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ORIGINAL PAPER

Synthesis, structure, and solvatochromic properties of pharmacologically active 5-substituted 5-phenylhydantoins

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Abstract A series of 5-substituted 5-phenylhydantoins was 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 were analyzed by means of the linear solvation energy relationship concept proposed by Kamlet and Taft. The lipophilicities of the investigated hydantoins were estimated by calculation of their log *P* values. The quantitative relationship between the ratio of the contributions of specific solvent interactions and the corresponding lipophilicity parameter is discussed. The correlation equations were combined with the corresponding ED_{50} values and different physicochemical parameters to generate new equations that demonstrate the reasonable relationships between solute–solvent interactions and the structure–activity parameters. In order to determine a spectroscopic assignment of the absorption bands in different solvents, quantum chemical calculations were done.

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Introduction

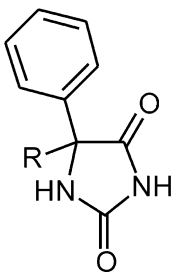
Hydantoins (imidazolidine-2,4-diones) have been demonstrated to possess good anticonvulsant activity [1]. Depending on the nature of the substitution on the hydantoin ring, a wide range of other pharmacological properties, e.g., antiarrhythmic [2], anti-inflammatory [3], anti-HIV [4], hypolipidemic [5], and antihypertensive activities [6], have also been identified.

Understanding the anticonvulsant activity of hydantoin derivatives has been a focus of research since 1938 when Merritt and Putnam found that 5,5-diphenylhydantoin (phenytoin) has anticonvulsant properties. In principle, three crucial points should be taken into account. The first and the second are related to the transport phenomena in vivo, depending on the general lipophilic properties of the hydantoin derivative, and the penetration of the latter through the blood–brain barrier (BBB) into the cell membranes, determined by the amount and position of the lipophilic parts of the molecule [7]. The *n*-octanol–water partition coefficient (log *P*) has been traditionally used to measure the lipophilicity of drugs as a predictor of solute–membrane partitioning [8]. The third point concerns the receptor interactions. Hydantoins target the neuronal voltage-gated sodium channels (NVSC) to reproduce the normal ion potential [9]. Regarding the molecular mode of action of phenytoin, Smythies [10] suggested that it forms an array of molecules stacked on a *β*-turn segment of the proteic part of a putative receptor site through the formation of hydrogen bonds with the carbonyl in position 2 and

the NH in position 3. However, phenytoin has two alternative C(=O)NH edges and two prochiral phenyl groups connected to the quaternary carbon in position 5. This arrangement suggests that other modes of hydrogen bond formation may also take place.

The capacity of organic molecules to form hydrogen bonds very significantly affects a wide range of their properties, including aqueous solubility, cell permeability, human intestinal absorption (HIA), BBB permeation, nonspecific plasma protein binding, and many others [11, 12]. Poupaert et al. [13] observed that the anticonvulsant activity of phenytoin-like compounds was reduced when the hydrogen-bonding groups (CO and NH) were removed from the phenytoin structure. This study was supported by Cortes et al. [14] as they observed the loss of the activity with changing the hydantoin skeleton to imidazolone or imidazolidinone by removing or modifying the hydrogen-bonding groups. In the present work, eleven compounds structurally related to phenytoin (**10**) with reported maximal electroshock seizure (MES) activities in rats were prepared [15, 16] (Fig. 1).

The focus of our research was the determination of the chemical behavior of the prepared phenytoin analogues in different solvents using UV/Vis spectroscopic methods. The UV absorption spectra were recorded in the region 200–400 nm in selected solvents of different polarity. In order to obtain an insight into the various modes of solvation determining the absorption energies, we interpreted the effects of solvent dipolarity/polarizability and hydrogen bonding on the absorption spectra by means of a linear solvation energy relationship (LSER) using the Kamlet–Taft equation [17] of the form:



No.	R
1	CH_3
2	C_2H_5
3	*n*-C_3H_7
4	*i*-C_3H_7
5	*n*-C_4H_9
6	*i*-C_4H_9
7	*t*-C_4H_9
8	*cyc*-C_5H_9
9	*cyc*-C_6H_{11}
10	C_6H_5
11	$C_6H_5CH_2$

Fig. 1 Structures of the investigated 5-substituted 5-phenylhydantoins

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

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 v_0 is the regression value of this solvent property in cyclohexane as the reference solvent. The regression coefficients s, b, and a in Eq. 1 measure the relative susceptibilities of the absorption frequencies to the indicated solvent parameters. This treatment of solvation effects assumes attractive solute–solvent interactions and allows one to estimate the ability of the investigated compounds to form hydrogen bonds. In order to determine a spectroscopic assignment of the absorption bands and analyze the solvent effects on the electronic charge distribution in the ground and excited state, we performed quantum chemical calculations using Gaussian 03 [18] for density functional theory (DFT) calculations and MOPAC 2009 [19] for semiempirical calculations.

The lipophilicities of the investigated hydantoins were estimated by the calculation of the log *P* values with the Advanced Chemistry Development (ACD) software Solaris v. 4.67. The calculated values of log *P* were correlated with the ratio of the contributions of specific solvent–solute interactions *a*/*b* calculated from Eq. 1. By employing the linear dependence thus obtained, we analyzed the pharmacological activity of the studied hydantoin derivatives. The correlation equations were combined with the corresponding ED_{50} values (the effective dose required to protect a rat against spasms induced by the maximum

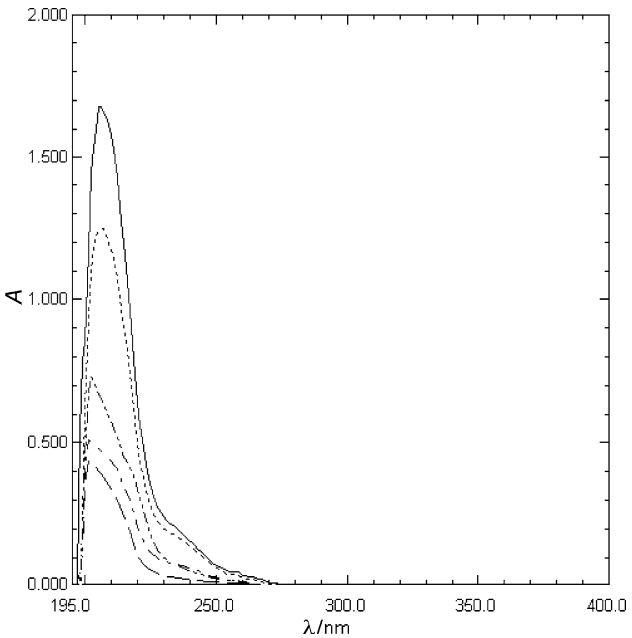


Fig. 2 UV spectra of compounds **1** (*continuous line*), **3** (*space-dashed line*), **5** (*dashed line*), **9** (*dash-single dotted line*), and **11** (*dash-double dotted line*) in ethanol

electric shock) and different physicochemical parameters to generate new equations demonstrating the reasonable relationships between solute–solvent interactions and the structure–activity parameters.

Results and discussion

All of the investigated molecules give similar UV absorption spectra with one band in the region 200–400 nm (Fig. 2). Their absorbance maxima in 15 solvents are collected in Table 1. In order to understand the photophysical facets of UV absorption, quantum chemical calculations were done. Two program packages were used to obtain information about excited states and electronic transition probabilities. The DFT calculations were done with Gaussian 03 [18] and the semiempirical calculations with MOPAC 2009 [19]. This detailed analysis of the components of electronic transitions revealed that the most intense transitions are essentially charge transfer transitions (Fig. 3). Several most intense excitations involve electron density shift from the imidazole moiety to the phenyl ring in compound **1**. As is shown in Figs. 2 and 3, there is good agreement between the computed and experimentally determined spectra. The relevant part of the computational output is given in the "Supplementary material".

Table 1 UV spectral data of the investigated compounds

Solvent/R	$\nu_{max}/10^3$ cm^{-1}										
	CH_3	C_2H_5	*n*-C_3H_7	*i*-C_3H_7	*n*-C_4H_9	*i*-C_4H_9	*t*-C_4H_9	*cyc*-C_5H_9	*cyc*-C_6H_{11}	C_6H_5	$C_6H_5CH_2$
Methanol	47.80	47.44	47.57	47.71	47.89	47.48	48.08	47.89	47.85	45.33	47.35
Ethanol	47.76	47.26	47.26	47.57	47.89	47.71	48.03	47.66	47.71	47.71	47.80
1-Propanol	46.86	46.38	46.43	46.30	46.00	47.53	47.80	46.55	46.34	46.30	46.30
2-Propanol	47.30	47.02	46.98	46.90	46.81	47.46	47.91	47.48	47.14	46.72	47.20
1-Butanol	47.04	46.99	46.77	46.25	45.75	46.82	47.26	47.30	46.99	46.77	47.04
2-Methylpropan-2-ol	46.69	46.51	46.51	46.51	46.51	46.78	47.38	47.30	46.64	46.21	46.82
Tetrahydrofuran	39.28	39.15	39.75	39.62	39.71	41.46	41.36	39.59	39.56	39.81	39.56
Diisopropyl ether	41.19	41.60	41.32	41.36	41.67	41.68	41.74	41.43	41.74	41.84	41.63
Methyl acetate	39.57	38.88	39.82	39.76	40.16	39.62	39.74	39.7	40.92	40.11	39.94
Ethyl acetate	39.03	39.12	39.49	38.97	38.97	40.34	40.97	38.85	38.74	38.73	38.88
Dioxane	40.72	40.52	40.49	40.62	40.49	40.78	41.12	40.55	40.49	40.29	40.55
N,*N*-Dimethylformamide	37.54	37.54	37.37	38.97	39.18	37.68	37.68	39.53	39.12	37.34	39.28
N,*N*-Dimethylacetamide	38.76	38.40	38.49	38.11	38.11	39.75	39.60	37.4	38.46	38.37	38.43
Dimethyl sulfoxide	39.78	39.59	37.85	38.26	37.79	38.70	39.49	39.59	39.71	38.46	37.91
Chloroform	41.15	41.15	40.95	41.12	41.08	41.16	41.22	40.98	41.46	40.95	41.12

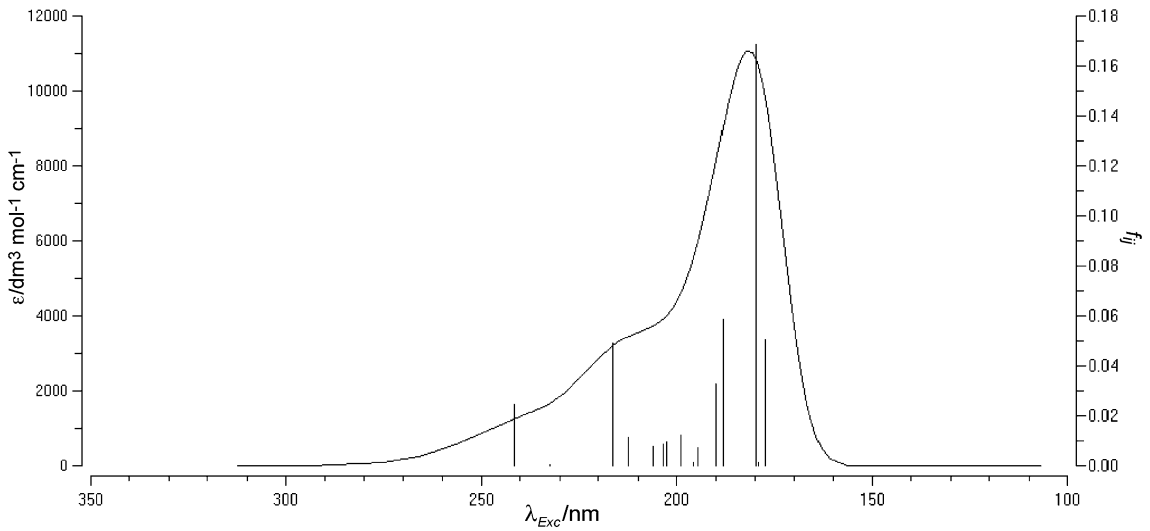


Fig. 3 Gaussview interpretation of UV–Vis spectrum of compound **1** derived from Gaussian 03 calculation

The effects of the solvent dipolarity/polarizability (nonspecific solvent interactions) and hydrogen bonding (specific solvent interactions) on the spectral shifts are interpreted by using the general Kamlet–Taft solvatochromic equation, Eq. 1. The correlation of the spectroscopic data with solvent parameters was performed by means of a multiple linear regression analysis. The parameters for the solvents used in correlations are listed in Table 2 and the coefficient values v_0, s, b, and a fit at the 95% confidence level are given in Table 3.

The negative sign of the s coefficient (Table 3) indicates a bathochromic shift with increasing solvent dipolarity/polarizability. This suggests that stabilization of the electron excited state relative to the ground state occurs. The positive signs of the a and b coefficients indicate a hypsochromic shift with increasing both solvent HBA basicity and HBD acidity and imply stabilization of the ground state relative to the electronic excited state. This is due to the interactions of HBD solvents with the hydantoin carbonyl moieties and the hydrogen bonding of the NH groups. The acidity of hydantoins is mostly the result of the NH group in position 3 which is flanked by two electron-withdrawing carbonyl groups.

Table 2 Kamlet–Taft solvent parameters [17]

Solvent	π^*	β	α
Methanol	0.6	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-Methylpropan-2-ol	0.41	1.01	0.68
Tetrahydrofuran	0.58	0.55	0
Diisopropyl ether	0.27	0.49	0
Methyl acetate	0.60	0.42	0
Ethyl acetate	0.55	0.45	0
Dioxane	0.55	0.37	0
N,*N*-Dimethylformamide	0.88	0.69	0
N,*N*-Dimethylacetamide	0.88	0.76	0
Dimethyl sulfoxide	1	0.76	0
Chloroform	0.58	0	0.44

The percentage contributions of the solvatochromic parameters (Table 4) for the investigated hydantoins show that most of the solvatochromism is due to the hydrogen bonding rather than to the nonspecific solute–solvent interactions. These results are in accordance with the preferred existence of the hydantoins as their lactam tautomer [20].

In our recent paper [21], we reported experimentally estimated lipophilicities of a representative number of hydantoin derivatives by reversed-phase high-performance thin-layer chromatography (HPTLC). Experimentally estimated lipophilicities, expressed as the chromatographic retention R_M^0 (silica gel stationary phase with acetonitrile–toluene mobile phase) for some of the 5-substituted 5-phenylhydantoins studied in this work are listed in Table 5. The R_M^0 values were correlated against the calculated log P data and the results are shown in Fig. 4. The satisfactory correlation attests that both R_M^0 and log P values can be used as a measure of the lipophilicity of the investigated compounds ($r = 0.945$, $s = 0.05$, $F = 42$).

Because the solvent parameters used in Eq. 1 reflect solute–solvent interactions, we interpreted the regression parameters in terms of the ability of the studied compounds to interact with their environment. Evidence for solvent effects on the structure–activity relationship of

Table 3 Regression fits for solvatochromic parameters (Eq. 1)

No.	R	$v_0/10^3$ cm^{-1}	$s/10^3$ cm^{-1}	$b/10^3$ cm^{-1}	$a/10^3$ cm^{-1}	r^a	SD^b	F^c
1	CH_3	40.69 (±0.91)	−4.09 (±1.27)	2.58 (±0.95)	8.05 (±0.68)	0.983	0.81	108
2	C_2H_5	40.99 (±0.86)	−4.70 (±1.21)	2.55 (±0.90)	7.72 (±0.64)	0.985	0.77	115
3	*n*-C_3H_7	41.99 (±0.68)	−6.03 (±0.95)	2.24 (±0.71)	7.58 (±0.51)	0.990	0.60	191
4	*i*-C_3H_7	41.41 (±0.78)	−4.82 (±1.08)	2.09 (±0.80)	7.65 (±0.58)	0.987	0.70	138
5	*n*-C_4H_9	41.81 (±0.97)	−5.21 (±1.35)	1.89 (±1.00)	7.51 (±0.72)	0.980	0.86	87
6	*i*-C_4H_9	42.13 (±0.86)	−5.76 (±1.20)	2.90 (±0.89)	7.03 (±0.64)	0.984	0.76	110
7	*t*-C_4H_9	42.13 (±0.92)	−5.63 (±1.29)	3.11 (±0.96)	7.27 (±0.69)	0.982	0.82	101
8	*cyc*-C_5H_9	40.79 (±0.96)	−4.46 (±1.34)	3.02 (±0.99)	7.84 (±0.72)	0.982	0.85	98
9	*cyc*-C_6H_{11}	40.14 (±0.92)	−3.93 (±1.29)	2.23 (±0.96)	7.59 (±0.69)	0.981	0.82	93
10	C_6H_5	42.09 (±0.87)	−6.57 (±1.24)	2.88 (±0.92)	6.63 (±0.66)	0.982	0.79	100
11	$C_6H_5CH_2$	41.60 (±0.72)	−5.43 (±1.01)	2.62 (±0.75)	7.52 (±0.54)	0.989	0.64	165

[a] Correlation coefficient

[b] Standard deviation

[c] Fisher test

Table 4 Percentage contributions of the solvatochromic parameters and values *a*/*b*

No.	P_{π^*}/%	P_{β}/%	P_{α}/%	*a*/*b*[a]
1	28	18	55	3.12
2	31	17	52	3.03
3	38	14	48	3.38
4	33	14	53	3.66
5	36	13	51	3.97
6	37	18	45	2.42
7	35	19	45	2.34
8	29	20	51	2.60
9	29	16	55	3.40
10	41	18	41	2.30
11	35	17	48	2.87

[a] Relation of regression coefficients of specific solvent interactions (Table 3)

5-substituted 5-phenylhydantoins was obtained by the correlation of the calculated log *P* values against the ratio of the contributions of the specific solvent interactions *a*/*b* (Fig. 5). All parameters are dependent on the structural features of the studied compounds. The log *P* parameter is a solvational characteristic, because it is directly related to the change in the Gibbs free energy of solvation of a solute distributed between two solvents. Abraham et al. [22] demonstrated that the hydrogen bond acidity of a solute plays a minor role, compared with the basicity, in partitioning between *n*-octanol and water. Although *n*-octanol is a stronger hydrogen bond base than water, the difference in hydrogen bond acidities between these two solvents affects the partitioning of a solute more significantly for the investigated set of compounds. The plot of log *P* versus *a*/*b* reveals a linear relationship for compounds **6**, **7**, **8**, **9**, **10**, and **11** ($r = 0.935$). However, the points for compounds **1**, **2**, **3**, **4**, and **5** form a separate line ($r = 0.855$) due to the different structural characteristics of substituents in position 5 (R is a lower homologue). In a previous study, a set of eight 3-substituted 5,5-diphenylhydantoins [23] was used to analyze the structural determinants governing the partitioning of the solute between *n*-octanol and water. An analogous linear relationship between log *P* and *a*/*b* was obtained, but with the opposite slope, compared with the dependencies in this work, and there was no separation of homologues. This is reasonable, because the compounds of such a set have reduced hydrogen-bonding ability due to lack of the proton at N3. The existence of these correlations (Fig. 5) supports the hypothesis of Poupaert et al. [13] that the hydrogen bonding is an essential factor in the anticonvulsant action of phenytoin-like compounds in terms of their transport properties.

In this work, we used a three-parameter quantitative structure–activity relationship (QSAR) model for the analysis of the anticonvulsant potencies for the set of eight 5-substituted 5-phenylhydantoins using the MES assay (ED_{50} values are converted into millimoles per kilo) and the obtained result is given by Eq. 2:

$$\log ED_{50} = 1.09(\pm 0.23)\log P - 0.69(\pm 0.36)\sigma^* + 0.35(\pm 0.12)E_s - 2.66(\pm 0.42) \quad (2)$$

($r = 0.942$, $s = 0.21$, $F = 11$, $n = 8$).

Table 5 Physicochemical properties and activity data of the studied compounds

No.	R	MW[a]	σ^* [b]	E_s^c	log P[d]	R_M^0 [e]	ED_{50}[f]/mg kg^{-1}
1	CH_3	190.2	0	0	1.00	−0.9006	–
2	C_2H_5	204.2	−0.1	−0.07	1.53	−0.8719	23
3	*n*-C_3H_7	218.3	−0.115	−0.36	2.06	−1.0133	66
4	*i*-C_3H_7	218.3	−0.19	−0.47	1.88	–	56
5	*n*-C_4H_9	232.3	−0.13	−0.39	2.59	−1.1615	620
6	*i*-C_4H_9	232.3	−0.125	−0.93	2.41	–	75
7	*t*-C_4H_9	232.3	−0.3	−1.54	2.23	–	57
8	*cyc*-C_5H_9	244.3	−0.2	−0.51	2.49	−1.1736	–
9	*cyc*-C_6H_{11}	258.3	−0.15	−0.79	3.06	−1.2137	–
10	C_6H_5	252.3	0.6	−2.55	2.52	−1.1476	18
11	$C_6H_5CH_2$	266.3	0.215	−0.38	2.74	–	200

[a] Molecular weight

[b] Taft electronic parameter [33]

[c] Taft steric parameter [33]

[d] Calculated by ACD Solaris v. 4.67

[e] Chromatographic retention R_M^0 (silica gel stationary phase with acetonitrile–toluene mobile phase) [21]

[f] Effective dose to protect rats against spasms induced by maximum electric shock, i.e., reported pharmacological activity [15, 16]

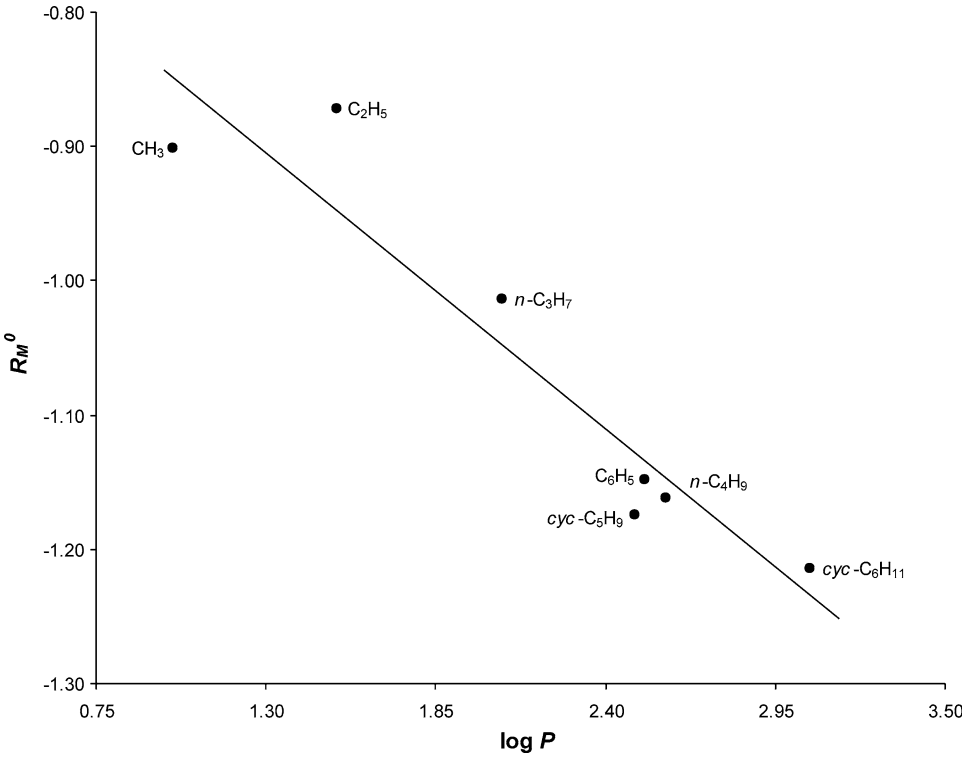


Fig. 4 Correlation between experimentally estimated and calculated lipophilicities

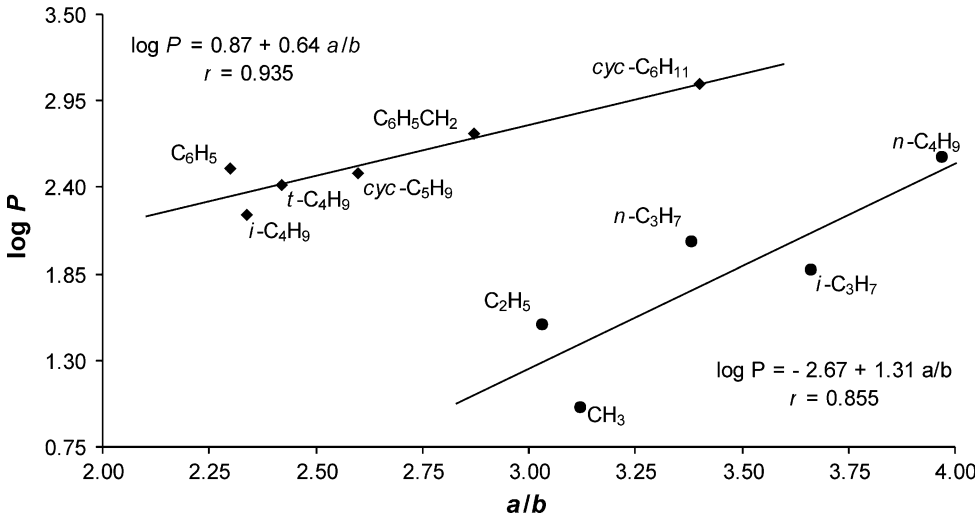


Fig. 5 Correlation between the calculated log *P* and the ratio of the specific solvent interactions

The σ^* term seems to imply a significant role for electron-withdrawing groups in position 5, whereas the positive coefficient for E_s suggests that bulky substituents produce a strong hydrophobic shield protecting the hydrogen bonds formed by the imidic part of the hydantoin ring and a β-bend protein segment from the water extrusion. This indicates that the receptors involved possess special stereochemical and electronic features. The phenyl ring appears to reach a hydrophobic surface. However, the definite identification of which binding sites are involved in the activity is difficult as most anticonvulsants interact with more than one receptor [24]. This also implies a particular importance of the C5 substitution for the pharmacokinetic phase of the drug action. Thus, the crucial factors in determining the anticonvulsant potency are the hydrogen bond acceptor, hydrogen bond donor, and an electronegative group being a large hydrophobic part of the molecule.

Conclusions

We investigated the solvational characteristics in ground and excited states of some hydantoin derivatives by monitoring UV absorbance maxima in different solvents.

Quantum chemical calculations were performed to determine a spectroscopic assignment of the absorption bands. The solvent-dependent spectral shifts were analyzed using the LSER method of Kamlet and Taft. The derived ratio of the specific solvent interactions of the investigated compounds was the cornerstone of the description of anticonvulsant potencies of the studied compounds, providing an indication of the interaction between the hydantoin moiety and its surroundings. The present study also shows that size and electronic properties of the substituent in position 5 are important structural features of such a set of compounds. The proposed approach can be applied to generate new models offering possibilities to optimize transport properties and activity simultaneously.

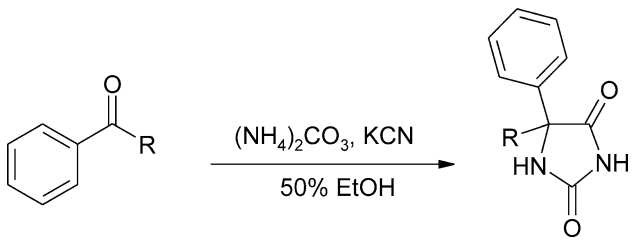
Experimental

Spectroscopic measurements

The ^{1}H and ^{13}C NMR spectral measurements were performed on a Varian-Gemini 200 spectrometer at 200 or 50 MHz, respectively. The spectra were recorded at room temperature in DMSO-d_6. The chemical shifts are expressed in ppm values referenced to TMS ($\delta_H = 0$ ppm) in ^{1}H NMR spectra, and the residual solvent signal ($\delta_C = 39.5$ ppm) in ^{13}C NMR spectra. FT-IR spectra were recorded with a Bomem MB 100 spectrophotometer. UV absorption spectra were measured with a Simadzu 1700 spectrophotometer. The UV spectra were taken in spectro quality solvents (Fluka) at a fixed concentration of 10^{-5} mol dm^{-3}.

General procedure for synthesis of 5-substituted 5-phenylhydantoins

All of the investigated compounds were synthesized by a modification of the method of Bucherer and Lieb [25]. The appropriate ketone was heated with ammonium carbonate and potassium cyanide in 50% aqueous ethanol. The obtained precipitate was filtered and crystallized from ethanol until constant melting point was achieved (Scheme 1). The ketones used in this preparation were commercially available (Fluka). The chemical structures and the purities of the synthesized hydantoins were confirmed by melting points, FT-IR, ^{1}H and ^{13}C NMR spectra and agree well with reported data (Table 6).



Scheme 1

Table 6 Synthesis of the investigated hydantoin derivatives

No.	R	Yield/%	m.p./°C	
			Found	Reported
1	CH_3	75	194–196	196–198 [26]
2	C_2H_5	72	196–199	194–196 [26]
3	*n*-C_3H_7	70	163–165	165–166 [27]
4	*i*-C_3H_7	80	209–211	210–212 [28]
5	*n*-C_4H_9	68	203–204	204–205 [27]
6	*i*-C_4H_9	70	176–178	177–178 [27]
7	*t*-C_4H_9	48	271–273	271–273 [15]
8	*cyc*-C_5H_9	52	223–225	–
9	*cyc*-C_6H_{11}	45	269–270	270 [29]
10	C_6H_5	85	293–295	290–293 [30]
11	$C_6H_5CH_2$	84	214–216	214–215 [31]

Method of calculation

Geometries of molecules were optimized using the semi-empirical PM6 method. Initial structures were prepared with the Vega ZZ graphic [32] interface. Gaussian 03 [18] calculations were done on a four-processor machine with Linux platform, using the following keywords: B3LYP/6-31G(d TD=NS,p) FCheck tates=15 cube=orbitals Pop=Full. MOPAC 2009 [19] was used on a two-processor PC using the following keywords: PM6 PRECISE C.I.=6 MECI vectors large 1SCF EPS=4.8 MMOK, for the geometry optimization, and PM6 PRECISE C.I.=6 MECI vectors large 1SCF EPS=4.8 MMOK graph, for the calculation of excited states.

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 deviation (SD), and Fisher criterion (F). The lipophilicities were estimated by the calculation of log P values with the Advanced Chemistry Development (ACD) software Solaris v. 4.67.

The corresponding physicochemical parameters of the studied compounds and their antiepileptic potencies in the MES test are collected in Table 5. For the details of the biological tests, the original articles should be consulted [15, 16].

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