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Cytotoxic activity of substituted chalcones in terms of molecular electronic properties

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ABSTRACT

Global chemical reactivity descriptors and lipophilicity (log*P*) were evaluated via density functional theory in order to clarify the structure–cytotoxic activity relationships of substituted chalcones. Stepwise multiple regression was employed to establish correlation between descriptors and cytotoxic activity against three cancer cell lines (HL-60, NALM-6 and WM-115) for 11 compounds. Regression analysis revealed that electrophilicity index and chemical potential significantly contributed in explaining of chalcones cytotoxic potential. Moreover, the established structure–activity relationships based on electronic structure properties allow indicating the substructures responsible for their cytotoxic activity. The study has also been supported by crystallographic data of 2-chloro-2′-hydroxychalcone.

The quantitative structure–activity relationships (QSAR) as the mathematical representation of biological activity in terms of structural descriptors have attracted considerable interests in the literature for many years. Utilization of electronic structures descriptors has shown to be valuable in many structure-activity studies. Chemical hardness (η) and softness (σ), chemical potential (μ) and electrophilicity index (ω)[1] are known as global reactivity descriptors. The electronic indexes have been successfully applied in describing and predicting the toxicity of polychlorinated biphenyls,[2] polyaromatic hydrocarbons,[3] celastroid triterpenoids[4] as well as pharmacological activity of numerous compounds, such as, for example, testosterone derivatives[5] and antimalarian chalcones.[6]

The aim of this study is to rationalize of a cytotoxic effect of 11 substituted chalcones (listed in Table 1) towards three cancer cell lines in terms of chemical descriptors that are derived from electronic structure calculation. Chalcones are an important class of natural molecules that display numerous promising pharmacological properties as have been recently reviewed.[7] Several derivatives of chalcones were tested as antibacterial,[8] antifungal[9] and anticancer[10,11] agents.

A basic skeletal structure of a chalcone moiety (Fig. 1) consists two aromatic rings (ring A and ring B) covalently linked by a α,β-unsaturated carbonyl short chain (link).

The proximity of the 2-hydroxyl group in ring A to the oxygen atom of the carbonyl group of the linkage induces the intramolecular hydrogen bond that stabilizes planar conformers. The conformation of these chalcones was confirmed by X-ray analysis of an exemplary compound **7** (Fig. 2).

The crystal data and details of structural determination are presented in Tables S1 and S2 and Ref. 12. Compound **7** crystallizes in space group $P2_12_12_1$ with two independent molecules in asymmetric unit. The molecule consist of two nearly planar six-membered aromatic rings (A, B—molecule **7a**, and A′, B′—molecule **7b**) with maximum deviation from best planes: 0.005, 0.006, 0.006 and 0.016 Å, respectively, for A, B, A′, and B′ rings. The inter-planar angle between ring A and ring B is 3.00(2)° and between A′, and B′ is 2.44 (2)°. Rings A, B and A′, B′ are connected by a three carbon, α,β-unsaturated chain with expected planar configuration along a double CC bond (torsional angles: C1–C7–C8–C9 equal to 179.92(2)° and C21–C27–C28–C29 equal to 179.64(2)°).

However, torsional angles of C7–C8–C9–O2 (**7a**) and C27–C28–C29–O22 (**7b**) are found at −8.10(2)° and −4.60(2)°, respectively, that indicate a small torsion of the link chain. In the crystal structure **7a** and **7b** are neighboring molecules that are involved in the network of hydrogen bonds: C2–H2...O21^{i} (symmetry code (i): 3/2−*x*, 1−*y*, −1/2+*z*) and C35–H35...O1^{ii} (symmetry code (ii): 1−*x*, *y*, *z*).

The molecules are interconnected by the network of H-bonds that forms a chained structure along *c* axis (Fig. S1, Table S2 in

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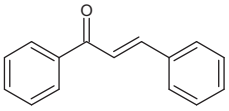
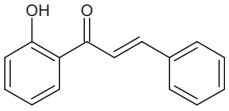
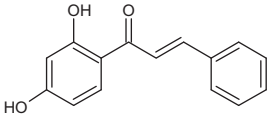
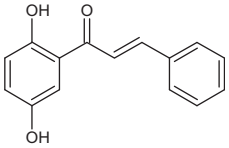
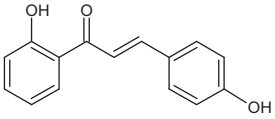
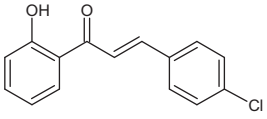
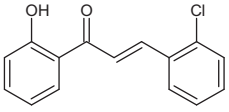
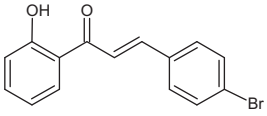
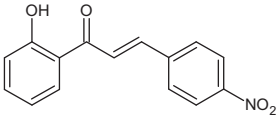
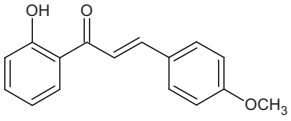
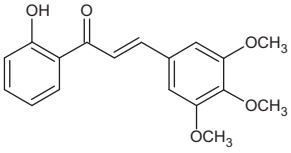
0960-894X/

Table 1
Structure of chalcone[19] derivatives used in the study

1		**2**	
3		**4**	
5		**6**	
7		**8**	
9		**10**	
11			

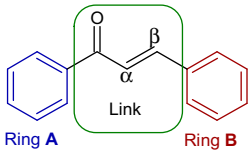


Figure 1. Chalcone scaffold.

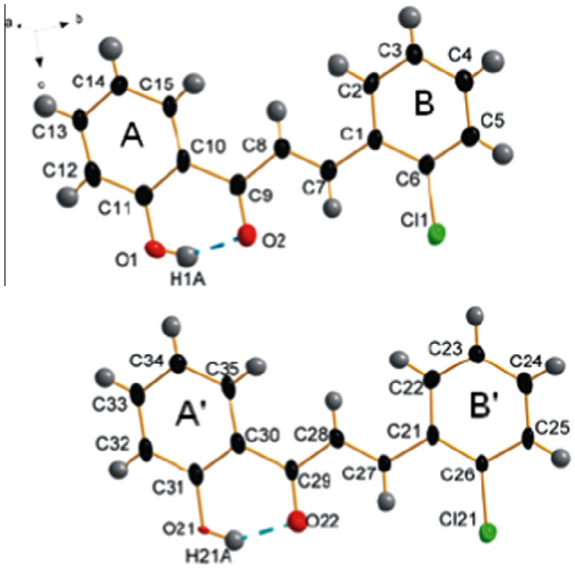


Figure 2. An ORTEP view of two molecules **7a** and **7b** of compound **7**. Displacement parameters for non-H atoms are drawn at the 50% probability level. The intramolecular O–H. . .O hydrogen bonds are displayed as blue dashed lines.

Supplementary file). Also the intramolecular hydrogen bond between 2-hydroxy group of ring A and oxygen of a nearby carbonyl group is confirmed in the crystal lattice (see Fig. 2). Furthermore, the π–π stacked interaction between the aromatic rings of the formed chains is also present with the average C–C separation distance of 3.32 Å (Fig. S1).

An initial evaluation of compounds for potential anticancer agents involves elaborate screening tests with human cancer cell lines. In this study cytotoxicity of chalcones and reference compounds was determined by the MTT (3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide) assay.

The compounds were evaluated for their ability to evoke cytotoxic effect toward three cancer cell lines: primary skin melanoma (WM-115), human leukemia promyelocytic (HL-60) and lymphoblastic (NALM-6). The results for compounds **1**–**11** are shown as IC_{50} values in Table 2. Chromanone, flavanone and cisplatin were used as references compounds. Cytotoxic activity (IC_{50}) of chalcones against both leukemia cells (HL-60 and NALM-6) varies in range from 5.3 to 55.0 μM. The cluster analysis, based on these data, shows two separate groups collecting compounds with different activity (Fig. 3). Many electrophiles are cytotoxic via covalent mechanism of action involving the formation of a chemical bond between cytotoxic compound and biomolecules (proteins, DNA). Compounds, which toxicity could be related to that mechanism, require electron-deficient sites susceptible to accept an electron pair from electron-rich biomolecules. Experimental data indicate that α,β-unsaturated carbonyl chemicals as an electrophiles evoke cytotoxicity due to Michael-type adducts with sulfhydryl groups on specific cysteine residues.[13] Covalency formed between these molecules closely relates to properties of their frontier orbitals.

Frontier molecular orbital energies, namely, the lowest unoccupied molecular orbital (E_{LUMO}) and the highest occupied molecular orbital (E_{HOMO}) were computed by DFT methods in order to