

## Synthesis and Antioxidant Properties of 5-Ethoxycarbonyl -6-Methyl 4- Alkyl (Aryl)-1-N- Alkyl(Aryl)-3,4-Dihydropyrimidine -2(1H)-Tions

**Sujayev Afsun Razzaq oqli**

ANAS Academician A.M.Guliyev Institute of  
 Chemistry of Additives, PhD in Chemistry  
*s.afsun@mail.ru*

**Garibov Emin Nazir oqli**

ANAS Academician A.M.Guliyev Institute of  
 Chemistry of Additives, PhD in Chemistry  
*e.garibov@yahoo.com*

**Nazarov Nazar Mohubbat oqli**

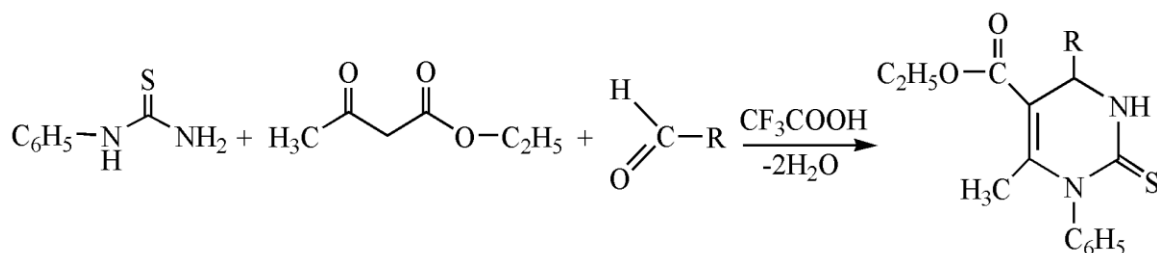
ANAS Academician A.M.Guliyev Institute of Chemistry of Additives  
*nazarov-nazar@rambler.ru*

**Abstract:** In the presence of trifluoroacetic acid on the basis of three-component condensation of N-alkyl (aryl)-thiocarbamide with its different aldehyde and ethyl ether of acetoacetic acid an efficient method for the synthesis of 5-ethoxycarbonyl-6-methyl 4-alkyl(aryl)-1-N-alkyl(aryl)-3,4-dihydropyrimidine -2(1H)-tions has been worked out. Antioxidant properties of synthesized compounds have been investigated.

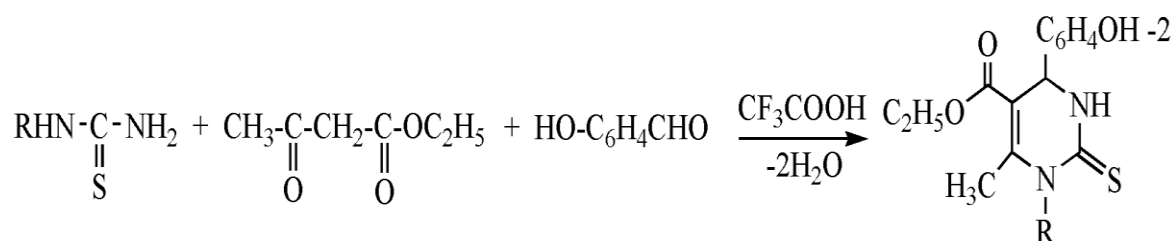
**Keywords:** three-component condensation, N-alkyl (aryl)-thiocarbamide, dihydro-pyrimidine, antioxidant properties.

In the presence of trifluoroacetic acid new effective synthesis method of 5-ethoxycarbonyl-6-methyl-4-alkyl(aryl)-1-N-alkyl(aryl)-3,4-dihydropyrimidine-2(1H)-tions (I-VIII) have been worked out.

It was determined that in the presence of trifluoroacetic acid from mutual influence of different aldehydes with ethyl acetoacetate and phenylthiocarbamid in the alcohol environment with 50-75% outputs the relevant 5-ethoxycarbonyl-6-methyl-4-alkyl(aryl)-1-N-phenyl-3, 4-dihydropyrimidine-2(1H)-tions, 5-ethoxycarbonyl-6-methyl-4(2-hydroxyphenyl)-1-N-phenyl-3,4-dihydropyrimidine-2(1H)-tions are obtained. Synthesis has been carried out on the following scheme:



R=H (I), C<sub>6</sub>H<sub>5</sub> (II), 2-HO-C<sub>6</sub>H<sub>4</sub> (III), 2-HO-5Br-C<sub>6</sub>H<sub>3</sub> (IV)



R=CH<sub>3</sub> (V), C(CH<sub>3</sub>)<sub>3</sub> (VI), C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub> (VII), CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> (VIII)

In NMR <sup>13</sup>C spectrum of carbons in (I) compound the carbon atoms in the molecule have the following signals for electron densities: 24, 29, 39, 51, 83, 118, 122, 124, 128, 133, 142, 150, 180 m.h. (C=S), 204 m.h. (C=O) (fig.1).

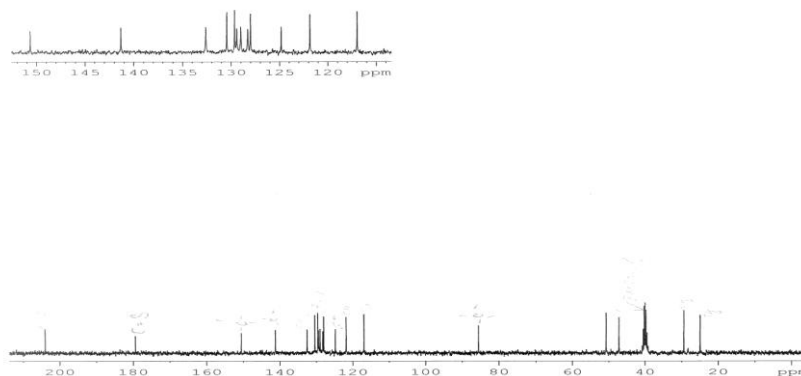


Fig1. In NMR <sup>13</sup>C spectrum of 5-asil-6-methyl-4(phenyl)-1-N-phenyl-3,4-dihydro pyrimidine-2 (1H) tion (I)

In the IQ spectrum of synthesized compounds the valence vibrations of NH bond are observed at the band of 3370-3040 cm<sup>-1</sup>. The valence vibrations of C=O bond in the acetyl group are consistent with 1635-1630 cm<sup>-1</sup> absorption band (fig. 2-3).

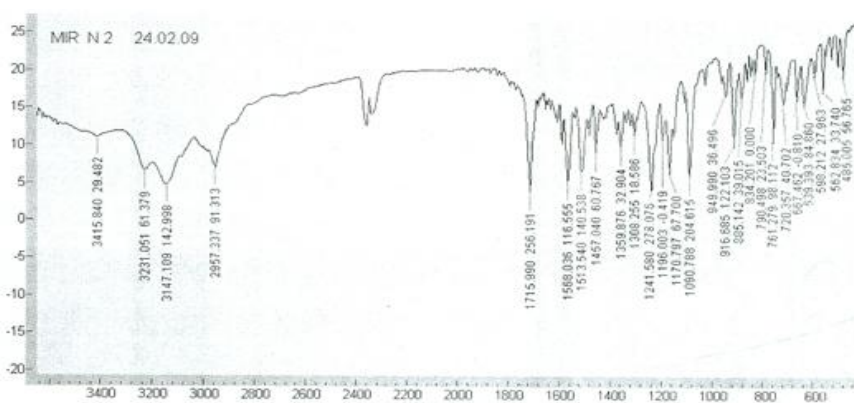


Fig2. In IQ spectrum of 5-Etoksikarbonil-6-methyl-4 (2-hidroksifenil) -1-N-phenyl-3,4-dihidropirimidin-2 (1H) tion (III)

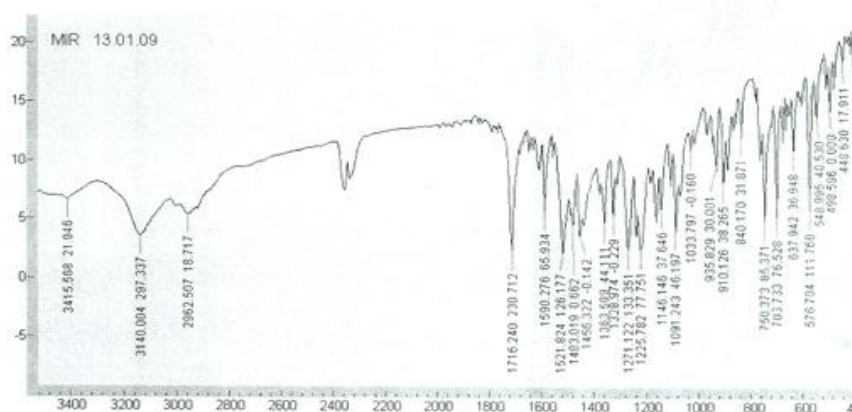
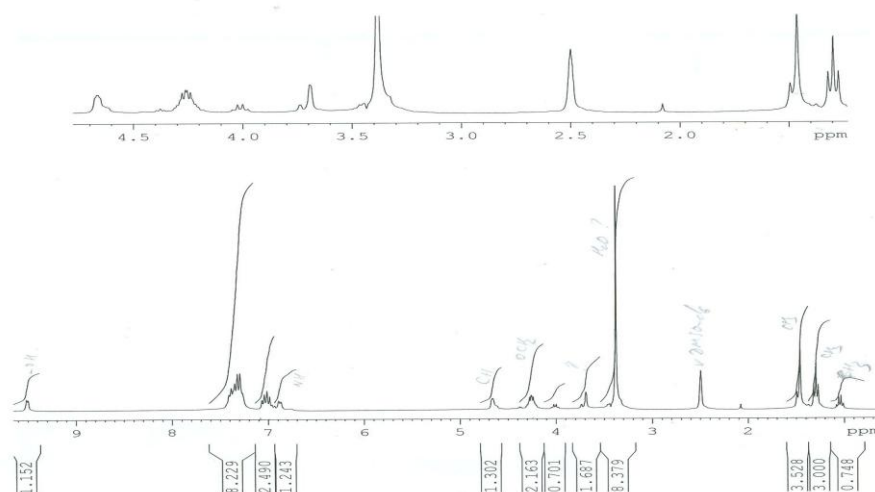


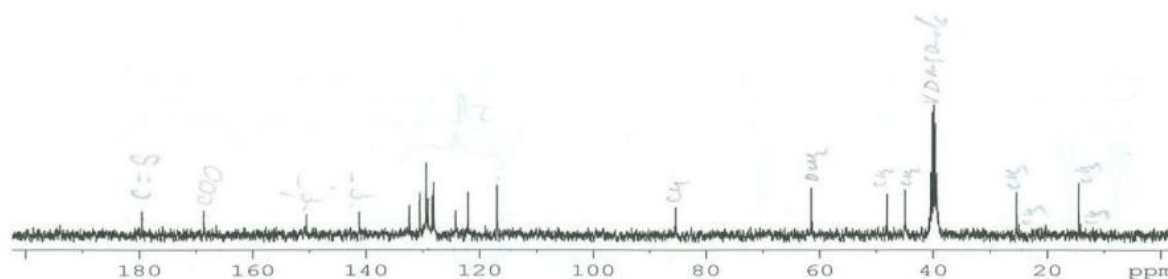
Fig3. IQ spectrum of 5-asil-6-methyl-4(2-hidroksifenil)-1-N-phenyl-3,4-dihidropirimidin-2(1H)-tion (V)

In the strongest area, in the NMR <sup>1</sup>H spectrum of 5-ethoxycarbonyl-6-methyl-4(2-hydroxyphenyl)-1-N-phenyl-3,4-dihydropyrimidine 2(1H)-tion (III) the signal of 3 hydrogens in the 135 m.h methyl group is observed form of singlet. The signal of three protons in methyl group located at acetyl group is identified as 2.35 m.h. at relatively weak area in the form of singlet. The signal of only proton in the methine proton is observed 4.85 m.h. Nonequivalent protons in two phenyl groups located at 3 and 6 position in molecule are identified in the form of multiplet in the 6.8-7.1 and 7.4 m.h areas. Singlet is compitable with the only proton positioned at NH fragment in the weakest area in the form of 9.35 m.h (fig.4). NMR <sup>1</sup>H spectrums of other 3,4-dihydropyrimidine-2(1H) tions (I-VIII) are compitable with NMR <sup>1</sup>H spectrum of (III) compound. They are distinguished only for the form of some functional groups.



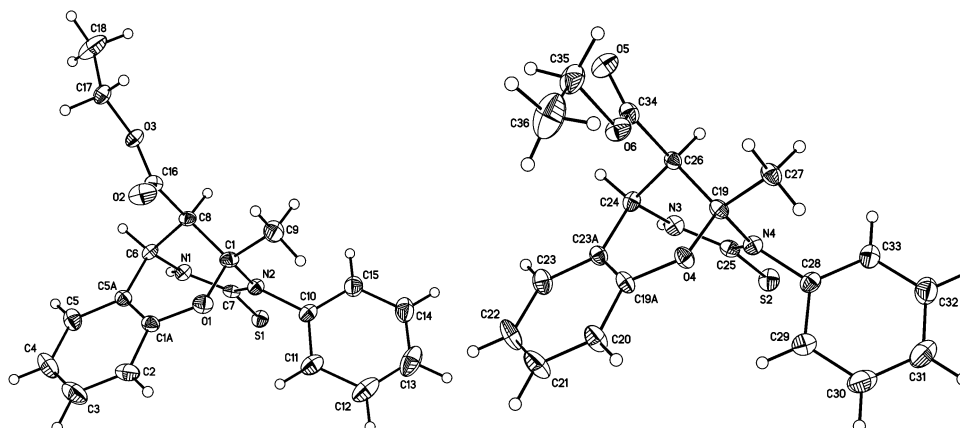
**Fig4.** In NMR  $^1\text{H}$  spectrum of 5-*etoksikarbonil*-6-*methyl*-4(2-*hidroksifenil*)-1-*N*-*phenil*-3,4-*dihidropirimidin*-2(1*H*) *tion* (III)

Carbon atoms in molecule at the  $^{13}\text{C}$  NMR (DMSO- $d_6$  m.h.  $\delta$ ) spectrum of carbons in (III) compound have the following signals for their electron densities (fig 5): 14.99, 25.89, 62.35, 86.28, 116.85, 122.55, 125.01, 126.21, 126.22, 128.87, 128.88, 130.01, 133.24, 142.16, 151.96, 167.91, 179.05.  $^1\text{H}$  NMR spectrum (DMSO- $d_6$  m.h.  $\delta$ ): 1.31 (t., 3H,  $\text{CH}_3$ ); 1.49 (s., 3H,  $\text{CH}_3$ ); 4.26 (k., 2H,  $\text{OCH}_2$ ); 4.67 (s.(d.), 1H, CH); 6.85 (d., 1H, NH); 7.02-7.35 (m., 9H, 2Ar); 9.49 (d., 1H, OH).



**Fig5.** In NMR  $^{13}\text{C}$  spectrum of 5-*etoksikarbonil*-6-*methyl*-4(2-*hidroksifenil*)-1-*N*-*phenil*-3,4-*dihidropirimidin*-2(1*H*) *tion* (III)

The crystal structure of synthesized 5-ethoxycarbonyl-6-methyl 4(2-hydroxyphenyl)-1-N-phenyl-3,4-dihydropyrimidine-2(1H)-one has been determined with X-ray structure analysis method. The structure and crystalline form of III compound have been shown in the figure 6,7, but the selected difference for bond length and valence angle has been described in the table 1. III Crystalline compound holds two crystallographical independent molecules in the central bicyclic fragment which are distinguished by carboxylate conformation (torsion angles in the (Me)C-C-C=O molecules are equal to  $-22.8(6)$  and  $162.8(3)^\circ$  fig.6).



**Fig6.** The molecular structure of the (III) compound.

## Synthesis and Antioxidant Properties of 5-Ethoxycarbonyl -6-Methyl 4- Alkyl (Aril)-1-N- Alkyl(Aril)-3,4-Dihydropyrimidine -2(1h)-Tions

III molecule holds complex three-organic compound system consisting of hexahydropyrimidine, dihydropyrimidin and benzol ring (Fig.6). In bicyclic fragment the cycles of hexahydropyrimidine and dihydropyrimidine- take a shape of symmetric platform (diversion of atoms C(6)/C(24), C(8)/C(26) and in the form of medium platform at two independent crystalline molecules C(1)/C(19), C(8)/C(26) – in compliance with 0.169/-0.236, 0.643/0.622 v $\alpha$  -0.086/-0.157, 0.649/0.611 Å.). In this case benzol cycle in practice directs to the cycle of hexahydropyrimidine prependercularly (the angle for two crystallographical independent molecules is 76.9 and 78.5°. Nitrogen atom in hexahydropyrimidine ring has plane-triangle conformation (valence angle of N(1), N(2), N(3) and N(4) nitrogen atom is 360.1, 359.8, 360.0 v $\alpha$  359.8°). The relevant conformation of three cyclic fragment were determined [1, 3-5] in the previously learned relative compounds. Trance structure of C-C and O-C bonds is substitutive surface with the carboxylate. (torsional corner in two independent crystallographical molecule is C-C-O-C 172.9(3) and 167.6(3)°) and is equatorial to hexahydropyrimidine cycle, it is axial to dihydropyrimidine cycle. In two crystallographical independent molecules phenyl substitute turns under the 78.8 and 81.6° angle.

As can be seen from Table 1 III molecule is placed at thiocarbamide fragment in compressed form– N(1)-C(7), C(7)-N(2) v $\alpha$  N(3)-C(25), C(25)-N(4) bond length becomes short, in C(7)=S(1) v $\alpha$  C(25)=S(2) bonds according to [2] it becomes long in comparison with statistical C-N single and C=S double bonds.

In this case in hexahydropyrimidine cycle the meaning of endo-cyclic valence angles is 120° at nitrogen atom in sp<sup>2</sup> hybrid form, at carbon atom it is 109.5° in sp<sup>3</sup> hybrid form (Table 1). In addition to, endo-cyclic valence angles in hexahydropyrimidine cycle influences to the determination of a endocyclic valence angles in dihydropyrimidine cycle. Thus, the meaning of endocyclic valence angles in dihydropyrimidine cycle is 120° at oxygen atom in accordance with sp<sup>2</sup> and sp<sup>3</sup> hybrid cases, at carbon atom combined with oxygen it is 120 and 109.5° (Table 1).

**Table1.** III structure of communication length [Å] and  $\omega$  corners valent [degrees] selected meaning

Rabitə	d	Rabitə	d	Rabitə	d	Rabitə	d
S(1)-C(7)	1.685(4)	N(2)-C(7)	1.358(4)	S(2)-C(25)	1.677(4)	N(4)-C(25)	1.371(4)
O(1)-C(1A)	1.372(4)	N(2)-C(1)	1.500(4)	O(4)-C(19A)	1.372(4)	N(4)-C(19)	1.489(4)
O(1)-C(1)	1.434(4)	C(1)-C(8)	1.510(5)	O(4)-C(19)	1.420(4)	C(19)-C(26)	1.519(5)
N(1)-C(7)	1.337(4)	C(5A)-C(6)	1.492(5)	N(3)-C(25)	1.335(4)	C(23A)-C(24)	1.505(4)
N(1)-C(6)	1.470(4)	C(6)-C(8)	1.519(4)	N(3)-C(24)	1.456(4)	C(24)-C(26)	1.525(4)

Künc	$\omega$	Künc	$\omega$	Künc	$\omega$
C(1A)-O(1)-C(1)	118.1(3)	N(1)-C(6)-C(8)	106.2(3)	O(4)-C(19)-C(26)	112.4(3)
C(7)-N(1)-C(6)	122.6(3)	C(5A)-C(6)-C(8)	109.8(3)	N(4)-C(19)-C(26)	107.9(3)
C(7)-N(2)-C(1)	123.4(3)	N(1)-C(7)-N(2)	118.2(3)	O(4)-C(19A)-C(23A)	122.7(3)
O(1)-C(1)-N(2)	108.1(3)	C(1)-C(8)-C(6)	106.8(3)	C(19A)-C(23A)-C(24)	120.2(3)
O(1)-C(1)-C(8)	112.3(3)	C(19A)-O(4)-C(19)	117.1(3)	N(3)-C(24)-C(23A)	112.1(3)
N(2)-C(1)-C(8)	107.5(3)	C(25)-N(3)-C(24)	122.5(3)	N(3)-C(24)-C(26)	105.5(3)
O(1)-C(1A)-C(5A)	122.5(3)	C(25)-N(4)-C(19)	123.5(3)	C(23A)-C(24)-C(26)	109.4(3)
C(1A)-C(5A)-C(6)	119.6(4)	O(4)-C(19)-N(4)	108.7(3)	N(3)-C(25)-N(4)	117.7(3)
N(1)-C(6)-C(5A)	111.3(3)			C(19)-C(26)-C(24)	106.1(3)

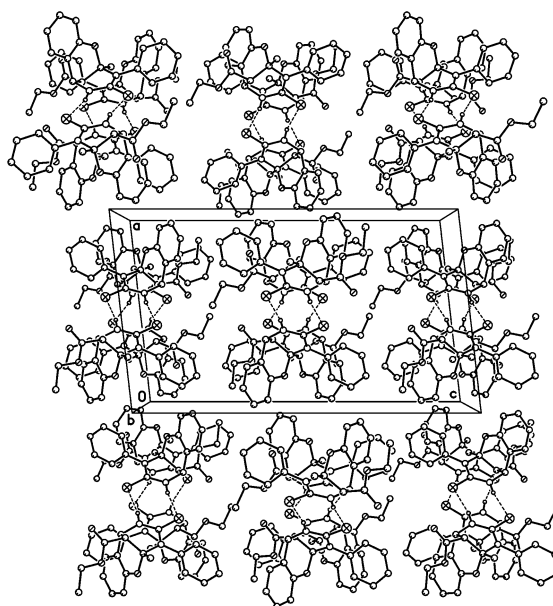
III compound is diastereoisomer C(1)/C(19), C(6)/C(24) and 8)/C(26) with three asymmetrical centre of carbon atom.

The crystal of the studied compound shows racemate - rac-1/19R\*, 6/24R\*, 8/26R in chiral atoms. Enantiomers in crystal form central symmetric dimer by the help of N-H...S intermolecular hydrogen bond (Figure 7, Table 2) . Dimers make for through b –axis. (Figure 7).

**Table2.** Dimensions of hydrogen bond in III structure. [Å and degree].

H rabbitəsinin növü	D*-H	H...A*	D...A	$\angle$ (D-H...A)
N(1)-H(1N)...S(1) [-x+1, -y+1, -z+1]	0.91	2.61	3.496(4)	166
N(3)-H(3N)...S(2) [-x+1, -y, -z+1]	0.91	2.44	3.345(4)	170

• D-protondonor; A-protonakseptor.



**Fig7.** *b* the location along the axis of the molecule III. Hydrogen bonds shown in bar lines.

Crystals for RSA are obtained by double double crystallization of (III) compound in ethanol.

X-ray structure studies of III compound have been carried out in Bruker APEX II CCD diffractometer ( $T=296$  K,  $\lambda\text{MoK}_\alpha$ -radiation, graphite monochromator,  $\varphi$ - $\nu$   $\omega$ -transfer,  $2\theta_{\max} = 46^\circ$ ).

The crystals of III compound ( $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ ,  $M_r=368.44$ ) are colorless,  $T_m=232^\circ\text{C}$ , with prismatic structured, sizes  $0.20 \times 0.10 \times 0.10$  mm<sup>3</sup>, one striped:  $a=12.627(2)$ ,  $b=13.649(2)$ ,  $c=21.574(3)$  Å,  $\beta=96.498(3)^\circ$ ,  $V=3694.1(10)$  Å<sup>3</sup>, space group  $P2_1/c$ ,  $Z=8$ ,  $d_s=1.325$  q/sm<sup>3</sup>,  $\mu=0.197$  mm<sup>-1</sup>. 24457 Reflection intensity has been measured (4985 non-arbitrary reflections  $R_{\text{int}}=0.095$ ) and semi-empirical correction against absorption by the help of SADABS [6] program has been made for them.

The structure of III combination has been determined with direct method and in hydrogenless atom it has been specified up to the least squares with anisotropic approximation in hydrogenless atoms. Hydrogens of amines have been detected in Fourier syntheses and recorded in positive and thermal parameters ( $U_{\text{izo}}(\text{H})=1.2U_{\text{ekv}}(\text{N})$ ). The coordinates of other hydrogen carbons were calculated on the basis of geometric information, were precised with the positive and thermal parameters (for methyl group  $U_{\text{ekv}}(\text{H})=1.5U_{\text{ekv}}(\text{C})$   $\nu$   $U_{\text{ekv}}(\text{H})=1.2U_{\text{ekv}}(\text{C})$ ). The last meaning of  $R_1=0.051$  used factors is  $I > 2\sigma(I)$  for 2748 independent reverberations and for all independent reverberations is  $wR_2=0.093$ . All reports have been carried out throught SHELXTL [7] program system.

The cumene such as model hydrocarbon was used in order to assess the activity of synthesized compounds as antioxidant. As a reaction model at  $60^\circ\text{C}$  in chlorbenzene solution the oxidation reaction occurring by the help of  $\alpha,\alpha'$ -azobisisobutyronitrile (AIBN) initiator was used.

In all studied experiences the thickness of AIBN is static and equal to  $\cdot 10^{-2}$  mol/l. For assessing antioxidant property of synthesized compounds their cumyl peroxide radicals and kinetics of their reactions with cumyl peroxide was searched. The thickness of compounds of which antioxidant property was studied was learned in the limit of  $5 \cdot 10^{-5}$  mol/l and  $5 \cdot 10^{-4}$  mol/l. From the conducted researches it became clear that the synthesized compounds detain the oxidation of cumene with insiator and it was determined that they split cumyl hydroperoxide into catalytic molecular products. The studied compounds (I-VII) including into the class of compounds having combined effect, as well as by interacting with cumyl peroxide break the chain of oxidation and split the cumyl hydroperoxide that formed during the reaction into catalytic molecular products.

#### ACKNOWLEDGMENT

This work was supported by the Science Development Foundation unde the President of the Republic of Azerbaijan -

Grant №EİF/GAM-2--2013-2(8)-25/15/4

## REFERENCES

- [1] Gerard Jenner. Effect of high pressure on Biginelli reactions. Steric hindrance and mechanistic considerations // *Tetrahedron Lett.*, 2004, v. 45, p. 6195-6198.
- [2] Ji-Tai Li, Jun-Fen Han, Jin-Hui Yang, Tong-Shuang Li. An efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by  $\text{NH}_2\text{SO}_3\text{H}$  under ultrasound irradiation // *Ultrasonics Sonochemistry*, 2003, v. 10, p. 119-122.
- [3] Limin Wang, Changtao Qian, He Tian, Yun. Lanthanide Triflate Catalyzed One-pot synthesis of dihydropyrimidin-2(1H)-thiones by a three-component of 1,3-Dicarbonyl Compounds, Aldehydes, and Thiourea Using a Solvent-Free Biginelli Condensation // *Synthetic Communications*, 2003, v. 33, p. 1459-1468.
- [4] Laue T., Plagens A. *Namen und Schlagwort-Reaktionen der Organischen Chemie*. Taubner, 2006, 94 P.
- [5] Lu Jun, Yinjuan Bai, Zhenjun Wang et al. One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using lanthanum chloride as a catalyst // *Tetrahedron Lett.*, 2000, v. 41, p. 9075-9078.
- [6] Subhas D. Bose, Madapa Sudharshan, Sanjay W. Chavhan. New protocol for Biginelli reaction-a practical synthesis of Monastrol /Dedicated to Dr. A. V. Rama Rao on his 70th birthday. *ARKIVOC* 2005, p. 228-236.
- [7] Sasaki S, Mizuno M, Naemura K, Tobe Y. Synthesis and Anion-Selective Complexation of Cyclophane-Based Cyclic Thioureas // *J. Org. Chem.*, 2000, v. 65 № 2, pp. 275-283.

## AUTHORS' BIOGRAPHY



**Sujayev Afsun Razzaqogli** is PhD in chemistry, scientist of “Theoretical bases of the synthesis and action mechanism of additives” laboratory of Institute of Chemistry of. He is an Organic chemist by profession. He has been conducting scientific research since 2003. The main directions of his scientific-research work cover the studying of N-substituted thiocarbamides and their various derivatives and their antioxidant, antimicrobial, antiviral effects. He has about 11 years’ research experience. He is the author of 30 scientific works (15 of them in prestigious foreign journals) and 1 inventions in general.



**Garibov Emin Nazirogli** is PhD in chemistry, post-doctoral of “Theoretical bases of the synthesis and action mechanism of additives” laboratory of Institute of Chemistry of. He is an Oil chemist by profession. He has been conducting scientific research since 2006. The main directions of his scientific-research work cover the studying of N-substituted thiocarbamides and their various derivatives and their antioxidant, antimicrobial, antiviral effects. He has about 10 years’ research experience. He is the author of 21 scientific works.



**Nazarov Nazar Mohubbatogli**, The project executive Nazarov works as a young scientific researcher in the institute of Chemistry of Additives. By the synthesis and transformations of various organic sulfur compounds, he became the winner of small grant competition declared in order to stimulate scientific research work of young scientists. He conducts researches on Synthesis and Transformations of various Organic Sulfur Compounds.