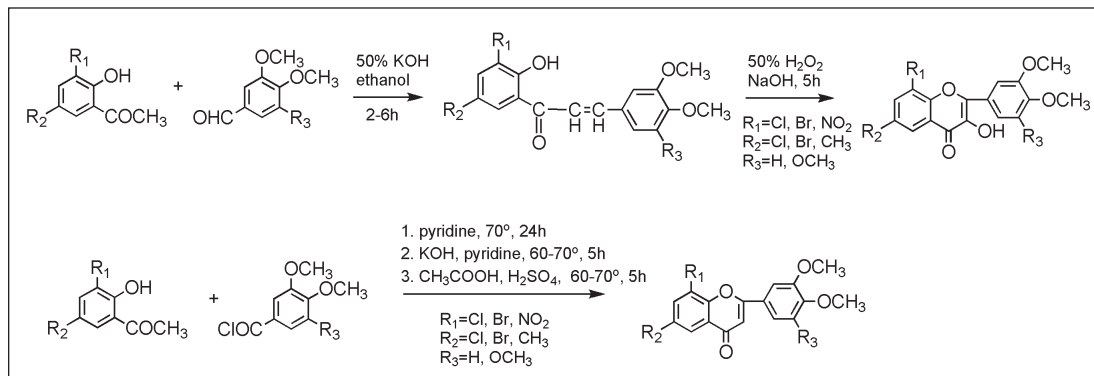


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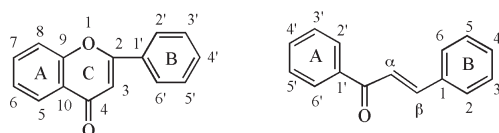
Eighteen substituted chalcones, flavones and 3-flavonols were synthesized and characterized using ^1H -NMR, IR and elemental analysis. The substitution pattern includes two halogen atoms, nitro and methyl groups in ring A as well as two or three methoxy groups in ring B.

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Introduction.

Flavonoids (benzo- γ -pyrones), as shown in Scheme 1, are a class of about 4,000 natural compounds present in all vascular plants. They appear to exhibit a wide range of biological activities including anti-oxidative [1-2], anti-inflammatory [3-5], cancer suppressing [6-9] and antiviral (anti-HIV) [10-12]. The average human diet contains about 1 g of flavonoids per day, assimilated through fruits, vegetables, red wine, tea *etc.* [13].

Scheme 1



Structure and numbering of flavones and chalcones

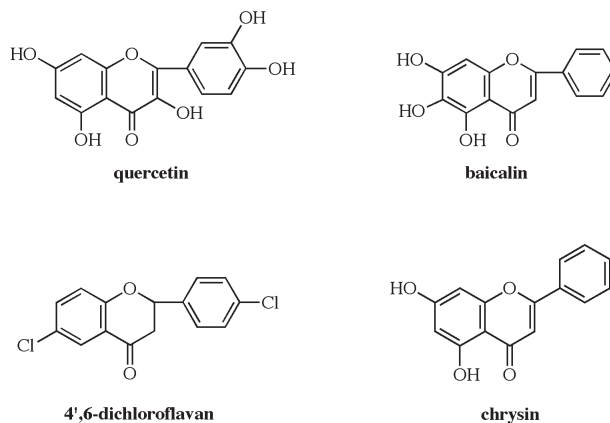
Most of the flavonoids have been isolated from plants in order to test their biological properties; others were synthetically produced in search of more potent drug candidates. The structure-activity relationship (SAR) in flavonoids is empirical, based on numerous data from testing different compounds. Although there are a lot of data in the literature, it is very difficult to outline a clear tendency that will lead to the optimized structure of high activity and low toxicity.

Among the most studied compounds, quercetin and baicalin (Scheme 2) are polyhydroxylated flavones [14-17]. It is believed that the important structural features leading to high biological activity are the presence of 5-OH and 3-OH groups. The latter, however, is considered

responsible for some mutagenic properties observed in quercetin, which disappeared after this group was methylated [12]. The solubility can be modified through selective introduction of lipophilic and hydrophilic substituents – most popular approach is to balance the number of the alkyl substituents and free hydroxyl groups.

The incorporation of electronegative elements, such as halogens and nitro groups, in the flavonoid structure, introduce new patterns of biological properties. 4',6-Dichloroflavan (Scheme 2) has been reported to be a potent antirhinovirus compound [12]. Halogenated and nitro-substituted flavones exhibit structure-dependent aryl hydrocarbon receptor (AhR) agonist and antagonist activities comparable to that observed for 2,3,7,8-tetrachlorodibenzo-*p*-

Scheme 2



Structures of flavonoid analogs

dioxin (TCDD) [18]. 8-Iodo, 8-bromo and 8-trifluoromethyl derivatives of chrysin (Scheme 2) exhibit strong activities against human gastric adenocarcinoma cell lines (SGC-7901) and colorectal adenocarcinoma (HT-29) cells [8,9]. One of the most recent studies reports the effect of some flavonoids on the central nervous system. Halogenated flavanones and flavones are considered potential benzodiazepine receptor ligands. Indeed, 6-bromoflavone and 6-bromo-3'-nitroflavone showed activities close or higher than that of diazepam [19].

The current paper reports our preliminary studies on the synthesis of halogenated and nitro-substituted chalcones and flavones. The compounds will be subject to biological testing to establish their anti-inflammatory, tumor suppressing and anti-HIV activities.

Results and Discussion.

The chalcone derivatives **5-10** were synthesized by Claisen condensation of appropriately substituted acetophenones and benzaldehydes in ethanol in the presence of 50% aqueous KOH. The reaction time as well as the yield varies depending on the corresponding reagents. The compounds containing the dimethoxybenzaldehyde unit were obtained with lower yields than the trimethoxy deriv-

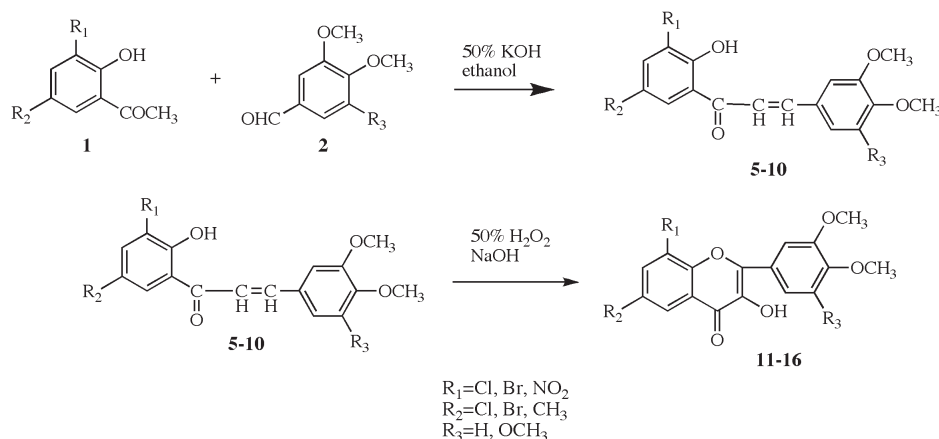
atives. The crude product was contaminated with some starting materials which could easily be removed by column chromatography on silica gel using CH_2Cl_2 :hexane as eluent (Scheme 3).

3-Hydroxyflavonols **11-16** were synthesized utilizing the Algar-Flynn-Oyamada reaction in the presence of 50% H_2O_2 and sodium hydroxide. The only reaction product observed was the corresponding 3-hydroxyflavonol (Scheme 3). The compounds have low solubility in the most common solvents. They were purified in small quantities by crystallizing the solid products in appropriate amounts of $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$. Attempts to purify them by column chromatography failed due to decomposition. 3-Hydroxyflavonols exhibit high melting points (Table 1) and some of them decompose at $\sim 250^\circ\text{C}$.

Flavones **17-22** were synthesized using a three step Baker-Venkataraman rearrangement. The crude product was purified by recrystallization and Chromatotron chromatography using CH_2Cl_2 :MeOH as eluent (Scheme 4).

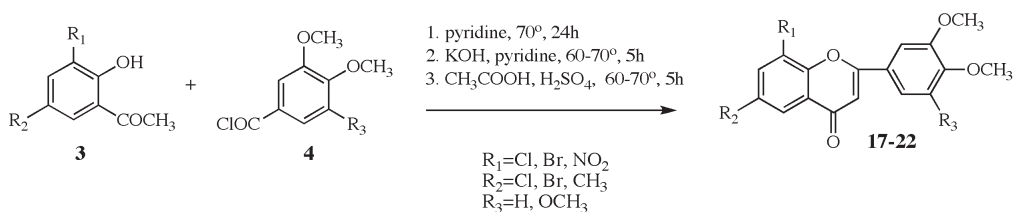
The structures of the synthesized compounds were confirmed by $^1\text{H-NMR}$, IR and elemental analysis. The compounds will be subject to cyclooxygenase-1 and cyclooxygenase-2 binding activity testing as well as anti-cancer testing.

Scheme 3



Synthesis of substituted chalcones and 3-flavonols

Scheme 4



Synthesis of substituted flavones.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus and were uncorrected. Infrared spectra were obtained on a Perkin Elmer FTIR 1430 spectrophotometer, using KBr pellets. ^1H nmr and ^{13}C nmr spectra were obtained with a Bruker HX-300 spectrometer and the chemical shifts were reported as parts per million (δ ppm) downfield. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Column chromatography as well as Chromatotron 8924 (Harrison Research) instruments were used for purification of the compounds. Davisil Chromatographic Silica gel (200-425 mesh) was used for column chromatographic separations and Silica gel Merck, TLC grade 7749 with gypsum binder and fluorescent indicator was used for the preparation of the Chromatotron rotors. All reactions and purification procedures were monitored using Whatman TLC plates with a fluorescent indicator. All solvents and chemicals were purchased from Fisher Scientific Company and Sigma-Aldrich Chemical Company and used without further purification.

Synthesis of Chalcones **5-10** [20-22].

The corresponding substituted acetophenones **1** were mixed with an equimolar amount of 3,4-dimethoxybenzaldehyde or 3,4,5-trimethoxybenzaldehyde, **2**, in ethanol (Scheme 3). 5 Milliliters of 50% aqueous KOH was added and the reaction mixture heated at 50-60 °C for 2-6 h. The product precipitated after cooling as yellow crystals, which were collected, recrystallized from $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ and finally purified by column chromatography, using CH_2Cl_2 :hexane 5:1 as eluent. The yields were 60-80%.

Synthesis of 3-Flavonols **11-16** [23-24].

2'-Hydroxychalcones **5-10** were synthesized as described above (Scheme 3). The reaction products were not isolated, but after cooling to room temperature, equivalent amounts of sodium hydroxide and 50% aqueous hydrogen peroxide were added. About 30 min later, thick yellow precipitate was formed. The mixture was stirred at room temperature for 5 h, the precipitate removed by filtration and air dried. The compounds were purified by recrystallization from $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$. The yields were 40-60%.

Table 1
Elemental Analysis and Melting Point Data for the Synthesized Compounds

	Compound	Composition	Elemental analysis Calculated/Found	m.p. °C
5	$\text{R}_1=\text{R}_2=\text{Cl}$, $\text{R}_3=\text{OCH}_3$	$\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{O}_5$	C56.41 H4.21 C56.31 H4.41	145-146
6	$\text{R}_1=\text{R}_2=\text{Br}$, $\text{R}_3=\text{OCH}_3$	$\text{C}_{18}\text{H}_{16}\text{Br}_2\text{O}_5$	C45.79 H3.42 C45.65 H3.74	152-153
7	$\text{R}_1=\text{NO}_2$, $\text{R}_2=\text{CH}_3$, $\text{R}_3=\text{OCH}_3$	$\text{C}_{19}\text{H}_{19}\text{NO}_7$	C61.12 H5.13 C61.11 H5.40	147-148
8	$\text{R}_1=\text{R}_2=\text{Cl}$, $\text{R}_3=\text{H}$	$\text{C}_{17}\text{H}_{14}\text{Cl}_2\text{O}_4$	C57.81 H4.00 C58.03 H4.39	163-164
9	$\text{R}_1=\text{R}_2=\text{Br}$, $\text{R}_3=\text{H}$	$\text{C}_{17}\text{H}_{14}\text{Br}_2\text{O}_4$	C46.18 H3.19 C46.29 H3.43	158-159
10	$\text{R}_1=\text{NO}_2$, $\text{R}_2=\text{CH}_3$, $\text{R}_3=\text{H}$	$\text{C}_{18}\text{H}_{17}\text{NO}_6$	C62.97 H4.99 C62.97 H5.33	153-154
11	$\text{R}_1=\text{R}_2=\text{Cl}$, $\text{R}_3=\text{OCH}_3$	$\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{O}_6$	C54.43 H3.55 C54.36 H3.85	198-199
12	$\text{R}_1=\text{R}_2=\text{Br}$, $\text{R}_3=\text{OCH}_3$	$\text{C}_{18}\text{H}_{14}\text{Br}_2\text{O}_6$	C44.47 H2.90 C44.12 H3.19	>260, decomp
13	$\text{R}_1=\text{NO}_2$, $\text{R}_2=\text{CH}_3$, $\text{R}_3=\text{OCH}_3$	$\text{C}_{19}\text{H}_{17}\text{NO}_8$	C58.92 H4.42 C58.97 H4.71	210-211
14	$\text{R}_1=\text{R}_2=\text{Cl}$, $\text{R}_3=\text{H}$	$\text{C}_{17}\text{H}_{12}\text{Cl}_2\text{O}_5$	C55.61 H3.29 C55.41 H3.45	215-216
15	$\text{R}_1=\text{R}_2=\text{Br}$, $\text{R}_3=\text{H}$	$\text{C}_{17}\text{H}_{12}\text{Br}_2\text{O}_5$	C44.77 H2.65 C44.81 H2.99	220-221
16	$\text{R}_1=\text{NO}_2$, $\text{R}_2=\text{CH}_3$, $\text{R}_3=\text{H}$	$\text{C}_{18}\text{H}_{15}\text{NO}_7$	C60.50 H4.23 C60.41 H4.21	195-196
17	$\text{R}_1=\text{R}_2=\text{Cl}$, $\text{R}_3=\text{OCH}_3$	$\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{O}_5$	C56.71 H3.70 C57.03 H3.81	155-156
18	$\text{R}_1=\text{R}_2=\text{Br}$, $\text{R}_3=\text{OCH}_3$	$\text{C}_{18}\text{H}_{14}\text{Br}_2\text{O}_5$	C45.99 H3.00 C46.28 H3.39	179-180
19	$\text{R}_1=\text{NO}_2$, $\text{R}_2=\text{CH}_3$, $\text{R}_3=\text{OCH}_3$	$\text{C}_{19}\text{H}_{17}\text{NO}_7$	C61.45 H4.61 C61.47 H5.01	135-136
20	$\text{R}_1=\text{R}_2=\text{Cl}$, $\text{R}_3=\text{H}$	$\text{C}_{17}\text{H}_{12}\text{Cl}_2\text{O}_4$	C58.14 H3.44 C58.37 H3.76	145-146
21	$\text{R}_1=\text{R}_2=\text{Br}$, $\text{R}_3=\text{H}$	$\text{C}_{17}\text{H}_{12}\text{Br}_2\text{O}_4$	C46.40 H2.75 C46.72 H3.12	134-135
22	$\text{R}_1=\text{NO}_2$, $\text{R}_2=\text{CH}_3$, $\text{R}_3=\text{H}$	$\text{C}_{18}\text{H}_{15}\text{NO}_6$	C63.34 H4.43 C62.95 H4.80	150-151

Table 2
NMR and IR Data for the Synthesized Compounds

Compound	¹ H-NMR (δ ppm)	IR (ν cm ⁻¹ KBr)
5	(DMSO-d ₆): δ 3.70, 3.79 (s, s, 9H, -CH ₃ O), 6.82 (s, 2H, Ar), 7.07-7.08 (d, 1H, Ar, J=3.0 Hz), 7.42-7.43 (d, 1H, Ar, J=3.0 Hz), 7.37-7.42 (d, 1H, CH=CH, J=15 Hz) 8.55-8.60 (d, 1H, CH=CH, J=15 Hz)	3400 (broad, OH), 1590 (C=O), 1610 (C=C Ar), 1590 (C=C), 1130 (C-O) cm ⁻¹ .
6	(DMSO-d ₆): δ 3.78, 3.80 (s, s, 9H, -CH ₃ O), 7.14 (s, 2H, Ar), 7.34-7.35 (d, 1H, J=3.0 Hz), 7.39-7.45 (d, 1H, J=18 Hz, CH=CH), 7.58-7.59 (d, 1H, J=3.0 Hz), 8.48-8.53 (d, 1H, J=18 Hz)	3390 (broad, OH), 1585 (C=O), 1600 (C=C Ar), 1595 (C=C), 1110 (C-O) cm ⁻¹ .
7	(DMSO-d ₆): δ 3.81, 3.84 (s, s, 9H, -CH ₃ O), 6.87 (s, 2H, Ar), 7.37-7.43 (d, 1H, J=18 Hz CH=CH), 7.48-7.49 (d, 1H, J=3.0 Hz, Ar), 8.08- 8.14 (d, 1H, J=18 Hz, CH=CH)	3390 (broad, OH), 1640 (C=O), 1612 (C=C Ar), 1580 (C=C), 1120 (C-O) cm ⁻¹ .
8	(DMSO-d ₆): δ 3.93, 3.97 (s, s, 6H, -CH ₃ O), 6.88-6.92 (m, 1H, Ar), 7.15-7.16 (d, 1H, J= 3.0 Hz, Ar), 7.24-7.29 (m, 1H, Ar), 7.34-7.39 (d, 1H, J=15 Hz, CH=CH), 7.54-7.57 (m, 1H, Ar), 7.80-7.81 (d, 1H, J=3.0 Hz, Ar), 7.91-7.96 (d, 1H, J=15 Hz, CH=CH)	3400 (broad, OH), 1650 (C=O), 1610 (C=C Ar), 1590 (C=C), 1125 (C-O) cm ⁻¹ .
9	(DMSO-d ₆): δ 3.07, 3.10 (s, s, 6H, -CH ₃ O), 6.88-6.92 (m, 1H, Ar), 7.15-7.16 (d, 1H, Ar), 7.26-7.30 (dd, 1H, Ar), 7.34-7.39 (d, 1H, J=15 Hz, CH=CH), 7.86-7.91 (d, 1H, J=15 Hz, CH=CH), 7.94-7.98 (m, 1H, Ar)	3390 (broad, OH), 1650 (C=O), 1611 (C=C Ar), 1590 (C=C), 1110 (C-O) cm ⁻¹ .
10	(DMSO-d ₆): δ 3.77, 3.80 (s, s, 6H, -CH ₃ O), 6.95-6.98 (d, 1H, J=9 Hz), 7.17 (s, 1H, Ar), 7.22- 7.23 (d, 1H, J=3.0 Hz, Ar), 7.40-7.45 (d, 1H, J=15 Hz, CH=CH), 7.65-7.66 (d, 1H, J=3.0 Hz, Ar), 7.98-8.03 (d, 1H, J=15 Hz, CH=CH)	3390 (broad, OH), 1640 (C=O), 1610 (C=C Ar), 1592 (C=C), 1120 (C-O) cm ⁻¹ .
11	(DMSO-d ₆): δ 3.68, 3.81 (s, s, 9H, -CH ₃ O), 7.83-7.84 (d, 1H, Ar, J=2.4 Hz), 7.85-7.86 (d, 1H, Ar, J=2.4 Hz), 8.08 (s, 2H, Ar)	3400 (broad, OH), 1650 (C=O), 1613 (C=C Ar), 1590 (C=C), 1131 (C-O) cm ⁻¹ .
12	(DMSO-d ₆): δ 3.68, 3.81 (s, s, 9H, -CH ₃ O), 7.98-7.99 (d, 1H, Ar, J=2.4 Hz), 8.01-8.02 (d, 1H, Ar, J=2.4 Hz), 8.19 (s, 2H, Ar)	3390 (broad, OH), 1655 (C=O), 1605 (C=C Ar), 1580 (C=C), 1115 (C-O) cm ⁻¹ .
13	(DMSO-d ₆): δ 3.76, 3.86 (s, s, 6H, -OCH ₃), 7.69 (s, 2H, Ar), 8.25-8.26 (d, 1H, J=3.0 Hz, Ar), 8.42-8.43 (d, 1H, J=3.0 Hz, Ar).	3410 (broad, OH), 1660 (C=O), 1613 (C=C Ar), 1595 (C=C), 1115 (C-O) cm ⁻¹ .
14	(DMSO-d ₆): δ 3.79 (s, 6H, -OCH ₃), 7.01- 7.04 (d, 1H, Ar, J=9.0 Hz), 7.81 (s, 1H, Ar), 7.87 (m, 1H, Ar), 8.12-8.15 (d, 1H, Ar, J=9.0 Hz), 8.44 (s, 1H, Ar)	3380 (broad, OH), 1645 (C=O), 1610 (C=C Ar), 1595 (C=C), 1120 (C-O) cm ⁻¹ .
15	(DMSO-d ₆): δ 3.29, 3.31 (s, s, 6H, -OCH ₃), 7.17-7.19 (d, 1H, Ar, J=6 Hz), 7.88-7.98 (m, 2H, Ar), 8.14-8.15 (d, 1H, J=3.0 Hz), 8.34- 8.35 (d, 1H, Ar, J=3.0 Hz)	3400 (broad, OH), 1656 (C=O), 1600 (C=C Ar), 1595 (C=C), 1130 (C-O) cm ⁻¹ .
16	(DMSO-d ₆): δ 3.77-3.80 (s, s, 6H, -OCH ₃), 6.97-6.99 (m, 2H, Ar), 8.16 (s, 1H, Ar), 8.33- 8.35 (dd, J=6 Hz, Ar), 8.48 (s, 1H, Ar)	3380 (broad, OH), 1660 (C=O), 1610 (C=C Ar), 1588 (C=C), 1130 (C-O) cm ⁻¹ .

Table 2 (continued)

Compound	¹ H-NMR (δ ppm)	IR (ν cm ⁻¹ KBr)
17	(deuteriochloroform): δ 3.87, 3.89 (s, 9H, -CH ₃ O), 8.01-8.02 (d, J=2.4 Hz, 1H, Ar), 7.67-7.68 (d, J=2.4 Hz, 1H, Ar), 6.74 (s, 1H, O=C-CH=), 7.14 (s, 2H, Ar)	1660 (C=O), 1613 (C=C Ar), 1592 (C=C), 1133 (C-O) cm ⁻¹ .
18	(deuteriochloroform): δ 3.93, 3.94 (s, 9H, -CH ₃ O), 8.27-8.28 (d, J=2.2 Hz, 1H, Ar), 8.02-8.03 (d, J=2.2 Hz, 1H, Ar), 6.80 (s, 1H, O=C-CH=), 7.23 (s, 2H, Ar)	1656 (C=O), 1610 (C=C Ar), 1591 (C=C), 1134 (C-O) cm ⁻¹ .
19	(deuteriochloroform): δ 3.87, 3.91 (s, 9H, -CH ₃ O), 8.24 (s, 1H, Ar), 8.19-8.20 (d, J=2.1 Hz, 1H, Ar), 6.79 (s, 1H, O=C-CH=), 7.23 (s, 2H, Ar), 2.49 (s, 3H, -CH ₃)	1654 (C=O), 1618 (C=C Ar), 1583 (C=C), 1126 (C-O) cm ⁻¹ .
20	(deuteriochloroform): δ 3.95, 3.96 (s, 6H, -CH ₃ O), 8.07-8.06 (d, J=2.3 Hz, 1H, Ar), 7.70-7.71 (d, J=2.6 Hz, 1H, Ar), 6.77 (s, 1H, O=C-CH=), 6.97-6.99 (d, J=8.4 Hz, 1H, Ar) 7.44-7.45 (d, J=2.0 Hz, 1H, Ar), (td, J=2.3, 8.7 Hz, 1H, Ar)	1654 (C=O), 1561 (C=C Ar), 1519 (C=C), 1278 (C-O) cm ⁻¹ .
21	(deuteriochloroform): δ 3.92, 3.93 (s, 6H, -CH ₃ O), 8.26-8.27 (d, J=2.4 Hz, 1H, Ar), 7.99-8.00 (d, J=2.2 Hz, 1H, Ar), 6.82 (s, 1H, O=C-CH=), 7.74-7.77 (dd, J=1.9 Hz, 6.4 Hz, 1H, Ar), 7.57-7.58 (d, J=1.6 Hz, 1H, Ar), 6.88-6.91 (d, J=8.5 Hz, 1H, Ar)	1677 (C=O), 1650 (C=C Ar), 1599 (C=C), 1235 (C-O) cm ⁻¹ .
22	(deuteriochloroform): δ 3.96, 4.00 (s, 6H, -CH ₃ O), 8.30 (s, 1H, Ar), 8.22-8.23 (d, J=2.0 Hz, 1H, Ar), 6.84 (s, 1H, O=C-CH=), 6.97-7.00 (d, J=8.9 Hz, 1H, Ar), 7.82-8.00 (dd, J=1.8 Hz, 50.3, 1H, Ar), 7.58-7.59 (d, J=2.0 Hz, 1H, Ar), 2.54 (s, 3H, -CH ₃)	1647 (C=O), 1615 (C=C Ar), 1531 (C=C), 1256 (C-O) cm ⁻¹ .

Synthesis of Flavones **17-22** [20, 25-26].

Compounds **3** (Scheme 4) were mixed with 1.7 times excess of 3,4,5-trimethoxy benzoyl chloride or 3,4-dimethoxy benzoyl chloride, **4**, correspondingly, in pyridine. The reaction mixture was heated at 70 °C for 4 h, and then poured onto ice containing 5 N HCl. The precipitate that formed was collected by vacuum filtration and air dried. The crude product was dissolved in pyridine in the presence of 10 times excess of KOH. The reaction was carried out for 4 h at 65 °C, and then the mixture poured onto an ice-5 N HCl bath. A yellow precipitate was formed, which was collected by filtration and air dried. The crude product was dissolved in acetic acid containing 1 mL concentrated H₂SO₄, heated at 60 °C for 4 h and left stirring overnight at room temperature. After 24 h, the reaction mixture was poured onto an ice-NaHCO₃ mixture, the product collected by filtration and recrystallized from ethanol. The pure flavone was obtained by purification on Chromatotron with CH₂Cl₂:MeOH 8:1 as eluent. The yields were 30-50%.

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REFERENCES AND NOTES

- [1] H. Bao, H. F. Ren, H. Endo, Y. Takagi, T. Hayashi, *Food Chemistry*, **86**, 517 (2004).
- [2] T. Miura, S. Muraoka, Y. Fujimoto, *Food and Chemical Toxicology* **41**, 759 (2003).
- [3] J. J. A. Hendricks, J. Alblas, S. M. A. van der Pol, E. A. F. van Tol, C. D. Dijkstra, H. E. de Vries, *Journal of Experimental Medicine*, **200**, 1667 (2004).
- [4] H. Y. Lin, S. C. Shen, Y. C. Chen, *Journal of Cellular Physiology*, **202**, 579 (2005).
- [5] Y. S. Chi, H. G. Jong, K. H. Son, H. W. Chang, S. S. Kang, and H. P. Kim, *Biochem. Pharmacol.*, **62**, 1185 (2001).
- [6] T. Zhang, X. L. Chen, L. B. Qu, J. L. Wu, R. Cui, Y. F. Zhao, *Bioorganic & Medicinal Chemistry*, **12**, 6097 (2004).
- [7] C. A. Rowe, M. P. Nantz, C. DeNiera, K. Green, S. T. Talcott, S. S. Percival, *Journal of Medicinal Food*, **7**, 402 (2004).
- [8] X. Zheng, J. G. Cao, W. D. Meng, and F. L. Qing, *Bioorganic and Medicinal Chemistry Letters*, **13**, 3423 (2003).
- [9] X. Zheng, W. D. Meng, Y. Y. Xu, J. G. Cao, and F. L. Qing, *Bioorganic and Medicinal Chemistry Letters*, **13**, 881 (2003).
- [10] W. Wang, Z. H. Ding, J. K. Liu, Y. T. Zheng, *Antiviral Research*, **64**, 189 (2004).
- [11] T. B. Ng, B. Huang, W. P. Fong, and H. W. Yeung, *Life Sci.*, **61**, 933 (1997).
- [12] A. J. Vlietnick, D. A. Vanden Berghe, and A. Haemers, *Plant Flavonoids in Biol. And Medicine II: Biochem., Cell. And Medicinal Properties*, 283 (1988).
- [13] G. Di Carlo, N. Mascolo, A. A. Izzo, and F. Capasso, *Life Sciences*, **65**, 337 (1999).
- [14] L. M. Larocca, M. Guistacchini, N. Maggiano, F. O. Ranalletti, M. Piantelli, E. Alcini, and A. Capelli, *J. Urol.*, **152**, 1029 (1994).

- [15] M. A. Avila, J.A. Velasco, J. Cansado, and V. Nitario, *Cancer Res.*, **54** 2424 (1994).
- [16] K. Ono, H. Nakane, M. Fukushima, J. C. Chermann, and F. Barre-Sinoussi, *Biochem. Biophys. Res. Commun.*, **160**, 982 (1989).
- [17] B. Q. Li, T. Fu, Y.D. Yan, N. W. Baylor, F. W. Ruscetti, and H. F. Kung, *Cell. And Mol. Biol. Res.*, **39**, 119 (1993).
- [18] Y. F. Lu, M. Santostefano, B. D. M. Cunningham, M. D. Threadgill, and S. Safe, *Biochemical Pharmacology*, **51**, 1077 (1996).
- [19] P. Bovichelli, R. Bernini, R. Antonioletti, and E. Mincione, *Tetrahedron Letters*, **43**, 5563 (2002).
- [20] N. N. Mateeva, R. N. Kode, and K. K. Redda, *J. Heterocyclic Chem.*, **39**, 1251 (2002).
- [21] D. K. Bhardwaj, A. K. Gupta, A. Jain and V. K. Shrawat, *Indian J. Chem.*, **27B**, 261 (1988).
- [22] K. Krohn, K. Steingroever, and M. M Rao, *Phytochemistry*, **61**, 931 (2002).
- [23] B. Cummins, M. X. Donnelly, J. F. Eades, H. Fletcher, F. O'Conneide, E. M. Philbin, J. Swirski, T. S. Wheeler, and R. K. Wilson, *Tetrahedron*, **19**, 449 (1963).
- [24] M. Bennett, A.J. Burke, and W. Ivo O'Sullivan, *Tetrahedron*, **52**, 7163-7178 (1996).
- [25] T. Horie, Y. Kawamura, H. Yamamoto and K. Yamashita, *Chem. Pharm. Bull.*, **43**, 2054 (1995).
- [26] C. J. Bennett, S. T. Caldwell, D. B. McPhail, P. C. Morrice, G. G. Duthie, R. C. Hartley, *Bioorganic & Medicinal Chemistry*, **12**, 2079 (2004).