Synthesis and antiadrenergic properties of β-substituted alcohols based on 6-hydroxymethylpyridoxine*

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An approach to the synthesis of epoxides based on 6-hydroxymethylpyridoxine acetals was developed. The epoxides obtained were involved in the ring opening reactions by nitrogen-, oxygen-, and sulfur-containing nucleophiles. Cytotoxicity and antiadrenergic properties of some synthesized compounds were studied on the models *in situ* and *in vivo*.

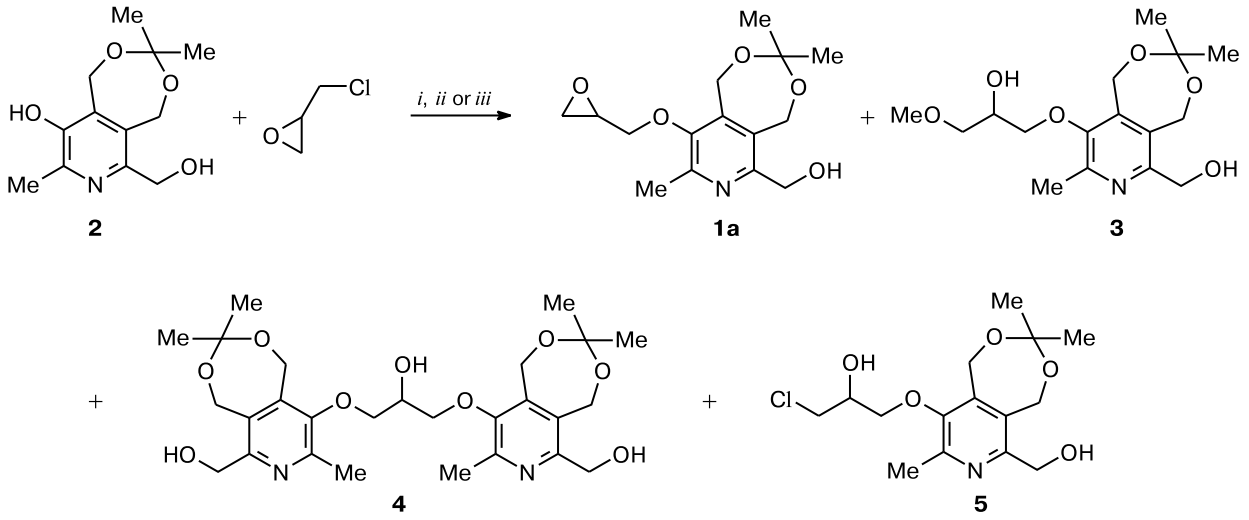
Key words: pyridoxine, 6-hydroxymethylpyridoxine, epoxides, β-substituted alcohols, antiadrenergic activity, β-blockers.

One of the most efficient approaches to the development of new pharmaceutical agent is modification of natural biologically active compounds, for example, vitamin B_6 (pyridoxine), which is one of key coenzymes involved in metabolism with more than 100 enzymes and in many biochemical processes.[1—5] Only one work[6] is known, in which a similar approach was used in the development of new β-adrenoblockers, structural analogues of known pharmaceutical drugs (metoprolol, betaxolol, propranolol, atenolol, *etc.*).[7,8]

In continuation of our systematic studies on the directed synthesis of physiologically active compounds based on 6-hydroxymethylpyridoxine,[9—13] in the present work we synthesized a series of β-substituted alcohols, studied their antiadrenergic and cytotoxic properties.

Pyridoxine derivative **1a** containing an oxirane fragment was obtained by the nucleophilic substitution reaction of 6-hydroxymethylpyridoxine acetonide **2** with racemic epichlorohydrin under various conditions (Scheme 1). The high-

Scheme 1



Reagents, conditions, and yields of the product 1a: *i*. MeOH, NaOH, 20 °C, 48 h, 25% yield; *ii*. MeOH, Et_3N, 20 °C, 48 h, 38% yield; *iii*. DMF, NaH, 70 °C, 24 h, 65% yield.

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est yield of the oxirane was achieved in the reaction of acetonide **2** with epichlorohydrin in DMF in the presence of sodium hydride. In other cases, the formation of the side products **3**—**5** and a considerable resinification of the reaction mixture were observed, whereas the yield of the target product **1a** was below 38%. According to the ^{1}H NMR spectroscopy data, the ratio of the products **1a** : **3** : **4** : **5** in the reaction mixture obtained by method *i* was 1 : 1 : 1 : 1, by method *ii* 1 : 0 : 0 : 1, by method *iii* 1 : 0 : 0 : 0.03. Unfortunately, attempted separation of the mixture of compounds **1a** and **5** by column chromatography or recrystallization was unsuccessful. The structure of the synthesized compounds was determined using 1D and 2D NMR spectroscopy, mass spectrometry, and in some cases by X-ray crystallography (Fig. 1).

The epoxide ring opening reaction in compound **1a** with nitrogen-, oxygen- and sulfur-containing nucleophiles (NuH) was used to obtain β-substituted alcohols **6**—**40** (Scheme 2, Table 1). The nucleophiles were primary and secondary amines, alcohols, and thiols, which differed in the size and lipophilicity of substituents at the nitrogen, oxygen, and sulfur atoms. It was found that the amination reaction under the influence of microwave irradiation leads to a considerable decrease in the reaction time and the increase in the yield of the target products. The selectivity of the epoxide ring opening in compound **1a** was confirmed by 1D and 2D NMR spectroscopy. In all the cases, the ring opening product was formed *via* the attack by nucleophile from the least substituted side.

Since the acetonide protection of the hydroxymethyl groups at positions 4 and 5 of the pyridoxine fragment can be easily removed by hydrolysis in the acidic medium of digestive tract,[14] a number of acetals **41**—**46** more stable to hydrolysis was synthesized, which contained only one methyl group at the acetal carbon atom of the seven-membered ring (see Scheme 1, Table 1). The starting epoxide **1b** was obtained similarly to compound **1a** by method *iii* (see Scheme 1) in 58% yield.

β-Substituted alcohols **6**—**46** were isolated by column chromatography on silica gel.

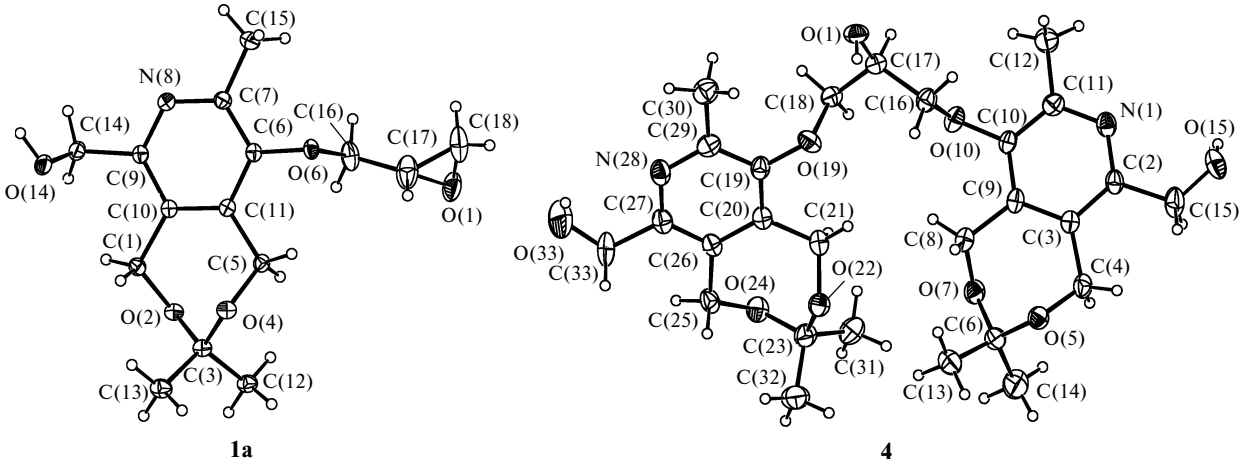
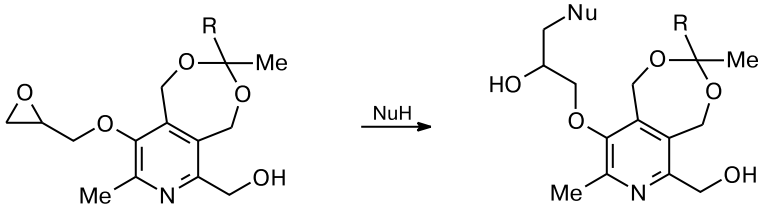


Fig. 1. The structures of compounds **1a** and **4** according to the X-ray diffraction data (disordering is not shown for clarity, ellipsoids of thermal vibrations are given with 30% probability).

Scheme 2*



R = Me (**1a**, **6**—**40**),
H (**1b**, **41**—**46**)

* Reaction conditions and NuH are given in Table 1.

Table 1. Synthesis[a] and cytotoxicity[b] of compounds **6—46**

Compound	NuH	Solvent	T /°C	Yield[c] (%)	IC_{50} /μmol L^{-1}
6	Pr^iNH_2	MeOH	100	73	>2820
7	Bu^tNH_2	MeOH	100	56	>2820
8	$EtC(Me)_2NH_2$	MeOH	100	37	1170
9	$C_{12}H_{25}NH_2$	MeOH	100	69	4.9
10	$PhNH_2$	MeOH	100	61	167
11	$C_6H_{11}NH_2$	MeOH	100	55	114
12	Et_2NH	MeOH	100	37	669
13	Bu_2NH	MeOH	100	55	98
14	$(C_8H_{17})_2NH$	MeOH	100	50	0.1
15	$(C_6H_{11})_2NH$	MeOH	100	67	10.4
16	Bn_2NH	MeOH	100	55	8.6
17	$(CH_2)_5NH$	MeOH	100	71	2550
18	$O(CH_2CH_2)_2NH$	MeOH	100	87	>2820
19	EtOH	EtOH	50	39	1995
20	Pr^iOH	Pr^iOH	50	68	340
21	PhOH	DMF	70	79	129
22	4-$Bu^tC_6H_4OH$	DMF	70	60	45
23	2,4-$(Bu^t)_2C_6H_3OH$	DMF	70	56	—[d]
24	4-Bu^t-2-$(HOCH_2)C_6H_3OH$	DMF	70	80	—[d]
25	3-HOC_5H_4N	DMF	70	58	—[d]
26	Pr^iSH	DMF	70	68	202
27	BuSH	DMF	70	46	—[d]
28	Bu^tSH	DMF	70	64	23
29	PhSH	DMF	70	71	—[d]
30	2-MeC_6H_4SH	DMF	70	30	—[d]
31	4-MeC_6H_4SH	DMF	70	73	—[d]
32	2-ClC_6H_4SH	DMF	70	82	—[d]
33	4-ClC_6H_4SH	DMF	70	74	16
34	2,4-$Cl_2C_6H_3SH$	DMF	70	51	0.2
35	2-FC_6H_4SH	DMF	70	25	38
36	4-FC_6H_4SH	DMF	70	67	—[d]
37	2-BrC_6H_4SH	DMF	70	71	—[d]
38	4-BrC_6H_4SH	DMF	70	67	42
39	BnSH	DMF	70	74	—[d]
40	H_2O	H_2O	50	31	—[d]
41	Pr^iNH_2	MeOH	100	48	> 2820
42	Bu^tNH_2	MeOH	100	93	2511
43	$EtC(Me)_2NH_2$	MeOH	100	47	466
44	$(CH_2)_5NH$	MeOH	100	65	1260
45	$O(CH_2CH_2)_2NH$	MeOH	100	70	1837
46	EtOH	EtOH	50	78	1990
Metoprolol	—	—	—	—	> 2820

[a] Reaction conditions and reagents: for compounds **6—18** and **41—45**, **1a** or **1b** (3.4 mmol), NuH (6.8 mmol), microwave irradiation, 1.5 h; for compounds **19**, **20**, and **46**, **1a** or **1b** (0.7 mmol), NaOH (0.7 mmol), 48 h; for compounds **21—39**, **1a** (0.5 mmol), NuH (1.0 mmol), NaH (1.0 mmol), 72—120 h; for compound **40**, **1a** (0.7 mmol), KOH (0.8 mmol), 72 h.

[b] Against human embryonic kidney cells HEK-239.

[c] Yields of isolated products.

[d] No data available.

Most of the synthesized compounds were found to be more toxic toward human embryonic kidney cells HEK-293 than known β_1-adrenoblocker metoprolol. Atrial myocardial contractile activity of one of the nontoxic compounds, derivative **6**, was studied *in situ* on the atrium myocardium bands of inbred rats (Fig. 2). In the concentrations of 0.1 and 1 μmol L^{-1}, neither metoprolol, nor compound **6** have considerable influence on the myocardial contractile activity (number of experiments $n = 5$, statistical significance $p > 0.05$). Upon increase in the concentration of compounds to 10 and 100 μmol L^{-1}, metoprolol causes reliable decrease in the contractile activity

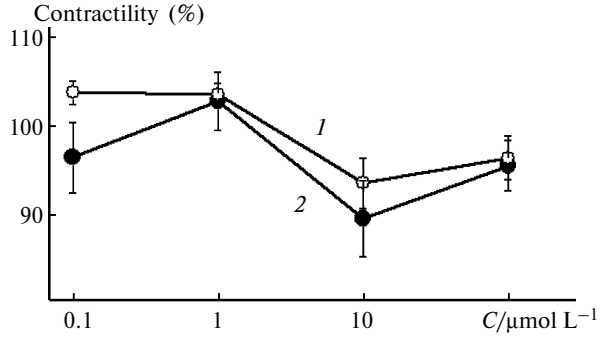


Fig. 2. The influence of compound **6** (*1*) and metoprolol (*2*) on atrial myocardial contractile activity in inbred rats.

to 89±4% ($n = 5$, $p < 0.05$) and 95±2% ($n = 4$, $p < 0.05$), respectively, whereas compound **6** did this to 93±3% ($n = 7$, $p < 0.05$) and 96±2% ($n = 6$, $p < 0.05$), respectively. Thus, compound **6** has a negative inotropic effect on the activity of the rat atrial myocardium comparable with that of metoprolol.

For the most safe compounds **6—8**, **10—13**, **17—21**, **26**, and **40—46**, the studies of cardiodepressive action were carried out *in vivo*, which was assessed by the decrease in the heart rate (HR) of white outbred mice after intragastric administration of compounds (Table 2). The maximal effect was observed for compound **17**, but only in half of mice in the group. The most stable decrease in HR in the

Table 2. Cardiodepressive activity of some synthesized compounds

Compound	Decrease in HR (%)		*N*	*t*/min		τ/min	
	M±m (δ)	$x_{0.5}$ ($x_{0.025}$) [$x_{0.975}$]		M±m (δ)	$x_{0.5}$ ($x_{0.025}$) [$x_{0.975}$]	M±m (δ)	$x_{0.5}$ ($x_{0.025}$) [$x_{0.975}$]
Metoprolol	36.34±3.25 (7.27)	33.64 (31.18) [46.08]	4	35.25±3.02 (6.75)	36 (28.23) [41]	74±4.8 (10.72)	72 (65.23) [88.03]
6	20.62	—*	1 from 3	20	—*	48	—*
8	27.21±4.56 (10.19)	28.35 (21.33) [35.02]	3 from 4	85.67±15.65 (34.99)	74 (58.8) [122.45]	84.5±15.67 (35.03)	67.5 (66) [131.9]
10	20.16±3.38 (7.56)	21.35 (12.55) [26.77]	3 from 3	54.67±8.56 (19.14)	49 (39.5) [74.65]	61.33±14.14 (31.63)	71 (28.25) [86.2]
11	14.28±2.07 (4.63)	14.28 (11.17) [17.4]	2 from 3	47±3.79 (8.49)	47 (41.3) [52.7]	67± 6.32 (14.14)	67 (57.5) [76.5]
13	25±4.1 (9.16)	24.61 (12.96) [34.72]	5 from 5	51.2±5.73 (12.81)	49 (39.4) [70.1]	66.2±6.64 (14.84)	62 (48.3) [83.4]
17	43.86±3.18 (7.12)	43.86 (39.08) [48.64]	2 from 5	67±1.9 (4.24)	67 (64.15) [69.85]	78.5±5.38 (12.02)	78.5 (70.43) [86.58]
18	24.39±4.24 (9.48)	20.35 (16.06) [37.22]	6	32±9.26 (20.72)	24.5 (11) [59.38]	48.84 ± 12.06 (26.96)	55 (5.42) [77.5]
19	28.88±3.71 (8.3)	33.13 (15.52) [35.41]	6	29.83±6.51 (14.57)	30.5 (9.5) [45.75]	70.33±6.84 (15.29)	69 (51.25) [89.25]
20	24.45±8.35 (18.68)	24.45 (6.14) [45.74]	4 from 5	33.27±17.58 (39.32)	28.03 (0.02) [75.43]	58.5±13.53 (30.25)	57.5 (25.73) [92.98]
21	28.5±2.94 (6.57)	28.01 (21.47) [36.35]	4 from 4	40.5±4.04 (9.04)	41.5 (30.45) [48.85]	82.5±0.93 (2.08)	82.5 (80.15) [84.85]
40	28.94±3.65 (8.17)	27.85 (21.72) [38.02]	4 from 6	27.83±5.11 (11.43)	31 (13.25) [40.38]	94±7.07 (15.81)	89 (29.38) [113.63]
41	17.8±6.52 (14.57)	15.3 (5.18) [32.55]	4 from 4	44.25±7.99 (17.86)	44 (24.28) [64.65]	70.75±11.65 (26.04)	75 (40.58) [93.7]
43	20.42±2.34 (5.24)	20.42 (16.91) [23.94]	3 from 3	26.5±4.74 (10.61)	26.5 (19.38) [33.63]	74.67±7.81 (17.47)	70 (60.5) [92.8]
44	10.41±3.67 (8.21)	8.68 (3.47) [18.82]	3 from 3	42.67±12.65 (28.29)	35 (19.8) [72.05]	92.33±2.02 (4.51)	92 (88.2) [96.75]
45	30.09±5.5 (12.45)	29.76 (16.34) [44.38]	4 from 4	31.5±3.94 (8.81)	31.5 (21.6) [41.4]	82±8.85 (19.78)	89.5 (55.48) [95.78]
46	21.08±5.02 (11.22)	25.31 (9.21) [29.36]	3 from 3	53±4.4 (9.85)	56 (42.7) [60.75]	102.33±6.64 (14.84)	106 (87) [114.55]
3	16.51±1.42 (3.18)	15.76 (13.67) [20.62]	4 from 6	37.67±15.88 (35.52)	29.5 (4.63) [89]	50.33±15.4 (34.44)	33 (28.25) [87.15]

Note: *N* is the number of animals; *t* is the time of the onset of maximal effect; τ is the duration of action of a compound; M±m is the arithmetic average value and the standard error of the arithmetic average value; δ is the deviation of the arithmetic average value; $x_{0.5}$, $x_{0.025}$, and $x_{0.975}$ is the median and percentiles 0.025 and 0.975, respectively.

* Statistical indices were not calculated.

whole group of animals was observed for compounds **19**, **21**, and **45**. The duration of cardiodepressive effect of many compound was comparable with that of metoprolol. The use of the acetal protection instead of the ketal one led to an increase in the duration of the effect of compounds. Compounds **7**, **12**, **26**, and **42** did not exhibit cardiodepressive action (experimental groups contained 3—5 animals).

To sum up, the screening of some pyridoxine derivatives synthesized in the present work revealed lead compounds, which are comparable with beta blocker metoprolol in both the onset of the maximal cardiodepressive effect and in its duration. It should be especially noted that the antiadrenergic activity was found not only in β-aminoalcohols, but also in β-alkoxy- and β-aryloxyalcohols. We believe that this opens additional possibilities for researches in the development of new adrenoblocker.

In conclusion, in the present work we developed an approach to the synthesis of new physiologically active pyridoxine derivatives by the ring opening reaction of epoxides based on 6-hydroxymethylpyridoxine with various nucleophiles. Some of the compounds obtained are of interest as lead compounds in the development of new antiadrenergic agents.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer (400.13 and 100.61 MHz, respectively). Chemical shifts are given relative to the residual signals of deuterated solvents. Electrospray ionization high resolution mass spectra were recorded on an AB Sciex 5600 mass spectrometer with a DuoSpray ion source (Turbo Ion Spray probe, voltage 5500 V, nebulizer gas pressure 25 psi (~1300 Torr)), registration in a positive ion mode, compounds were studied in solutions in a mixture of methanol—water (1 : 1). All the experiments with microwave irradiation were carried out in a Discover®-CEM laboratory microwave reactor working on a frequency 2.45 GHz with a continuous power of irradiation from 0 to 300 W. Melting points were determined using a Stanford Research Systems MPA-100 OptiMelt apparatus. Chromatographic purification of compounds obtained was carried out using Acros silica gel (60—200 mesh. Reaction progress and purity of compounds were monitored by TLC on Sorbfil PTLC-AF-A-UF plates.

X-ray diffraction study of crystals of compounds **1a** and **4** was carried out on a Bruker SMART Apex II diffractometer (graphite monochromator, λ(MoKα) = 0.71073 Å, 150 K, ω-scan technique). Crystallographic data and parameters of refinement for the structures are given in Table 3. Semiempirical allowance for absorption was made using the SADABS[15] program. The structures were solved by direct method using the SHELXS[16] program. Nonhydrogen atoms were refined first in isotropic and then in anisotropic approximation using the SHELXL-97[16] program. Hydrogen atoms at the carbon atoms were placed in calculated positions and refined using a riding model. Hydroxy hydrogen atoms were found from the difference Fourier synthesis, their positions were refined isotropically on final stage of refinement with the fixed bond distance of 0.85 Å. All the calculations were carried out using the WinGX[17] and APEX2[18] programs. In the crystal of compound **1a**, a disordering of the epoxide oxygen atom O(1) over two positions with about equal occupancy was found. In the crystal of compound **4**, a disordering of two hydroxy groups at the bridged atom C(17) and atom C(15) was found; the occupancies of two positions are about the same in both cases. In the crystal of compound **4**, apart from the molecule of the main compound, two solvent molecules of water were revealed. For one of them, the hydrogen atoms were localized

Table 3. Crystallographic data and parameters of X-ray diffraction experiment for structures **1a** and **4**

Parameter	**1a**	**4**
Molecular formula	$C_{15}H_{21}NO_5$	$C_{27}H_{38}N_2O_9 \cdot 2H_2O$
Molecular weight	295.33	568.61
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$C2/c$
Z	4	8
a/Å	15.109(6)	43.12(1)
b/Å	12.105(5)	7.879(3)
c/Å	7.975(3)	17.215(5)
β/deg	97.760(5)	107.758(4)
V/Å^3	1445(1)	5571(3)
d_{calc}/g cm^{-3}	1.357	1.356
μ/cm^{-1}	1.02	1.05
Number of measured reflections	12896	24585
Number of reflections with $I \geq \sigma(I)$	2566	1941
R_{int}	0.0435	0.1259
R_1 ($I > 2\sigma(I)$)	0.0661	0.0712
wR_2 ($I > 2\sigma(I)$)	0.1616	0.1590
R_1 (on all reflections)	0.0879	0.2187
R_2 (on all reflections)	0.1757	0.2026

from the difference Fourier synthesis, for the second, the hydrogen atoms were not found, however, they were included in the general structural formula. The crystallographic data for the structures of **1a** and **4** were deposited with the Cambridge Crystallographic Data Center (CCDC 1014072 and 1014073, respectively).

[3,3,8-Trimethyl-9-(oxiran-2-ylmethoxy)-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-6-yl]methanol (1a). ***Method i.*** Epichlorohydrin (1.0 mL, 12.5 mmol) was added to a solution of compound **2** (1.0 g, 4.2 mmol) and NaOH (0.2 g, 5 mmol) in methanol (15 mL). The reaction mixture was stirred for 48 h at room temperature. The solvent was evaporated at reduced pressure, the product was purified by column chromatography on silica gel (eluent ethyl acetate). The yield was 0.31 g (25%), colorless crystals, m.p. 150—152 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.49 (s, 6 H, 2 CH_3); 2.48 (s, 3 H, $CH_{3(Pyr)}$); 2.70 (dd, 1 H, CH, ^2J = 4.7 Hz, ^3J = 2.7 Hz); 2.89 (t, 1 H, CH_2, ^2J = = 4.7 Hz); 3.33 (m, 1 H, CH); 3.64 (dd, 1 H, CH, ^2J = 11.2 Hz, ^3J = 6.4 Hz); 4.09 (dd, 1 H, CH, ^2J = 11.2 Hz, ^3J = 2.6 Hz); 4.53 (s, 2 H, $CH_{2(Pyr)}$); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.82 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.96 ($CH_{3(Pyr)}$); 23.80 (2 CH_3); 44.52 (CH_2); 50.35 (CH); 58.91 (CH_2); 59.08 (CH_2); 61.24 (CH_2); 74.46 (CH_2); 102.80 (C); 129.54 (C_{Pyr}); 141.57 (C_{Pyr}); 148.40 (C_{Pyr}); 148.44 (C_{Pyr}); 149.43 (C_{Pyr}). MS, *m/z*: 296.1494 $[M + H]^+$. $C_{15}H_{22}NO_5$. Calculated for $C_{15}H_{23}NO_5$: 296.1498.

Method ii. Epichlorohydrin (1.0 mL, 12.5 mmol) was added to a solution of compound **2** (1.0 g, 4.2 mmol) and triethylamine (1.8 mL, 12.5 mmol) in methanol (15 mL). The reaction mixture was stirred for 48 h at room temperature. The solvent was evaporated at reduced pressure and the product was purified by column chromatography on silica gel (eluent ethyl acetate). The yield was 0.47 g (38%).

Method iii. Epichlorohydrin (1.0 mL, 12.5 mmol) was added to a solution of compound **2** (1.00 g, 4.2 mmol) and sodium hydride (0.10 g, 4.2 mmol) in dimethylformamide (15 mL). The reaction mixture was stirred for 24 h at 70 °C. The solvent was evaporated at reduced pressure, the product was purified by column chromatography on silica gel (eluent ethyl acetate). The yield was 0.80 g (65%).

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-methoxypropan-2-ol (3) was obtained as a side product in the reaction carried out by method *i*. The yield was 0.41 g (30%), colorless crystals, m.p. 107 °C. ^{1}H NMR (400 MHz, acetone-d_6), δ: 1.45 (s, 6 H, 2 CH_3); 2.44 (s, 3 H, $CH_{3(Pyr)}$); 3.36 (s, 3 H, CH_3); 3.53 (m, 2 H, CH_2, ^2J = 9.6 Hz, ^3J = 5.6 Hz); 3.83 (m, 2 H, CH_2, ^2J = 9.6 Hz, ^3J = = 4.9 Hz); 4.07 (m, 1 H, CH); 4.23 (br.s, 1 H, OH); 4.54 (s, 2 H, $CH_{2(Pyr)}$); 4.82 (s, 2 H, $CH_{2(Pyr)}$); 4.98 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, acetone-d_6), δ: 18.95 ($CH_{3(Pyr)}$); 23.98 (2 CH_3); 59.14 (CH_2); 59.23 (CH_2); 60.09 (OCH_3); 62.82 (CH_2); 70.04 (CH); 74.37 (CH_2); 75.68 (CH_2); 103.02 (C); 131.53 (C_{Pyr}); 142.32 (C_{Pyr}); 148.90 (C_{Pyr}); 150.22 (C_{Pyr}); 150.30 (C_{Pyr}). MS, *m/z*: 328.1758 $[M + H]^+$. $C_{16}H_{26}NO_6$. Calculated for $C_{16}H_{27}NO_6$: 328.1760.

1,3-Bis(6-hydroxymethyl-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yloxy)propan-2-ol (4) was obtained as a side product in the reaction carried out by method *i*. The yield was 0.63 g (28%), colorless crystals, m.p. 161 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.43 (s, 12 H, 4 CH_3); 2.41 (s, 6 H, 2 $CH_{3(Pyr)}$); 3.88 (m, 4 H, CH_2, ^2J = 9.7 Hz, ^3J = 5.1 Hz); 4.16 (br.m, 1 H, CH); 4.48 (br.d, 4 H, 2 $CH_{2(Pyr)}$, ^3J = 3.0 Hz); 4.89 (s, 4 H, 2 $CH_{2(Pyr)}$); 4.95 (s, 4 H, 2 $CH_{2(Pyr)}$); 5.08 (br.t, 2 H, OH); 5.51 (br.d, H, OH, ^3J = 5.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 18.64 ($CH_{3(Pyr)}$); 23.53 (2 CH_3); 58.19 (CH_2); 59.77 (CH_2); 63.45 (CH_2); 68.72 (CH); 74.60 (CH_2); 101.93 (C); 131.64 (C_{Pyr}); 140.70 (C_{Pyr}); 147.67 (C_{Pyr}); 149.16 (C_{Pyr}); 150.88 (C_{Pyr}). MS, *m/z*: 535.2654 $[M + H]^+$. $C_{27}H_{39}N_2O_9$. Calculated for $C_{27}H_{40}N_2O_9$: 535.2656.

1-Chloro-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (5) was obtained as a side product in the reaction carried out by methods *i*, *ii*, and *iii*. ^{1}H NMR (400 MHz, $CDCl_3$), δ (in the mixture with compound **1a**): 1.50 (s, 6 H, 2 CH_3); 2.49 (s, 3 H, $CH_{3(Pyr)}$); 3.79 (m, 2 H, CH_2Cl, ^2J = 11.2 Hz, ^3J = 5.4 Hz); 3.86 (d, 2 H, OCH_2, ^2J = 5.0 Hz); 4.20 (m, 1 H, CH); 4.55 (s, 2 H, $CH_{2(Pyr)}$); 4.71 (s, 2 H, $CH_{2(Pyr)}$); 4.95 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (experiment APT, 100 MHz, $CDCl_3$), δ (in the mixture with compound **1a**): 18.77 ($CH_{3(Pyr)}$); 23.73 (2 CH_3); 45.62 (CH_2); 58.74 (CH_2); 59.03 (CH_2); 61.11 (CH_2); 70.22 (CH); 73.48 (CH_2); 102.80 (C); 129.68 (C_{Pyr}); 141.64 (C_{Pyr}); 148.25 (C_{Pyr}); 148.45 (C_{Pyr}); 148.94 (C_{Pyr}). MS (in the mixture with compound **1a**), *m/z*: 332.1269 $[M + H]^+$. $C_{15}H_{23}ClNO_5$. Calculated for $C_{15}H_{24}ClNO_5$: 332.1265.

Oxirane ring opening with nitrogen-containing nucleophiles (general procedure). A corresponding amine (6.80 mmol) was added to a solution of epoxide (1 g, 3.39 mmol) in methanol (5 mL). The reaction was carried out under microwave radiation for 1.5 h at 100 °C. The solvent was evaporated at reduced pressure, the product was purified by column chromatography on silica gel (eluent ethyl acetate, then acetone).

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(isopropylamino)propan-2-ol (6) was obtained using isopropylamine as a nitrogen-containing nucleophile. The yield was 0.84 g (73%), colorless crystals, m.p. 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.09 (d, 6 H, 2 CH_3, ^3J = 6.2 Hz); 1.50 (s, 6 H, 2 CH_3); 2.49 (s, 3 H, $CH_{3(Pyr)}$); 2.71 (dd, 1 H, NCH_2, $^2J_{AB}$ = 12.0 Hz, $^3J_{AX}$ = 8.3 Hz); 2.88 (dd, 1 H, NCH_2, $^3J_{BX}$ = 3.9 Hz); 2.82 (sext, 1 H, $C(C\underline{H}_3)_2$); 3.74 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.6 Hz); 3.76 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.3.93—3.99 (m, 1 H, CH); 4.54 (s, 2 H, $CH_{2(Pyr)}$); 4.71 (s, 2 H, $CH_{2(Pyr)}$); 4.84 (br.s, 1 H, OH); 4.97 (s, 2 H, $CH_{2(Pyr)}$). 68 ($CH_{3(Pyr)}$); 20.98 (CH_3); 21.07 (CH_3); 23.64 (2 CH_3); 48.47 (CH_2); 50.07 (CH); 58.64 (CH_2); 59.23 (CH_2); 61.60 (CH_2); 67.53 (CH); 75.42 (CH_2); 102.62 (C); 130.01 (C_{Pyr}); 141.31 (C_{Pyr}); 148.16 (C_{Pyr}); 148.65 (C_{Pyr}); 149.09 (C_{Pyr}). MS, *m/z*: 339.2280 $[M + H]^+$. $C_{18}H_{31}N_2O_4$. Calculated for $C_{18}H_{32}N_2O_4$: 339.2284.

1-(*tert*-Butylamino)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (7) was obtained using *tert*-butylamine as a nitrogen-containing nucleophile. The yield was 0.70 g (56%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.06 (s, 9 H, 3 CH_3); 1.38 (s, 6 H, 2 CH_3); 2.32 (s, 3 H, $CH_{3(Pyr)}$); 2.61 (dd, 1 H, NCH_2, $^2J_{AB}$ = 11.4 Hz, $^3J_{AX}$ = 8.9 Hz); 2.73 (dd, 1 H, NCH_2, $^3J_{BX}$ = 3.2 Hz); 3. 61 (d, 2 H, OCH_2, ^3J = 4.8 Hz); 3.94 (m, 1 H, CH); 4.24 (br.s, 2 H, 2 OH); 4.45 (s, 2 H, $CH_{2(Pyr)}$); 4.67 (s, 2 H, $CH_{2(Pyr)}$); 4.84 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.93 ($CH_{3(Pyr)}$); 23.76 (2 CH_3); 27.00 (3 CH_3); 45.17 (CH_2); 55.49 (C); 58.79 (CH_2); 59.13 (CH_2); 61.39 (CH_2); 67.07 (CH); 75.32 (CH_2); 102.74 (C); 129.67 (C_{Pyr}); 141.40 (C_{Pyr}); 148.20 (C_{Pyr}); 148.46 (C_{Pyr}); 149.16 (C_{Pyr}). MS, *m/z*: 369.2390 $[M + H]^+$. $C_{19}H_{33}N_2O_5$. Calculated for $C_{19}H_{34}N_2O_5$: 369.2389.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]-dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(*tert*-pentylamino)propan-2-ol (8) was obtained using *tert*-amylamine as a nitrogen-containing nucleophile. The yield was 0.48 g (37%), colorless crystals, m.p. 73—74 °C. ^{1}H NMR (400 MHz, acetone-d_6), δ: 0.85 (t, 3 H, CCH_3, ^3J = 7.5 Hz); 1.03 (s, 6 H, 2 CH_3); 1.33—1.49 (m, 8 H, NCH_2, 2 CH_3); 2.43 (s, 3 H, $CH_{3(Pyr)}$); 2.66 (dd, 1 H, NCH_2, $^2J_{AB}$ = 11.2 Hz, $^3J_{AX}$ = 7.2 Hz); 2.77 (dd, 1 H, NCH_2, $^3J_{BX}$ = 4.4 Hz); 3.42 (br.s, 2 H, OH); 3.77 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 6.0 Hz); 3.88 (dd, 1 H, OCH_2, $^3J_{BX}$ = = 4.1 Hz); 3.96 (m, 1 H, CH); 4.54 (s, 2 H, $CH_{2(Pyr)}$); 4.83 (s, 2 H, $CH_{2(Pyr)}$); 4.99 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, acetone-d_6), δ: 8.51 ($\underline{C}H_3C$); 19.06 ($CH_{3(Pyr)}$); 23.96 (2 CH_3); 26.79 ($\underline{C}H_3C$); 26.81 ($\underline{C}H_3C$); 33.80 (CH_2); 45.08 (CH_2); 52.75 ($N\underline{C}CH_2$); 59.31 (CH_2); 60.14 (CH_2); 62.90 (CH_2); 70.56 (CH); 77.15 (CH); 102.97 (C); 131.61 (C_{Pyr}); 142.25 (C_{Pyr}); 148.83 (C_{Pyr}); 150.21 (C_{Pyr}); 150.42 (C_{Pyr}). MS, *m/z*: 383.2546 $[M + H]^+$. $C_{20}H_{35}N_2O_5$. Calculated for $C_{20}H_{36}N_2O_5$: 383.2546.

1-(Dodecylamino)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (9) was obtained using dodecylamine as a nitrogen-containing nucleophile. The yield was 1.12 g (69%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.85 (t, 3 H, CH_3, ^3J = 6.8 Hz); 1.16—1.34 (m, 19 H, 8 CH_2, CH_3); 1.47 (s, 6 H, 2 CH_3); 1.55 (m, 2 H, CH_2); 2.42 (s, 3 H, $CH_{3(Pyr)}$); 2.56—2.94 (m, 4 H, 2 NCH_2); 3.73 (m, 2 H, OCH_2); 4.08—4.15 (m, 1 H, CH); 4.28 (br.s, 2 H, OH); 4.52 (s, 2 H, $CH_{2(Pyr)}$); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.92 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.24 ($CH_{3(Aliph)}$); 18.78 ($CH_{3(Pyr)}$); 22.77 (CH_2); 23.71 (2 CH_3); 27.00 (CH_2); 27.36 (CH_2); 29.34 (CH_2); 29.43 (CH_2); 29.65 (CH_2); 29.72 (CH_2); 31.98 (CH_2); 49.17 (CH_2); 50.91 (CH_2); 58.65 (CH_2); 59.25 (CH_2); 61.64 (CH_2); 66.84 (CH_2); 75.08 (CH); 102.75 (C); 129.94 (C_{Pyr}); 141.30 (C_{Pyr}); 148.10 (C_{Pyr}); 148.68 (C_{Pyr}); 148.92 (C_{Pyr}). MS, *m/z*: 481.3647 $[M + H]^+$. $C_{27}H_{49}N_2O_5$. Calculated for $C_{27}H_{50}N_2O_5$: 481.3641.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]-dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(phenylamino)propan-2-ol (10) was obtained using aniline as a nitrogen-containing nucleophile. The yield was 0.80 g (61%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.37 (s, 3 H, CH_3); 1.38 (s, 3 H, CH_3); 2.30 (s, 3 H, $CH_{3(Pyr)}$); 3.13 (dd, 1 H, CH_2, ^2J = 12.8 Hz, ^3J = 7.4 Hz); 3.27 (dd, 1 H, CH_2, ^3J = 3.6 Hz); 3.66 (d, 2 H, CH_2, ^3J = 4.9 Hz); 4.09 (m, 1 H, CH); 4.42 (s, 2 H, $CH_{2(Pyr)}$); 4.61 (s, 2 H, $CH_{2(Pyr)}$); 4.81 (s, 2 H, $CH_{2(Pyr)}$); 6.51—7.10 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.67 ($CH_{3(Pyr)}$); 23.60 (2 CH_3); 46.51 (CH_2); 58.60 (CH_2); 59.11 (CH_2); 61.37 (CH_2); 68.99 (CH); 75.40 (CH_2); 102.66 (C); 113.23 (C_{Ar}); 117.99 (C_{Ar}); 129.29 (C_{Ar}); 129.82 (C_{Ar}); 141.30 (C_{Ar}); 147.98 (C_{Ar}); 148.15 (C_{Ar}); 148.35 (C_{Ar}); 149.10 (C_{Ar}). MS, *m/z*: 389.2080 $[M + H]^+$. $C_{21}H_{29}N_2O_5$. Calculated for $C_{21}H_{30}N_2O_5$: 389.2076.

1-(Cyclohexylamino)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (11) was obtained using cyclohexylamine as a nitrogen-containing nucleophile. The yield was 0.74 g (55%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.11—2.10 (m, 10 H, 5 CH_2); 1.45 (s, 6 H, 2 CH_3); 2.38 (s, 3 H, $CH_{3(Pyr)}$); 2.72 (m, 1 H, NH); 2.94 (dd, 1 H, NCH_2, $^2J_{AB}$ = 11.2 Hz, $^3J_{AX}$ = 9.6 Hz); 3.09 (dd, 1 H, NCH_2, $^3J_{BX}$ = 2.8 Hz); 3.65—3.78 (m, 2 H, OCH_2); 4.26 (m, 1 H, CH); 4.50 (s, 2 H, $CH_{2(Pyr)}$); 4.69 (s, 2 H, $CH_{2(Pyr)}$); 4.89 (s, 2 H, $CH_{2(Pyr)}$); 5.26 (br.s, 2 H, 2 OH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 18.76 ($CH_{3(Pyr)}$); 23.65 (2 CH_3); 24.07 (CH_2); 24.87 (CH_2); 28.22 (CH_2); 28.47 (CH_2); 46.43 (CH_2); 56.39 (CH_2); 58.25 (CH_2); 59.84 (CH_2); 63.53 (CH_2); 65.89 (CH); 75.16 (CH_2); 102.00 (C); 131.76 (C_{Pyr}); 140.77 (C_{Pyr}); 147.74 (C_{Pyr}); 148.96 (C_{Pyr}); 151.12 (C_{Pyr}). MS, *m/z*: 395.2546 $[M + H]^+$. $C_{21}H_{35}N_2O_5$. Calculated for $C_{21}H_{36}N_2O_5$: 395.2546.

1-(Diethylamino)-2-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (12) was obtained using diethylamine as a nitrogen-containing nucleophile. The yield was 0.46 g (37%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.05 (t, 6 H, 2 CH_3, ^3J = 7.2 Hz); 1.44 (s, 6 H, 2 CH_3); 2.41 (s, 3 H, $CH_{3(Pyr)}$); 2.55—2.78 (m, 6 H, 2 CH_2, NCH_2); 3.68 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.3 Hz, $^3J_{AX}$ = 5.6 Hz); 3.70 (m, 1 H, OCH_2, $^3J_{BX}$ = 4.4 Hz); 3.97—4.05 (m, 1 H, CH); 4.49 (s, 2 H, $CH_{2(Pyr)}$); 4.68 (s, 2 H, $CH_{2(Pyr)}$); 4.92 (s, 2 H, $CH_{2(Pyr)}$); 4.97 (br.s, 2 H, 2 OH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 11.37 ($CH_{3(Aliph)}$); 18.84 ($CH_{3(Pyr)}$); 23.68 (2 CH_3); 47.30 (CH_2); 55.68 (CH_2); 58.84 (CH_2); 59.04 (CH_2); 61.29 (CH_2); 66.18 (CH); 75.77 (CH_2); 102.61 (C_{Pyr}); 129.50 (C_{Pyr}); 141.36 (C_{Pyr}); 148.20 (C_{Pyr}); 148.25 (C_{Pyr}); 149.42 (C_{Pyr}). MS, *m/z*: 369.2390 $[M + H]^+$. $C_{19}H_{33}N_2O_5$. Calculated for $C_{19}H_{34}N_2O_5$: 369.2389.

1-(Dibutylamino)-2-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (13) was obtained using dibutylamine as a nitrogen-containing nucleophile. The yield was 0.79 g (55%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.91 (t, 6 H, 2 CH_3, ^3J = 7.2 Hz); 1.25—1.36 (m, 4 H, 2 CH_2); 1.38—1.51 (m, 4 H, 2 CH_2); 1.47 (s, 6 H, 2 CH_3); 2.46 (s, 3 H, $CH_{3(Pyr)}$); 2.42—2.54 (m, 2 H, CH_2); 2.55—2.64 (m, 4 H, NCH_2, CH_2); 3.71 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.7 Hz); 3.73 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.2 Hz); 3.95—4.02 (m, 1 H, CH); 4.52 (s, 2 H, $CH_{2(Pyr)}$); 4.69 (s, 2 H, $CH_{2(Pyr)}$); 4.76 (br.s, 2 H, OH); 4.96 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.06 ($CH_{3(Aliph)}$); 18.96 ($CH_{3(Pyr)}$); 20.60 ($CH_{2(Aliph)}$); 23.70 (2 CH_3); 29.06 ($CH_{2(Aliph)}$); 54.12 ($CH_{2(Aliph)}$); 57.04 (CH_2); 58.90 (CH_2); 61.20 (CH_2); 66.46 (CH); 75.95 (CH_2); 102.67 (C); 129.38 (C_{Pyr}); 141.45 (C_{Pyr}); 148.12 (C_{Pyr}); 148.37 (C_{Pyr}); 149.58 (C_{Pyr}). MS, *m/z*: 425.3016 $[M + H]^+$. $C_{23}H_{41}N_2O_5$. Calculated for $C_{23}H_{42}N_2O_5$: 425.3015.

1-(Dioctylamino)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (14) was obtained using dioctylamine as a nitrogen-containing nucleophile. The yield was 0.91 g (50%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.84 (t, 6 H, 2 CH_3, ^3J = 7.0 Hz); 1.15—1.33 (m, 20 H, CH_2); 1.34—1.48 (m, 4 H, CH_2); 1.46 (s, 6 H, 2 CH_3); 2.35—2.46 (m, 2 H, CH_2); 2.44 (s, 3 H, $CH_{3(Pyr)}$); 2.46—2.56 (m, 4 H, NCH_2, CH_2); 3.68 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.8 Hz); 3.72 (dd, 1 H, OCH_2, $^3J_{BX}$ = 3.7 Hz); 3.89—3.96 (m, 1 H, CH); 4.51 (s, 2 H, $CH_{2(Pyr)}$), 4.69 (s, 2 H, $CH_{2(Pyr)}$); 4.94 and 4.97 (both AB system, 2 H, $CH_{2(Pyr)}$, ^2J = 16.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.15 ($CH_{3(Aliph)}$); 18.90 ($CH_{3(Pyr)}$); 22.70 ($CH_{2(Aliph)}$); 23.71 (2 CH_3); 27.15 ($CH_{2(Aliph)}$); 27.46 ($CH_{2(Aliph)}$); 29.35 ($CH_{2(Aliph)}$); 29.58 ($CH_{2(Aliph)}$); 31.89 (CH_2); 54.29 (CH_2); 58.93 (CH_2); 61.23 (CH_2); 66.46 (CH); 75.95 (CH_2); 102.61 (C); 129.36 (C_{Pyr}); 141.40 (C_{Pyr}); 148.07 (C_{Pyr}); 148.33 (C_{Pyr}); 149.56 (C_{Pyr}). MS, *m/z*: 537.4268 $[M + H]^+$. $C_{31}H_{57}N_2O_5$. Calculated for $C_{31}H_{58}N_2O_5$: 537.4267.

1-(Dicyclohexylamino)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-

2-ol (15) was obtained using dicyclohexylamine as a nitrogen-containing nucleophile. The yield was 1.08 g (67%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.98—1.84 (m, 20 H, 10 CH_2); 1.56 (s, 6 H, 2 CH_3); 2.48 (s, 3 H, $CH_{3(Pyr)}$); 2.44—2.85 (m, 4 H, 2 CH, NCH_2); 3.68 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.9 Hz); 3.74 (dd, 1 H, OCH_2, $^3J_{BX}$ = 3.6 Hz); 3.88 (m, 1 H, CH); 4.53 (s, 2 H, $CH_{2(Pyr)}$); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.97 and 5.01 (both AB system, 2 H, $CH_{2(Pyr)}$, ^2J = 16.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 19.02 ($CH_{3(Pyr)}$); 23.74 (CH_3); 23.77 (CH_3); 26.03 (2 $CH_{2(Aliph)}$); 26.36 (2 $CH_{2(Aliph)}$); 26.47 (2 $CH_{2(Aliph)}$); 31.04 (NCH); 33.07 (NCH); 47.88 (CH_2); 58.24 (CH_2); 58.99 (CH_2); 59.06 (CH_2); 61.17 (CH_2); 66.14 (CH); 76.39 (CH_2); 102.66 (C); 129.26 (C_{Pyr}); 141.45 (C_{Pyr}); 147.94 (C_{Pyr}); 148.39 (C_{Pyr}); 149.69 (C_{Pyr}). MS, *m/z*: 477.3329 $[M + H]^+$. $C_{27}H_{45}N_2O_5$. Calculated for $C_{27}H_{46}N_2O_5$: 477.3328.

1-(Dibenzylamino)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (16) was obtained using dibenzylamine as a nitrogen-containing nucleophile. The yield was 0.92 g (55%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.49 (s, 6 H, 2 CH_3); 2.42 (s, 3 H, $CH_{3(Pyr)}$); 2.56—2.76 (m, 2 H, NCH_2Ph); 3.48—3.59 (m, 2 H, NCH_2Ph); 3.62 (dd, 1 H, NCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 6.0 Hz); 3.68 (dd, 1 H, NCH_2, $^3J_{BX}$ = 3.7 Hz); 3.78—3.90 (m, 2 H, OCH_2); 4.05 (m, 1 H, CH); 4.53 (s, 2 H, $CH_{2(Pyr)}$); 4.69 (s, 2 H, $CH_{2(Pyr)}$); 4.86 (s, 2 H, $CH_{2(Pyr)}$); 7.24—7.40 (m, 10 H, 2 Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 19.04 ($CH_{3(Pyr)}$); 23.79 (2 CH_3); 56.08 (CH_2); 58.82 (2 CH_2); 58.95 (2 CH_2); 61.08 (CH_2); 66.91 (CH); 75.89 (CH_2); 102.70 (C); 127.62 (C_{Ar}); 128.66 (C_{Ar}); 129.21 (C_{Ar}); 138.33 (C_{Ar}); 141.36 (C_{Ar}); 147.93 (C_{Ar}); 148.29 (C_{Ar}); 149.54 (C_{Ar}). MS, *m/z*: 493.2703 $[M + H]^+$. $C_{29}H_{37}N_2O_5$. Calculated for $C_{29}H_{38}N_2O_5$: 493.2702.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]-dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(piperidin-1-yl)propan-2-ol (17) was obtained using piperidine as a nitrogen-containing nucleophile. The yield was 0.91 g (71%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.46 (m, 2 H, CH_2); 1.47 (s, 6 H, 2 CH_3); 1.59 (m, 4 H, 2 CH_2); 2.37 (m, 2 H, NCH_2); 2.47 (m, 2 H, NCH_2); 2.49 (s, 3 H, $CH_{3(Pyr)}$); 2.62 (m, 2 H, NCH_2); 3.69 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = = 5.5 Hz); 3.74 (dd, 1 H, OCH_2, $^3J_{BX}$ = 3.7 Hz); 4.05 (m, 1 H, CH); 4.37 (br.s, 1 H, OH); 4.52 (s, 2 H, $CH_{2(Pyr)}$); 4.69 (s, 2 H, $CH_{2(Pyr)}$); 4.93 and 4.98 (both AB system, 2 H, $CH_{2(Pyr)}$, ^2J = = 16.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.90 ($CH_{3(Pyr)}$); 23.75 (2 CH_3); 24.10 (CH_2); 25.90 (2 CH_2); 54.81 (CH_2); 58.90 (CH_2); 59.03 (CH_2); 60.80 (CH_2); 61.21 (CH_2); 65.82 (CH); 75.74 (CH_2); 102.68 (C); 129.39 (C_{Pyr}); 141.44 (C_{Pyr}); 148.13 (C_{Pyr}); 148.38 (C_{Pyr}); 149.46 (C_{Pyr}). MS, *m/z*: 381.2390 $[M + H]^+$. $C_{20}H_{33}N_2O_5$. Calculated for $C_{20}H_{34}N_2O_5$: 381.2389.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro-[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-morpholinopropan-2-ol (18) was obtained using morpholine as a nitrogen-containing nucleophile. The yield was 1.13 g (87%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.47 (s, 6 H, 2 CH_3); 2.44 (m, 2 H, CH_2); 2.44 (s, 3 H, $CH_{3(Pyr)}$); 2.50 (dd, 1 H, NCH_2, $^2J_{AB}$ = 12.0 Hz, $^3J_{AX}$ = 4.7 Hz); 2.54 (dd, 1 H, NCH_2, $^3J_{BX}$ = 9.4 Hz); 2.64 (m, 2 H, CH_2); 3.59 (br.s, 1 H, OH); 3.66—3.80 (m, 6 H, 2 CH_2, OCH_2); 4.05 (m, 1 H, CH); 4.51 (s, 2 H, $CH_{2(Pyr)}$); 4.69 (s, 2 H, $CH_{2(Pyr)}$); 4.84 (br.s, 1 H, OH); 4.92 and 4.96 (both AB system, 2 H, $CH_{2(Pyr)}$, ^2J = 16.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.87 ($CH_{3(Pyr)}$); 23.74 (2 CH_3); 53.79 (CH_2); 58.82 (CH_2); 59.04 (CH_2); 60.65 (CH_2); 61.22 (CH_2); 65.93 (CH); 67.03 (CH_2); 75.43 (CH_2); 102.68 (C); 129.44 (C_{Pyr}); 141.40 (C_{Pyr}); 148.24 (C_{Pyr}); 148.34 (C_{Pyr}); 149.34 (C_{Pyr}). MS, *m/z*: 383.2182 $[M + H]^+$. $C_{19}H_{31}N_2O_6$. Calculated for $C_{19}H_{32}N_2O_6$: 383.2182.

Oxirane ring opening with aliphatic oxygen-containing nucleophiles (general procedure). Sodium hydroxide (0.7 mmol) was added to a solution of compound **1a** (0.21 g, 0.70 mmol) in ethanol or propan-2-ol (15.0 mL). The reaction mixture was stirred for 48 h at 50 °C. The solvent was evaporated at reduced pressure, the product was purified by column chromatography (eluent ethyl acetate).

1-Ethoxy-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (19) was obtained by the procedure described above using ethanol as an oxygen-containing nucleophile. The yield was 0.09 g (39%), colorless crystals, m.p. 104 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.21 (t, 3 H, CH_3, ^3J = 7.0 Hz); 1.48 (s, 6 H, 2 CH_3); 2.45 (s, 3 H, $CH_{3(Pyr)}$); 3.51—3.63 (m, 4 H, $CH_3C\underline{H}_2O$ + $CHC\underline{H}_2O$); 3.77 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.7 Hz); 3.79 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.7 Hz); 4.12 (m, 1 H, CH); 4.53 (s, 2 H, $CH_{2(Pyr)}$); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.94 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 15.20 (CH_3); 18.80 ($CH_{3(Pyr)}$); 23.76 (2 CH_3); 58.82 (CH_2); 59.06 (CH_2); 61.18 (CH_2); 67.08 (CH); 69.56 (CH_2); 71.02 (CH_2); 74.15 (CH_2); 102.75 (C); 129.42 (C_{Pyr}); 141.46 (C_{Pyr}); 148.20 (C_{Pyr}); 148.42 (C_{Pyr}); 149.27 (C_{Pyr}). MS, *m/z*: 342.1917 $[M + H]^+$. $C_{17}H_{28}NO_6$. Calculated for $C_{17}H_{29}NO_6$: 342.1917.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro-[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-isopropoxypropan-2-ol (20) was obtained using propan-2-ol as an oxygen-containing nucleophile. The yield was 0.17 g (68%), colorless crystals, m.p. 84—85 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.13 (d, 6 H, 2 CH_3, ^3J = 6.1 Hz); 1.44 (s, 6 H, 2 CH_3); 2.40 (s, 3 H, $CH_{3(Pyr)}$); 3.58 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.8 Hz); 3.60 (dd, 1 H, OCH_2, $^3J_{BX}$ = 5.0 Hz); 3.64 (sept, 1 H, $C\underline{H}(CH_3)_2$); 3.78 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.7 Hz); 3.80 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.6 Hz); 4.09 (m, 1 H, CH); 4.56 (s, 2 H, $CH_{2(Pyr)}$); 4.72 (s, 2 H, $CH_{2(Pyr)}$); 4.96 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.65 ($CH_{3(Pyr)}$); 22.06 ($\underline{C}H_3CH_3CH$); 22.14 ($CH_3\underline{C}H_3CH$); 23.76 (2 CH_3); 58.89 (CH_2); 59.04 (CH_2); 60.92 (CH_2); 68.49 (CH_2); 69.68 (CH); 72.53 (CH_2); 74.23 (CH_2); 102.79 (C); 129.66 (C_{Pyr}); 142.04 (C_{Pyr}); 148.07 (C_{Pyr}); 148.31 (C_{Pyr}); 149.43 (C_{Pyr}). MS, *m/z*: 356.2073 $[M + H]^+$. $C_{18}H_{30}NO_6$. Calculated for $C_{18}H_{31}NO_6$: 356.2073.

Oxirane ring opening with sulfur-containing and aromatic oxygen-containing nucleophiles (general procedure). The starting epoxide **1a** (0.15 g, 0.51 mmol) was added to a solution of sulfur-containing or aromatic oxygen-containing nucleophile (1.0 mmol) and sodium hydride (0.02 g, 1.0 mmol) in dimethylformamide (15.0 mL). The reaction mixture was stirred for 3—5 days at 70 °C, reaction progress was monitored by TLC. The solvent was evaporated at reduced pressure, the product was purified by column chromatography (eluent ethyl acetate).

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro-[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-phenoxypropan-2-ol (21) was obtained using phenol as an oxygen-containing nucleophile. The yield was 0.16 g (79%), colorless crystals, m.p. 114 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.47 (s, 6 H, 2 CH_3); 2.47 (s, 3 H, $CH_{3(Pyr)}$); 2.79 (br.s, 1 H, OH); 3.94 (d, 2 H, OCH_2, ^3J = 4.9 Hz); 4.17 (d, 2 H, OCH_2, ^3J = 5.4 Hz); 4.36 (m, 1 H, CH); 4.54 (s, 2 H,

$CH_{2(Pyr)}$); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.94 (s, 2 H, $CH_{2(Pyr)}$); 6.92—7.34 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.91 ($CH_{3(Pyr)}$); 23.74 (2 CH_3); 58.81 (CH_2); 59.03 (CH_2); 61.12 (CH_2); 68.20 (CH_2); 69.27 (CH); 73.75 (CH_2); 102.79 (C); 114.61 (C_{Ar}); 121.57 (C_{Ar}); 129.42 (C_{Ar}); 129.74 (C_{Ar}); 141.46 (C_{Ar}); 148.31 (C_{Ar}); 148.38 (C_{Ar}); 149.15 (C_{Ar}); 158.33 (C_{Ar}). MS, *m/z*: 390.1929 $[M + H]^+$. $C_{21}H_{28}NO_6$. Calculated for $C_{21}H_{29}NO_6$: 390.1917.

1-(4-*tert*-Butylphenoxy)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (22) was obtained using 4-*tert*-butylphenol as an oxygen-containing nucleophile. The yield was 0.14 g (60%), colorless crystals, m.p. 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.30 (s, 9 H, 3 CH_3); 1.47 (s, 6 H, 2 CH_3); 2.49 (s, 3 H, $CH_{3(Pyr)}$); 2.60 (br.s, 1 H, OH); 3.92 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.4 Hz); 3.93 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.8 Hz); 4.15 (d, 2 H, $CHC\underline{H}_2O$, ^3J = 5.3 Hz); 4.35 (m, 1 H, CH); 4.55 (s, 2 H, $CH_{2(Pyr)}$); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.81 (br.s, 1 H, OH); 4.94 (s, 2 H, $CH_{2(Pyr)}$); 6.85—7.34 (m, 4 H, C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.90 ($CH_{3(Pyr)}$); 23.73 (2 CH_3); 31.61 (3 CH_3); 34.22 ($\underline{C}(CH_3)_3$); 58.82 (CH_2); 59.05 (CH_2); 61.16 (CH_2); 68.29 (CH); 69.27 (CH_2); 73.81 (CH_2); 102.76 (C); 114.09 (2 CH_{Ar}); 126.50 (2 CH_{Ar}); 129.46 (C_{Ar}); 141.45 (C_{Ar}); 144.25 (C_{Ar}); 148.25 (C_{Ar}); 148.38 (C_{Ar}); 149.18 (C_{Ar}); 156.06 (C_{Ar}). MS, *m/z*: 446.2543 $[M + H]^+$. $C_{25}H_{36}NO_6$. Calculated for $C_{25}H_{37}NO_6$: 446.2543.

1-(2,4-Di-*tert*-butylphenoxy)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-propan-2-ol (23) was obtained using 2,4-di-*tert*-butylphenol as an oxygen-containing nucleophile. The yield was 0.14 g (56%), colorless crystals, m.p. 82—83 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.32 (s, 9 H, 3 CH_3); 1.41 (s, 9 H, 3 CH_3); 1.47 (s, 6 H, 2 CH_3); 2.48 (s, 3 H, $CH_{3(Pyr)}$); 3.04 (br.s, 1 H, OH); 3.95 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 6.2 Hz); 4.01 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.0 Hz); 4.18 (dd, 1 H, OCH_2, $^2J_{AB}$ = 10.0 Hz, $^3J_{AX}$ = = 5.4 Hz); 4.18 (dd, 1 H, OCH_2, $^3J_{BX}$ = 5.8 Hz); 4.44 (m, 1 H, CH); 4.55 (s, 2 H, $CH_{2(Pyr)}$); 4.72 (s, 2 H, $CH_{2(Pyr)}$); 4.96 (s, 2 H, $CH_{2(Pyr)}$); 6.80—7.40 (m, 3 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.90 ($CH_{3(Pyr)}$); 23.72 (2 CH_3); 30.19 (3 CH_3); 31.67 (3 CH_3); 34.40 ($\underline{C}CH_3$); 35.11 ($\underline{C}CH_3$); 58.78 (CH_2); 59.07 (CH_2); 61.20 (CH_2); 68.40 (CH); 69.60 (CH_2); 74.62 (CH_2); 102.76 (C); 111.56 (C_{Ar}); 123.63 (C_{Ar}); 124.21 (C_{Ar}); 129.54 (C_{Ar}); 137.18 (C_{Ar}); 141.45 (C_{Ar}); 143.41 (C_{Ar}); 148.33 (C_{Ar}); 149.17 (C_{Ar}); 154.80 (C_{Ar}). MS, *m/z*: 502.3169 $[M + H]^+$. $C_{29}H_{44}NO_6$. Calculated for $C_{29}H_{45}NO_6$: 502.3169.

1-(4-*tert*-Butyl-2-(hydroxymethyl)phenoxy)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]-pyridin-9-yl]oxy}propan-2-ol (24) was obtained using 4-*tert*-butyl-2-hydroxymethylphenol as an oxygen-containing nucleophile. The yield was 0.19 g (80%), colorless crystals, m.p. 64—65 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.28 (s, 9 H, 3 CH_3); 1.43 (s, 6 H, 2 CH_3); 2.40 (s, 3 H, $CH_{3(Pyr)}$); 3.84 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.7 Hz); 3.87 (dd, 1 H, OCH_2, $^3J_{BX}$ = 5.3 Hz); 4.16 (dd, 1 H, OCH_2, $^2J_{AB}$ = 10.0 Hz, $^3J_{AX}$ = 5.6 Hz); 4.19 (dd, 1 H, OCH_2, $^3J_{BX}$ = 3.9 Hz); 4.28 (m, 1 H, CH); 4.50 (s, 2 H, $CH_{2(Pyr)}$); 4.60 and 4.66 (both AB system, 2 H, $C\underline{H}_2OH$, $^2J_{AB}$ = 12.0 Hz); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.88 (s, 2 H, $CH_{2(Pyr)}$); 6.77—7.34 (m, 3 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.72 ($CH_{3(Pyr)}$); 23.65 (2 CH_3); 31.55 (3 CH_3); 34.19 ($\underline{C}(CH_3)_3$); 58.62 (CH_2); 59.22 (CH_2); 61.43 (CH_2); 61.93 (CH_2); 69.06 (CH); 69.52 (CH_2); 73.68 (CH_2); 102.73 (C); 111.96 (C_{Ar}); 125.97 (C_{Ar}); 127.01 (C_{Ar}); 128.70 (C_{Ar}); 129.81 (C_{Ar}); 141.34 (C_{Ar}); 144.10 (C_{Ar}); 148.30 (C_{Ar}); 148.47 (C_{Ar}); 149.17 (C_{Ar}); 154.78 (C_{Ar}). MS, *m/z*: 476.2648 $[M + H]^+$. $C_{26}H_{38}NO_7$. Calculated for $C_{26}H_{39}NO_7$: 476.2648.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]-dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(pyridin-3-yloxy)propan-2-ol (25) was obtained using 3-hydroxypyridine as an oxygen-containing nucleophile. The yield was 0.12 g (58%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.47 (s, 6 H, 2 CH_3); 2.45 (s, 3 H, $CH_{3(Pyr)}$); 3.94 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.4 Hz); 3.95 (1 H, OCH_2, $^3J_{BX}$ = 4.6 Hz); 4.17—4.26 (m, 2 H, OCH_2); 4.38 (m, 1 H, CH); 4.55 (s, 2 H, $CH_{2(Pyr)}$); 4.72 (s, 2 H, $CH_{2(Pyr)}$); 4.93 (s, 2 H, $CH_{2(Pyr)}$); 7.17—8.39 (m, 4 H, C_5H_4N). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.80 ($CH_{3(Pyr)}$); 23.68 (2 CH_3); 58.70 (CH_2); 59.10 (CH_2); 61.29 (CH_2); 68.79 (CH); 69.89 (CH_2); 73.72 (CH_2); 102.76 (C); 121.46 (CH_{Ar}); 124.17 (CH_{Ar}); 129.65 (C_{Ar}); 137.80 (C_{Ar}); 141.39 (C_{Ar}); 142.64 (C_{Ar}); 148.30 (C_{Ar}); 148.48 (C_{Ar}); 149.09 (C_{Ar}); 154.77 (C_{Ar}). MS, *m/z*: 391.1864 $[M + H]^+$. $C_{20}H_{27}N_2O_6$. Calculated for $C_{20}H_{28}N_2O_6$: 391.1864.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]-dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(isopropylthio)propan-2-ol (26) was obtained using isopropylthiol as a sulfur-containing nucleophile. The yield was 0.13 g (68%), colorless crystals, m.p. 65—66 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.25 (d, 6 H, 2 CH_3, ^3J = 6.7 Hz); 1.45 (s, 6 H, 2 CH_3); 2.40 (s, 3 H, $CH_{3(Pyr)}$); 2.70 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.2 Hz, $^3J_{AX}$ = 7.2 Hz); 2.81 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.7 Hz); 2.94 (sept, 1 H, $C\underline{H}(CH_3)_2$); 3.30 (br.s, 1 H, OH); 3.73 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.2 Hz, $^3J_{AX}$ = 5.8 Hz); 3.76 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.0 Hz); 4.01 (m, 1 H, CH); 4.49 (s, 2 H, $CH_{2(Pyr)}$); 4.68 (s, 2 H, $CH_{2(Pyr)}$); 4.90 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.84 ($CH_{3(Pyr)}$); 23.53 (2 CH_3); 23.69 (2 CH_3); 34.14 (CH_2); 35.62 (CH); 58.80 (CH_2); 59.04 (CH_2); 61.26 (CH_2); 69.26 (CH); 75.75 (CH_2); 102.66 (C); 129.54 (C_{Pyr}); 141.13 (C_{Pyr}); 148.25 (C_{Pyr}); 148.28 (C_{Pyr}); 149.14 (C_{Pyr}). MS, *m/z*: 372.1845 $[M + H]^+$. $C_{18}H_{30}NO_5S$. Calculated for $C_{18}H_{31}NO_5S$: 372.1845.

1-(Butylthio)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (27) was obtained using *n*-butylthiol as a sulfur-containing nucleophile. The yield was 0.09 g (46%), colorless crystals, m.p. 79 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.89 (t, 3 H, CH_3, ^3J = 7.3 Hz); 1.38 (m, 2 H, CH_2); 1.46 (s, 6 H, 2 CH_3); 1.55 (m, 2 H, CH_2); 2.41 (s, 3 H, $CH_{3(Pyr)}$); 2.54 (t, 2 H, CH_2, ^3J = 7.3 Hz); 2.68 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.2 Hz, $^3J_{AX}$ = 7.6 Hz); 2.80 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.5 Hz); 3.29 (br.s, 1 H, OH); 3.74 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.10 Hz); 3.76 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.11 Hz); 4.02 (m, 1 H, CH); 4.50 (s, 2 H, $CH_{2(Pyr)}$); 4.68 (s, 2 H, $CH_{2(Pyr)}$); 4.91 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 13.72 ($CH_{3(BuS)}$); 18.90 ($CH_{3(Pyr)}$); 21.96 (CH_2); 23.68 (2 CH_3); 31.80 (CH_2); 32.35 (CH_2); 35.74 (CH_2); 58.80 (CH_2); 59.03 (CH_2); 61.25 (CH_2); 69.03 (CH); 75.66 (CH_2); 102.70 (C); 129.51 (C_{Pyr}); 141.34 (C_{Pyr}); 148.26 (C_{Pyr}); 149.12 (C_{Pyr}). MS, *m/z*: 386.2008 $[M + H]^+$. $C_{19}H_{32}NO_5S$. Calculated for $C_{19}H_{33}NO_5S$: 386.2001.

1-(*tert*-Butylthio)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (28) was obtained using *tert*-butylthiol as a sulfur-containing nucleophile. The yield was 0.13 g (64%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.35 (s, 9 H, 3 CH_3); 1.49 (s, 6 H, 2 CH_3); 2.50 (s, 3 H, $CH_{3(Pyr)}$); 2.77 (dd, 1 H, SCH_2, $^2J_{AB}$ = 12.8 Hz, $^3J_{AX}$ = 7.0 Hz); 2.86 (dd, 1 H, SCH_2,

$^3J_{BX}$ = 5.6 Hz); 2.95 (br.s, 1 H, OH); 3.77 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 6.0 Hz); 3.81 (dd, 1 H, OCH_2, $^3J_{BX}$ = = 4.0 Hz); 4.07 (m, 1 H, CH); 4.56 (s, 2 H, $CH_{2(Pyr)}$); 4.72 (s, 2 H, $CH_{2(Pyr)}$); 4.97 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.80 ($CH_{3(Pyr)}$); 23.68 (2 CH_3); 31.03 (CH_2); 32.00 (CH_2); 42.66 ($\underline{C}(CH_3)_3$); 58.84 (CH_2); 59.04 (CH_2); 61.21 (CH_2); 69.70 (CH); 75.91 (CH_2); 102.68 (C); 129.61 (C_{Pyr}); 141.51 (C_{Pyr}); 148.26 (C_{Pyr}); 149.18 (C_{Pyr}). MS, *m/z*: 386.2001 $[M + H]^+$. $C_{19}H_{32}NO_5S$. Calculated for $C_{19}H_{33}NO_5S$: 386.2001.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]-dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(phenylthio)propan-2-ol (29) was obtained using thiophenol as a sulfur-containing nucleophile. The yield was 0.15 g (71%), colorless crystals, m.p. 85 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.39 (s, 6 H, 2 CH_3); 2.31 (s, 3 H, $CH_{3(Pyr)}$); 3.05 (dd, 1 H, CH_2, $^2J_{AB}$ = 13.7 Hz, $^3J_{AX}$= 7.0 Hz); 3.12 (dd, 2 H, SCH_2, $^3J_{BX}$ = 6.0 Hz); 3.46 (br.s, 1 H, OH); 3.71 (d, 2 H, OCH_2, ^3J = 4.7 Hz); 3.96 (m, 1 H, CH); 4.43 (s, 2 H, $CH_{2(Pyr)}$); 4.62 (s, 2 H, $CH_{2(Pyr)}$); 4.82 (s, 2 H, $CH_{2(Pyr)}$); 7.09—7.32 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.67 ($CH_{3(Pyr)}$); 23.56 (2 CH_3); 37.18 (CH_2); 58.63 (CH_2); 58.99 (CH_2); 61.28 (CH_2); 68.85 (CH); 75.31 (CH_2); 102.54 (C); 126.52 (C_{Ar}); 129.02 (C_{Ar}); 129.64 (C_{Ar}); 135.17 (C_{Ar}); 141.27 (C_{Ar}); 148.14 (C_{Ar}); 148.24 (C_{Ar}); 149.03 (C_{Ar}); 162.59 (C_{Ar}). MS, *m/z*: 406.1684 $[M + H]^+$. $C_{21}H_{28}NO_5S$. Calculated for $C_{21}H_{29}NO_5S$: 406.1688.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]-dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(2-tolylthio)propan-2-ol (30) was obtained using 2-methylthiophenol as a sulfur-containing nucleophile. The yield was 0.06 g (30%), colorless crystals, m.p. 107—108 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.49 (s, 6 H, 2 CH_3); 2.41 (s, 3 H, $CH_{3(Pyr)}$); 2.44 (s, 3 H, $CH_{3(Ph)}$); 3.12 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.6 Hz, $^3J_{AX}$ = 7.0 Hz); 3.19 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.9 Hz); 3.83 (d, 2 H, OCH_2, ^3J = 4.7 Hz); 4.06 (m, 1 H, CH); 4.53 (s, 2 H, $CH_{2(Pyr)}$); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.93 (s, 2 H, $CH_{2(Pyr)}$); 7.08—7.43 (m, 4 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.95 ($CH_{3(Pyr)}$); 20.63 ($CH_{3(Ar)}$); 23.76 (2 CH_3); 36.89 (CH_2); 58.85 (CH_2); 59.04 (CH_2); 61.18 (CH_2); 69.04 (CH); 75.48 (CH_2); 102.77 (C); 126.77 (C_{Ar}); 126.82 (C_{Ar}); 129.40 (C_{Ar}); 129.47 (C_{Ar}); 130.59 (C_{Ar}); 134.11 (C_{Ar}); 138.52 (C_{Ar}); 141.39 (C_{Ar}); 148.32 (C_{Ar}); 149.12 (C_{Ar}). MS, *m/z*: 420.1845 $[M + H]^+$. $C_{22}H_{30}NO_5S$. Calculated for $C_{22}H_{31}NO_5S$: 420.1845.

1-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]-dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(4-tolylthio)propan-2-ol (31) was obtained using 4-methylthiophenol as a sulfur-containing nucleophile. The yield was 0.16 g (73%), colorless crystals, m.p. 70—71 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.39 (s, 6 H, 2 CH_3); 2.22 (s, 3 H, $CH_{3(Pyr)}$); 2.30 (s, 3 H, $CH_{3(Ph)}$); 2.99 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.7 Hz, $^3J_{AX}$ = 7.0 Hz); 3.06 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.9 Hz); 3.47 (br.s, 1 H, OH); 3.69 (dd, 1 H, OCH_2, $^2J_{AB}$ = 10.0 Hz, $^3J_{AX}$ = 5.6 Hz); 3.70 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.1 Hz); 3.92 (m, 1 H, CH); 4.43 (s, 2 H, $CH_{2(Pyr)}$); 4.62 (s, 2 H, $CH_{2(Pyr)}$); 4.81 (s, 2 H, $CH_{2(Pyr)}$); 4.88 (br.s, 1 H, OH); 7.00—7.22 (m, 4 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.75 ($CH_{3(Pyr)}$); 21.03 ($CH_{3(Ar)}$); 23.64 (2 CH_3); 38.15 (CH_2); 58.70 (CH_2); 59.04 (CH_2); 61.30 (CH_2); 68.88 (CH); 75.37 (CH_2); 102.63 (C); 129.62 (C_{Ar}); 129.92 (2 $CH_{(Ar)}$); 130.74 (2 $CH_{(Ar)}$); 131.12 (C_{Ar}); 137.02 (C_{Ar}); 141.29 (C_{Ar}); 148.21 (C_{Ar}); 148.28 (C_{Ar}); 149.06 (C_{Ar}). MS, *m/z*: 420.1845 $[M + H]^+$. $C_{22}H_{30}NO_5S$. Calculated for $C_{22}H_{31}NO_5S$: 420.1845.

1-(2-Chlorophenylthio)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (32) was obtained using 2-chlorothiophenol as a sulfur-containing nucleophile. The yield was 0.18 g (82%), colorless crystals, m.p. 111 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.51 (s, 6 H, 2 CH_3); 2.45 (s, 3 H, $CH_{3(Pyr)}$); 3.19 (dd, 1 H, SCH_2, $^2J_{AB}$ = = 13.5 Hz, $^3J_{AX}$ = 6.9 Hz); 3.27 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.9 Hz); 3.51 (br.s, 1 H, OH); 3.86 (d, 2 H, OCH_2, ^3J = 4.7 Hz); 4.10 (m, 1 H, CH); 4.56 (s, 2 H, $CH_{2(Pyr)}$); 4.73 (s, 2 H, $CH_{2(Pyr)}$); 4.96 (s, 2 H, $CH_{2(Pyr)}$); 7.17—7.45 (m, 4 H, C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.85 ($CH_{3(Pyr)}$); 23.68 (2 CH_3); 36.51 (CH_2); 58.76 (CH_2); 59.04 (CH_2); 61.23 (CH_2); 68.91 (CH); 75.36 (CH_2); 102.74 (C); 127.42 ($CH_{(Ph)}$); 127.64 (C_{Ar}); 129.60 (C_{Ar}); 130.03 (C_{Ar}); 130.11 (C_{Ar}); 134.34 (C_{Ar}); 134.69 (C_{Ar}); 141.37 (C_{Ar}); 148.25 (C_{Ar}); 148.33 (C_{Ar}); 149.03 (C_{Ar}). MS, *m/z*: 440.1299 $[M + H]^+$. $C_{21}H_{27}ClNO_5S$. Calculated for $C_{21}H_{28}ClNO_5S$: 440.1298.

1-(4-Chlorophenylthio)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (33) was obtained using 4-chlorothiophenol as a sulfur-containing nucleophile. The yield was 0.17 g (74%), colorless crystals, m.p. 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.49 (s, 6 H, 2 CH_3); 2.45 (s, 3 H, $CH_{3(Pyr)}$); 2.93 (br.s, 1 H, OH); 3.13 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.7 Hz, $^3J_{AX}$ = 7.2 Hz); 3.22 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.6 Hz); 3.83 (d, 2 H, OCH_2, ^3J = 4.8 Hz); 4.04 (m, 1 H, CH); 4.54 (s, 2 H, $CH_{2(Pyr)}$); 4.71 (s, 2 H, $CH_{2(Pyr)}$); 4.82 (br.s, 1 H, OH); 4.91 (s, 2 H, $CH_{2(Pyr)}$); 7.26—7.36 (m, 4 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.99 ($CH_{3(Pyr)}$); 23.76 ($CH_{3(Ar)}$); 38.00 (2 CH_3); 58.18 (CH_2); 59.02 (CH_2); 61.14 (CH_2); 68.95 (CH); 75.28 (CH_2); 102.81 (C); 129.48 (C_{Ar}); 131.59 (C_{Ar}); 133.15 (C_{Ar}); 133.50 (C_{Ar}); 141.37 (C_{Ar}); 148.28 (C_{Ar}); 148.38 (C_{Ar}); 149.06 (C_{Ar}). MS, *m/z*: 440.1299 $[M + H]^+$. $C_{21}H_{27}ClNO_5S$. Calculated for $C_{21}H_{28}ClNO_5S$: 440.1298.

1-(2,4-Dichlorophenylthio)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]-oxy}propan-2-ol (34) was obtained using 2,4-dichlorothiophenol as a sulfur-containing nucleophile. The yield was 0.12 g (51%), colorless crystals, m.p. 122—123 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.47 (s, 6 H, 2 CH_3); 2.42 (s, 3 H, $CH_{3(Pyr)}$); 3.13 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.5 Hz, $^3J_{AX}$ = 7.0 Hz); 3.21 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.7 Hz); 3.77—3.86 (m, 2 H, OCH_2); 4.06 (m, 1 H, CH); 4.52 (s, 2 H, $CH_{2(Pyr)}$); 4.69 (s, 2 H, $CH_{2(Pyr)}$); 4.90 (s, 2 H, $CH_{2(Pyr)}$); 7.16—7.45 (m, 3 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.91 ($CH_{3(Pyr)}$); 23.72 (2 CH_3); 36.76 (CH_2); 58.76 (CH_2); 59.05 (CH_2); 61.19 (CH_2); 68.95 (CH); 75.30 (CH_2); 102.80 (C); 127.74 (C_{Ar}); 129.59 (C_{Ar}); 129.87 (C_{Ar}); 131.07 (C_{Ar}); 133.02 (C_{Ar}); 133.11 (C_{Ar}); 135.49 (C_{Ar}); 141.38 (C_{Ar}); 148.24 (C_{Ar}); 148.35 (C_{Ar}); 148.99 (C_{Ar}). MS, *m/z*: 474.0909 $[M + H]^+$. $C_{21}H_{26}Cl_2NO_5S$. Calculated for $C_{21}H_{27}Cl_2NO_5S$: 474.0909.

3-(2-Fluorophenylthio)-1-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (35) was obtained using 2-fluorothiophenol as a sulfur-containing nucleophile. The yield was 0.05 g (25%), colorless crystals, m.p. 98—100 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.46 (s, 6 H, 2 CH_3); 2.39 (s, 3 H, $CH_{3(Pyr)}$); 3.08 (dd, 1 H, SCH_2, $^2J_{AB}$ = = 13.6 Hz, $^3J_{AX}$ = 7.1 Hz); 3.16 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.8 Hz); 3.75—3.83 (m, 2 H, OCH_2); 3.98 (m, 1 H, CH); 4.50 (s, 2 H, $CH_{2(Pyr)}$); 4.68 (s, 2 H, $CH_{2(Pyr)}$); 4.90 (s, 2 H, $CH_{2(Pyr)}$); 7.01—7.47 (m, 4 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.80

($CH_{3(Pyr)}$); 23.68 (2 CH_3); 37.37 (CH_2S, ^4J = 1.2 Hz); 58.74 (CH_2); 59.04 (CH_2); 61.23 (CH_2); 69.08 (CH); 75.29 (CH_2); 102.72 (C); 116.04 (C_{Ar}, ^2J = 22.7 Hz); 121.58 (C_{Ar}, ^2J = 17.8 Hz); 124.79 (C_{Ar}, ^3J = 3.5 Hz); 129.53 (C_{Ar}, ^3J = 6.1 Hz); 129.58 (C_{Ar}); 133.42 (C_{Ar}); 141.37 (C_{Ar}); 148.28 (C_{Ar}, ^4J = 2.7 Hz); 148.29 (C_{Ar}); 149.05 (C_{Ar}); 161.97 (C_{Ar}, ^1J = 245.7 Hz). MS, *m/z*: 424.1594 $[M + H]^+$. $C_{21}H_{27}FNO_5S$. Calculated for $C_{21}H_{28}FNO_5S$: 424.1594.

3-(4-Fluorophenylthio)-1-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (36) was obtained using 4-fluorothiophenol as a sulfur-containing nucleophile. The yield was 0.14 g (67%), colorless crystals, m.p. 92—93 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.50 (s, 6 H, 2 CH_3); 2.47 (s, 3 H, $CH_{3(Pyr)}$); 2.71 (br.d, 1 H, OH, ^3J = 2.9 Hz); 3.09 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.8 Hz, $^3J_{AX}$ = 7.4 Hz); 3.19 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.5 Hz); 3.83 (dd, 1 H, OCH_2, $^2J_{AB}$ = 9.6 Hz, $^3J_{AX}$ = 5.6 Hz); 3.83 (dd, 1 H, OCH_2, $^3J_{BX}$ = 4.4 Hz); 4.01 (m, 1 H, CH); 4.54 (s, 2 H, $CH_{2(Pyr)}$); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.77 (br.s, 1 H, OH); 4.92 (s, 2 H, $CH_{2(Pyr)}$); 6.99—7.48 (m, 4 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 19.02 ($CH_{3(Pyr)}$); 23.78 (2 CH_3); 39.13 (CH_2); 58.84 (CH_2); 59.01 (CH_2); 61.12 (CH_2); 68.89 (CH); 75.33 (CH_2); 102.81 (C); 116.45 (C_{Ar}, ^2J = 22.0 Hz); 129.43 (C_{Ar}); 129.87 (C_{Ar}, ^4J = 3.3 Hz); 133.24 (C_{Ar}, ^3J = 8.1 Hz); 141.36 (C_{Ar}); 148.29 (C_{Ar}); 149.11 (C_{Ar}); 162.29 (C_{Ar}, ^1J = 247.4 Hz); 162.69 (C_{Ar}). MS, *m/z*: 424.1594 $[M + H]^+$. $C_{21}H_{27}FNO_5S$. Calculated for $C_{21}H_{28}FNO_5S$: 424.1594.

1-(2-Bromophenylthio)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (37) was obtained using 2-bromothiophenol as a sulfur-containing nucleophile. The yield was 0.18 g (71%), colorless crystals, m.p. 115—116 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.49 (s, 6 H, 2 CH_3); 2.43 (s, 3 H, $CH_{3(Pyr)}$); 3.17 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.3 Hz, $^3J_{AX}$ = 6.8 Hz); 3.25 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.8 Hz); 3.70 (br.s, 1 H, OH); 3.80—3.89 (m, 2 H, OCH_2); 4.10 (m, 1 H, CH); 4.53 (s, 2 H, $CH_{2(Pyr)}$); 4.71 (s, 2 H, $CH_{2(Pyr)}$); 4.94 (s, 2 H, $CH_{2(Pyr)}$); 7.00—7.61 (m, 4 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.82 ($CH_{3(Pyr)}$); 23.68 (2 CH_3); 36.78 (CH_2); 58.73 (CH_2); 59.05 (CH_2); 61.25 (CH_2); 68.81 (CH); 75.36 (CH_2); 102.71 (C); 127.51 (C_{Ar}); 127.58 (C_{Ar}); 128.01 (C_{Ar}); 129.41 (C_{Ar}); 129.52 (C_{Ar}); 129.63 (C_{Ar}); 133.27 (C_{Ar}); 141.36 (C_{Ar}); 148.22 (C_{Ar}); 148.32 (C_{Ar}); 149.00 (C_{Ar}). MS, *m/z*: 484.0793 $[M + H]^+$. $C_{21}H_{27}BrNO_5S$. Calculated for $C_{21}H_{28}BrNO_5S$: 484.0793.

1-(4-Bromophenylthio)-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (38) was obtained using 4-bromothiophenol as a sulfur-containing nucleophile. The yield was 0.17 g (67%), colorless crystals, m.p. 93—94 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.49 (s, 6 H, 2 CH_3); 2.44 (s, 3 H, $CH_{3(Pyr)}$); 2.98 (br.s, 1 H, OH); 3.13 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.7 Hz, $^3J_{AX}$ = 7.2 Hz); 3.21 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.6 Hz); 3.82 (d, 2 H, OCH_2, ^3J = 4.8 Hz); 4.04 (m, 1 H, CH); 4.53 (s, 2 H, $CH_{2(Pyr)}$); 4.70 (s, 2 H, $CH_{2(Pyr)}$); 4.91 (s, 2 H, $CH_{2(Pyr)}$); 7.20—7.52 (m, 4 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.99 ($CH_{3(Pyr)}$); 23.76 (2 CH_3); 37.74 (CH_2); 58.80 (CH_2); 59.01 (CH_2); 61.14 (CH_2); 68.93 (CH); 75.26 (CH_2); 102.80 (C); 120.95 (C_{Ar}); 129.43 (C_{Ar}); 131.65 (2 C_{Ar}); 132.37 (2 C_{Ar}); 134.20 (C_{Ar}); 141.35 (C_{Ar}); 148.26 (C_{Ar}); 148.35 (C_{Ar}); 149.04 (C_{Ar}). MS, *m/z*: 484.0793 $[M + H]^+$. $C_{21}H_{27}BrNO_5S$. Calculated for $C_{21}H_{28}BrNO_5S$: 484.0793.

1-Benzylthio-3-{[6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (39) was obtained using benzylthiol as a sulfur-containing nucleophile. The yield was 0.16 g (74%), colorless crystals, m.p. 98 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.44 (s, 6 H, 2 CH_3); 2.34 (s, 3 H, $CH_{3(Pyr)}$); 2.58 (dd, 1 H, SCH_2, $^2J_{AB}$ = 13.7 Hz, $^3J_{AX}$ = 7.2 Hz); 2.66 (dd, 1 H, SCH_2, $^3J_{BX}$ = 5.6 Hz); 3.60—3.68 (m, 2 H, OCH_2, ^3J = 4.8 Hz); 3.71 (s, 2 H, CH_2Ph); 3.91 (m, 1 H, CH); 4.09 (br.s, 1 H, OH); 4.48 (s, 2 H, $CH_{2(Pyr)}$); 4.66 (s, 2 H, $CH_{2(Pyr)}$); 4.85 (s, 2 H, $CH_{2(Pyr)}$); 7.18—7.40 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 18.72 ($CH_{3(Pyr)}$); 23.63 (2 CH_3); 34.67 (SCH_2); 36.68 (SCH_2); 58.70 (CH_2); 59.02 (CH_2); 61.25 (CH); 69.12 (CH_2); 75.62 (CH_2); 102.62 (C); 127.22 (C_{Ar}); 128.59 (C_{Ar}); 128.85 (C_{Ar}); 129.62 (C_{Ar}); 137.92 (C_{Ar}); 141.32 (C_{Ar}); 148.19 (C_{Ar}); 148.26 (C_{Ar}); 149.05 (C_{Ar}). MS, *m/z*: 420.1845 $[M + H]^+$. $C_{22}H_{30}NO_5S$. Calculated for $C_{22}H_{31}NO_5S$: 420.1845.

3-{[6-(Hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro-[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-1,2-diol (40). A solution of compound **1a** (0.20 g, 0.68 mmol) and KOH (0.05 g, 0.82 mmol) in water (25.0 mL) was stirred for 3 days at 50 °C. The solvent was evaporated at reduced pressure, the product was purified by column chromatography (eluent acetone). The yield was 0.07 g (31%), colorless crystals, m.p. 149—150 °C. ^{1}H NMR (400 MHz, CD_3OD), δ: 1.48 (s, 6 H, 2 CH_3); 2.45 (s, 3 H, $CH_{3(Pyr)}$); 3.66 (dd, 1 H, OCH_2, $^2J_{AB}$ = 11.2 Hz, $^3J_{AX}$ = 5.8 Hz); 3.68 (dd, 1 H, OCH_2, $^3J_{BX}$ = 5.7 Hz); 3.76 (dd, 1 H, OCH_2, $^2J_{AB}$ = = 9.6 Hz, $^3J_{AX}$ = 6.1 Hz); 3.86 (dd, 1 H, OCH_2, $^3J_{BX}$ = 3.9 Hz); 3.92—4.01 (m, 1 H, CH); 4.59 (s, 2 H, $CH_{2(Pyr)}$); 4.94 (s, 2 H, $CH_{2(Pyr)}$); 5.01 (s, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, CD_3OD), δ: 18.51 ($CH_{3(Pyr)}$); 23.97 (2 CH_3); 59.82 (CH_2); 61.22 (CH); 63.85 (CH_2); 64.19 (CH_2); 72.23 (CH_2); 75.80 (CH_2); 103.74 (C); 133.96 (C_{Pyr}); 143.44 (C_{Pyr}); 149.98 (C_{Pyr}); 151.24 (C_{Pyr}); 151.32 (C_{Pyr}). MS, *m/z*: 314.1604 $[M + H]^+$. $C_{15}H_{24}NO_6$. Calculated for $C_{15}H_{25}NO_6$: 314.1604.

[3,8-Dimethyl-9-(oxiran-2-ylmethoxy)-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-6-yl]methanol (1b) was obtained similarly to compound **1a** by method *iii*, using the corresponding acetal instead of ketal **2**. The yield was 0.68 g (58%), colorless crystals, m.p. 95—96 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (a mixture of diastereomers): 1.41 (d, 3 H, CH_3, ^3J = 5.2 Hz); 2.52 (s, 3 H, $CH_{3(Pyr)}$); 2.70 (td, 1 H, CH_2, ^2J = 4.7 Hz, ^3J = 2.7 Hz); 2.90 (t, 1 H, CH_2, ^3J = 4.5 Hz); 3.31—3.37 (m, 1 H, CH); 3.60—3.70 (m, 1 H, CH_2); 4.07—4.17 (m, 1 H, CH_2); 4.54—4.65 (m, 3 H, $CH_{2(Pyr)}$, C<u>H</u>CH_3); 4.84 (dd, 3 H, $CH_{2(Pyr)}$, OH, ^2J = 15.4 Hz); 5.10—5.18 (m, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (a mixture of diastereomers): 18.92 ($CH_{3(Pyr)}$); 19.36 (CH_3); 19.41 (CH_3); 44.43 (CH_2); 44.45 (CH_2); 50.23 (CH); 50.26 (CH); 61.18 (CH_2); 61.75 (CH_2); 61.86 (CH_2); 62.16 (CH_2); 62.21 (CH_2); 74.65 (CH_2); 74.73 (CH_2); 102.42 (CH); 102.52 (CH); 129.98 (C_{Pyr}); 141.90 (C_{Pyr}); 148.57 (C_{Pyr}); 148.97 (C_{Pyr}); 148.99 (C_{Pyr}); 149.46 (C_{Pyr}); 149.51 (C_{Pyr}). MS, *m/z*: 282.1336 $[M + H]^+$. $C_{14}H_{19}NO_5$. Calculated for $C_{14}H_{20}NO_5$: 282.1336.

1-{[6-(Hydroxymethyl)-3,8-dimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(isopropylamino)propan-2-ol (41) was obtained similarly to compound **6** from epoxide **1b** and isopropylamine. The yield was 0.55 g (48%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ (a mixture of diastereomers): 1.10 (d, 6 H, 2 CH_3, ^3J = 5.9 Hz); 1.33 (d, 3 H, CH_3, ^3J = 5.2 Hz); 1.91 (s, 1 H, NH); 2.38 (s, 3 H, $CH_{3(Pyr)}$); 2.69—2.94 (ABX system, 2 H, NC<u>H</u>$_2$CH, NC<u>H</u>$(CH_3)_2$); 3.61—3.72 (ABX system, 2 H, OC<u>H</u>$_2$CH); 4.01—4.11 (ABX system, 1 H, CH); 4.45—4.90 (m, 7 H, 2 $CH_{2(Pyr)}$, C<u>H</u>CH_3, 2 OH); 5.07 (m, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (a mixture of diaste-

reomers): 18.80 ($CH_{3(Pyr)}$); 19.35 (CH_3); 21.97 (CH_3); 22.01 (CH_3); 48.86 (CH_2); 49.30 (CH); 61.56 (CH_2); 61.66 (CH_2); 61.72 (CH_2); 62.43 (CH_2); 68.11 (CH); 76.16 (CH_2); 102.36 (CH); 102.41 (CH); 130.32 (C_{Pyr}); 141.64 (C_{Pyr}); 148.82 (C_{Pyr}); 148.92 (C_{Pyr}); 149.37 (C_{Pyr}). MS, *m/z*: 341.2072 $[M + H]^+$. $C_{17}H_{29}N_2O_5$. Calculated for $C_{17}H_{30}N_2O_5$: 341.2071.

1-(*tert*-Butylamino)-3-{[6-(hydroxymethyl)-3,8-dimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (42) was obtained similarly to compound **7** from epoxide **1b** and *tert*-butylamine. The yield was 1.11 g (93%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ (a mixture of diastereomers): 1.18 (s, 9 H, 3 CH_3); 1.30 (d, 3 H, CH_3, ^3J = 4.7 Hz); 1.88 (s, 1 H, NH); 2.35 (s, 3 H, $CH_{3(Pyr)}$); 2.73—2.93 (ABX system, 2 H, NC$\underline{H}_2$CH); 3.66 (ABX system, 2 H, OC$\underline{H}_2$CH); 4.06—4.16 (ABX system, 1 H, CH); 4.50 (s, 2 H, $CH_{2(Pyr)}$); 4.56 (d, 1 H, C$\underline{H}$CH$_3$, ^2J = 15.2 Hz); 4.76 (dd, 2 H, $CH_{2(Pyr)}$, ^2J = 15.3 Hz); 4.97—5.11 (m, 2 H, $CH_{2(Pyr)}$); 5.47 (br.s, 2 H, 2 OH). ^{13}C NMR (100 MHz, $CDCl_3$), δ (a mixture of diastereomers): 18.77 ($CH_{3(Pyr)}$); 19.29 (CH_3); 19.30 (CH_3); 24.67 (CH_2); 27.45 (3 CH_3); 44.62 (CH); 52.99 (CH_2); 61.61 (CH_2); 61.68 (CH_2); 67.63 (CH); 76.00 (CH_2); 102.29 (CH); 102.34 (CH); 130.40 (C_{Pyr}); 141.60 (C_{Pyr}); 148.84 (C_{Pyr}); 148.88 (C_{Pyr}); 149.35 (C_{Pyr}). MS, *m/z*: 355.2228 $[M + H]^+$. $C_{18}H_{31}N_2O_5$. Calculated for $C_{18}H_{32}N_2O_5$: 355.2227.

1-{[6-(Hydroxymethyl)-3,8-dimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(*tert*-pentylamino)propan-2-ol (43) was obtained similarly to compound **8** from epoxide **1b** and *tert*-amylamine. The yield was 0.59 g (47%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ (a mixture of diastereomers): 0.88 (t, 3 H, CH_3, ^3J = 7.5 Hz); 1.17 (s, 6 H, 2 CH_3); 1.35 (d, 3 H, CH_3, ^3J = 5.2 Hz); 1.53 (q, 2 H, C$\underline{H}_2$CH$_3$, ^3J = 7.4 Hz); 2.41 (s, 3 H, $CH_{3(Pyr)}$); 2.71—3.00 (ABX system, 2 H, NC$\underline{H}_2$CH); 3.66—3.79 (ABX system, 2 H, OC$\underline{H}_2$CH); 4.01—4.19 (ABX system, 1 H, CH); 4.54 (m, 2 H, $CH_{2(Pyr)}$); 4.58 (d, 1 H, C$\underline{H}$CH$_3$, ^2J = 15.2 Hz); 4.79 (dd, 2 H, $CH_{2(Pyr)}$, ^2J = 15.3 Hz); 5.02—5.14 (m, 2 H, $CH_{2(Pyr)}$); 5.26 (br.s, 2 H, 2 OH). ^{13}C NMR (100 MHz, $CDCl_3$), δ (a mixture of diastereomers): 8.21 (CH_3); 18.93 ($CH_{3(Pyr)}$); 19.37 (CH_3); 25.06 (CH_2); 25.11 (CH_2); 32.38 (CH_2); 44.41 (CH_2); 44.72 (CH_2); 55.79 (CH_2); 61.43 (CH_2); 61.79 (CH_2); 62.28 (CH_2); 62.31 (CH_2); 67.87 (CH); 76.07 (CH); 102.39 (CH); 102.41 (CH); 130.14 (C_{Pyr}); 141.69 (C_{Pyr}); 148.67 (C_{Pyr}); 148.90 (C_{Pyr}); 149.42 (C_{Pyr}). MS, *m/z*: 369.2384 $[M + H]^+$. $C_{19}H_{33}N_2O_5$. Calculated for $C_{19}H_{34}N_2O_5$: 369.2384.

1-{[6-(Hydroxymethyl)-3,8-dimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-(piperidin-1-yl)propan-2-ol (44) was obtained similarly to compound **17** from epoxide **1b** and piperidine. The yield was 0.81 g (65%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ (a mixture of diastereomers): 1.35 (d, 3 H, CH_3, ^3J = 5.2 Hz); 1.40—1.52 (m, 2 H, CH_2); 1.56—1.70 (m, 4 H, 2 CH_2); 2.41 (s, 3 H, $CH_{3(Pyr)}$); 2.47—2.77 (ABX system, 6 H, 2 CH_2, NC$\underline{H}_2$CH); 3.63—3.76 (ABX system, 2 H, OCH_2CH); 4.07—4.18 (ABX system, 1 H, CH); 4.47—4.61 (m, 3 H, C$\underline{H}$CH$_3$, $CH_{2(Pyr)}$); 4.65—4.81 (m, 4 H, $CH_{2(Pyr)}$, 2 OH, ^2J = 15.1 Hz); 5.04—5.15 (m, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (a mixture of diastereomers): 18.89 ($CH_{3(Pyr)}$); 19.38 (CH_3); 23.67 (CH_2); 25.29 (CH_2); 54.77 (CH_2); 60.80 (CH_2); 61.40 (CH_2); 61.80 (CH_2); 62.34 (CH_2); 65.63 (CH); 75.90 (CH_2); 102.41 (CH); 102.45 (CH); 130.08 (C_{Pyr}); 141.68 (C_{Pyr}); 148.57 (C_{Pyr}); 148.94 (C_{Pyr}); 149.45 (C_{Pyr}). MS, *m/z*: 367.2227 $[M + H]^+$. $C_{19}H_{31}N_2O_5$. Calculated for $C_{19}H_{32}N_2O_5$: 367.2227.

1-{[6-(Hydroxymethyl)-3,8-dimethyl-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}-3-morpholinopropan-2-ol (45) was obtained similarly to compound **18** from epoxide **1b** and morpholine. The yield was 0.87 g (70%), a yellow clear oily compound. ^{1}H NMR (400 MHz, $CDCl_3$), δ (a mixture of diastereomers): 1.30 (br.s, 3 H, CH_3); 2.00—2.69 (ABX system, 6 H, $N(CH_2)_2$, NC$\underline{H}_2$CH); 2.35 (s, 3 H, $CH_{3(Pyr)}$); 3.45—3.77 (ABX system, 6 H, 2 CH_2, OC$\underline{H}_2$CH); 3.98 (ABX system, 1 H, CH); 4.41—4.59 (m, 3 H, C$\underline{H}$CH$_3$, $CH_{2(Pyr)}$); 4.75 (dd, 2 H, $CH_{2(Pyr)}$, ^2J = 15.1 Hz); 5.03 (m, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (a mixture of diastereomers): 18.66 ($CH_{3(Pyr)}$); 19.22 (CH_3); 53.63 (CH_2); 60.51 (CH_2); 60.48 (CH_2); 61.56 (CH_2); 62.30 (CH_2); 65.87 (CH); 66.70 (CH_2); 75.63 (CH_2); 102.20 (CH); 102.24 (CH); 130.21 (C_{Pyr}); 141.52 (C_{Pyr}); 148.67 (C_{Pyr}); 148.78 (C_{Pyr}); 149.26 (C_{Pyr}). MS, *m/z*: 369.2020 $[M + H]^+$. $C_{18}H_{29}N_2O_6$. Calculated for $C_{18}H_{30}N_2O_6$: 369.2020.

1-Ethoxy-3-{[6-(hydroxymethyl)-3,8-dimethyl-1,5-dihydro-[1,3]dioxepino[5,6-*c*]pyridin-9-yl]oxy}propan-2-ol (46) was obtained similarly to compound **19** from epoxide **1b** and ethanol. The yield was 0.18 g (78%), colorless crystalline compound, m.p. 81—82 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (a mixture of diastereomers): 1.23 (t, 3 H, CH_3, ^3J = 7.0 Hz); 1.41 (d, 3 H, CH_3, ^3J = 5.3 Hz); 2.58 (s, 3 H, $CH_{3(Pyr)}$); 2.65 (br.s, 1 H, OH); 3.52—3.65 (ABX system, 4 H, $CH_3C\underline{H}_2O$, OC$\underline{H}_2$CH); 3.78—3.90 (ABX system, 2 H, CHC$\underline{H}_2$O); 4.08—4.21 (ABX system, 1 H, CH); 4.62—4.72 (m, 3 H, C$\underline{H}$CH$_3$, $CH_{2(Pyr)}$); 4.88 (dd, 2 H, $CH_{2(Pyr)}$, ^2J = 15.5 Hz); 5.12—5.22 (m, 2 H, $CH_{2(Pyr)}$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (a mixture of diastereomers): 15.23 (CH_3); 18.07 ($CH_{3(Pyr)}$); 19.30 (CH_3); 60.33 (CH_2); 61.72 (CH_2); 61.80 (CH_2); 62.13 (CH_2); 67.16 (CH); 69.57 (CH_2); 70.89 (CH_2); 74.92 (CH_2); 102.40 (CH); 102.45 (CH); 131.07 (C_{Pyr}); 148.13 (C_{Pyr}); 148.45 (C_{Pyr}); 149.97 (C_{Pyr}). MS, *m/z*: 328.1755 $[M + H]^+$. $C_{16}H_{26}NO_6$. Calculated for $C_{16}H_{27}NO_6$: 328.1755.

Biological studies. To improve the solubility in water, the compounds under study were converted to pyridinium tartrates using L-tartaric acid: the studied compound and L-tartaric acid (60 μmol each) were dissolved in MeOH, then the solvent was evaporated *in vacuo*.

Study of cytotoxicity of some pyridoxine derivatives. Cytotoxicity of some synthesized pyridoxine derivatives (see Table 1) was studied in HEK-293 cell line (human embryonic kidney cells 293) using a proliferative MTT-assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Promega). The cells were seeded in a 96-well plate at a concentration of 1000 cells per well and were cultured in DMEM culture meduum supplemented with 10% fetal calf serum, L-glutamine, and 1% penicillin—streptomycin (90 μL) according to the standard culturing conditions for 24 h. The cell viability was measured at 72 h post-treatment with test agent (10 μL). The concentration of the starting solutions was $2.82 \cdot 10^{-5}$ mol L^{-1}. Then, the medium was exchanged for the supplemented medium (80 μL), MTT solution (5 mg mL^{-1}) was added to a volume of 20 μL in each well and was incubated for 3.5 h. The solution was removed and DMSO (100 μL) was added to solubilize the formazan crystals. After 10 min, absorbance was determined at 555 nm (the reference wavelength 650 nm) by a TECAN plate reader. The results were presented in the percent ratio to the control sample, treat-

ed with PBS. For each compound tested, the IC_{50}, ($p < 0.05$) was generated from the dose—responce curve for each cell line.

Studies of atrial myocardial contractile activity in inbred rats upon action of compound 6. Experiments were carried out on isolated atrium strips of inbred rats (two-three months old, 280—320-g males). The study correspond to the "Guide for the Care and Use of Laboratory Animals" published by the American National Institute of Health (NIH, Publication No. 85-23, amended in 1996) and approved by the local ethics committee of the Kazan Federal University (No. 0.1.1.67-06/101/14, 12.06.2014). On the day of the experiment, rats were anesthetized by inhalation of 5% isoflurane (Abbott Laboratories), after which the hearts were rapidly excised and immersed in Krebs solution containing (mmol L^{-1}): NaCl, 137.0; NaH_2PO_4, 1.0; KCl, 5.0; $MgSO_4$, 1.0; $CaCl_2$, 2.2; $NaHCO_3$, 11.0; glucose, 11; ascorbic acid, 0.3; pH 7.2—7.4, atmosphere 95% O_2 and 5% CO_2.

To register the contractile activity of working myocardium, the 4—6-mm long and 0.2—0.4 mm in diameter tissue strips were excised from the right atrium and mounted in a special perfusion chamber (BIOPAC, Inc). In the experiment, the strips under constant perfusion with Krebs solution were stimulated by electric current with a frequency of 0.1 Hz using two silver electrodes. The strength of contractions was registered using a TDS 125C isometric transducer (BIOPAC, Inc). The effect of test compounds was analyzed in percents to the basal level. The Student's t-test for paired samples was used in the statistical processing of the results. Criterion $p < 0.05$ was considered reliable.

Studies of cardiodepressive effect of pyridoxine derivatives (see Table 2) were carried out on 24±6-g white outbred laboratory mice of both sexes. Experimental animals were kept in vivarium conditions (with natural lighting regime at a temperature of 22—24 °C and relative air humidity of 40—50%) using a standard diet (GOST R 50258-92). The studies were carried out according to the rules of good laboratory practice (GLP) in conducting preclinical studies in the Russian Federation, as well as to the rules and recommendations of the International European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (1986). Potential cardiodepressive effect of test compounds was studied in the experiments with narcotized mice. Compounds were administered once intraperitoneally and intragastrically in the dose of 60 mmol kg^{-1} 3±1 min before narcotization with isoflurane (1.5 vol.%) (EICKMEYER ISOFLO Vaporiser (EICKMEYER)). Electrocardiograms of animals were recorded in all standard leads during 1.5—2 h after administration of test compounds using a PowerLab 4/35 ADInstruments digital recording station. Metoprolol was used as a comparator drug. Cardiodepressive activity of compounds was assessed by heart rate reduction. Statistical processing of the results was carried out using the Microsoft Office Excel 2007 program with calculation of the activity arithmetic average value (M), its standard deviation (δ), and a standard error (m), as well as medians ($x_{0.5}$) and percentiles 0.025 and 0.975 ($x_{0.025}$ and $x_{0.975}$). The reliability of sample differences having normal distribution was evaluated using parametric Student's t-test. The differences at a 95% and higher probability level were considered as reliable ($p \leq 0.05$).

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