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Quantitative relationships between structure and cytotoxic activity of flavonoid derivatives. An application of Hirshfeld surface derived descriptors

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ABSTRACT

Quantitative relationships between the structure and cytotoxic activity of series flavonoid derivatives were examined. The first regression-based model, developed for 18 flavanone-2-pyrazoline hybrids, involved two interpretable descriptors: a Mor04v and partial atomic charge. The second model, developed for structurally diverse set of compounds, was based on descriptors derived from Hirshfeld surface analysis. This model suggests that cytotoxic activity of compounds can be successfully predicted based on a fraction of H···H contacts and a fraction of interactions involving a halogen atom. For non-halogen derivatives, the data reveal that cytotoxic activity is inversely proportional to the percentage of O···H and N···H close contacts to Hirshfeld surface, while directly proportional to the percentage of H···H interactions. Chlorine (**1k**) and bromine (**1l**) derivatives of compounds, containing flavanone fused with *N*-methyl-2-pyrazoline, exhibited high cytotoxic potential against HL-60 cancer cell line (IC_{50} < 10 μM). The cytotoxicity of **1k** and **1l** towards normal cells (HUVEC) was 10 and 25-fold lower, respectively.

Current treatment of cancer is based predominantly on cytotoxic drugs and despite their limitations, new conventionally cytotoxic agents are still needed. The prior aim in the development of cytotoxic compounds is to improve their efficiency as well as safety and tolerability.[1] Various strategies have been employed for new drug design, among which one of the most promising is the combination of two potentially active entities in a single compound.[2] The importance of heterocyclic compounds in drug discovery is well recognized and, flavanone and pyrazole derivatives are examples of compounds which are widely used in synthesis.[3–6] The main series of compounds presented in this study contains a pyrazole ring condensed with, previously published, 3-arylideno-flavanones which exhibited promising cytotoxicity against leukemia cell lines.[7]

Chemometric modeling which involve experimentally or computationally derived molecular descriptors is now well established and widely used in medicinal chemistry, particularly for finding and designing new drug candidates.[8,9] Modern studies of quantitative structure–activity relationships (QSAR),[10] are focused on improving the predictability of models through their rigorous validation,[11,12] as well as calculating new informative descriptors and developing more powerful machine learning approaches. A huge variety of molecular descriptors have been proposed; however, in the development of successful QSAR models, the selection of appropriate descriptors becomes crucial. The potential source of descriptors useful for QSAR study is X-ray crystallography. The pharmacological action of a great number of drugs is due to non-covalent interactions (hydrogen bonding, electrostatic or van der Waals forces) between a compound and an active site. Therefore, information about molecular structure and intermolecular interactions play an important role in such disciplines as pharmacology and structure-based drug design.[13,14]

The aim of this study was (i) to evaluate the cytotoxic activity of series pyrazole-fused flavanone derivatives, (ii) to develop regression-based QSAR model with the use of the interpretable descriptors: quantum chemical and derived from three-dimensional structure of the molecules, (iii) an attempt to apply non–covalent intermolecular interactions derived from Hirshfeld surface analysis[15] of crystal compounds as descriptors in modeling of quantitative structure–activity relationships.

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A series of flavanone-2-pyrazoline hybrids (**1a–s**) was synthesized (Table 1). These compounds were evaluated for their cytotoxicity toward human leukemia promyelocytic (HL-60) cancer cell line. The results of MTT (3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide) assay (details in Supplementary material) are shown as IC_{50} (in μM) values. Table 1 also contains values of cytotoxicity of three substituted chalcones (**3a–c**),[16] 3-benzylidene-flavanone (**4a**)[7] and compounds **2a**–**c** and four reference compounds flavanone, 3-benzylideneflavanone, cisplatin and etoposide.[17] Cytotoxic activity (IC_{50}) of compounds **1a–s** varies from 7 μM to ~540 μM. Almost all flavanone-2-pyrazoline hybrids demonstrate the tendency of decreasing cytotoxicity in relation to corresponding flavanone derivatives.[7] The only two compounds (**1k** and **1l**) with halogen substituents exhibit cytotoxic potency comparable to respective 3-(4-chlorobenzylidene)-flavanone and 3-(4-bromobenzylidene)-flavanone. In the previous study, chlorinated chalcones[16] showed comparable potency ($IC_{50} \approx 7$–8 μM) against HL-60 cell line. IC_{50} values of **1k** and **1l** are approximately 7-fold lower compared to the nonsubstituted compound **1a**. Replacement of chlorine with fluorine (**1j**) is detrimental to cytotoxic activity. All compounds possessing OH group as R^2 (**1h**, **1o**, **1r**) exhibit weak or moderate cytotoxicity. Moreover, the pairs of compounds **1m**, **1n** and **1o**, **1r** demonstrate comparable IC_{50}, thus their cytotoxic activity does not depend on substitution at N atom. The following two derivatives, 4-OCH_3 (**1g**) and 3-OH (**1h**), are approximately 10- to 6-fold less active than their nonsubstituted analog (**1a**).

Furthermore, the two most potent (IC_{50} < 10 μM) compounds in group 1 (**1k**, **1l**) as well as **3a** and **4a** were evaluated for their cytotoxic activity against normal human umbilical vein endothelial cells (HUVEC). The results are shown in Table 2. IC_{50} values were statistically compared with appropriate results for **1k**, **1l**, **3a** and **4a** against cancer cells. Unfortunately, **3a** and **4a** are comparably cytotoxic against the cancer as well as normal cells. On the other hand, cytotoxic activity of compounds **1k** and **1l** towards normal cells is 10 and 25-times lower than towards HL-60 cells, respectively. It seems that the presence of fused pyrazoline ring play one of the key roles in selectivity of cytotoxic effect. In fact, the halogenated derivatives of chalcone and 3-arylideneflavanone exhibit high cytotoxicity against both cancer and normal cells. The absence of carbonyl group in the flavanone–pyrazoline derivatives is believed to be a major factor in the selective killing of cancer cells by **1k** and **1l**.

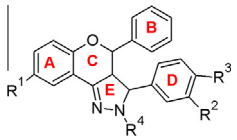
Table 2
Cytotoxic activity of selected compounds toward normal human umbilical vein endothelial cells (HUVEC)

Compound	IC_{50} (μM)	*p*-Value[a]
1k	70.9 ± 6.9	<0.001
1l	184.0 ± 20.8	<0.001
3a	7.8 ± 0.7	0.828
4a	6.9 ± 0.5	0.011

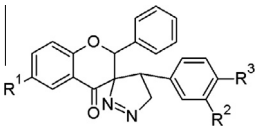
[a] *p*-Value from unpaired *t*-test; each mean of IC_{50} against normal cells HUVEC was compared with IC_{50} value against cancer cell line (from Table 1).

The molecular Hirshfeld surfaces of crystal compounds (depicted in Table 1) were explored with the use of Hirshfeld surface analysis undertaken in *CrystalExplorer* 3.1.[18] Hirshfeld surface analysis is an effective way to discern intermolecular interactions in solid state and also visualize them directly in an exploitable manner, namely, normalized contact distance (d_{norm}) surface, curvedness, shape index and 2D fingerprints.[19] These molecular fingerprints provide qualitative and quantitative information of close intermolecular contacts. The molecular structure of exemplary compounds **1e** and **2b**, as well as crystal data and structural determination details are presented in Supplementary Information (Fig. S1 and Tables S1 and S2) and Ref. 20.

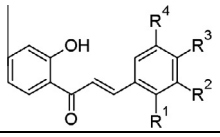
Table 1
Structure of compounds used in this study and their cytotoxic activity toward human leukemia promyelocytic cancer cell line HL-60. Cytotoxicity of reference compounds



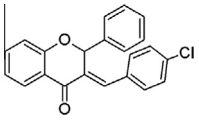
Compd	R^1	R^2	R^3	R^4	IC_{50}[b] (μM)
1a[a]	H	H	H	CH_3	54.1 ± 4.2
1b[a]	H	CN	H	CH_3	65.4 ± 8.2
1c	H	H	CN	CH_3	20.1 ± 1.9
1d	H	CH_3	H	CH_3	60.5 ± 5.3
1e[a]	H	H	CH_3	CH_3	27.8 ± 3.6
1f	H	OCH_3	H	CH_3	70.3 ± 4.9
1g	H	H	OCH_3	CH_3	541.3 ± 53.8
1h	H	OH	H	CH_3	343.5 ± 37.0
1i[a]	H	H	OH	CH_3	47.7 ± 3.7
1j	H	H	F	CH_3	97.7 ± 2.7
1k[a]	H	H	Cl	CH_3	7.4 ± 0.5
1l[a]	H	H	Br	CH_3	7.5 ± 0.4
1m[a]	OH	H	H	CH_3	37.7 ± 3.6
1n	OH	H	H	H	27.3 ± 2.9
1o	H	OH	H	H	50.0 ± 2.6
1p	H	H	OH	H	42.0 ± 3.1
1r	H	OH	H	OCH_3	51.7 ± 1.2
1s	H	H	D ring = 4-pyridyl		49.7 ± 3.6
Flavanone					51.1 ± 1.7
3-Benzylideneflavanone					33.3 ± 3.0



Compd	R^1	R^2	R^3	IC_{50} (μM)
2a[a]	H	CN	H	75.0 ± 3.2
2b[a]	H	OCH_3	H	74.9 ± 2.7
2c[a]	H	H	NO_2	54.6 ± 2.1



Compd	R^1	R^2	R^3	R^4	IC_{50} (μM)
3a[a]	Cl	H	H	H	7.7 ± 1.0[16]
3b[a]	H	H	OCH_3	H	48.7 ± 3.9[16]
3c[a]	H	OCH_3	OCH_3	OCH_3	39.3 ± 3.5[16]



4a[a]	5.8 ± 0.5[7]
Cisplatin	0.8 ± 0.1
Etoposide	0.025[17]

[a] Compounds for which crystal structure was determined.
[b] IC_{50}-concentration of a test compound required to reduce the fraction of surviving cells to 50% of that observed in the control, non-treated cells. Mean values of IC_{50} (in μM) ± standard deviation from 3 experiments each performed in quintuple.