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Activity of 4-Arylchromene Derivatives as Apoptosis Inductors and Potential Anticancer Drugs

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Abstract—The correlation models describing the quantitative structure-activity relationship have been developed for a series of the apoptosis-inducing 4-aryl-4*H*-chromenes and 4-aryl-2*H*-chromenes taking advantage of the fragment descriptors of the molecular structure. The set of models have been picked up, containing no more than 28 parameters and having the standard deviation of the predicted apoptosis-inducing activity of below 0.3 logarithmic units. Basing of the frequency of the descriptors in the 438 picked models, the structural elements crucial for the pro-apoptosis activity have been detected. The structural modifications have been suggested to enhance the studied activity of the compounds.

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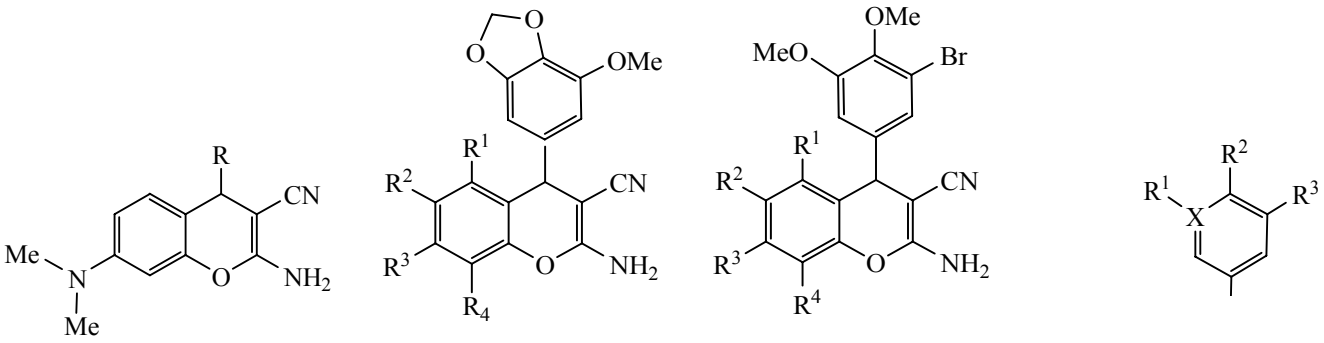
It is known that the abnormality of the apoptosis (programmed cell death) mechanisms may lead to the unlimited mitosis and thus induce the cancer and related diseases [1]. Therefore, the action of most modern anticancer drugs directs at the apoptosis normalization; and the drugs are usually the apoptosis inductors interacting with various targets. Recently, the compounds targeting at tubulin or the tubulin-based microtubules (Taxol, Vinblastine, etc) have been considered the most efficient antitumor agents [2–4]. However, the multiple drug resistance often developing in the tumor cells stimulates the search for new compounds, capable of binding to tubulin but aiming at other targets as well. 4-Arylchromenes are among such novel apoptosis inductors; they inhibit tubulin polymerization as well as destroy the capillary network of the tumor [5, 6].

In this work, we took advantage of the QSAR (quantitative structure-activity relationship) approach to predict the apoptosis-inductive activity of the compounds and to elucidate the crucial structural fragments responsible for the biological activity. In total, 15 sets (**I–XV**) of 4-aryl-4*H*-chromene and 4-aryl-2*H*-chromene derivatives were studied, their structures shown in Schemes 1–4. The experimental values of apoptosis-inductive activity of the compounds were extracted from the literature [4–9] (Table 1). The activity was determined as the activity of caspases (EC_{50}) cleaving the fluorescent substrate in the culture of cells pre-treated with the tested inductor [10]. The logarithms of experimental activity were used in the analysis for convenience.

In order to develop the QSAR equation, the compounds molecular structure was represented as a set of fragments, each of them being assigned to a non-hydrogen atom or group of atoms. Molecular descriptors were in turn numbers of the corresponding fragments or of pairs of fragments separated by certain number of chemical bonds [11–13].

The diversity of the analyzed chemical structures was reduced to 18 types of the fragments. The fragment type was determined by the nature of the corresponding atom and its chemical surrounding. For instance, oxygen atom corresponded to five types of the fragments: (1) oxygen atom in an alkoxy group (O), (2) oxygen atom in chromene backbone (O1), (3) oxygen atom in carbonyl group (O2), (4) oxygen atom in dioxymethylene group (OO), and (5) oxygen atom in hydroxyl group (OH). It was assumed that the atoms of various fragments differed in the interaction with the surrounding, and the set of the fragments determined the possible intramolecular interactions.

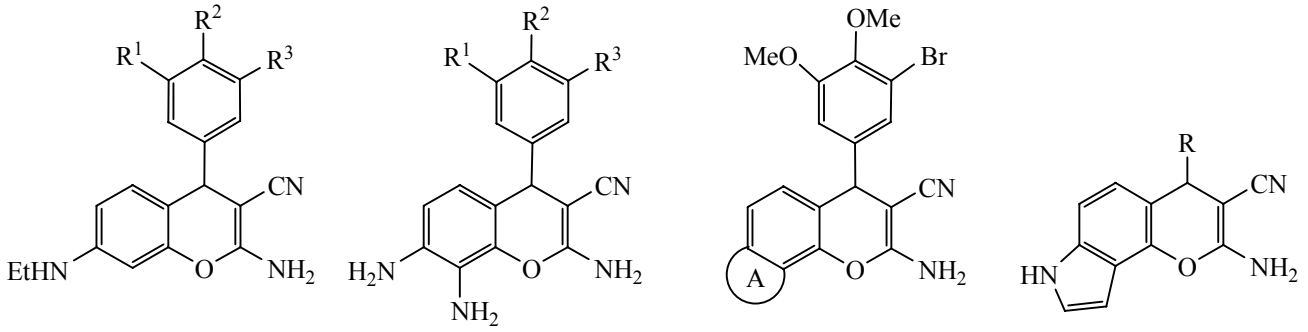
Scheme 1.



I (1–39) **II** (40–52) **III** (53–66) **IV** (67–75)

I, R = phenyl (1), 3-methylphenyl (2), 3-hydroxyphenyl (3), 2-methoxyphenyl (4), 3-methoxyphenyl (5), 4-methoxyphenyl (6), 3-trifluoromethoxyphenyl (7), 3-benzyloxyphenyl (8), 3-dodecyloxyphenyl (9), 3-cyanophenyl (10), 3-carboxyphenyl (11), 3-fluorophenyl (12), 3-chlorophenyl (13), 3-bromophenyl (14), 3,5-dimethoxyphenyl (15), 4,5-dimethoxyphenyl (16), 5,6-dimethoxyphenyl (17), 3-chloro-5-methoxyphenyl (18), 3-bromo-5-methoxyphenyl (19), 3,4,5-trymethoxyphenyl (20), 3,4,6-trimethoxyphenyl (21), 4,5,6-trimethoxyphenyl (22), 3-chloro-4,5-dimethoxyphenyl (23), 2-bromo-4,5-dimethoxyphenyl (24), 3-iodo-4,5-dimethoxyphenyl (25), 3-bromo-4-hydroxy-5-methoxyphenyl (26), cyclohexyl (27), 4-(3-bromo-4,5-dimethoxyphenyl)-4-methyl (28), 3-bromo-4,5-methylenedioxyphenyl (29), pyridin-3-yl (30), pyridin-4-yl (31), pyridin-2-yl (32), 5-methylpyridin-3-yl (33), 5-bromopyridin-3-yl (34), 3-methylpyridin-2-yl (35), 2-phenylethyl (36), quinolin-3-yl (37), 2-sulfanylphenyl (38), 4-bromo-2-sulfanylphenyl (39). **II**, $R^3 = NH_2$ (40), NHEt (41), NMe_2 (42), NEt_2 (43), NHPh (44), morpholin-4-yl (45), OMe (46), OH (47); $R^1 = R^3 = OMe$ (48); $R^2 = R^3 = OMe$ (49); $R^2 = Me$, $R^3 = NHEt$ (50); $R^3 = NMe_2$, $R^4 = Me$ (51); R^3, $R^4 = OCH_2O$ (52).[1] **III**, $R^3 = NH_2$ (53), NMe_2 (54), NHEt (55), OMe (56), OEt (57), OH (58), Br (59), Cl (60); $R^3 = R^4 = NH_2$ (61), Me (62); $R^3 = NH_2$, R^4 =Me (63);[1] $R^3 = OH$, $R^4 = NH_2$ (64); $R^3 = R^4 = OH$ (65), $R^3 = NMe_2$ and H instead of 2-NH_2 (66). **IV**, X = C, $R^3 = R^2 = R^1 = OMe$ (67), $R^1 = R^3 = OMe$ (68), $R^3 = OMe$ (69), Br (70), Cl (71), NO_2 (72), H (73); X = N, $R^3 = R^2 = R^1 = H$ (74); $R^3 = OMe$ (75).[1]

Scheme 2.

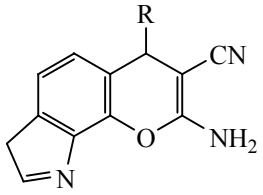


V (76–80) **VI** (81–87) **VII** (88–97) **VIII** (98–108)

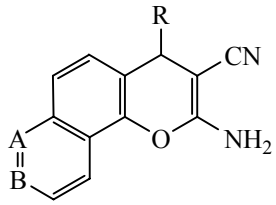
V, $R^3 = R^2 = R^1$ =OMe (76); $R^1 = R^3 = OMe$, $R^2 = H$ (77); $R^3 = OMe$, $R^1 = R^2 = H$ (78); $R^3 = Cl$, $R^1 = R^2 = H$ (79); $R^3 = NO_2$, $R^1 = R^2 = H$ (80). **VI**, $R^3 = Cl$, $R^1 = R^2 = OMe$ (81); $R^3 = I$, $R^1 = R^2 = OMe$ (82); $R^3 = Br$, $R^2 = OH$, $R^1 = OMe$ (83); $R^1 = R^3 = OMe$, $R^2 = H$ (84); $R^3 = CN$, $R^1 = R^2 = H$ (85); $R^3 = Br$, $R^1 = R^2 = H$ (86); R^3 =NO_2, $R^1 = R^2 = H$ (87). **VII**, A = benzo (88), 2,3-(N^7)-pyrido (89), 3,4-(N^8)-pyrido (90), 3,2-(N^{10})-pyrido (91), tetrahydrobenzo (92), N^7-8-methylpyrrolo (93); pyrrole-derivatives with Me (94), CH_2OH (95), and Et (96) at N^7, N^9-methylpyrrolo (97). **VIII**, R = 3-bromo-4,5-dimethoxyphenyl (98), 3-bromo-4-hydroxy-5-methoxyphenyl (99), 3,4,5-trimethoxyphenyl (100), 3,5-dimethoxyphenyl (101), 3-methoxyphenyl (102), phenyl (103), 3-nitrophenyl (104), 3-cyanophenyl (105), pyridin-3-yl (106), 5-methylpyridin-3-yl (107), 5-methoxypyridin-3-yl (108).

[1] When no substituent is stated, H is presumed.

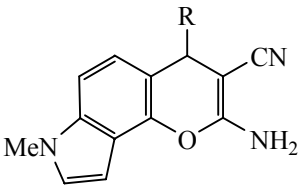
Scheme 3.



IX (109–114)



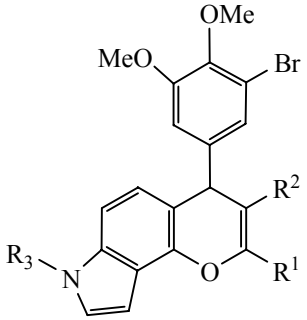
X (115–121)



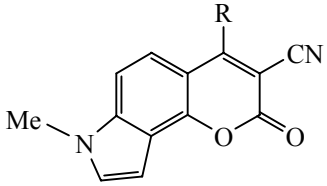
XI (122–127)

IX, R = 3-bromo-4,5-dimethoxyphenyl (109), 3-bromo-4-hydroxy-5-methoxyphenyl (110), 3,4,5-trimethoxyphenyl (111), 3,5-dimethoxyphenyl (112), 3-methoxyphenyl (113), 3-cyanophenyl (114). **X**, R = 3,4,5-trimethoxyphenyl, A = B = C (115); R = 3-iodo-4,5-dimethoxyphenyl, A = B = C (116); R = 3,4,5-trimethoxyphenyl, A = N, B = C (117); R = 3,4,5-trimethoxyphenyl, A = C, B = N (118); R = 3-iodo-4,5-dimethoxyphenyl, A = C, B = N (119); R = 5-bromo-3-pyridinyl, A = C, B = N (120); R = 5-methylpyridin-3-yl, A = C, B = N (121). **XI**, R = 3,4,5-trimethoxyphenyl (122), 3,5-dimethoxyphenyl (123), 3-methoxyphenyl (124), 3-methoxy-4,5-methyldioxyphenyl (125), 5-methylpyridin-3-yl (126), 5-methoxypyridin-3-yl (127).

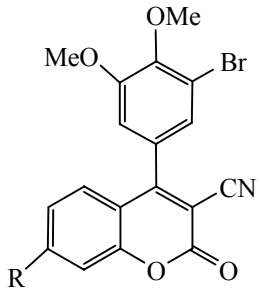
Scheme 4.



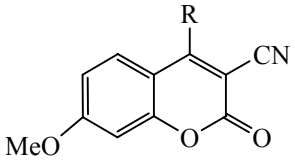
XII (128–132)



XIII (133–139)



XIV (140–143)



XV (144–145)

XII, $R^1 = R^3$ =H, R^2 = CN (128); R^1 = H, R^2 = CN, R^3 = Me (129); R^1 = H, R^2 = CN, R^3 = Et (130); $R^1 = NH_2$, $R^2 = CO_2Me$, R^3 = H (131); $R^1 = NH_2$, $R^2 = CO_2Et$, R^3 = H (132). **XIII**, R = 3-bromo-4,5-dimethoxyphenyl (133), 3,5-dimethoxyphenyl (134), 3-methoxyphenyl (135), 3-nitrophenyl (136), 3-bromophenyl (137), 3-methoxy-4,5-methylenedioxyphenyl (138), 5-methoxypyridin-3-yl (139). **XIV**, R = OMe (140), NH_2 (141), NMe_2 (142), Cl (143). **XV**, R = 3,5-dimethoxyphenyl (144), and 3-methoxyphenyl (145).

Table 1. Apoptosis-inductive activity of 4-arylchromene derivatives [4–9]

Run no.[a]	Experiment[b]		Calculation[c]	Run no.[a]	Experiment[b]		Calculation[c]
	EC_{50}, μmol/L[d]	log (EC_{50})	log (EC_{50})		EC_{50}, μmol/L[d]	log (EC_{50})	log (EC_{50})
Set I [5]				Set I [5]			
1	0.118	–0.93	–0.83	11	10.000	1.00	0.78
2	0.134	–0.87	–1.43	12	0.081	–1.09	–0.83
3	0.272	–0.57	–0.83	13	0.112	–0.95	–0.83
4	0.280	–0.55	0.25	14	0.064	–1.19	–1.27
5	0.065	–1.19	–1.31	15	0.023	–1.64	–1.80
6	1.600	0.20	–0.55	16	0.253	–0.60	–1.04
7	0.450	–0.35	–0.35	17	1.020	0.01	–0.24
8	2.520	0.40	0.38	18	0.076	–1.12	–1.31
9	10.000	1.00	1.13	19	0.031	–1.51	–1.75
10	0.063	–1.20	–0.83	20	0.045	–1.35	–1.52

Table 1. (Contd.)

Run no.[a]	Experiment[b]		Calculation[c]	Run no.[a]	Experiment[b]		Calculation[c]
	EC_{50}, μmol/L[d]	log (EC_{50})	log (EC_{50})		EC_{50}, μmol/L[d]	log (EC_{50})	log (EC_{50})
	Set I [5]				Set III [6]		
21	1.770	0.25	0.04	64	0.061	–1.21	–1.16
22	3.160	0.50	0.04	65	1.700	0.23	0.45
23	0.018	–1.74	–1.76	66	0.065	–1.19	–1.04
24	2.640	0.42	0.36		Set IV [6]		
25	0.018	–1.74	–1.43	67	0.026	–1.59	–1.43
26	0.041	–1.39	–1.75	68	0.015	–1.82	–1.70
27	0.290	–0.54	–0.60	69	0.052	–1.28	–1.22
28	7.300	0.86	0.66	70	0.052	–1.28	–1.18
29	0.245	–0.61	–0.60	71	0.080	–1.10	–0.74
30	0.068	–1.17	–1.07	72	0.089	–1.05	–0.74
31	0.381	–0.42	–0.25	73	0.360	–0.44	–0.74
32	0.465	–0.33	–0.43	74	0.170	–0.77	–0.97
33	0.011	–1.96	–1.66	75	0.047	–1.33	–1.46
34	0.033	–1.48	–1.51		Set V [6]		
35	0.244	–0.61	–0.73	76	0.049	–1.31	–1.05
36	0.430	–0.37	–0.11	77	0.055	–1.26	–1.13
37	1.820	0.26	0.28	78	0.110	–0.96	–1.03
38	0.200	–0.70	–0.65	79	0.120	–0.92	–0.92
39	0.150	–0.82	–1.09	80	0.110	–0.96	–0.92
	Set II [6]				Set VI [6]		
40	1.200	0.08	–0.10	81	0.024	–1.62	–1.60
41	0.330	–0.48	–0.36	82	0.049	–1.31	–1.28
42	0.073	–1.14	–0.65	83	0.023	–1.64	–1.21
43	0.480	–0.32	–0.62	84	0.092	–1.04	–0.88
44	10.000	1.00	1.16	85	0.390	–0.41	–0.65
45	10.000	1.00	0.87	86	0.150	–0.82	–1.09
46	0.160	–0.80	–1.22	87	0.390	–0.41	–0.65
47	5.800	0.76	0.76		Set VII [4, 7]		
48	10.000	1.00	1.10	88	0.073	–1.14	–1.60
49	10.000	1.00	1.04	89	0.065	–1.19	–1.11
50	1.100	0.04	–0.18	90	0.061	–1.21	–1.20
51	0.310	–0.51	–0.47	91	0.029	–1.54	–1.11
52	0.210	–0.68	–0.76	92	0.190	–0.72	–0.61
	Set III [6]			93	0.030	–1.52	–1.63
53	0.033	–1.48	–1.32	94	0.002	–2.70	–2.63
54	0.019	–1.72	–1.48	95	0.003	–2.52	–2.63
55	0.014	–1.85	–1.39	96	0.039	–1.41	–1.61
56	0.017	–1.77	–1.39	97	0.150	–0.82	–1.17
57	0.064	–1.19	–1.37		Set VIII [4]		
58	0.130	–0.89	–1.16	98	0.005	–2.30	–2.25
59	0.140	–0.85	–1.32	99	0.013	–1.89	–2.04
60	0.160	–0.80	–0.20	100	0.030	–1.52	–1.72
61	0.034	–1.47	–1.32	101	0.030	–1.52	–1.51
62	0.042	–1.38	–1.17	102	0.052	–1.28	–1.30
63	0.026	–1.59	–1.81	103	0.270	–0.57	–1.09

Table 1. (Contd.)

Run no.[a]	Experiment[b]		Calculation[c]	Run no.[a]	Experiment[b]		Calculation[c]
	EC_{50}, μmol/L[d]	log (EC_{50})	log (EC_{50})		EC_{50}, μmol/L[d]	log (EC_{50})	log (EC_{50})
Set VIII [4]				Set XI [7]			
104	0.068	–1.17	–1.09	126	0.003	–2.52	–2.31
105	0.043	–1.37	–1.09	127	0.003	–2.52	–2.10
106	0.110	–0.96	–1.32	Set XII [8]			
107	0.013	–1.89	–1.92	128	0.047	–1.33	–1.37
108	0.016	–1.80	–1.53	129	0.029	–1.54	–1.75
Set IX [4]				130	0.070	–1.15	–0.73
109	0.016	–1.80	–1.51	131	1.400	0.15	0.00
110	0.035	–1.46	–1.39	132	3.200	0.51	0.55
111	0.072	–1.14	–1.37	Set XIII [9]			
112	0.031	–1.51	–1.25	133	0.013	–1.89	–1.75
113	0.088	–1.06	–0.95	134	0.024	–1.62	–1.82
114	0.120	–0.92	–0.65	135	0.043	–1.37	–1.43
Set X [4]				136	0.043	–1.37	–1.04
115	0.027	–1.57	–1.46	137	0.024	–1.62	–1.34
116	0.064	–1.19	–1.56	138	0.027	–1.57	–1.43
117	0.160	–0.80	–0.88	139	0.019	–1.72	–1.66
118	0.120	–0.92	–1.07	Set XIV [9]			
119	0.064	–1.19	–1.16	140	0.042	–1.38	–0.94
120	0.120	–0.92	–0.93	141	0.820	–0.09	–0.24
121	0.230	–0.64	–1.08	142	0.280	–0.55	–0.40
Set XI [7]				143	6.900	0.84	0.24
122	0.004	–2.40	–2.27	Set XV [9]			
123	0.005	–2.30	–2.26	144	0.017	–1.77	–1.70
124	0.006	–2.22	–1.87	145	0.053	–1.28	–1.22
125	0.017	–1.77	–1.87				

[a] The number corresponds to the compound number in the scheme. [b] Experimental values were taken from [4–9]. [c] Activity values were calculated using the best model equation. Correlation coefficient $r = 0.9038$, standard deviation $s = 0.28$. [d] EC_{50} stands for concentration corresponding to 50% decomposition of the fluorescent substrate caspase 3 in the T47D cells previously treated with the corresponding derivative [10].

All the fragments used in the correlation equation are listed in Table 2.

Some of the atoms present in all the studied compounds were assigned to the "silent" fragment Q, its contribution being not directly introduced into the correlation equation, however, being reflected indirectly in the contributions from other fragments and in the free term. In particular, Q fragment was assigned to carbon atoms of chromene backbone, carbonyl carbon, carbon atom of dioxymethylene group, nitrogen atom of cyano group, and oxygen atoms of nitro group. The Q fragment approach could be considered assigning of several atom types to the same fragment, in order to simplify the correlation equation [12, 14].

The correlation equation (1) included the sum of single-fragment contributions depending on the fragment types and number, and the sum of pairwise contributions determined by the pairs of fragments separated by a certain number of chemical bonds [14].

$$P \approx \sum_t n_t P_t + \sum_{t,m,r} k_{t,m-r} P_{t,m-r} + \text{const}, \quad (1)$$

where n_t, number of fragments of type t and $k_{t,m-r}$, number of pairs of fragments t and m with the corresponding atoms separated by r chemical bonds.

Table 2. Fragments types and their designations

Atoms and groups	Fragment type
Aliphatic carbon	C
Aromatic carbon	C_{ar}
Cyano group	CN
Alkoxy group oxygen	O
Chromene backbone oxygen	O1
Carbonyl oxygen	O2
Dioxymethylene oxygen	OO
Hydroxyl group	OH
Amino group	N
Pyrrole nitrogen	N1
Pyridine nitrogen	N2
Nitro group nitrogen	NO
Fluorine	F
Chlorine	Cl
Bromine	Br
Iodine	I
Sulfur	S
"Silent" atom	Q

The contributions per fragment P_t, and $P_{t,m-r}$ were determined as parameters of the correlation equation by linear regression of the experimentally measured activities. In the case of the studied set of structures, the longest chain of chemical bonds was of 23. The above-mentioned 18 fragment types gave therefore 3951 descriptors in total. After the descriptors with zero values for all the structures were excluded along with the highly correlated ones (correlation coefficient of above 0.98, meaning that the descriptors added the same information to the model), 245 meaningful descriptors were left, their contributions P_t and $P_{t,m-r}$ forming the set of parameters to be included into the correlation model. In order to use the regression methods, the parameters were further screened taking advantage of the procedure described elsewhere [14]. The models with no more than 28 parameters and the standard deviation of the activity estimation of below 0.3 logarithmic units (about 10% of the activity range) were picked up into the promising models collection.

The so formed collection included 438 models. From the frequency of repetition in those models, 20 parameters were selected that were included into more than 50% of the models (Table 3). As suggested, the descriptors corresponding to those parameters reflected the crucial structural fragments determining the desired type of biological activity. If a certain descriptor gave the positive contribution into the sum (1), it was negatively correlated with the apoptosis-inductive activity; vice versa, the descriptors with negative contribution were likely desirable in the compound to enhance its activity. In the best correlation model, of 28 descriptors included, 12 ones were present in more than 50% of the picked up promising models. They were nos. 2, 3, 5, 7, 10, 11, 14, 15, 21, 22, 24, and 27 in Table 4.

Table 3. Repetition frequency of the selected descriptors in the picked out model

Descriptor	Number of compounds with nonzero descriptor	Repetition (models number)
Br,N-7	42	438
CN1-2	4	438
Br,C-9	5	437
I	4	437
F,C-1	1	427
OH,C_{ar}-5	2	426
O,Cl-3	2	379
O,C-10	64	374
O,O-8	3	368
C,C-7	5	364
C_{ar},C_{ar}-4	2	359
Br,C-8	5	334
N2,C-9	10	332
CN,O-5	5	310
C,C-8	3	298
O,C-2	4	283
N2,C-3	4	275
N1	42	250
C,C_{ar}-10	113	244
N,C_{ar}-7	132	238

The descriptors corresponding to halogen atoms revealed the contributions of both signs. In particular, the descriptor 7 in Table 4 showed that introduction of iodine could increase the compound activity. Indeed, compounds 25, 82, 116, and 119 (Table 1) bearing iodine atom in the *meta*-position of 4-aryl substituent

Table 4. Coefficients of the best model and their repetition frequency

Run no.	Descriptor	Coefficient	Number of compounds with non-zero descriptor	Repetition frequency (% of the total number of models)
1	Br,OH-9	–1.36±0.68	3	13
2	Br, C-8	–1.26±0.43	5	76
3	Cl, O-3	–0.72±0.41	2	87
4	C,N-6	–0.48±0.29	7	2
5	Br,N-7	–0.44±0.12	42	100
6	N,N1-6	–0.44±0.15	25	15
7	I	–0.40±0.30	4	100
8	Br, N1-9	–0.30±0.21	15	8
9	C,C_{ar}-2	–0.30±0.08	115	24
10	C,O-10	–0.18±0.06	64	85
11	C,C_{ar}-10	–0.09±0.05	113	56
12	C,C_{ar}-5	0.18±0.09	107	5
13	C,O-11	0.20±0.08	36	13
14	C_{ar},C_{ar}-4	0.31±0.09	2	82
15	C,F-1	0.32±0.19	1	97
16	N2	0.40±0.16	23	3
17	C,O-9	0.60±0.13	12	21
18	C_{ar},O1-6	0.63±0.19	146	7
19	N,O2-6	0.64±0.41	2	17
20	N,OO-9	0.67±0.21	9	27
21	Br,C-9	0.70±0.25	5	100
22	C,N1-2	1.0±0.35	4	100
23	C_{ar},O-5	1.07±0.19	5	23
24	Cl,O1-4	1.12±0.42	2	49
25	C,O-13	1.49±0.51	2	13
26	N,OH-6	1.52±0.57	4	21
27	C_{ar},OH-5	1.61±0.44	2	97
28	C,CN-3	2.73±0.58	3	17

were fairly active. On the other hand, descriptor 15 (Table 4) showed that the CF_3 should decrease the compound activity, that was confirmed by the low activity of compound 7.

The two-fragment descriptors including chlorine atom revealed negative (no. 3 in Table 4) as well as positive (no. 24 in Table 4) contributions. The Cl,O-3 descriptor coefficient was negative in the case of

compounds 23 and 81 (Table 1); in those compounds, chlorine was included in 4-(3-chloro-4,5-dimethoxyphenyl) moiety, and that structural fragment favored the high activity of the compounds. The Cl,O1-4 descriptor with positive coefficient corresponded to chlorine atom separated from chromene backbone oxygen by four bonds. Such fragments were found in two compounds, 60 and 143. Such chlorine location was considered unfavorable, as compound 60 showed moderate activity, and compound 143 was of low activity.

Bromine atom was included into paired descriptors with negative coefficients (nos. 1, 2, 5, and 8, in Table 4). Such descriptors were nonzero in the compounds with bromine atom located in the *meta*-position of the 4-aryl substituent. Thus, 3-bromo-4,5-dimethoxyphenyl was considered a fragment enhancing the compounds activity. The Br,C-9 descriptor with the positive coefficient (descriptor 21 in Table 4) reflected some special situations: (1) bromine atom located in the *ortho*-position of the 4-aryl substituent (compound 24, Table 1); (2) aliphatic carbons located in positions 7 and 8 of the chromene backbone (methyl groups in compound 62 and methylene groups in compound 92); (3) methyl group located at N^9 (compound 97); and (4) cyano group substituted with carboxymethyl one (compound 132). It should be noted that the listed compounds were of variable activity, as their other fragments corresponded to descriptors with coefficients of the both signs, either compensating each other or enhancing the total score.

Similarly, hydroxyl group in position 7 of chromene corresponded to the Br,OH-9 descriptor with large negative coefficient (no. 1 in Table 4) and to the N,OH-6 and C_{ar},OH-5 descriptors with large positive coefficients (nos. 26 and 27 in Table 4). The relatively high activity of compounds 58 and 64 could be explained by the favorable effect of 3-bromo-4,5-dimethoxyphenyl in position 4. In the low-active compound 47, such substituent was absent, and it was to be seen that the presence of hydroxyl group in position 7 suppressed the compound activity.

Positive coefficient of the C_{ar},C_{ar}-4 descriptor (no. 14 in Table 4) showed that the overloading of the substituent in position 4 of chromene backbone with aromatic groups could be a reason of low activity of compounds 8 and 37.

The pyridine fragment effect could not be revealed straightforwardly. The N2 descriptor (no. 16 in Table 4, coefficient of 0.40) gave positive contribution to the correlation equation; that could mean the unfavorable effect of the pyrimidine fragment. However, the C_{ar},O1-6 descriptor (no. 18 in Table 4, positive coefficient of 0.63) was nonzero in the cases of all compounds with aryl substituent in position 4 of chromene: it equaled 2 in the case of phenyl groups and 1 in the case of pyridine groups. Hence, the both descriptors gave the $0.63\times2 = 1.26$ contribution in the case of phenyl substituent and the $0.63 + 0.40 = 1.03$ contribution in the case of 4-pyridine derivatives; therefore, other conditions being the same, pyridinyl derivatives were somewhat favorable. That was confirmed by comparison of activities of compounds 126 and 124 (0.003 and 0.006 μmol/L, respectively).

Noteworthily, according to the developed models, the following fragments enhanced the apoptosis-inductive activity of the compounds: 3-bromo-4,5-dimethoxyphenyl in position 4 of chromene and pyrrolyl in position 7 or 8; that was confirmed by the experimental evaluation [5–7]. Such compounds derivatives were studied systematically and many of them were fairly active.

To conclude, within the studied compounds class, the following modifications can potentially enhance the compounds activity: (1) introduction of iodine and chlorine instead of bromine in the compound 94 (the predicted activities of 0.005 and 0.002 μmol/L, respectively) and (2) introduction of methyl in position 6 of chromene backbone in compound 94 allowing the advantageous Br,C-8 descriptor (no. 2 in Table 4) with large negative coefficient (the predicted activity of 0.001 μmol/L).

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