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SYNTHESIS OF PYRAZOLO[4,3-*c*]QUINOLINES AND THE C-C BOND CLEAVAGE DURING REDUCTIVE CYCLIZATION

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Abstract – An efficient synthesis of *o*-nitrophenyl tethered pyrazole-4-carbaldehydes was achieved *via* Vilsmeier-Haack formylation of hydrazone derivatives which were subjected to Claisen-Schmidt condensation and Morita-Baylis-Hillman (MBH) reaction with various methyl ketones and activated alkenes respectively to generate the corresponding chalcones and MBH adducts. However, successive Fe-mediated reductive cyclization was followed by an unusual C-C bond cleavage which afforded the pyrazolo[4,3-*c*]quinolines devoid of diverse substituents at C-4 position.

Synthesis of pyrazole fused heterocyclic frameworks occupies an important place in the field of pharmaceutical and medicinal chemistry as several biologically active compounds and blockbuster drugs hold pyrazole core in their structures (Figure 1).[1-7] Because of the widespread bioactivity and broad range of applications of pyrazole derivatives, their synthesis has gained considerable attention from synthetic chemists.[8-10] Compounds containing pyrazole motif exhibit excellent pharmacological properties such as antitumor, antimicrobial, anti-inflammatory, antiviral, antifungal, anticonvulsant, antidepressant, etc.[11-22] Several notable marketed drugs contain the pyrazole moieties such as Rimonabant, Celebrex and Sildenafil which are in the category of most selling drugs over the years and also Zometapine which is effectively used as an antidepressant drug (Figure 1).[11a, 23-27]

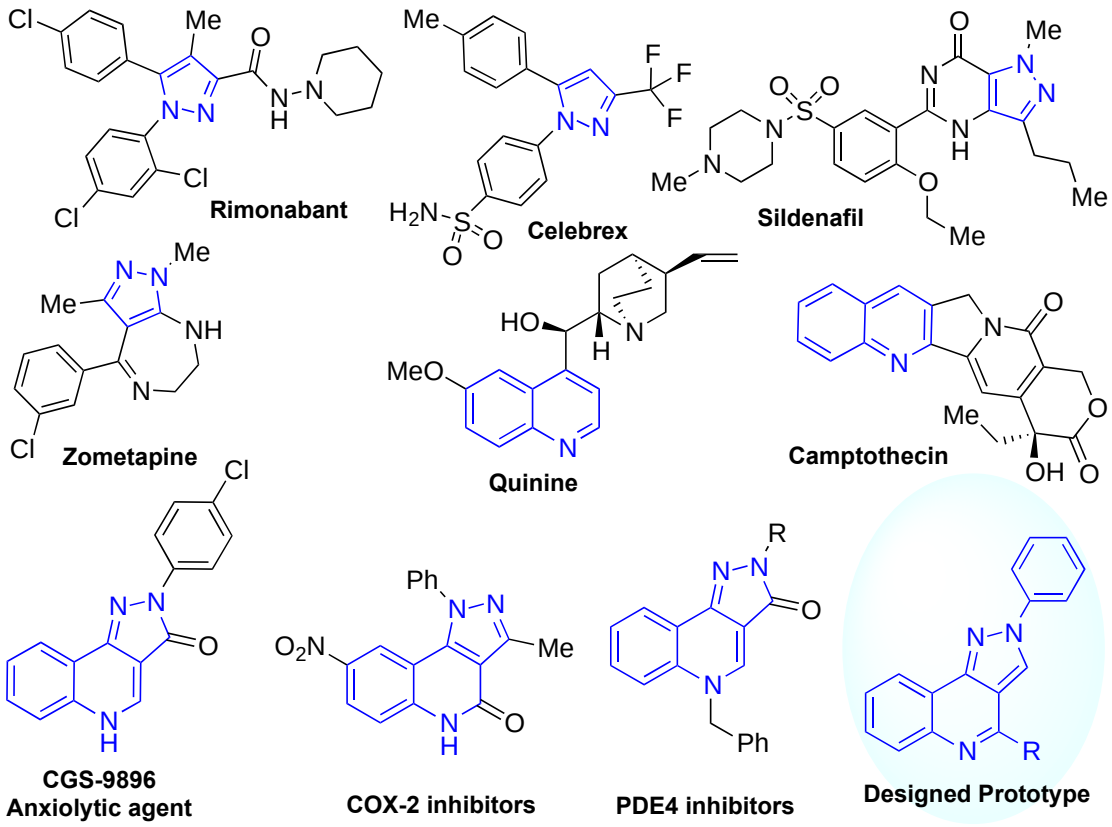


Figure 1. Selected examples of pyrazole and quinoline based drugs and bioactive compounds

Similarly, quinoline is another valuable class of nitrogen-containing heterocyclic framework which has attracted much attention of researchers due to their excellent medicinal profile.[28-32] Quinoline framework is also represented by several commercial drugs such as Chloroquine, Hydroxychloroquine, Ferroquine and Sitamaquine and bioactive natural products like Quinine and Camptothecin.[33-41] Inspired by the pharmacological profile of these two pharmacophores (i.e. pyrazole and quinoline), it was envisaged to incorporate them in a single framework; pyrazolo[4,3-*c*]quinoline. The medicinal potential of pyrazolo[4,3-*c*]quinoline containing a pyrazole moiety condensed with quinoline nucleus is well documented in literature.[42-44] The compounds containing this tricyclic ring system display potent anticancer[45] and anti-inflammatory acitivities,[46] high-affinity toward benzodiazepine receptor ligands.[47-48] They also act as interleukin inhibitors,[49] anxiolytic drugs (CGS-9896 which is used for producing long-lasting anxiolytic and anticonvulsant effects),[50a] selective cyclooxygenase-2 (COX-2),[50b] and phosphodiesterase 4 (PDE4) inhibitors.[51] To achieve the synthesis of diversely substituted pyrazolo[4,3-*c*]quinoline derivatives, a retrosynthetic analysis was performed which showed that pyrazolo[4,3-*c*]quinoline framework **III** can be generated *via* reductive cyclization of pyrazole tethered α,β-unsaturated ketones **II** which in turn can be afforded *via* Claisen-Schmidt condensation of **I** with methyl ketones as outlined in Figure 2.

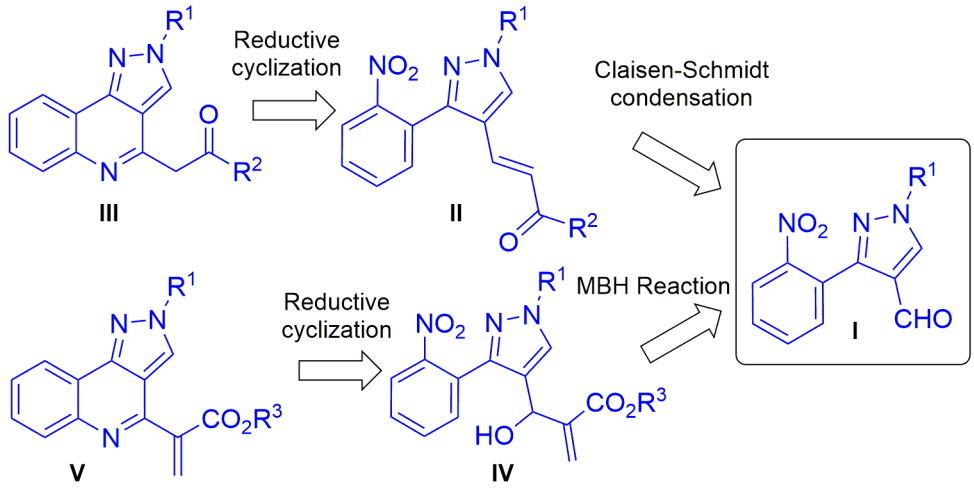
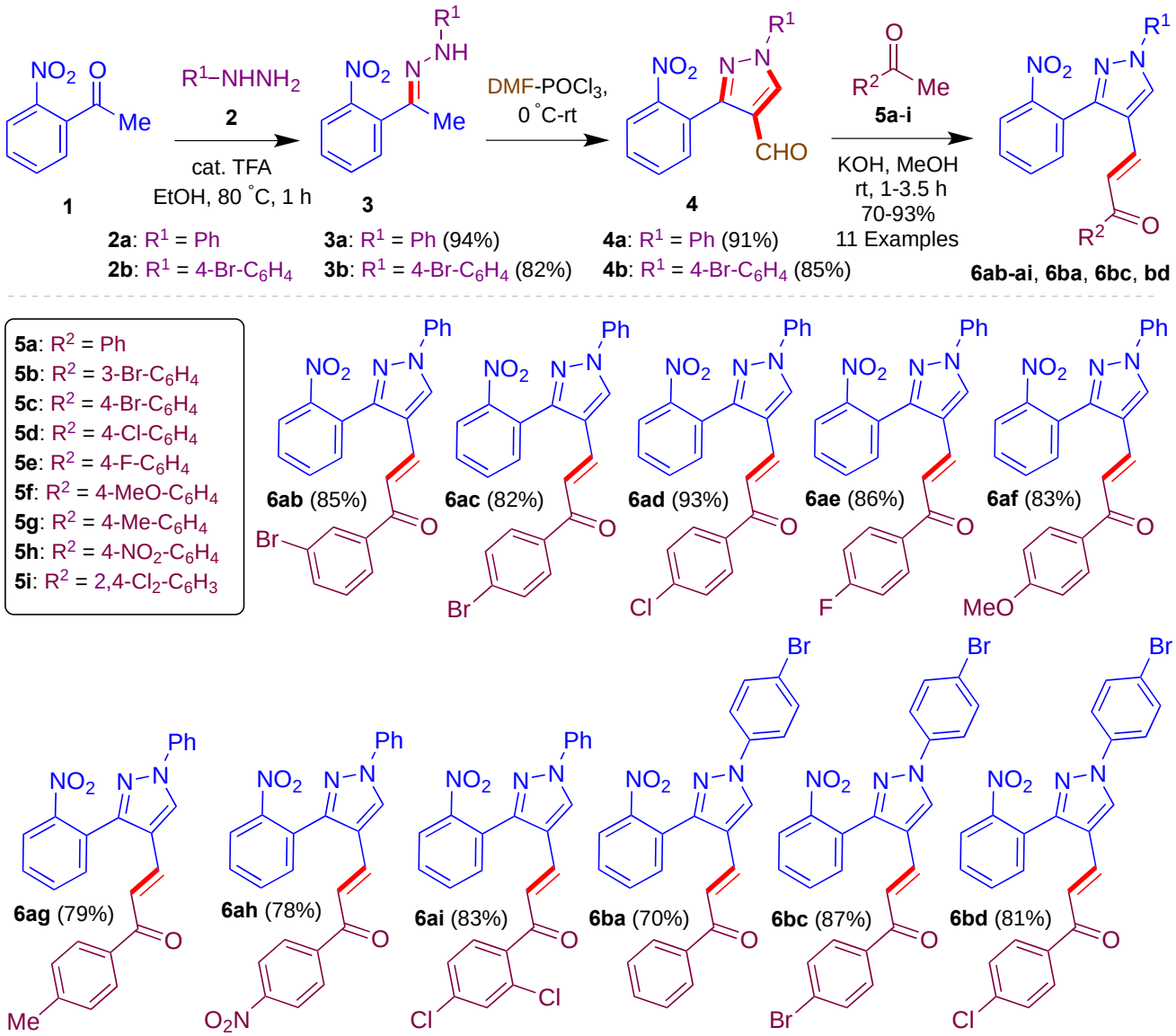


Figure 2. Retrosynthetic analysis for the synthesis of substituted pyrazolo[4,3-*c*]quinoline derivatives

Alternatively, the synthesis of **V** may be achieved *via* reductive cyclization of Morita-Baylis-Hillman (MBH) adduct **IV** afforded from **I** *via* MBH reaction with activated alkenes. Accordingly, 2-nitrophenyl substituted pyrazole-4-carbaldehydes were synthesized and subjected to Claisen-Schmidt condensation as well as MBH reaction and subsequently served in Fe-AcOH mediated reductive cyclization[52-54] to afford the diversely substituted pyrazolo[4,3-*c*]quinolines.

It has been revealed that the cleavage of C–C bond is a challenging task and only limited methods are available by employing transition metals such as Rh,[55,56] Ru,[57] Pd,[58,59] Pt,[60] Cu,[61,62] and Fe.[63,64] However, most of these strategies involve the C-C bond cleavage under oxidative conditions but the detailed studies involving C-C cleavage under reductive conditions remain scarce in literature.[54,65,66] Although Fe-mediated C-C bond cleavage under reductive conditions was previously envisioned,[54] but it was not quantified over variety of substrates. Interestingly, during present study, C-C bond cleavage was observed under similar reaction conditions rather on different group of molecules. In this context, studies were performed which are presented and discussed herein.

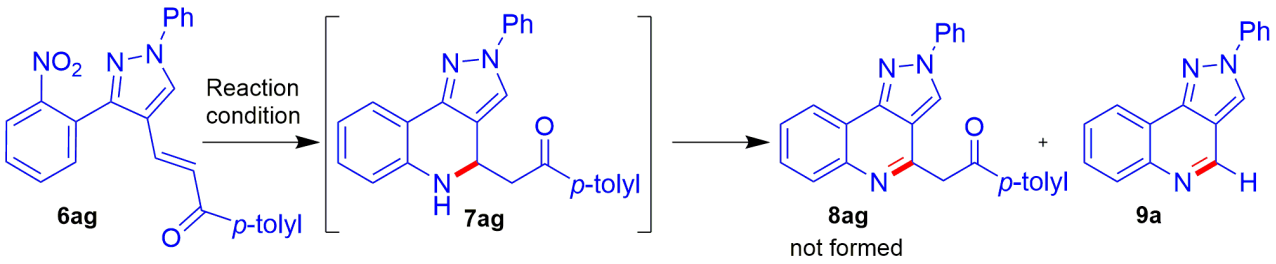
The present study commenced with the synthesis of 1-aryl-3-(2-nitrophenyl)-1*H*-pyrazole-4-carbaldehydes **4** which was achieved *via* modification in the previously documented procedure as depicted in Scheme 1.[67-70] The condensation of 2-nitroacetophenone (**1**) with phenylhydrazines **2a**, **b** in EtOH afforded the corresponding hydrazone derivatives **3a**, **b** under the catalysis of TFA which were further subjected to Vilsmeier-Haack formylation with DMF-$POCl_3$ to yield the desired 1-aryl-3-(2-nitrophenyl)-1*H*-pyrazole-4-carbaldehydes **4a**, **b**.



Scheme 1. Synthesis of 1-aryl-3-(2-nitrophenyl)-1*H*-pyrazole-4-carbaldehydes

To achieve the synthesis of diversely substituted pyrazolo[4,3-*c*]quinolines derivatives, **4a**, **b** were treated with diversely substituted aryl methyl ketones **5a-i** in presence of KOH in MeOH to afford the Claisen-Schmidt condensation products, (*E*)-3-[3-(2-nitrophenyl)-1-aryl-1*H*-pyrazol-4-yl]-1-arylprop-2-en-1-ones **6ab-ai**, **6ba**, **6bc**, and **bd** (**b** is a component from **4** and **d** is a component from **5**) (Scheme 1). The respective chalcones **6** were obtained within 1-3.5 h in good to excellent yields (70-93%) *via* filtration of solid product precipitated during the course of reaction and no column chromatographic purification was required.

Table 1. Results of optimization studies



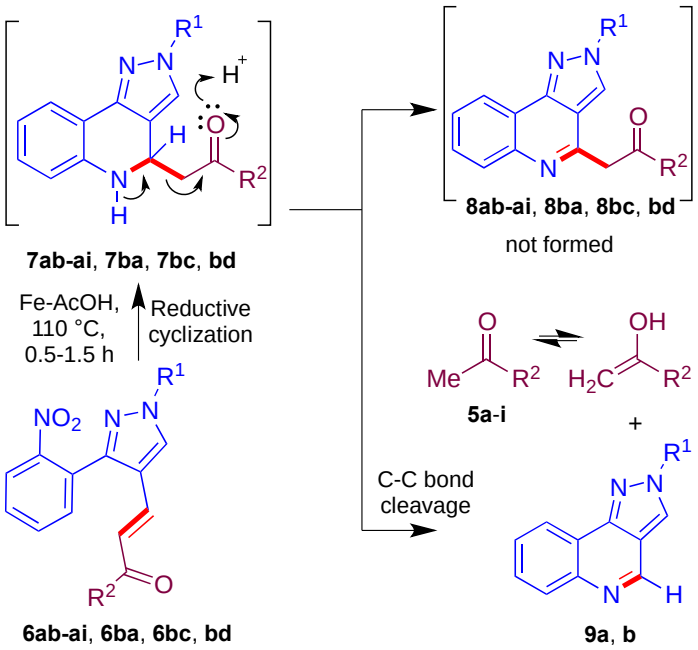
Entry	Reagent/Additive	Solvent	T (°C)	Time	**9a**, Yield %[a,b]
1	Fe powder/-	AcOH	110	1 h 45 min	71
2	**Fe powder/-**	**AcOH**	**110**	**1 h 15 min**	**84**
3	Zn dust/-	AcOH	110	2 h 30 min	59
4	Zn dust/-	AcOH:H_2O (1:1, v/v)	110	3 h	67[c]
5	$SnCl_2.2H_2O$/-	MeOH	80	12 h	43[c]
6	Fe powder/-	AcOH	80	3 h 45 min	60[c]
7	Fe powder/HCl (15 equiv.)	EtOH:H_2O (1:1, v/v)	110	2 h	63[c]

[a]Unless otherwise mentioned, All the reactions were performed with 1.2 mmol of **6ag** and 5.0 equiv. of reagent in 3 mL of solvent. [b]Isolated yields. [c]The reaction was carried out under N_2 atmosphere.

To achieve the synthesis of desired pyrazolo[4,3-*c*]quinoline, the optimization studies were performed with **6ag** as the model substrate. The chalcone derivative **6ag** was chosen as model substrate because of its electronic effects to emphasize the product formation. The compound **6ag** was then served in Fe-AcOH mediated reductive cyclization to afford the anticipated substituted pyrazolo[4,3-*c*]quinoline. The reaction was completed within 1 h 15 min and a short silica gel column chromatographic purification of product followed by spectroscopic analysis revealed that the expected product **8ag** underwent unusual C-C bond cleavage at C-4 position leading to the formation of pyrazolo[4,3-*c*]quinoline derivative **9a** instead of desired product **8ag**. Surprisingly, similar results were obtained when the reaction was executed under different conditions as summarized in Table 1.

When the reductive cyclization was performed with other substrates **6ab-ai**, **6ba**, **6bc**, and **bd**; similar products **9a**, **b** were obtained in all the cases due to the unexpected C-C bond cleavage in the products **7**/**8** under reductive conditions as summarized in Scheme 2.

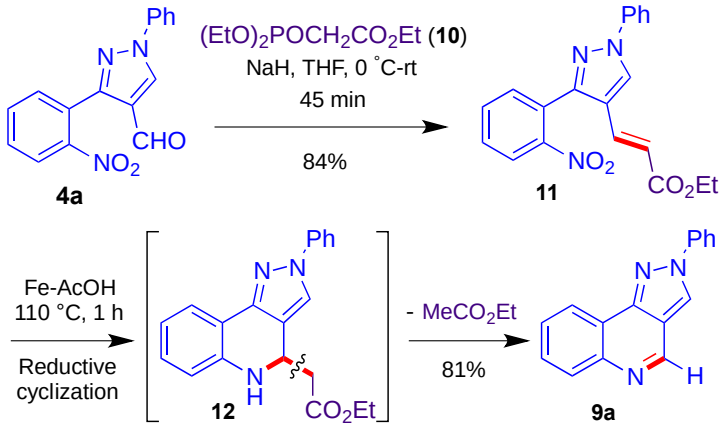
This unorthodox cleavage of C-C bond during reductive conditions[65,66] may be attributed to the protonation of carbonyl group, which induces the electronic deficiency in the carbon chain. The resulting enolate (enol) generated after C-C bond cleavage which is resonance stabilized together with entropy issues and aromaticity of the product (thermodynamic stability).



6ab: R^1 = Ph; R^2 = 3-Br-C_6H_4	**9a** (80%)
6ac: R^1 = Ph; R^2 = 4-Br-C_6H_4	**9a** (83%)
6ad: R^1 = Ph; R^2 = 4-Cl-C_6H_4	**9a** (79%)
6ae: R^1 = Ph; R^2 = 4-F-C_6H_4	**9a** (74%)
6af: R^1 = Ph; R^2 = 4-MeO-C_6H_4	**9a** (86%)
6ag: R^1 = Ph; R^2 = 4-Me-C_6H_4	**9a** (84%)
6ah: R^1 = Ph; R^2 = 4-NO_2-C_6H_4	**9a** (93%)
6ai: R^1 = Ph; R^2 = 2,4-Cl_2-C_6H_3	**9a** (82%)
6ba: R^1 = 4-Br-C_6H_4; R^2 = Ph	**9b** (71%)
6bc: R^1 = 4-Br-C_6H_4; R^2 = 4-Br-C_6H_4	**9b** (78%)
6bd: R^1 = 4-Br-C_6H_4; R^2 = 4-Cl-C_6H_4	**9b** (74%)

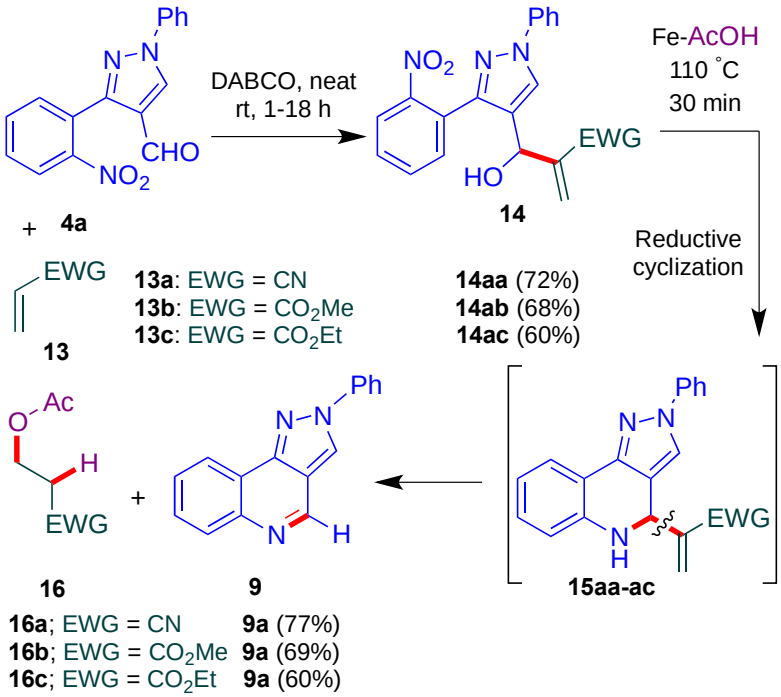
Scheme 2. Reductive cyclization mediated synthesis of pyrazolo[4,3-*c*]quinolines **9**

The applicability of the developed protocol was further extended to substrates **11**, which were obtained by Wittig reaction of **4a** and triethyl phosphonoacetate (**10**). It was observed that, the reaction of **11** under Fe-AcOH mediated reductive cyclization conditions gave indistinguishable results to yield **9a** in 81% (Scheme 3).



Scheme 3. Synthesis of pyrazolo[4,3-*c*]quinoline **9a** using Wittig product **11**

To generate diversely substituted pyrazolo[4,3-*c*]quinoline derivatives, we also attempted an alternate route through exploration of MBH chemistry as envisaged in retrosynthetic analysis (Figure 2). Accordingly, 1-phenyl-3-(2-nitrophenyl)-1*H*-pyrazole-4-carbaldehyde (**4a**) was reacted with different activated alkenes **13a-c** under neat conditions in presence of DABCO to prepare the corresponding MBH adducts for the first time.[71] It was observed that MBH reaction was very sluggish, however, afforded the desired adducts in good yields. Surprisingly, the treatment of MBH adducts **14aa-ac** with Fe-AcOH also led to the formation of pyrazolo[4,3-*c*]quinoline derivatives **9** devoid of substituents at C-4 position. Here also, the desired products **15aa-ac** underwent C-C bond cleavage during the course of reaction to furnish the product **9a** as revealed from TLC analysis, melting point and spectroscopic studies (Scheme 4).

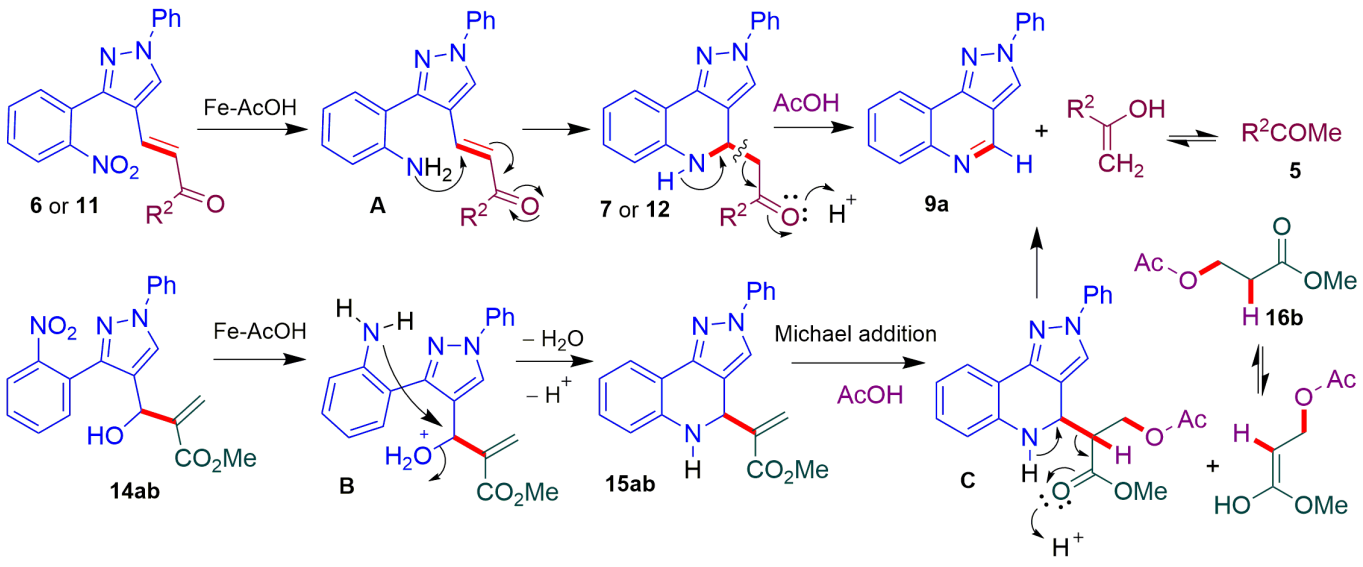


Scheme 4. Synthesis of pyrazolo[4,3-*c*]quinoline **9a** from MBH adducts **14aa-ac**

Based on the above observations, a plausible mechanism for the formation of pyrazolo[4,3-*c*]quinoline **9a** is delineated in Scheme 5.[54,72-74] It is anticipated that during Fe-AcOH mediated reductive cyclization in chalcones **6** and **11**, initially nitro group is reduced to amine **A**. Thereafter, amine derivative undergoes successive intramolecular Michael addition to give **7** or **12**. The protonation of carbonyl group of **7** or **12** induces the electronic deficiency in the carbon chain and triggers C-C bond cleavage instead of dehydrogenation to finally yield the pyrazolo[4,3-*c*]quinoline **9a**. Similarly, during the treatment of MBH adduct **14ab** with Fe-AcOH, nitro group is reduced to an amine and also the hydroxyl functionality gets protonated, thereafter nucleophilic substitution may take place to yield **15ab** as the intermediate. Subsequently, acetic acid can undergo Michael addition with **15ab** to give the addition product **C**.

Likewise, protonation of carbonyl group of **C** instigate the electronic deficiency in the carbon chain to undergo C-C bond cleavage to yield the pyrazolo[4,3-*c*]quinoline **9a** with the elimination of methyl β-acetoxypropionate (**16b**).

In conclusion, we herein attempted the synthesis of diversely substituted pyrazolo[4,3-*c*]quinolines *via* application of Fe-AcOH mediated reductive cyclization of Claisen-Schmidt condensation products and MBH adducts afforded from 1-aryl-3-(2-nitrophenyl)-1*H*-pyrazole-4-carbaldehydes. It was revealed that reaction conditions favored unusual C-C bond cleavage over dehydrogenation to afford the pyrazolo[4,3-*c*]quinolines instead of desired diversely C-4 substituted products. Similar kind of C-C bond cleavage was observed in case of Witting product and MBH adducts. This strange cleavage of C-C bond during reductive conditions was attributed to the protonation of carbonyl group and subsequent C-C bond cleavage prompted due to the electronic deficiency in the carbon chain. In case of MBH adducts, Michael addition of acetic acid and subsequent carbonyl group protonation results in C-C bond cleavage. It is also anticipated that acidic conditions and high temperature may also be responsible for preferred C-C bond cleavage over dehydrogenation. It is envisaged that the present study opens up avenues for exploration of possibility of C-C bond cleavage under reductive conditions.



Scheme 5. Plausible mechanism for the formation of pyrazolo[4,3-*c*]quinoline **9a**

EXPERIMENTAL

The chemicals and reagents were purchased from Sigma Aldrich, Acros, Avera Synthesis, Spectrochem Pvt. Ltd. and used without further purification. Commercially available anhydrous MeOH and THF (Spectrochem make) were used as such without further distillation. Thin layer chromatography (TLC) was performed using pre-coated aluminium plates purchased from E. Merck (silica gel 60 PF254, 0.25

mm). Column chromatography was performed using Spectrochem silica gel (60–120 mesh). Melting points were determined in an open capillary tubes on a Precision Digital melting point apparatus (LABCO make) containing silicon oil and are uncorrected. IR spectra were recorded using Agilent FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on Avance III Bruker spectrometer at operating frequencies of 400 MHz, 300 MHz (^{1}H) or 100 MHz (^{13}C) as indicated in the individual spectrum using $CDCl_3$ and DMSO-d_6 as a solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.26/77.28 ($CDCl_3$) and $\delta_{H/C}$ 2.51/39.50 (DMSO-d_6) relative to TMS as internal standards. Coupling constants *J* [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), overlapped and br (broad). The MS spectra were recorded on Xevo G2-SQ TOF (Water, USA) or Thermo Finnigan LCQ Advantage, Ion Trap Mass Spectrometer. Elemental analyses were performed on a Carlo–Erba's 108 or an Elementar's Vario EL III microanalyzer. The room temperature varied between 25 °C and 35 °C.

General procedure for the synthesis of (*E*)-2-aryl-1-[1-(2-nitrophenyl)ethylidene]hydrazines 3a, b as exemplified for 3a.

To a stirred solution of *o*-nitroacetophenone **1** (2.00 g, 12.12 mmol) in 10 mL of EtOH, phenylhydrazine (**2a**) (1.63 g, 15.09 mmol) and TFA in catalytic amount were added at rt. Thereafter, reaction mixture was refluxed at 80 °C till the completion of reaction which was monitored by TLC. After completion of the reaction, excess of EtOH was evaporated and content was poured into water, extracted with $CHCl_3$ (3 x 20 mL) and washed with 10% aq. $NaHCO_3$ solution (10 mL) followed by brine (10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under vacum to afford **3a** as orange oil (2.62 g; 94%) which was significantly pure and used as such for the next step. The analytical data of **3a** is consistent with known compound in the literature.[69]

General procedure for the synthesis of 1-aryl-3-(2-nitrophenyl)-1*H*-pyrazole-4-carbaldehydes 4a, b as exemplified for 4a.

To a cooled anhydrous DMF (15 mL), $POCl_3$ (6.36 mL, 68.02 mmol) was added dropwise at 0 °C and continued the stirring at 0 °C for 15 min. Then (*E*)-2-aryl-1-[1-(2-nitrophenyl)ethylidene]hydrazine derivative **3a** (2.62 g, 11.34 mmol) was added to the reaction mixture and stirred the reaction mixture at rt for additional 10 h. After completion of reaction as monitored by TLC, the content was poured over crushed ice under stirring. Thereafter, the content was neutralised with 10% aq. $NaHCO_3$ solution which resulted in precipitation of white solid product. The solid product was filtered under vacuum and dried in air to yield a yellow solid **4a** (3.02 g; 91%). The resulting product was analytically pure and we proceeded for next step without further purification. The analytical data of **4a** is consistent with known compound in the literature.[69]

General procedure for the synthesis of (*E*)-3-[3-(2-nitrophenyl)-1-aryl-1*H*-pyrazol-4-yl]-1-arylprop-2-en-1-ones 6ab-ai, 6ba, 6bc, and 6bd as exemplified for 6ab.

To a stirred solution of 3-bromoacetophenone (**5b**) (75 µL, 0.38 mmol) in MeOH (8 mL), KOH (0.14 g, 2.55 mmol) was added followed by addition of **4a** (0.15 g, 0.51 mmol) at rt and stirring was continued at rt till completion of reaction. After completion of reaction as monitored by TLC, the content was cooled and filtered under vaccum. The crude solid product was further washed with EtOAc:hexane (5:95, v/v) to obtain the pure product. The product was air dried under vacuum to yield a light yellow solid product, **6ab** (0.21 g; 85%) which was analytically pure.

(*E*)-1-(3-Bromophenyl)-3-[3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one (6ab).

Yield 0.21 g (85%), yellow solid, mp 161-162 °C, R_f 0.42 (hexane/EtOAc, 80/20, v/v). IR spectrum, ν, cm^{-1}: 1209 (CH=CH), 1404 and 1533 (NO_2), 1665 (C=O). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 7.09 (1H, d, *J* = 15.6 Hz, =C*H*); 7.34-7.41 (2H, m, ArH); 7.52 (2H, t, *J* = 7.7 Hz, ArH); 7.62-7.82 (8H, m, *H*C= and ArH); 7.97 (1H, s, ArH); 8.14 (1H, d, *J* = 7.8 Hz, ArH); 8.54 (1H, s, ArH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), *δ*, ppm: 119.0; 119.1; 119.5; 121.5; 122.8; 125.0; 126.0; 127.6; 127.9; 128.3; 129.6; 130.2; 131.1; 131.5; 132.8; 133.1; 133.8; 134.2; 136.2; 139.2; 140.0; 149.7; 149.8; 187.7. Mass spectrum, *m*/*z* (ES, %): 474.0 $[M+1]^+$, 476.0 $[M+1+2]^+$. Anal. Calcd for $C_{24}H_{16}BrN_3O_3$, %: C 60.77; H 3.40; N 8.86. Found, %: C 60.92; H 3.44; N 8.93.

(*E*)-1-(4-Bromophenyl)-3-[3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one (6ac).

Yield 0.20 g (82%), yellow solid, mp 138-139 °C, R_f 0.54 (hexane/EtOAc, 80/20, v/v). IR spectrum, ν, cm^{-1}: 1210 (CH=CH), 1404 and 1533 (NO_2), 1665 (C=O). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 7.10 (1H, d, *J* = 15.7 Hz, =C*H*); 7.35 (1H, t, *J* = 7.4 Hz, ArH); 7.47 (2H, t, *J* = 7.9 Hz, ArH); 7.45-7.76 (10H, m, *H*C= and ArH); 8.09 (1H, d, *J* = 7.6 Hz, ArH); 8.36 (1H, s, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), *δ*, ppm: 118.9; 119.4; 120.9; 124.8; 127.2; 127.3; 127.6; 127.8; 129.6; 129.9; 130.1; 131.2; 132.3; 133.0; 134.4; 136.8; 139.1; 149.5; 149.8; 188.7. Mass spectrum, *m*/*z* (ES, %): 474.0 $[M+1]^+$, 476.0 $[M+1+2]^+$. Anal. Calcd for $C_{24}H_{16}BrN_3O_3$, %: C 60.77; H 3.40; N 8.86. Found, %: C 60.99; H 3.46; N 8.94.

(*E*)-1-(4-Chlorophenyl)-3-[3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one (6ad).

Yield 0.21 g (93%), yellow solid, mp 134-135 °C, R_f 0.39 (hexane/EtOAc, 80/20, v/v). IR spectrum, ν, cm^{-1}: 1214 (CH=CH), 1407 and 1521 (NO_2), 1668 (C=O). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 7.04 (1H, d, *J* = 15.6 Hz, =C*H*); 7.27-7.29 (1H, m, ArH); 7.31-7.44 (4H, m, ArH); 7.51 (1H, s, ArH); 7.54-7.61 (2H, m, *H*C= and ArH); 7.66 (3H, d, *J* = 7.8 Hz, ArH); 7.73 (2H, d, *J* = 8.4 Hz, ArH); 8.03 (1H, d, *J* = 8.1 Hz, ArH); 8.30 (1H, s, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), *δ*, ppm: 118.9; 119.4; 121.0; 124.7; 127.2; 127.3; 127.6; 128.9; 129.6; 129.7; 130.0; 132.7; 133.0; 134.3; 136.4; 139.1;

149.6; 149.7; 188.5. Mass spectrum, *m*/*z* (ES, %): 430.1 $[M+1]^+$, 432.1 $[M+1+2]^+$. Anal. Calcd for $C_{24}H_{16}ClN_3O_3$, (%): C 67.06; H 3.75; N 9.78. Found, %: C 67.25; H 3.79; N 9.85.

(*E*)-1-(4-Fluorophenyl)-3-[3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one (6ae).

Yield 0.31 g (86%), yellow solid, mp 154-155 °C, R_f 0.57 (hexane/EtOAc, 80/20, v/v). IR spectrum, ν, cm^{-1}: 1217 (CH=CH), 1344 and 1524 (NO_2), 1658 (C=O). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 7.12-7.18 (3H, m, =C*H* and ArH); 7.38 (1H, t, *J* = 7.4 Hz, ArH); 7.51 (2H, t, *J* = 7.5 Hz, ArH); 7.60-7.70 (3H, m, *H*C= and ArH); 7.75 (3H, d, *J* = 8.1 Hz, ArH); 7.92 (2H, t, *J* = 6.9 Hz, ArH); 8.12 (1H, d, *J* = 7.8 Hz, ArH); 8.38 (1H, s, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), *δ*, ppm: 115.67 (d, *J* = 28.8 Hz); 119.0; 119.3; 121.1; 124.7; 127.2; 127.3; 127.5; 129.6; 130.0; 130.9 (d, *J* = 12.2 Hz); 132.7; 133.0; 134.0; 134.4; 139.1; 149.6; 149.7; 165.5 (d, *J* = 337 Hz); 188.2. Mass spectrum, *m*/*z* (ES, %): 414.1 $[M+1]^+$. Anal. Calcd for $C_{24}H_{16}FN_3O_3$, %: C 69.73; H 3.90; N 10.16. Found, %: C 69.89; H 3.95; N 10.26.

(*E*)-1-(4-Methoxyphenyl)-3-[3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one (6af).

Yield 0.30 g (83%), yellow solid, mp 142-143 °C, R_f 0.58 (hexane/EtOAc, 80/20, v/v). IR spectrum, ν, cm^{-1}: 1220 (CH=CH), 1503 and 1596 (NO_2), 1668 (C=O). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 3.86 (3H, s, OCH_3); 6.91 (2H, d, *J* = 8.0 Hz, ArH); 7.16 (1H, d, *J* = 15.6 Hz, =C*H*); 7.33 (1H, t, *J* = 7.4 Hz, ArH); 7.47 (2H, t, *J* = 7.9 Hz, ArH); 7.57 (1H, d, *J* = 15.6 Hz, *H*C=); 7.60-7.65 (2H, m, ArH); 7.72 (3H, t, *J* = 6.7 Hz, ArH); 7.86 (2H, d, *J* = 8.8 Hz, ArH); 8.07 (1H, d, *J* = 8.3 Hz, ArH); 8.34 (1H, s, ArH). Mass spectrum, *m*/*z* (ES, %): 426.1 $[M+1]^+$. Anal. Calcd for $C_{25}H_{19}N_3O_4$, %: C 70.58; H 4.50; N 9.88. Found, %: C 70.71; H 4.55; N 9.96.

(*E*)-3-[3-(2-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-(*p*-tolyl)prop-2-en-1-one (6ag).

Yield 0.22 g (79%), yellow solid, mp 147-148 °C, R_f 0.53 (hexane/EtOAc, 80/20, v/v). IR spectrum, ν, cm^{-1}: 1215 (CH=CH), 1354 and 1531 (NO_2), 1658 (C=O). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 2.41 (3H, s, $ArCH_3$); 7.17 (1H, d, *J* = 15.6 Hz, =C*H*); 7.24 (1H, s, ArH); 7.35 (1H, t, *J* = 7.4 Hz, ArH); 7.48 (2H, t, *J* = 7.9 Hz, ArH); 7.60 (1H, d, *J* = 15.6 Hz, *H*C=); 7.62-7.65 (2H, m, ArH); 7.73 (3H, d, *J* = 8.3 Hz, ArH); 7.78 (2H, d, *J* = 8.2 Hz, ArH); 8.09 (1H, d, *J* = 7.8 Hz, ArH); 8.35 (1H, s, ArH). Mass spectrum, *m*/*z* (ES, %): 410.1 $[M+1]^+$. Anal. Calcd for $C_{25}H_{19}N_3O_3$, %: C 73.34; H 4.68; N 10.26. Found, %: C 73.55; H 4.72; N 10.33.

(*E*)-1-(4-Nitrophenyl)-3-[3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one (6ah).

Yield 0.29 g (78%), yellow solid, mp 152-153 °C, R_f 0.50 (hexane/EtOAc, 80/20, v/v). IR spectrum, ν, cm^{-1}: 1214 (CH=CH), 1406 and 1538 (NO_2), 1660 (C=O); ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 7.08 (1H, d, *J* = 15.6 Hz, =C*H*); 7.37 (1H, t, *J* = 7.8 Hz, ArH); 7.49 (2H, t, *J* = 7.9 Hz, ArH); 7.61-7.70 (3H, m, *H*C= and ArH); 7.74 (2H, t, *J* = 8.3 Hz, ArH); 7.98 (2H, d, *J* = 8.2 Hz, ArH); 8.12 (1H,

d, *J* = 7.8 Hz, ArH); 8.30 (2H, d, *J* = 8.0 Hz, ArH); 8.38 (1H, s, ArH). Mass spectrum, *m*/*z* (ES, %): 441.1 $[M+1]^+$. Anal. Calcd for $C_{24}H_{16}N_4O_5$, %: C 65.45; H 3.66; N 12.72. Found, %: C 65.66; H 3.70; N 12.79.

(*E*)-1-(2,4-Dichlorophenyl)-3-[3-(2-nitrophenyl)-1-phenyl -1*H*-pyrazol-4-yl]prop-2-en-1-one (6ai).

Yield 0.33 g (83%), yellow solid, mp 159-160 °C, R_f 0.65 (hexane/EtOAc, 80/20, v/v). IR spectrum, ν, cm^{-1}: 1207 (CH=CH), 1367 and 1531 (NO_2), 1658 (C=O); ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 6.72 (1H, d, *J* = 15.6 Hz, =C*H*); 7.31-7.33 (2H, m, ArH); 7.35-7.38 (2H, m, ArH); 7.39 (1H, d, *J* = 15.6 Hz, *H*C=); 7.48 (2H, t, *J* = 7.9 Hz, ArH); 7.58-7.60 (1H, m, ArH); 7.61-7.66 (1H, m, ArH); 7.69-7.71 (3H, m, ArH); 8.07 (1H, dd, *J* = 7.9 Hz, ArH); 8.29 (1H, s, ArH). Mass spectrum, *m*/*z* (ES, %): 464.0 $[M+1]^+$. Anal. Calcd for $C_{24}H_{15}Cl_2N_3O_3$, %: C 62.08; H 3.26; N 9.05. Found, %: C 62.29; H 3.30; N 9.14.

(*E*)-3-[1-(4-Bromophenyl)-3-(2-nitrophenyl)-1*H*-pyrazol -4-yl]-1-phenylprop-2-en-1-one (6ba).

Yield 0.18 g (70%), yellow solid, mp 144-145 °C, R_f 0.55 (hexane/EtOAc, 70/30, v/v). IR spectrum, ν, cm^{-1}: 1217 (CH=CH), 1365 and 1530 (NO_2), 1665 (C=O). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 7.16 (1H, d, *J* = 15.7 Hz, =C*H*); 7.43-7.47 (2H, m, =C*H* and ArH); 7.53-7.68 (8H, m, *H*C= and ArH); 7.72-7.76 (1H, m, ArH); 7.85-7.87 (2H, m, ArH); 8.10 (1H, dd, *J* = 7.8 Hz, ArH); 8.33 (1H, s, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), *δ*, ppm: 119.5; 120.7; 120.9; 121.9; 124.8; 126.9; 127.1; 128.3; 128.6; 130.1; 132.6; 132.7; 132.8; 133.0; 133.4; 138.0; 138.2; 149.5; 150.0; 189.7. Mass spectrum, *m*/*z* (ES, %): 474.1 $[M+1]^+$, 476.1 $[M+1+2]^+$. Anal. Calcd for $C_{24}H_{16}BrN_3O_3$, %: C 60.77; H 3.40; N 8.8. Found, %: C 60.93; H 3.45; N 8.94.

(*E*)-1-(4-Bromophenyl)-3-[1-(4-bromophenyl)-3-(2-nitrophenyl)-1*H*-pyrazol-4-yl]prop-2-en-1-one (6bc).

Yield 0.46 g (87%), light yellow solid, mp 166-167 °C, R_f 0.62 (hexane/EtOAc, 30/70, v/v). IR spectrum, ν, cm^{-1}: 1210 (CH=CH), 1411 and 1560 (NO_2), 1646 (C=O); ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 7.17 (1H, d, *J* = 15.7 Hz, =C*H*); 7.26 (1H, s, ArH); 7.56-7.66 (8H, m, *H*C= and ArH); 7.72-7.78 (3H, m, ArH); 8.10 (1H, dd, *J* = 7.8 Hz, ArH); 8.34 (1H, s, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), *δ*, ppm: 120.8; 122.0; 124.8; 126.8; 127.2; 128.5; 129.3; 130.1; 132.7; 133.0; 135.4. Mass spectrum, *m*/*z* (ES, %): 551.9 $[M+1]^+$, 553.9 $[M+1+2]^+$. Anal. Calcd for $C_{24}H_{15}Br_2N_3O_3$, %: C 52.11; H 2.73; N 7.60. Found, %: C 52.30; H 2.77; N 7.67.

(*E*)-3-[1-(4-Bromophenyl)-3-(2-nitrophenyl)-1*H*-pyrazol-4-yl]-1-(4-chlorophenyl)prop-2-en-1-one (6bd).

Yield 0.22 g (81%), yellow solid, mp 136-137 °C, R_f 0.70 (hexane/EtOAc, 70/30, v/v). IR spectrum, ν, cm^{-1}: 1216 (CH=CH), 1399 and 1526 (NO_2), 1665 (C=O). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 7.10 (1H, d, *J* = 15.7 Hz, =C*H*); 7.41-7.44 (1H, m, =C*H*); 7.56-7.81 (11H, m, *H*C= and ArH); 8.11 (1H, d, *J* = 8.3 Hz, ArH); 8.33 (1H, s, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), *δ*, ppm: 119.3;

120.8; 121.0; 121.3; 124.8; 127.0; 127.1; 128.9; 129.8; 130.2; 132.6; 132.7; 133.1; 134.0; 136.3; 138.1; 139.2; 149.5; 150.1; 188.4. Mass spectrum, *m*/*z* (ES, %): 507.9 $[M+1]^+$, 509.9 $[M+1+2]^+$. Anal. Calcd for $C_{24}H_{15}BrClN_3O_3$, %: C 56.66; H 2.97; N 8.26. Found, %: C 56.84; H 3.01; N 8.33.

General procedure for synthesis of (2*E*)-ethyl 3-[3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2-propenoate (11).

To a cooled solution of triethyl phosphonoacetate (**10**) (0.34 g, 1.53 mmol) in anhydrous THF (5 mL), NaH (0.073 g, 3.04 mmol) was added and the reaction mixture was stirred at 0 ^oC for 15 min. Thereafter, **4a** (0.30 g, 1.02 mmol) was added to the reaction mixture and the mixture was stirred at rt till completion of reaction. After completion of reaction as monitored by TLC, content was poured into water, extracted with EtOAc (3 x 10 mL) and washed with 10% aq. $NaHCO_3$ solution (10 mL) followed by brine (10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under vacum to afford **11** as yellow solid (0.31 g; 84%).

(2*E*)-Ethyl 3-[3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2-propenoate (11)

The analytical data of **11** is consistent with known compound in the literature.[69]

General procedure for synthesis of Morita-Baylis-Hillman adducts 14aa-ac as exemplified for 14aa.

A solution of acrylonitrile (**13a**) (5 mL) and DABCO (0.17 g, 1.53 mmol) was stired at rt for 15 min. Thereafter, **4a** (0.30 g, 1.02 mmol) was added to the reaction mixture and the content was stirred at rt till completion (16 h). After completion of reaction as monitored by TLC, the content was poured into water, extracted with EtOAc (3 x 10 mL) and washed with 10% aq. $NaHCO_3$ solution (10 mL) followed by brine (10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under vacum to afford **14aa** as yellow oil (0.26 g; 72%) which was analytically pure.

2-{Hydroxy[3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl] methyl}acrylonitrile (14aa).

Yield 0.26 g (72%), yellow oil, R_f 0.39 (hexane/EtOAc, 70/30, v/v). IR spectrum, ν, cm^{-1}: 1358 and 1524 (NO_2), 1732 (CO_2Et), 2256 (CN) 3269(OH). ^1H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 2.64 (1H, d, *J* = 3.5 Hz, CHO*H*); 5.24 (1H, s, C*H*OH); 5.96 (1H, s, CH*H*); 6.05 (1H, s, C*H*H); 7.32 (1H, t, *J* = 7.4 Hz, ArH); 7.46 (2H, t, *J* = 7.9 Hz, ArH); 7.62 (2H, d, *J* = 7.4 Hz, ArH); 7.68-7.72 (3H, m, ArH); 8.04 (1H, d, *J* = 8.0 Hz, ArH); 8.10 (1H, s, ArH). Mass spectrum, *m*/*z* (ES, %): 347.1 $[M+1]^+$. Anal. Calcd for $C_{19}H_{14}N_4O_3$, %: C 65.89; H 4.07; N 16.18. Found, %: C 66.08; H 4.12; N 16.26.

Methyl β-hydroxy-α-methylene-3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-propanoate (14ab)

Yield 0.87 g (68%), yellow oil, R_f 0.48 (hexane/EtOAc, 70/30, v/v). IR spectrum, ν, cm^{-1}: 1352 and 1517 (NO_2), 1735 (CO_2Me), 3254(OH). ^1H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 3.65 (3H, s, CO_2CH_3); 5.52 (1H, d, *J* = 16.8 Hz, C*H*OH); 5.90 (1H, s, CH*H*); 6.25 (1H, s, C*H*H); 7.29 (1H, d, *J* = 7.3 Hz, ArH); 7.43 (2H, t, *J* = 7.8 Hz, ArH); 7.58 (1H, t, *J* = 4.0 Hz, ArH); 7.66 (4H, d, *J* = 7.1 Hz, ArH);

7.98 (2H, t, *J* = 9.7 Hz, ArH). Mass spectrum, *m*/*z* (ES, %): 380.1 $[M+1]^+$. Anal. Calcd for $C_{20}H_{17}N_3O_5$, %: C 63.32; H 4.52; N 11.08. Found, %: C 63.51; H 4.56; N 11.16.

Ethyl β-hydroxy-α-methylene-3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-propanoate (14ac)

Yield 0.80 g (60%), yellow oil, R_f 0.50 (hexane/EtOAc, 70/30, v/v). IR spectrum, ν, cm^{-1} : 1317 and 1516 (NO_2), 1732 (CO_2Et), 3349(OH). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 1.23-1.27 (3H, m, $CO_2CH_2CH_3$); 4.09-4.22 (2H, m, $CO_2CH_2CH_3$); 5.51 (1H, s, C*H*OH); 5.60 (1H, s, CH*H*); 6.24 (1H, s, C*H*H); 7.28 (1H, t, *J* = 8.7 Hz, ArH); 7.43 (2H, t, *J* = 7.9 Hz, ArH); 7.54-7.61 (1H, m, ArH); 7.67 (4H, t, *J* = 3.6 Hz, ArH); 7.96-8.04 (2H, m, ArH). Mass spectrum, *m*/*z* (ES, %): 394.1 $[M+1]^+$. Anal. Calcd for $C_{21}H_{19}N_3O_5$, %: C 64.12; H 4.87; N 10.68. Found, %: C 64.28; H 4.91; N 10.76.

General procedure for synthesis of pyrazolo[4,3-*c*]quinolines 9a, b from 6 as exemplified for 9a.

To a solution of **6ag** (0.80 g, 1.96 mmol) in glacial AcOH (5 mL), Fe powder (0.55 g, 9.76 mmol) was added and the reaction mixture was heated at 110 °C for 1 h and 15 min. After completion of reaction as monitored by TLC, the content was neautralized with 10% aq. $NaHCO_3$ and extracted with EtOAc (3 x 20 mL) and washed with brine solution (10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under vacum to yield the crude compound which was passed through a short silica gel column (60-120 mesh) using EtOAc/hexane (30/70; v/v) as an eluent to afford **9a** as a light yellow solid (0.40 g; 84%).

2-Phenyl-2*H*-pyrazolo[4,3-*c*]quinoline (9a).

The analytical data of **9a** is consistent with known compound in the literature.[69]

2-(4-Bromophenyl)-2*H*-pyrazolo[4,3-*c*]quinoline (9b).

Yield 0.19 g (71%), light yellow solid, mp 147-148 °C, R_f 0.53 (hexane/EtOAc, 70/30, v/v). IR spectrum, ν, cm^{-1}: 1605(C=N). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), *δ*, ppm (*J*, Hz): 7.64-7.74 (4H, m, ArH); 7.83-7.87 (2H, m, ArH); 8.12-8.14 (1H, m, ArH); 8.54 (1H, s, $ArH_{Pyrazole}$). 8.56-8.59 (1H, m, ArH); 9.22 (1H, s, $ArH_{Quinoline}$). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), *δ*, ppm: 117.4; 120.2; 122.0; 122.3; 122.8; 127.4; 129.1; 129.9; 132.9; 139.0; 144.8; 146.9; 148.6. Mass spectrum, *m*/*z* (ES, %): 324.0 $[M+1]^+$, 326.0 $[M+1+2]^+$. Anal. Calcd for $C_{16}H_{10}BrN_3$, %: C 59.28; H 3.11; N 12.96. Found, %: C 59.41; H 3.16; N 13.04.

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REFERENCES

1. S. Altomonte, G. L. Baillie, R. A. Rossb, and M. Zanda, *RSC Adv*., 2015, **5**, 13692.
2. R. Lan, Q. Liu, P. Fan, S. Lin, S. R. Fernando, D. McCallion, R. Pertwee, and A. Makriyannis, *J. Med. Chem.*, 1999, **42**, 769.
3. J. M. Renga, K. L. McLaren, and M. J. Ricks, *Org. Process. Res. Dev.*, 2003, **7**, 267.
4. T. H. Kuo, T. H. Lin, R. S. Yang, S. C. Kuo, W. M. Fu, and H. Y. Hung, *J. Med. Chem*., 2015, **58**, 4954.
5. S. Altomonte, G. L. Baillie, R. A. Ross, J. Riley, and M. Zanda, *RSC Adv*., 2014, **4**, 20164.
6. B. A. Thaher, M. Arnsmann, F. Totzke, J. E. Ehlert, M. H. G. Kubbutat, C. Schachtele, M. O. Zimmermann, P. Koch, F. M. Boeckler, and S. A. Laufer, *J. Med. Chem*., 2012, **55**, 961.
7. G. Szabo, B. Varga, D. Payer-Lengyel, A. Szemzo, P. Erdelyi, K. Vukics, J. Szikra, E. Hegyi, M. Vastag, B. Kiss, J. Laszy, I. Gyertyan, and J. Fischer, *J. Med. Chem*., 2009, **52**, 4329.
8. R. Aggarwal, V. Kumar, R. Kumar, and S. P. Singh, *Beilstein J. Org. Chem*., 2011, **7**, 179.
9. K. Makino, H. S. Kim, and Y. Kurasawa, *J. Heterocycl. Chem*., 1999, **36**, 321.
10. M. J. Naim, O. Alam, F. Nawaz, M. J. Alam, and P. Alam, *J. Pharm. Bioall. Sci*., 2016, **8**, 2.
11. (a) R. J. Katz, *Pharmacol., Biochem. Behav*., 1984, **21**, 487; (b) M. Manpadi, P. Y. Uglinskii, S. K. Rastogi, K. M. Cotter, Y. S. C. Wong, L. A. Anderson, A. J. Ortega, S. V. Slambrouck, W. F. A. Steelant, S. Rogelj, P. Tongwa, M. Y. Antipin, I. V. Magedov, and A. Kornienko, *Org. Biomol. Chem*., 2007, **5**, 3865.
12. S. Schenone, M. Radi, F. Musumeci, C. Brullo, and M. Botta, *Chem. Rev*., 2014, **114**, 7189.
13. R. Perez-Fernández, P. Goya, and J. Elguero, *ARKIVOC*, 2014, **ii**, 233.
14. M. Nayak, N. Rastogi, and S. Batra, *Eur. J. Org. Chem*., 2012, 1360.
15. A. Kamal, V. S. Reddy, A. B. Shaik, G. B. Kumar, M. V. P. S. Vishnuvardhan, S. Polepalli, and N. Jain, *Org. Biomol. Chem.*, 2015, **13**, 3416.
16. N. S. Jha, S. Mishra, A. S. Mamidi, A. Mishra, S. K. Jha, and A. Surolia, *RSC Adv*., 2016, **6**, 7474.
17. S. Nag, M. Nayak, and S. Batra, *Adv. Synth. Catal*., 2009, **351**, 2715.
18. C. Hamdouchi, J. Ezquerra, J. A. Vega, J. J. Vaquero, J. Alvarez-Builla, and B. A. Heinz, *Bioorg. Med. Chem. Lett*., 1999, **9**, 1391.
19. N. Dahan-Farkas, C. Langley, A. L. Rousseau, D. B. Yadav, H. Davids, and C. B. de Koning, *Eur. J. Med. Chem*., 2011, **46**, 4573.
20. P. N. Kalaria, J. A. Makawana, S. P. Satasia, D. K. Raval, and H.-L. Zhu, *Med. Chem. Commun*.,

2014, **5**, 1555.

21. M. Nayak and S. Batra, *Adv. Synth. Catal*., 2010, **352**, 3431.
22. M. Nayak and S. Batra, *Eur. J. Org. Chem*., 2012, 3677.
23. T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, and P. C. Isakson, *J. Med. Chem*., 1997, **40**, 1347.
24. V. K. Kotagiri, S. Suthrapu, J. M. Reddy, C. P. Rao, V. Bollugoddu, A. Bhattacharya, and R. Bandichhor, *Org. Process. Res. Dev.*, 2007, **11**, 910.
25. N. K. Terrett, A. S. Bell, D. Brown, and P. Ellis, *Bioorg. Med. Chem. Lett*., 1996, **6**, 1819.
26. P. J. Dunn, *Org. Process. Res. Dev.*, 2005, **9**, 88.
27. R. Paramashivappa, P. P. Kumar, P. V. S. Rao, and A. S. Rao, *J. Agric. Food Chem*., 2002, **50**, 7709.
28. V. V. Kouznetsov, L. Y. V. Mendez, and C. M. M. Gomez, *Curr. Org. Chem*., 2005, **9**, 141.
29. V. V. Kouznetsov, *Tetrahedron*, 2009, **65**, 2721.
30. M. S. Singh and K. Raghuvanshi, *Tetrahedron*, 2012, **68**, 8683.
31. S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchala, and H. D. Patel, *RSC Adv*., 2014, **4**, 24463.
32. S. Kumar, S. Bawa, and H. Gupta, *Mini-Rev. Med. Chem*., 2009, **9**, 1648.
33. S. L. Croft, S. Sundar, and A. H. Fairlamb, *Clin. Microbiol. Rev*., 2006, **19**, 111.
34. T. Eicher, S. Hauptmann, and A. Speicher, The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications, Second Edition, Wiley-VCH: Weinheim, 2003, p 316.
35. C. Biot, W. Daher, N. Chavain, T. Fandeur, J. Khalife, D. Dive, and E. D. Clercq, *J. Med. Chem*., 2006, **49**, 2845.
36. Y. L. Chen, C. J. Huang, Z. Y. Huang, C. H. Tseng, F. S. Chang, S. H. Yang, S. R. Lin, and C. C. Tzeng, *Bioorg. Med. Chem*., 2006, **14**, 3098.
37. Y. L. Zhao, Y. L. Chen, F. S. Chang, and C. C. Tzeng, *Eur. J. Med. Chem*., 2005, **40**, 792.
38. S. Vangapandu, M. Jain, K. Kaur, P. Patil, S. R. Patel, and R. Jain, *Med. Res. Rev*., 2007, **27**, 65.
39. W. Du, *Tetrahedron*, 2003, **59**, 8649.
40. J. F. Biard, S. Guyot, C. Roussakis, J. F. Verbist, J. Vercauteren, J. F. Weber, and K. Boukef, *Tetrahedron Lett*., 1994, **35**, 2691.
41. J. P. Marino, M. B. Rubio, G. Cao, and A. D. Dios, *J. Am. Chem. Soc*., 2002, **124**, 13398.
42. R. A. Mekheimer, E. A. Ahmed, and K. U. Sadek, *Tetrahedron*, 2012, **68**, 1637.
43. J. Yu, H. R. Moon, J. W. Lim, and J. N. Kim, *Bull. Korean Chem. Soc*., 2015, **36**, 203.
44. M. M. Maluleka and M. J. Mphahlele, *Tetrahedron*, 2013, **69**, 699.

45. R. R. Reis, E. C. Azevedo, M. C. de Souza, V .F. Ferreira, R. C. Montenegro, A. J. Araujo, C. Pessoa, L. V. Costa-Lotufo, M. O. de Moraes, J. D. Filho, A. M. de Souza, N. C. de Carvalho, H. C. Castro, C. R. Rodrigues, and T. R. Vasconcelos, *Eur. J. Med. Chem*., 2011, **46**, 1448.
46. R. Mekheimer, *Pharmazie*, 1994, **49**, 486.
47. L. Savini, P. Massarelli, C. Nencini, C. Pellerano, G. Biggio, A. Maciocco, G. Tuligi, A. Carrieri, N. Cinone, and A. Carotti, *Bioorg. Med. Chem*., 1998, **6**, 389.
48. A. Carotti, C. Altomare, L. Savini, L. Chiasserini, C. Pellerano, M. P. Mascia, E. Maciocco, F. Busonero, M. Mameli, G. Biggio, and E. Sanna, *Bioorg. Med. Chem*., 2003, **17**, 5259.
49. J. S. Skotnicki, S. C. Gilman, B. A. Steinbaugh, and J. H. Musser, U.S. Patent 4748246, 1988.
50. (a) N. J. Leidenheimer and M. D. Schechter, *Pharmacol., Biochem. Behav*., 1988, **31**, 249; (b) B. Baruah, K. Dasu, B. Vaitilingam, A. Vanguri, S. R. Casturi, and K. R. Yeleswarapu, *Bioorg. Med. Chem. Lett*., 2004, **4**, 445.
51. A. Gaurav and V. Gautam. *Curr. Enzym. Inhib*., 2016, **9**, 106.
52. V. Singh, V. Singh, and S. Batra, *Eur. J. Org. Chem*., 2008, 5446.
53. V. Singh, S. Hutait, and S. Batra, *Eur. J. Org. Chem*., 2009, 3454.
54. A. Mishra and S. Batra, *Eur. J. Org. Chem*., 2010, 4832.
55. T. Seiser and N. Cramer, *J. Am. Chem. Soc*., 2010, **132**, 5340.
56. Z.-Q. Lei, H. Li, Y. Li, X.-S. Zhang, K. Chen, X. Wang, J. Sun, and Z.-J. Shi, *Angew. Chem. Int. Ed*., 2012, **51**, 2690.
57. D. Nečas, M. Turský, and M. Kotora, *J. Am. Chem. Soc*., 2004, **126**, 10222.
58. S. Chiba, Y.-J. Xu, and Y.-F. Wang, *J. Am. Chem. Soc*., 2009, **131**, 12886.
59. A. J. Grenning and J. A. Tunge, *Angew. Chem. Int. Ed.*, 2011, **50**, 1688.
60. A. Gunay and W. D. Jones, *J. Am. Chem. Soc*., 2007, **129**, 8729.
61. T. Sugiishi, A. Kimura, and H. Nakamura, *J. Am. Chem. Soc*., 2010, **132**, 5332.
62. (a) C. He, S. Guo, L. Huang, and A. Lei, *J. Am. Chem. Soc*., 2010, **132**, 8273; (b) N. Vodnala, R. Gujjarappa, C. K. Hazra, D. Kaldhi, A. K. Kabi, U. Beifuss, and C. C. Malakar, *Adv. Synth. Catal*., 2019, **361**, 135.
63. H. Li, W. Li, W. Liu, Z. He, and Z. Li, *Angew. Chem. Int. Ed.*, 2011, **50**, 2975.
64. C. Qin, W. Zhou, F. Chen, Y. Ou, and N. Jiao, *Angew. Chem. Int. Ed.*, 2011, **50**, 12595.
65. A. Kamimura, K. Ikeda, T. Moriyama, and H. Uno, *Tetrahedron Lett*., 2013, **54**, 1842.
66. S. Tashiro, M. Yamada, and M. Shionoya, *Angew. Chem. Int. Ed.*, 2015, **54**, 5351.
67. A. H. Abadi, A. A. H. Eissa, and G. S. Hassan, *Chem. Pharm. Bull.*, 2003, **51**, 838.
68. Y-R. Li, C. Li, J-C. Liu, M. Guo, T-Y. Zhang, L. P. Sun, C. J. Zheng, and H-R. Piao, *Bioorg. Med. Chem. Lett*., 2015, **25**, 5052.

69. P. G. Baraldi, M. A. Tabrizi, D. Preti, A. Bovero, F. Fruttarolo, R. Romagnoli, N. A. Zaid, A. R. Moorman, K. Varani, and P. A. Borea, *J. Med. Chem*., 2005, **48**, 5001.
70. P. K. Sharma, S. Kumar, P. Kumar, P. Kaushik, D. Kaushik, Y. Dhingra, and K. R. Aneja, *Eur. J. Med. Chem*., 2010, **45**, 2650.
71. S. Nag, V. Singh, and S. Batra, *ARKIVOC*, 2007, **xiv**, 185.
72. H. Katayama and H. Hojo, *Org. Biomol. Chem*., 2013, **11**, 4405.
73. M. G. Uchuskin, A. S. Pilipenko, O. V. Serdyuk, I. V. Trushkov, and A. V. Butin, *Org. Biomol. Chem*., 2012, **10**, 7262.
74. A. J. Perkowski and D. A. Nicewicz, *J. Am. Chem. Soc*., 2013, **135**, 10334.