THE REACTION OF ALLOXAN WITH INDOLE AND FURANES. STRUCTURE OF 5-INDOL-3-YL-5-HYDROXYPYRIMIDINE-2,4,6(1H,3H,5H)-TRIONE

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Keywords: alloxan; indol; 2-methylfurane; 5-(indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione; 5-(5-methylfuran-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione; synthesis; structure.

The improved syntheses of 5-(indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (**1**), 5-(5-methylfuran-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (**2**), 5-(5-N,N-dimethylhydrazonylfuran-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (**3**), 5-(4-N,N-dimethyl-aminophenyl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (**4a**), and 5-(4-N,N-diethylaminophenyl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (**4b**) from alloxane in mild conditions were reported. The structure of 5-(indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (**1**) has been determined by XRD study.

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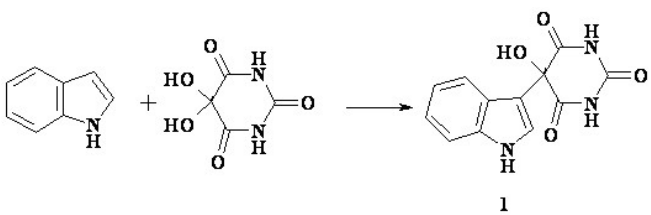
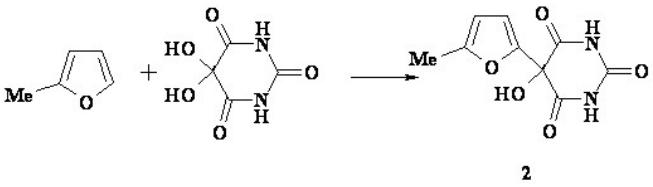
INTRODUCTION:

Recently, 5-(indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **1** was used as the precursor for the synthesis of the range of inhibitors of HAT enzymes[1]. These compounds find utility in any number of therapeutic applications, including treatment of cancer. Compound **1** was synthesized by the reaction of alloxan with indole in boiling ethanol solution in the presence of HCl (Scheme 1).[1]



Scheme 1.

Also, it was reported that alloxan hydrate condensed with 2-methylfurane in the presence of $Sc(OTf)_3$ at room temperature in MeCN solution selectively forming 5-(5-methylfuran-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **2** (Scheme 2).[2]



Scheme 2.

Compound **2** can be regarded as a precursor in the synthesis of 5-(5-methylfuran-2-yl)hydantoin.[1] It can be supposed that alloxan derivatives **1**, **2** may be synthesized in simpler route. This work was undertaken to simplification of syntheses of these compounds and derivatives and to study their structure.

EXPERIMENTAL

^{1}H spectra were recorded on VARIAN VXP-300 spectrometer (300 MHz) and VARIAN JEMINI 400 spectrometer (400 MHz); ^{13}C NMR spectra were recorded on VARIAN VXP-300 spectrometer (75 MHz) and VARIAN JEMINI 400 spectrometer (100 MHz), solvent: $(CD_3)_2SO$, with TMS as internal standard. Mass spectra were recorded on VG 70-70EQ mass spectrometer in fast atom bombardment (FAB) mode. The solvents were purified and dried according to standard procedures. MeOH was dried by distillation on Ca. Indole was purified by sublimation under vacuum (3 Hgmm). N,N-

Dimethylaniline, N,N-diethylaniline and N,N-dimetylhydrazone of 2-furylaldehyde were distillated under vacuum (2 Hgmm).

5-(Indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (1)

A solution of 5,5-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione dihydrate (422 mg, 2.153 mmol) in MeOH (5 ml) was added to a solution of indole (252 mg, 2.153 mmol)) in MeOH (5 ml), the reaction solution was kept at 20°C for 115 h, then solvent was evaporated under vacuum 4 Hgmm, the residue was stirred with PhH (10 ml), the solid was filtered out, dried under vacuum 20 Hgmm, then it was stirred with water (5 ml), the precipitate was filtered out and dried under vacuum 4 Hgmm, yielding (547 mg, 98 %) 5-(indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **1**, pinky white solid, m.p. 235 – 238°C (with decomp.); for solvate 2**(1)**•3THF m.p. 202 – 206°C (with decomp.) (THF – C_6H_{14}). ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) δ = 6.31 (1H, s, OH Alloxane); 7.00 (1H, t, ^3J = 7.2, H Ind); 7.10 (1H, t, ^3J = 7.6, H Ind); 7.13 (1H, s, (C2)H Ind); 7.38 (1H, d, ^3J = 8.4, H Ind); 7.81 (1H, d, ^3J = 8.0, H Ind); 11.26 (1H, s, NH Ind); 11.32 (2H, s, NHC(O) Alloxane). Mass spectrum, *m/z*, (I_{rel} %): 259 M^+ (87); 242 [M+H-H_2O] (100). Mass spectrum, KI, *m/z*, (I_{rel} %): 336 [M-H+2K]$^+$ (14); 298 [M+K]$^+$ (35); 231 (17); 205 (79); 192 (100). Anal. Calcd. for $C_{12}H_9N_3O_4$: C 55.60, H 3.50 , N 16.21. Found: C 55.52, H 3.83, N 16.07.

^{1}H NMR spectrum of solvate 2**(1)**•3THF (300 MHz, $(CD_3)_2SO$) δ = 1.74 (6H, s, CH_2 THF); 3.58 (6H, s, CH_2O THF); 6.31 (1H, s, OH); 6.99 (1H, t, ^3J = 7.2, H Ind); 7.10 (1H, t, ^3J = 7.5, H Ind); 7.14 (1H, d, ^3J = 1.8, (C2)H Ind); 7.37 (1H, d, ^3J = 7.8, H Ind); 7.82 (1H, d, ^3J = 7.8, H Ind); 11.25 (1H, s, NH Ind); 11.31 (2H, s, NHC(O) Alloxane). ^{13}C NMR spectrum of solvate 2**(1)** • 3THF (75 MHz, APT regime, $(CD_3)_2SO$) δ = 1) CH mode: 112.2; 119.6; 131.3; 122.1; 124.2 (C-2, C-4, C-5, C-6, C-7 Ind); 2) CH_2 and C_q mode: 25.5 (CH_2 THF); 67.4 (CH_2O THF); 74.8 (C-OH, Alloxane); 113.0; 125.0; 136.8 (C-4a, C-7a, C-3 Ind); 150.5 (NHC(=O)NH); 171.2 (C(=O)NH).

The crystals of 2(**1**)•3THF were grew from THF – C_6H_{14}, monoclinic, 2($C_{12}H_9N_3O_4$) • 3(C_4H_8O), at 293 K, *a* = 7.0510(4), *b* = 26.132(2), *c* = 20.600(1) Å, β = 96.978(5)°, *V* = 3767.5(4) Å^3, M_r = 734.76, Z = 4, space group $P2_1/n$, d_{calc}= 1.295 g/cm^3, μ(MoK_α) = 0.097 мм$^{-1}$, *F*(000) = 1552. Cell parameters and intensities of 41237 reflections (10952 independent reflections, R_{int}=0.043) were measured using "Xcalibur-3" diffractometer (*T*=293 K, graphite-monochromated MoK_α radiation, ω-scan, $2\theta_{max}$= 60°).

The structure was solved by direct method using the SHELXTL program package [5]. At structure refinement limitations were made on bond lengths in solvent molecules (Csp^3–Csp^3 1.54 Å, Csp^3–O 1.44 Å). Positions of the hydrogen atoms were located from electron density difference maps and refined using the riding model with U_{iso} = 1.2U_{eqv} of the carrier atom. The hydrogen atoms taking part in the formation of hydrogen bonds were refined in isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 10787 reflections was converged to wR_2 = 0.276 (R_1 = 0.086 for 4112 reflections with $F>4\sigma(F)$, S=0.929). The final atomic coordinates, and crystallographic data for molecule **1** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 1538278)

5-(5-Methylfuran-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (2)

The mixture of 5,5-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione dihydrate (215 mg, 1.005 mmol) and solution of 2-methtylfurane (287 mg, 3.499 mmol) in acetic acid (18 ml) was stirred at 23°C for 143 h, then the solvent was evaporated under vacuum 4 Hgmm, the residue was washed by cold water (5 ml), dried under vacuum 2 Hgmm, yielding (180 mg, 80%) 5-(5-methylfuran-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **2**, colorless crystals, m.p. 199 – 200°C (with decomp.) (THF – C_6H_{14}). ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) δ = 2.21 (3H, s, Me); 6.08 (1H, d, ^3J = 2.8, H-4 Fur); 6.27 08 (1H, d, ^3J = 2.8, H-3 Fur); 6.70 (1H, s, OH); 11.46 (2H, s, NH). ^{13}C NMR spectrum (75 MHz, APT regime, $(CD_3)_2SO$) δ = 1) CH and Me mode: 15.5 (Me); 107.4, 109.9 (C-3, C-4 Fur); 2) CH_2 and C_q mode: 73.8 (C–OH); 148.7, 150.3 (C-2, C-5 Fur); 153.1 (NHC(=O)NH); 169.0 (C(=O)NH). Mass spectrum, *m/z*, (I_{rel} %): 224 M^+ (34); 207 [M+H-H_2O] (100); 109 (48). Mass spectrum, KI, *m/z*, (I_{rel} %): 263 [M+K]$^+$ (74); 224 M^+ (44); 207 [M+H-H_2O] (100); 109 (41).

5-(5-N,N-Dimethylhydrazonylfuran-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (3)

5,5-Dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione dihydrate (444 mg, 2.262 mmol) was added to the solution of N,N-dimethylhydrazone of 2-furylaldehyde (313 mg, 2.262 mmol) in MeOH (12 ml), the reaction mixture was stirred at 12°C for 10 min, was kept at 12°C for 23 h, then solvent was evaporated under vacuum 10 Hgmm, the residue was washed by a) Et_2O (15 ml), b) i-PrOH (5.5 ml). The solid residue was dried under vacuum 4 Hgmm, yielding (344 mg, 54%) 5-(5-N,N-dimethylhydrazonylfuran-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **3**, yellow solid, m.p. 173 – 177°C (with decomp.). ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) δ = 2.87 (6H, s, NMe_2); 6.42 (2H, s, H Fur); 6.85 (1H, s, OH); 7.06 (1H, s, CH=N); 11.53 (2H, br. s, NH). ^{13}C NMR spectrum (100 MHz, APT regime, $(CD_3)_2SO$) δ = 1) CH and Me mode: 42.3 (NMe_2); 106.8, 110.5 (C-3, C-4 Fur); 121.4 (CH=N); 2) CH_2 and C_q mode: 73.3 (C–OH); 148.5, 149.7 (C-2, C-5 Fur); 152.9 (NHC(=O)NH); 168.2 (C(=O)NH). Mass spectrum, *m/z*, (I_{rel} %): 281 [M+H]$^+$ (68); 280 M^+ (100). Anal. Calcd. for $C_{11}H_{12}N_4O_5$: N 19.99. Found: N 19.58.

The i-PrOH filtrate was kept -22°C for 50 h, the formed precipitate was filtered off, washed by Et_2O (3 ml), dried under vacuum 4 Hgmm, additionally yielding (82 mg, 13%) compound **3**.

5-(4-N,N-Dimethylaminophenyl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (4a)

The mixture of 5,5-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione dihydrate (678 mg, 3.458 mmol),

N,N-dimethylaniline (419 mg, 3.458 mmol) and acetic acid (10 ml) was stirred at 20 °C for 24 h, the precipitate was filtered off, dried under vacuum 3 Hgmm, yielding (844 mg, 93%) 5-(4-N,N-dimethylaminophenyl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **4a**, white solid, m.p. 200–203 °C (with decomp.). ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) δ = 2.88 (6H, s, NMe_2); 6.36 (1H, br. s, OH); 6.71 (2H, d, ^3J = 8.8, (C-3)H, (C-5)H C_6H_4); 7.19 (2H, d, ^3J = 8.8, (C-2)H, (C-6)H C_6H_4); 11.41 (2H, s, NH). ^{13}C NMR spectrum (100 MHz, APT regime, $(CD_3)_2SO$) δ = 1) CH and Me mode: 39.8 (Me); 111.3 (C-3,C-5 C_6H_4); 125.9 (C-2,C-6 C_6H_4); 2) CH_2 and C_q mode: 76.3 (C–OH); 125.1 (C-1 C_6H_4); 149.9 (C-4 C_6H_4); 150.4 [NH(C=O)NH]; 171.1 [C(=O)NH]. Mass spectrum, *m/z*, (I_{rel} %): 264 $[M+H]^+$ (35); 263 M^+ (100); 246 $[M+H-H_2O]^+$(31). Mass spectrum, KI, *m/z*, (I_{rel} %): 340 $[M-H+2K]^+$(45); 302 $[M+K]^+$ (76); 263 M^+ (100); 246 $[M+H-H_2O]^+$(38). Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C 54.75; H 4.98; N 15.96. Found: C 54.81; H 5.05; N 15.72.

The acetic acid filtrate was evaporated under vacuum 3 Hgmm, the residue washed by water (3 ml), dried under vacuum 3 Hgmm, additionally yielding (44 mg, 4.8%) compound **4a**.

5-(4-N,N-Diethylaminophenyl)-5-hydroxypyrimidine-2,4,6(1H, 3H,5H)-trione (4b)

The mixture of 5,5-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione dihydrate (1.56 g, 7.96 mmol), N,N-diethylaniline (1.08 g, 7.237 mmol) and acetic acid (20 ml) was stirred at 20°C for 70 h, the negligible precipitate was filtered off, the filtrate was evaporated under vacuum 3 Hgmm, the residue was washed a) by CH_2Cl_2 (15 ml), b) by cold water (25 ml), dried under vacuum 3 Hgmm, yielding (2.05 g, 97%) 5-(4-N,N-diethylaminophenyl)-5-hydroxy-pyrimidine-2,4,6(1H,3H,5H)-trione **4b**, pinky white solid, m.p. 167 – 168°C (with decomp.). ^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$) δ = 1.06 (6H, t, ^3J = 6.8, $N(CH_2\underline{Me})_2$); 3.31 (4H, q, ^3J = 6.8, $N(\underline{CH_2}Me)_2$); 6.31 (1H, br. s, OH); 6.64 (2H, d, ^3J = 8.8, (C-3)H, (C-5)H C_6H_4); 7.15 (2H, d, ^3J = 8.8, (C-2)H, (C-6)H C_6H_4); 11.39 (2H, s, NH). ^{13}C NMR spectrum (100 MHz, $(CD_3)_2SO$) δ = 12.3 (Me); 43.6 (NCH_2); 76.3 (C–OH); 110.9 (C-3, C-5 C_6H_4); 123.7 9 (C-1 C_6H_4); 126.3 9 (C-2, C-6 C_6H_4); 147.4 9 (C-4 C_6H_4); 149.8 [NH(C=O)NH]; 171.0[C(=O)NH]. Mass spectrum, *m/z*, (I_{rel} %): 292 $[M+H]^+$ (30); 291 M^+ (63); 276 (72); 274 $[M+H-H_2O]^+$(34); 260 (10); 176 (100).

RESULTS AND DISCUSSION

Independently we had found that 5-(indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **1** could be synthesized with high yield by alloxan hydrate interaction with indole in methanol solution at room temperature (preliminary communications[3,4]). The structure of compound **1** has been proved by data of ^{1}H and ^{13}C NMR spectra and mass spectra. Earlier these data had been no reported[1]. Also the XRD study of 5-(indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **1** has been done (Figure 1).

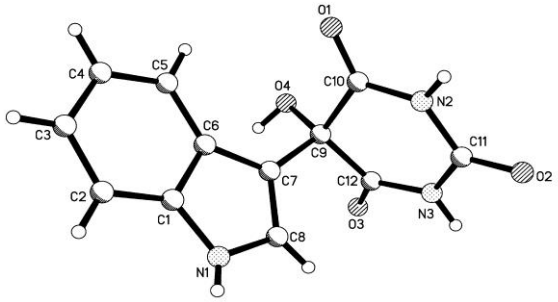


Figure 1. The molecular structure of 5-(indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **1**.

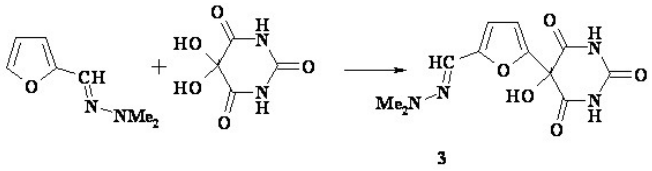
In the crystal compound, **1** exists as the solvate with tetrahydrofuran (THF) 1:1.5. There are two molecules of compound **1** (**A** and **B**) and three molecules of THF in the asymmetric part of the unit cell. The pyrimidinetrione cycle adopts a sofa conformation. Puckering parameters are: S = 0.39, Θ = 40.4°, Ψ = 4.9° in molecule **A** and S = 0.33, Θ = 36.1°, Ψ = 5.6° in molecule **B**. The deviation of C(9) atom from the mean plane of the remaining atoms of this ring is 0.37 Å in molecule **A**, and 0.30 Å in molecule **B**. The pyrimidinetrione cycle is turned toward to the plane of indole moiety (the C(6)-C(7)-C(9)-C(10) torsion angle is 65.8(2)° in molecule **A**, and 80.6(2)° in molecule **B**). The some difference of C(7)–C(9) bond connecting both heterocycle moiety is observed: in molecule **A** this bond is longer than the bond in molecule **B** (C(7A)–C(9A) bond length is 1.524(2) Å, C(7B)–C(9B) bond length is 1.507(2) Å). Also in both kinds **A** and **B** C(9)–C(10) bond such longer that C(9)–C(12) bond (length of C(9A)–C(10A) bond is 1.541(2) Å, C(9B)–C(10B) bond is 1.536(2) Å, C(9A)–C(12A) bond is 1.523(2) Å, C(9B)–C(12B) bond is 1.526(2) Å). In the molecule, **A** amide C=O bonds are similar (length of C(10A)–O(1A) bond is 1.207(2) Å, C(12A)–O(3A) bond is 1.211(2) Å).). In molecule **B** amide C=O bonds are such different (length of C(10B)–O(1B) bond is 1.213(2) Å, C(12B)–O(3B) bond is 1.222(2) Å).

The two from three solvate molecules of tetrahydrofuran are disordered over two twist conformations with equal population.

In the crystal molecules, **A** and **B** have a different supramolecular arrangement. Molecule **A** forms four intermolecular hydrogen bonds as the proton donor and three intermolecular hydrogen bonds as the proton acceptor. Molecule **B** forms four intermolecular hydrogen bonds as the proton donor and two intermolecular hydrogen bonds as the proton acceptor.

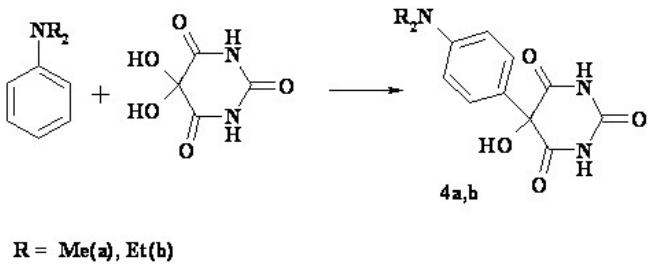
It was found that 5-(5-methylfuran-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **2** formed with high yield in alloxan hydrate reaction with 2-methylfurane in acetic acid solution at room temperature. In this reaction $Sc(OTf)_3$ presence is not need. The structure of compound **2** has been proved by data of ^{1}H and ^{13}C NMR spectra and mass spectra.

In the same manner, alloxane hydrate reacts with N,N-dimethylhydrazone of 2-furylaldehyde yielding 5-(5-N,N-dimethylhydrazonylfuran-2-yl)-5-hydroxypyrimidine-2,4,6 (1H,3H,5H)-trione **3** (Scheme 3). This reaction takes place in the acetic acid solution at room temperatures.



Scheme 3.

It was found that alloxane reacted with N,N-dimethylaniline and N,N-diethylaniline in acetic acid at room temperature yielding 5-(4-N,N-dimethylamino-phenyl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **4a** and 5-(4-N,N-diethylaminophenyl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **4b**, respectively (Scheme 4).



Scheme 4.

The structures of compounds **3**, **4a**, and 4**b** are consistent with the data of ^{1}H and ^{13}C NMR spectra and mass spectra. Compound **3**, **4a**, and 4**b** may be regard as precursors for the synthesis of respective hydantoins.

Conclusions

New improved syntheses of 5-(indol-3-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **1**, 5-(5-methyl-furan-2-yl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **2**, 5-(5-N,N-dimethylhydrazonylfuran-2-yl)-5-hydroxypyrimi-dine-2,4,6(1H,3H,5H)-trione **3**, 5-(4-N,N-dimethylamino-phenyl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **4a**, and 5-(4-N,N-diethylaminophenyl)-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione **4b** in mild conditions had been developed. The structure of 5-(indol-3-yl)-5-hyd-roxypyrimidine-2,4,6(1H,3H,5H)-trione **1** has been investigated by XRD study.

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References

[1]Kesicki, E. A., Wang, C., Patane, M. A., Kluge, A. F., J. H. Van Drie, Jr., *WO2016/44777*, **2016**, ABVIE Inc.

[2]Spesivaya, E. C., Konshin V. V., *III Int. Sci. Conf. "Achievements of Synthesis and Complexing,"* 21 – 25 April 2014, Moscow, RUDN University, Russia, Book of Abstracts, **2014**, 290.

[3]Shtamburg, V. V., Anishenko A. A., *VII Int. Conf. "Chemistry of Nitrogen-Containing Heterocycles (CNCH-2015)",* 9–13 November 2015, Kharkiv, Ukraine, Book of Abstracts, **2015**, P-7.

[4]Shtamburg, V. V., Anishenko A. A., Shtamburg, V. G., *XXIV Ukrainian Conference of Organic Chemistry*, 19 – 23 September 2016, Poltava, Ukraine, Book of Abstracts, **2016**, C-9, 89.

[5]Sheldrick G. M., *Acta Crystallogr., Sect. A*, **2008**, *A64*, 112-122. https://doi.org/10.1107/S0108767307043930

[6]Zefirov, N. S., Palyulin, V. A., Dashevskaya, E. E., *J .Phys. Org. Chem*., **1990**, *3*, 147–154. https://doi.org/10.1002/poc.610030304

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