Effects of Simple and Angular Chromones on Tumor Cell Respiration

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This paper is dedicated to Professor P. Joseph-Nathan for his 65th birthday.

A set of structurally related compounds incorporating a chromone moiety as an essential component of their structures were tested against the TA3 mouse carcinoma cell line and its multidrug-resistant variant TA3-MTX-R. A tentative structure–activity relationship was found for this family of substances, suggesting that a Michael addition at C-1 is involved in the mechanism that provokes the activities.

Keywords: Chromone, cancer, cell respiration.

Chromones and their structural analogues have motivated a great interest because of their usefulness as biologically active agents. The chromone moiety is the essential component of pharmacophores of a large number of bioactive molecules [1]. Several interesting biological properties of this type of compounds have been reported, including cytotoxic (anticancer) [2], neuroprotective [3], HIV-inhibitory [4], antimicrobial [5], antifungal [6], and antioxidant activity [7]. Several kinds of molecular mechanisms of action of flavonoids have been identified, such as carcinogen inactivation, antiproliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis, antioxidation and reversal of multidrug resistance [10]. Consequently, considerable attention and efforts are being devoted to the isolation of chromone derivatives from natural resources, their chemistry and synthesis, and evaluation of their biological activities. 4-Oxo-4*H*-benzopyran-3-carbaldehyde (3-formyl chromone) (**1**) is a very reactive system owing to the presence of aldehydic and pyrone carbonyl groups linked to the ethylenic C-2 position, which is very reactive toward Michael addition of nucleophiles. However, in the presence of Lewis acids the formyl group becomes more reactive than C2 [8]. This change of reactivity has been explained in terms of the theoretical electrophilicity index [9]. To date, some flavonoids have already entered clinical trials, for example, phenodioxol and flavopiridol (**2**). The last was identified as the first cyclindependent kinase inhibitor and entered phase II clinical trials [11].

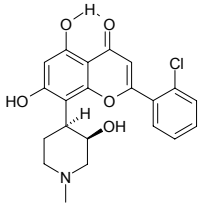

Figure 1: Flavopiridol (**2**)

Stigmatellin A, a chromone isolated from the myxobacterium *Stigmatella aurantiaca*, is a powerful inhibitor of electron transport in mitochondria and chloroplasts [12]. Stigmatellin is one of the most potent inhibitors of the ubiquinol oxidation site (*Q*o site) of complex-III and this property has made it of interest in agrochemistry [13]. In contrast, oxidation of either catechol or phenol moieties of a series of hydroxylated flavones, chromones and acetophenones, to yield quinoid structures, is a possibility that has been mentioned in relation to their mutagenic activity.

The interaction between leukocytes and the vascular endothelial cells via cellular adhesion molecules plays an important role in various inflammatory and immune diseases. Molecules that block these interactions have been identified as potential therapeutic targets for acute and chronic inflammatory diseases. A series of chromone derivatives have been screened for their ICAM-1 inhibitory activity on human endothelial cells, as well as their effect on NADPH-catalyzed rat microsomal lipid peroxidation. These results showed that compound **4** happens to be the most potent. In addition, compound **4** also significantly inhibited the TNF-a induced expression of VCAM-1 and E-selectin, which play key roles in various inflammatory diseases [14].

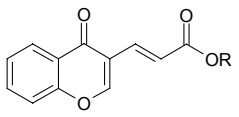

Figure 2: (*E*)-ethyl 3-(4-oxo-4*H*-chromen-3-yl) acrylate (**4**).

Previously, we have reported that compounds bearing a carbonyl group in the *ortho* position with regard to a phenol function, like flavopiridol, were able to cause inhibition of cellular respiration [15].

The oxygen uptake inhibition by TA3 and TA3-MTX-R cells is useful as a quick test for preliminary screening of possible anticancer activity. Generally, the IC_{50} for oxygen uptake inhibition is about one order of magnitude greater than the IC_{50} for cytotoxicity. In relation to these compounds, spectroscopic and reactivity studies of chromone 4 have also been reported [16,17].

The high reactivity towards Michael addition makes chromones susceptible to nucleophilic attack, inside the cell, resulting in covalent modifications of the nucleophilic sites present in biological molecules, such as thiols and amine groups in proteins. Besides, the phenolic moiety of hydroxyl chromones may generate phenoxy radicals that, in the presence of oxygen, might initiate a redox cycle, resulting in the inactivation of biological molecules by oxidation.

Phenolic compounds may either stimulate or inhibit oxidative damage to biomolecules and it is believed that they can behave as either antioxidants or pro-oxidants [18]. Their ability to inhibit the growth and proliferation of certain malignant cells *in vitro* is strongly dependent on their structural characteristics [19a-19c]. This kind of compound has been reported to display antiproliferative and cytotoxic properties in several tumor cell lines [19].

Based on these antecedents, we screened a set of simple and angular chromones for the inhibition of oxygen consumption by TA3 ascites tumor cells derived from mouse mammary adenocarcinoma and their multidrug-resistant variant TA3.MTX-R. This study is centered on the effects on their inhibitory activity of phenolic hydroxyl substitution, *ortho* to the carbonyl group, and the formyl replacement group at C-3 by either an acrylic ester or a hydroxymethyl group.

The studied chromones, shown in Tables 1 and 2, were synthesized by the Vilsmeier–Haack reaction. The acetophenones used as substrates for the synthesis of angular chromones were prepared through a two step sequence: Diels-Alder reaction of either butadiene or 2,3-dimethylbutadiene with acetyl benzoquinone, followed by a 1,5-sigmatropic rearrangement, in accord with Scheme 1, as reported previously [20].

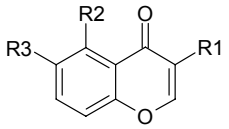

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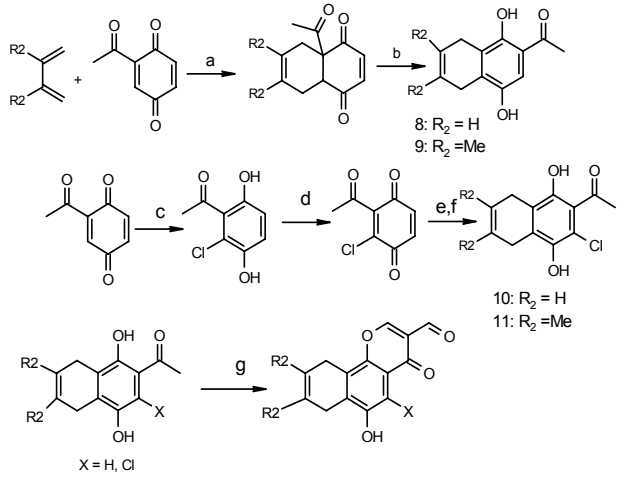
Table 1: Chromone derivatives.

Compd.	R1	R2	R3
1	CHO	H	H
2	CHO	OH	H
3	CHO	H	OMe
4	$CH{=}CHCO_2Et$	H	H
5	$CH{=}CHCO_2Et$	OH	H
6	CH_2OH	H	H
7	CH_2OH	OH	H

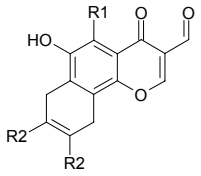
Compounds **1-3** are simple formyl chromones, meeting the primary requirement of a formyl group linked to C-3. Table 3 shows the IC_{50} values of the studied chromones against TA3 and TA3-MTX-R. It may be seen from this Table that these compounds show moderate activity against both cell lines,

displaying very similar activities, suggesting that the aromatic ring substitution is unimportant. However, the differences between the activities of formylchromones **1** and **2** with respect to derivatives **4** and **5**, obtained by replacement of the formyl group by a less electronegative group, such as acrylate, provokes a fall in the activity by a factor of 16-fold in both cell lines for the pair **1** and **4**, and about 9-fold in both lines for the pair **2** and **5**.



a) benzene, r.t., b) xylene, pyridine, reflux, c) HCl(g), d) AgO, e) diene, toluene, r.t, f) silicagel, toluene g) $POCl_3$, DMF

Scheme 1: Synthesis of angular formylchromones



12-15

Table 2: angular chromones synthesized.

Compds	R1	R2
12	H	H
13	H	Me
14	Cl	H
15	Cl	Me

Table 3: Inhibitory activities of chromones.

Compds.	IC_{50}(mM) TA3	IC_{50}(mM) TA3-MTX-R
1	0.11 ± 0.009	0.12 ± 0.05
2	0.11 ± 0.005	0.13 ± 0.009
3	0.17 ± 0.05	0.12 ± 0.005
4	0.92 ± 0.1	1.22 ± 0.09
5	1.90 ± 0.08	2.00 ± 0.09
6	inactive	inactive
7	inactive	inactive
12	inactive	inactive
13	inactive	inactive
14	0.12 ± 0.003	not measured
15	0.12 ± 0.006	not measured

In addition, when the formyl group was replaced by a hydroxymethyl group, the activity was abolished. This trend might be correlated with the change in the susceptibility of C-1 to act as a Michael acceptor. Although the inhibitory activity showed by **4** is low, it must be taken into account in relation to its published bioactivities, and in the design of analog compounds. The introduction of a third cycle in the molecules also abolished the activities (compounds **12** and **13**). However, the introduction of a chlorine atom (compounds **14** and **15**) led to recovery of the activities against the TA3 cell line, suggesting that lipophilicity is also important, probably due to improved cell penetration.

Experimental

All melting points are uncorrected and were determined on a Kofler hot stage apparatus. Infrared spectra (KBr discs) were recorded on a FT-IR Bruker IFS 55 spectrophotometer; wave numbers are reported in cm^{-1}. The ^{1}H and ^{13}C NMR spectra were obtained from a Bruker AVANCE DRX 300 spectrometer operating at either 300.13 MHz (^{1}H) or 75.47 MHz (^{13}C). Measurements were carried out at a probe temperature of 300K, using $CDCl_3$ containing tetramethylsilane (TMS) as internal standard. High resolution mass spectra were obtained on a MAT 95XP Thermo Finnigan spectrometer.

General procedure for preparation of formyl chromones 1-3 and 12-15: The formyl chromones were synthesized through the Vilsmeier–Haack reaction according to the following procedure: to a cooled dimethylformamide solution of the corresponding *o*-hydroxyacetophenone, phosphorus oxychloride was added dropwise and then the ice bath was removed. The stirred reaction mixture was kept at 75ºC overnight and then treated with ice-water to give the corresponding 3-formyl chromone derivative. The crude material was purified by column chromatography using silica gel and *n*-hexane/ethyl acetate (1:1 or 2:1) as eluent [8].

General procedure for the synthesis of bicyclic acetophenones 8-11: A solution of either acetylbenzoquinone [20] or the 3-chloro derivative [21] in toluene was placed in a rubber sealed tube and then either butadiene or 2,3-dimethylbutadiene was added. The reaction mixture was heated at 60ºC for 24 h. The solvent was then removed by vacuum evaporation, the crude material dissolved in a mixture of 5 mL xylene and 0.3 mL pyridine, and heated under reflux for 4 h. Vacuum evaporation of the solvent yielded the corresponding hydroquinone [21].

General procedure for the Wittig reaction: To a solution of chromone (**1** and **2**), one equivalent of ethyl (triphenylphosphoranylidene) acetate in toluene was added and heated under reflux for 2 h. A mixture of *cis* and *trans* derivatives was obtained, with the latter as the main product. Purification was in accord with procedures previously described [16,17].

General procedure for reduction of formyl chromones: About 1 g basic alumina and about 50 mg (5% of alumina weight) of formyl chromone (**1** and **2**), dissolved in 10 mL 2-propanol, were placed in a round-bottom flask containing a magnetic bar, and the mixture was stirred for 4 h at 75ºC. Vacuum filtration through celite, and rotatory evaporation of the solvent gave the crude alcohols (**6** and **7**), which were purified by column chromatography using ethyl acetate/*n*-hexane (1:1) as eluent [8].

Cell respiration: Oxygen uptake was measured polarographically at 25ºC with a Clark electrode No. 5331 (Yellow Springs Instruments) and using a YSI model 53 monitor linked to a 100 mV single channel Goerz RE 511 recorder. The 2.0 mL reaction mixture contained 150 mM NaCl, 3 mM KCl, and 10 mM Tris–HCl, pH 7.4, plus 5 mM glutamine as substrate, and 2.5 mg protein/mL of either TA3 ascites tumor cells derived from mouse mammary adenocarcinoma or their multidrug-resistant variant TA3.MTX-R, as described before [15].

3-Formyl-4[*H*]-1-benzopyran-4-one (**1**) [8]

MP: 149–151°C.
^{1}H NMR (300 MHz, $CDCl_3$): 7.52 (ddd, 1H, J_1 = 7.9 Hz, J_2 = 7.2 Hz, J_3 = 1.1 Hz, 6-H), 7.56 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.1 Hz, 8-H), 7.77 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 7.2 Hz, J_3 = 1.7 Hz, 7-H), 8.32 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 5-H), 8.57 (s, 1H, 2-H), 10.40 (s, 1H, CHO).

3-Formyl-5-hydroxy-4[*H*]-1-benzopyran-4-one (**2**) [8]

MP: 157°C.
^{1}H NMR: (300 MHz, $CDCl_3$) 6.91 (dd, 1H, J_1 = 0.7, J_2 = 8.3 Hz, 6-H), 6.99 (dd, 1H, J_1 = 0.7 Hz, J_2 = 8.3 Hz, 8-H), 7.61 (dd, 1H, J_1 = J_2 = 8.3 Hz, 7-H), 8.52 (s, 1, 2-H), 10.32 (s, 1H, CHO), 12.10 (s, 1H, OH).

3-Formyl-6-methoxy-4[*H*]-1-benzopyran-4-one (**3**) [8]

MP: 163-165°C.
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H, OCH_3), 7.32 (dd, 1H, J_1 = 9.2 Hz, J_2 = 3.0 Hz, 7-H), 7.48 (d, 1H, J = 9.2 Hz, 8-H), 7.66 (d, 1H, J_1 = 3.0 Hz, 5-H), 8.53 (s, 1H, 2-H), 10.41 (s, 1H, CHO).

***Trans*-ethyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate** (**4**) [16,17]

MP: 111.5–112.5ºC.
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, 3H, J = 7.2 Hz, CH_3), 4.26 (q, 2H, J = 7.2 Hz, CH_2), 7.28 (d, 1H, J = 15.9 Hz, H-10), 7.49 (d, 1H, J = 15.9 Hz, H-9), 7.45 (ddd, 1H, J_1 = 8.0 Hz, J_2 = 7.2 Hz, J_3 = 1.1 Hz, H-6), 7.49 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.0 Hz, H-8), 7.70 (ddd, 1H, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 1.6 Hz, H-7), 8.12 (s, 1H, H-2), 8.28 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz, H-5).

***Trans*-ethyl 3-(5-hydroxy-4-oxo-4*H*-chromen-3-yl) acrylate** (**5**) [16,17]

MP: 158.5–159.5ºC.
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, 3H, J = 7.1 Hz, CH_3), 4.30 (q, 2H, J = 7.1 Hz, CH_2), 6.85 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.7 Hz, H-6), 6.93 (dd, 1H, J_1 = 8.4 Hz, J_2 = 0.7 Hz, H-8), 7.21 (d, 1H, J = 15.9 Hz, H-10), 7.38 (d, 1H, J = 15.9 Hz, H-9), 7.56 (dd, 1H, J_1 = 8.4 Hz, J_2 = 8.3 Hz, H-7), 8.10 (s, 1H, H-2), 12.49 (s, 1H, OH).

3-(Hydroxymethyl)-4-oxo-4*H*-1-benzopyrane (**6**) [8]

MP: 109–110ºC.
^{1}H NMR: (300 MHz, $CDCl_3$): δ 3.00 (t, 1H, J = 6.3 Hz, CH_2O*H*), 4.59 (dd, 2H, J_1 = 6.3 Hz, J_2 = 0.7 Hz, CH_2OH), 7.43 (ddd, 1H, J_1 = 7.9 Hz, J_2 = 7.3 Hz, J_3 = 1.0 Hz, 6-H), 7.48 (1H, d, J = 8.6 Hz, 8-H), 7.70 (ddd, 1H, J_1 = 8.6 Hz, J_2 = 6.9 Hz, J_3 = 1.6 Hz, 7-H), 7.95 (t, 1H, J = 0.7 Hz, 2-H), 8.24 (dd, 1H, J_1 = 7.9 Hz, J_2=1.6 Hz, 5-H).

5-Hydroxy-3-(hydroxymethyl)-4-oxo-4*H*-1-benzo pyrane (**7**) [8]

MP: 102–104ºC.
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58 (s, 2H, CH_2O*H*), 5.12 (t, 1H, J = 0.8 Hz, CH_2OH), 6.82 (dd, 1H, J_1 = 8 Hz, J_2 = 0.9 Hz, 6-H), 6.92 (1H, dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 8-H), 7.55 (dd, 1H, J_1 = J_2= 8.4 Hz, 7-H),7.94 (t, 1H, J = 0.8 Hz, 2-H), 12.25 (s, 1H, 5-H).

1-(1,4-Dihydroxy-5,8-dihydro-2-naphthalenyl) ethanone (**8**)

MP: 170-171ºC.
IR (KBr): 3270, 3032, 1614.6, 1523.8, 1393.2 cm^{-1}.
^{1}H NMR: (300 MHz, $CDCl_3$): δ 2.57 (s, 3H, $COCH_3$), 3.32 (s, 4H, 2 x CH_2, 4-H, 7-H), 4.44 (s, 1H, OH, 3-H), 5.84-5.99 (m, 2H, 5-H, 6-H), 6.99 (s, 1H, Ar-H), 12.32 (s, 1H, OH, 8-H).
HRMS: m/z [M^+] calcd. for $C_{12}H_{12}O_3$: 204.07864; found: 204.07794.
Yield: 53%.

1-(1,4-Dihydroxy-5,8-dihydro-6,7-dimethyl-2-naphthalenyl) ethanone (**9**)

MP: 168-169ºC.
IR (KBr): 3270, 1626.1, 1529, 1417.8, 1388.6 cm^{-1}.
^1H NMR: (300 MHz, $CDCl_3$) δ: 1.79 (s, 6H, 2 x CH_3), 2.57 (s, 3H, $COCH_3$), 3.23 (s, 4H, 2 x CH_2, 4-H, 7-H), 4.43 (s, 1H, OH, 3-H), 6.98 (s, 1H, Ar-H), 12.31 (s, 1H, OH, 8-H).
HRMS: m/z [M^+] calcd for $C_{14}H_{16}O_3$: 232.10995; found: 232.10921.
Yield: (89% x 72%).

1-(3-Chloro-1,4-dihydroxy-5,8-dihydro-2-naphthalenyl) ethanone (**10**)

MP: 142-144ºC.
IR (KBr): 3400, 2980, 1615, 1460.1 cm^{-1}.
^1H NMR: (300 MHz, $CDCl_3$) δ: 2.81 (s, 3H, $COCH_3$), 3.21-3.39 (m, 4H, 2 x CH_2, 4-H, 7-H), 5.52 (s, 1H, OH, 3-H), 5.80-5.94 (m, 2H, 5-H, 6-H), 12.74 (s, 1H, OH, 8-H).
HRMS: m/z [M^+] calcd. for $C_{12}H_{11}O_3Cl$: 238.03967; found: 238.03852.
Yield: 75%.

1-(3-Chloro-1,4-dihydroxy-5,8-dihydro-6,7-dimethyl-2-naphthalenyl) ethanone (**11**)

MP: 175-176ºC.
IR (KBr): 3400, 1617.7, 1582.8, 1463.3 cm^{-1}.
^1H NMR**:** (300 MHz, $CDCl_3$): δ 1.77 (s, 6H, 2 x CH_3), 2.81 (s, 3H, $COCH_3$), 3.16-3.29 (m, 4H, 2 x CH_2, 4-H, 7-H), 5.53 (s, 1H, OH, 3-H), 12.76 (s, 1H, OH, 8-H).
HRMS: m/z [M^+] calcd. for $C_{14}H_{15}O_3Cl$: 266.07097; found 266.06986.
Yield: 82%

6-Hydroxy-4-oxo-7,10-dihydro 4*H*-benzo[*h*]cromen-3-carbaldehyde (**12**)

MP**:** 225-228ºC (sublimate).
IR (KBr): 3250, 1693.3, 1636.9, 1586.5, 1455.3 cm^{-1}.
^1H NMR: (300 MHz, DMSO-d_6) δ: 3.27-3.35 (m, 2H, 7-H or 10-H), 3.43-3.52 (t, 2H, 7-H or 10-H), 5.88 (s, 2H, 8-H, 9-H), 7.43 (s, 1H, Ar-H), 8.48 (s, 1H, 2-H), 10.30 (s, 1H, CHO).
HRMS: m/z [M^+] calcd. for $C_{14}H_{10}O_4$: 242.05791; found:242.05703.
Yield: 74%.

6-Hydroxy-8,9-dimethyl-4-oxo-7,10-dihydro-4*H* benzo[*h*]chromen-3-carbaldehyde (**13**)

MP: 255-256ºC (decomposed).
IR (KBr): 3300, 1703.2, 1630, 1590.4, 1455.7 cm^{-1}.
^1H NMR: (300 MHz, DMSO-d_6) δ: 1.82 (s, 6H, 2 x CH_3), 3.24-3.32 (s, 2H, 7-H or 10-H), 3.40-3.51 (s, 2H, 7-H or 10-H), 7.43 (s, 1H, Ar-H), 8.59 (s, 1H, 2-H), 10.31 (s, 1H, CHO).
HRMS: m/z [M^+] calcd. for $C_{16}H_{14}O_4$: 270.08921; found: 270.08719.
Yield: 73%.

5-Chloro-6-hydroxy-4-oxo-7,10-dihydro-4*H* benzo[*h*]chromen-3-carbaldehyde (**14**)

MP: 175-177ºC.
IR (KBr): 3401.9, 1703.7, 1695.1, 1586.4 cm^{-1}.
^1H NMR: (300 MHz, DMSO d_6) δ: 3.39-3.56 (m, 4H, 2 x CH_2, 7-H, 10-H), 5.94 (s, 2H, 8-H, 9-H), 6.31 (s, 1H, OH), 8.46 (s, 1H, 2H), 10.35 (s, 1H, CHO).
HRMS: m/z [M^+] calcd. for $C_{14}H_9O_4Cl$: 276.01894; found: 276.01575.

5-Chloro-6-hydroxy-8,9-dimethyl-4-oxo-7,10-dihydro-4*H*-benzo[*h*]cromen-3-carbaldehyde (**15**)

MP: 118-121ºC.
IR (KBr): 3300, 1701.7, 1651.3, 1587.1, 1466 cm^{-1}.
^1H NMR: (300 MHz, DMSO-d_6): δ 1.88 (s, 6H, 2 x CH_3), 3.31-3.44 (m, 4H, 2 x CH_2, 7-H, 10-H), 6.35 (s, 1H, OH), 8.5 (s, 1H, 2-H), 10.38 (s, 1H, CHO).
HRMS: m/z [M^+] calcd. for $C_{16}H_{13}O_4Cl$: 30.01894; found: 304.05225.
Yield: 73%.

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