CHEMIJA. 2011. Vol. 22. No. 1. P. 65–72

Synthesis and structure of 3,3'-[(4-alkoxyphenyl)imino] bis(N'-phthaloyl- or N'-benzylidenepropanohydrazide) derivatives

Ingrida Tumosienė[1],

Gema Mikulskienė[2],

Kristina Kantminienė[3],

Zigmuntas J. Beresnevičius[1]*

[1] *Department of Organic Chemistry, Kaunas University of Technology, Radvilėnų pl. 19, LT-50254 Kaunas, Lithuania*

[2] *Department of Bioorganic Compounds Chemistry, Vilnius University Institute of Biochemistry, Mokslininkų 12, LT-08662 Vilnius, Lithuania*

[3] *Department of General Chemistry, Kaunas University of Technology, Radvilėnų pl. 19, LT-50254 Kaunas, Lithuania*

The title compounds were synthesized from the respective hydrazides and phthalic anhydride or aromatic aldehydes and characterized by elemental analysis, mass spectrometry, NMR spectra, and molecular modeling. The structural features of these disubstituted amines with different spatial arrangement of their identical substituents have been specifically reflected by ^{1}H and ^{13}C NMR spectra. An analysis of the inseparable mixtures of isomers existing in d_6-DMSO solution on purpose to ascertain the cause of a supplementary set of resonances in the NMR spectra of the study compounds is reported.

Key words: propanohydrazide, substituted amine, NMR spectra, isomers, molecular modeling

INTRODUCTION

N-Substituted β-amino acids and their derivatives are structural units of various natural compounds and exhibit a broad spectrum of biological activity. Acid hydrazides are synthons for the synthesis of various compounds, e. g., hydrazones and heterocyclic compounds, as reported previously [1, 2]. Hydrazones find application in electrophotography [3], dye synthesis, and polymer industry as plasticizers and stabilizers. Acid hydrazones exhibit anticonvulsive [4], anti-inflammatory, and antithrombotic activities [5]. Various hydrazones have been reported to possess antimicrobial [6–8] and antiproliferative properties [9]. It is natural to expect that increasing the number of functional groups or structural fragments in the molecule of the compound containing such a group or fragment and possessing useful properties will lead to the strengthening of those useful properties. Therefore, we have recently turned our attention to the disubstituted [10, 11] and tetrasubstituted amines [12]. On the other hand, acid hydrazones are interesting compounds for the structure investigation since they can exist as mixtures of rotamers and positional isomers in solutions due to the presence of an amide group and an azomethine fragment. NMR spectroscopy and molecular modeling have proved to be an exceptional tool for elucidating the structure and probable composition of isomers. Actually, experimental NMR spectra are the result of a statistically averaged molecular characteristic caused by the dynamic process such as conformational equilibrium as well

* Corresponding author. E-mail: zigmuntas.beresnevicius@ktu.lt

as intra and / or intermolecular interactions. The results are not completely consistent with those of the studies in which molecules possess one chain with amide and azomethine fragments [13–27].

The present study is a continuation of our efforts in the synthesis and investigation of amide and azomethine derivatives in the light of spectroscopic and computational methods.

RESULTS AND DISCUSSION

Dihydrazides **1** and **2** were synthesized by heating under reflux the appropriate 3,3'-(arylimino)di(propanoic acid) with hydrazine and subsequently removing the water formed [11]. The reaction of dihydrazides **1** and **2** with phthalic anhydride in dioxane at the reflux temperature provided phthaloyl hydrazides **3** and **4** (Scheme). Unreacted phthalic anhydride was hydrolyzed with aqueous Na_2CO_3 solution. Benzylidenehydrazides **5** and **6** were prepared by the synthesis method usual for hydrazones, i.e. respective dihydrazides **1** and **2** were heated under reflux with aromatic aldehydes in methanol.

The synthesized compounds were characterized by elemental analysis, mass spectrometry, and NMR spectra. Their structural features were investigated in detail by NMR spectroscopy and molecular modeling. The assignments of NMR resonances were based on the chemical shifts theory and signal intensity arguments, multiplicities, and a comparison with the structurally related compounds. Solutions for NMR spectra were prepared in d_6-DMSO whose interaction with the solute molecules had been reflected by NMR spectra. The NMR spectral analysis combined with molecular modeling allowed to perceive the isomer formation of the synthesized compounds in the d_6-DMSO solutions.

The characteristic resonances of quadruple intensity, observed in the aromatic region of ^{13}C NMR spectra at 129.5 ppm, 123.7 ppm, 135.2 ppm, and 165.1 ppm and attributed to C-3', C-4', C-5', and C-2' carbons, respectively, confirmed the presence of the phthaloyl group moiety in **3** and **4** [28, 29]. Traces of spectral lines attributed to the rotamers formed due to the amide fragment were found in the region of 9.9–10.9 ppm in ^1H NMR spectra.

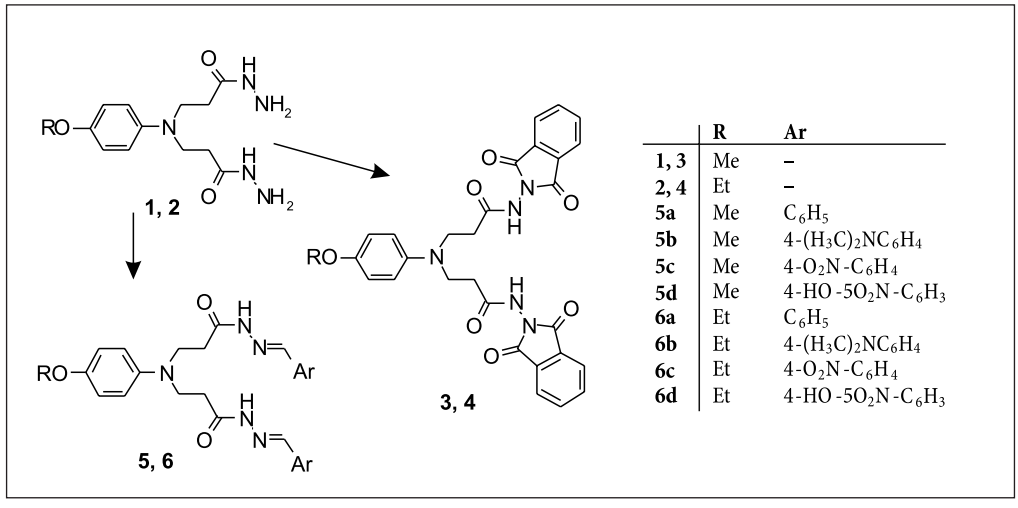
The isomer formation, the distribution of charges, the spatial arrangement of fragments, and the composition of close contacts in molecular models of benzilydenehydrazine derivatives **5** and **6** depend on the nature and location of the substituents of benzene in the azomethine group as well as on the conformation of the amide group, and are reflected by NMR spectra. The real NMR spectra of these compounds consist of a set of resonances corresponding to the stabile isomers or the time-averaged structures of the molecule present in the solution.

Theoretically, ten isomers of these compounds can be expected due to the presence of two identical aliphatic chains in their structure. Molecular models of all possible isomers were made and optimized (MM2) to the minimum of the total steric energy (Table 1). Attempts were made to relate these values with the probability of the existence of each isomer.

The dependence of the total steric energies on the structure of a particular isomer for the molecular models of **6** was analogous as the ones for **5**; therefore, data on **6** are not presented in Table 1.

The interlocation of aliphatic chains was different due to the *E* / *Z* distribution of amide fragments and *cis* / *trans* location in the azomethine group. It was perceived that both aliphatic chains in the molecules tried to occupy such a spatial position that would be convenient for the formation of close contacts between amides [11]. The measured (from model) lengths of close contacts (2.5–2.9 Å) were similar to the length of the hydrogen bond.

The isomers whose optimized models form one and two close contacts should be more stabile and possess a lower energy value as an illustration of the possibility of a real existence. Such tendency has not been observed among the data presented in Table 1. Consequently, it was concluded that in compounds of this structure, along with the intramolecular



	R	Ar
1, 3	Me	–
2, 4	Et	–
5a	Me	C_6H_5
5b	Me	$4\text{-}(H_3C)_2NC_6H_4$
5c	Me	$4\text{-}O_2N\text{-}C_6H_4$
5d	Me	$4\text{-}HO\text{-}5O_2N\text{-}C_6H_3$
6a	Et	C_6H_5
6b	Et	$4\text{-}(H_3C)_2NC_6H_4$
6c	Et	$4\text{-}O_2N\text{-}C_6H_4$
6d	Et	$4\text{-}HO\text{-}5O_2N\text{-}C_6H_3$

Scheme. Synthesis of 3,3'-[(4-alkoxyphenyl)imino]bis(N'-phthaloyl or N'-benzylidenepropanohydrazide) derivatives

Table 1. **Total steric energies of all possible isomers of models for 5**

Isomers*	Total steric energies of models for 5 (kJ/mol)			
	5a	5b	5c	5d
E/trans–E/trans	–62.57	–20.30	–53.15	–50.89
E/trans–E/cis	–59.47	–17.03	–55.66	–56.20
E/trans–Z/cis	–39.80	1.30	–14.40	–55.41
E/trans–Z/trans	–38.75	5.02	–22.85	–52.94
Z/trans–Z/trans	–33.56	2.59	–27.04	–47.29
Z/trans–E/cis	–34.53	4.73	–45.87	–44.53
Z/trans–Z/cis	–34.32	4.31	–32.56	–69.09
E/cis–E/cis	–44.74	2.72	–38.25	–91.15
E/cis–Z/cis	–30.89	11.09	–18.33	–68.68
Z/cis–Z/cis	–38.63	–8.41	–14.40	–60.01

* The conformation of the amide group / the configuration of the azomethine group of the first aliphatic chain – the conformation of the amide group / the configuration of the azomethine group of the second aliphatic chain.

bonds, there exist intermolecular bonds among donor–acceptor groups of the molecules of separate isomers or solvent molecules.

Usually, most information about the existing isomers can be obtained from the NH group resonances. The averaging of NH signals in ^{1}H NMR spectra complicated the analysis of the possible isomers.

A correlation between the total steric energy (Table 1) and the intensity of NH resonance (Fig. 1) was observed only in case of **5d**. The resonance of the most shielded hydrogen

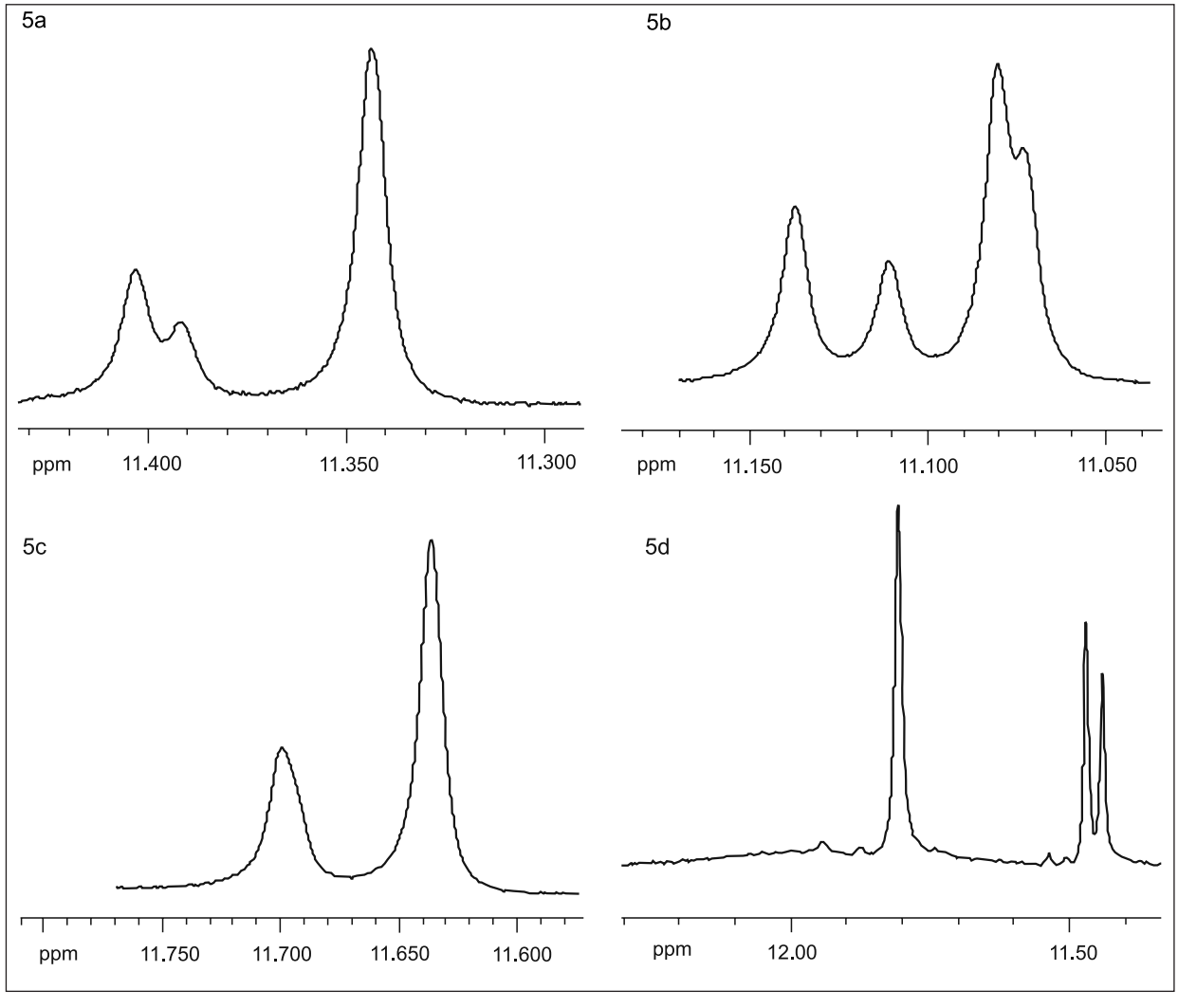


Fig. 1. Resonances of NH group in ^{1}H NMR spectra of **5**

of the NH group was assigned to the *Z*/*cis*–*Z*/*cis* isomer (total steric energy –60.01 kJ/mol), the adjacent one was assigned to the *E*/*cis*–*Z*/*cis* isomer (total steric energy –68.68 kJ/mol), and the resonance of the most deshielded hydrogen was ascribed to the *E*/*cis*–*E*/*cis* isomer (total steric energy –91.15 kJ/mol). A similar trend was observed in the ^{13}C NMR spectra of **5d**. In this case, more than one resonance was assigned to each carbon atom. Part of the aromatic region (resonances of carbon atoms of aromatic rings in the azomethine group) of **5d** is presented in Fig. 2. Each carbon atom of these aromatic rings resonated at three positions.

In the case of the *trans* location of the substituent in an azomethine fragment, no correlation between total steric energy and the intensity of resonances could be found. It should be concluded that the *cis* location of the substituent of the azomethine group dominated. As for compounds **5 a–c**, the resonances of NH protons were averaged from several states of the molecule.

The information obtained from models of compounds **5a** (*E*/*trans*–*E*/*trans* isomer) and **5d** (*E*/*cis*–*E*/*cis* isomer), presented in Fig. 3 and Table 2, was used to clarify the influence of the spatial location of the aliphatic chains on

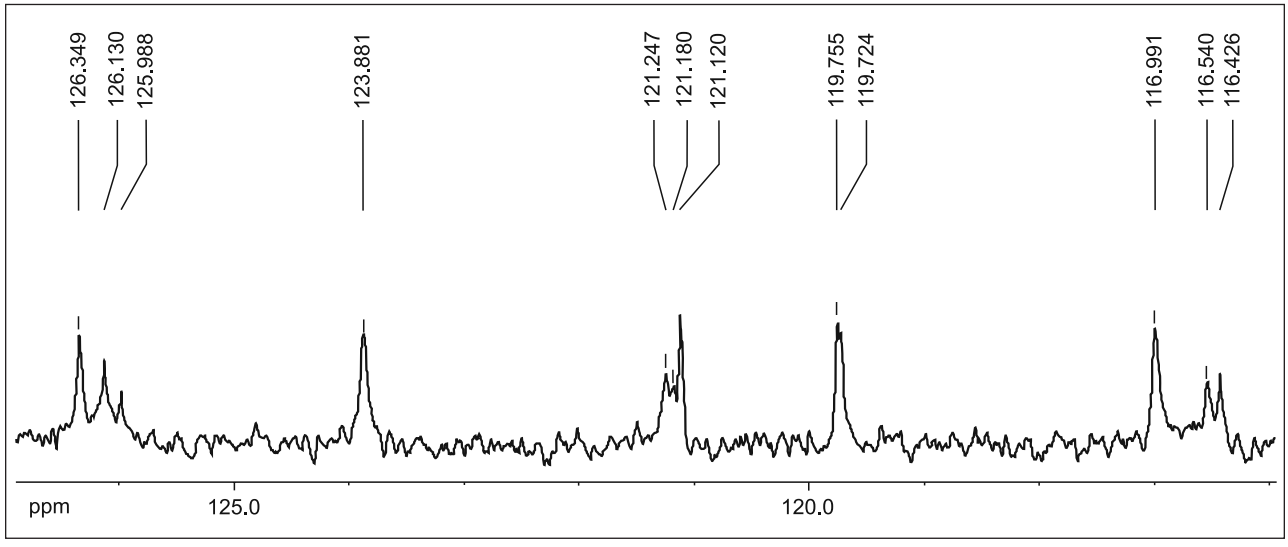


Fig. 2. Part of aromatic region in ^{13}C NMR spectra of **5d**

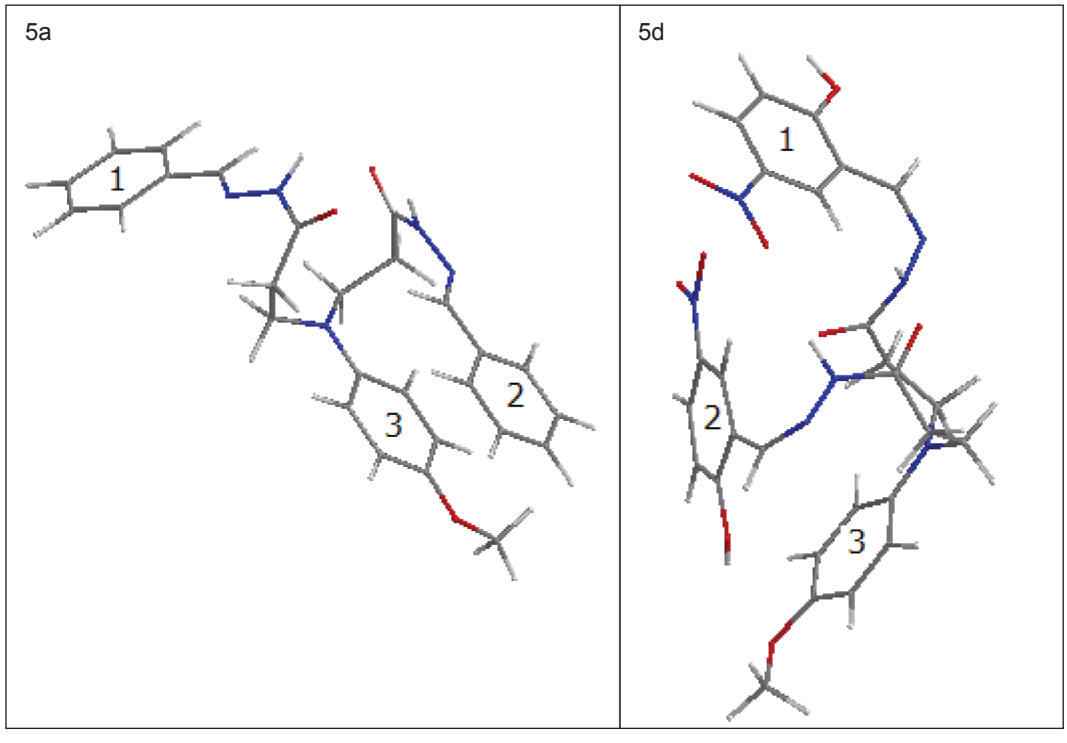


Fig. 3. A view of **5a** (*E*/*trans*–*E*/*trans* isomer) and **5d** (*E*/*cis*–*E*/*cis* isomer) models

Table 2. **Values of Hückel charges (a. u.) in 5a (*E/trans–E/trans* isomer) and 5d (*E/cis–E/cis* isomer) models**

Benzene rings	Atoms	Hückel charges		Aliphatic chains	Other atoms	Hückel charges	
		5a	5d			5a	5d
1	C-1′	0.037	–0.065	1	**C** = N	–0.032	0.022
	C-2′	–0.063	0.292		C = **N**	–0.063	–0.015
	C-3′	–0.026	–0.122		**N**H	0.434	0.363
	C-4′	–0.059	–0.009		**C** = O	0.407	0.372
	C-5′	–0.027	0.054		C = **O**	–0.743	–0.758
	C-6′	–0.060	–0.056		**C**H_2CO	–0.121	–0.124
2	C-1′	0.035	–0.061		**C**H_2N	0.022	0.030
	C-2′	–0.052	0.296		**O**H	–	–0.188
	C-3′	–0.029	–0.121		**N**O_2	–	1.264
	C-4′	–0.051	–0.005		N**O**$_2$	–	–0.746/–0.776
	C-5′	–0.026	0.034	Common	N	0.148	0.149
	C-6′	–0.054	–0.006	2	**C**H_2N	0.320	0.032
3	C-1	0.087	0.082		**C**H_2CO	–0.130	–0.125
	C-2	–0.164	–0.164		**C** = O	0.348	0.352
	C-3	–0.101	–0.105		C = **O**	–0.796	–0.780
	C-4	0.141	0.153		**N**H	0.446	0.388
	C-5	–0.112	–0.118		**C** = N	0.012	0.038
	C-6	–0.165	–0.164		C = **N**	–0.038	–0.065
	OCH_3	–0.211	–0.209		**O**H	–	–0.204
	O**C**H_3	0.078	0.079		**N**O_2	–	1.248
	–	–	–		N**O**$_2$		–0.773/–0.780

charge distribution. The models of **5a** and **5d** correspond to the lowest values of total steric energy (Table 1). Usually, substituents redistribute the charge in the molecules. The distribution of the charge of each aliphatic chain in these models also depends on their different spatial location (Table 2).

Very fast dynamic processes average the charge values of the corresponding atoms of each aliphatic chain for separate isomers, and consequently only a few sets of resonances are observed in the NMR spectra.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova (300 MHz) spectrometer operating in the Fourier transform mode. Chemical shifts (δ) are reported in parts per million (ppm), calibrated from TMS (0 ppm) as an internal standard for ^{1}H NMR, and d_6-DMSO (39.5 ppm) for ^{13}C NMR. Melting points were determined on an automatic APA1 melting point apparatus and are uncorrected. Mass spectra were obtained with a Waters (Micromas) ZQ 2000 spectrometer. The monitoring of the reaction course and of the purity of the synthesized compounds was carried out using TLC on Silufol 254 and Silufol UV-254 plates.

The molecular modeling of the study compounds was carried out using Chem 3D Ultra 9.0 (Licence Cambridge Software Package, Serial number 031 406391 4800).

3,3'-[(4-Methoxyphenyl)imino]di(propanohydrazide) (1) was synthesized as described in [11]. Yield 63%.

3,3'-[(4-Ethoxyphenyl)imino]di(propanohydrazide) (2) was synthesized as described in [11]. Yield 79%.

3,3'-[(4-Methoxyphenyl)imino]bis(N'-phthaloylpropanohydrazide) (3). A solution of **1** (1.47 g, 5 mmol), phthalic anhydride (2.95 g, 20 mmol) and dioxane (30 ml) was heated under reflux for 4 h, then water (20 ml) and Na_2CO_3 (1.6 g, 20 mmol) were added. The crystals formed were filtered and recrystallized from acetone and water mixture to get **3**. Yield 1.25 g (47%). M. p. 109–110 °C. ^{1}H NMR δ: 2.58 (t, 4H, *J* = 6.8 Hz, CH_2CO); 3.47–3.61 (m, 4H, CH_2N); 3.69 (s, 3H, OCH_3); 6.72–6.90 (m, 4H, H_{ar}); 7.90–7.99 (m, 8H, H_{phthal}); 9.89 (s, 0.2H, NH); 10.72 (s, 1.6H, NH); 10.86 (s, 0.2H, NH). ^{13}C NMR δ: 31.08 ($\underline{CH_2}$CO); 47.39 (CH_2N); 55.34 (CH_3O); 114.92 (C-2,6 + C-3,5); 123.72 (C-4'); 129.49 (C-3'); 135.23 (C-5'); 141.20 (C-1); 151.54 (C-4); 165.12 (C-2'); 167.31; 170.32 (CONH). MS (ESI, 20 V): *m/z* (%): 556 $[M + H]^+$ (90). Anal. calcd for $C_{29}H_{25}N_5O_7$, %: C, 62.69; H, 4.54; N, 12.61. Found, %: C, 62.49; H, 4.63; N, 12.31.

3,3'-[(Ethoxyphenyl)imino]bis(N'-phthaloylpropanohydrazide) (4) was prepared from **2** (1.54 g, 5 mmol) and phthalic anhydride (2.95 g, 20 mmol) according to the synthesis procedure of **3**. Yield 1.4 g (52%). M. p. 105–106 °C (from acetone–water mixture). ^{1}H NMR δ: 1.30 (t, 3H, *J* = 6.9 Hz, $\underline{CH_3}CH_2O$); 2.57 (t, 4H, *J* = 6.9 Hz, CH_2CO); 3.57 (t, 4H, *J* = 6.9 Hz, CH_2N); 3.94 (q, 2H, *J* = 6.9 Hz, $CH_3\underline{CH_2}O$); 6.67 (d, 2H, *J* = 9.3 Hz, H_{ar}); 6.87 (d, 2H, *J* = 9.3 Hz, H_{ar}); 7.91–7.98 (m, 8H, H_{phthal}); 9.89 (br s, 0.6H, NH); 10.73 (br s, 1.4H, NH). ^{13}C NMR δ: 14.86 ($\underline{CH_3}CH_2O$); 31.09 ($\underline{CH_2}$CO); 47.35 (CH_2N); 63.32

($CH_3\underline{CH_2}O$); 114.81 (C-2,6); 115.63 (C-3,5); 123.70 (C-4'); 129.48 (C-3'); 135.22 (C-5'); 141.16 (C-1); 150.70 (C-4); 165.10 (C-2'); 170.30 (CONH). MS (ESI, 20 V): *m/z* (%): 570 $[M + H]^+$ (100). Anal. calcd for $C_{30}H_{27}N_5O_{7,}$ %: C, 63.26; H, 4.78; N, 12.29. Found, %: C, 63.21; H, 4.76; N, 12.28.

General procedure for preparation of 3,3'-[(4-alkoxyphenyl)imino]bis[(N'-benzylidene)propanohydrazides] 5, 6. A mixture of dihydrazide **1** or **2** (5 mmol) and aromatic aldehyde (20 mmol) in methanol (100 ml) was heated under reflux and cooled down. The crystals formed were filtered, washed with diethyl ether, and recrystallized from DMF–water mixture.

3,3'-[(4-Methoxyphenyl)imino]bis[(N'-benzylidene)propanohydrazide] (5a) was prepared from **1** and benzaldehyde by refluxing the reaction mixture for 0.5 h. Yield 87 %. M. p. 202–203 °C (from DMF–water mixture). ^{1}H NMR δ: 2.41–2.52 (m, 1.6H, CH_2CO); 2.87–2.93 (m, 2.4H, CH_2CO); 3.51–3.66 (m, 4H, CH_2N); 3.67 (s, 3H, CH_3O); 6.76–6.87 (m, 4H, $H_{ar(2-6)}$); 7.37–7.67 (m, 10H, $H_{ar(2'-6')}$); 7.99, 8.00 (2 s, 1.2H, CH = N); 8.13, 8.14 (2 s, 0.8H, CH = N); 11.34 (s, 1.2H, NH); 11.39, 11.40 (2 s, 0.8H, NH). ^{13}C NMR δ: 30.19, 30.39 ($\underline{CH_2}CO$); 32.33, 32.53 ($\underline{CH_2}CO$); 47.01, 47.34 (CH_2N); 55.21, 55.26 (CH_3O); 113.91, 114.28 (C-2,6), 114.76, 115.08 (C-3,5); 126.64, 126.95 (C-2',6'); 128.71 (C-3',5'); 129.66, 129.87 (C-4'); 134.16, 134.26 (C-1'); 141.61, 141.66 (C-1); 142.97, 145.99 (CH = N); 150.96, 151.12 (C-4); 167.24, 167.30, 173.00 (CO). MS (ESI, 30 V): *m/z* (%): 472 $([M + H]^+$ (100). Anal. calcd for $C_{27}H_{29}N_5O_3$, %: C, 68.77; H, 6.20; N, 14.85. Found, %: C, 68.52; H, 6.11; N, 14.83.

3,3'-[(4-Methoxyphenyl)imino]bis[N'-(4-dimethylaminobenzylidene)propanohydrazide] (5b) was prepared from **1** and *p-N,N*-dimethylaminobenzaldehyde by refluxing the reaction mixture for 5 h. Yield 65%. M. p. 146–147 °C (from DMF–water mixture). ^{1}H NMR δ: 2.39–2.47 (m, 1.6H; CH_2CO); 2.81–3.00 (m, 2.4H, CH_2CO); 2.90, 2.91 (2 s, 7.2H, $N(CH_3)_2$); 2.94, 2.97 (2 s, 4.8H, $(CH_3)_2N$); 3.50–3.63 (m, 4H, CH_2N); 3.67, 3.68, 3.69 (3 s, 3H, CH_3O); 6.64–7.66 (m, 12H, H_{ar}); 7.88 (s, 1.2H, CH = N); 8.00 (s, 0.8H, CH = N); 11.07, 11.08 (2s, 1.2H, NH), 11.11, 11.14 (2 s, 0.8H, NH). ^{13}C NMR δ: 30.31, 30.51 ($\underline{CH_2}CO$); 32.27, 32.52 ($\underline{CH_2}CO$); 39.22, 39.75 ($(CH_3)_2N$); 47.01, 47.44 (CH_2N); 48.63 (CH_2N); 55.15, 55.22, 55.28 (CH_3O); 111.72 (C-3',5'); 113.77, 114.19 (C-2,6); 114.75, 115.07 (C-3,5); 121.58, 121.65 (C-1'); 127.93, 128.31 (C-2',6'); 129.24 (C-2',6'); 141.73, 141.81 (C-1); 143.73, 143.89 (CH = N); 146.85, 146.92 (CH = N); 150.85, 151.06, 151.92 (C-4); 151.18, 151.36 (C-4'); 166.64, 166.72, 172.42 (CO). MS (ESI, 30 V): *m/z* (%): 558 $[M + H]^+$ (100). Anal. calcd for $C_{31}H_{39}N_7O_3$, %: C, 66.76; H, 7.05; N, 17.58. Found, %: C, 66.89; H, 7.34; N, 17.39.

3,3'-[(4-Methoxyphenyl)imino]bis[N'-(4-nitrobenzylidene)propanohydrazide] (5c) was prepared from **1** and *p*-nitrobenzaldehyde by refluxing the reaction mixture for 0.5 h. Yield 80%. M. p. 182–183 °C (from DMF–water mixture). ^{1}H NMR δ: 2.86–2.91 (m, 1.6H, CH_2CO); 2.43–3.58 (m, 2.4H, CH_2CO); 3.50–3.66 (m, 4H, CH_2N); 3.66 (s, 3H, CH_3O); 6.74–8.23 (m, 12H, H_{ar}); 11.64 (s, 0.8H, NH); 11.70 (s, 1.2H, NH). ^{13}C NMR δ: 30.12, 30.30 ($\underline{CH_2}CO$); 32.39, 32.63 ($\underline{CH_2}CO$); 47.16, 47.37 (CH_2N); 55.14, 55.22 (CH_3O); 114.11, 114.42 (C-2,6); 114.78, 115.20 (C-3,5); 123.89, 124.24 (C-3',5'); 127.46, 127.84 (C-2',6'); 140.49, 140.65 (C-1'); 141.64, 141.65 (C-1); 143.54 (CH = N); 147.43 (C-4'); 147.67 (CH = N); 151.08, 151.22 (C-4); 167.81, 173.58 (CO). MS (ESI, 30 V): *m/z* (%): 562 $[M + H]^+$ (100). Anal. calcd for $C_{27}H_{27}N_7O_7$, %: C, 57.75; H, 4.85; N, 17.46. Found, %: C, 57.76; H, 5.12; N, 17.44.

3,3'-[(4-Methoxyphenyl)imino]bis[N'-(2-hydroxy-5-nitrobenzylidene)propanohydrazide] (5d) was prepared from **1** and 2-hydroxy-5-nitrobenzenecarbaldehyde by refluxing the reaction mixture for 1 h. Yield 85%. M. p. 240–241 °C (from DMF–water mixture). ^{1}H NMR δ: 2.44–2.56 (m, 2H, CH_2CO); 2.83–2.91 (m, 2H, CH_2CO); 3.53–3.68 (m, 4H, CH_2N); 3.60, 3.62, 3.67 (s, 3H, CH_3O); 6.70–8.47 (m, 12H, $H_{ar,}$ + CH = N); 11.44, 11.47 (2 s, 1H, NH); 11.81 (s, 1H, NH); 11.95 (br s, 2H, OH). ^{13}C NMR δ: 30.56, 30.30 ($\underline{CH_2}CO$); 32.25, 32.50 ($\underline{CH_2}CO$); 47.24, 47.37 (CH_2N); 47.67 (CH_2N); 114.27, 114.78, 115.19 (C-2,6 + C-3,5); 116.43, 116.54, 116.72 (C-3'); 119.72, 119.76, 121.12 (C-1'); 121.18, 121.25, 123.88 (C-6'); 125.99, 126.13, 126.34 (C-4'); 137.58, 137.65, 137.74, 139.81, 139.91 (C-5'); 141.43, 141.48 (CH = N); 141.70 (C-1); 142.93, 142.95 (CH = N); 151.20, 151.57 (C-4); 161.66, 161.75, 162.49 (C-2'); 167.53, 172.93, 173.93 (CO). MS (ESI, 45 V): *m/z* (%): 594 $[M + H]^+$ (50). Anal. Calcd for $C_{27}H_{27}N_7O_9$, %: C, 54.62; H, 4.58; N, 16.51. Found, %: C, 54.53; H, 4.35; N, 16.21.

3,3'-[(4-Ethoxyphenyl)imino]bis[(N'-benzylidene)propanohydrazide] (6a) was prepared from **2** and benzaldehyde by refluxing the reaction mixture for 0.5 h. Yield 86%. M. p. 180–181 °C (from DMF–water mixture). ^{1}H NMR δ: 1.28, 1.29 (2 t, 3H, J = 6.9 Hz, $\underline{CH_3}CH_2O$); 2.41–2.57 (m, 1.6H, CH_2CO); 2.82–2.91 (m, 2.4H, CH_2CO), 3.51–3.65 (m, 4H, CH_2N); 3.93 (q, 2H, J = 6.9 Hz, $CH_3\underline{CH_2}O$); 6.68–6.84 (m, 4H, $H_{ar(2-6)}$); 7.34–7.61 (m, 10H, $H_{ar(2-6)}$); 7.99, 7.98 (2 s, 1.2H, CH = N); 8.12, 8.14 (2 s, 0.8H, CH = N); 11.34 (s, 1.2H, NH); 11.39, 11.40 (2 s, 0.8H, NH). ^{13}C NMR δ: 14.85 ($\underline{CH_3}$ CH_2O); 30.20, 30.40 ($\underline{CH_2}CO$); 32.35, 32.55 ($\underline{CH_2}CO$); 46.99, 47.33 (CH_2N); 63.25 ($\underline{CH_3}CH_2O$); 113.92, 114.26 (C-2,6); 115.48 (C-3,5); 126.64, 126.96 (C-2',6'); 128.72 (C-3',5'); 129.67, 129.88 (C-4'); 134.16, 134.27 (C-1'); 141.58, 141.64 (C-1); 142.97, 145.99 (CH = N); 150.18, 150.32 (C-4); 167.25, 173.00 (CO). MS (ESI, 15 V): *m/z* (%): 486 $([M + H]^+$ (100). Anal. calcd for $C_{28}H_{31}N_5O_{2,}$ %: C, 69.26; H, 6.43; N, 14.42. Found, %: C, 69.19; H, 6.25; N, 14.40.

3,3'-[(4-Ethoxyphenyl)imino]bis[N'-(4-dimethylaminobenzylidene)propanohydrazide] (6b) was prepared from **2** and *p-N,N*-dimethylaminobenzaldehyde by refluxing the

reaction mixture for 5 h. Yield 71%. M. p. 112–113 ºC (from DMF–water mixture). ^{1}H NMR δ: 1.29 (t, 3H, *J* = 6.9 Hz, $\underline{CH_3}CH_2O$); 2.39–2.46 (m, 1.6H, CH_2CO); 2.80–2.88 (m, 2.4H, CH_2CO); 2.92, 2.93 (2 s, 7.2H, $(CH_3)_2N$); 2.95 (s, 4.8H, $(CH_3)_2N$); 3.47–3.66 (m, 4H, CH_2N); 3.92 (q, 2H, *J* = 6.9 Hz, $CH_3\underline{CH_2}O$), 6.65–7.49 (m, 12H, H_{ar}); 7.87 (2 s, 1.2H, CH = N); 8.00 (s, 0.8H, CH = N); 11.07 (s, 1.2H, NH), 11.10, 11.25 (2 s, 0.8H, NH). ^{13}C NMR δ: 14.88 ($CH_3\underline{CH_2}O$); 30.24, 30.44 ($\underline{CH_2}CO$); 32.33, 32.51 ($\underline{CH_2}CO$); 39.22, 39.78 ($N(CH_3)_2$); 47.07 (CH_2N); 47.42, 47.65 (CH_2N); 63.20, 63.25 ($CH_3\underline{CH_2}O$); 111.75 (C-3',5'); 113.80, 114.22 (C-2,6); 115.48, 115.77 (C-3,5); 121.57, 121.64 (C-1'); 127.96, 128.31 (C-2',6'); 141.58, 141.64, 141.69 (C-1); 143.82, 143.87 (CH = N); 146.83, 146.89 (CH = N); 151.19, 151.60 ((C-4), + (C-4')); 166.00, 166.69, 172.41 (CO). MS (ESI, 20 V): *m/z* (%): 572 $[M + H]^+$ (100). Anal. calcd for $C_{32}H_{41}N_7O_3$, %: C, 67.23; H, 7.23; N, 17.15. Found, %: C, 67.05; H, 7.29; N, 16.97.

3,3'-[(4-Ethoxyphenyl)imino]bis[N'-(4-nitrobenzylidene)propanohydrazide] (6c) was prepared from **2** and *p*-nitrobenzaldehyde by refluxing the reaction mixture for 0.5 h. Yield 86%. M. p. 187–188 ºC (from DMF–water mixture). ^{1}H NMR δ: 1.29–1.34 (m, 3H, $\underline{CH_3}CH_2O$); 2.43–2.58 (m, 1.6H, CH_2CO); 2.89–2.93 (m, 2.4H, CH_2CO); 3.29–3.45 (m, 1.6H, CH_2N); 3.55–3.68 (m, 2.4H, CH_2N); 3.88–3.98 (m, 2H, $CH_3\underline{CH_2}O$); 6.72–8.33 (m, 14H, H_{ar} + CH = N); 11.67 (s, 0.8H, NH); 11.74 (s, 1.2H, NH). ^{13}C NMR δ: 14.82 ($\underline{CH_3}CH_2O$); 30.04, 30.26 ($\underline{CH_2}CO$); 32.44, 32.67 ($\underline{CH_2}CO$); 47.26, 47.39 (CH_2N); 63.14, 63.22 ($CH_3\underline{CH_2}O$); 114.21, 114.46 (C-2,6); 115.35, 115.43 (C-3,5); 123.81, 123.91 (C-3',5'); 127.44, 127.83, 127.91 (C-2',6'); 140.44, 140.65 (C-1'); 141.55 (C-1); 143.52 (CH = N); 147.40 (C-4'); 147.66 (CH = N); 150.37, 150.47 (C-4); 167.80, 173.61 (CO). MS (ESI, 30 V): *m/z* (%): 576 $[M + H]^+$ (100). Anal. calcd for $C_{28}H_{29}N_7O_7$, %: C, 58.43; H, 5.08; N, 17.03. Found, %: C, 58.02; H, 4.99; N, 17.01.

3,3'-[(4-Ethoxyphenyl)imino]bis[N'-(2-hydroxy-5-nitrobenzylidene)propanohydrazide] (6d) was prepared from **2** and 2-hydroxy-5-nitrobenzenecarbaldehyde by refluxing the reaction mixture for 1 h. Yield 65%. M. p. 222–223 ºC (from DMF–water mixture). ^{1}H NMR δ: 1.21–1.29 (m, 3H, $\underline{CH_3}CH_2O$); 2.43–2.58 (m, 2H, CH_2CO); 2.83–2.91 (m, 2H, CH_2CO); 3.53–3.65 (m, 4H, CH_2N); 3.78–3.94 (m, 2H, $CH_3\underline{CH_2}O$); 6.68–8.48 (m, 12H, H_{ar} + CH = N); 11.45, 11.48 (2 s, 1H, NH); 11.82 (s, 1H, NH); 11.95 (br s, 2H, OH). ^{13}C NMR δ: 30.31, 30.56 ($\underline{CH_2}CO$); 32.26, 32.54 ($\underline{CH_2}CO$); 47.23, 47.37 (CH_2N); 47.69, 47.79 (CH_2N); 114.08, 114.26, 115.14, 115.47 (C-2,6 + C-3,5); 116.42, 116.53, 116.53, 116.99 (C-3'); 119.74, 121.11 (C-1'); 121.19, 121.26, 123.88 (C-6'); 125.97, 126.11, 126.34 (C-4'); 137.54, 137.71, 139.80, 139.90 (C-5'); 141.42 (CH = N); 141.65 (C-1), 142.93 (CH = N); 150.41, 150.76 (C-4); 161.63, 161.74, 162.51 (C-2'); 167.54, 172.95, 173.10 (CO). MS (ESI, 30 V): *m/z* (%): 608 $[M + H]^+$ (100). Anal. Calcd for $C_{28}H_{29}N_7O_9$: C, 55.35; H, 4.81; N, 16.14. Found: C, 55.65; H, 5.11; N, 15.89.

CONCLUSIONS

3,3'-[(4-Alkoxyphenyl)imino]bis(N'-benzylidenepropanohydrazide) derivatives were synthesized from the corresponding dihydrazides on treatment with aromatic aldehydes or phthalic anhydride.

The synthesized compounds were characterized by the elemental analysis, mass spectrometry, and NMR spectra. Their structural features were investigated in detail by NMR spectroscopy and molecular modeling.

Theoretically, ten isomers of these compounds can be expected. In the case of 3,3'-[(4-methoxyphenyl)imino]bis[N'-(2-hydroxy-5-nitrobenzylidene)propanohydrazide], it was possible to note that the substituent of the azomethine group was located in the *cis* position.

Received 14 October 2010
Accepted 21 October 2010

References

1. I. Tumosienė, K. Kantminienė, A. Pavilonis, Ž. Maželienė, Z. J. Beresnevičius, *Heterocycles*, **78**, 59 (2009).
2. I. Tumosienė, Z. J. Beresnevičius, *Monatsh. Chem.*, **140**, 1523 (2009).
3. V. Getautis, J. V. Gražulevičius, M. Daškevičienė, T. Malinauskas, V. Jankauskas, J. Sidaravičius, A. Undzėnas, *Eur. Polymer J.*, **43**, 3597 (2007).
4. J. V. Ragavendran, D. Sriram, S. K. Patel, I. V. Reddy, N. Bharathwajan, J. Stables, P. Yogeeswari, *Eur. J. Med. Chem.*, **42**, 146 (2007).
5. S. Rollas, G. Kűçűkgűzel, *Molecules*, **12**, 1910 (2007).
6. C. Loncle, J. M. Brunel, N. Vidal, M. Dherbomez, Y. Letourneux, *Eur. J. Med. Chem.*, **39**, 1067 (2004).
7. K. A. Metwally, L. M. Abdel-Aziz, E. M. Lashine, M. I. Husseiny, R. H. Badawy, *Bioorg. Med. Chem. Lett.*, **14**, 8675 (2006).
8. A. J. M. Rasras, T. H. Al-Tel, A. F. Al-Aboudi, R. A. Al-Qawasmeh, *Eur. J. Med. Chem.*, **45**, 2307 (2010).
9. W.-Y. Liu, H.-Y. Li, B.-X Zhao, D.-S. Shin, S. Lian, J.-Y. Miao, *Carbohydr. Res.*, **344**, 1270 (2009).
10. I. Tumosienė, E. Jakienė, Z. J. Beresnevičius, G. Mikulskienė, *Cheminė technologija*, **3**, 58 (2006).
11. I. Tumosienė, I. Z. J. Beresnevičius, K. Kantminienė, G. Mikulskienė, *Chemija*, **19**, 44 (2008).
12. V. Novikovaitė, E. Jakienė, Z. J. Beresnevičius, G. Mikulskienė, *Cheminė technologija*, **2**, 33 (2006).
13. S. H. Huang, Z. W. Bai, J. W. Feng, *Magn. Reson. Chem.*, **47**, 423 (2009).
14. C. Zalaru, F. Dumitrascu, C. Draghici, E. Cristea, I. Tarcomnicu, *Arkivoc*, **ii**, 308 (2009).
15. C. O'Callaghan, T. B. H. McMurry, J. E. O'Brien, *J. Chem. Res.* (S), **453**, (M) 1101 (2001).
16. D. S. María, R. M. Claramunt, I. Alkorta, J. Elguero, *Magn. Reson. Chem.*, **47**, 472 (2009).
17. A. M. Pansuriya, M. M. Savant, C. V. Bhuva, J. Singh, Y. T. Naliapara, *Arkivoc*, **vii**, 79 (2009).

18. I. Iriepa, A. I. Madrid, E. Gálvez, J. Bellanato, *J. Mol. Struct*., **787**, 8 (2006).
19. M. Sayyed, S. Mokle, M. Bokhare, A. Mankar, S. Surwase, S. Bhusare, Y. Vibhute, *Arkivoc*, **i**, 187 (2006).
20. K. J. Puri, R. Singh, V. K. Chahal, R. P. Sharma, *Arkivoc*, **xi**, 247 (2009).
21. H. Kagechika, T. Himi, E. Kawachi, K. Shudo, *J. Med. Chem*., **32**, 2292 (1989).
22. H. Suezawa, T. Yuzuri, M. Hirota, Y. Ito, Y. Hamada, *Bull. Chem. Soc. Jpn*., **62**, 328 (1900).
23. R. Benassi, A. Benedetti, F. Taddei, R. Cappelletti, D. Nardi, A. Tajana, *Org. Magn. Reson.*, **20**, 26 (2005).
24. R. Quintanilla-Licea, J. Colunga-Valladares, A. Caballero-Quintero, C. Rodríguez-Padilla, R. Tamez-Guerra, R. Gómez-Flores, N. Waksman, *Molecules*, **7**, 662 (2002).
25. N. Díaz, D. Suárez, R. T. L. Sordo, *Eur. J. Org. Chem*., **4**, 793 (2001).
26. H. S. V. Deepak, A. Joy, N. Suryaprakash, K. V. Ramanathan, *Magn. Reson. Chem*., **42**, 409 (2004).
27. L. Lefrançois, M. Hébrant, C. Tondre, J. J. Delpuech, C. Berthon, C. Madic, *J. Chem. Soc. Perkin. Trans.*, **2**, 1149 (1999).
28. A. K. Singh, J. Sooriyakumar, M. Kadarkaraisamy, J. E. Drake, M. B. Hursthouse, M. E. Light, R. J. Butcher, *Polyhedron*, **21**, 667 (2002).
29. H. Ceric, M. Šindler-Kulyk, *Arkivoc*, **vii**, 237 (2009).

Ingrida Tumosienė, Gema Mikulskienė, Kristina Kantminienė, Zigmuntas J. Beresnevičius

3,3'–[(4-ALKOKSIFENIL)IMINO]BIS(N'-FTALOIL- ARBA N'-BENZILIDENPROPANHIDRAZIDŲ) DARINIŲ SINTEZĖ IR STRUKTŪROS TYRIMAS

S a n t r a u k a

3,3'-[(4-Alkoksifenil)imino]bis(N'-ftaloil- arba N'-benzilidenpropanhidrazidai) susintetinti iš atitinkamų dihidrazidų, veikiant pastaruosius ftalio rūgšties anhidridu arba aromatiniais aldehidais. Gautųjų junginių struktūra įrodyta, panaudojant elementinės analizės, masių spektrometrijos ir BMR spektrų duomenis. Šių dipakeistų aminų struktūros ypatybės ištirtos BMR spektroskopijos ir molekulių modeliavimo metodais. Jų molekulės d_6-DMSO tirpale egzistuoja izomerų mišinių pavidalu ir teoriškai jos gali sudaryti dešimt izomerų. Dėl vidinių ir tarpmolekulinių sąveikų bei skirtingo amino pakaitų išsidėstymo erdvėje kai kurios struktūros yra energetiniu požiūriu palankesnės, o tai sąlygoja papildomų linijų rinkinių atsiradimą BMR spektruose.