DMSO (3.0 mL) was added KOH (42 mg, 0.75 mmol, 5 equiv) and the mixture was heated at 120 °C for 2–3 h. After completion of the reaction (TLC), the mixture was diluted with H₂O and extracted with EtOAc (3×25 mL). The combined extracts were washed with brine, dried (anhyd Na₂SO₄), filtered, and concentrated in vacuo. The crude material was purified by silica gel (100–200 mesh) column chromatography using EtOAc–PE to afford **12**.

3-(Naphthalen-1-yl)-1*H*-pyrazolo[4,3-*c*]quinoline (12a)

Yield: 40.7 mg (92%); white solid; mp >300 °C.

¹H NMR (DMSO- d_6 , 600 MHz): δ = 14.6 (s, 1 H), 9.05 (s, 1 H), 8.52 (d, J = 7.5 Hz, 1 H), 8.32 (d, J = 8.4 Hz, 1 H), 8.15 (d, J = 7.8 Hz, 1 H), 8.09 (d, J = 7.8 Hz, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 7.90 (d, J = 7.2 Hz, 1 H), 7.83–7.76 (m, 2 H), 7.71 (t, J = 7.5 Hz, 1 H), 7.60 (t, J = 7.2 Hz, 1 H), 7.55 (t, J = 7.5 Hz, 1 H).

 ^{13}C NMR (DMSO- $d_6,$ 150 MHz): δ = 146.1, 145.8, 144.9, 141.5, 134.1, 131.5, 129.9, 129.7, 129.6, 129.5, 129.0, 128.9, 127.5, 127.2, 126.7, 126.2, 126.1, 122.6, 116.1, 115.9.

HRMS (EI): *m*/*z* calcd for C₂₀H₁₃N₃ [M]⁺: 295.1109; found: 295.1109.

3-Phenyl-1H-pyrazolo[4,3-c]quinoline (12b)¹⁵

Yield: 33.0 mg (90%); white solid; mp >300 °C.

¹H NMR (DMSO- d_6 , 600 MHz): δ = 14.48 (s, 1 H), 9.51 (s, 1 H), 8.45 (d, J = 7.8 Hz, 1 H), 8.15 (d, J = 7.8 Hz, 1 H), 8.11 (d, J = 7.2 Hz, 2 H), 7.79 (t, J = 7.5 Hz, 1 H), 7.74 (t, J = 7.5 Hz, 1 H), 7.57 (t, J = 7.2 Hz, 2 H), 7.49–7.48 (m, 1 H).

 ^{13}C NMR (DMSO- $d_6,\,600$ MHz): δ = 146.2, 146.0, 144.7, 142.0, 133.0, 129.9, 129.6, 129.5, 129.0, 127.8, 127.4, 122.5, 115.9, 114.3.

HRMS (EI): *m*/*z* calcd for C₁₆H₁₁N₃ [M]⁺: 245.0953: found: 245.0957.

3-(4-Methoxyphenyl)-1H-pyrazolo[4,3-c]quinoline(12c)

Yield: 39.2 mg (95%); white solid; mp >300 °C.

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¹H NMR (DMSO- d_6 , 600 MHz): δ = 14.4 (s, 1 H), 9.46 (s, 1 H), 8.44 (d, J = 7.8 Hz, 1 H), 8.13 (d, J = 7.8 Hz, 1 H), 8.03 (d, J = 9.0 Hz, 2 H), 7.78 (t, J = 7.5 Hz, 1 H), 7.72 (t, J = 7.5 Hz, 1 H), 7.12 (d, J = 9.0 Hz, 2 H), 3.84 (s, 3 H).

¹³C NMR (DMSO-*d*₆, 150 MHz): δ = 144.8, 129.9, 129.4, 129.1, 127.3, 122.5, 115.0, 55.7.

HRMS (EI): *m*/*z* calcd for C₁₇H₁₃N₃O [M]⁺: 275.1059; found: 275.1030.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591737. X-ray crystallographic data of **5d**, **5e**, **6b**, and **6d**, experimental procedures, and spectral data of compounds **8** and **9** and copies of ¹H, ¹³C NMR spectra of compounds **5–8** and **12** are included.

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- (14) CCDC 1537223 (**5d**), CCDC 1537224 (**5e**), CCDC 1537225 (**6b**) and CCDC 1537226 (**6d**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
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