Procesing '21

ZBORNIK RADOVA

34. Međunarodni kongres o procesnoj industriji

3. i 4. jun 2021
Novi Sad

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pisanih za 34. Međunarodni kongres o procesnoj industriji
PROCESING ′21

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2021

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Fakultet tehničkih nauka Univerziteta u Novom Sadu, Novi Sad

Izdavač
Savez mašinskih i elektrotehničkih
inženjera i tehničara Srbije (SMEITS)
Društvo za procesnu tehniku
Kneza Miloša 7a/II,
11000 Beograd

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pri SMEITS-u
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PREDGOVOR

U ovom zborniku su kompletni radovi koje je Naučno-stručni odbor 34. Međunarodnog kongresa o procesnoj industriji Procesing '21. posle obavljenih recenzija prihvatio za izlaganje.

Zbornik radova će biti objavljen elektronski i na sajtu www.izdanja.smeits.rs.

Međunarodni karakter Procesinga '21 i ove godine ostvaren je inostranim učesnicima sa radovim, kao i članovima naučnog odbora. Zvanični jezici za izlaganje radova na kongresu su srpski i engleski.

Osnovni ciljevi kongresa su inoviranje i proširivanje znanja inženjera u procesnoj industriji, energetici, rudarstvu, komunalnom sektoru (vodovodima, toplanama) i podrška istraživačima u predstavljanju ostvarenih rezultata istraživačkih projekata.

Tematika Procesinga '21 obuhvata osnovne procesne operacije – mehaničke, hidromehaničke, toplotne, difuzione, hemijske i biohemijske, kao i procesna postrojenja i opremu (aparate i mašine).

Program Procesinga '21 obuhvata oblasti: projektovanja i razvoja u procesnoj industriji; konstruisanja mašina, aparata i uređaja; pripreme i vođenja izgradnje i montaže industrijskih postrojenja; industrijskih i laboratorijskih merenja; ispitivanja i atestiranja materijala, proizvoda, mašina i aparata; istraživanja i razvoja nove opreme i industrijskih sistema.

U program Procesinga '21 po tradiciji, pored prezentacije radova uključena su tri Okrugla stola iz aktuelnih tema u oblasti procesne tehnike:

- *Cirkularna ekonomija – alat za održivost industrije,*
- *Tretman voda u industriji – iskustva i buduće potrebe,*
- *Gasovi u industriji – primeri dobre prakse.*

Procesing '21 organizuje Društvo za procesnu tehniku pri SMEITS-u, a u Naučnom i Organizacionom odboru prisutni su predstavnici svih Mašinskih fakulteta u Srbiji kao i Tehnoloških i drugih fakulteta u okviru kojih je oblast procesne tehnike zastupljena u nastavi.

Pomoć u organizovanju Procesinga '21 dali su članovi Katedre za procesnu tehniku Mašinskog fakulteta Univerziteta u Beogradu i Departmana za energetiku i procesnu tehniku Fakulteta tehniničkih nauka iz Novog Sada.

Sa Tehnološko-metalurškog fakulteta u Beogradu, pored drugih vidova saradnje kroz Društvo za procesnu tehniku prijavljen je i značajan broja radova za ovogodišnji Procesing.

U Beogradu
juli 2021.

SADRŽAJ

Inženjerstvo životne sredine i održivi razvoj u procesnoj industriji

Procesi i postrojenja u pripremi i prečišćavanju vode u procesnoj industriji

Procesne tehnologije

Gasna tehnika

Osnovne i pomoćne operacije, aparati i mašine u procesnoj industriji

Energetska efikasnost u procesnoj industriji

Menadžment kvaliteta i standardizacija u organizacijama

Radovi koji će biti objavljeni u časopisu „Procesna tehnika“ u 2021. godini

SINTEZA DISUPSTITUISANIH DERIVATA PIROLIDIN-2,5-DIONA PRIMENOM MIKROTALASNOG POSTUPKA I EVALUACIJA NJIHOVIH FARMAKOKINETIČKI RELEVANTNIH SVOJSTAVA

SYNTHESIS OF DISUBSTITUTED PYRROLIDINE-2,5-DIONE DERIVATIVES USING THE MICROWAVE PROCEDURE AND EVALUATION OF THEIR PHARMACOKINETICALLY RELEVANT PROPERTIES

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Derivati sukcinimida (pirolidin-2,5-diona) predstavljaju organska jedinjenja širokog spektra farmakološke aktivnosti. Derivati ovog jedinjenja poznati su antikonvulzivi (etosukcinimid, metosukcinimid i fensukcinimid), antipsihotici, sedativi, antikancerogeni i antivirusni agensi. U okviru ovog rada, primenom modifikovanog mikrotalasnog postupka, sintetisani su pirolidin-2,5-dioni koji u položajima 1 i 4 sadrže meta i/ili para-supstituisanu fenil-grupu. Njihova struktura potvrđena je određivanjem temperature topljenja, primenom FT-IR/ATR, ^{1}H NMR, ^{13}C NMR i UV-Vis spektroskopskih metoda i elementarne analize. Položaj apsorpcionih maksimuma novosintetisanih jedinjenja u različitim rastvaračima razmatran je sa apsekta specifičnih i nespecifičnih interakcija koje se uspostavljaju između molekula rastvorene supstance i molekula rastvarača. Uticaj hemijske strukture na farmakološki potencijal derivata pirolidin-2,5-diona, procenjen je primenom „pravila broja pet“, Veberovog, Eganovog i Gozovog emirijskog kriterijuma, kao i primenom različitih in silico metoda. Dobijene vrednosti molekulskih deskriptora potom su upoređene sa vrednostima karakterističnim za referentne lekove kao što su metosukcinimid i etosukcinimid. Dobijene vrednosti molekulskih deskriptora ukazuju da proučavana jedinjenja zadovoljavaju sve empirijske kriterijume neophodne za dalja ispitivanja lekova.

Ključne reči: *Pirolidin-2,5-dion; Mikrotalasna sinteza; Solvatohromizam, Farmakološka aktivnost.*

Succinimide (pyrrolidine-2,5-dione) derivatives represent organic compounds with a broad spectrum of pharmacological activity. Succinimide derivatives are well known anticonvulsants (ethosuccinimide, metosuccinimide and fensuccinimide), antipsychotics, sedatives, anticancer and antiviral agents. In this work, using a modified microwave procedure, succinimide derivatives bearing a meta and/or para-substituted phenyl group in position 1 and 4 were synthetized and completely structurally characterized by melting point, FT-IR/ATR, ^{1}H NMR, ^{13}C NMR and UV-Vis spectra and elemental analysis. The position of the absorption maxima of newly synthesized compounds in different solvents is considered from the aspect of specific and nonspecific interactions established between the molecules. The influence of the chemical structure on the pharmacological potential of succinimide derivatives was evaluated using the "rule of five", Veber, Egan and Ghose's empirical criteria, as well as using different in silico methods. The obtained values of molecular descriptors were then compared with the characteristic values for reference drugs such as methosuccinimide and ethosuccinimide. Calculated molecular descriptors indicate that the investigated compounds fulfill necessary empirical criteria which qualify them as interesting drug candidates.

Key words: *Pyrrolidine-2,5-dione; Microwave synthesis; Solvatochromism; Pharmacological activity.*

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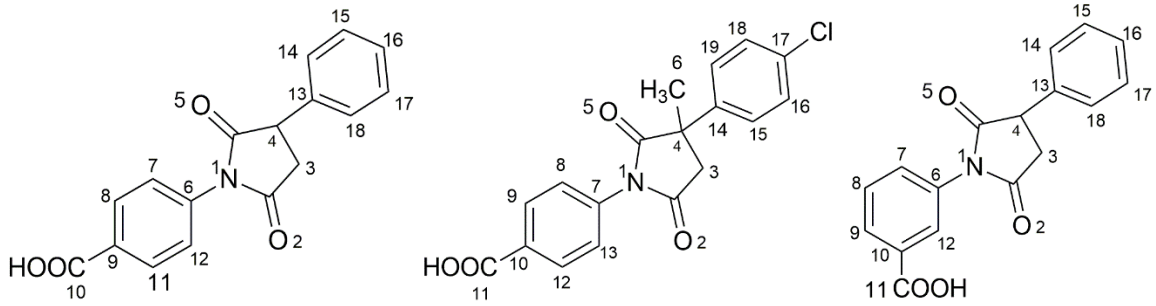
1 Introduction

A large number of five-membered heterocyclic molecules which represent very interesting structural motifs in the synthesis of new potentially pharmacologically active compounds are known in the literature. Succinimide (pyrrolidine-2,5-dione) belongs to the group of cyclic imides whose synthetic analogues possess a wide range of activities. Namely, derivatives of this five-membered heterocycle are widely used as antiepileptics (anticonvulsants), CNS depressants, analgesics, antitumor drugs, cytostatics, antituberculotics, antimicrobial/antifungal agents [1].



(1) (2) (3)

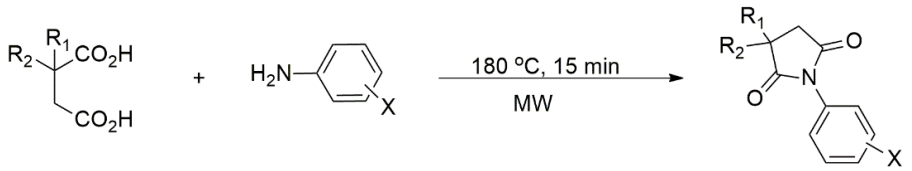
Figure 1*. The chemical structure of the investigated compounds.*

Succinimide derivatives are mainly used in medicine as anticonvulsant drugs, under the names zarontin, milontin and celontin. In addition, a large number of 2-arylsuccinimides such as 3-phenyl-2,3-dimethylsuccinimide and its *N*-methyl derivative exhibit anticonvulsant properties and are generally used in the treatment of milder forms of epilepsy because they do not induce sedation. Disubstituted analogs such as *N*-methyl-2-phenyl-2-ethyl- and N-methyl-2-phenyl-3-methylsuccinimides are examples of non-toxic antiepileptics suitable for minor forms of seizures. Derivatives of this cyclic core are used in the treatment of various disorders of the central and peripheral nervous system, primarily tremors, partial tremors associated with Parkinson's disease and multiple sclerosis [2]. As part of the study of the relationship between the structure and pharmacological activity of succinimide derivatives, three new derivatives (Figure 1) were synthesized using a modified microwave procedure known from the literature. All these compounds were synthesized for the first time in this paper and were completely structurally characterized by different spectroscopic techniques. The solvatochromic properties of these cyclic imides were analyzed by determining the UV-absorption maxima in the selected set of solvents and correlating the achieved values of the absorption maxima with different solvent parameters using the appropriate linear equations. The assessment of the pharmacokinetic profile was performed by predicting their ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties, i.e. bioavailability, using various empirical rules and software packages.

2 Experimental

2.1 General procedure for the synthesis of disubstituted pyrrolidine-2,5- diones

Disubstituted pyrrolidine-2,5-dione derivatives were synthesized according to a modified method from the literature (Scheme 1). The disubstituted succinic acid (1 mol) was mixed with the corresponding monosubstituted aniline (1.16 mol) in a microwave synthesis reactor and then the resulting reaction mixture was heated at 180 °C for 15 minutes. After cooling to room temperature, the product formed is purified by recrystallization from ethanol.



R_1	R_2	X
CH_3	4-Cl-C_6H_4-	4-CO_2H
H	C_6H_5-	4-CO_2H
H	C_6H_5-	3-CO_2H

Compounds	R_1	R_2	X
1	CH_3	4-Cl-C_6H_4-	4-CO_2H
2	H	C_6H_5-	4-CO_2H
3	H	C_6H_5-	3-CO_2H

Scheme 1. *Synthesis of the investigated compounds.*

4-(3-(4-Chlorophenyl)-3-methyl-2,5-dioxopirrolidine-1-yl)benzoic acid (1): White crystalline solid; Yield: 66%; m.p. = 163−172°C, FTIR/ATR (ν/ cm^{-1}): 1696, 13 (C=O), 1682 (C=O), 1674 (C=O), 1662, 1635, 1626, 1622, 1595, 1574, 1558, 1526, 1520, 1512, 1496, 1454, 1440, 1422, 1384, 1344, 1309, 1286, 1281, 1234, 1169, 1128, 1002, 964, 865, 842, 821, 768, 695, 533, 528, 520, 504, 472, 461, 451; ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 11.0 (s, 1H, COOH), 8.07 (d, 2H, *J* = 8.4 Hz, C_6H_4), 7.51 (d, 2H, *J* = 10.0 Hz, C_6H_4), 7.37 (d, 2H, *J* = 8.4 Hz, C_6H_4), 7.27 (d, 2H, *J* = 8.4 Hz, C_6H_4), 3.59 (s, 1H, -CH-), 3.09–2.92 (m, 2H, -CH_2-), 1.78 (s, 3H,-CH_3-); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 175.8 (C2), 174.9 (C5), 169.3 (C11), 137.1 (C7), 134.1 (C14), 133.2 (C17), 131.0 (C15,19), 130.5 (C9,12), 129.3 (C16,18), 124.3 (C8,13), 45.6 (C3,4), 24.5 (C6); Elementary analysis: Calculated for: $C_{18}H_{14}ClNO_4$ (343.76): C, 62.89; H, 4.10; N, 4.07; Found (%):C, 63.05; H, 4.26; N, 4.07.

4-(2,5-Dioxo-3-phenylpyrrolidine-1-yl)benzoic acid (2): White crystalline solid; Yield: 72%; m.p. = 172−175°C, FTIR/ATR (ν/ cm^{-1}): 1705, (C=O), 1682, (C=O), 1604, (C=O), 1585, 1491, 1422, 1383, 1366, 1310, 1271, 1197, 1184, 1169, 1125, 1095, 927, 829, 792, 766, 768, 719, 703, 669, 646, 631, 540, 515, 503, 435; ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 11.0 (s, 1H, COOH), 8.04 (d, 2H, *J* = 8.4 Hz, -C_6H_4-), 7.46 (d, 2H, *J* = 8.4 Hz, -C_6H_4-), 7.40–7.27 (m, 5H, -C_6H_5-), 4.01 (s, 1H, -CH-), 3.15–2.90 (m, 2H, -CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 176.5 (C2), 170.7 (C5), 169.6 (C10), 136.3 (C13), 130.5 (C8,11), 129.6 (C14,18), 129.2 (C15,17), 128.5 (C9), 127.6 (C16), 124.3 (C7,12), 38.0 (C4), 32.9 (C3); Elementary analysis: Calculated for $C_{17}H_{13}NO_4$ (295.29): C, 69.15; H, 4.44; N, 4.74; Found (%):C, 69.00; H, 4.69; N, 4.74.

3-(2,5-Dioxo-3-phenylpyrrolidine-1-yl)benzoic acid (3): White crystalline solid; Yield: 76%; m.p. = 193−196°C, FTIR/ATR (ν/ cm^{-1}): 1700, (C=O), 1682, (C=O), 1653, (C=O), 1603, 1588, 1497, 1425, 1387, 1310, 1280, 1234, 1190, 1178, 1167, 1127, 1101, 1076, 1017, 950, 928, 865, 767, 749, 696, 645, 638, 615, 519, 502, 489, 474, 466; ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 11.0 (s, 1H, COOH), 8.45 (s, 1H, -C_6H_4-), 7.95 (s, 1H, -C_6H_4-), 7.77 (s, 1H, -C_6H_4-), 7.64 (s, 1H, -C_6H_4-), 7.49–7.31 (m, 5H, -C_6H_5-), 3.56 (s, 1H, -CH-), 2.75–2.50 (m, 2H, -CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 176.5 (C2), 170.7 (C5), 166.3 (C11), 136.3 (C13), 135.2 (C7), 133.3 (C9,12), 133.1 (C6,8), 129.6 (C14,18), 129.2 (C15,17), 128.3 (C10),

127.6 (C16), 38.0 (C4), 32.9 (C3); Elementary analysis: Calculated for $C_{17}H_{13}NO_4$ (295.29): C, 69.15; H, 4.44; N, 4.74; Found (%): C, 69.06; H, 4.50; N, 4.74.

2.2 Methods for the characterization of the synthesized compounds

All synthesized compounds were characterized using the following experimental techniques:

- FT-IR/ATR, ^{1}H NMR, ^{13}C NMR spectroscopy to confirm chemical structure,
- Absorption spectroscopy for solvatochromic analysis.

The FT-IR/ATR spectra of all synthesized compounds were recorded in the wavelength range 400–4000 cm^{-1} using a Bomem MB Series spectrophotometer. NMR spectra were recorded on a Bruker 300 spectrophotometer at 400 MHz and 100 MHz. All spectra were recorded at room temperature in deuterated dimethylsulfoxide (DMSO-d_6). Chemical shifts are expressed in ppm relative to the reference TMS (tetramethylsilane) (δH = 0 ppm) in the 1H NMR spectra, and the residual solvent signal DMSO (δC = 39.5 ppm) in the 13C NMR spectra.

The 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} in the wavelength range 200–400 nm. The obtained UV-Vis spectra in ethanol is presented in Figure 2 and the values of absorption maxima are given in Table 1. Elemental analysis of all studied compounds was performed using a microanalyzer of the element Elemental Vario EL III.

2.3 In silico optimization of the synthesized compounds

Prediction of the potential pharmacological activity of the newly synthesized compounds was performed using a set of empirical methods for which the values of molecular descriptors were determined using various online software packages (Molinspiration [3], SwissADME [4], PreADMET [5], PkcSM [6] and DataWarrior [7]).

3 Results and discussion

3.1 Solvatochrome analysis

The solvatochromic properties of the new succinimides (**1–3**) were investigated by determining the appropriate UV-Vis absorption spectra in a selected set of solvents of different polarity in the wavelength range 200–400 nm. Representative UV-Vis spectra in ethanol is presented in Figure 2 and the values of absorption maxima are given in Table 1.

***Table 1**: Wavelengths of the absorption maxima of investigated compounds (**1–3**) in a selected set of solvents.*

λ_{max} (nm)				
Compound/Solvent	Methanol	Ethanol	1-Propanol	Acetonitrile
1	223	222	225	224
2	288	281	288	284
3	228 282	229	258 281	238 274
Referent compound [11]	213	216	218	/

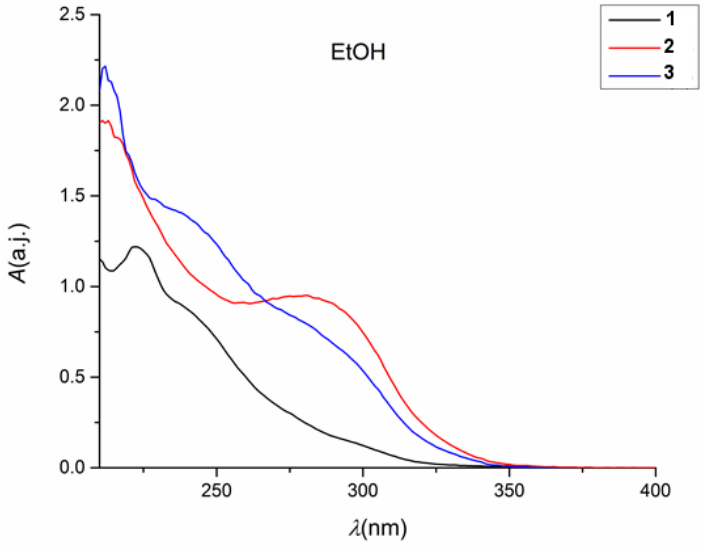


***Figure 2**: Absorption spectra of investigated compounds (**1–3**) in ethanol.*

The observed trends in the shift of absorption maxima are in accordance with previous results achieved for succinimide derivatives [8–10]. Namely, the absorption spectra of all studied compounds are characterized by the presence of one dominant band originating from the $\pi \rightarrow \pi^*$ transition and corresponding to the absorption maximum of lower energy. In addition, on the absorption spectrum

of 3-(2,5-dioxo-3-phenylpyrrolidin-1-yl)benzoic acid (**3**), a wide band of lower intensity in the range of wavelengths of 275–290 nm is present. Table 1 shows that the introduction of substituents in the *m*- and/ or *p*-position of the phenyl group results in a batochromic shift of the absorption maxima in polar protic solvents relative to the previously synthesized unsubstituted succinimide derivative, i.e. 3-methyl-1,3-diphenylpyrrolidine-2,5-dione taken as reference compound [11]. From obtained data, it can be concluded that *m*/*p*-substituents on the phenyl core attached to the *N*-atom of the succinimide ring have the greatest influence on the shift of the absorption maxima. The redshift of the absorption maxima of the studied disubstituted succinimides is a consequence of $\pi \rightarrow \pi^*$ transitions involving the π-electronic system of the mentioned molecules. π–delocalization is mostly the result of the transfer (displacement) of the π-electron density from the phenyl core to the carbonyl groups of the succinimide ring as a consequence of the electronic effects of the substituents present. In addition, the planarity of the studied molecules also contributes to the resonant transfer of π-electron density from the phenyl core to the succinimide ring, which results in a batochromic shift of the absorption maxima. The change in the polarity of the solvent has a weaker effect on the shift of the absorption maxima in all studied molecules.

3.2 Multiparametric optimization of molecular descriptors of disubstituted succinimides

The main goal of rational drug design and drug evaluation is to establish a quantitative relationship between structure and calculated molecular parameters based on the chemical structure and physicochemical characteristics of molecules on the one hand, and their pharmacological role in the body on the other. To create new anticonvulsants, the pharmacokinetic profile of disubstituted succinimides (**1**–**3**) was assessed by predicting their ADMET properties, i.e. bioavailability, by applying different empirical rules and appropriate software packages. The use of computer methods in the rational design of drugs (Computer-Aided Drug Design), enables more efficient and economical detection of new drugs, as well as optimization of their properties. For the theoretical assessment of the existence of pharmacological activity, the rules of good bioavailability are most often applied, among which the most well-known is the Lipinski's "rule of five". In accordance with the "rule of number five", good oral absorption can be expected for compounds whose set of physicochemical parameters is in the following ranges: partition coefficient (logP) < 5, number of hydrogen bond donors (HBD) < 5, number of hydrogen bond acceptors (HBA) < 10 , relative molecular weight (MW) < 500. Molecules that are considered to have properties similar to standard drugs must not show more than one deviation from Lipinski's rule. According to Veber's criteria, adequate oral bioavailability is achieved in molecules that have less than 10 rotatable bonds (nrb) and a topological polar surface area (TPSA) of less than 140 $Å^2$. According to the modified versions of these two concepts, in the case of compounds whose physicochemical properties satisfy the following ranges: 160 ≤ relative molecular mass; –0.4 ≤ WlogP < 5.6; 40 ≤ molar refractivity (MR) ≤ 130; 20 ≤ number of atoms (NA) ≤ 70 (Ghose's criteria) and WlogP ≤ 5.88, TPSA < 131.6 Å2 (Egan's criteria), there is a high probability of therapeutic effects [12].

***Table 2**. Physico-chemical properties of the investigated compounds [3,4].*

Compound	MW, g/mol	NA	nrb	HBD	HBA	MR	TPSA, $Å^2$
1	343.76	24	3	1	4	92.63	74.68
2	295.29	22	3	1	4	82.93	74.68
3	295.29	22	3	1	4	82.93	74.68
metho-succini-mide	203.24	15	1	0	2	60.42	37.38
etho-succini-mide	141.17	10	1	1	2	40.51	46.17

Table 3*. Values of the partition coefficient of the investigated compounds [4].*

Compound	$logP_{o/w}$ (XLOGP3)	$logP_{o/w}$ (WLOGP)	$logP_{o/w}$ (MLOGP)
1	2.91	2.88	3.28
2	1.93	2.05	2.54
3	1.93	2.05	2.54
methosuccinimide	1.20	0.95	1.91
ethosuccinimide	0.38	0.07	0.65

Based on the values of molecular descriptors covered by these rules (Tables 2 and 3), it can be concluded that the examined succinimide derivatives meet all the stated empirical criteria, i.e. meet the theoretical condition for adequate bioavailability and the appropriate pharmacological potential [12]. When compared with standard anticonvulsant succinimides such as metosuccinimide and ethosuccinimide, the introduction of substituents at the succinimide ring results in an increase in molecular weight. Based on the calculated value of the polar surface of the molecules (Table 2), it is expected that in *in vivo* conditions, the tested succinimide derivatives will show better intestinal absorption and passage through the blood-brain barrier. A moderate number of rotatable bonds that do not exceed 3 in all compounds, also contribute to the optimal passage of the studied molecules through the blood-brain barrier. According to the literature data, drugs that act on the central nervous system should have less than 8 rotatable bonds [12].

The data illustrated in Table 3, show that different values of the partition coefficient were obtained for the same compound, which is a consequence of a different mathematical algorithm for calculating this parameter within the software packages used. The highest values of the partition coefficient were obtained for 4-(3-(4-chlorophenyl)-3-methyl-2,5-dioxopyrrolidin-1-yl)benzoic acid (**1**), which allows this molecule to pass more successfully through the blood-brain barrier to passive diffusion as well as more successful binding to active sites at appropriate receptors, which is especially important for achieving the optimal concentration of drugs that act on the central nervous system.

According to the physico-chemical characteristics of potentially pharmacologically active derivatives of succinimide, for the assessment and optimization of the efficacy, it is necessary to know their pharmacokinetics. Using the relevant software packages, the pharmacokinetic potential of the newly synthesized compounds was predicted by determining the most important molecular descriptors. The obtained results (Tables 4 and 5) show that all studied molecules show a good predisposition for optimal intestinal absorption as well as that these values are similar to those determined for the reference drugs methosuccinimide and ethosuccinimide. Also, using appropriate software packages, the interaction of individual investigated cyclic ureides with cytochrome P450 isoenzymes (CYP450) such as: CYP1A2, CYP2C19, CYP2C9, CYP2D6 was confirmed. The results presented in Table 5 indicate that depending on the substituent present, the studied molecules may act as activators and inhibitors of individual isoenzymes. It is important to note that the newly synthesized compounds do not have tumorigenic potential, which was confirmed by the application of the software package DataWarrior [12]. Based on the optimal values of molecular descriptors obtained by applying appropriate computer programs, it can be concluded that the succinimide derivatives synthesized in this paper meet all the necessary empirical criteria which further qualifies them as interesting candidates for drugs.

4 Conclusion

In order to create new anticonvulsant drugs, succinimide derivatives which in positions 1 and 4 possess *meta*- and/or *para*-substituted phenyl group have been synthesized. The chemical structure of the newly synthesized compounds was confirmed by determining the melting point, FT-IR/ATR, ^{1}H NMR, ^{13}C NMR and UV-Vis spectra and elemental analysis. The results of the solvatochromic analysis show that the absorption spectra of all studied compounds are characterized by the presence

of one dominant band originating from the $\pi \rightarrow \pi^*$ transition and corresponding to the absorption maximum of lower energy. The introduction of substituents in the *meta*- and/or *para*-position of the phenyl core results in a batochromic shift of the absorption maxima in polar protic solvents relative to the unsubstituted succinimide derivative, i.e. 3-methyl-1,3-diphenylpyrrolidine-2,5-dione used as reference compound. The influence of the chemical structure on the pharmacological potential of succinimide derivatives was assessed by applying the "rule of five", Veber's, Egan's and Ghose's empirical criteria, as well as by applying various *in silico* methods. Compared to the reference drugs metosuccinimide and ethosuccinimide, all synthesized molecules have good intestinal absorption and passage through the blood-brain barrier and depending on the nature of the substituent present in the *meta*/*p*ara-position of the phenyl core may act as potential activators/inhibitors of individual P450 isoenzymes.

Table 4. *Pharmacokinetic profile of the investigated compounds-Absorption*

	SwissADME	pkCSM	SwissADME	PreADMET	SwissADME	PreADMET
Compound	Gastrointestinal absorption	Gastrointestinal absorption %	The compound penetrates the blood-brain barrier	The compound penetrates the blood-brain barrier (C_{brain}/C_{blood})	The compound is a P-gp inhibitor	The compound is a P-gp inhibitor
1	High	97.45	Yes	-0.487	No	No
2	High	98.78	Yes	-0.288	No	No
3	High	99.18	Yes	-0.288	No	No
methosuccinimide	High	95.89	Yes	-0.018	No	No
ethosuccinimide	High	93.49	Yes	-0.267	No	No

Table 5. *Pharmacokinetic profile of the investigated compounds-Metabolism and Toxicity.*

	[4]	[6]	[4]	[6]	[4]	[6]	[4]	[6]	[7]
Compound	The compound is an inhibitor of the enzyme CYP1A2	The compound is an inhibitor of the enzyme CYP1A2	The compound is an inhibitor of the enzyme CYP2C19	The compound is an inhibitor of the enzyme CYP2C19	The compound is an inhibitor of the enzyme CYP2C9	The compound is an inhibitor of the enzyme CYP2C9	The compound is an inhibitor of the enzyme CYP2D6	The compound is an inhibitor of the enzyme CYP2D6	The compound possess mutagenic / tumourigenic potential
1	No	No	Yes	Yes	Yes	Yes	No	No	No
2	No	No	No	No	No	No	No	No	No
3	No	No	No	No	No	No	No	No	No
methosuccinimide	No	No	No	No	No	No	No	No	No
ethosuccinimide	No	No	No	No	No	No	No	No	No

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M72