

Synthesis and Aminomethylation of 2-Amino-4-(2-chlorophenyl)-6-(dicyanomethyl)- 1,4-dihydropyridine-3,5-dicarbonitrile N-Methylmorpholinium Salt

A. O. Kurskova^a, V. V. Dotsenko^{b,c,*}, K. A. Frolov^a, N. A. Aksenov^c, I. V. Aksenova^c,
B. S. Krivokolysko^d, A. A. Peresyphkina^e, E. A. Chigorina^{f,g}, and S. G. Krivokolysko^{a,d}

^a ChemEx Laboratory, V. Dahl Lugansk State University, Lugansk, 91034 Ukraine

^b Kuban State University, Krasnodar, 350040 Russia

^c North Caucasian Federal University, Stavropol, 355009 Russia

^d Lugansk State Medical University named after St. Luke, Lugansk, 91045 Ukraine

^e Belgorod State National Research University, Belgorod, 308015 Russia

^f National Research Center “Kurchatov Institute” – IREA, Moscow, 107076 Russia

^g National Research Center “Kurchatov Institute”, Moscow, 123182 Russia

*e-mail: victor_dotsenko_@mail.ru

Received January 6, 2022; revised February 15, 2022; accepted February 17, 2022

Abstract—Sequential reaction of 2-chlorobenzaldehyde, cyanothioacetamide, and malononitrile dimer in the presence of an excess of *N*-methylmorpholine resulted in the formation of *N*-methylmorpholinium salt of 2-amino-4-(2-chlorophenyl)-6-(dicyanomethyl)-1,4-dihydropyridine-3,5-dicarbonitrile. The resulting salt reacts under Mannich conditions with primary amines and an excess of formaldehyde to form substituted 2-alkylamino-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitriles. Structure of the key compound was confirmed by single crystal X-ray diffraction analysis.

Keywords: cyanothioacetamide, 2-aminopropene-1,1,3-tricarbonitrile, aminomethylation, 1,4-dihydropyridines, calculated biological activity

DOI: 10.1134/S1070363222050061

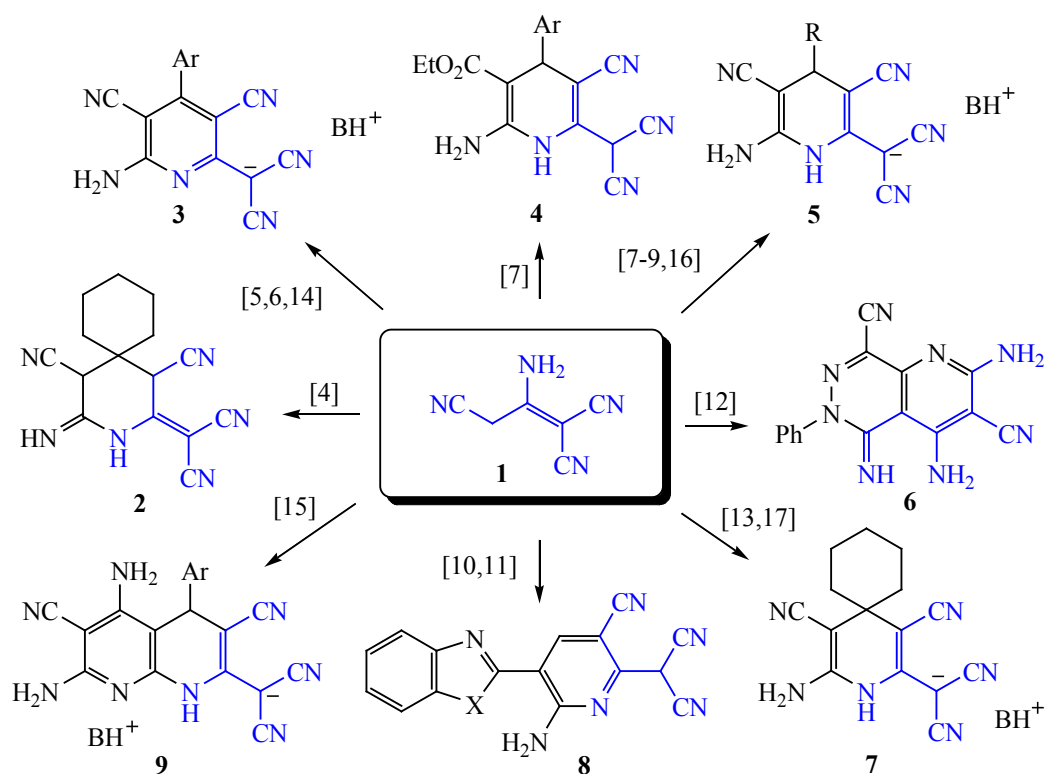
2-Aminopropene-1,1,3-tricarbonitrile **1**, easily available [1] by dimerization of malononitrile, is a reactive methylene active nitrile and is widely used in various cyclization reactions (see reviews [2, 3]). In reactions with unsaturated nitriles or their precursors, the malononitrile dimer forms partially saturated and/or polyfunctional derivatives of 2-(dicyanomethyl)- and 2-(dicyanomethylene)pyridine **2–9** [4–17] (Scheme 1).

Despite the rich synthetic potential, there are scarce data on the preparation of such pyridine derivatives [2, 3]. The potential for the practical use of such compounds has not been fully realized. Thus, anticancer [18], molluscicidal [8], and antibacterial [19, 20] effects of a number of 2-(dicyanomethyl)pyridines have been reported. A

series of 3-cyano-2-(dicyanomethylene)pyridines with pronounced fluorescent and photoluminescent properties has been described in [21–23].

Continuing our research in the field of malononitrile dimer chemistry [24–28], we obtained new functional 2-(dicyanomethyl)pyridine derivatives and studied their properties. It has been previously shown that 2-cyanothioacrylamides can react with malononitrile dimer in the presence of bases to eliminate hydrogen sulfide and form dicyanomethanides **5** (Ar = 2-IC₆H₄) and **7** (Scheme 2) [13, 17]. On the other hand, the three-component reaction of acetaldehyde, dimer **1**, and cyanothioacetamide leads to the formation of thioamide **10** [29].

Scheme 1.



B = base (morpholine, *N*-methylmorpholine).

We found that the sequential reaction of 2-chlorobenzaldehyde, cyanothioacetamide [30, 31], and malononitrile dimer **1** in EtOH in the presence of an excess of *N*-methylmorpholine at 25°C proceeds with the formation of 2-amino-4-(2-chlorophenyl)-6-(dicyanomethyl)-1,4-dihydropyridine-3,5-dicarbonitrile *N*-methylmorpholinium salt **11** in 68% yield (Scheme 3). This reaction includes the intermediate formation of 3-(2-chlorophenyl)-2-cyanoprop-2-enethioamide **12** [32], the Michael addition of the malononitrile dimer anion, and the cyclocondensation of adduct **13** with elimination of H₂S to afford the target salt **11**.

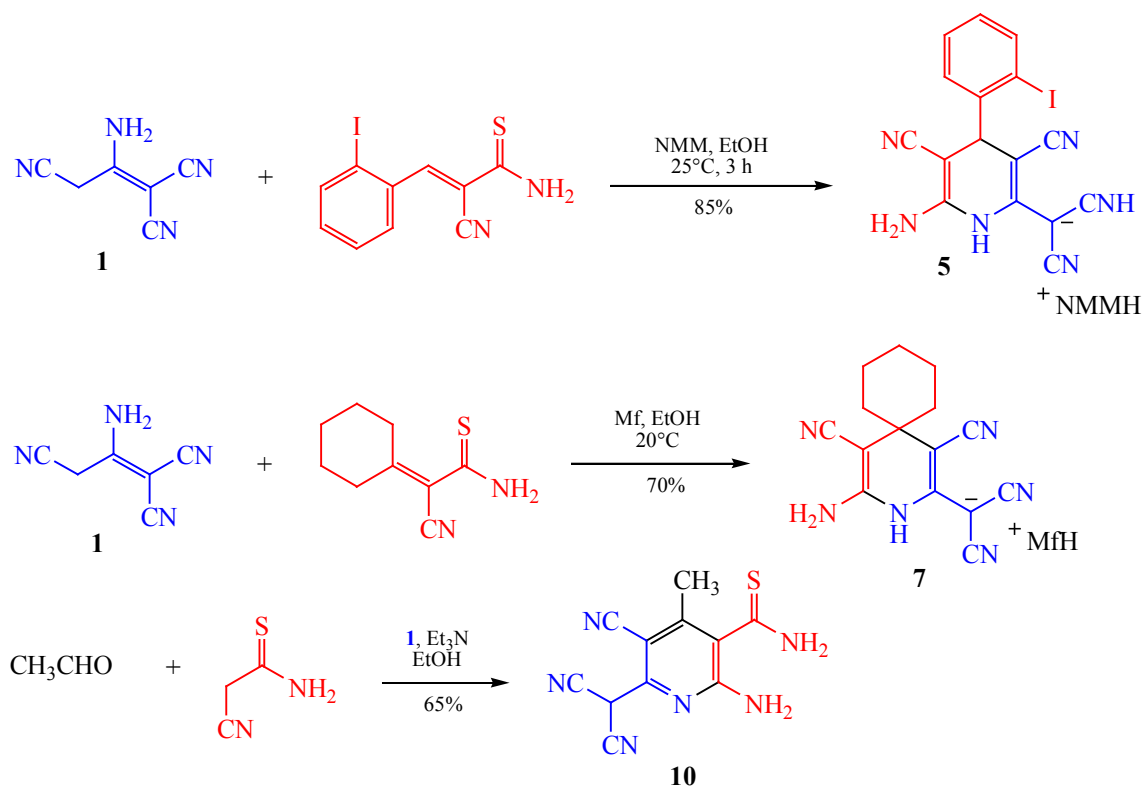
Previously, we found that aminomethylation of isostructural analogs of compound **11**, 1,4-dihydropyridine-2-thiolates and -selenolates **14**, under the action of an excess of HCHO and primary amines leads to the formation of new tricyclic system derivatives, namely 3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene **15** [33, 34]. Some of compounds **15** showed antiviral activity

against tick-borne encephalitis virus [35]. At the same time, the Mannich reaction involving 2-(dicyanomethylene)pyridine **2** under similar conditions [4] yields only 2-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-en-1,5-dicarbonitriles **16** (Scheme 4).

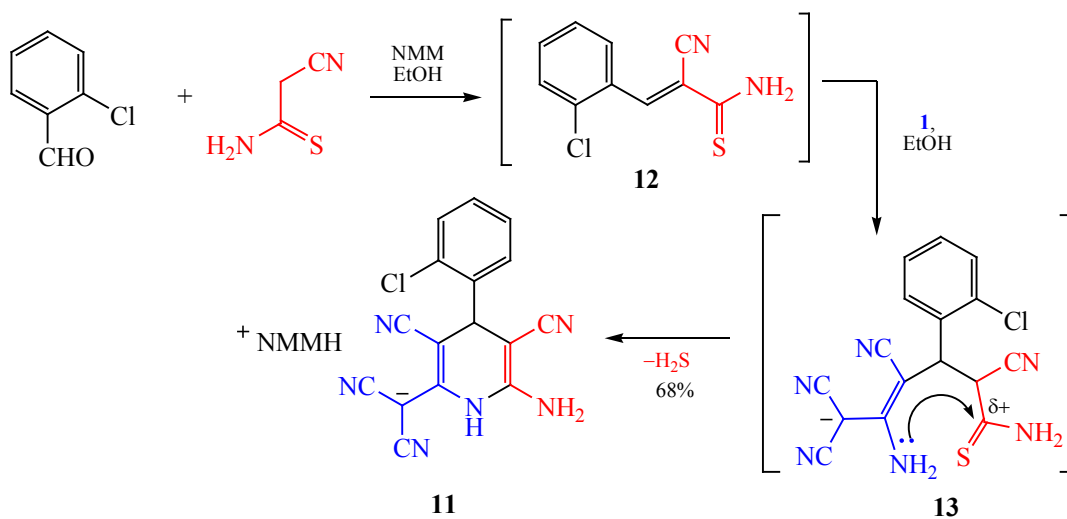
It seemed appropriate to study the behavior of dicyanomethanide **11** in the Mannich reaction. Alkoxy-methylation/aminomethylation products, namely substituted 2-(*R*-amino)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-en-1,5-dicarbonitriles **17** and **18** were obtained in moderate yields (41–69%) upon short-term reflux of compound **11** with a twofold (or equimolar) amount of primary amine and an excess of 37% aqueous HCHO in various alcohols (MeOH, EtOH, PrOH, *i*-PrOH, BuOH) (Scheme 5).

The reaction tolerates both aliphatic and aromatic amines. Presumably, in each case, the process begins with aminomethylation at the most active nucleophilic positions 3 and 5 of compound **11** to form the 3,7-diazabicyclo[3.3.1]-

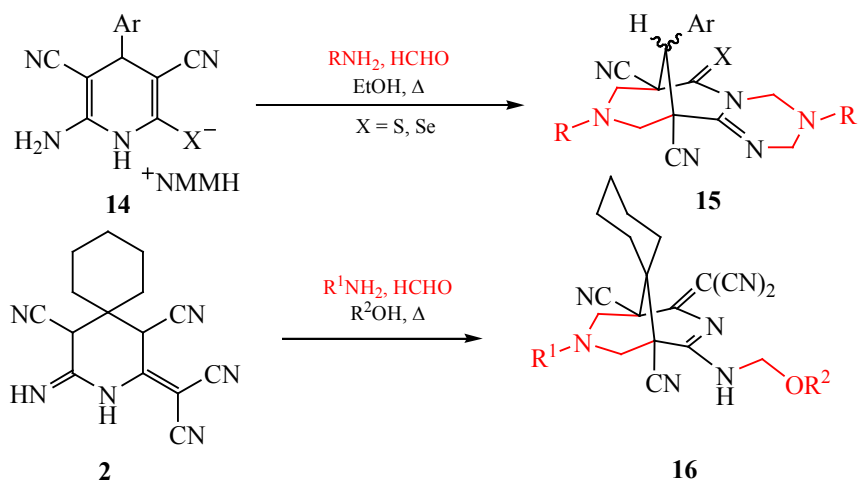
Scheme 2.

NMM = *N*-methylmorpholine; Mf = morpholine.

Scheme 3.

NMM = *N*-methylmorpholine; Mf = morpholine.

Scheme 4.



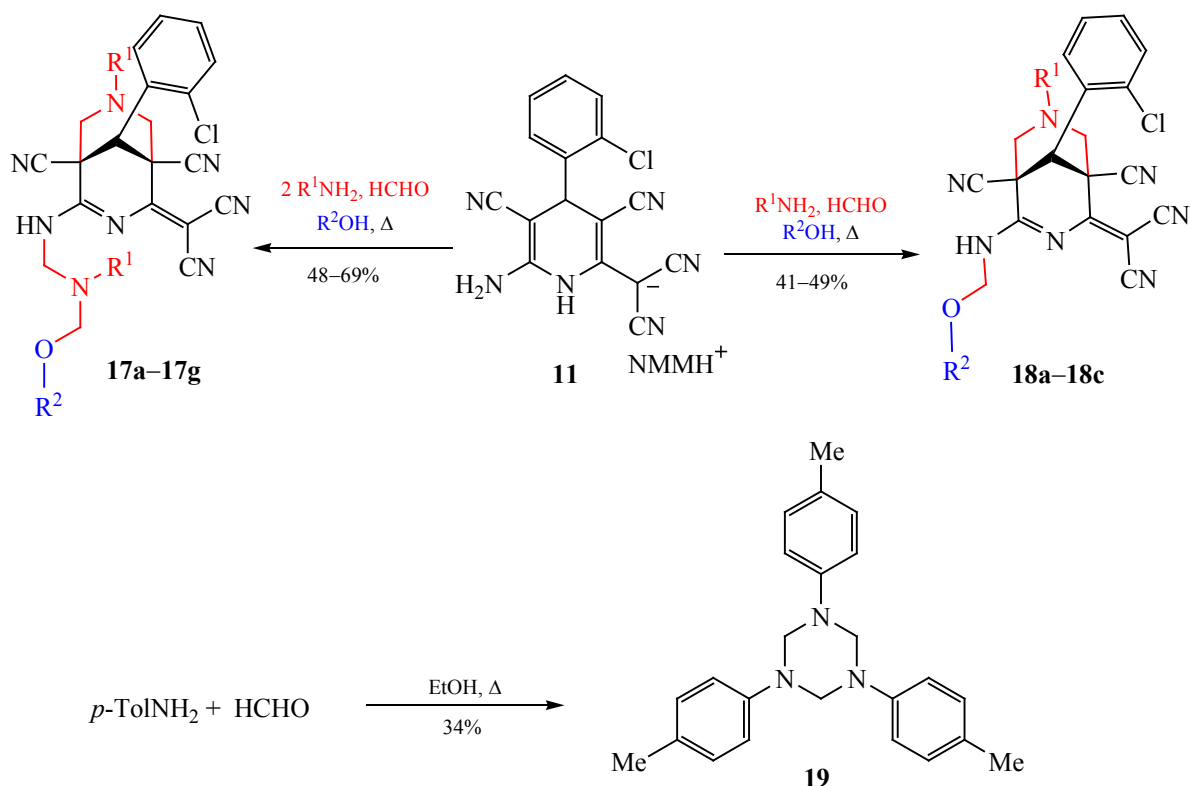
non-2-ene system. The choice of the reaction direction in favor of the formation of products **17** or **18** is apparently determined by the presence or absence of an excess of amine in the reaction medium. Closure of the 1,3,5-triazine ring was not observed in any of the cases. In our opinion, this is due to the low nucleophilicity of the endocyclic nitrogen atom owing to the strong electron-withdrawing effect of the dicyanomethylene fragment. The nature of the amines used and the chosen solvents do not have a fundamental effect on regioselectivity of the aminomethylation process. At the same time, the reaction of the salt **11** with *p*-toluidine in ethanol resulted in the isolation of the well-known [36] product of its reaction with formaldehyde, 1,3,5-tri(4-methylphenyl)-1,3,5-perhydrotriazine **19**. However, it should be noted that compound **19** is also an aminomethylating agent and can successfully act as this agent in the absence of any catalysts (see, for example, recent examples in the review [37]). The absence of reaction with compound **11** can be explained by the relatively low solubility of 1,3,5-perhydrotriazine **19** in aqueous alcohol and removal from the reaction medium.

Structure of compounds **17–19** was determined using mass spectroscopy, ^1H and ^{13}C NMR spectroscopy (DEPTQ), as well as IR spectroscopy method. In addition, structure of compound **17c** was studied using single-crystal X-ray diffraction analysis (Fig. 1).

3,7-Diazabicyclo[3.3.1]nonanes (bispidins) and related compounds are widely used as biologically active compounds [38, 39], complexing agents for metals [40],

radionuclides [41], as initial reagents for the synthesis of natural compounds [42], materials for imaging in positron emission tomography [43], platforms for chiral catalysts [44, 45]. Recently, 3,7-diazabicyclononane derivatives have been successfully used as initial templates for constructing complex supramolecular assemblies [46–49]. Recently, submicromolar inhibitors of the main SARS-CoV-2 protease have been found among bispidins [50]. Based on the foregoing, it seemed appropriate to study the profile of the possible biological activity of new compounds by means of molecular docking. Possible protein targets for the obtained compounds were predicted using the GalaxySagittarius protein ligand docking protocol [51] based on the GalaxyWeb web server [52, 53]. The 3D structures of the studied compounds were preliminarily optimized by means of molecular mechanics in the MM2 force field to optimize the geometry and minimize the energy. Docking using the GalaxySagittarius protocol was carried out in the Binding compatibility prediction and Re-ranking using docking modes. Table S1 (see Supplementary Materials) shows docking results for each of compounds **17a–17g**, **18a–18c** for 20 target-ligand complexes with the lowest binding free energy ΔG_{bind} and the best estimate of the protein-ligand interaction. Predicted protein targets are identified by ID in the Protein Data Bank (PDB) and in the UniProt database. As you can see from Table S1, common receptors for compounds **17a–17g**, **18a–18c** are blood coagulation factor XI (PDB ID 5e2p) and ephrin receptor (ephrin type-A receptor 2, PDB ID 5ia5), which

Scheme 5.



$R^1 = \text{Me}$, $R^2 = \text{Et}$ (**17a**); $R^1 = \text{Me}$, $R^2 = \text{Pr}$ (**17b**); $R^1 = \text{furfuryl}$, $R^2 = \text{Et}$ (**17c**); $R^1 = \text{furfuryl}$, $R^2 = \text{Me}$ (**17d**); $R^1 = \text{furfuryl}$, $R^2 = \text{Bu}$ (**17e**); $R^1 = \text{Ph}$, $R^2 = \text{Et}$ (**17f**); $R^1 = i\text{-Pr}$, $R^2 = \text{Et}$ (**17g**); $R^1 = \text{Me}$, $R^2 = \text{Et}$ (**18a**); $R^1 = \text{Me}$, $R^2 = i\text{-Pr}$ (**18b**); $R^1 = i\text{-Pr}$, $R^2 = i\text{-Pr}$ (**18c**).

plays an important role in the pathogenesis of some cancer forms (melanoma, Kaposi's sarcoma). Three-dimensional visualization of the docking results was implemented using the UCSF Chimera software package [54, 55] and is shown in Fig. 2. In general, compounds **17a–17g**, **18a–18c** can be considered as promising objects for further screening in order to find new agents for the treatment and therapy of oncological diseases and circulatory system diseases.

In conclusion, we proposed a method for the synthesis of new 2-amino-4-(2-chlorophenyl)-6-(dicyanomethyl)-1,4-dihydropyridine-3,5-dicarbonitrile *N*-methylmorpholinium salt and studied its aminomethylation. It was found that the reaction proceeds with the participation of solvent molecules and the formation of 4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-en-1,5-dicarbonitrile derivatives. The formation of 1,3,5-triazine fused derivatives was not revealed. Possible

protein targets were determined for the synthesized compounds by molecular docking.

EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX-400 NMR spectrometer [400.40 (¹H), 100.63 (¹³C), 40.55 MHz (¹⁵N)] in DMSO-*d*₆ relative to internal TMS or residual solvent signals. IR spectra were recorded on a Bruker Vertex 70 IR Fourier spectrometer with an ATR attachment on a diamond crystal. Mass spectra were obtained on a MX1321 instrument using a direct sample injection system at an ionization chamber temperature of 200°C and an ionizing electron energy of 70 eV. Elemental analysis was carried out on a C,H,N analyzer Carlo Erba 1106, measurement error $\pm 0.4\%$. Purity of the obtained compounds was monitored by TLC on Silufol UV254 plates, eluting with acetone–hexane (1 : 1) and developing with iodine vapor or UV detector. Melting

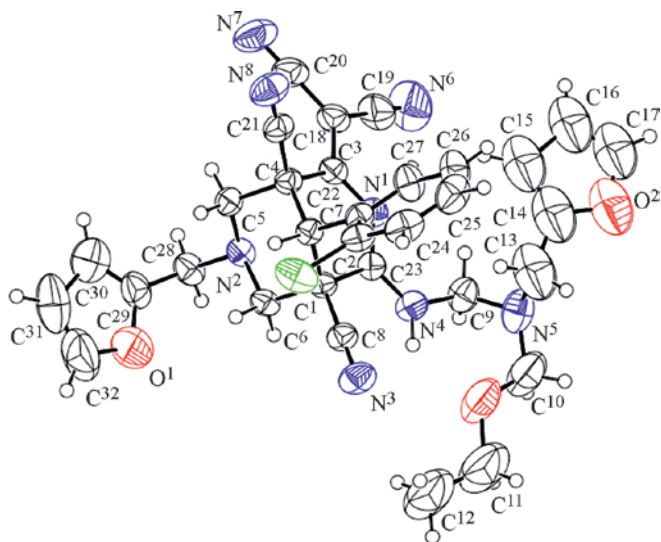


Fig. 1. General view of the molecule of compound **17c** in the crystal.

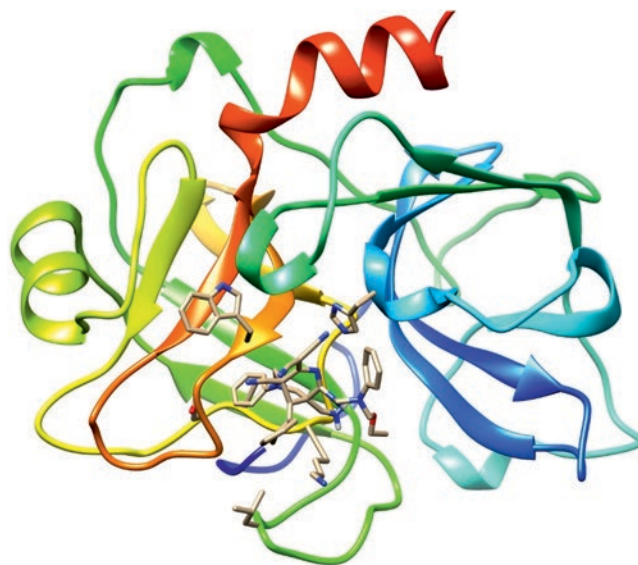


Fig. 2. Predicted structure of the protein-ligand complex for compound **17f** and blood coagulation factor XI (PDB ID 5e2p).

points were determined on a Kofler instrument and were not corrected.

Commercially available reagents were used; cyanothioacetamide [56] and malononitrile dimer **1** [1] were obtained by known methods.

2-Amino-4-(2-chlorophenyl)-6-(dicyanomethyl)-1,4-dihydropyridine-3,5-dicarbonitrile *N*-methylmorpholinium salt (11). A mixture of 0.84 mL (7.5 mmol) of 2-chlorobenzaldehyde, 0.75 g (7.5 mmol) of cyanothioacetamide and 1 drop of *N*-methylmorpholine in 15–20 mL of ethanol was stirred at 20°C. After 10 min, 1.00 g (7.5 mmol) of malononitrile dimer **1** and 1.5 mL (15 mmol) of *N*-methylmorpholine were added to the resulting orange suspension of 3-(2-chlorophenyl)-2-cyanothioacrylamide **12**. After dissolution of all starting components, the reaction mixture was stirred for 2 h at 20°C and kept for 12 h. The resulting precipitate was filtered off, washed with cold EtOH and dried for 3 h at 60°C. Yield 68%, gray-beige finely crystalline powder, mp 185–187°C. IR spectrum, ν , cm^{-1} : 2217 br, 2193 br ($\text{C}\equiv\text{N}$), 3325 br ($\text{N}-\text{H}$, N^+-H). ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 2.78 s (3H, Me), 3.17–3.20 m (4H, CH_2NCH_2), 3.73–3.76 m (4H, CH_2OCH_2), 4.56 s (1H, C^4H), 6.03 br. s (2H, NH_2), 7.19–7.22 m, 7.30–7.35 m (each 2H, Ar), 7.85 s (1H, NH), 8.13 s (1H, N^+H ,

integral intensity of signal is underestimated, probably due to deuterium exchange). ^{13}C NMR spectrum DEPTQ ($\text{DMSO}-d_6$), δ_{C} , ppm: 38.4* (C^4), 42.6* (Me), 52.7 (CH_2NCH_2), 55.1 (C^3), 63.4 [$\text{C}(\text{C}\equiv\text{N})_2$], 63.5 (CH_2OCH_2), 65.5 (C^5), 114.2 ($\text{C}^3\text{C}\equiv\text{N}$), 120.8 ($\text{C}\equiv\text{N}$), 121.2 ($\text{C}\equiv\text{N}$), 121.6 ($\text{C}\equiv\text{N}$), 127.8* ($\text{CH}-\text{Ar}$), 128.2* ($\text{CH}-\text{Ar}$), 129.1* ($\text{CH}-\text{Ar}$), 130.0* ($\text{CH}-\text{Ar}$), 131.1 (C^1-Ar), 144.0, 147.5 (CCl , C^2), 151.2 (C^6). Here and below, signals in antiphase are marked with an asterisk. Found, %: C 59.61; H 4.67; N 23.03. $\text{C}_{21}\text{H}_{20}\text{ClN}_7\text{O}$. Calculated, %: C 59.79; H 4.78; N 23.24. M 421.9.

General procedure for the preparation of compounds 17–19. A mixture of 0.84 g (2 mmol) of salt **11**, 4 mmol (for **17** or **19**) or 2 mmol (for **18**) of the corresponding primary amine, 3.5 mL of 37% aqueous HCHO in 20 mL of alcohol (MeOH, EtOH, PrOH, *i*-PrOH or BuOH) was brought to a reflux and completely homogenized. The hot solution was filtered through a paper filter and kept for 24–72 h. The resulting precipitate was separated, washed with ethanol and dried for 3 h at 60°C.

7-Methyl-2-([methyl(ethoxymethyl)amino]-methyl)-9-(2-chlorophenyl)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (17a). Yield 57%, yellow fine crystalline

powder, mp 191–193°C. IR spectrum, ν , cm^{-1} : 2173 m ($\text{C}\equiv\text{N}$), 2205 m ($\text{C}\equiv\text{N}$), 2248 m ($\text{C}\equiv\text{N}$), 3320 br (NH). ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 1.05 t (3H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 6.9 Hz), 2.30–2.36 m (6H, 2MeN), 2.71–2.96 m (2H, C^6H , C^8H), 3.15–3.26 m (2H, C^6H , C^8H), 3.43 q (2H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 6.9 Hz), 4.31–4.33 m (2H, NCH_2N), 4.51–4.72 m (3H, NCH_2O , C^9H), 7.08–7.15 m (1H, Ar), 7.36–7.49 m (2H, Ar), 7.58–7.65 m (1H, Ar), 9.95 br. s (1H, NH, integral intensity of the signal is underestimated, probably due to deuterium exchange). ^{13}C NMR spectrum DEPTQ ($\text{DMSO}-d_6$), δ_{C} , ppm: 18.6* ($\text{CH}_3\text{CH}_2\text{O}$), 40.4, 41.6 (C^1 , C^5), 43.7* (MeN), 46.7* (MeN), 47.9* (C^9), 56.0, 59.9 (C^6 , C^8), 60.8 ($\text{CH}_3\text{CH}_2\text{O}$), 60.9 [$\text{C}(\text{C}\equiv\text{N})_2$], 65.9 (NCH_2N), 78.1 (NCH_2O), 113.9 ($\text{C}\equiv\text{N}$), 114.6 ($\text{C}\equiv\text{N}$), 115.1 ($\text{C}\equiv\text{N}$), 115.2 ($\text{C}\equiv\text{N}$), 127.8* (CH-Ar), 128.8* (CH-Ar), 130.9* (CH-Ar), 131.1 (C^1 -Ar), 131.3* (CH-Ar), 135.5 (CCl), 161.9 (C^2), 168.5 (C^4). Mass spectrum, m/z (I_{rel} , %): 432 (4) [$M - \text{EtO}$] $^+$, 431 (13) [$M - \text{EtO} - 1$] $^+$, 376 (7) [$M - \text{EtOCH}_2\text{N}(\text{Me})\text{CH}_2 + 1$] $^+$, 307 (10) [$M - \text{EtOCH}_2\text{N}(\text{Me})\text{CH}_2\text{NH} - \text{CH}_2\text{N}(\text{Me})\text{CH}_2 + 4$] $^+$. Found, %: C 60.35; H 2.65; N 23.32. $\text{C}_{24}\text{H}_{25}\text{ClN}_8\text{O}$. Calculated, %: C 60.44; H 5.28; N 23.49. M 477.0.

7-Methyl-2-({[methyl(propoxymethyl)amino]methyl}amino)-9-(2-chlorophenyl)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (17b). Yield 48%, bright yellow fine crystalline powder, mp 203–205°C. IR spectrum, ν , cm^{-1} : 2167 m ($\text{C}\equiv\text{N}$), 2195 m ($\text{C}\equiv\text{N}$), 2225 m ($\text{C}\equiv\text{N}$), 3323 br (NH). ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 0.82 t (3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 7.5 Hz), 1.39–1.42 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$), 2.30–2.35 m (6H, MeN), 2.63–2.95 m (2H, C^6H , C^8H), 3.15–3.33 m (4H, C^6H , C^8H , $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$), 4.31–4.36 m (2H, NCH_2N), 4.49–4.77 m (3H, NCH_2O , C^9H), 7.07–7.14 m (1H, Ar), 7.38–7.50 m (2H, Ar), 7.58–7.67 m (1H, Ar), 9.95 br. s (1H, NH, integral intensity of the signal is underestimated, probably due to deuterium exchange). Due to the low solubility of the compound in $\text{DMSO}-d_6$ an informative ^{13}C DEPTQ NMR spectrum could not be obtained. Found, %: C 60.94; H 5.41; N 22.58. $\text{C}_{25}\text{H}_{27}\text{ClN}_8\text{O}$. Calculated, %: C 61.16; H 5.54; N 22.82. M 491.0.

7-(2-Furylmethyl)-2-({[2-furylmethyl(ethoxymethyl)amino]methyl}amino)-9-(2-chlorophenyl)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (17c). Yield 68%, orange crystalline powder, mp 161–163°C. IR spectrum, ν , cm^{-1} : 2185 m ($\text{C}\equiv\text{N}$), 2197 m ($\text{C}\equiv\text{N}$), 2220 m ($\text{C}\equiv\text{N}$), 2250 m ($\text{C}\equiv\text{N}$), 3330 br (NH). ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm:

1.05 t (3H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 7.1 Hz), 3.25–3.42 m (4H, C^6H_2 , C^8H_2), 3.44 q (2H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 7.1 Hz), 3.61–3.93 m (4H, NCH_2 -furyl), 4.14–4.34 m (2H, NCH_2N), 4.49–5.03 m (3H, NCH_2O , C^9H), 6.25–6.44 m (4H, furyl), 7.04–7.65 m (6H, Ar, furyl), 9.95 br. s (1H, NH, integral intensity of the signal is underestimated, probably due to deuterium exchange). ^{13}C NMR spectrum DEPTQ ($\text{DMSO}-d_6$), δ_{C} , ppm: 18.6* (MeCH_2O), 40.7, 45.8 (C^1 , C^5), 46.9* (C^9), 51.1 (CH_2 -furyl), 56.0, 58.2 (C^6 , C^8), 60.9 [$\text{C}(\text{C}\equiv\text{N})_2$], 62.4 (MeCH_2O), 66.1 (NCH_2N), 83.2 (NCH_2O), 109.5*, 110.5* (C^3 , C^4 -furyl), 113.4 ($\text{C}\equiv\text{N}$), 114.4 ($\text{C}\equiv\text{N}$), 115.0 ($\text{C}\equiv\text{N}$), 115.1 ($\text{C}\equiv\text{N}$), 128.2*, 128.7*, 130.7* (CH-Ar), 130.9 (C^1 -Ar), 131.3* (CH-Ar), 135.4 (C-Cl), 142.6*, 143.2* (C^5 -furyl), 149.8 (C^2 -furyl), 161.8 (C^2), 168.5 (C^4). Mass spectrum, m/z (I_{rel} , %): 564 (14) [$M - \text{EtO}$] $^+$, 563 (28) [$M - \text{EtO} - 1$] $^+$, 454 (8) [$M - \text{EtOCH}_2\text{NCH}_2$ -furyl - 1] $^+$, 442 (9) [$M - \text{EtOCH}_2\text{N}(\text{CH}_2$ -furyl) $\text{CH}_2 + 1$] $^+$. Found, %: C 62.82; H 4.58; N 18.16. $\text{C}_{32}\text{H}_{29}\text{ClN}_8\text{O}_3$. Calculated, %: C 63.10; H 4.80; N 18.40. M 609.1.

2-({[Methoxymethyl(2-furylmethyl)amino]methyl}amino)-7-(2-furylmethyl)-9-(2-chlorophenyl)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (17d). Yield 59%, orange fine crystalline powder, mp 158–160°C. IR spectrum, ν , cm^{-1} : 2167 m ($\text{C}\equiv\text{N}$), 2200 m ($\text{C}\equiv\text{N}$), 2245 m ($\text{C}\equiv\text{N}$), 3310 br (N-H). ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 3.27–3.44 m (7H, C^6H_2 , C^8H_2 , MeO), 3.62–3.92 m (4H, NCH_2 -furyl), 4.13–4.34 m (2H, NCH_2N), 4.39–5.10 m (3H, NCH_2O , C^9H), 6.19–6.45 m (4H, furyl), 7.06–7.64 m (6H, Ar, furyl), 9.95 br. s (1H, NH, integral intensity of the signal is underestimated, probably due to deuterium exchange). ^{13}C NMR spectrum DEPTQ ($\text{DMSO}-d_6$), δ_{C} , ppm: 40.8, 41.7 (C^1 , C^5), 46.9* (MeO), 47.1* (C^9), 51.1 (CH_2 -furyl), 57.8, 58.2 (C^6 , C^8), 60.9 [$\text{C}(\text{C}\equiv\text{N})_2$], 66.3 (NCH_2N), 81.6 (NCH_2O), 109.5*, 110.5* (C^3 , C^4 -furyl), 113.8 ($\text{C}\equiv\text{N}$), 114.6 ($\text{C}\equiv\text{N}$), 115.0 ($\text{C}\equiv\text{N}$), 115.1 ($\text{C}\equiv\text{N}$), 127.9* (CH-Ar), 128.8* (CH-Ar), 130.7* (CH-Ar), 131.0 (C^1 -Ar), 131.3* (CH-Ar), 135.4 (CCl), 143.1*, 143.3* (C^5 -furyl), 149.8 (C^2 -furyl), 161.8 (C^2), 168.5 (C^4). Found, %: C 62.38; H 4.45; N 18.58. $\text{C}_{31}\text{H}_{27}\text{ClN}_8\text{O}_3$. Calculated, %: C 62.57; H 4.57; N 18.83. M 595.1.

2-({[Butoxymethyl(2-furylmethyl)amino]methyl}amino)-7-(2-furylmethyl)-9-(2-chlorophenyl)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (17e). Yield 63%, yellow fine crystalline powder, mp 145–147°C. IR spectrum, ν , cm^{-1} : 2165 m ($\text{C}\equiv\text{N}$), 2193 m ($\text{C}\equiv\text{N}$), 2225 m ($\text{C}\equiv\text{N}$),

3375 br (N–H). ^1H NMR spectrum (DMSO- d_6), δ , ppm: 0.85 t (3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 7.2 Hz), 1.25–1.29 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 1.35–1.38 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 3.24–3.42 m (6H, C^6H_2 , C^8H_2 , $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 3.74–3.91 m (4H, NCH_2 -furyl), 4.35 br. s, 4.49 br. s (2H, NCH_2N), 4.58 s (1H, C^9H), 4.67–4.90 m (2H, NCH_2O), 6.23–6.45 m (4H, furyl), 7.05–7.64 m (6H, Ar, furyl), 9.95 br. s (1H, NH, integral intensity of signal is underestimated, probably due to deuterium exchange). ^{13}C NMR spectrum DEPTQ (DMSO- d_6), δ_{C} , ppm: 13.9* ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 18.7 ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 34.7 ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 40.9, 41.9 (C^1 , C^5), 46.9* ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 47.1* (C^9), 51.1 (CH_2 -furyl), 58.2, 60.4 (C^6 , C^8), 61.1 ($\text{C}(\text{C}\equiv\text{N})_2$), 68.4 (NCH_2N), 81.6 (NCH_2O), 109.4*, 110.4* (C^3 , C^4 -furyl), 113.8 ($\text{C}\equiv\text{N}$), 114.6 ($\text{C}\equiv\text{N}$), 115.0 ($\text{C}\equiv\text{N}$), 115.1 ($\text{C}\equiv\text{N}$), 127.9* (CH-Ar), 128.8* (CH-Ar), 130.7* (CH-Ar), 130.9 (C^1 -Ar), 131.3* (CH-Ar), 135.4 (C-Cl), 143.2* (C^5 -furyl), 149.8 (C^2 -furyl), 161.8 (C^2), 168.5 (C^4). Found, %: C 63.94; H 5.08; N 17.34. $\text{C}_{34}\text{H}_{33}\text{ClN}_8\text{O}_3$. Calculated, %: C 64.09; H 5.22; N 17.59. *M* 637.1.

7-Phenyl-2-([phenyl(ethoxymethyl)amino]methyl)amino-9-(2-chlorophenyl)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (17f). Yield 74%, brown fine crystalline powder, mp 155–157°C. IR spectrum, ν , cm^{-1} : 2175 m ($\text{C}\equiv\text{N}$), 2195 m ($\text{C}\equiv\text{N}$), 2247 m ($\text{C}\equiv\text{N}$), 3390 br (N–H). ^1H NMR spectrum (DMSO- d_6), δ , ppm: 1.06 t (3H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 6.9 Hz), 3.43 q (2H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 6.9 Hz), 4.02–4.11 m (2H, C^6H , C^8H), 4.24–4.36 m (2H, C^6H , C^8H), 4.55–4.93 m (5H, NCH_2N , C^9H , NCH_2O), 6.77–7.67 m (14H, 3Ar), 10.19 br. s (1H, NH, integral intensity of the signal is underestimated, probably due to deuterium exchange). Due to the low solubility of the compound in DMSO- d_6 an informative ^{13}C DEPTQ NMR spectrum could not be registered. Mass spectrum, m/z (I_{rel} , %): 557 (6) [$M - \text{EtO} + 1$] $^+$, 556 (6) [$M - \text{EtO}$] $^+$, 555 (7) [$M - \text{EtO} - 1$] $^+$, 495 (20) [$M - \text{Ph} - \text{Et}$] $^+$, 452 (12) [$M - \text{EtOCH}_2\text{NPh}$] $^+$, 451 (13) [$M - \text{EtOCH}_2\text{NPh} - 1$] $^+$, 450 (25) [$M - \text{EtOCH}_2\text{NPh} - 2$] $^+$. Found, %: C 67.71; H 4.69; N 18.45. $\text{C}_{34}\text{H}_{29}\text{ClN}_8\text{O}_3$. Calculated, %: C 67.94; H 4.86; N 18.64. *M* 601.1.

7-Isopropyl-2-([isopropyl(ethoxymethyl)amino]methyl)amino-9-(2-chlorophenyl)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (17g). Yield 69%, yellow fine crystalline powder, mp 189–192°C. IR spectrum, ν , cm^{-1} : 2177 m ($\text{C}\equiv\text{N}$), 2200 m ($\text{C}\equiv\text{N}$), 2197 m ($\text{C}\equiv\text{N}$), 2250 m ($\text{C}\equiv\text{N}$),

3330 br (N–H). ^1H NMR spectrum (DMSO- d_6), δ , ppm: 0.94–0.95 m (12H, $\text{Me-}i\text{-Pr}$), 1.05 t (3H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 6.9 Hz), 1.10 m, 1.16 m (2H, NCH , $i\text{-Pr}$), 2.73–3.07 m (2H, C^6H , C^8H), 3.16–3.32 m (2H, C^6H , C^8H), 3.43 q (2H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 6.9 Hz), 4.29–4.34 m (2H, NCH_2N), 4.51 br. s (1H, C^9H), 4.71 m, 4.80 m (2H, NCH_2O), 7.08–7.14 m (1H, Ar), 7.39–7.47 m (2H, Ar), 7.58–7.64 m (1H, Ar), 9.78 br. s (1H, NH, integral intensity of the signal is underestimated, probably due to deuterium exchange). Due to the low solubility of the compound in DMSO- d_6 an informative ^{13}C DEPTQ NMR spectrum could not be registered. Mass spectrum, m/z (I_{rel} , %): 488 (12) [$M - \text{EtO}$] $^+$, 487 (28) [$M - \text{EtO} - 1$] $^+$, 404 (14) [$M - \text{EtOCH}_2\text{N}(i\text{-Pr})\text{CH}_2 + 1$] $^+$. Found, %: C 63.00; H 6.14; N 20.89. $\text{C}_{28}\text{H}_{33}\text{ClN}_8\text{O}$. Calculated, %: C 63.09; H 6.24; N 21.02. *M* 533.1.

7-Methyl-9-(2-chlorophenyl)-4-(dicyanomethylene)-2-(ethoxymethylamino)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (18a). Yield 44%, orange fine crystalline powder, mp 193–195°C. IR spectrum, ν , cm^{-1} : 2160 m ($\text{C}\equiv\text{N}$), 2193 m ($\text{C}\equiv\text{N}$), 2215 m ($\text{C}\equiv\text{N}$), 3337 br (N–H). ^1H NMR spectrum (DMSO- d_6), δ , ppm: 1.11 t (3H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 7.0 Hz), 2.34 br. s (3H, MeN), 3.18–3.38 m (4H, C^6H_2 , C^8H_2), 3.51 q (2H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HH}}$ 7.0 Hz), 4.54 s (1H, C^9H), 4.85 d, 5.08 d (2H, NCH_2O , $^3J_{\text{HH}}$ 9.9 Hz), 7.05 d. d (1H, Ar, $^3J_{\text{HH}}$ 7.6, $^4J_{\text{HH}}$ 1.8 Hz), 7.42–7.50 m (2H, Ar), 7.66 d. d (1H, Ar, $^3J_{\text{HH}}$ 7.7, $^4J_{\text{HH}}$ 1.6 Hz), 10.32 br. s (1H, NH, integral intensity of the signal is underestimated, probably due to deuterium exchange). ^{13}C NMR spectrum DEPTQ (DMSO- d_6), δ_{C} , ppm: 14.9* ($\text{CH}_3\text{CH}_2\text{O}$), 40.6, 42.2 (C^1 , C^5), 43.3* (MeN), 46.8* (C^9), 59.8, 60.8 [C^6 , C^8 , signal overlay with $\text{C}(\text{C}\equiv\text{N})_2$], 64.3 ($\text{CH}_3\text{CH}_2\text{O}$), 71.8 (NCH_2O), 113.3 ($\text{C}\equiv\text{N}$), 114.1 ($\text{C}\equiv\text{N}$), 114.9 ($\text{C}\equiv\text{N}$), 115.0 ($\text{C}\equiv\text{N}$), 127.8* (CH-Ar), 128.7* (CH-Ar), 130.8* (CH-Ar), 130.9 (C^1 -Ar), 131.5* (CH-Ar), 135.5 (CCl), 159.6 (C^2), 167.3 (C^4). Found, %: C 60.85; H 4.57; N 22.58. $\text{C}_{22}\text{H}_{20}\text{ClN}_7\text{O}$. Calculated, %: C 60.90; H 4.65; N 22.60. *M* 433.9.

2-(Isopropoxymethylamino)-7-methyl-9-(2-chlorophenyl)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (18b). Yield 49%, yellow fine crystalline powder, mp 172–174 °C. IR spectrum, ν , cm^{-1} : 2195 m ($\text{C}\equiv\text{N}$), 2220 m ($\text{C}\equiv\text{N}$), 3330 br (N–H). ^1H NMR spectrum (DMSO- d_6), δ , ppm: 1.03 d (6H, Me_2CH , $^3J_{\text{HH}}$ 6.1 Hz), 2.48 s (3H, MeN), 2.66–2.92 m (2H, C^6H , C^8H), 3.08–3.28 m (2H, C^6H , C^8H), 3.76–3.78 m (1H, CH $i\text{-Pr}$), 4.31 br. s (1H, C^9H), 4.47–4.76 m (2H, NCH_2O), 7.06–7.17 m (1H, Ar),

7.37–7.47 m (2H, Ar), 7.58–7.65 m (1H, Ar), 9.03 br. s (1H, NH, integral intensity of the signal is underestimated, probably due to deuterium exchange). ^{13}C NMR spectrum DEPTQ (DMSO- d_6), δ_{C} , ppm: 25.5 (2Me, *i*-Pr), 40.6, 40.8 (C¹, C⁵), 43.3 (MeN), 47.9 (C⁹), 60.0*, 60.8* (C⁶, C⁸), 60.9* [$\underline{\text{C}}(\text{C}\equiv\text{N})_2$], 62.0 (CH, *i*-Pr), 85.9 (NCH₂O), 113.5* (C \equiv N), 114.9* (C \equiv N), 116.3* (C \equiv N), 117.7* (C \equiv N), 127.9 (CH-Ar), 128.7 (CH-Ar), 130.8 (CH-Ar), 131.3 (CH-Ar), 131.7* (C¹-Ar), 135.4* (CCl), 159.6* (C²), 167.4* (C⁴). Found, %: C 61.54; H 4.94; N 21.81. C₂₃H₂₂ClN₇O. Calculated, %: C 61.67; H 4.95; N 21.89. *M* 447.9.

7-Isopropyl-2-(isopropoxymethylamino)-9-(2-chlorophenyl)-4-(dicyanomethylene)-3,7-diazabicyclo[3.3.1]non-2-ene-1,5-dicarbonitrile (18c). Yield 41%, orange fine crystalline powder, mp 241–243°C. IR spectrum, ν , cm⁻¹: 2170 m (C \equiv N), 2195 m (C \equiv N), 3303 br (N–H). ^1H NMR spectrum (DMSO- d_6), δ , ppm: 0.95 m (6H, $\underline{\text{Me}}_2\text{CHN}$), 1.03 d (6H, $\underline{\text{Me}}_2\text{CHO}$, $^3J_{\text{HH}} = 6.1$ Hz), 2.61–2.92 m (2H, C⁶H, C⁸H), 3.08–3.27 m (2H, C⁶H, C⁸H), 3.34–3.36 m (1H, $\underline{\text{Me}}_2\text{CHN}$), 3.75–3.78 m (1H, $\underline{\text{Me}}_2\text{CHO}$), 4.33 br. s (1H, C⁹H), 4.51–4.54 m, 4.76–4.80 m (2H, NCH₂O), 7.07–7.18 m (1H, Ar), 7.38–7.48 m (2H, Ar), 7.57–7.64 m (1H, Ar), 9.88 br. s (1H, NH, integral intensity of the signal is underestimated, probably due to deuterium exchange). ^{13}C NMR spectrum DEPTQ (DMSO- d_6), δ_{C} , ppm: 17.4*, 18.4* ($\underline{\text{Me}}_2\text{CHN}$), 25.5* ($\underline{\text{Me}}_2\text{CHO}$), 41.1, 41.9 (C¹, C⁵), 47.7* (C⁹), 53.3* ($\underline{\text{Me}}_2\text{CHN}$), 55.3, 55.7 (C⁶, C⁸), 62.0* ($\underline{\text{Me}}_2\text{CHO}$), 63.3 [$\underline{\text{C}}(\text{C}\equiv\text{N})_2$], 81.9 (NCH₂O), 113.9 (C \equiv N), 114.6 (C \equiv N), 115.3 (C \equiv N), 116.5 (C \equiv N), 128.0* (CH-Ar), 128.8* (CH-Ar), 130.8* (CH-Ar), 131.2* (CH-Ar), 131.3 (C¹-Ar), 135.4 (CCl), 162.2 (C²), 169.2 (C⁴). Found, %: C 63.00; H 5.21; N 20.49. C₂₅H₂₆ClN₇O. Calculated, %: C 63.08; H 5.51; N 20.60. *M* 476.0.

1,3,5-Tri(4-methylphenyl)-1,3,5-triazinane (19). Yield 34%, colorless crystals, mp 125–127°C (mp 125°C [43]). ^1H NMR spectrum (DMSO- d_6), δ , ppm: 2.17 br. s (9H, 3Me), 4.74 br. s (6H, 3CH₂), 6.94 d (6H, 3Ar, $^3J_{\text{HH}} = 8.7$ Hz), 6.99 d (6H, 3Ar, $^3J_{\text{HH}} = 8.7$ Hz). ^{13}C NMR spectrum DEPTQ (DMSO- d_6), δ_{C} , ppm: 20.1 (Me), 67.7* (CH₂), 117.0 (CH-Ar), 128.6* (C⁴-Ar), 129.4 (CH-Ar), 146.0* (C¹-Ar). Found, %: C 80.57; H 7.59; N 11.59. C₂₄H₂₇N₃. Calculated, %: C 80.63; H 7.61; N 11.75. *M* 357.5.

Single crystal X-ray diffraction analysis.

Experimental material for a crystal of compound **17c** (C₃₂H₂₉ClN₈O₃) was obtained on a Bruker APEX-II CCD

diffractometer at 296.15 K. The structure was solved by a direct method using the Olex2 [57] and ShelXD [58] software package and refined using the SHELXL package [59]. The structure was refined by full-matrix least squares in the anisotropic approximation for non-hydrogen atoms by F^2 . The main characteristics and unit cell parameters of **17c**: crystal size 0.32 × 0.3 × 0.29 mm, triclinic crystal system, space group *P*-1, *M* 609.08; unit cell parameters: *a* 11.6884(7), *b* 12.1570(7), *c* 12.2224(7) Å, α 99.2520(10)°, β 113.6070(10)°, γ 93.6220(10)°, *V* 1555.00(16) Å³, *Z* 2, d_{calc} 1.301 g/cm³; $\mu(\text{CuK}\alpha)$ 0.170 mm⁻¹, *F*(000) 636.0, θ 3.42°–56.64°; reflection index intervals: $-15 \leq h \leq 15$, $-16 \leq k \leq 16$, $-16 \leq l \leq 16$; 18091 reflections were measured, 7738 were independent [R_{int} 0.0166], 7738 reflections show $I > 2\sigma(I)$. Number of refined parameters was 355. Final divergence factors were R_1 0.0838 and wR_2 0.2590, R_1 0.1018 and wR_2 0.2840 for all reflections, GOOF by F^2 was 1.072; $\Delta\rho_{\text{max}}$ and $\Delta\rho_{\text{min}}$ 0.95 and -0.87 e/Å³. Crystal data for compound **17c** were deposited in the Cambridge Crystallographic Data Center (CCDC 2081885).

AUTHOR INFORMATION

A.O. Kurskova, ORCID: <http://orcid.org/0000-0001-9014-3248>

V.V. Dotsenko, ORCID: <http://orcid.org/0000-0001-7163-0497>

K.A. Frolov, ORCID: <http://orcid.org/0000-0002-8045-7582>

N.A. Aksenov, ORCID: <http://orcid.org/0000-0002-7125-9066>

I.V. Aksenova, ORCID: <http://orcid.org/0000-0002-8083-1407>

A.A. Peresyphkina, ORCID: <http://orcid.org/0000-0003-2829-9860>

E.A. Chigorina, ORCID: <https://orcid.org/0000-0002-9398-1455>

S.G. Krivokolisko, ORCID: <http://orcid.org/0000-0001-9879-9217>

ACKNOWLEDGMENTS

Analytical studies were carried out using the equipment of the Center for Analytical research was done using equipment of NRC “Kurchatov Institute” – IREA Shared Knowledge Center., as well as the Scientific and Educational Center “Diagnostics of the Structure and Properties of Nanomaterials” and the Center

for Collective Use “Ecological Analytical Center” of the Kuban State University.

FUNDING

This work was financially supported by the Kuban Science Foundation within the framework of the scientific project MFI-20.1-26/20 (application no. MFI-20.1/45), as well as by the Ministry of Education and Science of the Russian Federation (topic 0795-2020-0031).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

SUPPLEMENTARY INFORMATION

The online version contains supplementary material available at <https://doi.org/10.1134/S1070363222050061>.

REFERENCES

- Mittelbach, M., *Monatsh. Chem.*, 1985, vol. 116, no. 5, p. 689.
<https://doi.org/10.1007/BF00798796>
- Dotsenko, V.V., Krivokolysko, S.G., and Semenova, A.M., *Chem. Heterocycl. Compd.*, 2018, vol. 54, no. 11, p. 989.
<https://doi.org/10.1007/s10593-018-2383-y>
- Shaabani, A. and Hooshmand, S.E., *Mol. Divers.*, 2018, vol. 22, no. 1, p. 207.
<https://doi.org/10.1007/s11030-017-9807-y>
- Kurskova, A.O., Dotsenko, V.V., Frolov, K.A., Akse-
nov, N.A., Aksenova, I.V., Shcherbakov, S.V., Ovcha-
rov, S.N., Krivokolysko, D.S., and Krivokolysko, S.G.,
Russ. J. Gen. Chem., 2021, vol. 91, no. 6, p. 971.
<https://doi.org/10.1134/S1070363221060037>
- Kurskova, A.O., Dotsenko, V.V., Frolov, K.A.,
Aksenov, N.A., Aksenova, I.V., Krivokolysko, B.S.,
and Krivokolysko, S.G., *Russ. J. Gen. Chem.*,
2021, vol. 91, no. 8, p. 1471.
<https://doi.org/10.1134/S1070363221080089>
- Helmy, N.M., El-Baih, F.E.M., Al-Alshaikh, M.A.,
and Moustafa, M.S., *Molecules*, 2011, vol. 16, no. 1,
p. 298.
<https://doi.org/10.3390/molecules16010298>
- Fahmy, S.M., Abd Allah, S.O., and Mohareb, R.M.,
Synthesis, 1984, no. 11, p. 976.
<https://doi.org/10.1055/s-1984-31045>
- Abdelrazek, F.M., Michael, F.A., and Mohamed, A.E.,
Arch. Pharm., 2006, vol. 339, no. 6, p. 305.
<https://doi.org/10.1002/ardp.200500259>
- Hafiz, I.S.A., Rashad, M.E.E., Mahfouz, M.A.E., and
Elnagdi, M.H., *J. Chem. Res. Miniprint*, 1998, no. 11,
p. 2946.
- Fadda, A. and Refat, H., *Monatsh. Chem.*, 1999,
vol. 130, p. 1487.
<https://doi.org/10.1007/s007060050308>
- Zaki, M.E.A., Fadda, A.A., Samir, K., and Amer, F.A.,
Chem. Heterocycl. Compd., 2003, vol. 39, p. 1242.
<https://doi.org/10.1023/B:COHC.0000008274.04008.c2>
- Kandeel, Z.E.-S., Abdelrazek, F.M., and Elnagdi, M.H.,
Heterocycles, 1986, vol. 24, no. 9, p. 2455.
<https://doi.org/10.3987/R-1986-09-2455>
- Sharanin, Yu.A., Krivokolysko, S.G., and Dyachen-
ko, V.D., *Russ. J. Org. Chem.*, 1994, vol. 30, no. 4, p. 620.
- Fuentes, L., Vaquero, J.J., and Soto, J.L., *Synthesis*,
1982, vol. 1982, no. 4, p. 320.
<https://doi.org/10.1055/s-1982-29798>
- Bardasov, I.V., Alekseeva, A.U., Ershov, O.V., and
Belikov, M.Yu., *Tetrahedron Lett.*, 2015, vol. 56, no. 40,
p. 5434.
<https://doi.org/10.1016/j.tetlet.2015.08.013>
- Elnagdi, M.H., Harb, A.F., Elghandour, A.H.H.,
Hussien, A.H.M., and Metwally, S.A.M., *Gazz. Chim.
Ital.*, 1992, vol. 122, no. 8, p. 299.
- Dyachenko, V.D. and Litvinov, V.P., *Doklady Chem.*,
1997, vol. 355, no. 1–3, p. 153.
- Mohareb, R.M., Abouzied, A.S., and Abbas, N.S.,
Anti-Cancer Agents Med. Chem., 2017, vol. 17, no. 14,
p. 1951.
<https://doi.org/10.2174/1871520617666170725153523>
- El-Sayed, E.H. and Fadda, A.A., *J. Heterocycl. Chem.*,
2018, vol. 55, no. 10, p. 2251.
<https://doi.org/10.1002/jhet.3276>
- Hassan, M.I. and Hassane, A., *Egypt. J. Chem.*, 2019,
vol. 62, Special Issue (Part 1) Innovation in Chemistry,
p. 103.
<https://doi.org/10.21608/EJCHEM.2019.14725.1907>
- Ievlev, M.Y., Mayorov, N.S., Shishlikova, M.A.,
Belikov, M.Y., Bardasov, I.N., and Ershov, O.V., *Chem.
Heterocycl. Compd.*, 2021, vol. 57, no. 10, p. 1051.
<https://doi.org/10.1007/s10593-021-03021-2>
- Chunikhin, S.S., Ershov, O.V., Yatsenko, A.V.,
Tafeenko, V.A., Dmitrieva, N.E., and Ievlev, M.Y.,
CrystEngComm, 2021, vol. 23, no. 15, p. 2816.
<https://doi.org/10.1039/D1CE00028D>
- Ershov, O.V., Chunikhin, S.S., Ievlev, M.Y.,
Belikov, M.Y., and Tafeenko, V.A., *CrystEngComm*,
2019, vol. 21, no. 36, p. 5500.
<https://doi.org/10.1039/C9CE01089K>
- 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., Pa-

- payanina, E.S., Mazepa, A.V., and Magerramov, A.M., *Chem. Heterocycl. Compd.*, 2016, vol. 52, no. 7, p. 473.
<https://doi.org/10.1007/s10593-016-1918-3>
25. Tverdokhlebo, N.M., Khoroshilov, G.E., and Dotsenko, V.V., *Tetrahedron Lett.*, 2014, vol. 55, p. 6593.
<https://doi.org/10.1016/j.tetlet.2014.10.046>
26. Dotsenko, V.V., Chigorina, E.A., and Krivokolysko, S.G., *Chem. Heterocycl. Compd.*, 2017, vol. 53, N. 5, p. 626.
<https://doi.org/10.1007/s10593-017-2103-z>
27. Dyadyuchenko, L.V., Dotsenko, V.V., Muraviev, V.S., Dmitrieva, I.G., Aksenov, N.A., and Aksenova, I.V., *Russ. Chem. Bull.*, 2021, vol. 70, no. 7, p. 1363.
<https://doi.org/10.1007/s11172-021-3224-1>
28. Dotsenko, V.V., Bepalov, A.V., Russkikh, A.A., Kindop, V.K., Aksenov, N.A., Aksenova, I.V., Shcherbakov, S.V., and Ovcharov, S.N., *Russ. J. Gen. Chem.*, 2021, vol. 91, no. 6, p. 951.
<https://doi.org/10.1134/S1070363221060013>
29. Sadek, K.U., Selim, M.A., Elmaghraby, M.A., and El-nagdi, M.H., *Pharmazie*, 1993, vol. 48, no. 6, p. 419.
<https://doi.org/10.24355/dbbs.084-201901181427-0>
30. Dyachenko, V.D., Dyachenko, I.V., and Nenajdenko, V.G., *Russ. Chem. Rev.*, 2018, vol. 87, no. 1, p. 1.
<https://doi.org/10.1070/RCR4760>
31. Maggeramov, A.M., Shikhaliev, N.G., Dyachenko, V.D., Dyachenko, I.V., Nenajdenko, V.G., *α -Tsyantioatsetamid (α -Cyanothioacetamide)*, Moscow: Tekhnosfera, 2018, 224 p.
32. Brunskill, J.S.A., De, A., and Ewing, D.F., *J. Chem. Soc. Perkin Trans. I*, 1978, no. 6, p. 629.
<https://doi.org/10.1039/p19780000629>
33. Dotsenko, V.V., Krivokolysko, S.G., Chernega, A.N., and Litvinov, V.P., *Monatsh. Chem.*, 2007, vol. 138, no. 1, p. 35.
<https://doi.org/10.1007/s00706-006-0569-y>
34. Dotsenko, V.V., Frolov, K.A., Chigorina, E.A., Khrustaleva, A.N., Bibik, E. Yu., and Krivokolysko, S.G., *Russ. Chem. Bull.*, 2019, vol. 68, no. 4, p. 691.
<https://doi.org/10.1007/s11172-019-2476-5>
35. Orlov, A.A., Eletskaia, A.A., Frolov, K.A., Golinet, A.D., Palyulin, V.A., Krivokolysko, S.G., Kozlovskaya, L.I., Dotsenko, V.V., and Osolodkin, D.I., *Arch. Pharm.*, 2018, vol. 351, no. 6, paper no. 1700353.
<https://doi.org/10.1002/ardp.201700353>
36. Dotsenko, V.V., Frolov, K.A., and Krivokolysko, S.G., *Chem. Heterocycl. Compd.*, vol. 48, no. 4, p. 642.
<https://doi.org/10.1007/s10593-012-1038-7>
37. Liang, D., Xiao, W.-J., and Chen, J.-R., *Synthesis*, 2020, vol. 52, no. 17, p. 2469.
<https://doi.org/10.1055/s-0040-1707160>
38. Tomassoli, I. and Gündisch, D., *Curr. Top. Med. Chem.*, 2016, vol. 16, no. 11, p. 1314.
<https://doi.org/10.2174/1568026615666150915111434>
39. Nonat, A.M., Roux, A., Sy, M., and Charbonnière, L.J., *Dalton Trans.*, 2019, vol. 48, no. 44, p. 16476.
<https://doi.org/10.1039/C9DT03480C>
40. Comba, P., Kerscher, M., Rück, K., and Starke, M., *Dalton Trans.*, 2018, vol. 47, no. 28, p. 9202.
<https://doi.org/10.1039/C8DT01108G>
41. Sacchetti, A. and Rossetti, A., *Eur. J. Org. Chem.*, 2021, vol. 2021, no. 10, p. 1491.
<https://doi.org/10.1002/ejoc.202001439>
42. Stephan, H., Walther, M., Fähnemann, S., Ceroni, P., Molloy, J.K., Bergamini, G., Heisig, F., Müller, C.E., Kraus, W., and Comba, P., *Chem. Eur. J.*, 2014, vol. 20, no. 51, p. 17011.
<https://doi.org/10.1002/chem.201404086>
43. Mozhaitsev, E.S., Ponomarev, K.Y., Patrusheva, O.S., Medvedko, A.V., Dalinger, A.I., Rogachev, A.D., Komarova, N.I., Korchagina, D.V., Suslov, E.V., Volcho, K.P., Salakhutdinov, N.F., and Vatsadze, S.Z., *Russ. J. Org. Chem.*, 2020, vol. 56, no. 11, p. 1969.
<https://doi.org/10.1134/S1070428020110123>
44. Suslov, E.V., Ponomarev, K.Y., Patrusheva, O.S., Kuranov, S.O., Okhina, A.A., Rogachev, A.D., Munkuev, A.A., Ottenbacher, R.V., Dalinger, A.I., Kalinin, M.A., Vatsadze, S.Z., Volcho, K.P., and Salakhutdinov, N.F., *Molecules*, 2021, vol. 26, no. 24, p. 7539.
<https://doi.org/10.3390/molecules26247539>
45. Dalinger, A.I., Medved'ko, A.V., Kalinin, M.A., Sereda, V.A., Churakov, A.V., and Vatsadze, S.Z., *Russ. Chem. Bull.*, 2021, vol. 70, no. 5, p. 1002.
<https://doi.org/10.1007/s11172-021-3180-9>
46. Medved'ko, A.V., Dalinger, A.I., Nuriev, V.N., Semashko, V.S., Filatov, A.V., Ezhov, A.A., Churakov, A.V., Howard, J.A.K., Shiryaev, A.A., Baranchikov, A.E., Ivanov, V.K., and Vatsadze, S.Z., *Nanomaterials*, 2019, vol. 9, no. 1, p. 89.
<https://doi.org/10.3390/nano9010089>
47. Antipin, I.S., Alifimov, M.V., Arslanov, V.V., Buriilov, V.A., Vatsadze, S.Z., Voloshin, Ya.Z., Volcho, K.P., Gorbachuk, V.V., Gorbunova, Yu.G., Gromov, S.P., Dudkin, S.V., Zaitsev, S.Yu., Zakharova, L.Ya., Ziganshin, M.A., Zolotukhina, A.V., Kalinina, M.A., Karakhanov, E.A., Kashapov, R.R., Koif-

- man, O.I., Konovalov, A.I., Korenev, V.S., Maksimov, A.L., Mamardashvili, N.Zh., Mamardashvili, G.M., Martynov, A.G., Mustafina, A.R., Nugmanov, R.I., Ovsyannikov, AS, Padnya, P.L., Potapov, A.S., Selektor, S.L., Sokolov, M.N., Solovieva, S.E., Stoikov, I.I., Stuzhin, P.A., Suslov, E.V., Ushakov, E.N., Fedin, V.P., Fedorenko, S.V., Fedorova, O.A., Fedorov, Yu.V., Chvalun, S.N., Tsivadze, A.Yu., Shtykov, S.N., Shurpik, D.N., Shcherbina, M.A., and Yakimova, L.S., *Russ. Chem. Rev.*, 2021, vol. 90, no. 8, p. 895.
<https://doi.org/10.1070/RCR5011>
48. Vatsadze, S.Z., Medved'ko, A.V., Bodunov, A.A., and Lyssenko, K.A., *Mendeleev Commun.*, 2020, vol. 30, no. 3, p. 344.
<https://doi.org/10.1016/j.mencom.2020.05.028>
49. Medved'ko, A.V., Krut'ko, D.P., Gaisen, S.V., Churakov, A.V., Minyaev, M.E., Moiseeva, A.A., Lemenovskiy, D.A., Yu, H., Wang, L., and Vatsadze, S.Z., *J. Organomet. Chem.*, 2021, vol. 949, paper no. 121945.
<https://doi.org/10.1016/j.jorganchem.2021.121945>
50. Shcherbakov, D., Baev, D., Kalinin, M., Dalinger, A., Chirkova, V., Belenkaya, S., Khvostov, A., Krut'ko, D., Medved'ko, A., Volosnikova, E., Sharlaeva, E., Shanshin, D., Tolstikova, T., Yarovaya, O., Maksyutov, R., Salakhutdinov, N., and Vatsadze, S., *ACS Med. Chem. Lett.*, 2022, Vol. 13, no. 1, p. 140.
<https://doi.org/10.1021/acsmchemlett.1c00299>
51. Yang, J., Kwon, S., Bae, S.H., Park, K.M., Yoon, C., Lee, J.H., and Seok, C., *J. Chem. Inf. Model.*, 2020, vol. 60, no. 6, p. 3246.
<https://doi.org/10.1021/acs.jcim.0c00104>
52. *GalaxyWEB*. A web server for protein structure prediction, refinement, and related methods. Computational Biology Lab, Department of Chemistry, Seoul National University, S. Korea.
<http://galaxy.seoklab.org/index.html>
53. Ko, J., Park, H., Heo, L., and Seok, C., *Nucleic Acids Res.*, 2012, vol. 40, no. W1, p. W294.
<https://doi.org/10.1093/nar/gks493>
54. Pettersen, E.F., Goddard, T.D., Huang, C.C., Couch, G.S., Greenblatt, D.M., Meng, E.C., and Ferrin, T.E., *J. Comput. Chem.*, 2004, vol. 25, no. 13, p. 1605.
<https://doi.org/10.1002/jcc.20084>
55. *UCSF Chimera*. Visualization system for exploratory research and analysis developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco, US.
<https://www.rbvi.ucsf.edu/chimera/>
56. Dotsenko, V.V., Krivokolysko, S.G., Polovinko, V.V., and Litvinov, V.P., *Chem. Heterocycl. Compd.*, 2012, vol. 48, no. 2, p. 309.
<https://doi.org/10.1007/s10593-012-0991-5>
57. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K., and Puschmann, H., *J. Appl. Cryst.*, 2009, vol. 42, p. 339.
<https://doi.org/10.1107/S0021889808042726>
58. Sheldrick, G.M., *Acta Crystallogr. (A)*, 2008, vol. 64, p. 112.
<https://doi.org/10.1107/S0108767307043930>
59. Sheldrick, G.M., *Acta Crystallogr. (C)*, 2015, vol. 71, p. 3.
<https://doi.org/10.1107/S2053229614024218>