RSC Advances

RSC Publishing

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c3ra41830h

Copper triflate-mediated synthesis of 1,3,5-triarylpyrazoles in [bmim][PF_6] ionic liquid and evaluation of their anticancer activities†

V. Kameshwara Rao,[a] Rakesh Tiwari,[b] Bhupender S. Chhikara,[b] Amir Nasrolahi Shirazi,[b] Keykavous Parang[b] and Anil Kumar*[a]

Received 16th April 2013,
Accepted 13th June 2013

DOI: 10.1039/c3ra41830h

www.rsc.org/advances

A simple, efficient, and environment friendly protocol for the synthesis of 1,3,5-triarylpyrazoles and 1,3,5-triarylpyrazolines in [bmim][PF_6] 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 the requirement for an additional oxidizing reagent. The catalyst can be reused for up to four cycles without much loss in the catalytic activity. The pyrazoles (**4a–o**) and pyrazolines (**3a–n**) were evaluated for their antiproliferative activity in SK-OV-3, HT-29, and HeLa human cancer cells lines. Among all the 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 the 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$\kappa\beta$ kinase β (IKKβ or IKK-2) inhibitors,[8] and anti-inflammatory agents.[9] Pyrazole derivatives have been shown to have a good binding affinity towards estrogen receptors.[10–12] Some of the pyrazole derivatives have been reported to possess antidepressant, anti-convulsant,[13] anti-inflammatory, and anti-arthritic[14] activities. Pyrazole scaffolds constitute the basic framework of several drug molecules such as celecoxib (a non-steroidal anti-inflammatory drug)[14] and rimonabant (an anorectic antiobesity drug) (Fig. 1).

Pyrazoles have received considerable attention from 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 their corresponding pyrazoles. For this oxidative aromatization of pyrazolines to pyrazoles, various reagents have been employed such as I_2,[17] $Bi(NO_3)_3{\cdot}5H_2O$,[18] MnO_2,[19] DDQ,[20] Pd/C,[21] NaOEt,[22] $PhI(OAc)_2$,[23] TBBDA,[24] and ionic liquids.[25,26] However, many of these oxidative methods suffer from relatively high oxidant loading, the use of strong oxidants and chlorinated organic solvents, harsh conditions, poor yields, and a longer reaction time. Thus, the development of an environmentally benign process with the use of alternative solvents such as ionic liquids in place of organic solvents, and a catalytic amount of ecofriendly catalyst to 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 a copper triflate-mediated protocol for the synthesis of pyrazoles by the reaction of hydrazines with α,β-unsaturated ketones in a 1-butyl-3-methylimidazolium hexafluoropho-

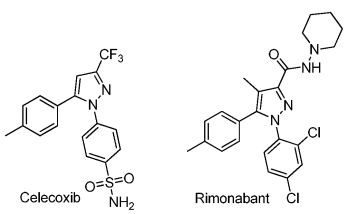
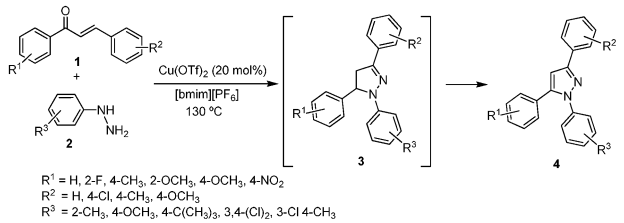


Fig. 1 Chemical structure of drug molecules, celecoxib and rimonabant containing a pyrazole scaffold.

[a]*Department of Chemistry, Birla Institute of Technology and Science, Pilani 333031, Rajasthan, India. E-mail: anilkumar@pilani.bits-pilani.ac.in*

[b]*Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA*

† Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR for **4a–o** and **3a–n** can be found in the online version of this article. See DOI: 10.1039/c3ra41830h



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

sphate ([bmim][PF_6]) 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 mol%), 1-(4-*tert*-butylphenyl)-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (**3a**) was obtained in 62% yield (Table 1, entry 8). Further optimization of the 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][PF_6] gave the desired product 1-(4-*tert*-butylphenyl)-3,5-diphenyl-1*H*-pyrazole (**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. The use of $Ce(OTf)_3$ in [bmim][PF_6] resulted in 75% yield of **3a** along with 10% of **4a**, whereas use of *p*TSA in [bmim][PF_6] gave 69% of **3a** (Table 1, entry 11 and 12). There was not much increase in the 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 15% **3a** (Table 1, entries 1–3). These data indicate that $Cu(OTf)_2$ was involved in the 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][PF_6] ionic liquids, and only **3a** was isolated in 20% yield along with the starting material; the yield of **3a** did not increase with increasing the time up to 2 h.

The structure of **4a** was confirmed by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry. In the ^{1}H NMR spectrum, a singlet was observed at δ 6.81 for the proton at the C_4-position of the pyrazole ring along with other protons on aryl substituents. In the ^{13}C NMR, a peak appeared at δ 104.97 for the C_4-carbon of the pyrazole ring. The presence of a peak at *m*/*z* 355.2173 for the $[M + H]^+$ ion with molecular formula $C_{25}H_{27}N_2^+$ 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, NO_2, OCH_3, CH_3 and $-C(CH_3)_3$ 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%).

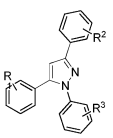
By monitoring the model reaction between 1,2-diphenylprop-2-en-1-one (**1**) and *tert*-butylphenylhydrazine hydrochloride (**2**) in the presence of 20 mol% $Cu(OTf)_2$ in [bmim][PF_6] at different time intervals, it was found that in the first 30 min pyrazoline (**3a**) was the major product, which was oxidized to pyrazole in the reaction as time progressed. We thus decided

Table 1 Optimization of reaction conditions for the synthesis of **4a**[a]

Subst. 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[de]
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	*p*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

[a] Reaction conditions: chalcone (1.0 mmol), arylhydrazine (1.2 mmol), catalyst (*x* mol%), solvent (2 mL), 130 °C, 2 h. [b] Isolated yield. [c] Only 20% of **3a** was formed after 30 min in the absence of $Cu(OTf)_2$ under similar conditions. [d] At 100 °C, complete conversion of **3a** to **4a** was not observed and it requires a longer reaction time. [e] When isolated **3a** was used, 95% yield of **4a** was obtained. [f] Reflux conditions.

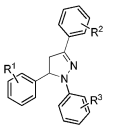
Table 2 Synthesized 1,3,5-triarylpyrazoles (**4a–o**)



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

[a] Isolated yield. [b] In four consecutive recycling experiments **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

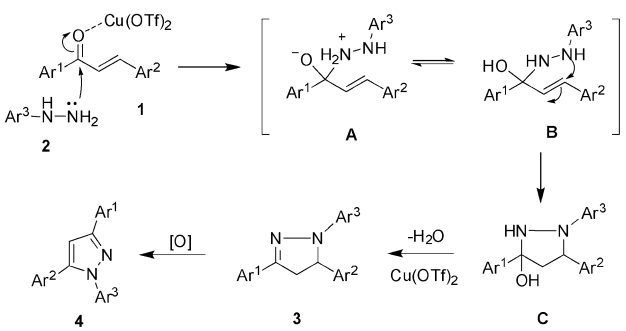
[a] Isolated yield.

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 α,β-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 the synthesized compounds were elucidated by ^{1}H NMR and ^{13}C NMR spectroscopic data (ESI†).

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 the 1,2-addition of hydrazine to chalcone mediated by $Cu(OTf)_2$. 3-Hydroxypyrazoline (**C**) undergoes elimination in the presence of $Cu(OTf)_2$ to give the 1,3,5-triarylpyrazoline derivative (**3**). Oxidative aromatization of **3** in the presence of $Cu(OTf)_2$ yields the corresponding 1,3,5-triarylpyrazole (**4**). We did not observe the 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 the presence of $Cu(OTf)_2$. It appears that ionic liquid helps in the stabilization of charged intermediates generated by the coordination of $Cu(OTf)_2$ to the carbonyl of chalcone and thereby increases the electrophilicity of chalcone.

Further, we investigated the possibility of recycling the catalyst. After performing the first cycle, the product was extracted with an ethyl acetate–hexane mixture, and $Cu(OTf)_2$ in ionic liquid was properly dried under vacuum. The fresh chalcone and 4-*tert*-butyl phenylhydrazine hydrochloride were added to the recovered ionic liquid containing $Cu(OTf)_2$ and the reaction was carried out under the 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 the 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 Fig. 2 and 3, respectively. Fig. 2 shows that among all the 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-Triarylpyrazoline 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. The 2-methylsubstituted compound **3b** showed the highest potency with 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



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

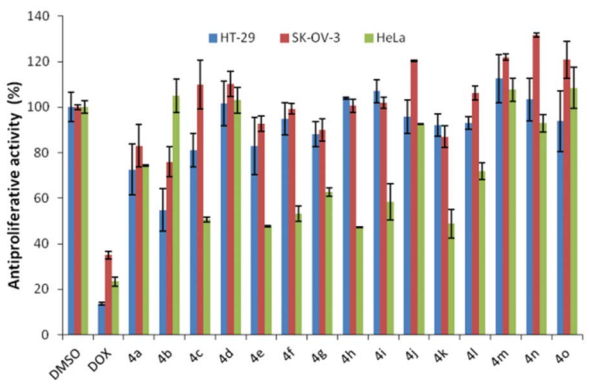


Fig. 2 Antiproliferative activity of **4a–o**.

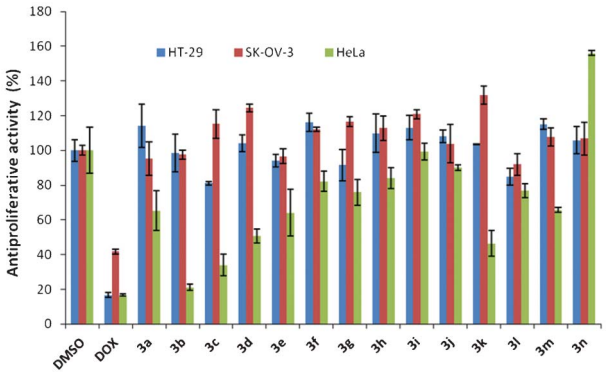


Fig. 3 Antiproliferative activity of **3a–n**.

this derivative could lead to the synthesis of a promising candidate that selectively targets 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 $CDCl_3$ as the 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 the presence of sodium hydroxide, as reported in literature.[33]

Experimental procedure for the synthesis of 3 and 4

Chalcone (1.0 mmol), arylhydrazine hydrochloride (1.2 mmol) and $Cu(OTf)_2$ (0.2 mmol, 20 mol%) were added to a 10 mL round bottom flask containing [bmim][PF_6] 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 the reaction as indicated by TLC, the reaction mixture was extracted with an ethyl acetate–hexane mixture and the solvent was removed under vacuum. The crude compound was purified by passing it 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-1*H*-pyrazole (3a). Pale green solid, m.p. 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{25}H_{27}N_2^+$ 355.2169, found 355.2176 $[M + H]^+$.

4,5-Dihydro-3,5-diphenyl-1-*o*-tolyl-1*H*-pyrazole (3b). Brown liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{22}H_{20}N_2Na^+$ 335.1519, found 335.1532 $[M + Na]^+$.

1-(3,4-Dichlorophenyl)-4,5-dihydro-3,5-diphenyl-1*H*-pyrazole (3c). Pale yellow solid, m.p. 133–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{21}H_{17}Cl_2N_2^+$ 367.0763, found 367.0782 $[M + H]^+$.

1-(3-Chloro-4-methylphenyl)-4,5-dihydro-3,5-diphenyl-1*H*-pyrazole (3d). Pale yellow solid, m.p. 121–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{22}H_{20}ClN_2^+$ 347.1310, found 347.1321 $[M + H]^+$.

1-(3,4-Dichlorophenyl)-4,5-dihydro-5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole (3e). Yellow solid, m.p. 133–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{22}H_{19}Cl_2N_2O^+$ 397.0869, found 397.0874 $[M + H]^+$.

1-(3-Chloro-4-methylphenyl)-4,5-dihydro-5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole (3f). Off white solid, m.p. 120–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{23}H_{22}ClN_2O^+$ 377.1415, found 377.1427 $[M + H]^+$.

1-(3,4-Dichlorophenyl)-4,5-dihydro-5-(3-methoxyphenyl)-3-*p*-tolyl-1*H*-pyrazole (3g). Off white solid, m.p. 184–185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{23}H_{21}Cl_2N_2O^+$ 411.1025, found 411.1043 $[M + H]^+$.

1-(3,4-Dichlorophenyl)-4,5-dihydro-3,5-di-*p*-tolyl-1*H*-pyrazole (3h). Off white solid, m.p. 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{23}H_{21}Cl_2N_2^+$ 395.1076, found 395.1102 $[M + H]^+$.

1-(3-Chloro-4-methylphenyl)-4,5-dihydro-3,5-di-*p*-tolyl-1*H*-pyrazole (3i). Pale yellow solid, m.p. 135–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{24}H_{24}ClN_2^+$ 375.1623, found 375.1635 $[M + H]^+$.

1-(4-*tert*-Butylphenyl)-4,5-dihydro-3,5-di-*p*-tolyl-1*H*-pyrazole (3j). Pale green solid, m.p. 108–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{27}H_{31}N_2^+$ 383.2482, found 383.2503 $[M + H]^+$.

1-(4-*tert*-Butylphenyl)-3-(4-chlorophenyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazole (3k). Pale green solid, m.p. 81–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 161.34 (d, $J_{C,F}$ = 248.25 Hz), 145.64, 142.36, 134.25, 131.26, 129.22, 128.75, 127.64 (d, $J_{C,F}$ = 3.9 Hz), 126.88, 125.87 (d, $J_{C,F}$ = 3.8 Hz), 124.84 (d, $J_{C,F}$ = 3.5 Hz), 123.99, 115.80, 115.52, 113.00, 58.19 (d, $J_{C,F}$ = 3.0 Hz), 42.11, 33.99, 31.46; HRMS (ESI) calcd for $C_{25}H_{25}ClFN_2^+$ 407.1685, found 407.1712 $[M + H]^+$.

3-(4-Chlorophenyl)-5-(2-fluorophenyl)-4,5-dihydro-1-*o*-tolyl-1*H*-pyrazole (3l). Off white solid, m.p. 153–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 161.99 (d, $J_{C,F}$ = 244.5 Hz), 147.05, 143.62, 134.29, 131.52 (d, $J_{C,F}$ = 18.7 Hz), 131.08, 129.20 (d, $J_{C,F}$ = 8.2 Hz), 128.75, 128.23 (d, $J_{C,F}$ = 4.0 Hz), 126.82, 126.08, 124.54 (d, $J_{C,F}$ = 3.5 Hz), 123.40, 118.36, 115.60, 115.31, 60.09 (d, $J_{C,F}$ = 2.5 Hz), 41.0, 20.42; HRMS (ESI) calcd for $C_{22}H_{19}ClFN_2^+$ 365.1215, found 365.1208 $[M + H]^+$.

1-(4-*tert*-Butylphenyl)-4,5-dihydro-3-(4-methoxyphenyl)-5-(4-nitrophenyl)-1*H*-pyrazole (3m). Dark red solid, m.p. 124–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{26}H_{28}N_3O_3^+$ 430.2125, found 430.2136 $[M + H]^+$.

1-(3-Chloro-4-methylphenyl)-4,5-dihydro-3-(4-methoxyphenyl)-5-(4-nitrophenyl)-1*H*-pyrazole (3n). Dark red solid, m.p. 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{23}H_{20}ClN_3NaO_3^+$ 444.1085, found 444.1108 $[M + Na]^+$.

1-(4-*tert*-Butylphenyl)-3,5-diphenyl-1*H*-pyrazole (4a). Off white solid, m.p. 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{25}H_{27}N_2^+$ 355.2169, found 355.2173 $[M + H]^+$.

3,5-Diphenyl-1-*o*-tolyl-1*H*-pyrazole (4b). Off white solid, m.p. 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{22}H_{19}N_2^+$ 311.1543, found 311. 1536 $[M + H]^+$.

1-(3,4-Dichlorophenyl)-3,5-diphenyl-1*H*-pyrazole (4c). Pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{21}H_{15}Cl_2N_2^+$ 365.0607, found 365. 0589 $[M + H]^+$.

1-(3-Chloro-4-methylphenyl)-3,5-diphenyl-1*H*-pyrazole (4d). Off white solid; m.p. 113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{22}H_{18}ClN_2^+$ 345.1153, found 345. 1138 $[M + H]^+$.

1-(3,4-Dichlorophenyl)-5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole (4e). Off white solid, m.p. 99–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{22}H_{17}Cl_2N_2O^+$ 395.0712, found 395.0696 $[M + H]^+$.

1-(3-Chloro-4-methylphenyl)-5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole (4f). Off white solid, m.p. 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{23}H_{20}ClN_2O^+$ 375.1259, found 375.1273 $[M + H]^+$.

1-(3,4-Dichlorophenyl)-5-(3-methoxyphenyl)-3-*p*-tolyl-1*H*-pyrazole (4g). Off white solid, m.p. 135–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{23}H_{19}Cl_2N_2O^+$ 409.0869, found 409.0882 $[M + H]^+$.

1-(3,4-Dichlorophenyl)-3,5-di-*p*-tolyl-1*H*-pyrazole (4h). Off white solid, m.p. 129–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 2H), δ 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, $CDCl_3$) δ 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 $C_{23}H_{19}Cl_2N_2^+$ 393.0920, found 393.0897 $[M + H]^+$.

1-(3-Chloro-4-methylphenyl)-3,5-di-*p*-tolyl-1*H*-pyrazole (4i). Off white solid, m.p. 96–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{24}H_{22}ClN_2^+$ 373.1466, found 373.1483 $[M + H]^+$.

1-(4-*tert*-Butylphenyl)-3,5-di-*p*-tolyl-1*H*-pyrazole (4j). Off white solid, m.p. 160–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{27}H_{29}N_2^+$ 381.2325, found 381.2327 $[M + H]^+$.

1-(4-*tert*-Butylphenyl)-3-(4-chlorophenyl)-5-(2-fluorophenyl)-1*H*-pyrazole (4k). Off white solid, m.p. 141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, 1H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.19 (d, $J_{C,F}$ = 244.5 Hz), 150.65 (d, $J_{C,F}$ = 2.3 Hz), 138.05, 137.58, 133.65, 131.75, 131.20, 130.61 (d, $J_{C,F}$ = 8.1 Hz), 128.80, 127.04, 125.87, 124.33, 123.78, 118.78 (d, $J_{C,F}$ = 14.8 Hz), 116.28, 116.00, 106.44 (d, $J_{C,F}$ = 2.0 Hz), 34.62, 31.29; HRMS (ESI) calcd for $C_{25}H_{22}ClFN_2Na^+$ 427.1348, found 427.1351 $[M + Na]^+$.

3-(4-Chlorophenyl)-5-(2-fluorophenyl)-1-*o*-tolyl-1*H*-pyrazole (4l). Dark red solid, m.p. 134–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 161.15 (d, $J_{C,F}$ = 248.25 Hz), 150.72, 139.42, 139.14, 135.55, 133.67, 131.79, 131.16, 130.66 (d, $J_{C,F}$ = 8.23 Hz), 129.02, 128.94 (d, $J_{C,F}$ = 12.2 Hz), 127.81, 127.12, 126.47, 124.04 (d, $J_{C,F}$ = 3.7 Hz), 118.31 (d, $J_{C,F}$ = 14.3 Hz), 116.23, 115.94, 105.35 (d, $J_{C,F}$ = 3.2 Hz), 17.69; HRMS (ESI) calcd for $C_{22}H_{16}ClFN_2Na^+$ 385.0878, found 385.0885 $[M + Na]^+$.

1-(4-*tert*-Butylphenyl)-3-(4-methoxyphenyl)-5-(4-nitrophenyl)-1*H*-pyrazole (4m). Pale green solid, m.p. 134–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{26}H_{25}N_3NaO_3^+$ 450.1788, found 450.1793 $[M + Na]^+$.

1-(3-Chloro-4-methylphenyl)-3-(4-methoxyphenyl)-5-(4-nitrophenyl)-1*H*-pyrazole (4n). Pale green solid, m.p. 109–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{23}H_{19}ClN_3O_3^+$ 420.1109, found 420.1121 $[M + H]^+$.

1-(4-Methoxyphenyl)-3,5-diphenyl-1*H*-pyrazole (4o). Off white solid, m.p. 121–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{22}H_{18}N_2NaO^+$ 349.1311, found 349.1298 $[M + Na]^+$.

Cell culture and cell proliferation assay

Cell culture. Human ovarian adenocarcinoma (SK-OV-3), colon adenocarcinoma (HT-29) and cervical adenocarcinoma (HeLa) cells were obtained from the American Type Culture Collection. Cells were grown on 75 cm^2 cell culture flasks with EMEM (Eagle's minimum essential medium), supplemented with 10% fetal bovine serum, and a 1% penicillin–streptomycin solution (10 000 units of penicillin and 10 mg of streptomycin in 0.9% NaCl) in a humidified atmosphere of 5% CO_2, 95% air at 37 °C.

Cell proliferation assay. The cell proliferation assay was carried out using a CellTiter 96 aqueous one solution cell proliferation assay kit (Promega, USA). Briefly, upon reaching about 75–80% confluency, 5000 cells/well were plated in a 96-well microplate in 100 μL media. After seeding for 72 h, the cells were treated with 50 μM compound in triplicate. Doxorubicin (10 μM) was used as the positive control. At the end of the sample exposure period (72 h), 20 μL 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 a microplate reader. The blank control was recorded by measuring the absorbance at 490 nm with wells containing the medium mixed with CellTiter 96 aqueous solution but no cells. Results were expressed as a 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 [bmim][PF_6] 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 reagents 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 the antiproliferative activities of these classes of compounds.

Acknowledgements

We thank University Grant Commission, New Delhi Project # 39-733/2010 (SR) and the National Science Foundation, Grant Number CHE 0748555, and American Cancer Society grant number RSG-07-290-01-CDD American Cancer Society Grant #RSG-07-290-01-CDD for their financial support. VKR is thankful to CSIR, New Delhi for SRF. We also thank the National Institute of General Medical Sciences of the National Institutes of Health under grant number 8 P20 GM103430-12 for sponsoring the core facility.

References

1 D. Kumar and S. P. Singh, *Heterocycles*, 2004, **63**, 145–173.
2 S. R. Donohue, R. F. Dannals, C. Halldin and V. W. Pike, *J. Med. Chem.*, 2011, **54**, 2961–2970.
3 L. Yan, P. Huo, J. S. Debenham, C. B. Madsen-Duggan, J. Lao, R. Z. Chen, J. C. Xiao, C.-P. Shen, D. S. Stribling, L. P. Shearman, A. M. Strack, N. Tsou, R. G. Ball, J. Wang, X. Tong, T. J. Bateman, V. B. G. Reddy, T. M. Fong and J. J. Hale, *J. Med. Chem.*, 2010, **53**, 4028–4037.
4 M. Gao, M. Wang and Q.-H. Zheng, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3704–3709.
5 R. L. Dow, P. A. Carpino, J. R. Hadcock, S. C. Black, P. A. Iredale, P. DaSilva-Jardine, S. R. Schneider, E. S. Paight, D. A. Griffith, D. O. Scott, R. E. O'Connor and C. I. Nduaka, *J. Med. Chem.*, 2009, **52**, 2652–2655.
6 J. H. M. Lange, H. K. A. C. Coolen, H. H. van Stuivenberg, J. A. R. Dijksman, A. H. J. Herremans, E. Ronken, H. G. Keizer, K. Tipker, A. C. McCreary, W. Veerman, H. C. Wals, B. Stork, P. C. Verveer, A. P. den Hartog, N. M. J. de Jong, T. J. P. Adolfs, J. Hoogendoorn and C. G. Kruse, *J. Med. Chem.*, 2003, **47**, 627–643.
7 S. Kumar, S. Bawa, S. Drabu, R. Kumar and H. Gupta, *Recent Pat. Anti-Infect. Drug Discovery*, 2009, **4**, 154–163.
8 J. Xie, G. I. Poda, Y. Hu, N. X. Chen, R. F. Heier, S. G. Wolfson, M. T. Reding, P. J. Lennon, R. G. Kurumbail, S. R. Selness, X. Li, N. N. Kishore, C. D. Sommers, L. Christine, S. L. Bonar, N. Venkatraman, S. Mathialagan, S. J. Brustkern and H.-C. Huang, *Bioorg. Med. Chem.*, 2011, **19**, 1242–1255.
9 E. Nassar, H. A. Abdel-Aziz, H. S. Ibrahim and A. M. Mansour, *Sci. Pharm.*, 2011, **79**, 507–524.
10 G. A. Nishiguchi, A. L. Rodriguez and J. A. Katzenellenbogen, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 947–950.
11 V. C. Jordan, *J. Med. Chem.*, 2003, **46**, 1081–1111.
12 S. R. Stauffer, C. J. Coletta, R. Tedesco, G. Nishiguchi, K. Carlson, J. Sun, B. S. Katzenellenbogen and J. A. Katzenellenbogen, *J. Med. Chem.*, 2000, **43**, 4934–4947.
13 Z. Özdemir, H. B. Kandilci, B. Gümüşel, Ü. Çalış and A. A. Bilgin, *Eur. J. Med. Chem.*, 2007, **42**, 373–379.
14 M. Ezawa, D. S. Garvey, D. R. Janero, S. P. Khanapure, L. G. Letts, A. Martino, R. R. Ranatunge, D. J. Schwalb and D. V. Young, *Lett. Drug Des. Discovery*, 2005, **2**, 40–43.
15 S. Fustero, M. Sánchez-Roselló, P. Barrio and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984–7034.
16 S. Kumar, H. Ila and H. Junjappa, *J. Org. Chem.*, 2009, **74**, 7046–7051.
17 S. Ponnala and D. Prasad Sahu, *Synth. Commun.*, 2006, **36**, 2189–2194.
18 D. Azarifar and B. Maleki, *Synth. Commun.*, 2005, **35**, 2581–2585.
19 Y. R. Huang and J. A. Katzenellenbogen, *Org. Lett.*, 2000, **2**, 2833–2836.
20 G. T. Cin, S. Demirel and A. Cakici, *J. Organomet. Chem.*, 2011, **696**, 613–621.
21 N. Nakamichi, Y. Kawashita and M. Hayashi, *Org. Lett.*, 2002, **4**, 3955–3957.
22 A. R. Katritzky, M. Wang, S. Zhang, M. V. Voronkov and P. J. Steel, *J. Org. Chem.*, 2001, **66**, 6787–6791.
23 S. P. Singh, D. Kumar, O. Prakash and R. P. Kapoor, *Synth. Commun.*, 1997, **27**, 2683–2689.
24 R. G. A. Vaghei and D. Maleki, *B. J. Chin. Chem. Soc.*, 2004, **51**, 1373–1376.
25 D. N. Moreira, C. P. Frizzo, K. Longhi, N. Zanatta, H. G. Bonacorso and M. A. P. Martins, *Monatsh. Chem.*, 2008, **139**, 1049–1054.
26 D. N. Moreira, K. Longhi, C. P. Frizzo, H. G. Bonacorso, N. Zanatta and M. A. P. Martins, *Catal. Commun.*, 2010, **11**, 476–479.

27 V. K. Rao, M. S. Rao and A. Kumar, *J. Heterocycl. Chem.*, 2011, **48**, 1356–1360.
28 A. Kumar and V. K. Rao, *Synlett*, 2011, **2011**, 2157–2162.
29 V. K. Rao, B. S. Chhikara, R. Tiwari, A. N. Shirazi, K. Parang and A. Kumar, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 410–414.
30 V. K. Rao, B. S. Chhikara, A. N. Shirazi, R. Tiwari, K. Parang and A. Kumar, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3511–3514.
31 D. Kumar, V. B. Reddy, A. Kumar, D. Mandal, R. Tiwari and K. Parang, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 449–452.
32 A. Kumar, I. Ahmad, B. S. Chhikara, R. Tiwari, D. Mandal and K. Parang, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1342–1346.
33 S. Syam, S. I. Abdelwahab, M. A. Al-Mamary and S. Mohan, *Molecules*, 2012, **17**, 6179–6195.