One-Pot Synthesis of 1,3,5-Triarylpyrazoles

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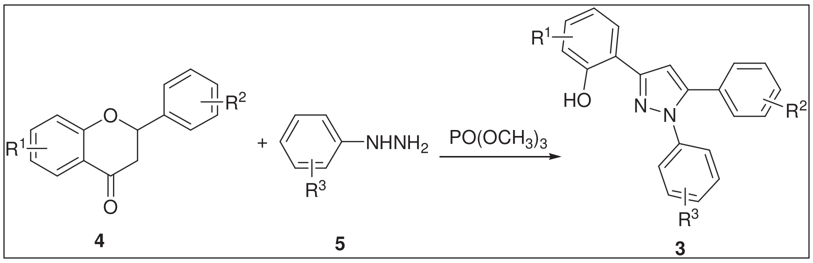

A series of novel 1,3,5-triarylpyrazoles **3a–3x** were synthesized from flavanones, arylhydrazines, and trimethyl phosphate in an one-pot procedure. Facile reaction process, easy after-reaction workshop, and good yields are the distinct characteristics of the developed protocol. The target compounds were characterized by element analysis, infrared ray (IR), ^{1}H NMR spectra, and electrospray ionization-mass spectrometry. The structure of representative compound **3h** ($C_{23}H_{20}N_2O_3$, M_r = 372.42) was further confirmed by X-ray diffraction. It crystallizes in monoclinic, space group P $2_1/c$, a = 8.9720(5), b = 24.5523(13), c = 8.9687(6) Å, α = 90.0000, β = 102.6417(17), γ = 90.0000°, V = 1927.76(20) Å^3, Z = 4, μ(MoKα) = 0.086, F(000) = 784, D_c = 1.283 g/cm^3, the final R = 0.0349 and wR = 0.0844 for 1668 observed reflections ($I > 2\sigma(I)$)

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INTRODUCTION

Triaryl-substituted pyrazoles received substantial attention for their various biological activities, such as anticancer [1–3], anti-inflammatory [4], and so on [5]. Reported methods for the synthesis of 1,3,5-triarylpyrazoles, as cycloaddition using 3-aryl-2,3-epoxy-1-phenyl-1-propanones or cyclocondensation from 1,3-diphenylpropane-1,3-dione [6–9], usually result in the formation of isomers and involve multiple synthetic steps [10]. Thus, with the aim of refining and simplifying the synthetic protocol, we delivered a facile and efficient method for the synthesis of 1,3,5-triaryl-substituted pyrazoles from flavanones, arylhydrazines, and $PO(OCH_3)_3$ in a one-pot procedure.

RESULTS AND DISCUSSION

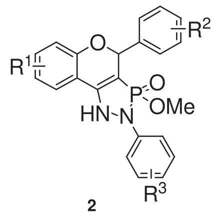
The synthetic procedure to obtain compound **3** (1,3,5-triarylpyrazoles) was discovered accidentally in one of our previous studies on pyrazole compound **2**. Treating **1** ((*E*)-1-phenyl-2-(2-phenyl-2,3-dihydrochromen-4-ylidene) hydrazine) with $PO(OCH_3)_3$ in solvent at temperature gave **3** in high yields instead of **2** (Scheme 1). Since **1** could be obtained through the reaction between compound **4** (2-phenyl-2,3-dihydrochromen-4-one) and compound **5** (1-phenylhydrazine), we supposed that compound **3** might be obtained directly from the reaction between compounds **4** and **5** in the presence of $PO(OCH_3)_3$ in an one-pot procedure (Scheme 2), which was proved to be feasible as follows.

Various substituted flavanones (**4**) and arylhydrazines (**5**) were investigated to explore the optimal reaction condition, as well as the scope of our method. As shown in Table 1, substrates with aromatic ring bearing electron-withdrawing group, electron-detonating group, and no substituent were involved, and most substrates led the corresponding products in moderate to good yields. Flavanone bearing methoyxl group tended to lead a slightly higher yield, while flavanone bearing electron-withdrawing group resulted in low yield and the reaction did not go smoothly at low temperature. High reaction temperature, up to 200°C, was required when 4-dinitrophenylhydrazine and 4-methylsulfonyl phenyl hydrazine were used as the reactants. It was also noteworthy to mention that ortho-substituted phenylhydrazine significantly decreased reaction yield (**3k**), due to steric effect.

Products **3a–3x** were characterized by element analysis, IR, ^{1}H NMR spectra, and electrospray ionization-mass spectrometry (ESI-MS). The structure of compound **3h** was further confirmed by X-ray analysis (Figs. 1 and 2, CCDC(687044)). The selected bond lengths, bond angles, and torsion angles of **3h** are listed in Tables 3 and 4, respectively. Further details can be found in Table 2.

Structure analysis indicated that all ring atoms in the pyrazole moiety were nearly coplanar. The N(2)─C(4) bond length was 1.363(2), which was remarkably shorter

Scheme 1



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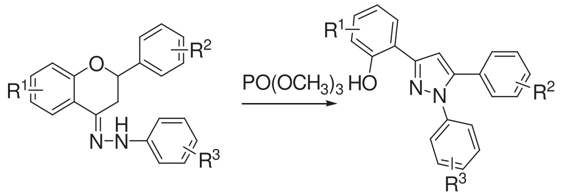
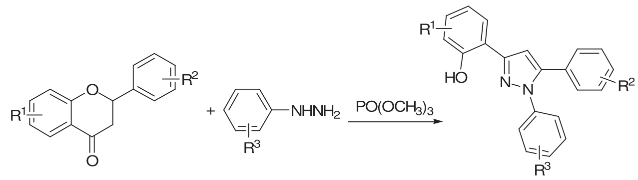


1 3

Scheme 2



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than a normal C—N bond (1.50 Å) but close to a typical C—N bond (1.32 Å) [11]. It was considered that atom N(2) made three sp2–sp2 σ bonds with its neighboring atoms. Its lone pair electrons made Π bond with the other four electrons (three from carbon atoms, one from nitrogen atoms N(1)). The dihedral shaped by pyrazole plane and aryl ring C(5)—C(6)—C(7)—C(8)—C(9)—C(10) was 167.5°, which also illustrated a coplanar structure. Due to the result of conjugation effect of aryl rings, the bond distances of N(2)—C(19) (1.425 Å), C(4)—C(13) (1.475(2) Å), C(2)—C(5) (1.472(2) Å) were shorter than that of typical C—N (1.50 Å) and C—C bond (1.54 Å). In addition, X-ray analysis also revealed that the existence of an intramolecular hydrogen bond in the crystal and the bond length of O(3)—H(1)…N(1) was 2.548(2) (Table 5).

We speculated the mechanistic pathway for formation of pyrazoles as follows (Scheme 3). First, (*E*)-1-phenyl-2-(2-phenyl-2,3-dihydrochromen-4-ylidene)hydrazine was obtained by the reaction of 2-phenyl-2,3-dihydrochromen-4-one with 1-phenylhydrazine, and the arylhydrazone pyrone ring was opened. Then electronic rearrangement happened and 2-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)phenol was obtained. Finally, objective compound of 1,3,5-triarylpyrazole was successfully synthesized using PO$(OCH_3)_3$ as oxidant [11,12].

Table 1

One-pot synthesis of 1,3,5-triarylpyrozoles **3a–3x**.

Entry	Compound	R^1	R^2	R^3	Condition	Yield (%)
1	**3a**	H	H	H	120°C, 2 h	54
2	**3b**	H	4-MeO	H	120°C, 12 h	56
3	**3c**	H	4-Cl	4-NO_2	200°C, 12 h	40
4	**3d**	H	4-Cl	H	120°C, 12 h	45
5	**3e**	H	H	4-Cl	130°C, 12 h	58
6	**3f**	H	H	4-NO_2	200°C, 6 h	53
7	**3g**	H	H	4-SO_2Me	180°C, 6 h	45
8	**3h**	4,6-diMeO	H	H	110°C, 6 h	65
9	**3i**	4,6-diMeO	4-Me	H	110°C, 6 h	67
10	**3j**	4,6-diMeO	3-MeO	H	110°C, 6 h	64
11	**3k**	4,6-diMeO	3-MeO	2-Cl	110°C, 6 h	29
12	**3l**	4,6-diMeO	4-MeO	H	110°C, 6 h	72
13	**3m**	4,6-diMeO	4-MeO	4-F	110°C, 6 h	64
14	**3n**	4,6-diMeO	H	4-Cl	110°C, 6 h	67
15	**3o**	4,6-diMeO	3,4-diMeO	H	110°C, 6 h	72
16	**3p**	4,6-diMeO	H	4-NO_2	120°C, 24 h	48
17	**3q**	4,6-diMeO	H	4-Br	120°C, 6 h	59
18	**3r**	4-MeO	H	H	120°C, 6 h	60
19	**3s**	4-MeO	4-Cl	H	120°C, 6 h	53
20	**3t**	5-COOH	H	H	120°C, 24 h	49
21	**3u**	4-MeO	4-MeO	4-Br	120°C, 12 h	54
22	**3v**	5-Cl	H	H	130°C, 12 h	48
23	**3w**	5-Me	H	H	120°C, 12 h	51
24	**3x**	5-Me	3-CH_2OCH_2-4	H	120°C, 12 h	53

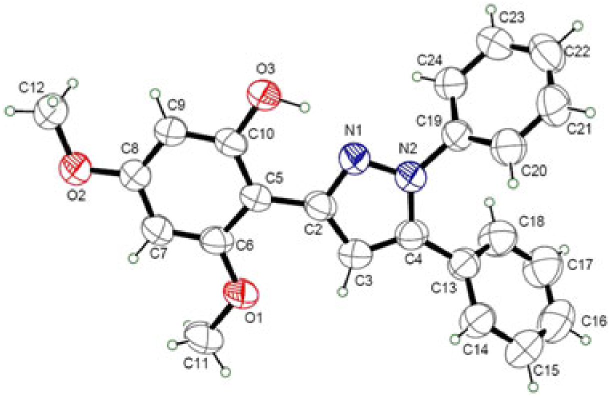


Figure 1. Molecule structure of compound of **3h**.

CONCLUSION

In summary, we have successfully developed a novel facile one-pot procedure for the synthesis of 1,3,5-triaryl substituted pyrazoles from flavanones, arylhydrazines, and $PO(OCH_3)_3$. The reaction products were prepared in moderate to good yield with different substituents.

EXPERIMENTAL

Melting points were determined on a Buchi B-540 apparatus and were uncorrected. All ^1H NMR spectra were recorded on a Brüker AM 400 with tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in δ values (ppm) relative to internal TMS and *J* values were reported in Hertz. IR spectra were recorded using KBr pellets on a Bruker Vector-22 FTIR spectrophotometer. The elemental analysis was measured on a EA-300 analyzer and the MS(ESI) were measured on Esquire-LC-00075. X-ray diffraction data were collected on a Rigaku RAXIS-RAPID.

Representative procedure for preparation of 3h. 5,7-Dimethoxylflavanone (1) was prepared according to the literature [13]. Then the mixture of compound 1 (0.284 g, 1 mmol), phenylhydrazine hydrochloride 2 (0.173 g, 1.2 mmol), and $PO(OCH_3)_3$ (1 mL) was stirred at 110°C for 12 h. After cooling to room temperature, the reaction mixture was then added into water (20 mL) and then extracted with EtOAc

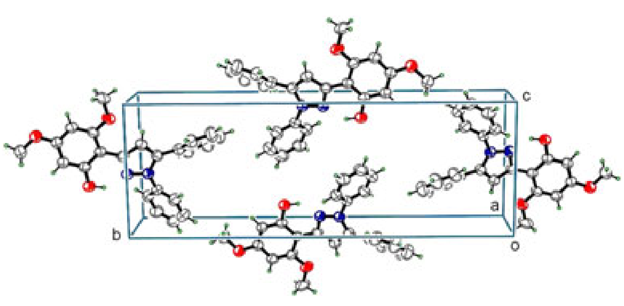


Figure 2. Packing arrangement in a unit cell of **3h**.

Table 2

Details of X-ray diffraction studies.

Complex	**3h**
CCDC No.	687044
Formula	$C_{23}\,H_{20}\,N_2\,O_3$
M_r (g/mol)	372.42
Crystal color	Colorless
Crystal habit	Needle
Crystal dimensions (mm)	0.32 × 0.18 × 0.11
Crystal system	Monoclinic
Space group	P 2_1/c
Z	4
a (Å)	8.9720(5)
b(Å)	24.5523(13)
c(Å)	8.9687(6)
α (°)	90
β (°)	102.6417(17)
γ (°)	90
Temperature (K)	296(1)
Volume (Å^3)	1927.8(2)
D calcd. (g/cm^3)	1.283
Radiation	MoKα (λ = 0.71075 Å)
Absorption coefficient, μ (mm^{-1})	0.086
F(000)	784.0
θ range(°) for data correction	0.997–27.44
Observed reflections	18,904
Independent reflections	4403(R_{int} = 0.046)
Data/restraints/parameters	4403/0/254
Maximum shift/error	0.00
Goodness-of-fit on F^2	1.001
Final R indices[$I > 2\sigma(I)$]	R_1 = 0.0349, wR_2 = 0.0844
Extinction coefficient	272(16)
Largest diffraction peak and hole (e; Å^{-3})	0.40 and −0.34

(10 mL × 3); the extract was then washed with brine and concentrated to give residue, which was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (b.p.: 60–90°C, v/v 1:5) to afford white powder as the pure product (0.241 g, 65%). Single crystals of the title compound were obtained by evaporating the petroleum ether/ethyl acetate (5:1) solution slowly. The structure was solved by direct methods with CrystalStructure 3.7.0 [14–16].

2-(1,5-Diphenyl-1H-pyrazol-3-yl)phenol 3a. Yield: 54%. White powder, mp 83–85°C. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.84 (s, 1H, —OH), 7.64 (dd, 1H, *J* = 7.6 Hz, 1.2 Hz, H-6″), 7.38–7.23 (m, 11H, H- 2′, 3′, 4′, 5′, 6′, 5″, 2‴, 3‴, 4‴, 5‴, 6‴), 7.05 (dd, 1H, *J* = 7.6 Hz, 1.2 Hz, H-3″), 6.95 (td, 1H, *J* = 7.6 Hz, 1.2 Hz, H-4″), 6.88 (s, 1H, H-4); IR (KBr)v: 3057, 2926, 1652, 1622, 1595, 1498, 1363, 1296, 1250, 827, 758, 694 cm^{-1}; Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97; Found: C, 80.58; H, 5.20; N, 9.08; MS (ESI): *m/z* = 313 [M+H]$^+$.

2-(5-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)phenol 3b. Yield: 56%. White powder, mp 90–92°C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63(dd, 1H, *J* = 7.6 Hz, 1.6 Hz, H-6″), 7.38–7.30 (m, 5H, H-2′, 3′, 4′, 5′, 6′), 7.25 (td, 1H, *J* = 7.6 Hz, 1.2 Hz, H-5″), 7.15 (d, 2H, *J* = 9.2 Hz, H-2‴, 6‴), 7.05 (dd, 1H, *J* = 7.6 Hz, 1.2 Hz, H-3″), 6.96 (td, 1H, *J* = 7.6 Hz, 1.2 Hz, H-4″), 6.82 (s, 1H, H-4), 6.80 (d, 2H, H-3‴, 5‴); IR (KBr)v: 3057, 2927, 1652, 1623, 1585, 1499, 1457, 1362, 1255, 837,

Table 3

Selected bond lengths (Å) and bond angles (°) of **3h**.

Bond	Distance	Bond	Distance	Bond	Distance
N(1)—N(2)	1.364(2)	N(1)–C(2)	1.341(2)	N(2)—C(4)	1.363(2)
N(2)—C(19)	1.425(2)	C(4)–C(13)	1.425(2)	C(2)—C(5)	1.473(2)
O(1)—C(6)	1.374(2)	O(2)–C(8)	1.380(2)	O(3)—C(10)	1.364(2)
Bond	Angle (°)	Bond	Angle (°)	Bond	Angle (°)
N(1)—N(2)—C(4)	111.1(1)	N(1)—C(2)—C(3)	109.6(2)	C(2)—C(3)—C(4)	106.6(2)
N(2)—C(4)—C(3)	106.6(2)				

Table 4

Selected torsion angles (°) of **3h**.

Bond	Angle (°)	Bond	Angle (°)
N(1)–N(2)–C(19)–C(24)	−49.8(2)	C(19)–N(2)–C(4)–C(13)	−7.2(2)
N(1)–C(2)–C(5)–C(10)	−5.0(2)	C(3)–C(2)–C(5)–C(6)	−5.1(2)
C(2)–N(1)–N(2)–C(4)	−0.2(2)	C(4)–N(2)–C(19)–C(20)	−49.5(2)
N(2)–C(4)–C(13)–C(18)	−44.4(2)		

798, 759, 695 cm^{-1}; Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18; Found: C, 77.33; H, 5.27; N, 8.03; MS (ESI): m/z = 343 $[M+H]^+$.

2-(5-(4-Chlorophenyl)-1-(4-nitrophenyl)-1H-pyrazol-3-yl) phenol 3c. Yield: 40%. Yellow powder, mp 148–150°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.58 (s, 1H, OH), 8.19 (d, 2H, J = 9.2 Hz, H-3′, 5′), 7.63(dd, 1H, J = 7.6 Hz, 1.6 Hz, H-6″), 7.47 (d, 2H, J = 9.2 Hz, H-2′, 6′), 7.40 (d, 2H, J = 8.4 Hz, H-3″′, 5″′), 7.36 (d, 2H, J = 8.4 Hz, H-2″′, 6″′), 7.25 (td, 1H, J = 7.6 Hz, 1.2 Hz, H-5′), 7.05 (dd, 1H, J = 7.6 Hz, 1.2 Hz, H-3″), 7.25 (td, 1H, J = 7.6 Hz, 1.2 Hz, H-4″), 6.92 (s, 1H, H-4); IR (KBr)v: 3060, 1636, 1622, 1584, 1498, 1446, 1362, 1344, 1297, 1249, 830, 799, 759 cm^{-1}; Anal. Calcd for $C_{21}H_{14}ClN_3O_3$: C, 64.37; H, 3.60; N, 10.72; Found: 64.31; H, 3.58; N, 10.69; MS (ESI): m/z = 392 $[M+H]^+$.

2-(5-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)phenol 3d. Yield: 45%. White powder, mp 134–136°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.75 (s, 1H, —OH), 7.63 (dd, 1H, J = 8.0 Hz, 1.6 Hz, H-6″), 7.42–7.21 (m, 10H, H-2′, 3′, 4′, 5′, 6′, 5″, 2″′, 3″′, 5″′, 6″′), 7.05 (dd, 1H, J = 8.0 Hz, 1.2 Hz, H-3″), 6.95 (td, 1H, J = 8.0 Hz, 1.2 Hz, H-4″), 6.87 (s, 1H, H-4); IR (KBr)v: 3063, 1637, 1622, 1584, 1499, 1446, 1362, 1297, 1249, 830, 799, 759, 692 cm^{-1}; Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08; Found: 72.65; H, 4.38; N, 8.13; MS (ESI): m/z = 347 $[M+H]^+$.

Table 5

Hydrogen-bonding Geometry (Å) of **3h**.

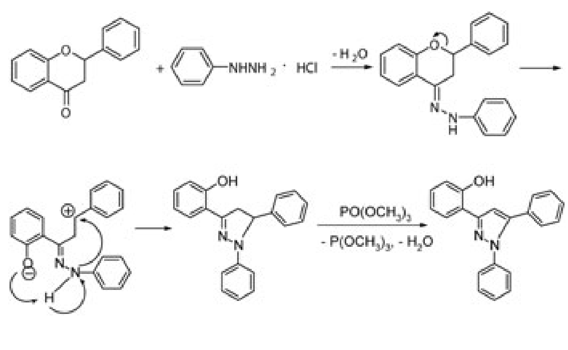
D—H…A	D—H	H…A	D…A	D—H…A
O(3)—H(1)…N(1)	0.945	1.716	2.548(2)	144.8

Symmetry codes: x, y, z.

2-(1-(4-Chlorophenyl)-5-phenyl-1H-pyrazol-3-yl)phenol 3e. Yield: 58%. White powder, mp 144–146°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.84 (s, 1H, —OH), 7.64 (dd, 1H, J = 7.6 Hz, 1.2 Hz, H-6″), 7.38–7.23 (m, 10H, H-2′, 3′, 5′, 6′, 5″, 2″′, 3″′, 4″′, 5″′, 6″′), 7.05 (dd, 1H, J = 8.0 Hz, 1.6 Hz, H-3″), 6.95 (td, 1H, J = 8.0 Hz, 1.6 Hz, H-4″), 6.89 (s, 1H, H-4); IR (KBr)v: 3058, 1632, 1622, 1584, 1499, 1458, 1361, 1290, 1263, 830, 795, 759, 692 cm^{-1}; Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08; Found: 72.69; H, 4.39; N, 8.12; MS (ESI): m/z = 347 $[M+H]^+$.

2-(1-(4-Nitrophenyl)-5-phenyl-1H-pyrazol-3-yl)phenol 3f. Yield: 53%. White powder, mp 150–152°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.51 (s, 1H, —OH), 8.19 (d, 2H, J = 9.2 Hz, H-3′, 5′), 7.64 (dd, 1H, J = 7.6 Hz, 1.2 Hz, H-6″), 7.46 (d, 2H, J = 9.2 Hz, H-2′, 6′), 7.38–7.23 (m, 6H, H-5″, 2″′, 3″′, 4″′, 5″′, 6″′), 7.05 (dd, 1H, J = 7.6 Hz, 1.2 Hz, H-3″), 6.95 (td, 1H, J = 7.6 Hz, 1.2 Hz, H-4″), 6.91 (s, 1H, H-4); IR (KBr)v: 3059, 1632, 1586, 1499, 1438, 1362, 1347, 1297, 839, 794, 766 cm^{-1}; Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76; Found: 70.52; H, 4.26; N, 11.81; MS (ESI): m/z = 358 $[M+H]^+$.

Scheme 3



2-(1-(4-(Methylsulfonyl)phenyl)-5-phenyl-1H-pyrazol-3-yl) phenol 3g. Yield: 30%. White powder, mp 96–98°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.54 (s, 1H, —OH), 7.92 (d, 2H, J = 8.4 Hz, H-3′, 5′), 7.64 (dd, 1H, J = 8.0 Hz, 1.6 Hz, H-6″), 7.53 (d, 2H, J = 8.4 Hz, H-2′, 6′), 7.45–7.39 (m, 3H, H-3″′, 4″′, 5″′), 7.32–7.27 (m, 3H, H-5″, 2″′, 6″′), 7.07 (d, 1H, J = 8.0 Hz, H-3″), 6.97 (td, 1H, J = 8.0 Hz, 0.8 Hz, H-4″), 6.93 (s, 1H, H-4), 3.09 (s, 3H, -SO_2CH_3); IR (KBr)v: 3057, 1652, 1622, 1585, 1497, 1450, 1361, 1318, 1297, 1249, 917, 825, 762 cm^{-1}; Anal. Calcd for $C_{22}H_{18}N_2O_3S$: C, 67.67; H, 4.65; N, 7.17; Found: 67.74; H, 4.61; N, 7.24; MS (ESI): m/z = 391 [M+H]$^+$.

2-(1,5-Diphenyl-1H-pyrazol-3-yl)-3,5-dimethoxyphenol 3h. Yield: 65%. White powder, mp 155–156°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.97 (s, 1H, —OH), 7.36–7.26 (m, 10H, H-5″′, 6″′, 2′, 3′, 4′, 5′, 6′, 2″′, 3″′, 4″′), 7.19 (s, 1H, H-4), 6.28 (d, 1H, J = 2.0 Hz, H-5″), 6.15 (d, 1H, J = 2.0 Hz, H-3″), 3.92 (s, 3H, —OCH_3), 3.84 (s, 3H, —OCH_3); IR (KBr)v: 3064, 1628, 1595, 1498, 1434, 1383, 1287, 1217, 822, 766, 738, 697 cm^{-1}; Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52; Found: 74.29; H, 5.44; N, 7.58; MS (ESI): m/z = 373 [M+H]$^+$.

3,5-Dimethoxy-2-(1-phenyl-5-*p*-tolyl-1H-pyrazol-3-yl)phenol 3i. Yield: 67%. White amorphous powder, mp 174–176°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.98 (s, 1H, —OH), 7.36–7.28 (m, 5H, H-2′, 3′, 4′, 5′, 6′), 7.20 (d, 2H, J = 8.0 Hz, H-2″′, 6″′), 7.16 (s, 1H, H-4), 7.14 (d, 2H, J = 8.0 Hz, H-3″′, 5″′), 6.26 (d, 1H, J = 1.2 Hz, H-5″), 6.13 (d, 1H, J = 1.2 Hz, H-3″), 3.92 (s, 3H, —OCH_3), 3.83 (s, 3H, —OCH_3), 2.37 (s, 3H, CH_3); IR (KBr)v: 3058, 2928, 1630, 1597, 1500, 1434, 1383, 1287, 860, 825, 799, 697 cm^{-1}; Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25; Found: 74.46; H, 5.40; N, 7.52; MS (ESI): m/z = 387 [M+H]$^+$.

3,5-Dimethoxy-2-(5-(3-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)phenol 3j. Yield: 56%. White powder, mp 141–142°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 7H, H-2′, 3′, 4′, 5′, 6′, 5″′, 6″′), 6.98 (s, 1H, H-4), 6.89–6.86 (m, 2H, H-2″′, 4″′), 6.22 (d, 1H, J = 2.0 Hz, H-5″), 6.09 (d, 1H, J = 2.0 Hz, H-3″), 3.91 (s, 3H, —OCH_3), 3.81 (s, 6H, —OCH_3×2); IR (KBr)v: 3049, 1635, 1595, 1499, 1427, 1385, 1290, 933, 880, 822, 766, 738, 690 cm^{-1}; Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96; Found: C, 71.51; H, 5.58; N, 7.05; MS (ESI): m/z = 403 [M+H]$^+$.

2-(1-(2-Chlorophenyl)-5-(3-methoxyphenyl)-1H-pyrazol-3-yl)-3,5-dimethoxyphenol 3k. Yield: 29%. White powder, mp 135–137°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, J = 7.6 Hz, 1.6 Hz, H-6′), 7.49 (dd, J = 7.6 Hz, 1.2 Hz, H-3′), 7.37–7.22 (m, 4H, H-2′, 4′, 5′, 5″′, 6″′), 7.11 (s, 1H, H-4), 6.89–6.86 (m, 2H, H-2″′, 4″′), 6.24 (d, 1H, J = 2.0 Hz, H-5″), 6.11 (d, 1H, J = 2.0 Hz, H-3″), 3.91 (s, 3H, —OCH_3), 3.81 (s, 6H, —OCH_3×2); IR (KBr)v: 3058, 1629, 1599, 1497, 1427, 1388, 1288, 1156, 884, 752, 690 cm^{-1}; Anal. Calcd for $C_{24}H_{21}ClN_2O_4$: C, 65.98; H, 4.84; N, 6.41; Found: C, 66.06; H, 4.81; N, 6.52; MS (ESI): m/z = 437 [M+H]$^+$.

3,5-Dimethoxy-2-(5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)phenol 3l. Yield: 72%. White powder, mp 180–182°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.31 (d, 5H, H-2′, 3′, 4′, 5′, 6′), 7.23 (d, 2H, J = 8.8 Hz, H-2″′, 6″′), 7.01(s, 1H, H-4), 6.90 (d, 2H, J = 8.8 Hz, H-3″′, 5″′), 6.22 (d, 1H, J = 2.0 Hz, H-5″), 6.09 (d, 1H, J = 2.0 Hz, H-3″), 3.91 (s, 3H, —OCH_3), 3.81 (s, 3H, —OCH_3), 3.76 (s, 3H, —OCH_3); IR (KBr)v: 3030, 2827, 1633, 1600, 1499, 1433, 1378, 1277, 858, 799, 762, 695 cm^{-1}; Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96; Found: C, 71.55; H, 5.56; N, 6.90; MS (ESI): m/z = 403 [M+H]$^+$.

2-(1-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)-3,5-dimethoxyphenol 3m. Yield: 56%. White powder, mp 115–117°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 2H, H-3′, 5′); 7.25–7.20 (m, 4H, H-2′, 6′, 2″′, 6″′), 7.11(s, 1H, H-4), 6.88 (d, 2H, J = 8.8 Hz, H-3″′, 5″′), 6.24 (d, 1H, J = 2.0 Hz, H-5″), 6.11 (d, 1H, J = 2.0 Hz, H-3″), 3.91 (s, 3H, —OCH_3), 3.83 (s, 3H, —OCH_3), 3.77 (s, 3H, —OCH_3); IR (KBr)v: 3088, 1649, 1587, 1499, 1434, 1383, 1288, 1156, 904, 766 cm^{-1}; Anal. Calcd for $C_{24}H_{21}FN_2O_4$: C, 68.56; H, 5.03; N, 6.66; Found: C, 68.71; H, 5.11; N, 6.59; MS (ESI): m/z = 421 [M+H]$^+$.

2-(1-(4-Chlorophenyl)-5-phenyl-1H-pyrazol-3-yl)-3,5-dimethoxyphenol 3n. Yield: 67%. White powder, mp 149–151°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 9H, H-2′, 3′, 5′, 6′, 2″′, 3″′, 4″′, 5″′, 6″′), 7.15(s, 1H, H-4), 6.24 (d, 1H, J = 2.0 Hz, H-5″), 6.11 (d, 1H, J = 2.0 Hz, H-3″), 3.89 (s, 3H, —OCH_3), 3.81 (s, 3H, —OCH_3); IR (KBr)v: 3030, 2927, 1644, 1590, 1503, 1431, 1388, 1278, 917, 876, 752, 697 cm^{-1}; Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89; Found: C, 67.83; H, 4.66; N, 6.81; MS (ESI): m/z = 407 [M+H]$^+$.

2-(1-(4-Bromophenyl)-5-(3,4-dimethoxyphenyl)-1H-pyrazol-3-yl)-5-methoxyphenol 3o. Yield: 56%. White powder, mp 182–183°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.81 (s, 1H, —OH), 7.51 (d, 1H, J = 8.8 Hz, H-6″), 7.48 (d, 2H, J = 8.8 Hz, H-3′, 5′), 7.21 (d, 2H, J = 8.8 Hz, H-2′, 6′), 6.85 (s, 2H, H-4, 5″′), 6.74 (s, 2H, H-2″′, 6″′), 6.59 (d, 1H, J = 2.0 Hz, H-3″), 6.53 (dd, 1H, J = 8.8 Hz, 2.0 Hz, H-5″), 3.91 (s, 3H, —OCH_3), 3.84 (s, 3H, —OCH_3), 3.74 (s, 3H, —OCH_3); IR (KBr)v: 3046, 1652, 1597, 1489, 1431, 1380, 1288, 904, 766 cm^{-1}; Anal. Calcd for $C_{24}H_{21}BrN_2O_4$: C, 59.89; H, 4.40; N, 5.82; Found: C, 60.01; H, 4.37; N, 5.81; MS (ESI): m/z = 481 [M+H]$^+$.

3,5-Dimethoxy-2-(1-(4-nitrophenyl)-5-phenyl-1H-pyrazol-3-yl)phenol 3p. Yield: 48%. White powder, mp 177–178°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.58 (s, 1H, OH), 8.19 (d, 2H, J = 9.2 Hz, H-3′, 5′), 7.47 (d, 2H, J = 9.2 Hz, H-2′, 6′), 7.44–7.39 (m, 3H, H-3″′, 4″′, 5″′), 7.34–7.31 (m, 2H, H-2″′, 6″′), 7.24 (s, 1H, H-4), 6.27 (d, 1H, J = 2.0 Hz, H-5″), 6.14 (d, 1H, J = 2.0 Hz, H-3″), 3.91 (s, 3H, —OCH_3), 3.84 (s, 3H, —OCH_3); IR (KBr)v: 3058, 2970, 1653, 1585, 1521, 1457, 1362, 933, 887, 822, 735, 692 cm^{-1}; Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07; Found: C, 66.29; H, 4.56; N, 10.13; MS (ESI): m/z = 418 [M+H]$^+$.

2-(1-(4-Bromophenyl)-5-phenyl-1H-pyrazol-3-yl)-3,5-dimethoxyphenol 3q. Yield: 56%. White powder, mp 144–146°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.78 (s, 1H, H-OH), 7.46 (d, 2H, J = 8.8 Hz, H-3′, 5′), 7.38–7.35 (m, 3H, H-3″′, 4″′, 5″′), 7.32–7.29 (m, 2H, H-2″′, 6″′), 7.19 (d, 2H, J = 8.8 Hz, H-2′, 6′), 7.18 (s, 1H, H-4), 6.26 (d, 1H, J = 2.4 Hz, H-5″), 6.13 (d, 1H, J = 2.4 Hz, H-3″), 3.91 (s, 3H, —OCH_3), 3.84 (s, 3H, —OCH_3); IR (KBr)v: 3059, 1643, 1598, 1497, 1438, 1361, 1290, 1070, 933, 886, 738, 692 cm^{-1}; Anal. Calcd for $C_{23}H_{19}BrN_3O_5$: C, 61.21; H, 4.24; N, 6.21; Found: C, 61.12; H, 4.29; N, 6.32; MS (ESI): m/z = 418 [M+H]$^+$.

2-(1,5-Diphenyl-1H-pyrazol-3-yl)-5-methoxyphenol 3r. Yield: 60%. White powder, mp 146–148°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.94 (s, 1H, OH), 7.52 (d, 1H, J = 8.0 Hz, H-6″), 7.38–7.27 (m, 10H, H-2′, 3′, 4′, 5′, 6′, 2″′, 3″′, 4″′, 5″′, 6″′), 6.78 (s, 1H, H-4), 6.60 (d, 1H, J = 2.8 Hz, H-3″), 6.53 (dd, 1H, J = 8.0 Hz, 2.8 Hz, H-5″), 3.83 (s, 3H, —OCH_3); IR (KBr)v: 3064, 1632, 1585, 1498, 1439, 1361, 1286, 1263, 977, 830, 799, 763, 694 cm^{-1}; Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18; Found: C, 77.29; H, 5.35; N, 8.24; MS (ESI): m/z = 343 [M+H]$^+$.

2-(5-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)-5-methoxyphenol 3s. Yield: 53%. White powder, mp 152–154°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.85 (s, 1H, —OH), 7.51 (d, 1H, J = 8.8 Hz, H-6″), 7.40–7.29 (m, 7H, H-3‴, 5‴, 2′, 3′, 4′, 5′, 6′), 7.22 (d, 2H, J = 8.8 Hz, H-2‴, 6‴), 6.78 (s, 1H, H-4), 6.59 (d, 1H, J = 2.4 Hz, H-3″), 6.53 (dd, 1H, J = 8.8 Hz, 2.4 Hz, H-5″), 3.83 (s, 3H, —OCH_3); IR (KBr)v: 3063, 2951, 1637, 1558, 1489, 1445, 1369, 1289, 1093, 947, 836, 795, 759, 697 cm^{-1}; Anal. Calcd for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 9.41; Found: C, 70.19; H, 4.65; N, 9.33; MS (ESI): m/z = 377 [M+H]$^+$.

3-(1,5-Diphenyl-1H-pyrazol-3-yl)-4-hydroxybenzoic acid 3t. Yield: 49%. White powder, mp 241–242°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.56 (s, 1H, —OH), 8.46 (d, 1H, J = 2.0 Hz, H-2″), 8.03 (dd, 1H, J = 8.8 Hz, 2.0 Hz, H-4″), 7.41–7.29 (m, 10H, H-2′, 3′, 4′, 5′, 6′, 2‴, 3‴, 4‴, 5‴, 6‴), 7.10 (d, 1H, J = 8.8 Hz, H-5″), 7.02 (s, 1H, H-4); IR (KBr)v: 3424, 1690, 1633, 1588, 1489, 1433, 1363, 1286, 830, 758, 690 cm^{-1}; Anal. Calcd for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.53; N, 7.86; Found: C, 74.26; H, 4.49; N, 7.80; MS (ESI): m/z = 357 [M+H]$^+$.

5-Methoxy-2-(5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)phenol 3u. Yield: 52%. White powder, mp 181–183°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.53 (s, 1H, —OH), 7.86 (d, 1H, J = 7.2 Hz, H-6″), 7.44 (d, 1H, J = 15.2 Hz, H-4), 7.15 (d, 2H, J = 9.2 Hz, H-2‴, 6‴), 6.80 (d, 2H, H-3‴, 5‴), 6.49 (dd, 1H, J = 7.2Hz, 2.4 Hz, H-5″), 6.48 (d, 1H, J = 2.4 Hz, H-3″), 3.96 (s, 3H, —OCH_3), 3.94 (s, 3H, —OCH_3); IR (KBr)v: 3057, 1622, 1590, 1498, 1433, 1358, 1263, 877, 830, 799, 694 cm^{-1}; Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52; Found: C, 74.24; H, 5.44; N, 7.46; MS (ESI): m/z = 373 [M+H]$^+$.

4-Chloro-2-(1,5-diphenyl-1H-pyrazol-3-yl)phenol 3v. Yield: 48%. White powder, mp 98–100°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.83 (s, 1H, OH), 7.59 (d, 1H, J = 2.4 Hz, H-6″), 7.39–7.26 (m, 10H, H-2′, 3′, 4′, 5′, 6′, 2‴, 3‴, 4‴, 5‴, 6‴), 7.18 (dd, 1H, J = 8.8 Hz, 2.4 Hz, H-4″), 6.98 (d, 1H, J = 8.8 Hz, H-3″), 6.85 (s, 1H, H-4); IR (KBr)v: 3057, 1637, 1595, 1498, 1456, 1361, 1263, 977, 830, 787, 765, 695 cm^{-1}; Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08; Found: C, 72.63; H, 4.41; N, 7.94; MS (ESI): m/z = 347 [M+H]$^+$.

2-(1,5-Diphenyl-1H-pyrazol-3-yl)-4-methylphenol 3w. Yield: 51%. White powder, mp 94–96°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.49 (s, 1H, —OH), 7.42 (d, 1H, J = 1.6 Hz, H-6″), 7.39–7.24 (m, 10H, H-2′, 3′, 4′, 5′, 6′, 2‴, 3‴, 4″′, 5‴, 6‴), 7.06 (dd, 1H, J = 8.0 Hz, 1.6Hz, H-4″), 6.95 (d, 1H, J = 8.0 Hz, H-3″), 6.87 (s, 1H, H-4), 2.34 (s, 3H, —CH_3); IR (KBr)v: 3066, 1639, 1594, 1498, 1433, 1362, 1279, 1263, 917, 830, 755, 692 cm^{-1}; Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58; Found: C, 80.79; H, 5.51; N, 8.63; MS (ESI): m/z = 327 [M+H]$^+$.

2-(5-(Benzo[d][1,3]dioxol-5-yl)-1-phenyl-1H-pyrazol-3-yl)-4-methylphenol 3x. Yield: 53%. White powder, mp 80–82°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.62 (s, 1H, —OH), 7.42 (d, 1H, J = 2.0 Hz, H-6″), 7.40–7.31 (m, 5H, H-2′, 3′, 4′, 5′, 6′), 7.05 (dd, 1H, J = 8.4 Hz, 2.0 Hz, H-4″), 6.94 (d, 1H, J = 8.4 Hz, H-3″), 6.79 (m, 3H, H-2‴, 5‴, 6‴), 6.72 (s, 1H, H-4), 5.99 (s, 2H, —OCH_2O—), 2.34 (s, 3H, —CH_3); IR (KBr)v: 3058, 1642, 1589, 1499, 1444, 1362, 1263, 925, 830, 763, 694 cm^{-1}; Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56; Found: C, 74.68; H, 4.86; N, 7.63; MS (ESI): m/z = 371 [M+H]$^+$.

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