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Sm-Catalyzed Synthesis and Biological Activity of Acyclic and Cyclic Azadiperoxides

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Abstract—Acyclic diaminodiperoxides and cyclic azadiperoxides are synthesized by the reaction of 1,1-bis(hydroperoxy)cycloalkanes with formaldehyde and primary arylamines in the presence of Sm-containing catalysts [$SmCl_3 \cdot 6H_2O$, $Sm(NO_3)_3 \cdot 6H_2O$, $SmCl_3/\gamma\text{-}Al_2O_3$, and $Sm(NO_3)_3/\gamma\text{-}Al_2O_3$]. The chemoselectivity of this three-component reaction depends on the position of the substituent (F,Cl) in the phenyl ring of the primary arylamines. Signals of the cyclic aminoperoxides were assigned considering the conformation dynamics of the tetraoxazocane cycle with two rigid peroxide bonds. The structure of the acyclic diaminodiperoxides was reliably determined by X-ray diffraction analysis. The synthesized acyclic diaminodiperoxides were found to exhibit anticancer activity.

Keywords: acyclic diaminodiperoxides, cyclic azadiperoxides, arylamines, catalysis, heterocyclization, chemoselectivity, conformational analysis, X-ray diffraction analysis, anticancer activity.

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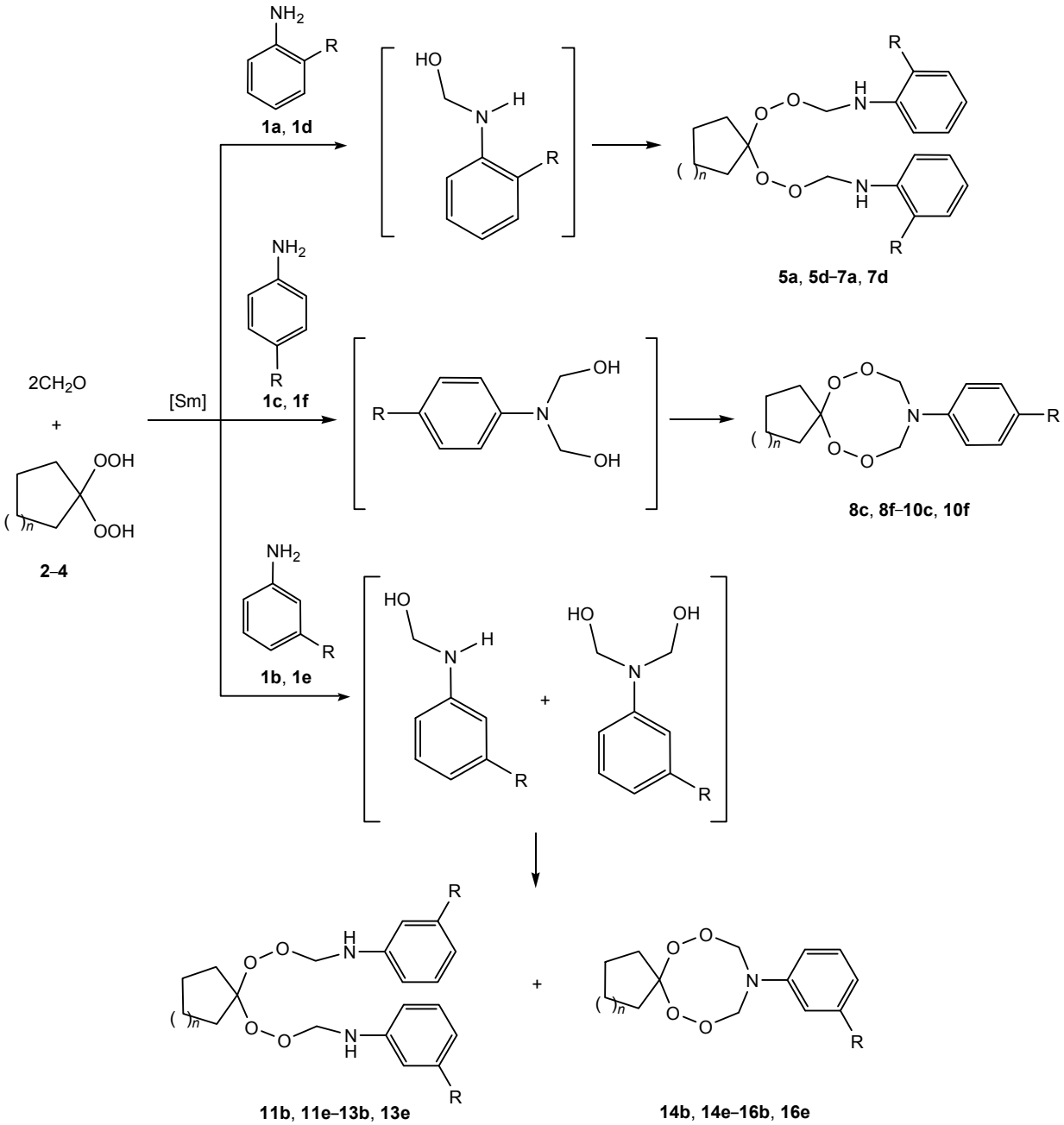
The ability of peroxides to exhibit antimalarial, anticancer, and anthelmintic activity of the compounds of depends on the molecular structure, as well as on whether they contain heteroatomic substituents [1–13]. Nitrogen-containing asymmetric peroxides are most promising for the treatment of malaria.

Azaperoxides are difficult or sometimes impossible to synthesize, which is associated with the low resistance of the peroxyl group to the action of amines [14]. Earlier [15, 16] we developed selective synthesis of aminodiperoxides by the recyclization of pentaoxacanes [17] in the presence of primary amines. Proceeding with this research, as well as with the aim to develop an efficient synthetic approach to acyclic and cyclic aminodiperoxides, we have studied the three-component heterocyclization of 1,1-bis(hydroperoxy)-cycloalkanes with formaldehyde and primary arylamines, catalyzed by Sm salts [$SmCl_3 \cdot 6H_2O$, $Sm(NO_3)_3 \cdot 6H_2O$, $SmCl_3/\gamma\text{-}Al_2O_3$, $Sm(NO_3)_3/\gamma\text{-}Al_2O_3$].

Amidodiperoxides formed within 2–3 min upon the addition of a solution of an aromatic amine in THF at 15–20°C to a mixture of 1,1-bis(hydroperoxy)cycloalkane and formaldehyde in the presence of catalytic amounts of $Sm(NO_3)_3 \cdot 6H_2O$ (5 mol %). The reaction direction depends on the position of the substituent (F, Cl) in the benzene ring of arylamines **1a–1f**. The reaction of *o*-chloro(fluoro)anilines **1a**, **1d** with formaldehyde and 1,1-bis(hydroperoxycycloalkanes **2–4** gave *N*,*N*′-[cycloalkane-1,1-diyl (diperoxymethanediyl)]dianilines **5a**, **5d–7a**, **7d** in yields of 63–75%. The analogous reaction with *p*-chloro(fluoro)anilines **1c**, **1f** instead of arylamines **1a**, **1d** formed cyclic tetraoxazaspiroalkanes **8c**, **8f–10c**, **1f** in yields of 75–87%. The three-component condensation with *m*-chloro-(fluoro)anilines **1b**, **1e** produce 1 : 1 mixtures of acyclic **11b**, **11e–13b**, **13e** and cyclic aminoperoxides **14b**, **14e–16b**, **16e** (Scheme 1).

Presumably, ortho substituents (F, Cl) in the benzene ring create steric hindrance to the condensation of anilines **1a–1f** with two formaldehyde molecules, and the reaction involves the intermediate formation of aminoalcohols, which further react with 1,1-bis(hydroperoxy)cycloalkane to form acyclic products **5–7**. If the substituent occupies the *para*-position, no steric hindrance takes place, and the reaction involves the intermediate formation of 2-aryl-

Scheme 1.

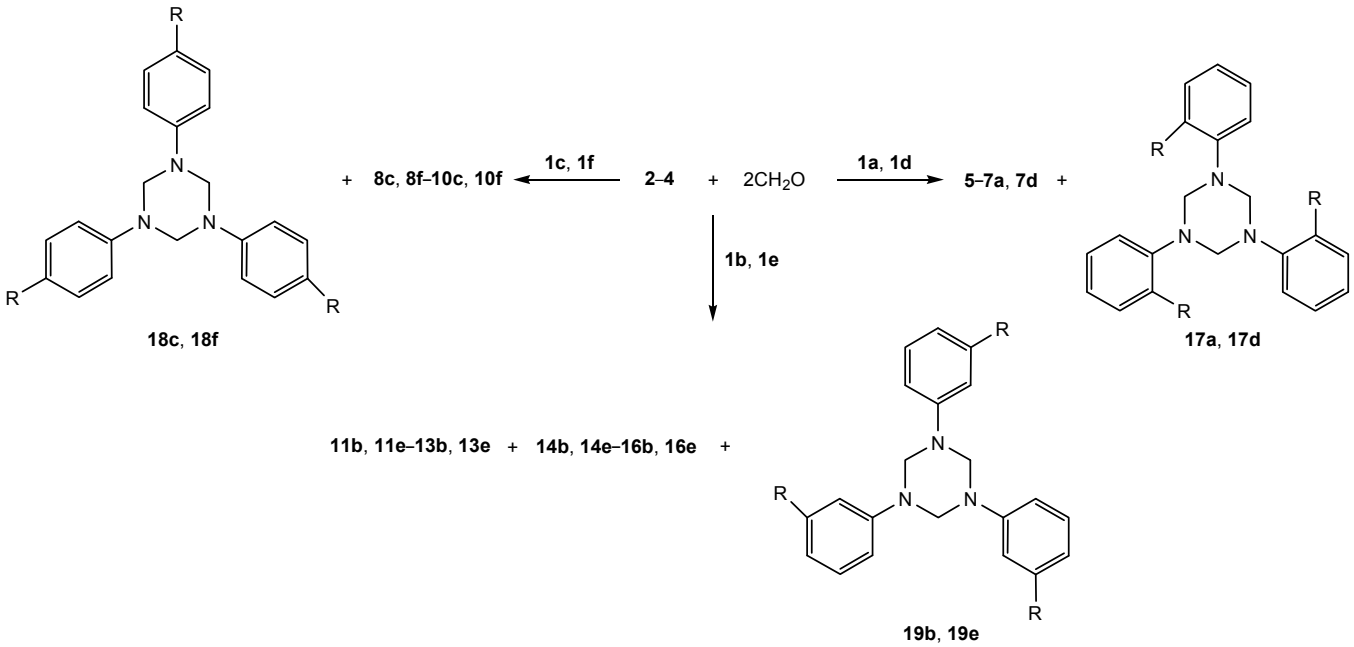


R = Cl (**a–c**), F (**d–f**); *n* = 1 (**2**, **5**, **8**, **11**, **14**), 2 (**3**, **6**, **9**, **12**,**15**), 3 (**4**, **7**, **10**, **13**, **16**); [Sm] = $Sm(NO_3)_3 \cdot 6H_2O$.

2-azapropane-1,3-diols, whose subsequent reaction with 1,1-bis(hydroperoxy)cycloalkane leads to cyclic peroxides. With *meta*-substituted aniline, both reaction pathways are realized; as a result, both cyclic and acyclic aminoperoxides are formed (Scheme 1).

In the absence of catalyst, along with the two mentioned pathways, the competitive weakly basic condensation of aniline derivatives **1a–1f** with formaldehyde, catalyzed by 1,1-bis(hydroperoxy)cycloalkanes **2–4**, occurs [18] to form symmetrical 1,3,5-triaryl-1,3,5-triazinanes **17a**, **17d**, **18c**, **18f**, **19b**, and **19c**. The reactions of *o*-chloro(fluoro)anilines **1a** and **1d** with formaldehyde and 1,1-bis(hydroperoxy)cycloalkanes **2–4** give rise to acyclic *N,N′*-[cycloalkane-1,1-diyl(bisperoxymethanediyl)]dianilines **5a**, **5d–7a**, and **7d** an 1,3,5-tris(2-halophenyl)-1,3,5-triazinanes **17a** and **17d** in a 1 : 2 ratio (Scheme 2, Table 1). The three-

Scheme 2.



R = Cl (**a–c**), F (**d–f**).

component condensation with *p*-haloanilines **1c** and **1f** forms cyclic tetraoxazaspiroalkanes **8c**, **8f–10c**, **10f** and triazines **18c**, **18f**. The three-component condensation with *m*-chloro(fluoro)anilines **1b** and **1e** gives rise to a mixture of acyclic 1,1-bis[*N*-(peroxymethyl)-*N*-aryl-amino]cycloalkanes **11b**, **11e–13b**, and **13e**, cyclic tetra-oxazaspiroalkanes **14b**, **14e–16b**, **16e** and 1,3,5-tris[3-chloro(fluoro)phenyl]-1,3,5-triazinanes **19b**, **19e** (the ratios of the products are listed in the table).

The structure of aminoperoxides **13b**, **12b**, **12e**, and **9f** was established by single-crystal X-ray diffraction (XRD) analysis (Fig. 1, Table 2). The XRD data were collected at room temperature (293 K).

Table 1. Yields, %, of triazinanes **17a**, **17d**, **18c**, **18f**, **19b**, **19e** and acyclic **5a**, **5d–7a**, **7d**, **11b**, **11e–13b**, **13e** and cyclic amino-peroxides **8c**, **8f–10c**, **10f**, **14b**, **14e–16b**, **16e**

Run no.	R	Triazinane	Acyclic diaminodiperoxide	Cyclic azadiperoxide
1	*o*-F	50 (**17d**)	30 (**5d**)	–
	m-F	45 (**19e**)	23 (**11e**)	20 (**14e**)
	p-F	60 (**18f**)	–	29 (**8f**)
	o-Cl	52 (**17a**)	25 (**5a**)	–
	m-Cl	55 (**19b**)	20 (**11b**)	18 (**14b**)
	p-Cl	64 (**18c**)	–	31 (**8c**)
2	*o*-F	49(**17d**)	24 (**6d**)	–
	m-F	46 (**19e**)	19 (**15e**)	15 (**15e**)
	p-F	48 (**18f**)	–	20 (**9f**)
	o-Cl	62 (**17a**)	25 (**6a**)	–
	m-Cl	50 (**19b**)	25 (**15b**)	25 (**15b**)
	p-Cl	53 (**18c**)	–	20 (**9c**)
3	*o*-F	64(**17d**)	26 (**7d**)	–
	m-F	60 (**19e**)	27 (**13e**)	22 (**16e**)
	p-F	58 (**18f**)	–	23 (**10f**)
	o-Cl	56 (**17a**)	22 (**7a**)	–
	m-Cl	59 (**19b**)	20 (**13b**)	26 (**16b**)
	p-Cl	48 (**18c**)	–	18 (**10c**)

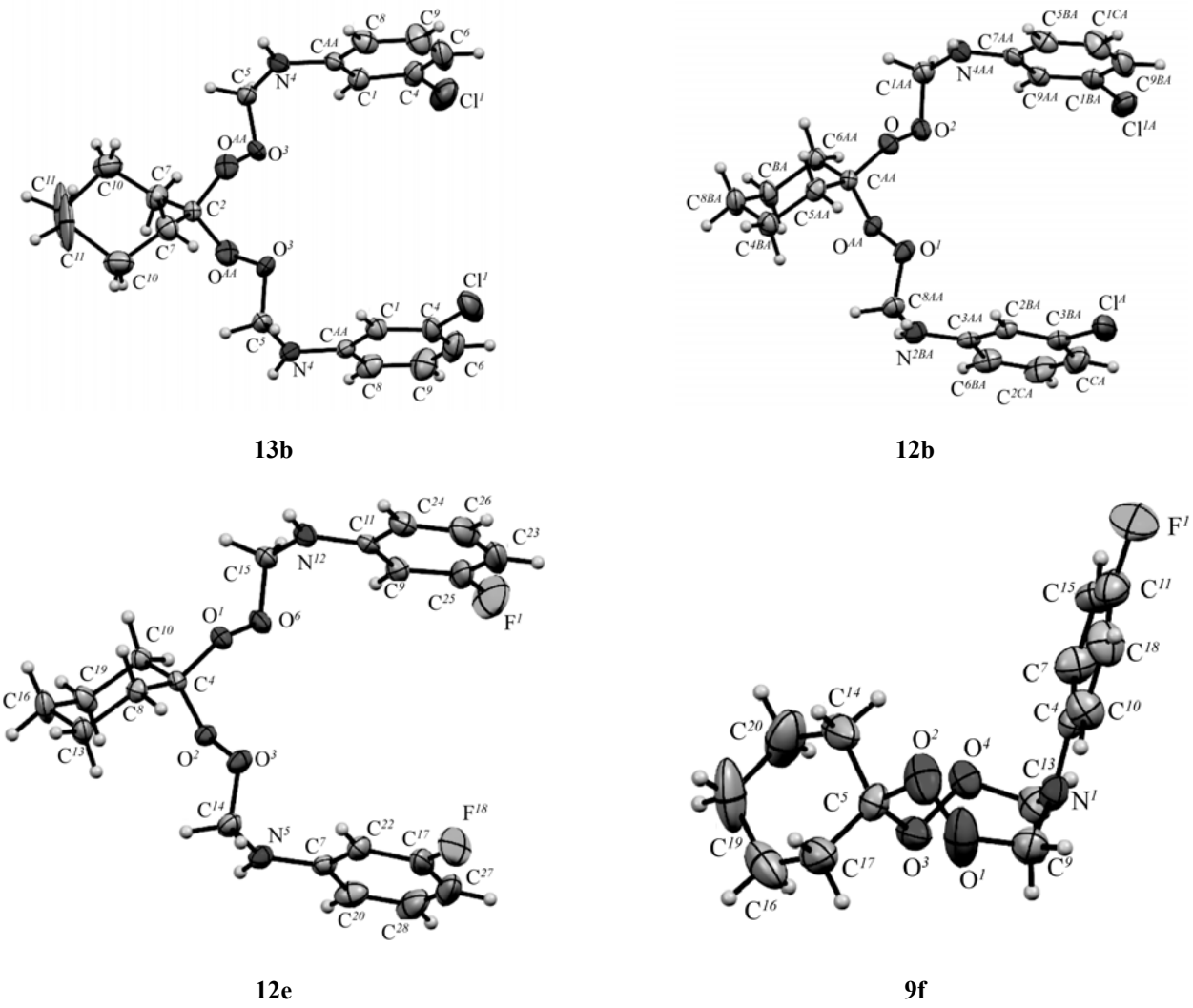


Fig. 1. Structures of aminoperoxides **13b**, **12b**, **12e**, and **9f** by XRD data. The nonhydrogen atoms are presented by thermal ellipsoids drawn at a 30% probability level.

Compounds **13b**, **12b**, and **9f** form orthorhombic crystals, whereas the monoclinic crystal system is characteristic of compound **12e**. Molecule **13b** (Fig. 1) in the crystal takes a special position and is located on the symmetry axis C_2, which passes through the C^2 atom and bisector of the $H^AC^{11}H^B$ angle. Molecules **12e**, **12b**, and **9f** in the respective crystals are in general positions. Aminoperoxide **13b** has its own second-order symmetry axis C_2, whereas the other aminoperoxides have no symmetry elements, i.e. they only have the first-order axis C_1. The cyclohexane fragment in molecules **12b**, **12e**, and **9f** takes a *chair* conformation, and the seven-membered carbocycle in compound **13b** has a *twist* conformation. The bond lengths and angles are contained in the ciffiles. Aminoperoxide **9f** has a tetraoxazocane fragment which takes a *twist–boat–chair* conformation, and the *p*-fluoroaryl substituent is axial with respect to this fragment.

The cyclic aminoperoxides were studied by ^{1}H and ^{13}C NMR spectroscopy to find that at room temperature they exist as equilibrium mixtures of conformers with different spatial organization of the ring. The ^{1}H and ^{13}C NMR spectra of the synthesized cyclic azaperoxides show double sets of proton and carbon signals both in DMSO and in $CDCl_3$ and Tol-d_6. In the ^{1}H NMR spectra in apolar solvents of, for example, compound **9c**, the $NC\underline{H}_2$ methylene proton signals appear as doubled doublets at 5.18 and

Table 2. Crystallographic data and refinement parameters of structures **9f**, **12b**, **12e**, and **13b**

Parameter	**9f**	**12b**	**12e**	**13b**
T, K	293	293	293	293
Brutto formula	$C_{14}H_{18}FNO_4$	$C_{20}H_{24}Cl_2N_2O_4$	$C_{20}H_{24}F_2N_2O_4$	$C_{21}H_{26}Cl_2N_2O_4$
M, Da	283.29	427.31	394.41	441.34
Syngony	Rhombic	Rhombic	Monoclinic	Rhombic
Space group	*P*bca (№ 61)	*P*212121 (№ 19)	*P*21/n (№ 14)	*P*21212 (№ 18)
a, Å	12.4485(6)	5.8964(4)	12.3217(8)	5.6933(12)
b, Å	10.2927(6)	15.0223(9)	5.7679(6)	15.024(3)
c, Å	21.8055(10)	23.2043(18)	27.155(2)	12.615(3)
α, deg	90	90	90	90
β, deg	90	90	92.820(12)	90
γ, deg	90	90	90	90
Volume, Å^3	2793.9(2)	2055.4(2)	1927.6(3)	1079.1(4)
Z	8	4	4	2
d_{calc}, g/cm^3	1.347	1.381	1.359	1.358
μ, mm^{-1}	0.107	0.344	0.107	0.330
$2\theta_{max}$, deg	58.06	58.56	62.10	58.40
Measured reflections	14961	13324	4979	6240
Unique reflections (R_{int})	3246(R_{int} 0.0522)	4882 (R_{int} 0.0222)	3513 (R_{int} 0.0131)	2342 (R_{int} 0.0366)
R_1 [$I \geq 2\sigma(I)$]	0.0939	0.0527	0.0903	0.09631
wR_2	0.2702	0.1531	0.3009	0.2441
CCDC	1585916	1575320	1575321	1575319

5.00 ppm (^2J 14.3 Hz) and 4.94 and 4.89 ppm (^2J 12.0 Hz), with the intensity ratio ~1 : 2.7 (Fig. 2).

The HSQC experiment showed that the more intense upfield doublets are connected with the upfield carbon signal at 85.1 ppm. When the temperature is decreased to 243 K, this proton signal coalesces, whereas at 218 K it splits into two signals, and the spectrum shows signals of three conformers (Fig. 2). Simultaneously, the pair of signals at 4.93 and 5.15 ppm, which are presumably averaged signals of different heteroring conformers, too, transform into two doubled doublets (Fig. 2).

For structural assessment of the conformers we determined minima on the potential energy surface (PES) of compound **9c** by B3LYP/6-31G(d,2p) computations in the gas phase (Gausian 09). It was found that the eight-membered *N*,*O*-heteroring can take the conformations *chair–chair* **A**, *twist–chair* **B**, and *boat–chair* **C**; therewith, the **B'** conformer, which is slightly higher in energy on the PES and has different dihedral angles of the oxazocine ring, is also optimized for the *twist* form (Fig. 3). The most favored are the energetically close conformers **A** and **B**, the latter of which crystallizes.

When assigning the signals of the conformers, we noticed a strongly pronounced deshielding effect of the proton signals of one of the methylene groups of the spirocyclohexane fragment, located α to the quaternary carbon atom, for the minor conformer, whose signals are observed in the weak-field region and does not

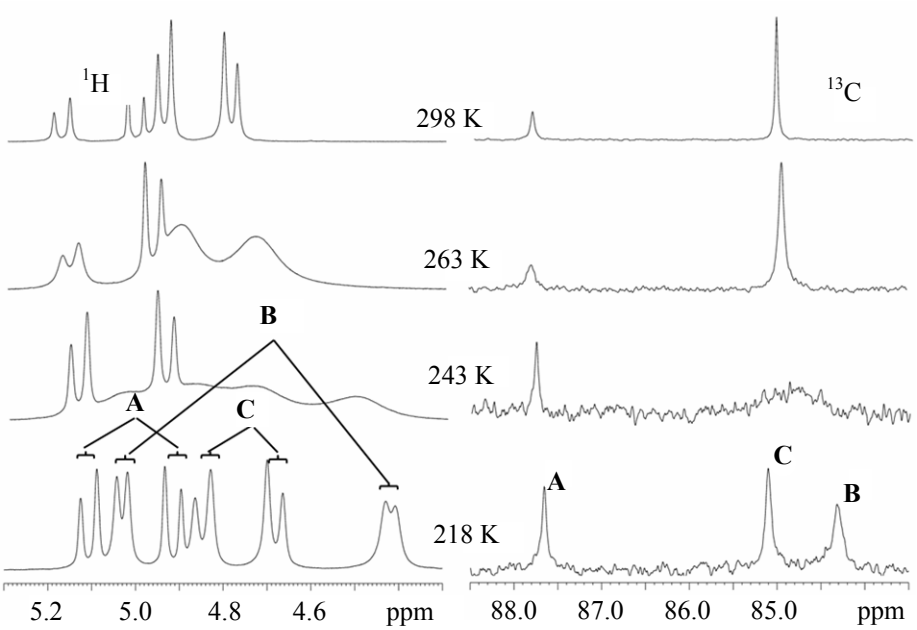
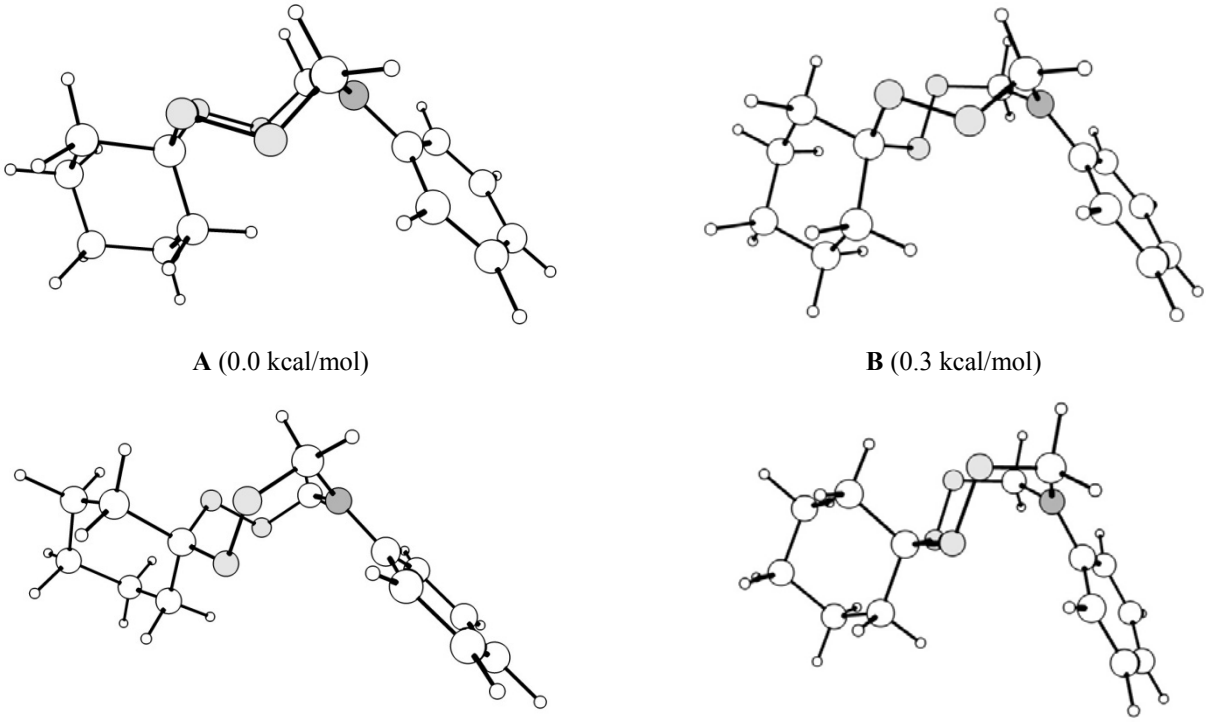


Fig. 2. Fragment ^{1}H and ^{13}C NMR spectra of compound **9c** in toluene (NCH_2O signals region).

change in the 223–298 K range. This observation allowed us to suggest that, among the theoretically found stable conformers, such situation can be realized in the *chair–chair* conformer **A**, where the aryl and cycloxane fragments are proximate to each other (d_{calc} 2.8 Å). Evidence for this suggestion was obtained from NOE experiments (Fig. 4) and calculated chemical shifts of the characteristic carbon atoms (Table 3).



A (0.0 kcal/mol)

B (0.3 kcal/mol)

B' (1.4 kcal/mol)

C (3.2 kcal/mol)

Fig. 3. Stable ring conformers in compound **9c**.

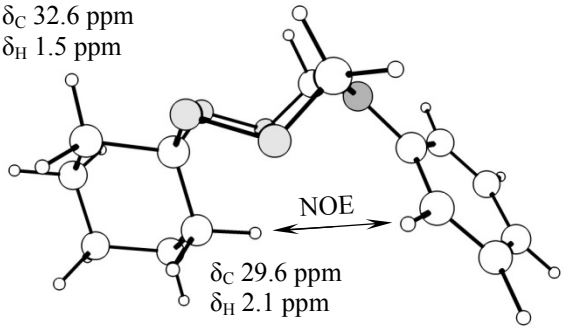


Fig. 4. Assignment of the NMR signals of conformer **A** by NOESY data.

The ^{1}H and ^{13}C NMR signals of the other conformers are impossible to assign with a high degree of reliability because of the closeness of their; moreover, the signals of the cyclohexane fragment strongly undergo strong broadening with decreasing temperature. Apparently, the carbon signal at 84.3 ppm, which is connected to the methylene proton signals with quite different chemical shifts (Δδ 0.6 ppm) and the geminal constant $^{2}J_{B}$ of 9.8 Hz in the HSQC spectrum (Fig. 2), belongs to conformer **B** (or **B** + **B'**). Because the diastereotopicity of the corresponding protons in conformers **A** and **C**, whose structure is a combination of the classical *chair* and *boat* conformations, is less pronounced, the ^{2}J constants are also close (~14.4 Hz). Using dynamic low-temperature NMR spectroscopy, we estimated the barriers to inversion of the heteroring [$\Delta G^{\neq}$ 12.2 kcal/mol (±0.1 kcal/mol)] between structures **B** (and/or **B'**) and **C**.

Extrapolating the resulting data to compounds **8c**, **8f**, **9f**, **10c**, and **10f**, as well as **14b**, **14e–16b**, and **16e**, which show the same NMR spectral characteristic, we established at room temperature the eight-membered aminoperoxides preferentially exist as *chair–chair* conformers **A**, whereas the *boat–chair* **C** and *twist–boat* conformers **B** are present in equilibrium. It should be noted that the conformationally rigid peroxide fragments, too, give a series of singlets in the ^{1}H NMR spectra of linear diperoxides.

Table 3. Calculated and experimental ^{13}C NMR chemical shifts of conformers **A**, **B**, and **C** of compound **9f**

Conformer	CH_{2calc}	CH_{2exp}	C_{calc}	C_{exp}
A	97.1	87.6	124.6	111.4
B	92.5	84.3	120.6	108.8
C	93.5	85.1	122.3	108.8

The APCI mass spectrum of acyclic diperoxide **7a** displays peaks of the $[C_7H_7ClN]^{+\bullet}$ and $[C_7H_7ClNO]^{+\bullet}$ radical cations formed by C–O or O–O bond cleavage.

Under APCI conditions, the studied cyclic diperoxides mainly form positive ions due to concurrent cleavage of the C–O and O–O, C–O and C–N, and C–O and C–O bonds in the protonated molecule.

The APCI mass spectra of compounds **9c**, **9f**, **10f**, **14b**, **15b**, **15e**, **16b**, and **16e** display peaks of three characteristic fragment ions $[C_7H_6HlgN + H]^{+}$, $[C_7H_6HlgNO + H]^{+}$, and $[C_8H_8HlgNO_3 + H]^{+}$, which are common for all these compounds, as well as peaks of the associates of these ions with one or two solvent (acetonitrile) molecules.

In additions, the mass spectra of compounds **9f**, **10f**, **14b**, **15e**, **16b**, and **16e** show peaks characteristic of these compounds. The $[C_8H_8FNO + H]^{+}$ ion peak (*m/z* 154) are observed in the mass spectra of compounds **10f** and **16e**, which is likely to be explained by the presence of a 7-membered ring and a fluorine atom in their structures. The mass spectrum of compound **16b** shown another peak, which is characteristic of this compound: $[C_8H_8ClN + H]^{+}$, *m/z* 154. The mass spectra of compounds **9f**, **14b**, and **15e** show molecular ion $[M + H]^{+}$ peaks at *m/z* 284, 286, and 284, respectively, which we associate with the presence of a six-membered (**9f** and **15e**) or a 5-member ring (**14b**), taking into account the absence of molecular ions in the spectra of **10f** and **16e** containing a 7-membered ring. The fluorine substituent, too, stabilizes the molecular ion, as judged from the fact that chloro derivatives **9c** and **15b** do not give molecular ions.

Biological activity assay. The newly synthesized cyclic and acyclic aminoperoxides **10f**, **13b**, **12b**, and **12e** were tested for anticancer activity *in vitro* on 60 cell lines of different human cancers (lungs, colon, central nervous system, ovary, kidney, prostate, breast, leukemia, and melanoma) by the protocols available at the US National Cancer Institute [19–24] (concentration 10^{-5} M). Each cell line was inoculated and preincubated in a microtiter plate, after which the test compound was added, and the culture was incubated for 48 h. The results are presented as percent growth of the treated cells compared to untreated control cells. According to the NCI criteria (growth inhibition of any cancer cell line to ~ 32% or less), compound **10f** was inactive, whereas compounds **13b**, **12b**, and **12e**, that

inhibit cell growth or causes death of certain cell lines, were have been identified as active.

Acyclic diaminodiperoxide **13b** is active against SR leukimia (5.27%), LOX IMVI melanoma (–85.23%), IGROV1 ovarian cancer (7.21%), and UO-31 kidney cancer cells (–47.31%). Compound **12b** is active against K-562 (–40.99%) and SR leukemia (–41.42%), A549/ATCC breast cancer (3.10%), HOP-92 (–46.34%), NCI-H522 (14.69%), LOX IMVI melanoma cells (–86.08%), IGROV1 ovarian cancer (–33.19%), and 786-0 (10.78%) and UO-31 kidney cancer cells (–73.73%). Aminoperoxide **12e** inhibits growth of SR leukemia (31.48%), LOX IMVI melanoma (–68.86%), and UO-31 kidney cancer cells (–58.17%). It appears that compounds **13b**, **12b**, and **12e** may be promising as potential anticancer agents for more detailed in vitro studies.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered on a Bruker Avance 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ and DMSO-d_6, internal reference TMS. The 2D homonuclear (COSY) and heteronuclear experiments (HSQC, HMBC) were accomplished by standard Bruker procedures at the same operating frequencies. The APCI mass spectra were obtained on a Shimadzu LCMS-2010EV system in the positive ion mode at the ionization electrode potential of 4.5 kV; APCI interface temperature 250°C, heater temperature 200°C, desolvation line temperature 230°C; nebulizer gas (nitrogen) flow rate 1.5 L min^{-1}; RF lens voltage (Q-massive) 5 V, flow rate of mobile phase (acetonitrile–water, 83 : 17) 0.1 mL min^{-1}.

Elemental analysis of performed on a Carlo Erba 1106 analyzer. Reaction progress was monitored by TLC on Sorbfil (PTSKh-AF-C), eluent C_6H_{12}–EtOAc, 10 : 1, developer iodine vapor. Column chromatography was performed on KSK silica gel (100–200 μm).

X-ray diffraction analysis was performed on a Rigaku/Oxford Diffraction Xcalibur/Gemini EOS diffractometer with an EOS CCD area detector (graphite monchromator, MoK_α radiation, λ 0.71073 Å, ω-scanning, $2\theta_{max}$ 62°). Data collection and processing were performed using CrysAlis^{Pro} Oxford Diffraction software [25]. The structure was solved by the direct method and refined by full-matrix least squares with anisotropic temperature factors for nonhydrogen atoms. The hydrogen atoms were located by difference Fourier synthesis and refined with isotropic displacement parameters. Calculations were performed using SHELX [26].

Quantum-chemical calculations were performed using Gaussian 09 [27]. Geometry optimization, vibrational analysis, and calculation of the entropy and thermodynamic corrections to total energy were performed at the B3LYP6-31G(d,p) level of theory [28–30]. Thermodynamic parameters were determined at 298 K. The NMR shifts were calculated by the GIAO method [31] incorporated in Gaussian 09. The quantum-chemical data were processed using ChemCraft [32].

Anticancer activity in vitro. The anticancer activity assay developed at the US National Cancer Institute is described in [19–24] and at www.dtp.nci.nih.gov.

Heterocyclization of 1,1-bis(hydroperoxy)cycloalkanes with formaldehyde and primary amines, catalyzed by $Sm(NO_3)_3\cdot 6H_2O$ (*general procedure*). Tetrahydrofuran (5 mL), 37% aqueous formaldehyde (1.46 mL, 20 mmol), and corresponding 1,1-bis(hydroperoxy)alkane were loaded at ~20°C into a Schlenk flask mounted on a magnetic stirrer, after which $Sm(NO_3)_3\cdot 6H_2O$ [0.022 g, 5 mol % with respect to 1,1-bis(hydroperoxy)cycloalkane)] and, after 15-min stirring, 1 mmol of arylamine were added. The reaction mixture was stirred for 6 h at ~20°C and then THF was evaporated. Diethyl ether (10 mL) was dded to the residue, and the mixture was washed with water (4 × 5 mL). The ether layer was dried over $MgSO_4$ and concentrated to isolate aminoperoxides stable at room temperature. Reaction progress was monitored by TLC, eluent C_6H_{12}–EtOAc, 5 : 1, developer iodine vapor.

***N*,*N*′-[Cyclopentane-1,1-diyl(bisperoxymethanediyl)]di(2-chloroaniline) (5a).** Yield 0.31 g (75%), yellow oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.36–1.46 m (4H, H_2C), 1.60–1.72 m (4H, H_2C), 5.24–5.20 m (4H, OH_2CN), 6.74–6.77 m (2H, HC), 6.97–6.99 m (2H, HC), 7.14–7.16 m (2H, HC), 7.28–7.30 m (2H, HC). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.7, 30.1, 85.6, 109.4, 115.2, 117.4, 121.6, 130.1, 135.4, 147.7. Found, %: C 55.10; H 5.34; Cl 16.97; N 6.76. $C_{19}H_{22}Cl_2N_2O_4$. Calculated, %: C 55.22; H 5.37; Cl 17.15; N 6.78.

***N*,*N*′-[Cyclopentane-1,1-diyl(bisperoxymethanediyl)]di(2-fluoroaniline) (5d).** Yield 0.26 g (70%), light yellow oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm:

1.57–1.75 m (4H, H_2C), 1.84–1.99 m (4H, H_2C), 5.08 d (4H, OH_2CN, *J* 10 Hz), 5.19 d (4H,OH_2CN, *J* 10 Hz), 6.70–6.96 m (6H, HC), 7.02–7.08 m (4H, HC). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.5, 33.1, 79.9, 110.1, 113.9, 115.1 d (*J* 15 Hz), 119.0 d (*J* 7 Hz), 124.5, 134.3, 151.6 d (*J* 190 Hz). Found, %: C 59.96; H 5.81; F 9.90; N 7.33. $C_{19}H_{22}F_2N_2O_4$. Calculated, %: C 59.99; H 5.83; F 9.99; N 7.36.

***N*,*N*′-[Cyclohexane-1,1-diyl(bisperoxymethanediyl)]di(2-chloroaniline) (6a).** Yield 0.28 g (67%), light yellow oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.32–1.40 m (6H, H_2C), 1.68–1.76 m (4H, H_2C), 5.24–5.29 m (4H, OH_2CN), 6.58–6.62 m (2H, HC), 6.68–6.71 m (2H, HC), 7.04–7.15 m (2H, HC), 7.26–7.28 m (2H, HC). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.5, 25.3, 30.5, 78.4, 109.4, 113.4, 118.9, 119.0, 128.2, 129.5, 142.6. Found, %: C 56.20; H 5.63; Cl 16.50; N 6.54. $C_{20}H_{24}Cl_2N_2O_4$. Calculated, %: C 56.22; H 5.66; Cl 16.59; N 6.56.

***N*,*N*′-[Cyclohexane-1,1-diyl(bisperoxymethanediyl)]di(2-fluoroaniline) (6d).** Yield 0.29 g (74%), light yellow oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.32–1.46 m (6H, H_2C), 1.67–1.73 m (4H, H_2C), 5.18–5.24 m (4H, H_2C), 6.64–6.68 m (2H, HC), 6.72–6.79 m (4H, HC), 6.94–6.98 m (4H, HC), 7.02–7.06 m (4H, HC). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.4, 25.3, 30.5, 78.4, 109.2, 115.1 d, (*J* 15 Hz), 118.1 d (*J* 6 Hz), 124.9, 136.3 d (*J* 88 Hz), 151.3 d (*J* 189 Hz). Found, %: C 60.88; H 6.11; F 9.57; N 7.07. $C_{20}H_{24}F_2N_2O_4$. Calculated, %: C 60.90; H 6.13; F 9.63; N 7.10.

***N*,*N*′-[Cycloheptane-1,1-diyl(bisperoxymethanediyl)]di(2-chloroaniline) (7a).** Yield 0.3 g (72%), light yellow oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.41–1.61 m (8H, H_2C), 1.89–1.95 m (4H, H_2C), 5.19–5.22 m (4H, NCH_2O), 6.71–6.80 m (4H, HC), 7.08–7.11 m (2H, HC), 7.30–7.33 m (4H, HC). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.7, 30.1, 33.2, 78.1, 113.5, 113.6, 114.2, 118.8, 119.0, 128.2, 129.6, 142.6. Mass spectrum (APCI), *m/z* (I_{rel}, %): 197 (36) $[C_7H_6ClNO + H + CH_3CN]^+$, 181 (54) $[C_7H_6ClN + H + CH_3CN]^+$, 156 (8) $[C_7H_6ClNO + H]^+$, 140 (100) $[C_7H_6ClN + H]^+$. Found, %: C 57.12; H 5.91; Cl 15.97; N 6.32. $C_{21}H_{26}Cl_2N_2O_4$. Calculated, %: C 57.15; H 5.94; Cl 16.06; N 6.35.

***N*,*N*′-[Cycloheptane-1,1-diyl(bisperoxymethanediyl)]di(2-fluoroaniline) (7d).** Yield 0.27 g (68%), light yellow oil. ^1H NMR spectrum ^1H ($CDCl_3$), δ, ppm: 1.43–1.69 m (8H, H_2C), 1.88–1.99 m (4H, H_2C), 5.20–5.22 m (4H, H_2C), 6.70–6.79 m (2H, HC), 6.96–6.99 m (2H, HC), 7.04–7.13 m (4H, HC). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.7, 30.5, 33.5, 78.6, 109.0, 113.94, 114.74 d (*J* 15 Hz), 116,97, 118.46 d (*J* 6 Hz), 124.51, 134.10, 151.68 d (*J* 190 Hz). Found, %: C 61.73; H 6.40; F 9.25; N 6.83. $C_{21}H_{26}F_2N_2O_4$. Calculated, %: C 61.75; H 6.42; F 9.30; N 6.86.

9-(4-Chlorophenyl)-6,7,11,12-tetraoxa-9-azaspiro[4.7]dodecane (8c). Yield 0.21 g (75%), light yellow powder, mp 61–62°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.11–2.14 m (2H, H_2C, conformer **A**), 1.56–1.69 m (4H, H_2C), 1.81–1.91 m (4H, H_2C), 5.35 and 5.74 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.35–5.38 m (4H, OH_2CN, conformers **B** + **C**), 6.52–6.74 m (2H, HC), 7.04–7.12 m (2H, HC). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.6, 32.9, 86.0 (conformer **A**), 87.0 (conformers **B** + **C**), 115.0, 115.9, 116.8, 129.1, 144.7. Mass spectrum (APCI), *m/z* (I_{rel}, %): 284 (4) $[M + H]^+$, 227 (84) $[C_8H_8FNO_3 + H + CH_3CN]^+$, 186 (24) $[C_8H_8FNO_3 + H]^+$, 181 (100) $[C_7H_6FNO + H + CH_3CN]^+$, 165 (51) $[C_7H_6FN + H + CH_3CN]^+$, 140 (15) $[C_7H_6FNO+H]^+$, 124 (26) $[C_7H_6FN + H]^+$. Found, %: C 54.63; H 5.62; Cl 12.37; N 4.87. $C_{13}H_{16}ClNO_4$. Calculated, %: C 54.65; H 5.64; Cl 12.41; N 4.90.

9-(4-Fluorophenyl)-6,7,11,12-tetraoxa-9-azaspiro[4.7]dodecane (8f). Yield 0.21 g (79%), colorless crystals, mp 47–49°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.11–2.14 m (2H, H_2C, conformer **A**), 1.56–1.69 m (4H, H_2C), 1.81–1.91 m (4H, H_2C), 5.35 and 5.74 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.35–5.38 m (4H, OH_2CN, conformers **B**+**C**), 6.52–6.74 m (2H, HC), 7.04–7.12 m (2H, HC). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.3, 32.7, 86.4 (conformer **A**), 87.5 (conformers **B** + **C**), 115.7 d (*J* 18 Hz), 119.12 d (*J* 6 Hz), 119.7, 143. 9 d (*J* 8 Hz), 157.58 d (*J* 189 Hz). Found, %: C 57.97; H 5.96; F 7.05; N 5.17. $C_{13}H_{16}FNO_4$. Calculated, %: C 57.99; H 5.99; F 7.06; N 5.20.

10-(4-Chlorophenyl)-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecane (9c). Yield 0.23 g (79%), white powder, mp 93–94°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.41–1.45 m (4H, H_2C), 1.50–1.61 m (4H, H_2C), 1.65–1.81 m (4H, H_2C), 2.03 br.s (4H, H_2C, conformer **A**), 5.30 d and 5.62 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.39 d (4H, OH_2CN, conformers **B** + **C**, *J* 12 Hz), 7.01–7.04 m (2H, HC), 7.25–7.28 m (4H, HC). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.6, 25.2, 30.1, 85.9, 109.3, 118.6, 129.1, 145.5 (conformer **A**), 22.7, 25.1, 29.5, 88.7, 113.0, 119.9, 129.3, 145.5 (conformers **B** + **C**). Mass spectrum (APCI), *m/z* (I_{rel}, %): 243

(100) $[C_8H_8ClNO_3 + H + CH_3CN]^+$, 238 (13) $[C_7H_6ClNO + H + 2CH_3CN]^+$, 202 (9) $[C_8H_8ClNO_3 + H]^+$, 197 (47) $[C_7H_6ClNO + H + CH_3CN]^+$, 181 (27) $[C_7H_6ClN + H + CH_3CN]^+$, 156 (11) $[C_7H_6ClNO + H]^+$, 140 (28) $[C_7H_6ClN + H]^+$. Found, %: C 56.07; H 6.03; Cl 11.80; N 4.63. $C_{14}H_{18}ClNO_4$. Calculated, %: C 56.10; H 6.05; Cl 11.83; N 4.67.

10-(4-Fluorophenyl)-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecane (9f). Yield 0.23 g (82%), light brown crystals, mp 50–50°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35–1.41 m (2H, H_2C), 1.43–1.46 m (4H, H_2C), 1.65–1.66 m (4H, H_2C), 1.90 br.s (4H, H_2C, conformer **A**), 5.36 d and 5.76 d (4H, OH_2CN, conformer **A**, *J* 12 Hz,), 5.36–5.37 m (4H, OH_2CN, conformers **B** + **C**), 7.07–7.14 m (4H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.7, 25.1, 30.1, 86.1, 108.7, 115.8 d (*J* 17 Hz), 118.7 d (*J* 7 Hz), 143.6, 157.46 d (*J* 188 Hz, conformer **A**), 22.8, 24.9, 29.5, 88.6, 111.0, 116.2 d (*J* 18 Hz), 119.8 d (*J* 7 Hz), 143.6, 157.5 d (*J* 188 Hz, conformers **B** + **C**). Found, %: C 59.33; H 6.35; F 6.67; N 4.91. $C_{14}H_{18}FNO_4$. Calculated, %: C 59.36; H 6.40; F 6.71; N 4.94.

11-(4-Chlorophenyl)-8,9,13,14-tetraoxa-11-azaspiro[6.7]tetradecane (10c). Yield 0.27 g (87%), light yellow oil. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.40–1.59 m (8H, H_2C), 1.85–1.93 m (4H, H_2C), 2.06 br.s (4H, H_2C, conformer **A**), 5.24 and 5.36 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.25–5.30 m (4H, OH_2CN, conformers **B** + **C**), 6.99–7.02 m (2H, HC), 7.15–7.17 m (2H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.7, 30.0, 33.9, 85.9, 114.5, 115.7, 118.6, 128.9, 145.5 (conformer **A**), 22.8, 30.2, 34.2, 87.4, 114.9, 116.3, 119.0, 129.2, 144.9 (conformers **B** + **C**). Found, %: C 57.40; H 6.39; Cl 11.27; N 4.43. $C_{15}H_{20}ClNO_4$. Calculated, %: C 57.42; H 6.42; Cl 11.30; N 4.46.

11-(4-Fluorophenyl)-8,9,13,14-tetraoxa-11-azaspiro[6.7]tetradecane (10f). Yield 0.25 g (85%), light yellow crystals, mp 79–81°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.36–1.58 m (8H, H_2C), 1.94–1.99 m (2H, H_2C), 2.00–2.01 m (4H, H_2C, conformer **A**), 5.36 and 5.60 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.36–5.37 m (4H, OH_2CN, conformers **A** + **B** + **C**), 7.09–7.12 m (4H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.6, 29.8, 32.4, 85.9, 113.9, 115.7 d (*J* 17 Hz), 118.5 d (*J* 7 Hz), 143.7, 157.4 d (*J* 188 Hz, conformer **A**), 22.0, 29.6, 31.1, 85.9, 113.9, 116.2 d (*J* 17 Hz), 120.3 d (*J* 7 Hz), 143.7, 157.4 d (*J* 188 Hz, conformers **B** + **C**). Mass spectrum (APCI), *m/z* (I_{rel}, %): 227 (71) $[C_8H_8FNO_3 + H + CH_3CN]^+$, 222 (19) $[C_7H_6FNO + H + 2CH_3CN]^+$, 186 (18) $[C_8H_8FNO_3 + H]^+$, 181 (100) $[C_7H_6FNO + H + CH_3CN]^+$, 165 (67) $[C_7H_6FN + H + CH_3CN]^+$, 154 (15) $[C_8H_8FNO + H]^+$, 140 (10) $[C_7H_6FNO + H]^+$, 124 (39) $[C_7H_6FN + H]^+$. Found, %: C 60.57; H 6.76; F 6.36; N 4.69. $C_{15}H_{20}FNO_4$. Calculated, %: C 60.60; H 6.78; F 6.39; N 4.71.

***N*,*N*′-[Cyclopentane-1,1-diyl(bisperoxymethanediyl)]di(3-chloroaniline) (11b).** Yield 0.18 g (44%), light yellow oil. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.45–1.48 m (4H, H_2C), 1.56–1.63 m (4H, H_2C), 5.11–5.12 m (4H, NCH_2O), 6.95–6.99 m (2H, CH, *J* 10 Hz), 7.05–7.07 m (2H, HC), 7.26–7.29 m (4H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 24.3, 32.9, 75.6, 115.4, 116.6, 119.9, 120.8, 130.9, 134.0, 148.4. Found, %: C 55.20; H 5.34; Cl 17.12; N 6.75. $C_{19}H_{22}Cl_2N_2O_4$. Calculated, %: C 55.22; H 5.37; Cl 17.15; N 6.78.

***N*,*N*′-[Cyclopentane-1,1-diyl(bisperoxymethanediyl)]di(3-fluoroaniline) (11e).** Yield 0.19 g (50%), light yellow oil. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.45–1.48 m (4H, H_2C), 1.56–1.64 m (4H, H_2C), 5.13–5.14 m (4H, NCH_2O), 6.71–74 m (2H, HC), 6.91–6.94 m (4H, HC), 7.26–7.30 m (2H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 24.3, 33.9, 78.5, 103.1 d (*J* 25 Hz), 107.2 d (*J* 21 Hz), 112.7, 119.2, 130.1 d (*J* 17 Hz), 148.1, 162.7 d (*J* 191 Hz). Found, %: C 59.96; H 5.80; F 9.97; N 7.34. $C_{19}H_{22}F_2N_2O_4$. Calculated, %: C 59.99; H 5.83; F 9.99; N 7.36.

***N*,*N*′-[Cyclohexane-1,1-diyl(bisperoxymethanediyl)]di(3-chloroaniline) (12b).** Yield 0.22 g (55%), colorless crystals, mp 98–99°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.33–1.41 m (6H, H_2C), 1.66–1.68 m (4H, H_2C), 5.11–5.13 m (4H, NCH_2O), 6.64–6.73 m (4H, HC), 6.84–6.85 m (2H, HC), 7.07–7.12 m (2H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.4, 25.3, 30.5, 78.4, 109.2, 112.3, 112.8, 117.5, 130.8, 134.0, 148.5. Found, %: C 56.20; H 5.63; Cl 16.57; N 6.53%. $C_{20}H_{24}Cl_2N_2O_4$. Calculated, %: C 56.22; H 5.66; Cl 16.59; N 6.56.

***N*,*N*′-[Cyclohexane-1,1-diyl(bisperoxymethanediyl)]di(3-fluoroaniline) (12e).** Yield 0.17 g (45%), colorless crystals, mp 118–119°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.33–1.40 m (4H, H_2C), 1.66–1.67 m (6H, H_2C), 5.10–5.12 m (4H, NCH_2O), 6.42–6.58 m (6H, HC), 7.09–7.23 m (4H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.4, 25.3, 30.6, 78.5, 100.1, 104.2 d (*J* 17 Hz), 109.2, 109.8, 130.7 d (*J* 8 Hz),

149.1, 163.6 d (*J* 191 Hz). Found, %: C 60.87; H 6.11; F 9.60; N 7.07. $C_{20}H_{24}F_2N_2O_4$. Calculated, %: C 60.90; H 6.13; F 9.63; N 7.10.

***N*,*N*′-[Cycloheptane-1,1-diyl(bisperoxymethanediyl)]di(3-chloroaniline) (13b).** Yield 0.18 g (43%), colorless crystals, mp 83–84°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39–1.42 m (8H, H_2C), 1.76–1.78 m (4H, H_2C), 5.11–5.12 m (4H, NCH_2O), 6.65–6.67 m (2H, HC), 6.83–6.84 m (2H, HC), 7.09–7.12 m (2H, HC), 7.20–7.23 m (2H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.6, 30.3, 33.3, 78.3, 112.3, 112.9, 114.5, 117.5, 130.8, 134.0, 148.6. Found, %: C 57.13; H 5.91; Cl 16.03; N 6.32. $C_{21}H_{26}Cl_2N_2O_4$. Calculated, %: C 57.15; H 5.94; Cl 16.06; N 6.35.

***N*,*N*′-[Cycloheptane-1,1-diyl(bisperoxymethanediyl)]di(3-fluoroaniline) (13e).** Yield 0.18 g (47%), light yellow oil. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39–1.47 m (4H, H_2C), 1.59–1.63 m (4H, H_2C), 1.75–1.76 m (4H, H_2C), 5.09–5.12 m (4H, NCH_2O), 6.40–6.44 m (2H, HC), 6.54–6.58 m (2H, HC), 7.08–7.13 m (2H, HC), 7.20–7.22 m (2H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.6, 30.2, 33.2, 78.4, 100.1, 104.1 d (*J* 17 Hz), 109.7, 114.4 d (*J* 20 Hz), 130.7 d (*J* 9 Hz), 149.7 d (*J* 8 Hz), 163.7 d (*J* 190 Hz). Found, %: C 61.73; H 6.39; F 9.27; N 6.83. $C_{21}H_{26}F_2N_2O_4$. Calculated, %: C 61.75; H 6.42; F 9.30; N 6.86.

9-(3-Chlorophenyl)-6,7,11,12-tetraoxa-9-azaspiro[4.7]dodecane (14b). Yield 0.15 g (56%), colorless crystals, mp 70–71°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.45–1.48 m (4H, H_2C), 1.56–1.63 m (4H, H_2C), 1.98–2.01 m (4H, H_2C, conformer **A**), 5.44 and 5.81 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.43–5.46 d (4H, OH_2CN, conformers **B** + **C**), 6.95–6.99 m (1H, HC), 7.05–7.07 m (1H, HC), 7.15–7.16 m (1H, HC), 7.26–7.29 m (1H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 24.3, 33.0, 85.6 (conformer **A**), 87.6 (conformers **B** + **C**), 115.4, 116.6, 119.9, 120.0, 130.9, 134.0, 148.4. Mass spectrum (APCI), *m/z* (I_{rel}, %): 286 (17) $[M + H]^+$, 243 (81) $[C_8H_8ClNO_3 + H + CH_3CN]^+$, 238 (14) $[C_7H_6ClNO + H + 2CH_3CN]^+$, 202 (37) $[C_8H_8ClNO_3 + H]^+$, 197 (100) $[C_7H_6ClNO + H + CH_3CN]^+$, 190 (22) $[C_7H_6ClNO + Cl]^-$, 181 (93) $[C_7H_6ClN + H + CH_3CN]^+$, 156 (19) $[C_7H_6ClNO + H]^+$, 154 (100) $[C_7H_6ClNO - H]^-$, 140 (53) $[C_7H_6ClN + H]^+$. Found,%: C 54.63; H 5.62; Cl 12.39; N 4.87. $C_{13}H_{16}ClNO_4$. Calculated, %: C 54.65; H 5.64; Cl 12.41; N 4.90.

9-(3-Fluorophenyl)-6,7,11,12-tetraoxa-9-azaspiro-[4.7]dodecane (14e). Yield 0.13 g (50%), yellow oil. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.45–1.48 m (4H, H_2C), 1.56–1.64 m (4H, H_2C), 1.98–2.01 m (4H, H_2C, conformer **A**), 5.44 and 5.81 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.43–5.46 m (4H, OH_2CN, conformers **B** + **C**), 6.71–6.74 m (1H, HC), 6.91–6.94 m (2H, HC), 7.26–7.30 m (1H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 24.3, 33.0, 85.6 (conformer **A**), 87.6 (conformers **B** + **C**), 103.9 d (*J* 20 Hz), 107.4 d (*J* 20 Hz), 112.6, 119.9, 130.8 d (*J* 8 Hz), 148.9 d (*J* 8 Hz), 163.3 d (*J* 191 Hz). Found, %: C 57.97; H 5.96; F 7.03; N 5.17. $C_{13}H_{16}FNO_4$. Calculated, %: C 57.99; H 5.99; F 7.06; N 5.20.

10-(3-Chlorophenyl)-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecane (15b). Yield 0.13 g (45%), yellow oil. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35–1.42 m (6H, H_2C), 1.55–1.64 m (4H, H_2C), 1.84–1.85 m (4H, H_2C, conformer **A**), 5.35 and 5.84 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.39–5.44 m (4H, OH_2CN, conformers **B** + **C**), 6.94–6.99 m (1H, HC), 7.01–7.06 m (1H, HC), 7.14–7.15 m (1H, HC), 7.26–7.30 m (1H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.7, 25.1, 30.0, 85.4 108.9, 115.2, 116.3, 120.7, 130.9, 134.0, 148.3 (conformer **A**); 22.8, 24.9, 29.4, 87.7 111.0, 115.9, 117.1, 121.5, 131.3, 134.0, 148.3 (conformers **B** + **C**). Mass spectrum (APCI), *m/z* (I_{rel}, %): 243 (45) $[C_8H_8ClNO_3 + H + CH_3CN]^+$, 238 (12) $[C_7H_6ClNO + H + 2CH_3CN]^+$, 202 (14) $[C_8H_8ClNO_3 + H]^+$, 197 (100) $[C_7H_6ClNO + H + CH_3CN]^+$, 181 (67) $[C_7H_6ClN + H + CH_3CN]^+$, 156 (18) $[C_7H_6ClNO + H]^+$, 140 (47) $[C_7H_6ClN+H]^+$. Found, %: C 56.07; H 6.02; Cl 11.80; N 4.62. $C_{14}H_{18}ClNO_4$. Calculated, %: C 56.10; H 6.05; Cl 11.83; N 4.67.

10-(3-Fluorophenyl)-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecane (15e). Yield 0.15 g (55%), light yellow powder, mp 48–49°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35–1.44 m (6H, H_2C), 1.55–1.66 m (4H, H_2C), 1.84–1.85 m (4H, H_2C, conformer **A**), 5.36 and 5.83 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.39–5.44 m (4H, OH_2CN, conformers **B** + **C**), 6.70–6.77 m (1H, HC), 6.88–6.94 m (2H, HC), 7.26–7.32 m (1H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.7, 25.1, 30.1, 85.3, 103.6 d (*J* 21 Hz), 107.3 d (*J* 17 Hz), 108.8, 112.4, 130.8 d (*J* 8 Hz), 148.9, 163.3 d (*J* 197 Hz, conformer **A**); 22.7, 24.9, 29.4, 87.6, 103.6 d (*J* 21 Hz), 107.3 d (*J* 17 Hz), 108.8, 113.2, 130.8 d (*J* 8 Hz), 148.9, 163.3 d (*J* 197 Hz, conformers **B** + **C**). Mass spectrum (APCI), *m/z* (I_{rel}, %): 284 (7) $[M + H]^+$, 227 (56) $[C_8H_8FNO_3 + H + CH_3CN]^+$, 186 (40) $[C_8H_8FNO_3 + H]^+$, 181 (100) $[C_7H_6FNO + H + CH_3CN]^+$, 165 (71) $[C_7H_6FN + H + CH_3CN]^+$, 140 (32)

$[C_7H_6FNO + H]^+$, 124 (50) $[C_7H_6FN + H]^+$. Found, %: C 59.34; H 6.38; F 6.68; N 4.91. $C_{14}H_{18}FNO_4$. Calculated, %: C 59.36; H 6.40; F 6.71; N 4.94.

11-(3-Chlorophenyl)-8,9,13,14-tetraoxa-11-aza-spiro[6.7]tetradecane (16b). Yield 0.17 g (57%), light yellow powder, mp 60–61°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35–1.48 m (8H, H_2C), 1.55–1.56 m (4H, H_2C), 1.92–2.00 m (4H, H_2C, conformer **A**), 5.34 and 5.79 d (4H, OH_2CN, conformer **A**, *J* 12 Hz), 5.37–5.41 m (4H, OH_2CN, conformers **B** + **C**), 6.94–6.96 m (1H, HC), 7.03–7.05 m (1H, HC), 7.13–7.14 m (1H, HC), 7.25–7.29 m (1H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.7, 29.8, 32.4, 85.1 115.2, 116.4, 120.7, 130.9, 134.0, 136.3, 148.04. Mass spectrum (APCI), *m/z* (I_{rel}, %):243 (61) $[C_8H_8ClNO_3 + H + CH_3CN]^+$, 238 (17) $[C_7H_6ClNO + H + 2CH_3CN]^+$, 202 (23) $[C_8H_8ClNO_3 + H]^+$, 197 (100) $[C_7H_6ClNO + H + CH_3CN]^+$, 181 (66) $[C_7H_6ClN + H + CH_3CN]^+$, 156 (12) $[C_7H_6ClNO + H]^+$, 154 (23) $[C_8H_8ClN + H]^+$, 140 (39) $[C_7H_6ClN + H]^+$. Found, %: C 57.39; H 6.39; Cl 11.27; N 4.44. $C_{15}H_{20}ClNO_4$. Calculated, %: C 57.42; H 6.42; Cl 11.30; N 4.46.

11-(3-Fluorophenyl)-8,9,13,14-tetraoxa-11-aza-dispiro[6.7]tetradecane (16e). Yield 0.15 g (53%), white powder, mp 66–68°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35–1.48 m (8H, H_2C), 1.54–1.56 m (4H, H_2C), 1.93–1.98 m (4H, H_2C, conformer **A**), 5.35 and 5.78 d (4H, OH_2CN, conformer **A**), 5.35–5.40 m (4H, OH_2CN, conformers **B** + **C**), 6.68–6.72 m (1H, HC), 6.89–6.91 m (2H, HC), 7.25–7.29 m (1H, HC). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.6, 29.8, 32.4, 85.1 (conformer **A**), 87.56 (conformers **B** + **C**), 103.7 d (*J* 20 Hz), 107.2 d (*J* 17 Hz), 112.5, 114.0, 130.8 d (*J* 8 Hz), 148.9 d (*J* 8 Hz), 163.3 d (*J* 191 Hz). Mass spec-trum (APCI), *m/z* (I_{rel}, %): 227 (40) $[C_8H_8FNO_3 + H + CH_3CN]^+$, 222 (10) $[C_7H_6FNO + H + 2CH_3CN]^+$, 186 (29) $[C_8H_8FNO_3 + H]^+$, 181 (100) $[C_7H_6FNO + H + CH_3CN]^+$, 165 (84) $[C_7H_6FN + H + CH_3CN]^+$, 140 (17) $[C_7H_6FNO + H]^+$, 154 (22) $[C_8H_8FNO + H]^+$, 124 (42) $[C_7H_6FN + H]^+$. Found, %: C 60.57; H 6.76; F 6.36; N 4.68. $C_{15}H_{20}FNO_4$. Calculated, %: C 60.60; H 6.78; F 6.39; N 4.71.

1,3,5-Triaryl-1,3,5-triazinanes 17a, 17d, 18c, 18f, 19b, and 19e. The ^{1}H and ^{13}C NMR spectra are consistent with those reported in [18].

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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