First Example of Catalytic Synthesis of Difurazanohexahydrohexaazapyrenes and *in Vitro* Study of Their Antitumor Activity

Elena B. Rakhimova,*^{ID} Victor Yu. Kirsanov, Ekaterina S. Mescheryakova, Leonard M. Khalilov, Askhat G. Ibragimov, Lilya U. Dzhemileva, Vladimir A. D'yakonov,^{ID} and Usein M. Dzhemilev

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, 141 Prospekt Oktyabrya, 450075 Ufa, Russian Federation

Supporting Information

ABSTRACT: Catalytic method for synthesis of hexahydrohexaazapyrenes bearing two annelated furazan moieties has been successfully developed. Structures of synthesized hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes have been determined on the basis of NMR data using 2D techniques, MALDI TOF/TOF mass spectrometry, and X-ray analysis. Primary screening of hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes for cytotoxic activity against the K562, Jurkat, U937, and HeLa tumor cell lines has been performed. Studies on the induction of apoptosis and the effect of the synthesized compounds on the cell cycle have been successfully implemented. The synthesized compounds have been found to induce apoptosis of cancer cells in the K562, Jurkat, U937, and HeLa lines.

KEYWORDS: Catalysis, heterocyclization, 1,3,5-triazinanes, 1,4,5,8-tetraazadifurazano[3,4-*c*][3,4-*h*]decalin, 2,8-disubstituted hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes, cytotoxic activity

R = cycloalkyl, norbornyl
6 examples, 54–63% yield

Apoptosis
of cancer cells
in lines K562, Jurkat,
U937 and HeLa

Intensive development of heterocyclic chemistry is stipulated by a broad range of practical applications for heterocyclic compounds.¹ Studies directed toward synthesis of heterocyclic compounds have resulted in development of efficient chemical reactions with participation of heterocyclic fragments as “building blocks” or synthones of a predetermined structure. One of such practically significant synthones is 1,2,5-oxadiazole (furazan). A characteristic feature of the furazan cycle that influences chemical reactivity of its derivatives² is the presence of N–O–N chain, which renders the heterocycle with an essentially electron acceptor functionality. However, the degree of bond fixation in the heterodienic fragment of furazan is very high, and its derivatives are not susceptible to tautomerism. According to ref 3, the furazan ring constitutes a part of high energy materials, while the polynitrogenous derivatives of furazanopyrazine have been proposed for use as explosives.^{4,5} Aforesaid studies have contributed to the development of methods for the synthesis of furazanopyrazines^{6–9} and have stimulated investigations into their physical¹⁰ and biological^{11,12} properties. Heterocycles containing an oxadiazole moiety possess antiatherogenic,¹³ antimalarial,¹⁴ and antimicrobial^{15,16} activities, as well as neuroprotective¹⁷ and antiproliferative¹⁸ effects.

In continuation of our research in the field of synthesis of annelated polyazapolycycles^{19–23} and aiming at development of an efficient method for producing previously undescribed hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes promising for practical use, we have studied a reaction for catalytic cycloaminomethylation of tetraazadifurazanodecalin. Such an approach to the design of annelated polyazapolycycles is based

on our previously obtained positive results for a one-pot synthesis of hexaazaperhydropyrenes^{19,20} or hexaazaperhydrodibenzotetracenes²¹ via cyclocondensation of tetraazadecalin or tetraazaperhydrodibenzotetracene with cycloaminomethylation reagents. 1,3,5-Trisubstituted 1,3,5-triazinanes have been recognized as efficient reagents for the reactions of aminomethylation^{24–26} and cycloaddition.^{27–31} During our preliminary experiments, it had been shown that noncatalytic interaction between 1,3,5-tricyclopropyl-1,3,5-triazinane and 1,4,5,8-tetraazadifurazano[3,4-*c*][3,4-*h*]decalin (**1**) at 20 °C results in formation of 2,8-dicyclopropyl-substituted hexahydrodioxadecaazadicyclopenta[*e,l*]pyrene (**2**) with the yield no more than 10%. To increase the yield of the target heterocycle **2**, we have carried out the reaction of 1,3,5-tricyclopropyl-1,3,5-triazinane with 1,4,5,8-tetraazadifurazano[3,4-*c*][3,4-*h*]decalin in the presence of nickel catalyst that we had previously utilized in heterocyclization reactions.^{19–21} Under the action of NiCl₂·6H₂O (5 mol %), heterocyclization between 1,4,5,8-tetraazadifurazano[3,4-*c*][3,4-*h*]decalin and 1,3,5-tricyclopropyl-1,3,5-triazinane proceeds in a MeOH–DMSO mixed solvent to produce hexahydrodioxadecaazadicyclopenta[*e,l*]pyrene **2** with 63% yield. Upon increasing concentration of the NiCl₂·6H₂O catalyst up to 10 mol %, no significant changes in the yield of the heterocycle **2** has been observed. Choice of the solvent mixture (MeOH–DMSO) is stipulated by good solubility of

Received: January 18, 2019

Accepted: February 28, 2019

Published: March 5, 2019

initial reagents therein. However, the amount of DMSO for dissolving the initial 1,4,5,8-tetraazadifurano[3,4-*c*][3,4-*h*]-decalin has to be minimal since its excess in the reaction medium significantly reduces the yield of target polyazapoly-cycle 2. Replacing cyclopropyl moiety at the nitrogen atom of initial triazinane with other cycloalkyl substituents ($R =$ cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl) has no noticeable effect on the yield of resulting difurazanohexahydrohexaazapyrenes. It should be noted that 1,3,5-tricycloalkyl-1,3,5-triazinanes have been generated *in situ* and further involved into cycloaminomethylation reaction without prior isolation to attain more efficient synthesis of target hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes. Under optimized conditions (5 mol % $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, 20 °C, 3 h, solvent mixture MeOH–DMSO), heterocyclization between 1,4,5,8-tetraazadifurano[3,4-*c*][3,4-*h*]decalin and 1,3,5-tricycloalkyl-1,3,5-triazinanes has selectively produced 2,8-dicycloalkyl-substituted hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes (3–7) with 55–58% yield (Scheme 1). Proposed synthesis

Scheme 1. Recyclization of 1,3,5-Tricyclopropyl-1,3,5-triazinanes with 1,4,5,8-Tetraazadifurano[3,4-*c*][3,4-*h*]decalin

of polyazapolycycles with *bis*-annulated furazan rings, involving 1,4,5,8-tetraazadifurano[3,4-*c*][3,4-*h*]decalin as an initial substrate, opens a roadway toward producing a wide range of novel biologically important compounds.

^1H NMR spectra of the compounds 2–6 are characterized by the presence of two doublet signals (2J , geminal = 12 Hz) in the regions of 4.21–4.39 and 4.95–5.01 ppm, whose signals correspond to methylene protons of the carbon atoms located between two nitrogen atoms in positions H-1, H-3, H-7, and H-9. Broadened signals in the region between 4.75 and 4.85 ppm attribute to skeleton protons H-12c and H-12d. In ^{13}C NMR spectra, appearance of three signals is characteristic of a furazan-containing hexacyclic skeleton of the compounds 2–6. Two signals in the regions of 65.1–68.2 and 147.5–147.7 ppm attribute to the carbon atoms located between the nitrogen atoms in positions C-1, C-3, C-7, C-9 and C-3b, C-6a, C-9b, C-12a, respectively. The signal between 67.9 and 68.3 ppm corresponds to the carbon atoms in positions C-12c and C-12d. It should be noted that in ^1H and ^{13}C NMR spectra of the compound 7, due to the presence of two chiral centers at C-1' and C-1'', formation of a diastereomeric pair has been observed along with diastereomeric splitting^{32,33} of the signals attributable to both norbornane fragments and a hexahydrodioxadecaazadicyclopenta[*e,l*]pyrene ring. Signal assessment has been conducted based on two-dimensional homonuclear- (COSY, NOESY) and heteronuclear (HSQC, HMBC) NMR experiments. Structures proposed for the compounds 2–7 have been confirmed by recording molecular peaks in the mass spectra of positive ions (MALDI TOF/TOF, resolution 0.001 ae).

Structures of 2,8-dicyclohexyl- (4) and 2,8-dibicyclo[2.2.1]-hept-2-yl-substituted hexahydrodioxadecaazadicyclopenta[*e,l*]pyrene (7) have been also confirmed by X-ray crystal analysis (Figure 1). According to X-ray diffraction data, the compounds

Figure 1. Crystal structures of compounds 4 and 7. Asymmetric unit of the compound 7 (7a)

4 and 7 crystallize in the centrosymmetric triclinic space group $P\bar{1}$. Compound 7 crystallizes with two DMSO molecules (Figure 1, 7a), on the contrary to the compound 4, whose asymmetric unit comprises only the molecules of the target compound. Central saturated polyazapolycyclic skeleton has C_1 symmetry. Preferred conformation for the triazinane and piperazine rings in crystal state is *chair*, which is preserved upon formation of a polycyclic structure, in accordance to what we had observed earlier.^{20–22} However, in the cases of the compounds 4 and 7, the triazinane rings adopt a *chair* conformation, whereas the piperazine rings adopt a *sofa* conformation. Additional changes occur in a ring fusion mode and in orientation of nitrogen atoms N2 and N8. Thus, in the structures 4 and 7, four heterocyclic rings demonstrate *cis* fusion. Norbornane substituents in the compound 7 are *cis*-oriented and occupy an axial position relative to the polycyclic skeleton. In the compound 4, cyclohexane substituents that adopt the *chair* conformation are orthogonal with regard to one another and occupy axial and equatorial positions, accordingly, relative to the polyazapolycyclic skeleton of the molecule.

Based on the results of the earlier experiments^{19–21} and the literature data,^{34,35} one can assume that a catalytic reaction cycle between 1,4,5,8-tetraazadifurano[3,4-*c*][3,4-*h*]decalin (1) and 1,3,5-tricycloalkyl-1,3,5-triazinane includes a phase of heteroatom coordination with the central metal ion of the catalyst.³⁶ This coordination contributes to the shift of electron density from the heteroatom to the metal ion, thus leading to the formation of a carbocation. Subsequent nucleophilic addition of a secondary nitrogen atom in 1 to a carbocation generated under the reaction conditions results in heterocyclization, whereupon hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes are formed.

We have suggested that thus-synthesized compounds can act as agents that induce apoptosis of tumor cells via modulating activity of the key enzymes involved there into, in particular, the caspases.^{37,38} Often, while comprising several functional groups and radicals and while transforming into various forms of metabolites, heterocyclic compounds can exert a complex

Table 1. Cytotoxic Activities of the Synthesized Hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes 2–7 Measured on the Tumor Cell Cultures Jurkat, K562, U937, and HeLa (CC₅₀, μ M)

compd	Jurkat	K562	U937	HeLa
2	0.27 $\pm$ 0.014	0.31 $\pm$ 0.022	0.25 $\pm$ 0.027	0.42 $\pm$ 0.031
3	0.51 $\pm$ 0.023	0.64 $\pm$ 0.032	0.57 $\pm$ 0.011	0.98 $\pm$ 0.027
4	0.53 $\pm$ 0.037	0.59 $\pm$ 0.014	0.54 $\pm$ 0.024	1.04 $\pm$ 0.048
5	0.57 $\pm$ 0.028	0.69 $\pm$ 0.043	0.59 $\pm$ 0.032	1.21 $\pm$ 0.036
6	0.62 $\pm$ 0.032	0.74 $\pm$ 0.017	0.58 $\pm$ 0.028	1.37 $\pm$ 0.032
7	0.16 $\pm$ 0.015	0.21 $\pm$ 0.019	0.11 $\pm$ 0.048	0.32 $\pm$ 0.027

effect on a cell. Acting as antimetabolites, these compounds interact with the key intracellular molecules (DNA, RNA, proteins, various coenzymes, etc.) that ultimately lead to the death of tumor cells. Therefore, the search for new compounds possessing high antitumor activity is of an undoubted interest. In this regard, we have studied the processes of induction and modulation of apoptosis using newly synthesized 2,8-disubstituted hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes. Frequently used in practical oncology etoposide has been selected as a reference drug. It has been established that the cytotoxic effect of hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes, as determined by the MTT assay in four human tumor cell lines, has a pronounced dose-dependent nature, individual for each compound. Cytotoxicity screening in the U937 cell line by the MTT assay has shown that compounds 2 and 7 have the lowest CC₅₀ values (0.25 and 0.11 μ M, respectively) (Table 1).

The compounds studied hereby induce cell apoptosis in the lines K562, Jurkat, U937, and HeLa. According to the results obtained upon determination of fluorescence intensity level in cells incubated with the test compounds 4 and 7 and stained with Annexin Alexa Fluor 488 and 7AAD, a significant increase in the CC₅₀ values has been demonstrated for all analyzed compounds, whereas in the variants with etoposide, the dye fluorescence intensity has conformed to the studied compounds. The highest percentage of apoptotic cells has been obtained in the U937 cell line upon its treatment with the test compound 7 (Figure 2), wherein said effect is clearly dependent on the dose of the test compound.

Figure 2. U937 tumor cells treated with the test compound 7 in different concentrations and stained with annexin V/7AAD. Flow cytometry data: (A) control; (B) 7, 0.2 μ M; (C) 7, 0.1 μ M; (D) 7, 0.05 μ M; (E) 7, 0.025 μ M. The histogram shows the apoptosis rate (%); * p < 0.05 when compared with the control group (n = 5).

The results of flow cytometry conducted in the cell line U937 in 24 h after the treatment with the test compound 7 have demonstrated an appearance of a hypodiploid peak attributable to DNA (preG₀ cell population), an increase in the proportion of cells in S-phase and a decrease in the G₂ peak (Figure 3); all these events together being indicative of the ability of a substance to affect all phases of the cell cycle that ultimately leads to cell death.

In conclusion, in the present study we have demonstrated that intermolecular heterocyclization of 1,3,5-tricycloalkyl-

Figure 3. Cell cycle phases of U937 cells treated with the test compound 7: (A) control; (B) 7, 0.2 μ M; (C) 7, 0.1 μ M; (D) 7, 0.05 μ M; (E) 7, 0.025 μ M. Incubation time of U937 cells with 7 is 24 h. The DNA histograms of U937 cells' cell cycle were analyzed by flow cytometry for PI staining. The G₀/G₁%, S%, and G₂+M% phases of the cells were analyzed using flow cytometry. Flow cytometric histograms are representative of three separate experiments. Proliferating index (PI) value (%) = [S + (G₂+M)] / [(G₀/G₁) + S + (G₂+M)] $\times$ 100. Data are presented with the means $\pm$ SD and mean values of three independent experiments. * p < 0.05 and ** p < 0.01, compared with the control group.

1,3,5-triazinanes with 1,4,5,8-tetraazadifurano[3,4-*c*][3,4-*h*]-decalin catalyzed by NiCl₂·6H₂O provides for an effective method for the synthesis of novel 2,8-dicycloalkyl-substituted hexahydrodioxadecaazadicyclopenta[*e,l*]pyrenes with profound antitumor activity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.9b00019.

Experimental procedures^{39–43} and full characterization for compounds 2–7 (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rakhimovaelena@mail.ru.

ORCID

Elena B. Rakhimova: 0000-0002-7908-1354

Vladimir A. D'yakonov: 0000-0002-7787-5054

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

This research has been financially supported by the Russian Foundation for Basic Research (Grants 18-33-00528, 18-29-09068) and the President of Russian Federation for Government Support of Leading Scientific Schools (Grant NS-5240.2018.3). The research has been carried out in accordance with the approved plans for research projects at the Institute of Petrochemistry and Catalysis of the Russian Academy of Sciences (RAS) on the topic titled "Metal Complex Catalysis

in the Synthesis of Hetero- and Metalloheterocycles". State Registration No. AAAA-A17-117012610060-7 (2017–2019).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Structural studies of synthesized compounds have been performed on the unique equipment in the Centre of Common Usage "Agidel" at the Institute of Petrochemistry and Catalysis of RAS.

REFERENCES

- (1) Lamberth, C.; Dinges, J. *Bioactive Heterocyclic Compound Classes: Pharmaceuticals and Agrochemicals*; Wiley-VCH Verlag & Co, 2012; p 670.
- (2) Sheremetev, A. B.; Makhova, N. N.; Friedrichsen, W. Monocyclic furazans and furoxans. *Adv. Heterocycl. Chem.* **2001**, *78*, 65–188.
- (3) Sheremetev, A. B.; Yudin, I. L. Advances in the chemistry of furazano[3,4-b]pyrazines and their analogues. *Russ. Chem. Rev.* **2003**, *72* (1), 87–100.
- (4) Willer, R. L. 1,4,5,8-tetranitro-1,4,5,8-tetraazadifurazano-[3,4-c][3,4-h]Decalin. Patent US 4503229. Chem. Abstr. 1035-409-9, 1985.
- (5) Willer, R. L. Synthesis of 1,4-dinitrofurazano(3,4-b)piperazine. Patent US 4539405. Chem. Abstr. 1049-160-9, 1986.
- (6) Gasco, A.; Ruà, G.; Menziani, E.; Nano, G. M.; Tappi, G. Studies in the chemistry of 1,2,5-oxadiazole. I. Synthesis of some furazanopyrazines from 3,4-diamino-1,2,5-oxadiazole. *J. Heterocycl. Chem.* **1969**, *6*, 769–770.
- (7) Eremeev, A. V.; Andrianov, V. G.; Piskunova, I. P. Synthesis of furazano[3,4-b]pyrazine derivatives. *Chem. Heterocycl. Compd.* **1978**, *5*, 500–502.
- (8) Bratton, L. D.; Unangst, P. C.; Rubin, J. R.; Trivedi, B. K. Preparation of 6-, 7-, and 8-substituted derivatives of 2-oxa-1,3,4,10-tetraazacyclopenta[b]fluoren-9-one. *J. Heterocycl. Chem.* **2001**, *38*, 1103–1111.
- (9) Pirogov, S. V.; Mel'nikova, S. F.; Tselinskii, I. V. Reaction of diaminofurazane with ninhydrin. *Chem. Heterocycl. Compd.* **1997**, *12*, 1473–1474.
- (10) Roy, M. S.; Saxena, D.; Manmeeta; Sharma, G. D. Doping effect of viologen on rectification, charge transport processes and photovoltaic properties of furazano(3,4-b)piperazine thin film device. *J. Mater. Sci.: Mater. Electron.* **2001**, *12*, 45–50.
- (11) Andreichenkov, Yu. S.; Nekrasov, D. D.; Bargteil, B. A.; Zalesov, B. S. 6-Phenacylidene-5-oxo-4,5,6,7-tetrahydrofurazano[3,4-b]pyrazine exhibiting tranquilizing activity. Patent RU 1042321. Chem. Abstr. 1267-017-7, 1997.
- (12) Sheremetev, A. B.; Betin, V. L.; Yudin, I. L.; Kulagina, V. O.; Khropov, Yu. V.; Bulargina, T. V.; Kots, A. Ya.; Aherementev, A. V. Derivatives of tetrafurazano[3,4-b:3',4'-f:3'',4''-j: 3''', 4'''-n] [1,4,5,8,9,12,13,16]octaazabicyclo[14.2.2]eicosa-4,8,12-triene and method of obtaining them. Patent RU 2167161. Chem. Abstr. 1385-596-7, 2001.
- (13) Cabrera, M.; López, G. V.; Gómez, L. E.; Breijo, M.; Pintos, C.; Botti, H.; Raymondo, S.; Vettorazzi, A.; López de Cerain, A.; Monge, A.; Rubbo, H.; Gonzalez, M.; Cerecetto, H. Genetic toxicology and preliminary in vivo studies of nitric oxide donor tocopherol analogs as potential new class of antiatherogenic agents. *Drug Chem. Toxicol.* **2011**, *34* (3), 285–293.
- (14) Cameron, A.; Read, J.; Tranter, R.; Winter, V. J.; Sessions, R. B.; Brady, R. L.; Vivas, L.; Easton, A.; Kendrick, H.; Croft, S. L.; Barros, D.; Lavandera, J. L.; Martin, J. J.; Risco, F.; García-Ochoa, S.; Gamo, F. J.; Sanz, L.; Leon, L.; Ruiz, J. R.; Gabarro, R.; Mallo, A.; de las Heras, F. G. Identification and activity of a series ofazole-based compounds with lactate dehydrogenase-directed anti-malarial activity. *J. Biol. Chem.* **2004**, *279* (30), 31429–31439.
- (15) Sravya, G.; Yamini, G.; Padmavathi, V.; Padmaja, A. Synthesis and antimicrobial activity of styryl/pyrrolyl/pyrazolyl sulfonylmethyl-1,3,4-oxadiazolyl amines and styryl/pyrrolyl/pyrazolyl sulfonylmethyl-1,3,4-thiadiazolyl amines. *Eur. J. Med. Chem.* **2016**, *122*, 647–655.
- (16) Babu, Y. H.; Kumar, M. A.; Srinivasulu, K.; Reddy, C. S.; Raju, C. N. Synthesis and antimicrobial activity of novel 2-(heteryl-carboxamido)-2,3-dihydro-1H-1,2,5-oxadiazolo[3,4-c] [1,3,2]-diazaphosphole-2-oxides. *ARKIVOC* **2006**, *xv*, 189–197.
- (17) Schiefer, I. T.; VandeVrede, L.; Fa, M.; Arancio, O.; Thatcher, G. R. J. Furoxans (1,2,5-oxadiazole-N-oxides) as novel no mimetic neuroprotective and procognitive agents. *J. Med. Chem.* **2012**, *55*, 3076–3087.
- (18) Sheremetev, A. B.; Dmitriev, D. E.; Lagutina, N. K.; Raihstat, M. M.; Kiselyov, A. S.; Semenova, M. N.; Ikizalp, N. N.; Semenov, V. V. New functionalized aminofurazans as potential antimitotic agents in the sea urchin embryo assay. *Mendeleev Commun.* **2010**, *20*, 132–134.
- (19) Rakhimova, E. B.; Kirsanov, V. Yu.; Zainullin, R. A.; Ibragimov, A. G.; Dzhemilev, U. M. New Catalytic Method for the Synthesis of 2,7-Dicycloalkyl-hexaazaperhydropyrenes. *J. Chem.* **2016**, *2016*, 8406172.
- (20) Rakhimova, E. B.; Kirsanov, V. Yu.; Meshcheryakova, E. S.; Khalilov, L. M.; Kutepov, B. I.; Ibragimov, A. G.; Dzhemilev, U. M. One-pot catalytic synthesis of 2,7-bis-substituted 4,9(10)-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes. *Tetrahedron* **2017**, *73* (49), 6880–6886.
- (21) Rakhimova, E. B.; Kirsanov, V. Yu.; Meshcheryakova, E. S.; Khalilov, L. M.; Ibragimov, A. G.; Dzhemilev, U. M. First synthesis of 2,9-disubstituted *cis*-2,3a,7b,9,10a,14b-hexaazaperhydropyridibenzotetra-cenes. *Synlett* **2018**, *29*, 1861–1866.
- (22) Rakhimova, E. B.; Ismagilov, R. A.; Meshcheryakova, E. S.; Khalilov, L. M.; Ibragimov, A. G.; Dzhemilev, U. M. An efficient catalytic method for the synthesis of 2,7-dialkyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes. *Tetrahedron Lett.* **2014**, *55* (46), 6367–6369.
- (23) Rakhimova, E. B.; Kirsanov, V. Yu.; Ibragimov, A. G.; Dzhemilev, U. M. Efficient catalytic synthesis of 2,7-diaryl(hetaryl)-4,9-dimethylperhydro-2,3a,5a,7,8a,10a-hexaazapyrenes. *Russ. J. Org. Chem.* **2018**, *54* (7), 1085–1089.
- (24) Oda, S.; Sam, B.; Krische, M. J. Hydroaminomethylation Beyond Carbonylation: Allene–Imine Reductive Coupling by Ruthenium-Catalyzed Transfer Hydrogenation. *Angew. Chem., Int. Ed.* **2015**, *54*, 8525–8528.
- (25) Lian, X.; Lin, L.; Fu, K.; Ma, B.; Liu, X.; Feng, X. A new approach to the asymmetric Mannich reaction catalyzed by chiral *N,N'*-dioxide–metal complexes. *Chem. Sci.* **2017**, *8*, 1238–1242.
- (26) Gong, J.; Li, S.-W.; Qurban, S.; Kang, Q. Enantioselective Mannich reaction employing 1,3,5-triaryl-1,3,5-triazines catalyzed by chiral-at-metal rhodium complexes. *Eur. J. Org. Chem.* **2017**, *25*, 3584–3593.
- (27) Ji, D.; Sun, J. [3 + 2]-Cycloaddition of azaoxyallyl cations with hexahydro-1,3,5-triazines: access to 4-imidazolidinones. *Org. Lett.* **2018**, *20*, 2745–2748.
- (28) Zhu, C.; Xu, G.; Sun, J. Gold-catalyzed formal [4 + 1]/[4 + 3] cycloadditions of diazo esters with triazines. *Angew. Chem., Int. Ed.* **2016**, *55*, 11867–11871.
- (29) Peng, S.; Cao, S.; Sun, J. Gold-catalyzed regiodivergent[2 + 2+2]-cycloadditions of allenes with triazines. *Org. Lett.* **2017**, *19*, 524–527.
- (30) Garve, L. K. B.; Jones, P. G.; Werz, D. B. Ring-Opening 1-Amino-3-aminomethylation of Donor-Acceptor Cyclopropanes via 1,3-Diazepanes. *Angew. Chem., Int. Ed.* **2017**, *56*, 9226–9230.
- (31) Garve, L. K. B.; Kreft, A.; Jones, P. G.; Werz, D. B. Synthesis of 2-unsubstituted pyrrolidines and piperidines from donor–acceptor cyclopropanes and cyclobutanes: 1,3,5-triazines as surrogates for formylimines. *J. Org. Chem.* **2017**, *82*, 9235–9242.
- (32) Khalilov, L. M.; Spivak, A. Yu.; Vasil'eva, E. V.; Fatykhov, A. A.; Prokhorova, N. A.; Tolstikov, G. A. ¹³C NMR spectra of biologically

active compounds XI. Diastereomeric effects in C-glycosides. *Chem. Nat. Compd.* **1991**, 27, 318–322.

(33) Khalilov, L. M.; Panasenko, A. A.; Muslukhov, R. R.; Tolstikov, G. A. Diastereomeric effects on chiral axes in the ^{13}C -NMR spectra of diallenes. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1988**, 37, 1569–1572.

(34) Mokrov, G. V.; Likhoshesterov, A. M.; Lezina, V. P.; Gudasheva, T. A.; Bushmarinov, I. S.; Antipin, M. Yu. Synthesis and selected properties of *N*-substituted pyrrolo[2,1-*c*]-1,3-diazacycloalkano[1,2-*a*]pyrazinones. *Russ. Chem. Bull.* **2010**, 59, 1254–1266.

(35) Krohn, K.; Cludius-Brandt, S. Acid-Induced Rearrangement Reactions of α -Hydroxy-1,3-dithianes. *Synthesis* **2010**, 8, 1344–1348.

(36) Kukushkin, Yu. N. *Reactivity of Coordination Compounds* [in Russian]; Khimiya: Leningrad, 1987, 288.

(37) Majumder, P. K.; Pandey, P.; Sun, X.; Cheng, K.; Datta, R.; Saxena, S.; Kharbanda, S.; Kufe, D. Mitochondrial Translocation of Protein Kinase C δ in Phorbol Ester-induced Cytochrome *c* Release and Apoptosis. *J. Biol. Chem.* **2000**, 275 (29), 21793–21796.

(38) Volkova, T. O.; Malysheva, I. E.; Nemova, N. N. Phorbol 12-myristate 13-acetate prevents apoptosis in erythroleukemia K562 cells induced by some nucleosides. *Russ. J. Dev. Biol.* **2005**, 36 (1), 14–20.

(39) Willer, R. L.; Moore, D. W. Synthesis and chemistry of some furazano- and furoxano[3,4-*b*]piperazines. *J. Org. Chem.* **1985**, 50, 5123–5127.

(40) *CrysAlis PRO/2012*; Agilent Ltd.: Yarnton, Oxfordshire, England, 2012.

(41) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **2009**, 42, 339–341.

(42) Sheldrick, G. M. A short history of SHELX. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, A64, 112–122.

(43) Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; Van De Streek, J. Mercury: visualization and analysis of crystal structures. *J. Appl. Crystallogr.* **2006**, 39, 453–457.