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Solvent Effects on the Structure-Property Relationship of Some Potentially Pharmacologically Active 3-(4-Substituted Benzyl)-5-Ethyl-5-Phenyl- and 3-(4-Substituted Benzyl)-5,5-Diphenylhydantoins

Sleem F. Hmuda · Nemanja P. Trišović · Nataša V. Valentić · Gordana S. Uščumlić

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Abstract Two series of 3-(4-substituted benzyl)-5-ethyl-5-phenyl- and 3-(4-substituted benzyl)-5,5-diphenylhydantoins were synthesized and their UV absorption spectra were recorded in the region 200–400 nm in selected solvents of different polarity. The effects of solvent dipolarity/polarizability and solvent/solute hydrogen bonding interactions on the spectral shifts were analyzed by means of the linear solvation energy relationship (LSER) methodology of Kamlet and Taft. The quantitative relationships between hydrogen bonding interactions and the lipophilicity and blood-brain permeation of the studied compounds were discussed. Satisfactory linear dependences were obtained for moderate electron-donating and electron-withdrawing substituents at the benzyl moiety, while the strong electron-withdrawing substituent (NO_2) significantly modifies the solvation characteristics of the molecule. The paper clearly demonstrates how the solvatochromic comparison method may be applied to estimate the contributions of various modes of solvation to the pharmaceutically relevant properties of these newly synthetized hydantoin derivatives.

Keywords Hydantoin derivatives · Absorption frequencies · Kamlet-Taft equation · Hydrogen bonding · Lipophilicity · Blood-brain barrier permeability

1 Introduction

Hydantoins (imidazolidine-2,4-diones) have been widely used in biological screenings resulting in numerous pharmaceutical applications. Many of them have been identified as antiarrhytmics [1], antimuscarinics [2], antidiabetics [3] and drugs in cancer therapy [4]. However, the hydantoin derivatives are most commonly used in epilepsy treatment. Phenytoin (5,5-diphenylhydantoin) is a major anticonvulsant drug being very effective in controlling a variety of seizure disorders while impairing neurological function little, if at all [5]. Moreover, several 5-phenylhydantoins are known to be active anticonvulsants (nirvanol, etothoin,

S.F. Hmuda · N.P. Trišović · N.V. Valentić (✉) · G.S. Uščumlić
Department of Organic Chemistry, Faculty of Technology and Metallurgy, University of Belgrade, Karnegijeva 4, PO Box 3503, 11120 Belgrade, Serbia
e-mail: naca@tmf.bg.ac.rs

mephenytoin). The observed activities usually do not arise only from the heterocycle itself, but from the different substituents attached to it [6]. In this context, much attention has been paid to the determination of the structural elements of pharmacologically active drugs that are responsible for both their beneficial biological activity and unwanted side effects.

The lipophilicity of compounds is very important from physicochemical and biological viewpoints. Transport phenomena *in vivo* and through membranes proved to be dependent on lipophilic contributions [7]. In the case of hydantoins, lipophilic interactions have been used to explain the binding to receptor or receptor sites [8]. The *n*-octanol/water partitioning coefficient ($\log_{10} P$) has been traditionally used to measure the lipophilicity of drugs as a predictor of solute/membrane partitioning [9]. Because of the complexity of solvent effects, this property reflects well intermolecular interactions in condensed media. For the anticonvulsant assays, the optimal lipophilicity for penetration through the blood-brain barrier appears to exist at about $\log_{10} P = 2$.

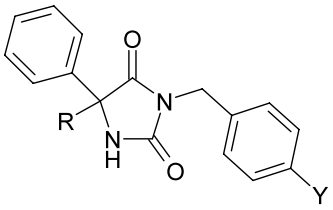
Knowledge of the equilibrium distribution between blood and brain is a fundamental aspect of drug design. The blood-brain barrier (BBB) is a complicated system formed of tight junctions between brain parenchymal capillary cells in the choroid plexus and external tissue capillary cells [10]. Its role is to maintain the homeostasis of the CNS and effective penetration is desirable for drugs targeting CNS diseases. Relatively lipophilic drugs can cross the BBB by passive diffusion, influenced by their hydrogen-bonding capacity. The more capable of hydrogen bonding a molecule is, the more hydrophilic it will be and the more it will distribute toward blood rather than the brain, since blood is more water-like and less lipid like than brain [11]. The general solvation equation for the interpretation of the BBB permeation of Abraham [12] shows that the solute dipolarity/polarizability, hydrogen-bond acidity, and hydrogen-bond basicity favor blood and the solute size favors the brain.

In the course of structure-property studies of various hydantoin derivatives, we have focused much attention on the estimation of their ability to form hydrogen bonds. Two sets of newly synthesized derivatives of nirvanol (5-ethyl-5-phenylhydantoin) and phenytoin (5,5-diphenylhydantoin) with potential for pharmaceutical applications are assembled in this work (Fig. 1). It has been of interest to prepare such sets of compounds so that their pharmacologically relevant properties might be compared with that of the parent compounds, so that lead candidates for future characterization in the maximal electroshock seizure (MES) test could be identified. The focus of our research has been to the determination of their chemical behavior in different solvents using UV/Vis spectroscopic methods. The UV absorption spectra have been recorded in the region 200–400 nm in twelve solvents of different polarity.

The effects of solvent dipolarity/polarizability and hydrogen bonding on the spectral shifts were interpreted by means of a linear solvation energy relationship using the Kamlet-Taft equation [13] of the form:

$$\nu = \nu_0 + s\pi^* + b\beta + a\alpha \tag{1}$$

where π^* is an index of the solvent dipolarity/polarizability; 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 ν_0 is the regression value of this solvent property with cyclohexane as reference solvent. The regression coefficients s, b and a in Eq. 1 measure the relative susceptibilities of the absorption frequencies to the solvent parameters.This treatment of solvation effects assumes attractive interactions between a solute and its environment and allows estimation of the ability of the investigated compounds to form hydrogen bonds.



No.	R	Y
1	C_2H_5	H
2	C_2H_5	CH_3
3	C_2H_5	Cl
4	C_2H_5	Br
5	C_2H_5	NO_2
6	C_6H_5	H
7	C_6H_5	CH_3
8	C_6H_5	Cl
9	C_6H_5	Br
10	C_6H_5	NO_2

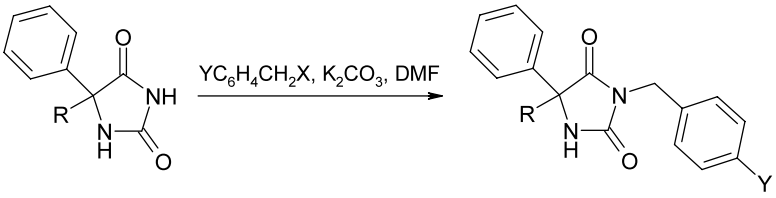
Fig. 1 Structures of the investigated 3-(4-substituted benzyl)-5-ethyl-5-phenyl- and 3-(4-substituted benzyl)-5,5-diphenylhydantoins

To analyze the role of hydrogen bonding in their pharmacologically relevant properties, we correlated the *n*-octanol/water partitioning coefficient ($\log_{10} P$) and blood-brain penetration property data ($\log_{10} BB$) against regression coefficients from Eq. 1. The corresponding values are *in silico* calculated, because their experimental determination is time-consuming, expensive and difficult. The lipophilicities of the investigated hydantoin derivatives were estimated by the calculation of $\log_{10} P$ values with the Advanced Chemistry Development (ACD) Software Solaris v. 4.67. The blood-brain barrier penetration property data ($\log_{10} BB$) were obtained by the ChemSilico program. The correlation equations demonstrate reasonable relationships between solute–solvent interactions and structure–property parameters.

2 Experimental

2.1 Chemicals and Materials

All the investigated compounds were synthesized following the procedure presented in the synthesis scheme (Scheme 1) [14]. The appropriate hydantoin was dissolved in DMF and potassium carbonate (4.4 equivalents) was added. 4-Substituted benzyl halide (1.1 equivalents) was then added and the reaction mixture was stirred for 24 h. The reaction mixture was poured into three volumes of water and extracted with ethyl acetate. The ethyl acetate extracts were washed with 5% NaOH and water, and brine, and then dried over $MgSO_4$. The solvent was removed and the resulting solid was recrystallized from ethanol until a constant melting point was achieved.



Scheme 1 Synthesis of the investigated compounds

2.2 Spectral Analysis

The chemical structures and purities of the synthesized compounds were confirmed by their melting points, ^{1}H NMR, FT-IR and UV spectra. Their full characterization is presented in Table 1.

The ^{1}H NMR spectra of DMSO-d_6 solutions (TMS as internal standard) were measured with a Varian-Gemini 200 MHz spectrometer.

The FT-IR spectra were recorded with a Bomem MB 100 spectrophotometer.

The UV absorption spectra were measured with a Shimadzu 1700 spectrophotometer. The UV spectra were taken in spectroquality solvents (Fluka) at 10^{-5} mol·dm^{-3} concentration.

2.3 Methods of Calculation

The lipophilic activity of the investigated hydantoin derivatives was estimated by the calculation of $\log_{10} P$ values with the Advanced Chemistry Development (ACD) Software Solaris v. 4.67. The blood-brain barrier penetration property data ($\log_{10} BB$) were obtained by the ChemSilico program (http://chemsilico.com).

The corresponding physicochemical characteristics and pharmacologically relevant data of the studied compounds are collected in Table 2.

2.4 Regression Analysis

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

3 Results and Discussion

The UV absorption frequencies of the investigated hydantoin derivatives in twelve solvents are given in Table 3. Hydrogen bonding and solvent polarity are the key factors in controlling pathways of energy dissipation following electronic excitation. The red shift of the absorption band when the solvent polarity is decreased supports its n-π^* nature, since in protic solvents, the n-electrons are expected to be blocked by the solvent proton through intermolecular hydrogen bonds and consequently the excitation of n-electrons is difficult. These results are in accordance with our previously published data [18, 19].

The effects of solvent dipolarity/polarizability and hydrogen bonding are interpreted by means of the LSER concept using Eq. 1. The solvent parameters are collected in the Table 4.

Table 1 Characterization of investigated 3-(4-substituted benzyl)-5-ethyl-5-phenyl- and 3-(4-substituted benzyl)-5,5-diphenylhydantoins

No.	R	Y	mp (°C)	lit. mp (°C)	IR (KBr) ν_{max} (cm^{-1})	^1H NMR δ (ppm) (DMS-*d*6)
1	C_2H_5	H	138–140	139–140 [15]	3212 (N–H) 1768 (C=O) 1707 (C=O)	9.12 [s, 1H, (*N* − 1)H], 7.30–7.44 [m, 5H, Ph], 7.21–7.27 [m, 5H, CH_2–Ph], 4.56 [s, 2H, N–CH_2–], 1.88–2.22 [m, 2H, –CH_2–], 0.75 [t, 3H, –CH_3]
2	C_2H_5	CH_3	164–167		3269 (N–H) 1762 (C=O) 1710 (C=O)	9.10 [s, 1H, (*N* − 1)H], 7.32–7.43 [m, 5H, Ph], 7.23–7.31 [m, 4H, –C_6H_4–CH_3], 4.49 [s, 2H, N–CH_2–], 2.24 [s, 3H, –C_6H_4–CH_3], 1.89–2.16 [m, 2H, –CH_2–], 0.74 [t, 3H, –CH_3]
3	C_2H_5	Cl	165–168		3259 (N–H) 1763 (C=O) 1710 (C=O)	9.13 [s, 1H, (*N* − 1)H], 7.40–7.55 [m, 5H, Ph], 7.23–7.36 [m, 4H, –C_6H_4–Cl], 4.54 [s, 2H, N–CH_2–], 1.86–2.21 [m, 2H, –CH_2–], 0.74 [t, 3H, –CH_3]
4	C_2H_5	Br	170–173		3245 (N–H) 1763 (C=O) 1710 (C=O)	9.13 [s, 1H, (*N* − 1)H], 7.30–7.53 [m, 5H, Ph], 7.21–7.29 [m, 4H, –C_6H_4–Br], 4.53 [s, 2H, N–CH_2–], 1.87–2.21 [m, 2H, –CH_2–], 0.74 [t, 3H, –CH_3]
5	C_2H_5	NO_2	174–176		3269 (N–H) 1764 (C=O) 1711 (C=O)	9.23 [s, 1H, (*N* − 1)H], 7.46–7.57 [m, 5H, Ph], 7.36–7.43[m, 4H, –C_6H_4–NO_2], 4.71 [s, 2H, N–CH_2–], 1.91–2.25 [m, 2H, –CH_2–], 0.78 [t, 3H, –CH_3]
6	C_6H_5	H	145–146	145-146 [16]	3275 (N–H) 1760 (C=O) 1715 (C=O)	9.81 [s, 1H, (*N* − 1)H], 7.32–7.44 [m, 10H, 2Ph], 7.23–7.31 [m, 5H, CH_2–Ph], 4.66 [s, 2H, N–CH_2–]
7	C_6H_5	CH_3	110–112		3262 (N–H) 1760 (C=O) 1711 (C=O)	9.77 [s, 1H, (*N* − 1)H], 7.30–7.44 [m, 10H, 2Ph], 7.07–7.16 [m, 4H, –C_6H_4–CH_3], 4.60 [s, 2H, N–CH_2–], 2.24 [s, 3H, –C_6H_4–CH_3]

Table 1 (*Continued*)

No.	R	Y	mp (°C)	lit. mp (°C)	IR (KBr) ν_{max} (cm^{-1})	^1H NMR δ (ppm) (DMS-*d*6)
8	C_6H_5	Cl	140–142		3325 (N–H) 1773 (C=O) 1704 (C=O)	9.84 [s, 1H, (*N* − 1)H], 7.28–7.43 [m, 10H, 2Ph], 7.24–7.28 [m, 4H, –C_6H_4–Cl], 4.64 [s, 2H, N–CH_2–]
9	C_6H_5	Br	130–133		3318 (N–H) 1773 (C=O) 1705 (C=O)	9.82[s, 1H, (*N* − 1)H], 7.22–7.50 [m, 10H, 2Ph], 7.15–7.20 [m, 4H, –C_6H_4–Br], 4.61 [s, 2H, N–CH_2–]
10	C_6H_5	NO_2	174–177		3219 (N–H) 1770 (C=O) 1712 (C=O)	9.89 [s, 1H, (*N* − 1)H], 7.34–7.51 [m, 10H, 2Ph], 7.24–7.31 [m, 4H, –C_6H_4–NO_2], 4.78 [s, 2H, N–CH_2–]

Table 2 Physicochemical parameters and pharmacologically relevant data of the investigated compounds

No.	R	Y	σ_I[a]	σ_R[b]	$\log_{10} P$[c]	$\log_{10} BB$[d]
1	C_2H_5	H	0	0	3.25	−0.01
2	C_2H_5	CH_3	−0.01	−0.16	3.71	−0.03
3	C_2H_5	Cl	0.47	−0.25	3.84	−0.05
4	C_2H_5	Br	0.47	−0.25	4.02	−0.07
5	C_2H_5	NO_2	0.67	0.10	2.98	−0.49
6	C_6H_5	H	0	0	3.89	−0.14
7	C_6H_5	CH_3	−0.01	−0.16	4.35	−0.11
8	C_6H_5	Cl	0.47	−0.25	4.49	−0.13
9	C_6H_5	Br	0.47	−0.25	4.67	−0.16
10	C_6H_5	NO_2	0.67	0.10	3.62	−0.42

[a]Inductive substituent constant [17]

[b]Resonance substituent constant [17]

[c]Calculated by ACD Solaris v. 4.67

[d]Blood-brain penetration property data ($\log_{10} BB$) were calculated by ChemSilico

The correlation of the spectroscopic data was carried out in terms of multiple linear regression. Stepwise regression analysis was used to determine the most significant parameters. It has been found that absorption frequencies of studied compounds in selected solvents show a satisfactory correlation with the π^* and α parameters (Eq. 2). The β parameter isn't statistically significant. Hydantoins are weak acids which dissociate at the $N-3$ atom, because this allows more efficient delocalization of the negative charge than ionization at $N-1$. It has been demonstrated that 3-substituted hydantoins show no appreciable ionization [20]. The regression values ν_0, s and a fit at the 95% confidence level are presented in Table 5. The success of Eq. 2 is shown in Fig. 2 by means of a plot of calculated values of ν_{max} versus observed values ν_{max} in different solvents ($R = 0.984$, $S = 0.76$, $F = 3539$).

$$\nu = \nu_0 + s\pi^* + a\alpha \tag{2}$$

The negative sign of the s coefficient in the solvatochromic equation (Table 5) indicates a bathochromic shift with increasing solvent dipolarity/polarizability. This suggests stabilization of the electronic excited state relative to the ground state occurs. The positive sign of the

Table 3 UV absorption frequencies of the investigated compounds in the selected solvents

Solvent	$\nu_{max} \times 10^{-3}$ (cm^{-1})									
	Compound									
	1	2	3	4	5	6	7	8	9	10
Methanol	47.80	46.64	47.76	47.80	47.08	46.51	46.13	45.54	45.79	47.08
Ethanol	47.85	47.39	46.30	46.40	47.06	47.28	46.30	46.51	46.40	47.39
1-propanol	47.76	46.43	45.75	46.21	47.44	46.86	46.08	46.13	45.96	47.39
2-propanol	48.12	47.80	47.21	47.98	48.69	47.30	46.38	47.76	46.00	48.12
1-butanol	46.38	45.79	45.37	45.41	46.25	45.91	45.33	45.09	44.88	45.91
2-methyl-2-propanol	46.37	46.30	45.87	45.58	46.34	46.00	45.75	45.96	44.40	46.13
Diisopropyl ether	41.84	41.91	41.95	42.12	37.94	41.43	41.43	41.70	41.77	37.99
Dimethyl sulfoxide	38.76	37.94	38.70	38.58	36.68	38.64	38.55	38.64	38.64	36.93
Methyl acetate	39.67	39.64	39.64	39.62	37.98	39.62	39.60	39.62	39.60	37.91
Ethyl acetate	38.85	38.82	38.88	38.88	37.74	39.65	39.62	39.65	39.62	37.74
N,*N*-dimethylformamide	37.54	37.59	37.57	37.51	36.68	37.71	37.62	37.65	37.62	36.66
N,*N*-dimethylacetamide	37.15	36.71	36.85	37.23	35.87	37.15	36.93	37.04	37.17	36.00

Table 4 Solvent parameters [13]

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
2-methyl-2-propanol	0.41	1.01	0.68
Diisopropyl ether	0.27	0.49	0.00
Dimethyl sulfoxide	1.00	0.76	0.00
Methyl acetate	0.60	0.42	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

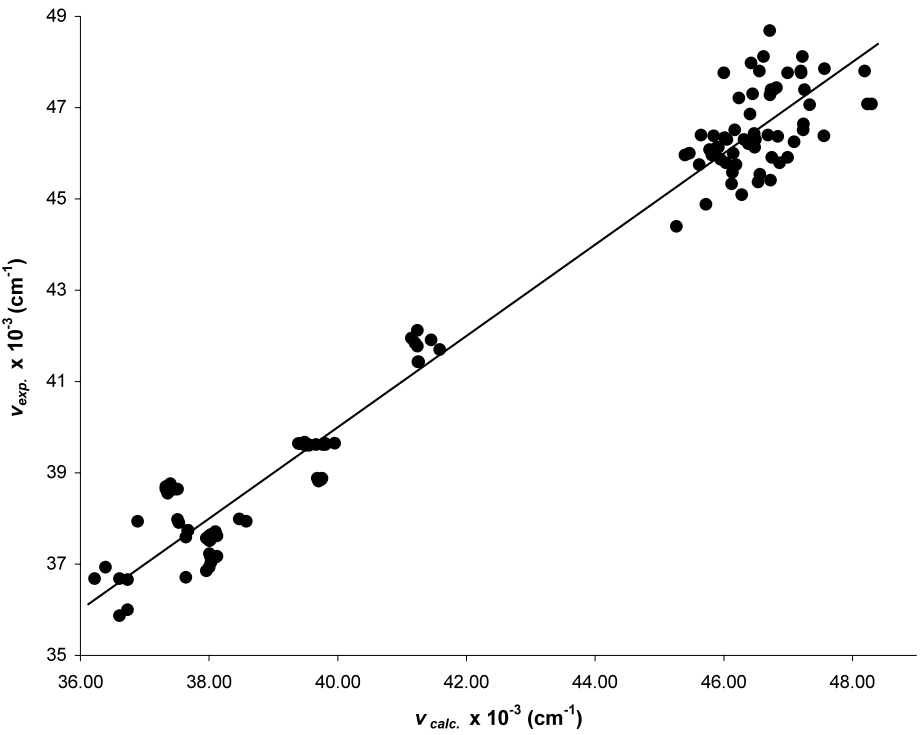


Fig. 2 Experimental versus calculated values of ν from Eq. 2

a coefficient for all compounds indicates a hypsochromic shift with increasing solvent hydrogen bond acidity. This implies stabilization of the ground state relative to the electronic excited state.

The percentage contributions of the solvatochromic parameters (Table 6) for the studied compounds show that the most of the solvatochromism is due to the solvent acidity (specific

Table 5 Regression fits to the solvatochromic parameters

No.	R	Y	$\nu_0 \times 10^{-3}$ (cm^{-1})	$s \times 10^{-3}$ (cm^{-1})	$a \times 10^{-3}$ (cm^{-1})	R^a	S^b	F^c
1	C_2H_5	H	42.61 (±1.00)	−5.21 (±1.36)	9.36 (±0.70)	0.985	0.87	148
2	C_2H_5	CH_3	43.14 (±0.98)	−6.25 (±1.33)	8.44 (±0.68)	0.984	0.85	141
3	C_2H_5	Cl	42.56 (±1.07)	−5.23 (±1.45)	8.14 (±0.74)	0.979	0.93	104
4	C_2H_5	Br	42.67 (±1.14)	−5.30 (±1.55)	8.29 (±0.79)	0.977	0.99	94
5	C_2H_5	NO_2	39.45 (±1.09)	−3.23 (±1.48)	11.60 (±0.76)	0.987	0.94	168
6	C_6H_5	H	42.64 (±0.86)	−5.16 (±1.16)	8.27 (±0.70)	0.987	0.74	166
7	C_6H_5	CH_3	42.70 (±0.77)	−5.34 (±1.04)	7.51 (±0.53)	0.988	0.67	179
8	C_6H_5	Cl	43.16 (±1.13)	−5.83 (±1.54)	7.42 (±0.79)	0.974	0.98	83
9	C_6H_5	Br	42.62 (±0.90)	−5.11 (±1.22)	6.97 (±0.62)	0.981	0.78	114
10	C_6H_5	NO_2	39.24 (±0.98)	−2.85 (±1.33)	11.51 (±1.12)	0.989	0.85	201

[a]Correlation coefficient

[b]Standard error

[c]Fisher test

Table 6 Percentage contribution of the solvatochromic effects

No.	R	Y	$P_{\pi*}$(%)	P_α(%)
1	C_2H_5	H	35.76	64.24
2	C_2H_5	CH_3	42.52	57.48
3	C_2H_5	Cl	39.12	60.88
4	C_2H_5	Br	39.03	60.97
5	C_2H_5	NO_2	21.72	78.28
6	C_6H_5	H	38.42	61.58
7	C_6H_5	CH_3	41.56	58.44
8	C_6H_5	Cl	44.00	56.00
9	C_6H_5	Br	42.30	57.70
10	C_6H_5	NO_2	19.86	80.14

solute/solvent interactions) rather than to the solvent dipolarity/polarizability (nonspecific solute/solvent interactions). These results are in accordance with the preferred existence of all studied molecules in their imido tautomeric forms. In order to obtain an insight into sub-

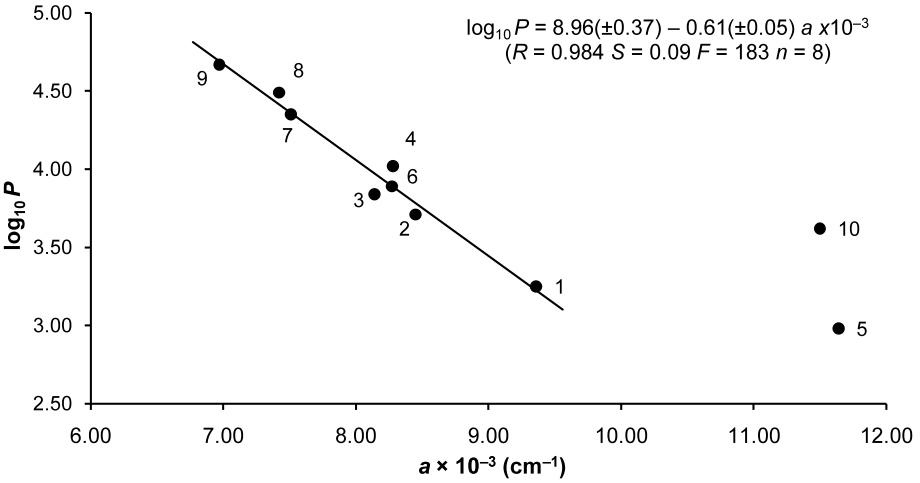


Fig. 3 Correlation between the $\log_{10} P$ values and the regression coefficient a from Eq. 2, for the studied compounds

stituent effects favoring particular modes of solvation in the ground and excited states of the compounds, we analyzed the ratio a/s, as a convenient measure of the relative contributions of indicated solvent properties, by using Taft's dual substituent parameter (DSP) method [21] in the form:

$$a/|s| = (a/|s|)_0 + \rho_I \sigma_I + \rho_R \sigma_R \tag{3}$$

The obtained correlation (Eq. 4) indicates that the main effect through which these substituents influence the solvation characteristics of the derivatives is the resonance effect while the inductive effect is less significant (the blending constant, defined as ρ_R/ρ_I, is 2.83).

$$a/|s| = 1.95(\pm 0.15) + 1.85(\pm 0.31)\sigma_I + 5.24(\pm 0.61)\sigma_R \tag{4}$$
$$(R = 0.971, S = 0.27, F = 59, n = 10)$$

Because the solvent parameters used in Eq. 2 reflect solute/solvent interactions, the regression coefficients obtained in Eq. 4 are interpreted in terms of the ability of the studied compounds to interact with their environment.

We estimated lipophilicities of the investigated hydantoin derivatives by calculation of $\log_{10} P$ values with Advanced Chemistry Development (ACD) Software Solaris v. 4.67 (Table 2). The $\log_{10} P$ parameter is a solvation characteristic, since it is directly related to the change in the Gibbs energy of solvation of a solute between two solvents [22]. The calculated values of $\log_{10} P$ were correlated against the regression coefficient a from Eq. 2 as a measure of the solute hydrogen-bond accepting ability. The result of this correlation is shown in Fig. 3. The plot of $\log_{10} P$ values versus a reveals a satisfactory linear relationship for eight compounds, excluding the points for compounds with the strong electron-withdrawing substituent NO_2, which can be represented by Eq. 5:

$$\log_{10} P = 8.96\,(\pm 0.37) - 0.61\,(\pm 0.05)\,a \times 10^{-3} \tag{5}$$
$$(R = 0.984, S = 0.09, F = 183, n = 8)$$

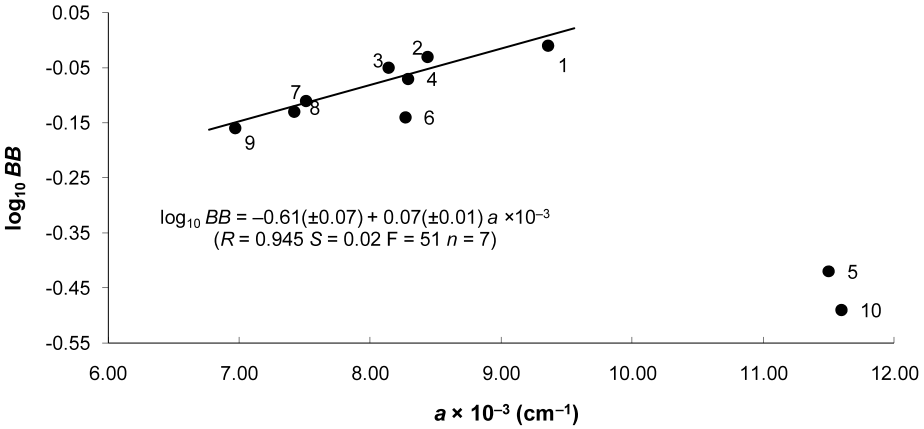


Fig. 4 Correlation between the blood-brain penetration property data ($\log_{10} BB$) and the regression coefficient a, from Eq. 2, for the studied compounds

The solute hydrogen-bond basicity favors partitioning in water rather than in n-octanol, since water is the more acidic medium. This correlation is in agreement with Abraham's characterization of the n-octanol/water system, suggesting that the hydrogen-bond accepting ability, polarity and size of a solute are good descriptors with which to model its lipophilicity [23, 24].

Limited performance of $\log_{10} P$ has been known for predicting the blood-brain equilibrium ratio [25]. We used the a coefficient from Eq. 2 to model the BBB penetration property data of the investigated hydantoin derivatives. The BBB penetration property data ($\log_{10} BB$), calculated by the ChemSilico program, is based on a measure of the partitioning of a compound across the blood–brain barrier (Table 2). The property is expressed as the ratio of the concentration in the brain to that in the blood:

$$BB = [brain] / [blood] \tag{6}$$

Correlating the data indicating likely brain penetration against the a coefficient from Eq. 2, we have derived a predictive model for seven compounds (Eq. 7), excluding the points 5, 6 and 10:

$$\log_{10} BB = -0.61\,(\pm 0.07) + 0.07\,(\pm 0.01)\,a \times 10^{-3} \tag{7}$$
$$(R = 0.945,\ S = 0.02,\ F = 51,\ n = 7)$$

The plots of the investigated pharmacologically relevant properties versus a give satisfactory linear dependences for moderate electron-donating and electron-withdrawing substituents on the benzyl moiety. The data for the hydantoin derivatives with a strong electron-withdrawing substituent (NO_2) do not follow this correlation. This substituent significantly changes solvation characteristics of the molecule and thus its lipophilicity is decreased due to increased relative contributions of the specific interactions to the overall solvation effects. This is in accordance with well accepted rule saying if the number of nitrogens and oxygens, N+O, is five or less in a molecule, then it has high chances of entering the brain [26].

It can be seen that the hydrogen bond basicity of the investigated hydantoin derivatives has an effect on the blood-brain barrier permeation. Previous investigation showed that the

BBB permeability can be increased by lowering the overall hydrogen-bonding ability of a compound by shielding with nonpolar groups [27]. However, this might be expected up to the point where the hydrophobic region of the receptor is filled, and thereafter the activity and thus the penetration through the BBB decreases due to steric hindrance during the interaction of the ligand and receptor.

The results obtained in this work can be used to determine how to modify the structure of lipophilic hydantoin derivatives to improve their activity.

4 Conclusion

In the summary, the satisfactory correlation of the UV absorption frequencies of the studied 3-(4-substituted benzyl)-5-ethyl-5-phenyl- and 3-(4-substituted benzyl)-5,5-diphenylhydantoins with Eq. 2 indicates that the correct model was selected. This means that this model gives a correct interpretation of the linear solvation energy relationship for the complex system of hydantoin derivatives in the selected solvent set. In such a case, where both solvents and substrates are hydrogen bond donors and acceptors, it is quite difficult to untangle the solvent dipolarity/polarizability, hydrogen bond basicity and hydrogen bond acidity properties. The investigated hydantoin derivatives show significant terms in π^* and α, but the solvent basicity term is negligible due to the lack of a suitable HBD moiety. It was pointed out that substituents of the benzyl moiety affect their ability to interact with molecular environments.

This investigation also demonstrates how the solvatochromic comparison method may be used to correlate and rationalize multiple interacting solvent effects on the pharmacologically relevant properties of the selected set of compounds. The proposed approach can help in assessing their potential pharmaceutical application.

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