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Complete assignments of ^{1}H and ^{13}C NMR data for 21 naphthalenyl-phenyl-pyrazoline derivatives

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To find potent new chemotherapy drugs, we designed and synthesized a series of naphthochalcones bearing naphthalenyl-phenyl-pyrazoline moieties. The complete ^{1}H and ^{13}C NMR data for these compounds are reported here and can be used to identify further new naphthochalcones bearing the desired pyrazoline moieties. Copyright © 2013 John Wiley & Sons, Ltd.

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Keywords: NMR; ^{1}H NMR; ^{13}C NMR; 2D NMR; flavonoid; naphthochalcone; pyrazoline

Introduction

Chalcones are secondary plant metabolites that belong to the flavonoids and have a C6-C3-C6 skeleton (Fig. 1A). Unlike most flavonoids consisting of A-, C-, and B-rings, chalcones have an α,β-unsaturated carbonyl group instead of a closed C-ring, as shown in Fig. 1B. They are made by chalcone synthase in the biosynthetic pathway of plants or synthesized via the aldol condensation of acetophenone and benzaldehyde. Chalcones have antibacterial and antimalarial properties, activate nuclear factor erythroid 2 p45-related factor 2 and a basic-leucine zipper transcription factor in cytoplasm, and inhibit the activity of nuclear factor kappa-light-chain-enhancer in activated B cells (NF-κB).[1–4] Given these diverse biological activities, various chalcones have been isolated from natural sources and synthesized. Several chalcones inhibit NF-κB on HCT116 human colorectal cancer cells via tumor necrosis factor alpha (TNFα).[5] The effects of 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone on cell proliferation, cell cycle distribution, and programmed cell death in cultures of human colorectal carcinoma HCT116 have been described.[6] The cytotoxic effects of 2',5'-dihydroxychalcone on HCT116 have also been evaluated.[7] Because compounds containing pyrazoline moieties show anti-colon cancer activity,[8] we tried to replace the α,β-unsaturated carbonyl group of chalcone with a pyrazoline, as shown in Fig. 1C. Another class of flavonoids, naphthoflavones (benzoflavones), has an additional benzene ring attached to the A-ring of flavone (Fig. 1D). Recently, 7,8-benzoflavone was identified as a potent inhibitor of the breast cancer resistance protein,[9,10] and the effects of 5,6-benzoflavone on chemically-induced mammary carcinogenesis have been reported.[11] Therefore, we designed naphthochalcones bearing pyrazoline moieties to enhance these effects (Fig. 1E). In this research, 21 naphthalenyl-phenyl-pyrazoline derivatives were synthesized, of which, only three have been reported previously.[12–14] Here, we report the complete ^{1}H and ^{13}C nuclear magnetic resonance (NMR) data for the 21 naphthalenyl-phenyl-pyrazolines synthesized in this study. These NMR data can help us to identify newly isolated or synthesized naphthochalcones bearing pyrazoline moieties.

Experimental

Synthesis

Naphthalenyl-phenyl-pyrazoline derivatives **1–21** were synthesized as shown in Scheme 1. Claisen–Schmidt condensation of 2'-hydroxy-1'-acetonaphthone (**I**) with methoxy- substituted benzaldehydes (**II**) under basic conditions afforded (*E*)-1-(2-hydroxynaphthalen-1-yl)-3-(methoxyphenyl)prop-2-en-1-ones (benzochalcones) (**III**), as we reported previously.[15] Benzochalcones (**III**), treated with *p*-chlorophenyl hydrazine (**IV**) in refluxing ethanol, produced novel 1,3,5-trisubstituted pyrazoline derivatives (**1–4**) with good yields. When the benzochalcones (**III**) were reacted with hydrazine (**V**), new 3,5-disubstituted pyrazoline derivatives (**5–8**) were obtained. Claisen–Schmidt condensation of 1'-hydroxy-2'-acetonaphthone with methoxy-substituted benzaldehydes (**II**) gave the corresponding (*E*)-1-(1-hydroxynaphthalen-2-yl)-3-(methoxyphenyl)prop-2-en-1-ones (**VI**), which were treated with hydrazine to produce the desired, new 3,5-disubstituted pyrazoline

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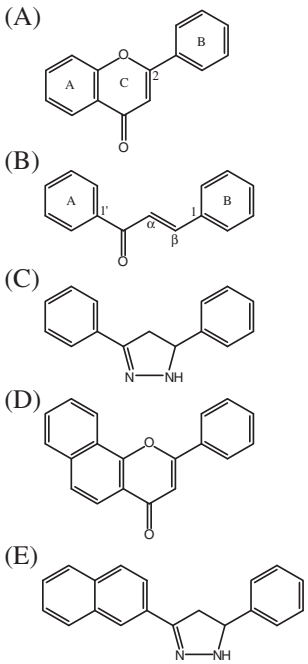

Figure 1. The structures of (A) flavonoid, (B) chalcone, (C) 3,5-diphenyl-4,5-dihydro-pyrazoline, (D) 7,8-benzoflavone, and (E) naphthochalcone bearing pyrazoline moieties.

derivatives (**9–17**). The same procedures were used to synthesize additional pyrazolines (**18–21**) but starting from benzochalcones, (*E*)-1-(2-hydroxy-methoxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (**VII**). The reaction mechanism for the formation of pyrazolines from chalcones is well established[16,17]: primary amines of arylhydrazine initially form an imine with the carbonyl part of chalcones, followed by the attachment of another nitrogen to the carbon-carbon double bond for pyrazoline ring formation, eventually giving only one regioisomer.

NMR spectra

All of the synthetic naphthalenyl-phenyl-pyrazoline derivatives, except for **1**, **3**, **4**, **19**, and **20**, were dissolved in DMSO-d_6, and the remaining five derivatives were dissolved in $CHCl_3$-d. The ^1H and ^{13}C chemical shifts of the deuterated solvent were referenced to tetramethylsilane (TMS). The NMR samples were prepared at approximately 50 mM and transferred to 2.5-mm NMR tubes. The NMR experiments were carried out using a Bruker Avance 400 spectrometer system (9.4 T; Bruker, Karlsruhe, Germany) at 298 K. For one-dimensional (1D) ^1H NMR spectra, the relaxation delay, 90° pulse, spectral width, and digital resolution were 1 s, 11.8 μs, 5555 Hz, and 0.17 Hz/point, respectively. For the ^{13}C NMR and distortionless enhancement by polarization transfer (DEPT) experiments, the same parameters were 3 s, 15.0 μs, 20,964 Hz, and 0.32 Hz/point, respectively. For two-dimensional (2D) correlation spectra (COSY, HMQC, and HMBC) all data were acquired with 2 K × 256 data points ($t_2 \times t_1$). The delay for the long-range coupling of HMBC was 70 ms. The zero-filling of 2 K and the sine-squared bell window function were applied before Fourier transformation using XWin-NMR (Bruker).[18] All NMR data were analyzed using Sparky.[19]

Mass spectra

To confirm the structures of the 21 synthesized naphthalenyl-phenyl-pyrazoline derivatives, high-resolution electron impact mass spectra (HREIMS) were obtained and analyzed in the Korea Basic Science Institute at Daegu, using a JMS700 spectrometer (JEOL, Tokyo, Japan).

Results and Discussion

The structures and nomenclature of naphthalenyl-phenyl-pyrazolines **1–21** are shown in Fig. 2. Naphthalenyl-phenyl-pyrazoline derivatives **1–4** have a 1-[1-(4-chlorophenyl)-5-(methoxyphenyl)-pyrazolin-3-yl] naphthalen-2-ol moiety, **5–8** are 1-[5-(methoxyphenyl)-pyrazolin-3-yl] naphthalen-2-ols, **9–17** are 2-[5-(methoxyphenyl)-pyrazolin-3-yl]naphthalen-1-ols, and **18–21** have a 2-[5-(naphthalen-1-yl)-pyrazolin-3-yl]phenol moiety. All of the naphthalenyl-phenyl-pyrazoline derivatives, except **1**, **5**, and **12**,[12–14] are new compounds.

The procedures used to assign the NMR data of the compound with the most complex structure **(2)** are explained in detail here. Of the 27 carbons of compound **2**, 25 ^{13}C peaks were observed in the ^{13}C NMR spectrum. Two signals at 113.9 and 128.7 ppm were assigned C-2"/C-6" and C-3"/C-5", respectively, because they had double the intensity of the neighboring signals. Based on the interpretation of the HMBC spectrum, C-1" and C-4" were determined. Because the ^{13}C peak at 46.0 ppm was a triplet in the DEPT spectrum, it was assigned to C-py-4 of the pyrazoline group. C-py-3 and C-py-5 were determined easily based on the connectivities of the COSY and HMBC spectra. The ^1H and ^{13}C peaks of 2-hydroxynaphthalene were assigned by comparisons with reported NMR data.[15,18] The C-1 of the dimethoxyphenyl group showed long-range coupling with H-py-4 of the pyrazoline group in HMBC. In addition, two long-range couplings of C-1 were observed with two protons at 6.63 and 6.48 ppm. Whereas the former was a doublet peak, the latter was a doublet of a doublet; thus, they were assigned to H-3 and H-5, respectively. The two carbon peaks at 98.9 and 105.0 ppm were C-3 and C-5, respectively, based on the direct correlations between the proton and carbon in HMQC. The ^1H peak at 7.05 ppm should be H-6. Because the ^{13}C peak at 157.2 ppm was long range coupled to H-py-5 in HMBC, it was identified as C-2. Therefore, the ^{13}C peak at 159.9 ppm was assigned to C-4. Two methoxy protons at 3.87 and 3.73 ppm showed long-range coupling with two ^{13}C peaks at 157.2 and 159.9 ppm, respectively, so these two protons were assigned 2-OCH_3 and 4-OCH_3, respectively. The proton signal of the 2'-hydroxyl group contained in naphthalene was found at 10.23 ppm. The important connections obtained from the COSY and HMBC experiments are shown in Fig. S1. As a result, derivative **2** was determined to be 1-[1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-pyrazolin-3-yl]naphthalen-2-ol. This result was confirmed by the HREIMS data, as its observed molecular mass was 458.1395 and calculated mass was 458.1397. The complete assignments of the ^1H and ^{13}C NMR data of **2** are listed in Tables 1 and 2, respectively. Similarly, the ^1H and ^{13}C NMR data of the other 20 naphthalenyl-phenyl-pyrazoline derivatives were acquired and are listed in Tables 1 and 2, respectively.

The H-py-5s of the pyrazoline rings in **18–21** were the most deshielded among the compounds tested here and were connected to naphthalene directly. The second deshielded chemical shifts of H-py-5s were observed in **1–4**, in which two phenyl groups were neighbors. Likewise, the H-py-1s of **18–21** were the most deshielded, and the naphthalene was linked in the

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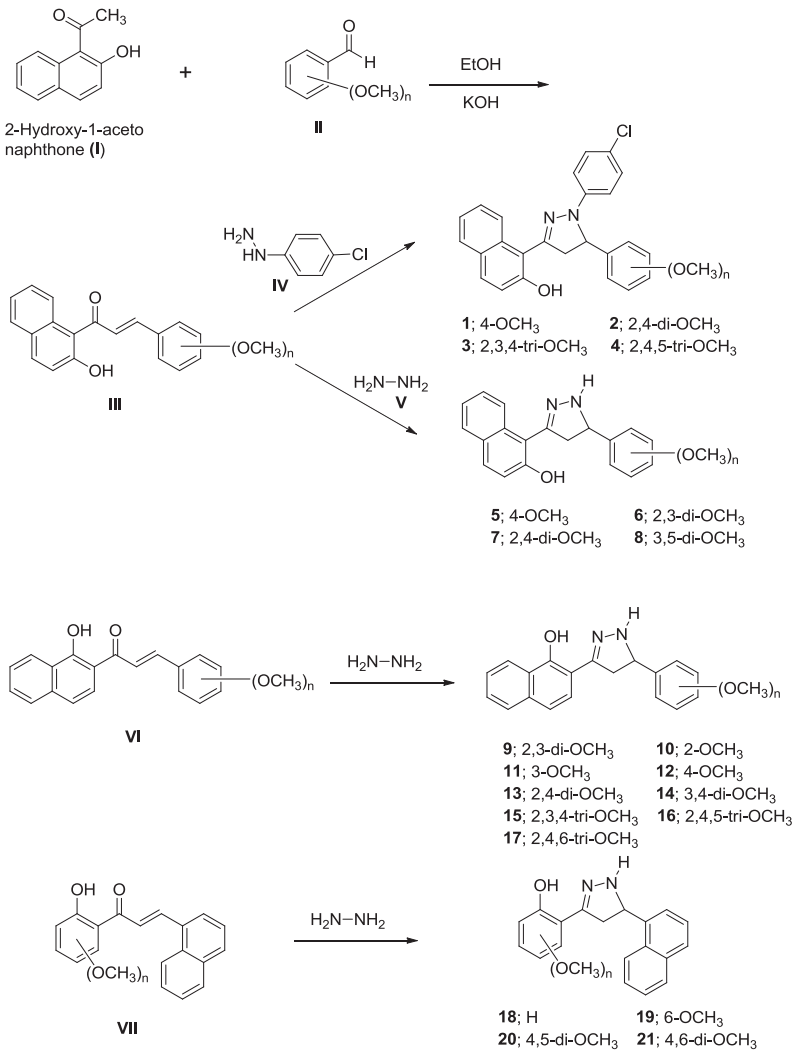
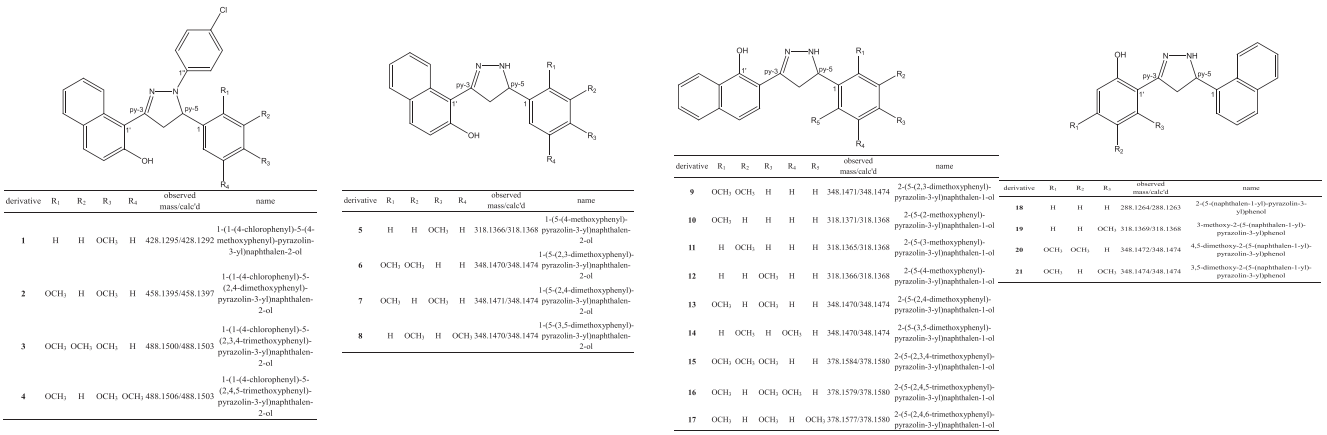


Scheme 1. The synthetic methods used to prepare naphthalenyl-phenyl-pyrazoline derivatives **1–21**.



derivative	R_1	R_2	R_3	R_4	observed mass/calc'd	name
1	H	H	OCH_3	H	428.1295/428.1292	1-(1-(4-chlorophenyl)-5-(4-methoxyphenyl)-pyrazolin-3-yl)naphthalen-2-ol
2	OCH_3	H	OCH_3	H	458.1395/458.1397	1-(1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-pyrazolin-3-yl)naphthalen-2-ol
3	OCH_3	OCH_3	OCH_3	H	488.1500/488.1503	1-(1-(4-chlorophenyl)-5-(2,3,4-trimethoxyphenyl)-pyrazolin-3-yl)naphthalen-2-ol
4	OCH_3	H	OCH_3	OCH_3	488.1506/488.1503	1-(1-(4-chlorophenyl)-5-(2,4,5-trimethoxyphenyl)-pyrazolin-3-yl)naphthalen-2-ol

derivative	R_1	R_2	R_3	R_4	observed mass/calc'd	name
5	H	H	OCH_3	H	318.1366/318.1368	1-(5-(4-methoxyphenyl)-pyrazolin-3-yl)naphthalen-2-ol
6	OCH_3	OCH_3	H	H	348.1470/348.1474	1-(5-(2,3-dimethoxyphenyl)-pyrazolin-3-yl)naphthalen-2-ol
7	OCH_3	H	OCH_3	H	348.1471/348.1474	1-(5-(2,4-dimethoxyphenyl)-pyrazolin-3-yl)naphthalen-2-ol
8	H	OCH_3	H	OCH_3	348.1470/348.1474	1-(5-(3,5-dimethoxyphenyl)-pyrazolin-3-yl)naphthalen-2-ol

derivative	R_1	R_2	R_3	R_4	R_5	observed mass/calc'd	name
9	OCH_3	OCH_3	H	H	H	348.1471/348.1474	2-(5-(2,3-dimethoxyphenyl)-pyrazolin-3-yl)naphthalen-1-ol
10	OCH_3	H	H	H	H	318.1371/318.1368	2-(5-(2-methoxyphenyl)-pyrazolin-3-yl)naphthalen-1-ol
11	H	OCH_3	H	H	H	318.1365/318.1368	2-(5-(3-methoxyphenyl)-pyrazolin-3-yl)naphthalen-1-ol
12	H	H	OCH_3	H	H	318.1366/318.1368	2-(5-(4-methoxyphenyl)-pyrazolin-3-yl)naphthalen-1-ol
13	OCH_3	H	OCH_3	H	H	348.1470/348.1474	2-(5-(2,4-dimethoxyphenyl)-pyrazolin-3-yl)naphthalen-1-ol
14	H	OCH_3	H	OCH_3	H	348.1470/348.1474	2-(5-(3,5-dimethoxyphenyl)-pyrazolin-3-yl)naphthalen-1-ol
15	OCH_3	OCH_3	OCH_3	H	H	378.1584/378.1580	2-(5-(2,3,4-trimethoxyphenyl)-pyrazolin-3-yl)naphthalen-1-ol
16	OCH_3	H	OCH_3	OCH_3	H	378.1579/378.1580	2-(5-(2,4,5-trimethoxyphenyl)-pyrazolin-3-yl)naphthalen-1-ol
17	OCH_3	H	OCH_3	H	OCH_3	378.1577/378.1580	2-(5-(2,4,6-trimethoxyphenyl)-pyrazolin-3-yl)naphthalen-1-ol

derivative	R_1	R_2	R_3	observed mass/calc'd	name
18	H	H	H	288.1264/288.1263	2-(5-(naphthalen-1-yl)-pyrazolin-3-yl)phenol
19	H	H	OCH_3	318.1369/318.1368	3-methoxy-2-(5-(naphthalen-1-yl)-pyrazolin-3-yl)phenol
20	OCH_3	OCH_3	H	348.1472/348.1474	4,5-dimethoxy-2-(5-(naphthalen-1-yl)-pyrazolin-3-yl)phenol
21	OCH_3	H	OCH_3	348.1474/348.1474	3,5-dimethoxy-2-(5-(naphthalen-1-yl)-pyrazolin-3-yl)phenol

Figure 2. The structures, nomenclature, and mass analysis data of naphthalenyl-phenyl-pyrazolines **1–21**.

α-position. Whereas the C-py-3s of the pyrazoline ring in **9–17** were deshielded more than in the other compounds, the C-py-4s of **9–17** were shielded more than others. The C-py-5s of **5–8** were also more deshielded than in the other compounds. More polysubstituted naphthalenyl-phenyl-pyrazoline derivatives synthesized in the future can be identified based on the NMR data reported here.

Table 1. The ^{1}H NMR chemical shifts of naphthalenyl-phenyl-pyrazoline derivatives **1–21**

Position	1	2	3	4	5	6	7	8	9	10	11
H-py*-1	—	—	—	—	7.46 (d, 3.5)	7.37 (d, 3.6)	7.28 (d, 3.0)	7.48 (d, 3.0)	7.75 (d, 3.5)	7.73 (d, 3.0)	7.90 (d, 3.6)
H-py*-4	3.68 (dd, 16.7, 7.6)	3.08 (dd, 17.6, 6.1)	3.61 (dd, 16.7, 6.7)	3.55 (dd, 16.8, 7.0)	3.08 (dd, 16.1, 10.2)	3.00 (dd, 16.2, 10.5)	2.95 (dd, 16.2, 9.9)	3.10 (dd, 16.2, 9.9)	3.04 (dd, 16.7, 10.3)	3.00 (dd, 16.7, 10.1)	3.10 (dd, 16.6, 10.7)
	4.31 (dd, 16.7, 11.3)	4.02 (dd, 17.6, 12.0)	4.34 (dd, 16.7, 11.8)	4.33 (dd, 16.8, 11.5)	3.54 (dd, 16.1, 10.6)	3.59 (dd, 16.2, 10.6)	3.55 (dd, 16.2, 10.1)	3.56 (dd, 16.2, 10.2)	3.73 (dd, 16.7, 10.8)	3.70 (dd, 16.7, 10.6)	3.73 (dd, 16.6, 10.8)
H-py*-5	5.21 (dd, 11.3, 7.6)	5.51 (dd, 12.0, 6.1)	5.49 (dd, 11.8, 6.7)	5.56 (dd, 11.5, 7.0)	4.85 (ddd, 10.6, 10.2, 3.5)	5.12 (ddd, 10.6, 10.5, 3.6)	5.02 (ddd, 10.1, 9.9, 3.0)	4.83 (ddd, 10.2, 9.9, 3.0)	5.12 (ddd, 10.8, 10.3, 3.5)	5.10 (ddd, 10.6, 10.1, 3.0)	4.89 (ddd, 10.8, 10.7, 3.6)
H-2	7.24 (d, 8.8)	—	—	—	7.41 (d, 8.7)	—	—	6.67 (d, 2.2)	—	—	7.02 (d, 1.6)
H-3	6.88 (d, 8.8)	6.63 (d, 2.3)	—	6.56 (s)	6.93 (d, 8.7)	—	6.58 (d, 2.3)	—	—	7.04 (dd, 8.2, 1.0)	—
H-4	—	—	—	—	—	6.98 (dd, 8.0, 1.4)	—	6.41 (dd,2.2, 2.2)	7.00 (dd, 7.0, 2.7)	7.28 (m)	6.87 (m)
H-5	6.88 (d, 8.8)	6.48 (dd, 8.5, 2.3)	6.56 (d, 8.6)	—	6.93 (d, 8.7)	7.09 (dd, 8.0, 8.0)	6.53 (dd, 8.4, 2.3)	—	7.05 (m)	6.95 (ddd, 7.5, 7.5, 1.0)	7.29 (dd, 8.1, 8.1)
H-6	7.24 (d, 8.8)	7.05 (d, 8.5)	6.84 (d, 8.6)	6.68 (s)	7.41 (d, 8.7)	7.19 (dd, 8.0, 1.4)	7.42 (d, 8.4)	6.67 (d, 2.2)	7.05 (m)	7.43 (m)	7.01 (m)
H-3'	7.27 (d, 9.0)	7.23 (d, 9.0)	7.27 (d, 8.9)	7.27 (d, 8.9)	7.21 (d, 9.0)	7.20 (d, 9.0)	7.20 (d, 9.0)	7.21 (d, 8.9)	7.41 (d, 9.0)	7.41 (d, 8.7)	7.43 (s)
H-4'	7.75 (d, 9.0)	7.81 (d, 9.0)	7.75 (d, 8.9)	7.75 (d, 8.9)	7.78 (d, 9.0)	7.78 (d, 9.0)	7.78 (d, 9.0)	7.79 (d, 8.9)	7.43 (d, 9.0)	7.43 (d, 8.7)	7.43 (s)
H-5'	7.77 (d, 8.0)	7.82 (d, 8.0)	7.77 (d, 8.0)	7.77 (dd, 8.0, 1.3)	7.81 (d, 8.0)	7.80 (d, 8.0)	7.80 (d, 8.0)	7.81 (d, 8.0)	7.86 (d, 7.6)	7.85 (d, 7.5)	7.86 (d, 7.6)
H-6'	7.31 (ddd, 8.0, 6.9, 1.2)	7.32(ddd, 8.0, 6.9, 1.0)	7.31 (ddd, 8.0, 6.9, 1.0)	7.31 (ddd, 8.0, 6.9, 1.3)	7.30 (ddd, 8.0, 6.9, 1.0)	7.30 (ddd, 8.0, 6.9, 1.0)	7.30 (ddd, 8.0, 6.9, 1.0)	7.30 (ddd, 8.0, 6.9, 1.0)	7.54 (m)	7.54 (m)	7.54 (m)
H-7'	7.4 (ddd, 8.5, 6.9, 1.2)	7.47 (ddd, 8.6, 6.9, 1.0)	7.42 (ddd, 8.6, 6.9, 1.0)	7.42 (ddd, 8.5, 6.9, 1.3)	7.43 (ddd, 8.6, 6.9, 1.0)	7.43 (ddd, 8.5, 6.9, 1.0)	7.42 (ddd, 8.5, 6.9, 1.0)	7.43 (ddd, 8.5, 6.9, 1.0)	7.51 (m)	7.51 (m)	7.52 (m)
H-8'	7.92 (d, 8.5)	8.26 (d, 8.6)	7.96 (d, 8.6)	7.96 (d, 8.5)	8.13 (d, 8.6)	8.13 (d, 8.5)	8.11 (d, 8.5)	8.13 (d, 8.5)	8.25 (d, 7.8)	8.24 (d, 7.9)	8.25 (d, 7.9)
H-2''/ H-6''	6.93 (d, 8.9)	6.89 (d, 9.0)	6.93 (d, 8.8)	6.93 (d, 9.0)	—	—	—	—	—	—	—
H-3''/ H-5''	7.16 (d, 8.9)	7.19 (d, 9.0)	7.18 (d, 8.8)	7.17 (d, 9.0)	—	—	—	—	—	—	—
2-OCH_3	—	3.87 (s)	3.88 (s)	3.89 (s)	—	3.77 (s)	3.80 (s)	—	3.80 (s)	3.85 (s)	—
3-OCH_3	—	—	3.99 (s)	—	—	3.81 (s)	—	3.75 (s)	3.82 (s)	—	3.76 (s)
4-OCH_3	3.78 (s)	3.73 (s)	3.81 (s)	3.88 (s)	3.75 (s)	—	3.76 (s)	—	—	—	—
5-OCH_3	—	—	—	3.65 (s)	—	—	—	3.75 (s)	—	—	—
1'-OH	—	—	—	—	—	—	—	—	12.32 (s)	12.33 (s)	12.28 (s)
2'-OH	12.11 (s)	10.23 (bs)	12.07 (s)	12.12 (s)	10.66 (bs)	10.65 (bs)	10.70 (bs)	10.61 (bs)	—	—	—

Position	12	13	14	15	16	17	18	19	20	21
H-py*-1	7.84 (d, 3.4)	7.65 (d, 3.2)	7.88 (d, 3.6)	7.69 (d, 2.5)	7.69 (d, 3.7)	7.11 (bs)	7.94 (d, 3.0)	7.80 (d, 3.6)	7.70 (d, 3.8)	7.59 (d, 4.0)
H-py*-4	3.07 (dd, 16.6, 10.6)	2.99 (dd, 16.6, 10.0)	3.10 (dd, 16.6, 10.7)	3.03 (dd, 16.6, 10.3)	2.98 (dd, 16.6, 10.7)	3.30 (dd, 16.5, 8.3)	2.96 (dd, 16.7, 10.6)	3.08 (dd, 17.5, 10.3)	2.95 (dd, 16.6, 10.4)	3.03 (dd, 17.5, 10.4)
	3.68 (dd, 16.6, 10.8)	3.63 (dd, 16.6, 10.4)	3.69 (dd, 16.6, 10.8)	3.69 (dd, 16.6, 10.7)	3.65 (dd, 16.6, 10.8)	3.41 (dd, 16.5, 12.6)	3.92 (dd, 16.7, 11.0)	3.98 (dd, 17.5, 10.9)	3.90 (dd, 16.7, 10.8)	3.95 (dd, 17.5, 10.7)
H-py*-5	4.86 (ddd, 10.8, 10.6, 3.4)	5.02 (ddd, 10.4, 10.0, 3.2)	4.85 (ddd, 10.8, 10.7, 3.6)	5.02 (ddd, 10.7, 10.3, 2.5)	5.05 (ddd, 10.8, 10.7, 3.7)	5.35 (dd, 12.6, 8.3)	5.60 (ddd, 11.0, 10.6, 3.0)	5.54 (ddd, 10.9, 10.3, 3.6)	5.56 (ddd, 10.8, 10.4, 3.8)	5.49 (ddd, 10.7, 10.4, 4.0)
H-2	7.36 (d, 8.7)	—	6.62 (d, 2.3)	—	—	—	7.71 (d, 7.1)	7.69 (d, 7.1)	7.72 (d, 7.1)	7.69 (d, 7.1)
H-3	6.74 (d, 8.7)	6.60 (d, 2.4)	—	—	6.74 (s)	6.25 (s)	7.50 (dd, 8.1, 7.1)	7.50 (dd, 8.2, 7.1)	7.50 (dd, 8.1, 7.1)	7.50 (dd, 8.1, 7.1)
H-4	—	—	6.43 (d, 2.3)	—	—	—	7.86 (d, 8.1)	7.86 (d, 8.2)	7.86 (d, 8.2)	7.85 (d, 8.1)
H-5	6.74 (d, 8.7)	6.51 (dd, 8.4, 2.4)	—	6.80 (d, 8.7)	—	6.25 (s)	7.97 (d, 7.6)	7.96 (d, 7.6)	7.97 (d, 7.7)	7.96 (d, 7.6)
H-6	7.36 (d, 8.7)	7.30 (d, 8.4)	6.62 (d, 2.3)	7.13 (d, 8.7)	7.07 (s)	—	7.56 (ddd, 7.6, 6.8, 1.2)	7.55 (ddd, 7.6, 6.8, 1.2)	7.56 (ddd, 7.7, 6.8, 1.2)	7.55 (ddd, 7.6, 6.8, 1.2)
H-7	—	—	—	—	—	—	7.59 (ddd, 8.2, 6.8, 1.2)	7.59 (ddd, 8.2, 6.8, 1.2)	7.60 (ddd, 8.2, 6.8, 1.2)	7.58 (ddd, 8.1, 6.8, 1.2)
H-8	—	—	—	—	—	—	8.18 (d, 8.2)	8.16 (d 8.2)	8.19 (d, 8.2)	8.16 (d, 8.1)
H-3'	7.43 (s)	7.41 (d, 8.8)	7.41 (d, 8.8)	7.42 (d, 8.8)	7.41 (d, 8.9)	7.38 (d, 8.6)	6.92 (dd, 8.2, 1.0)	6.49 (d, 8.2)	6.58 (s)	6.14 (s)
H-4'	7.43 (s)	7.43 (d, 8.8)	7.44 (d, 8.8)	7.44 (d, 8.8)	7.43 (d, 8.9)	7.42 (d, 8.6)	7.22 (ddd, 8.2, 7.5, 1.5)	7.14 (dd, 8.2, 8.2)	—	—
H-5'	7.85 (d, 7.3)	7.85 (d, 7.6)	7.85 (d, 7.6)	7.86 (d, 7.7)	7.86 (d, 7.6)	7.85 (d, 7.4)	6.85 (ddd, 7.7, 7.5, 1.0)	6.53 (d, 8.2)	—	6.07 (s)
H-6'	7.54 (m)	7.53 (m)	7.54 (m)	7.54 (m)	7.54 (m)	7.53 (m)	7.27 (dd, 7.7, 1.5)	—	6.79 (s)	—
H-7'	7.52 (m)	7.51 (m)	7.52 (m)	7.51 (m)	7.51 (m)	7.50 (m)	—	—	—	—
H-8'	8.25 (d, 7.8)	8.23 (d, 7.8)	8.25 (d, 7.9)	8.25 (d, 7.8)	8.24 (d, 7.9)	8.24 (d, 7.8)	—	—	—	—
2-OCH_3	—	3.83 (s)	—	3.85 (s)	3.83 (s)	3.66 (s)	—	—	—	—
3-OCH_3	—	—	3.75 (s)	3.78 (s)	—	—	—	—	—	—
4-OCH_3	3.75 (s)	3.75 (s)	—	3.77 (s)	3.80 (s)	3.77 (s)	—	—	—	—
5-OCH_3	—	—	3.75 (s)	—	3.69 (s)	—	—	—	—	—
6-OCH_3	—	—	—	—	—	3.66 (s)	—	—	—	—
4'-OCH_3	—	—	—	—	—	—	—	—	3.76 (s)	3.74 (s)
5'-OCH_3	—	—	—	—	—	—	—	—	3.66 (s)	—
6'-OCH_3	—	—	—	—	—	—	—	3.68 (s)	—	3.66 (s)
1'-OH	12.31 (s)	12.34 (s)	12.26 (s)	12.34 (s)	12.34 (s)	12.59 (s)	—	—	—	—
2'-OH	—	—	—	—	—	—	11.23 (s)	12.20 (s)	11.08 (s)	12.50 (s)

* py denotes pyrazoline. Multiplicity and coupling constants are given in parentheses.

Magnetic Resonance in Chemistry

Table 2. The ^{13}C NMR chemical shifts of naphthalenyl-phenyl-pyrazoline derivatives **1–21**

Position	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
C-py*-3	150.5	148.2	150.7	151.3	149.1	148.9	149.2	148.9	153.1	153.2	153.3
C-py*-4	48.8	46.0	47.6	47.4	44.9	44.3	43.3	44.7	40.5	39.5	41.0
C-py*-5	63.8	57.1	58.8	58.4	63.0	57.5	57.4	63.3	56.4	56.4	62.1
1	132.7	121.1	125.9	119.7	134.7	136.3	122.6	145.6	135.8	129.8	143.8
2	127.2	157.2	150.8	150.6	127.9	146.2	157.6	104.5	146.3	156.6	112.3
3	114.7	98.9	142.4	97.6	113.7	152.2	98.3	160.5	152.3	110.8	159.3
4	159.4	159.9	153.6	149.5	158.4	111.7	159.7	98.9	112.0	128.4	112.8
5	114.7	105.0	107.5	143.6	113.7	123.9	104.3	160.5	124.0	120.3	129.6
6	127.2	127.1	121.2	110.5	127.9	118.6	127.0	104.5	118.6	126.3	118.9
1'	109.1	112.0	109.3	109.5	112.4	112.4	112.5	112.4	153.2	153.1	153.2
2'	157.4	154.3	157.2	157.3	154.5	154.4	154.5	154.5	110.0	110.1	110.0
3'	119.2	118.2	119.2	119.3	118.3	118.3	118.3	118.3	124.7	124.7	124.7
4'	131.9	130.4	131.7	131.9	129.9	129.8	130.0	129.9	118.5	118.5	118.5
5'	129.4	128.2	129.3	129.5	128.1	128.1	128.1	128.1	127.5	127.5	127.5
6'	123.1	122.9	123.1	123.2	122.7	122.7	122.7	122.7	127.0	127.0	127.1
7'	126.8	126.9	126.8	126.9	125.4	126.4	126.4	126.4	125.4	125.4	125.5
8'	123.2	124.1	123.3	123.4	124.2	124.2	124.2	124.2	122.3	122.3	122.3
9'	131.9	132.6	132.0	132.1	132.5	132.5	132.4	132.5	123.9	123.9	123.9
10'	129.0	128.0	129.0	129.1	128.0	128.0	128.0	128.0	133.7	133.7	133.7
1''	142.6	143.6	142.5	142.9	—	—	—	—	—	—	—
2''	114.8	113.9	114.4	114.7	—	—	—	—	—	—	—
3''	129.1	128.7	129.1	129.2	—	—	—	—	—	—	—
4''	125.0	121.6	124.6	124.9	—	—	—	—	—	—	—
5''	129.1	128.7	129.1	129.2	—	—	—	—	—	—	—
6''	114.8	113.9	114.4	114.7	—	—	—	—	—	—	—
2-OCH_3	—	55.7	60.9	56.4	—	60.2	55.4	—	60.3	55.5	—
3-OCH_3	—	—	61.0	—	—	55.6	—	55.1	55.7	—	55.0
4-OCH_3	55.3	55.2	56.0	56.3	55.0	—	55.2	—	—	—	—
5-OCH_3	—	—	—	56.7	—	—	—	55.1	—	—	—

Position	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
C-py*-3	153.3	153.3	153.4	153.3	153.5	153.4	152.3	151.1	152.9	151.7
C-py*-4	41.0	39.5	41.0	40.4	39.8	38.2	40.7	44.8	41.2	44.8
C-py*-5	61.7	56.2	62.2	56.5	56.2	50.5	58.8	58.6	58.5	58.4
1	134.0	122	144.6	127.8	121.0	110.4	138.0	138.3	138.2	138.4
2	127.9	157.6	104.7	151.1	151.1	159.2	123.1	123.1	123.1	123.2
3	113.8	98.5	160.5	152.7	98.5	91.3	125.5	125.5	125.5	125.5
4	158.6	159.8	99.0	141.7	148.8	160.3	127.6	127.5	127.5	127.5
5	113.8	104.4	160.5	107.8	142.5	91.3	128.6	128.7	128.7	128.7
6	127.9	127	104.7	121.3	111.7	159.2	125.7	125.7	125.7	125.7
7	—	—	—	—	—	—	126.2	126.3	126.2	126.2
8	—	—	—	—	—	—	123.5	123.5	123.6	123.5
9	—	—	—	—	—	—	130.5	130.5	130.5	130.5
10	—	—	—	—	—	—	133.5	133.5	133.5	133.5
1'	153.2	153.1	153.2	153.2	153.2	153.0	116.8	106.5	107.9	100.0
2'	110.0	110.1	110.0	110.1	110.1	110.3	156.7	158.6	152.1	160.1
3'	124.7	124.7	124.7	124.7	124.7	124.7	115.7	102.2	100.4	93.9
4'	118.5	118.4	118.5	118.4	118.4	118.2	129.7	130.0	150.5	161.1
5'	127.5	127.4	127.5	127.5	127.5	127.4	119.1	109.2	141.7	90.5
6'	127.0	127.0	127.1	127.0	127.0	126.7	127.7	157.9	111.3	158.9
7'	125.5	125.4	125.5	125.4	125.4	125.3	—	—	—	—
8'	122.3	122.3	122.3	122.3	122.3	122.3	—	—	—	—
9'	123.9	123.9	123.9	123.9	123.9	123.9	—	—	—	—
10'	133.7	133.6	133.7	133.7	133.7	133.4	—	—	—	—
2-OCH_3	—	55.5	—	60.9	56.3	55.8	—	—	—	—

(Continues)

Table 2. (Continued)

Position	12	13	14	15	16	17	18	19	20	21
3-OCH_3	—	—	55.1	55.8	—	—	—	—	—	—
4-OCH_3	55.1	55.2	—	60.3	55.8	55.2	—	—	—	—
5-OCH_3	—	—	55.1	—	56.3	—	—	—	—	—
6-OCH_3	—	—	—	—	—	55.8	—	—	—	—
4'-OCH_3	—	—	—	—	—	—	—	—	55.5	55.2
5'-OCH_3	—	—	—	—	—	—	—	—	56.3	—
6'-OCH_3	—	—	—	—	—	—	—	55.7	—	55.6

* py denotes pyrazoline.

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References

[1] S. F. Nielsen, M. Larsen, T. Boesen, K. Schonning, H. Kromann. *J. Med. Chem.* **2005**, *48*, 2667.
[2] E. M. Guantai, K. Ncokazi, T. J. Egan, J. Gut, P. J. Rosenthal, R. Bhampidipati, A. Kopinathan, P. J. Smith, K. Chibale. *J. Med. Chem.* **2011**, *54*, 3637.
[3] V. Kumar, S. Kumar, M. Hassan, H. Wu, R. K. Thimmulappa, A. Kumar, S. K. Sharma, V. S. Parmar, S. Biswal, S. V. Malhotra. *J. Med. Chem.* **2011**, *54*, 4147.
[4] P. Lorenzo, R. Alvarez, M. A. Ortiz, S. Alvarez, F. J. Piedrafita, A. R. de Lera. *J. Med. Chem.* **2008**, *51*, 5431.
[5] S. Y. Shin, Y. Woo, J. Hyun, Y. Yong, D. Koh, Y. H. Lee, Y. Lim. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6036.
[6] H. Ko, Y. J. Kim, E. C. Amor, J. W. Lee, H. C. Kim, H. J. Kim, H. O. Yang. *J. Cell. Biochem.* **2011**, *112*, 2471.
[7] N. H. Nam, Y. Kim, Y. J. You, D. H. Hong, H. M. Kim, B. Z. Ahn. *Eur. J. Med. Chem.* **2003**, *38*, 179.
[8] D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, L. Zaprutko, A. Gzella, R. Lesyk. *Eur. J. Med. Chem.* **2009**, *44*, 1396.
[9] X. Wang, M. E. Morris. *J. Pharm. Sci.* **2008**, *97*, 4546.
[10] S. Zhang, X. Wang, K. Sagawa, M. E. Morris. *Drug Metab. Dispos.* **2005**, *33*, 341.
[11] R. A. Lubet, B. M. Heckman, S. L. De Flora, V. E. Steele, J. A. Crowell, M. M. Juliana, C. J. Grubbs. *Oncol. Rep.* **2011**, *26*, 731.
[12] D. Koh. *J. Appl. Biol. Chem.* **2011**, *54*, 143.
[13] P. R. Athappan, P. Shanthi, C. Natarajan. *Indian J. Chem. A.* **1998**, *37A*, 136.
[14] V. B. Kadu, A. G. Dashi. *Orient. J. Chem.* **1997**, *13*, 285.
[15] D. Hwang, J. Hyun, G. Jo, D. Koh, Y. Lim. *Magn. Reson. Chem.* **2011**, *49*, 41.
[16] N. Gokhan-Kelekci, S. Koyunoglu, S. Yabanoglu, K. Yelekci, O. Ozgen, G. Ucar, K. Erol, E. Kendi, A. Yesilada. *Bioorg. Med. Chem.* **2009**, *17*, 675.
[17] B. N. Acharya, D. Saraswat, M. Tiwari, A. K. Shrivastava, R. Ghorpade, S. Bapna, M. P. Kaushik. *Eur. J. Med. Chem.* **2010**, *45*, 430.
[18] D. Hwang, G. Jo, J. Hyun, S. D. Lee, D. Koh, Y. Lim. *Magn. Reson. Chem.* **2012**, *50*, 62.
[19] T. D. Goddard, D. G. Kneller, *University of California: San Francisco* **2008**.