

**Using the Ni-[(Benzylpropyl)amino]benzophenone complex in the Glaser reaction for the synthesis of bis  $\alpha$ -amino acids**

Anna F. Mkrtchyan<sup>a,b\*</sup>, Liana A. Hayriyan<sup>b</sup>, Ani J. Karapetyan<sup>a,b</sup>, Anna S. Tovmasyan<sup>a,b</sup>, Avetis H. Tsaturyan<sup>a,b</sup>, Victor N. Khrustalev<sup>c,d</sup>, Viktor I. Maleev<sup>e</sup>, Ashot S. Saghyan<sup>a,b</sup>

<sup>a</sup>*Institute of Pharmacy, Yerevan State University, 1 Alex Manoogian Str., 0025 Yerevan, Armenia*

<sup>b</sup>*Scientific and Production Center "Armbiotechnology" of NAS RA, 14 Gyurjyan Str., 0056 Yerevan, Armenia*

<sup>c</sup>*Peoples' Friendship University of Russia (RUDN University). 117198 Moscow, Russian Federation;*

<sup>d</sup>*N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation;*

<sup>e</sup>*A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

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# 1. General Experimental Details

All the alkyl halides were obtained from commercial sources and used without further purification. The initial **1 (a-e)** complexes were prepared from following literature data [1,2]. TLC analyses were performed on glass plates coated with silica gel 60 F<sub>254</sub>. Column chromatography was performed on silica gel (60×120 mesh) on a glass column. Mps (mp) were determined by «Elektrothermal». <sup>1</sup>H and <sup>13</sup>C NMR spectra («Mercury-300 Varian» 300 MHz respectively) were recorded using TMS as an internal standard (0 ppm). Elemental analyses were done by elemental analyzer EURO EA 3000. The enantiomeric purity of the amino acids was determined by HPLC («Waters Alliance 2695 HPLC System») on the chiral phase Diaspher-110- Chirasil-E-PA 6:0 mkm 4.0 x 250 mm, and a mixture of 20% of MeOH and of 80% of a 0:1 M aqueous solution of NaH<sub>2</sub>PO<sub>4</sub> x 2H<sub>2</sub>O was used as the eluent. The optical rotation was measured on a Perkin Elmer-341 polarimeter. X-ray diffraction data were collected on a three-circle Bruker APEX-II CCD diffractometer ( $\lambda$ MoK $\alpha$ -radiation, graphite monochromator,  $\varphi$  and  $\omega$  scan mode) and corrected for absorption using the SADABS program [3]. The data were indexed and integrated using the SAINT program [4]. The initial complexes **1 (a-e)** were used in the form of an enantiomerically pure (*S,S*)-diastereomer, as expected, all amino acids were obtained with a high diastereomeric excess, since epimerization of the C $_{\alpha}$ -chiral center of the amino acid moiety in the studied cross-coupling systems was excluded. Obtaining crystals of dimeric complex **3a** is confirmed (*S*)-absolute configuration of its amino acid moiety. In addition, compound **3b** was selected to check the enantiomeric purity of the synthesized amino acids via HPLC on a chiral-phase column. The enantiomeric purity from starting material **2b** (*ee* >99%) was maintained during the Glaser reaction and subsequent cleavage gave **3b** with *ee* >99%.

## 2. General procedure: Glaser cross-coupling reaction

To a mixture of **1 (a-e)** (1.0 eq.) and of copper iodide (1 eq.) was added 20 mL solution of 1,4-dioxane and 20 mL solution of triethyl amine. The reaction mixture was stirred at 90 °C temperature under the air for 12-24 h. The reaction was monitored by TLC. The reaction mixture was extracted by chloroform, and then got rid of the deposits of copper iodide. The product was purified by column chromatography using EtOAc/CHCl<sub>3</sub> = 3:1 as eluent (SiO<sub>2</sub>).

## 3. General procedure: Isolation of amino acids

Isolation of amino acids from the complexes were carried out according to the following literature data<sup>5</sup>. The suspension of the complex in CH<sub>3</sub>OH was slowly added to a vigorously stirred 2 M aqueous HCl solution at 50-60 °C. The amino acid was isolated from the aqueous layer on Dowex-50 (H<sup>+</sup> form).

## 4. HPLC on a chiral phase of 3b

### HPLC-Waters2695

Separations Module – Waters 2487, Dual Absorbance Detector

**Column:** BioChem Mack (Russian)

**Sorbent:** 110-CHirasel-E

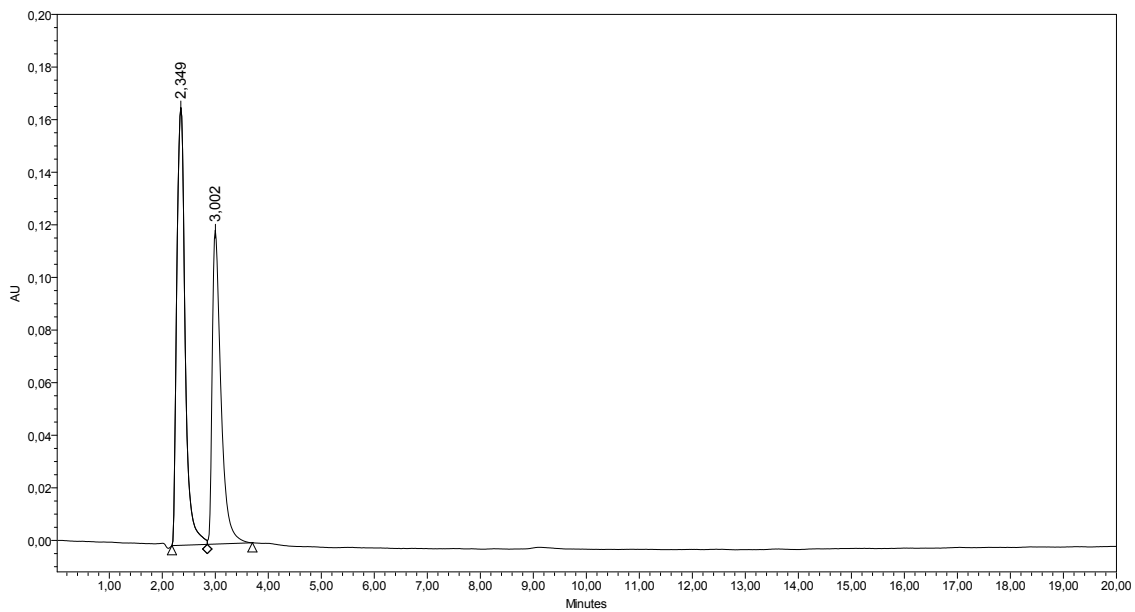
**Eluent:** 95% H<sub>2</sub>O + HClO<sub>4</sub> (pH 3)

5% MeCN

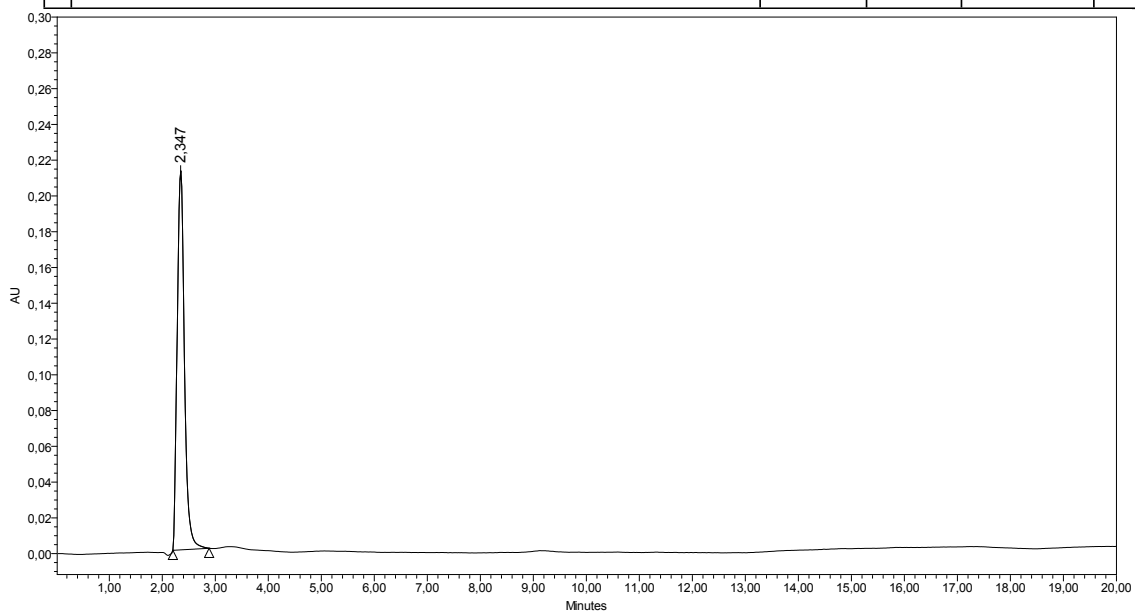
**Flow:** 0.3

**Det (UV):** 200 nm

**time:** 30 min



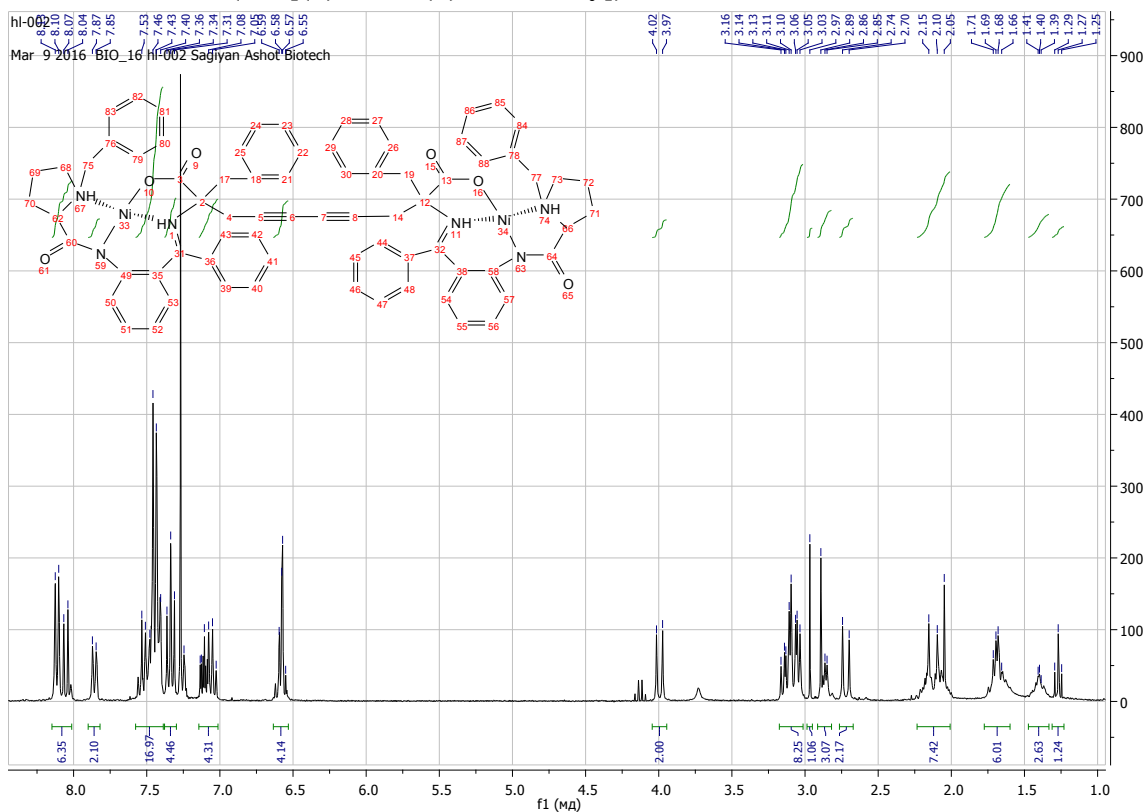
	Name	Retention Time	Area	% Area	Height
1	<b>(S,S)- 2,9-diamino-2,9-dibenzyldeca-4,6-diynedioic acid (3b)</b>	2,349	1829656	57,31	166784
2	<b>(R,R)- 2,9-diamino-2,9-dibenzyldeca-4,6-diynedioic acid</b>	3,002	1363141	42,69	119372



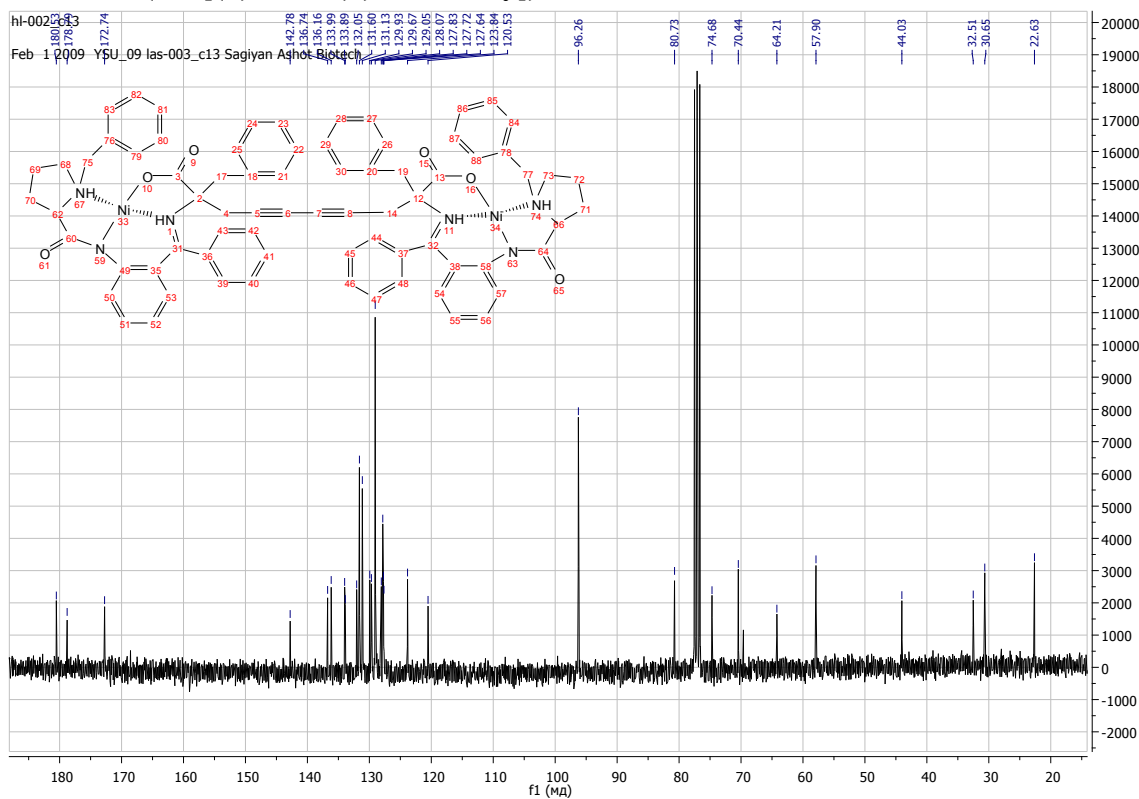
	Name	Retention Time	Area	% Area	Height
1	<b>(S,S)- 2,9-diamino-2,9-dibenzyldeca-4,6-diynedioic acid (3b)</b>	2,347	2024939	100,00	212387

# 5. NMR Spectra

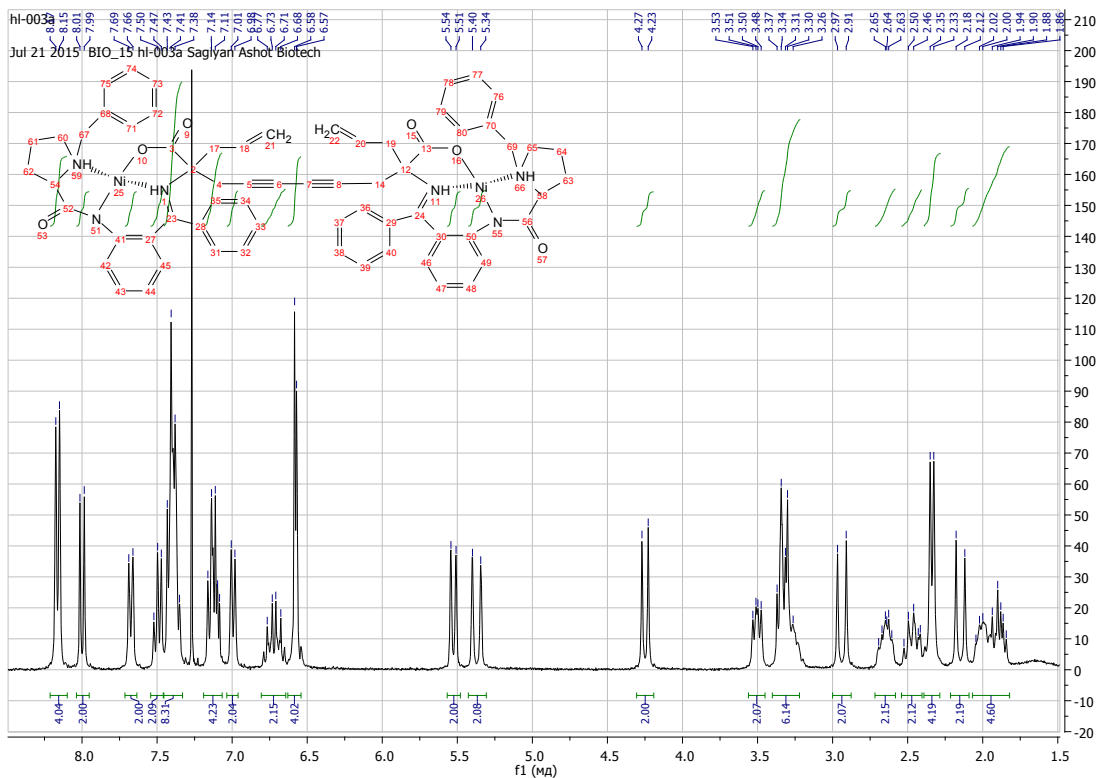
## 2b, $^1\text{H}$ NMR *Bis*-( $\text{Ni}^{\text{II}}$ [(*S*)-BPB-(*S*)-Bnz-PGly]), $\text{CDCl}_3$



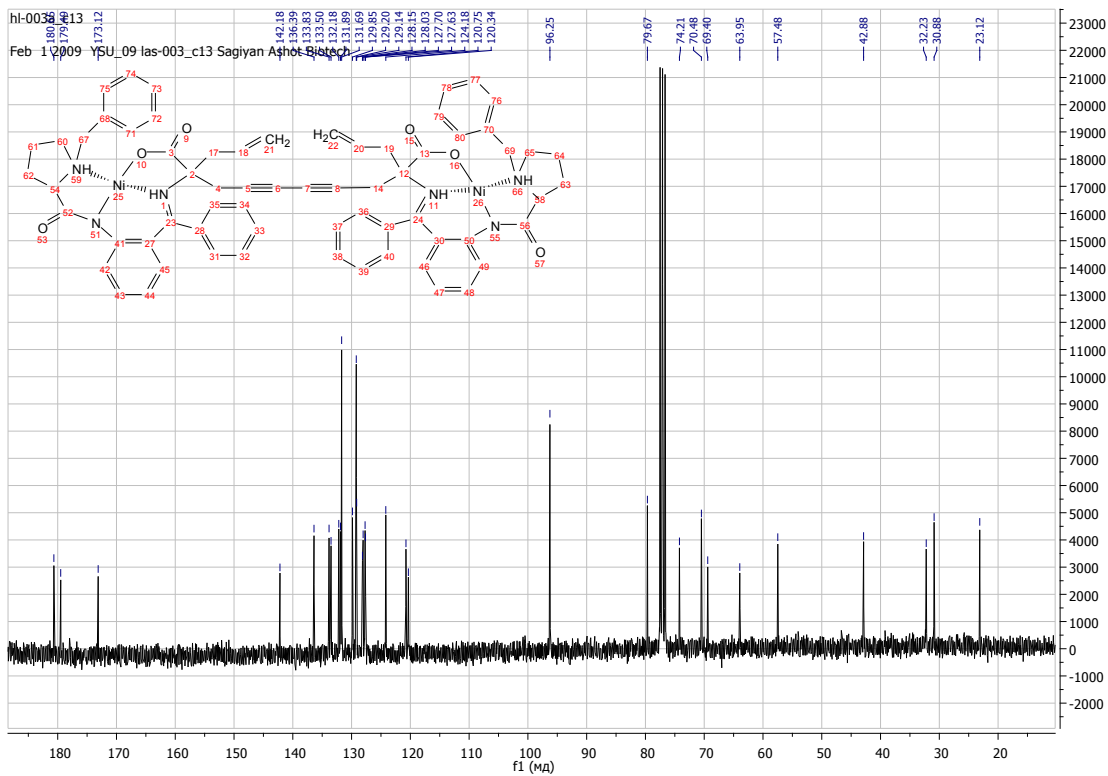
## 2b, $^{13}\text{C}$ NMR *Bis*-( $\text{Ni}^{\text{II}}$ [(*S*)-BPB-(*S*)-Bnz-PGly]), $\text{CDCl}_3$



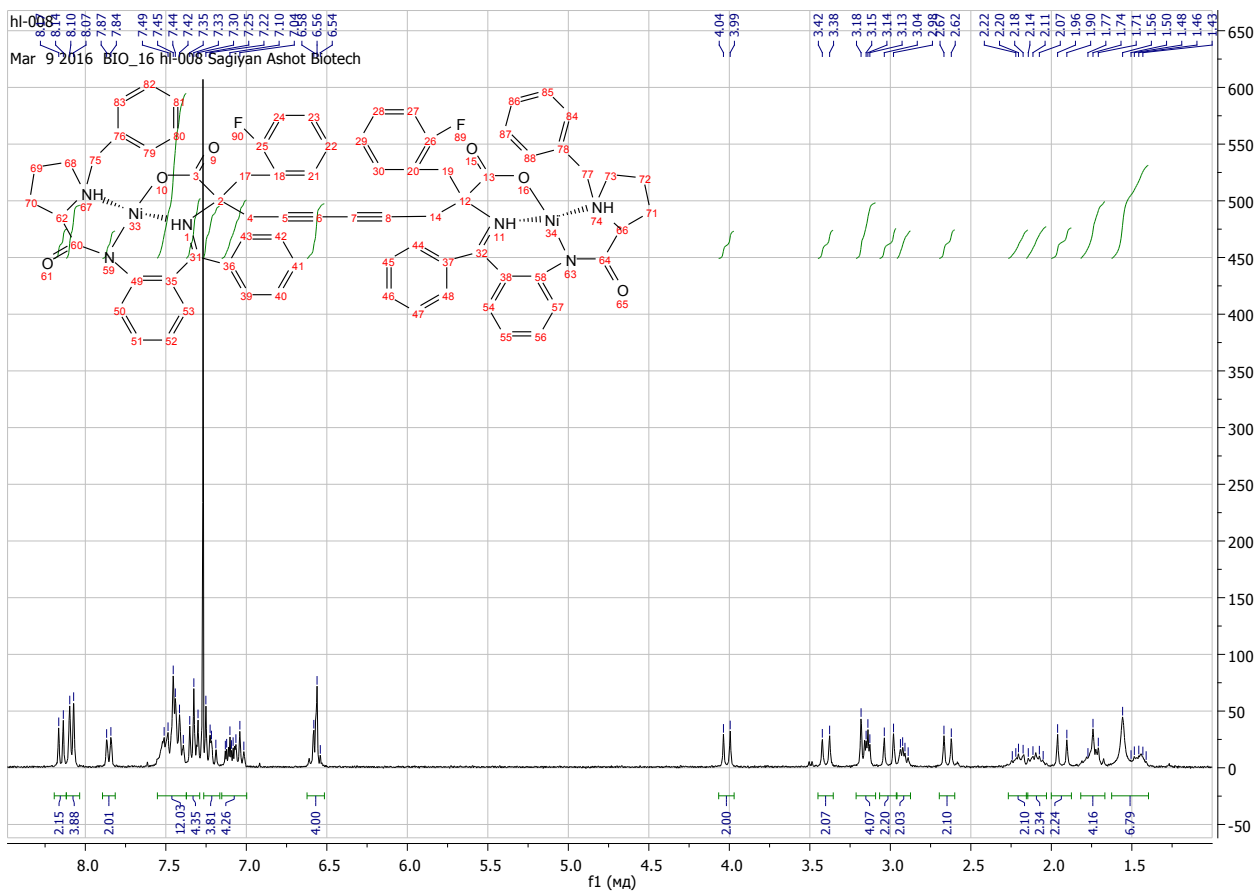
**2c,  $^1\text{H}$  NMR Bis- (Ni<sup>II</sup>[(S)-BPB-(S)-Allyl-PGly]), CDCl<sub>3</sub>**



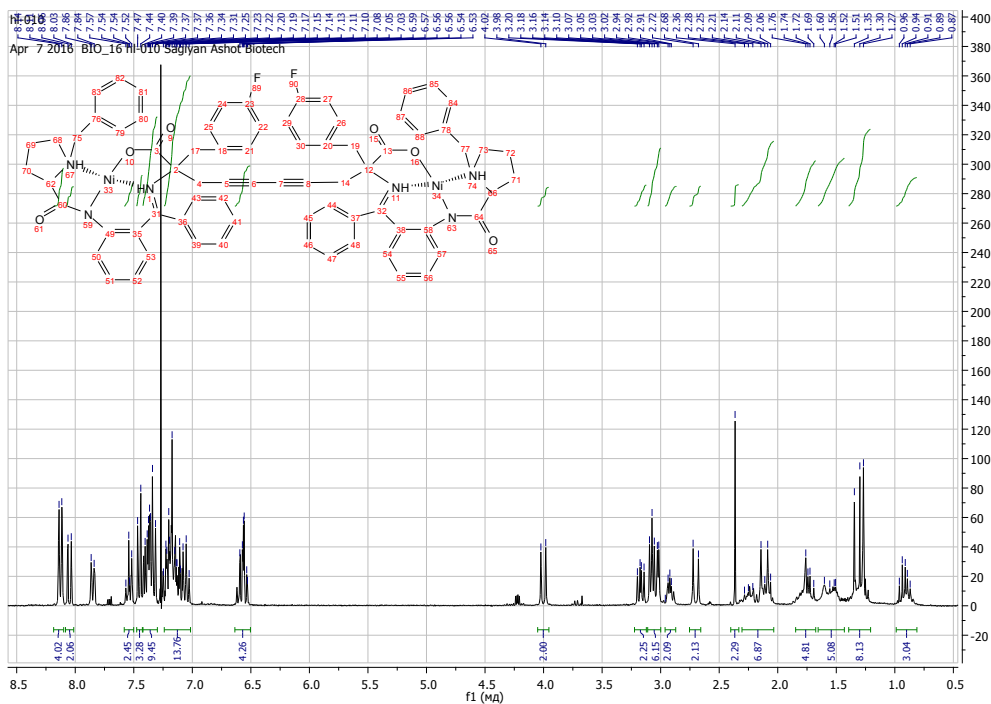
**2c,  $^{13}\text{C}$  NMR Bis- (Ni<sup>II</sup>[(S)-BPB-(S)-Allyl-PGly]), CDCl<sub>3</sub>**



**2d, <sup>1</sup>H NMR Bis-(Ni<sup>II</sup>[(S)-BPB-(S)-2-F-Bnz-PGly]), CDCl<sub>3</sub>**

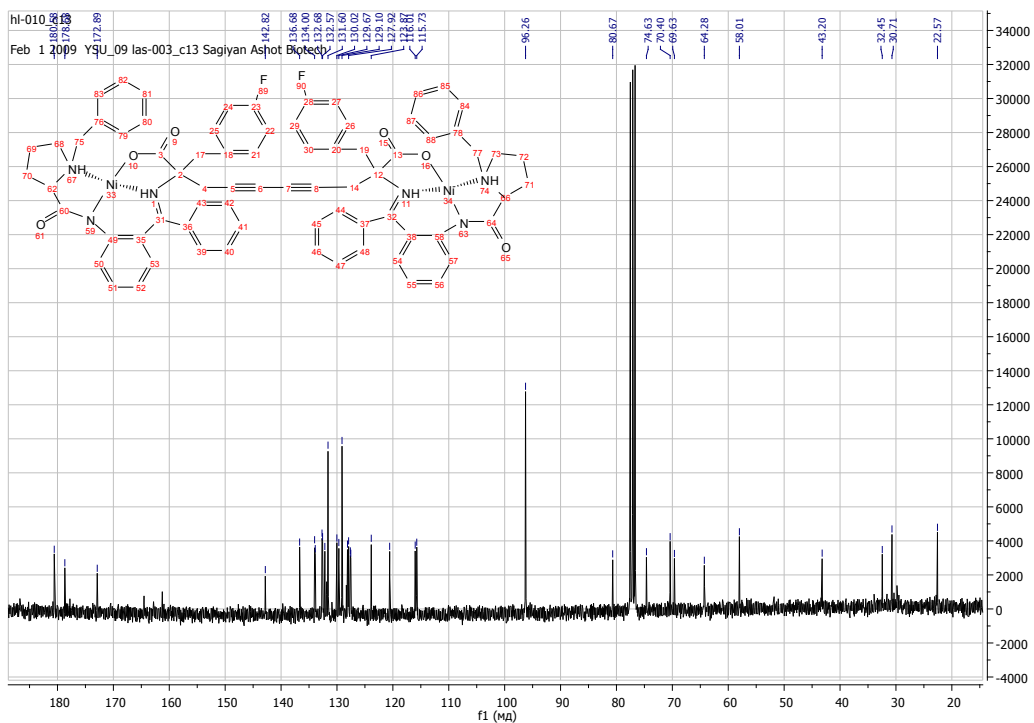


**2e, <sup>1</sup>H NMR Bis-(Ni<sup>II</sup>[(S)-BPB-(S)-4-F-Bnz-PGly]), CDCl<sub>3</sub>**

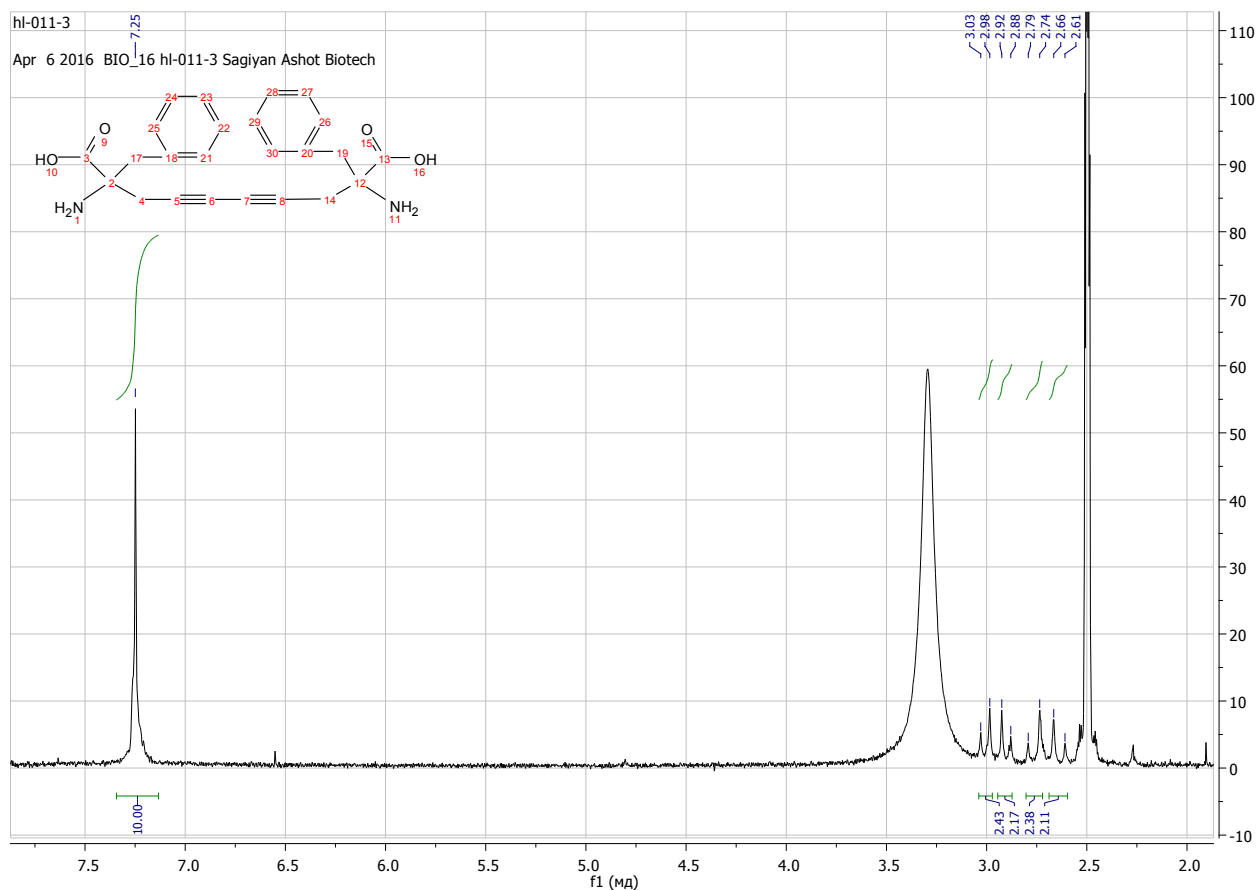




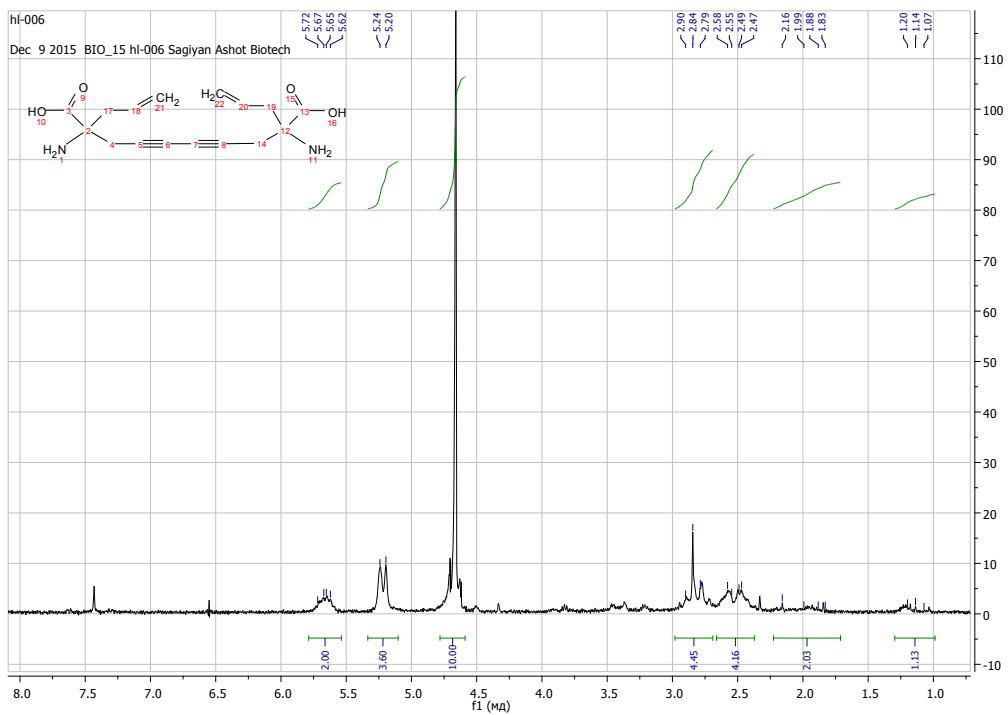
**2e,  $^{13}\text{C}$  NMR Bis- (Ni<sup>II</sup>[(S)-BPB-(S)-4-F-Bnz-PGly]), CDCl<sub>3</sub>**



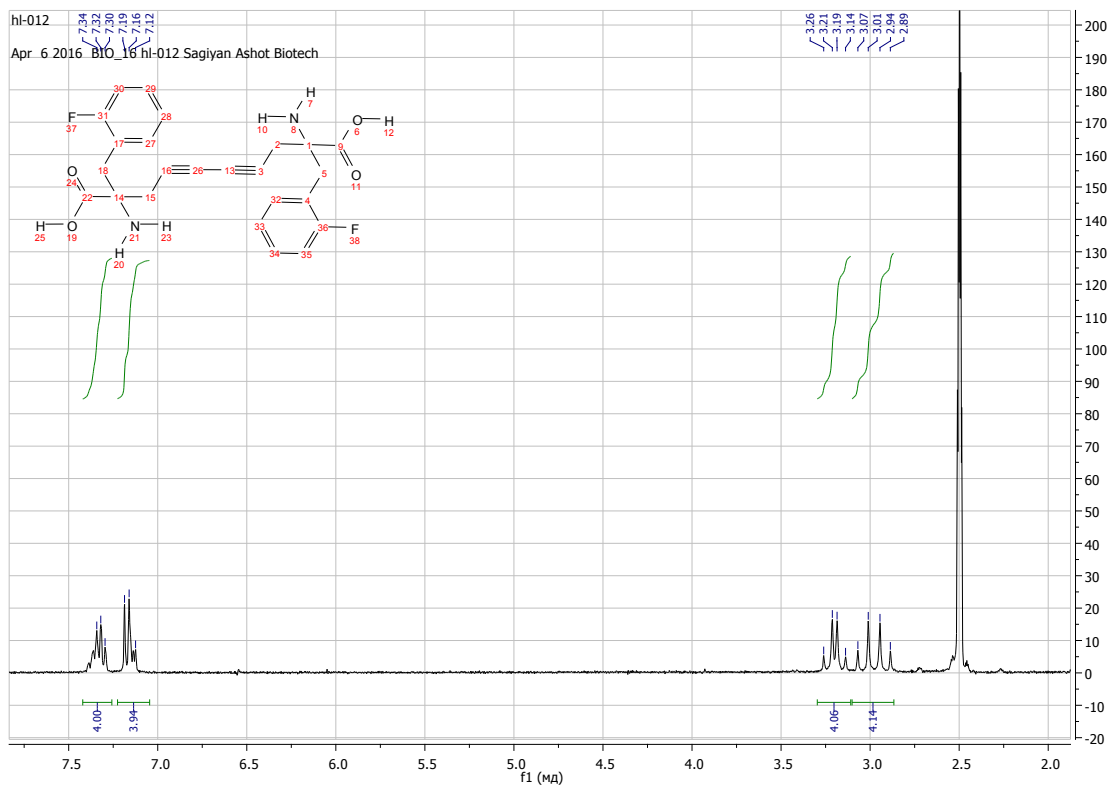
**3b,  $^1\text{H}$  NMR, 2S,9S-diamino-2,9-dibenzyldeca-4,6-diyndioic acid, DMSO**



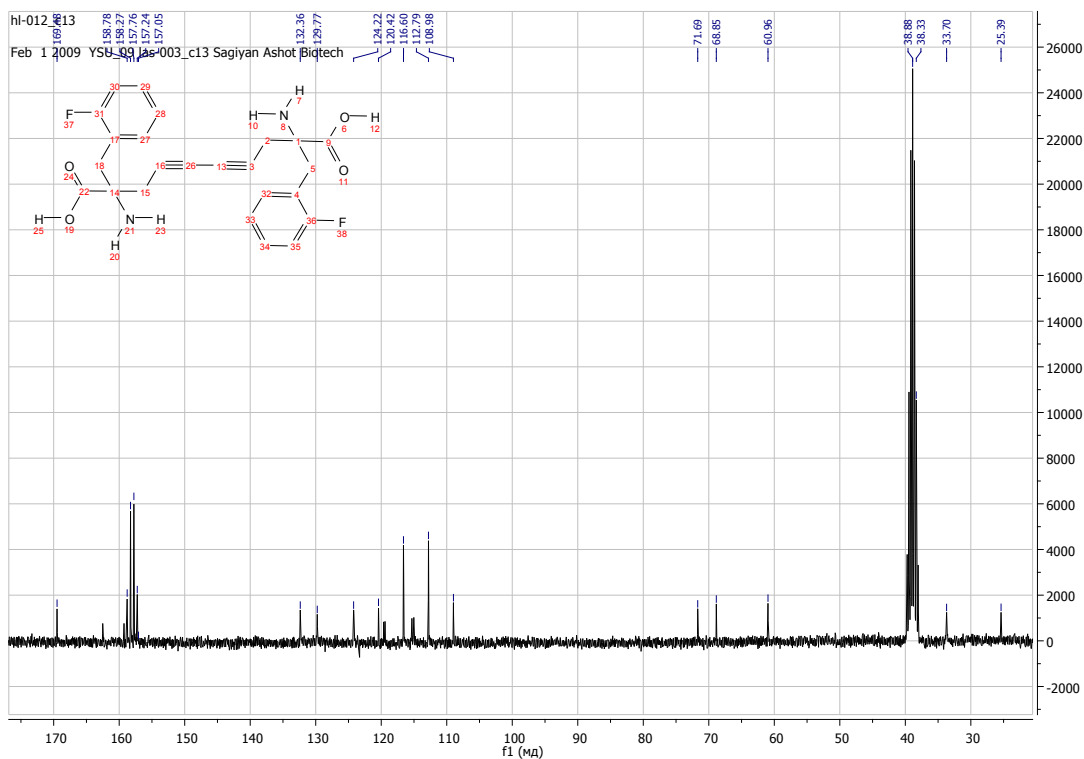
### 3c, <sup>1</sup>H NMR, 2*S*,9*S*-diallyl-2,9-diaminodeca-4,6-diynedioic acid, D<sub>2</sub>O



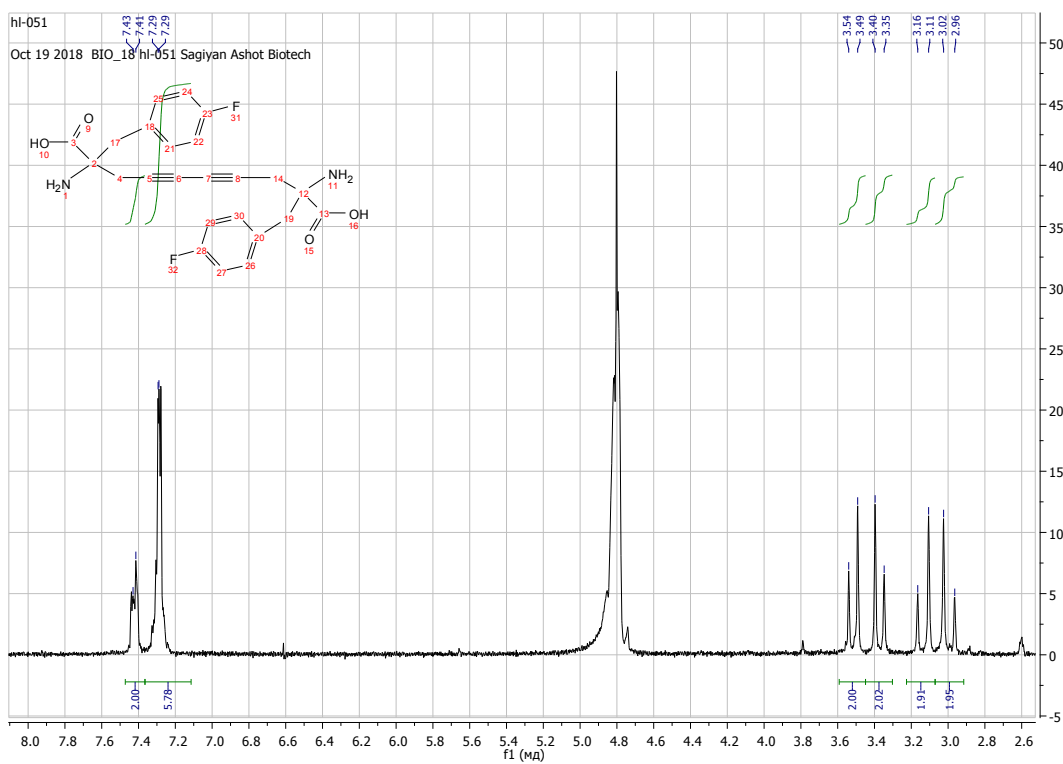
### 3d, <sup>1</sup>H NMR, 2*S*,9*S*-diamino-2,9-bis(2-fluorobenzyl)deca-4,6-diynedioic acid, DMSO+TFAA



### 3d, <sup>13</sup>C NMR, 2*S*,9*S*-diamino-2,9-bis(2-fluorobenzyl)deca-4,6-diyndioic acid, DMSO+TFAA



### 3e, <sup>1</sup>H NMR, 2*S*,9*S*-diamino-2,9-bis(4-fluorobenzyl)deca-4,6-diyndioic acid, DMSO+TFAA



## 6. Crystal X-ray diffraction

**Single-crystal X-ray diffraction.** The crystal of **3a** (CCDC 1959274, C<sub>60</sub>H<sub>52</sub>N<sub>6</sub>O<sub>6</sub>Ni<sub>2</sub>, *M* = 1070.46) is monoclinic, space group *P*2<sub>1</sub>, at *T* = 100 K: *a* = 12.983(3) Å, *b* = 12.994(3) Å, *c* = 33.620(7) Å, *β* = 91.884(4)°, *V* = 5669(2) Å<sup>3</sup>, *Z* = 4, *d*<sub>calc</sub> = 1.254 g/cm<sup>3</sup>, *F*(000) = 2232, *μ* = 0.718 mm<sup>-1</sup>, 56162 total reflections, 23063 independent reflections, *R*<sub>int</sub> = 0.0704, 2*θ*<sub>max</sub> = 53.01°, *T*<sub>min</sub> = 0.830, *T*<sub>max</sub> = 0.860, *R*<sub>1</sub> = 0.0766 (for 17022 independent reflections with *I* > 2*σ*(*I*)), *wR*<sub>2</sub> = 0.1998 (for all independent reflections), *S* = 1.064. X-ray diffraction data were collected on a three-circle Bruker APEX-II CCD diffractometer (λMoK<sub>α</sub>-radiation, graphite monochromator, *φ* and *ω* scan mode) and corrected for absorption using the SADABS program [6]. The data were indexed and integrated using the SAINT program[7]. The structure was solved by direct methods and refined by full-matrix least squares technique on *F*<sup>2</sup> with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [*U*<sub>iso</sub>(H) = 1.5*U*<sub>eq</sub>(C) for the CH<sub>3</sub>-groups and 1.2*U*<sub>eq</sub>(C) for the other groups]. The absolute structure of **3a** was determined by the refinement of Flack parameter which has become equal to 0.08(2). The calculations were carried out using the SHELXTL program [8].

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[2] A.S. Saghyan, A.F. Mkrtchyan, A.J. Karapetyan, Z.Z. Mardiyan, L.A. Hayriyan, H.M. Simonyan *International Journal of Chemical Engineering and Applications*, 2016, 7, 413-416.

[3] G. M. Sheldrick, *SADABS*, v. 2.03, Bruker/Siemens Area Detector Absorption Correction Program; Bruker AXS Inc., Madison, WI, 2003.

[4] Bruker, *SAINTE*, v. 8.27A, Bruker AXS Inc., Madison, WI, 2012.

[5] Yu.N.Belokon', A.S. Saghiyan, S.M. Djamgaryan, B.I. Bakhmutov, V.M. Belikov., *Tetrahedron*, 1988, 44, 5507-5514.

[6] G. M. Sheldrick, *SADABS*, v. 2.03, Bruker/Siemens Area Detector Absorption Correction Program; Bruker AXS Inc., Madison, WI, 2003.

[7] Bruker, *SAINTE*, v. 8.27A, Bruker AXS Inc., Madison, WI, 2012.

[8] G. M. Sheldrick, *Acta Cryst.* 2015, C71, 3-8.