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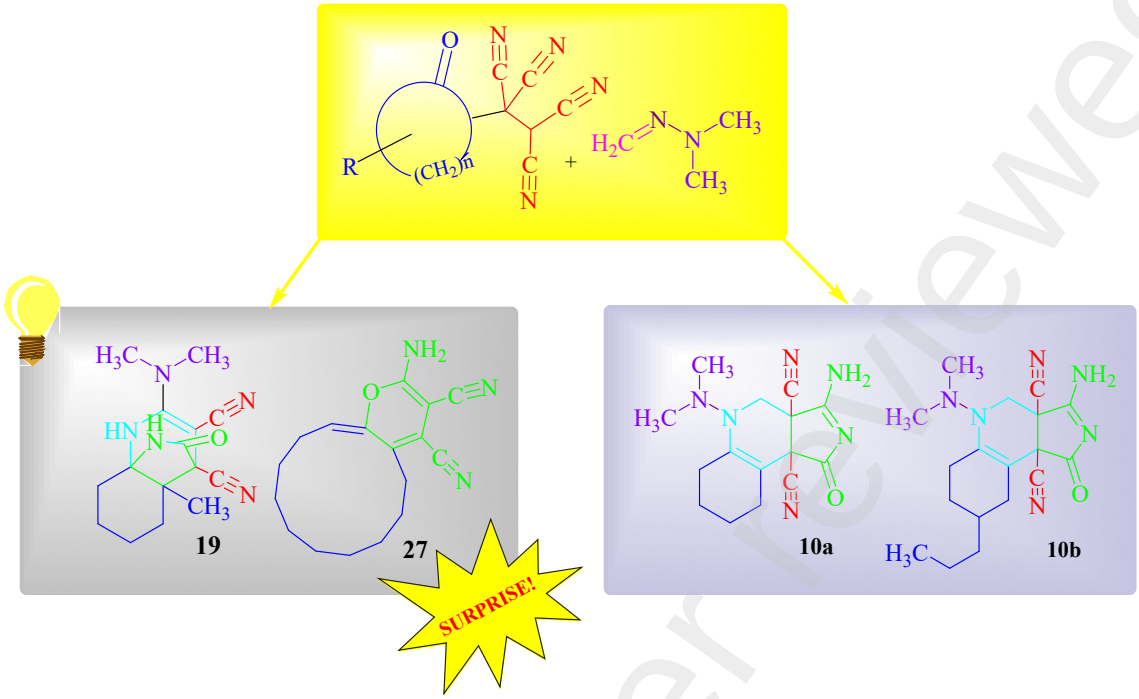
Graphical abstract



New Multifunctional Synthon in Organic Chemistry

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Abstract

"Heptyl" (unsymmetrical dimethylhydrazine - UDMH) is actively used as fuel for rocket engines in many countries around the world. Nonetheless, it constantly loses its properties due to absorption of moisture which cannot be azeotroped. Its long term application is of special concern. UDMH's transportation and processing is complicated since it is an extremely toxic compound of the 1st hazard class. Its disposal via burning gives much more toxic oxidation products. The safest way to neutralize it is instantaneous interaction with formalin solution to

form less toxic 1,1-dimethyl-2-methylenehydrazone (MDH), which is polymerized in an acidic media, and the resulting product is burned forming a huge amount of nitrogen oxides. The purpose of this work is to reveal the synthetic possibilities and practical application of MDH. We would like to pay international chemical community's attention to this extremely promising metastable compound to the purposes of molecular design, pharmaceutical and medicinal chemistry.

Keywords: unsymmetrical dimethylhydrazine, methylene dimethylhydrazone, tetracyanoethylene, tetracyanoketones, Thorp-Ziegler type cyclization

Introduction

1,1-Dimethylhydrazine, despite well-known advantages, has disadvantages that put it on the verge of its possible application as a high-temperature fuel. UDMH is characterized by extremely high toxicity, teratogenicity, the ability to absorb water from the atmosphere with the loss of positive properties [1]. The most effective way to utilize it is an instantaneous exothermic reaction with formalin [1,2], which leads to the formation of much less toxic 1,1-dimethyl-2-methylenehydrazone (MDH). The purpose of our work is to attract chemical community's attention and to show some unusual synthetic possibilities and practical application of MDH. We have studied the synthetic possibilities of MDH in reactions with CH acids.

We used tetracyanoethylated ketones (TCK), which have a tendency to cascade transformations, are the most sustainable, and have a high synthetic potential (pKa 2.8–3.6). The main properties of DMH [1] are proposed to be catalytic cyclization of TCK in cascade transformations with the formation of -5-hydroxypyrrolidin-2-one (5-hydroxylactam) (figure 1) which is a part of many biologically active compounds.

These include inhibitors of various classes of enzymes. For example, HIV-1 integrase [3] (an enzyme that catalyzes the incorporation of the HIV-1 DNA virus into the chromosome of the host cell), tyrosine kinase [4] (an enzyme that catalyzes the transfer of the phosphate residue of the ATP molecule to the amino acid residue of tyrosine), telomerase [5] (an enzyme that adds a specific sequence to the end of a DNA chain and stabilizes chromosomes). It should be noted that a heterocyclic derivative is a structural component of agonists (chemical compounds interacting with a receptor, causes its biological response) of serotonin [6], chemokine [7] receptors (a peptide that regulates the movement of leukocytes and their migration from blood to tissue) and their migration, and endothelin [5] (the most powerful vasoconstrictor receptor,

consisting of 21 amino acids). The compound 5-hydroxypyrrolidin-2-one is a component of drugs for treatment nervous or intellectual activity, memory, and mental fatigue disorders [8].

Results and Discussion

It is readily apparent that MDH reacts with CH-acids (TCK) via all of the structural fragments: the methylene group (A), and the dimethylamine fragment (B). Surprises turned out the discovered: both the decomposition with the formation of started compounds (E) and its deeper degradation on dimethylamine and formaldoxime (C). In turn, intermediate C is capable of producing salt (direction D, Figure 2).

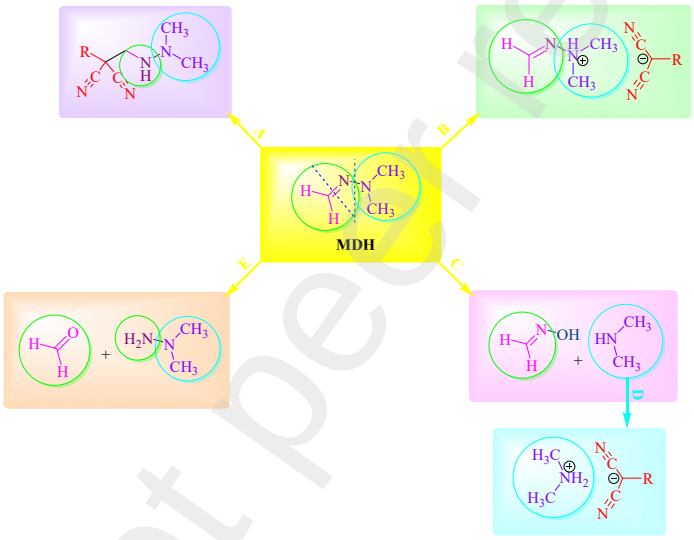

Figure 1: MDH reaction centers.

All of the noted directions are represented in the examples below. Moreover, high-resolution mass spectra of the isolated products (without purification) were recorded to determine the minor stages of the processes (MSMP), which can become essential, if it is necessary. Target compounds were isolated by recrystallization. Thus, cyclohexanone-1,1,2,2-tetracarbonitrile [9], 1a and its 4-propyl-substituted analogue 1b (Figure 3) react similarly: at the first stage of the process along the A route (Figure 2), then according to figure 3 .

After The Michael addition adduct 3 probably undergoes intramolecular cyclization which is very important for stabilizing the subsequent course of the process by the interaction of the nucleophilic secondary amine of the dimethylhydrazine moiety 3 at the electrophilic carbon of the cyclic carbonyl group to form hydrazinoalcohol 4. In the latter, due to the proximity of the hydroxyl and carbonitrile groups, probably, there is an intramolecular cyclization according to the Thorp-Ziegler type [10,11] into a cyclic imino ester 5, which rearranges through the

intermediate 6 into a cyclic amide 7. In the latter ring opening leads to the amidotricarbonitrile 8. The proximity of the reaction centers (carbonitrile and amide groups) promotes Thorp-Ziegler type cyclization with the third ring formation in the structures 8,9 and final stabilization in 3-amino-5-(dimethylamino)-1-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[3,4-c]quinoline-3a,9b-dicarbonitrile. MSMP for minor stages determining show that the main process goes along the direction of Scheme 1 (according to the Michael reaction). In addition, in the high-resolution mass spectrum of the precipitate, after the end of the processes, the following minor target compounds were found: the adduct of 10 and dimethylamine (M + 343.1250), which indicates degradation at a certain stage of MDH along the path C (Fig.1) and addition of dimethylamine (DMA) at the double bond of tricycle 10 to form compounds: 3-amino-5,9a-bis(dimethylamino)-1-oxo-4,5,5a, 6,7,8,9,9a-octahydro-1H -pyrrolo[3,4-c]quinoline-3a,9b-dicarbonitrile (11a) and 3-amino-5,9a-bis(dimethylamino)-1-oxo-8-propyl-4,5,5a,6,7,8,9,9a-octahydro-1H-pyrrolo[3,4-c]quinoline-3a,9b-dicarbonitrile – m/z 385.1719 (11b).

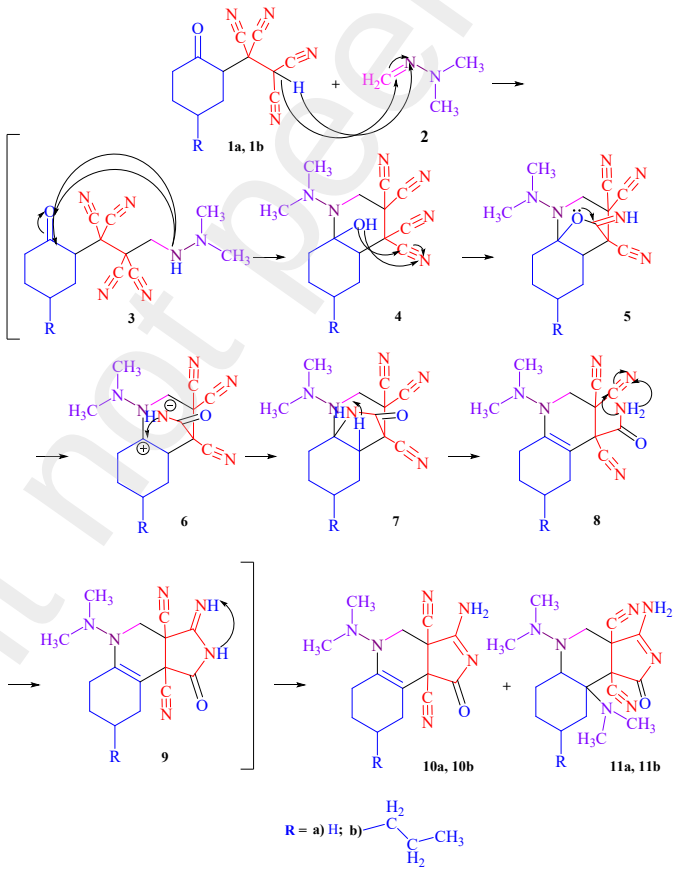

Figure 2: Cyclohexanone and 4-propylcyclohexanone derivatives reactions with MDH

Quite unusually, TCK based on α-methylcyclohexanone enters into this reaction. Due to the fact that the methyl group and the tetracarbonitrile moiety are in the same (α-position) to the carbonyl group, obviously that the former creates hindrances (Fig.5-7) for the critical, for stabilization, stage of the reaction along the direction A - cyclization to hexahydropyridine

(figure 3, compound 4). We consider that in this case only direction D can be realized (Fig.2). Furthermore, the bond cleavage between DMH nitrogens is followed by the salt formation and an adduct is formed with the released DMA, the latter probably adds to the electrophilic carbon of the terminal carbonitrile group (Fig.4, intermediate 14, after rearrangement - 18). It is stabilized by cyclization to hexahydropyridinol 16 followed by intramolecular cyclization via imino ester 17 to tricyclic amide 19.

MSMP, besides the main ion m/z 286.1668+, a molecular ion of the sodium adduct with the target tricyclic cycloamide 19 and also compound 20 with m/z 308.1484+ were found due to the fact that traces of an aqueous solution of sodium hydroxide were definitely present in the reaction. In addition, a dimerization product of the compounds 19 m/z 571.3257+ (comp. 31) and 19 s 20 with m/z 593.3060+ (22) was also found as a minor compound.

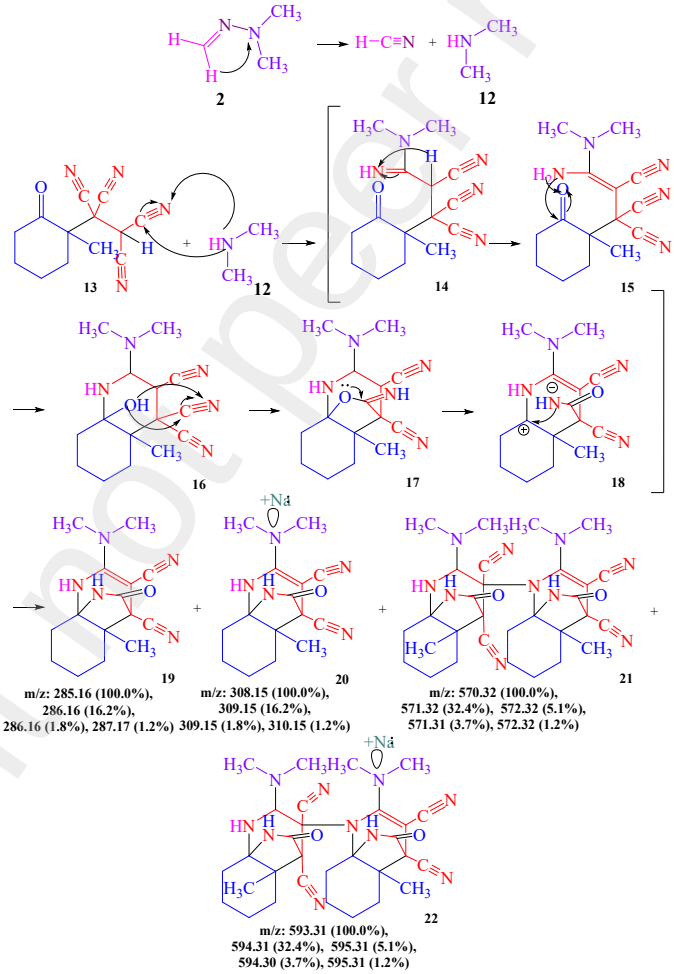

Figure 4: Tetracyanomethylcyclohexanone and MDH interaction

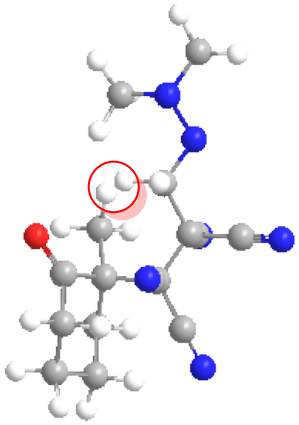

Figure 5: 2-Methylcyclohexanone derivative 13

According to the structure 13, between circled hydrogen atoms it is observed a trans-annular repulsion, which makes ring closing into a six-membered cycle impossible. There are no hindrances in the structures of other TCK, and the atoms arrangement does not prevent the cyclization (Fig. 6-7).

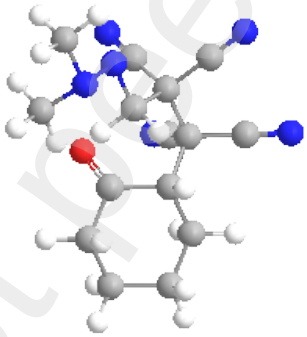

Figure 6: Cyclohexanone derivative 1a

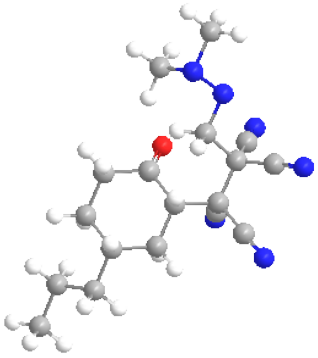

Figure 7: Cyclohexanone derivative 1a

A macrocyclic derivative from cyclododecanone (23, Fig. 8) is stable and does not interact with MDH, but the latter is probably an unusual catalyst for the elimination of hydrogen cyanide in the first stage (product 24, Fig. 8) and enolization of the adduct (compound 25, Fig. 8) with the formation of bicyclic enaminonitrile 26 followed by intramolecular Thorpe-Ziegler type reaction

(Fig. 8). The hydroxyl group 26 undergoes further chemical transformations - elimination (compound 27) and nucleophilic substitution (products 28 and 29). Besides the catalytic effect, MDH under the process conditions is consumed via the paths C, D (Fig. 8) and released dimethylamine, which probably replaces the hydroxyl group 27 with the formation of the product 28 (Fig. 8) m/z 329.2340+. In addition, both the adduct ion 29 and the dimethylhydrazine moiety m/z 344.2455+ were recognized in the high-resolution mass spectrum that indicates another possibility of degradation of an origin MDH along the E direction (Fig. 2).

Simultaneously, a similar transformation occurs with the starting ketone 23. The latter decomposes unusually under the process conditions and decomposes to the starting ketone and tetracyanoethylene (Fig. 2, direction E).

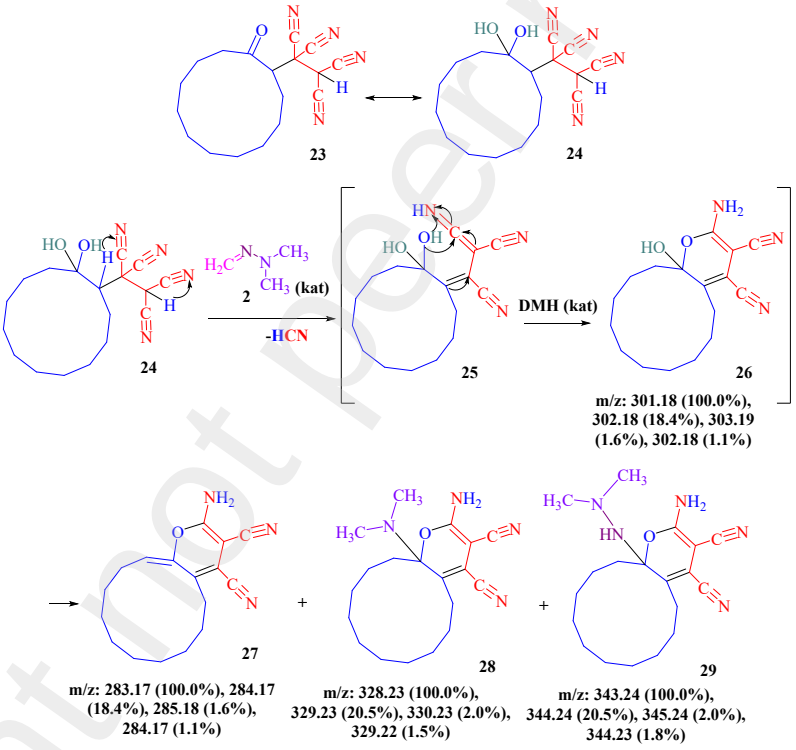

Figure 8: Tetracyanocyclododecanone and MDH interaction

MDMH interacts with released tetracyanoethylene (TCNE) at the hydrogen atom of the amino group. Earlier in the publication [12] we reported about this interaction leading to tricyanohydrazine derivatives 30 that are potential antimicrobial dyes and photosensitizers. 30 is obtained with a low yield.

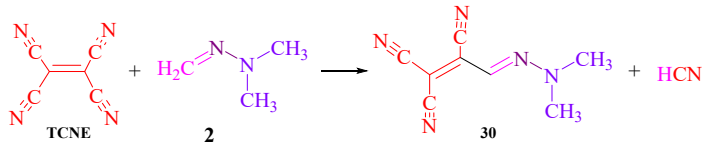

Figure 9: TCNE and MDH interaction

The interaction of MDH at the CH-acid center (direction A) allows performing the reaction with tetracyanoethene ($TCNEH_2$) that leads to the formation of a five-membered ring - 5-amino-1-(dimethylamino) -1,2-dihydro-3H-pyrrole-3 ,3,4-tricarbonitrile (33).

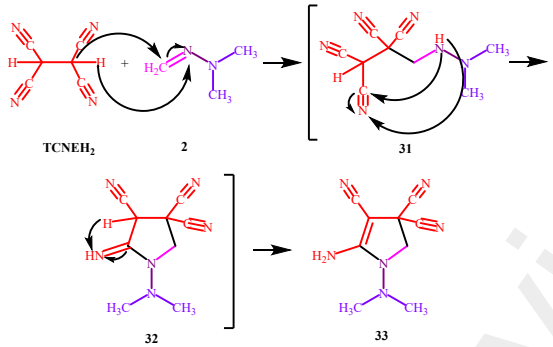

Figure 10: $TCNEH_2$ and MDH interaction

One of the DMH analogs is known to be N,N-dimethylethane-1,2-diamine, which has spaced reaction centers, biological activity against acute pancreatitis [13] and, in the structure of phenothiazine derivatives, reduces the resistance of cancer cells to drugs [14].

N,N-Dimethyl-2-(methyleneamino)ethan-1-amine (MDEA) reacts with the cyclohexanone adduct (a) similarly to the methylene derivative of unsymmetrical dimethylhydrazine (MDEA). The presence of a dimethylamino group outside the structure makes it easy to alkylate it and give these compounds 42, 43 obvious solubility in aqueous solutions that of great importance for pharmaceutical studies.

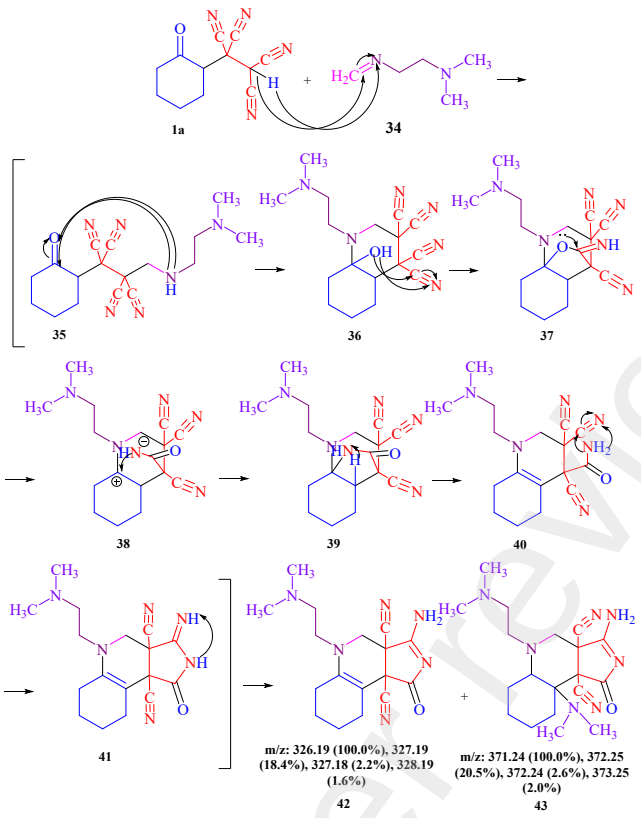

Figure 11: $TCNEH_2$ and MDH interaction

All of the agents were acquired from commercial suppliers and used without further purification. The progress of the reactions and the purity of the products were monitored by TLC on Sorbfil plates (spots were visualized under UV light, when treated with iodine vapor, or when heated). Melting and decomposition points were determined on an Optimelt MPA100 instrument. IR spectra were recorded on an FSM-1202 spectrometer with Fourier transform for samples dispersed in Nujol. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d6 with TMS internal standard on a Bruker AVANCE400 WB spectrometer at an operating frequency of 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C.

HRMS mass spectra were obtained on a quadrupole time-of-flight (t, qTOF) AB Sciex Triple TOF 5600 mass spectrometer (AB SCIEX PTE. Ltd., Singapore) using turbo-ion spray source (nebulizer gas nitrogen, a positive ionization polarity, needle voltage 5500 V). Recording of the spectra was performed in “TOF MS” mode with collision energy 10 eV, declustering potential 100 eV and with resolution more than 30 000 full-width half-maximum. Samples with the analyte concentration 5 µmol/L were prepared by dissolving the test compounds in methanol (hypergrade for LC-MS , Merck) .

Data sets for single crystal **10a**, **10b, 19** and **27** were collected on a Rigaku XtaLab Synergy S instrument with a HyPix detector and a PhotonJet microfocus X-ray tube using Cu Kα (1.54184 Å) radiation at low temperature. Images were indexed and integrated using the CrysAlisPro data reduction package. Data were corrected for systematic errors and absorption using the ABSPACK module: numerical absorption correction based on Gaussian integration over a multifaceted crystal model and empirical absorption correction based on spherical harmonics according to the point group symmetry using equivalent reflections. The GRAL module was used for analysis of systematic absences and space group determination. The structure was solved by direct methods using SHELXT [15] and refined by the full-matrix least-squares on F^2 using SHELXL [16]. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were inserted at the calculated positions and refined as riding atoms. The figures were

generated using Mercury 4.1 [17] program. Crystals were obtained by slow evaporation method. Crystal data and structure refinement parameters summarized in Table 1.

Crystal Data for **10a**: $C_{15}H_{18}N_6O$ (*M* =298.35 g/mol): triclinic, space group P-1 (no. 2), *a* = 13.9756(12) Å, *b* = 15.0773(15) Å, *c* = 18.0923(13) Å, *α* = 112.010(8)°, *β* = 93.942(7)°, *γ* = 112.380(9)°, *V* = 3167.3(5) Å^3, *Z* = 8, *T* = 104(7) K, μ(Cu Kα) = 0.683 mm^{-1}, *Dcalc* = 1.251 g/cm^3, 34121 reflections measured (5.436° ≤ 2Θ ≤ 156.656°), 12415 unique (R_{int} = 0.1673, R_{sigma} = 0.1628) which were used in all calculations. The final R_1 was 0.0845 (I > 2σ(I)) and wR_2 was 0.2282 (all data). CCDC number 2152262.

Crystal Data for **10b**: $C_{22}H_{32}N_6O_3$ (*M* =428.53 g/mol): triclinic, space group P-1 (no. 2), *a* = 9.42370(10) Å, *b* = 11.97650(10) Å, *c* = 11.99720(10) Å, *α* = 111.2460(10)°, *β* = 111.1820(10)°, *γ* = 93.9690(10)°, *V* = 1145.11(2) Å^3, *Z* = 2, *T* = 102.2(9) K, μ(Cu Kα) = 0.690 mm^{-1}, *Dcalc* = 1.243 g/cm^3, 33743 reflections measured (8.14° ≤ 2Θ ≤ 153.026°), 4548 unique (R_{int} = 0.0349, R_{sigma} = 0.0172) which were used in all calculations. The final R_1 was 0.0422 (I > 2σ(I)) and wR_2 was 0.1101 (all data). CCDC number 2152263.

Crystal Data for **19**: $C_{15}H_{19}N_5O$ (*M* =285.35 g/mol): triclinic, space group P-1 (no. 2), *a* = 7.5867(2) Å, *b* = 9.1339(3) Å, *c* = 10.8470(4) Å, *α* = 76.621(3)°, *β* = 82.305(3)°, *γ* = 81.452(3)°, *V* = 719.26(4) Å^3, *Z* = 2, *T* = 100(1) K, μ(Cu Kα) = 0.703 mm^{-1}, *Dcalc* = 1.318 g/cm^3, 17589 reflections measured (8.424° ≤ 2Θ ≤ 152.906°), 2865 unique (R_{int} = 0.0345, R_{sigma} = 0.0220) which were used in all calculations. The final R_1 was 0.0399 (I > 2σ(I)) and wR_2 was 0.0993 (all data). CCDC number 2152264.

Crystal Data for **27**: for $C_{17}H_{21}N_3O$ (*M* =283.37 g/mol): triclinic, space group P-1 (no. 2), *a* = 8.5574(5) Å, *b* = 9.7008(6) Å, *c* = 9.7930(4) Å, *α* = 102.032(4)°, *β* = 103.106(4)°, *γ* = 101.505(5)°, *V* = 747.97(7) Å^3, *Z* = 2, *T* = 99.9(10) K, μ(Cu Kα) = 0.632 mm^{-1}, *Dcalc* = 1.258 g/cm^3, 7141 reflections measured (9.618° ≤ 2Θ ≤ 153.2°), 2981 unique (R_{int} = 0.0614, R_{sigma} = 0.0595) which were used in all calculations. The final R_1 was 0.0821 (I > 2σ(I)) and wR_2 was 0.2326 (all data). CCDC number 2152265.

Table 1. Crystal data and structure refinement for 10a, 10b, 19 and 27.

Identification code	10a	10b	19	27
Empirical formula	$C_{15}H_{18}N_6O$	$C_{22}H_{32}N_6O_3$	$C_{15}H_{19}N_5O$	$C_{17}H_{21}N_3O$
Formula weight	298.35	428.53	285.35	283.37
Temperature/K	104(7)	102.2(9)	100(1)	99.9(10)
Crystal system	triclinic	triclinic	triclinic	triclinic
Space group	P-1	P-1	P-1	P-1
a/Å	13.9756(12)	9.42370(10)	7.5867(2)	8.5574(5)
b/Å	15.0773(15)	11.97650(10)	9.1339(3)	9.7008(6)
c/Å	18.0923(13)	11.99720(10)	10.8470(4)	9.7930(4)
α/°	112.010(8)	111.2460(10)	76.621(3)	102.032(4)
β/°	93.942(7)	111.1820(10)	82.305(3)	103.106(4)
γ/°	112.380(9)	93.9690(10)	81.452(3)	101.505(5)
Volume/Å^3	3167.3(5)	1145.11(2)	719.26(4)	747.97(7)
Z	8	2	2	2
ρ_{calc}mg/mm^3	1.251	1.243	1.318	1.258
μ/mm^{-1}	0.683	0.690	0.703	0.632
F(000)	1264.0	460.0	304.0	304.0

Crystal size/mm³	0.18 × 0.08 × 0.02	0.208 × 0.191 × 0.123	0.1 × 0.05 × 0.04	0.15 × 0.1 × 0.04
2Θ range for data collection	5.436 to 156.656°	8.14 to 153.026°	8.424 to 152.906°	9.618 to 153.2°
Index ranges	-17 ≤ h ≤ 17, -18 ≤ k ≤ 18, -15 ≤ l ≤ 22	-10 ≤ h ≤ 11, -14 ≤ k ≤ 14, -15 ≤ l ≤ 14	-9 ≤ h ≤ 8, -11 ≤ k ≤ 11, -12 ≤ l ≤ 13	-10 ≤ h ≤ 10, -12 ≤ k ≤ 12, -11 ≤ l ≤ 12
Reflections collected	34121	33743	17589	7141
Independent reflections	12415[R(int) = 0.1673]	4548[R(int) = 0.0349]	2865[R(int) = 0.0345]	2981[R(int) = 0.0614]
Data/restraints/parameters	12415/0/801	4548/45/302	2865/0/193	2981/0/190
Goodness-of-fit on F^2	1.003	1.034	1.021	1.090
Final R indexes [I>=2σ (I)]	R_1 = 0.0845, wR_2 = 0.1731	R_1 = 0.0422, wR_2 = 0.1082	R_1 = 0.0399, wR_2 = 0.0966	R_1 = 0.0821, wR_2 = 0.2250

N,N-dimethyl-2-methylenehydrazone (MDH) and N,N-dimethyl-2-(methyleneamino)ethan-1-amine (MDEA) were obtained by the general procedure [2] in 36% and 38% yields, respectively.

Dimethylamine (12) was obtained according to the method [18] with a yield of 85%.

Synthesis of 2-(Dimethylamino)-4a-methyl-10-oxo-5,6,7,8-tetrahydro-1H-8a,4-(epimino)quinoline-3,4(4aH)-dicarbonitrile (19)

In turn 0 0.03 g (0.0007 mol) 12 and 0.2 g (0.0008 mol) 13 were dissolved in ethyl acetate. The reaction mixture was stirred at 0°C. The completeness of the reaction was monitored by TLC, 13 was used as a reference sample. An hour later, precipitate of sand-colored crystals was observed. The target product was filtered off on a Schott filter, washed with cold ethyl acetate. Sediment weight 0.09 g. Yield: 45%. Melting point: 249°C.

1-(2-Oxocyclohexyl)ethane-1,1,2,2-tetracarbonitrile (1a), 1-(2-oxo-5-propylcyclohexyl)ethane-1,1,2,2-tetracarbonitrile (1b), 1 -(1-methyl-2-oxohexyl-)ethane-1,1,2,2-tetracarbonitrile (12c), 1-(2-oxocyclododecyl)ethane-1,1,2,2-tetracarbonitrile (23h) were obtained according to the general procedure [9] with yields of 74%, 75%, 66%, and 61%, respectively.

Synthesis of 3-Amino-5-(dimethylamino)-1-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[3,4-c]quinoline-3a,9b-dicarbonitrile (10a), 3 -amino-5-(dimethylamino)-1-oxo-8-(propyl)-4,5,6,7,8,9-hexahydro-1H-pyrrolo[3,4-c]quinoline-3a,9b-dicarbonitrile (10b), 2-(dimethylamino)-4a-methyl-10-oxo-5,6,7,8-tetrahydro-1H-8a,4-(epimino)quinoline-3,4(4aH)-dicarbonitrile (19) , (E) -2-amino-6,7,8,9,10,11,12,13-octahydro-5H-cyclododeca [b] pyran-3,4-dicarbonitrile (28), 3-amino-5- (2-(dimethylamino)ethyl-1-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[3,4-c]quinoline-3a,9b-dicarbonitrile (44)

The compounds were synthesized according to the general procedure with yields of 84%, 75%, 48%, 64%, 62%, respectively. 0.06 g (0.0008 mol) of MDMG and 0.2 g (0.0009 mol) of TCA were successively dissolved in ethyl acetate, and the resulting solutions were mixed. The completeness of the reaction was monitored by TLC, MDMG was used as a reference sample. An hour later, sand-coloured crystals precipitated. The target product was filtered off on a Schott filter, washed with cold ethyl acetate. Precipitate weight 0.21 g

3-Amino-5-(dimethylamino)-1-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[3,4-c]quinoline-3a,9b-dicarbonitrile (10a)

Found , C 60.28; H 6.31; N 28.05. $C_{15}H_{18}N_6O$. Calculated %: C 60.39; H 6.08; N 28.17.

3-Amino-5-(dimethylamino)-1-oxo-8-(propyl)- 4,5,6,7,8,9-hexahydro-1H-pyrrolo[3,4-c]quinoline-3a,9b- dicarbonitrile (10b)

Found, C, 63.48; H 7.13; N 24.65. $C_{18}H_{24}N_6O$. Calculated %: C 63.51; H 7.11; N 24.69.

2-(Dimethylamino)-4a-methyl-10-oxo-5,6,7,8-tetrahydro-1H-8a,4-(epimino)quinoline-3,4(4aH)-dicarbonitrile (19)

Found, C 63.08; H 6.69; N 24.55. $C_{15}H_{19}N_5O$. Calculated %: C 63.14; H 6.71; N 24.54.

(E)2-Amino-6,7,8,9,10,11,12,13-octahydro-5H-cyclododeca [b]pyran-3,4-dicarbonitrile (27)

Found C, 72.03; H 7.42; N 14.80. $C_{17}H_{21}N_3O$. Calculated %: C 72.06; H 7.47; N 14.83.

Synthesis 5-Amino-1-(dimethylamino)-1,2-dihydro-3H-pyrrole-3,3,4-tricarbonitrile (33)

To a solution of 1 mmol of ethane-1,1,2,2-tetracarbonitrile in 2 ml of ethyl acetate was added 1.1 mmol of 1,1-dimethyl-2-methylenehydrazine. The mixture was kept at room temperature for 14 hours (TLC control) and cooled. The precipitate was filtered off, washed with 2 ml of cold ethyl acetate. Yield 81%. Found, %: C 53.61; H 4.72; N 41.67. $C_9H_{10}N_6$. Calculated %: C 53.46; H 4.98; N 41.56.

3-Amino-5-(2-(dimethylamino)ethyl-1-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[3,4-c]quinoline-3a,9b-dicarbonitrile (42)

Found C 62.53 H 6.75 N 25.80 $C_{17}H_{22}N_6O$ Calculated % C 62.56 H 6.79 N 25.75.

Table 1. Yield, melting point, IR, MNR ^1H, ^{13}C, mass-spectra data.

Structural number	Yield	Melting point	IR(Nujol), ν, sm^{-1}	MNR ^1H δ, ppm, J, Hz (DMSO-d_6)	ЯМР ^{13}C ppm, (DMSO-d_6)	HMRS(ESI), m/z
10a	84%	217-219	1659 (s) (C=C), 1736 (vs) (C=O), 2241 (w) (C≡N), 3291 (vs, br) (NH_2)	9.63 (d, J = 78.4 Hz, 2H, NH_2), 3.54 (dd, J = 156.4, 11.7 Hz, 2H, CH_2^4), 2.33 (s, 6H, $N(CH_3)_2$), 2.24 – 2.10 (m, 2H, CH_2^7), 1.65 – 1.54 (m, 2H, CH_2^9), 1.53 – 1.29 (m, 2H, CH_2^8).	178.15 (C=O), 177.07 (C^2), 144.94 ($(C^{11,6})_2$), 116.16 ($C≡N^{21}$), 115.24 ($C≡N^{16}$), 59.76 (C^{12}), 52.94 (C^3), 51.08 (CH_2^4), 39.52 ($N(CH_3)_2$), 24.92 (CH_2^7), 24.55(CH_2^8) , 22.01 (CH_2^9), 21.88 (CH_2^{10}).	Calcd. $C_{15}H_{18}N_6O$: 298.1500 $[M]^+$, Found.: 299.1620; Calcd. $C_{15}H_{18}N_6O+N(CH_3)_2$: 343.2100 $[M+N(CH_3)_2]^+$, Found: 343.1250
10b	75%	214-216	1640 (s) (C=C), 1745 (s) (C=O), 2251 (s) (C≡N), 3494 (vs, br) (NH_2)	9.61 (d, J = 115.6 Hz, 2H, NH_2), 3.58 (dd, J = 307.2, 11.7 Hz, 2H, CH_2^6), 2.12 – 2.03 (m, 2H, CH_2^{13}), 1.91 (dd, J = 15.8, 11.2 Hz, 1H, CH^{11}), 1.72 (dd, J = 23.8, 9.1 Hz, 2H, CH_2^{12}), 1.49 – 1.42 (m, 2H, CH_2^{14}), 1.27 (ddd, J = 41.6, 14.6, 6.8 Hz, 2H, CH_2^{15}), 1.04 (s, 3H, NCH_3^{17}), 1.03 (s, 3H, NCH_3^{18}), 0.88 (t, J = 7.1 Hz, 3H,	178.07 (C=O), 177.15 (C^5), 145.03 ($(C^{8,9})_2$), 116.19 ($C≡N^{20}$), 115.30 ($C≡N^{19}$), 41.14 (C^3), 39.55 ($N(CH_3)_2$), 37.85 (CH^6), 31.91(CH_2^{14}), 28.41(C^4), 25.53 ($(CH_2^{10,12})_2$) 24.94 19.63 ($(CH_2^{15,13})_2$), 14.18 (CH_3).	Calcd. $C_{18}H_{24}N_6O$ 340.20 $[M]^+$, Found: 341.2090; Calcld. $C_{18}H_{24}N_6O+N(CH_3)_2$: 385.2600 $[M+N(CH_3)_2]^+$, Found: 385.1719

				CH_3).		
19	48%	>250	1579 (s) (C=C), 1717 (vs) (C=O), 2168 (vs) (=C-C≡N), 2242 (w) (C≡N), 3167 (br), 3282 (w) (NH)	8.42 (s, 1H, NH^1), 7.06 (s, 1H, NH^6), 2.91 (s, 6H, $N(CH_3)_2$), 2.03 – 1.07 (m, 8H, $(CH_2^{12-7})_4$), 0.89 (s, 3H, CH_3)	168.68 (C=O), 157.75 (C^5), 120.99 (C≡N), 115.88 (C≡N), 71.98 (C^7), 40.09 ($N(CH_3)_2$), 31.86 (CH_2^8), 26.66 (CH_2^{11}), 20.86 (CH_2^9), 20.06 (CH_2^{10}), 13.72 (CH_3).	Calcd. $C_{15}H_{19}N_5O$: 285.1600 $[M]^+$, Found: 286.1668; Calcd. $C_{15}H_{19}N_5O{\cdot}Na^+$: 308.1500 $[M+Na]^+$, Found: 308.1484; Calcd. $C_{15}H_{19}N_5O{\times}2$: 570.3200 $[M{\times}2]^+$, Found: 571.3257; Calcd. $[C_{15}H_{19}N_5O]_2{\cdot}Na^+$: 593.3100 $[M{\times}2+Na]^+$; Found: 593.3060
27	64%	210-212	1547 (s) (C=C), 1658 (vs) (C=C), 1731 (w) (=C-O), 2182 (s), 2233 (s) (C≡N), 3379 (w, br) (NH_2)	8.12 (s, 2H, NH_2), 5.27 (t, J = 7.9 Hz, 1H, CH^{15}), 2.20 (q, J = 6.5 Hz, 2H, CH_2^{14}), 1.67 – 1.08 (m, 16H, $(CH_2^{13-6})_8$).	163.23 (C^2), 116.93 ($C{\equiv}N^{20}$), 115.23 ($C{\equiv}N^{18}$), 104.31 (CH^{15}), 27.53 (CH_2^{13}), 24.65 ($(CH_2^{9-7})_3$), 23.42 (CH_2^{14}), 21.47 (CH_2^{10}).	Calcd. $C_{17}H_{21}N_3O$: 283.1700 $[M]^+$, Found: 284.1763; Calcd. $C_{17}H_{22}N_3O_2$: 301.1800 $[M+OH]^+$, Found: 302.1871; Calcd. $C_{19}H_{27}N_4O$: 328.2300 $[M+N(CH_3)_2]^+$, Found: 329.2340; Calcd. $C_{19}H_{28}N_5O$: 343.2400 $[M+NH\text{-}N(CH_3)_2]^+$; Found: 344.2455
33	81%	163-165	1646 (vs) (C=C), 2112 (vs), 2165 (s) (C≡N), 3177 (w, br), 3240 (w, br), 3362 (w, br), 3386 (w, br) (NH_2)	7.56 (s, 2H, NH_2), 4.05 (s, 2H, CH_2^5), 2.43 (s, 6H, $N(CH_3)_2$).	161.85 (C^3), 117.70 ($C{\equiv}N^9$), 115.14 ($(C{\equiv}N^{11,10})_2$), 48.42 (CH_2^5), 46.42 (C^2), 42.24 ($N(CH_3)_2$), 34.59 (C^1)	Calcd. $C_9H_{10}N_6$: 202.1000 $[M]^+$, Found: 203.1047
42	62%	235-236	1661 (s) (C=C), 1748 (vs) (C=O), 2253 (w) (C≡N), 3291 (br), 3403 (w, br) (NH_2)	9.60 (s, 2H, NH_2), 3.66-3.48 (m, 2H, CH_2^4), 3.25-3.00 (m, 2H, CH_2^7), 2.29 (dh, J=7.9, 6.1 Hz, 2H, CH_2^8), 2.18-2.15 (m, 4H, $(CH_2^{19,18})_2$ 2.14 (s, 6H, $N(CH_3)_2$), 1.69-1.39 (m, 2H, CH_2^9).	179.31 (C=O), 177.80 (C^2), 142.47 ($(C^{11,6})_2$), 117.16 ($C{\equiv}N^{23}$), 116.05 ($C{\equiv}N^{16}$), 58.90 (CH_2^{19}), 54.11 (C^3), 51.78 (C^{12}), 51.11 (C^4), 47.74 (CH_2^{18}), 46.24 ($N(CH_3)_2$), 25.94 (CH_2^7), 25.78 (CH_2^8), 22.93 (CH_2^9), 22.70 (CH_2^{10}).	

Conclusion

Thus, 1,1-dimethyl-2-methylenehydrazine is able to enter into reactions with all elements of its structure and in some cases (for example, cyclization reactions and rearrangement of ketone adducts a-h) possesses catalytic properties making it as an indispensable starting compound for the synthesis of various organic structures. It should be stated that the extreme availability of this reagent is of great importance.

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References

[1] S.V. Kolesnikov, General information about fuel — 1,1 dimethylhydrazine, "Oxidation of asymmetric dimethylhydrazine (heptyl) and identification of its transformation products in straits": — Monograph. — *Novosibirsk: SibAK Publishing House*. — K60, 110, ISBN 978-5-4379-0359-9, 2014

[2] F. Klages, G. Nober, F. Kircher, M. Bock, "Untersuchungen in der Hydrazinreihe. I. Die Darstellung von Tri- und Tetra-alkyl-hydrazinen". *Justus Liebig's Annalen Der Chemie.* 547(1), 1–38, doi:10.1002/jlac.19415470102, 1941

[3] M. Fardis, H. Jin, S. Jabri, R. Z. Cai, M. Mish, M. Tsiang, & C. U. Kim, "Effect of substitution on novel tricyclic HIV-1 integrase inhibitors," *Bioorganic & Medicinal Chemistry Letters.* 16(15), 4031–4035, doi:10.1016/j.bmcl.2006.05.008, 2006.

[4] R. Yamada, K. Fukuda, M. Kawanishi, Y. Ohmori, M. Nasu, M. Seto, Y. Sasaki, T. Sunazuka, L. Zhuorong, N. Funato, H. M. I. Yoshihiro, Y. Iwai, S. Ōmura, "Synthesis and activity of staurosporine analogs with a lactone functionality," *Bioorganic & Medicinal Chemistry Letters,* 6(16), 1893–1896, doi:10.1016/0960-894x(96)00343-5, 1996.

[5] S. B. Singh, M. A. Goetz, E. T. Jones, G. F. Bills, R. A. Giacobbe, L. Herranz, S. Stevens-Mile, D. L. Williams, "Oteromycin: A Novel Antagonist of Endothelin Receptor," *The J. of Organic Chemistry,* 60(21), 7040–7042, doi:10.1021/jo00126a071, 1995.

[6] F. Micheli, A. Pasquarello, G. Tedesco, D. Hamprecht, G. Bonanomi, A. Checchia, A. Jaxa-Chamiec, F. Damiani, S. Davalli, D. Donati, C. Gallotti, M. Petrone, M. Rinaldi, G. Riley, T. S. Silvia, M. Wood, "Diaryl substituted pyrrolidinones and pyrrolones as 5-HT2C inhibitors: Synthesis and biological evaluation" *Bioorganic & Medicinal Chemistry Letters*, 16(15), 3906–3912, doi:10.1016/j.bmcl.2006.05.034, 2006.

[7] G. Butora, G. J. Morriello, S. Kothandaraman, D. Guiadeen, A. Pasternak, W. H. Parsons, M. MacCoss, P. P. Vicario, M. A. Cascieri, L. Yang, "4-Amino-2-alkyl-butyramides as small molecule CCR2 antagonists with favorable pharmacokinetic properties," *Bioorganic & Medicinal Chemistry Letters*, 16(18), 4715–4722, doi:10.1016/j.bmcl.2006.07.011, 2006

[8] E. Toja, C. Gorini, C. Zirotti, F. Barzaghi, G. Galliani, "Amnesia-reversal activity of a series of 5-alkoxy-1-arylsulfonyl-2-pyrrolidinones," *European J. of Medicinal Chemistry*, 26(4), 403–413, doi:10.1016/0223-5234(91)90101-r, 1991.

[9] C. L. Dickinson, "Cyanocarbon Chemistry. XV.1A New Synthesis of 3,4-Dicyano-2(1H)-pyridones," *J. of the American Chemical Society* 82(16), 4367–4369, doi:10.1021/ja01501a063, 1960.

[10] S. Lin, & J. March, "March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th Edition," *Molecules*, 6(12), 1064–1065, doi:10.3390/61201064, 2001.

[11] J. Schaefer, J. Bloomfield, "Diekmann condensation (Including the Thorpe-Ziegler condensation). Organic reactions," 15(Ya), 1-203. ISSN: 0078-6179, 1967

[12] M. A. Maryasov, V. V. Davydova, O. E. Nasakin, S. A. Shteingolts, O. A. Lodochnikova, "Synthesis of 2,2-Dimethylhydrazonebut-2-enenitriles and [(2,2-Dimethylhydrazono)methyl]phenylacrylonitriles for Development of Antimicrobial Fluorescent Dyes," *General chemistry J.,* 91, 1613–1618, doi: 10.1134/S007036322109002, 2021.

[13] S. Luo, P. Li, S. Li, Z. Du, X. Hu, Y. Fu, Z. Zhang, "N,N-Dimethyl Tertiary Amino Group Mediated Dual Pancreas- and Lung-Targeting Therapy against Acute Pancreatitis," *Molecular Pharmaceutics,* 14(5), 1771–1781, doi:10.1021/acs.molpharmaceut.7b00028, 2017.

[14] D. Takács, O. Egyed, L. Drahos, P. Szabó, K. Jemnitz, M. Szabó, Z. Veres, J. Visy, J. Molnár, Z. Riedl, G. Hajós, "Synthesis and pharmacological investigation of new N-hydroxyalkyl-2-aminophenothiazines exhibiting marked MDR inhibitory effect," *Bioorganic & Medicinal Chemistry*, 21(13), 3760–3779, doi:10.1016/j.bmc.2013.04.034, 2013.

[15] G. M. Sheldrick, "SHELXT: Integration of space group definition and structural solution. Act of Crystallogr.," 71, 3-8, 2015.

[16] G. M., Sheldrick, "A Brief History of SHELX. Act of Crystallogr.," 64, 112-122, 2007.

[17] C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. R. Taylor, M. Tauler, J. Van De Strick, *J. Appl. Crystallogr. Visualization and analysis of crystal structures,* 39, 453-457, 2006.

[18] K. Banert, T. Pester, "Too Short-Lived or Not Existing Species: N-Azidoamines Reinvestigated," *The J. of Organic Chemistry,* doi:10.1021/acs.joc.9b00034, 2019.