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Solvent effects on the absorption spectra of potentially pharmacologically active 5-alkyl-5-arylhydantoins: a structure–property relationship study

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Abstract: To obtain insight into the interactions of potential anticonvulsant drugs with their surrounding, two series of 5-methyl-5-aryl- and 5-ethyl-5--arylhydantoins were synthesized and their absorption spectra were recorded in the region from 200 to 400 nm in a set of selected solvents. The effects of solvent dipolarity/polarizability and solvent–solute hydrogen bonding interactions on the absorption maxima shifts were analyzed by means of the linear solvation energy relationship (LSER) concept of Kamlet and Taft. The ratio of the contributions of specific and non-specific solvent–solute interactions were correlated with the corresponding absorption, distribution, metabolism, and excretion (ADME) properties of the studied compounds. The correlation equations were combined with different physicochemical parameters to generate new equations, which demonstrate the reasonable relationships between the solvent–solute interactions and the structure–activity parameters.

Keywords: hydantoin derivatives; Kamlet–Taft Equation; human intestinal absorption; lipophilicity, binding affinity.

INTRODUCTION

Hydantoin (imidazolidine-2,4-dione) is the core structure of different biologically active compounds, such as antibacterial[1] and antifungal agents,[2] free radical scavengers[3] and serotonin and fibrinogen receptor antagonists.[4] 5-Phenylhydantoins are commonly used in the treatment of epilepsy and related disorders. Phenytoin (5,5-diphenylhydantoin) is one of the oldest non-sedative anticonvulsant drugs,[5] whereas mephenytoin (3-methyl-5-ethyl-5-phenylhydantoin) is considered only after other less toxic anticonvulsants have failed.[6] Nirvanol, the 3-demethylated metabolite of mephenytoin, was the first hydantoin derivative used

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briefly in the treatment of chorea, but it was abandoned due to its hypnotic–sedative effect.[7] Anticonvulsant drugs require long-term application and should have only minor unfavourable effects. For this reason, the synthesis and modelling of the behaviour of new hydantoin derivatives significantly contributes to a rational search for new anticonvulsant drugs.

The anticonvulsant activity of hydantoin derivatives is mediated by their interaction with and inhibition of the brain Na^+ channels.[8] Their common pharmacophore core contains at least one aromatic ring at C5, which forms aromatic–aromatic interactions, and a polar imide group, which interacts with the receptor site through a low-energy amino–aromatic hydrogen bond. Poupaert *et al.* tested a limited series of compounds structurally related to phenytoin and observed that the anticonvulsant activity decreased with a reduction in their ability to form hydrogen bonds.[9] Brouillette *et al.* demonstrated that 5-alkyl-5-phenylhydantoins have an affinity for Na^+ channels comparable to that of phenytoin, with the optimal length of the aliphatic chain corresponding to pentyl, hexyl or heptyl.[10,11] In this context, it was proposed that the structure–activity and structure–property relationships of hydantoin anticonvulsants have molecular size and hydrogen bonding as their primary determinants.[12–14]

Since most drug candidates fail in preclinical and clinical trials because of their unfavourable ADME (absorption, distribution, metabolism and excretion) properties, ADME modelling has attracted significant attention over the last two decades. The lipophilicity of drugs, as expressed by their octanol–water partitioning coefficient (log *P*), has been proven to be the most important parameter in the study of transport phenomena *in vivo* and through biological membranes. Insufficient lipophilicity results in poor membrane permeability of a drug, whereas excessive lipophilicity is a common cause of poor solubility that could lead to incomplete absorption following oral administration.[15] Concerning central nervous system (CNS) active drugs, the ideal candidates must be able to penetrate the blood–brain barrier (BBB) effectively. It was suggested that the optimum log *P* value for diffusion into the brain is around 2.[16]

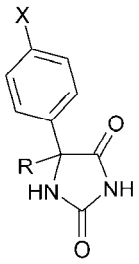
In this work, two series of 5-methyl-5-aryl- and 5-ethyl-5-arylhydantoins were assembled (Fig. 1) as a part of a larger investigation on the contribution of hydrogen bonding to the pharmacologically relevant properties of hydantoin derivatives and their potential application as anticonvulsant drugs. Kleinpeter *et al.* estimated the lipophilicities of a representative number of hydantoins using RP-HPLC[17] and concluded that some of the derivatives studied in this work (**1**, **5**, **6**, **7**, **9**, **10** and **11**) are expected to interact with and penetrate native membranes and be bioactive.

A first insight into the interactions of the investigated molecules with their surrounding can be derived from solvatochromic studies in which specific and non-specific interactions can be separated.[18] Hereto, their absorption spectra

have been recorded in the region 200–400 nm in twelve solvents. The effects of solvent dipolarity/polarizabilty (non-specific solvent–solute interactions) and hydrogen bonding (specific solvent–solute interactions) on the absorption spectra shifts were interpreted using the Kamlet–Taft equation[19] in the form:

$$v = v_0 + s\pi^* + b\beta + a\alpha \quad (1)$$

where v is the wavenumber, π^* is an index of the solvent dipolarity/polarizabilty, β is a measure of the solvent hydrogen bonding acceptor (HBA) basicity, α is a measure of the solvent hydrogen bonding donor (HBD) acidity and v_0 is the regression value of this solute property in cyclohexane as the reference solvent. The regression coefficients s, b and a in Eq. (1) measure the relative susceptibilities of the absorption maxima shift to the indicated solvent parameters.



1:	R = Me, X = H	**7:**	R = Et, X = H
2:	R = Me, X = OH	**8:**	R = Et, X = OH
3:	R = Me, X = Me	**9:**	R = Et, X = Me
4:	R = Me, X = MeO	**10:**	R = Et, X = MeO
5:	R = Me, X = Cl	**11:**	R = Et, X = Cl
6:	R = Me, X = Br	**12:**	R = Et, X = Br

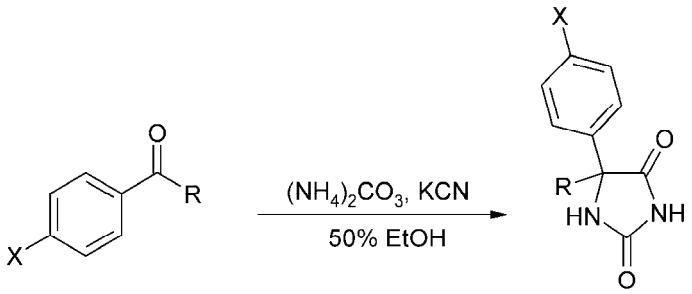
Fig. 1. Structures of the investigated 5-methyl-5-(4-substituted phenyl)- and 5-ethyl-5-(4-substituted phenyl)hydantoins.

To analyze the role of hydrogen bonding in their ADME properties, octanol–water partitioning coefficient (log P), human intestinal absorption (*Abs*) and protein binding affinity (k_A) data have been correlated with the regression coefficients from Eq. (1). The obtained correlation equations demonstrate reasonable relationships between solvent–solute interactions and structure–property parameters.

EXPERIMENTAL

Synthesis of the investigated compounds

All of the investigated 5-methyl-5-aryl- and 5-ethyl-5-arylhydantoins were synthesized by a modification of the method of Bucherer[20] (Scheme 1). The appropriate ketone (0.020 mol) was dissolved in 50 % ethanol (50 cm^3) and ammonium carbonate (7.70 g, 80.0 mmol) plus potassium cyanide (2.60 g, 40.0 mmol) were added. This mixture was warmed under a condenser at 60 °C for 15 h, after which the solution was concentrated to approximately two-thirds of its initial volume and chilled in an ice-bath. The mass was filtered on a Büchner funnel. The product was dissolved in 5 % sodium hydroxide solution, filtered from unreacted ketone and reprecipitated by acidification with hydrochloric acid. Recrystallization of the white solid from 60 % ethanol yielded a crystalline product. The ketones used in these preparations were commercially available (Fluka). The chemical structure and the purities of the synthesized compounds were confirmed by their melting points and ^{1}H-NMR, ^{13}C-NMR, FT-IR and UV spectra.



Scheme 1. Synthetic route to the investigated 5-alkyl-5-(4-substituted phenyl)hydantoins.

Spectroscopic measurements

The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC 250 spectrometer at 200 MHz for the ^{1}H-NMR and 50 MHz for the ^{13}C-NMR spectra. The spectra were recorded at room temperature in DMSO-d_6. The chemical shifts are expressed in ppm referred to TMS (δ_H = 0 ppm) in the ^{1}H-NMR and the residual solvent signal (δ_H = 39.5 ppm) in the ^{13}C-NMR spectra. The FT-IR spectra were recorded on a Bomem MB 100 spectrometer. The absorption spectra were measured in spectroquality solvents (Fluka) at 10^{-5} mol dm^{-3} concentration using a Shimadzu 1700 spectrophotometer. All melting points are uncorrected and are presented in °C. Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS (HRMS) instrument (LC: series 1200). Elemental analysis was performed using a Vario EL III elemental analyzer.

Physicochemical characterization of the investigated compounds

The physicochemical characterization of compounds **1**–**6** has already been reported,[21] whereas the yields and the characterization of compounds **7**–**12** are given in the Supplementary material to this paper.

Methods of calculation

The correlation analysis was realised using Microsoft Excel 2003, which considers the 95% confidence level. The goodness-of-fit is discussed using the correlation coefficient (R), standard error of the estimate (S) and the Fisher's criterion (F).

In the absence of appropriate experimental data in the literature, computer methods were used to predict the ADME properties of the investigated hydantoin derivatives. Their lipophilicity was estimated by calculation of their log P values with Advanced Chemistry Development (ACD) software Solaris, v. 4.67. The human intestinal absorption data (*Abs*) and protein binding values (f_b) were obtained with the ChemSilico program.[23]

The corresponding physicochemical characteristics and ADME data of the investigated molecules are collected in Table I.

TABLE I. Physicochemical properties and ADME data of the investigated molecules

No.	R	X	σ_I[a]	σ_R[b]	log P[c]	*Abs*[d] / %	f_b[d] / %	log k_A[e]
1	Me	H	0	0	0.999	91.8	37.435	2.71
2	Me	OH	0.24	–0.43	0.263	89.4	40.823	2.85
3	Me	Me	–0.01	–0.13	1.459	93.3	67.904	3.97
4	Me	MeO	0.3	–0.43	0.914	89.4	52.849	3.33
5	Me	Cl	0.47	–0.16	1.594	93.7	69.988	4.07

TABLE I. Continued

No.	R	X	σ_I[a]	σ_R[b]	log P[c]	Abs[d] / %	f_b[d] / %	log k_A[e]
6	Me	Br	0.47	–0.16	1.771	94.0	75.079	4.32
7	Et	H	0	0	1.530	92.8	48.188	3.15
8	Et	OH	0.24	–0.43	0.794	91.0	49.223	3.19
9	Et	Me	–0.01	–0.13	1.991	93.9	74.736	4.30
10	Et	MeO	0.3	–0.43	1.446	90.8	61.883	3.70
11	Et	Cl	0.47	–0.16	2.126	94.3	76.844	4.42
12	Et	Br	0.47	–0.16	2.302	94.4	80.989	4.67

[a]Inductive substituent parameter;[24] [b]resonance substituent parameter;[24] [c]calculated with ACD Solaris, v. 4.67; [d]calculated with ChemSilico; [e]the protein binding affinities were obtained by Eq. (3)

RESULTS AND DISCUSSION

Absorption spectra of the investigated molecules were recorded in twelve solvents of different polarities and the corresponding absorption maxima are presented in Table II. The absorption spectra were characterized by one band with a weak low-energy shoulder, which is typical for 5-phenylhydantoins. The main absorptions resulted from an intramolecular charge transfer (ICT), corresponding to a migration of electron density from the hydantoin moiety to the phenyl ring. The bathochromic shift of the absorption bands with increasing solvent dipolarity/polarizability is in accordance with previously published data.[12–14]

TABLE II. Absorption maxima of the investigated molecules in the set of selected solvents

Compound/ Solvent	$\nu_{max}\times10^{-3}$ / cm^{-1}											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Methanol	47.89	44.56	45.80	44.80	45.21	44.96	46.51	43.63	45.83	44.17	45.00	44.76
Ethanol	47.48	44.52	45.66	44.76	45.16	44.92	47.13	44.44	45.75	45.21	45.33	45.04
1-Propanol	47.50	44.62	45.45	45.00	44.88	45.51	47.08	44.60	45.87	45.21	44.68	44.56
2-Propanol	47.94	44.90	46.21	44.80	45.00	44.82	48.17	45.70	47.57	46.59	45.21	45.05
1-Butanol	47.60	44.85	46.00	45.44	46.00	45.33	47.04	44.96	45.83	45.45	45.63	44.13
Diethyl ether	40.62	40.42	40.91	40.52	40.55	40.52	40.88	40.75	40.72	40.45	40.49	40.39
Disopropyl ether	41.77	39.03	41.28	40.25	41.28	41.18	41.77	41.67	41.74	41.70	41.18	41.02
Tetrahydro-furan	39.18	38.79	39.15	39.09	39.12	39.06	39.43	39.31	39.28	39.34	39.28	39.25
Dimethyl sulfoxide	37.45	36.05	36.76	36.39	37.26	37.20	37.48	36.37	36.74	36.98	37.28	37.34
Ethyl acetate	38.58	36.39	38.66	36.60	38.46	38.28	39.62	36.51	39.28	36.88	38.76	38.32
N,*N*-Dimethyl-formamide	37.79	36.20	37.73	37.51	37.76	37.70	37.65	36.18	36.79	36.39	37.31	38.71
N,*N*-Dimethyl-acetamide	37.12	36.07	36.79	36.41	37.7	37.37	37.57	36.18	37.15	36.50	37.25	37.43

The effects of the solvent dipolarity/polarizability and hydrogen bonding on the absorption maxima shifts were evaluated by multiple regression analysis using the solvent parameter set of Kamlet and Taft (Table III). It was found that

absorption maxima of the investigated molecules in selected solvents show a satisfactory correlation with the π^*, β and α parameters. The fitted regression values of v_0, s, b and a at the 95 % confidence level are presented in Table IV. The success degree of Eq. (1) is shown in Fig. 2 by means of a plot of v_{max} calculated *versus* v_{max} observed in different solvents (R = 0.991, S = 0.50, F = 8048).

TABLE III. Solvent parameters[19]

Solvent	π^*	β	α
Methanol	0.60	0.62	0.93
Ethanol	0.54	0.77	0.83
1-Propanol	0.52	0.83	0.78
2-Propanol	0.48	0.95	0.76
1-Butanol	0.47	0.88	0.79
Diethyl ether	0.27	0.47	0.00
Diisopropyl ether	0.27	0.49	0.00
Tetrahydrofuran	0.58	0.55	0.00
Dimethyl sulfoxide	1.00	0.76	0.00
Ethyl acetate	0.55	0.45	0.00
N,*N*-Dimethylformamide	0.88	0.69	0.00
N,*N*-Dimethylacetamide	0.88	0.76	0.00

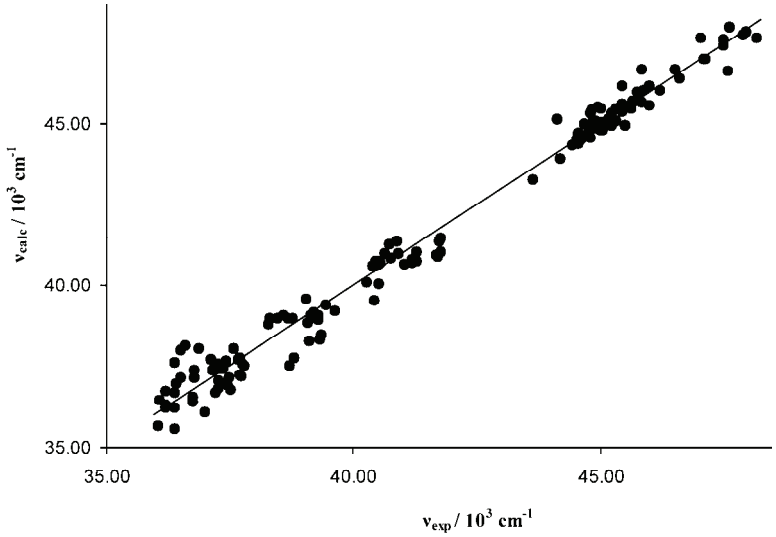


Fig. 2. Experimental *vs*. calculated values of v from Eq. (1).

The investigated compounds showed positive solvatochromism with regards to π^* (as indicated by the negative s coefficients in Table IV), which indicates that the dipole moment of the excited state is higher than in the ground state. Thus, considerable differences between the dipole moments in the ground and excited state are characteristic for ICT processes. The positive a and b coeffi-

cients indicate hypsochromic shifts of absorption maxima with increasing solvent hydrogen bond acidity and basicity (Table IV). This can be explained by the hydrogen bond formation between protic solvents and the hydantoin carbonyl moieties, which reduced their electron density and thus decreased the ICT character of the chromophoric system. On the other hand, the interactions of the NH groups played only a minor role, which is represented by the small percentage contribution of the *b* coefficient compared to those of *a* and *s* (Table V). These results are also in accordance with the preferred existence of the investigated molecules in their imido tautomer.

TABLE IV. Regression fits to the solvatochromic parameters

No.	R	X	$v_0\times10^{-3}$ / cm^{-1}	$s\times10^{-3}$ / cm^{-1}	$b\times10^{-3}$ / cm^{-1}	$a\times10^{-3}$ / cm^{-1}	R^a	S^b	F^c
1	Me	H	41.51(±0.68)	–6.51(±0.80)	2.59(±1.34)	9.15(±0.52)	0.996	0.48	351
2	Me	OH	39.80(±1.02)	–6.56(±1.20)	3.22(±2.01)	6.99(±0.78)	0.988	0.72	106
3	Me	Me	41.85(±0.49)	–6.88(±0.58)	2.11(±0.97)	7.16(±0.74)	0.997	0.34	463
4	Me	MeO	40.29(±1.08)	–6.55(±1.26)	3.28(±2.11)	6.65(±0.82)	0.985	0.76	89
5	Me	Cl	41.22(±0.54)	–5.89(±0.63)	2.30(±1.06)	6.41(±0.41)	0.998	0.38	310
6	Me	Br	41.18(±0.61)	–6.45(±0.72)	2.60(±1.06)	6.36(±0.46)	0.994	0.43	238
7	Et	H	41.43(±0.63)	–7.43(±0.74)	4.16(±1.24)	7.65(±0.48)	0.996	0.44	346
8	Et	OH	40.47(±1.13)	–9.67(±1.32)	6.34(±2.22)	5.04(±0.86)	0.984	0.79	83
9	Et	Me	41.79(±0.89)	–8.06(±0.95)	3.57(±1.59)	6.96(±0.62)	0.993	0.57	187
10	Et	MeO	39.96(±1.11)	–9.14(±1.30)	6.94(±2.19)	5.53(±0.85)	0.986	0.78	92
11	Et	Cl	41.49(±0.47)	–6.13(±0.55)	1.98(±0.93)	6.45(±0.36)	0.997	0.33	409
12	Et	Br	41.29(±0.40)	–5.73(±0.47)	1.88(±0.79)	6.19(±0.31)	0.997	0.28	505

[a]Correlation coefficient; [b]standard error; [c]Fisher's test

Table V. Percentage contribution of the solvatochromic effects

No.	R	X	P_{π^*} / %	P_β / %	P_α / %
1	Me	H	35.67	14.19	50.14
2	Me	OH	39.12	19.20	41.68
3	Me	Me	42.60	13.07	44.33
4	Me	MeO	39.75	19.90	40.35
5	Me	Cl	40.30	15.76	43.93
6	Me	Br	41.86	16.87	41.27
7	Et	H	38.62	21.62	39.76
8	Et	OH	45.94	30.12	23.94
9	Et	Me	43.36	19.20	37.44
10	Et	MeO	42.30	32.11	25.59
11	Et	Cl	42.10	13.60	44.30
12	Et	Br	41.52	13.62	44.86

To investigate the importance of various types of interactions in determining the anticonvulsant potencies of the investigated compounds, a multiple regression approach was applied to analyze the factors which govern their ADME properties. ADME data, whether experimentally measured or computationally pre-

dicted, provide key insights into how a drug will ultimately be treated or accepted by the body.

The evidence for solvent effects on the structure–property relationships of the investigated molecules was first demonstrated by plotting the calculated human intestinal absorption (HIA) values against the ratio $a/|s|$ as a convenient measure of the relative contributions of the dominant modes of solvation (Fig. 3). The HIA values (*Abs*) calculated by the ChemSilico program are expressed as the percentage of a drug absorbed by the intestine (Table I). The plot of the *Abs* values *versus* $a/|s|$ reveals that the molecules, where OH and MeO are attached to the phenyl ring (**2**, **4**, **8** and **10**), behave differently and their intestinal absorption percentages when compared to the others are somewhat lower. This can be expected, because these substituents may act as an additional site for hydrogen-bonding with the surrounding solvent molecules.

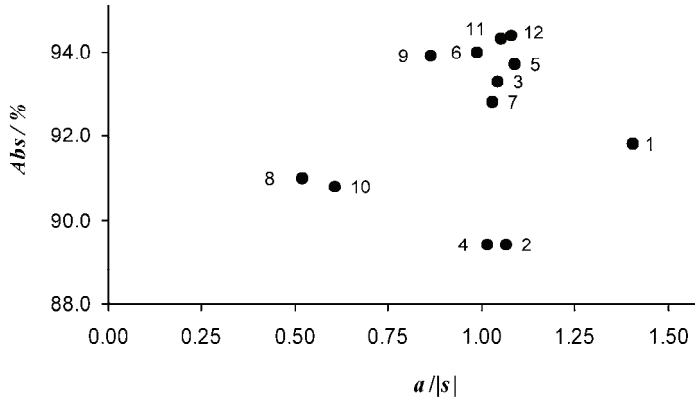


Fig. 3. Correlation between the *Abs* values and the ratio of the contributions of the specific and non-specific solvent–solute interactions ($a/|s|$).

The improved correlation, which includes all of the investigated molecules, was derived through the additional inclusion of the resonance (σ_R) and inductive (σ_I) constants of substituents in *para* position of the phenyl group (Eq. 2):

$$Abs = 98.05(\pm1.65) - 3.94(\pm1.38)a/|s| + 4.68(\pm1.28)\sigma_I + 13.45(\pm2.02)\sigma_R \quad (2)$$
$$(R = 0.928,\ S = 0.81,\ F = 16,\ n = 12)$$

It can be seen that Eq. (2) has a meaning similar to the corresponding model of Abraham,[25] when one realizes that the *a* and *s* coefficients refer to the hydrogen bond basicity and dipolarity/polarizability of the investigated molecules, respectively. The Abraham approach is based on the theoretical cavity model of solvent–solute interactions and successfully correlates different physicochemical properties of solutes.[26] Eq. (2) shows that the hydrogen bond basicity of the investigated molecules decreases intestinal absorption, whereas the dipolarity/po-

larizability enhances it. Generally, substituents on the phenyl ring at C5 exhibit two opposing effects: the conjugative electron donation, which decreases drug intestinal absorption, and the inductive electron withdrawal, which acts in the opposite direction.

Furthermore, the same approach was applied in the analysis of factors that determine octanol–water partitioning (log *P*) and protein binding affinity (k_A). The log *P* parameter, calculated with Advanced Chemistry Development (ACD) software Solaris, v. 4.67 (Table I), is a solvational characteristic, since it is directly related to the change in the Gibbs energy of solvation of a drug between octanol and water.[27] The protein binding values (f_b, fraction bound) are given as the percentage of the total plasma concentration of a drug that is bound to all plasma proteins (Table I). Human serum albumin (HSA), the most abundant protein in blood plasma (concentration 0.53–0.75 mM), has multiple hydrophobic binding sites and binds diverse drugs.[28] The percentage data were converted into an equivalent binding affinity k_A using the following formula (Eq. (3)) derived from the mass law. k_A is the binding affinity to HSA under the assumption that binding occurs exclusively to HSA, a binary complex is formed, and an excess of albumin (concentration 0.6 mM, [HSA]) is present compared to the concentration of the drug:[29]

$$\log k_A = \log \frac{[f_b]}{1-[f_b]} - \log[\mathrm{HSA}] \quad (3)$$

Reasonable statistics were obtained for 10 compounds with the exclusion of compounds **3** and **9** bearing substituents with electron-donating inductive effect (Eqs. (4) and (5)):

$$\log P = 2.56(\pm0.75) - 1.08(\pm0.58)a/|s| + 2.34(\pm0.61)\sigma_I + 3.43(\pm0.84)\sigma_R \quad (4)$$
$$(R = 0.907,\ S = 0.33,\ F = 9,\ n = 10)$$
$$\log k_A = 3.88(\pm0.51) - 0.79(\pm0.40)a/|s| + 3.60(\pm0.41)\sigma_I + 2.21(\pm0.57)\sigma_R \quad (5)$$
$$(R = 0.965,\ S = 0.22,\ F = 27,\ n = 10)$$

Evidently, all equations ((2), (4) and (5)) show clear similarities. It should be pointed out that parameters $a/|s|$, σ_I and σ_R are not normalized to each other, so the regression coefficients in these equations do not provide adequate measures of the relative contributions of the indicated types of solvent–solute interactions and substituent effects to the analyzed ADME properties. On the other hand, they all interpret the contribution of the hydrogen bond basicity and dipolarity/polarizability to the lipophilicity and intestinal absorption of the investigated molecules in the same manner as the Abraham models.[26,30] The obtained correlations also suggest that the introduction of an electron-withdrawing substituent at the *para* position of the phenyl group at C5 may produce derivatives with improved pharmacokinetic properties.

CONCLUSIONS

The reasonable correlations of absorption maxima of 5-methyl-5-aryl- and 5-ethyl-5-arylhydantoins with the solvent parameter set of Kamlet and Taft indicated that the selected model interpreted their LSER correctly. In this case, where both solvent and solute are hydrogen bond donors and acceptors, it was quite difficult to quantitatively estimate and separate the overall solvent effect into the contributions of specific and non-specific interactions. However, such a separation provided further possibility to establish the structure–property relationships of the investigated molecules. The obtained models represented how various types of interactions and electronic effects of substituents on the phenyl ring at C5 influenced their biological partitioning and binding to plasma proteins. The approach proposed in this work provided the means to analyze pharmacokinetic properties of hydantoin derivatives, not yet pharmacologically tested, which are difficult to determine experimentally.

SUPPLEMENTARY MATERIAL

Physical and spectral data for compounds **7**–**12** are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

УТИЦАЈ РАСТВАРАЧА НА АПСОРПЦИОНЕ СПЕКТРЕ ПОТЕНЦИЈАЛНО ФАРМАКОЛОШКИ АКТИВНИХ 5-АЛКИЛ-5-АРИЛХИДАНТОИНА: ПРОУЧАВАЊЕ ОДНОСА СТРУКТУРЕ И СВОЈСТАВА

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Да би се проценио начин на који потенцијални антиконвулзивни лекови интерагују са својим окружењем, две серије 5-метил-5-(4-супституисаних фенил)- и 5-етил-5-(4-супституисаних фенил)хидантоина су синтетисане и њихови апсорпциони спектри су снимљени у интервалу таласних дужина од 200 до 400 nm у сету изабраних растварача. Ефекти диполарности/поларизабилности растварача и водоничног везивања између молекула растварача и растворене супстанце на померање апсорпционих максимума анализирани су применом метода линеарне корелације енергије солватације (LSER), односно Камлет–Тафтовом једначином. Однос доприноса специфичних и неспецифичних интеракција између молекула растварача и растворене супстанце корелисани су са одговарајућим АДМЕ својствима проучаваних једињења. Корелационе једначине су даље комбиноване са различитим физичко–хемијским параметрима при чему су добијене нове једначине које на задовољавајући начин описују односе између интеракција између молекула растварача и растворене супстанце и својстава која одређују њихову активност у организму.

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