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The Structure–Activity Correlation in a Series of Stilbene Derivatives and Related Compounds, the Inducers of Apoptosis

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Abstract—The structure–property correlation based on the fragment description of the molecular structure is used for the calculation of the antiproliferative and apoptosis-inducing activity of a series of the *trans*- and *cis*-stilbene derivatives and related compounds. To construct a simple model, from the entire set of fragment descriptors the most efficient ones were selected using an original algorithm. The result is a large collection of similar by accuracy simple models involving different variables. The fragment contributions that appears in the models most often correspond to the elements of molecular structure that are most important for the activity, and we can assume that the more such elements in the structure of a compound, the more active it is.

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Apoptosis is the genetically programmed cell death, that is a general biological process characteristic of multicellular biological systems allowing them to be exempted from aging or diseased cells that have become dangerous for the organism. Any violation of this process can cause a variety of diseases. In particular, at the violation of the apoptosis system, when cells start to divide unlimitedly, apppear oncologic diseases, and for the treatment are used the substances inducing apoptosis. At the end of the last century, great attention has been paid to resveratrol (*trans*-3,5,4'-trihydroxystilbene), long known as the biologically active substance (Fig. 1, no. 1), [1]. It turned out that resveratrol can be used for prevention and treatment of cancer diseases [2]. This substance is capable of activation different signaling pathways leading to inhibition of growth of the tumor cells [3]. Stilbene skeleton is a basic element of a number of biologically active compounds and is used as a privileged structure in the design of compounds with apoptosis-inducing characteristics [4–10]. For a rational approach to the synthesis of stilbene derivatives with the desired properties is necessary to investigate the structure–activity correlation, to identify the structural elements that increase the activity of the stilbene skeleton. Molecular design of derivatives of resveratrol with a pronounced antiphlogistic activity was recently described in [11]. The purpose of this study is revealing the quantitative structure–activity relations to identify fragments of the structure responsible for the apoptotic activity of some stilbene derivatives and the derivatives of 2-phenylnaphthalene and terphenyls, that are close to them by the shape of the molecular frame (Table 1). The results of this analysis may be useful for designing new medicines. The experimental values of the antiproliferative (IC_{50}) and apoptosis-inducing (AC_{50}) activity of these compounds were taken from the literature [4, 8]. For compounds with weak apoptosis-inducing activity were taken boundary values of concentrations (Table 2, nos. 2, 7, 8, 14, 22, and 37).

Description of building the models. To build the correlation structure–property was used representation of the molecular structure through its fragments: to the heavy atoms or groups of the atoms are assigned the fragments of different types. The correlation ratio was chosen as a sum of unifragmental contributions associated with an atom of a certain type, and pair contributions, determined by the type and number of pairs of atoms and the number of bonds separating them [12–14].

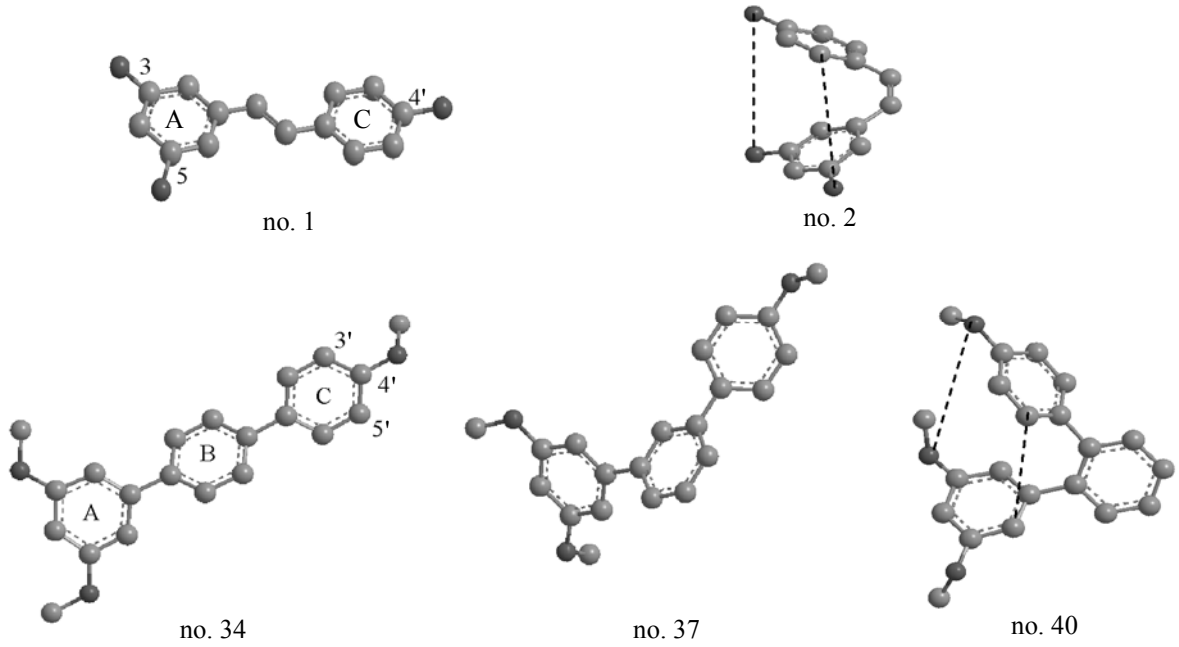


Fig. 1. Molecular structure of some compounds considered in this paper. The dashed lines show some of the approached atoms in the *cis*-stilbene derivative (no. 2) and in the ortho-terphenyl derivative (no. 40).

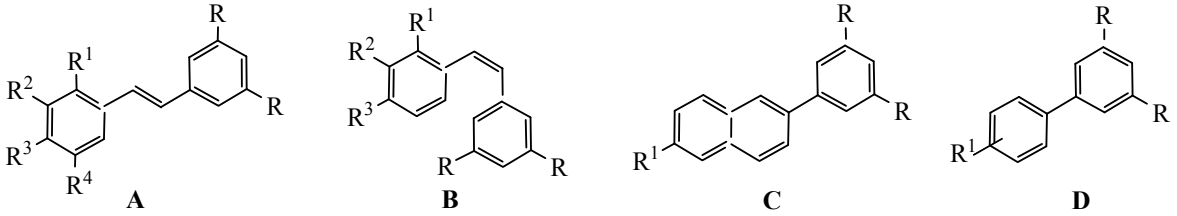
$$P \approx \sum_t n_t P_t + \sum_{t,m,r} k_{t,m-r} P_{t,m-r} + \text{const.} \quad (1)$$

Here, n_t is the number of fragments associated with the atoms of a certain type t; $k_{t,m-r}$ is the number of pairs of fragments, which correspond to atoms of types t and m, separated by r chemical bonds. The fragment contributions of P_t, $P_{t,m-r}$ are the parameters of the correlation equations determined from the experimentally measured activities by the methods of linear regression. The numbers n_t and $k_{t,m-r}$ describe quantitatively the molecular structure.

This description of the molecular structure allows explicitly reflect its features. It helps in the interpretation of the resulting correlation models and gives a possibility to forecast the changes in activity at the modification of the molecular structure of compound. However, this approach conveys the molecular topology, but does not consider the steric arrangement of atoms. The set of stilbene derivatives includes several pairs of stereoisomers. The stereoisomers differ significantly from each other by their activity. To account for this difference, while choosing the types of fragments we considered the fact that carbon atoms of **A** and **B** rings, as well as substituents in these rings are closer to each other in the *cis*-isomer, and hence interact more strongly than in the corresponding *trans*-isomers (Fig. 1, nos. 1 and 2). Therefore they were marked as the fragments of different types. A similar assumption was made for the *ortho*-compounds (no. nos. 38–40, Table 1). Silicon atoms in the *cis*- and *trans*-isomers are marked as the fragments of the same type, because, we believe that their interaction with other atoms at their spatial rapproachment is varied insignificantly. Types of fragments and their designations are given in Table 3.

As noted previously [15], one of the limitations of the describing the molecular structure through its fragments is the large number of contributions to the correlation relation. For a number of the stilbene derivatives and related compounds the maximum distance between the fragments in a molecule was equal to 14 chemical bonds. Thus, the total number of contributions taking into account all the possible combinations of "fragment type–distance" was 1104. The descriptors yielding the same contribution for all compounds in the set were excluded and from the group of correlated descriptors (the correlation coefficient > 0.98) was retained only one. Finally, we got a set of 104 descriptors, also too much for the construction and interpretation of correlation models. To simplify the models, further should be selected the variables using certain criteria, exploring the entire space of descriptors as completely as possible. Typically, the characteristic of the model accuracy can

Table 1. Stilbene, 2-phenylnaphthalene, and terphenyl derivatives considered in this paper



A **B** **C** **D**

no.	Structure	R	R^1	R^2	R^3
1	**A**	OH	H	H	OH
2	**B**	OH	H	H	OH
3	**A**	OMe	H	H	OH
4	**B**	OMe	H	H	OH
5	**A**	OMe	H	OH	
6	**A**	OMe	OH	H	
7	**A**	OMe	H	H	$OSi(Me)_2CMe_3$
8	**B**	OMe	H	H	$OSi(Me)_2CMe_3$
9	**A**	OMe	H	H	OMe
10	**A**	OMe	H	H	NH_2
11	**B**	OMe	H	H	NH_2
12	**A**	OMe	H	OH	OH
13	**B**	OMe	H	OH	OH
14	**A**	OH	H	OH	OMe
15	**B**	OH	H	OH	OMe
16	**A**	OMe	H	OH	OMe
17	**B**	OMe	H	OH	OMe
18	**A**	OMe	H	OMe	OH
19	**B**	OMe	H	OMe	OH
20	**A**	OMe	OH	OMe	
21	**A**	OH	H	OEt	OH
22	**A**	OH	H	NH_2	OMe
23	**B**	OH	H	NH_2	OMe
24	**A**	OMe	H	NH_2	OMe
25	**B**	OMe	H	NH_2	OMe
26[a]	**A**	OMe	OH	H	H
27[b]	**A**	OMe	H	OMe	OH
28[c]	**A**	OMe	H	CMe_3	OH
29	**C**	OH	OH	–	–
30	**C**	OMe	OH	–	–
31	**C**	OMe	OMe	–	–
32	**D**	OH	*p*-Ph-4-OH	–	–
33	**D**	OMe	*p*-Ph-4-OH	–	–
34	**D**	OMe	*p*-Ph-4-OMe	–	–
35	**D**	OH	*m*-Ph-4-OH	–	–
36	**D**	OMe	*m*-Ph-4-OH	–	–
37	**D**	OMe	*m*-Ph-4-OMe	–	–
38	**D**	OH	*o*-Ph-4-OH	–	–
39	**D**	OMe	*o*-Ph-4-OH	–	–
40	**D**	OMe	*o*-Ph-4-OMe	–	–

[a] R^4 = Cl. [b] R^4 = OMe. [c] $R^4 = CMe_3$. In other cases R^4 = H.

Table 2. Antiproliferative (IC_{50}) and apoptosis-inducing (AC_{50}) activity of stilbene, 2-phenylnaphthalene, and terphenyl derivatives

no.[a]	Experiment		Calculated log (IC_{50})[d]	Experiment		Calculated log (IC_{50})[d]
	AC_{50}, μM [4, 8][b]	log (IC_{50})[c]		AC_{50}, μM [4, 8][b]	log (AC_{50})[c]	
1	5	0.70	0.77	50	1.70	1.66
2	42	1.62	1.46	200 (>200)	2.30	2.06
3	35	1.54	0.73	70	1.85	1.26
4	2	0.30	0.75	5	0.70	1.32
5	23	1.36	0.81	58	1.76	0.92
6	9	0.95	0.81	35	1.54	1.56
7	48	1.68	1.47	200 (>200)	2.30	2.20
8	50	1.70	1.73	200 (>200)	2.30	2.40
9	2.5	0.40	0.49	4	0.60	0.74
10	4	0.60	1.15	15	1.18	1.56
11	2.5	0.40	0.75	8	0.90	0.94
12	0.8	–0.10	0.39	1	0.00	0.62
13	0.05	–1.30	–1.41	0.1	–1.00	–1.01
14	48	1.68	1.59	200 (>200)	2.30	2.28
15	40	1.60	1.81	70	1.85	2.06
16	0.7	–0.15	0.15	0.9	–0.05	0.10
17	0.03	–1.52	–1.41	0.04	–1.40	–1.39
18	25	1.40	0.92	40	1.60	1.57
19	20	1.30	0.75	38	1.58	1.32
20	3.5	0.54	1.00	15	1.18	1.87
21	11	1.04	0.97	18	1.26	1.33
22	80	1.90	1.93	200 (>200)	2.30	2.28
23	40	1.60	1.46	68	1.83	1.69
24	4	0.60	0.49	8	0.90	0.74
25	0.03	–1.52	–1.52	0.04	–1.40	–1.40
26	14	1.15	0.81	29	1.46	1.56
27	20	1.30	1.12	79	1.90	1.88
28	84	1.92	2.10	100 (>100)	2.00	1.88
29	28	1.45	1.45	48	1.68	1.66
30	10	1.00	1.12	19	1.28	1.26
31	76	1.88	1.94	91	1.96	1.87
32	7	0.85	0.75	25	1.40	1.32
33	2.5	0.40	0.70	3	0.48	0.97
34	75	1.88	1.74	100 (>100)	2.00	1.87
35	27	1.43	1.59	63	1.80	1.91
36	4.8	0.68	0.70	23	1.36	0.97
37	50	1.70	1.74	100 (>100)	2.00	1.87
38	3.5	0.54	0.75	9	0.95	0.94
39	5	0.70	0.75	10	1.00	0.94
40	7	0.85	0.75	15	1.18	0.94
			R^2 0.8909; s 0.34			R^2 0.9057; s 0.34

[a] The numbering of the compounds is the same as in Table 1. [b] IC_{50} is the concentration at which occurs 50% inhibition of cell growth, AC_{50} is the concentration at which the apoptosis is induced in 50% of the cells (determined using cells of acute myeloid leukemia, line LH60). [c] For the convenience, the experimental values are converted to a logarithmic scale. [d] Expression (1) is used, with the parameters given in Table 4.

Table 3. Types of fragments and their designations

Fragment type	Atoms and groups
C1	Aromatic carbon atoms
C2	Aromatic carbon atoms in rings **A** and **B** of the stylbene *cis*-isomer and in rings A and **C** of *ortho*-terphenyl
C3	Aliphatic carbon atom
C4	The carbon atoms in the double bond
O1	Hydroxy group
O2	Hydroxy group in the stylbene *cis*-isomers and *ortho*-terphenyls
OC1	Methoxy group
OC2	Methoxy group in the stylbene *cis*-isomers and *ortho*-terphenyls
N1	Amino group
N-	Amino group in stylbene *cis*-isomers
Si	Silicon
Cl	Chlorine

Table 4. The parameters of expression (1) for the most accurate models

IC_{50}		AC_{50}	
contribution	value	contribution	value
Const	0.754±0.203	Const	0.944±0.271
$P_{O1,O1-4}$	2.519±0.299	$P_{O1,O1-4}$	2.158±0.623
$P_{C4,O2-4}$	0.351±0.242	P_{Si}	1.458±0.542
$P_{OC1,C1-4}$	0.197±0.066	$P_{C4,O2-5}$	0.374±0.177
$P_{C3,C3-2}$	0.163±0.093	P_{OC1}	0.308±0.119
$P_{C4,O1-4}$	–0.341±0.210	$P_{O1,C1-10}$	–0.297±0.135
$P_{O1,C1-10}$	–0.421±0.213	$P_{OC1,O1–9}$	–0.320±0.193
$P_{O1,O1-10}$	–0.700±0.241	$P_{O1,O1-10}$	–0.574±0.331
$P_{C4,OC1-6}$	–0.858±0.305	$P_{C4,OC1-6}$	–1.126±0.444
$P_{OC2,N2-9}$	–1.137±0.292	$P_{OC2,N2-9}$	–1.172±0.369
$P_{OC2,O2-9}$	–1.257±0.540	$P_{OC2,O2-9}$	–1.352±0.269

serve as such criteria (for example, the correlation coefficient of the experimentally measured activity and the activity calculated with the equation of the model) [16]. In constructing the structure–activity correlation for the compounds with antiproliferative and apoptotic-inducing activity we selected the descriptors that would allow obtaining a model with 10 variables and the standard deviation of no more than 10% of the range of changes in the activity, using our original single-step algorithm.

As described in [17], the stepwise regression was applied by an iterative way from different starting points. The models including no more than 10 variables, and giving the standard deviation of the calculated values of activity from the experimentally measured of no more than 0.37 logarithmic units of activity were accumulated in the collection. The algorithm stops when in the previous step the models with a new set of nine descriptors did not appear, to which could be applied the stepwise regression. For antiproliferative activity 13 iterations were required, and 112 models with 10 variables were accumulated. For the apoptosis-inducing activity the algorithm stopped after 21 iterations, the collection contained 80 models. In Table 2 along with the experimental values of both activities are given the results of calculations of the estimates of activity with the best by accuracy models with 10 variables. It follows from the data in Table 2 that the values of both types of activity for all pairs of isomers of stilbene derivatives (compounds nos. 1 and 2, 3 and 4, 10 and 11, 16 and 17, 18 and 19, 22 and 23, 24 and 25) and terphenyl (compounds nos. 32 and 38, 33 and 39, 34 and 40) are reproduced correctly. Analysis of the value of the contribution of selected descriptors (see Table 4) in the best models for both activities allows us to note that there are six matching contributions (marked in bold letters). Among them only the contribution $P_{O1,O1-4}$, corresponding to two hydroxy groups separated by four bonds, has a positive value in the correlation, that is, unfavorable for the appearance of both types of activity. Such a pair of fragments found in the *trans*-isomer of stilbenes with two hydroxy groups in ring **A**, and in similar 2-phenylnaphthalenes and *para*- and *meta*-terphenyls. Some of these compounds really show low activity (Table 2, nos. 14 and 22). The other matching contributions are negative, that is, favorable for the manifestation of bioactivity. The $P_{O1,O1-10}$ and $P_{O1,C1-10}$ compensate by their small negative value the

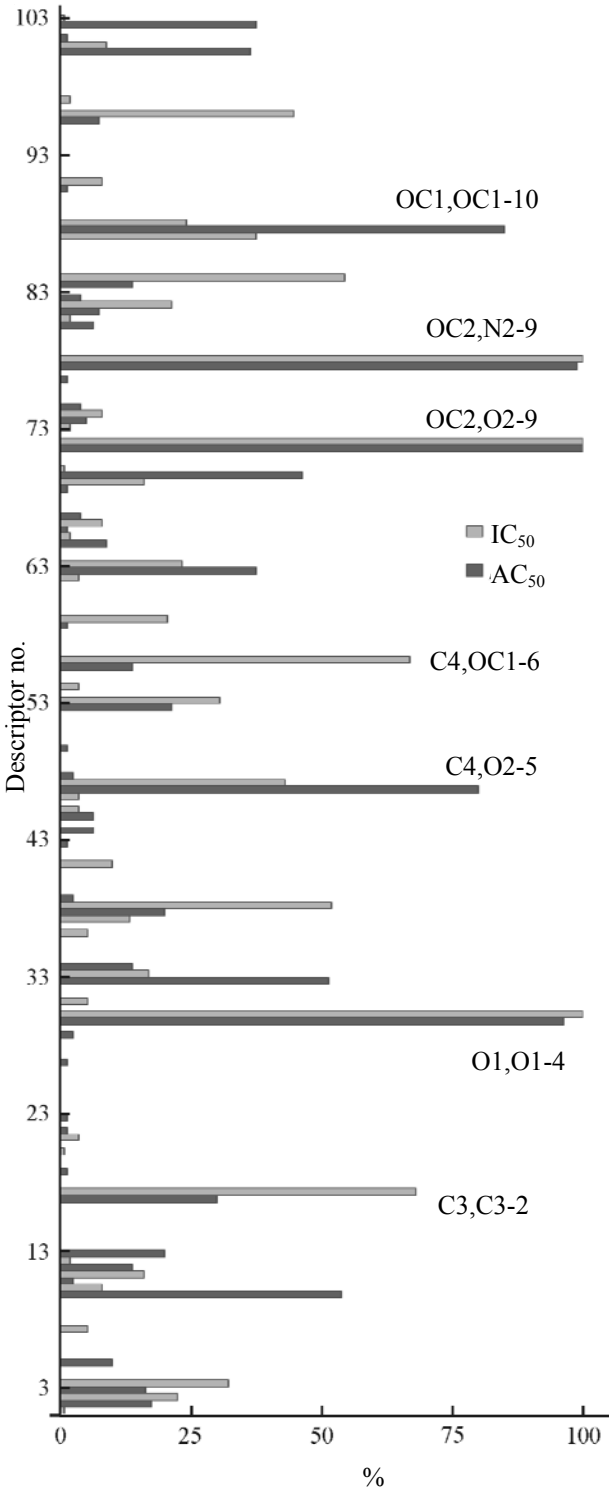


Fig. 2. Frequency (in%)of appearance of descriptors in a set of models. Gray color marks the antiproliferative activity, black color, the apoptosis-inducing activity. On the ordinate are the numbers of descriptors.

impact of the contribution of $P_{O1,O1\text{-}4}$ in the corresponding *trans*-stilbenes and increase the activity of 2-phenylnaphthalenes and *para*- and *meta*-terphenyls (Table 2, nos. 32 and 35). A negative contribution of $P_{C4,OC1\text{-}6}$ occurred in *trans*-stilbenes with methoxy group in B ring only, gives an increase in activity (e.g., compounds no. 9 and 16). The large negative contributions $P_{OC2,N2\text{-}9}$ and $P_{OC2,O2\text{-}9}$ are very important for the stilbene *cis*-isomers.

For the entire set of models in the collections the frequency of occurrence of descriptors was analyzed. Since the model selected for a collection by the criterion of highest accuracy, they are all close to the best model. It appeared that some descriptors are present in most models, and the elements of molecular structure corresponding to these descriptors are likely to play a significant role in the manifestation of antiproliferative and apoptosis-inducing activity. The frequencies of occurrence of different descriptors in the models are shown in Fig. 2. The histogram shows seven descriptors occurring in more than 2/3 of the collected models. Three descriptors, O1,O1-4, OC2,O2-9 and OC2,N2-9 are most frequently encountered in the correlation for both activities. This suggests that for both antiproliferative and apoptosis-inducing activity the same elements of the structure are important, which may indicate the similarity of molecular mechanisms. The descriptor O1,O1-4 reflects the presence of two hydroxy groups at a distance of 4 bonds in *trans*-stilbenes and close to them by the structure 2-phenylnaphthalenes and *para*- and *meta*-terphenyls. Its large positive contribution (see Table 4) indicates that such configurations of fragments should be avoided in designing a more active compound. Negative contributions of the descriptors OC2,O2-9 and OC2,N2-9, on the contrary, enhance activity, and the designer must try to enhance the number of respective fragments. Contributions of the descriptors OC2,O2-9 and OC2,N2-9 appear in the *cis*-stilbene, with the 3'-NH_2 and 3'-OH substituents in **B** ring when the A ring contains two methoxy groups (compound nos. 13, 17 and 25). We can therefore expect that the *cis*-isomer of compound no. 5 will be more active than the *trans*-analog. It is interesting to note that the same distance between the substituents can be obtained at modifying *ortho*-terphenyls. Introducing 3'-MeO group to the **C** ring of compound no. 38 and 3'-NH_2 or 3'-OH group into the **C** ring of compounds nos. 39 and 40, we can expect an increase in activity. Descriptors C3,C3-2 and C4,O2-5 give a positive contribution to the correlation

ratio. The former appears only in compounds with *tert*-butyl substituents (Table 5, compounds nos. 7, 8 and 28). It can be assumed that the presence of such hydrophobic substituents is unfavorable for the considered types of activity, especially for the apoptosis-inducing activity. Another descriptor, C4,O2-5 is associated with a pair of fragments, the hydroxy group–carbon atom at the double bond in *cis*-stilbene, and just this contribution reduced significantly the apoptosis-inducing activity of *cis*-resveratrol (compound no. 2). This fact suggests that the methoxy group as a substituent is rather preferable than the hydroxy groups. The descriptors C4,OC1-6 and OC1,OC1-10 give a small negative contribution to the correlation ratio. They appear in the *trans*-stilbene and related compounds with methoxy substituents, and this also can be considered as an argument in favor of preference of these groups as substituents.

Thus, based on the fragment representation of the molecular structure of a number of *cis*-and *trans*-stilbene, 2-phenyl-naphthalene, and terphenyl derivatives we obtained correlation relationships, which provide estimates of antiproliferative and apoptosis-inducing activity of the considered compounds with a good accuracy. The atoms which in some conformers are closer in the space and interact more strongly are represented as the fragments of different types. This technique allowed correct reflection of the ratio of activity of the pairs of conformers: *cis*- and *trans*-stilbenes, and *para*- and *ortho*-terphenyls. The analysis of frequently occurring descriptors in the collections of the models similar by accuracy allowed to suggest a way of modifying the structure of compounds to improve the activity of both the types. According to the correlation, the introduction of OMe, NH_2, and OH groups into the 3'-position of **C** ring of some *ortho*-terphenyls would produce a more active compounds.

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