A LFER Study of UV Absorption Frequencies of Biologically Active (*E*)-4-Aryl-4-oxo-2-butenoic Acids in Different Solvents. Implication on Behavior Within Cell Membrane. Part 1. Methanol.

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Introduction

One type of drug resistance is the ability of the organism to exclude the drug from the site of action by preventing the uptake of the drug. Plasma membrane can adjust its net charge (or hydrophobic character) by varying proportion of anionic to cationic groups. In this way a drug bearing the same kind of charge can be repelled from the membrane.[1]

On the other hand, it is known that compounds may have different UV absorption maxima in different solvents, as a consequence of solvent polarity,[2] H-bond donor/acceptor ability *etc*. Number of articles report correlation of UV absorption frequencies of phenyl-substituted compounds and literature substituent's parameters. Such studies aimed to quantify changes of UV maxima within congener set of compounds in the different solvents, and explain obtained results in term of influence of solvent polarity, H-bond donor/acceptor ability *etc.* (LSER).[3] The main trend observed in these studies was usage of the sets of congener compounds bearing conveniently chosen substituents in the same position on phenyl ring; often *para*- or *meta*-, and less often *ortho*-position.[4] Such studies can be considered as model studies. Not many attempts were done to study a congener set of compounds bearing several substituents at different positions on phenyl rings.[5]

To explain previously proven high antiproliferative and antibacterial activity of (*E*)-4-aryl-4-oxo-2-butenoic acids[6] and their derivatives,[7] with most active congeners bearing *ortho*-alkyl substituents, a need for inclusion of *ortho*-, *para*- and *ortho*-, *meta*-substituted congeners in various correlations was imposed.

To get insight in the behavior of title compounds within cell membrane[8] (as the part of the broader study of the most active congeners in different solvents), we have studied the extended correlation of UV absorption maxima of sixteen (*E*)-4-aryl-4-oxo-2-butenoic acids in methanol with the σ substituent constants and with a descriptor assessed by molecular modeling.

Results

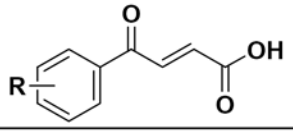
Title compounds (**1-17**) were synthesized and characterized as previously reported.[6] UV/Vis spectra were recorded on GBC Cintra 6 UV/Vis spectrophotometer in concentration range $5 \cdot 10^{-5}$ to $1 \cdot 10^{-4}$ *M* in methanol. Concentrations were set to have the absorption maxima (A_{max}) close to 1. Typical spectrum of (*E*)-4-aryl-4-oxo-2-butenoic acids is shown on *Figure 1* for 4-(2-ethyl-4-*i*-propylphenyl)-4-oxo-2-butenoic acid (**17**). The bands having maxima between 258.9 and 287.5 nm (secondary band) were used for correlations. Structures of compounds used in present communication, UV maxima, as well as σ values, and indicator variable used for correlations are given in the *Table 1*. Sigma (σ) values,[9] derived for benzoic acid analogs (implied analogy with benzoyl derivatives, Ph-C(O)-R) were used. Multiple linear regressions were done using extended Hammett correlations of the type:

$$\lambda_{max(R)} / \lambda_{max(H)} = \rho_1 \sigma_p + \rho_2 \sigma_m + \rho_3 \sigma_o + C \qquad \text{Equation 1}$$

$$\lambda_{max(R)} / \lambda_{max(H)} = \rho_1 \sigma_p + \rho_2 \sigma_m + \rho_3 \sigma_o + \alpha I + C \qquad \text{Equation 2}$$

Where $\boldsymbol{\lambda}_{\mathbf{max}(R)}$ is a wavelengths of the absorption maximum for compounds **2-16** (*Table 1*), while $\boldsymbol{\lambda}_{\mathbf{max}(H)}$ is wavelength of the absorption maximum of unsubstituted acid (**1**). Weights of *ortho*-, *meta*-, and *para*-substituents were factorized using appropriate sigmas for each particular position. Using *Eq. 1* on compounds (**2-15**) very good correlation was obtained (Correlation 1, *Table 2*), however inclusion of compounds **16** and **17** resulted in inferior correlation (Correlation 2, *Table 2*). Addition of an indicator variable (***I***) (seventh column of the *Table 1*), using *Eq. 2* (Correlation 3, *Table 2*) for compounds **16** and **17** gave correlation of the comparable quality as correlation 1.

Table1. *Structures of compounds, UV maxima, σ values, and indicator variable*



Compound Nº	R-	λ_{max}	σ_p	σ_m	σ_o	I
1	H-	258,925	0	0	0	0
2	4-Me-	281,965	–0,14	0	0	0
3	4-Et-	287,512	–0,32*	0	0	0
4	4-*i*-Pr-	283,245	–0,15	0	0	0
5	4-*n*-Bu-	282,819	–0,16	0	0	0
6	4-*tert*-Bu-	284,099	–0,20	0	0	0
7	4-F-	275,992	0,06	0	0	0
8	4-Cl-	273,005	0,23	0	0	0
9	4-Br-	272,579	0,23	0	0	0
10	2,5-di-Me-	276,419	0	–0,06	0,29	0
11	2,4-di-Me-	282,819	–0,14	0	0,29	0
12	3,4-di-Me-	286,232	–0,14	–0,06	0	0
13	3-NO_2-4-Me-	248,685	–0,31	0,76	0	0
14	2-Cl-4-Me-	269,165	–0,14	0	1,28	0
15	2,5-di-*i*-Pr-	274,991	0	–0,04	0,56	0
16	2,4-di-*i*-Pr-	287,085	–0,15	0	0,56	1
17	2-Et-5-*i*-Pr-	284,525	0	–0,04	0,41	1

*σ_p^+

Table 2. *Correlations obtained using Eq. 1 (Corr. 1 and 2) and Eq.2 (Corr. 3)*

Correlation	ρ_1	ρ_2	ρ_3	α	C	*n*	r	*sd*	F
1	*–0,109 (±0,009)*	*–0,196 (±0,008)*	*–0,040 (±0,004)*	/	*1,076 (±0,002)*	*14*	*0,993*	*0,005*	*228,0*
2	*–0,110 (±0,024)*	*–0,200 (±0,020)*	*–0,030 (±0,010)*	/	*1,079 (±0,004)*	*16*	*0,946*	*0,014*	*34,3*
3	*–0,111 (±0,009)*	*–0,196 (±0,008)*	*–0,040 (±0,004)*	*0,035 (±0,004)*	*1,076 (±0,002)*	*16*	*0,993*	*0,005*	*189,9*

On the *Figure 2*, plot λ_{max} measured *vs.* λ_{max} predicted, obtained using correlation 3 is shown. For the sake of clarity, λ_{max} values, *not* $\lambda_{max(R)} \setminus \lambda_{max(H)}$ are used.

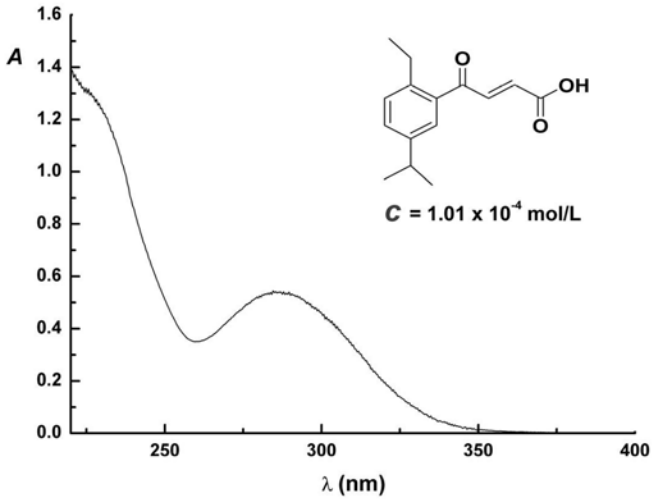


Figure 1. *Spectrum of (E)- 4-(2-ethyl-4-i-propylphenyl)-4-oxo-2-butenoic acid.*

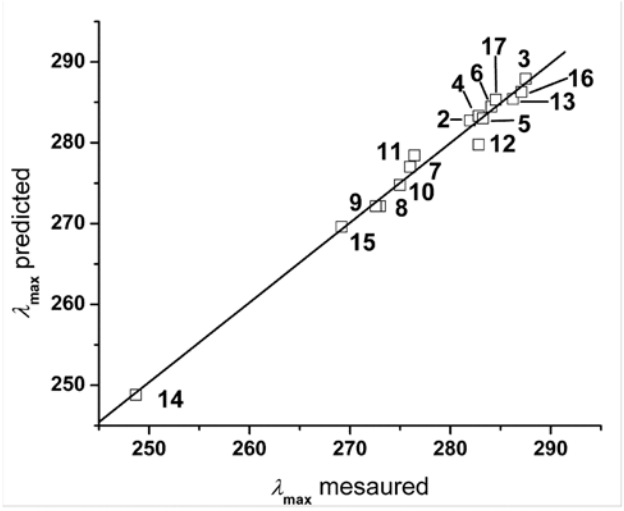
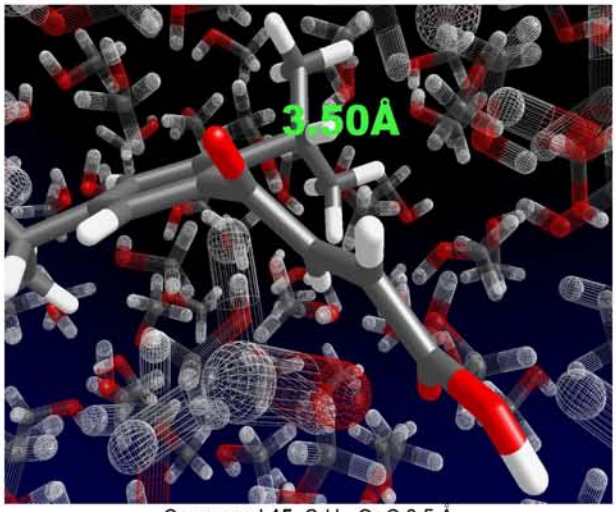


Figure 2. *Plot (λ_{max} measured) vs. (λ_{max} predicted), obtained using correlation 3 (Table2).*

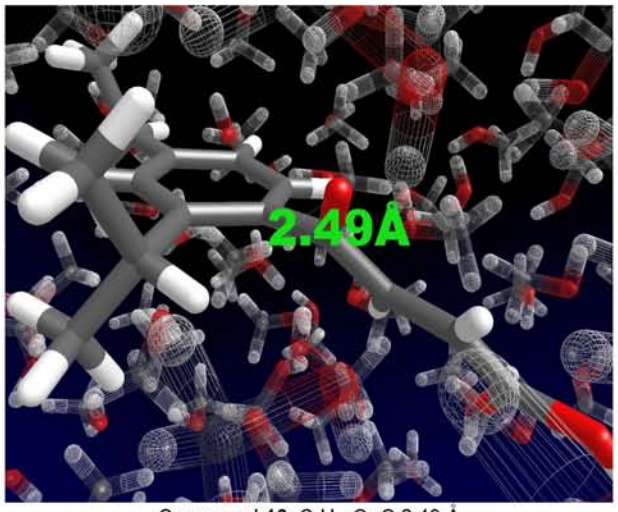
Whilst last equation looks statistically good established, one can ask why ***I*** is introduced for last two compounds (**16**, **17**) and didn't apply for compounds **14** and **15,** bearing bulky substituents on the *ortho*- position, too. Molecular modeling gives partial answer to that. Geometry optimization of compounds (**14-17**) was done by the semi-empirical PM3 molecular orbital method, following solvatation with 15 Å sphere (0.8 Å vdW overlap) MeOH, using VegaZZ 2.0.5 package.[10] In this way obtained clusters were further optimized in Hyperchem 7.5.2[11] on the molecular mechanics level, using MM+ force field (bond, angle, torsion, non-bonded, electrostatic and hydrogen-bonded interactions were account). Resulted clusters were returned back to VegaZZ 2.0.5, and geometries of studied molecules (**14-17**) examined. For the compounds **14-17** is obvious that angle between planes of phenyl rings and the rest of the molecule (-C(O)-CH=CH-COOH) are > 30 °, as is expected. However, for compounds **16** and **17** keto oxygen's are more closer to *ortho*-substituent H- of α C (having *same* distance C=O····H-C α (2,49 Å)) than in compounds **14** and **15**. In the compounds **14** and **15**, keto oxygen's are on the distance >3.0 Å from the *ortho*-substituent α-C hydrogen in the compound **15**, or *ortho*-Cl- (compound **14**). This is illustrated comparing geometries of **15** and **16** (*Figures 3* and *4*, respectively). Are such geometries a consequence of weak C-H····O=C< bonds, or the result of mere balance of intramolecular forces (spatial arrangement between planes of aryl rings and the rest of molecules) is not instantly clear.

One can complain for low diversity of substituents using in present study. The alkyl substituted compounds are the most active, and as such, are the major topic of interest of our group. To improve statistical significance of obtained correlations, some halo- and nitro-substituted compound were introduced in the whole set (**7-9**, **13**,**14**). The disadvantage in the correlations was the using of σ^+ value for compound **3**, whilst for other compounds σ values were used. This can't be explained so far.



Compound **15**, C-H····O=C 3.5 Å

Figure 3. *Optimized geometry of (E)-4-(2,5-di-i-Pr-phenyl)-4-oxo-2-butenoic acids (**15**) (solid) surrounded with 15 Å MeOH sphere (wire).*



Compound **16**, C-H····O=C 2.49 Å

Figure 4. *Optimized geometry of (E)-4-(2,4-di-i-Pr-phenyl)-4-oxo-2-butenoic acids (**16**) (solid) surrounded with 15 Å MeOH sphere (wire).*

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Linearna korelacija slobodne energije (LFER) ULj/Vid apsorpcionih maksimuma biološki aktivnih (*E*)-4-aril-4-okso-2-butenskih kiselina u različitim rastvaračima kao model ponašanja unutar ćelijske membrane. Prvi deo. Metanol

U okviru šire studije biološki najaktivnijih kongenera (E)-4-aril-4-okso-2-butenskih kiselina u različitim rastvaračima, a u cilju dobijanja korisnih podataka o mogućem ponašanju jedinjenja unutar ćelijske membrane, u ovom saopštenju je opisana korelacija ULj/Vid apsorpcionih maksimuma sedamnaest (E)-4-aril-4-okso-2-butenskih kiselina u metanolu, upotrebom literaturnih sigma (σ) konstanti i deskriptora dobijenih molekulskim modelovanjem. Kao rezultat su prikazane tri korelacije koje imaju veoma dobre statističke parametre. Rezultati molekulskog modelovanja daju moguće objašnjenje za odstupanje najaktivnijih kongenera (koji imaju voluminozne orto-supstituente) od klasičnih korelacija Hammett-ovog tipa. Uključivanjem u korelacije parametara dobijenih molekulskim modelovanjem dobijeni su rezultati koi se mogu primeniti na širi skup srodnih jedinjenja.