A Concise One-Pot Synthesis of 3,4-Diaryl-1*H*-pyrazoles from Natural Isoflavones and Hydrazine Hydrate

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An efficient protocol has been developed for the preparation of a series of new 3,4-diaryl-1*H*-pyrazoles, potential pharmacological and agricultural targets, by the reaction of hydrazine hydrate with different natural isoflavones or their derivatives. The target compounds were obtained in good-to-excellent yields (80–95%; *Table 2*) under fairly mild reaction conditions (80°) tolerating various functional groups. The new compounds were fully characterized, and the single-crystal X-ray structures of 3,5-diethoxy-2-[4-(4-ethoxyphenyl)-1*H*-pyrazol-3-yl]phenol (**26**) and of the peracetylated compound 2-{1-acetyl-4-[4-acetoxy-3-(diacetylamino)phenyl]-1*H*-pyrazol-3-yl}-5-acetoxyphenyl acetate (**35**) were solved (*Figure*).

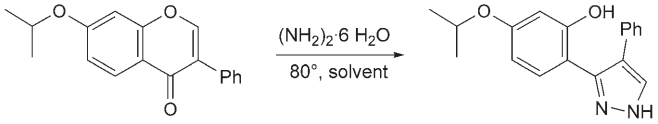
Introduction. – The chemistry of 1*H*-pyrazoles is particularly interesting because of their potential application in medicinal chemistry as analgesic [1][2], anti-inflammatory [3][4], antitumor [5][6], antimicrobial [7][8], or therapeutic agents [9], as well as based on their wide applications in agriculture as potent insecticides [10][11] and herbicides [12][13], although scarcely found in nature [14]. Due to many promising pharmacological, agrochemical, and analytical applications, 3,4-diarylpyrazoles are being used as inhibitors of heat-shock protein 90 (HSP90) and as therapeutics of cancer. Therefore, 3,4-diarylpyrazoles have been the focus of many synthetic targets over the past decades [15].

Recently, *Xie et al.* [16] and *Dymock et al.* [17] reported the synthesis of some 3,4-diarylpyrazoles by reacting hydrazine (NH_2-NH_2) with synthetic isoflavones. It is well-known that natural isoflavones display a wide range of biological activities [18]. For instance, soybean isoflavones (daidzein and genistein) have antidysrhythmic [19], antioxidant [20], and cardiovascular-inhibiting [21] properties. Ipriflavone is used in the prevention and treatment of osteoporosis [22]; and irisolidone (= 5,7-dihydroxy-6,4′-dimethoxyisoflavone) is an effective antidiabetic [23]. However, it is necessary to modify the structure of natural isoflavones to increase their biological activities and generally poor solubilities.

Recently, we reported the synthesis of several new water-soluble isoflavones [24]. In order to enhance their biological activity and to develop more-powerful new drugs, we herein report the high-throughput synthesis of a series of new 3,4-diarylpyrazoles by means of a one-pot procedure based on the reaction of hydrazine with natural isoflavones.

Results and Discussion. – Initially, we screened several solvents, including MeOH, EtOH, THF, MeCN, DMF, and BuOH, for the model reaction between ipriflavone (= 7-(1-methylethoxy)-3-phenyl-4*H*-1-benzopyran-4-one; 1 mmol) with hydrazine hydrate (5 mmol) at 80°. The results of these studies are summarized in *Table 1*. EtOH was found to be the best solvent in terms of reaction time (90 min) and yield (92%; *Entry 1*). Reasonable results were also obtained with other solvents, but the conversion of ipriflavone to the corresponding 3,4-diarylpyrazole appears to be sluggish at 80° (*Entries 2–6*). Therefore, we decided to use EtOH for further studies.

Table 1. *Solvent Effects on the Reaction of Ipriflavone with Hydrazine Hydrate*



Entry	Solvent	Time [min]	Yield [%][a])
1	EtOH	90	92
2	MeOH	150	85
3	THF	160	60
4	MeCN	120	72
5	BuOH	140	78
6	DMF	130	55

[a]) Yields refer to the pure, recrystallized product.

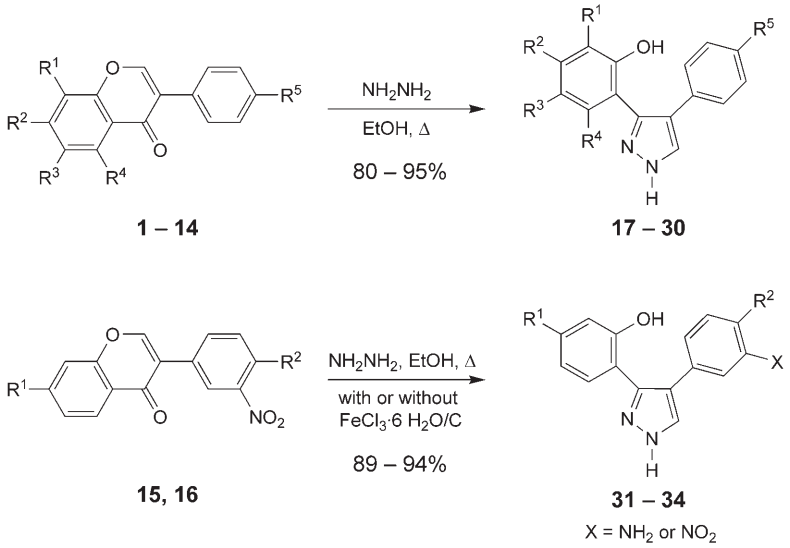
With the optimized reaction conditions at hand, the structurally divergent isoflavones **1**–**16** were reacted with hydrazine hydrate to illustrate the scope of this type of synthesis of 3,4-diarylpyrazoles[1]). All substrates smoothly reacted within 0.75–6 h to afford the target compounds in excellent yields, as shown in *Scheme 1* and *Table 2*. Although the reaction solvent was the same as in the procedure elaborated by *Dymock et al.* [17], the reaction time was nearly halved.

All products were characterized by IR, ^{1}H- and ^{13}C-NMR, and HR-MS (see *Exper. Part*). The structures of compounds **26** and **35** were further established by single-crystal X-ray diffraction (*Fig. 1*). In the crystal structure of **26**, only one tautomer was found, the one with the H-atom at the N(2)-atom (species **B** in *Scheme 2* below).

As shown in *Table 2*, the synthesis of 3,4-diarylpyrazoles lacking OH groups in both aromatic rings is accomplished in high yields. If the benzopyranone ring bears no OH group at C(5) (*Entries 2*, *3*, and *5*), the products were formed in nearly quantitative yields; otherwise, the yield was lower (*Entries 8* and *9*). These results are not surprising because isoflavones with a 5-OH group react with more difficulty than those without electron-donating substituents at this position, probably because their intermediate benzene-1,3,5-triol is easily oxidized. The usefulness of this methodology lies in the fact that the reactions are carried out rapidly under very mild conditions. Moreover, the method is compatible with many functional groups such as MeO, NO_2, Br, i-Pr, *etc.*

[1]) For systematic compound names, see *Exper. Part* (names in parentheses).

Scheme 1



Nitroisoflavone and hydrazine may either react directly or in the presence of $FeCl_3$ as catalyst. In the latter case, simultaneous reduction of the NO_2 group occurs, leading to the corresponding amines **32** or **34** (*Scheme 1*). Because pyrazoles often exist in tautomeric forms (*Scheme 2*) [25], the structures of compounds **20**, **32**, and **34** could not be unambiguously determined by regular ^{1}H- and ^{13}C-NMR experiments performed in (D_6)DMSO. However, deuterium (^{2}H)-exchange experiments simplified the spectra and allowed us to assign the different signals (see *Exper. Part*).

A *Michael*-addition mechanism can be proposed for the reaction of hydrazine with isoflavones (*Scheme 3*). Thus, nucleophilic attack of hydrazine at the C(2)-atom of an isoflavone **C** gives rise to the intermediate **D**, whose benzopyranone ring opens to **E**. The latter then attacks the C=O group, which, upon loss of H_2O and protonation, leads to the final pyrazole product **F** [26].

Conclusions. – We have further elaborated and optimized the reaction of hydrazine hydrate with different natural isoflavones to access pharmacologically and agriculturally interesting 3,4-diarylpyrazoles. The mild reaction condition, short reaction times, simple workup, excellent yields, and the use of an environmentally benign solvent (EtOH) offer advantages over other procedures for the synthesis of these compounds. On the basis of the present investigation, we are currently carrying out further research on possible industrial, pharmacological, and agricultural applications of 3,4-diarylpyrazoles.

Table 2. *Synthesis of 3,4-Diaryl-1*H*-pyrazoles by Reaction of Various Isoflavones with Hydrazine Hydrate at 80° in EtOH.* For details, see *Exper. Part.*

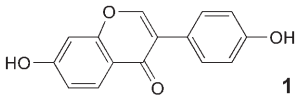
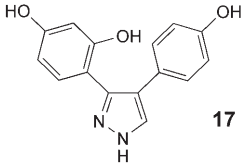
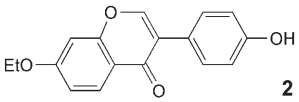
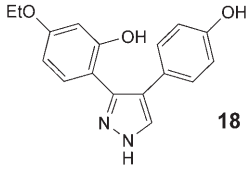
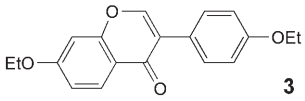
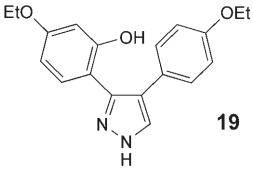
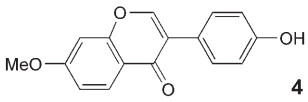
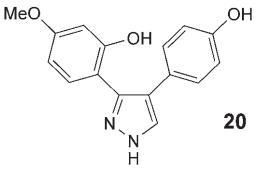
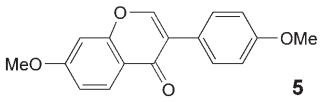
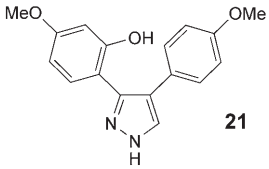
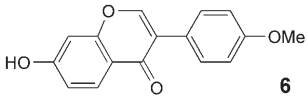
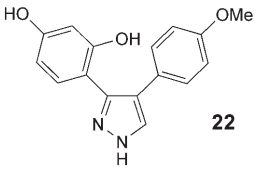
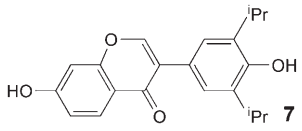
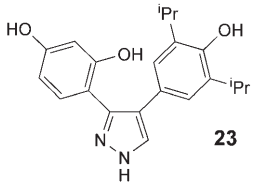
Entry	Substrate	Product	Time [h]	Yield [%][a])
1	 **1**	 **17**	2.5	85
2	 **2**	 **18**	2.0	93
3	 **3**	 **19**	1.5	95
4	 **4**	 **20**	2.0	89
5	 **5**	 **21**	0.75	93
6	 **6**	 **22**	1.0	93
7	 **7**	 **23**	2.5	80

Table 2 (cont.)

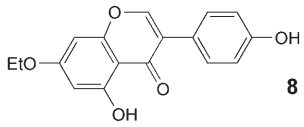
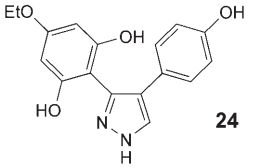
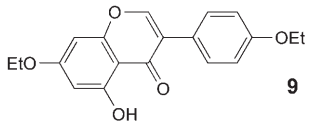
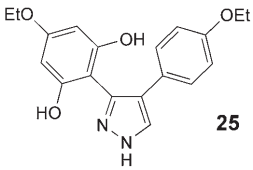
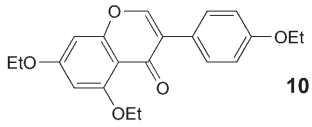
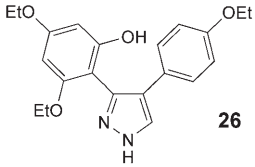
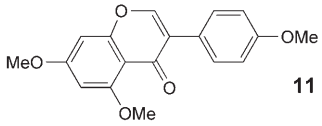
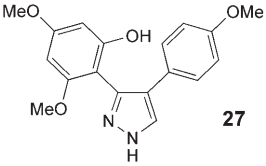
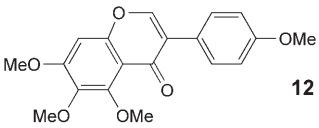
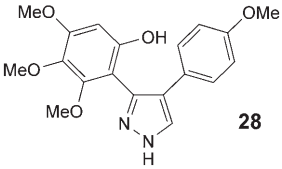
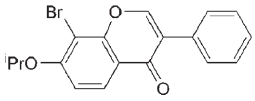
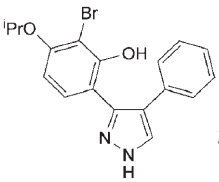
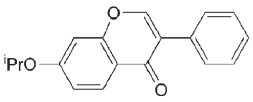
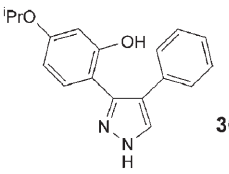
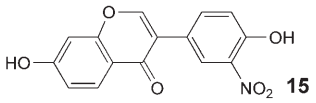
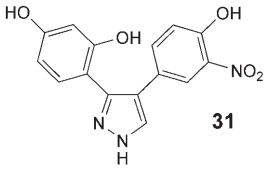
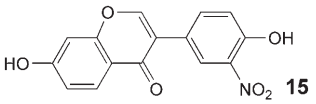
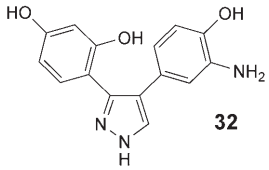
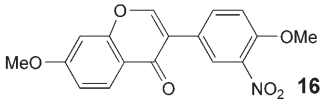
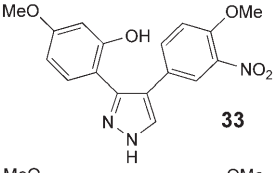
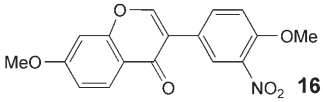
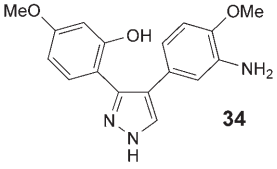
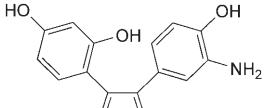
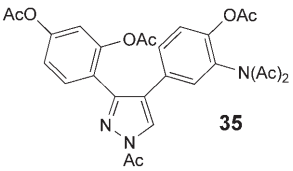
Entry	Substrate	Product	Time [h]	Yield [%][a])
8	 **8**	 **24**	2.5	82
9	 **9**	 **25**	2.0	84
10	 **10**	 **26**	1.5	90
11	 **11**	 **27**	1.5	93
12	 **12**	 **28**	1.5	90
13	 **13**	 **29**	2.0	94
14	 **14**	 **30**	1.5	92

Table 2 (cont.)

Entry	Substrate	Product	Time [h]	Yield [%][a])
15	 **15**	 **31**	2.0	94
16	 **15**	 **32**	6.0	89[b])
17	 **16**	 **33**	1.0	90
18	 **16**	 **34**	6.0	91[b])
19	 **32**	 **35**	1.0	95

[a]) Yields of pure, isolated products. [b]) Reaction carried out with $FeCl_3 \cdot 6\,H_2O$/C as catalyst.

Experimental Part

General. Thin-layer chromatography (TLC): *silica gel 60 GF*$_{254}$ plates; visualization under UV light (254 nm). Melting points (m.p.) are uncorrected. IR Spectra: *Nicollet 170SX* FT-IR spectrophotometer; as KBr pellets; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: at 300/75 MHz, resp., in (D_6)DMSO, unless otherwise indicated; chemical shifts δ in ppm rel. to Me_4Si (=0 ppm), coupling constants J in Hz. HR-ESI-MS: *Bruker Daltonics APEX-II 4.7E* FT-ICR mass spectrometer; in m/z. X-Ray crystallography: *Bruker Smart-1000 CCD* diffractometer.

General Procedure (*GP 1*) *for the Synthesis of* **17**–**31** *and* **33**. Hydrazine hydrate was added to an EtOH soln. of the appropriate isoflavone at 60–85°, and the mixture was stirred at 85° for the time specified (*Table 2*). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into H_2O, the precipitate was filtered, and washed with H_2O until the

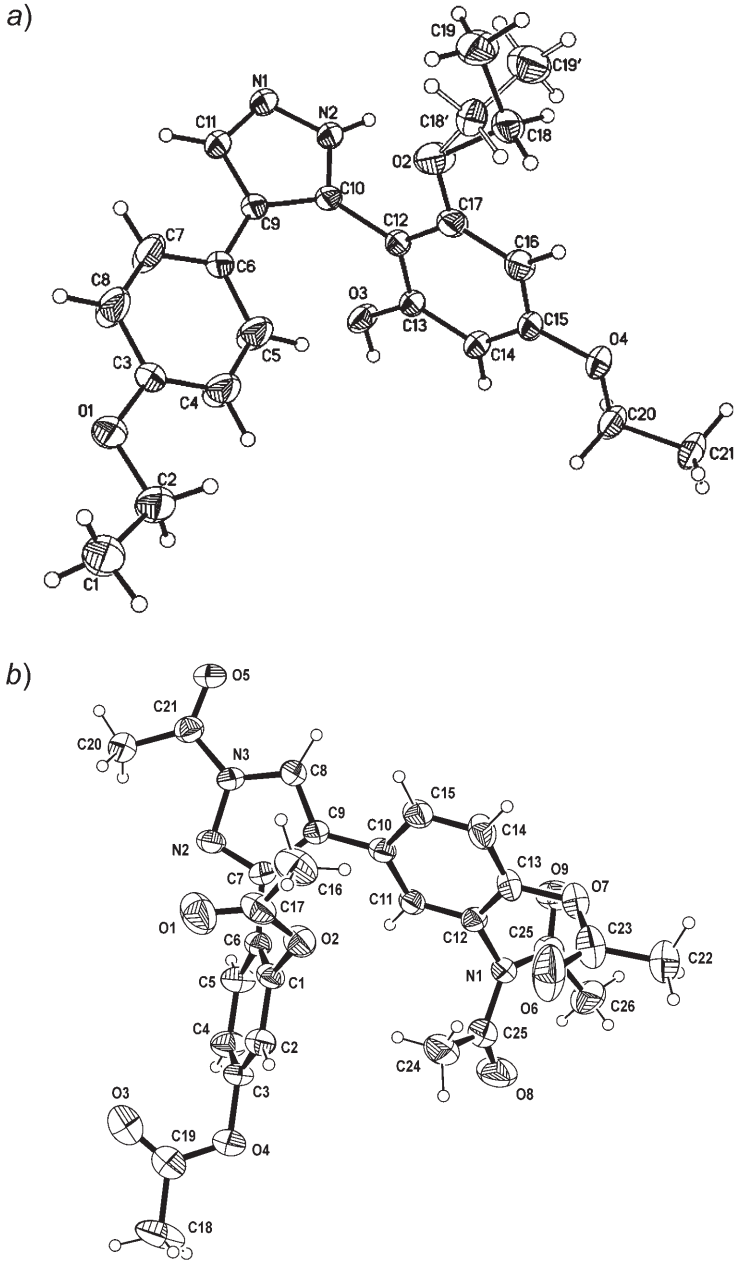
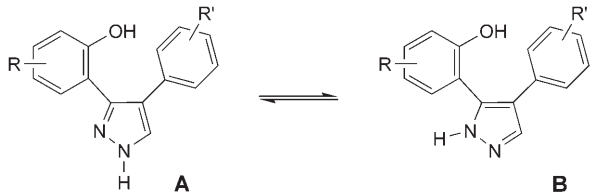


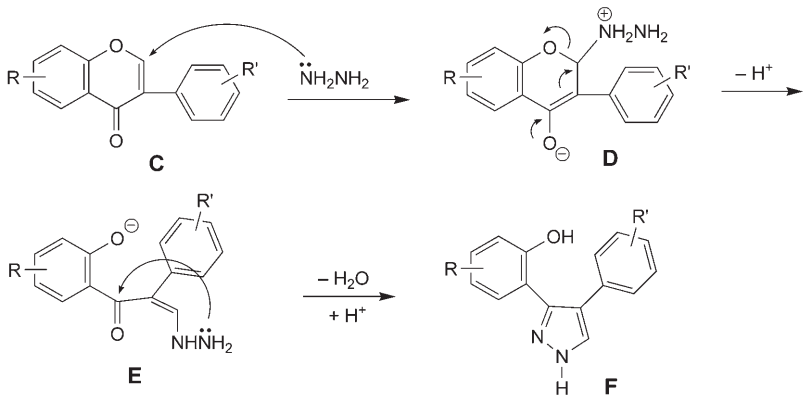
Figure. *Single-crystal X-ray structures of* a) **26** *and* b) **35**. Displacement ellipsoids are shown at the 30%-probability level. In the case of **26**, one Et group is disordered. For details, see *Table 3* and *Exper. Part.*

filtrate was neutral. The precipitate was recrystallized from EtOH to afford the corresponding pure products in yields of 80–95% (see *Table 2*).

Scheme 2. *Alternative Tautomeric Forms of 3,4-Diarylpyrazoles*



Scheme 3. *Proposed Mechanism for the Reaction of Isoflavones with Hydrazine Hydrate*



*3-(2,4-Dihydroxyphenyl)-4-(4-hydroxyphenyl)-1*H*-pyrazole* (=*4-[4-(4-Hydroxyphenyl)-1*H*-pyrazol-3-yl]benzene-1,3-diol*; **17**). Colorless solid. M.p. 179.6–181.4°. IR: 3137, 1617, 1559, 1505, 1457, 1387, 1250, 1177, 1055, 978, 834. ^{1}H-NMR: 6.24 (*d*, *J* = 8.4, 1 H); 6.41 (*s*, 1 H); 6.71 (*d*, *J* = 8.4, 2 H); 6.93 (*d*, *J* = 8.4, 1 H); 7.12 (*d*, *J* = 8.4, 2 H); 8.05–8.36 (*m*, 5 H). ^{13}C-NMR: 103.4; 107.2; 107.9; 115.8; 120.1; 123.7; 129.1; 131.5; 133.4; 140.6; 156.7; 157.2; 159.7. HR-ESI-MS: 269.0926 ($[M+H]^+$, $C_{15}H_{13}N_2O_3^+$; calc. 269.0926).

*3-(4-Ethoxy-2-hydroxyphenyl)-4-(4-hydroxyphenyl)-1*H*-pyrazole* (=*5-Ethoxy-2-[4-(4-hydroxyphenyl)-1*H*-pyrazol-3-yl]phenol*; **18**). Colorless solid. M.p. 245.6–247.8°. IR: 3306, 3024, 2973, 1628, 1516, 1486, 1441, 1383, 1237, 1166, 1038, 987, 894, 832. ^{1}H-NMR: 1.33 (*t*, *J* = 6.7, 3 H); 3.99 (*q*, *J* = 6.7, 2 H); 6.37–6.69 (*m*, 4 H); 7.08 (*s*, 3 H); 7.63–7.85 (*m*, 1 H). ^{13}C-NMR: 15.1; 63.4; 102.4; 105.7; 115.6; 119.4; 128.1; 128.9; 130.1; 132.6; 137.9; 142.2; 156.4; 156.9; 159.6. HR-ESI-MS: 297.1229 ($[M+H]^+$, $C_{17}H_{17}N_2O_3^+$; calc. 297.1239).

*3-(4-Ethoxy-2-hydroxyphenyl)-4-(4-ethoxyphenyl)-1*H*-pyrazole* (=*5-Ethoxy-2-[4-(4-ethoxyphenyl)-1*H*-pyrazol-3-yl]phenol*; **19**). Colorless crystals. M.p. 120.3–121.8°. IR: 3364, 2979, 2871, 1634, 1586, 1525, 1436, 1384, 1240, 1184, 1163, 1133, 1113, 1090, 1046, 987, 824, 784. ^{1}H-NMR: 1.31 (*t*, *J* = 6.3, 6 H); 3.98 (*m*, 4 H); 6.30–6.46 (*m*, 2 H); 6.81–6.99 (*m*, 3 H); 7.17 (*d*, *J* = 6.3, 2 H); 7.78 (*m*, 1 H); 10.10 (*m*, 1 H); 12.87 (*m*, 1 H). ^{13}C-NMR: 15.2; 63.4; 102.5; 105.7; 114.8; 119.1; 126.7; 128.2; 129.8; 132.3; 138.1; 146.6; 157.2; 158.1; 160.5. HR-ESI-MS: 325.1548 ($[M+H]^+$, $C_{19}H_{21}N_2O_3^+$; calc. 325.1552).

*3-(2-Hydroxy-4-methoxyphenyl)-4-(4-hydroxyphenyl)-1*H*-pyrazole* (=*2-[4-(4-Hydroxyphenyl)-1*H*-pyrazol-3-yl]-5-methoxyphenol*; **20**). Colorless crystals. M.p. 230.7–232.5°. IR: 3370, 3282, 2608, 1621, 1595, 1569, 1533, 1510, 1482, 1432, 1354, 1249, 1165, 1115, 1027, 953, 829. ^{1}H-NMR ((D$_6$)DMSO): 3.72 (*s*, 3 H); 6.34–6.74 (*m*, 4 H); 7.11 (*d*, *J* = 7.2, 3 H); 7.76 (*m*, 1 H); 9.33 (*m*, 1 H); 10.24 (*m*, 1 H); 12.87 (*m*, 1 H). ^{1}H-NMR ((D$_6$)DMSO/D$_2$O): 3.78 (*s*, 3 H); 6.45 (*d*, *J* = 7.8, 1 H); 6.58 (*s*, 1 H); 6.78 (*d*, *J* = 8.4, 2 H); 7.10 (*d*, *J* = 8.4, 2 H); 7.17 (*d*, *J* = 8.4, 2 H); 7.80 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 55.5; 102.0;

105.2; 110.8; 115.7; 119.4; 120.7; 125.2; 128.3; 129.5; 130.2; 132.3; 135.3; 138.0; 146.1; 155.9; 156.7; 157.3; 160.4; 161.0. ^{13}C-NMR ((D_6)DMSO/D_2O): 55.4; 101.8; 105.5; 110.6; 115.7; 119.7; 125.0; 128.7; 131.4; 138.0; 146.5; 155.3; 156.5; 160.7. HR-ESI-MS: 283.1072 ($[M+H]^+$, $C_{16}H_{15}N_2O_3^+$; calc. 283.1083).

*3-(2-Hydroxy-4-methoxyphenyl)-4-(4-methoxyphenyl)-1*H*-pyrazole* (*=5-Methoxy-2-[4-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]phenol*; **21**). Colorless crystals. M.p. 150.5–151.6°. IR: 3431, 2921, 2728, 2603, 1621, 1597, 1564, 1534, 1507, 1480, 1434, 1386, 1323, 1202, 1172, 1100, 1062, 1033, 950, 833. ^{1}H-NMR: 3.72 (*s*, 6 H); 6.33–6.49 (*m*, 2 H); 6.84–7.21 (*m*, 5 H); 7.84 (*m*, 1 H); 10.14 (*m*, 1 H); 12.89 (*m*, 1 H). ^{13}C-NMR: 55.5; 102.0; 105.2; 114.3; 119.1; 125.9; 128.1; 129.9; 132.3; 138.2; 146.3; 156.2; 157.3; 161.3. HR-ESI-MS: 297.1233 ($[M+H]^+$, $C_{17}H_{17}N_2O_3^+$; calc. 297.1239).

*3-(2,4-Dihydroxyphenyl)-4-(4-methoxyphenyl)-1*H*-pyrazole* (*=4-[4-(4-Methoxyphenyl)-1*H*-pyrazol-3-yl]benzene-1,3-diol*; **22**). Colorless crystals. M.p. 209.2–211.0°. IR: 3334, 2933, 2540, 1729, 1611, 1573, 1519, 1408, 1353, 1295, 1247, 1157, 1116, 1064, 1025, 956, 868, 814, 733. ^{1}H-NMR: 3.72 (*s*, 3 H); 6.33 (*m*, 2 H); 6.88 (*m*, 3 H); 7.22 (*d*, *J* = 8.4, 2 H); 7.78 (*m*, 1 H); 9.92 (*m*, 2 H); 12.83 (*m*, 1 H). ^{13}C-NMR: 55.5; 103.4; 107.0; 114.3; 118.9; 126.9; 129.9; 132.1; 136.1; 138.0; 146.4; 157.1; 158.0; 159.2. HR-ESI-MS: 283.1080 ($[M+H]^+$, $C_{16}H_{15}N_2O_3^+$; calc. 283.1083).

*3-(2,4-Dihydroxyphenyl)-4-(4-hydroxy-3,5-diisopropylphenyl)-1*H*-pyrazole* (*=4-[4-[4-Hydroxy-3,5-bis(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl]benzene-1,3-diol*; **23**). Colorless solid. M.p. 232.0–233.2°. IR: 3429, 2963, 2621, 1612, 1563, 1496, 1466, 1383, 1316, 1255, 1177, 1104, 1058, 971, 954, 839. ^{1}H-NMR: 1.08 (*d*, *J* = 6.0, 12 H); 3.26 (*m*, 2 H); 6.23 (*s*, 1 H); 6.42 (*s*, 1 H); 6.96 (*s*, 3 H); 7.75 (*m*, 1 H); 9.49 (*s*, 1 H). ^{13}C-NMR: 23.4; 26.5; 103.1; 106.6; 109.6; 119.9; 122.0; 125.6; 129.9; 132.1; 135.4; 137.6; 149.3; 157.0; 158.8. HR-ESI-MS: 353.1863 ($[M+H]^+$, $C_{21}H_{25}N_2O_3^+$; calc. 353.1865).

*3-(2,6-Dihydroxy-4-ethoxyphenyl)-4-(4-hydroxyphenyl)-1*H*-pyrazole* (*=5-Ethoxy-2-[4-(4-hydroxyphenyl)-1*H*-pyrazol-3-yl]benzene-1,3-diol*; **24**). Pink crystals. M.p. 259.6–261.3°. IR: 3274, 3155, 2984, 2557, 1631, 1587, 1512, 1447, 1356, 1284, 1231, 1199, 1173, 1143, 1120, 1055, 958, 820. ^{1}H-NMR: 1.31 (*t*, *J* = 6.7, 3 H); 3.91 (*q*, *J* = 6.7, 2 H); 5.95 (*s*, 2 H); 6.60 (*d*, *J* = 8.1, 2 H); 7.11 (*d*, *J* = 8.1, 2 H); 7.65 (*s*, 1 H); 9.21 (*m*, 3 H); 12.37 (*s*, 1 H). ^{13}C-NMR: 15.2; 63.2; 98.9; 114.6; 115.5; 120.1; 125.9; 127.3; 131.9; 137.2; 155.6; 158.3; 160.5. HR-ESI-MS: 313.1183 ($[M+H]^+$, $C_{17}H_{17}N_2O_4^+$; calc. 313.1188).

*3-(2,6-Dihydroxy-4-ethoxyphenyl)-4-(4-ethoxyphenyl)-1*H*-pyrazole* (*=5-Ethoxy-2-[4-(4-ethoxyphenyl)-1*H*-pyrazol-3-yl]benzene-1,3-diol*; **25**). Pink crystals. M.p. 188.7–190.1°. IR: 3395, 3339, 2977, 2933, 2362, 1622, 1581, 1513, 1476, 1445, 1392, 1351, 1286, 1247, 1164, 1107, 1047, 949, 843, 813. ^{1}H-NMR: 1.29 (*t*, *J* = 6.5, 6 H); 3.92 (*q*, *J* = 6.5, 4 H); 5.97 (*s*, 2 H); 6.76 (*d*, *J* = 7.8, 2 H); 7.23 (*d*, *J* = 7.8, 2 H); 7.74 (*s*, 1 H). ^{13}C-NMR: 14.7; 62.7; 62.8; 93.0; 98.9; 114.2; 119.3; 126.4; 127.0; 135.4; 156.3; 157.8; 160.0. HR-ESI-MS: 341.1492 ($[M+H]^+$, $C_{19}H_{21}N_2O_4^+$; calc. 341.1501).

*3-(2,4-Diethoxy-6-hydroxyphenyl)-4-(4-ethoxyphenyl)-1*H*-pyrazole* (*=3,5-Diethoxy-2-[4-(4-ethoxyphenyl)-1*H*-pyrazol-3-yl]phenol*; **26**). Pink crystals. M.p. 168.4–169.6°. IR: 3341, 3101, 2980, 2930, 2874, 1624, 1586, 1526, 1507, 1478, 1440, 1393, 1355, 1287, 1239, 1172, 1116, 1092, 1046, 941, 828, 807, 706. ^{1}H-NMR: 0.92 (*t*, *J* = 5.4, 3 H); 1.33 (*m*, 6 H); 3.79 (*q*, *J* = 5.4, 2 H); 3.99 (*q*, *J* = 5.8, 4 H); 6.10 (*s*, 1 H); 6.15 (*s*, 1 H); 6.79 (*d*, *J* = 7.8, 2 H); 7.19 (*d*, *J* = 7.8, 2 H); 7.75 (*s*, 1 H); 9.52 (*s*, 1 H); 12.48 (*s*, 1 H). ^{13}C-NMR: 14.7; 15.1; 63.3; 63.4; 63.9; 91.8; 94.6; 100.7; 113.7; 114.6; 119.8; 127.2; 127.6; 137.2; 156.9; 158.0; 159.2; 160.8. HR-ESI-MS: 369.1804 ($[M+H]^+$, $C_{21}H_{25}N_2O_4^+$; calc. 369.1814).

*3-(6-Hydroxy-2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)-1*H*-pyrazole* (*=3,5-Dimethoxy-2-[4-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]phenol*; **27**). Colorless solid. M.p. 172.0–173.7°. IR: 3439, 2973, 2939, 2832, 2618, 1618, 1539, 1462, 1419, 1385, 1287, 1249, 1204, 1153, 1107, 1044, 955, 882, 832, 803. ^{1}H-NMR: 3.54 (*s*, 3 H); 3.68 (*s*, 3 H); 3.75 (*s*, 3 H); 6.14 (*s*, 2 H); 6.78 (*d*, *J* = 8.4, 2 H); 7.19 (*d*, *J* = 8.4, 2 H); 7.76 (*s*, 1 H). ^{13}C-NMR: 55.4; 55.5; 55.9; 90.5; 94.1; 114.2; 119.9; 127.2; 127.3; 137.7; 142.3; 157.6; 157.9; 158.1; 160.2; 161.7. HR-ESI-MS: 327.1338 ($[M+H]^+$, $C_{18}H_{19}N_2O_4^+$; calc. 327.1345).

*3-(6-Hydroxy-2,3,4-trimethoxyphenyl)-4-(4-methoxyphenyl)-1*H*-pyrazole* (*=3,4,5-Trimethoxy-2-[4-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]phenol*; **28**). Colorless solid. M.p. 106.5–107.2°. IR: 3490, 3332, 2936, 1612, 1559, 1510, 1464, 1409, 1338, 1287, 1245, 1177, 1111, 1074, 1021, 973, 823. ^{1}H-NMR: 3.37 (*s*, 3 H); 3.65 (*s*, 3 H); 3.68 (*s*, 3 H); 3.78 (*s*, 3 H); 6.37 (*s*, 1 H); 6.80 (*d*, *J* = 8.4, 2 H); 7.21 (*d*, *J* = 8.4, 2 H); 7.76 (*s*, 1 H); 9.41 (*s*, 1 H); 12.6 (*s*, 1 H). ^{13}C-NMR: 55.4; 56.0; 60.8; 61.0; 96.2; 103.2; 114.3; 120.5; 127.1; 127.4; 135.0; 137.6; 142.3; 146.2; 153.1; 155.4; 157.7. HR-ESI-MS: 327.1439 ($[M+H]^+$, $C_{19}H_{21}N_2O_5^+$; calc. 357.1450).

*3-(3-Bromo-2-hydroxy-4-isopropoxyphenyl)-4-phenyl-1*H-*pyrazole* (=*2-Bromo-3-(1-methylethoxy)-6-(4-phenyl-1*H-*pyrazol-3-yl)phenol*; **29**). Colorless solid. M.p. 171.6–173.4°. IR: 3379, 2974, 2926, 1617, 1507, 1421, 1372, 1290, 1226, 1161, 1110, 1043, 766. ^{1}H-NMR ($CDCl_3$): 1.36 (*d*, *J* = 6.0, 6 H); 4.52 (*m*, 1 H); 6.27 (*d*, *J* = 8.7, 1 H); 7.10 (*d*, *J* = 8.7, 1 H); 7.37 (*s*, 4 H); 7.63 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 22.1; 72.1; 105.7; 111.0; 120.3; 127.4; 128.6; 129.5; 130.4; 133.2; 139.6; 147.4; 155.0; 156.3; 157.0. HR-ESI-MS: 373.0542 ($[M+H]^+$, $C_{18}H_{18}N_2BrO_2^+$; calc. 373.0552).

*3-(2-Hydroxy-4-isopropoxyphenyl)-4-phenyl-1*H-*pyrazole* (=*5-(1-Methylethoxy)-2-(4-phenyl-1*H-*pyrazol-3-yl)phenol*; **30**). Colorless crystals. M.p. 129.2–130.9°. IR: 3262, 2973, 1624, 1577, 1514, 1443, 1361, 1276, 1162, 983, 924, 843, 756. ^{1}H-NMR ($CDCl_3$): 1.32 (*d*, *J* = 6.0, 6 H); 4.50 (*m*, 1 H); 6.21 (*d*, *J* = 6.3, 1 H); 6.58 (*s*, 1 H); 7.09 (*d*, *J* = 8.7, 1 H); 7.37 (*s*, 5 H); 8.13 (*s*, 1 H); 8.98 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 22.1; 69.8; 102.6; 103.5; 107.3; 109.6; 120.2; 127.3; 128.6; 129.2; 129.5; 133.3; 147.1; 157.3; 158.9. HR-ESI-MS: 295.1443 ($[M+H]^+$, $C_{18}H_{19}N_2O_2^+$; calc. 295.1447).

*3-(2,4-Dihydroxyphenyl)-4-(3-nitro-4-hydroxyphenyl)-1*H-*pyrazole* (=*4-[4-(4-Hydroxy-3-nitrophenyl)-1*H-*pyrazol-3-yl]benzene-1,3-diol*; **31**). Red crystals. M.p. 240.6–242.9°. IR: 3365, 3123, 2953, 2843, 1637, 1593, 1531, 1477, 1439, 1386, 1349, 1269, 1193, 1094, 1009, 831. ^{1}H-NMR: 6.28 (*s*, 1 H); 6.40 (*s*, 1 H); 6.94 (*d*, *J* = 8.1, 2 H); 7.04 (*d*, *J* = 8.7, 1 H); 7.46 (*d*, *J* = 8.7, 1 H); 7.91 (*d*, *J* = 8.1, 2 H); 9.77 (*s*, 2 H); 10.79 (*s*, 1 H); 12.90 (*s*, 1 H). ^{13}C-NMR: 103.3; 107.2; 108.4; 117.2; 119.6; 122.5; 126.3; 132.2; 134.2; 137.0; 138.1; 143.2; 150.6; 156.9; 159.5. HR-ESI-MS: 314.0770 ($[M+H]^+$, $C_{15}H_{12}N_3O_5^+$; calc. 314.0777).

*3-(2-Hydroxy-4-methoxyphenyl)-4-(3-nitro-4-methoxyphenyl)-1*H-*pyrazole* (=*5-Methoxy-2-[4-(4-methoxy-3-nitrophenyl)-1*H-*pyrazol-3-yl]phenol*; **33**). Colorless crystals. M.p. 172.2–174.2°. IR: 3554, 3317, 3053, 1618, 1569, 1533, 1470, 1408, 1246, 1180, 1120, 1071, 950, 843. ^{1}H-NMR: 3.75 (*s*, 3 H); 3.89 (*s*, 3 H); 6.46 (*d*, *J* = 7.8, 1 H); 6.51 (*s*, 1 H); 7.09 (*d*, *J* = 8.4, 1 H); 7.28 (*d*, *J* = 8.7, 1 H); 7.51 (*d*, *J* = 7.8, 1 H); 7.78 (*s*, 1 H); 7.93 (*s*, 1 H); 9.89 (*s*, 1 H); 12.92 (*s*, 1 H). ^{13}C-NMR: 55.5; 57.1; 102.1; 105.4; 114.8; 117.2; 122.9; 127.4; 131.8; 132.8; 138.5; 139.7; 150.5; 157.0; 160.5; 161.2. HR-ESI-MS: 342.1089 ($[M+H]^+$, $C_{17}H_{16}N_3O_5^+$; calc. 342.1090).

General Procedure (*GP 2*) *for the Synthesis of Compounds* **32** *and* **34**. Hydrazine hydrate (5 mmol) was added to a soln. of the corresponding isoflavone (1 mmol) in EtOH. Then, $FeCl_3 \cdot 6\,H_2O$ (0.2 g; 0.0014 g/C) was added at 80°, and the mixture was stirred at this temp. for 6 h. The mixture was filtered, and the filtrate was kept overnight. The formed precipitate was filtered off and purified by recrystallization from EtOH to afford the product.

*3-(2,4-Dihydroxyphenyl)-4-(3-amino-4-hydroxyphenyl)-1*H-*pyrazole* (=*4-[4-(3-Amino-4-hydroxyphenyl)-1*H-*pyrazol-3-yl]benzene-1,3-diol*; **32**). Prepared according to *GP 2*. Colorless solid. M.p. 290–292.3°. IR: 3387, 3306, 3211, 3005, 2579, 1615, 1557, 1467, 1406, 1332, 1295, 1224, 1178, 1117, 953, 910, 819, 753, 707. ^{1}H-NMR ((D_6)DMSO): 4.36–4.50 (*m*, 4 H); 6.09–6.84 (*m*, 10 H); 7.03 (*s*, 1 H); 7.06 (*s*, 1 H); 7.46 (*s*, 1 H); 7.73 (*s*, 1 H); 8.81–9.07 (*m*, 2 H); 9.38–9.50 (*m*, 3 H); 10.91 (*s*, 1 H); 12.42 (*s*, 1 H); 12.99 (*s*, 1 H). ^{1}H-NMR ((D_6)DMSO/D_2O): 4.49 (*s*, 2 H); 6.35 (*d*, *J* = 7.8, 1 H); 6.47–6.51 (*m*, 2 H); 6.73 (*m*, 2 H); 7.10 (*d*, *J* = 7.8, 1 H); 7.78 (*s*, 1 H). ^{13}C-NMR: 103.2; 107.1; 109.8; 115.0; 115.2; 117.5; 120.0; 125.6; 128.9; 131.3; 136.1; 143.2; 155.7; 156.7; 158.3. HR-ESI-MS: 284.1034 ($[M+H]^+$, $C_{15}H_{14}N_3O_3^+$; calc. 284.1035).

*3-(2-Hydroxy-4-methoxyphenyl)-4-(3-amino-4-methoxyphenyl)-1*H-*pyrazole* (=*2-[4-(3-Amino-4-methoxyphenyl)-1*H-*pyrazol-3-yl]-5-methoxyphenol*; **34**). Prepared according to *GP 2*. Colorless solid. M.p. 184.9–186.5°. IR: 3426, 3296, 2932, 1626, 1543, 1510, 1466, 1439, 1370, 1256, 1182, 1112, 1063, 1028, 988, 820, 755. ^{1}H-NMR ((D_6)DMSO): 3.71 (*s*, 12 H); 4.57 (*s*, 2 H); 4.71 (*s*, 2 H); 6.29–7.15 (*m*, 12 H); 7.52 (*s*, 1 H); 7.80 (*s*, 1 H); 9.74 (*s*, 1 H); 10.97 (*s*, 1 H); 12.55 (*s*, 1 H); 13.10 (*s*, 1 H). ^{1}H-NMR ((D_6)DMSO/D_2O): 3.74 (*s*, 6 H); 4.04 (*s*, 2 H); 6.40–6.52 (*m*, 3 H); 6.67–6.74 (*t*, 2 H); 7.10 (*s*, 1 H); 7.70 (*s*, 1 H). ^{13}C-NMR: 55.5; 55.7; 101.8; 105.3; 111.1; 114.3; 116.5; 119.9; 125.5; 126.6; 130.2; 137.3; 145.8; 156.0; 156.8; 160.6. HR-ESI-MS: 312.1338 ($[M+H]^+$, $C_{17}H_{18}N_3O_3^+$; calc. 312.1348).

*2-{4-[4-Acetoxy-3-(diacetylamino)phenyl]-1-acetyl-1*H-*pyrazol-3-yl}-5-acetoxyphenyl Acetate* (**35**). For X-ray diffraction, compound **32** (1 mmol) was peracetylated by exposure to Ac_2O (8 mmol) in anh. pyridine (5 ml) at 80° for 1 h. The mixture was poured into ice-water. The precipitate was filtered off, washed neutral with H_2O, and purified by recrystallization from EtOH. Yield of **35**: 95%. Colorless crystals. M.p. 205.4–207.3°. IR: 3429, 3149, 3063, 2997, 2932, 1770, 1722, 1617, 1498, 1431, 1376, 1191, 1137, 1013, 910, 838, 719. ^{1}H-NMR ($CDCl_3$): 1.99 (*s*, 3 H); 2.21–2.30 (*m*, 14 H); 2.74 (*s*, 3 H); 7.04 (*d*, *J* = 6.3,

3 H); 7.25 (*d*, $J = 8.4$, 1 H); 7.41 (*m*, 2 H); 8.42 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 20.7; 21.1; 21.5; 26.2; 116.9; 119.5; 122.3; 124.2; 126.7; 129.1; 129.6; 130.4; 131.9; 146.5; 149.0; 151.8; 168.3; 169.2; 172.3. HR-ESI-MS: 558.1479 ($[M+Na]^+$, $C_{27}H_{25}N_3NaO_9^+$; calc. 558.1488). X-Ray: see *Figure* and section below.

X-Ray Crystal Structures of Compounds **26** *and* **35**[2]). Diffraction data were collected on a *Bruker Smart-1000 CCD* diffractometer with graphite-monochromated MoK_α radiation (λ 0.71073 Å) using the ($\omega - 2\theta$) scan technique. The structures were solved by direct methods and refined on F^2 by full matrix least-squares with the SHELXL-97 program. All non-H-atoms were refined anisotropically. All H-atoms were treated using a riding model. The crystals used for the diffraction study showed no decomposition during data collection. In the crystal structure of **26**, an Et group (C(18), C(19), C(18′), C(19′); *Figure*) was disordered over 0.60 and 0.40 occupied positions, so the bond lengths C(18)–C(19) and C(18′)–C(19′) were restraint in the refinement. The crystallographic data of the two compounds are collected in *Table 3*.

Table 3. *Crystallographic Data of* **26** *and* **35**

	26	**35**
Empirical formula	$C_{21}H_{24}N_2O_4$	$C_{27}H_{25}N_3O_9$
Color, shape	pink, block	colorless, plate
M_r [g/mol]	368.42	535.50
Crystal size [mm]	$0.39 \times 0.30 \times 0.20$	$0.37 \times 0.28 \times 0.27$
Temperature [K]	296(2)	296(2)
Wavelength [Å]	0.71073	0.71073
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/c$
Unit-cell parameters [Å, °]:	$a = 8.3072(7)$	$a = 13.676(3)$
	$b = 17.8746(15)$	$b = 13.952(3)$
	$c = 13.5921(11)$	$c = 14.091(3)$
	$\beta = 106.0580(10)$	$\beta = 99.560(4)$
Volume [Å^3]	1939.5(3)	2651.4(9)
Z	4	4
Calculated density [g/cm^3]	1.262	1.342
Absorption coefficient [mm^{-1}]	0.088	0.102
θ-Range [°] for data collection	1.93 to 25.10	2.07 to 25.10
Limiting indices	$-9 \le h \le 9$	$-16 \le h \le 16$
	$16 \le k \le 21$	$-16 \le k \le 13$
	$-16 \le l \le 13$	$-16 \le l \le 15$
Reflections collected	9,634	13,381
Independent reflections	3,447 [R(int) = 0.0234]	4,720 [R(int) = 0.0632]
Absorption correction	multiscan	multiscan
Completeness to θ_{max}	99.9%	99.9%
Data/restraints/parameters	3,447/2/268	4,720/0/359
Goodness-of-fit on F^2	1.071	1.012
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0606$, $wR_2 = 0.1638$	$R_1 = 0.0513$, $wR_2 = 0.1073$
R Indices (all data)	$R_1 = 0.0899$, $wR_2 = 0.1886$	$R_1 = 0.1537$, $wR_2 = 0.1271$
Largest diff. peak and hole [e/Å^3]	0.260, −0.221	0.301, −0.205

[2]) The crystallographic data of **26** and **35** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication numbers CCDC-641949 and -641950, resp. Copies of the data can be obtained, free of charge, at http://www.ccdc.cam.ac.uk/data_request/cif.

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