Tetrahedron 68 (2012) 7941–7948

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 1,3-diaryl-1*H*-benzo[*g*]indazoles

Meng-Yang Chang [a,*], Hang-Yi Tai [a], Yeh-Long Chen [a], Ru-Ting Hsu [b]

[a] Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan
[b] Department of Nursing, ShuZen College of Medicine and Management, Luju, Kaohsiung 821, Taiwan

ARTICLE INFO

Article history:
Received 3 June 2012
Received in revised form 20 June 2012
Accepted 3 July 2012
Available online 10 July 2012

Keywords:
1*H*-Benzo[*g*]indazoles
Aldol condensation
Knorr pyrazole synthesis
One-pot combination
Oxidative cleavage annulation

ABSTRACT

A facile three-step synthetic route toward 1,3-diaryl-1*H*-benzo[*g*]indazoles **1a**–**1n** starting with 3,4-dimethoxy-2-allylbenzaldehyde (**6**) in modest total yield is described. The facile route was carried by aldol condensation of aldehyde **6** with aryl methyl ketones **5a**–**5d** in alkaline MeOH at reflux, Knorr pyrazole synthesis of the resulting chalcones **4a**–**4d** with aryl hydrazines **3a**–**3e** in EtOH at reflux followed by DDQ-mediated aromatization in toluene at reflux, and oxidative cleavage annulation of olefins **2a**–**2n** with the one-pot combination of OsO_4/$NaIO_4$/HOAc in the aqueous THF at reflux.

1. Introduction

During the last decade, functionalized 1*H*-indazoles have become a versatile class of compounds that have found use in drug discovery.[1] Due to the particular pharmaceutical interest concerning the specific substitution pattern of 1*H*-indazoles, some synthetic methods have been developed.[2] In 1961, Knorr and Huisgen reported the first example of substituted 1*H*-indazoles, and recent developments have been characterized by transition metal-mediated synthesis.[3,4] In regard to the general preparation of 1*H*-indazole derivatives, there have been a few reports on the synthesis of polycyclic benzannulated 1*H*-indazoles.[5] The adopted synthetic routes are described in Fig. 1. Basically, the key formation of pyrazole skeleton presents a major challenge for constructing the tricyclic angular 1*H*-benzo[*g*]indazole or linear 1*H*-benzo[*f*]indazole. While 1*H*-benzo-indazoles and their derivatives with this specific substitution pattern have been developed, new methods for their preparation are still needed.

In continuation of our investigation with the one-pot combination of OsO_4/$NaIO_4$/HOAc,[6a] a facile three-step route is employed to create the framework of 6,7-dimethoxy-1,3-diaryl-1*H*-benzo[*g*]indazoles **1a**–**1n**, starting with 3,4-dimethoxy-2-allylbenzaldehyde (**6**), via (1) NaOH-mediated aldol condensation of **6** with **5a**–**5d** in MeOH at reflux, (2) Knorr pyrazole synthesis of the resulting **4a**–**4d** with **3a**–**3e** in EtOH at reflux, followed by DDQ-mediated aromatization in toluene at reflux, and then (3) oxidative cleavage annulation of **2a**–**2n** with the combination of OsO_4/$NaIO_4$/HOAc in the aqueous THF at reflux (Fig. 2).

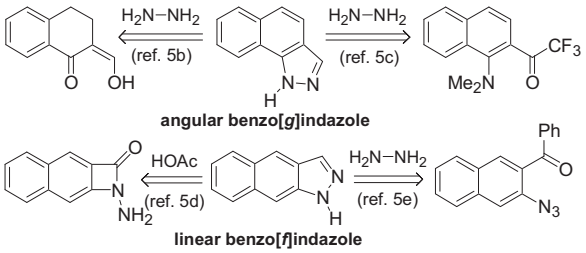


Fig. 1. Synthetic routes of 1*H*-benzo-indazoles.

2. Results and discussion

The starting material, 2-allylbenzaldehyde **6**, was provided from commercially available isovanillin (**7**) in moderate overall three-step yields according to the reported procedures with the reaction sequence of O-allylation and the Claisen rearrangement followed by O-methylation.[6,7]

Next, synthesis of **4a**–**4f** was examined by the NaOH-mediated aldol condensation of **6** with **5a**–**5f** in MeOH. After screening six ketones **5a**–**5f** with different functional groups (Ar_1=**a**, Ph; **b**, 4-F–Ph; **c**, 3,4,5-$(MeO)_3$–Ph; **d**, 2-MeO–Ph; **e**, 2-NO_2–Ph; **f**, 4-NO_2–Ph), (*E*)-isomers **4a**–**4f** were isolated in 25–89% yields, as

* Corresponding author. Tel.: +886 7 3121101x2220; e-mail addresses: mychang@kmu.edu.tw, mychang624@yahoo.com.tw (M.-Y. Chang).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.07.011

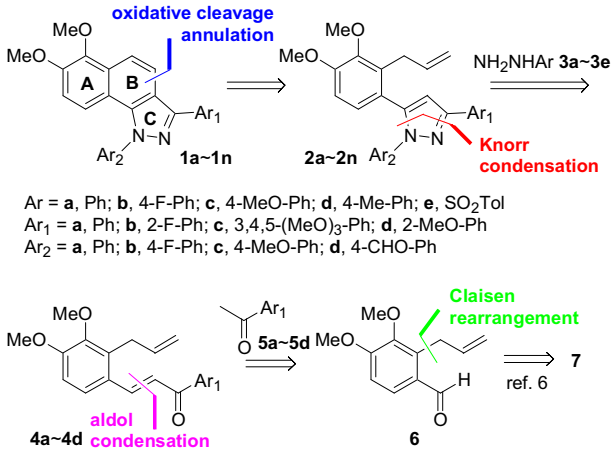
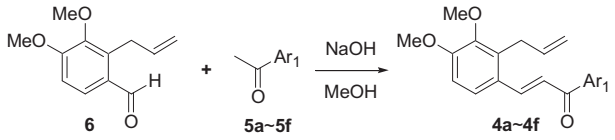


Fig. 2. Retrosynthetic route toward benzo[*g*]indazoles **1a**–**1n**.

shown in Scheme 1. We found that **4e** and **4f** provided poorer yields (25% and 38%) than the others at reflux for 5 h due to the stronger electron-withdrawing effect of nitro group.



Ar_1 = **4a**, Ph (82%); **4b**, 2-F-Ph (50%); **4c**, 3,4,5-$(MeO)_3$-Ph (89%); **4d**, 2-MeO-Ph (75%); **4e**, 2-NO_2-Ph (25%); **4f**, 4-NO_2-Ph (38%)

Scheme 1. Aldol condensation of **6** with **5a**–**5f**.

Furthermore, **2a**–**2n** (Ar_2=**a**, Ph; **b**, 4-F–Ph; **c**, 4-MeO–Ph; **d**, 4-CHO–Ph) were obtained as single isomers with 64–83% yield via the treatment of **4a**–**4d** with five arylhydrazines **3a**–**3e** (Ar=**a**, Ph; **b**, 4-F–Ph; **c**, 4-MeO–Ph; **d**, 4-Me–Ph; **e**, SO_2Tol) in refluxing EtOH followed by DDQ-mediated aromatization of the resulting dihydropyrazole in toluene at reflux (see Table 1 and Scheme 2). Moreover, the Ar_2 group in the N1-position of the pyrazole (C ring) is in relative opposite configuration, as expected for the regiochemistry of Knorr condensation. Another regioisomer **8** was not observed during the process.[8] The protocol is broadly applicable for the synthesis of substituted pyrazoles. The structure of **2k** was determined using single-crystal X-ray analysis.[9]

In particular, when the oxidative dehydrogenation of dihydropyrazole skeleton with 4-methylphenyl group (Ar=4-Me–Ph) was treated with DDQ, the 4-methylphenyl group of three pyrazoles **2d**, **2h**, and **2l** was further converted to 4-formylphenyl group (Ar_2=4-CHO–Ph) via the benzylic oxidation. For synthesizing **2n** (Ar=SO_2Tol), no benzylic oxidative product was observed in the DDQ-mediated reaction. With the experimental results, we envisioned that *p*-tolyl group with electron-donating amino group could be easily oxidized to the benzaldehyde skeleton; therefore, a rapid synthetic route for establishing the 4-formylphenyl group could easily result. With the previous synthetic experience, we attempted to construct the B ring of the tricyclic 1*H*-benzo[*g*]indazoles **1a**–**1n** by the useful combination of OsO_4/$NaIO_4$/HOAc via the facile one-pot oxidative cleavage of **2a**–**2n** and subsequent intramolecular ring-closure. Reports in the literature have described the improved procedure for the oxidative cleavage of olefins by the OsO_4/$NaIO_4$ system.[10] In order to initiate the work, one-pot oxidative cleavage of the olefinic group of **2a** was first examined. When the reaction condition was treated at rt, **1a** provided with good yields within a period of 4 h. After adjusting the reaction temperature from rt to 60 °C and time from 4 to 2 h, the desired **1a** with poorer yield was observed. The possible mechanism for the formation of **1a** is described in Scheme 3. The initial event may be considered as the formation of **I** with the proton/oxocarbenium ions from HOAc-mediated annulation. Intermediate **II** with six-membered ring is yielded via the nitrogen lone pair of pyrazole skeleton promoted cascade-type ring-closure on the intermediate **I**. After hydrogen abstraction of **III** and sequential oxidative dehydration of the resulting **IV**, the tricyclic skeleton of 1*H*-benzo[*g*]indazole **1a** was produced. Under the above mentioned one-pot combination condition, **1b**–**1l** with different electron-withdrawing and electron-donating aryl substituents were provided in the 60–74% yields, as shown in Table 1. The structures of **1i** and **1j** were determined using single-crystal X-ray analysis (Figs. 3 and 4).[9]

The formation of 14 cycloadducts was confirmed through spectral analysis. For example, the ^{1}H NMR spectrum of **1c** exhibited two doublets δ 7.94 (J=9.2 Hz) and 7.32 (J=9.2 Hz) for the CH protons of the B ring. The CH protons of the A ring exhibited two doublets δ 7.11 (J=8.8 Hz) and 7.08 (J=8.8 Hz). Finally, compound **1c** was confirmed by high-resolution mass spectrometry, which showed a peak at m/z 411.1713 [M^++1].

3. Conclusion

In summary, we have successfully presented a synthetic route for the synthesis of 1,3-diaryl-1*H*-benzo[*g*]indazoles **1a**–**1n** via aldol condensation, Knorr pyrazole synthesis, and oxidative cleavage annulation with the one-pot combination of OsO_4/$NaIO_4$/HOAc. This synthesis starts from simple starting material and reagents, and provides a potential methodology for chemical biology research of combretastatin-A4 (CA4).

4. Experimental section

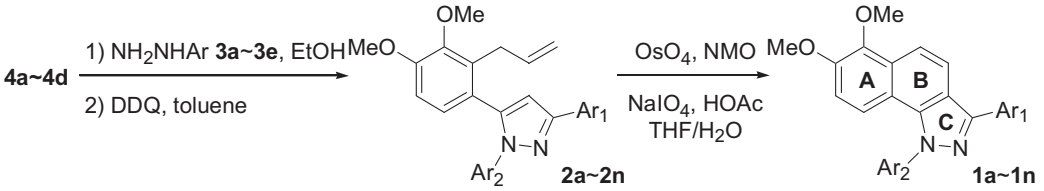
4.1. General

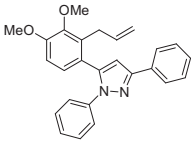
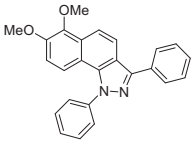
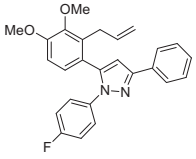
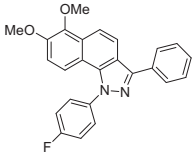
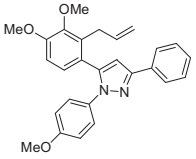
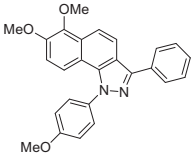
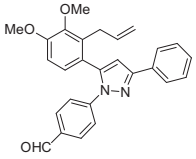
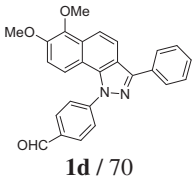
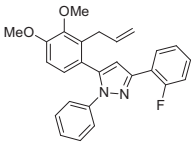
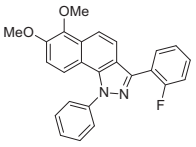
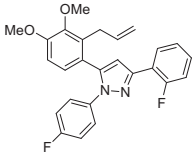
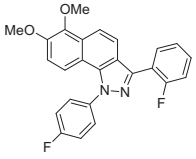
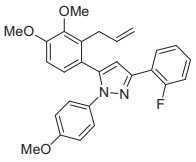
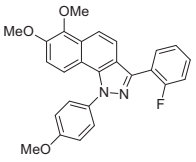
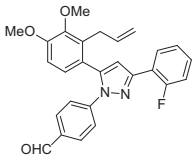
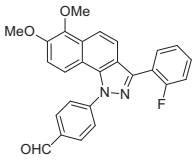
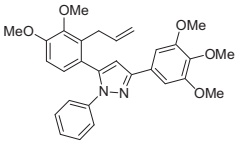
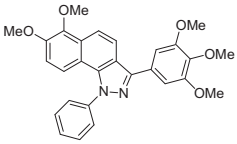
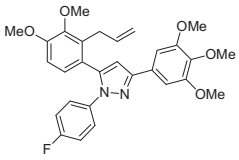
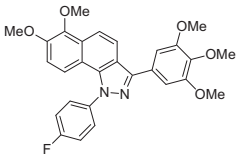
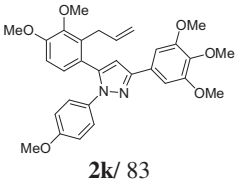
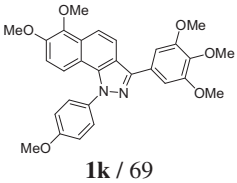
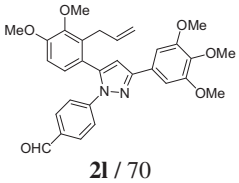
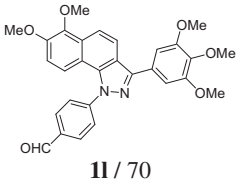
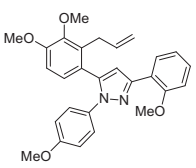
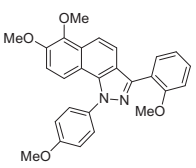
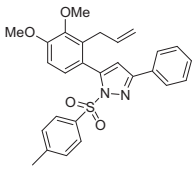
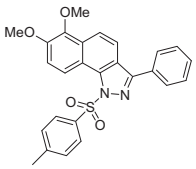
All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous $MgSO_4$ before concentration in vacuo. Melting points were determined with an SMP3 melting apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 200/400 and at 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in hertz. High-resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN-OS-Rapid Analyzer or Elementar Vario EL III.

4.2. A representative synthetic procedure of compounds 4a–4f

NaOH (160 mg, 4.0 mmol) was added to a solution of skeleton **6** (2.0 mmol) in MeOH (20 mL) at rt. Then methyl aryl ketones **5a**–**5f** (2.1 mmol) were added to the reaction mixture. The reaction mixture was stirred at reflux for 3 h. The reaction mixture was concentrated to yield the residue. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc=10:1 to 6:1) afforded compounds **4a**–**4f**.

Table 1
Synthesis of 1,3-diaryl-1*H*-benzo[*g*]indazoles **1a**–**1n**[a–c]

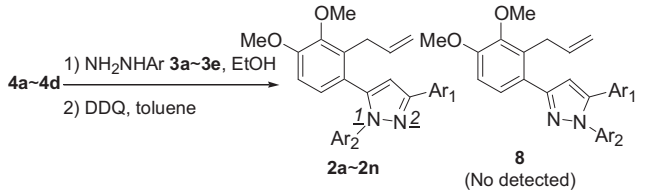


Entry	Product **2**/yield (%)[a]	Product **1**/yield (%)[b]	Entry	Product **2**/yield (%)[a]	Product **1**/yield (%)[b]
1	 **2a** / 80	 **1a** / 74	8	 **2b** / 74	 **1b** / 69
2	 **2c** / 82	 **1c** / 63	9	 **2d** / 69	 **1d** / 70
3	 **2e** / 80	 **1e** / 72	10	 **2f** / 74	 **1f** / 63
4	 **2g** / 79	 **1g** / 60	11	 **2h** / 64	 **1h** / 74
5	 **2i** / 82	 **1i** / 67	12	 **2j** / 80	 **1j** / 63
6	 **2k**/ 83	 **1k** / 69	13	 **2l** / 70	 **1l** / 70
7	 **2m** / 72	 **1m** / 66	14	 **2n** / 68	 **1n** / 73

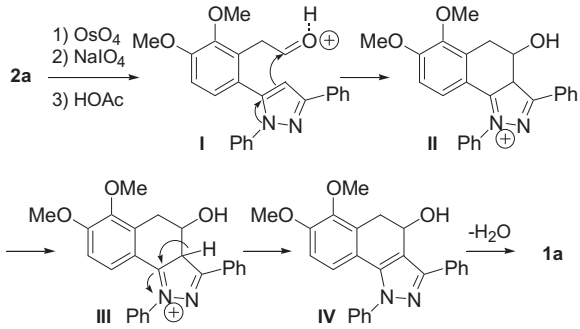
[a] For the optimal reaction conditions: (i) compounds **4a**–**4d** (1.5 mmol, 1.0 equiv), compounds **3a**–**3d** (1.6 mmol), EtOH (20 mL), reflux, 3 h; (ii) DDQ (2.0 mmol), toluene (15 mL), reflux, 3 h.

[b] For the optimal reaction conditions: (i) compounds **2a**–**2n** (1.0 mmol), OsO_4 (2.5% in THF, 1 mL), NMO (50% in H_2O, 2.2 mmol), THF/H_2O (v/v=1:1, 20 mL), rt, 2 h; (ii) $NaIO_4$ (1.2 mmol), rt, 1 h; (iii) HOAc (1 mL), rt, 1 h.

[c] The isolated products were >95% pure as determined by ^1H NMR analysis.



Scheme 2. Synthesis of **2a**–**2n**.



Scheme 3. The possible mechanism of **2a**.

*4.2.1. 3-(6-Allyl-2,3-dimethoxy-phenyl)-1-phenyl-propenone (**4a**)* Yield=82% (505 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{21}O_3$ 309.1491, found 309.1489; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03–7.98 (m, 3H), 7.59–7.47 (m, 4H), 7.35 (d, J=15.6 Hz, 1H), 6.87 (d, J=8.8 Hz, 1H), 6.02–5.92 (m, 1H), 5.04 (dq, J=2.0, 10.0 Hz, 1H), 4.91 (dq, J=2.0, 17.2 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 3.62 (dt, J=2.0, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.71, 154.50, 147.30, 142.67, 138.38, 136.58, 134.29, 132.54, 128.52 (2×), 128.47 (2×), 127.49, 122.95, 121.84, 115.85, 110.43, 60.95, 55.73, 30.08.

*4.2.2. 3-(2-Allyl-3,4-dimethoxy-phenyl)-1-(2-fluoro-phenyl)-propenone (**4b**)* Yield=50% (326 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{20}FO_3$ 327.1397, found 327.1399; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, J=1.6, 15.6 Hz, 1H), 7.76 (dt, J=1.6, 7.6 Hz, 1H), 7.51 (d, J=8.8 Hz, 2H), 7.26–7.12 (m, 3H), 7.85 (d, J=8.8 Hz, 1H), 5.98–5.88 (m, 1H), 5.01 (dq, J=1.6, 10.4 Hz, 1H), 4.86 (dq, J=1.6, 16.8 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.59 (dt, J=1.6, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.29 (d, J=2.3 Hz), 160.93 (d, J=251.0 Hz), 154.60, 147.22, 142.87, 136.48, 134.32, 133.47 (d, J=9.1 Hz), 130.81 (d, J=2.3 Hz), 127.11, 125.20 (d, J=6.0 Hz), 124.35 (d, J=3.1 Hz), 123.10 (2×), 116.36 (d, J=22.8 Hz), 115.75, 110.46, 60.87, 55.66, 30.02.

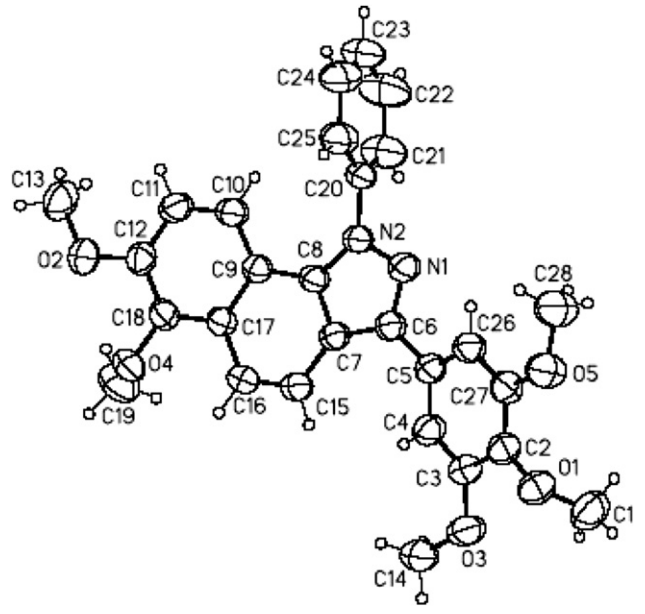


Fig. 3. X-ray structure of **1i**.

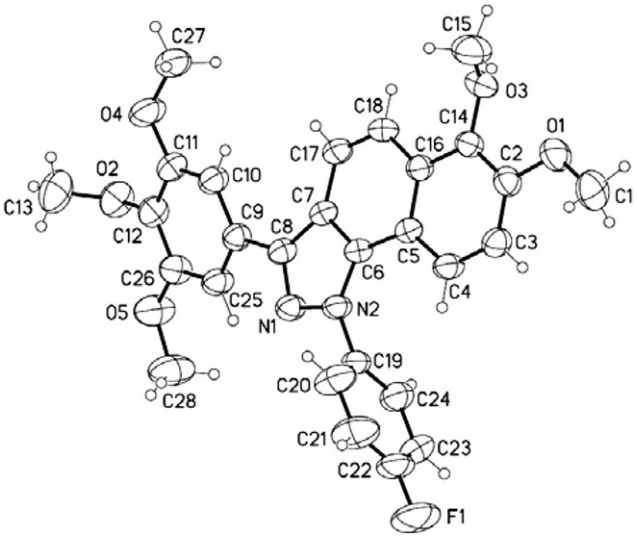


Fig. 4. X-ray structure of **1j**.

*4.2.3. 3-(2-Allyl-3,4-dimethoxy-phenyl)-1-(3,4,5-trimethoxy-phenyl)-propenone (**4c**)* Yield=89% (708 mg); yellowish solid; mp=125–126 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{23}H_{27}O_6$ 399.1808, found 399.1813; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J=15.6 Hz, 1H), 7.50 (d, J=8.8 Hz, 1H), 7.28 (d, J=15.6 Hz, 1H), 7.24 (s, 2H), 6.86 (d, J=8.8 Hz, 1H), 6.01–5.91 (m, 1H), 5.02 (dq, J=2.0, 10.0 Hz, 1H), 4.91 (dq, J=2.0, 17.2 Hz, 1H), 3.92 (s, 6H), 3.91 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.61 (dt, J=2.0, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.30, 154.48, 153.04, 147.31, 142.57 (2×), 142.16, 136.57, 134.19, 133.66, 127.53, 123.07, 121.56, 115.85, 110.40, 105.94 (2×), 60.94, 56.29 (3×), 55.71, 30.15.

*4.2.4. 3-(2-Allyl-3,4-dimethoxy-phenyl)-1-(2-methoxy-phenyl)-propenone (**4d**)* Yield=75% (507 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{21}H_{23}O_4$ 339.1596, found 339.1603; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J=15.6 Hz, 1H), 7.54 (d, J=1.6, 7.6 Hz, 1H), 7.44 (d, J=8.4 Hz, 1H), 7.43–7.38 (m, 1H), 7.15 (d, J=15.6 Hz, 1H), 7.00–7.93 (m, 2H), 6.81 (d, J=8.8 Hz, 1H), 5.93–5.83 (m, 1H), 4.96 (dq, J=1.6, 10.4 Hz, 1H), 4.82 (dq, J=1.6, 16.8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.55 (dt, J=1.6, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.12, 157.56, 154.05, 146.94, 141.30, 136.30, 133.71, 132.24, 129.80, 129.15, 127.20, 126.52, 122.74, 120.34, 115.42, 111.28, 110.29, 60.59, 55.41 (2×), 29.56.

*4.2.5. 3-(2-Allyl-3,4-dimethoxy-phenyl)-1-(2-nitro-phenyl)-propenone (**4e**)* Yield=25% (177 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{20}NO_5$ 354.1342, found 354.1348; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, J=0.8, 8.4 Hz, 1H), 7.75 (dt, J=1.2, 7.6 Hz, 1H), 7.64 (dt, J=1.6, 7.6 Hz, 1H), 7.48 (dd, J=1.6, 7.6 Hz, 1H), 7.45 (d, J=8.8 Hz, 1H), 7.38 (d, J=16.0 Hz, 1H), 6.85 (d, J=8.8 Hz, 1H), 6.4 (d, J=16.0 Hz, 1H), 5.77–5.67 (m, 1H), 4.86 (dq, J=1.6, 10.0 Hz, 1H), 4.71 (dq, J=1.6, 16.8 Hz, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.38 (dt, J=1.6, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.28, 154.90, 147.21, 144.54, 136.46,

136.26 (2×), 133.88, 130.33, 128.96, 126.41, 125.81, 124.42, 123.21 (2×), 115.64, 110.60, 60.95, 55.75, 30.02.

*4.2.6. 3-(2-Allyl-3,4-dimethoxy-phenyl)-1-(4-nitro-phenyl)-propenone (**4f**)* Yield=38% (268 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{20}NO_5$ 354.1342, found 354.1348; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J*=15.2 Hz, 1H), 7.91 (d, *J*=8.8 Hz, 2H), 7.50 (d, *J*=8.4 Hz, 1H), 7.35 (d, *J*=15.2 Hz, 1H), 6.85 (d, *J*=8.4 Hz, 1H), 6.72 (d, *J*=8.8 Hz, 2H), 6.02–5.92 (m, 1H), 5.03 (dq, *J*=2.0, 10.0 Hz, 1H), 4.93 (dq, *J*=2.0, 17.2 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.62 (dt, *J*=2.0, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.26, 154.15, 150.33, 147.29, 143.06, 141.03, 136.63, 134.06, 130.98 (2×), 127.97, 122.82, 121.85, 115.78, 114.24 (2×), 110.41, 60.91, 55.71, 30.12.

4.3. A representative synthetic procedure of compounds 2a–2n

Aryl hydrazines **3a**–**3e** (1.6 mmol) were added to a solution of compounds **4a**–**4d** (1.5 mmol) in EtOH (20 mL) at rt. The reaction mixture was stirred at reflux for 3 h. The reaction mixture was concentrated to yield the residue. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Without further purification, DDQ (450 mg, 2.0 mmol) was added the resulting product in toluene (15 mL) at rt. The reaction mixture was stirred at reflux for 3 h. The reaction mixture was concentrated to yield the residue. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc=8:1 to 4:1) afforded compounds **2a**–**2n**.

*4.3.1. 5-(2-Allyl-3,4-dimethoxy-phenyl)-1,3-diphenyl-1H-pyrazole (**2a**)* Yield=80% (475 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{26}H_{25}N_2O_2$ 397.1916, found 397.1922; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.91 (m, 2H), 7.46–7.42 (m, 2H), 7.36–7.18 (m, 6H), 6.89 (d, *J*=8.4 Hz, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 6.74 (s, 1H), 5.82–5.72 (m, 1H), 4.91 (dq, *J*=2.0, 10.0 Hz, 1H), 4.80 (dq, *J*=2.0, 17.2 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.30 (d, *J*=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.15, 151.36, 147.54, 142.71, 140.14, 136.51, 133.32, 133.17, 128.65 (2×), 128.61 (2×), 127.89, 126.72, 126.66, 125.74 (2×), 123.92 (2×), 123.80, 115.36, 110.19, 106.56, 60.77, 55.58, 31.92. Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.92; H, 6.31; N, 7.38.

*4.3.2. 5-(2-Allyl-3,4-dimethoxy-phenyl)-1-(4-fluoro-phenyl)-3-phenyl-1H-pyrazole (**2b**)* Yield=74% (460 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{26}H_{24}FN_2O_2$ 415.1822, found 415.1826; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.91 (m, 2H), 7.46–7.42 (m, 2H), 7.37–7.26 (m, 3H), 6.99–6.94 (m, 2H), 6.87 (d, *J*=8.4 Hz, 1H), 6.78 (d, *J*=8.4 Hz, 1H), 6.74 (s, 1H), 5.83–5.74 (m, 1H), 4.92 (dq, *J*=2.0, 10.0 Hz, 1H), 4.80 (dq, *J*=2.0, 17.2 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.31 (d, *J*=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.10 (d, *J*=245.6 Hz), 153.20, 151.39, 147.54, 142.74, 136.41, 136.29 (d, *J*=3.1 Hz), 133.26, 132.99, 128.65, 128.61 (2×), 127.96, 126.66, 125.69 (2×), 125.66 (d, *J*=8.3 Hz), 123.41, 115.58, 115.41, 115.36, 110.21, 106.46, 60.54, 55.54, 31.88.

*4.3.3. 5-(2-Allyl-3,4-dimethoxy-phenyl)-1-(4-methoxy-phenyl)-3-phenyl-1H-pyrazole (**2c**)* Yield=82% (524 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{27}H_{27}N_2O_3$ 427.2022, found 427.2025; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J*=7.2 Hz, 2H), 7.47–7.41 (m, 2H), 7.36–7.32 (m, 1H), 7.22 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=8.0 Hz, 1H), 6.80–6.75 (m, 3H), 6.72 (s, 1H), 5.83–5.73 (m, 1H), 4.92 (dq, *J*=2.0, 10.4 Hz, 1H), 4.80 (dq, *J*=2.0, 17.2 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.31 (d, *J*=5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.35, 153.11, 150.81, 147.45, 142.84, 136.59, 133.32, 133.04, 132.82, 128.64 (2×), 127.98, 126.79, 125.82 (2×), 125.62 (2×), 123.49, 115.39, 113.86 (2×), 110.15, 106.05, 60.79, 55.59, 55.43, 31.91.

*4.3.4. 4-[5-(2-Allyl-3,4-dimethoxy-phenyl)-3-phenyl-pyrazol-1-yl]-benzaldehyde (**2d**)* Yield=69% (439 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{27}H_{25}N_2O_3$ 425.1865, found 425.1871; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.93 (d, *J*=7.2 Hz, 2H), 7.78 (d, *J*=8.8 Hz, 2H), 7.52–7.43 (m, 4H), 7.39–7.35 (m, 1H), 6.89 (d, *J*=8.4 Hz, 1H), 6.81 (d, *J*=8.4 Hz, 1H), 6.78 (s, 1H), 5.81–5.72 (m, 1H), 4.88 (dq, *J*=1.6, 10.0 Hz, 1H), 4.77 (dq, *J*=1.6, 16.8 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.30 (d, *J*=4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.14, 153.51, 152.29, 147.72, 144.72, 143.19, 136.16, 133.87, 133.17, 132.49, 130.32 (2×), 128.71 (2×), 128.39, 126.49, 125.85 (2×), 123.29 (3×), 115.56, 110.44, 107.85, 60.84, 55.62, 31.91.

*4.3.5. 5-(2-Allyl-3,4-dimethoxy-phenyl)-3-(2-fluoro-phenyl)-1-phenyl-1H-pyrazole (**2e**)* Yield=80% (497 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{26}H_{24}FN_2O_2$ 415.1822, found 415.1829; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (dt, *J*=1.6, 7.6 Hz, 1H), 7.34–7.08 (m, 8H), 6.89 (d, *J*=4.0 Hz, 1H), 6.89 (d, *J*=8.4 Hz, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 5.81–5.70 (m, 1H), 4.90 (dq, *J*=1.6, 10.0 Hz, 1H), 4.81 (dq, *J*=1.6, 16.8 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.31 (d, *J*=6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.30 (d, *J*=248.3 Hz), 153.18, 147.55, 140.07, 136.38, 133.44, 131.87, 129.17 (d, *J*=8.3 Hz), 128.68 (2×), 128.43, 128.10 (2×), 126.71, 124.25, 124.21, 124.01, 123.70, 116.03 (d, *J*=22.0 Hz), 115.44, 110.19, 110.07, 109.97, 60.78, 55.60, 31.94.

*4.3.6. 5-(2-Allyl-3,4-dimethoxy-phenyl)-1,3-bis-(2-fluoro-phenyl)-1H-pyrazole (**2f**)* Yield=74% (480 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{26}H_{23}F_2N_2O_2$ 433.1728, found 433.1733; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (dt, *J*=1.6, 7.6 Hz, 1H), 7.34–7.26 (m, 3H), 7.22 (dt, *J*=8.0, 9.2 Hz, 1H), 7.15 (ddd, *J*=0.8, 8.0, 10.8 Hz, 1H), 6.99–6.93 (m, 2H), 6.89 (d, *J*=4.0 Hz, 1H), 6.87 (d, *J*=8.4 Hz, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 5.82–5.72 (m, 1H), 4.91 (dq, *J*=1.6, 10.0 Hz, 1H), 4.81 (dq, *J*=1.6, 16.8 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.31 (d, *J*=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.21 (d, *J*=145.6 Hz), 160.28 (d, *J*=248.6 Hz), 153.24, 147.57, 146.19, 142.44 (d, *J*=22.2 Hz), 136.29, 133.40, 129.25 (d, *J*=8.3 Hz), 128.41 (d, *J*=3.8 Hz), 126.75, 125.79, 125.71, 124.24 (d, *J*=3.1 Hz), 123.35, 120.94 (d, *J*=12.1 Hz), 116.16, 115.94, 115.64, 115.49, 115.41, 110.22, 109.93 (d, *J*=10.6 Hz), 60.77, 55.58, 31.91.

*4.3.7. 5-(2-Allyl-3,4-dimethoxy-phenyl)-3-(2-fluoro-phenyl)-1-(4-methoxy-phenyl)-1H-pyrazole (**2g**)* Yield=79% (526 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{27}H_{26}FN_2O_3$ 445.1928, found 445.1932; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (dt, *J*=2.0, 7.6 Hz, 1H), 7.32–7.26 (m, 1H), 7.24–7.19 (m, 3H), 7.14 (ddd, *J*=0.8, 8.0, 11.2 Hz, 1H), 6.88 (d, *J*=8.8 Hz, 1H), 6.87 (s, 1H), 6.81–6.77 (m, 2H), 6.76 (d, *J*=8.8 Hz, 1H), 5.83–5.73 (m, 1H), 4.91 (dq, *J*=2.0, 10.0 Hz, 1H), 4.82 (dq, *J*=2.0, 17.2 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.32 (d, *J*=6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.24 (d, *J*=248.0 Hz), 158.31, 153.06, 147.47, 145.69, 142.30, 136.47, 133.44, 133.38, 129.01 (d, *J*=8.3 Hz), 128.44 (d, *J*=3.8 Hz), 126.83, 125.48 (2×), 124.19 (d, *J*=3.1 Hz), 123.70, 121.17 (d, *J*=12.1 Hz), 115.98 (d, *J*=22.0 Hz), 115.40, 113.83 (2×), 110.13, 109.52 (d, *J*=10.7 Hz), 60.76, 55.56, 55.38, 31.92.

*4.3.8. 4-[5-(2-Allyl-3,4-dimethoxy-phenyl)-3-(2-fluoro-phenyl)-pyrazol-1-yl]-benzaldehyde (**2h**)* Yield=64% (424 mg); yellowish solid; mp=114–115 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{27}H_{24}FN_2O_3$ 443.1771, found 443.1778; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 8.17 (dt, J=2.0, 7.6 Hz, 1H), 7.80–7.76 (m, 2H), 7.52–7.49 (m, 2H), 7.36–7.31 (m, 1H), 7.24

(dt, *J*=1.2, 7.6 Hz, 1H), 7.18–7.13 (m, 1H), 6.93 (d, *J*=8.0 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 6.80 (d, *J*=8.4 Hz, 1H), 5.80–5.70 (m, 1H), 4.87 (dq, *J*=2.0, 10.0 Hz, 1H), 4.78 (dq, *J*=2.0, 17.2 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.31 (br d, *J*=5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 191.07, 160.36 (d, *J*=248.7 Hz), 158.51, 147.74, 147.18, 144.71, 142.80 (d, *J*=2.3 Hz), 136.02, 133.98, 133.28, 130.29 (2×), 129.65 (d, *J*=9.1 Hz), 128.46 (d, *J*=3.0 Hz), 126.55, 124.30 (d, *J*=3.8 Hz), 125.35 (2×), 123.20 (d, *J*=7.5 Hz), 120.55 (d, *J*=12.1 Hz), 116.11 (d, *J*=21.9 Hz), 115.58, 111.18 (d, *J*=9.9 Hz), 110.44, 60.81, 55.61, 31.92.

*4.3.9. 5-(2-Allyl-3,4-dimethoxy-phenyl)-1-phenyl-3-(3,4,5-trimethoxy-phenyl)-1H-pyrazole (**2i**)* Yield=82% (598 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{29}H_{31}N_2O_5$ 487.2233, found 487.2236; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.32–7.19 (m, 5H), 7.15 (s, 2H), 6.89 (d, *J*=8.4 Hz, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 6.68 (s, 1H), 5.78–5.71 (m, 1H), 4.89 (dq, *J*=1.6, 10.0 Hz, 1H), 4.79 (dq, *J*=1.6, 16.8 Hz, 1H), 3.95 (s, 6H), 3.89 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 3.28 (d, *J*=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 153.46, 153.04, 151.22, 147.54, 142.90, 139.96, 138.11, 136.48, 133.30, 128.82, 128.68 (2×), 126.80, 126.68, 125.38, 123.99 (2×), 123.62, 115.33, 110.19, 106.51, 103.00 (2×), 60.94, 60.76, 56.21 (2×), 55.59, 31.93.

*4.3.10. 5-(2-Allyl-3,4-dimethoxy-phenyl)-1-(4-fluoro-phenyl)-3-(3,4,5-trimethoxy-phenyl)-1H-pyrazole (**2j**)* Yield=80% (605 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{29}H_{30}FN_2O_5$ 505.2139, found 505.2142; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.30–7.25 (m, 2H), 7.13 (s, 2H), 6.98–6.92 (m, 2H), 6.86 (d, *J*=8.4 Hz, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 6.68 (s, 1H), 5.79–5.70 (m, 1H), 4.89 (dq, *J*=1.6, 10.0 Hz, 1H), 4.78 (dq, *J*=1.6, 16.8 Hz, 1H), 3.94 (s, 6H), 3.88 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.28 (d, *J*=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.36, 159.91, 153.44, 153.22, 151.26, 147.51, 142.89, 138.12, 136.35, 126.16, 133.21, 128.68, 126.61, 125.76, 125.67, 123.26, 115.58, 115.36 (2×), 110.19, 106.40, 102.92 (2×), 60.88, 60.72, 56.15 (2×), 55.53, 31.87.

*4.3.11. 5-(2-Allyl-3,4-dimethoxy-phenyl)-1-(4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-1H-pyrazole (**2k**)* Yield=83% (642 mg); yellowish solid; mp=105–106 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{30}H_{33}N_2O_6$ 517.2339, found 517.2343; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.20 (d, *J*=8.8 Hz, 2H), 7.13 (s, 2H), 6.86 (d, *J*=8.4 Hz, 1H), 6.76 (d, *J*=8.8 Hz, 2H), 6.75 (d, *J*=8.4 Hz, 1H), 6.66 (s, 1H), 5.81–5.71 (m, 1H), 4.90 (dq, *J*=1.6, 10.0 Hz, 1H), 4.80 (dq, *J*=1.6, 17.2 Hz, 1H), 3.93 (s, 6H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.29 (d, *J*=6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.28, 153.39 (2×), 153.04, 150.82, 147.39, 142.80, 137.94, 136.54, 133.23, 133.18, 128.90, 126.68, 125.52 (2×), 123.51, 115.25, 113.75 (2×), 110.08, 105.93, 102.89 (2×), 60.86, 60.69, 56.13 (2×), 55.50, 55.33, 31.86. Single-crystal X-ray diagram: crystal of compound **2k** was grown by slow diffusion of EtOAc into a solution of compound **2k** in CCl_4 to yield colorless prism. The compound crystallizes in the trigonal crystal system, space group *R*-3, *a*=21.0478(6) Å, *b*=21.0478(6) Å, *c*=32.2300(11) Å, *V*=12,365.3(7) Å^3, *Z*=18, d_{calcd}=1.373 g/cm^3, *F*(000)=5376, 2*θ* range 1.28–26.39°, *R* indices (all data) *R*1=0.0915, *wR*2=0.2338.

*4.3.12. 4-[5-(2-Allyl-3,4-dimethoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-pyrazol-1-yl]-benzaldehyde (**2l**)* Yield=70% (540 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{30}H_{31}N_2O_6$ 515.2182, found 515.2187; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.93 (s, 1H), 7.77 (d, *J*=8.8 Hz, 2H), 7.49 (d, *J*=8.8 Hz, 2H), 7.14 (s, 2H), 6.89 (d, *J*=8.4 Hz, 1H), 6.80 (d, *J*=8.4 Hz, 1H), 6.72 (s, 1H), 5.77–5.67 (m, 1H), 4.85 (dq, *J*=1.6, 10.0 Hz, 1H), 4.75 (dq, *J*=1.6, 16.8 Hz, 1H), 3.95 (s, 6H), 3.89 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.27 (br d, *J*=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 191.05, 153.47 (2×), 153.44, 152.15, 147.65, 144.62, 143.25, 138.34, 136.07, 133.84, 133.08, 130.26 (2×), 128.20, 126.41, 123.25 (2×), 123.14, 115.46, 110.39, 107.75, 102.97 (2×), 60.88, 60.77, 56.14 (2×), 55.56, 31.87.

*4.3.13. 5-(2-Allyl-3,4-dimethoxy-phenyl)-3-(2-methoxy-phenyl)-1-(4-methoxy-phenyl)-1H-pyrazole (**2m**)* Yield=72% (492 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{28}H_{29}N_2O_4$ 457.2127, found 457.2133; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.12 (dd, *J*=1.6, 7.6 Hz, 1H), 7.31 (dt, *J*=1.6, 8.8 Hz, 1H), 7.22 (d, *J*=8.8 Hz, 2H), 7.06–6.98 (m, 2H), 6.98 (s, 1H), 6.89 (d, *J*=8.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 2H), 6.75 (d, *J*=8.8 Hz, 1H), 5.84–5.74 (m, 1H), 4.91 (dq, *J*=1.6, 10.0 Hz, 1H), 4.84 (dq, *J*=1.6, 16.8 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.34 (br d, *J*=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.10, 156.91, 152.91, 147.93, 147.44, 141.71, 141.43, 136.64, 133.63, 133.47, 132.38, 128.80, 128.66, 126.89, 125.46 (2×), 120.84, 115.30, 113.75 (2×), 111.31, 110.35, 110.08, 60.89, 55.57, 55.44, 55.38, 32.00.

4.4. A representative synthetic procedure of compounds 1a–1n

A solution of 2.5% OsO_4 (1 mL, in THF) was added to a solution of compounds **2a**–**2n** (1.0 mmol) in the co-solvent of THF (10 mL) and water (10 mL). NMO (50% in water, 500 mg, 2.2 mmol) was added to the reaction mixture at rt. The reaction mixture was stirred at rt for 2 h. Then, $NaIO_4$ (257 mg, 1.2 mmol) was added to the reaction mixture at rt. The reaction mixture was stirred at rt for 1 h. HOAc (1 mL) was added to the reaction mixture at rt. The reaction mixture was stirred at rt for 1 h. The overall synthetic procedure had to be monitored by TLC until the reaction was completed. Aqueous $NaHSO_3$ () (10%, 5 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexanes/EtOAc) afforded compounds **1a**–**1n**.

*4.4.1. 6,7-Dimethoxy-1,3-diphenyl-1H-benzo[g]indazole (**1a**)* Yield=74% (281 mg); yellowish solid; mp=105–106 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{25}H_{21}N_2O_2$ 381.1603, found 381.1610; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.03–7.95 (m, 4H), 7.68–7.52 (m, 7H), 7.46–7.42 (m, 1H), 7.33 (d, *J*=9.2 Hz, 1H), 7.07 (d, *J*=9.2 Hz, 1H), 4.02 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 149.46, 146.40, 144.08, 141.77, 137.92, 133.16, 129.60 (2×), 129.14, 128.96, 128.80 (2×), 128.18, 128.05 (2×), 127.54 (2×), 119.64, 118.68, 118.15, 116.85, 116.35, 113.12, 61.26, 56.39.

*4.4.2. 1-(4-Fluoro-phenyl)-6,7-dimethoxy-3-phenyl-1H-benzo[g]indazole (**1b** Yield=69% (275 mg); yellowish solid; mp=171–172 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{25}H_{20}FN_2O_2$ 399.1509, found 399.1513; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.01–7.95 (m, 4H), 7.66–7.62 (m, 2H), 7.56–7.52 (m, 2H), 7.47–7.42 (m, 1H), 7.33–7.28 (m, 3H), 7.10 (d, *J*=9.2 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.77 (d, *J*=247.7 Hz), 149.55, 146.55, 144.14, 138.06, 137.84, 137.80, 132.96, 129.49, 129.40, 129.01, 128.84 (2×), 128.29, 128.02 (2×), 119.59, 118.40, 117.00, 116.69, 116.47, 116.19, 113.21, 61.27, 56.38.

*4.4.3. 6,7-Dimethoxy-1-(4-methoxy-phenyl)-3-phenyl-1H-benzo[g]indazole (**1c**)* Yield=63% (258 mg); yellowish solid; mp=152–153 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{26}H_{23}N_2O_3$ 411.1709, found 411.1713; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.02–7.99 (m, 3H), 7.94 (d, *J*=9.2 Hz, 1H), 7.57–7.51 (m, 4H), 7.45–7.41 (m, 1H), 7.32 (d, *J*=9.2 Hz, 1H), 7.11 (d, *J*=8.8 Hz, 2H), 7.08 (d, *J*=8.8 Hz, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 160.07, 149.40, 146.03, 144.03, 138.14, 134.69, 133.31, 128.86 (2×), 128.77 (2×), 128.58, 128.08,

128.01 (2×), 119.66, 118.56, 117.84, 116.62, 116.46, 114.70 (2×), 113.10, 61.25, 56.37, 55.65.

*4.4.4. 4-(6,7-Dimethoxy-3-phenyl-benzo[g]indazol-1-yl)-benzaldehyde (**1d**)* Yield=70% (286 mg); yellowish solid; mp=125–126 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{26}H_{21}N_2O_3$ 409.1552, found 409.1556; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.12 (d, J=8.8 Hz, 2H), 8.03–7.98 (m, 4H), 7.89 (d, J=8.8 Hz, 2H), 7.57–7.53 (m, 2H), 7.48–7.44 (m, 2H), 7.12 (d, J=9.2 Hz, 1H), 4.03 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.16, 149.63, 147.82, 146.63, 144.20, 137.65, 135.86, 132.75, 130.86, 129.18, 128.90 (2×), 128.51 (2×), 128.03 (2×), 127.33 (2×), 119.56, 119.16, 118.72, 117.59, 116.02, 113.29, 61.31, 56.40.

*4.4.5. 3-(2-Fluoro-phenyl)-6,7-dimethoxy-1-phenyl-1H-benzo[g]indazole (**1e**)* Yield=72% (287 mg); yellowish solid; mp=143–144 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{25}H_{20}FN_2O_2$ 399.1509, found 399.1513; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J=9.2 Hz, 1H), 7.86 (dt, J=2.0, 7.6 Hz, 1H), 7.80 (dd, J=3.6, 9.2 Hz, 1H), 7.68–7.58 (m, 5H), 7.46–7.41 (m, 1H), 7.34 (d, J=9.2 Hz, 1H), 7.31–7.25 (m, 2H), 7.07 (d, J=9.2 Hz, 1H), 4.01 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.20 (d, J=247.9 Hz), 149.50, 144.18, 142.09, 141.77, 137.52, 131.50 (d, J=3.1 Hz), 130.09 (d, J=7.5 Hz), 129.58 (2×), 129.16, 129.06, 127.49 (2×), 124.42 (d, J=3.8 Hz), 120.88 (d, J=15.2 Hz), 120.06 (d, J=7.6 Hz), 119.26, 118.63, 116.71, 116.30, 116.11 (d, J=21.9 Hz), 113.11, 61.25, 56.38.

*4.4.6. 1,3-Bis-(2-fluoro-phenyl)-6,7-dimethoxy-1H-benzo[g]indazole (**1f**)* Yield=63% (262 mg); yellowish solid; mp=128–129 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{25}H_{19}F_2N_2O_2$ 417.1415, found 417.1422; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J=0.4, 9.2 Hz, 1H), 7.82 (dt, J=1.6, 8.0 Hz, 1H), 7.78 (dd, J=3.2, 9.2 Hz, 1H), 7.66–7.60 (m, 2H), 7.45–7.39 (m, 1H), 7.31–7.23 (m, 5H), 7.07 (d, J=9.2 Hz, 1H), 3.99 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.75 (d, J=247.1 Hz), 160.14 (d, J=247.8 Hz), 149.54, 144.20, 142.22, 137.80 (d, J=3.1 Hz), 137.63, 131.39 (d, J=3.8 Hz), 130.16 (d, J=8.3 Hz), 129.35 (d, J=8.3 Hz), 129.06, 124.42 (d, J=3.1 Hz), 120.68 (d, J=14.4 Hz), 119.98 (d, J=6.8 Hz), 119.21, 118.31, 116.81, 116.63, 116.40, 116.22, 116.11, 116.01, 113.16, 61.21, 56.33.

*4.4.7. 3-(2-Fluoro-phenyl)-6,7-dimethoxy-1-(4-methoxy-phenyl)-1H-benzo[g]indazole (**1g**)* Yield=60% (257 mg); yellowish solid; mp=130–131 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{26}H_{22}FN_2O_3$ 429.1615, found 429.1619; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, J=0.8, 9.2 Hz, 1H), 7.85 (dt, J=2.0, 8.0 Hz, 1H), 7.79 (dd, J=3.6, 9.2 Hz, 1H), 7.57–7.54 (m, 2H), 7.45–7.39 (m, 1H), 7.33 (dd, J=0.8, 9.2 Hz, 1H), 7.30–7.23 (m, 2H), 7.12–7.08 (m, 2H), 7.07 (d, J=9.2 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.15 (d, J=247.1 Hz), 160.10, 149.43, 144.12, 141.69, 137.72, 134.60, 131.47 (d, J=1.9 Hz), 129.98 (d, J=8.3 Hz), 128.97, 129.78 (2×), 124.37 (d, J=3.7 Hz), 120.92 (d, J=14.4 Hz), 120.06 (d, J=7.6 Hz), 118.93, 118.51, 116.49, 116.37, 116.06 (d, J=21.2 Hz), 114.67 (2×), 113.08, 61.20, 56.34, 55.59.

*4.4.8. 4-[3-(2-Fluoro-phenyl)-6,7-dimethoxy-benzo[g]indazol-1-yl]-benzaldehyde (**1h**)* Yield=74% (315 mg); yellowish solid; mp=146–147 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{26}H_{20}FN_2O_3$ 427.1458, found 427.1462; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.14–8.11 (m, 2H), 8.00 (dd, J=0.4, 9.2 Hz, 1H), 7.91–7.88 (m, 2H), 7.83 (dt, J=2.0, 7.6 Hz, 1H), 7.79 (dd, J=3.6, 9.2 Hz, 1H), 7.49–7.43 (m, 2H), 7.32–7.26 (m, 2H), 7.12 (d, J=9.2 Hz, 1H), 4.02 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.11, 160.18 (d, J=247.9 Hz), 149.69, 146.51, 144.29, 143.52, 137.26, 135.98, 131.37 (d, J=3.8 Hz), 130.84 (2×), 130.46 (d, J=8.3 Hz), 129.29, 127.36 (2×), 124.51 (d, J=3.8 Hz), 120.41 (d, J=15.1 Hz), 120.19, 119.95 (d, J=6.8 Hz), 118.65, 117.46, 116.21 (d, J=22.0 Hz), 115.93, 113.26, 61.29, 56.39.

*4.4.9. 6,7-Dimethoxy-1-phenyl-3-(3,4,5-trimethoxy-phenyl)-1H-benzo[g]indazole (**1i**)* Yield=67% (315 mg); yellowish solid; mp=160–161 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{28}H_{27}N_2O_5$ 471.1920, found 471.1918; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 2H), 7.67–7.58 (m, 5H), 7.31 (d, J=9.2 Hz, 1H), 7.21 (s, 2H), 7.07 (d, J=9.2 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 6H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.58, 149.51, 146.37, 144.09, 141.68, 138.27, 137.96, 129.60 (2×), 129.20, 128.96, 128.72, 127.56 (2×), 119.41, 118.65, 118.02, 116.96, 116.30, 113.20 (2×), 105.31 (2×), 61.24, 60.96, 56.37, 56.28 (2×). Anal. Calcd for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.95. Found: C, 71.78; H, 5.87; N, 6.12. Single-crystal X-ray diagram: crystal of compound **1i** was grown by slow diffusion of EtOAc into a solution of compound **1i** in CH_2Cl_2 to yield colorless prism. The compound crystallizes in the triclinic crystal system, space group P-1, a=9.7753(5) Å, b=11.3174(6) Å, c=11.6471(6) Å, V=1191.77(11) Å^3, Z=2, d_{calcd}=1.311 g/cm^3, F(000)=496, 2θ range 1.86–26.41°, R indices (all data) R1=0.0644, wR2=0.1455.

*4.4.10. 1-(4-Fluoro-phenyl)-6,7-dimethoxy-3-(3,4,5-trimethoxy-phenyl)-1H-benzo[g]indazole (**1j**)* Yield=63% (307 mg); yellowish solid; mp=213–214 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{28}H_{26}FN_2O_5$ 489.1826, found 489.1820; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J=9.2 Hz, 1H), 7.95 (d, J=9.2 Hz, 1H), 7.66–7.62 (m, 2H), 7.33–7.29 (m, 3H), 7.21 (s, 2H), 7.10 (d, J=9.2 Hz, 1H), 4.02 (s, 3H), 3.98 (s, 6H), 3.96 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.84 (d, J=247.8 Hz), 153.61, 149.67, 146.42, 144.15, 138.40, 138.11, 137.54, 137.51, 129.55, 129.47, 129.07, 128.27, 119.34, 118.41, 117.90, 117.23, 116.75, 116.52, 116.07, 113.30, 105.30 (2×), 61.27, 60.97, 56.36, 56.29 (2×). Anal. Calcd for $C_{28}H_{25}FN_2O_5$: C, 68.84; H, 5.16; N, 5.73. Found: C, 69.10; H, 5.32; N, 5.98. Single-crystal X-ray diagram: crystal of compound **1j** was grown by slow diffusion of EtOAc into a solution of compound **1j** in CH_2Cl_2 to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group P-1, a=9.6671(4) Å, b=11.4385(5) Å, c=11.6125(5) Å, V=1195.10(9) Å^3, Z=2, d_{calcd}=1.358 g/cm^3, F(000)=512, 2θ range 2.20–26.41°, R indices (all data) R1=0.0599, wR2=0.1151.

*4.4.11. 6,7-Dimethoxy-1-(4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-1H-benzo[g]indazole (**1k**)* Yield=69% (345 mg); yellowish solid; mp=198–199 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{29}H_{29}N_2O_6$ 501.2026, found 501.2028; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (br s, 2H), 7.54 (d, J=6.8 Hz, 2H), 7.31 (d, J=9.2 Hz, 1H), 7.22 (s, 2H), 7.10 (d, J=6.8 Hz, 2H), 7.07 (d, J=9.2 Hz, 1H), 4.00 (s, 3H), 3.97 (s, 6H), 3.94 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.04, 153.47 (2×), 149.38, 145.87, 143.93, 138.10, 138.06, 134.42, 128.80 (3×), 119.33, 118.48, 117.59, 116.69, 116.29, 114.63 (3×), 113.09, 105.12 (2×), 61.14, 60.88, 56.25, 56.17 (2×), 55.54.

*4.4.12. 4-[6,7-Dimethoxy-3-(3,4,5-trimethoxy-phenyl)-benzo[g]indazol-1-yl]-benzaldehyde (**1l**)* Yield=70% (349 mg); yellowish solid; mp=214–215 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{29}H_{27}N_2O_6$ 499.1869, found 499.1876; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.12 (d, J=8.4 Hz, 2H), 8.03 (d, J=8.4 Hz, 1H), 7.96 (d, J=8.4 Hz, 1H), 7.89 (d, J=8.4 Hz, 2H), 7.44 (d, J=9.2 Hz, 1H), 7.20 (s, 2H), 7.12 (d, J=9.2 Hz, 1H), 4.03 (s, 3H), 3.98 (s, 6H), 3.97 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.08, 153.61 (2×), 149.66, 147.71, 146.47, 144.17, 138.46, 137.67, 135.90, 130.81 (2×), 129.15, 128.21, 127.35 (2×), 119.31, 118.97,

118.68, 117.68, 115.92, 113.32, 105.23 (2×), 61.27, 60.95, 56.36, 56.25 (2×).

*4.4.13. 6,7-Dimethoxy-3-(2-methoxy-phenyl)-1-(4-methoxy-phenyl)-1H-benzo[g]indazole (**1m**)* Yield=66% (290 mg); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{27}H_{25}N_2O_4$ 441.1814, found 441.1822; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, J=0.4, 9.2 Hz, 1H), 7.71 (d, J=9.2 Hz, 2H), 7.57 (d, J=8.8 Hz, 2H), 7.43 (dt, J=2.0, 8.0 Hz, 1H), 7.36 (d, J=9.2 Hz, 1H), 7.11–7.07 (m, 4H), 7.06 (d, J=9.2 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.91, 157.26, 149.25, 144.31, 144.07, 137.43, 134.83, 131.74, 129.75, 129.91, 128.83 (2×), 122.14, 121.10, 120.81, 119.45, 118.58, 116.56, 115.68, 114.56 (2×), 112.84, 111.10, 61.17, 56.35, 55.59, 55.44.

*4.4.14. 6,7-Dimethoxy-3-phenyl-1-tosyl-1H-benzo[g]indazole (**1n**)* Yield=73% (334 mg); yellowish solid; mp=159–160 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{26}H_{23}N_2O_4S$ 459.1379, found 459.1383; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (dd, J=0.8, 9.6 Hz, 1H), 8.11 (dd, J=0.8, 8.8 Hz, 1H), 7.84–7.81 (m, 2H), 7.78 (d, J=8.8 Hz, 1H), 7.72 (d, J=8.4 Hz, 2H), 7.54–7.46 (m, 4H), 7.15 (d, J=8.4 Hz, 2H), 4.08 (s, 3H), 4.01 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.76, 149.99, 145.12, 143.21, 141.18, 134.35, 131.36, 130.07, 129.50 (2×), 129.45, 128.79 (2×), 128.48 (2×), 127.85 (2×), 123.01, 122.17, 120.41, 118.51, 117.53, 114.34, 61.25, 56.35, 21.60.

Acknowledgements

The authors would like to thank the National Science Council of the Republic of China for its financial support (NSC 99-2113-M-037-006-MY3).

Supplementary data

Scanned photocopies of ^{1}H and ^{13}C NMR spectral data were supported.

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.011.

References and notes

1. (a) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; Ochoa de Ocariz, C. *Mini-Rev. Med. Chem.* **2005**, *5*, 869; (b) Murineddu, G.; Lazzari, P.; Ruiu, S.; Sanna, A.; Loriga, G.; Manca, I.; Falzoi, M.; Dessi, C.; Curzu, M. M.; Chelucci, G.; Pani, L.; Pinna, G. A. *J. Med. Chem.* **2006**, *49*, 7502.
2. For reviews on the syntheses of indazoles, see: (a) Schimdt, A.; Beutler, A.; Snovydovych, B. *Eur. J. Org. Chem.* **2008**, 4073; (b) Schimdt, A.; Dreger, A. *Curr. Org. Chem.* **2011**, *15*, 1423.
3. Huisgen, R.; Knorr, R. *Naturwissenschaften* **1961**, *48*, 716.
4. (a) Inamoto, K.; Katsuno, M.; Yoshino, T.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695; (b) Vina, D.; Olmo, E. D.; Lopez-Perez, J. L.; Feliciano, A. S. *Org. Lett.* **2007**, *9*, 525; (c) O'Dell, D. K.; Nicholas, K. M. *Heterocycles* **2004**, *63*, 373.
5. (a) Shvartsberg, M. S.; Ivanchikova, I. D.; Fedenok, L. G. *Tetrahedron Lett.* **1994**, *35*, 6749; (b) Hashem, M. M.; Berlin, K. D.; Chesnut, R. W.; Durham, N. N. *J. Med. Chem.* **1976**, *19*, 229; (c) Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1990**, 481; (d) Bashir, N.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 868; (e) Adger, B. M.; Bradbury, S.; Keating, M.; Rees, C. W.; Storr, R. C.; Williams, M. T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 31; (f) Saracoglu, N.; Durucasu, I.; Balci, M. *Tetrahedron* **1995**, *51*, 10979; (g) Grimshaw, J.; Mannus, D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2096; (h) Olivera, R.; SanMartin, R.; Dominguez, E. *Synlett* **2000**, 1028.
6. (a) Chang, M.-Y.; Wu, M.-H.; Lee, N.-C.; Lee, M.-F. *Tetrahedron Lett.* **2012**, *53*, 2125; (b) Chang, M.-Y.; Wu, M.-H. *Tetrahedron Lett.* **2012**, *53*, 3173.
7. (a) Chattopadhyay, S. K.; Biswas, T.; Maity, S. *Synlett* **2006**, 2211; (b) Tsai, J.-C.; Li, S.-R.; Chen, L.-Y.; Chen, P. Y.; Jhong, J. Y.; Shu, C.-J.; Lo, Y.-F.; Lin, C.-N.; Wang, E.-C. *J. Chin. Chem. Soc.* **2008**, *55*, 1317.
8. (a) Congiu, C.; Onnis, V.; Vesci, L.; Castorina, M.; Pisano, C. *Bioorg. Med. Chem.* **2010**, *18*, 6238; (b) Gokhan-Kelekci, N.; Yabanoglu, S.; Kupeli, E.; Salgın, U.; Ozgen, O.; Ucar, G.; Yesilada, E.; Kendi, E.; Yesilada, A.; Bilgin, A. A. *Bioorg. Med. Chem.* **2007**, *15*, 5775; (c) Bonesi, M.; Loizzo, M. R.; Statti, G. A.; Michel, S.; Tillequin, F.; Menichini, F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1990; (d) Bhat, B. A.; Dhar, K. L.; Puri, S. C.; Saxena, A. K.; Shanmugavel, M.; Qazi, G. N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3177; (e) Johnson, M.; Younglove, B.; Lee, L.; LeBlanc, R.; Holt, H. J.; Hills, P.; Mackay, H.; Brown, T.; Mooberry, S. L.; Lee, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5897.
9. CCDC 884931 (**2k**), 878329(**1i**), and 878847 (**1j**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
10. (a) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217; (b) Nielsen, T. E.; Meldal, M. *Org. Lett.* **2005**, *7*, 2695; (c) Nielsen, T. E.; Le Quement, S. T.; Meldal, M. *Org. Lett.* **2007**, *9*, 2469.