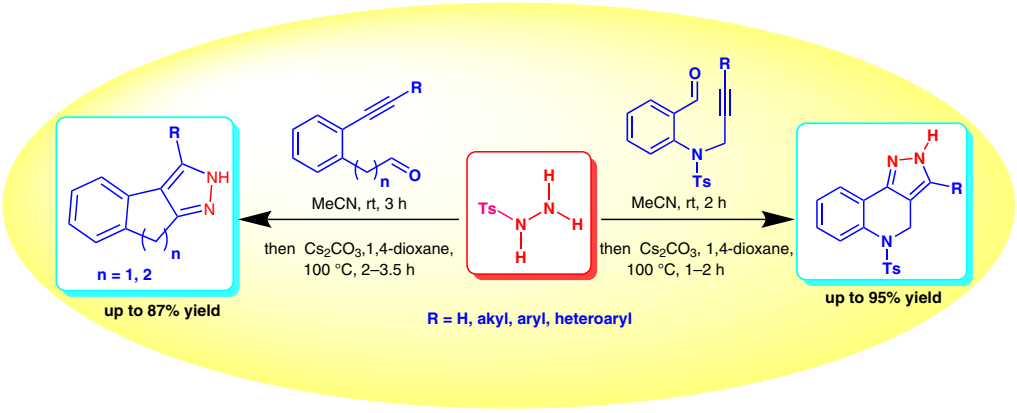
Synthesis M. Jash et al. Paper

Intramolecular Cycloaddition Approach to Fused Pyrazoles: Access to 4,5-Dihydro-2*H*-pyrazolo[4,3-*c*]quinolines, 2,8-Dihydroindeno[2,1-*c*]pyrazoles, and 4,5-Dihydro-2*H*-benzo[*e*]indazoles

Moumita Jash
Bimolendu Das
Suparna Sen
Chinmay Chowdhury*

Organic & Medicinal Chemistry Division, CSIR-Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Kolkata-700032, India
chinmay@iicb.res.in



Received: 26.09.2017
Accepted after revision: 10.11.2017
Published online: 12.12.2017
DOI: 10.1055/s-0036-1591737; Art ID: ss-2017-z0621-op

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-promoted 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, quinoline

Pyrazoles, considered as privileged structural motif in medicinal chemistry,[1] are prevalent in core structures of natural products[2] 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 IC_{50} of 0.014 μM, 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

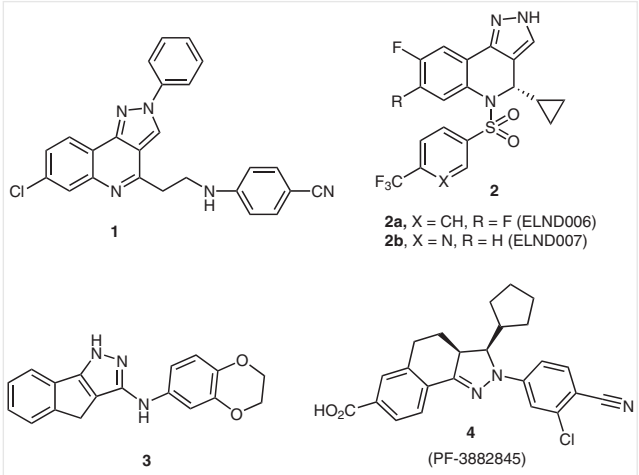


Figure 1 Biologically active fused polycyclic pyrazoles

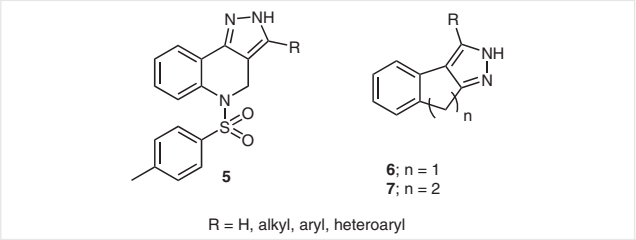
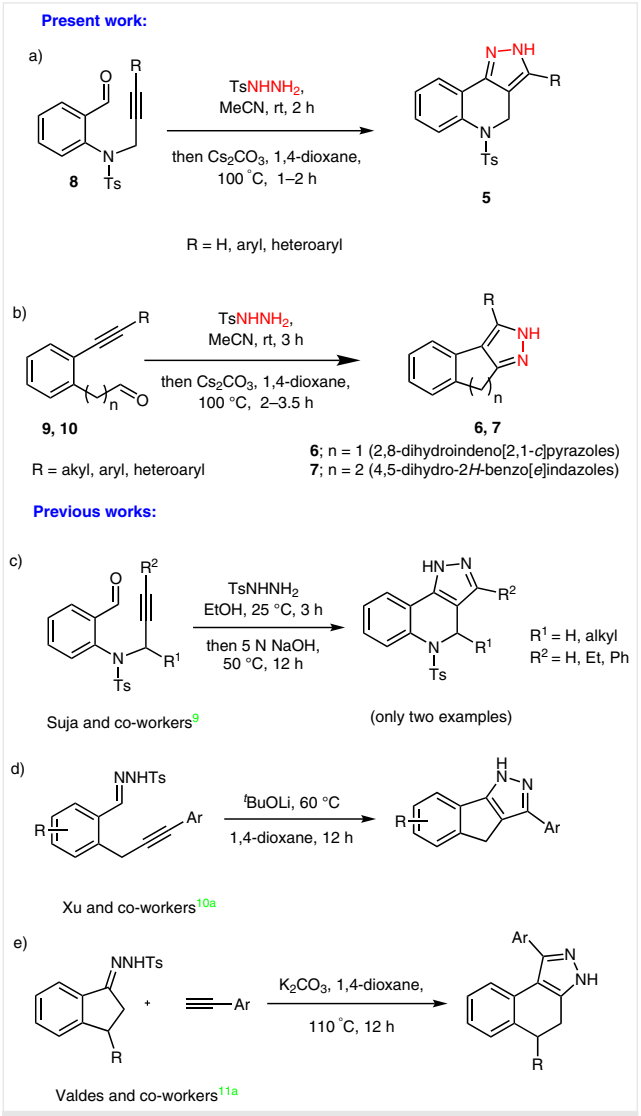


Figure 2 Fused pyrazoles **5–7** as synthetic targets

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-2*H*-pyrazolo-[4,3-*c*]quinolines **5** (Scheme 1, a), 2,8-dihydroindeno[2,1-*c*]-pyrazoles **6** and 4,5-dihydro-2*H*-benzo[*e*]indazoles **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*-BuOLi. 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-2-yn-1-yl]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 (NH_2NHTs) 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 higher-boiling 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



Scheme 1 Synthesis of pyrazole-fused heterocycles **5** and carbocycles **6**, **7** using intramolecular [3+2]-cycloaddition reactions

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.

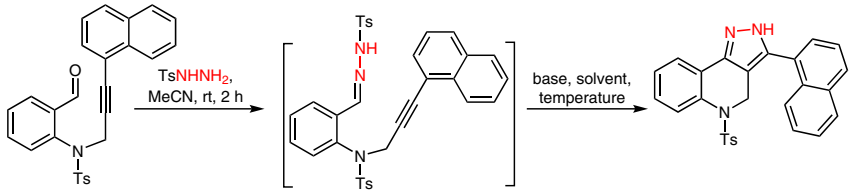
Having established the optimized reaction conditions, we next sought to extend the scope and generality of the procedure employing a variety of substituents R at the alkyne moiety of substrate **8** as shown in Scheme 2. Indeed, a series of products **5a–j** could easily be synthesized within 1–2 hours and in good to excellent yields (64–95%). Introduction of the phenyl ring as substituent (R = Ph) as in substrate **8**, yielded 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., CF_3, NO_2, CO_2Me) 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 substrate having a terminal alkyne moiety (instead of an internal alkyne) worked best, furnishing the product **5j** (95%) within 1 hour; this experiment suggested that the steric interactions play an important role during cycloaddition.

Based 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 ^{13}C NMR, and HRMS) and analytical data. In addition, single crystal X-ray[14] 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

Table 1 Optimization of the Reaction Conditions for the One-Pot Synthesis of **5a**[a]



8a **11a** **5a**

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_2CO_3	MeCN	reflux	3.0	38
4	Cs_2CO_3	MeCN	reflux	2.0	55
5	DBU	1,4-dioxane	100	1.5	60
6	Cs_2CO_3	1,4-dioxane	100	1.0	88
7	CsOAc	1,4-dioxane	100	1.5	64
8	Cs_2CO_3	THF	reflux	2.0	75
9	Cs_2CO_3	DMF	100	1.5	48
10	*t*-BuOK	1,4-dioxane	100	1.5	67
11	NaH	1,4-dioxane	100	2.0	52

[a] Reaction conditions: **8a** (0.25 mmol), NH_2NHTs (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*-toluenesulfonyl 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 corresponding product **6a** was formed within 2 hours in 60% isolated yield, whereas substrate **9b** (R = Ph) required 3 hours to furnish the product **6b** in 85% yield. Employment of a heteroaryl substituent (e.g., R = pyridyl) in substrate **9c** ne-

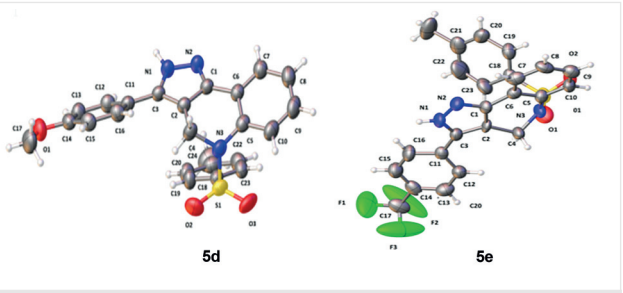
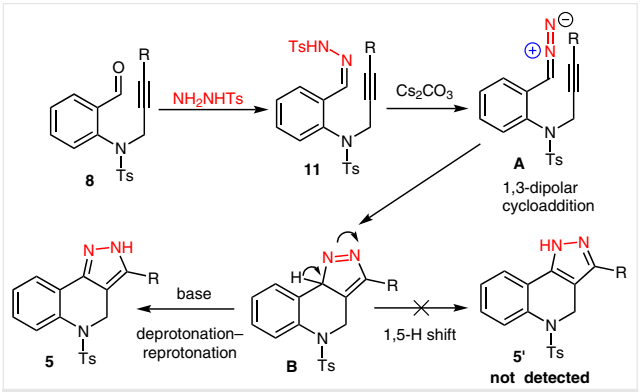
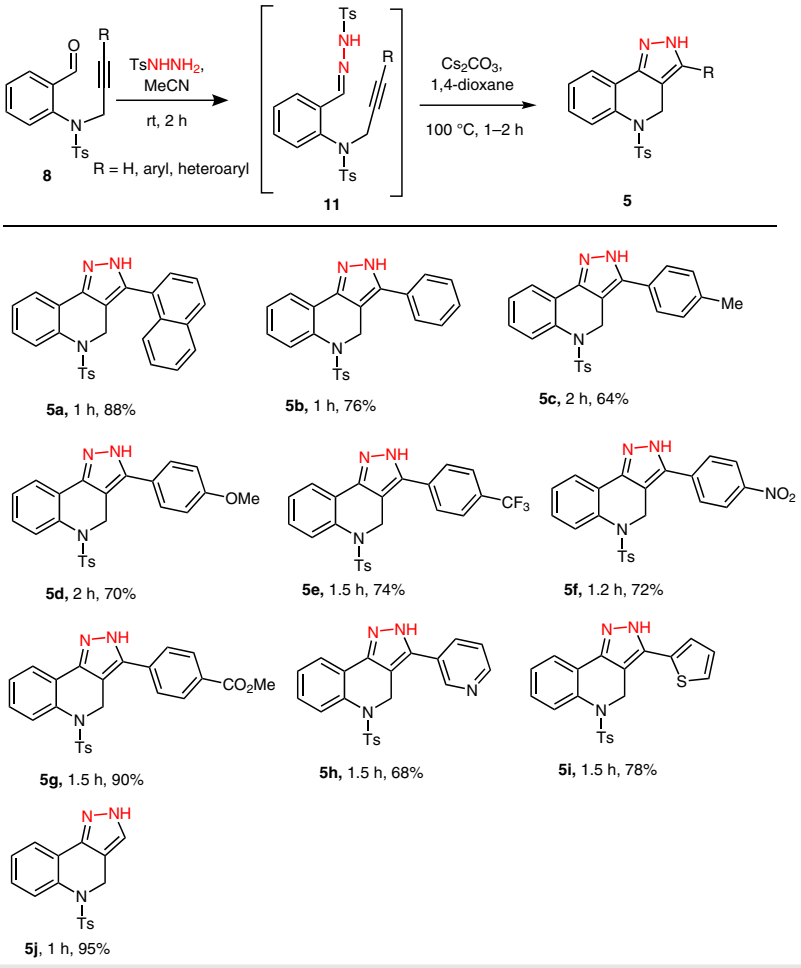


Figure 3 ORTEP diagram of compound **5d** and **5e** (drawn at 50% probability level)



Scheme 3 Plausible mechanism for the formation of products **5**



Scheme 2 One-pot synthesis of pyrazolo[4,3-c]dihydroquinolines **5**. *Reagents and conditions*: **8** (0.25 mmol), NH_2NHTs (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, CO_2Me) 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 ^{13}C 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).

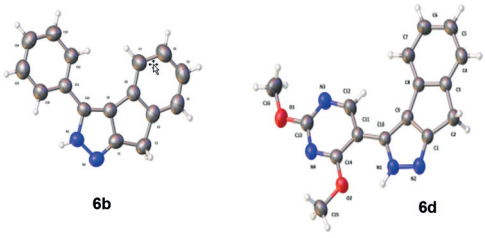
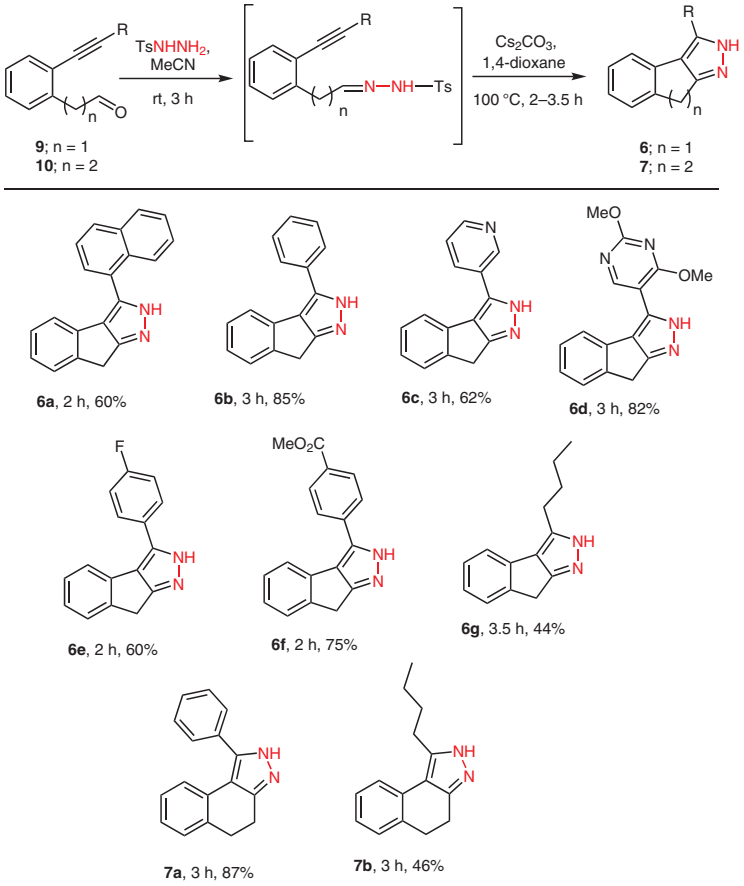


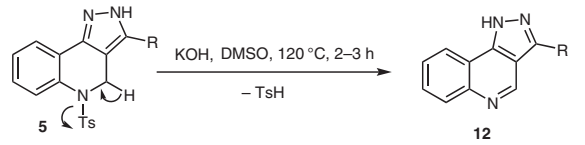
Figure 4 ORTEP diagram of **6b** and **6d** (drawn at 50% probability level)

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**



Scheme 4 Synthesis of carbocycle fused pyarazoles **6**, **7**. *Reagents and conditions*: **9**/**10** (0.25 mmol), NH_2NHTs (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., Cs_2CO_3, K_2CO_3, Na_2CO_3, 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).



5a: R = 1-naphthyl
5b: R = Ph
5d: R = 4-MeOC$_6$H$_4$

12a: R = 1-naphthyl (92%)
12b: R = Ph (90%)
12c: R = 4-MeOC$_6$H$_4$ (95%)

Scheme 5 Base-promoted transformation of **5** to pyrazolo[4,3-*c*]quinolines **12**

The structures of the products **12** were established from spectroscopic (^{1}H and ^{13}C 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_2Cl_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 4 Å 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. ^{1}H and ^{13}C 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 [$CDCl_3$: ^{1}H NMR 7.26 ppm (s); ^{13}C NMR 77.0 ppm; DMSO-d_6: ^{1}H NMR 2.54 ppm (s); ^{13}C NMR 39.5 ppm]. Coupling constants (*J*) are expressed in hertz (Hz) and standard abbreviations are used to denote spin multiplicities. All ^{13}C 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-2*H*-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 Cs_2CO_3 (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 Na_2SO_4), 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-2*H*-pyrazolo[4,3-*c*]quinoline (5a)

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

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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-2*H*-pyrazolo[4,3-*c*]quinoline (5b)

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

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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-2*H*-pyrazolo[4,3-*c*]quinoline (5c)

Yield: 66.4 mg (64%); pale yellow gum.

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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-2*H*-pyrazolo[4,3-*c*]quinoline (5d)

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

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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*-pyrazolo[4,3-*c*]quinoline (5e)

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

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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.

^{1}H NMR ($CDCl_3$ + 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).

^{13}C NMR ($CDCl_3$ + 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.

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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-2*H*-pyrazolo[4,3-*c*]quinoline (5h)

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

^{1}H NMR ($CDCl_3$ + 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).

^{13}C NMR ($CDCl_3$ + 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.

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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-2*H*-pyrazolo[4,3-*c*]quinoline (5j)

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

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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 Cs_2CO_3 (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 Na_2SO_4), 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.

^{1}H NMR ($CDCl_3$, 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).

^{13}C NMR ($CDCl_3$, 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 $C_{20}H_{14}N_2$ [M]$^+$: 282.1157; found: 282.1148.

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

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

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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 $C_{16}H_{12}N_2$ [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.

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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 $C_{15}H_{11}N_3$ [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.

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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.

^{1}H NMR ($CDCl_3$, 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).

^{13}C NMR ($CDCl_3$, 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 $C_{16}H_{11}FN_2$ [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.

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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.

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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.

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

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

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

^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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 $C_{17}H_{14}N_2$ [M]$^+$: 246.1157; found: 246.1142.

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

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

^{1}H NMR ($CDCl_3$, 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 $C_{15}H_{18}N_2$ [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 H_2O and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with brine, dried (anhyd Na_2SO_4), 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.

^{1}H 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 $C_{20}H_{13}N_3$ [M]$^+$: 295.1109; found: 295.1109.

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

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

^{1}H 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 $C_{16}H_{11}N_3$ [M]$^+$: 245.0953: found: 245.0957.

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

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

^{1}H 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).

^{13}C 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 $C_{17}H_{13}N_3O$ [M]$^+$: 275.1059; found: 275.1030.

Funding Information

M.J. thanks UGC, New Delhi for a fellowship. Partial Financial support from WB-DBT (GAP 340) is gratefully acknowledged.

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 ^{1}H, ^{13}C NMR spectra of compounds **5**–**8** and **12** are included.

References

(1) (a) Khan, M. F.; Alam, M. M.; Verma, G.; Akhtar, W.; Akhter, M.; Shaquiquzzaman, M. *Eur. J. Med. Chem.* **2016**, *120*, 170. (b) Kumar, H.; Saini, D.; Jai, S.; Jain, N. *Eur. J. Med. Chem.* **2013**, *70*, 248. (c) Küçükgüzel, Ş. G.; Şenkardeş, S. *Eur. J. Med. Chem.* **2015**, *97*, 786. (d) McDonald, E.; Jones, K.; Brough, P. A.; Drysdale, M. J.; Workman, P. *Curr. Top. Med. Chem.* **2006**, *6*, 1193.

(2) Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. *Eur. J. Med.Chem.* **2013**, *69*, 735.

(3) For example: (a) *Celecoxib*, a COX-2 inhibitor: Hassan, G. S.; Abou-Seri, S. M.; Kamel, G.; Ali, M. M. *Eur. J. Med. Chem.* **2014**, *76*, 482. (b) *Fezolamine*, an antidepressant: Luttinger, D.; Hlasta, D. J. *Annu. Rep. Med. Chem.* **1987**, *22*, 21. (c) *Difenamizole*, an analgesic: Kameyama, T.; Nabeshima, T. *Neuropharmacology* **1978**, *17*, 249.

(4) (a) For anticancer activity: Wentland, P. M. U.S. Patent 5,334,595, **1994**. (b) For selective cyclooxygenase-2 (COX-2) inhibitory: Baruah, B.; Dasu, K.; Vaitilingam, B.; Vanguri, A.; Casturi, S. R.; Yeleswarapu, K. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 445. (c) For A3 adenosine receptor antagonistic: Baraldi, P. G.; Tabrizi, M. A.; Preti, D.; Bovero Fruttarolo, F.; Romagnoli, R.; Zaid, N. A.; Moorman, A. R.; Varani, K.; Borea, P. A. *J. Med. Chem.* **2005**, *48*, 5001. (d) For phosphodiesterase-4 (PDE4) inhibitory activity: Crespo, M. I.; Gracia, J.; Puig, C.; Vega, A.; Bou, J.; Beleta, J.; Domenech, T.; Ryder, H.; Segarra, V.; Palacios, J. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2661. (e) For antiulcer activity: Kalayanov, G. D.; Kang, S. K.; Cheon, H. G.; Lee, S. G.; Yum, E. K.; Kim, S. S.; Choi, J. K. *Bull. Korean Chem. Soc.* **1998**, *19*, 667. (f) For γ-secretase inhibitory activity: Truong, A. P.; Aubele, D. L.; Probst, G. D.; Neitzel, M. L.; Semko, C. M.; Bowers, S.; Dressen, D.; Hom, R. K.; Konradi, A. W.; Sham, H. L.; Garofalo, A. W.; Keim, P. S.; Wu, J.; Dappen, M. S.; Wong, K.; Goldbach, E.; Quinn, K. P.; Sauer, J.-M.; Brigham, E. F.; Wallace, W.; Nguyen, L.; Hemphill, S. S.; Bova, M. P.; Basi, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4920.

(5) (a) Skotnicki, J. S.; Gilman, C. S.; Steinbaugh, B. A.; Musser, J. H. U.S. Patent 4,748,246, **1988**; *Chem. Abstr.* **1988**, *109*, 110425u (b) Probst, G.; Aubele, D. L.; Bowers, S.; Dressen, D.; Garofalo, A. W.; Hom, R. K.; Konradi, A. W.; Marugg, J. L.; Mattson, M. N.; Neitzel, M. L.; Semko, C. M.; Sham, H. L.; Smith, J.; Sun, M.; Truong, A. P.; Ye, X. M.; Xu, Y.-Z.; Dappen, M. S.; Jagodzinski, J. J.; Keim, P. S.; Peterson, B.; Latimer, L. H.; Quincy, D.; Wu, J.; Goldbach, E.; Ness, D. K.; Quinn, K. P.; Sauer, J.-M.; Wong, K.; Zhang, H.; Zmolek, W.; Brigham, E. F.; Kholodenko, D.; Hu, K.; Kwong, G. T.; Lee, M.; Liao, A.; Motter, R. N.; Sacayon, P.; Santiago, P.; Willits, C.; Bard, F.; Bova, M. P.; Hemphill, S. S.; Nguyen, L.; Ruslim, L.; Tanaka, K.; Tanaka, P.; Wallace, W.; Yednock, T. A.; Basi, G. S. *J. Med. Chem.* **2013**, *56*, 5261.

(6) (a) Murineddu, G.; Asproni, B.; Ruiu, S.; Deligia, F.; Falzoi, M.; Pau, A.; Thomas, B. F.; Zhang, Y.; Pinna, G. A.; Pani, L.; Lazzari, P. *Open Med. Chem. J.* **2012**, *6*, 1. (b) Minegishi, H.; Fukashiro, S.; Ban, H. S.; Nakamura, H. *ACS Med. Chem. Lett.* **2013**, *4*, 297. (c) Liu, Y.-N.; Wang, J.-J.; Ji, Y.-T.; Zhao, G.-D.; Tang, L.-Q.; Zhang, C.-M.; Guo, X.-L.; Liu, Z.-P. *J. Med. Chem.* **2016**, *59*, 5341. (d) Schenone, S.; Bruno, O.; Ranise, A.; Brullo, C.; Bondavalli, F.; Filippelli, W.; Mazzeo, F.; Capuano, A.; Falcone, G. *Farmaco* **2003**, *58*, 845. (e) Meyers, M. J.; Arhancet, G. B.; Hockerman, S. L.; Chen, X.; Long, S. A.; Mahoney, M. W.; Rico, J. R.; Garland, D. J.; Blinn, J. R.; Collins, J. T.; Yang, S.; Huang, H.-C.; McGee, K. F.; Wendling, J. M.; Dietz, J. D.; Payne, M. A.; Homer, B. L.; Heron, M. I.; Reitz, D. B.; Hu, X. *J. Med. Chem.* **2010**, *53*, 5979.

(7) (a) Jash, M.; Das, B.; Chowdhury, C. *J. Org. Chem.* **2016**, *81*, 10987. (b) Kundu, P.; Mondal, A.; Chowdhury, C. *J. Org. Chem.* **2016**, *81*, 6596. (c) Kundu, P.; Mondal, A.; Das, B.; Chowdhury, C. *Adv. Synth. Catal.* **2015**, *357*, 3737. (d) Chowdhury, C.; Das, B.; Mukherjee, S.; Achari, B. *J. Org. Chem.* **2012**, *77*, 5108.

(8) For a recent review, see: (a) Mekheimer, R. A.; Ahmed, E. A.; Sadek, K. U. *Tetrahedron* **2012**, *68*, 1637. (b) Alizadeh, A.; Moafi, L.; Ghanbaripour, R.; Abadi, M. H.; Zhu, Z.; Kubicki, M. *Tetrahedron* **2015**, *71*, 3495. (c) Maluleka, M. M.; Mphahlele, M. J. *Tetrahedron* **2013**, *69*, 699. (d) Rivilli, M. J. L.; Moyano, E. L.; Yranzo, G. I. *Tetrahedron Lett.* **2010**, *51*, 478. (e) Duggineni, S.; Sawant, D.; Saha, B.; Kundu, B. *Tetrahedron* **2006**, *62*, 3228. (f) Kasiotis, K. M.; Fokialakis, N.; Haroutounian, S. A. *Synthesis* **2006**, 1791.

(9) Divya, K. V. L.; Meena, A.; Suja, T. D. *Synthesis* **2016**, *48*, 4207.

(10) For structural isomers of dihydroindeno[2,1-*c*]pyrazoles **6**, see: (a) Zheng, Y.; Zhang, X.; Yao, R.; Wen, Y. C.; Huang, J.; Xu, X. *J. Org. Chem.* **2016**, *81*, 11072. (b) Mor, S.; Nagoria, S.; Kumar, A.; Monga, J.; Lohan, S. *Med. Chem. Res.* **2016**, *25*, 1096. (c) Hamilton, R. W. *J. Heterocycl. Chem.* **1976**, *13*, 545.

(11) For structural isomers of 4,5-dihydrobenzo[*e*]indazoles **7**, see: (a) Péréz-Aguilar, M. C.; Valdés, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 7219. For structurally related compounds of **7**, see: (b) Yang, W.; Ye, S.; Fanning, D.; Coon, T.; Schmidt, Y.; Krenitsky, P.; Stamos, D.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 2501. (c) Sivaprasad, G.; Sridhar, R.; Perumal, P. T. *J. Heterocycl. Chem.* **2006**, *43*, 389.

(12) (a) Wu, L.-L.; Ge, Y.-C.; He, T.; Zhang, L.; Fu, X.-L.; Fu, H.-Y.; Chen, H.; Li, R.-X. *Synthesis* **2012**, *44*, 1577. (b) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381. (c) Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13729. (d) Kong, Y.; Tang, M.; Wang, Y. *Org. Lett.* **2014**, *16*, 576.

(13) Interestingly, it was observed that product **5f** exists with its tautomeric form **5'f** (see Scheme 3) in a ratio of 10:8 when NMR is recorded in DMSO-d_6; in $CDCl_3$ this tautomerization appears to be blocked and **5f** exists as a single isomer. This happens because dimethyl sulfoxide is possibly capable of making hydrogen bond with pyrazole NH leading to tautomerization.

(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.

(15) Savchenko, T. I.; Silin, O. V.; Kovalenko, S. M.; Musatov, V. I.; Nikitchenko, V. M.; Ivachtchenko, A. V. *Synth. Commun.* **2007**, *37*, 1321.