

## EVALUATION OF SOLVENT AND SUBSTITUENT EFFECTS ON ABSORPTION SPECTRA OF SPIROHYDANTOINS DERIVED FROM $\alpha$ -TETRALONE

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### Abstract

A convenient and efficient approach toward the synthesis of six 3-(4-substituted benzyl)-6,7-benzo-1,3-diazaspiro[4.5]decane-2,4-diones (**1–6**) by Bucherer-Bergs reaction and further alkylation at position 3 of the hydantoin ring is reported. Further, their chemical structure was confirmed by melting points, elemental analysis, FT-IR, NMR and UV-Vis spectroscopic methods. To gain an insight into interactions which the investigated spirohydantoin establish with their environment, their absorption spectra were recorded in selected solvents of different polarity and the solvent effects on the UV-Vis absorption band positions, intensity and shape, were discussed. Substituent effects on the solvatochromism of compounds **1–6** were analyzed using the Hammett's equation. Considering the broad applications of hydantoin derivatives, as well as the fact that their relative importance may increase in the future, results obtained in this study serve as a basis for further investigations.

### Introduction

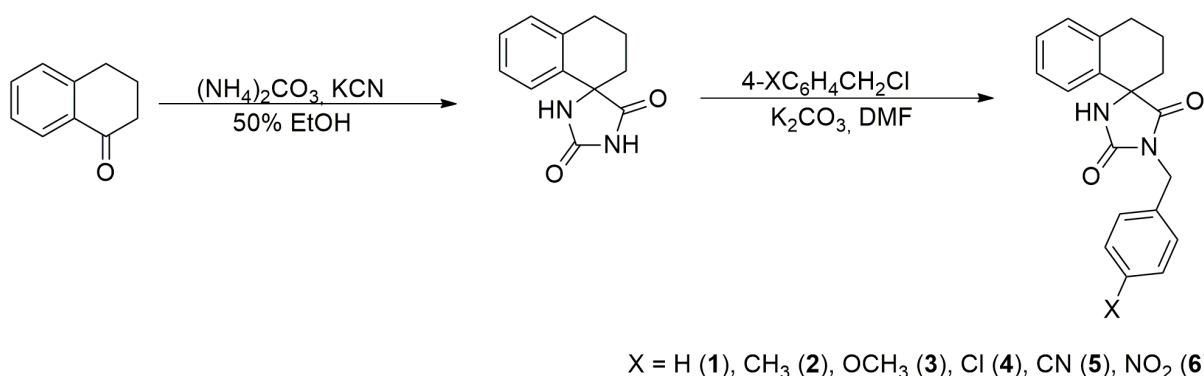
The hydantoin (imidazolidine-2,4-dione) ring is an important structural fragment of a large number of pharmacologically active compounds [1]. Derivatives of this five-membered cyclic ureide are known anticonvulsants (Dilantin, Cerebyx, Peganon), nonsteroidal antiandrogenic agents (Anandron), antibiotics (Furadantin), muscle relaxants (Dantrium) [2], antiarrhythmics (Azimilide), keratolytics (Alantoin), astringents and antacids [3]. By introducing substituents in N3 and C5 positions of this bioactive nucleus, various analogs with potential pharmacological application are obtained. Structure-activity relationship (SAR) analysis of 3-benzyloxy-5-alkylhydantoin revealed that substitution of benzene ring with chlorine and bromine atoms, as well as the presence of slightly longer lipophilic substituents such as isopropyl and isobutyl groups at C5 position, may be essential for its antiproliferative activity [4]. The antileukemic activity of 1-(3-bromopropyl)-3-methyl-5,5-diphenylimidazolidine-2,4-dione and 1-(3-bromobutyl)-3-methyl-5,5-diphenylimidazolidine-2,4-dione towards human acute histiocytic lymphoma U937 cells and human promyelocytic leukemia HL-60 cells is based on temporary changes in the leukemia cell viability, volume and count [5]. Antiviral activity of 5,5-diphenyl-3-[3-(4-phenyl-1H-1,2,3-triazol-1-yl)propyl]imidazolidin-2,4-dione is based on prevention of adsorption and penetration of human metapneumovirus into host cells [6]. *In vivo* studies have shown that *N*-arylsulfonyl derivatives of imidazolidin-2,4-dione represent new hypoglycemic agents because they effectively reduce blood glucose levels compared to the standard drug glipizide [7]. Potentially pharmacologically active compounds often bear numerous functional groups capable of forming hydrogen bonds, making them soluble and giving them the ability to form specific interactions with their biomolecular targets [8]. Hydrogen bonding influences the interactions of potentially pharmacologically active

organic compounds at different levels of complexity, going from those with other small molecules, up to the highest supramolecular assemblies, *e.g.*, proteins and membranes. These interactions considerably affect the pharmacological activity, pharmacokinetics and physicochemical properties of drugs, hence making hydrogen bonding an important subject of study in drug discovery and development [9]. Therefore, solvatochromic study gives an insight into possible different solute–solvent interactions mimicking the interactions of potentially pharmacologically active organic compounds with their environment. In continuation of our long-term research on the influence of chemical structure on the potential pharmacological activity of imidazolidin-2,4-dione derivatives, six 3-(4-substituted benzyl)-6,7-benzo-1,3-diazaspiro[4.5]decane-2,4-diones were synthesized (Scheme 1). To gain insight into the ways in which those compounds interact with their environment, their absorption spectra were recorded in a selected set of solvents. The influence of substituents on the position of the absorption spectra was evaluated in detail using Hammett's equation.

## Experimental

### General procedure for the synthesis of compounds 1–6

The synthetic route was carried out according to Scheme 1. Starting from commercially available  $\alpha$ -tetralone, the modified Bucherer-Bergs reaction was carried out by the use of ammonium carbonate and potassium cyanide to afford the 3',4'-dihydro-2H-spiro[imidazolidine-4,1'-naphthalene]-2,4-dione [10]. In the following step, alkylation at position 3 of the hydantoin ring was conducted with various *p*-substituted benzyl-chlorides in the presence of  $K_2CO_3$  in *N,N*-dimethylformamide (DMF) [11]. Their chemical structure was confirmed by melting points, elemental analysis, FT-IR, NMR and UV–Vis spectroscopic methods.



Scheme 1. Synthetic pathway of the investigated compounds.

The melting points were measured on an Electrothermal melting point apparatus. The FT-IR spectra of the synthesized compounds were recorded in the range of 400 to 4000  $cm^{-1}$  using Bomem MB spectrophotometer. Elemental analysis of the investigated compounds were carried out using microanalyzer Elemental Vario EL III. Absorption spectra were recorded on a Shimadzu 1700 spectrophotometer in solvents of spectroscopic purity (Fluka) at a fixed concentration of  $10^{-5}$  mol  $dm^{-3}$ .  $^1H$  NMR spectra were recorded on a Bruker Ascend 400 spectrophotometer at 400 MHz in deuterated dimethyl sulfoxide (DMSO- $d_6$ ).

*3-(Benzyl)-6,7-benzo-1,3-diazaspiro[4.5]decane-2,4-dione* (1): White crystalline substance; m.p. 126–129 °C; yield: 75 %; IR (KBr,  $\nu/cm^{-1}$ ): 3246, 2931, 1770, 1701;  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 8.88 (s, 1H, NH), 7.66 (t, 1H,  $J$  = 8 Hz, Ar(benzyl)-H), 7.33 (t, 2H,  $J$  = 8 Hz, Ar(benzyl)-H), 7.27 (d, 2H,  $J$  = 8 Hz, Ar(benzyl)-H), 7.25–7.22 (m, 1H, Ar(tetralin)-H), 7.19–

7.11 (m, 2H, Ar(tetralin)-H), 6.93 (d, 1H,  $J = 8$  Hz, Ar(tetralin)-H), 4.57 (s, 2H; N-CH<sub>2</sub>), 2.82–2.79 (m, 2H; CH<sub>2</sub>), 2.10–2.04 (m, 2H; CH<sub>2</sub>), 1.95–1.81 ppm (m, 2H; CH<sub>2</sub>); Anal. Calcd. For C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C, 74.49, H, 5.92, N, 9.14. Found: C, 74.46, H, 5.95, N, 9.14.

*3-(4-Methylbenzyl)-6,7-benzo-1,3-diazaspiro[4.5]decane-2,4-dione (2)*: White crystalline substance; m.p. 153–156 °C; yield: 71 %; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3269, 2945, 2876, 1756, 1703, 1686; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 8.89$  (s, 1H, NH), 7.19 (m, 1H, Ar(tetralin)-H), 7.21–7.15 (m, 6H, Ar(tetralin)-H + Ar(benzyl)-H), 6.90 (d, 1H,  $J = 8.0$  Hz, Ar(tetralin)-H), 4.56 (s, 2H, N-CH<sub>2</sub>), 2.83–2.77 (m, 2H, CH<sub>2</sub>), 2.45 (s, 3H, CH<sub>3</sub>), 2.11–2.04 (m, 2H; CH<sub>2</sub>), 1.99–1.85 ppm (m, 2H; CH<sub>2</sub>); Anal. Calcd. For C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: C, 74.98, H, 6.29, N, 8.74. Found: C, 74.96, H, 6.31, N, 8.74.

*3-(4-Methoxybenzyl)-6,7-benzo-1,3-diazaspiro[4.5]decane-2,4-dione (3)*: White crystalline substance; m.p. 136–138 °C; yield: 56 %; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3249, 3025, 2951, 1770, 1698; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 8.90$  (s, 1H, NH), 7.24 (d, 2H,  $J = 8.4$  Hz, Ar(benzyl)-H), 7.23 (m, 1H, Ar(tetralin)-H), 7.18–7.13 (m, 2H, Ar(tetralin)-H), 6.93 (d, 2H,  $J = 8.4$  Hz, Ar(benzyl)-H), 6.90 (d, 1H,  $J = 8.0$  Hz, Ar(tetralin)-H), 4.55 (s, 2H, N-CH<sub>2</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 2.81–2.78 (m, 2H, CH<sub>2</sub>), 2.13–2.05 (m, 2H, CH<sub>2</sub>), 1.95–1.81 ppm (m, 2H, CH<sub>2</sub>) [12]; Anal. Calcd. For C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>: C, 71.41, H, 5.99, N, 8.33. Found: C, 71.36, H, 6.04, N, 8.30.

*3-(4-Chlorobenzyl)-6,7-benzo-1,3-diazaspiro[4.5]decane-2,4-dione (4)*: White crystalline substance; m.p. 130–133 °C; yield: 82 %; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3232, 3105, 2932, 1767, 1703; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 8.91$  (s, 1H, NH), 7.36 (d, 2H,  $J = 8.4$  Hz, Ar(benzyl)-H), 7.31 (d, 2H,  $J = 8.4$  Hz, Ar(benzyl)-H), 6.92–6.89 (m, 4H, Ar(tetralin)-H), 4.51 (s, 2H, N-CH<sub>2</sub>), 2.89–2.86 (m, 2H, CH<sub>2</sub>), 2.19–1.94 (m, 2H, CH<sub>2</sub>), 1.92–1.85 ppm (m, 2H, CH<sub>2</sub>); Anal. Calcd. For C<sub>19</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>2</sub>: C, 66.96, H, 5.03, N, 8.22. Found: C, 66.94, H, 5.05, N, 8.22.

*3-(4-Cyanobenzyl)-6,7-benzo-1,3-diazaspiro[4.5]decane-2,4-dione (5)*: White crystalline substance; m.p. 182–185 °C; yield: 83 %; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3365, 2935, 2865, 2225, 1774, 1708; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 8.93$  (s, 1H, NH), 7.55 (d, 2H,  $J = 8$  Hz, Ar(benzyl)-H), 7.43 (d, 2H,  $J = 8$  Hz, Ar(benzyl)-H), 7.20–7.15 (m, 3H, Ar(tetralin)-H), 6.88–6.84 (m, 1H, Ar(tetralin)-H), 4.52 (s, 2H, N-CH<sub>2</sub>), 2.79–2.75 (m, 2H, CH<sub>2</sub>), 2.12–2.04 (m, 2H, CH<sub>2</sub>), 1.90–1.85 ppm (m, 2H, CH<sub>2</sub>); Anal. Calcd. For C<sub>20</sub>H<sub>17</sub>ClN<sub>3</sub>O<sub>2</sub>: C, 72.49, H, 5.17, N, 12.68. Found: C, 72.51, H, 5.14, N, 12.68.

*3-(4-Nitrobenzyl)-6,7-benzo-1,3-diazaspiro[4.5]decane-2,4-dione (6)*: Yellow crystalline substance; m.p. 170–173 °C; yield: 88 %; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3204, 3097, 2933, 2840, 1770, 1708; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 8.94$  (s, 1H, NH), 8.11 (d, 2H,  $J = 8$  Hz, Ar(benzyl)-H), 7.92 (d, 2H,  $J = 8.4$  Hz, Ar(benzyl)-H), 7.22–7.05 (m, 4H, Ar(tetralin)-H), 4.55 (s, 2H, N-CH<sub>2</sub>), 2.79–2.75 (m, 2H, CH<sub>2</sub>), 2.12–2.04 (m, 2H, CH<sub>2</sub>), 1.95–1.90 ppm (m, 2H, CH<sub>2</sub>); Anal. Calcd. For C<sub>19</sub>H<sub>17</sub>ClN<sub>3</sub>O<sub>4</sub>: C, 64.95, H, 4.88, N, 11.96. Found: C, 64.94, H, 4.89, N, 11.96.

## Results and discussion

### Solvatochromic analysis

Solvatochromic properties of six synthesized compounds were investigated by recording the corresponding UV-Vis absorption spectra in a selected set of solvents of different polarity in the wavelength range 200–400 nm. The values of the wavelengths originating from the higher energy absorption maxima are shown in Table 1, and a representative spectra recorded in ethanol are presented in Figure 1. The observed trends in the change in the intensity of the absorption maximum are in accordance with our previous results [13]. Namely, the absorption spectra of all investigated compounds are characterized by the presence of one dominant band originating from the  $\pi \rightarrow \pi^*$  transition and corresponding to the absorption maximum of higher lower energy. Figure 1 shows that the introduction of a substituent in the *p*-position of the phenyl ring results in a bathochromic shift of the absorption maximum in relation to the

unsubstituted compound (**1**) in all solvents. In general, with increasing electron-donor as well as electron-acceptor characteristics of the substituent, there is a shift of the absorption maximum towards higher wavelengths. Based on the described trends, it can be concluded that electron-donor groups exert a significant influence on the shift of the electron density from the *p*-substituted benzyl group to the hydantoin ring, contributing to the bathochromic shift [14]. The effect of electron-accepting substituents on the shift of the electron density in the studied molecules is opposite, and also results in positive solvatochromism compared to the unsubstituted compound **1**.

Table 1. The absorption spectra of compounds (**1–6**) in a selected set of solvents.

Solvent/ Compound	$\lambda_{max}$ (nm)					
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
Methanol	207	214	222	216	231	269
Ethanol	212	215	225	218	232	270
1-Propanol	216	218	229	221	230	272
1-Butanol	215	216	228	219	234	273
Acetonitrile	210	216	220	215	232	274
Diethyl eter	214	215	228	218	233	273
Cyclohexane	215	216	219	219	235	272

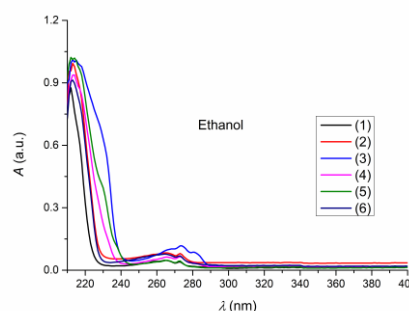


Figure 1. The absorption spectra of compounds (**1–6**) in ethanol.

The position of the absorption maxima are more affected by the substitution pattern than the polarity of solvent. The dominant influence of substituents on the shape, intensity and position of the electronic spectra of compounds **1–6** was analyzed using linear free energy correlation. The obtained results are represented by the diagram  $\nu_{max} = f(\sigma_p)$  (Figure 2), as well as by the corresponding equations, especially for electron-donor (equation 1) and electron-acceptor (equation 2) substituents:

$$\nu_{max} = 47.42(\pm 0.82) + 9.431(\pm 0.48)\sigma_p \quad (R = 0.905; s = 0.854; F = 4; n = 3) \quad (1)$$

$$\nu_{max} = 47.91(\pm 2.03) - 11.048(\pm 3.08)\sigma_p \quad (R = 0.895; s = 2.45; F = 8; n = 3) \quad (2)$$

The obtained nonlinear dependence is an indicator of the different effect of substituents on the shift of the electron density in the analyzed series of compounds, where the electron-acceptor effect is significantly stronger compared to the electron-donor effect ( $\rho_A = -11.048$ ;  $\rho_D = 9.431$ ).

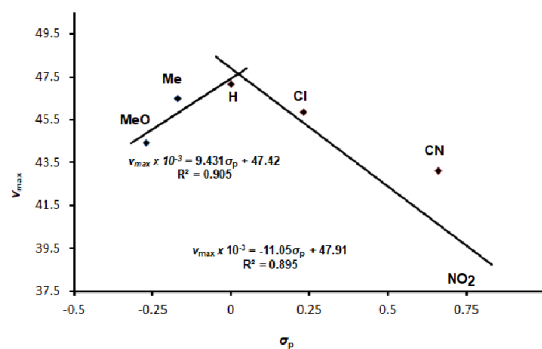


Figure 2. The correlation of  $\nu_{max}$  and  $\sigma_p$  for compounds **1–6** in a selected set of solvents

## Conclusion

In this study, we synthesized six 3-(4-substituted benzyl)-6,7-benzo-1,3-diazaspiro[4.5]decane-2,4-diones and confirmed their chemical structure by melting points, elemental analysis, FT-IR, NMR and UV-Vis spectroscopic methods. Substituent effects on the solvatochromism of compounds **1–6** was analyzed using the Hammett's equation. The obtained nonlinear dependence showed that the electron-acceptor effect is significantly stronger compared to the electron-donor effect ( $\rho_A = -11.048$ ;  $\rho_D = 9.431$ ). Considering obtained results, we can conclude that, the investigated spirohydantoin represents interesting starting point for the preparation of new pharmacologically active compounds and better understanding of the structure-activity relationship.

## Acknowledgements

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## References

- [1] J.L. Monteiro, B. Pieber, A.G. Corrêa, C.O. Kappe, *Synlett*. 27 (2016) 83.
- [2] L. Konnert, F. Lamaty, J. Martinez, E. Colacino, *Chem. Rev.* 17 (2017) 13757.
- [3] A. Czopek, A. Zagórska, M. Kołaczkowski, A. Bucki, B. Gryzłó, J. Rychtyk, M. Pawłowski, A. Siwek, G. Satała, A. Bojarski, M. Kubacka, B. Filipek, *Acta Pol. Pharm.-Drug Res.* 73 (2016) 1545.
- [4] A.A. Mostafa, A.N. Al-Rahmah, R.S. Kumar, A. Manilal, A. Idhayadhulla, *Int. J. Pharmacol.* 12 (2016) 290.
- [5] K. Śladowska, J. Handzlik, K. Kieć-Kononowicz, L. Mazur, *Indian J. Exp. Biol.* 54 (2016) 553.
- [6] G. Mendes, G.H. Aspesi, A.L.A. Arruda, M.T.V. Romanos, C.K.Z. Andrade, *J. Braz. Chem. Soc.* 27 (2016) 2.
- [7] A. Hussain, M.K. Kashif, M.M. Naseer, U.A. Rana, S. Hameed, *Res. Chem. Intermed.* 41 (2015) 7313.
- [8] B. Kuhn, P. Mohr, M. Stahl, *J. Med. Chem.* 53 (2010) 2601.
- [9] G.M. Ghiandoni, E. Caldeweyher, *Sci. Rep.* 13 (2023) 4143.
- [10] E. Naydenova, N. Pencheva, J. Popova, N. Stoyanov, M. Lazarova, B. Aleksiev, *Farmaco* 57 (2002) 189.
- [11] H. Suzuki, M.B.B. Kneller, D.A. Rock, J.P. Jones, W.F. Trager, A.E. Rettie, *Arch. Biochem. Biophys.* 429 (2004) 1.
- [12] A.M. Lazić, I.S. Đorđević, L.D. Radovanović, D.M. Popović, J.R. Rogan, G.V. Janjić, N.P. Trišović, *ChemPlusChem* 85 (2020) 1220.
- [13] N. Trišović, N. Valentić G. Ušćumlić, *Chem. Cent. J.* 5 (2011) 1.
- [14] D.C. Lavanya, K. Yesudas, N.S. Makarov, R.V. Jayathirtha, K. Bhanuprakash, J.W. Perry, *J. Mater. Chem. C* 3 (2015) 3730.