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ORIGINAL PAPER

Solvent Effects on the Structure-Activity Relationship of Pharmacological Active 3-Substituted-5,5-Diphenylhydantoins

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Abstract Absorption spectra of eight 3-substituted-5,5-diphenylhydantoins have been recorded in fourteen solvents in the range 200–400 nm. The effect of solvent dipolarity/polarizability and solvent/solute hydrogen bonding interactions are analyzed by means of the linear solvation energy relationship (LSER) concept proposed by Kamlet and Taft. The lipophilic activity of the investigated hydantoins was estimated by the calculation of $\log_{10} P$ values with the Advanced Chemistry Development Software. The calculated values of $\log_{10} P$ were correlated with the ratio of the contributions of specific solvent interactions, and, by employing the linear dependence thus obtained, the pharmacological activity of the studied hydantoin derivatives is discussed.

Keywords Hydantoins · Absorption frequencies · Solvent effect · Kamlet–Taft equation · Pharmacological activity · Lipophilicity parameter · Specific solvent interactions

1 Introduction

Hydantoins (2,4-imidazolidinediones) are important anticonvulsant drugs [1, 2]. Also, they have a number of other biological activities as antiarrhythmic drugs [3, 4], bactericides [5], fungicides [5] and drugs in cancer therapy [6]. Understanding the anticonvulsant activity of hydantoins has been a focus of research since 1938 when Merrit and Putman found that 5,5-diphenylhydantoin (phenytoin) showed anticonvulsant properties [5]. Hydantoins target the trans–membrane sodium channel in neurons to reproduce the normal ion potential. Membrane interactions have been discussed with regard to transport phenomena through the blood–brain barrier to the receptor binding site [7]. Transport phenomena in vivo and through membranes proved to be dependent on lipophilic contributions. The importance of lipophilicity has been known for a long time [8]. For anticonvulsant assays, it is known that an optimal lipophilicity for penetration through the blood–brain barrier appears to exist at

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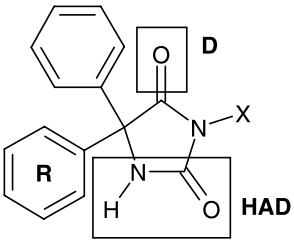

R hydrophobic unit
D electron donor group
HAD hydrogen donor/acceptor unit

X = H, CH_2OH, CH_2OCH_3, $CH_2OC_2H_5$, CH_2OCOCH_3, $CH_2OCH_2C_6H_5$, $CH_2C_6H_5$, COC_6H_5

Fig. 1 Anticonvulsant pharmacophore model for the 3-substituted-5,5-diphenylhydantoins studied

about $\log_{10} P = 2$ [9]. Also, lipophilic interactions were used to explain the binding of hydantoin derivatives to receptors or receptor parts [10–12]. The previously reported results [13] clearly confirmed the hypothesis that hydrogen bonding was an essential factor in the anticonvulsant action of these compounds. Following this idea, a pharmacophore model was proposed that is based on a hydrogen bonding acceptor, a hydrogen bonding donor and an electronegative group with a large hydrophobic part of the molecule in a defined spatial arrangement [12]. The position of hydrogen donors or electron donors in combination with an aromatic ring in a specific orientation was found to be crucial (Fig. 1) [12, 14].

Our research on the pharmacological activity of hydantoin derivatives has been focused on determination of the structural and chemical behavior of compounds in different solvents using UV/vis spectroscopic methods. To the best of our knowledge, the influence of the solvent on the UV absorption frequencies of hydantoins has not been systematically presented before. In this work, eight 3-substituted-5,5-diphenylhydantoins (Fig. 1) were synthesized and their ultraviolet absorption spectra have been recorded in the region, 200–400 nm, in fourteen solvents of different polarity. The effect of solvent dipolarity/polarizability and hydrogen bonding on the absorption spectra are interpreted by means of a linear solvation energy relationship (LSER) using a Kamlet–Taft equation [15] of the form:

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

where π^* is a measure of the solvent dipolarity/polarizability [16], β is the scale of the solvent hydrogen bond acceptor (HBA) basicities [17], α is the scale of the solvent hydrogen bond donor (HBD) acidities [18] and ν_o is the regression value of the solute property in the reference solvent cyclohexane. The regression coefficients s, b and a in Eq. 1 measure the relative sensitivities of the solvent-dependent solute property (absorption frequencies) to the indicated solvent parameters.

Linear free-energy relationships (LFER) are widely used to characterize chemical and biochemical processes. A particular type of LFER is the linear solvation energy relationship (LSER) proposed by Kamlet et al. [19] for physico-chemical and biochemical processes that depend on solute–solvent interactions. The LSER have been widely applied to different partition processes, mainly liquid–liquid extraction such as octanol–water partitioning and chromatographic processes [20]. The LSER developed by Kamlet and Taft is one of the most ambitious and successful quantitative treatments of solvent effects by means of a multiparameter equation [21–24].

The lipophilic activity of the investigated hydantoins in this work was estimated by the calculation of $\log_{10} P$ values with the Advanced Chemistry Development (ACD) Software

Solarius V. 4.67. The calculated values of $\log_{10} P$ were correlated with the ratio of the contributions of specific solvent interactions a/b calculated from Eq. 1 and, employing the linear dependence thus obtained, the pharmacological activity of the studied hydantoin derivatives is discussed.

2 Experimental

2.1 Chemicals and Materials

All of the investigated 3-alkoxymethyl-5,5-diphenylhydantoins were synthesized by the reaction of the 5,5-diphenylhydantoin sodium salt suspended in *N*,*N*-dimethylformamide with the corresponding chloromethylalkylether in the presence of base, using a modified literature procedure [25]. The experimental investigation included modification of the synthetic procedure in terms of catalyst, isolation techniques, as well as purification and identification of the products.

3-Hydroxymethyl-5,5-diphenylhydantoin was prepared by the reaction of 5,5-diphenylhydantoin (commercial available Fluka) with 37% aqueous formaldehyde in ethyl alcohol and sodium hydroxide. Isolation of the product from the reaction mixture and the purification process are as previously reported [26]. 3-Acetoxymethyl-5,5-diphenylhydantoin was synthesized by the reaction of 3-hydroxymethyl-5,5-diphenylhydantoin with acetic anhydride [27]. 3-Benzyl-5,5-diphenylhydantoin was prepared by the reaction of 5,5-diphenylhydantoin and benzylchloride in alcoholic solution in the presence of sodium hydroxide [28]. 3-Benzoyl-5,5-diphenylhydantoin was synthesized by the reaction of the 5,5-diphenylhydantoin sodium salt and benzoylchloride in dry benzene [29].

2.2 Spectral Analysis

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

FT-IR spectra were recorded with a Bomem MB 100 spectrophotometer. ^{1}H NMR spectra of DMSO-d6 solutions (TMS as internal standard) were measured with a Varian-Gemini 200 MHz spectrometer. UV absorption spectra were measured with a Shimadzu 1700 spectrophotometer. The UV spectra were taken in spectroquality solvents (Fluka) at 10^{-5} mol·L^{-1} concentration.

2.3 Regression Analysis

The correlation analysis was carried out using Microsoft Excel computer software, 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's significance test (F).

3 Results and Discussion

The ultraviolet absorption frequencies of the 3-substituted-5,5-diphenylhydantoin in fourteen protic and aprotic solvents in the range, 200–400 nm, are given in Table 2. The effects

Table 1 Physical and spectroscopic data for 3-substituted-5,5-diphenylhydantoins[a]

No.	Substituent X	mp[b] (°C)	Lit. mp.[b] (°C)	IR (KBr) ν_{NH} (cm^{-1})	IR (KBr) $\nu_{C=O}$ (cm^{-1})	^{1}H NMR (DMSO-*d*6) δ (ppm)
1	H	293–5	293–5	3273	1773	9.17 [s, 2H, (N-1)H],
				3208	1742	7.30 [s, 10H, 2Ph]
2	CH_2OH	184–6	184–6 [26]	3337	1769	9.67 [s, 1H, (N-1)H],
					1708	7.27–7.51 [m, 10H, 2Ph],
						6.30–6.49 [t, 1H, OH],
						4.84–4.87 [d, 2H, N–CH_2]
3	CH_2OCH_3	126–7	127–8 [25]	3181	1781	9.82 [s, 1H, (N-1)H],
					1741	7.26–7.46 [m, 10H, 2Ph],
						4.83 [s, 2H, N–CH_2],
						3.22 [s, 3H, CH_3]
4	$CH_2OC_2H_5$	127–9		3174	1778	9.82 [s, 1H, (N-1)H],
					1726	7.26–7.46 [m, 10H, 2Ph],
						4.87 [s, 2H, N–CH_2],
						3.41–3.52 [q, 2H, OCH_2],
						1.01–1.08 [t, 3H, CH_3]
5	CH_2OCOCH_3	161–2	162–3 [27]	3380	1789	9.96 [s, 1H, (N-1)H],
					1737	7.28–7.52 [m, 10H, 2Ph],
					1728	5.48 [s, 2H, N–CH_2],
						2.0 [s, 3H, $COCH_3$]
6	$CH_2OCH_2C_6H_5$	150–2	151–2 [25]	3174	1777	9.85 [s, 1H, (N-1)H],
					1715	7.20–7.46 [m, 15H, 2Ph + CH_2Ph],
						4.98 [s, 2H, N–CH_2],
						4.54 [s, 2H, OCH_2]
7	$CH_2C_6H_5$	145–6	145–6 [28]	3275	1760	9.84 [s, 1H, (N-1)H],
					1715	7.23–7.42 [m, 15H, 2Ph + CH_2Ph],
						4.66 [s, 2H, N–CH_2]
8	COC_6H_5	150–1	149–51 [29]	3335	1797	10.27 [s, 1H, (N-1)H],
					1748	7.34–7.83 [m, 15H, 2Ph + CH_2Ph]
					1718	

[a]The 5,5-diphenylhydantoins was commercially available (Fluka)

[b]Melting point, mp

of the solvent dipolarity/polarizability (nonspecific solvent interactions) and hydrogen bonding (specific solvent interactions) on the investigated hydantoins are interpreted by means of the LSER concept using Eq. 1. The solvent parameters [30] are given in Table 3. Correlation of the spectroscopic data was carried out by means of a multiple linear regression analysis. It was found that absorption frequencies for hydantoin derivatives in eleven selected solvents (except chloroform, acetonitrile and dioxane) show a satisfactory correlation with the π^*, β and α parameters. These results are in accordance with our unpublished data for 3-(4-substituted benzyl)- and 3-(4-substituted benzoyl)-5,5-diphenylhydantoins and Kamlet–Taft's conclusion [31] that differences between the solvent dipolarity/polarizability are significantly greater between different solvent classes than within the individual classes.

Table 2 Ultraviolet absorption frequencies of 3-substituted-5,5-diphenylhydantoins in different solvents

No.	Solvent/Substituent X	$\nu_{max} \times 10^{-3}$ (cm^{-1})							
		H	CH_2OH	CH_2OCH_3	$CH_2OC_2H_5$	CH_2OCOCH_3	$CH_2OCH_2C_6H_5$	$CH_2C_6H_5$	COC_6H_5
1	Methanol	47.39	47.39	46.58	46.30	46.73	46.95	45.09	46.95
2	Ethanol	47.39	46.51	46.37	46.08	46.08	47.39	47.08	47.85
3	Propan-1-ol	45.87	44.84	45.13	45.05	45.45	44.05	45.41	47.17
4	Propan-2-ol	44.44	44.44	44.52	44.25	44.25	44.25	47.48	46.95
5	Butan-1-ol	45.25	45.05	44.78	44.64	44.64	44.84	46.04	47.95
6	Ethyl acetate	38.76	38.91	38.95	38.83	38.76	38.76	39.71	38.91
7	Diisopropyl ether	41.07	41.15	41.18	41.07	41.15	41.15	41.63	41.43
8	Tetrahydrofuran	39.60	39.53	39.72	39.53	39.53	39.53	38.82	39.06
9	*N*,*N*-Dimethylacetamide	37.17	37.31	37.48	37.24	37.31	34.72	39.36	37.31
10	*N*,*N*-Dimethylformamide	37.45	37.45	37.64	37.45	37.45	37.45	37.43	37.17
11	Acetone	39.53	39.53	39.46	39.86	38.91	38.83	40.88	36.80
12	Chloroform	40.90	40.98	40.90	40.86	40.90	40.82	40.86	40.88
13	Acetonitrile	48.78	48.31	48.51	48.40	47.62	48.54	48.80	47.72
14	Dioxane	40.16	40.24	40.28	40.22	40.24	40.16	40.36	40.18

Table 3 Solvent parameters [30]

Solvent	π^*	α	β
Methanol	0.60	0.93	0.62
Ethanol	0.54	0.83	0.77
Propan-1-ol	0.52	0.78	0.83
Propan-2-ol	0.48	0.76	0.95
Butan-1-ol	0.47	0.79	0.88
Ethyl acetate	0.55	0	0.45
Diisopropyl ether	0.27	0	0.49
Tetrahydrofuran	0.58	0	0.55
N,*N*-Dimethylacetamide	0.88	0	0.76
N,*N*-Dimethylformamide	0.88	0	0.69
Acetone	0.71	0.08	0.48
Chloroform	0.58	0.44	0
Acetonitrile	0.75	0.19	0.31
Dioxane	0.55	0	0.37

Table 4 Regression fits to the solvatochromic parameters (Eq. 1)[a]

No.	Substituent X	ν_0 (10^{-3} cm^{-1})	s (10^{-3} cm^{-1})	a (10^{-3} cm^{-1})	b (10^{-3} cm^{-1})	R[b]	S[c]	F[d]
1	H	43.83 (±1.14)	−4.02 (±1.36)	9.54 (±0.77)	−4.27 (±1.78)	0.989	0.68	109
2	CH_2OH	43.95 (±0.86)	−3.94 (±1.02)	9.05 (±0.58)	−4.49 (±1.33)	0.993	0.51	171
3	CH_2OCH_3	43.47 (±0.84)	−4.37 (±1.00)	8.19 (±0.57)	−2.96 (±1.32)	0.993	0.51	159
4	$CH_2OC_2H_5$	43.62 (±0.82)	−4.28 (±0.98)	8.18 (±0.56)	−3.46 (±1.28)	0.993	0.49	161
5	CH_2OCOCH_3	43.44 (±0.91)	−4.52 (±1.09)	8.33 (±0.62)	−3.14 (±1.42)	0.992	0.55	142
6	$CH_2OCH_2C_6H_5$	45.47441 (±1.76)	−5.82 (±2.11)	9.72 (±1.19)	−6.04 (±2.76)	0.977	1.06	48
7	$CH_2C_6H_5$	41.52 (±1.79)	−6.16 (±2.13)	6.22 (±1.21)	3.51 (±2.79)	0.969	1.07	36
8	COC_6H_5	41.56 (±1.13)	−8.68 (±1.35)	8.50 (±0.76)	4.17 (±1.76)	0.993	0.68	165

[a]Chloroform, acetonitrile and dioxane were excluded from the correlation set

[b]Correlation coefficient

[c]Standard error of the estimate

[d]Fisher's test

The results of the multiple regressions are presented in Tables 4 and 5. The coefficient values ν_o, s, b and a fit at the 95% confidence level are given in Table 4. The degree of success of

Table 5 Percentage contributions of the solvatochromic parameters

No.	Substituent X	$P_{\pi*}$ (%)	P_{α} (%)	P_{β} (%)
1	H	22.55	53.50	23.95
2	CH_2OH	22.54	51.77	25.69
3	CH_2OCH_3	28.16	52.77	19.07
4	$CH_2OC_2H_5$	26.88	51.38	21.74
5	CH_2OCOCH_3	28.27	52.09	19.64
6	$CH_2OCH_2C_6H_5$	26.97	45.04	27.99
7	$CH_2C_6H_5$	38.77	39.14	22.09
8	COC_6H_5	40.65	39.81	19.54

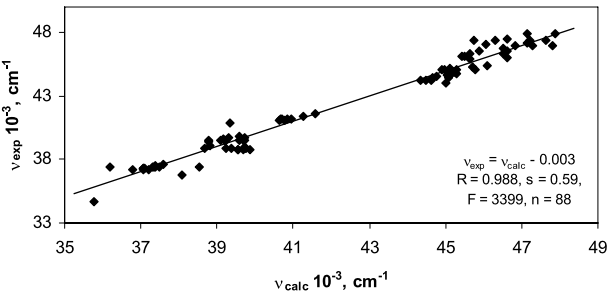

Fig. 2 Plot of ν_{max} observed against ν_{max} calculated from Eq. 1 for 3-substituted-5,5-diphenylhydantoins

Eq. 1 is shown in Fig. 2 by means of a plot of ν_{max} calculated versus ν_{max} observed in different solvents. The negative signs of the *s* and *b* coefficients in the total solvatochromic equation (Table 4) for all 3-substituted-5,5-diphenylhydantoins (excluding the positive sign of the *b* coefficient for $CH_2C_6H_5$ and COC_6H_5 groups as substituents) indicates a bathochromic shift with both increasing solvent polarity and solvent hydrogen bond acceptor basicity. This suggests that stabilization of the electron's excited state relative to the ground state occurs. The positive sign of the *a* coefficient for all hydantoins indicates a hypsochromic shift with increasing solvent hydrogen bond donor acidity. This implies stabilization of the ground state relative to the electronic excited state. The percentage contributions of the solvatochromic parameters (Table 5) for the investigated hydantoins show that most of the solvatochromism is due to solvent basicity and acidity (specific solute–solvent interactions) rather than to the solvent dipolarity/polarizability (nonspecific solute–solvent interactions). These results are in accordance with the preferred existence of the hydantoins as their lactam tautomer [5] and the previously reported hypothesis by Poupaert et al. [13] that hydrogen bonding is an essential factor in the anticonvulsant action of 5,5-diphenylhydantoin derivatives.

The results of our previous investigation of the solvent effects on the absorption frequencies of 5,5-dimethylhydantoin [32] and 1,3-bis-substituted-5,5-dimethylhydantoins [32] showed that multiple linear regression of the ν_{max} and π^*, α and β solvent parameters gave poor results for all 5,5-dimethylhydantoins because the β parameter is not significant in these correlations. This can be explained by the ability of these hydantoins to create a strong intermolecular hydrogen bond that decreases the hydrogen-bond accepting influence of the solvent and lipophilic activity of the molecules. These results are in accordance with the extensive study of 5,5-dialkylhydantoin derivatives [33] and the conclusion about the non-activity of these molecules.

Table 6 Values of the ratios of the solvatochromic coefficients a/b, lipophilic parameter $\log_{10} P$ and pharmacologic activity parameter MES for 3-substituted-5,5-diphenylhydantoins

No.	Substituent X	a/b	$\log_{10} P$[a]	MES[b] ED_{50}, $mg \cdot kg^{-1}$ (activity reported)
1	H	2.23	2.52	~7.5
2	CH_2OH	2.02	1.34	–
3	CH_2OCH_3	2.77	1.98	~6
4	$CH_2OC_2H_5$	2.36	2.84	–
5	CH_2OCOCH_3	2.65	2.24	<12.5
6	$CH_2OCH_2C_6H_5$	1.61	4.18	>25
7	$CH_2C_6H_5$	1.77	3.89	>200
8	COC_6H_5	2.04	3.40	–

[a]Values of ACD $\log_{10} P$ calculated by the Advanced Chemistry Development Software Solaris V.4.67

[b]Maximal electroshock seizures (pharmacological test) [25, 34]

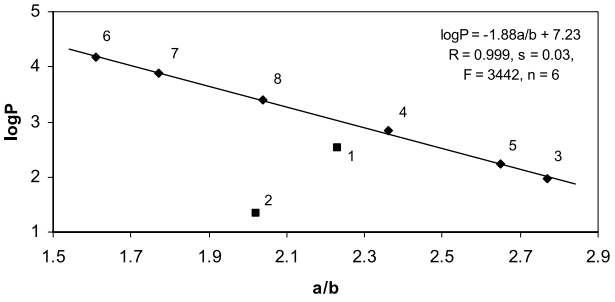

Fig. 3 Correlation of $\log_{10} P$ values with ratios of contribution of specific solvent interactions a/b for 3-substituted-5,5-diphenylhydantoins

Vida et al. [25] earlier reported that both 3-acetoxymethyl and 1,3-bis(acetoxymethyl)-5,5-diphenylhydantoin showed good activity against maximal electroshock seizures (MES test). They also reported [34] that 3-alkoxymethyl derivatives of diphenylhydantoin possess activity against maximal electroshock seizures but, unlike the non-substituted diphenylhydantoin, were also effective against chemoshock. The results of these studies have been summarized in Table 6 for some of the compounds investigated in our present work.

Additional evidence for solvent effects on the structure-activity relationship of hydantoin derivatives was obtained by the correlation of calculated lipophilic $\log_{10} P$ values with the ratio of the contributions of specific solvent interactions a/b, with both parameters being dependent on the structural characteristics of the investigated hydantoins (Table 6). The results of the correlation are shown in Fig. 3. The plot of $\log_{10} P$ values versus a/b gives a satisfactory linear correlation (excluding the point of CH_2OH substituent) that can be represented by Eq. 2:

$$\log_{10} P = -1.89(\pm 0.20)(a/b) + 7.18(\pm 0.45)$$
$$(R = 0.972, \quad S = 0.21, \quad F = 87, \quad n = 7). \tag{2}$$

The data for 3-hydroxymethyl-5,5-diphenylhydantoin (a very important intermediate in the preparation of the phenytoin prodrug) did not follow Eq. 2. The existence of this correlation (Fig. 3) is strong evidence for the proportionality between the lipophilic parameters and the specific solvatochromic effect of the investigated 3-substituted-5,5-diphenylhydantoins that show good activity against maximal electroshock seizures as reported previously

[25, 34] (Table 6). The correlation of $\log_{10} P$ with a/b values for 3-substituted-5,5-diphenylhydantoins, excluding the data of both 3-hydroxymethyl-5,5-diphenylhydantoin and 5,5-diphenylhydantoin (unsubstituted molecule), gave excellent results as presented by Eq. 3:

$$\log_{10} P = -1.88(\pm 0.03)(a/b) + 7.23(\pm 0.07)$$
$$(R = 0.999, \quad S = 0.03, \quad F = 3442, \quad n = 6). \tag{3}$$

The satisfactory correlation of the ultraviolet absorption frequencies of the investigated 3-substituted-5,5-diphenylhydantoins with Eq. 1 indicates that the correct model was selected. This means that this model gives a correct interpretation of the linear solvation energy relationships for the complex system of hydantoin derivatives in the selected solvents. In this case, where both solvents and substrates are hydrogen-bond donors and acceptors, it has proven to be quite difficult to untangle the solvent dipolarity/polarizability, hydrogen bond donor acidity and hydrogen bond acceptor basicity properties. For these reasons, we consider that the results presented in this work may be utilized to quantitatively estimate and separate the overall solvent effect into specific and nonspecific contributions using a LSER method. The satisfactory correlation of the lipophilic parameters, $\log_{10} P$, of the investigated pharmacological active hydantoins with the ratio of the contributions of the specific solvent-solute interactions supports the previously reported [12] pharmacophore model, which is based on a hydrogen-bond acceptor, a hydrogen-bond donor, and an electronegative group with a large hydrophobic part of the molecule.

Following the model proposed in this work, the pharmacological activity of some hydantoin derivatives can be explained and the corresponding potential activity/nonactivity of the studied hydantoins, not yet pharmacologically tested, may be predicted.

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References

1. Lopez, A.C., Trigo, C.G.: In: Katrizky, A.R. (ed.) The Chemistry of Hydantoins. Advances in Heterocyclic Chemistry. Academic Press, New York (1985)
2. Scholl, S., Koch, A., Henning, D., Kempter, G., Kleinpeter, E.: The influence of structure and lipophilicity of hydantoin derivatives on anticonvulsant activity. Struct. Chem. **10**, 355–366 (1999)
3. Knabe, J., Baldauf, J., Ahlhem, A.: Racemates and enantiomers of basic substituted 5-phenylhydantoins. Syntheses and antiarrhythmic activity. Pharmazie **52**, 912–919 (1997)
4. Anger, T., Madge, D.J., Mulla, M., Riddall, D.: Medicinal chemistry of neuronal voltage-gated sodium channel blockers. J. Med. Chem. **44**, 115–137 (2001)
5. Kleinpeter, E.: The structure of hydantoins in solution and in the solid state. Struct. Chem. **8**, 161–173 (1997)
6. Rodgers, T.R., LaMontagne, M.P., Markovac, A., Ach, A.B.: Hydantoins as antitumor agents. J. Med. Chem. **20**, 591–594 (1977)
7. Meldrum, B.S.: Identification and preclinical testing of novel antiepileptic compounds. Epilepsia **38**, S7–S15 (1997)
8. Seydel, J.K., Schaper, K.J.: In: Schemische Struktur und Biologische Wirkung von Wirkstoffen, Metoden der Quantitativen Structur–Wirkungsanalyse. Verlag Chemie, Weinheim (1979)
9. Hacksell, U.: In: Krogsgaard-Larsen, P., Madsen, U. (eds.) A Textbook of Drug Design and Development. Harwood Academic Publishers, Amsterdam (1996)
10. Brouillette, W.J., Brown, G.B., DeLorey, T.M., Liang, G.: Sodium channel binding and anticonvulsant activities of hydantoin containing conformationally constrained 5-phenyl substituents. J. Pharm. Sci. **79**, 871–874 (1990)

11. Brouillette, W.J., Jestkov, V.P., Brown, M.L., Akhtar, M.S., DeLorey, T.M., Brown, G.B.: Bicyclic hydantoins with a bridgehead nitrogen. Comparison of anticonvulsant activities with binding to the neuronal voltage-dependent sodium channel. J. Med. Chem. **37**, 3289–3293 (1994)
12. Unverferth, K., Engel, J., Höfgen, N., Rostock, A., Günther, R., Lankau, H.J., Menzer, M., Rolfs, A., Liebscher, J., Müller, B., Hofmann, H.J.: Synthesis. anticonvulsant activity, and structure-activity relationships of sodium channel blocking 3-aminopyrroles. J. Med. Chem. **41**, 63–73 (1998)
13. Poupaert, J.H., Vandervarst, D., Guiot, P., Moustafa, M.M.M., Dumont, P.: Structure–activity relationship of phenytoin-like anticonvulsant drugs. J. Med. Chem. **27**, 76–78 (1984)
14. Jones, G.L., Woodbury, D.M.: Anticonvulsant structure–activity relationships: historical development and probable causes of failure. Drug Dev. Res. **2**, 333–355 (1982)
15. Kamlet, M.J., Abboud, J.L.M., Taft, R.W.: An examination of linear solvation energy relationships. Prog. Phys. Org. Chem. **13**, 485–630 (1981)
16. Abboud, J.L.M., Kamlet, M.J., Taft, R.W.: Regarding a generalized scale of solvent polarities. J. Am. Chem. Soc. **99**, 8325–8327 (1977)
17. Kamlet, M.J., Taft, R.W.: The solvatochromic comparison method. I. The β-scale of solvent hydrogen-bond acceptor (HBA) basicities. J. Am. Chem. Soc. **98**, 377–383 (1976)
18. Kamlet, M.J., Taft, R.W.: Linear solvation energy relationships. Part 3. Some reinterpretations of solvent effects based on correlations with solvent π^* and α values. J. Chem. Soc. Perkin Trans. **2**, 349–356 (1979)
19. Kamlet, M.J., Doherty, R.M., Abboud, J.L.M., Abraham, M.H., Taft, R.W.: Solubility: a new look. Chemtech **16**, 566–576 (1986)
20. Carr, P.W., Doherty, R.M., Kamlet, M.J., Taft, R.W., Melander, W., Horvath, C.: Study of temperature and mobile-phase effects in reversed-phase high–performance liquid chromatography by the use of the solvatochromic comparison method. Anal. Chem. **58**, 2674–2680 (1986)
21. Ušćumlić, G.S., Mijin, D.Ž., Valentić, N.V., Vajs, V., Sušić, B.: Substituent and solvent effects on the UV/Vis absorption spectra of 5-(4-substituted arylazo)-6-hydroxy-4-methyl-3-cyano-2-pyridones. Chem. Phys. Lett. **397**, 148–153 (2004)
22. Mijin, D.Ž., Ušćumlić, G.S., Perišić-Janjić, N.U., Valentić, N.V.: Substituent and solvent effects on the UV/vis absorption spectra of 5-(3- and 4-substituted arylazo)-4,6-dimethyl-3-cyano-2-pyridones. Chem. Phys. Lett. **418**, 223–229 (2006)
23. Magnes, B.Z., Pines, D., Strashnikova, N., Pines, E.: Hydrogen-bonding interactions of photoacids: Correlation of optical solvatochromism with IR absorption spectra. Solid State Ionics **168**, 225–233 (2004)
24. Spange, S., Kunzmann, D., Sens, R., Roth, I., Seitfert, A., Thiel, W.R.: Solvatochromic azamethine dyes for probing the polarity of gold-cluster-functionalized silica particles. Chem. Eur. J. **9**, 4161–4167 (2003)
25. Vida, J.A., Samour, C.M., Reinhard, J.F.: Anticonvulsants. 1. Alkoxymethyl derivatives of barbiturates and diphenylhydantoin. J. Med. Chem. **14**, 187–189 (1971)
26. Mai, K.H.X., Patil, G.: Preparation of 2-(1-hydroxyalkyl)-5,5-diphenylhydantoins as drug intermediates. U.S. Patent 4,709,042 (1987); Chem. Abstr. **108**, 94560 (1987)
27. Vida, J.A., Wilber, W.R., Reinhard, J.F.: Anticonvulsants. 2. Acyloxymethyl and halomethyl derivatives of barbituric acid and diphenylhydantoin. J. Med. Chem. **14**, 190–193 (1971)
28. Hoffmann, C.: Synthesis of some 3-substituted 5,5-diphenylhydantoins. Bull. Soc. Chim. Fr., 45–47 (1950)
29. Muccioli, G.G., Wouters, J., Poupaert, J.H., Norberg, B., Poppitz, W., Scriba, E.K.G., Lambert, D.M.: Versatile access to benzhydryl-phenylureas through an unexpected rearrangement during microwave-enhanced synthesis of hydantoins. Org. Lett. **5**, 3599–3602 (2003)
30. Kamlet, M.J., Abboud, J.L.M., Abraham, M.H., Taft, R.W.: Linear solvation energy relationships. 23. A comprehensive collection of the solvatochromic parameters, π^*, α, and β, and some methods for simplifying the generalized solvatochromic equation. J. Org. Chem. **48**, 2877–2887 (1983)
31. Taft, R.W., Abboud, J.-L.M., Kamlet, M.J.: Solvatochromic comparison method. 20. Linear solvation energy relationships. 12. The dδ term in the solvatochromic equations. J. Am. Chem. Soc. **103**, 1080–1086 (1981)
32. Ušćumlić, G.S., Kshad, A.A., Mijin, D.Ž.: Synthesis and investigation of solvent effects on the ultraviolet absorption spectra of 1,3-bis-substituted-5,5-dimethylhydantoins. J. Serb. Chem. Soc. **68**, 699–706 (2003)
33. Ware, E.: The chemistry of the hydantoins. Chem. Rev. **46**, 403–70 (1950)
34. Vida, J.A., O'Dea, M.H., Samour, C.M., Reinhard, J.F.: Anticonvulsants. 5. Derivatives of 5-ethyl-5-phenylhydantoin and 5,5-diphenylhydantoin. J. Med. Chem. **18**, 383–385 (1975)