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Copper triflate-mediated synthesis of 1,3,5-triarylpyrazoles in [bmim][PF₆] ionic liquid and evaluation of their anticancer activities

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Abstract

A simple, efficient, and environment friendly protocol for the synthesis of 1,3,5-triarylpyrazole and 1,3,5-triarylpyrazolines in [bimm][PF₆] ionic liquid mediated by Cu(OTf)₂ is described. The reaction protocol gave 1,3,5-triarylpyrazoles in good to high yields (71-84%) *via* a one-pot addition–cyclocondensation between chalcones and arylhydrazines, and oxidative aromatization without requirement for an additional oxidizing reagent. The catalyst can be reused up to four cycles without much loss in the catalytic activity. The pyrazoles (**4a-o**) and pyrazolines (**3a-n**) were evaluated for antiproliferative activity in SK-OV-3, HT-29, and HeLa human cancer cell lines. Among all compounds, **3b** inhibited cell proliferation of HeLa cells by 80% at a concentration of 50 μM.

Introduction

Pyrazoles and their derivatives are well recognized as an important class of heterocyclic compounds that have found extensive use in the pharmaceutical, material, and agrochemical industries.¹ Compounds containing pyrazole moiety have exhibited diverse biological activities. For example, 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylate derivatives can act as cannabinoid-1 (CB1) receptor antagonists,²⁻⁷ I kinase (IKK or IKK-2) inhibitors,⁸ and anti-inflammatory agents.⁹ Pyrazole derivatives have been shown to have good binding affinity towards estrogen receptor.¹⁰⁻¹² Some of the pyrazole derivatives have been reported to possess anti-depressant, anti-convulsant,¹³ anti-inflammatory, and anti-arthritis¹⁴ activities. Pyrazole scaffold constitutes the basic framework of several drug molecules such as celecoxib (a non-steroidal anti-inflammatory drug)¹⁴ and rimonabant (an anorectic antiobesity drug) (Figure 1). Pyrazoles have received considerable attention of chemists because of their diverse bioactivities. Thus, a number of synthetic strategies have been developed for their synthesis.^{15, 16} The most common approach for the synthesis of substituted pyrazoles is the condensation of α,β-unsaturated carbonyl compounds with hydrazines. However, this strategy results in the formation of 4,5-dihydro-1*H*-pyrazoles (pyrazolines) that need to be further oxidized to corresponding pyrazoles. For this oxidative

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aromatization of pyrazolines to pyrazoles, various reagents have been employed such as I₂,¹⁷ Bi(NO₃)₃·5H₂O,¹⁸ MnO₂,¹⁹ DDQ,²⁰ Pd/C,²¹ NaOEt,²² PhI(OAc)₂,²³ TBBDA,²⁴ and ionic liquid.^{25, 26} However, many of these oxidative methods suffer from relatively high oxidant loading, use of strong oxidants and chlorinated organic solvents, harsh conditions, poor yields, and longer reaction time. Thus, development of environmentally benign process with the use of alternative solvents such as ionic liquids in place of organic solvent and a catalytic amount of ecofriendly catalyst that avoid harsh oxidizing reagents is highly desirable.

As part of our ongoing work on the development of novel reaction methodologies using metal triflates,²⁷⁻²⁹ and evaluation of small molecules as anticancer agents,²⁹⁻³² herein we report copper triflate-mediated protocol for the synthesis of pyrazoles by reaction of hydrazines with α,β -unsaturated ketones in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF₆]) ionic liquid (Scheme 1) and evaluation of their anti-proliferative activity against different cancer cell lines.

Results and discussion

In the standardization experiment, when 1,2-diphenylprop-2-en-1-one (**1**) and 4-*tert*-butylphenylhydrazine hydrochloride (**2**) were reacted in ethanol under reflux in the presence of Cu(OTf)₂ (20 mole%), 1-(4-*tert*-butylphenyl)-3,5-diphenyl-4,5-dihydro-1H-pyrazole (**3a**) was obtained in 62% yield (Table 1, entry 8). Further optimization of reaction conditions was carried out by changing solvents, catalysts, and catalyst loading. As shown in Table 1, the use of 20 mol% Cu(OTf)₂ in [bmim][PF₆] gave the desired product **4a** in excellent yield (82%) (Table 1, entry 2). When Cu(OTf)₂ was replaced with other catalysts such as *p*TSA, Sc(OTf)₃, Ce(OTf)₃, Zn(OTf)₂, AgOTf, or Yb(OTf)₃, a mixture of **3a** and **4a** was observed. Use of Ce(OTf)₃ in [bmim][PF₆] resulted in 75% yield of **3a** along with 10% of **4a** whereas use of *p*TSA in [bmim][PF₆] gave 69% of **3a** (Table 1, entry 11-12). There was not much increase in yield of **4a** on changing the amount of Cu(OTf)₂ from 20 mol% to 30 mol%. However, reducing the amount of Cu(OTf)₂ to 10 mol% decreased the yield of **4a** to 64% along with the formation of **3a** in 15% (Table 1, entries 1-3). These data indicate that Cu(OTf)₂ was involved in aerobic oxidation of **3a** to **4a**. It is necessary to mention that **4a** was not formed in the absence of Cu(OTf)₂ in [bmim][PF₆] ionic liquids, and only **3a** was isolated in 20% yield along with starting material and yield of **3a** did not increase with increasing time upto 2h.

The structure of **4a** was confirmed by ¹H NMR, ¹³C NMR, and high-resolution mass spectrometry. In the ¹H NMR spectra, a singlet was observed at δ 6.81 for the proton at C₄-position of pyrazole ring along with other protons on aryl substituents. In the ¹³C NMR, a peak appeared at δ 104.97 for the C₄-carbon of pyrazole ring. Presence of peak at m/z 355.2173 for [M + H]⁺ ion with molecular formula C₂₅H₂₇N₂⁺ confirmed the structure of **4a**. To explore the synthetic scope and versatility of the protocol, a series of arylhydrazines (**2**) were reacted with different α,β -carbonyl compounds (**1**) under the optimal reaction conditions. The results are summarized in Table 2. Various functional groups, such as F, Cl, NO₂, OCH₃, CH₃ and -C(CH₃)₃ on arylhydrazines and chalcones were well tolerated under these conditions affording corresponding 1,3,5-substituted pyrazoles (**4a-o**) in good to high yields (71–84%).

By monitoring the model reaction between 1,2-diphenylprop-2-en-1-one (**1**) and *tert*-butylphenylhydrazine hydrochloride (**2**) in the presence of 20 mol% Cu(OTf)₂ in [bmim][PF₆] at different time interval it was found that in first 30 minutes pyrazoline (**3a**) was the major product, which got oxidized to pyrazole in the reaction as time progresses. We thus decided to synthesize the pyrazolines using this protocol in order to evaluate them in our

biological assay. The reaction of **1** and **2** afforded 1,3,5-triarylpyrazolines (**3a–o**) *via* a one-pot addition–cyclocondensation process in good to high yields (60–84%). Several , -unsaturated carbonyl compounds with both electron-rich and electron-deficient arenes were successfully applied to this reaction. The results of pyrazoline synthesis are summarized in Table 3. The chemical structures of all synthesized compounds were elucidated by ¹H NMR and ¹³C NMR spectroscopic data (Supporting information).

Based on the intermediate formed as pyrazoline **3a** and structure of the product **4a**, the reaction is proposed to proceed through the sequential steps as shown in Scheme 2. The first step is believed to be 1,2-addition of hydrazine to chalcone mediated by Cu(OTf)₂. The 3-hydroxypyrazoline (**C**) undergoes elimination in the presence of Cu(OTf)₂ to give 1,3,5-triarylpyrazoline derivative (**3**). Oxidative aromatization of **3** in the presence of Cu(OTf)₂ yields corresponding 1,3,5-triarylpyrazole (**4**). We did not observe formation of **4a**, when isolated **3a** was treated with Cu(OTf)₂ under nitrogen atmosphere. This further confirms that **3a** is converted to **4a** *via* oxidation with atmospheric oxygen in presence of Cu(OTf)₂. It appeared that ionic liquid helps in stabilization of charged intermediate generated by coordination of Cu(OTf)₂ to carbonyl of chalcone and thereby increases electrophilicity of chalcone.

Further, we investigated the possibility of recycling of the catalyst. After performing the first cycle, the product was extracted with ethyl acetate/hexane mixture, and Cu(OTf)₂ in ionic liquid was properly dried under vacuum. Furthermore, the fresh chalcone and 4-tert-butyl phenylhydrazine hydrochloride were added to recovered ionic liquid containing Cu(OTf)₂ and the reaction was carried out under same conditions. The above procedure was repeated four times to give **4a** in high yields (82, 80, 78, and 79%) without much loss of catalytic activity (Table 2, footnote b).

To evaluate the anti-cancer activity of synthesized compounds, all derivatives (**4a–o** and **3a–n**) were evaluated for their inhibitory activity on the proliferation of human ovarian adenocarcinoma (SK-OV-3), human colon adenocarcinoma (HT-29), and human cervical adenocarcinoma (HeLa) cells. Doxorubicin (Dox) and DMSO were used as positive and negative controls, respectively. The antiproliferative activity results of compounds **4a–o** and **3a–n** at 50 μM after 72 h incubation are shown in Figures 2 and 3, respectively. Figure 2 shows that among all 1,3,5-triarylpyrazoles derivatives (**4a–o**), **4c**, **4e**, **4f**, **4g**, **4h**, **4i**, and **4k** inhibit the proliferation of HeLa cells by 50%, 55%, 45%, 39%, 54%, 42%, and 50%, respectively. However, they did not exhibit significant inhibitory potency in HT-29 and SK-OV-3 cells. 1,3,5-Triarylpyrazolines derivatives (**3a–n**) showed high to weak antiproliferative activity against HeLa cells after 72 h incubation. Compounds **3c**, **3d**, **3e**, **3k**, **3l**, and **3m** inhibited the proliferation of HeLa cells by 62%, 50%, 35%, 58%, 23%, and 40%, respectively. 2-Methylsubstituted compound **3b** showed the highest potency by 80% inhibition of HeLa cells. They showed modest to weak potency in SK-OV-3 and HT-29 cells. Among all derivatives, compound **3b** showed comparable potency to doxorubicin (10 μmol) in HeLa cells. Further modification on the chemical structure of this derivative could lead to the synthesis of a promising candidate that selectively target HeLa cells.

Experimental

General

All chemicals were obtained from commercial suppliers and used without further purification. Melting points were determined in open capillary tubes on a MPA120-Automated Melting Point apparatus and are uncorrected. NMR spectra were recorded on a Bruker (300 MHz) NMR spectrometer using CDCl₃ as solvent and the chemical shifts were expressed in ppm. Metal triflates were purchased from Sigma-Aldrich and used as received.

All other reagents and solvents were purchased from Merck (India), Spectrochem Chemicals, S. D. Fine Chemicals, India and used without further purification unless otherwise specified. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). The α,β -unsaturated ketones (chalcones) **1** were prepared by the treatment of an appropriate acetophenone with benzaldehydes in presence of sodium hydroxide as reported in literature³³

Experimental procedure for synthesis of **3** and **4**

Chalcone (1.0 mmol), arylhydrazine hydrochloride (1.2 mmol), Cu(OTf)₂ (0.2 mmol, 20 mol%) were added to a 10 mL round bottom flask containing [bmim][PF₆] ionic liquid (2 mL). The reaction mixture was heated at 130 °C with stirring for 30 min (for **3**) or 1-2.5 h (for **4**). After completion of reaction as indicated by TLC, the reaction mixture was extracted with ethyl acetate-hexane mixture and the solvent was removed under vacuum. The crude compound was purified by passing through a bed of silica gel (100-200 mesh) to give pure **3** or **4**.

1-(4-tert-Butylphenyl)-4,5-dihydro-3,5-diphenyl-1H-pyrazole (3a)—Pale green solid, m.p. 148-150 °C; ¹H NMR (300 MHz, CDCl₃) 7.71 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.29 (m, 8H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 5.19 (dd, *J* = 12.2, 8.0 Hz, 1H), 3.80 (dd, *J* = 17.0, 12.4 Hz, 1H), 3.11 (dd, *J* = 17.0, 8.0 Hz, 1H), 1.25 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) 146.30, 142.97, 142.90, 141.92, 132.88, 129.14, 128.53, 128.46, 127.54, 126.00, 125.71, 124.81, 113.14, 65.06, 43.70, 33.96, 31.48; HRMS (ESI) calcd for C₂₅H₂₇N₂⁺ 355.2169, found 355.2176 [M + H]⁺.

4,5-Dihydro-3,5-diphenyl-1-o-tolyl-1H-pyrazole (3b)—Brown liquid; ¹H NMR (300 MHz, CDCl₃) 7.70 (d, *J* = 7.3 Hz, 2H), 7.41 – 7.30 (m, 5H), 7.29 – 7.19 (m, 3H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.05 – 6.85 (m, 3H), 5.26 (t, *J* = 10.8 Hz, 1H), 3.69 (dd, *J* = 16.5, 11.1 Hz, 1H), 3.19 (dd, *J* = 16.4, 10.5 Hz, 1H), 2.43 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 148.13, 144.28, 141.00, 132.99, 131.47, 131.25, 128.69, 128.55, 127.66, 126.93, 126.01, 125.65, 123.28, 119.27, 67.66, 42.67, 20.46; HRMS (ESI) calcd for C₂₂H₂₀N₂Na⁺ 335.1519, found 335.1532 [M + Na]⁺.

1-(3,4-Dichlorophenyl)-4,5-dihydro-3,5-diphenyl-1H-pyrazole (3c)—Pale yellow solid, m.p. 133-134 °C; ¹H NMR (300 MHz, CDCl₃) 7.71 (d, *J* = 7.4 Hz, 2H), 7.42 – 7.31 (m, 5H), 7.30 – 7.23 (m, 4H), 7.14 (d, *J* = 8.9 Hz, 1H), 6.73 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.22 (dd, *J* = 12.2, 6.7 Hz, 1H), 3.85 (dd, *J* = 17.3, 12.3 Hz, 1H), 3.16 (dd, *J* = 17.3, 6.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) 148.22, 144.02, 141.52, 132.65, 132.15, 130.30, 129.35, 129.15, 128.65, 127.98, 125.95, 125.75, 121.59, 114.94, 112.47, 64.18, 43.78; HRMS (ESI) calcd for C₂₁H₁₇Cl₂N₂⁺ 367.0763, found 367.0782 [M + H]⁺.

1-(3-Chloro-4-methylphenyl)-4,5-dihydro-3,5-diphenyl-1H-pyrazole (3d)—Pale yellow solid, m.p. 121-122 °C; ¹H NMR (300 MHz, CDCl₃) 7.71 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.27 (m, 8H), 7.21 (d, *J* = 2.1 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.20 (dd, *J* = 12.3, 7.2 Hz, 1H), 3.82 (dd, *J* = 17.1, 12.3 Hz, 1H), 3.12 (dd, *J* = 17.1, 7.2 Hz, 1H), 2.23 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 147.15, 143.90, 142.17, 134.68, 132.52, 130.92, 129.22, 128.77, 128.58, 127.73, 125.93, 125.85, 125.81, 114.08, 111.56, 64.51, 43.65, 19.03; HRMS (ESI) calcd for C₂₂H₂₀ClN₂⁺ 347.1310; found 347.1321 [M + H]⁺.

1-(3,4-Dichlorophenyl)-4,5-dihydro-5-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (3e)—Yellow solid, m.p. 133-134 °C; ¹H NMR (300 MHz, CDCl₃) 7.71 (d, *J* = 6.5 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 3H), 7.29 – 7.24 (m, 1H), 7.16 (t, *J* = 8.6 Hz, 3H), 6.85 (d, *J* = 8.6

Hz, 2H), 6.75 (dd, $J = 8.7, 2.7$ Hz, 1H), 5.18 (dd, $J = 12.1, 6.7$ Hz, 1H), 3.83 (dd, $J = 9.9, 7.3$ Hz, 1H), 3.77 (s, 3H), 3.13 (dd, $J = 17.3, 6.7$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) 159.23, 148.23, 144.06, 133.53, 132.60, 132.23, 130.26, 129.10, 128.64, 126.96, 125.92, 121.51, 114.95, 114.67, 112.54, 63.72, 55.29, 43.81, HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}^+$ 397.0869, found 397.0874 $[\text{M} + \text{H}]^+$.

1-(3-Chloro-4-methylphenyl)-4,5-dihydro-5-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (3f)—Off white solid, m.p. 120-121 °C; ^1H NMR (300 MHz, CDCl_3) 7.71 (d, $J = 7.1$ Hz, 2H), 7.37 (dd, $J = 12.8, 5.3$ Hz, 3H), 7.23 – 7.17 (m, 3H), 6.96 (d, $J = 8.3$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 2H), 6.73 (d, $J = 6.2$ Hz, 1H), 5.16 (dd, $J = 12.1, 7.1$ Hz, 1H), 3.82 (d, $J = 4.0$ Hz, 1H), 3.76 (s, 3H), 3.10 (dd, $J = 17.1, 7.1$ Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 159.07, 147.17, 143.94, 134.63, 134.21, 132.60, 130.90, 130.05, 128.73, 128.57, 127.05, 125.86, 125.79, 114.55, 114.09, 111.63, 64.04, 55.27, 43.68, 19.03; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{22}\text{ClN}_2\text{O}^+$ 377.1415, found 377.1427 $[\text{M} + \text{H}]^+$.

1-(3,4-Dichlorophenyl)-4,5-dihydro-5-(3-methoxyphenyl)-3-p-tolyl-1H-pyrazole (3g)—Off white solid, m.p. 184-185 °C; ^1H NMR (300 MHz, CDCl_3) 7.59 (d, $J = 8.1$ Hz, 2H), 7.30 – 7.10 (m, 5H), 6.89 – 6.75 (m, 3H), 6.73 (dd, $J = 8.9, 2.6$ Hz, 1H), 5.13 (dd, $J = 12.2, 6.9$ Hz, 1H), 3.89 – 3.78 (m, 1H), 3.75 (s, 3H), 3.13 (dd, $J = 17.2, 6.9$ Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 160.36, 148.48, 144.25, 143.36, 139.34, 132.59, 130.44, 130.26, 129.35, 125.93, 121.42, 117.96, 114.88, 113.09, 112.42, 111.36, 64.14, 55.26, 43.85, 21.44; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{21}\text{Cl}_2\text{N}_2\text{O}^+$ 411.1025, found 411.1043 $[\text{M} + \text{H}]^+$.

1-(3,4-Dichlorophenyl)-4,5-dihydro-3,5-di-p-tolyl-1H-pyrazole (3h)—Off white solid, m.p. 115-116 °C; ^1H NMR (300 MHz, CDCl_3) 7.60 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 2.6$ Hz, 1H), 7.21 – 7.16 (m, 2H), 7.13 – 7.11 (m, 4H), 6.73 (dd, $J = 8.9, 2.5$ Hz, 1H), 5.16 (dd, $J = 12.2, 6.7$ Hz, 1H), 3.80 (dd, $J = 17.2, 12.2$ Hz, 1H), 3.11 (dd, $J = 17.2, 6.7$ Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 148.41, 144.20, 139.27, 138.67, 137.64, 132.57, 130.23, 129.96, 129.44, 129.34, 125.90, 125.69, 121.27, 114.84, 112.41, 63.90, 43.91, 21.43, 21.11; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{21}\text{Cl}_2\text{N}_2^+$ 395.1076, found 395.1102 $[\text{M} + \text{H}]^+$.

1-(3-Chloro-4-methylphenyl)-4,5-dihydro-3,5-dip-tolyl-1H-pyrazole (3i)—Pale yellow solid, m.p. 135-136 °C; ^1H NMR (300 MHz, CDCl_3) 7.59 (d, $J = 8.1$ Hz, 2H), 7.20 – 7.18 (m, 2H), 7.17 – 7.14 (m, 3H), 7.13 – 7.09 (m, 2H), 6.94 (d, $J = 8.4$ Hz, 1H), 6.74 – 6.68 (m, 1H), 5.14 (dd, $J = 12.1, 7.2$ Hz, 1H), 3.77 (dd, $J = 17.1, 12.2$ Hz, 1H), 3.08 (dd, $J = 17.1, 7.2$ Hz, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 147.37, 144.12, 139.33, 138.83, 137.33, 134.62, 130.88, 129.84, 129.81, 129.39, 129.28, 128.61, 125.79, 125.78, 125.64, 114.00, 111.51, 64.25, 43.81, 21.41, 21.11, 19.02; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{24}\text{ClN}_2^+$ 375.1623; found 375.1635 $[\text{M} + \text{H}]^+$.

1-(4-tert-Butylphenyl)-4,5-dihydro-3,5-di-p-tolyl-1H-pyrazole (3j)—Pale green solid, m.p. 108-109 °C; ^1H NMR (300 MHz, CDCl_3) 7.59 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 11.0$ Hz, 1H), 7.26 – 7.20 (m, 3H), 7.19 – 7.13 (m, 4H), 7.01 (d, $J = 8.7$ Hz, 2H), 5.13 (dd, $J = 12.2, 8.1$ Hz, 1H), 3.76 (dd, $J = 17.0, 12.3$ Hz, 1H), 3.06 (dd, $J = 17.0, 8.1$ Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) 146.54, 143.15, 141.66, 140.13, 138.46, 137.11, 129.76, 129.22, 128.60, 125.93, 125.66, 124.97, 113.07, 64.82, 43.87, 33.94, 31.48, 21.39, 21.12; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{31}\text{N}_2^+$ 383.2482, found 383.2503 $[\text{M} + \text{H}]^+$.

1-(4-tert-Butylphenyl)-3-(4-chlorophenyl)-5-(2-fluorophenyl)-4,5-dihydro-1H-pyrazole (3k)—Pale green solid, m.p. 81-82 °C; ^1H NMR (300 MHz, CDCl_3) 7.63 (d, $J = 8.5$ Hz, 2H), 7.33 (d, $J = 8.5$ Hz, 2H), 7.23 (d, $J = 9.1$ Hz, 4H), 7.09 (dd, $J = 20.6, 9.0$ Hz, 2H), 6.99 (d, $J = 8.7$ Hz, 2H), 5.52 (dd, $J = 12.4, 7.5$ Hz, 1H), 3.83 (dd, $J = 17.1, 12.4$ Hz, 1H), 3.05 (dd, $J = 17.1, 7.5$ Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) 161.34 (d, $J_{\text{C,F}} = 248.25$ Hz), 145.64, 142.36, 134.25, 131.26, 129.22, 128.75, 127.64 (d, $J_{\text{C,F}} = 3.9$ Hz), 126.88, 125.87 (d, $J_{\text{C,F}} = 3.8$ Hz), 124.84 (d, $J_{\text{C,F}} = 3.5$ Hz), 123.99, 115.80, 115.52, 113.00, 58.19 (d, $J_{\text{C,F}} = 3.0$ Hz), 42.11, 33.99, 31.46; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{ClFN}_2$ + 407.1685, found 407.1712 [M + H] $^+$.

3-(4-Chlorophenyl)-5-(2-fluorophenyl)-4,5-dihydro-1-o-tolyl-1H-pyrazole (3l)—Off white solid, m.p. 153-154 °C; ^1H NMR (300 MHz, CDCl_3) 7.62 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.2$ Hz, 3H), 7.22 – 7.12 (m, 2H), 7.05 – 6.97 (m, 3H), 6.95 – 6.87 (m, 2H), 5.65 (t, $J = 10.8$ Hz, 1H), 3.73 (dd, $J = 16.4, 11.3$ Hz, 1H), 3.11 (dd, $J = 16.4, 10.3$ Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 161.99 (d, $J_{\text{C,F}} = 244.5$ Hz), 147.05, 143.62, 134.29, 131.52 (d, $J_{\text{C,F}} = 18.7$ Hz), 131.08, 129.20 (d, $J_{\text{C,F}} = 8.2$ Hz), 128.75, 128.23 (d, $J_{\text{C,F}} = 4.0$ Hz), 126.82, 126.08, 124.54 (d, $J_{\text{C,F}} = 3.5$ Hz), 123.40, 118.36, 115.60, 115.31, 60.09 (d, $J_{\text{C,F}} = 2.5$ Hz), 41.0, 20.42; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{19}\text{ClFN}_2$ + 365.1215, found 365.1208 [M + H] $^+$.

1-(4-tert-Butylphenyl)-4,5-dihydro-3-(4-methoxyphenyl)-5-(4-nitrophenyl)-1H-pyrazole (3m)—Dark red solid, m.p. 124-125 °C; ^1H NMR (300 MHz, CDCl_3) 8.20 (d, $J = 8.6$ Hz, 2H), 7.64 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 8.6$ Hz, 2H), 7.21 (d, $J = 8.7$ Hz, 2H), 6.92 (dd, $J = 8.7, 3.7$ Hz, 4H), 5.25 (dd, $J = 12.2, 8.0$ Hz, 1H), 3.90 – 3.79 (m, 1H), 3.83 (s, 3H), 3.06 (dd, $J = 17.0, 7.9$ Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) 160.33, 150.33, 147.43, 146.46, 142.70, 142.39, 127.27, 127.04, 125.87, 125.04, 124.51, 114.09, 113.08, 64.35, 55.36, 43.59, 33.98, 31.44; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_3$ + 430.2125, found 430.2136 [M + H] $^+$.

1-(3-Chloro-4-methylphenyl)-4,5-dihydro-3-(4-methoxyphenyl)-5-(4-nitrophenyl)-1H-pyrazole (3n)—Dark red solid, m. p. 120-122 °C; ^1H NMR (400 MHz, CDCl_3) 8.19 (d, $J = 6.7$ Hz, 2H), 7.64 (d, $J = 6.9$ Hz, 2H), 7.46 (d, $J = 6.9$ Hz, 2H), 7.12 (s, 1H), 6.94 (dd, $J = 22.2, 7.2$ Hz, 3H), 6.62 (d, $J = 6.0$ Hz, 1H), 5.26 (dd, $J = 9.3, 6.0$ Hz, 1H), 4.07 – 3.87 (s, 1H), 3.83 (s, 3H), 3.07 (dd, $J = 15.8, 5.5$ Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) 160.56, 149.55, 147.52, 147.27, 143.74, 134.87, 131.09, 127.43, 126.93, 126.41, 124.66, 124.59, 114.15, 114.02, 111.43, 63.80, 55.38, 43.58, 19.02; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{ClN}_3\text{NaO}_3$ + 444.1085, found 444.1108 [M + Na] $^+$.

1-(4-tert-Butylphenyl)-3,5-diphenyl-1H-pyrazole (4a)—Off white solid, m.p. 149-150 °C; ^1H NMR (400 MHz, CDCl_3) 7.92 (d, $J = 7.3$ Hz, 2H), 7.42 (t, $J = 7.5$ Hz, H), 7.37 – 7.25 (m, 10H), 6.81 (s, 1H), 1.31 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) 151.74, 150.54, 144.30, 137.68, 133.17, 130.73, 128.76, 128.63, 128.46, 128.21, 127.92, 125.87, 125.80, 124.79, 104.97, 34.65, 31.35; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{27}\text{N}_2$ + 355.2169, found 355.2173 [M + H] $^+$.

3,5-Diphenyl-1-o-tolyl-1H-pyrazole (4b)—Off white solid, m.p. 95-96 °C; ^1H NMR (300 MHz, CDCl_3) 7.92 (d, $J = 7.4$ Hz, 2H), 7.42 (t, $J = 7.5$ Hz, 2H), 7.36 – 7.28 (m, 3H), 7.27 – 7.18 (m, 7H), 6.87 (s, 1H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 151.76, 145.48, 139.56, 135.71, 133.24, 131.11, 130.27, 129.01, 128.65, 128.46, 128.23, 128.14, 127.91, 127.88, 126.68, 125.80, 103.20, 17.72; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{19}\text{N}_2$ + 311.1543, found 311.1536 [M + H] $^+$.

1-(3,4-Dichlorophenyl)-3,5-diphenyl-1H-pyrazole (4c)—Pale yellow liquid; ^1H NMR (300 MHz, CDCl_3) 7.90 (d, $J=7.3$ Hz, 2H), 7.62 (d, $J=2.4$ Hz, 1H), 7.44 (t, $J=7.4$ Hz, 2H), 7.39–7.35 (m, 4H), 7.33 (s, 1H), 7.29 (dd, $J=6.6, 2.9$ Hz, 2H), 7.08 (dd, $J=8.6, 2.4$ Hz, 1H), 6.81 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) 152.62, 144.57, 139.34, 132.93, 132.60, 131.19, 130.30, 130.05, 128.84, 128.79, 128.75, 128.35, 126.71, 125.87, 123.95, 106.05; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{15}\text{Cl}_2\text{N}_2$ + 365.0607, found 365.0589 [M + H] $^+$.

1-(3-Chloro-4-methylphenyl)-3,5-diphenyl-1H-pyrazole (4d)—Off white solid; m.p. 113–114 °C; ^1H NMR (300 MHz, CDCl_3) 7.91 (d, $J=7.3$ Hz, 2H), 7.50 (s, 1H), 7.43 (t, $J=7.3$ Hz, 2H), 7.36–7.27 (m, 6H), 7.13 (d, $J=8.1$ Hz, 1H), 7.04 (d, $J=8.0$ Hz, 1H), 6.80 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 152.15, 144.43, 138.87, 135.29, 134.51, 132.90, 130.78, 130.35, 128.76, 128.69, 128.60, 128.52, 128.12, 125.84, 125.69, 123.26, 105.41, 19.74; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{18}\text{ClN}_2$ + 345.1153, found 345.1138 [M + H] $^+$.

1-(3,4-Dichlorophenyl)-5-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (4e)—Off white solid, m.p. 99–100 °C; ^1H NMR (300 MHz, CDCl_3) 7.89 (d, $J=7.4$ Hz, 2H), 7.64 (d, $J=2.3$ Hz, 1H), 7.43 (t, $J=7.4$ Hz, 2H), 7.38–7.21 (m, 2H), 7.21 (d, $J=8.6$ Hz, 2H), 7.09 (dd, $J=8.6, 2.3$ Hz, 1H), 6.89 (d, $J=8.6$ Hz, 2H), 6.75 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 159.98, 152.53, 144.43, 139.47, 132.90, 132.70, 131.07, 130.28, 130.09, 128.72, 128.28, 126.72, 125.84, 123.96, 122.34, 114.23, 105.57, 55.34; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}$ + 395.0712, found 395.0696 [M + H] $^+$.

1-(3-Chloro-4-methylphenyl)-5-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (4f)—m.p. 147–148 °C; Off white solid, ^1H NMR (300 MHz, CDCl_3) 7.90 (d, $J=7.3$ Hz, 2H), 7.51 (d, $J=1.6$ Hz, 1H), 7.42 (t, $J=7.4$ Hz, 2H), 7.33 (t, $J=7.2$ Hz, 1H), 7.26–7.12 (m, 3H), 7.04 (dd, $J=8.1, 1.7$ Hz, 1H), 6.87 (d, $J=8.6$ Hz, 2H), 6.74 (s, 1H), 3.82 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 159.74, 152.05, 144.28, 138.99, 135.17, 134.49, 132.99, 130.77, 130.04, 128.65, 128.04, 125.82, 125.71, 123.28, 122.71, 114.04, 104.91, 55.30, 19.73; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{ClN}_2\text{O}$ + 375.1259, found 375.1273 [M + H] $^+$.

1-(3,4-Dichlorophenyl)-5-(3-methoxyphenyl)-3-p-tolyl-1H-pyrazole (4g)—Off white solid, m.p. 135–136 °C; ^1H NMR (300 MHz, CDCl_3) 7.79 (d, $J=7.8$ Hz, 2H), 7.64 (d, $J=1.7$ Hz, 1H), 7.35 (d, $J=8.6$ Hz, 1H), 7.29–7.21 (m, 3H), 7.10 (dd, $J=8.5, 1.8$ Hz, 1H), 6.91 (d, $J=8.3$ Hz, 1H), 6.87–6.74 (m, 3H), 3.76 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 159.69, 152.65, 144.29, 139.37, 138.20, 132.87, 131.36, 131.07, 130.24, 129.85, 129.75, 129.44, 126.62, 125.75, 123.88, 121.23, 114.38, 114.32, 105.96, 55.33, 21.35; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}$ + 409.0869, found 409.0882 [M + H] $^+$.

1-(3,4-Dichlorophenyl)-3,5-di-p-tolyl-1H-pyrazole (4h)—Off white solid, m.p. 129–130 °C; ^1H NMR (300 MHz, CDCl_3) 7.78 (d, $J=7.8$ Hz, 2H), 7.63 (d, $J=2.7$ Hz, 2H), 7.34 (d, $J=8.6$ Hz, 1H), 7.24 (d, $J=7.4$ Hz, 2H), 7.20–7.13 (m, 4H), 7.08 (dd, $J=9.0, 2.7$ Hz, 1H), 6.74 (s, 1H), 2.39 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 152.62, 144.56, 139.50, 138.81, 138.12, 132.87, 130.99, 130.23, 129.85, 129.46, 129.42, 128.63, 127.18, 126.71, 125.75, 123.96, 105.68, 21.34, 21.33; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{Cl}_2\text{N}_2$ + 393.0920, found 393.0897 [M + H] $^+$.

1-(3-Chloro-4-methylphenyl)-3,5-di-p-tolyl-1H-pyrazole (4i)—Off white solid, m.p. 96–97 °C; ^1H NMR (300 MHz, CDCl_3) 7.79 (d, $J=7.7$ Hz, 2H), 7.52 (s, 1H), 7.23 (d, $J=8.2$ Hz, 2H), 7.15 (q, $J=8.5$ Hz, 5H), 7.03 (d, $J=8.0$ Hz, 1H), 6.73 (s, 1H), 2.38 (s, 3H), 2.36 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) 152.15, 144.41, 139.03, 138.41, 137.84, 135.10, 134.46, 130.72, 130.15, 129.35, 129.27, 128.60, 127.48, 125.72, 123.29, 105.03, 21.33, 21.30, 19.73; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{22}\text{ClN}_2$ + 373.1466, found 373.1483 [M + H] $^+$.

1-(4-tert-Butylphenyl)-3,5-di-p-tolyl-1H-pyrazole (4j)—Off white solid, m.p. 160-161 °C; ^1H NMR (300 MHz, CDCl_3) 7.80 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.6$ Hz, 2H), 7.28 (d, $J = 8.7$ Hz, 2H), 7.21 – 7.16 (m, 4H), 7.11 (d, $J = 8.1$ Hz, 2H), 6.74 (s, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) 151.73, 150.35, 144.26, 138.04, 137.81, 137.59, 130.41, 129.30, 129.15, 128.59, 127.87, 125.82, 125.69, 124.79, 104.56, 31.35, 21.33, 21.30; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{29}\text{N}_2^+$ 381.2325, found 381.2327 [M + H] $^+$.

1-(4-tert-Butylphenyl)-3-(4-chlorophenyl)-5-(2-fluorophenyl)-1H-pyrazole (4k)—Off white solid, m.p. 141-142 °C; ^1H NMR (300 MHz, CDCl_3) 7.85 (d, $J = 8.2$ Hz, 2H), 7.36 (dd, $J = 14.7, 8.4$ Hz, 5H), 7.29 – 7.18 (m, 3H), 7.16 – 7.03 (m, 2H), 6.83 (s, 2H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) 161.19, 157.88, 150.65 (d, $J_{\text{C,F}} = 2.3$ Hz), 138.05, 137.58, 133.65, 131.75, 131.20, 130.61 (d, $J_{\text{C,F}} = 8.1$ Hz), 128.80, 127.04, 125.87, 124.33, 123.78, 118.78 (d, $J_{\text{C,F}} = 14.8$ Hz), 116.28, 116.00, 106.44 (d, $J = 2.0$ Hz), 34.62, 31.29; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{22}\text{ClFN}_2\text{Na}^+$ 427.1348, found 427.1351 [M + Na] $^+$.

3-(4-Chlorophenyl)-5-(2-fluorophenyl)-1-o-tolyl-1H-pyrazole (4l)—Dark red solid, m.p. 134-135 °C; ^1H NMR (300 MHz, CDCl_3) 7.83 (d, $J = 8.5$ Hz, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.25 – 7.12 (m, 5H), 7.08 – 6.92 (m, 3H), 6.86 (d, $J = 1.2$ Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 161.15 (d, $J_{\text{C,F}} = 248.25$ Hz), 150.72, 139.42, 139.14, 135.55, 133.67, 131.79, 131.16, 130.66 (d, $J_{\text{C,F}} = 8.23$ Hz), 129.02, 128.94 (d, $J_{\text{C,F}} = 12.2$ Hz), 127.81, 127.12, 126.47, 124.04 (d, $J_{\text{C,F}} = 3.7$ Hz), 118.31 (d, $J_{\text{C,F}} = 14.3$ Hz), 116.23, 115.94, 105.35 (d, $J_{\text{C,F}} = 3.2$ Hz), 17.69; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{16}\text{ClFN}_2\text{Na}^+$ 385.0878, found 385.0885 [M + Na] $^+$.

1-(4-tert-Butylphenyl)-3-(4-methoxyphenyl)-5-(4-nitrophenyl)-1H-pyrazole (4m)—Pale green solid, m.p. 134-135 °C; ^1H NMR (300 MHz, CDCl_3) 8.16 (d, $J = 8.7$ Hz, 2H), 7.84 (d, $J = 8.7$ Hz, 2H), 7.42 (dd, $J = 12.6, 8.6$ Hz, 4H), 7.28 – 7.21 (m, 2H), 6.96 (d, $J = 8.7$ Hz, 2H), 6.85 (s, 1H), 3.85 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) 159.79, 152.04, 151.37, 147.21, 141.81, 137.11, 136.94, 129.18, 127.07, 126.26, 125.29, 124.92, 123.79, 114.12, 105.54, 55.32, 34.74, 31.30; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{N}_3\text{NaO}_3^+$ 450.1788, found 450.1793 [M + Na] $^+$.

1-(3-Chloro-4-methylphenyl)-3-(4-methoxyphenyl)-5-(4-nitrophenyl)-1H-pyrazole (4n)—Pale green solid, m.p. 109-110 °C; ^1H NMR (300 MHz, CDCl_3) 8.19 (d, $J = 8.0$ Hz, 2H), 7.83 (d, $J = 7.9$ Hz, 2H), 7.57 – 7.38 (m, 3H), 7.19 (d, $J = 7.6$ Hz, 1H), 6.97 (d, $J = 7.6$ Hz, 3H), 6.84 (s, 1H), 3.85 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 159.94, 152.44, 147.38, 141.92, 138.32, 136.55, 136.16, 134.94, 131.14, 129.25, 127.13, 125.86, 125.01, 123.91, 123.38, 114.18, 106.02, 55.34, 19.78; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{ClN}_3\text{O}_3^+$ 420.1109, found 420.1121 [M + H] $^+$.

1-(4-Methoxyphenyl)-3,5-diphenyl-1H-pyrazole (4o)—Off white solid, m.p. 121-122 °C; ^1H NMR (300 MHz, CDCl_3) 7.91 (d, $J = 7.6$ Hz, 2H), 7.42 (t, $J = 7.5$ Hz, 2H), 7.36 – 7.25 (m, 8H), 6.86 (d, $J = 8.9$ Hz, 2H), 6.81 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) 158.85, 151.63, 144.34, 133.45, 133.17, 130.62, 128.84, 128.63, 128.45, 128.17, 127.89, 126.75, 125.78, 114.11, 104.64, 55.50; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{NaO}^+$ 349.1311, found 349.1298 [M + Na] $^+$.

Cell Culture and Cell Proliferation Assay

Cell culture—Human ovarian adenocarcinoma cells (SK-OV-3), colon adenocarcinoma (HT-29) and cervical adenocarcinoma (HeLa) were obtained from American Type Culture

Collection. Cells were grown on 75 cm² cell culture flasks with EMEM (Eagle's minimum essential medium), supplemented with 10% fetal bovine serum, and 1% penicillin/streptomycin solution (10,000 units of penicillin and 10 mg of streptomycin in 0.9% NaCl) in a humidified atmosphere of 5% CO₂, 95% air at 37 °C.

Cell proliferation assay—Cell proliferation assay was carried out using CellTiter 96 aqueous one solution cell proliferation assay kit (Promega, USA). Briefly, upon reaching about 75-80% confluency, 5000 cells/well were plated in 96-well microplate in 100 EL media. After seeding for 72 h, the cells were treated with 50 EM compound in triplicate. Doxorubicin (10 EM) was used as the positive control. At the end of the sample exposure period (72 h), 20 EL CellTiter 96 aqueous solution was added. The plate was returned to the incubator for 1 h in a humidified atmosphere at 37 °C. The absorbance of the formazan product was measured at 490 nm using microplate reader. The blank control was recorded by measuring the absorbance at 490 nm with wells containing medium mixed with CellTiter 96 aqueous solution but no cells. Results were expressed as the percentage of the control (without compound set at 100%).

Conclusions

In summary, we have developed a simple, efficient and environmentally friendly protocol for the synthesis of 1,3,5-triarylpyrazoles and 1,3,5-triarylpyrazolines in [bimm][PF₆] ionic liquid mediated by Cu(OTf)₂. The reaction protocol exhibited tolerance with different functional groups, generating pyrazoles in good to high yields (71-82%) without any requirement for additional reagent for the oxidation of *in situ* generated pyrazolines. The catalyst can be reused up to four cycles without much loss in catalytic activity. The pyrazoles (**4a-o**) and pyrazolines (**3a-n**) were evaluated for antiproliferative activity. Compound **3b** inhibited cell proliferation of HeLa cells by 80% at a concentration of 50 μM. All other synthesized derivatives exhibited a modest inhibition against the proliferation of SK-OV-3, HT-29 and HeLa cells. Further structure-activity relationship studies are required for optimizing antiproliferative activities of these classes of compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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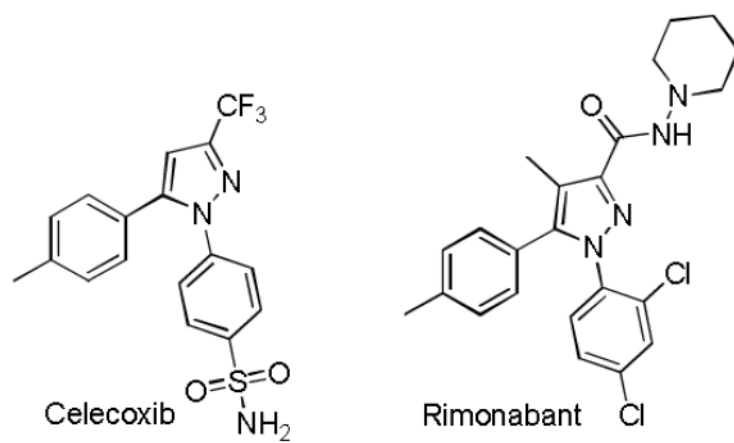


Fig. 1. Chemical structure of drug molecules, celecoxib and rimonabant containing pyrazole scaffold

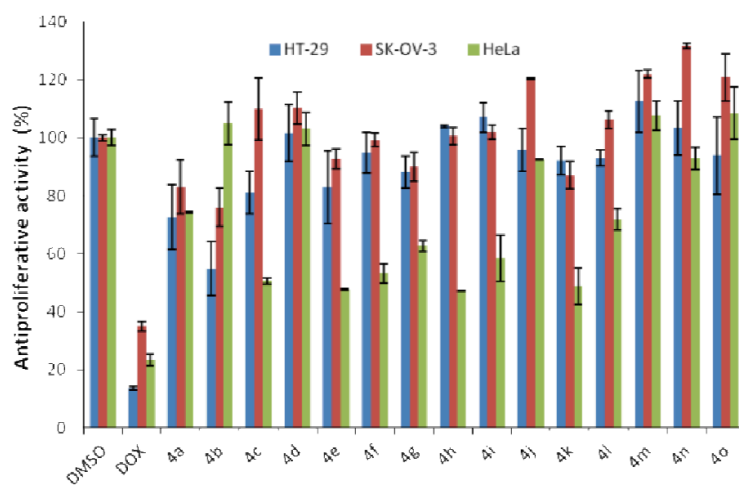


Fig. 2.
Antiproliferative activity of **4a-o**

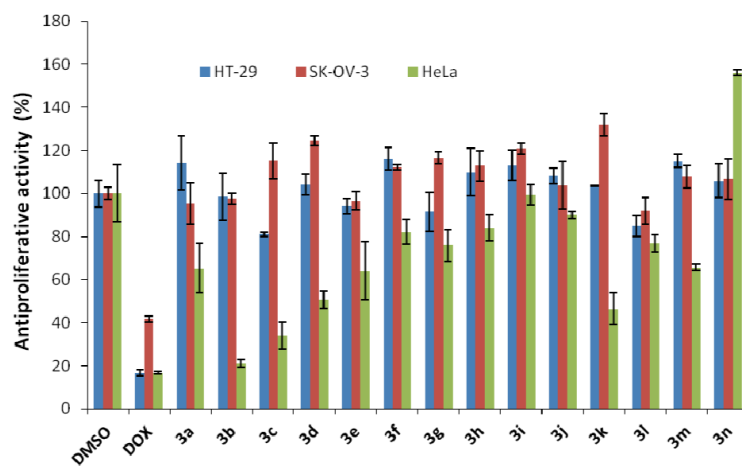
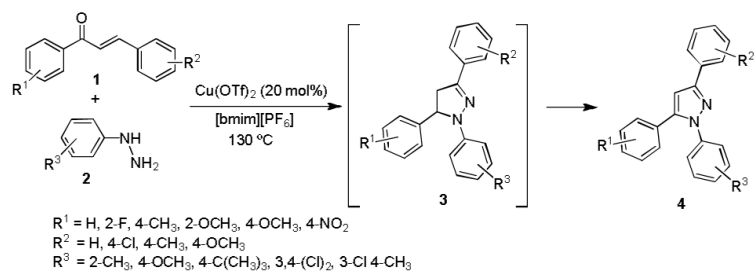
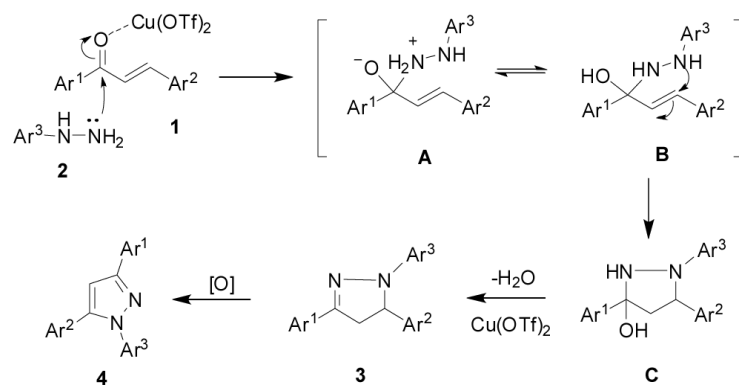


Fig. 3.
Antiproliferative activity of **3a-n**



Scheme 1.
Synthesis of substituted 1,3,5-triarylpyrazoles



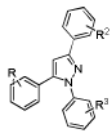
Scheme 2.
Proposed mechanism for synthesis of 1,3,5-triarylpyrazole

Table 1Optimization of reaction conditions for the synthesis of **4a**.^a

S. No.	Catalyst	Mol (%)	Solvent	Yield (3a) (%) ^b	Yield (4a) (%) ^b
1	Cu(OTf) ₂	10	[bmim][PF ₆]	15	64 ^c
2	Cu(OTf) ₂	20	[bmim][PF ₆]	-	82 ^{d,e}
3	Cu(OTf) ₂	30	[bmim][PF ₆]	-	84
4	Cu(OTf) ₂	20	[bmim][BF ₄]	35	50
5	Cu(OTf) ₂	20	[bmim][Br]	50	21
6	Cu(OTf) ₂	20	DMSO	-	15
7	Cu(OTf) ₂	20	DMF	-	33
8	Cu(OTf) ₂	20	Ethanol	62 ^f	-
9	Cu(OTf) ₂	20	PEG	60	-
10	Sc(OTf) ₃	20	[bmim][PF ₆]	61	19
11	Ce(OTf) ₃	20	[bmim][PF ₆]	75	10
12	<i>p</i> TSA	20	[bmim][PF ₆]	69	-
13	Zn(OTf) ₂	20	[bmim][PF ₆]	55	30
14	AgOTf	20	[bmim][PF ₆]	15	65
15	Yb(OTf) ₃	20	[bmim][PF ₆]	58	22

^aReaction condition: Chalcone (1.0 mmol), arylhydrazine (1.2 mmol), catalyst (x mol%), solvent (2 mL), 130 °C, 2 h.^bIsolated yield.^cOnly 20% of **3a** was formed after 30 min in the absence of Cu(OTf)₂ under similar conditions.^dAt 100 °C, complete conversion of **3a** to **4a** was not observed and it requires longer reaction time.^eWhen isolated **3a** was used 95% yield of **4a** was obtained.^fReflux condition.

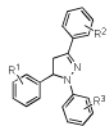
Table 2

Synthesized 1,3,5-triarylpyrazoles (**4a-o**)

Compd.	R ¹	R ²	R ³	Time (h)	Yield (%) ^a
4a	H	H	4-C(CH ₃) ₃	2	82 ^b
4b	H	H	2-CH ₃	2	81
4c	H	H	3,4-Cl	3	80
4d	H	H	3-Cl, 4-CH ₃	2.5	72
4e	4-OMe	H	3,4-Cl	2	71
4f	4-OMe	H	3-Cl, 4-CH ₃	2	77
4g	3-OMe	4-CH ₃	3,4-Cl	2	79
4h	4-CH ₃	4-CH ₃	3,4-Cl	2	74
4i	4-CH ₃	4-CH ₃	3-Cl, 4-CH ₃	2	77
4j	4-CH ₃	4-CH ₃	4-C(CH ₃) ₃	1.5	77
4k	2-F	4-Cl	4-C(CH ₃) ₃	2	84
4l	2-F	4-Cl	2-CH ₃	2	82
4m	4-NO ₂	4-OMe	4-C(CH ₃) ₃	1	75
4n	4-NO ₂	4-OMe	3-Cl, 4-CH ₃	1	81
4o	H	H	4-OMe	1.5	78

^aIsolated yield.^bIn four consecutive recycle experiment **4a** was observed in 82, 80, 78, and 79% yield, respectively.

Table 3

Synthesized 1,3,5-triarylpyrazolines (**3a-n**)

Compd.	R ¹	R ²	R ³	Time (Min.)	Yield (%) ^a
3a	H	H	4-C(CH ₃) ₃	30	84
3b	H	H	2-CH ₃	30	66
3c	H	H	3,4-Cl	30	77
3d	H	H	3-Cl, 4-CH ₃	30	68
3e	4-OMe	H	3,4-Cl	30	72
3f	4-OMe	H	3-Cl, 4-CH ₃	30	78
3g	3-OMe	4-CH ₃	3,4-Cl	30	60
3h	4-CH ₃	4-CH ₃	3,4-Cl	30	72
3i	4-CH ₃	4-CH ₃	3-Cl, 4-CH ₃	30	74
3j	4-CH ₃	4-CH ₃	4-C(CH ₃) ₃	30	79
3k	2-F	4-Cl	4-C(CH ₃) ₃	30	63
3l	2-F	4-Cl	2-CH ₃	30	65
3m	4-NO ₂	4-OMe	4-C(CH ₃) ₃	20	72
3n	4-NO ₂	4-OMe	3-Cl, 4-CH ₃	20	80

^aIsolated yield.