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Assessing the pharmacological potential of selected xanthene derivatives

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Abstract: A convenient and efficient approach toward the synthesis of seven aromatically substituted xanthendiones **1**–**7** and one structurally-related xanthenone **8** through condensation of dimedone and the appropriate aromatic aldehyde is reported. Further, their chemical structure was confirmed by melting points, elemental analysis, FT-IR, ^{1}H-, ^{13}C-NMR and UV–Vis spectroscopic methods. The relationship between the chemical structure and pharmacological activity was determined empirically using appropriate software packages and *in vitro* using the 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) method. The results of *in silico* prediction suggested that all investigated compounds possess good oral bioavailability. The results of the ABTS assay indicate that five compounds possess the ability to scavenge the $ABTS^{\bullet+}$ radical cation. Based on the comparison of the IC_{50} values, the activity of the compounds was found to be as follows: **6** > **1** > **7** > **2** > **8**. The effects of solvent dipolarity/polarizability and solute solvent–hydrogen-bonding interactions on the shifts of the absorption maxima were rationalized by means of the linear solvation energy relationship concepts proposed by Kamlet–Taft and Catalán.

Keywords: heterocycles; chemoinformatics prediction models; antioxidant activity; LSER analysis; solvatochromism.

INTRODUCTION

The expansion of degenerative diseases induced by oxidative stress and incorporation of free radicals, including atherosclerosis, ischemic heart disease, diabetes mellitus and cancer, presents one of the main problems of today's society.[1,2] Scientists are in a constant search for a novel scaffold with structural diversity and complexity to play a fundamental role in the drug discovery pipeline. Herein, fused benzene or hetero benzene rings in linear, angular or clustered arrangements present interesting compounds due to their chemical structures and

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biological activities.[3] Moreover, numerous compounds containing fused rings with oxygenated phenyl moieties, are used as anticancer and anti-inflammatory agents[4–6] and have shown to inhibit the growth of cancer cells.[7] On this behalf, an oxygen-incorporating tricyclic compound, xanthene, arises as an interesting structural scaffold with various beneficial heterogeneous pharmacological activities.[8] The literature review showed that xanthene nucleus has been reported to be a versatile and suitable towards obtaining compounds for different biological targets.[9] For example, xanthendiones (1,8-dioxooctahydroxanthenes) are a special class of oxygen-incorporating tricyclic compounds[9] bearing as a basic feature a pyran nucleus fused on either side with cyclohex-2-enone rings.[10] They are often found as a structural motif in natural products with a wide range of biological activities, such as: antioxidant[11–14] antimicrobial,[11,12,15] trypanocidal,[16] antiinflammatory,[16] antiproliferative[11,12] and anticancer.[17,18] Besides, xanthendiones are effective inhibitors of tryparothione reductase, bone morphogenetic protein (BMP-2)-targeted osteogenic agents, selective positive allosteric modulators of the δ-opioid receptors and estrogen receptors.[19]

As expected, the substitution pattern of the xanthene core will define the respective pharmacological response of the synthesized molecule.[9] Bhat *et al*. demonstrated that xanthendiones with electron-withdrawing halogen substituents show a broad spectrum of antibacterial activity against both Gram-positive and Gram-negative bacteria. Also, xanthendiones bearing the nitro group in *meta* position of the phenyl ring are two times more potent against *Candida albicans* and four times more potent against *Aspergillus clavatus* when compared to referent drug griseofulvin.[15] Moreover, Zukić *et al.*[9] showed that slight variations in structure lead to different activities of xanthendiones. Compounds bearing two hydroxy groups in *meta* and *para* position of the phenyl ring possess high antioxidant activity, while compounds bearing bromine atom in their structure exhibit high antimicrobial activity against *Escherichia coli* and *Salmonella aureus*.[12] Results of the antitubercular screening indicated that xanthene derivatives with the electron-withdrawing substituents possess prominent antimycobacterial activity against the MTB H37Ra and *Mycobacterium bovis* BCG.[19] Recent studies have shown that incorporating heterocyclic rings in molecular structure ameliorates antibacterial ability of newly synthesized compounds.[20] Small heterocycle-structured molecules targeting RNA in living cells and providing successful therapeutic agents have been reported in the literature.[21] For example, docking studies showed that these xanthendiones exhibit high binding affinity towards the amino acid residues of ATP binding pocket of human PIM1 kinase receptor through van der Waals interactions, steric favorable interactions and hydrogen bonding, thus being promising anticancer drugs.[15] Ilangovan *et al.*[8] demonstrated that 14-aryl-14*H*-dibenzo[*a*,*j*]xanthene derivatives act as good radical scavengers against DPPH and $ABTS^{\bullet+}$ due to the presence of butterfly-like planar naphthal-

ene rings on both sides of pyran ring and the presence of strong electron-donating substituents on the phenyl ring. Besides their pharmacological activity, xanthendiones can also be used in the preparation of stable laser dyes, fluorescent sensors and protein labeling fluorophores used in laser technology, functional materials for visualization of biomolecular assemblies, photodynamic therapy and as antagonists.[18]

Drug discovery is an inventive process of finding new potentially pharmacologically active compounds based on a combination of computational, experimental and clinical models and the knowledge of biological targets.[22] Drug-likeness of the compounds should present appropriate absorption, distribution, metabolism, excretion–toxicity (ADMET) properties leading progression from pre-clinical assessment to clinical evaluation. The rules of good bioavailability are often applied, among which the most popular is Lipinski's rule. According to the "rule of five", good oral absorption can be expected for compounds whose set of physicochemical parameters is in the following ranges: partition coefficient (log *P*) < 5, number of hydrogen bond donors < 5, number of hydrogen bond acceptors < 10, relative molecular mass < 500.[23] Potentially pharmacologically active compounds often bear numerous functional groups capable of forming hydrogen bonds, making them soluble and giving them the ability to form specific interactions with their biomolecular targets.[24] Hydrogen bonding influences the interactions of potentially pharmacologically active organic compounds at different levels of complexity, going from those with other small molecules, up to the highest supramolecular assemblies, *e.g.*, proteins and membranes. These interactions considerably affect the pharmacological activity, pharmacokinetics and physicochemical properties of drugs, hence making hydrogen bonding an important subject of study in drug discovery and development.[25] Therefore, solvatochromic study gives an insight into possible different solute–solvent interactions mimicking the interactions of potentially pharmacologically active organic compounds with their environment.

Keeping in mind the above stated application and activities of xanthene derivatives, seven xanthendiones (**1**–**7**) and one structurally-related xanthenone (**8**) are synthesized and thoroughly characterized. Sulfur and oxygen-containing heterocycles are widely used because of their key function in fulfilling needs in medicinal chemistry,[26–28] and therefore are incorporated into xanthendione scaffolds in compounds **3** and **4**. In aspiration to achieve new and high potent antioxidant agents, herein, we examined radical scavenging properties of the synthetized compounds using the 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) method. *In silico* prediction was performed in order to evaluate pharmacokinetic profiles of the synthesized compounds related to absorption properties and biophysical-kinetic profiles of the synthesized compounds related to metabolism properties. The effects of specific solvent-solute interactions (hydro-

gen bonding) which are related to the molecular structure of a compound and nonspecific solvent–solute interactions (dipolarity/polarizability of solvents) on the absorption maxima shifts were interpreted by using the linear solvation energy relationship (LSER) concept proposed by Kamlet, Taft and Catalán.[29,30]

EXPERIMENTAL

The general information

All chemicals, reagents and solvents were supplied by Sigma–Aldrich and were used without further purification.

Spectroscopic measurements

^{1}H-NMR spectra were recorded on a Bruker Ascend 400 spectrophotometer at 400 MHz, while ^{13}C-NMR spectra were recorded at 100 MHz at to the same device. ^{1}H- and ^{13}C-NMR spectra of compounds **1** and **7** were recorded at room temperature in deuterated dimethyl sulfoxide (DMSO-d_6), while the ^{1}H- and ^{13}C-NMR spectra of compounds **2**–**6** and **8** were recorded in deuterated chloroform ($CDCl_3$). The chemical shifts are expressed in ppm in relation to the reference TMS (δ_H = 0 ppm). FT-IR spectra of all synthesized compounds were recorded in the range from 400 to 4000 cm^{-1} using a Thermo Scientific Nicolet iS10 spectrometer, within the spectral resolution range of 400–4000 cm^{-1}. Elemental analysis of all studied compounds was performed using a microanalyzer brand Elemental Vario EL III.

*General procedure for synthesis of compounds **1–8***

The synthesis of compounds **1**–**7** is illustrated in Scheme 1, while the synthesis of compound **8** is presented in Scheme 2.[31] 3,5-Dibromo-4-hydroxybenzaldehyde and 3-chloro-4--hydroxybenzaldehyde, used for further synthesis of compounds **2** and **7**, respectively, were synthesized according to the procedures illustrated on Schemes S-1 and S-2 (Supplementary material to this paper). 5,5-Dimethylcyclohaxane-1,3-dione (2 mmol) was dissolved in water prior to the addition of 1 mmol of corresponding aldehyde. The reaction mixture was stirred at room temperature for 60 min while the course of the reaction was monitored by TLC. The reaction was completed for 60 min. Solid product was isolated by simple filtration and dried.[32] Obtained solid product (1 mmol) was dissolved in absolute ethanol (10 mL) in an Erlenmeyer flask (50 mL) with gentle heating. Furthermore, water (2.5 mL) and HCl (6 M, six drops) were added to the solution, and the mixture was boiled for 5 min. After cooling, water was added dropwise until the mixture became cloudy. The suspension was cooled at 0 °C, for 10 min. Crystals were collected by vacuum filtration and washed with several portions (10 mL total volume) of ice cold ethanol:water (1:1 volume ratio) to yield compounds **1**–**8**. The solid products **1**–**8** were fully characterized by FT-IR, ^{1}H- and ^{13}C-NMR spectra (Supplementary material, Figs. S-1–S-8) and elemental analysis.

In-silico *prediction*

Determination of the relevant molecular descriptors for all synthesized compounds was assessed employing the following software packages: SwissADME (Swiss Institute of Bioinformatics, Switzerland[33]) and PreADMET (East China University of Science and Technology, China[34]).

Antioxidant activity

The antioxidant activity of investigated compounds **1**–**8** was determined using ABTS radical-scavenging assay.[35] A stock solution of ABTS$^{\bullet+}$ was prepared in the reaction of ABTS (4.912 mL, 7 mM in phosphate-buffered saline (PBS)) and potassium persulfate (0.088 mL,

140 mM in distilled water). After 16 h of incubation in the dark, the stock solution was diluted with methanol until the recorded absorbance at 734 nm was 0.700±0.02. Subsequently, 20 μL of the methanolic solutions of the investigated compounds (5 mM) were mixed with 2 mL of the ABTS radical solution, shaken and stored in the dark for 10 min. Afterward the absorbance was measured at 734 nm. Each test was done in triplicate. The inhibition percentage of $ABTS^{\bullet+}$ was calculated using the formula:

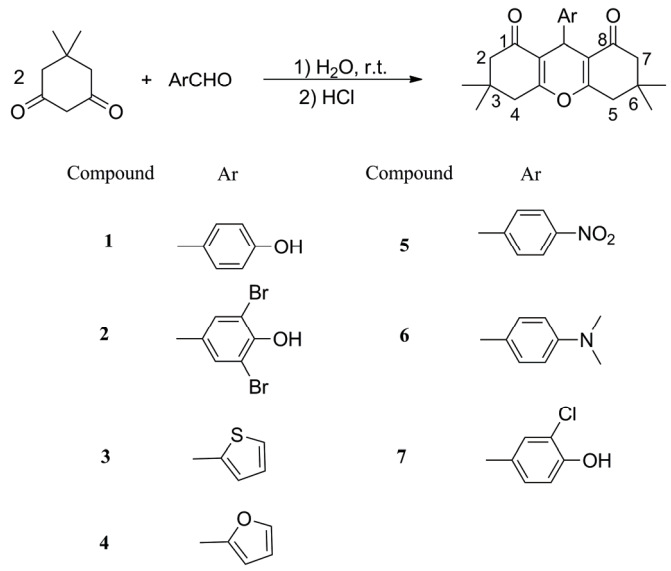
$$\text{Inhibition} = 100(A_c - A_s)/A_c \quad (1)$$

where A_c is the absorbance of the control solution (20 μL of methanol in 2 mL of ABTS solution) and A_s is the absorbance of the sample solution. Ascorbic acid was used as a standard antioxidant. The antioxidant ability of the most promising derivatives **1**, **2** and **6**–**8** was further evaluated by determination of the IC_{50} values. The methanolic solutions of the synthesized compounds and ascorbic acid were prepared at concentrations ranging from 5 to 0.5 mM, and obtained IC_{50} were compared. The tests were performed in triplicate. The resulting IC_{50} values are presented as means with standard deviation (±*SD*) from three experiments ($n = 3$).

RESULTS AND DISCUSSION

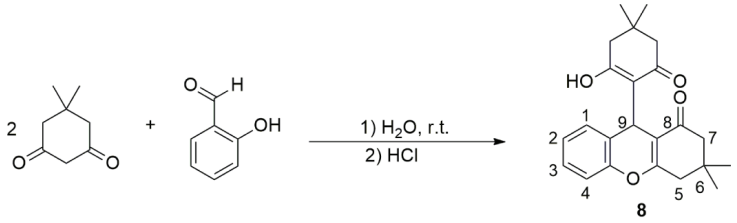
Synthesis and characterization

The synthesis of compounds **1**–**7** is illustrated in Scheme 1, while the synthesis of compound **8** is presented in Scheme 2. 3,5-Dibromo-4-hydroxybenzaldehyde and 3-chloro-4-hydroxybenzaldehyde, used for further synthesis of compounds **2** and **7**, respectively, were synthesized according to procedures illustrated on Schemes S-1 and S-2. The synthesis of compounds **1**–**7** involves the formation of a Knoevenagel product **A**, which, through the addition of **B**, was further converted in the Michael adduct intermediate **C** (Scheme S-3 of the Sup-



Scheme 1. Synthesis of compounds **1**–**7**.

plementary material). Nucleophilic attack of the –OH group on the C=C moiety gave compounds **1**–**7**.[36,37] On the other hand, when using salicylaldehyde in the reaction with dimedone, the reaction course occurs according to Scheme S-4 (Supplementary material) and results in a formation of 9-(2-hydroxy-4,4-dimethyl-6--oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**8**).[38,39]



8

Scheme 2. Synthesis of compound **8**.

*Multiparameter optimization of molecular descriptors of **1**–**8***

First essential aspect of the potentially pharmacologically active compounds, to be considered, is their drug-likeness. Therefore, the pharmacokinetic profile of compounds **1**–**8** was evaluated by predicting the appropriate ADMET characteristics, using various empirical rules and appropriate software packages.

Molecules considered to have properties similar to standard drugs must not show more than one deviation from Lipinski's rule. According to Veber's criterion, adequate oral bioavailability is achieved with molecules that have less than 10 rotatable bonds and a topological polar surface of less than 140 Å^2.[40] According to the modified versions of these two concepts, for compounds whose physicochemical properties satisfy the following ranges: 160 ≤ relative molecular mass ≤ 500; –0.4 ≤ WLOGP < 5.6; 40 ≤ molar refractivity ≤ 130; 20 ≤ number of atoms ≤ 70 (Goose's criterion) and WLOGP ≤ 5.88, *TPSA* (topological polar surface area) < 131.6 Å^2 (Egan's criterion), there is a high probability of manifesting therapeutic effects.[41] Based on the values of the molecular descriptors described in these rules (Tables S-I and S-II, Supplementary material), it can be concluded that the examined compounds (except compound **2** with the molecular weight > 500 g/mol and log *P* > 5) meet all the stated empirical criteria. Tables S-I and S-II show that they fulfill the theoretical condition for adequate biological availability in the body and therefore possess a pharmacological potential. Based on the calculated values of the topological polar surface area of the molecule, it is expected that in *in vivo* conditions, the investigated compounds will show good intestinal absorption. Furthermore, a small number of rotatable bonds suggests that significant conformational changes upon solvation and binding to appropriate receptors are not expected.[23]

Hence, the complete series of compounds was further examined with SwissADME and PreADMET *in silico* tools regarding their BBB permeation,

P-gp inhibition, inhibition of cytochrome P450 (CYP) (1A2, 2C19, 2C9, 2D6, 3A4) and considerations were performed in accordance with the information gathered. Comprehensive results are presented in Supplementary material (Tables S-II and S-III).[9] The data presented in Table S-II show that different partition coefficient values were obtained for the same compound, which is a consequence of different mathematical algorithms for calculating this parameter within the used software packages.[19,20] The highest values of the partition coefficient were obtained for compound **2**, which enables this molecule to more successfully pass through the blood–brain barrier by passive diffusion, as well as to more successfully bind to the active sites on the corresponding receptors.

Obtained data indicated that compounds **1**, **4**, **6** and **7** were found to be BBB permeant and only compound **5** was found not to be P-gp inhibitor.[9] According to obtained results, it can be concluded that all investigated compounds possess high gastrointestinal absorption, inhibit isoenzymes CYP2C19 and CYP2C9 and don't inhibit isoenzymes CYP1A2 and CYP2D6**.** Based on the optimal values of the molecular descriptors obtained by applying appropriate software packages, it can be concluded that the compounds synthesized in this work meet all the necessary empirical criteria, which further qualify them as interesting drug candidates.

*Antioxidant activity of the investigated compounds **1**–**8***

Evaluation of the antioxidant properties of the synthesized compounds was assessed using the ABTS assay and the scavenging activity was further compared to the activity of ascorbic acid (Fig. 1a). As antioxidants provide either hydrogen atoms or electrons to neutralize the single electron originating from free radicals, exploring effective antioxidants is of importance in medicinal chemistry.[42] The obtained data indicate variable activity of the compounds, designating that substituents in position 9 of xanthendiones affect the antioxidant ability of the molecules. Considering most of the compounds bear *p*-substituted phenyl scaffold (**1**, **2** and **5**–**7**) as a substituent in position 9 of xanthendione moiety, the choice of thiophene and furan rings should be further explained, in this section, from the aspect of antioxidant activity. Compounds **1** (with the 4-hydroxy phenyl ring), **2** (3,5-dibromo-4-hydroxy substituted phenyl ring), **6** (with the 4-dimethylamino substituted phenyl ring), **7** (with the 3-chloro-4-hydroxy substituted phenyl ring) and **8** exhibited excellent ability to scavenge the $ABTS^{\bullet+}$, comparing to the inhibition of ascorbic acid. Other compounds (**3**–**5**) showed weak or no antioxidant properties. Despite the expected data, wherein incorporating thiophene and furan nuclei with other heterocyclic compounds improves antioxidant activity,[26–28,43,44] compounds **3** and **4** do not exhibit significant amelioration in activity when compared to analogues. Incorporating these scaffolds, as pharmacophores of choice for designing antioxidant drugs, known for the excellent results through various

mechanisms of action,[26–28,43,44] has shown to have little to no effect on the antioxidant potential as substituents on xanthendione moiety in this case.

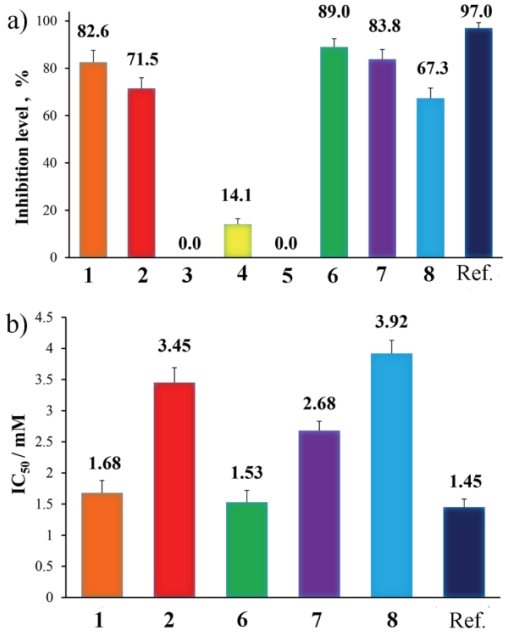


Fig. 1. The antioxidant properties of investigated compounds compared to the ascorbic acid. a) The scavenging activity at the sample concentration of 5mM; b) the IC_{50} values of compounds **1**, **2** and **6**–**8** and ascorbic acid used as reference.

The antioxidant activity of candidates **1**, **2** and **6**–**8** was further evaluated by the determination of IC_{50} values (Fig. 1b). The high IC_{50} values generally suggest low antioxidant activity. The IC_{50} values of the samples, ranging from 1.53 to 3.92 mM, indicate that these compounds demonstrate good antioxidant capacity in comparison to IC_{50} value of ascorbic acid (1.45 mM). Based on the comparison of the IC_{50} values, the activity of these compounds was found to be as follows: **6** > **1** > **7** > **2** > **8**. Based on the obtained results and literature survey, it could be concluded that the antioxidant activity is mainly associated with the presence of –OH group in the *para*-position of the phenyl ring which is in line with the well-established fact that phenolic functionality has considerable scavenging potential.[43,45] Notably, the most potent compound **6** bears *p*-dimethylamino group in the phenyl ring indicating that this group imparts significant antioxidant activity and is in accordance with the literature data.[46,47]

*Solvatochromic analysis of the investigated compounds **1**–**8***

It is known that the physicochemical and photochemical properties of different π-conjugated structures are influenced by the extent of their π-electron con-

jugation and the nature of functional groups attached to the conjugated chain as well as the nature of the surrounding medium.[48] Bearing this in mind, we directed our solvatochromic research towards an extensive analysis of the influence of specific and non-specific solvent interactions on the absorption maxima shift of these compounds containing different chromophores and auxochromes.

The solvatochromic properties of compounds **1**–**8** were investigated by determining the corresponding UV–Vis absorption spectra in a selected solvent set of different polarity (seven protic, ten aprotic and two nonpolar solvents) in the wavelength range 200–500 nm. The UV–Vis absorption spectra of the investigated compounds **1**–**8** showed no dependence of compound concentration suggesting that no dimmers of higher aggregates are formed. Representative UV–Vis spectra are presented in Figs. S-9–S-11 (Supplementary material), while the values of the absorption maxima are given in Table S-IV (Supplementary material). The observed trends in the absorption maxima shifts are in accordance with previously published results.[49–51] Namely, the absorption spectra of all investigated compounds are characterized by the presence of one dominant band corresponding to the $\pi \rightarrow \pi^*$ transition, which appears in the wavelength range of 220–270 nm in the polar protic solvents and the range of 280–300 nm in polar aprotic solvents and non-polar solvents. In addition, based on the data presented in Table S-IV, when polar protic solvents are used, all investigated compounds show additional absorption maxima in the wavelength range of 290–300 nm. This splitting of the absorption band could be attributed to a protonation reaction which is likely to occur at the carbonyl moieties and hydroxyl groups.[30] In the case of compound **6**, a shoulder at *ca.* 250 nm appears in diethyl ether and acetonitrile. Based on the data given in Table S-IV and the absorption spectra presented in Figs. S-9–S-11, it can be concluded that increasing solvent polarity causes bathochromic shifts of absorption maximas.

The influence of the solvent parameters (the effects of solvent polarity and hydrogen bonding) on the position of the absorption maxima is of very complex nature and was therefore analyzed mathematically in more detail[52] using general solvatochromic equations established by Kamlet–Taft (Eq. (2)) and Catalán (Eq. (3)):

$$\nu_{max} = \nu_{max}0 + a\alpha + b\beta + s\pi^* \quad (2)$$

$$\nu_{max} = \nu_{max0} + aSA + bSB + cSP + dSdP \quad (3)$$

where ν_{max} is a solvent-dependent physicochemical property in a given solvent, ν_{max0} is a statistical quantity that corresponds to the absorption frequency in cyclohexane as a reference solvent, α is a measure of the acidity of the solvent, describing its ability to donate a proton when establishing a hydrogen bond, β is a measure of the basicity of the solvent, *i.e.*, its ability to receive a proton when establishing a hydrogen bond, π^* is a measure of dipolarity/polarizability of the solvent, (Table S-V, Supplementary material).[53]

SA is a measure of the acidity of the solvent, *i.e.*, it describes its ability to donate a proton when establishing a hydrogen bond, *SB* is a measure of the basicity of the solvent, *i.e.*, its ability to receive a proton when establishing a hydrogen bond and *SPP* is a measure of dipolarity/polarizability of the solvent. Parameters *SA*, *SB* and *SPP* (Table S-V) are equivalent to the Kamlet–Taft α, β and π^* solvatochromic parameters.

In 2004, Catalán and Hopf[27] developed another important solvatochromic parameter, known as solvent polarizability, *SP*. *a*, *b*, *c* and *d* are regression coefficients describing the sensitivity of properties α, β and π^*, that is *SA*, *SB*, *SPP* and *SP* to the different solute–solvent interactions.

The values of the regression coefficients with a probability of 95 %, together with the percentage contribution of solvatochromic parameters are shown in Tables S-VI and S-VII (Supplementary material). The respective correlation coefficients obtained for both solvent parameter sets are in a good agreement with each other, therefore both models are equally suitable for describing specific/nonspecific solute–solvent interactions. Based on the high values of the obtained regression coefficients and the Fisher parameter, the results of the correlation of absorption frequencies with solvatochromic parameters can be considered satisfactory.

The data presented in Table S-VI indicate a bathochromic shift of the absorption maxima with the increasing solvent polarity expressed by the negative coefficient *s*. This indicates that a better stabilization of the excited state of the molecule compared to its ground state was confirmed. The negative values of coefficient *b* (compounds **1**–**3** and **7**, Table S-VI) indicate that the solvent basicity affects the molecule more in the excited than in the ground state. In the same manner, the negative values of the coefficient *a* (compounds **1**, **3**, **4**, **6** and **7**, Table S-VI) indicate that the solvent acidity affects the molecule more in the excited than in the ground state. The negative values of *a* term could be explained by the strong intermolecular hydrogen bonding of hydrogen bond donor (HBD) solvents with the carbonyl moieties of investigated compounds, which further reduces their electron density and thus increases the push–pull character of the chromophore. Based on the values of the percentages of solvatochromic parameters (Table S-VI), it can be concluded that for compounds **2** and **5**–**7**, the dipolarity/polarizability of the solvent is more dominant in relation to its acid––base properties, while with compounds **3**, **4** and **8**, the acidity of the solvent is more dominant and with compound **1** the basicity of the solvent. The strongest influence of the acidity of the solvent in compounds **3** and **4** can be ascribed to furanyl- and thiophenyl-groups used as substituents in position 9 of the xanthendione moiety.[52]

Analogously to the previously applied model, it was observed that the negative values of the coefficients *a*, *b*, *c* and *d* in the Catalán model (Table S-VII)

indicate that the solvent effects are more pronounced in the excited than in the ground state of the studied molecules. It is also confirmed that the dipolar investigated compounds (with the exception of compounds **3** and **5**) show positive solvatochromism with regard to dipolarity/polarizability as indicated by negative *c* and *d* terms (Table S-VII). Considering the solvent acidity, the exception from the series are compounds **5** and **6**, where positive values of the coefficient *a* indicate that the hydrogen bonding better stabilizes the ground than the excited state of the molecule. The disagreement between the results obtained by these two models is influenced by different solvatochromic probes used for the determination of the parameters, thus reflecting different solvent–solute interactions. The Kamlet–Taft empirical parameters are obtained as average experimental values of numerous solvatochromic probes, while Catalán's empirical solvent scales are based on well-defined reference probe systems.[54]

CONCLUSION

In this study, we synthesized seven aromatically substituted xanthendiones **1**–**7** and one structurally-related xanthenone **8** and screened their potential pharmacokinetic properties using convenient chemoinformatics prediction models (SwissADME and PreADMET). The results of chemoinformatics prediction models showed that almost all investigated compounds (with the exception of copound **2**) meet Lipinski's rule of five and its extensions, such as Veber's, Egan's and Goose's criterion, indicating their good oral bioavailability. The antioxidant screening carried out according to the ABTS assay revealed the antiradical properties of the investigated compounds. This study also revealed that the antioxidant activities were in the following order: **6** > **1** > **7** > **2** > **8**, based on the comparison of their IC_{50} values. Compound **6** is the most active with IC_{50} value comparable with IC_{50} value of ascorbic acid. The results obtained by general solvatochromic equations established by Kamlet–Taft and Catalán indicate that the position of the UV–Vis absorption maxima depends on the nature (polarity, acidity and basicity) of the solvent. With their high antioxidant activities and good oral bioavailability, the investigated compounds have set the path for the preparation of new pharmacologically active compounds and a better understanding of the structure–activity relationship.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12258, or from the corresponding author on request.

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ИЗВОД

ОДРЕЂИВАЊЕ ФАРМАКОЛОШКЕ АКТИВНОСТИ ДЕРИВАТА КСАНТЕНА

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У овом раду, представљена је једноставна метода у два корака за синтезу седам деривата ксантендиона и једног деривата ксантенона који садрже различите ароматичне супституенте, полазећи од димедона и одговарајућих ароматичних алдехида. Карактеризација синтетисаних једињења извршена је одређивањем температуре топљења, као и применом елементалне анализе, FT-IR, ^{1}H-NMR и ^{13}C-NMR спектроскопских метода. Веза између хемијске структуре ових једињења и њихове фармаколошке активности успостављена је емпиријски коришћењем одговарајућих софтверских пакета (за предикцкцију фармаколошке активности) и *in vitro* одређивањем њихове антиоксидативне активности применом ABTS методе. Резултати ABTS методе показују да од целокупне серије тестираних једињења, пет једињења показује значајну антиоксидативну активност. На основу међусобног поређења IC_{50} вредности испитиваних једињења показано је да њихова антиоксидативна активност опада у следећем низу: **6** > **1** > **7** > **2** > **8**. Једињење **6** је најактивније у анализираној серији и има IC_{50} вредност приближне вредности као аскорбинска киселина. Резултати солватохромних једначина које су развили Камлет (Kamlet), Тафт (Taft) и Каталан (Catalán), указују да положај апсорпционих максимума проучаваних једињења зависи од природе (поларности и кисело-базних својстава) употребљених растварача. Са високим вредностима антиоксидативне активности и добром оралном биорасположивошћу, деривати ксантендиона и ксантенона са ароматичним супституентима, представљају добру полазну основу за синтезу нових фармаколошки активних једињења и боље разумевање утицаја структуре на фармаколошку активност.

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