Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.rs • www.shd.org.rs/JSCS

J. Serb. Chem. Soc. 74 (11) 1195–1205 (2009)
JSCS–3910

UDC 547.783+542.913+54.02:532.74
Original scientific paper

Synthesis, structure and solvatochromism of 5-methyl-5-(3- or 4-substituted phenyl)hydantoins

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(Received 1 July 2008, revised 8 July 2009)

Abstract: Several 5-methyl-5-(3- or 4-substituted phenyl)hydantoins were prepared and their ultraviolet absorption spectra were recorded in the region 200––400 nm in twelve solvents of different polarity. The effect of solvent dipolarity/polarizability and solvent/solute hydrogen bonding interactions were 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 calculation of log *P* values with Advanced Chemistry Development Software. The calculated values of log *P* were correlated with the contribution of hydrogen bond donor–solvent interactions. By employing the thus obtained linear dependence, the pharmacological activity of the studied hydantoin derivatives is discussed.

Keywords: hydantoins; absorption frequencies; LSER; lipophilicity parameter; specific solvent interactions; pharmacological activity.

INTRODUCTION

Hydantoins (imidazolidine-2,4-diones) are important anticonvulsant drugs.[1,2] The anticonvulsant activity of hydantoins has been known since 1938 when Merrit and Putman[3] found that 5,5-diphenylhydantoin (phenitoin) showed anti-epileptic activity. In addition, a number of other pharmacological activities of hydantoin derivatives are known, such as in their use as anti-arrhythmic,[4] anti-inflammatory[5] and antitumor compounds.[6]

Both the electron distribution and the stereochemistry of hydantoins are important for their pharmacological activity. Following this idea, a pharmacophore model was proposed based on a hydrogen bonding acceptor, a hydrogen bonding donor and an electronegative group with a large hydrophobic part of the molecule

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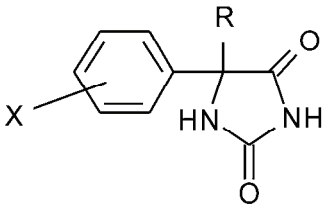
doi: 10.2298/JSC0911195D

in a defined spatial arrangement.[7] The position of the hydrogen donor in combination with an aromatic ring in a specific orientation was found to be crucial.[7,8] Previously reported results[9] clearly confirmed the hypothesis that hydrogen bonding is an essential factor in the anticonvulsant action of these compounds. In order to define the impact of a hydrogen bond forming ability on the anti-epileptic activity, Poupaert *et al.*[9] tested some phenitoin-related compounds in the maximal electroshock seizure (MES test). A net stepwise decrease of the anticonvulsant activity was observed when the hydantoin ring structure was altered into succinimide and pyrrolidinone and when these rings were N-methylated. The pharmacological data analyzed in terms of structure-activity relationships (SAR) indicate the importance of the capability of forming hydrogen bonds.

Our research on the pharmacological activity of hydantoin derivatives has



Compound	R	X
1	CH_3	4-NH_2
2	CH_3	4-OH
3	CH_3	4-OCH_3
4	CH_3	4-CH_3
5	CH_3	H
6	CH_3	4-Cl
7	CH_3	4-Br
8	CH_3	4-NO_2
9	CH_3	4-CN
10	C_6H_5	H
11	CH_3	3-NO_2
12	CH_3	3-OCH_3
13	CH_3	3-CH_3
14	CH_3	3-Cl

Fig. 1. Structure of the investigated 5-methyl-5-(3- or 4-substituted phenyl)hydantoins.

been focused on the determination of the structural and chemical behavior of compounds in different solvents using UV–Vis spectroscopic methods.[10] 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, fourteen 5-methyl-5-(3- or 4-substituted phenyl)hydantoins (Fig. 1) were synthesized and their ultraviolet absorption spectra were recorded in the region 200–400 nm in twelve solvents of different polarity. The effect of solvent dipolarity/polarizability and hydrogen bonding on the absorption spectra were interpreted by means of the linear solvation energy relationship (LSER) using a Kamlet–Taft equation[11] of the form:

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

where π^* is a measure of the solvent dipolarity/polarizability,[12] β is the scale of the solvent hydrogen bond acceptor (HBA) basicity,[13] α is the scale of the solvent hydrogen bond donor (HBD) acidity[14] and v_0 is the regression value of the solute property in cyclohexane as the reference solvent. 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*.[15] 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.[16] The LSER developed by Kamlet and Taft is one of the most ambitious and successful quantitative treatments of solvent effects by means of a multiparametar equation.[17–19]

The importance of lipophilicity in a structure-activity relationship has been known for a long time. Thus, transport phenomena *in vivo* and through membranes proved to be dependent on lipophilic contributions. The lipophilic activity of the hydantoins investigated in this work was estimated by calculation of log *P* values with Advanced Development (ACD) Software Solaris, version 4.67. The calculated values of log *P* were correlated with the contributions of hydrogen bond donor specific solvent interactions as calculated from Eq. (1). Based on a so obtained linear dependence, the pharmacological activity of the studied hydantoin derivatives is discussed.

RESULTS AND DISCUSSION

The chemical structures and the purities of the synthesized hydantoins were confirmed by melting point measurements as well as ^{1}H-NMR, FT-IR and UV spectroscopy. For the hydantoins **1**–**11** the obtained results were in agreement

with literature data (Table I). For the newly synthesized compounds **12**–**14** (3-OCH_3, 3-CH_3, 3-Cl) which, to the best of our knowledge, have not been registered in the literature, full characterization is presented below.

TABLE I. Physical and spectroscopic data for 5-methyl-5-(3- or 4-substituted phenyl)hydantoins

Compound No.	M.p.[a] °C	Lit. m.p.[a] °C	^{1}H-NMR (200 MHz, DMSO–d_6, δ / ppm)	
			(N-1)H	R, X, (N-3)H
1	181–184	182–184[20]	*s*, 8.30	(N-3)H (*s*, 10.30), Ph (*d*, 7.02), Ph (*d*, 6.45), NH_2 (*s*, 5.00), 5-Me (*s*, 1.50)
2	240–243	244[21]	*s*, 8.47	(N-3)H (*s*, 9.53), Ph (*d*, 7.28), Ph (*d*, 6.78), 5-Me (*s*, 1.63)
3	208–210	210–212[22]	*s*, 8.40	Ph (*d*, 7.35), Ph (*d*, 6.92), OMe (*s*, 3.73), 5-Me (*s*, 1.63)
4	200–204	203–204[23]	*s*, 8.57	Ph (*m*, 7.56–7.13), Me (*s*, 2.30), 5-Me (*s*, 1.67)
5	194–196	195–196[24]	*s*, 8.50	Ph (*s*, 7.37), 5-Me (*s*, 1.63)
6	258–260	260–261[23]	*s*, 8.57	Ph (*m*, 7.48–7.22), 5-Me (*s*, 1.67)
7	274–276	276–277[25]	*s*, 8.63	Ph (*m*, 7.73–7.33), 5-Me (*s*, 1.67)
8	228–230	227–229[26]	*s*, 8.70	Ph (*d*, 8.22), Ph (*d*, 7.72), 5-Me (*s*, 1.70)
9	203–205	206[27]	*s*, 8.70	Ph (*m*, 8.00–7.40), 5-Me (*s*, 1.70)
10	293–295	293–295[b]	*s*, 9.17	Ph (*s*, 7.30)
11	184-191	185–193[26]	*s*, 8.87	Ph (*m*, 8.33–7.50), 5-Me (*s*, 1.73)

[a]Melting point; [b]commercially available (Fluka)

*5-(3-Methoxyphenyl)-5-methylhydantoin (**12**)*. M.p. 125–130 °C; white crystals. IR (KBr, cm^{-1}): 3277, 3201, 1772, 1721, 1610, 1511, 1459, 1397, 1257, 803. ^{1}H-NMR (200 MHz, 25 °C, DMSO-d_6, δ / ppm): 10.74 (1H, *s*, N-3), 8.83 (1H, *s*, N-1), 7.22–6.74 (4H, *m*, Ph), 3.75 (3H, *s*, OMe), 1.62 (3H, *s*, 5-Me). ^{13}C-NMR (50 MHz, 25 °C, DMSO-d_6, δ/ ppm): 177.1, 159.6, 156.5, 141.9, 130.0, 117.9, 113.2, 111.8, 64.2, 55.5, 25.5.

*5-Methyl-5-(3-methylphenyl)hydantoin (**13**)*. M.p. 175–180 °C; white crystals. IR (KBr, cm^{-1}): 3267, 3200, 1779, 1719, 1608, 1508, 1424, 1378, 1239, 769. ^{1}H-NMR (200 MHz, 25 °C, DMSO-d_6, δ / ppm): 10.76 (1H, *s*, N-3), 8.47 (1H, *s*, N-1), 7.33–6.93 (4H, *m*, Ph), 2.33 (3H, *s*, Me), 1.67 (3H, *s*, 5-Me). ^{13}C-NMR (50 MHz, 25 °C, DMSO-d_6, δ/ ppm): 176.7, 158.5, 155.8, 139.6, 138.4, 116.2, 111.4, 108.6, 63.6, 54.2, 25.7.

*5-(3-Chlorophenyl)-5-methylhydantoin (**14**)*. M.p. 180–182 °C; white crystals. IR (KBr, cm^{-1}): 3281, 3204, 1772, 1713, 1606, 1491, 1401, 1299, 1241, 801. ^{1}H-NMR (200 MHz, 25 °C, DMSO-d_6, δ / ppm): 10.88 (1H, *s*, N-3), 8.62 (1H, *s*, N-1), 7.60–7.20 (4H, *m*, Ph), 1.67 (3H, *s*, 5-Me). ^{13}C-NMR (50 MHz, 25 °C, DMSO-d_6, δ/ ppm): 176.4, 158.2, 156.3, 139.0, 132.8, 128.5, 127.4, 126.2, 63.7, 25.1.

The infrared spectra of all the synthesized hydantoins showed two carbonyl bands at about 1702 and 1778 cm^{-1} and intense N–H bands in the region 3174––3292 cm^{-1}.

The ultraviolet absorption frequencies of the 5-methyl-5-(3- or 4-substituted phenyl)hydantoins in twelve solvents in the range 200–400 nm are given in Table II.

The effects of the solvent dipolarity/polarizability (nonspecific solvent interactions) and hydrogen bonding (specific solvent interactions) on the investigated hydantoins were interpreted using the general solvation equation, Eq. (1). Correlation of the spectroscopic data with solvent parameters[28] was performed by means of multiple linear regression analysis. It was found that the absorption frequencies for the hydantoin derivatives in twelve selected solvents showed a satisfactory correlation with the π^*, β and α parameters. The results of the multiple regressions are presented in Tables III and IV. The values of the coefficient v_0, *s* and *b*, and the fit at the 95 % confidence level are given in Table III.

A plot of the v_{max} values calculated using Eq. (1) *versus* the v_{max} values observed in different solvents is presented in Fig. 2. The negative sign of the coefficient *s* in the total solvatochromic equation (Table III) indicates a bathochromic shift with increasing solvent dipolarity/polarizability. The positive signs of the coefficients *a* and *b* (excluding the negative sign of the coefficient *b* for the 4-OH, 4-NO_2 and 3-NO_2 substituents) indicate a hypsochromic shift with increasing solvent hydrogen bond donor acidity and acceptor basicity and imply stabilization of the ground state relative to the electronic excited state. The percentage contributions of the solvatochromic parameters (Table III) for the investigated hydantoins show that most of the solvatochromism (except for the 4-NO_2 and 3-NO_2 substituents) is due to solvent acidity and basicity (specific solute––solvent interactions) rather than to the solvent dipolarity/polarizability (nonspecific solute–solvent interactions). The solvent acidity effect is predominant in all the investigated molecules, except for 5-methyl-5-(3- or 4-nitrosubstituted phenyl)hydantoins. These results are in accordance with the preferred existence of hydantoins in the lactam tautomeric form,[3] and the previously reported hypothesis of Poupaert *et al.*[9] that hydrogen bonding is an essential factor in the anticonvulsant action of 5,5-diphenylhydantoin derivatives.

The evidence for the solvent effects on the structure–activity relationship of hydantoin derivatives was obtained by correlation of the calculated lipophilic log *P* values with the contributions of hydrogen-bond donor solvent interactions, *a*. Both parameters depend on the structure of the hydantoins. The results of the correlation are shown in Fig. 3. The plot of the log *P* values *versus a* gives a satisfactory linear correlation for moderate electron-donating and electron-accepting substituents.

TABLE II. UV–Vis spectral data ($\nu_{max}\times10^{-3}$ / cm^{-1}) of 5-methyl-5-(3- or 4-substituted phenyl)hydantoins

Solvent	Compound													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Methanol	40.45	44.72	44.56	44.68	44.48	45.33	45.29	37.48	43.86	45.29	38.49	44.96	44.64	44.80
Ethanol	40.58	44.68	44.13	44.44	44.72	45.13	45.09	37.40	43.59	45.21	38.43	45.09	44.80	44.64
Propan-1-ol	40.39	44.64	44.21	44.60	44.88	44.88	44.08	37.37	44.25	45.25	38.64	44.84	44.92	44.80
Propan-2-ol	40.39	44.76	44.37	44.52	44.56	45.83	45.75	37.43	43.52	45.05	38.55	44.88	44.68	44.48
Methyl acetate	33.94	37.51	36.58	37.88	39.31	37.76	37.74	37.37	36.79	39.06	38.31	38.11	39.06	37.59
Ethyl acetate	34.04	37.26	36.58	38.08	39.59	37.62	37.59	37.23	36.82	38.49	38.34	37.91	38.76	37.54
N,N-Dimethylacetamide	33.56	36.02	35.59	36.82	38.46	37.62	37.57	36.34	36.71	38.91	36.00	37.31	37.59	37.31
Ethylene glycol	40.62	44.96	43.67	44.05	44.05	43.90	43.48	37.01	43.67	44.31	37.99	44.52	44.25	44.52
Tetrahydrofuran	33.76	37.34	36.76	37.74	38.91	37.76	37.71	37.37	37.82	38.76	38.40	37.85	38.17	38.11
Dioxane	33.67	37.37	35.77	37.45	38.85	37.23	37.17	37.37	37.62	38.61	38.37	37.54	37.88	38.05
Dimethyl sulfoxide	33.50	36.10	36.39	36.66	38.02	37.65	37.62	36.18	36.68	37.79	36.87	37.29	37.48	37.01
2-Methylpropan-2-ol	40.98	41.42	42.99	44.25	44.33	43.86	43.82	37.57	43.74	45.70	38.88	44.37	44.44	44.44

TABLE III. Regression fits to the solvatochromic parameters (Eq. (1))

Compound	v_0	s	b	a	R^a	S^b	F^c	n^d
1	34.09	–1.92 (±0.71)	1.83 (±0.71)	7.54 (±0.35)	0.995	0.43	247	12
2	39.02	–1.56 (±1.37)	–1.82 (±1.36)	9.23 (±0.68)	0.986	0.78	91	12
3	36.81	–1.92 (±0.72)	1.46 (±0.72)	8.79 (±0.35)	0.996	0.44	303	12
4	39.15	–3.21 (±0.53)	0.94 (±0.53)	7.84 (±0.26)	0.998	0.29	597	12
5	40.46	–2.96 (±0.80)	0.82 (±0.50)	6.26 (±0.39)	0.995	0.34	284	12
6	37.61	–2.02 (±0.74)	2.52 (±0.74)	7.89 (±0.36)	0.995	0.45	264	12
7	37.66	–2.33 (±0.68)	2.74 (±0.68)	7.70 (±0.35)	0.994	0.47	229	12
8	38.85	–2.05 (±0.17)	–0.82 (±0.17)	0.43 (±0.08)	0.981	0.10	66	12
9	37.89	–2.24 (±0.23)	1.37 (±0.60)	7.49 (±0.32)	0.993	0.48	198	12
10	39.41	–2.99 (±0.63)	2.32 (±0.62)	6.92 (±0.31)	0.996	0.38	299	12
11	40.85	–3.40 (±0.64)	–1.40 (±0.63)	0.85 (±0.32)	0.918	0.39	14	12
12	38.52	–2.29 (±0.66)	1.34 (±0.61)	8.01 (±0.36)	0.998	0.27	712	12
13	39.66	–2.92 (±0.56)	0.98 (±0.51)	7.22 (±0.28)	0.994	0.45	208	12
14	38.65	–2.40 (±0.25)	1.14 (±0.58)	7.93 (±0.33)	0.997	0.32	496	12

[a]Correlation coefficient; [b]standard error of the estimate; [c]Fisher's test; [d]number of solvents used in the calculations

TABLE IV. Percentage contributions of the nonspecific ($P\pi^*$) and specific ($P\alpha$ and $P\beta$) solvent interaction and the log P values

Compound	$P\pi^*$ / %	$P\alpha$ / %	$P\beta$ / %	Log P
1	16.98	66.82	16.20	–0.283
2	12.38	73.22	14.40	0.263
3	15.80	72.22	11.98	0.914
4	26.77	65.37	7.86	1.459
5	29.45	62.35	8.20	0.999
6	16.25	63.51	20.24	1.594
7	18.24	60.31	21.45	1.771
8	62.11	13.05	24.85	0.729
9	20.19	67.46	12.36	0.436
10	24.47	56.58	18.95	2.524
11	60.19	15.10	24.71	0.729
12	19.67	68.79	11.53	0.914
13	26.28	64.89	8.82	1.459
14	20.96	69.12	9.92	1.594

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 5-methyl-5-(4-substituted phenyl)hydantoins and 5,5-diphenylhydantoin that show good anticonvulsant activity as reported previously.[2,29] The data for hydantoins with substituents in the *meta* positions in the benzene ring did not follow this correlation (Fig. 3). These results are in accordance with their previously reported[25] non-anticonvulsant activity.

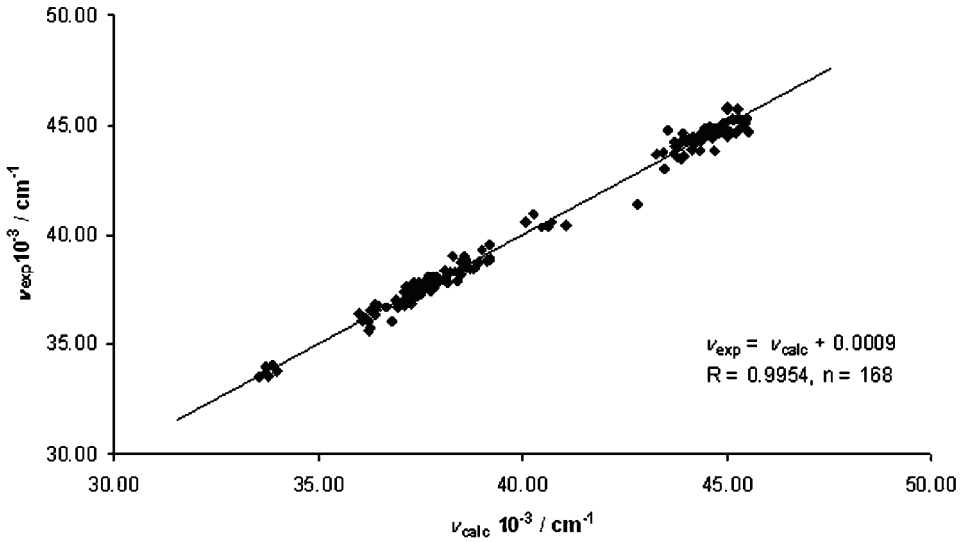


Fig. 2. Plot of ν_{max} observed against ν_{max} calculated from Eq. (1) for 5-methyl-5-(3- or 4-substituted phenyl)hydantoins.

Strong electron-donors and acceptors decrease the lipophilic activity of the investigated hydantoins. These compounds also did not follow correlation presented in Fig. 3.

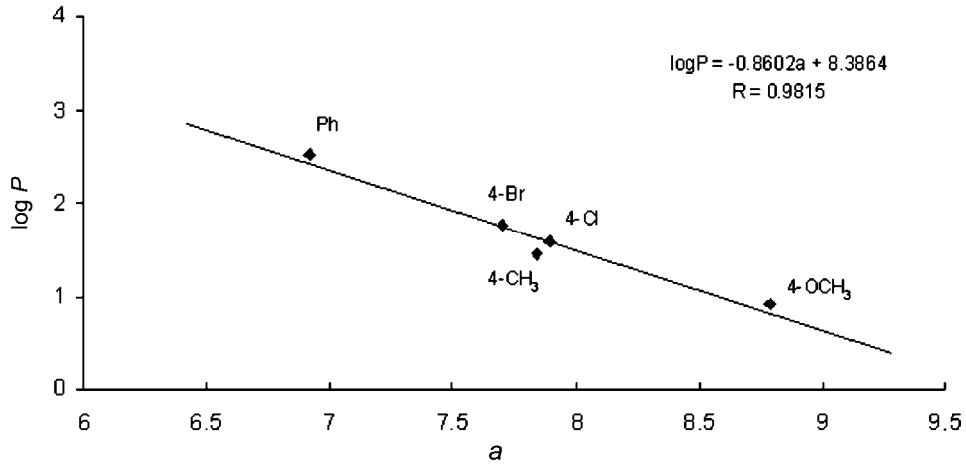


Fig. 3. Correlation of the log *P* values with the contribution of hydrogen bond solvent interaction, *a*, for 5-methyl-5-(4-substituted phenyl)hydantoins.

The satisfactory correlation of the ultraviolet absorption frequencies of the investigated 5-methyl-5-(3- or 4-substituted phenyl)hydantoins with Kamlet–Taft general solvatochromic equation indicates that the selected models give a correct

interpretation of the linear solvation energy relationships of the complex hydantoin system in the solvents used. This demonstrates that an equation with three solvatochromic parameters π^*, β and α can be used to evaluate the effects on both types of hydrogen bonding and the solvent dipolarity/polarizability effects for pharmacologically active hydantoins. For these reasons, it is considered that the results presented in this work may be utilized to quantitatively separate the overall solvent effect into specific and nonspecific contributions using a LSER method. The satisfactory correlation of the lipophilic parameters log *P* of the investigated pharmacologically active hydantoins[2,29] with the contribution of the hydrogen bond donor solvent interactions supports the previously reported[7] pharmacophore model based on a hydrogen-bond acceptor, a hydrogen-bond donor, and an electronegative group with a large hydrophilic 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/non-activity of the studied hydantoins, not yet pharmacologically tested, may be predicted.

EXPERIMENTAL

All of the investigated 5-methyl-5-(3- or 4-substituted phenyl)hydantoins were synthesized by a modification of the method of Bucherer.[30] Following this procedure, 0.020 mol of ketone was dissolved in 50 ml of 50 % ethanol and 0.080 mol of ammonium carbonate plus 0.040 mol of potassium cyanide were added. This mixture was warmed under a condenser at a temperature of 58–60 °C for 15 h, after which the solution was concentrated to approximately two-thirds of the 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 structures and the purities of the synthesized hydantoins **1**–**14** were confirmed by their melting points, as well as ^{1}H-NMR, FT-IR and UV spectroscopy.

The FT-IR spectra were recorded on a Bomem MB 100 spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra of DMSO-d_6 solutions (TMS as the internal standard) were measured with a Varian-Gemini 200 MHz spectrometer. 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.

The correlation analysis was performed 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 the Fisher's significance test, *F*.

Acknowledgements. The authors acknowledge the financial support of the Ministry of Science and Technical Development of the Republic of Serbia (Project 142063).

ИЗВОД

СИНТЕЗА, СТРУКТУРА И СОЛВАТОХРОМИЗАМ 5-МЕТИЛ-5-(3- ИЛИ 4-СУПСТИТУИСАНИХ ФЕНИЛ)-ХИДАНТОИНА

НАТАЛИЈА Д. ДИВЈАК, НЕБОЈША Р. БАЊАЦ, НАТАША В. ВАЛЕНТИЋ и ГОРДАНА С. УШЋУМЛИЋ

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У оквиру проучавања утицаја структуре на фармаколошку активност хидантоина, у овом раду синтетизовано је четрнаест једињења и одређени су њихови UV апсорпциони максимуми у дванаест растварача различите поларности. Апсорпциони максимуми су корелисани Камлет–Тафтовом (*Kamlet–Taft*) солватохромном једначином и извршена је квантитативна процена протон-донорских и протон-акцепторских карактеристика проучаваних једињења, које су од великог значаја за њихову физиолошку активност. Израчунате вредности log *P* корелисане су са уделом протон-донорских карактеристика растварача и на основу добијених линеарних зависности за молекуле са умереним елктрон-донорским и електрон-акцепторским супституентима, дискутована је веза између фармаколошке активности хидантоина и интеракција са молекулима растварача.

(Примљено 1. јула 2008, ревидирано 8. јула 2009)

REFERENCES

1. A. C. Lopez, C. G. Trigo, in *The Chemistry of Hydantoins. Advances in Heterocycles Chemistry,* A. R Katrizky, Ed., Academic Press, New York, 1985
2. S. Scholl, A. Koch, D. Henning, G. Kemter, E. Kleinpeter, *Struct. Chem.* **10** (1999) 355
3. E. Kleinpeter, *Struct. Chem.* **8** (1997) 161
4. J. Knabe, J. Baldauf, A. Aklhem, *Pharmacie* **52** (1997) 912
5. K. E. Schuite, W. V. von Eur, *J. Med. Chem.* **13** (1978) 25
6. T. R. Rodgers, M. P. LaMontage, A. Markovac, A. B. Ach, *J. Med. Chem.* **20** (1977) 591
7. K. Unverferth, J. Engel, N. Höfgen, A. Rostock, R. Günther, H. J. Lankom, M. Menzer, A. Rolfs, J. Liebscher, B Müller, H. J. Hofmann, *J. Med. Chem.* **41** (1998) 63
8. G. L. Jones, D. M. Woodbury, *Drug Dev. Res.* **2** (1982) 333
9. J. H. Poupaert, D. Vandervarst, P. Guiot, M. M. Moustata, P. Dumont, *J. Med. Chem.* **27** (1984) 76
10. N. Banjac, G. Ušćumlić, N. Valentić, D. Mijin, *J. Solution Chem.* **36** (2007) 869
11. M. J. Kamlet, J. L. M. Abboud, R. W. Taft, *Prog. Phys. Org. Chem.* **13** (1981) 485
12. J. L. M. Abboud, M. J. Kamlet, R. W. Taft, *J. Am. Chem. Soc.* **99** (1977) 8325
13. M. J. Kamlet, R. W. Taft, *J. Am. Chem. Soc.* **98** (1976) 377
14. M. J. Kamlet, R. W. Taft, *J. Chem. Soc., Perkin Trans. 2* (1979) 349
15. M. J. Kamlet, R. M. Doherty, J. L. M. Abboud, M. H. Abraham, R. W. Taft, *Chemtech* **16** (1986) 566
16. P. W. Carr, R. M. Doherty, M. J. Kamlet, R. W. Taft, W. Melander, C. Horvath, *Anal. Chem.* **58** (1986) 2674
17. D. Ž. Mijin, G. S. Ušćumlić, N. U. Perišić Janjić, N. V. Valentić, *Chem. Phys. Lett.* **418** (2006) 223
18. J. Nikolić, G. Ušćumlić, *J. Serb. Chem. Soc.* **72** (2007) 1217
19. S. Spange, R. Sevs, K. Zimmermann, A. Seifert, I. Roth, S. Anders, K. Hofmann, *New J. Chem.* **27** (2003) 520
20. H. R. Henze, L. M. Long, R. J. Speer, T. R. Thompson, *J. Am. Chem. Soc.* **65** (1943) 323

21. P. C. Wang, C. S. Wang, S. P. Crain, U.S. No. 4,672,101 (1987)
22. M. C. E. Carron, C. L. C. Carron, B. P. Bucher, Fr. No. 5,677 M (1968)
23. R. E. Nitz, W. Persch, A. Schmidt, *Arzneim.-Forsch*. **5** (1955) 357
24. A. S. Endler, E. I. Becker, *J. Am. Chem. Soc.* **77** (1955) 6608
25. H. R. Henze, A. F. Isabell, *J. Am. Chem. Soc.* **76** (1954) 4152
26. T. A. Connors, W. C. J. Ross, J. G. Wilson, *J. Am. Chem. Soc.* (1960) 2294
27. W. Holla, G. Beck, B. Kammermeier, B. Kulitzscher, J. Michalowsky, U.S. No. 6,018,053 (2000)
28. J. A. Vida, C. M. Samour, J. F. Reinhard, *J. Med. Chem.* **14** (1971) 187
29. C. E. Maurice, L. C. Claude, P. B. Bernard, Fr. No. 5677 (1968)
30. H. Bucherer, W. Steiner, *J. Pract. Chem.* **140** (1934) 291.