ANTINEOPLASTIC ACTIVITY AND CYTOTOXICITY OF FLAVONES, ISOFLAVONES, AND FLAVANONES[1]

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ABSTRACT.—Several hundred flavonoid derivatives, natural and synthetic, which have been tested in the screening program of the National Cancer Institute, have been examined for indications of structure-activity relationships which might exist among these compounds. No such relationships are apparent. In spite of occasional activity these compounds do not warrant further detailed pursuit as anti-tumor agents.

Recent review articles (1) and research publications (2, 3, 4) in the phytochemical literature have referred to the cytotoxic activity of flavonoid compounds. The small number of these reports might suggest that few data are available in this area. In fact, during the last ten years there has been a considerable sustained activity in the testing of such compounds, prepared by many investigators, by the National Cancer Institute. It is our purpose in this paper to summarize hitherto unpublished test data, kindly made available by the N.C.I. Our primary aim is to make the data available in a convenient form, thereby providing a basis for studying such structure-activity relationships as may exist among these compounds.

Both naturally occurring and synthetic compounds were tested. The data are presented in Tables 1–3. The compounds are arranged in groups according to similarity of substituent types, so that differences in biological activity may be discerned between groups having different substituents, and within groups having differently arrayed substituents. No test data were available for isoflavanones.

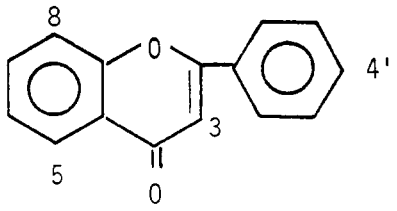
Although none of these compounds shows PS or LE activity,[2] it will be seen that twelve of the compounds exhibit *in vivo* activity against CA, LL, WA, and FV systems.[2] Insofar as activity in these systems represents antineoplastic activity, it can be seen that there is no obvious correlation for these compounds between KB activity (where data are available), and antineoplastic activity. To a degree, the types of data available reflect the screening procedures current when the compounds were submitted for testing; often, compounds for which only KB data are available were tested more recently than those which are quoted as inactive in a number of systems. Some compounds, e.g. the flavanones having doubly oxygenated substituents at poisition 3, show cytotoxicity *vs.* KB while displaying (where data are available) no activity against what would now be regarded as "second generation" screening systems.

Perusal of the data available, tabulated as above, has revealed to us no structure-activity correlation general enough to serve as a working hypothesis for a rationale of the activity of these compounds. It might be possible, however, to consider that the cytotoxicity *vs.* KB of the potential α-diketonic flavanones represents a

[1]Part VII in the Northeastern series of publications on Antitumor Plants. For Part VI see, P. W. Le Quesne, S. B. Levery, M. D. Menachery, T. F. Brennan, and R. F. Raffauf, *J. Chem. Soc. Perkin I*, in the press.

[2]See Abbreviations to the Tables.

TABLE 1. *Flavones.*



N.S.C. No.	Description	ED_{50} KB μg/mL	*In vivo* tumor systems
19028			CA−, LE−, SA−
69566	Oxime		LE−, SA−
127487	7-OS; 3',4'-MDO		LE−
93401	2'-F		LE−, LL−, SA−
93396	3'-F		LE−, LL−, SA−
93392	4'-F		LE−, LL−, SA−
22356	3'-OH	8.5	LE−
22357	4'-OH		CA−, LE−, SA−
73613	3'-NO_2	2.0	CA−, LE−, SA−
68222	3'-OSO_2Me	>100	
102045	3',4'-MDO		LE−
65033	2',3',4'-triMeO	13–100	CA−, LE−, LL−, SA−
19031	2',4'-diMeO; 5'-Br		CA−, SA−
66222	7,8,2'-triMeO	4–27	CA−, LE−, LL−, SA−
26744	6-OH	18	SA−, WA−; LL+
93394	6-F		LL−, SA−
94258	7-OH		LE−, LL−, SA−
123383	7-OH; 3',4'-diMeO		LE−
127572	7-OH; 3',4',5'-triMeO		LE−
123414	7-OH; 4'-MeO		LE−
93405	7-F	22	
93381	6,8-diF	15	LE−, SA−
5-Hydroxy-			
26745		20	LL−, SA−; WA+
123408	4'-MeO		LE−
407436	7-OH	13	LE−, WA−
83244	7,4'-diOH	7.4	LE−, 8P−, DL−
76061	7-OH; 4'-MeO	>100	CA−, LE−, PS−, SA−
128305	7-OH; 3',4'-diMeO		LE−
123410	7-OH; 3',4',5'-triMeO		LE−
115554	7-OH; 2',4',6'-triMeO		LE−
80687	7-MeO	49	LE−, 8P−, DL−
94547	7,4'-diMeO	45–81	LE−, LL−, PS−, SA−
195196	7,4'-diMeO; 3'-OH	19–29	
407303	7-OS; 4'-OH	>100	SA−
134765	7-Me; 3',4'-diMeO		LE−
127567	7-Me; 3',4',5'-triMeO		LE−
115553	8,2'-diAc; 3',5'-diOH		LE−
128304	7,8-diOH		LE−
122415	6-MeO; 7,4'-diOH	22	
106403	6,4-diMeO; 7-OH	3–25	LE−, PS−, SA−, WA−
122413	6,3',4'-triMeO; 7-OH	45	
122416	6-MeO; 7,3',4'-triOH	18–28	
106402	6,7,4'-triMeO; 3'-OH	2–4	
167408	7,4'-diOH; 8-CS; 3'-MeO		LE−
76988	6,7,8,4'-tetraOH	22	LL−, WA−
79323	6,7,8-triMeO; 4'-OH	0.7–100	LL−, SA−; FV+, WA+
79093	6,7,8,4'-tetraMeO	5–20	FV−, LE−, LL−, SA−, WA−
84889	6,7,8,3',4',5'-hexaMeO		
133101	3,4-diOH; 8-CS	25	

TABLE 1. *Continued.*

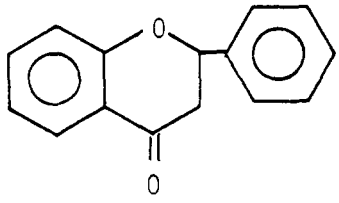
N.S.C. No.	Description	ED_{50} KB μg/mL	*In vivo* tumor systems
5-Methoxy-			
53907	7,4'-diMeO; 6-OH		CA−, LE−, SA−
53906	6,7-diMeO; 4'-OH	19	CA−, LE−, SA−
53908	6,7,4'-triMeO	27	CA−, LE−, SA−
66067	6,7,8,-triMeO; 4'-OAc	3–46	CA−, LL−, SA−
53909	4',6,7,8-tetraMeO	15	CA−, LE−, SA−, Pl−; PX+
68281	6,7,8-triMeO; 4'-EtO	30	LE−, SA−
71304	6,7,8-triMeO; 4'-PrO		
83281	6,7,8-triMeO; 4'-*i*PrO	>100	
83280	6,7,8-triMeO; 4'-AllylO	26	
76751	6,7,8,3',4'-pentaMeO	3–28	LL−, WA−
71301	6,7,8,2',4'-pentaMeO	15	LL−, SA−
71302	6,7,8,3',5'-pentaMeO	3–30	LL−, SA−; FV+
71300	6,7,8,2',5'-pentaMeO	4–12	SA−; FV+
102343	6,7,8-triMeO; 3',4'-MDO		LE−, WA−
83279	6,7,8,2',4',5'-hexaMeO	13	LL−; WA+
67580	6,7,8,3',4',5'-hexaMeO	0.5–7	CA−, LE−, LL−, SA−
67830	6,7,8,2',3',4',5',6'-octaMeO	4–30	LL−
5-Methyl-			
121858	7-OH; 4'-MeO		LE−
123384	7-OH; 3',4'-diMeO		LE−
123385	7-OH; 3',4',5'-triMeO		LE−
3-Hydroxy-			
57653		0.2–8	Bl−, CA−, LE−, LL−, PS−, SA−
58587	Zr-CPX		CA−, LE−, SA−
58586	Pb-CPX		CA−, LE−, SA−
58585	Zn-CPX		CA−, LE−, SA−
102030	4'-MeO		LE−
102048	4'-Cl		LE−, WA−
102042	4'-Me		LE−
78633	2',6'-diOH	>100	FV−, LE−, SA−
78635	2',6'-diMeO	1–16	FV−, LE−, PS−, SA−
102051	3',4'-diMeO		LE−
78634	3',4',6'-triMeO	5–10	FV−, LE−, SA−
46668	7-OH; 4'-Cl		LE−, SA−
407010	7,3',4'-triOH	>100	LE−, LL−, PS−, SA−
407331	7,3',4',5'-tetraOH	25	
102029	7,4'-diMeO		LE−
102057	7,3',4'-triMeO		LE−
19029	6-Me	2–35	Bl−, CA−, LE−, LL−, PS−, SA−
19024	6-Me; 4'-MeO	2–38	CA−, LE−, LL−, SA−
401510	7-MeO	26	
407229	5,7-diOH	>100	
407289	5,7,4'-triOH	26	
407294	5,7-diOH; 4'-MeO	20	
9219	5,7,3',4'-tetraOH	25	WA+
57655	Aluminum dvt. of 9219		CA−, LE−, SA−
19801	5,7,2',4'-tetraOH		CA−, LE−, PS−, SA−
58588	Zr dvt. if 9219		CA−, LE−, SA−
19802	5,3',4'-triOH; 7-MeO		CA−, LE−, SA−
115917	5,3',4'-triOH; 7-OS	28	
102049	5,7,3',4'-tetraMeO		LE−
407290	5,7,3',4',5'-pentaOH	15	Bl−, LE−
115916	5,6,7,3',4'-pentaOH	27	
3-Methoxy-			
31882	5,7-diOH; 4'-MeO		LE−, SA−; CA+
154016	5,7,3',4'-tetraOH	17	
168805	5,4'-diOH; 7,3'-diMeO		LE−
106970	5,7,3'-triOH; 4'-MeO	2	PS−
168804	5,7-diOH; 3',4'-diMeO		LE−

TABLE 1. *Continued.*

N.S.C. No.	Description	ED_{50} KB μg/ml	*In vivo* tumor systems
61837	5-OH; 7,3',4'-triMeO	41	CA−, LE−, SA−
408169	Co dvt. of 5-OH; 6,3',4'-triMeO	34	
408170	Sn dvt. of same	50	
408171	Zn dvt. of same	37	
168806	5-OH; 3',4'-diMeO; 7-(3''-Me-2-butenyl)		LE−
106969	5,7,3'-triOH; 6,4'-diMeO	0.4–3	PS−
115922	5,7,3',4'-tetraMeO	25	
31884	5,7-diAcO; 4'-MeO		LE−, SA−; CA+
3-Glycosyloxy-(Various sugars)			
115918	5,7,3',4'-tetraOH	26	
167410	6,8,3',4'-tetraOH		LE−
9222	7-OS; 4'-OH		LE−, CA−, PS−, SA−
9220	5,7,3',4'-tetraOH	>100	CA−, LE−, LL−, SA−, DL−; WA+
19804	7-MeO; 3',4',5-triOH	8.5	CA−, LE−, LL−, SA−
408168	Cd dvt. of 115918	8.5	
407304	5,7,3',4'-tetraOH	>100	CA−, LE−, LL−, PS−, SA−, DL−, WA−
9221	same as 407304		
134057	6,7-diMeO; 4',5-diOH		LE−
19803	5,6,3',4',5'-pentaOH	8.3	CA−, LE−, LL−, SA−
Miscellaneous			
61836	3,7,3',4'-tetraAcO; 5-OH	22	CA−, LE−, SA−
65031	3-NH_2	>100	CA−, LE−, SA−
67942	3-NHAc	>100	CA−, LE−, SA−
69569	3-$NHSO_2Me$	10	SA−
71096	3-NH_2; 6-Cl	>100	FV−, LE−, SA−
74877	3-Cl; 2'-OH	22	
97706	3,6-diCl; 2'-*i*PrO; 5'-Me	60	
74876	3,6-diCl	>100	
74931	3,6-diCl; 2',4',6'-triMe	>100	SA+
74899	3,6-diCl; 2'-*i*PrO; 4'-Me	22	
74882	3-Cl; 6-Me	>100	
80479	3-Me; 7-MeO	43	LE−, SA−; FV+
114649	3-Me; 8-$COOCH_2CH_2$-piperidyl(HCl)	>100	LE−
114650	3-Me; 7-MeO; 8-CH_2NMe_2(HCl)	22	LE−
169869	free base of 114650		Bl−, LE−
67938	3-NH_2, N,N-bis-methyl-sulfonamide	>100	CA−, LE−, SA−
115919	3,5,7,3',4'-pentaAcO		LE−

point of departure for further analogue synthesis. It is also possible that some of the compounds may inhibit mitotic spindle formation, owing to their possession of contiguous alkoxy-groups deviating from strict coplanarity (5). However, the data suggest that a flavonoid compound having activity *vs.* KB of 1–30 μg/ml is unlikely to be of further interest as an antineoplastic compound.

TABLE 2. *Flavanones.*

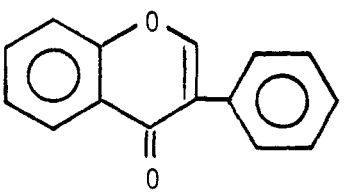


N.S.C. No.	Description	ED_{50} KB $\mu g/mL$	*In vivo* tumor systems
Chloro Derivatives			
54892	3-Cl		CA−, SA−
39251	6-Cl	1–8.5	CA−, LE−, SA−
50188	2'-Cl		CA−, LE−, SA−
50189	3'-Cl		LE−, SA−; CA+
50190	4'-Cl		CA−, LE−, SA−
39249	6,4'-diCl		CA−, LE−, SA−
39250	6,2'-diCl		CA−, LE−, SA−
39248	6,2',4'-triCl		CA−, LE−, SA−, DL−
54882	2,3-diCl		CA−, LE−, SA−
54872	2,3,6,4'-tetraCl		SA−
2-Methoxy-			
102050	3-(OH)(MeO); 6-MeO		LE−, WA−
102055	3-diOH	19	
102056	3-(OH)(MeO); 3',4'-diMeO		LE−
102035	3-diOH; 4'-MeO		LE−, WA−
102036	3-(OH)(MeO); 7,4'-diMeO		LE−, WA−
102040	3-(OH)(MeO); 4'-Cl		LE−
102041	3-(OH)(MeO); 4'-Me		LE−, WA−
102043	3-diOH; 7-MeO	20	
102044	3-(OH)(MeO); 7,4',4'-triMeO		LE−
102047	3-diOH; 7,4'-diMeO	2.8	
95848	3-(OH)(MeO)	34	LE−
102032	3-(OH)(CH_2NO_2)		LE−
3-Hydroxy-			
59264	7,3',4'-triOH		CA−, LE−, SA−, LL−
59266	7,3',4',5'-tetraOH	23	CA−, LE−, SA−
2801	5,7,3',4'-tetraOH	40–100	CA−, SA−, WA−
36398	6,7,3',4'-tetraOH		EA−, LE−, PS−, SA−
3-Methoxy-			
135827	5,4'-diOH; 6,7,3'-triMeO		LE−
135828	5,3'-OS; 6,7,4'-triMeO		LE−
5-Hydroxy-			
57654	7,3'-diOH; 4'-MeO		CA−, LE−, SA−
61835	7,3'-diOH; 4'-MeO; Pb CPX	42	CA−, LE−, SA−
170987	7-OS; 5,2',5'-triOH; 4'-MeO	>100	LE−
180246	6-Me; 7,4'-diOH	57	LE−
93745	7-OS; 4'-OH; *i*PrOH CPX	>100	8P−, LE−, SA−
5548	7-OS; 4'-OH		DL−; WA+
11855	7,4'-diOH		LE−, SA−
31048	7-OS; 3'-OH; 4'-MeO		CA−, LE−, SA−
34875	7,4'-diOH		CA−, LE−, LL−, SA−
43318	7-OH		CA−, LE−, SA−
44184	7-OS; 3'-OH; 4'-MeO		CA−, LE−, SA−
135064	4'-OH; 7-OS		SA−, WA−
407228	7-MeO; 4'-OH	13	
5-Methoxy-			
55274	6,7-diMeO; 4'-OH		CA−, LE−, SA−
56293	6,4'-diOH; 7-MeO		CA−, LE−, SA−
58249	6-OH; 7,4'-diMeO		CA−, LE−, SA−
65887	6,7,8-triMeO; 4'-OH	26	CA−, LE−, SA−
51170	6,7,4'-triMeO		CA−, LE−, SA−

TABLE 2. *Continued.*

N.S.C. No.	Description	ED_{50} KB μg/mL	*In vivo* tumor systems
Miscellaneous			
407308	5-OS; 7-MeO; 4'-OH	>100	SA−
5884	6-Me; 8-MeO	26	CA−, LE−, SA−
16721	3'-MeO; 4'-OH		LE−, SA−
37458	5,7,3'-triAcO; 4'-MeO		CA−, LE−, SA−
39252	6,4'-diMeO		CA−, LE−, SA−
102034	3=O		LE−
65028	3=NOH	35	CA−, LE−, SA−
102052	2-EtO; 3-(OH)(EtO)		LE−, WA−
50184	6-MeO		CA−, LE−; SA+
50185	3',4'-diMeO		CA−, LE−, SA−
50186	6,2'-diMeO	24	CA−, LE−, SA−
50187	4'-MeO		CA−, LE−, SA−
67943	3-NH_2(HCl)	3–5	CA−, LE−, SA−
69568	3-$NHSO_2Me$	10	LE−, SA−
71094	3-NH_2(HCl); 4'-MeO	>100	SA−
50393			CA−, FV−, LE−, SA−

TABLE 3. *Isoflavones.*



N.S.C. No.	Description	ED_{50} KB μg/mL	*In vivo* tumor systems
5-Hydroxy-			
36586	7,4'-diOH	6.7	CA−, LE−, SA−
123538	7-OH; 4'-MeO		LE−
5-Methoxy-			
64963	6,7,4'-triMeO	34	SA−; FV+
74436	6,4'-diOH; 7-MeO		FV−
77466	6,7,8,4'-tetraMeO		FV+
2-Methyl-			
61625	7-OH; 2'-Br	66	CA−, LE−, SA−
108339	7-AcO		LE−
108340	7-OH		LE−, WA−
Miscellaneous			
74435	5,7-diMe; 6,4'-diEtO		FV−
88178	2-COOEt; 5,7-diOH; 4'-MeO	21	LE−, SA−; LL+
93360	7-OH; 4'-MeO		LE−
93361	7-AcO; 2-Me; 4'-MeO		
93362	7-PrO; 2-Et; 4'-MeO		
100796	7-OH; 3',4'-MDO		LE−, WA−
135405			LE−

Abbreviations to the Tables

Compound descriptions
Ac=Acetyl
CPX=Complex

MDO = Methylenedioxy
S = Sugar residue
Other abbreviations have their usual significance.

Tumor systems
Bl = B16 Melanocarcinoma
CA = Adenocarcinoma 755
DL = Dunning leukemia
FV = Friend virus leukemia
LE = L-1210 lymphoid leukemia
LL = Lewis lung carcinoma
PS = P-388 Lymphocytic leukemia
PX = Plasmacytoma No. 1/cytoxan NSC 38280
Pl = Plasmacytoma No. 1
8P = P-1798 Lymphosarcoma
SA = Sarcoma 180
WA = Walker carcinosarcoma 256 (s.c.)

NOTE: The absence of specific data in the KB test system indicates that such data are not available for that system. All compounds rated positive in the *in vivo* systems mentioned had T/C <140% with the exception of the following: 71302 (179% in one test), 83279 (160, 147%), 9219 (230, 180%), 31882 (302%), 31884 (164%), 80479 (162%), 50189 (160%), 5548 (168, 157%), 64693 (332, 229%).

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