ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 1, pp. 19–24. © Pleiades Publishing, Ltd., 2019.
Russian Text © A.M. Semenova, R.V. Oganesyan, V.V. Dotsenko, E.A. Chigorina, N.A. Aksenov, I.V. Aksenova, E.E. Netreba, 2019, published in Zhurnal Obshchei Khimii, 2019, Vol. 89, No. 1, pp. 25–30.

Reaction of 5-Amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile with Hydroxycyclohexanones

A. M. Semenova[a,b], R. V. Oganesyan[a], V. V. Dotsenko[a,c]*, E. A. Chigorina[d], N. A. Aksenov[c], I. V. Aksenova[c], and E. E. Netreba[e]

[a] *Kuban State University, ul. Stavropol'skaya 149, Krasnodar, 350040 Russia*
**e-mail: victor_dotsenko_@mail.ru*

[b] *North Caucasian State Humanitarian and Technological Academy, Medical Institute, Cherkessk, Russia*

[c] *North Caucasus Federal University, Stavropol, Russia*

[d] *National Research Center "Kurchatov Institute" – IREA, Moscow, Russia*

[e] *Taurida Academy of V.I. Vernadsky Crimean Federal University, Simferopol, Russia*

Received July 5, 2018; revised July 5, 2018; accepted July 13, 2018

Abstract—The reaction of 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile with 3-aryl-5-hydroxy-5-methyl-2,4-di(ethoxycarbonyl)cyclohexanones in acetic acid furnished previously unknown 4,5,6,7,8,9-hexahydropyrazolo[1,5-*a*]quinazoline derivatives.

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

DOI: 10.1134/S1070363219010043

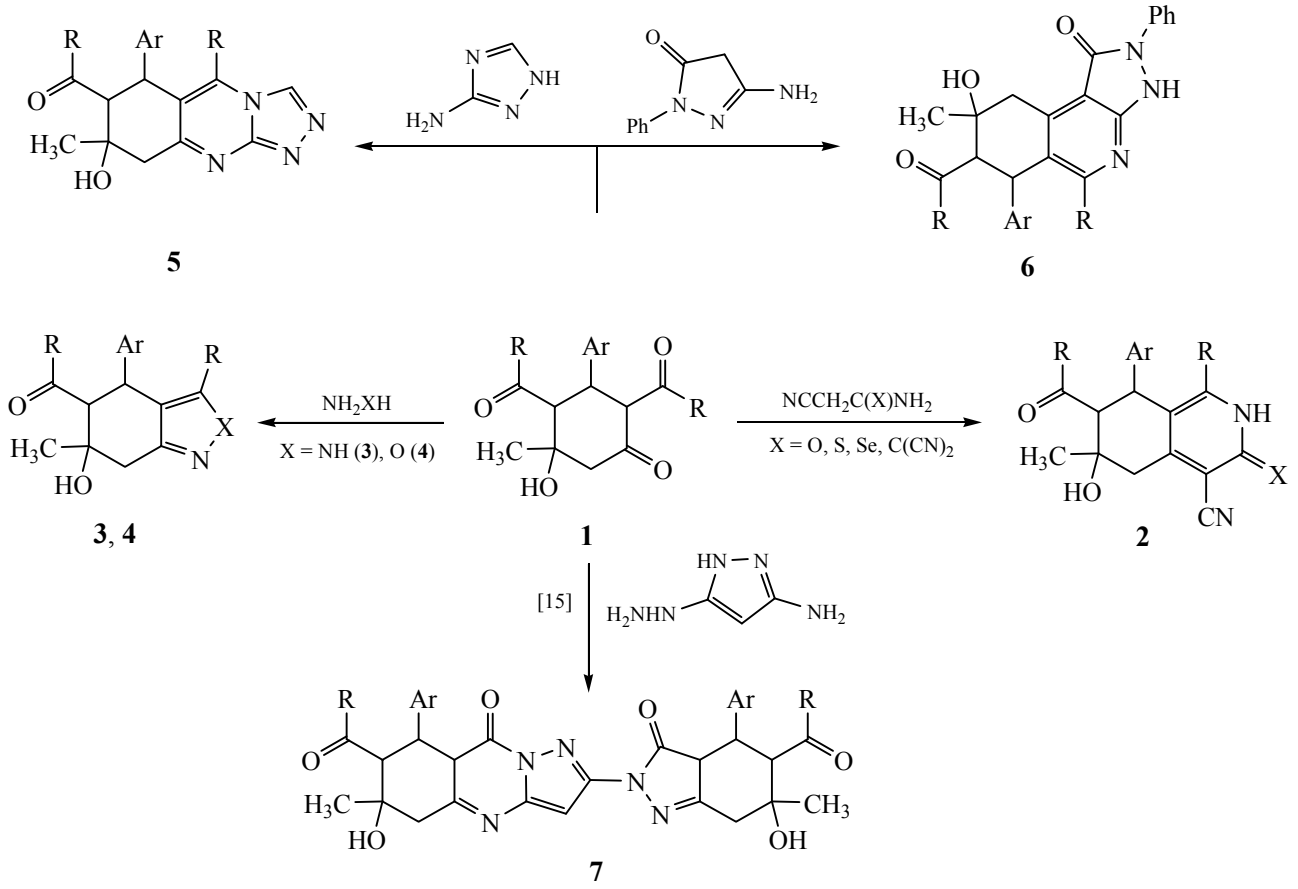
Cyclic 1,3-dicarbonyl compounds 2,4-di[RC(O)]-3-aryl-5-hydroxy-5-methylcyclohexanones **1** (β-cycloketols), available by the reaction of aromatic aldehydes with acetoacetic ester, are prospective reagents for fine organic synthesis. According to reviews [1, 2], β-cycloketol can serve as a starting point for obtaining substituted carbocycles, 2-oxabicyclo[2.2.2]octanes, enaminoketones and -esters, etc. At the same time, it should be noted that the data on heterocyclization reactions with β-cycloketol are scarce. Thus, preparation of isoquinolines **2** [3–7], indazoles **3** [1, 8–10], benzo[*c*]isoxazoles **4** [1, 9, 10], [1,2,4]triazolo[3,4-*b*]-quinazolines **5** [11] and pyrazolo[3,4-*c*]isoquinolines **6** [12] via condensation reactions of cycloketols with various 1,2- and 1,3-binucleophilic agents have been reported (Scheme 1).

The last two transformations are of particular interest, because, despite the considerable attention paid to the condensation reactions of aminoazoles with 1,3-bioelectrophils (see [13, 14]), only some examples of such reactions involving β-cycloketols were found. So, we managed to find the only and recent mention of the reaction of cycloketol with 5-amino-3-hydrazinopyrazole, leading to the formation of 6,7,8,8a-tetrahydropyrazolo[5,1-*b*]quinazoline-9(5*H*)-one **7** [15] (Scheme 1). It is worth noting that the analytical data presented in [15] (mass spectrometry and IR spectroscopy) are obviously not enough to confirm the structure of the claimed product.

Continuing research in the field of the chemistry of malononitrile dimer derivatives [16–19] and condensation reactions based on 3(5)-aminopyrazoles [20, 21], herein we reported the reaction of 3-aryl-5-hydroxy-5-methyl-2,4-di(ethoxycarbonyl)cyclohexanones **1a**, **1b** with 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **7** (Scheme 2). Aminopyrazole **7** is easily formed by the reaction of malononitrile dimer **8** with hydrazine hydrate [22] and, due to the presence of a number of amino and cyano groups, can enter into condensation reactions with the formation of functional derivatives [23–25]. β-Ketoesters (and β-cycloketols in particular) have not previously been reacted with aminopyrazole **7**. Due to the fact that the probable products of the pyrazoloquinoxaline series are of interest for pharmacology [26–28], the study of this interaction seems promising.

We found that cycloketols **1a**, **1b** react with 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **7**

Scheme 1.



in boiling AcOH to form previously unknown 4,5,6,7,8,9-hexahydropyrazolo[1,5-*a*]quinazoline derivatives **9a** and **9b** with low yields (15–22%, Scheme 2).

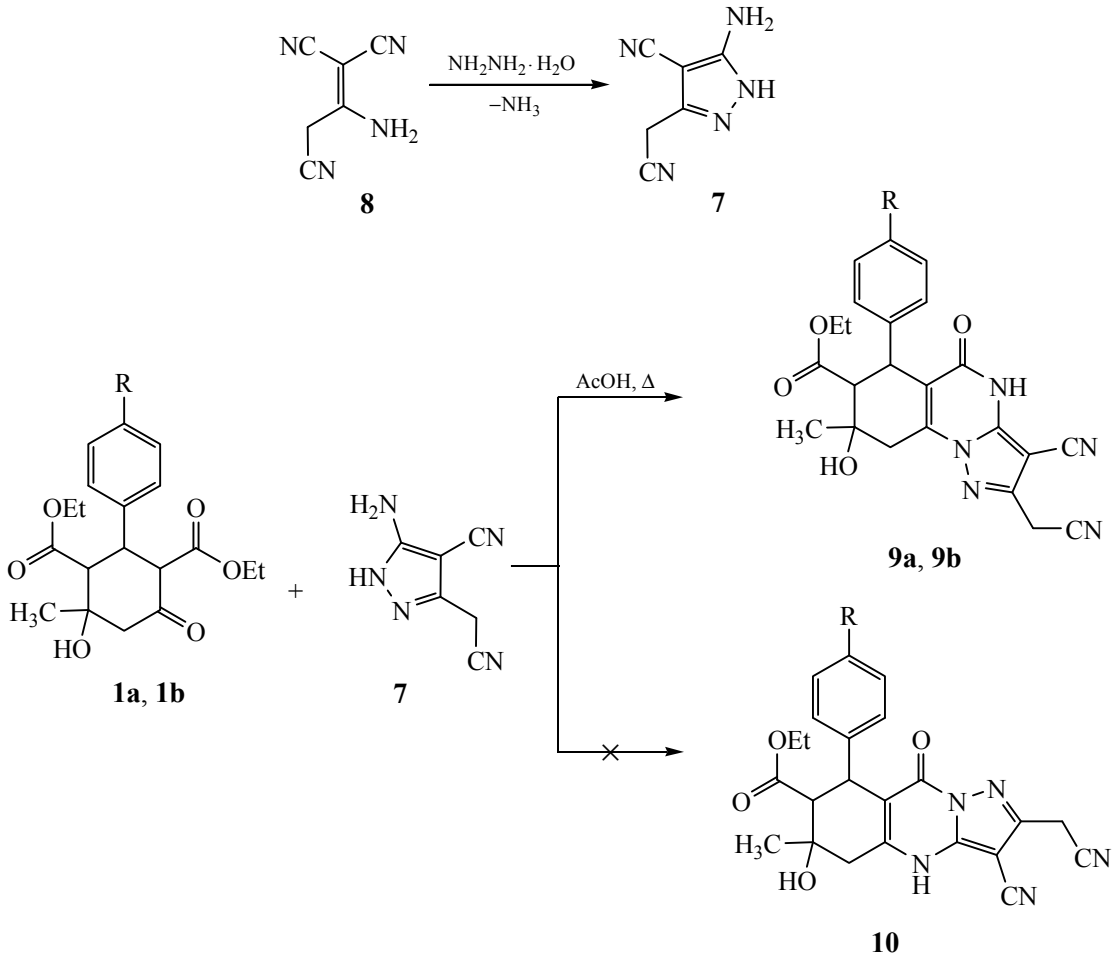
Structures of compounds **9a** and **9b** were confirmed by the IR, ^{1}H and ^{13}C NMR (DEPTQ) spectroscopy data, as well as 2D NMR experiments (NOESY, ^{1}H–^{13}C HSQC, HMBC). Heteronuclear correlations for compound **9a** are given in the Table.

In the IR spectra of compounds **9a** and **9b**, two absorption bands are observed, corresponding to the stretching vibrations of the conjugate and non-conjugate nitrile groups (2226–2230 and 2261–2262 cm^{-1}, respectively), as well as two carbonyl groups: ester (1717–1720 cm^{-1}) and amide (1678–1688 cm^{-1}). The position of the latter band evidences against the isomeric structure **10** (Scheme 2), since the "azolide" C=O group in similar structures is characterized by absorption in the higher frequency range (~1710 cm^{-1}) [29]. In addition, the obtained results correlate well with the literature data for related pyrazolo[1,5-*a*]pyrimidine structures with the C(O)NH fragment [21, 30]. In the ^{1}H NMR spectra, the proton signals of only one ester group are detected, as well as the characteristic broadened signals of C(O)NH protons at 13.29–13.44 ppm. NOESY experiment did not detect correlations between the NH proton signal and the methylene unit in the carbocyclic fragment, which would to expect if a structure **10** is formed.

Another feature of the structure of compounds **9a** and **9b** is the nonequivalence of the methylene protons of the OCH_2CH_3 fragment, which probably arises as a result of the formation of an intramolecular hydrogen bond between HO and COOEt groups. As a result, the OCH_2 proton signals resonate as a complex ABX_3 system instead of the expected quartet. The protons of the methylene $C^{9}H_2$ group are recorded by two doublets with $^{2}J \approx 17.0$ Hz.

In summary, we found for the first time that β-cycloketols react with 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile, a representative of the 3(5)-aminopyrazole series, to form hexahydropyrazolo[1,5-*a*]-quinazoline derivatives. Structure of the latter was

Scheme 2.



R = OMe (**a**), NO_2 (**b**).

confirmed by a complex of spectral data. Taking into account both the variety of available aminoazole and aminoazine substrates, as well as the availability of 2,4-diacyl(alkoxycarbonyl)-5-hydroxy-5-methylcyclohexanones, the detected transformation opens up a promising and practically unexplored direction in the chemistry of fused quinazoline derivatives. Optimization of the synthesis conditions, possibilities and limitations of this reaction will be the object of our further studies.

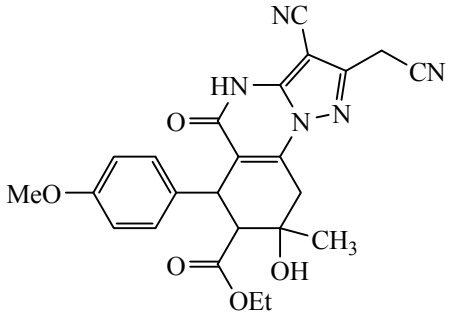
EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance III HD 400MHz [400 (^{1}H) and 101 MHz (^{13}C)] instrument from a DMSO-d_6 solution. IR spectra were recorded on a Bruker Vertex 70 IR Fourier spectrometer with an ATR. Elemental analysis for C, H, N was performed on a Carlo Erba 1106 instrument. Purity of the obtained compounds was monitored by TLC on Sorbfil-A plates, eluting with acetone–hexane mixture (1 : 1) and developing with iodine vapor or UV detector.

The starting 3-(4-R-phenyl)-5-hydroxy-5-methyl-2,4-di(ethoxycarbonyl)cyclohexanones **1a** and **1b** were obtained according to the known procedure [31]. 5-Amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **7** was obtained from malononitrile dimer by the known method [22].

Ethyl 8-hydroxy-6-(4-methoxyphenyl)-8-methyl-5-oxo-3-cyano-2-(cyanomethyl)-4,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolin-7-carboxylate (9a). A mixture of 380 mg (1 mmol) of 5-hydroxy-5-methyl-3-(4-methoxyphenyl)cyclohexanone-2,4-dicarboxylic acid diethyl ether **1a**, 5 mL of glacial AcOH and 150 mg (1 mmol) of pyrazole **7** was refluxed for 4 h (control by TLC), then cooled. The precipitate was filtered off and washed with EtOH. Yield 22%, white

Main HSQC and HMBC $^{1}H–^{13}C$ correlations for compound **9a**



9a

δ_H, ppm	δ_C, ppm	
	$^{1}H–^{13}C$ HSQC	$^{1}H–^{13}C$ HMBC
1.09	14.1*	59.8
1.28	27.6*	41.5, 58.5*, 68.1
2.65–2.71	41.5, 58.5*	27.6, 40.1, 58.6*, 68.2, 108.5, 135.6, 148.0, 171.4
3.22	41.5	68.3, 108.7, 148.0
3.69	54.9*	157.5
3.94–4.15	59.8	14.1*, 171.4
4.27	40.2*	58.6*, 108.6, 128.7*, 135.6, 148.0, 153.8, 171.4
4.34	16.7	73.2, 116.2, 153.7
4.86	–	–
6.76	113.3*	113.3*, 135.6, 157.5
7.04	128.7*	40.2*, 113.3*, 128.7*, 157.5
13.29	–	–

amorphous powder. IR spectra, ν, cm^{-1}: 3476 (O–H), 3182, 3076 (N–H), 2262, 2226 (C≡N), 1720 ($C=O_{ether}$), 1688 ($C=O_{amide}$), 1649, 1593 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.09 t (3H, $C\underline{H}_3CH_2O$, ^{3}J = 7.1 Hz), 1.28 s (3H, $C^{8}C\underline{H}_3$), 2.65–2.71 two overlapped doublets (2H, H^{9} + H^{7}), 3.22 d (1H, H^{9}, ^{2}J = 17.1 Hz), 3.69 s (3H, CH_3O), 3.94–4.15 m (2H, $CH_3C\underline{H}_2O$, ABX_3-system), 4.27 d (1H, H^{6}, ^{3}J = 10.2 Hz), 4.34 s (2H, CH_2CN), 4.86 br. s (1H, OH), 6.76 d (2H, H^{3} + H^{5}, Ar, ^{3}J = 8.4 Hz), 7.04 d (2H, H^{2} + H^{6}, Ar, ^{3}J = 8.4 Hz), 13.29 br. s (1H, NH). ^{13}C DEPTQ NMR spectrum, δ_C, ppm (here and hereafter, an *asterisk* denotes the antiphase signals): 14.5* ($\underline{C}H_3CH_2O$), 16.7 ($\underline{C}H_2CN$), 27.6* ($C^{8}\underline{C}H_3$), 40.2* (C^{6}), 41.5 (C^{9}), 54.9* (CH_3O), 58.6* (C^{7}), 59.8 ($CH_3\underline{C}H_2O$), 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 ($\underline{C}O_2Et$). Found, %: C 62.60; H 5.07; N 15.11. $C_{24}H_{23}N_5O_5$. Calculated, %: C 62.46; H 5.02; N 15.18.

Ethyl 8-hydroxy-8-methyl-6-(4-nitrophenyl)-5-oxo-3-cyano-2-(cyanomethyl)-4,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazoline-7-carboxylate (9b) was obtained similarly from 1.34 g (3.4 mmol) of 5-hydroxy-5-methyl-3-(4-nitrophenyl)cyclohexanone-2,4-dicarboxylic acid diethyl ester **1b** and 0.5 g (3.4 mmol) of pyrazole **7**; reaction time – 7 h. Yield 15%, beige amorphous powder. IR spectra, ν, cm^{-1}: 3476 (O–H), 3231, 3179, 3074 (N–H), 2261, 2230 (C≡N), 1717 ($C=O_{ether}$), 1678 ($C=O_{amide}$), 1645, 1589 (C=C), 1522 [$\nu_{as}(NO_2)$], 1348 [$\nu_{s}(NO_2)$]. ^{1}H NMR spectrum, δ, ppm: 1.04 t (3H, $C\underline{H}_3CH_2O$, ^{3}J = 7.1 Hz), 1.29 s (3H,

$C^8C\underline{H}_3$), 2.70 d (1H, H^9, ^2J = 17.3 Hz), 2.76 d (1H, H^7, ^3J =10.3 Hz), 3.27 d (1H, H^9, ^2J = 17.3 Hz), 3.91–4.05 m (2H, $CH_3C\underline{H}_2O$, ABX_3-system), 4.33 s (2H, CH_2CN), 4.43 d (1H, H^6, ^3J = 10.3 Hz), 5.02 br. s (1H, OH), 7.43 d (2H, $H^2 + H^6$, Ar, ^3J = 8.6 Hz), 8.09 d (2H, $H^3 + H^5$, Ar, ^3J = 8.6 Hz), 13.44 br. s (1H, NH). ^{13}C DEPTQ NMR spectrum, d_C, ppm: 14.1* ($\underline{C}H_3CH_2O$), 16.7 ($\underline{C}H_2CN$), 27.4* ($C^8\underline{C}H_3$), 41.1* (C^6), 41.4 (C^9), 57.5* (C^7), 60.1 ($CH_3\underline{C}H_2O$), 68.1 (C^8), 73.5 (C^3), 107.1 (C^{5a}), 111.8 (CN), 116.1 ($CH_2\underline{C}N$), 123.2* (C^2, C^6 Ar), 129.2* (C^3, C^5 Ar), 146.0 (C^1 Ar), 147.99 (C^{9a} and C^{3a}), 148.02 (C^{3a} and C^{9a}), 148.2 (C^4 Ar), 152.1 (C^2), 153.9 (C^5), 170.8 ($\underline{C}O_2Et$). Found, %: C 57.95; H 4.30; N 17.71. $C_{23}H_{20}N_6O_6$. Calculated, %: C 57.98; H 4.23; N 17.64.

FUNDING

This work was financially supported by the Ministry of Education and Science of Russia (project no. 4.5547.2017/8.9, V.V. Dotsenko and I.V. Aksenova; project no. 4.1196.2017/4.6, N.A. Aksenov) using equipment of Environmental Analytical Center of the Kuban State University (unique identifier RFMEFI59317X0008).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Kriven'ko, A.P. and Sorokin, V.V., *Zameshcennye tsyklogeksanolones* (Substituted Cyclohexanolones), Saratov: Saratovsk. Univ., 1999, p. 20.
2. Ismiev, A.I., Magerramov, A.M., Sukach, V.A., and Vovk, M.V., *Zh. Org. Farm. Khim*., 2016, vol. 14, no. 4 (56), p. 16.
3. Ozols, A.I., Pelcher, Yu.Ê., Kalme, Z.A., Popelis, Yu.Yu., Turovskis, I.V., and Duburs, G.Ya., *Chem. Heterocycl. Compd*., 1996, vol. 32, no. 1, p. 52. doi 10.1007/BF01169354
4. Dyachenko, V.D., Sukach, S.M., and Dyachenko, A.D., *Chem. Heterocycl. Compd*., 2015, vol. 51, no. 1, p. 51. doi 10.1007/s10593-015-1658-9
5. Dyachenko, V.D. and Karpov, E.N., *Russ. J. Org. Chem*., 2014, vol. 50, no. 12, p. 1787. doi 10.1134/S1070428014120136
6. Sukach, S.M. and Dyachenko, V.D., *Russ. J. Org. Chem*., 2015, vol. 51, no. 7, p. 1020. doi 10.1134/S1070428015070210
7. Dyachenko, V.D. and Sukach, S.M., *Chem. Heterocycl. Compd*., 2010, vol. 46, no. 12, p. 1467. doi 10.1007/s10593-011-0693-4
8. Gein, V.L., Nosova, N.V., Potemkin, K.D., Aliev, Z.G., and Kriven'ko, A.P., *Russ. J. Org. Chem*., 2005, vol. 41, no. 7, p. 1016. doi 10.1007/s11178-005-0287-7
9. Sorokin, V.V., Grigoryev, A.V., Ramazanov, A.K., and Krivenko, A.P., *Chem. Heterocycl. Compd*., 1999, vol. 35, no. 6, p. 671. doi 10.1007/BF02251624
10. Smirnova, N.O., Plotnikov, O.P., Vinogradova, N.A., Sorokin, V.V., and Kriven'ko, A.P., *Pharm. Chem. J*., 1995, vol. 29, no. 1, p. 49. doi 10.1007/BF02219464
11. Poplevina, N.V., Kuznetsova, A.A., and Krivenko, A.P., *Chem. Heterocycl. Compd*., 2010, vol. 46, no. 9, p. 1148. doi 10.1007/s10593-010-0644-5
12. Dyachenko, V.D. and Sukach, S.M., *Russ. J. Gen. Chem*., 2012, vol. 82, no. 2, p. 305. doi 10.1134/S1070363212020211
13. Anwar, H.F. and Elnagdi, M.H., *Arkivoc*, 2009, p. 198. doi 10.3998/ark.5550190.0010.107
14. Abu Elmaati, T.M. and El-Taweel, F.M., *J. Heterocycl. Chem*., 2004, vol. 41, no. 2, p. 109. doi 10.1002/jhet.5570410201
15. Etman, H.A., Sadek, M.G., and Khalil, A.G.M., *Res. J. Pharm. Biol. Chem. Sci*., 2015, vol. 6, no. 2, p. 247.
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., and Magerramov, A.M., *Chem. Heterocycl. Compd*., 2016, vol. 52, no. 7, p. 473. doi 10.1007/s10593-016-1918-3
17. Dotsenko, V.V., Krivokolysko, S.G., Chernega, A.N., and Litvinov, V.P., *Russ. Chem. Bull*., 2003, vol. 52, no. 4, p. 969. doi 10.1023/A:1024420930528
18. Tverdokhleb, N.M., Khoroshilov, G.E., and 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., and Krivokolysko, S.G., *Chem. Heterocycl. Compd.*, 2017, vol. 53, no. 5, p. 626. doi 10.1007/s10593-017-2103-z
20. Ledenyova, I.V., Didenko, V.V., Dotsenko, V.V., and Shikhaliev, K.S., *Tetrahedron Lett*., 2014, vol. 55, no. 6, p. 1239. doi 10.1016/j.tetlet.2014.01.010
21. Kolosov, M.A., Beloborodov, D.A., Orlov, V.D., and Dotsenko, V.V., *New J. Chem*., 2016, vol. 40, no. 9, p. 7573. doi 10.1039/c6nj00336b
22. Carboni, R.A., Coffman, D.D., and Howard, E.G., *J. Am. Chem. Soc*., 1958, vol. 80, no. 11, p. 2838. doi 10.1021/ja01544a061
23. Metwally, N.H., Abdallah, M.A., and Almabrook, S.A., *J. Heterocycl. Chem*., 2017, vol. 54, no. 1, p. 347. doi 10.1002/jhet.2590

24. Ragab, E.A., Metwally, N.H., and Mohamed, M.S., *Synth. Commun*., 2017, vol. 47, no. 2, p. 148. doi 10.1080/00397911.2016.1257722
25. Elkholy, A., Al-Qala, F., and Elnagdi, M.H., *Arkivoc*, 2008, p. 124.
26. Metwally, N.H. and Mohamed, M.S., *Synth. Commun*., 2018, vol. 48, no. 7, p. 721. doi 10.1080/00397911.2017.1399208
27. Garg, M., Chauhan, M., Singh, P.K., Alex, J.M., and Kumar, R., *Eur. J. Med. Chem*., 2015, vol. 97, p. 444. doi 10.1016/j.ejmech.2014.11.051
28. Yet, L., *Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis*, New York: John Wiley & Sons, 2018, p. 9.
29. Elnagdi, M.H., Sallam, M.M.M., and Ilias, M.A.M., *Helv. Chim. Acta*, 1975, vol. 58, no. 7, p. 1944. doi 10.1002/hlca.19750580710
30. Zayed, E.M., Ghozlan, S.A.S., and Ibrahim, A.A.H., *Monatsh. Chem.*, 1984, vol. 115, no. 4, p. 431. doi 10.1007/BF00810004
31. Finar, I.L., *J. Chem. Soc*., 1961, no. 2, p. 674. doi 10.1039/JR9610000674