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Microwave-assisted one-pot synthesis in water of carbonylpyrazolo[3,4-*b*]pyridine derivatives catalyzed by InCl_3 and sonochemical assisted condensation with aldehydes to obtain new chalcone derivatives containing the pyrazolopyridinic moiety†

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Pyrazolo[3,4-*b*]pyridine derivatives have been synthesized via one-pot condensation of 3-methyl-1-phenyl-1*H*-pyrazolo-5-amine (1), formaldehyde (as paraformaldehyde) (2) and β -diketones (3) under microwave irradiation in aqueous media catalyzed by InCl_3 . This process has been found to be useful in the preparation of new *N*-fused heterocycle products in good to excellent yields. Further treatment of pyrazolopyridines (4a and 4e) with aldehyde aromatics (5a–l) afforded chalcone analogs.

Introduction

Over the years it has been found in the literature that nitrogen-containing heterocycles have shown wide spectrums of biological activities for accessing pharmaceutical and medicinal products. Recent studies have shown that greater than 90% of molecules currently under analysis by pharmaceutical companies include nitrogen heterocycles, where pyrrole, imidazole, pyrazole, pyrimidine, pyridine, and derivatives constitute the most important family of these compounds.¹ Fused pyridine systems such as pyrazolopyridines and their related derivatives have been identified as a potentially interesting scaffold for biologically active compounds because of their structural analogy to purine bases, an important constituent of DNA and RNA nucleosides.^{2–5} The pyrazolopyridines, which comprise five isomers (I–V); [3,4-*b*], [3,4-*c*], [4,3-*c*], [4,3-*b*] and [1,5-*a*] (Fig. 1).

In particular pyrazolo[3,4-*b*]pyridines (I) has aroused great interest in recent years due to a wide variety of biological

activities associated with it. Analgesic, anti-microbial, antipyretic, anxiolytic, antagonists stereoselective of A1 receptors in humans, vasodilating, anti-chagasic, respiration stimulating, inhibitors of phosphodiesterase 4B (PDBE4B), bronchodilating, and of this system have been reported in the literature (Fig. 2).^{6–14}

Due to their attractive pharmacological properties, pyrazolo[3,4-*b*]pyridines have attracted the attention of chemists who have researched ways to obtain the desired properties through different synthetic strategies. The most common reactions include: (a) condensation of pyrazole-5-amine derivatives and activated carbonyl groups;^{15–17} (b) reaction of 5-aminopyrazoles, 1,3-dicarbonyl derivatives or equivalents and aldehydes through of Hantzsch-type reaction;^{18–20} (c) through Povarov-type [4 + 2], cycloaddition between 5-aminopyrazoles, aromatic aldehydes, and cycloalkanones in acetic acid;²¹ and (d) Friedländer condensation of 5-aminopyrazole-4-carbaldehydes with α -

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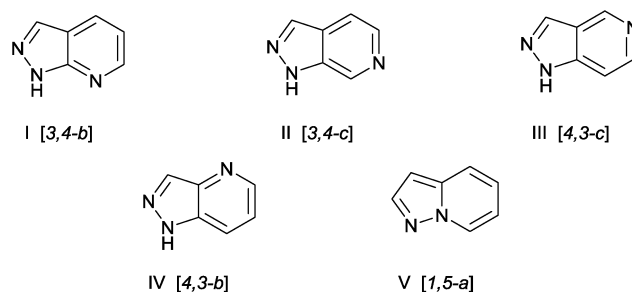


Fig. 1 Pyrazolopyridine Isomers.

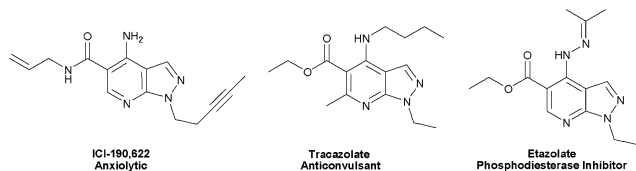


Fig. 2 Examples of pyrazolo[3,4-*b*]pyridines biologically active.

methylene ketones such as acetone or acetophenones with potassium hydroxide as basic catalyst.^{22–24}

The methods described in the literature presents several disadvantages such as the use of toxic solvents for the environment, long reaction times, several steps of synthesis, these contradict the current trends of green chemistry,²⁵ as a result of the importance that presents these heterocycles in the medicinal field, different researchers have designed environmentally friendly and efficient synthetic routes, for example have used water as solvent under microwave irradiation (MWI) using catalysts organic or inorganic.^{26,27} Recently, InCl_3 has emerged as useful Lewis acid catalyst in organic synthesis due to its compatibility with both organic and aqueous media in comparison with frequently used Lewis acids such as BF_3 , TiCl_4 , and AlCl_3 react violently with water and cannot be used under aqueous conditions. The fact that its non-toxic nature enables the chemists to handle its reactions very easily and its lower heterophilicity makes it an ideal catalyst or reagent for the C–C bond formation reactions. In this context, over the past few years, InCl_3 has received increasing attention as a novel type of water tolerant Lewis acid catalyst for organic synthesis with high chemo-, regio-, and stereoselectivity.

For example, InCl_3 has been utilized in Diels–Alder,²⁸ Friedel–Crafts,^{29,30} Michael-type,^{31–34} Mannich type,^{35,36} Mukaiyama–aldol,^{37,38} von Pechmann reaction,³⁹ Hosomi–Sakurai allylation reactions,^{40,41} neat or in water under mild conditions. As InCl_3 has these unique properties compared to other Lewis acids which include stability and recoverability from water, we are interested to apply it to other carbon–carbon bond formation reactions in water.

In general, the synthetic methodologies described in the literature are based on the starting materials. Starting from the variety of α,β -unsaturated synthons can build diverse pyrazolo[3,4-*b*]pyridine core. Herein, we wish to report a simple method for the synthesis of pyrazolo[3,4-*b*]pyridines derivatives *via* one-pot three-component reaction between 5-aminopyrazoles derivatives **1**, paraformaldehyde **2** and β -diketones **3** catalyzed by InCl_3 in aqueous media. Low environmental impact strategy, based on the construction of pyridine ring onto pyrazole combining reuse of catalyst, water and microwave irradiation.

We report the use of this nucleus of pyrazolo[3,4-*b*]pyridines for structural diversification from carbonyl carbon coupled aromatic aldehydes generating analogs of chalcones. Comparison yields and reaction times are reported by using a conventional method and use ultrasound for the obtaining of new derivatives. The target molecules were obtained in good to excellent isolated yields.

Results and discussion

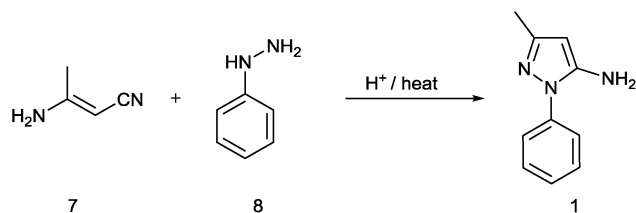
Initially, held the synthesis of compound **1**; prepared from (2*E*)-3-aminobut-2-enenitrile **7** and 1-phenyl hydrazine **8** was synthesized by conventional methods according to the literature (Scheme 1).⁴²

The three-component coupling reaction of **1**, paraformaldehyde **2** and indandione **3e** under MWI in water was studied comprehensively as a representative example for obtaining pyrazolo[3,4-*b*]pyridines. For comparison was studied the effect of three different reaction conditions: reflux using AcOH, reflux using water and InCl_3 and the use of water and InCl_3 with MWI (Scheme 2 and Table 1).

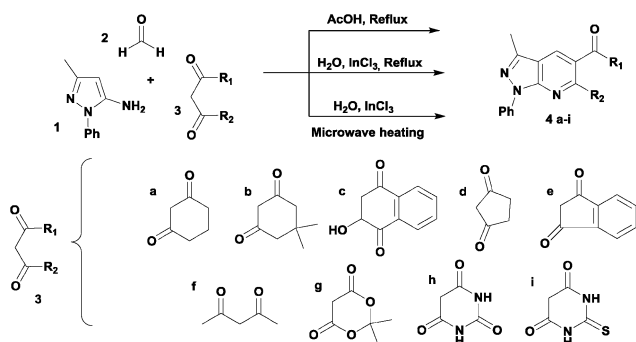
Previously, Dzvinchuk *et al.*⁴³ synthesized **4a** in 87% yield from the reaction of 1,3-cyclohexanedione **3a**, **1** and 4-(dimethylamino)-benzaldehyde in boiling acetic acid for 2 h. In this reaction *N,N*-dimethylaniline was obtained as a byproduct. Zheng *et al.*⁴⁴ reported the synthesis of **4b** in 15% yield from a two-step reaction. Recently Sumesh *et al.*,⁴⁵ reported the synthesis of **4a** and **4b** in 98% yield a one-step using *L*-proline, and water for 2 h.

In order to understand how the working temperature and the presence of different amounts of catalyst influence the performance and reaction time under MWI conditions was studied the behavior of compound **4e** which facilitated establish the optimal reaction conditions (Table 2).

As shown in Table 2, the expected product was obtained in good yield in water under MWI when is working with a temperature of 150 °C; InCl_3 at 15% mol. It is also observed that by inducing the reaction at the same temperature (150 °C),



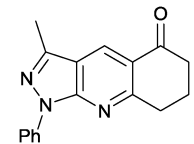
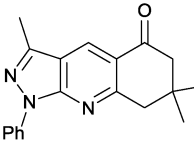
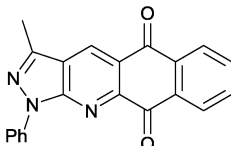
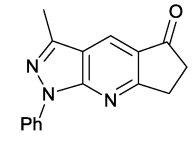
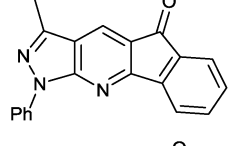
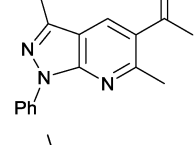
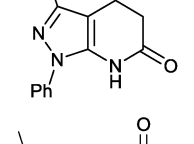
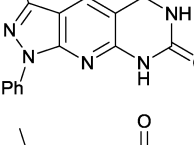
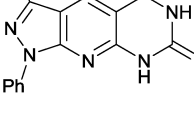
Scheme 1 Synthesis of starting material **1** needed for synthesis of pyrazolo[3,4-*b*]pyridine derivatives **4a–i**.



Scheme 2 Reaction conditions to obtain pyrazolo[3,4-*b*]pyridines **4a–i**.



Table 1 Comparison of yields pyrazolo[3,4-*b*]pyridines (4a–i)

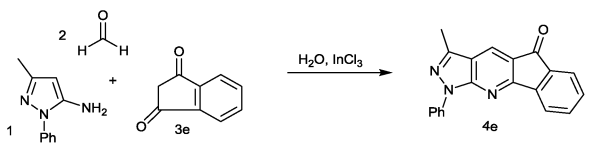
Compound	<i>m/z</i>	Mp (°C)	Conventional method		Microwave irradiation method	
			Time (h)/yield (%)		Time (min)/yield (%)	
			AcOH	H ₂ O/InCl ₃	H ₂ O/InCl ₃	
4a		277	128–130 123–124 (ref. 45)	4/60	16/33	15/75
4b		305	152–154 165–166 (ref. 45) 164.5–166 (ref. 43)	4/62	4/75	15/85
4c		339	211–213	9/48	7/52	10/80
4d		263	215–217	8/66	7/60	15/82
4e		311	246–248	1/44	5/72	10/91
4f		265	98–100 96 (ref. 46)	6/50	10/65	17/90
4g		227	276–278	4/47	8/50	12/67
4h		293	300–302	3/52	7/60	15/95
4i		309	>300	3/44	8/45	20/91

and increasing the amount of catalyst (20% mol), the yield does not change. With these results in hand, different pyrazolo[3,4-*b*]pyridine derivatives **4a–i** were prepared using various β -diketones **3a–i** (Table 1).

The possibility to recover and recycle InCl₃ also offers another significant advantage. Because InCl₃ is soluble in reaction medium and the products are insoluble in water, the recovered filtrate containing the catalyst could be recycled.



Table 2 Temperature screening for the synthesis of 3-methyl-1-phenylindeno[2,3-*e*]pyrazolo[3,4-*b*]pyridin-5(1*H*)-one **4e** in MWI at 300 W. Reactions are performed on a 1 mmol scale of the reactants under MWI

				
Entry	Catalyst (mol%)	Reaction temp. °C	Reaction time (min)	Isolated yield (%)
1	0	80	45	0
2	5	100	30	23
3	10	120	10	80
4	15	150	10	90
5	20	150	15	90
6	25	150	10	87

Studies using amine (**1**), formaldehyde (**2**), and diketone (**3e**) as model substrates showed that the recovered filtrate could be successively recycled in subsequent reactions without any significant decrease of yield of **4e**. A marginal loss of the yield was observed in first two runs (91% and 89%), while in third and fourth run the yield dropped to 75% and 65%, respectively.

With the optimized protocol in hand, the scope of this domino process was then assessed through the variation of β -diketones **3a–i** (Table 1). As a general trend, this reaction is tolerant to a large variety of β -diketones (linear, cyclical, heterocycles). Diversely adducts could be prepared in good yields (up to 95%), demonstrating the versatility of this one-pot process. This variety results very attractively for the establishment of structure–activity relationships after biological evaluation.

InCl_3 in water under microwave radiation turns out to be advantageous for the synthesis of these compounds as shown in the Table 1. In conventional method, the yield of all the products is lower as compared to the yield obtained by synthesis by

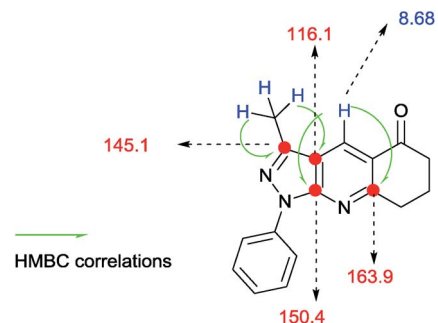
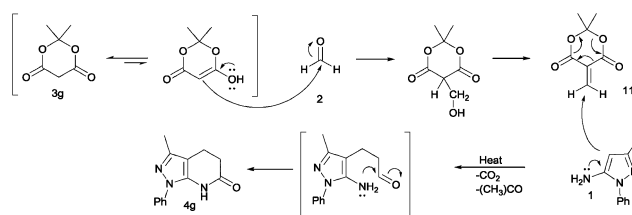


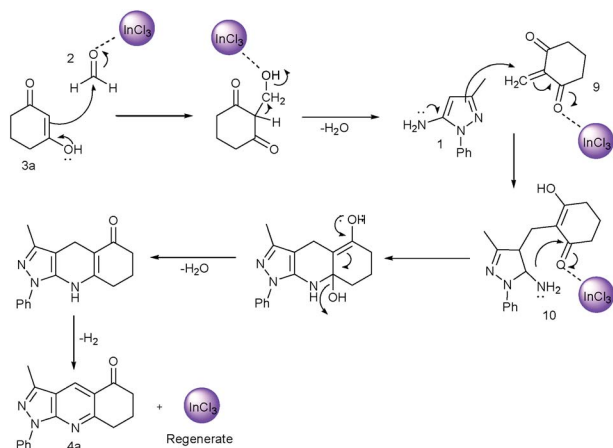
Fig. 3 Structural determination of compound **4a**.



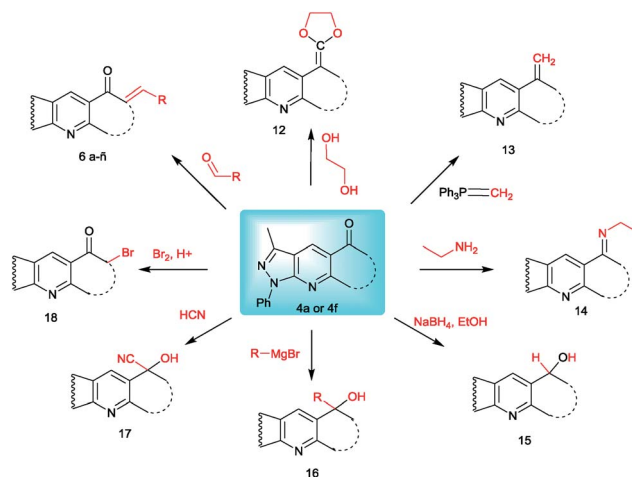
Scheme 4 Plausible mechanism for the formation of pyrazolo[3,4-*b*]pyridine **4g**.

MWI technique. Microwave irradiation method facilitates the polarization of the reacting molecule causing reactions to occur at higher rate.

A reasonable mechanism for the formation of product **4a** is outlined in Scheme 3. The formation of **4a** is expected to proceed *via* initial condensation of aldehyde **2** with β -diketones **3a** to give an intermediate [**9**], it may be proposed that the InCl_3 catalyst facilitates the formation the intermediate [**9**] by increasing the electrophilicity of the carbonyl group of the aldehyde which further undergoes Michael addition with **1** to give an open-chain intermediate [**10**], which is subsequently cyclized, dehydrated and dehydrogenated to afford the aromatized product **4a** (Fig. 3).



Scheme 3 Plausible mechanism for the formation of pyrazolo[3,4-*b*]pyridine derivative **4a**.



Scheme 5 Synthetic versatility of carbonyl carbon.



Table 3 Synthesis of heterocyclic analogues of chalcones

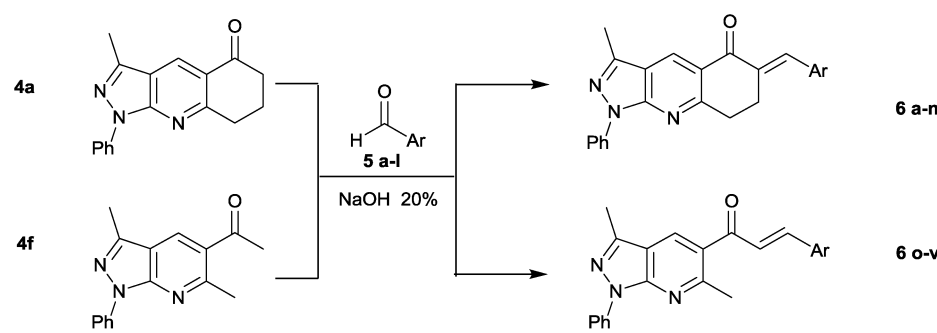
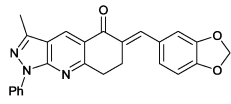
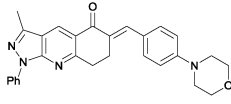
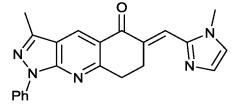
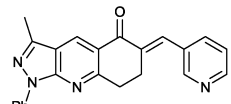
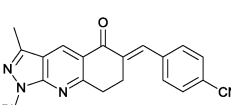
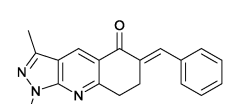
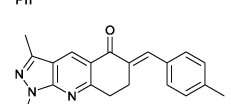
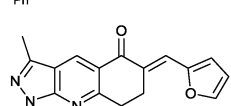
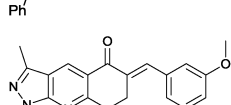
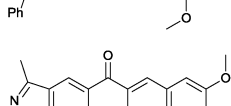
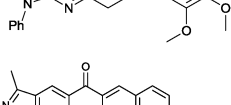
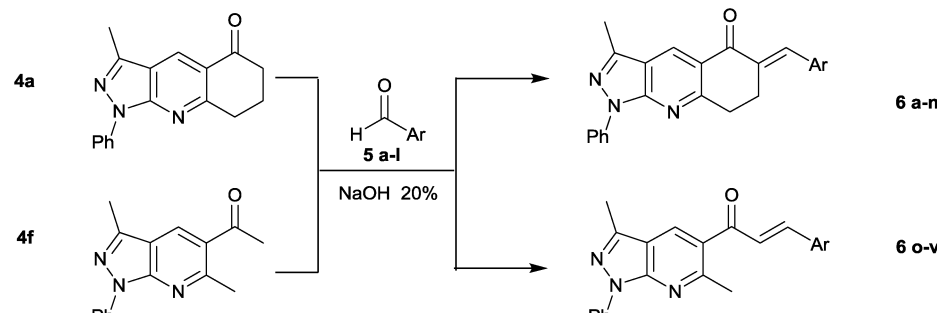
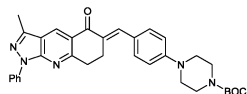
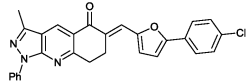
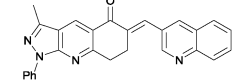
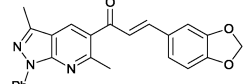
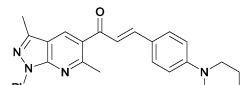
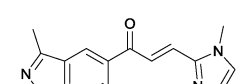
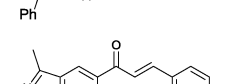
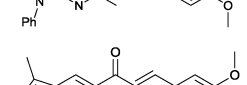
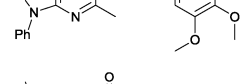
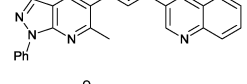
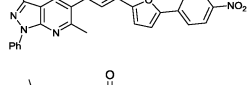
				
Entry	Structure	Conventional method (h per yield)	Ultrasonic method (min per yield)	Mp (°C)
6a		2/50	10/50	175–177
6b		2/52	20/65	187–189
6c		3/48	10/72	210–212
6d		2/51	15/52	165–167
6e		2/65	15/72	123–125
6f		3/67	10/80	189–191
6g		3/50	15/61	178–180
6h		2/61	10/83	180–182
6i		2/49	15/90	179–181
6j		3/57	15/92	177–179
6k		4/37	20/72	176–178



Table 3 (Contd.)

				
Entry	Estructure	Conventional method (h per yield)	Ultrasonic method (min per yield)	Mp (°C)
6l		3/45	20/67	108–110
6m		4/75	15/98	170–172
6n		3/62	15/87	211–213
6o		4.5/65	10/63	134–136
6p		3/79	10/82	230–232
6q		4/88	15/93	150–152
6r		2/70	10/72	186–188
6s		3/81	15/91	180–182
6t		2.5/85	10/87	195–197
6u		4/83	10/90	>300
6v		2.5/68	10/75	>300



However, the compound **4g** does not fit this mechanism. Derivatives of Meldrum's acid (1,3-dioxane-4,6-dione) are excellent precursors for the production of a variety of ketones, propadienones, iminopropadienones, and other reactive molecules by flash vacuum thermolysis (FVT),⁴⁷ via a pseudo-retro-Diels–Alder reaction, eliminating acetone and carbon dioxide. Mechanistically the formation of the product (**4g**) can be visualized by initial Knoevenagel condensation of aldehyde **2** and 6,6-dimethyl-1,3,5-trioxane-2,4-dione (**3h**) resulting in adduct **11**, followed by a Michael type nucleophilic addition of C-5 of the pyrazole ring (**1**) to the enone intermediate [**11**]; in the next step loss of acetone and CO₂ and subsequent cyclodehydration to furnish the desired compound (Scheme 4).

Ketones engage in many organic reactions. The most important reactions follow from the susceptibility of the carbonyl carbon toward nucleophilic addition and the tendency for the enolates to add to electrophiles, most reactions of carbonyl compounds take place by one of four general mechanisms: nucleophilic addition (12–17), nucleophilic acyl substitution, alpha substitution (18), and carbonyl condensation (6a–v) (Scheme 5).

In order to create structural diversity from the carbonyl carbon available, we synthesize chalcones derivatives using pyrazolopyridine **4f** or **4a** and aldehydes aromatic **5a–l** in a typical condensation of Claisen–Schmidt in ethanol with basic catalysis. In this reaction, we evaluate the advantages of sonochemical method over conventional method as is shown in Table 3.

A comparison of the results obtained under ultrasonic irradiations with those of conventional stirring in ethanol (Table 3) revealed that the reaction under ultrasonic irradiation proceeds in much lower reaction times and excellent yields. The rate acceleration using ultrasonic irradiations may be due to cavitation phenomena, in which the energy being transmitted more efficiently to the substrates.^{48–50}

The yields of compound **6** were excellent. It is worth noting that the electronic nature of the substituents affects only to a lesser extent the yields of the products and the reaction proceeds quite well with both electron-withdrawing and electron-releasing substituents on chalcones analogues.

Compounds of the series **4** and **6** were easily characterized by ¹H-NMR, ¹³C-NMR, IR and mass spectra. The FT-IR spectra of

synthesized pyrazolopyridines derivatives **4** and **6** showed bands at stretching frequencies in the range of 1584–1598 cm^{−1} and 1488–1502 cm^{−1}, which are characteristic of (–C=N) and (–C=C) groups. ¹H-NMR spectra were similar between them in each set, and were characterized by the presence of three groups of signals (aromatic protons, protons near heteroatoms and aliphatic protons). Each series was identified a signal around 8 ppm, typical for γ-unsubstituted pyridine ring shown as in Fig. 3 and 4.

Experimental

The experiments were performed in a discover microwave apparatus (CEM Corporation, Matthews, NC, USA); the ultrasonic irradiation was performed by using a Branson ultrasonic cleaner bath, model 1510, 115 v, 1.9 L with mechanical timer (60 min with continuous hold) and heater switch, 47 kHz. All the products were characterized by spectral data (IR, MS, ¹H-NMR, ¹³C-NMR). ¹H and ¹³C NMR spectra (400 MHz for proton and 100 MHz for carbon) were recorded on an AM-400 spectrometer (Bruker, Rheinstetten, Germany), using CDCl₃, DMSO-*d*₆ and CD₃OD as solvents. Tetramethylsilane (TMS) was used as an internal standard. Chemical shifts (δ) and *J* values are reported in ppm and Hz, respectively, relative to the solvent peak CDCl₃ at 7.24 ppm for protons and 77 ppm for carbon atoms; DMSO-*d*₆ 2.5 ppm for protons and 39.7 ppm for carbon atoms, and CD₃OD with 3.35 and 4.78 ppm for protons and 49.3 ppm for carbon. Signals are designated as follows: s, singlet; d, doublet; q, quartet; t, triplet; m, multiplet. IR spectra (KBr pellets, 500–4000 cm^{−1}) were recorded on a NEXUS 670 FT-IR spectrophotometer (Thermo Nicolet, Madison, WI, USA). High-resolution mass spectrometry ESI-MS and ESI-MS/MS analyses were conducted in a high-resolution hybrid quadrupole (Q) and orthogonal time-of-flight (TOF) mass spectrometer (Waters/Micromass Q-TOF micro, Manchester, UK) with a constant nebulizer temperature of 100 °C. Melting points (uncorrected) were measured on a Electrothermal IA9100 melting point apparatus (Stone, Staffs, UK). Reaction progress was monitored by means of thin-layer chromatography using silica gel 60 (Merck, Darmstadt, Germany). All reagents were purchased from either Merck or Sigma Aldrich (St. Louis, MO, USA) and used without further purification. Final purification of all products for analysis was carried out by recrystallization.

General procedure for the preparation of pyrazolopyridine 4a–j

Conventional method (reflux). (a) A solution of 5-aminopyrazole (**1**, 1 mmol), *p*-formaldehyde (**2**, 1 mmol) and β-diketone (**3**, 1 mmol) in acetic acid (15 mL) was heated at 80 °C (oil bath) for 4–11 h. Then, the reaction mixture was filtered hot and the resulting solid products were washed with ethanol, dried in air and recrystallized from ethanol.

(b) A mixture of 5-aminopyrazole (**1**, 1 mmol), *p*-formaldehyde (**2**, 1 mmol) and β-diketone (**3**, 1 mmol) was placed in a 50 mL round-bottomed flask; 10 mL of water and InCl₃ (15% mol) were added. The mixture was stirred under reflux for 4–16 h. The progress of the reaction was monitored by TLC using

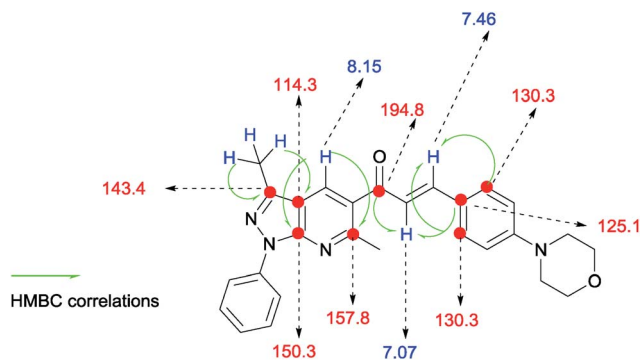


Fig. 4 HMBC-assisted NMR-based structural determination of compound **6p**.



petroleum ether/ethylacetate (60 : 40) as eluent. The reaction mixture was allowed to cool to room temperature. The precipitate formed was collected by filtration at pump washed with a mixture hexane/ethanol.

Synthesis assisted by microwave

A mixture of 5-aminopyrazole (1, 1 mmol), *p*-formaldehyde (2, 1 mmol), β -diketone (3, 1 mmol), InCl_3 (15% mol), and water (3 mL) were subjected to MWI (maximum power 300 W during 10–20 min at a controlled temperature of 483 K) using a focused microwave reactor (CEM Discover, Matthews, NC, USA). The aqueous phase extracted with EtOAc (2 \times 10 mL). The combined organic layers was dried over Na_2SO_4 and evaporated; to give the corresponding derivatives 4a–j.

3-Methyl-1-phenyl-7,8-dihydrocyclohexa[2,3-*e*]pyrazolo[3,4-*b*]pyridin-5(6*H*)-one (4a). Yield: 75% (207.9 mg); orange crystals; mp 128–130 °C; IR (KBr, cm^{-1}): 3063, 2949, 2883, 1680, 1593, 1505, 1419, 1260, 1183, 1015, 904, 778, 748, 667, 559, 530; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} = 2.11 (q, J = 6.0 Hz, 2H), 2.57 (s, 3H, CH_3), 2.68 (t, J = 6.5 Hz, 1H), 3.15 (t, J = 6.5 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 8.0 Hz, 2H), 8.23 (d, J = 8.7 Hz, 2H), 8.68 (s, 1H); ^{13}C NMR (100 MHz $\text{DMSO}-d_6$) δ_{C} : 12.1 (CH_3), 21.3 (CH_2), 33.0 (CH_2), 38.2 (CH_2), 116.1 (C), 120.1 (2 \times CH), 122.9 (C), 125.7 (CH), 129.1 (2 \times CH), 130.3 (CH), 138.7 (C), 145.1 (C), 150.4 (C), 163.9 (C), 196.5 (C); HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}$ $[\text{M} + \text{K}]^+$ 316.0858 found 316.4317.

3,7,7-Trimethyl-1-phenyl-7,8-dihydrocyclohexa[2,3-*e*]pyrazolo[3,4-*b*]pyridin-5(6*H*)-one (4b). Yield: 85% (259.5 mg); yellow solid; mp 152–154 °C; IR (KBr, cm^{-1}): 3064, 2954, 2929, 2869, 1678, 1591, 1507, 1374, 1244, 1119, 1023, 936, 757, 672, 556, 511; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} : 1.02 (s, 6H), 2.58 (m, 5H), 3.07 (s, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.7 Hz, 2H), 8.24 (d, J = 8.2 Hz, 2H), 8.68 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 12.2 (CH_3), 27.7 (CH_3), 32.5 (CH_3), 46.6 (CH_2), 51.5 (CH_2), 99.5 (C), 116.1 (C), 120.3 (2 \times CH), 122.0 (C), 125.9 (CH), 129.2 (2 \times CH), 130.2 (CH), 138.8 (C), 145.4 (C), 151.0 (C), 162.8 (C), 196.7 (C); HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$ $[\text{M}]^+$ 305.1528 found 305.2056.

3-Methyl-1-phenyl-7,8-dihydrocyclopenta[2,3-*e*]pyrazolo[3,4-*b*]pyridin-5,10-dione (4c). Yield: 80% (271.4 mg); brown solid; mp 211–213 °C; IR (KBr, cm^{-1}): 3476, 3052, 2921, 1683, 1665, 1505, 1290, 1276, 1114, 1094, 1027, 971, 785, 756, 661, 592; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} = 2.58 (s, 3H, CH_3), 7.32 (t, J = 7.2 Hz, 1H), 8.22 (d, J = 8.3 Hz, 2H), 8.24 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 12.0 (CH_3), 118.5 (C), 120.0 (2 \times CH), 124.6 (C), 126.0 (CH), 126.5 (CH), 126.8 (CH), 128.1 (CH), 129.0 (2 \times CH), 131.0 (CH), 132.5 (C), 133.4 (C), 134.4 (C), 138.2 (C), 145.4 (C), 147.5 (C), 150.2 (C), 180.4 (C), 181.3 (C); HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 362.0905 found 362.2862.

3-Methyl-1-phenyl-6,7-dihydrocyclopenta[2,3-*e*]pyrazolo[3,4-*b*]pyridin-5(1*H*)-one (4d). Yield: 82% (215.9 mg); yellow solid; mp 215–217 °C; IR (KBr, cm^{-1}): 3392, 3036, 2919, 1735, 1630, 1592, 1493, 1423, 1292, 1241, 1153, 1021, 754, 664, 615, 528; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} = 2.59 (s, 3H, CH_3), 7.35 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.9 Hz, 2H), 8.21 (d, J = 7.7 Hz, 2H), 8.54 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 12.2 (CH_3), 28.5 (CH_2), 36.1 (CH_2), 116.9 (C), 120.5 (2 \times CH), 125.0 (C), 126.0

(CH), 127.2 (2 \times CH), 129.2 (CH), 138.6 (C), 145.8 (C), 152.9 (C), 174.6 (C), 203.4 (C); HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{ONa}$ $[\text{M} + \text{Na}]^+$ 286.0956 found 286.0114.

3-Methyl-1-phenylindeno[2,3-*e*]pyrazolo[3,4-*b*]pyridin-5(1*H*)-one (4e). Yield: 91% (283.3 mg); yellow solid; mp 246–248 °C; IR (KBr, cm^{-1}): 3390, 3054, 2923, 1716, 1613, 1589, 1502, 1337, 1290, 1138, 1028, 809, 781, 727, 636, 553; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} = 2.61 (s, 3H, CH_3), 7.38 (t, J = 7.4 Hz, 1H), 7.95 (d, J = 7.2 Hz, 1H), 8.28 (d, J = 7.7 Hz, 2H), 8.47 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 11.3 (CH_3), 116.0 (C), 120.5 (2 \times CH), 120.7 (CH), 122.6 (C), 122.9 (CH), 125.7 (CH), 126.4 (CH), 128.5 (2 \times CH), 131.3 (CH), 134.8 (CH), 136.3 (C), 138.3 (C), 141.8 (C), 145.5 (C), 152.2 (C), 163.5 (C), 188.9 (C); HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{OK}$ $[\text{M} + \text{K}]^+$ 350.4350 found 349.4350.

1-(3,6-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)etanone (4f). Yield: 90% (238.7 mg); yellow solid; mp 100–102 °C; IR (KBr, cm^{-1}): 3065, 2960, 2924, 2853, 1679, 1611, 1592, 1503, 1436, 1236, 1119, 1026, 944, 755, 692, 585; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} = 2.63 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 7.31 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 8.0 Hz, 2H), 8.25 (d, J = 7.7 Hz, 2H), 8.87 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 12.2 (CH_3), 25.8 (CH_3), 29.4 (CH_3), 114.4 (C), 120.1 (2 \times CH), 125.7 (CH), 127.2 (C), 129.1 (2 \times CH), 133.3 (CH), 138.9 (C), 144.3 (C), 149.5 (C), 158.5 (C), 199.6 (C); HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{16}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 266.1293 found 266.2751.

3-Methyl-1-phenyl-4,5-dihydro-1*H*-pyrazol[3,4-*b*]pyridine (4g). Yield: 67% (152.2 mg); green crystals; mp 276–278 °C; IR (KBr, cm^{-1}): 3063, 2938, 2917, 2860, 1595, 1570, 1503, 1435, 1385, 1144, 1123, 1062, 950, 911, 785, 712, 690; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} = 1.95 (s, 3H), 3.16 (d, J = 3.7 Hz, 2H), 3.57 (d, J = 15.8 Hz, 1H), 4.26 (t, J = 14.3 Hz, 2H), 7.28 (t, J = 6.9 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.95 (d, J = 8.53 Hz, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 12.1 (CH_3), 47.5 (CH_2), 63.0 (CH_2), 104.3 (C), 119.8 (2 \times CH), 125.6 (CH), 129.3 (2 \times CH), 135.8 (C), 139.2 (C), 144.8 (C), 145.0 (C); HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_2$ $[\text{M} + 2\text{H}]^+$ 229.1215 found 229.1577.

3-Methyl-1-phenyl-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4h). Yield: 95% (278.6 mg); yellow solid; mp 300–302 °C; IR (KBr, cm^{-1}): 3169, 3050, 2822, 1716, 1618, 1592, 1493, 1418, 1381, 1242, 1166, 1030, 851, 796, 761, 575; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} = 2.24 (s, 3H), 7.51 (m, 4H), 7.71 (s, 1H), 8.11 (s, 1H), 12.14 (s, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 12.3 (CH_3), 103.9 (C), 114.3 (C), 120.3 (2 \times CH), 125.9 (CH), 129.2 (2 \times CH), 132.8 (C), 138.8 (CH), 145.4 (C), 150.7 (C), 151.1 (C), 161.1 (C), 162.4 (C); HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_2$ $[\text{M} + 2\text{H}]^+$ 295.1069 found 295.1305.

3-Methyl-1-phenyl-7-sulfanylidene-1,6,7,8-tetrahydro-5*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-5-one (4i). Yield: 91% (281.5 mg); red solid; mp > 300 °C; IR (KBr, cm^{-1}): 3322, 3108, 3045, 2917, 1641, 1600, 1496, 1415, 1378, 1337, 1152, 1094, 920, 781, 698, 677, 527; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} = 2.60 (s, 3H), 7.31 (t, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 2H), 8.23 (d, J = 8.0 Hz, 2H), 8.82 (s, 1H), 11.46 (s, 1H), 11.77 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 12.7 (CH_3), 104.3 (C), 106.7 (C), 124.6 (2 \times CH), 128.3 (CH), 129.7 (2 \times CH), 136.8 (CH), 143.8 (CH), 151.1 (C), 153.6 (C), 162.0 (C), 177.1 (C); calcd for $\text{C}_{30}\text{H}_{23}\text{N}_{10}\text{O}_2\text{S}_2$ $[\text{2M} + \text{H}]^+$ 619.1447 found 619.1970.



General procedure for the synthesis of chalcones 6a–i

A mixture of pyrazolo[3,4-*b*]pyridine (**4a** or **4f** 1 mmol), appropriate aromatic aldehyde (1 mmol), KOH (1 mmol) and ethanol (2 mL), was sonicated for 5–20 min in the water bath of an ultrasonic cleaner bath. The progress of the reaction was monitored by TLC using dichloromethane : ethyl acetate (9 : 1 v/v) as eluent. The reaction mixture was cooled in ice-water bath. The formed precipitate was filtered, washed with mixture water : ethanol (1 : 1) and purified by recrystallization with mixture ethanol : hexane (1 : 1) to give the target compounds in high yields of 50–98%.

(E)-6-((Benzo[d][1,3]dioxol-5-yl)methylene)-7,8-dihydro-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]quinolin-5(6H)-one (6a). Yield: 50% (204.7 mg); yellow solid; mp 221–223 °C; IR (KBr, cm⁻¹): 3065, 2897, 1658, 1592, 1488, 1317, 1239, 1036, 923, 816, 747; ¹H NMR (400 MHz, CD₃Cl); δ_H 2.67 (s, 3H), 3.24 (s, 4H), 6.02 (s, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 7.00 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.86 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 2H), 8.81 (s, 1H); ¹³C NMR (100 MHz, CD₃Cl); 12.5 (CH₃), 26.3 (CH₂), 32.7 (CH₂), 101.4 (CH₂), 108.5 (CH), 109.8 (CH), 117.0 (C), 120.9 (2× CH), 123.8 (C), 125.3 (CH), 125.9 (CH), 129.0 (2× CH), 129.6 (CH), 131.3 (C), 133.0 (CH), 137.6 (C), 139.1 (C), 145.1 (C), 147.8 (C), 148.3 (C), 151.0 (C), 162.5 (C), 187.0 (C); HRMS (ESI, *m/z*): calcd for C₂₅H₁₉N₃O₃Na [M + Na]⁺ 432.1324 found 432.1360.

(E)-6-(4-Morpholinobenzylidene)-7,8-dihydro-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]quinolin-5(6H)-one (6b). Yield: 65% (292.9 mg); yellow solid; mp 175–177 °C IR (KBr, cm⁻¹): 3062, 2955, 2920, 2894, 2851, 1664, 1589, 1508, 1421, 1378, 1184, 1114, 923; ¹H NMR (400 MHz, CD₃Cl); δ_H 2.45 (s, 3H), 3.03 (s, 8H) 3.63–3.66 (m, 4H), 6.53 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 2H), 7.04–7.09 (m, 1H), 7.23–7.31 (m, 4H), 7.68 (s, 1H), 8.08 (d, *J* = 7.8 Hz, 2H), 8.58 (s, 1H); ¹³C NMR (100 MHz, CD₃Cl); 12.5 (CH₃), 26.3 (CH₂), 32.7 (CH₂), 48.1 (CH₂), 66.6 (CH₂), 114.4 (2× CH), 116.9 (CH), 120.8 (CH), 124.0 (C), 125.8 (CH), 126.4 (C), 129.0 (2× CH), 131.1 (CH), 131.6 (C), 131.9 (2× CH), 137.9 (CH), 139.1 (C), 145.0 (C), 151.0 (C), 151.4 (C), 162.5 (C), 187.0 (C); HRMS (ESI, *m/z*): calcd for C₂₈H₂₆N₄O₂Na [M + Na]⁺ 473.1948 found 473.1105.

(E)-7,8-Dihydro-3-methyl-6-((1-methyl-1H-imidazol-2-yl)methylene)-1-phenyl-1H-pyrazolo[3,4-*b*]quinolin-5(6H)-one (6c). Yield: 72% (265.9 mg); yellow solid; mp 210–212 °C; IR (KBr, cm⁻¹): 3097, 3062, 2952, 2920, 2877, 1676, 1612, 1592, 1505, 1415, 1256, 1210, 1111, 1016, 889, 750; ¹H NMR (400 MHz, CD₃Cl) 2.62 (s, 3H), 3.26 (t, *J* = 6.6 Hz, 1H), 3.74 (m, 5H), 6.95 (s, 1H), 7.22 (d, *J* = 6.6 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.60 (s, 1H), 7.80 (s, 1H), 8.24 (d, *J* = 8.0 Hz, 2H), 8.74 (s, 1H); ¹³C NMR (100 MHz, CD₃Cl); 12.5 (CH₃), 25.7 (CH₂), 32.3 (CH₂), 33.2 (CH₃), 116.9 (C), 119.2 (CH), 120.8 (CH), 120.9 (2× H), 122.9 (CH), 123.5 (C), 125.8 (C), 125.9 (CH), 129.0 (2× CH), 130.2 (CH), 131.2 (CH), 136.1 (C), 139.0 (C), 143.9 (C), 145.0 (C), 151.0 (C), 163.3 (C), 187.0 (C); HRMS (ESI, *m/z*): calcd for C₂₂H₁₉N₅O [M + K]⁺ 408.1221 found 408.1104.

(E)-7,8-Dihydro-3-methyl-1-phenyl-6-((pyridin-3-yl)methylene)-1H-pyrazolo[3,4-*b*]quinolin-5(6H)-one (6d). Yield: 52% (190.5 mg); beige solid; mp 165–167 °C; IR (KBr, cm⁻¹): 3050, 2937, 2917, 2842, 1951, 1872, 1751, 1658, 1615, 1514, 1482, 1418, 1328, 1268, 1195, 1097, 1016, 758; ¹H NMR (400 MHz, CD₃Cl) 2.61 (s, 3H), 3.14–3.21 (m, 4H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.30–7.33 (m, 1H),

7.44 (t, *J* = 7.8 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.59 (s, 1H), 7.80 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 2H), 8.53 (s, 1H); 8.67 (s, 1H); 8.74 (s, 1H); ¹³C NMR (100 MHz, CD₃Cl); 12.8 (CH₃), 26.5 (CH₂), 32.9 (CH₂), 117.4 (C), 121.2 (2× CH), 123.6 (CH), 126.3 (CH), 129.3 (2× CH), 131.8 (CH), 133.7 (CH), 136.8 (CH), 137.0 (C), 139.3 (C), 145.4 (C), 149.7 (CH), 150.9 (CH), 151.4 (C), 162.7 (C), 186.8 (C); HRMS (ESI, *m/z*): calcd for C₂₃H₁₈N₄O₂Na [M + Na]⁺ 389.1373 found 389.1219.

4-((E)-7,8-Dihydro-3-methyl-5-oxo-1-phenyl-1H-pyrazolo[3,4-*b*]quinolin-6(5H)-ylidene)methylbenzonitrile (6e). Yield: 72% (281.1 mg); brown solid; mp 123–125 °C; IR (KBr, cm⁻¹): 3062, 2949, 2920, 2851, 2231, 1942, 1867, 1667, 1595, 1508, 1485, 1328, 1268, 1204, 1120, 1022, 854, 755; ¹H NMR (400 MHz, CD₃Cl) 2.65 (s, 3H), 3.13–3.20 (m, 4H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.47–7.52 (m, 4H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.84 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 2H), 8.78 (s, 1H); ¹³C NMR (100 MHz, CD₃Cl); 12.7 (CH₃), 26.5 (CH₂), 32.8 (CH₂), 112.3 (C), 117.4 (C), 118.7 (C), 121.1 (C), 121.1 (2× CH), 123.5 (C), 126.3 (CH), 129.3 (2× CH), 130.5 (2× CH), 131.8 (CH), 132.5 (2× CH), 135.1 (CH), 137.4 (C), 139.2 (C), 140.4 (C), 145.4 (C), 151.3 (C), 162.5 (C), 186.7 (C); HRMS (ESI, *m/z*): calcd for C₂₅H₁₈N₄O [M + H]⁺ 391.1559 found 390.9908.

(E)-6-Benzylidene-7,8-dihydro-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]quinolin-5(6H)-one (6f). Yield: 80% (292.3 mg); white solid; mp 189–191 °C; IR (KBr, cm⁻¹): 3062, 3045, 2966, 2940, 2920, 1661, 1609, 1583, 1511, 1485, 1418, 1268, 1201, 1016, 941, 790, 764; ¹H NMR (400 MHz, CD₃Cl) 2.48 (s, 3H), 3.03 (s, 4H), 7.05–7.10 (m, 1H), 7.15–7.32 (m, 6H), 7.74 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 8.61 (s, 1H); ¹³C NMR (100 MHz, CD₃Cl); 12.5 (CH₃), 26.1 (CH₂), 32.7 (CH₂), 117.0 (C), 120.8 (2× CH), 123.6 (CH), 125.9 (CH), 128.5 (2× CH), 128.8 (CH), 129.0 (2× CH), 129.9 (2× CH), 131.3 (CH), 134.5 (C), 135.5 (C), 137.5 (CH), 139.1 (C), 145.0 (C), 151.0 (C), 162.5 (C), 187.0 (C); HRMS (ESI, *m/z*): calcd for C₂₄H₁₉N₃O₂Na [M + Na]⁺ 388.1426 found 388.1700.

(E)-3-Methyl-6-(4-methylbenzylidene)-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[3,4-*b*]quinolin-5-one (6g). Yield: 61% (231.4 mg); white solid; mp 178–180 °C; IR (KBr, cm⁻¹): 3045, 2952, 2923, 1658, 1589, 1418, 1265, 1172, 1016, 813, 753; ¹H NMR (400 MHz, CD₃Cl); 2.40 (s, 3H), 2.66 (s, 3H), 3.23 (s, 4H), 7.23–7.30 (m, 3H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.48–7.50 (m, 2H), 7.92 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 2H), 8.80 (s, 1H); ¹³C NMR (100 MHz, CD₃Cl); 12.5 (CH₃), 21.4 (CH₃), 26.2 (CH₂), 32.7 (CH₂), 117.0 (C), 120.8 (2× CH), 123.7 (C), 125.9 (CH), 129.0 (2× CH), 129.2 (2× CH), 130.0 (2× CH), 131.2 (CH), 132.6 (C), 133.7 (C), 137.6 (CH), 139.1 (C), 139.1 (C), 145.0 (C), 151.0 (C), 162.5 (C), 187.1 (C); HRMS (ESI, *m/z*): calcd for C₂₅H₂₂N₃O [M + H]⁺ 380.1763 found 380.1763.

(E)-6-((Furan-2-yl)methylene)-7,8-dihydro-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]quinolin-5(6H)-one (6h). Yield: 83% (294.9 mg); beige solid; mp 180–182 °C; IR (KBr, cm⁻¹): 3140, 3123, 3053, 2955, 2897, 2842, 1742, 1658, 1664, 1609, 1545, 1499, 1317, 1265, 1198, 1068, 961, 880; ¹H NMR (400 MHz, CD₃Cl) 2.65 (s, 3H), 3.30 (t, *J* = 6.0 Hz, 2H) 3.40–3.44 (m, 2H), 6.53 (s, 1H), 6.74 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.59 (s, 1H), 7.64 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 2H), 8.78 (s, 1H); ¹³C NMR (100 MHz, CD₃Cl); 12.5 (CH₃), 25.6 (CH₂), 32.3 (CH₂), 112.3 (CH), 116.9 (C), 117.2 (CH), 120.9 (2× CH), 123.4 (CH),



123.8 (C), 125.9 (CH), 129.0 (2× CH), 130.7 (C), 131.2 (CH), 139.1 (C), 144.7 (CH), 145.0 (C), 150.9 (C), 152.2 (C), 162.8 (C), 186.7 (C); HRMS (ESI, m/z): calcd for $C_{22}H_{17}N_3O_2Na$ $[M + Na]^+$ 378.1218 found 378.0209.

(E)-6-(3,5-Dimethoxybenzylidene)-3-methyl-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[3,4-*b*]quinolin-5-one (6i). Yield: 90% (382.9 mg); yellow solid; mp 179–181 °C; IR (KBr, cm^{-1}): 3004, 2935, 2833, 1653, 1598, 1519, 1421, 1328, 1253, 1143, 1022, 764; 1H NMR (400 MHz, CD_3Cl) 2.90 (s, 3H), 3.50 (s, 4H) 4.17 (s, 6H) 7.16 (d, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.52 (m, 1H), 7.74 (t, $J = 8.0$ Hz, 2H), 8.13 (s, 1H), 8.53 (d, $J = 8.0$ Hz, 2H), 9.04 (m, 1H); ^{13}C NMR (100 MHz, CD_3Cl) 12.4 (CH₃), 26.2 (CH₂), 32.6 (CH₂), 55.9 (CH₃), 110.9 (CH), 113.3 (CH), 116.9 (C), 120.8 (2× CH), 123.4 (CH), 123.7 (C), 125.8 (CH), 128.3 (C), 128.9 (2× CH), 131.1 (CH), 132.7 (C), 137.7 (CH), 139.1 (C), 145.0 (C), 148.7 (C), 149.8 (C), 150.9 (C), 162.4 (C), 186.9 (C); HRMS (ESI, m/z): calcd for $C_{26}H_{24}N_3O_3$ $[M + H]^+$ 426.1818 found 426.1818.

(E)-3-Methyl-1-phenyl-6-(3,4,5-trimethoxybenzylidene)-1,6,7,8-tetrahydro-5H-pyrazolo[3,4-*b*]quinolin-5-one (6j). Yield: 92% (419.1 mg); yellow solid; mp 177–179 °C; IR (KBr, cm^{-1}): 2935, 2836, 2593, 1661, 1598, 1505, 1323, 1259, 1123, 1007, 834, 747; 1H NMR (400 MHz, CD_3Cl) 2.60 (s, 3H), 3.20 (s, 4H) 3.83 (s, 9H) 6.64 (s, 2H), 7.22 (m, 1H), 7.44 (t, $J = 7.5$ Hz, 2H), 7.81 (s, 1H), 8.23 (d, $J = 8.0$ Hz, 2H), 8.74 (s, 1H); ^{13}C NMR (100 MHz, CD_3Cl) 12.4 (CH₃), 26.2 (CH₂), 32.7 (CH₂) 56.2 (CH₃), 60.9 (CH₃), 107.4 (2× CH), 117.0 (C), 120.8 (2× CH), 123.6 (C), 125.9 (CH), 129.0 (2× CH), 130.9 (C), 131.2 (CH), 133.8 (C), 137.7 (CH), 138.9 (C), 139.0 (C), 145.0 (C), 151.0 (C), 153.1 (C), 162.4 (C), 186.9 (C); (ESI, m/z): calcd for $C_{27}H_{25}N_3O_4K$ $[M + K]^+$ 494.1482 found 494.1456.

(E)-3-Methyl-1-phenyl-6-(4-(prop-2-yn-1-yloxy)benzylidene)-1,6,7,8-tetrahydro-5H-pyrazolo[3,4-*b*]quinolin-5-one (6k). Yield: 72% (302.0 mg); white solid; mp 176–178 °C; IR (KBr, cm^{-1}): 3288, 3241, 2932, 1658, 1505, 1412, 1276, 1218, 1178, 1019, 842, 764; 1H NMR (400 MHz, CD_3Cl) 2.25 (s, 1H), 2.67 (s, 3H), 3.24 (s, 4H) 4.73 (s, 2H) 7.04 (d, $J = 8.0$ Hz, 2H), 7.28 (t, $J = 7.3$ Hz, 1H), 7.52 (m, 4H), 7.90 (s, 1H), 8.29 (d, $J = 8.0$ Hz, 2H), 8.80 (m, 1H); ^{13}C NMR (100 MHz, CD_3Cl) 12.5 (CH₃), 26.2 (CH₂), 32.7 (CH₂), 55.8 (CH₂), 75.9 (CH), 78.1 (C), 114.9 (2× CH), 117.0 (C), 120.9 (2× CH), 123.8 (C), 125.9 (CH), 128.9 (C), 129.0 (2× CH), 131.2 (2× CH), 131.8 (CH), 132.9 (C), 137.2 (CH), 139.1 (C), 145.0 (C), 151.0 (C), 158.0 (C), 162.5 (C), 187.0 (C); (ESI, m/z): calcd for $C_{27}H_{21}N_3O_2K$ $[M + K]^+$ 458.1271 found 458.1261.

tert-Butyl-(E)-4-((3-methyl-5-oxo-1-phenyl-1,5,7,8-tetrahydro-6H-pyrazolo[3,4-*b*]quinolin-6-ylidene)methyl)phenyl)piperazine-1-carboxylate (6l). Yield: 67% (326.5 mg); brown solid; mp 108–110 °C; IR (KBr, cm^{-1}): 3065, 2958, 2877, 1681, 1592, 1517, 1421, 1265, 1175, 1106, 906, 750; 1H NMR (400 MHz, CD_3Cl) 1.44 (s, 9H), 2.16 (m, 2H), 2.58 (s, 3H), 2.68 (t, $J = 6.0$ Hz, 2H), 7.19 (m, 6H), 3.54 (bs, 2H), 6.87 (d, $J = 8.0$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.45 (t, $J = 8.0$ Hz, 3H), 8.23 (m, 3H), 8.66 (s, 1H); ^{13}C NMR (100 MHz, CD_3Cl) 12.5 (CH₃), 21.9 (CH₂), 26.3 (CH₂), 28.4 (CH₃), 32.7 (CH₂), 33.7 (CH₂), 38.8 (CH₂), 48.0 (CH₂), 80.0 (C), 115.1 (CH), 116.7 (C), 120.8 (2× CH), 123.0 (C), 124.0 (C), 125.8 (CH), 125.9 (CH), 126.5 (C), 129.0 (2× CH), 130.4 (CH), 131.1 (CH), 131.6 (C), 131.9 (CH), 137.9 (CH), 139.2 (C), 145.1 (C), 151.2 (C), 154.6 (C), 163.8 (C), 187.0 (C); HRMS (ESI, m/z): calcd for $C_{33}H_{36}N_5O_3$ $[M + H]^+$ 550.2818 found 550.2818.

(E)-6-((5-(4-Chlorophenyl)furan-2-yl)methylene)-3-methyl-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[3,4-*b*]quinolin-5-one (6m). Yield: 98% (456.6 mg); yellow solid; mp 170–172 °C; IR (KBr, cm^{-1}): 3065, 2949, 1664, 1589, 1421, 1320, 1239, 1201, 1091, 1036, 912, 787; 1H NMR (400 MHz, CD_3Cl) 2.65 (s, 3H), 3.35 (t, $J = 6.1$ Hz, 2H), 3.46 (m, 2H) 6.77 (s, 1H), 6.82 (s, 1H), 7.28 (t, $J = 7.2$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 2H), 7.50 (t, $J = 7.3$ Hz, 2H), 7.63 (d, $J = 8.0$ Hz, 3H), 8.30 (d, $J = 8.0$ Hz, 2H), 8.77 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.5 (CH₃), 25.8 (CH₂), 108.3 (CH), 117.0 (C), 119.8 (CH), 120.9 (2× CH), 123.1 (CH), 123.8 (C), 125.4 (2× CH), 125.9 (CH), 128.3 (C), 129.0 (2× CH), 129.1 (2× CH), 130.6 (C), 131.1 (CH), 134.2 (C), 139.2 (C), 145.0 (C), 151.0 (C), 152.0 (C), 155.0 (C), 162.7 (C), 186.4 (C); HRMS (ESI, m/z): calcd for $C_{28}H_{20}ClN_3O_2$ $[M]^+$ 465.1244 found 465.1226.

(E)-3-Methyl-1-phenyl-6-(quinolin-3-ylmethylene)-1,6,7,8-tetrahydro-5H-pyrazolo[3,4-*b*]quinolin-5-one (6n). Yield: 87% (362.3 mg); yellow solid; mp 211–213 °C; IR (KBr, cm^{-1}): 3053, 2961, 2917, 1667, 1600, 1514, 1253, 1114, 1022, 747; 1H NMR (400 MHz, CD_3Cl) 2.68 (s, 3H), 3.30 (s, 4H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 2H), 7.59 (t, $J = 8.0$ Hz, 1H), 7.76 (t, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 8.04 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 8.21 (s, 1H), 8.28 (d, $J = 8.0$ Hz, 2H), 8.84 (s, 1H), 9.01 (s, 1H); ^{13}C NMR (100 MHz, CD_3Cl) 12.8 (CH₃), 26.7 (CH₂), 32.9 (CH₂), 117.4 (C), 121.2 (2× CH), 123.7 (C), 126.3 (CH), 127.6 (CH), 127.7 (C), 128.4 (CH), 129.0 (C), 129.3 (2× CH), 129.6 (CH), 130.7 (CH), 131.8 (CH), 133.9 (CH), 136.8 (CH), 136.9 (C), 139.3 (C), 145.4 (C), 147.8 (C), 151.4 (C), 151.6 (CH), 162.6 (C), 186.8 (C); HRMS (ESI, m/z): calcd for $C_{27}H_{20}N_4OK$ $[M + K]^+$ 455.1274 found 455.1271.

(E)-3-(Benzo[*d*][1,3]dioxol-5-yl)-1-(3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)prop-2-en-1-one (6o). Yield: 63% (250.3 mg); yellow solid; mp 186–188 °C; IR (KBr, cm^{-1}): 3082, 2990, 2894, 2787, 1655, 1589, 1577, 1444, 1308, 1184, 1033, 984, 754; 1H NMR ($CDCl_3$, 400 MHz) δ_H : 2.63 (s, 3H), 2.81 (s, 3H), 6.01 (s, 2H), 6.82 (d, $J = 8.0$ Hz, 1H), 7.12–7.04 (m, 3H), 7.28 (t, $J = 7.4$ Hz, 1H), 7.52–7.45 (m, 3H), 8.16 (s, 1H), 8.32 (d, $J = 7.5$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C : 12.4 (CH₃), 24.7 (CH₃), 101.6 (CH₂), 106.5 (CH), 108.5 (CH), 114.2 (C), 120.6 (2× CH), 123.9 (CH), 125.3 (CH), 125.5 (CH), 128.7 (C), 128.7 (C), 128.9 (2× CH), 129.8 (CH), 139.2 (C), 143.3 (C), 145.7 (CH), 148.4 (C), 150.1 (C), 150.1 (C), 158.0 (C), 193.8 (C); HRMS (ESI, m/z): calcd for $C_{24}H_{19}N_3O_3Na$ $[M + Na]^+$ 420.1324 found 420.0670.

(E)-1-(3,6-Dimethyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-3-(4-morpholinophenyl)prop-2-en-1-one (6p). Yield: 82% (359.6 mg); yellow solid; mp 230–232 °C; IR (KBr, cm^{-1}): 3069, 2961, 2921, 2892, 2849, 1953, 1885, 1737, 1668, 1600, 1508, 1380, 1303, 1180, 1123, 923, 761; 1H NMR ($CDCl_3$, 400 MHz) δ_H : 2.65 (s, 3H), 2.81 (s, 3H, CH₃), 3.27 (t, $J = 4.6$ Hz, 4H), 3.86 (t, $J = 4.5$ Hz, 4H), 6.89 (d, $J = 8.3$ Hz, 2H), 7.07 (d, $J = 15.9$ Hz, 1H), 7.29 (t, $J = 7.4$ Hz, 1H), 7.46 (d, $J = 16.1$ Hz, 1H), 7.53–7.50 (m, 4H), 8.15 (s, 1H), 8.33 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C : 12.5 (CH₃), 24.6 (CH₃), 47.8 (2× CH₂), 66.5 (2× CH₂), 114.2 (C), 114.5 (2× CH), 120.7 (2× CH), 122.9 (CH), 125.0 (C), 125.6 (CH), 129.0 (2× CH), 129.3 (C), 129.7 (CH), 130.2 (2× CH), 139.4 (C), 143.3 (C), 146.5 (CH), 150.2 (C), 152.9 (C), 157.8 (C),



194.7 (C); HRMS (ESI, m/z): calcd for $C_{27}H_{26}N_4O_2Na$ $[M + Na]^+$ 461.1953 found 461.8987.

(E)-1-(3,6-Dimethyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-3-(1-methyl-1H-imidazol-2-yl)prop-2-en-1-one (6q). Yield: 93% (332.4 mg); yellow solid; mp 150–152 °C; IR (KBr, cm^{-1}): 3107, 2955, 2923, 2847, 1685, 1602, 1555, 1504, 1376, 1300, 1241, 1175, 1124, 1033, 972, 830, 756; 1H NMR ($CDCl_3$, 400 MHz) δ_H : 2.86 (s, 3H), 3.12 (s, 3H), 4.02 (s, 3H), 7.51–7.43 (m, 3H), 7.72 (t, $J = 7.5$ Hz, 2H), 7.85 (d, $J = 15.1$ Hz, 1H), 8.05 (d, $J = 15.1$ Hz, 1H), 8.51 (d, $J = 8.0$ Hz, 2H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C : 12.5 (CH₃), 25.5 (CH₃), 33.0 (CH₃), 114.4 (C), 120.8 (2× CH), 124.13 (CH), 125.7 (CH), 125.9 (CH), 127.7 (CH), 128.0 (C), 128.9 (2× CH), 130.6 (CH), 131.1 (CH), 139.2 (C), 143.5 (C), 143.9 (C), 150.2 (C), 159.4 (C), 191.3 (C); HRMS (ESI, m/z): calcd for $C_{21}H_{19}N_5OK$ $[M + K]^+$ 396.1227 found 396.9227.

(E)-1-(3,6-Dimethyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (6r). Yield: 72% (276.1 mg); yellow solid; mp 134–136 °C; IR (KBr, cm^{-1}): 3163, 3069, 3001, 2915, 2841, 1962, 1805, 1739, 1654, 1503, 1420, 1300, 1251, 1169, 1029, 983, 820, 758; 1H NMR ($CDCl_3$, 400 MHz) δ_H : 2.64 (s, 3H), 2.82 (s, 3H), 3.83 (s, 3H), 6.92 (d, $J = 8.8$ Hz, 2H), 7.10 (d, $J = 15.8$ Hz, 1H), 7.28 (t, $J = 7.5$ Hz, 1H), 7.55–7.48 (m, 5H), 8.16 (s, 1H), 8.32 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C : 12.8 (CH₃), 25.0 (CH₃), 55.6 (CH₃), 114.5 (C), 114.7 (2× CH), 121.0 (2× CH), 124.2 (CH), 125.9 (CH), 127.3 (C), 129.2 (2× CH), 130.1 (CH), 130.6 (2× CH), 139.6 (C), 143.7 (C), 146.3 (CH), 150.5 (C), 158.2 (C), 162.2 (C), 194.6 (C); HRMS (ESI, m/z): calcd for $C_{24}H_{21}N_3O_2Na$ $[M + Na]^+$ 406.1531 found 406.1426.

(E)-1-(3,6-Dimethyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (6s). Yield: 91% (403.6 mg); yellow solid; mp 180–182 °C; IR (KBr, cm^{-1}): 3062, 2998, 2929, 2836, 1954, 1875, 1760, 1681, 1595, 1508, 1418, 1300, 1239, 1120, 1004, 822, 755; 1H NMR ($CDCl_3$, 400 MHz) δ_H : 3.09 (s, 3H), 3.25 (s, 3H), 4.34 (s, 9H), 7.55 (d, $J = 15.9$ Hz, 1H), 7.73 (t, $J = 7.3$ Hz, 1H), 7.85 (d, $J = 15.9$ Hz, 1H), 7.98–7.92 (m, 4H), 8.60 (s, 1H), 8.76 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C : 12.5 (CH₃), 24.7 (CH₃), 56.2 (2× CH₃), 61.0 (CH₃), 105.7 (2× CH), 114.3 (C), 120.8 (2× CH), 125.7 (CH), 125.8 (CH), 128.8 (C), 129.0 (2× CH), 129.7 (C), 129.9 (CH), 139.3 (C), 140.8 (C), 143.4 (C), 146.5 (CH), 150.3 (C), 153.5 (2× C), 157.8 (C), 194.7 (C); HRMS (ESI, m/z): calcd for $C_{26}H_{25}N_3O_4Na$ $[M + Na]^+$ 466.1743 found 465.9858.

(E)-1-(3,6-Dimethyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-3-(quinolin-3-yl)prop-2-en-1-one (6t). Yield: 87% (351.9 mg); brown solid; mp 195–197 °C; IR (KBr, cm^{-1}): 3058, 2918, 2850, 1874, 1793, 1737, 1602, 1511, 1384, 1251, 1126, 1031, 979, 906, 866, 756; 1H NMR ($CDCl_3$, 400 MHz) δ_H : 2.66 (s, 3H), 2.87 (s, 3H), 7.29 (t, $J = 7.4$ Hz, 1H), 7.53–7.46 (m, 3H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.79–7.73 (m, 2H), 7.86 (d, $J = 8.3$ Hz, 1H), 8.12 (d, $J = 8.5$ Hz, 1H), 8.33–8.27 (m, 4H), 9.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C : 12.6 (CH₃), 25.0 (CH₃), 114.3 (C), 120.8 (2× CH), 125.8 (CH), 127.30 (C), 127.4 (C), 127.6 (CH), 128.2 (CH), 128.4 (C), 129.0 (2× CH), 129.5 (CH), 130.4 (CH), 130.9 (2× CH), 136.2 (CH), 139.2 (C), 142.2 (CH), 143.6 (C), 148.8 (C), 149.3 (CH), 150.3 (C), 158.5 (C), 193.1 (C); HRMS (ESI, m/z): calcd for $C_{26}H_{21}N_4O$ $[M + H]^+$ 405.1715 found 405.0341.

(E)-1-(3,6-Dimethyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-3-(5-(4-nitrophenyl)furan-2-yl)prop-2-en-1-one (6u). Yield: 90% (418.0 mg); yellow solid; mp > 300 °C; IR (KBr, cm^{-1}): 2982, 2929, 1729, 1684, 1592. 1H NMR ($CDCl_3$, 400 MHz) δ_H : 2.67 (s, 3H, CH₃), 2.86 (s, 3H), 6.87 (d, $J = 3.4$ Hz, 1H), 6.99 (d, $J = 3.4$ Hz, 1H), 7.32–7.26 (m, 2H), 7.41 (d, $J = 15.6$ Hz, 1H), 7.52 (t, $J = 7.5$ Hz, 2H), 7.88 (d, $J = 8.8$ Hz, 2H), 8.34–8.25 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C : 12.5 (CH₃), 24.9 (CH₃), 111.6 (CH), 114.3 (C), 118.8 (CH), 120.7 (2× CH), 124.4 (2× CH), 124.7 (2× CH), 125.7 (CH), 125.8 (CH), 128.5 (C), 129.0 (2× CH), 130.1 (CH), 130.7 (CH), 135.1 (CH), 139.2 (C), 143.5 (C), 147.1 (C), 150.3 (C), 152.3 (C), 153.9 (C), 158.2 (C), 193.0 (C); HRMS (ESI, m/z): calcd for $C_{27}H_{21}N_4O_4$ $[M + H]^+$ 465.1563 found 465.1836.

(E)-1-(3,6-Dimethyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-3-(4-nitrophenyl)prop-2-en-1-one (6v). Yield: 75% (298.8 mg); orange solid; mp > 300 °C; IR (KBr, cm^{-1}): 3063, 2983, 1725, 1626, 1586; 1H NMR ($CDCl_3$, 400 MHz) δ_H : 2.66 (s, 3H), 2.86 (s, 3H), 7.30 (t, $J = 7.3$ Hz, 1H), 7.38 (d, $J = 15.8$ Hz, 1H), 7.52 (t, $J = 7.7$ Hz, 2H), 7.64 (d, $J = 15.8$ Hz, 1H), 7.76 (d, $J = 8.3$ Hz, 2H), 8.32–8.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C : 12.5 (CH₃), 25.1 (CH₃), 114.3 (C), 120.8 (CH × 2), 124.2 (CH × 2), 125.9 (CH), 127.8 (C), 129.0 (2× CH), 129.1 (2× CH), 129.2 (CH), 130.5 (CH), 139.2 (C), 140.5 (C), 142.2 (CH), 143.6 (C), 148.7 (C), 150.3 (C), 158.6 (C), 192.6 (C). Calcd for $C_{23}H_{18}N_4O_3K$ $[M + K]^+$ 437.1016 found 437.1286.

Conclusions

In summary, we developed an efficient three-component reaction of 3-methyl-1-phenyl-1H-pyrazolo-5-amine, para-formaldehyde and β -diketones under MWI in aqueous media catalyzed by $InCl_3$. Compared with previous methods, this new protocol has the advantages of simple operation, higher yields, low cost and is an environmentally benign procedure. Synthetic versatility showed for carbonyl group allows generating great structural variety, which facilitates the obtaining of a greater number of compounds with biological activity on different therapeutic targets depending on the group that originates. In the preparation of chalcones employment of sonication reduced times reaction from hours to minutes. These new compounds present a privileged core from a biological point of view.

Conflicts of interest

There are no conflicts to declare.

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