The reaction of 5-amino-3-(cyanomethyl)-1H-pyrazol-4-carbonitrile with beta-cycloketols

Victor V. Dotsenko[1-3]*, Aminat M. Semenova[1,4], Elena A. Chigorina[5], Nikolay A. Aksenov[3], Inna V. Aksenova[3]

[1]Kuban State University, 149 Stavropolskaya str, Krasnodar, 350040 Russia
e-mail: victor_dotsenko@bigmir.net
[2]ChemEx Lab, Vladimir Dal' Lugansk National University, 20A/7 Molodezhny, Lugansk, 91034 Russia
[3]Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., 355009 Stavropol, Russia
[4]North Caucasus Humanitarian Technological Academy, Medical Institute, 36 Stavropolskaya str., 369000 Cherkessk, Russia
[5]The Federal State Unitary Enterprise "Institute of Chemical Reagents and High Purity Chemical Substances" of National Research Centre "Kurchatov Institute", 3 Bogorodsky Val, Moscow, 107076, Russia

Abstract

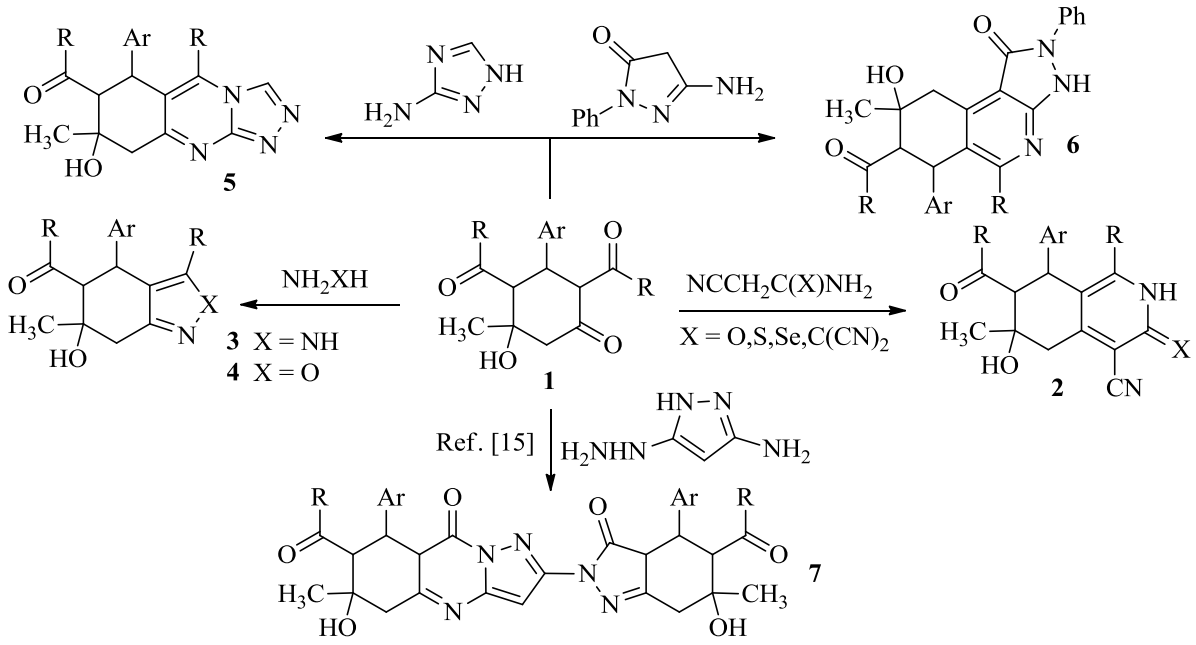
The reaction of 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile with 3-aryl-2,4-di(ethoxycarbonyl)-5-hydroxy-5-methylcyclohexanones in boiling acetic acid leads to the formation of new 4,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolines. The mechanism is discussed. The structure of the products was confirmed by means of ^{1}H и ^{13}C (DEPTQ) NMR, as well as 2D NMR (NOESY, ^{1}H–^{13}C HSQC, HMBC).

Keywords
β-cycloketols, aminopyrazole, cyclocondensation, pyrazolo[1,5-a]quinazoline

β-Cycloketols (2,4-di-(RC(O))-3-aryl-5-hydroxy-5-methylcyclohexanones) **1** which are easily accessible by the reaction of aromatic aldehydes with 1,3-dicarbonyls $RC(O)CH_2C(O)CH_3$, were recognized as promising reagents for organic synthesis. According to the literature [1,2], β-cycloketols are good precursors of a variety of carbocycles, enamine ketones and esters, etc. However, the heterocyclization reactions of β-cycloketols are not well studied. Thus, the literature describes the preparation of isoquinolines **2** [3-7], indazoles **3** [8-10], benzo[c]isoxazoles **4** [9,10], [1,2,4]triazolo[3,4-

b]quinazolines **5** [11] and pyrazolo[3,4-c]isoquinolines **6** [12] (Scheme 1) by reactions of beta-cycloketols with various 1,2- and 1,3-dinucleophilic agents. Despite the large attention paid to reactions of aminoazoles with 1,3-dielectrophilic agents (see reviews [13, 14]), only a few examples of reactions involving β-cycloketols were found in the literature. Thus, the reaction of cycloketols with 5-amino-3-hydrazinopiazole was reported to give 6,7,8,8a-tetrahydropyrazolo[5,1-b]quinazolin-9(5H)-one **7** [15] (Scheme 1).

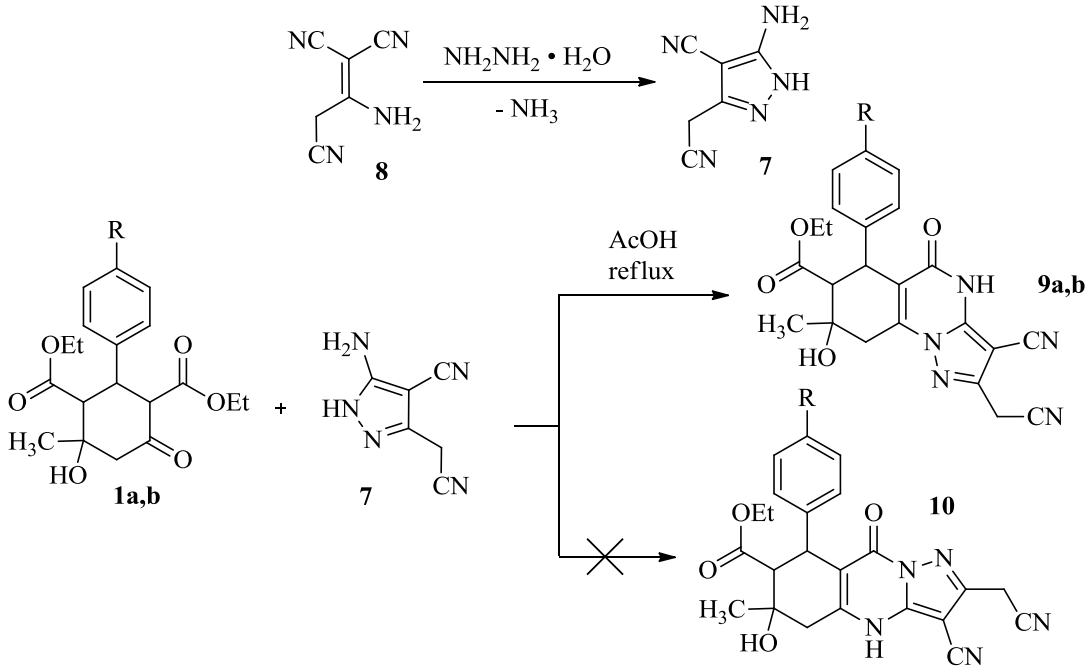
Scheme 1



In continuation of our studies in the chemistry of the malononitrile dimer [16–19], herein we report the reaction of 3-aryl-5-hydroxy-5-methyl-2,4-di (ethoxycarbonyl)cyclohexanones **1a,b** with 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile **7** (Scheme 2). Aminopyrazole **7** can be easily prepared by the reaction of malononitrile dimer **8** with hydrazine hydrate [20].

We found that cycloketols **1a,b** react with 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile **7** in boiling AcOH to give previously not described 4,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolines **9a,b** in low yields (15-22%). The structure of compounds **9a,b** was confirmed by means of IR spectrophotometry, ^{1}H and ^{13}C NMR (DEPTQ), and by the results of 2D NMR experiments (NOESY, ^{1}H–^{13}C HSQC, HMBC) for **9a** (Figures 1-3). Presumably, the reaction proceeds through the initial attack of pyrazole NH group at C-1 followed by intramolecular attack of the NH_2 group to ester carbonyl.

Scheme 2



1, 9: **a** R = OMe; **b** R = NO_2

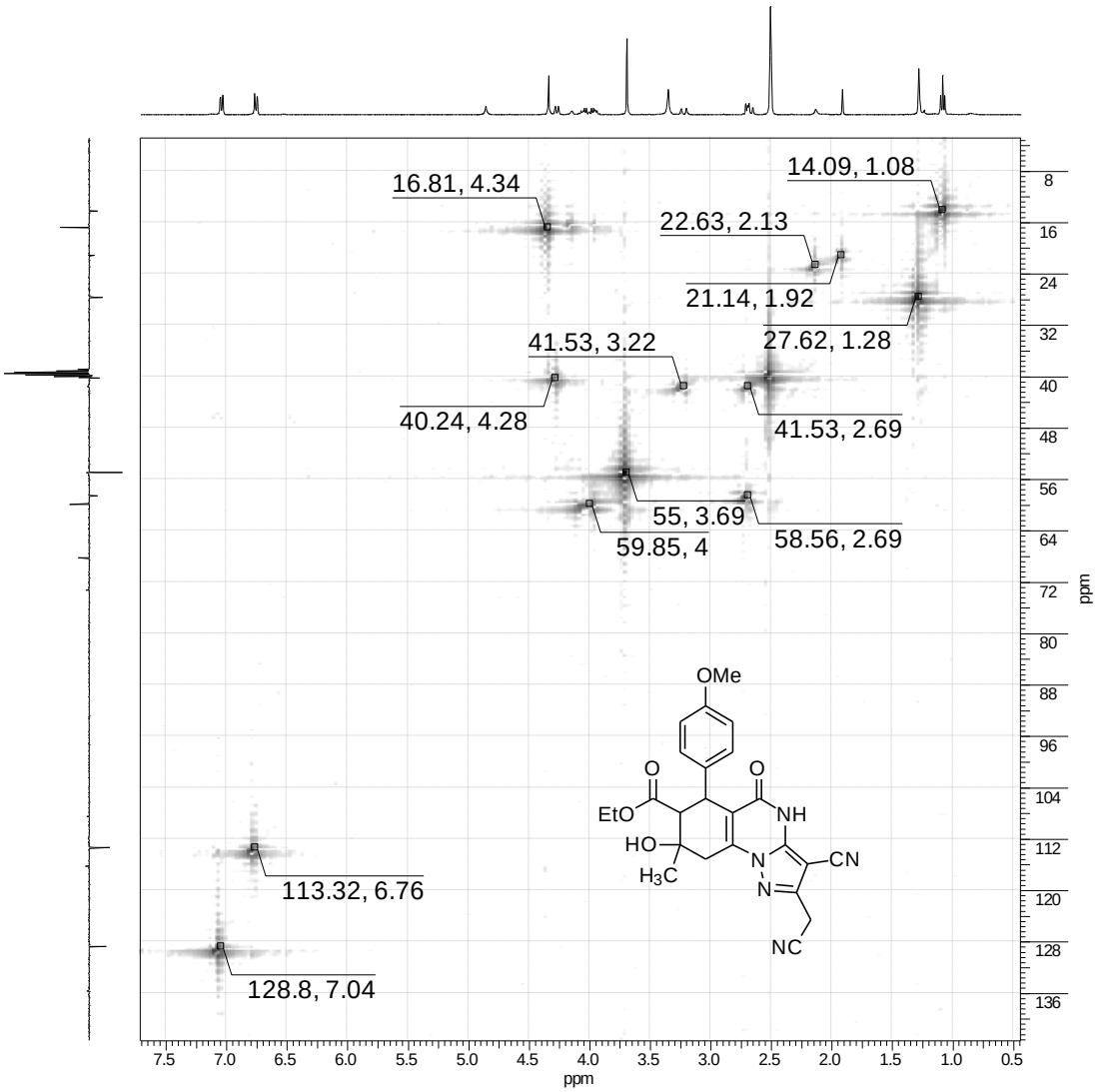


Fig. 1. HSQC $^{1}H–^{13}C$ NMR (400/101 MHz, DMSO-d_6) spectrum of **9a**.

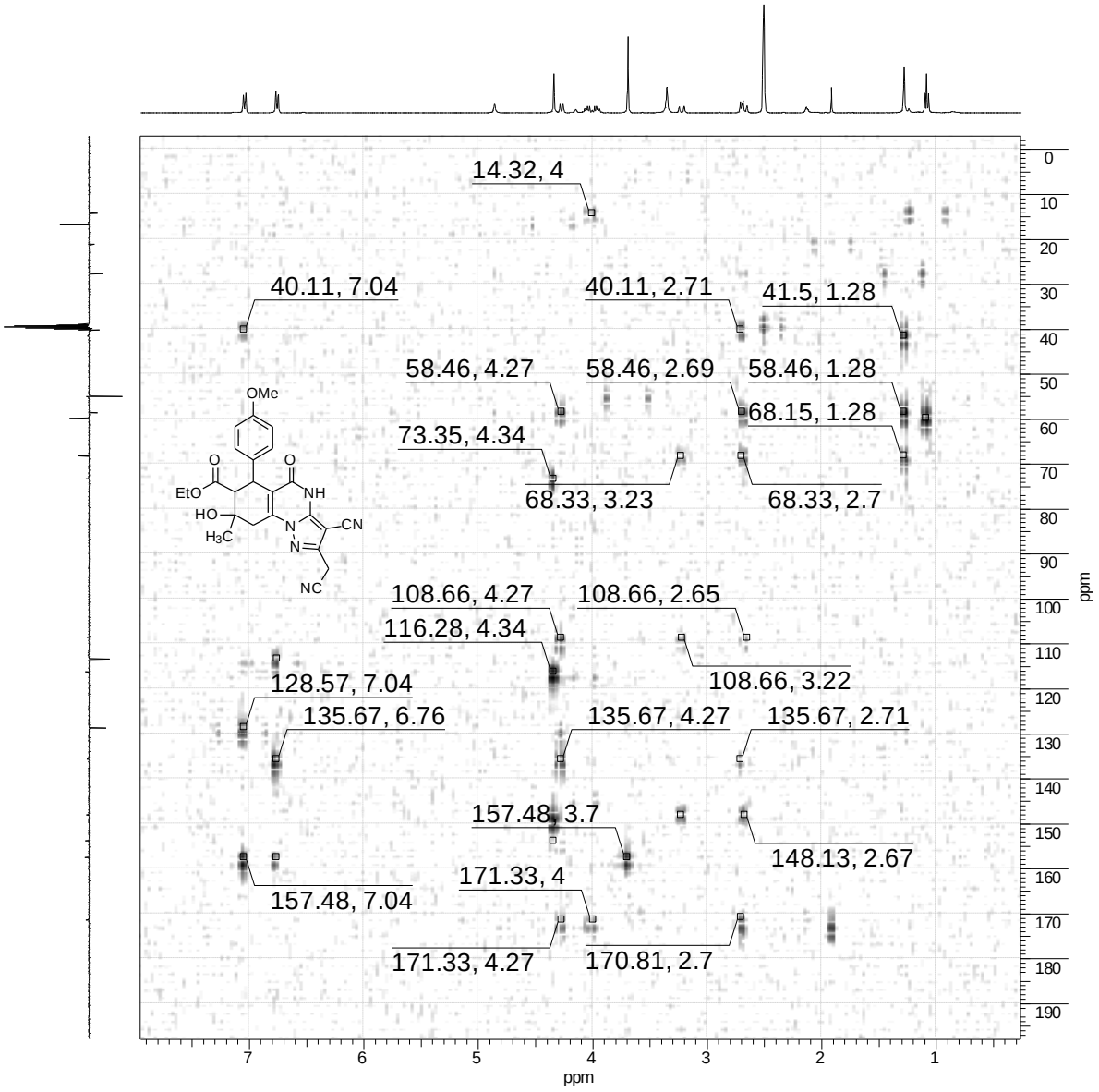


Fig. 2. HMBC ^{1}H–^{13}C NMR (400/101 MHz, DMSO-d_6) spectrum of **9a**.

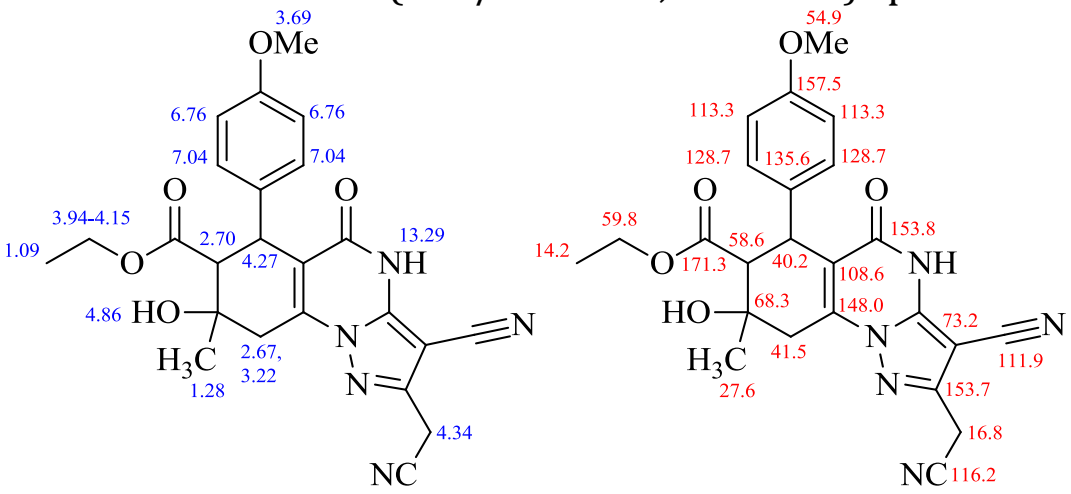


Fig. 3. The chemical shifts in the ^{1}H NMR (left) and ^{13}C NMR (right) spectra of **9a**.

Experimental

IR spectra were recorded on a Bruker Vertex 70 spectrometer. NMR spectra were recorded on a Bruker Avance III HD (400 MHz) in DMSO-d_6 using TMS as an internal standard. Selected experimental procedures are given.

Ethyl 3-cyano-2- (cyanomethyl)-8-hydroxy-6-(4-methoxyphenyl)-8-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolin-7-carboxylate (9a). A mixture of 380 mg (1 mmol) of diethyl 5-hydroxy-5-methyl-3- (4-methoxyphenyl)cyclohexanone-2,4-dicarboxylate (**1a**), 5 ml of glacial AcOH and 150 mg (1 mmol) of pyrazole **7** was heated under reflux for 4 h (TLC control). The precipitate was filtered off and washed with EtOH. Yield 22%, beige amorphous powder.

IR spectrum, ν, cm^{-1}: 3476 (O–H), 3182, 3076 (N–H), 2262, 2226 (2 C≡N), 1720 (C=O ester), 1688 (C=O amide), 1649, 1593 (C=C).
^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.09 t (3H, C$\underline{H}_3$CH$_2$O, ^3J 7.1 Hz), 1.28 s (3H, C^{8}C$\underline{H}_3$), 2.65-2.71 two d overlapped (2H, H^9 and H^7), 3.22 d (1H, H^9, ^2J 17.1 Hz), 3.69 s (3H, CH$_3$O), 3.94-4.15 m (ABX$_3$) (2H, CH$_3$C$\underline{H}_2$O), 4.27 d (1H, H^6, ^3J 10.2 Hz), 4.34 s (2H, CH$_2$CN), 4.86 br.s (1H, OH), 6.76 d (2H, H^3 and H^5 Ar, ^3J 8.4 Hz), 7.04 d (2H, H^2 & H^6 Ar, ^3J 8.4 Hz), 13.29 br.s (1H, NH). NMR ^{13}C DEPTQ (101 MHz, DMSO-d_6), δ_C, ppm.: 14.5* ($\underline{C}$H$_3$CH$_2$O), 16.7 ($\underline{C}$H$_2$CN), 27.6* (C$^8\underline{C}$H$_3$), 40.2* (C^6), 41.5 (C^9), 54.9* (CH$_3$O), 58.6* (C^7), 59.8 (CH$_3\underline{C}$H$_2$O), 68.2 (C^8), 73.2 (C^3), 108.5 (C^{5a}), 111.9 (CN), 113.3* (C^3, C^5 Ar), 116.2 (CH$_2\underline{C}$N), 128.7* (C^2, C^6 Ar), 135.6 (C^1 Ar), 148.0 (C^{9a}), 148.1 (C^{3a}), 153.7 (C^2), 153.8 (C^5), 157.5 (C^4 Ar), 171.4 ($\underline{C}$O$_2$Et). *Opposite signals.

References

1. Kriven'ko A.P., Sorokin V.V. Substituted cyclohexanolons. Saratov, 1999. P. 20 (in Russian).

2. Ismiev A.I., Maharramov A.M.., Sukach V.A.., Vovk M.V. // J. Org. Pharm. Chem. 2016. Vol. 14. № 4 (56). P. 16. (In Russian).
URL: ophcj.nuph.edu.ua/article/download/ophcj.16.905/85180.

3. Ozols A. I., Pelcher Yu.Ê., Kalme Z. A., Popelis Yu. Yu., Turovskis I.V., Duburs G.Ya. // Chem. Heterocycl. Compds. 1996. Vol. 32. N. 1. P. 52. DOI 10.1007/BF01169354.

4. Dyachenko V.D., Sukach S.M., Dyachenko A.D. // Chem. Heterocycl. Compds. 2015. Vol. 51. N 1. P. 51. doi 10.1007/s10593-015-1658-9.

5. Dyachenko V.D., Karpov E.N. // Russ. J. Org. Chem. 2014. Vol. 50. N 12. P. 1787. doi 10.1134/S1070428014120136.

6. Sukach S.M., Dyachenko V.D. // Russ. J. Org. Chem. 2015. Vol. 51. N 7. P. 1020. doi 10.1134/S1070428015070210.

7. Dyachenko V.D., Sukach S.M. // Chem. Heterocycl. Compds. 2010. Vol. 46. N 12. P. 1467. doi 10.1007/s10593-011-0693-4.

8. Gein V.L., Nosova N.V., Potemkin K.D., Aliev Z.G., Kriven'ko A.P. // Russ. J. Org. Chem. 2005. Vol. 41. N 7. P. 1016. doi 10.1007/s11178-005-0287-7.

9. Sorokin V.V., Grigoryev A.V., Ramazanov A.K., Krivenko, A.P. // Chem. Heterocycl. Compds. 1999. Vol. 35. N 6. P. 671. doi 10.1007/BF02251624.

10. Smirnova N.O., Plotnikov O.P., Vinogradova N.A., Sorokin V.V., Kriven'ko A.P. // Pharm. Chem. J. 1995. Vol. 29. N 1. P. 49. doi 10.1007/BF02219464.

11. Poplevina N.V., Kuznetsova A.A., Krivenko A.P. // Chem. Heterocycl. Compds. 2010. Vol. 46. N 9. P. 1148. doi 10.1007/s10593-010-0644-5.

12. Dyachenko V.D., Sukach S.M. // Russ. J. Gen. Chem. 2012. Vol. 82. N 2. P. 305. doi 10.1134/S1070363212020211.

13. Anwar H.F., Elnagdi M.H. // ARKIVOC. 2009 (i). P. 198. doi http://dx.doi.org/10.3998/ark.5550190.0010.107.

14. Abu Elmaati T.M., El-Taweel F.M. // J. Heterocycl. Chem. 2004. Vol. 41. N 2. P 109. doi 10.1002/jhet.5570410201.

15. Etman H.A., Sadek M.G., Khalil A.G.M. // Res. J. Pharm. Biol. Chem. Sci. 2015. Vol. 6. N 2. P. 247. Avail. URL: https://www.rjpbcs.com/pdf/2015_6(2)/[41].pdf

16. Dotsenko V.V., Ismiev A.I., Khrustaleva A.N., Frolov K.A., Krivokolysko S.G., Chigorina E.A., Snizhko A.P., Gromenko V.M., Bushmarinov I.S., Askerov R.K., Pekhtereva T.M., Suykov S.Yu., Papayanina E.S., Mazepa A.V., Magerramov A.M. // Chem. Heterocycl. Compds. 2016. Vol. 52. N. 7. P. 473. doi 10.1007/s10593-016-1918-3.

17. Dotsenko V.V., Krivokolysko S.G., Chernega A.N., Litvinov V.P. // Russ. Chem. Bull., Int. Ed. 2003. Vol. 52. N 4. P. 969. doi 10.1023/A:1024420930528.

18. Tverdokhleb N.M., Khoroshilov G.E., Dotsenko V.V. // Tetrahedron Lett. 2014. Vol. 55. P. 6593. doi 10.1016/j.tetlet.2014.10.046.

19. Dotsenko V.V., Chigorina E.A., Krivokolysko S.G. // Chem. Heterocycl. Compds. 2017. Vol. 53. N. 5. P. 626. doi 10.1007/s10593-017-2103-z.

20. Carboni R.A., Coffman D.D., Howard E.G. // J. Am. Chem. Soc. 1958. Vol. 80. N 11. P. 2838. doi 10.1021/ja01544a061