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Research Article

Tumor interactional equation with biological and drug environment

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ABSTRACT

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Today, chemotherapy is an aggressive form of chemical drug therapy meant to destroy cancerous tumors in the human body. Since the human body system can be considered as a solvent/biological environment, by obtaining effective interactional equations in anticancer drugs, real behavior interactional of these drugs in the body environment can be predicted. To this end, the spectroscopic technique is a promising investigative and diagnostic tool that can assist in uncovering the interactional equation of cancerous tumors and provide quantifiable molecular information for diagnosis and treatment evaluation. To investigate the interactional equation of cancerous tissues and the type of their interactional behavior, samples were taken from these tissues, and the mathematical model of cancerous tissue interaction was presented using Kamlet–Taft polarity parameters. This equation probes anticancer drug molecular interactional reactions with cancerous tumors in a sample to obtain information on their effective coefficient in the body and/or inter/intra molecular interactions. These interactions contain detailed information about the behavior of drugs used in cancer treatment and cancer tissues, which can be very useful for choosing treatment methods.

KEYWORDS

Spectroscopy, Biological environment, Cancerous tumor, Kamlet–Taft, Molecular interactions

I. INTRODUCTION

Cancer is the second-leading cause of death in the world and its genesis and progression are extremely complex. Cancer can be treated or stopped by chemotherapy, radiotherapy, and surgery procedures alone or in combination. Meanwhile, chemotherapy is a more effective and common treatment approach for cancer treatment, prevention of slow growth, and tumor reduction. The basics of chemotherapy include the use of drugs alone or in combination to inhibit cell proliferation and tumor growth [1],[2]. However, the emergence of new drugs and their drug resistance has turned the focus of scientists towards natural products including fruits, vegetables, teas, spices, and soy-based foods. Chalcone and its analogs are one of the privileged groups of natural compounds that are widely found in various plants. Chalcones (Fig.1) contain two aromatic rings (ring A and ring B) and α, β–unsaturated carbonyl group.

They have a delocalized π-electron-containing order in their aromatic rings. Chalcones are highly attractive molecules due to their broad biological activities with clinical potential against various diseases, especially for their anti-tumor activity. In addition, being inexpensive, available, and having low toxicity are a few advantages of chalcones, in comparison to other alternative medicinal compounds [3]–[5]. Many studies have shown anticancer activity of these compounds against various tumor cells. It has been found that the incorporation of different substituent groups on their two aromatic rings increases the anticancer and other activities [6]–[10].

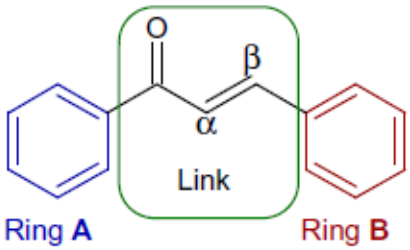


Fig. **1** Chalcone scaffold

Since the human body can be considered as a solvent/biological environment, by obtaining effective interactional equations in chalcone antitumor drugs, their real interactional behavior in the body environment can be predicted. When a drug is dissolved in various solvent environments, the solvatochromic effect occurs, and the spectrum of the substance changes. These spectral changes are due to drug-solvent interactions. Based on the studies, drug-solvent interactions could be non-specific, such as electrostatic, and/or specific in nature, such as electron donor-acceptor interactions or hydrogen bonding interactions [11]–[23]. To characterize these drug-solvent interactions, multiple regression analysis has been used, as proposed by Kamlet–Taft [24].

$$X = X_0 + a\alpha + b\beta + s\pi^* \qquad (1)$$

The Kamlet–Abboud–Taft (KAT) solvent polarity parameters consist of the solvent's dipolarity/polarizability (π^*) [25], solvent basicity (β) [26], and, solvent acidity (α) [27], X_0 is the regression intercept corresponding to the reference solvent or gaseous phase, and the coefficients *a*, *b*, and *s*, respectively, reflect the degree of regression for the interactions between the solvent's dipolarity/polarizability, solvent's basicity, and solvent's acidity.

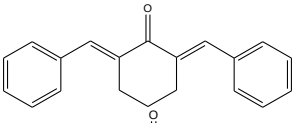
In this experimental work, KAT polarity parameters (π^*, β, and α) of breast and brain tumors were reported with the solvatochromic method, using the DR_{II} and coumarin 504 standard probe. Moreover, interactional behavior of six different chemical structures of chalcone drug with these tumors was investigated. This behavior probes chalcone antitumor drug molecular interactional reactions with cancerous tumors in a sample to obtain information on their effective coefficient in the body and/or inter/intra-molecular interactions. These interactions contain detailed information about the behavior of chalcone drugs used in cancer treatment and cancer tissues, which can be very useful for choosing treatment methods.

II. Experimental Section

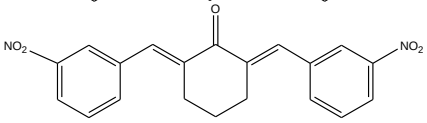
A. *Materials*

Synthesis and purification of the studied chalcones (Fig.2) were carried out as described in reference [28] and were used as solutes. Spectroscopy-grade solvent-sensitive standard dyes and coumarin 504 (Table 1) were obtained from Sigma Aldrich (Taufkirchen, Germany) and used without further purification. Disperse azo dye (DR_{II}) was synthesized and purified according to the common procedure in our laboratory and used as a probe.

Chalcone (I)



Chalcone (II)



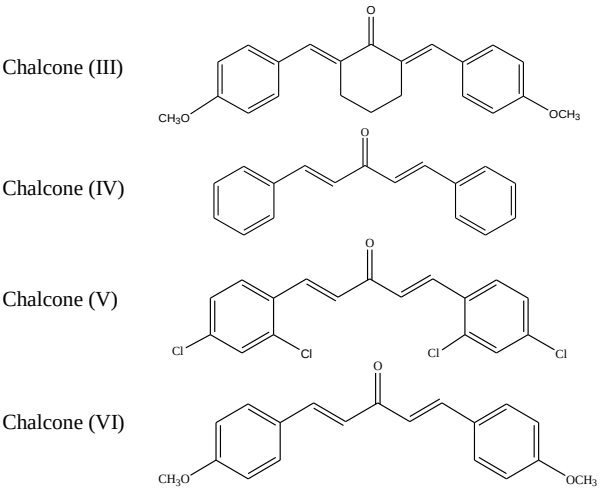
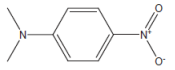
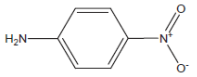
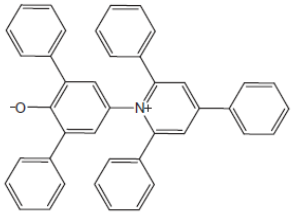
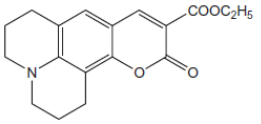
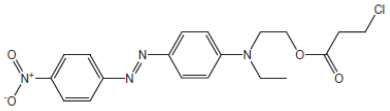


Fig.**2** Chemical structure of chalcones

TABLE 1: SOLVATOCHROMIC INDICATORS AND DYES USED

Dyes	Chemical structure
N, *N*-dimethyl-*4*-nitro aniline	
4-nitro aniline	
Reichardt's betaine dye 2,6-Diphenyl-4-(2,4,6-triphenyl-1-pyridinio) phenolate	
Coumarin 504	
2,3,5,6-1*H*,4*H*-Tetrahydro-9-cabethoxyquinolizino-[9,9a,1-*gh*]coumarin	
DR_{II}	
4-nitro-4-(*N*-ethyl, *N*-(2-(3-chloropropanoyloxy)ethyl azobenzene	

B. *Absorption spectroscopy*

After making an extremely dilute solution of polarity indicator dye, (10^{-5}M), the absorption spectra of 300–800 nm were recorded via a double beam Shimadzu UV-2450 Scan UV–visible spectrophotometer.

C. *Determination of the solvent polarity parameters via the solvatochromic method*

The solvatochromism technique was employed to define the KAT parameters with the wavenumber of the maximum absorption of each indicator expressed in kK (1000 cm^{-1}). To this end, we used all solvatochromic indicators listed in Table 1. After starting the experiment and recording the initial spectra, due to the fact that the absorption spectrum of two dyes, *4*-nitroaniline, and *N*, *N*-diethyl-*4*-nitroaniline, is located in the ultraviolet region and it is not possible to continue working with these dyes, it is necessary to use an alternative dye with a suitable regression coefficient. Moreover, in some cases, Richard's dye was not dissolved in tissues. Therefore, suitable substitute dyes were used. For this reason, a study was conducted on the dyes of the azo and coumarin family. Azo family dyes are an important group of dyes that have attracted the attention of many researchers due to their linear structure, color stability, and interchangeable spatial forms [29],[30]. DR_{II} dye to replace *4*-nitroaniline and *N*, *N*-diethyl-*4*-nitroaniline, and Coumarin 504 dye to replace Richard's dye were investigated. Coumarin 504 has a good linear relationship with Richard's dye, making it possible to measure α and $E_T(30)$ parameters with high accuracy. The obtained results are given in Figs.2, 3 and 4.

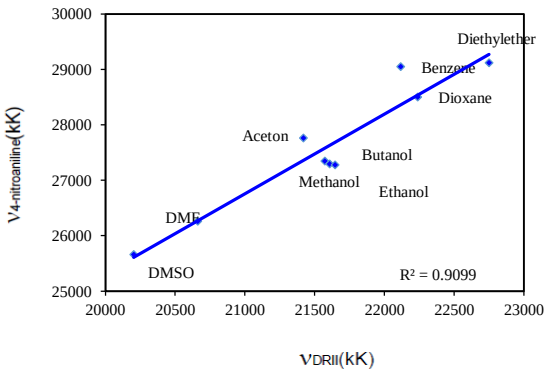


Fig.**3** Wavenumber of *4*-nitroaniline versus wavenumber of DR_{II}

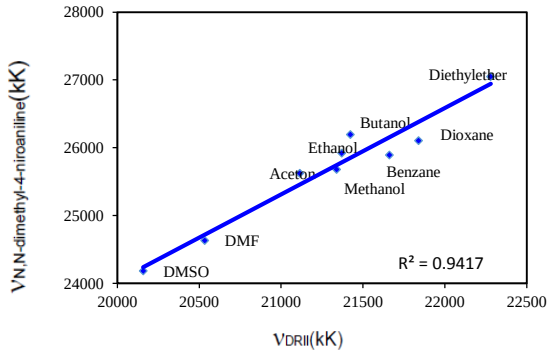


Fig.**4** Wavenumber of *N*, *N*-diethyl-*4*-nitroaniline versus wavenumber of DR_{II}

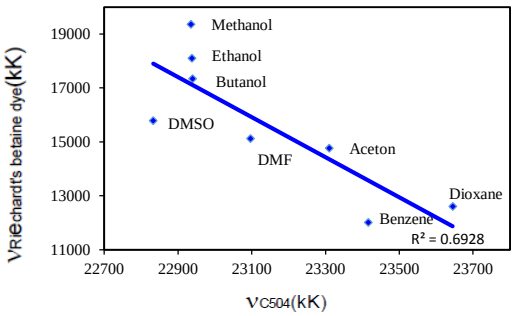


Fig.**5** Wavenumber of *N*, *N*-diethyl-*4*-nitroaniline versus wavenumber of DR_{II}

KAT parameters are calculated using the maximum absorption in the obtained absorption spectrum. In this case, the obtained maximum absorption wavelength from the recorded spectra is used as a wavenumber in cm^{-1} of 1000. The obtained relations from the above diagrams are respectively:

$$\nu_{(4-nitroaniline)} = 1.68\nu_{(DRII)} - 8402.40 = 0.95 \quad (2)$$

$$\nu_{(N,N-Dimethyl-4-nitroaniline)} = 1.19\nu_{(DRII)} + 594.39R = 0.98 \quad (3)$$

$$\nu_{(Reichardt-betaine-dye)} = -7.48\nu_{(C504)} + 188778R = 0.90 \quad (4)$$

After determining the wavenumber of the standard probe in each of the chalcone samples and tissues, the KAT and Reichardt parameters are calculated via the following relationships [29], [30]:

$$E_T(30) = \frac{28591.5}{\lambda_{max(Reichardt)}} \quad (5)$$

$$E_T^N = \frac{E_T(30)_{Solvent} - 30.7}{32.4} \quad (6)$$

$$\pi^* = \frac{\nu_{(N,N-dimethyl-4-nitroaniline)} - 28.18}{-3.52} \quad (7)$$

$$\beta = \frac{0.98\nu_{(N,N-dimethyl-4-nitroaniline)} - \nu_{(4-nitroaniline)} + 3.49}{2.75} \quad (8)$$

$$\alpha = \frac{E_T(30) - 14.6\pi^* - 30.31}{16.5} \quad (9)$$

III. RESULTS AND DISCUSSION

A. *Preparation of tissue samples*

First, samples of cancer tissues that were removed from the patient's body during surgery were prepared. On the other hand, these tissues can have various contaminations, and at the same time, to make the tissues similar to the original structure, the conventional methods of cutting these materials in layers were avoided. On the other hand, it was not possible to confirm the cellular structure of the desired tissue due to the effect on the test process, and instead, the sample taken out of the patient's body was immediately washed completely with saline solution and a cut was made from its central part. Next, the extra parts, i.e. the surface parts of this tissue, were cut and removed with a microtome device. Then the sample was placed inside the standard dye solution. After one hour, a slice of the desired tissue that had absorbed the dye was obtained using a cutting method with a sharp blade and placing the sample inside the unolith. It should be noted that in absorption spectroscopy, the non-uniformity of the sample surface has no effect on the spectroscopic results. Therefore, there was no need for very high precision in uniform cutting. Furthermore, the samples should be transparent against the light transmission, and the examined samples have relatively good transparency in the wavelength range of 420 nm. As a result, the standard dyes that have absorption lower than this wavelength were replaced by using the linear comparison

method with other reference dyes (C504 and DR_{II} dyes). The prepared slice with a diameter of about 1 mm and length and width of 3 and 1 cm, respectively was placed on the quartz cells and immediately the absorption spectrum of the sample was recorded in the range of 350 to 800 nm. Since the absorbed dyes have absorption between 450 and 650 nm, this wavelength range was chosen. The entire process was carried out in less than 10 minutes and each experiment was repeated eight times, and its average was reported.

B. *Investigation of interactional behavior of cancerous tissues*

After obtaining the wavenumber of the used dyes in this experiment, these numbers were converted to the wavenumber of solvent polarity dyes to be used in the KAT equations. Using these wavenumbers the KAT equations of solvent polarity parameters for breast and brain tissues were calculated and the results are given in Tables 2 and 3.

TABLE2. SOLVATOCHROMIC POLARITY OF BREAST TUMOR AT ROOM TEMPERATURE

Breast Tumor	α	β	π^*	$E_T(30)$	E_T^N
1	0.26	0.54	0.55	42.69	0.37
2	0.33	0.55	0.56	43.66	0.40
3	0.29	0.58	0.62	44.31	0.42
4	0.35	0.68	0.81	48.20	0.54
5	0.49	0.49	0.46	45.44	0.46
6	0.36	0.57	0.61	45.39	0.45
7	0.27	0.50	0.48	42.15	0.35
8	0.28	0.52	0.50	42.21	0.35
Average	0.33	0.55	0.57	44.25	0.37

TABLE3. SOLVATOCHROMIC POLARITY OF A BRAIN TUMOR AT ROOM TEMPERATURE

Brain Tumor	α	β	π^*	$E_T(30)$	E_T^N
1	0.80	0.86	0.09	43.52	0.39
2	1.44	0.73	0.89	67.04	1.12
3	1.66	0.69	0.82	69.65	1.20
4	1.56	0.64	0.73	66.65	1.11
5	0.72	0.63	0.04	41.56	0.33
6	0.56	0.55	0.08	41.80	0.34
7	0.63	0.59	0.07	41.50	0.33
8	0.87	0.72	0.16	40.35	0.30
Average	0.95	0.57	0.36	51.50	0.64

As expected, the obtained values for breast tumors show that β and π^* values are higher than α values (Table 2). On the other hand, according to our previous research [4] the effective coefficients of β and π^* in chalcones I, II, and III (*b* and *s*) are higher than the other chalcones. Therefore, the absorption of these chalcones (I, II and III) is more than others, and hence it is better absorption in the breast tissue. Therefore, the interactional equation for breast tissue is:

$$X = 31240 - 130\alpha - 390\beta - 750\pi^* \quad (9)$$

In contrast, the obtained values for brain tumors have different trends. They show that α and β values are higher than π^*values (Table 3). Based on our previous research [5] the effective coefficients of α and β in chalcones IV, V, and VI (*a* and *b*) are higher than the others. As a result, the absorption of these chalcones (IV, V, and VI) is greater than other chalcones. Meaning that they have better drug effectiveness. Therefore, the interactional equation for brain tissue is:

$$X = 31598 - 476\alpha - 328\beta - 747\pi^* \quad (10)$$

IV. CONCLUSION

Chalcone is well known in the medicinal fields as an important antitumor drug. The presence of different functional groups in the chemical structure of chalcones leads to their different biological, medicinal, and therapeutic characteristics. In this experimental work, KAT polarity parameters (π^*, β, and α) of breast and brain tumors were obtained through the solvatochromic method using the DR_{II} and coumarin 504 standard probe. In addition, interactional behaviors of six chalcones with different substituent groups in their chemical structures with these tumors were investigated. Our results indicate the interesting properties of chalcone antitumor drugs and their performance based on different substituent groups can be modified in different biological environments. Consequently, chalcone with its

unique structures can be used as a good candidate for treating different tumor tissues.

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