

Spectroscopic and quantum chemical elucidation of newly synthesized 1-aryl-3-methyl-3-phenylpyrrolidine-2,5-diones as potential anticonvulsant agents

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Abstract

Novel succinimide derivatives were synthesized from 3-methyl-3-phenylsuccinic acid and substituted anilines under solvent-free conditions by using microwave irradiation. All obtained compounds were characterized by ultraviolet (UV), Fourier-transform infrared (FT-IR), ¹H and ¹³C nuclear magnetic resonance (NMR) spectroscopy as well as by elemental analysis. The influence of the substituent electronic effects on spectroscopic data was analyzed by applying the Hammett equation. Moreover, a detailed interpretation and comparison of experimentally obtained and theoretically calculated FT-IR, UV and NMR spectra was performed. Density functional theory (DFT) calculated data of the investigated succinimides were obtained and analyzed in order to determine their structural, spectroscopic and electronic properties. Furthermore, ADMET factor profiling and *in-silico* prediction of potential biological activities of novel succinimide derivatives have been performed.

Keywords: Succinimide; electronic effect; spectroscopic analysis; quantum chemical calculation

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1. INTRODUCTION

Nitrogen-containing five- and six-membered heterocycles are ubiquitous in nature. These compounds are common constituents of natural products as well as of medicinally relevant structures and, as such, maintain significance in the research community over the years. Among them, succinimides (pyrrolidine-2,5-diones) represent renowned pharmacophores in drug discovery due to their versatile biological activity. Derivatives of this cyclic imide are used as anticonvulsant agents [1-3], among which ethosuximide, methsuximide, and phensuximide are important commercial drugs [4,5]. Substituted succinimides are recognized as promising antitumor [6], antitubercular [7], hypotensive [8], antimicrobial and antioxidant agents [9-11], and are used in treatments of glaucomas [12] and tremors [13]. The succinimide ring has been extensively studied in peptides and proteins since it is a cyclic intermediate in post-translational modifications of asparaginyl deamidation and aspartyl isomerization and thus it is responsible for protein aging [14-16]. Some of these succinimide derivatives represent important intermediates in the synthesis of drugs [17,18] and other organic compounds [19,20]. Chromones, naphthoquinones, and xanthenes bearing succinimide are shown to be highly cytotoxic comparable to activity of the anticancer agent doxorubicin [21]. Besides their significant biological role, they are, also, used as dopants necessary for generation of blue phases, which are considered to be the next-

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generation of fast liquid crystals displays [22], as well as an efficient and recyclable catalyst in form of succinimide sulfonic acid [23]. They also found applications in water-soluble reactive copolymers and polymers [24,25].

The initial analysis in drug discovery includes determination of quantitative structure-activity (properties) relationships (QSA(P)R) and ADME-Tox (refers to Absorption, Distribution, Metabolism, Excretion, and Toxicology) analysis, whereas, for succinimide derivatives, lipophilicity is used as an adequate property [26-29]. The resulting candidates *N*-phenyl substituted succinimides appear promising in research and development of new antiepileptic drugs.

Due to wide applications of succinimide derivatives, estimation and determination of their structure, and relations to the corresponding spectral properties is of utmost importance for understanding of physico-chemical properties [30-32]. The idea of this study was to create derivatives of the commercial drug methsuximide (celontin) in which the *N*-methyl group would be replaced by 3- and 4-substituted phenyl groups (Fig. 1). Thus, twelve novel 1-aryl-3-methyl-3-phenylpyrrolidine-2,5-diones were synthesized and characterized. Quantitative determination of substituent effects on the ultraviolet (UV), Fourier-transform infrared (FT-IR) and nuclear magnetic resonance (NMR) spectra has been performed using a linear free-energy relationship (LFER) concept. Moreover, we have also performed a comparative study between theoretically calculated properties and experimentally obtained results. Prediction of potential biological activities of the investigated succinimides is tested using the *in-silico* ADMET factor profiling.

2. MATERIALS AND METHODS

2.1. Chemistry

All chemicals used during the synthesis have been purchased from Sigma-Aldrich Chemicals (Sigma-Aldrich Corp., St. Louis, MO, USA) or Merck Chemicals (Merck KGaA, Darmstadt, Germany), as follows: acetophenone ($\geq 98\%$, Sigma-Aldrich), ethyl cyanoacetate ($\geq 98\%$, Merck KGaA), ammonium acetate ($\geq 98\%$, Sigma-Aldrich), benzene ($\geq 99.8\%$, Merck KGaA), potassium cyanide (97%, Merck KGaA), ethanol (95 %, Sigma-Aldrich), hydrochloric acid (37%, Sigma-Aldrich), 4-aminophenol ($\geq 98\%$, Sigma-Aldrich), 4-methoxyaniline (99%, Sigma-Aldrich), 4-methylaniline (99.6%, Sigma-Aldrich), aniline ($\geq 99.5\%$, Sigma-Aldrich), 4-fluoroaniline (99%, Sigma-Aldrich), 4-chloroaniline (98%, Sigma-Aldrich), 3-chloroaniline (99%, Sigma-Aldrich), 4-bromoaniline ($\geq 99\%$, Sigma-Aldrich), 3-bromoaniline (98%, Sigma-Aldrich), 4-aminobenzoic acid (99%, Sigma-Aldrich), 4-aminobenzonitrile (98%, Sigma-Aldrich), 4-nitroaniline ($\geq 99\%$, Sigma-Aldrich), DMSO- d_6 ($\geq 99\%$, Sigma-Aldrich), ethanol ($\geq 99.8\%$, Sigma-Aldrich). Microwave synthesis has been completed in Anton Paar Monowave 300 (Ashland, VA, USA) microwave reactor. FT-IR spectra of the investigated derivatives processed in the form of KBr pellets have been determined using an ABB Bomem MB Series 100 Fourier transform infrared (FT-IR) spectrophotometer (Quebec City, Canada). Nuclear magnetic resonance (NMR) spectra have been performed on a Bruker AC 250 spectrometer (Bruker, Germany) at 200 MHz for the ^1H NMR and 50 MHz for the ^{13}C NMR spectra. All NMR spectra of investigated derivatives have been recorded at room temperature in deuterated dimethyl sulfoxide (DMSO- d_6) using tetramethylsilane (TMS) as an internal standard. Elemental analyses have been performed using an Elemental Vario EL III microanalyzer (Elementar, Germany). Ultraviolet absorption spectra of the compounds in ethanol were recorded in the range 200–400 nm using Shimadzu 1700 UV-Vis spectrophotometer (Shimadzu, Japan).

2.2. Synthesis of 1-aryl-3-methyl-3-phenylpyrrolidine-2,5-diones (1–12)

All explored succinimide derivatives have been synthesized using 3-methyl-3-phenyl succinic acid and different substituted anilines under solvent-free conditions by microwave irradiation (MW). The corresponding succinic acid has been synthesized by previously reported procedures (Fig. 1) [33-35].

Generally, the mixture of the synthesized 3-methyl-3-phenyl succinic acid (1 mmol) and substituted aniline (1.1 mmol) have been stirred in a microwave reactor under solvent-free conditions ($V = 25$ mL, $t = 15$ min, $T = 180$ °C). The mixture was cooled and subsequently dissolved in ethyl acetate, consecutively washed with 10 mL of 5 % $\text{HCl}_{(\text{aq})}$, 10 mL of saturated $\text{NaHCO}_{3(\text{aq})}$, and two times with 10 mL of distilled water. The organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was recrystallized from acetone and chemical structures of the newly synthesized 1-aryl-3-methyl-3-phenylpyrrolidine-2,5-diones (1–12) have been

confirmed by determination of the melting point, FT-IR, ^1H and ^{13}C NMR spectroscopy, and elemental analysis. The characterization data are shown in Supplementary material (Section: Characterization).

2.3. Computational details

The density functional theory (DFT) calculations of the investigated dyes have been performed by using the "Gaussian 09 program" package (Gaussian Inc., Wallingford, CT, USA) [36] with B3LYP [36] and M06-2X [38] methods and 6-311G(d,p) basis set. Default convergence criteria were used without any constraint on the geometry. The stability of the optimized geometry was verified by frequency calculations, which gave real values for all the obtained frequencies. Optimized structural parameters have been utilized in the calculations of vibrational frequencies, electronic properties and isotropic chemical shifts.

Harmonic frequencies are calculated by the B3LYP/6-311G(d,p) method and then scaled by 0.9668 [39]. Assignments of the calculated wavenumbers are supported by the animation option of the GaussView 5.0 graphical interface of Gaussian programs [40], which performed a visual presentation of the shape of vibration modes.

Nuclear magnetic resonance (NMR) chemical shifts calculations were performed by using the Gauge-Independent Atomic Orbital (GIAO) method, at the same levels of theory in DMSO as a solvent. The ^1H and ^{13}C isotropic chemical shifts are listed in relation to the corresponding values for TMS. The solvent effect was introduced by the Conductor Polarizable Continuum Model (CPCM) [41]. Frontier Molecular Orbitals (FMO) analysis has been performed in an attempt to clarify the charge transfer within investigated succinimides.

3. RESULTS AND DISCUSSION

3.1. Synthetic pathway and characterization analysis

1-Aryl-3-methyl-3-phenylsuccinimides (**1–12**), investigated here, have been prepared according to the synthetic procedure presented in Figure 1 [33–35]. The last step represents modification of standard condensation procedures for closure of the succinimide ring and includes the use of MW radiation under solvent-free conditions, which significantly shortened the reaction time (15 min vs. 3 h of conventional heating) and improved yields.

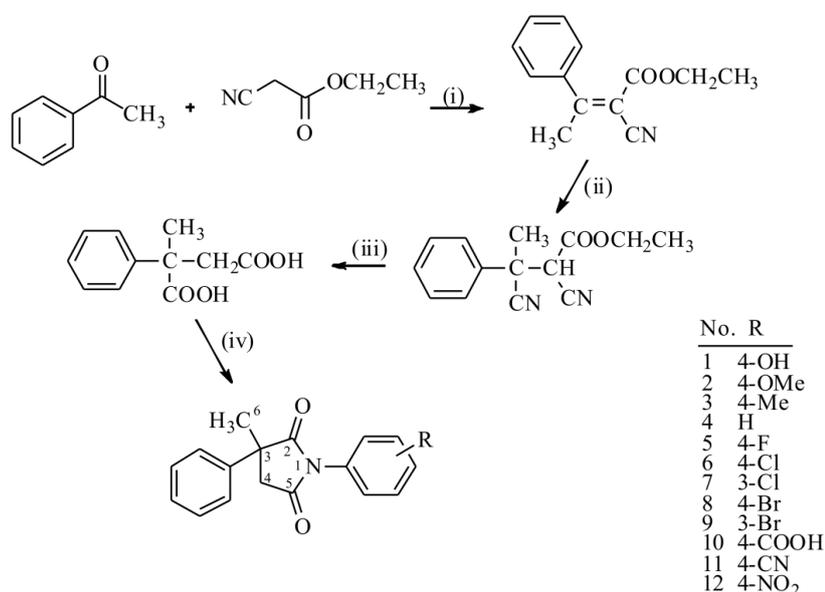


Figure 1. The synthetic route of novel 1-aryl-3-methyl-3-phenylsuccinimides. (i) NH_4OAc , C_6H_6 , reflux, 6 h; (ii) KCN, 50% ethanol, reflux, heated until a clear solution was formed (iii); 12 M HCl, reflux, 12 h (iv) substituted aniline, MW irradiation, 15 min, 180 °C

FT-IR spectra analysis of the investigated compounds revealed two characteristic stretching absorptions of carbonyl groups (C=O) originating from the succinimide ring in the regions 1773–1784 cm^{-1} (low intensity) and 1684–1709 cm^{-1} (strong intensity). All necessary C–H stretching of aromatic rings and the aliphatic chain were observed at their

characteristic absorption positions. ^1H NMR and ^{13}C NMR spectra unequivocally confirmed structures of the investigated compounds. From the ^1H NMR spectrum, characteristic aromatic protons, which belong to 3- or 4-substituted phenyl group, as well as aromatic protons from the phenyl group in the position 3 of the succinimide ring, were observed and all their positions are presented in the Supplementary data. Aromatic protons in *p*-substituted phenyl ring (for strong electron-acceptors and electron-donating groups) exhibit peaks as two doublets, while for unsubstituted and *m*-substituted phenyl group multiplet signals have been observed. Moreover, aromatic protons from the phenyl group in position 3 of the succinimide ring produced peaks as multiplet signals, which are overlapped with peaks which originate from the *p*(*m*)-substituted phenyl ring with moderate or weak substituents electronic effects. Corresponding methyl protons (3-methyl group on the succinimide ring) are observed as one strong singlet in the range from 1.77 to 1.73 ppm. Moreover, protons from the methylene group in the succinimide ring ($-\text{CH}_2-$) is observed as a characteristic AB quartet in the range 3.23–3.14 ppm with the coupling constant $J_{AB} = 18$ Hz. Additionally, ^{13}C NMR spectra of the investigated compounds exhibited all distinctive signals at the appropriate positions (Supplementary material).

3.2. Electronic effects of substituents on the spectroscopic data (Hammett's analysis)

As previously observed [32], the main influence on UV absorption wavenumbers is manifested through the electronic nature of the substituents at the phenyl ring attached to nitrogen on the succinimide core. Also, almost negligible effect of the solvent polarity and their other characteristics were observed on the changes of UV absorption positions [32]. Due to that and only with the aim to get an insight and confirm the strength of electronic effects of substituents on the UV-Vis absorption maxima, the UV absorption spectra of the investigated 1-aryl-3-methyl-3-phenylsuccinimides were recorded in ethanol in the range of 200–400 nm (Table S1, Fig. S1, Supplementary material). From the Figure S1 it can be observed that the UV absorption wavenumbers strongly depend on the nature of substituent electronic effects. As expected and previously reported [32], all substituents cause bathochromic band shifts relative to the unsubstituted compound **4**. The weak electron-donating methyl group induces the smallest positive changes on UV spectra, while the strongest electron-withdrawing $-\text{NO}_2$ group exhibits the largest bathochromic shift compared to the unsubstituted compound **4**. Shifts of the UV absorption bands are assigned to different $\pi \rightarrow \pi^*$ transitions involving the corresponding π -electron system of the investigated succinimides. The π -delocalization is essentially a result of transmission of π -electrons from the phenyl ring, provoked by electronic effects of substituents in the *p*- or *m*-position, to carbonyl groups of the succinimide ring. These bathochromic shifts of UV maxima, which are observed for all investigated compounds, support the evidence that a $\pi \rightarrow \pi^*$ transition is liable for these UV absorption shifts. Moreover, planarity of a molecule is one of the main features, which highly influences transmission of the resonance effect through the molecule and therefore significantly influences the contribution of the electron density delocalization to the UV absorption of each compound.

UV absorption maxima and the transmission of electronic effects were analyzed by a linear free-energy relationship (LFER) applying the simple Hammett equation [42]:

$$s = \rho \sigma + hs \quad (1)$$

where s is the absorption wavenumber (ν_{max}) as the substituent-dependent value, ρ expresses the sensitivity of ν_{max} to the substituent effects (proportionality constant), σ measures the electronic effect of substituents (substituent constant), and h is the intercept (*i.e.*, describes ν_{max} of the unsubstituted member of the series).

The plot ν_{max} vs. the Hammett substituent constants $\sigma_{p/m}$ [43] exhibits deviations from the Hammett linearity, therefore the electronic effect of the electron-donating and electron-accepting substituents are taken into consideration separately (Fig. 2). For the electron-donating substituents, the ρ value is significantly higher than 1, demonstrating high sensitivity of UV maxima toward these substituents. Also, the values of $\rho \gg 1$ indicate that the negative charge is built (or the positive charge is lost) on the succinimide ring, which is completely in agreement with possible resonance structures of these molecules with electron-donating substituents, where free electrons from substituents are shifted forward the imide part of the succinimide core. Moreover, the same trend in sensitivity is obtained for electron-accepting substituents, but the sign of ρ value indicates completely opposite effects than those described above. The value of $\rho \ll 0$ is obtained for electron-accepting substituents indicating formation of positive charges or reduction of negative charges on the chromophore succinimide ring.

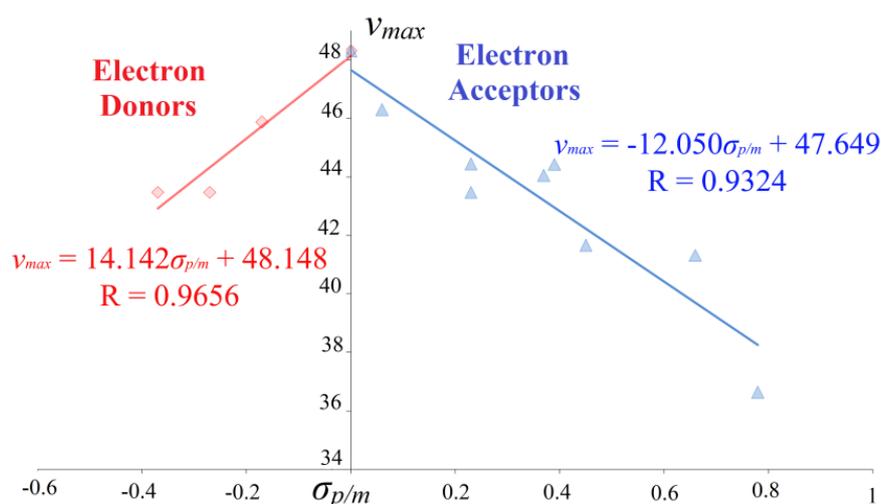


Figure 2. Experimental data and best linear fits of ν_{max} vs. $\sigma_{p/m}$ for investigated 1-aryl-3-methyl-3-phenylpyrrolidine-2,5-diones

Further, ^{13}C NMR chemical shifts for the two carbonyl atoms (C=O, C2, and C5) in the succinimide core (Fig. 1) for all 1-aryl-3-methyl-3-phenylsuccinimides were analyzed by LFER using Eq. (1), with the aim to get an insight into the quantitative assessment of substituent effects on the NMR data. All investigated ^{13}C NMR chemical shifts are presented in Table S2 (Supplementary material) as the substituent chemical shifts (SCS, δ) compared to the unsubstituted compound **4**. From the Table S2 it can be observed that electron-donating substituents cause downfield shifts, while electron-accepting substituents induce upfield shifts. Almost negligibly better correlations of ^{13}C SCSs for investigated carbonyl atoms (Table 1) are obtained with $\sigma_{p/m}$ substituent constants as compared to those with electrophilic substituent constants (σ_p^+) (Eq.(1)). Electronic effects of the substituents did not influence the SCS of the remaining two carbon atoms of the succinimide ring.

Table 1. Results of the SCS data correlations according to Eq. (1).

Parameter	ρ	h	R^a	s^b	F^c	n^d
$\delta_{\text{C}(2)}$	-0.709 (± 0.0387)	f^e	0.9854	0.0461	335	12
$\delta_{\text{C}(5)}$	-0.759 (± 0.0434)	f^e	0.9841	0.0517	306	12

^aCorrelation coefficient; ^bStandard error of the estimate; ^cFisher's test; ^dNumber of compounds included in the correlation;

^eNegligible value with a high standard error.

Values of correlation coefficients, R , from Table 1 show that influences of electronic effects of the substituent on the C2 and C5 chemical shifts were not statistically different. According to the ρ value, a moderate to small impact of substituent electronic effects on the electron density of investigated atoms is observed. The obtained results are entirely in accordance with the molecular structure of 1-aryl-3-methyl-3-phenylpyrrolidine-2,5-dione as well as with the mechanism of electron density transmission of the substituent electronic effects within the molecule [32].

2.3. DFT calculations

2.3.1. Conformational stability

A conformational analysis was performed to find all stable conformers of all investigated compounds. Conformational changes of the investigated compounds are possible in the position of substituents (methyl and phenyl groups) and small changes may be detected in positions 3 and 4 of the succinimide ring. In this work only the positions of 3-phenyl groups are investigated in detail. Positions of the *N*-phenyl group have been investigated in our previous work [32], and rotation of the methyl group does not contribute significantly to the energy of investigated systems. For a better insight into energy changes connected to rotation of the phenyl group in the position 3, potential energy scans (PES) for two possible orientations of the *N*-phenyl group were performed by the B3LYP/6-311G(d,p) method in vacuum



and ethanol. During the calculation, all geometrical parameters were simultaneously relaxed, while the torsion angle of the phenyl group in position 3 was varied in steps of 5° from 0–180°. Figure 4 represents the reaction coordinate for conformers with the *N*-phenyl group torsion angle of ~44°, while the reaction coordinate for the torsion angle of ~136° is shown in Figure S2, Supplementary material.

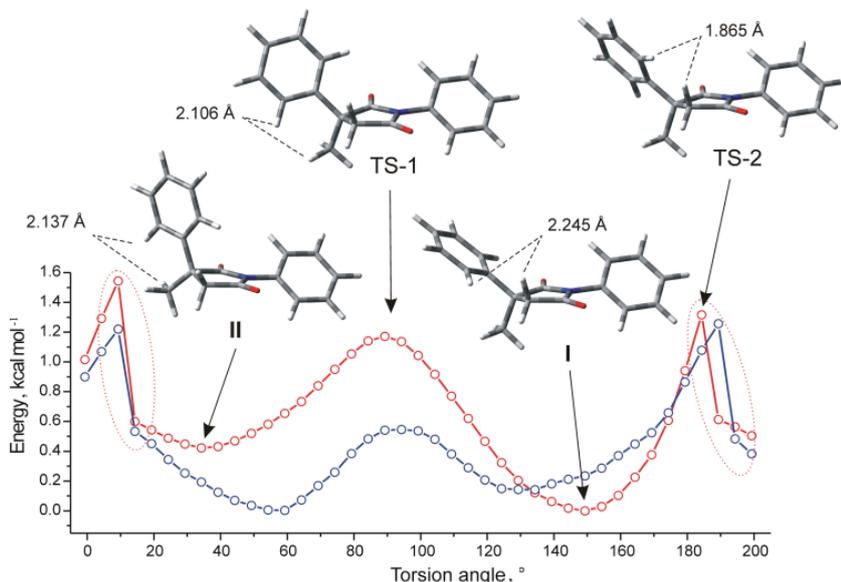


Figure 3. Potential energy scans for rotation of the phenyl group in position 3 in vacuum (red) and ethanol (blue) performed by the B3LYP/6-311G(d,p) method

Stable positions of the 3-phenyl group are determined with steric effects between other present groups. The succinimide ring in investigated molecules is almost planar and only the C3 atom deviates from the plane for no more than $\pm 6^\circ$, while the C4 atom shows a negligible deviation ($\pm 3^\circ$) but in the opposite direction, and thus the succinimide ring forms an unstable envelope conformation. The energetically most important repulsive interaction is between hydrogen atoms of CH₂ and 3-phenyl groups (see **TS-2** in Fig. 3). This interaction is responsible for the effect that while the 3-phenyl group is passing over the CH₂ group, the succinimide ring must rapidly flip from one envelope conformation to another, which can be seen as an irregularity on the reaction coordinate (see the part designated with a red circle in Fig. 3).

In contrast to the previously studied 1-(4-chlorophenyl)-3-phenylsuccinimide, which does not contain a methyl group in the position 3 and shows only one stable position for the 3-phenyl group [30], the compounds studied here show that rotation of the 3-phenyl group yields two stable conformers (**I** and **II**). The main reason for this may be attributed to the additional repulsion between methyl and phenyl groups in the position 3, which is strongest when the phenyl group and C3-CH₃ bond are in the same plane (see **TS-1** in Fig. 3). It must be noted that the overall energy change connected to the 3-phenyl group rotation is very small, less than 1.5 kcal mol⁻¹, which signifies that this group is very mobile. So, this group can easily adjust its position under the external influence. For comparison, the rotation barrier height for rotation of the ethyl group in 1-phenyl-3-ethyl-3-methylpyrrolidine-2,5-dione is ~5.5 kcal mol⁻¹ [44].

Also, a significant difference can be observed in Figure 3 in profiles of the reaction coordinates in vacuum and ethanol. The most evident difference is in the energy of conformers **I** and **II**. The vacuum environment favors the conformer **I** with the 3-phenyl group in the equatorial position, which is in agreement with the common view that the sterically bulkiest substituent tends to take this position. Contrary, in a polar solvent (ethanol), conformer **I** becomes less favored. The main reason for such behavior is in dipole moments of conformers. Calculations show that conformers **I** and **II** in vacuum have dipole moments of 1.456 and 1.575 D, respectively. So, the least polar conformer is the most stable one. Calculated dipole moments in ethanol are 1.741 and 1.834 D, respectively, and the conformer **II** becomes the most stable. A polar solvent tends to increase the dipole moment and additionally localizes hydrophobic and hydrophilic parts of the molecule, changing the envelope conformation of the succinimide ring, and consequently

bringing the phenyl groups into close proximity. Also this occurrence exposes the imide group for better interactions with solvent molecules.

Results show that four conformers are possible for the molecule with a symmetric substituent and eight conformers for that with an asymmetric substituent. Complete geometry optimizations of these conformers were performed by B3LYP and M06-2X methods with a 6-311G(d,p) basis set in vacuum and two solvents (ethanol and DMSO). According to a Boltzmann analysis, all conformers are simultaneously present in the solution at room temperature, so that the calculated properties of all conformers are used in the dynamic form (the Boltzmann averaging procedure is applied) for geometry correlation studies. In the same time, the most stable geometry of the compound **4** was used for vibrational and NMR studies. Geometries of all stable isomers for the compound **4** obtained by using the B3LYP method are shown in Figure 4 and 5. Calculated energies and statistical Boltzmann distribution weighted values of all stable isomers for the compound **4** by using B3LYP and M06-2X methods in vacuum, ethanol and DMSO are shown in Table S3 (Supplementary material).

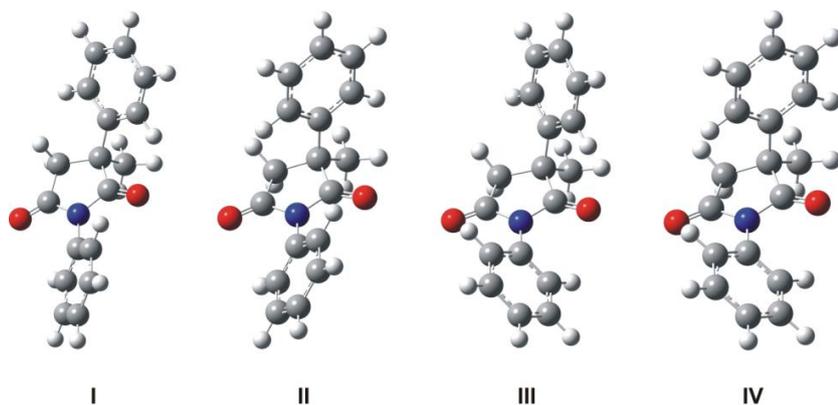


Figure 4. Geometries of all stable isomers for the compound **4** obtained by the B3LYP method

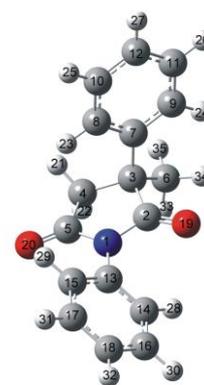


Figure 5. Atom numbering of investigated succinimide **4**

2. 3. 2. Vibrational and NMR spectral analyses of the investigated succinimide **4**

2. 3. 2. 1. Vibrational spectral analysis

The compound **4** was chosen as a representative example of the investigated series of succinimides. A meticulous analysis of experimental and calculated infrared spectra of the unsubstituted succinimide **4** was carried out to support the structural analysis. Wavenumbers which are the most important for the structure of this compound are presented in Table 2. The experimental and calculated spectra are shown in Figure S3 (Supplementary material) and the atom numbering scheme is presented in Figure 5.

Stretching vibrations of C–H and C–C aromatic bonds are characteristic for two phenyl moieties in the molecule **4**. Two broad and weak bands, in the calculated spectrum, at 3102 and 3112 cm^{-1} are assigned to symmetric stretching vibrations of the C–H group and asymmetric stretching vibrations are at 3084 and 3089 cm^{-1} with a counterpart in the experimental FT-IR spectrum at 2977 cm^{-1} . In-plane bending vibrations of C–H groups appear in the region 1050–1595 cm^{-1} and mix with C–C stretching as well as bending vibrations of aliphatic methyl and methylene group. The out-of-plane bending vibration of C–H groups in phenyl moieties are observed as intense bands at 652 and 756 cm^{-1} in the FT-IR spectrum while the corresponding calculated values are 695 and 743 cm^{-1} . Stretching vibrations of aromatic C–C bonds are observed at 1599 cm^{-1} and correlate with calculated values at 1569 and 1589 cm^{-1} . In-plane and out of plane bending vibrations of aromatic C–C groups correlate well, Table 2.

The most significant bands of the succinimide ring are in the region 1700–1800 cm^{-1} and belong to stretching vibrations of two carbonyl groups. The two carbonyl bond stretching vibrations are combined to produce symmetric and asymmetric stretching vibrations. Symmetric stretching vibrations are observed as a sharp and very intense peak at 1702 cm^{-1} while asymmetric stretching vibrations are observed as a weak band at 1778 cm^{-1} . Medium intense IR bands at 569, 780 and 1123 cm^{-1} are identified as C=O out-of-plane and in-plane bending vibrations. The corresponding theoretical wavenumbers of 564, 787 and 1173 cm^{-1} are well correlated to the experimental ones. The succinimide ring

C–C and C–N stretching vibration modes of the investigated molecule are predicted at 1182 and 1333 cm^{-1} by the B3LYP/6-311G(d,p) method and observed at 1186 and 1293 cm^{-1} in the FT-IR spectrum. The out-of-plane and in-plane bending vibrations of C–C and C–N groups of the succinimide moiety are observed at 876, 932 and 569, 756 cm^{-1} , respectively and calculated counterparts are at 859, 985 and 564, 748 cm^{-1} .

Frequencies of C–H phenyl ring vibrations are found to be higher than those of CH_2 and CH_3 groups. Also, symmetric modes have higher frequencies than the asymmetric ones for the phenyl C–H group, while it is the opposite for CH_2 and CH_3 groups. Calculated symmetric and asymmetric stretching modes for methyl and methylene aliphatic groups are at 2930, 2956 and 2986, 3020 cm^{-1} , respectively and correlate with the experimental finding at 2901 cm^{-1} . Bands at 1457 and 1293 cm^{-1} are attributed to CH_2 scissoring and wagging vibrations, respectively. A moderately strong peak at 1074 cm^{-1} is assigned to twisting vibrations and two peaks at 569 and 876 cm^{-1} in the FT-IR spectrum are assigned to rocking vibrations of the CH_2 group. Symmetric and asymmetric deformation vibration modes of the CH_3 group are predicted at 1363 and 1478 cm^{-1} , respectively, and observed at 1382 and 1493 cm^{-1} in the FT-IR spectrum. Methyl rocking vibrations of the investigated compound are coupled with in-plane bending vibrations of aromatic C–H and C–C bonds, in-plane bending vibrations of C–N–C as well as with twisting vibrations of the CH_2 group and display moderately strong peaks at 1050 and 1074 cm^{-1} in the FT-IR spectrum.

Table 2. The observed FT-IR and calculated (B3LYP/6-311G(d,p)) frequencies for the compound 4.

IR exp ^a	Unscaled B3LYP Frequency, cm^{-1}	Scaled B3LYP	IR intensity, K mmol^{-1}	Assignments
	3219	3112	1.4	$\nu_s\text{CH}$
	3209	3102	3.04	$\nu_s\text{CH}$
2977	3195	3089	24.18	$\nu_{as}\text{CH}$
	3190	3084	22.93	$\nu_{as}\text{CH}$
	3124	3020	4.86	$\nu_{as}\text{CH}_2$
2901	3089	2986	30.45	$\nu_{as}\text{CH}_3$
	3058	2956	8.53	$\nu_s\text{CH}_2$
	3031	2930	22.46	$\nu_s\text{CH}_3$
1778	1845	1784	54.11	$\nu_{as}\text{C}=\text{O}$
1702	1780	1721	518.06	$\nu_s\text{C}=\text{O}$
1595	1644	1589	17.8	$\nu\text{CC} + \beta\text{HCC}$
	1623	1569	2.53	$\nu\text{CC} + \beta\text{HCC}$
	1531	1480	44.33	βHCC
1493	1529	1478	54.98	$\beta\text{HCC} + \delta_{as}\text{CH}_3$
1457	1465	1416	5.9	ψCH_2
1382	1410	1363	36.14	$\delta_s\text{CH}_3$
1293	1379	1333	378.7	$\nu\text{NC} + \delta_s\text{CH}_3 + \omega\text{CH}_2$
1186	1223	1182	48.5	$\nu\text{NC} + \nu\text{CC} + \beta\text{CCH} + \tau\text{CH}_2$
1123	1213	1173	42.44	$\rho\text{CH}_3 + \beta\text{HCC} + \beta\text{CO}$
	1194	1154	33.57	$\tau\text{CH}_2 + \beta\text{HCC}$
1074	1167	1128	71.15	$\tau\text{CH}_2 + \beta\text{HCC} + \rho\text{CH}_3$
1050	1127	1090	20.67	$\beta\text{CNC} + \beta\text{HCC} + \rho\text{CH}_3$
932	1019	985	2.04	βCCC
876	889	859	31.2	$\beta\text{CCC} + \rho\text{CH}_2$
780	814	787	14.61	$\gamma\text{CCO} + \tau\text{CCCC}$
756	769	743	32.58	$\gamma\text{CNC} + \gamma\text{HCC}$
652	719	695	44.48	γHCC
569	583	564	3.3	$\gamma\text{CCO} + \rho\text{CH}_2$
480	517	500	10.23	$\tau\text{CCCC} + \tau\text{CNCC} + \tau\text{HCCC}$
444	503	486	8.03	τCCCC

^aHarmonic frequency; ν – stretching; ν_s –symmetric stretching; ν_{as} –asymmetric stretching; β –in plane bending; γ –out-of-plane bending; τ –torsion; δ_s –symmetric deformation; δ_{as} –asymmetric deformation; ψ –scissoring; ρ –rocking; ω –wagging

2. 3. 2. 2. NMR spectral analysis

Experimental and theoretical values for ^1H and ^{13}C NMR chemical shifts of the molecule **4** are given in Table 3 and the atom numbering scheme is presented in Figure 5. The ^{13}C and ^1H NMR spectra of the compound **4** are recorded in DMSO- d_6 and presented in Figures S4 and S5 (Supplementary material).

The two carbon atoms (C3 and C4) of the succinimide ring resonating at 44.64 and 47.69 ppm in the ^{13}C NMR spectrum show good agreement with computed values 52.89 and 55.13 ppm, respectively. Carbon atoms C2 and C5 of two carbonyl groups (deshielded because of electronegative oxygen atoms) are presented in the downfield at 180.12 and 174.72 ppm and supported well with computed shifts at 190.75 and 183.54 ppm. The methyl carbon atom C6 is observed at 24.46 ppm and the computed chemical shift is at 26 ppm. Carbon atoms of two phenyl groups appeared in the regions 125.94–142.45 and 134.04–152.88 ppm in the experimental and calculated spectrum, respectively.

In the ^1H NMR spectrum, a singlet appearing at 1.75 ppm with three protons integral is assigned to protons of the methyl group and shows good agreement with theoretical values at 1.54, 1.90 and 1.91 ppm for H35, H34 and H33, respectively. A quartet appearing at 3.18 ppm is assigned to methylene protons (H21 and H22) and calculated values of 2.89 and 3.09 ppm, respectively, correlate well. Peaks at 7.32–7.56 ppm, with respect to TMS, indicate the presence of aromatic hydrogen atoms of two phenyl groups.

Table 3. Calculated and experimental ^1H and ^{13}C NMR isotropic chemical shifts (with respect to TMS in DMSO solution) of the compound **4** (atom positions were numbered as in Figure 5).

^1H NMR	Chemical shift, ppm		^{13}C NMR	Chemical shift, ppm	
	calc.	exp.		calc.	exp.
H21	3.09	3.18	C2	190.75	180.12
H22	2.89	3.18	C3	55.13	47.69
H23	7.78	7.46	C4	52.89	44.64
H24	7.51	7.32	C5	183.54	174.72
H25	7.70	7.45	C6	26.00	24.46
H26	7.68	7.42	C7	152.88	142.45
H27	7.60	7.37	C8	132.45	125.94
H28	7.68	7.44	C9	134.42	125.94
H29	7.53	7.53	C10	134.98	128.99
H30	7.84	7.56	C11	135.81	128.99
H31	7.82	7.52	C12	134.04	128.82
H32	7.79	7.49	C13	142.20	132.47
H33	1.91	1.75	C14	135.14	127.25
H34	1.90	1.75	C15	134.79	127.25
H35	1.54	1.75	C16	135.85	128.54
			C17	135.93	128.54
			C18	135.97	128.99

2. 3. 2. 3. Electronic analysis

Frontier molecular orbitals (FMO), HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital), define the way a molecule interacts with other species and present helpful information for characterization of the molecule chemical reactivity [45]. In order to predict and determine possible charge transfers in the investigated molecules, the energy levels of HOMO and LUMO are computed at the B3LYP/6-311G(d,p) level. Compositions of frontier molecular orbitals along with their energies and energy gaps for compounds **2**, **4**, **10** and **12** are sketched in Figure 6. Energies of HOMO and LUMO and energy gaps for all investigated succinimides in vacuum, ethanol and DMSO are shown in Table S4 (Supplementary material).

From Figure 6 it is evident that electron densities of HOMO and LUMO for the compound **2** are separated on the 1-(4-methoxyphenyl) and 3-phenyl moiety, respectively. Therefore, an intramolecular charge transfer is possible in the molecule **2**. On the contrary, in the molecule **12**, the electron density of HOMO is dominantly populated on the 3-phenyl group and LUMO is located on the 1-(4-nitrophenyl) ring due to the strong electron accepting nitro substituent inducing a shift of π electron density from the 3-phenyl group toward the 1-aryl moiety. The electron density of HOMO and LUMO for the compound **4** is spread over succinimide and phenyl rings and such distribution cause a weaker intramolecular



charge transfer ICT than that in the substituted succinimides. The energy difference between the HOMO and LUMO for the compound **4** is obtained as 5.93 eV and confirms the low chemical reactivity of this succinimide. Interestingly, succinimides **2**, **10** and **12** with an electron-donor and an electron-acceptor substituent have smaller energy gaps of 5.34, 5.34 and 4.60 eV, respectively, which could explain the increase of their reactivity relative to the compound **4**. In conclusion, the ICT is more feasible in the compound **12**.

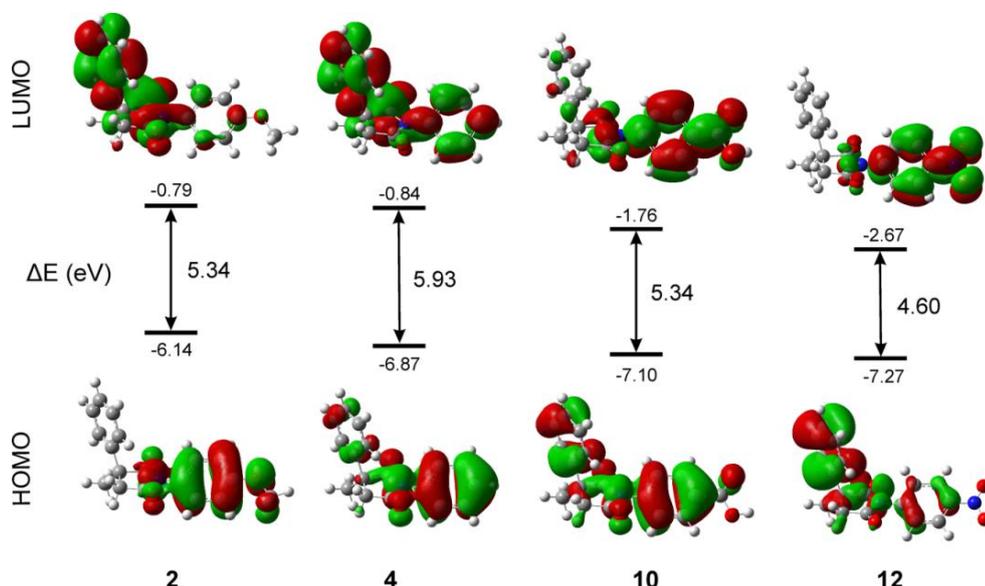


Figure 6. HOMO and LUMO of selected investigated succinimides: compounds **2**, **4**, **10** and **12**

2. 4. Comparison of experimentally and computationally obtained data

As planarity of a molecule is one of the most important molecular properties, which influences transition of electron density through the molecular skeleton, determination of relationships between torsion angles (θ) and spectroscopic data is important. With this aim, we have correlated UV absorption wavenumbers of the investigated compounds in ethanol with the corresponding $\cos^2 \theta$ of the Boltzmann distribution of the most stable conformers (θ is obtained by the B3LYP/6-311G(d,p) method). Excellent linear correlations (for donors: $\nu_{\max} = 43.804 \times \cos^2 \theta + 38.063$, $R^2 = 0.9331$; for acceptors: $\nu_{\max} = -40.415 \cos^2 \theta + 56.774$, $R^2 = 0.9101$) were obtained and the results are entirely in accordance with the previously described LFER model (Fig. 3). Further, correlations of C2 and C5 SCS with $\cos^2 \theta$ show excellent linear trends ($\delta_{C(C2)} = -2.221 \cos^2 \theta + 0.471$, $R^2 = 0.9093$; $\delta_{C(C5)} = -2.372 \cos^2 \theta + 0.492$, $R^2 = 0.9029$). Moreover, excellent correlations of $\cos^2 \theta$ with Hammett substituent constants were obtained (data not shown), which is again in agreement with the previously described LFER concept. Also, excellent agreements of experimentally and computationally obtained SCS data were obtained ($\delta_{C(C2)\text{exp}} = 0.631 \delta_{C(C2)\text{calc}} - 0.022$, $R^2 = 0.9197$; $\delta_{C(C5)\text{exp}} = 0.633 \delta_{C(C5)\text{calc}} - 0.012$, $R^2 = 0.9383$). Excellent agreements of theoretical with experimental data directly indicate high validity and precision of the proposed models.

2. 5. ADMET and PASS profiling

Structural properties of the investigated succinimides have been tested by the Lipinski's empirical 'rule of five' in order to determine which of them is pharmacokinetically active [46]. A compound has potentially a good *in vivo* permeability, if following the rules are satisfied: MW < 500; the compound bears 5 atoms that are proton-donors of hydrogen bonds (–OH and –NH); the compound has a maximum of 10 hydrogen bond acceptor atoms (N and O) and the logarithm of the octanol–water partition coefficient ($\log P$) is lower than 5 [47]. The fifth rule refers to the structural parameters and includes the number of rotatable bonds (lower than 8), molar refractivity (in the range of 40–130 Å³) as well as a small polar surface area (< 140 Å²) [47–49]. All structural parameters mentioned above are applied to the investigated succinimides and methsuximide. The corresponding data are presented in Table S4 (Supplementary material) where the partition coefficient ($\log P$) and the polar surface area are calculated by using the program Molinspiration [50].

Table S5 shows that all investigated succinimides meet the empirical criteria 'rule of five' being candidate molecules for pharmaco-dynamic phase investigations. Since $\log P$ is associated with the solubility and permeability of a molecule, this physicochemical parameter is one of the most important in estimation of the molecule capability for transfer through the cell membrane. The investigated succinimide derivatives are moderately lipophilic compounds, whereby all halogen substituents, methoxy and methyl groups induce an increase in the hydrophobic character compared to the unsubstituted molecule (compound **4**). Further, the synthesized molecules exhibit a low number of rotatable bonds (Table S5), which can provoke moderate conformational changes of the molecule due to binding to a receptor. Moreover, as the polar surface area (PSA) is a very important descriptor for drug transport properties and all investigated succinimides possess convenient values of this parameter, it can be expected that these potentially biologically active candidates will be transported without difficulties. Finally, it can be noted that all investigated compounds exhibit similar 'rule of five' properties to those of the commercially available anticonvulsant methsuximide.

The PASS (Prediction of Activity Spectra) online tool [51] is used for prediction of protein and ligand interactions. In this study, the PASS results (Table S6, Supplementary material). indicate that the novel series of succinimides are very promising drug candidates, based on the comparison of the P_a/P_i ratio of the parent compound - methsuximide, whereby few derivatives are principally segregate on this ratio.

4. CONCLUSION

In this paper, twelve novel derivatives of the commercially available drug methsuximide have been synthesized as potential anticonvulsant agents. The compounds were thoroughly characterized by different spectroscopic techniques. LFER analysis revealed that spectral properties are strongly influenced by electronic properties of the substituents. Quantum chemical calculations of energies, geometrical structure and vibrational wavenumbers of the investigated succinimides have been carried out by using DFT showing excellent agreements with the experimental data. The *in-silico* PASS prediction and ADMET profiling results regarding potential biological activities of investigated succinimides are encouraging enough to merit further *in vitro* and *in vivo* investigation.

Supplementary Material

Additional supporting material may be found journal web site: https://www.ache-pub.org.rs/index.php/HemInd/article/view/493/pdf_1

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LITERATURA

- [1] Hargreaves MK, Pritchard JG, Dave HR. Cyclic carboxylic monoimides. *Chem Rev.* 1970; 70: 439 – 469.
- [2] Kamiński K, Obniska J. Design, synthesis, and anticonvulsant activity of *N*-phenylamino derivatives of 3,3-dialkyl-pyrrolidine-2,5-diones and hexahydro-isoindole-1,3-diones. *Bioorgan Med Chem.* 2008; 16: 4921 – 4931.
- [3] Kamiński K, Rzepka S, Obniska J. Synthesis and anticonvulsant activity of new 1-[2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]pyrrolidine-2,5-diones. *Bioorgan Med Chem Lett.* 2011; 21: 5800 – 5803.
- [4] Patsalos PN. Properties of antiepileptic drugs in the treatment of idiopathic generalized epilepsies. *Epilepsia.* 2005; 46: 140–148.
- [5] Porter RJ, Penry JK, Lacy JR, Newmark ME, Kupferberg HJ. Plasma concentrations of phensuximide, methsuximide, and their metabolites in relation to clinical efficacy. *Neurology.* 1979; 29: 1509 – 1513.
- [6] Jensen PB, Sokilde B, Carstensen EV, Langer SW, Creighton A, Sehested M, Jensen L. Succinimide and maleimide derivatives and their use as topoisomerase II catalytic inhibitors. EP 1373494, 2004
- [7] Korhalkar AA, Khadse BG, Sengupta SR. Synthesis of 2-hetero/aryl-*N*-(*p*-fluorobenzene) succinimide derivatives as antitubercular agents. *Indian Drugs.* 1992; 29: 306 – 307.



- [8] Khadilkar BM, Bhayade SR. Synthesis and hypotensive activity of some succinimide derivatives. *Indian J Chem B*. 1993; 32: 338 – 342.
- [9] Shetgiri NP, Nayak BK. Synthesis and antimicrobial activity of some succinimides. *Indian J Chem B*. 2005; 44B: 1933 – 1936.
- [10] Zentz F, Guillou RL, Labia R, Sirot D, Linard B, Valla A. Syntheses, *in vitro* antibacterial and cytotoxic activities of a series of 3-substituted succinimides. *Farmaco*. 2004; 59: 879 – 886.
- [11] Bansode TN, Shelke JV, Dongre VG. Synthesis and antimicrobial activity of some new *N*-acyl substituted phenothiazines. *Eur J Med Chem*. 2009; 44: 5094 – 5098.
- [12] Sharir M. Succinimide derivatives as ocular hypotensive agents. WO 2007057889, 2007.
- [13] Prince DA. Succinimides and oxazolidinediones for treating tremor. US 4981867, 1991.
- [14] Kumar S, Prakash S, Gupta K, Dongre A, Balaram P, Balaram H. Unexpected functional implication of a stable succinimide in the structural stability of *Methanocaldococcus jannaschii* glutaminase. *Nat Commun*. 2016; 7: 12798.
- [15] Takahashi O, Kirikoshi R, Manabe N. Roles of intramolecular and intermolecular hydrogen bonding in a three-water-assisted mechanism of succinimide formation from aspartic acid residues. *Molecules*. 2014; 19: 11440 – 11452.
- [16] Grassi L, Regl C, Wildner S, Gadermaier G, Huber CG, Cabrele C, Schubert M. Complete NMR Assignment of succinimide and its detection and quantification in peptides and intact proteins. *Anal Chem*. 2017; 89: 11962 – 11970.
- [17] Kleemann A, Engel J. *Pharmaceutical Substances: Syntheses, Patents, Applications*. Stuttgart, Germany: Georg Thieme Verlag; 2001.
- [18] Popović-Đorđević J, Vitnik V, Vitnik Ž, Ivanović M. Glutarimides: biological activity, general synthetic methods and physicochemical properties. *Hem Ind*. 2015; 69: 523 – 536.
- [19] Liu SL, Li Y, Guo JR, Yang GC, Li XH, Gong JF, Song MP. An approach to 3-(Indol-2-yl)succinimide derivatives by manganese-catalyzed C-H activation. *Org Lett*. 2017; 19: 4042 – 4045.
- [20] Chauhan P, Kaur J, Chimni SS. Asymmetric organocatalytic addition reactions of maleimides. A promising approach towards the synthesis of chiral succinimide derivatives. *Chem-Asian J*. 2013; 8: 328 – 346.
- [21] Han SH, Kim S, De U, Mishra NK, Park J, Sharma S, Kwak JH, Han S, Kim HS, Kim IS. Synthesis of succinimide-containing chromones, naphthoquinones, and xanthenes under Rh(III) catalysis: evaluation of anticancer activity. *J Org Chem*. 2016; 81: 12416 – 12425.
- [22] Kishikawa K, Furukawa Y, Watanabe T, Kohri M, Taniguchi T, Kohmoto S. Why chiral tartaric imide derivatives give large helical twisting powers in nematic liquid crystal phases: substituent-effect approach to investigate intermolecular interactions between dopant and liquid crystalline molecules. *Liq Cryst*. 2017; 44: 956 – 968.
- [23] Shirini F, Khaligh NG. Succinimide-*N*-sulfonic acid: An efficient catalyst for the synthesis of xanthene derivatives under solvent-free conditions. *Dyes Pigments*. 2012; 95: 789 – 794.
- [24] Peng H, Kather M, Rübsum K, Jakob F, Schwaneberg U, Pich A. Water-soluble reactive copolymers based on cyclic *N*-vinylamides with succinimide side groups for bioconjugation with proteins. *Macromolecules*. 2015; 48: 4256 – 4268.
- [25] Doll KM, Shogrent RL, Holser RA, Willett JL, Swift G. Polymerization of L-aspartic acid to polysuccinimide and copoly(succinimide-aspartate) in supercritical carbon dioxide. *Lett Org Chem*. 2005; 2: 687 – 689.
- [26] Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. *Brit J Pharmacol*. 2011; 162: 1239 – 1249.
- [27] Milosevic NP, Kojic V, Curcic J, Jakimov D, Milic N, Banjac N, Uscumlic G, Kaliszan R. Evaluation of *in silico* pharmacokinetic properties and *in vitro* cytotoxic activity of selected newly synthesized *N*-succinimide derivatives. *J Pharmaceut Biomed*. 2017; 137: 252 – 257.
- [28] Perisic-Janjic N, Kaliszan R, Milosevic N, Uscumlic G, Banjac N. Chromatographic retention parameters in correlation analysis with *in silico* biological descriptors of a novel series of *N*-phenyl-3-methyl succinimide derivatives. *J Pharmaceut Biomed*. 2013; 72: 65 – 73.
- [29] Perisic-Janjic N, Kaliszan R, Wiczling P, Milosevic N, Uscumlic G, Banjac N. Reversed-phase TLC and HPLC retention data in correlation studies with *in silico* molecular descriptors and druglikeness properties of newly synthesized anticonvulsant succinimide derivatives. *Mol Pharmaceutics*. 2011; 8: 555 – 563.
- [30] Chamundeeswaria SPV, Samuela EJJ, Sundaraganesan N. Quantum mechanical and spectroscopic (FT-IR, FT-Raman, ¹³C, ¹H and UV) investigations of antiepileptic drug Ethosuximide. *Spectrochim Acta A*. 2011; 83: 478 – 489.
- [31] Vitnik VD, Vitnik Ž, Banjac NR, Valentić NV, Uščumlić GS, Juranić IO. Quantum mechanical and spectroscopic (FT-IR, ¹³C, ¹H NMR and UV) investigations of potent antiepileptic drug 1-(4-chlorophenyl)-3-phenylsuccinimide. *Spectrochim Acta A*. 2014; 117: 42 – 53.
- [32] Banjac NR, Božić BD, Mirković JM, Vitnik VD, Vitnik Ž, Valentić NV, Uščumlić GS. Experimental and theoretical study on the structure-property relationship of novel 1-aryl-3-methylsuccinimides. *J Mol Struct*. 2017; 1129: 271 – 282.
- [33] Miller CA, Long LM. Anticonvulsants. I. *N*-R- α -R1- α -phenylsuccinimides. *J Am Chem Soc*. 1951; 73: 4895 – 4898.
- [34] Miller CA, Long LM. Anticonvulsants. III. A study of *N*, α , β -trialkylsuccinimides. *J Am Chem Soc*. 1953; 75: 373 – 375.
- [35] Katritzky AR, Nair SK, Witek RM, Hutchins SM. Synthesis of 3,3-diarylpyrrolidines from diaryl ketones. *ARKIVOC*. 2003; V: 9 – 18.
- [36] Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, et al. *Gaussian 09, Revision D.01*. Wallingford CT: Gaussian, Inc.; 2009.
- [37] Becke AD. Density-functional thermochemistry. III. The role of exact exchange. *J Chem Phys*. 1993; 98: 5648 – 5652.

- [38] Zhao Y, Truhlar DG. Density functionals with broad applicability in chemistry. *Accounts Chem Res.* 2008; 41: 157 – 167.
- [39] Scott AP, Radom L. Harmonic vibrational frequencies: an evaluation of Hartree-Fock, Moeller-Plesset, quadratic configuration interaction, density functional theory, and semiempirical scale factors. *J Phys Chem.* 1996; 100: 16502 – 16513.
- [40] Dennington R, Keith T, Millam J. *GaussView, Version 5.0.9.* Shawnee Mission, Semichem Inc., KS; 2009.
- [41] Cossi M, Rega M, Scalmani G, Barone V. Energies, structures, and electronic properties of molecules in solution with the C-PCM solvation model. *J Comput Chem.* 2003; 24: 669 – 681.
- [42] Hammett LP. Effect of structure upon the reactions of organic compounds. Benzene derivatives. *J Am Chem Soc.* 1937; 59: 96 – 103.
- [43] Brown H, Okamoto Y. Electrophilic Substituent Constants. *J Am Chem Soc.* 1958; 80: 4979 – 4987.
- [44] Petković Cvetković J, Božić B, Banjac N, Petrović J, Soković M, Vitnik V, Vitnik Ž, Uščumlić G, Valentić N. Synthesis, antimicrobial activity and quantum chemical investigation of novel succinimide derivatives. *J MolStruct.* 2019; 1181: 148 –156.
- [45] Fleming I. *Frontier Orbitals and Organic Chemical Reactions.* New York, USA: John Wiley and Sons; 1976.
- [46] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliver Rev.* 1997; 23: 3 – 25.
- [47] Remko M, Swary M, Bickelhaupt FM. Theoretical study of structure, pKa, lipophilicity, solubility, absorption, and polar surface area of some centrally acting antihypertensives. *Bioorgan Med Chem.* 2006; 14: 1715 – 1728.
- [48] Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem.* 2002; 45: 2615 – 2623.
- [49] Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. a qualitative and quantitative characterization of known drug databases. *J Comb Chem.* 1999; 1: 55 – 68.
- [50] Molinspiration (2019). Calculation of Molecular Properties and Bioactivity Score. Molinspiration Cheminformatics [online].
- [51] Lagunin AI, Stepanchikova A, Filimonov D, Poroikov V., PASS: prediction of activity spectra for biologically active substances. *Bioinformatics.* 2000; 16: 747-748.

SAŽETAK

Spektroskopska i kvantno-hemijska proučavanja novih 1-aril-3-metil-3-fenilpirolidin-2,5-diona kao potencijalnih antikonvulzivnih jedinjenja

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(Naučni rad)

Novi derivati sukcinimida sintetisani su polazeći od 3-metil-3-fenilcetilbarne kiseline i supstituisanih analina u mikrotalasnom reaktoru u odsustvu rastvarača. Sva jedinjenja su okarakterisana primenom UV-vidljive spektroskopije, infracrvene spektroskopije sa Furijeovom transformacijom (FT-IR), protonske nuklearne magnetne rezonancije (¹H NMR), nuklearne magnetne rezonancije ugljenika-13, (¹³C NMR), kao i elementalnom analizom. Uticaj elektronskih efekata supstituenata na spektroskopske podatke analiziran je upotrebom Hametove jednačine. Takođe, izvršena je detaljna interpretacija, kao i poređenje eksperimentalno dobijenih i teorijski izračunatih FT-IR, UV i NMR spektara. Pored toga, urađeno je ADMET (engl. absorption, distribution, metabolism, excretion and toxicity) profilisanje i *in-silico* predviđanje potencijalne biološke aktivnosti nosintetisanih derivata sukcinimida.

Ključne reči: Sukcinimidi; Elektronski efekat; Spektroskopska analiza; Kvantno-hemijski proračun

