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ORIGINAL PAPER

Antioxidant activity of flavonoids: a QSAR modeling using Fukui indices descriptors

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Abstract A QSAR model to predict the antioxidant activity of flavonoid compounds was developed. New electronic structure descriptors which are Fukui indices are correlated to the radical scavenging of flavonoids. These indices are obtained at DFT/B3LYP level of chemical quantum theory. The $\log IC_{50}$ experimental values of antioxidant activity are taken from the literature. The model is based on the multilinear regression method. Both experimental and calculated data of 36 flavonoids compounds were analyzed. A good correlation coefficient (R^2=0.8159) is obtained and the antioxidant activities of test compounds are well predicted.

Keywords DFT · Flavonoids · Fukui indices · MLR · QSAR

Introduction

Flavonoids represent a highly diverse class of polyphenolic secondary metabolites which are abundant in plants. These natural products are easily extracted from many different plants [1]. They may be further divided into several subclasses, i.e., flavones, flavanones, flavonols, flavanols (also called catechins), and anthocyanidins. Flavonoids show extensive biological activities with low toxicity. Their use as potential therapeutic compounds against a variety of diseases is of great interest [2]. Some flavonoids possess significant anti-hepatotoxic [3], anti-HIV-1 [4, 5], antitumor [6], and anti-inflammatory activities [7–9].

One of the most interesting biological properties of flavonoids is their antioxidant activity [10, 11]. The antioxidant properties of flavonoids are often claimed to be responsible for the protective effects of these compounds against cardiovascular disease, certain forms of cancer, photosensitivity diseases, and inflammations [12, 13]. They can also inhibit a wide range of enzymes involved in oxidation reactions, such as 5-lipoxygenase, cyclooxygenase, monooxygenase, or xanthine oxidase [14–16]. These biological activities include the formation of reactive-oxygen suppressing species, either by inhibition of enzymes or by chelating trace elements involved in free-radical production, scavenging reactive species, and regulating or protecting antioxidant defenses [17]. At least two mechanisms involved in the antioxidant processes are known: a direct hydrogen atom transfer process or an electron transfer process [18, 19].

$$FIO^{-}H + RO^{\cdot} \rightarrow F1^{-}O^{\cdot} + ROH$$

So this activity depends mainly on the substitution pattern of the hydroxyl groups, that is to say, on the availability of phenolic hydrogens and on the possibility of stabilizing the resulting flavonoid phenoxyl radicals. Figure 1 presents the general structure of flavonoids, our ring notation and our atom numbering. The structural requirements considered essential for effective radical scavenging by flavonoids are the presence of 3', 4'-dihydroxy group (catechol) in the B ring and/or the presence of the 3-OH group in the C ring. In addition, the 5-OH group in combination with a 4-oxo moiety (1, 4-pyrone moiety) and C2=C3 double bond may increase the radical scavenging activity [20–22].

Numerous authors have investigated the antioxidant activity of flavonoids, and many attempts have been made to

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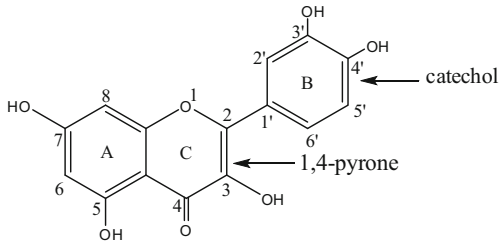

Fig. 1 General structure of flavonoid, ring notation, and atom numbering

establish the relationship between flavonoid structure and their radical scavenging activity [20, 23].

Quantitative structure-activity relationships (QSAR) models have been extensively developed in order to estimate and predict antioxidant activity of flavonoids using descriptors derived from chemical structure and various physicochemical parameters [24–27]. In order to establish an excellent QSAR equation, it is very important to select pertinent descriptors which are strongly related to the activity under study. The descriptors have to be carefully evaluated. In the literature, the quantum ones are calculated using semi-empirical methods such as AM1 [28] and PM3 [29]. However, some recent QSAR studies have revealed that the use of the density functional theory (DFT), instead of semi-empirical methods shows a better correlation between calculated results and experimental data [30–32]. It is well known that the DFT methods are more accurate then semi-empirical ones. Furthermore, conceptual DFT leads to some reactivity indexes not accessible with other quantum methods. The Fukui functions are some of these indexes. They represent a local reactivity of the studied compounds. They are given by [33]:

$$f(\overrightarrow{r}) = \left(\frac{\partial \rho(r)}{\partial N}\right) v(r) \quad (1)$$

where $\rho(r)$ is the electronic density, N is the number of electrons and v(r) is a constant external potential. The reactivity of an atom k in a molecule can be described, by a condensed Fukui function f_k. As ρ(r) is a discontinuous function of N, Yang and Parr [34, 35] have proposed approximated atomic indices f_k by applying the finite difference approximation to the condensed electronic population on any atom. Three indices were defined to describe nucleophilic, electrophilic, and radical attack. These can be written respectively as:

$$\begin{aligned} f_k^+ &= [q_k(N+1) - q_k(N)] \\ f_k^- &= [q_k(N) - q_k(N\text{-}1)] \\ f_k^0 &= [q_k(N+1) - q_k(N\text{-}1)]/2 \end{aligned} \quad (2)$$

$q_k(N)$: electronic population of k atom in neutral molecule.
$q_k(N+1)$: electronic population of k atom in anionic molecule.
$q_k(N-1)$: electronic population of k atom in cationic molecule.

In this approximation, the indices depend widely on the used population analysis approach. The electronic population around an atom k can be evaluated using Mulliken [36], Hirshfield [37], or natural orbital [38] approximations. These indices are some of the widely used local density functional descriptors to model chemical reactivity and site selectivity [34, 39]. The atom with the highest Fukui indices is the most reactive compared to the other atoms in the molecule.

As shown before the flavonoids compounds act by chemical reactions in their antioxidant activity, so this property can be related to reactivity indices as Fukui functions.

The aim of our study is the comprehension and development of a QSAR model of the relationship between some Fukui indices, which are electronic descriptors, and antioxidant activity of flavonoids. DFT based molecular descriptors such as hardness, group-philicity, ionization potential etc. have been used previously in QSAR models [40–43]. In the present paper we present a QSAR model where we introduce a new descriptor, namely the Fukui indices. These quantum chemical descriptors are employed to make a better predictive model of antioxidant activity. We have used the experimental results obtained through the DPPH test of antioxidant properties of flavonoids and derivatives compounds [44]. The classes of flavonoids considered in this work are: flavones (denoted as A, 17 compounds), flavon-3-ol (denoted as B, 15 compounds), flavanols (denoted as C, 3 compounds), and flavan-3-ol (denoted as D, 1 compound), for a total of 36 compounds. The choice of atoms whose Fukui indices are calculated was based on a study conducted by Anouar et al. [45]. The most probable nucleophilic, electrophilic or radical sites obtained by Anouar et al. [45] are shown by arrows in Fig. 2. The C ring is the most reactive part for all molecules. In the case of quercetin and morin the radical reactions should occur preferentially in B ring.

In our work we choose to study the Fukui indices of C(4) and O(4) atoms. This carbonyl group may have an important

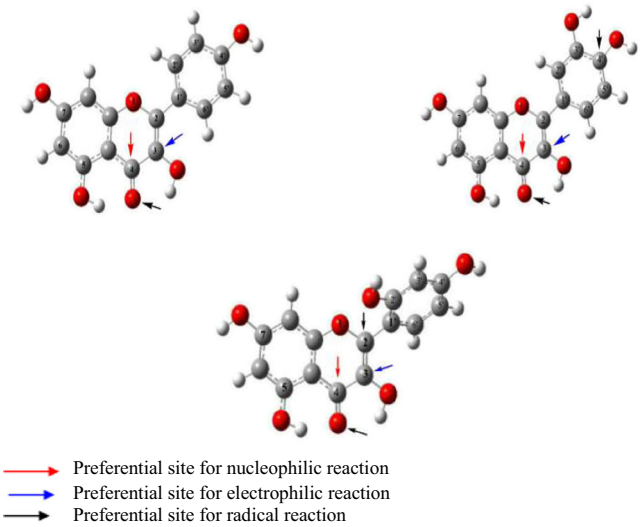

Fig. 2 Different reactive sites for kaempferol, quercetin, morin, and myricetin [45]

effect on the antioxidant activity, especially by dispossessing the charge by means of the resonance effect. This effect depends widely on the carbonyl molecular environment.

Calculation details

Experimental data

The antioxidants activities are expressed in terms of IC_{50} which is defined as the molar concentration of compound necessary to cause 50 % cell growth inhibition. All original IC_{50} values are usually converted to logarithm of IC_{50} (log-IC_{50}) in QSAR study. Table 1 lists the individual studied compounds and their corresponding antioxidant activity. These values were taken from literature by Seyoum et al. [44]. The multiple linear regression (MLR) method [46] was employed with the aim to obtain a correlation between the Fukui indices and the antioxidant activity of these compounds.

Descriptor calculation

It is evident from the previous work of De Proft et al. [47] that B3LYP and B3PW91 functional provide comparatively good results on Fukui indices. The choice of computational levels and basis sets requires a compromise between accuracy and computational time.

Hence in the present investigation, all molecular structures used in the study to develop QSAR models have been optimized using B3LYP functional and 6-31G** basis sets [48–51]. All the calculations have been performed using Gaussian03 software [52].Calculation of vibrational frequencies has been performed after geometry optimization on the same theory level to be sure that no optimized structure could display any imaginary frequency. Radical electronic structures have been calculated through Kohn-Sham formalism with unrestricted spin DFT/UB3LYP [53]. The optimized structures have then been used to calculate molecular descriptors which are Fukui indices.

The atomic charges for all the above molecules have been obtained in the framework of B3LYP theory using Mulliken Population Analysis (MPA) [36] and Natural Population Analysis (NPA) [37].

QSAR model

The QSAR model presented in this paper is developed on 24 flavonoids. These compounds were divided into two groups: one for training and one for testing. The training set and the testing one contains respectively 19 and five compounds. The purpose of the training set is to derivate the model. Their external prediction power is evaluated by the correct anticipation ability of antioxidant activity of the compounds of the corresponding test set.

Table 1 Experimental values of the antioxidant activity of the compounds considered in this work [44].

	Compounds	$IC_{50}(\mu M)$
1A	Luteolin-5-O-glucoside (5-O-glucoside, 7,3' ,4' –OH)	5.73±0.13
2A	Luteolin (5,7,3' ,4' -OH)	11.04±0.38
3A	7,8-Dihydroxyflavone (7,8-OH)	15.50±0.12
4A	8-Hydroxyacacetin (5,7,8-OH,4' -OMe)	20.28±0.20
5A	Luteolin 7-O-glucoside (7-O-glu,5,3' ,4' -OH)	28.17±0.69
6A	Cosmosiin (7-O-glucoside-5,4' -OH)	85.67±6.64
7A	8-Hydroxyflavone (8-OH)	166.43±3.61
8A	Vicenin-2 (6,8-C-glucoside,5,7,4'-OH)	171.28±5.26
9A	4'Methoxy3,6,8trichloro5,7dihydroxy (3,6,8-Cl,5,7-OH,4'-OMe)	201.52±9.34
10A	5,7-Dihydroxy-3',4'dimethoxyflavone (5,7-OH,3',4'-OMe)	313.18±19.89
11A	Diosmin (7-O-rutinoside,5,3' -OH,4' -OMe)	442.26±26.21
12A	Apigenin(5,7,4' -OH)	463.40±22.28
13A	Diosmetin(5,7,3'-OH,4'-OMe)	465.13±15.32
14A	Chrysin(5,7-OH)	492.57±23.94
15A	Acacetin (5,7-OH,4'-OMe)	529.80±29.55
16A	5-Hydroxy-3',4',7-trimethoxyflavone (5-OH,7,3',4'-OMe)	539.84±27.78
17A	7-Hydroxy-5-methyl4'methoxyflavone (5-Me,7-OH,4'-OMe)	808.71±25.45
1B	Quercetagetin (3,5,6,7,3',4'-OH)	9.02±0.16
2B	Rutin (3-rutinoside,5,7,3',4'-OH)	9.40±0.31
3B	Isoquercitrin (3-O-glucoside,5,7,3',4'-OH)	9.45±0.06
4B	Hyperoside (3-O-galactoside,5,7, 3',4'-OH)	10.01±0.00
5B	Quercetin (3,5,7,3',4'-OH)	10.89±0.03
6B	Robinetin (3,7,3' ,4',5'-OH)	11.02±0.56
7B	Rhamnetin (3,5,3',4'-OH,7-OMe)	13.50±0.79
8B	Fisetin (3,7,3' ,4'-OH)	14.06±0.21
9B	Quercetin 3,5-di-O-glucoside (3,5-O-glucoside,7,3',4'-OH)	14.41±0.93
10B	Morin (3,5,7,2',4'-OH)	17.27±0.13
11B	Kaempferol (3,5,7,4'-OH)	28.05±0.28
12B	Galangin (3,5,7-OH)	71.64±1.07
13B	Quercetin 3,7,3',4'–tertarmethylether (5,-OH,3, 7,3',4'-OMe)	261.40±17.93
14B	Kaempferol 3,5-di-O-glucoside (3,5-O-glucoside,7,4'-OH)	528.37±21.26
15B	3-Hydroxyflavone (3-OH)	695.93±11.67
1C	Taxifolin (3,5,7,3',4'-OH)	9.27±0.26
2C	Hesperetin (5,7,3'-OH,4'-OMe)	236.63±0.86
3C	Hesperidin7-O-rutinoside, 5,3'-OH,4'-OMe)	281.41±2.62
1D	(−)-Epicatechin (3,5,7,3',4'-OH)	16.09±0.41

A: Flavone class

B: Flavon-3-ol class

C: Flavanone class

D: Flavan-3-ol class

The antioxidant activity of the training set compounds was initially modeled using MLR analysis [46]. The general purpose of multiple regression is to quantify the relationship between several independent predictor variables and a criterion variable. The variables with insignificant regression coefficients will be omitted in the final equation.

The statistical quality of the developed models is examined by different statistical parameters [54] like square of correlation coefficient (R^2), the Fisher ratio values (F), and the standard deviation (s). Many authors consider higher $R^2>0.6$ as an indicator that the model is highly predictive [55].

Results and discussion

Atomic charges

In order to determine the Fukui indices, the study of the charge distribution was carried out by considering two types of charge analysis: Natural Population Analysis (NPA) and Mulliken Population Analysis (MPA). The population analysis is a mathematical way of partitioning the electronic density to obtain the atomic charges, bond orders, and other related information [56]. The fundamental assumption used by the Mulliken scheme for partitioning the electronic density is that the overlap of two orbitals is shared equally between them. This does not completely reflect the electronegativity of the individual elements. The weakness in the Mulliken approach arises from the fact that it employs a nonorthogonal basis set [57, 58]. This method has the advantage of simplicity but its results tend to vary with the size of the employed basis set [59] and do not respect the electronegativity nature of atoms in molecules. The (NPA) exhibits an improved numerical stability and better describes the electronic distribution in compounds of high ionic character, such as those which contain metallic atoms, or carbon structures with OH groups, such as the molecule considered in this study [60].

The calculated atomic charge values from the natural population analysis (NPA) and Mulliken population analysis (MPA) procedures using the DFT method are listed in Table 2.

In the flavonoids ring all hydrogen and carbon atoms have a net positive charge; in particular, the hydrogen, owing to being bound with the more electronegative oxygen atom. The presence of large amounts of negative charge on the O(4) atom, which is an acceptor atom, may suggest the presence of intramolecular hydrogen bonding in the cristal phase.

Table 2 The partial charge of O(4) and C(4) atoms calculated using the Mulliken and natural population analyses (NPA) methods

	Mulliken approach		*NPA approach*	
	O(4)	C(4)	O(4)	C(4)
1A	−0.511	0.417	−0.565	0.491
2A	−0.511	0.419	−0.565	0.490
3A	−0.526	0.406	−0.581	0.496
4A	−0.510	0.414	−0.565	0.491
5A	−0.508	0.418	−0.563	0.491
6A	−0.508	0.419	−0.563	0.491
7A	−0.521	0.408	−0.576	0.495
8A	−0.502	0.435	−0.636	0.494
9A	−0.571	0.453	−0.538	0.484
10A	−0.512	0.419	−0.567	0.490
11A	−0.504	0.418	−0.558	0.491
12A	−0.511	0.419	−0.566	0.490
13A	−0.511	0.418	−0.566	0.490
14A	−0.507	0.418	−0.562	0.491
15A	−0.511	0.418	−0.566	0.490
16A	−0.512	0.418	−0.566	0.491
17A	−0.542	0.404	−0.595	0.491
1B	−0.557	0.402	−0.604	0.452
2B	−0.535	0.421	−0.601	0.477
3B	−0.548	0.424	−0.607	0.468
4B	−0.504	0.409	−0.568	0.479
5B	−0.558	0.404	−0.603	0.453
6B	−0.558	0.403	−0.603	0.454
7B	−0.572	0.384	−0.622	0.454
8B	−0.545	0.425	−0.604	0.469
9B	−0.577	0.401	−0.605	0.453
10B	−0.557	0.404	−0.603	0.453
11B	−0.554	0.404	−0.600	0.456
12B	−0.525	0.401	−0.585	0.454
13B	−0.546	0.425	−0.604	0.468
14B	−0.562	0.386	−0.612	0.456
1C	−0.495	0.345	−0.562	0.531
2C	−0.468	0.381	−0.542	0.552
3C	−0.459	0.384	−0.533	0.556
1D	-	−0.236	-	0.507

The maximum of negative charge is obtained of the oxygen atom O(4) of flavon-3-ol (class B) in comparison with the other classes (Fig. 3). This class of compound is characterized by a double bond (C2=C3) and a group of hydroxyl in position 3. The double bond between C2=C3 and the carbonyl function in C4 provides a stabilizing electron delocalization of the phenoxy radical. On the other hand, the

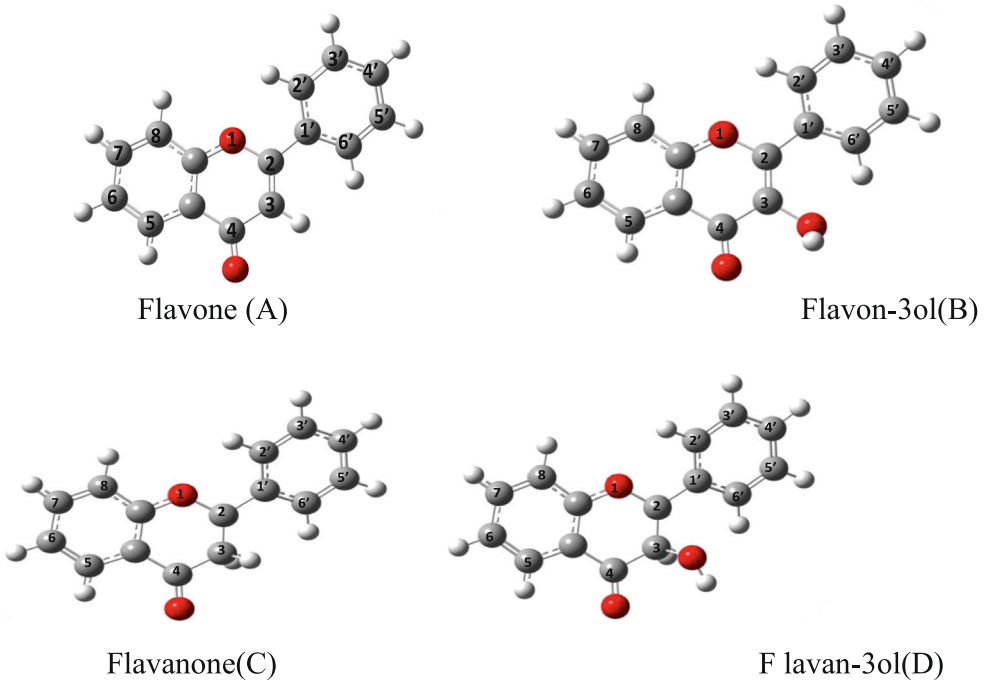

Fig. 3 Central chemical structure of the four classes of studied flavonoids and atom numbering

presence of a hydroxyl group in position 3 therefore enhances the antioxidant properties in the case of the unsaturated C ring.

The maximum of positive charge of the C(4) carbon atom is obtained in the case of flavanone (class C) in comparison with the other classes. This may be due to the absence of the double bond.

The carbon atom C(4) of hesperidin7-O-rutinoside (5, 3'-OH, 4'-OMe) has the highest positive (0.556) charge. This compound has a small antioxidant activity compared to other compounds of class (C). IC_{50}=281.41±2.62 μM.

The oxygen atom O(4) of rhamnetin (3, 5, 3', 4'-OH, 7-OMe) has the highest negative (−0.622) charge when compared with all the others compounds. This compound has a high antioxidant activity in comparison to the others compounds of class (C). IC_{50}=13.50± 0.79 μM.

Fukui indices

Because the antioxidant and antifungal activities can be mediated by bioactive receptor site (nucleophiles or electrophiles center), it is considered that the condensed Fukui functions can give relevant information regarding the reactive sites of flavonoids and the type of biochemical reaction in which they participate; for this reason they were determined and used as the descriptor for QSAR modeling.

Table 3 present the Fukui indices evaluated using MPA population analysis. As is observed in this Table, high f_k^+, f_k^- and f_k^0 values are associated mostly with the oxygen atom. The more important sites for the nucleophilic attack of all flavonoids used in this study are the oxygen atoms of (C4=O4) groups of hesperetin (2C) characterized by the presence of OH group in positions 3, 5, and 7, whereas the preferred site for the electrophilic attack are the oxygen atoms of the hesperidin7-O-rutinoside (3C). This compound has a small antioxidant activity compared to other compounds of class (C). It was observed that this compound is characterized by the presence of a rutinoside group in position 7 and the simple bond between (C2=C3).

Table 3 allows a comparison of Fukui indices and antioxidant $\log IC_{50}$ between the studied flavonoids. We note that, in general, the variations in Fukui indices are accompanied with variations in $\log IC_{50}$. However, the compounds 17A, 2B, 3B, 4B, 9B, 11B, 13B, 14B, 15B, 1C, 2C, 3C, and 1D do not respect this correlation. For example the 17A compound presents a Fukui indices value close to that of compound 16A but their $\log IC_{50}$ values are different.

QSAR models

Due to the above remarks we decided to exclude the compounds 17A, 2B, 3B, 4B, 9B, 11B, 13B, 14B, 15B, 1C, 2C, 3C, and 1D from the QSAR model construction. The present QSAR model is developed on the flavonoids who present a good correlation. The training set contains the compounds: 1A, 2A, 3A, 4A, 5A, 6A, 7A, 8A, 9A, 10A, 11A, 12A, 13A,

Table 3 Fukui indices at B3LYP/6-31G** using MPA and experimental [44] value ($logIC_{50}$) of antioxidant activity

Compounds	f_k^+		f_k^-		f_k^0		$logIC_{50}$ (μ*M*)
	O(4)	C(4)	O(4)	C(4)	O(4)	C(4)	
1A	0.091	0.06	0.061	0.014	0.076	0.037	0.7581
2A	0.091	0.06	0.057	0.012	0.074	0.036	1.0429
3A	0.092	0.056	0.067	0.012	0.0795	0.034	1.1903
4A	0.091	0.06	0.054	0.014	0.0725	0.037	1.3070
5A	0.092	0.062	0.057	0.013	0.0745	0.037	1.4497
6A	0.092	0.063	0.06	0.012	0.076	0.037	1.9328
7A	0.096	0.059	0.089	0.014	0.0925	0.029	2.2212
8A	0.076	0.067	0.035	0.011	0.0555	0.039	2.2337
9A	0.089	0.066	0.047	0.014	0.068	0.040	2.3043
10A	0.089	0.059	0.052	0.011	0.0705	0.035	2.4957
11A	0.087	0.057	0.054	0.012	0.0705	0.034	2.6456
12A	0.09	0.059	0.061	0.013	0.0755	0.036	2.6659
13A	0.09	0.059	0.058	0.013	0.074	0.036	2.6675
14A	0.09	0.057	0.068	0.016	0.079	0.036	2.6924
15A	0.09	0.058	0.061	0.013	0.075	0.035	2.7241
16A	0.088	0.058	0.054	0.012	0.071	0.035	2.7322
17A	0.088	0.058	0.054	0.012	0.071	0.035	2.9077
1B	0.091	0.087	0.054	0.023	0.072	0.055	0.9552
2B	0.09	0.073	0.051	0.014	0.070	0.043	0.9731
3B	0.092	0.076	0.053	0.015	0.072	0.045	0.9754
4B	0.087	0.064	0.05	0.017	0.068	0.040	1.0004
5B	0.091	0.087	0.053	0.023	0.071	0.055	1.0370
6B	0.089	0.077	0.056	0.019	0.072	0.048	1.0421
7B	0.089	0.086	0.051	0.023	0.07	0.054	1.1303
8B	0.089	0.078	0.058	0.02	0.073	0.049	1.1479
9B	0.091	0.075	0.052	0.014	0.071	0.044	1.1586
10B	0.091	0.087	0.056	0.024	0.073	0.055	1.2372
11B	0.091	0.087	0.054	0.023	0.072	0.055	1.4479
12B	0.09	0.085	0.056	0.024	0.073	0.054	1.8551
13B	0.092	0.081	0.052	0.019	0.072	0.054	2.4173
14B	0.09	0.075	0.057	0.015	0.073	0.045	2.7229
15B	0.09	0.085	0.056	0.024	0.073	0.054	2.8425
1C	0.096	0.059	0.089	0.014	0.092	0.036	0.9670
2C	0.116	0.109	0.037	0.014	0.076	0.061	2.3740
3C	0.110	0.09	0.072	0.024	0.091	0.057	2.4493
1D	0.108	0.09	0.051	0.02	0.079	0.055	1.2065

14A, 15A, 16A, 1B, 4B, 5B, 6B,7B, 8B, 10B, 12B. The MLR model was constructed with 19 molecules and the five remaining molecules (2A, 8A, 14A, 5B, 7B) were used as the test set.

The predicted $logIC_{50}$ values for the compounds are listed in Table 4. Figure 4 presents the correlation graph between experimental and predicted $logIC_{50}$ values.

Considering the balance of the QSAR quality and the number of employed descriptors, an optimal QSAR equation was obtained for 19 compounds in the training set using multiple linear regression analysis as follows:

$$n = 19, R^2 = 0.8160, \quad F = 20.69, S^2 = 0.0968$$
$$\mathrm{LogIC}_{50} = 27.073 - 690.29D_1 - 369.10D_2 + 831.87D_3$$

where n is the number of molecules in training set, R^2 is the square of correlation coefficient, F is the Fisher's F-value, S^2 is the regression standard deviation, D_1 is the first molecular

Table 4 experimental [44] and calculated value ($logIC_{50}$) of antioxidant activity

Compounds	Experimental $logIC_{50}$	Calculated $logIC_{50}$
1A	0.7581	0.7581
2A[a]	1.04296	1.1616
3A	1.19030	1.5977
4A	1.30706	1.1226
5A	1.44978	1.4505
6A	1.59382	1.6847
7A	2.22123	2.0927
8A[a]	1.9678	1.9523
9A	2.1590	1.9926
10A	2.30921	2.6350
11A	2.66595	2.1397
12A	2.6675	2.3204
13A	2.356	3.022
14A[a]	2.3876	2.5545
15A	2.3954	2.2669
16A	2.5713	2.8558
1B	0.9552	1.0357
4B	1.0004	1.1227
5B[a]	1.037	0.9419
6B	1.0421	1.4037
7B[a]	1.130	1.0289
8B	1.147	1.4974
10B	1.237	1.1294
12B	1.855	1.4037

a-Selected molecules for the whole test

descriptor (f_k^+), D_2 is the second molecular descriptor (f_k^-), and D_3 is the third molecular descriptor (f_k^0).

In Tables 5, X, DX, and t-test are the regression coefficients, standard errors of the regression coefficients, and significance of coefficient determination, respectively.

Table 5 The QSAR model parameters

No	X	±ΔX	t –test	Descriptors
0	27.073	3.7680	7.1849	Intersection
1	−690.29	117.71	−5.8642	$D_1-(f_k^+)$
2	- 369.10	106.82	−3.4552	$D_2-(f_k^-)$
3	831.87	215.03	3.8686	$D_3-(f_k^0)$

Correlation coefficient for the training set is excellent (R^2= 0.816).

Correlation graph points (Fig. 4) are all close to ideal line with slope=1 and y-axis origin=0. The model thus explains every molecule activity of training set with minor error.

The predicted ranges of the antioxidant activity of the developed QSAR model are in good agreement with the experimental data. The predicted range for the model is 0.7581–3.022 compared with the experimental range of 0.7581–2.6675, which are very close. There are three outliers from this model: the compounds 3A, 13A, and 12B. This result can be related to the fact of being the only compounds having no substituent on B ring.

As noted above, the presence of hydroxyls groups on B ring is the most significant structural parameter for the antioxidant activity [61]. Phenoxy radicals are stabilized by a hydroxyl in ortho to the one that loses its hydrogen atom. Actually, stability comes from delocalization of the electron and creation of a hydrogen bond which is necessary to obtain an optimal antioxidant activity.

The developed QSAR model is a good predictive model since the calculated antioxidant $logIC_{50}$ of the test set compounds are close to the experimental ones. We note the large discrepancy between calculated and experimental data for the compound 14A. It is supposed that the replacement of hydroxyl group by methoxyl on position 4' is not well represented in our QSAR model. Actually, in comparison to other

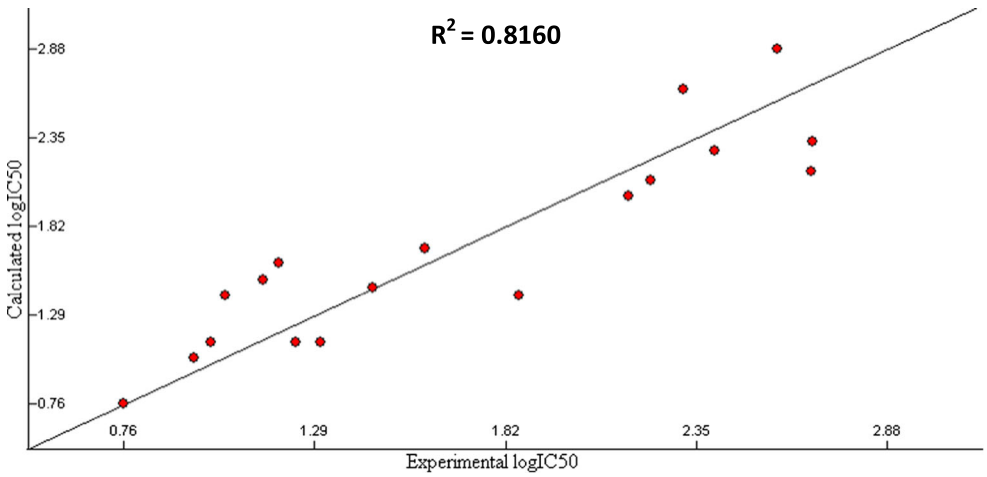

Fig. 4 Linear regression line between experimental and calculated $logIC_{50}$ using the developed QSAR model

compounds of the test set (5B, 7B), the compound 14A has a methoxyl group on 4' position in replacement of a hydroxyl.

Conclusions

The main objective of this paper is the comprehension and development of a new QSAR model of the relationship between some electronic descriptors of their carbonyl atoms and antioxidant activity of flavonoids. The QSAR studies of a series of flavonoids have been carried out using the conceptual density functional theory (DFT). The most significant outcome of the work is the introduction of a new descriptor namely, Fukui indices. An optimal QSAR equation with three parameters, i.e., f_k^+, f_k^-, and f_k^0 showing good statistic quality in the regression (R^2=0.8160). The QSAR equation indicates that the Fukui indices are a useful descriptor in determining the antioxidant radical scavenging activity. This descriptor is one of the widely used local density functional descriptors to model chemical reactivity and site selectivity.

We note that the chosen descriptors are not sufficient to develop a QSAR model using the data of only 36 flavonoids. However, the good obtained result will be extended by introducing Fukui indices of other atoms of other series of molecules.

In conclusion, a good QSAR model for the antioxidant activity of flavonoids was developed using DFT based descriptors. Therefore, DFT based QSARs could be expected to help to facilitate a future design of additional substituted flavonoids with good antioxidant activity, so the QSAR studies can offer important insights into designing high activity compounds prior to synthesis.

References

1. Burda S, Oleszek W (2001) J Agric Food Chem 49:2774–2779
2. Leibovitz BE, Mueller JA (1993) J Optimal Nutr 2:17–35
3. Soike H, Leng-Peschlow E (1987) Planta Med 53:37–39
4. Fesen MR, Hirogchi S, Yung J, Kohn KW, Pommier Y (1994) Biochem Pharmacol 48:595–608
5. Hu C, Chem K, Shi Q, Kilkuskie RE, Cheng Y, Lee KH (1994) J Nat Prod 57:42–51
6. Deschner EE, Ruperig J, Wong G, Newmark HL (1991) Carcinogenesis 12:1193–1196
7. Pathak D, Pathak K, Singla AK (1991) Fitoterapia 62:371–389
8. Landolfi R, Mower RL, Steiner M (1984) Biochem Pharmacol 32: 1525–1530
9. Carvalho JCT, Ferreira LP, Santos LS, Corrêa MJC, Campos LMO, Bastos JK, Sarti SJ (1999) J Ethnopharmacol 64:173–177
10. Ishitsuka H, Ohsawa C, Ohiwa T, Umeda I, Suhara Y (1982) Agents Chemother 22:611–616
11. Hannongbua S, Lawtrakul L, Limtrakul J (1996) J Comput Aided Mol Des 10:145–152
12. Stevens JF, Ivancic M, Deinzer M, Wollernweber E (1999) J Nat Prod 62:392–394
13. Kawakita T, Kaneko M, Nornoto K (1996) Biol Pharm Bull 19:936
14. Halliwell B, Gutteridge JMC, Cross CE (1992) J Lab Clin Med 119: 598–620
15. Gao D, Tawa R, Masaki H, Okano Y, Sakurai H (1998) Chem Pharm Bull 46:1383–1387
16. Cos P, Ying L, Calomme M, Hu JP, Cimanga K, Van Poel B, Pieters L, Vlietinck AJ, Vanden Berghe D (1998) J Nat Prod 61:71–76
17. Van Acker SABE, van den Berg DJ, Tromp MNJL, Griffioen DH, van Bennekom WP, van der Vijgh WJF, Bast A (1996) Free Radic Biol Med 20:331–342
18. Wrigth JS, Johnson ER, Di Labio GA (2001) J Am Chem Soc 123: 1173–1183
19. Leopoldini M, Prieto I, Russo N, Toscano M (2004) J Phys Chem B 108:92–94
20. Nenadis N, Wang L-F, Tsimidou M, Zhang H-Y (2004) J Agric Food Chem 52:4669–4674
21. Roginsky V, Lissi EA (2005) Food Chem 92:235–254
22. Villa~no D, Ferna'ndez-Pacho'n MS, Troncoso AM, Garcı'a-Parrilla MC (2005) Anal Chim Acta 538:391–398
23. Heim KE, Tagliaferro AR, Bobilya DJ (2002) J Nutr Biochem 13: 572–584
24. Rice-Evans CA, Miller NJ, Paganga G (1996) Free Radic Biol Med 20:933–956
25. Amić D, Davidović Amic D, Bes˘lo D, Trinajstic N (2003) Croat Chem Acta 76:55–61
26. Rackova L, Firakova S, Kostalova D, Stefek M, Sturdik E, Majekova M (2005) Bioorg Med Chem 13:6477–6484
27. Farkas O, Jakus J, He'berger K (2004) Molecules 9:1079–1088
28. Clare BW, Supuran CT (1998) J Mol Struct (THEOCHEM) 428: 109–121
29. Clare BW, Supuran CT (1999) Eur J Med Chem 34:463–474
30. Zhang L, Wan J, Yang G (2004) Bioorg Med Chem 12:6183–6191
31. Wan J, Zhang L, Yang G, Zhan C-G (2004) J Chem Inf Comput Sci 44:2099–2105
32. Sarkar A, Mostafa G (2009) J Mol Model 15:1221–1228
33. Petersson WG, Al-Laham A (1991) J Chem Phys 94:6081–6090
34. Parr RG, Yang W (1984) J Am Chem Soc 106:4049–4050
35. Yang W, Mortier W.J (1986) J. Am. Chem. Soc 108 :5708–5711
36. Mulliken RS (1955) J Chem Phys 23:1833–1840
37. Hirshfeld FL (1977) Theor Chim Acta 44:129–138
38. Reed AE, Weinhold F (1983) J Chem Phys 78:4066–4073
39. Fukui K (1982) Science 218:747–754
40. Thakur A, Thakur M, Kakani N, Joshi A, Thakur S, Gupta A (2004) ARKIVOC xiv:36–42
41. Karelson M, Lobanov VS, Katritzky AR (1996) Chem Rev 96:1027–1044
42. Vracko M, Gasteiger J (2002) Internet Electron. J Mol Des 1:527–544
43. Lameir J, Alves CN, Moliner V, Silla E (2006) Eur J Med Chem 41: 616–623
44. Seyoum A, Kaleab A, Fathy K (2006) Phytochemistry 67:2058–2070
45. Anouar EH, Marakchi K, Komiha N, Kabbaj OK, Dhaouadi Z, Lahmar S (2009) Phys Chem News 45:107–113
46. Kowalski BR (1984) Chemometrics: mathematics and statistics in chemistry. Reidel, Dordrecht
47. De Proft F, Jan Martin ML Geerlings P (1996) Chem Phy Lett 256: 400–408
48. Chang R (2001) Chemistry, 7th edn. McGraw-Hill, New York
49. Parr RG, Yang W (1989) Density-functional theory of atoms and molecules. Oxford University Press, New York
50. Mulliken RS (1934) J Chem Phys 2:782–793
51. Yang W, Parr RG (1985) Proc Natl Acad Sci U S A 82:6723–6726

52. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA, Vreven T Jr, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene MX, Knox JE, Hratchian HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2003) *Gaussian03*, Revision B.05. Gaussian, Inc, Pittsburgh
53. Reed AE, Curtiss LA, Weinhold F (1988) Chem Rev 88:899–926
54. Snedecor GW, Cochran WG (1967) Statistical methods. Oxford & Ibh, New Delhi
55. Zhang S, Wei L, Bastow K, Zheng W, Brossi A, Lee KH, Tropsha A (2007) J Comput Aided Mol Des 21:97–112
56. Young D (2001) Computational chemistry. Wiley, New York
57. Mulliken RS (1955) Electronic population analysis on LCAO-MO molecular wave functions. J Chem Phys 23:1833–1841
58. Mulliken RS (1962) Criteria for the construction of good self-consistent-field molecular orbital wave functions, and the significance of LCAO-MO population analysis. J Chem Phys 36:3428–3439
59. Reed AE, Curtiss LA, Weinhold F (1988) Intermolecular interactions from a natural bond orbital, donor–acceptor viewpoint. Chem Rev 88:899–926
60. Reed AE, Weinstock RB, Weinhold F (1985) J Chem Phys 83:735–746
61. Sroka Z (2005) Antioxidative and antiradical properties of plant phenolics. Naturforsch C 60:833–843