DOI 10.1007/s11094-018-1763-z
Pharmaceutical Chemistry Journal, Vol. 52, No. 1, April, 2018 (Russian Original Vol. 52, No. 1, January, 2018)

SYNTHESIS AND ANTICONVULSIVE ACTIVITY OF 3- AND 4-BENZOYLPYRIDINE OXIME DERIVATIVES

L. A. Zhmurenko,[1] T. A. Voronina,[1] S. A. Litvinova,[1] L. N. Nerobkova,[1] I. O. Gaidukov,[1] G. V. Mokrov,[1] and T. A. Gudasheva[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 52, No. 1, pp. 19 – 28, January, 2018.

Original article submitted June 21, 2017.

We present here the synthesis of 3- and 4-benzoylpyridine oxime derivatives with potential anticonvulsant action. The most active compound in the maximum electric shock test was 4-benzoylpyridine O-2-morpholinoethyloxime oxalate (1a), i.p. doses of 60 – 150 mg/kg of which increased the survival of mice to 100%. The best effect in the corasol antagonism test was obtained with 4-benzoylpyridine O-(isonicotinoyl)oxime (2c), i.p. doses of 12.5 mg/kg of which increased the survival of mice to 67% and the latent period of onset of generalized tonic-clonic convulsions to 52 sec. Compound 1a had low toxicity (the i.p. LD_{50} in mice was 316 mg/kg) and a therapeutic index of 21.

Keywords: 3- and 4-benzoylpyridine oximes, anticonvulsant activity, maximum electric shock test, corasol antagonism test.

Every year throughout the world roughly 2.4 million people are diagnosed with epilepsy. Searches for novel anticonvulsant substances for the prophylaxis and treatment of epilepsy are a current and relevant task as present antiepileptics do not completely satisfy clinical requirements and have a multitude of side effects [1, 2].

Studies at the V. V. Zakusov Science Research Institute of Pharmacology include the search for novel substances for the treatment of epilepsy. This report presents the results of studies on the synthesis and investigation of compounds with potential anticonvulsant activity among 3- and 4-benzoylpyridine oximes.

The target compounds were constructed using a pharmacophore approach. The structures of known selective serotonin reuptake inhibitors (SSRI) were used. The main effect of SSRI is known to be the antidepressant action, though some members of this class, such as zimelidine [3] and fluoxetine [4] (Fig. 1) show marked antiepileptic activity.

Analysis of the structures of zimelidine and fluoxetine led to the suggestion that pharmacophore elements required for anticonvulsant activity can be identified (Fig. 2*a*). The molecule should contain one amine-containing and two aromatic pharmacophores. These groups should be joined via a linker at least three σ bonds long. Working from this pharmacophore model, we constructed a group of amine-containing 3- and 4-benzoylpyridine oxime derivatives (Fig. 2*b*). The aromatic pharmacophores in these compounds contained phenyl and pyridine rings, while the amine-containing components were a disubstituted amine and the linker was an alkyloxime fragment.

With the aim of widening the concept of the structural requirements for compounds with anticonvulsant properties, we also suggested using O-acylated derivatives of 3- and 4-benzoylpyridine oximes in which the amine-containing pharmacophore was replaced with an aromatic acyl fragment (Fig. 2*c*).

EXPERIMENTAL CHEMICAL SECTION

Target compounds were synthesized using the following general scheme.

[1] V. V. Zakusov Science Research Institute of Pharmacology, 8 Baltiicheskaya Street, 125315 Moscow, Russia; e-mail: g.mokrov@gmail.com

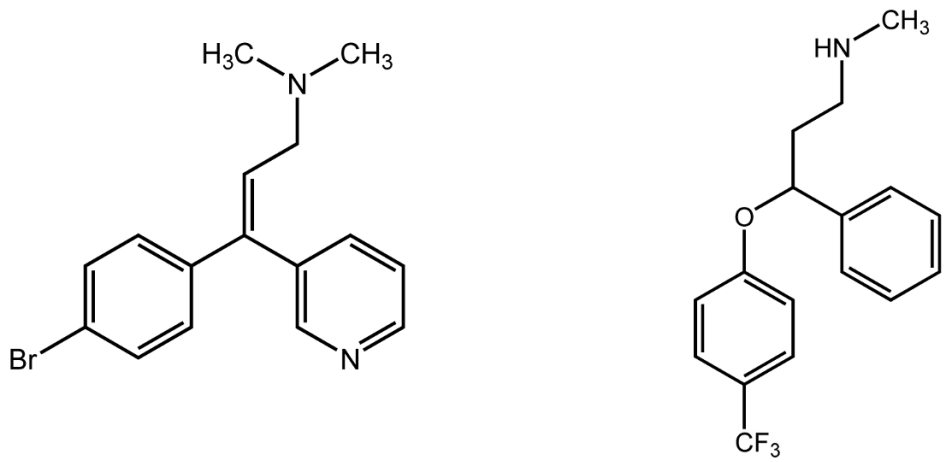


Fig. 1. Compounds with anticonvulsant activity used for the design of new structures.

Reaction of benzoylpyridine oximes (**3a-c**) [5, 6] with aminoalkylchlorides (**4**) in the presence of sodium hydride in DMFA yielded bases (**5a-i**). Interaction of these latter with oxalic acid in ethanol yielded the corresponding 3- and 4-benzoylpyridine O-(aminoalkyloxime) oxalates (**1a-i**).

Boiling of oximes **3a-c** with acid chlorides 6 in the presence of triethylamine in benzene yielded 3- and 4-benzoylpyridine O-(acyloximes) (**2a-l**).

The structures of target compounds **1a-i** and **2a-l** were verified by PMR spectroscopy and their purity by elemental analysis.

All compounds could exist as *sin-anti* isomers, like the starting oximes [6, 7]. ^{1}H NMR spectroscopy was used to identify the ratio of *sin* and *anti* isomers of the study compounds. This established that some compounds contained both isomers: **1b** (85:15), **1f** (70:30), **1h** (35:65), **1i** (70:30), **2a** (95:5), **2f** (40:60), **2g** (40:60), **2i** (30:70), **2j** (40:60), **2k** (50:50), and **2l** (30:70), while several compounds consisted of only one isomer: **1a**, **c**, **d**, **g**, **2b-e**, and **2h**. Published data suggest that the main isomer is the Z isomer, as structurally similar oximes are Z isomers [7].

Melting temperatures were determined on a Kofler bench and were not corrected. Reaction courses were monitored and the identities of study substances were confirmed by TLC in a system consisting of chloroform and methanol (9:1 or 9.5:0.5) on Kieselgel 60 F254 plates with detection in UV light. Elemental analysis data for 3- and 4-benzoylpyridine oxime derivatives (**1a-i** and **2a-l**) corresponded to their molecular formulas. Physicochemical properties are shown in Table 1.

4-Benzoylpyridine O-2-morpholinoethyloxime oxalate (1a). NaH (0.90 g, 0.022 mol) in 7 ml of dry DMFA was supplemented dropwise with a solution of 2.24 g (0.011 mol) of 4-benzoylpyridine oxime (**3a**) [5] in 20 ml of DMFA with cooling with water (10 – 15°C); the reaction was mixed for 1 h and 2.56 g (0.017 mol) of chloroethylmorpholine (base, prepared from 3.5 g

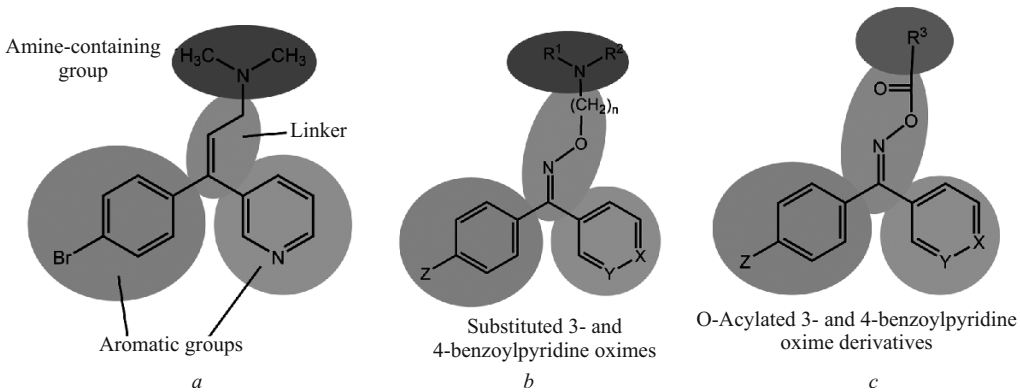
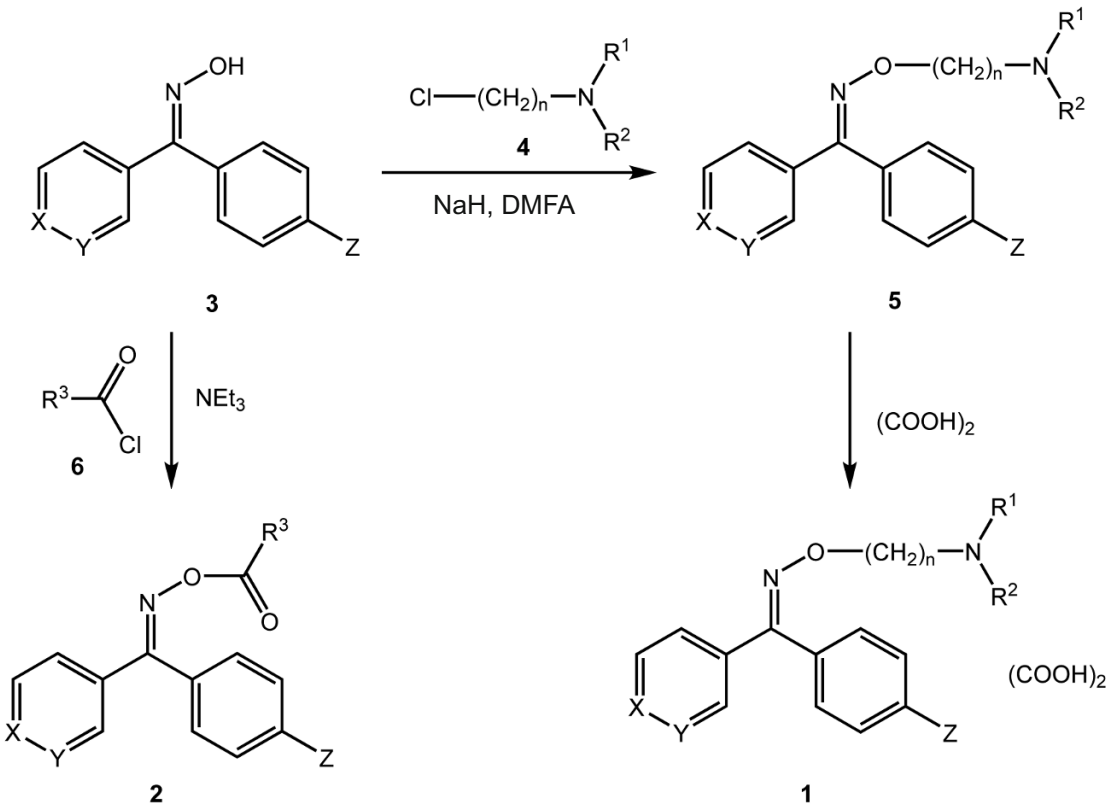
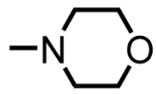
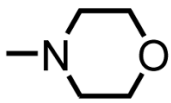
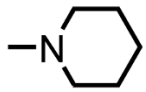
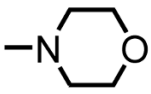
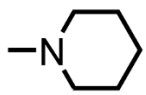
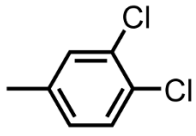
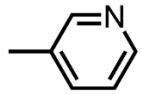
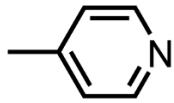
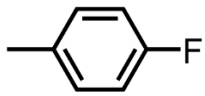
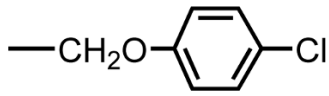
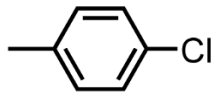
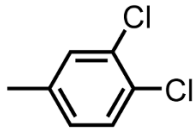
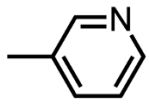
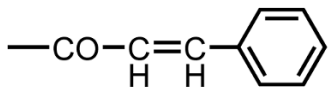
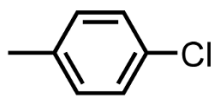
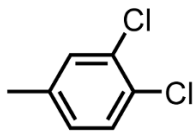
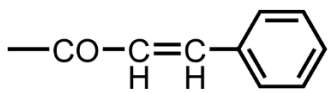


Fig. 2. Pharmacophore model of the structure of bis-aryl compounds with anticonvulsant activity (using zimelidine as an example) (*a*). Amine-containing 3- and 4-benzoylpyridine oxime derivatives corresponding to this pharmacophore model (*b*). O-acylated derivatives of 3- and 4-benzoylpyridine oxime derivatives (*c*).



Compound	X	Y	Z	*n*	NR^1R^2	R^3
1a	N	H	H	2		
1b	N	H	H	2	$N(CH_3)_2$	
1c	N	H	H	3	$N(CH_3)_2$	
1d	H	N	Cl	2		
1e	H	N	Cl	2		
1f	H	N	Cl	2	$N(CH_3)_2$	
1g	H	N	F	2		
1h	H	N	F	2		
1i	H	N	F	2	$N(CH_3)_2$	
2a	N	H	H			

Compound	X	Y	Z	*n*	NR^1R^2	R^3
2b	N	H	H			
2c	N	H	H			
2d	N	H	H			
2e	N	H	H			
2f	H	N	Cl			
2g	H	N	Cl			
2h	H	N	Cl			
2i	H	N	Cl			
2j	H	N	F			
2k	H	N	F			
2l	H	N	F			

of the hydrochloride of the amine) was added and mixing was continued for a further 2 h at room temperature and 220 ml of water was added; the reaction was extracted three times with ethyl acetate (40 ml each); extract was dried over $MgSO_4$ and evaporated; the residue (quantitative yield, as an oil) was dissolved in 5 ml of ethanol, supplemented with 0.9 g of oxalic acid in 2 ml of ethanol; the resulting precipitate was collected by filtration; the yield was 3 g of compound **1a**.

Compounds **1b-i** were prepared by an analogous route. Data on compounds **1a-i** are presented in Table 1. The synthesis of compounds **1b** and **1c** is described in patent [8] and that of compounds **1c** and **1f** is described in [6].

4-Benzoylpyridine O-(3,4-dichlorobenzoyl)oxime (2a). A mixture of 0.99 g (0.005 mol) of 4-benzoylpyridine oxime (**3a**), 1.26 g (0.006 mol) of 3,4-dichlorobenzoyl acid chloride, and 0.60 g (0.006 mol) of dry triethylamine in 10 ml of dry benzene was boiled for 2 h, left for one day, and treated with water (the precipitate dissolved); the benzene solution was washed with saturated $NaHCO_3$ solution followed by water, dried over $MgSO_4$ and evaporated; the oil was triturated under petroleum ether, and product was recrystallized from ethanol. The yield was 1.30 g.

Compounds **2b-l** were prepared by the same method. Data on compounds **2a-l** are presented in Table 1.

EXPERIMENTAL BIOLOGICAL SECTION

Experiments were performed on white mongrel male mice weighing 20 – 26 g. Experimental animals were obtained from Stolbovaya, Scientific Center for Biomedical Technologies (Moscow District). Animal keeping was in compliance with the corresponding rules for laboratory practice (GLP) and normative documents "Sanitary Epidemiological Requirements for the Fittings, Equipment, and Facilities of Animal Houses", approved by the Chief State Sanitary Physician, April 6, 1973, No. 1045-73 and Russian Federation Ministry of Health and Social Development Decree No. 708n, "Approval of Rules for Laboratory Practice", August 23, 2010.

Anticonvulsant activity of 3- and 4-benzoylpyridine oxime derivatives in a model of primary generalized convulsions evoked by maximum electric shock (MES). Each dose of compound was tested on 8-10 animals. MES was created using the certified instrument RodentShockerRS, type 221 (Harvard Apparatus GmbH, Germany). Using special corneal electrodes, animals received electric shocks (500/300 V/mA: 144 mA, duration 0.3 sec). Tonic extension of the hind and forelimbs were recorded, along with deaths. The anticonvulsant effects of the test compounds were assessed in terms of the ability to prevent the development of tonic extension and death. Compounds were given i.p. 40 min before MES [9 – 11].

Anticonvulsant activity of 3- and 4-benzoylpyridine oxime derivatives in a model of primary generalized convulsions evoked by corasol. Each dose of compound was tested on 8 – 10 animals. Experimental groups received i.p. test compounds dissolved in physiological saline at doses of 1 and 50 mg/kg 40 min before corasol. Control animals received the same volume of i.p. physiological saline. Convulsive seizures were induced in the animals by s.c. administration of corasol (10 mg/kg) in the cervical area of the back, which induced convulsions in 100% of mice. Animal observations were made 30 – 60 min after corasol injections. The latent period of the first generalized seizure with loss of reflex turning (LP) was measured, along with the number of dead animals [9, 12].

Acute toxicity of 3- and 4-benzoylpyridine oxime derivatives. Derivatives of 3- and 4-benzoylpyridine oximes were given as single i.p. doses. Animal deaths were recorded to determine LD_{50} values at 24 h and 14 days after dosage. The therapeutic index (TI) was calculated as $TI = LD_{50}/ED_{50}$.

Results were analyzed statistically in MS Excel 2010 and BioStat 2009 (Analyst Soft Inc.). Normal data distributions were confirmed using the Shapiro-Wilks test. Significant differences between groups were identified using the nonparametric Kruskal-Wallis test and Fisher's exact test.

LD_{50} values were calculated by probit analysis (Finney method) in Statplus V5.

The anticonvulsant activity of the compounds synthesized here was evaluated using two models in mice: the maximum electric shock method (MES) and the corasol antagonism test. The MES method modeled primary generalized seizures, i.e., grand mal convulsive seizures [9 – 11].

In the corasol antagonism test, convulsions were induced by the chemical action of the $GABA_A$ receptor antagonist corasol, and these modeled primary generalized seizures of the petit mal type [9, 12].

Both models are basic tests for assessing the actions of substances with anticonvulsant activity.

RESULTS AND DISCUSSION

The actions of MES were found to induce tonic extension and death in 90% of mice. Single i.p. doses 0.25 – 150 mg/kg of compounds **1a**, **1c**, **1d**, **1f**, **1g**, **2a**, **2b**, **2g**, **2k**, and **2l** decreased the proportions of animals with tonic extension and increased the proportions of surviving animals as compared with controls. Thus, mice given compound **1a** at doses of 20 and 40 mg/kg showed disappearance of tonic convulsions and increases in survival to 67% (in both cases), while doses of 60 – 150 mg/kg increased survival to 100% (Table 2). Compound **1c** at a dose of 5 mg/kg significantly increased survival to 63% compared with the 10% in controls. An increase in the dose of **1c** from 20 to 40 mg/kg increased the proportion of animals without tonic extension, which led to an increase in survival to 88%. Compound **1d** at a dose of 100 mg/kg prevented the development of tonic convulsions in 75% of cases, and an increase in the dose to 150 mg/kg increased survival to 100%. Compound **1f** at doses of 1.5 and 3 mg/kg and compound **1g** at doses of 20 and 40 mg/kg increased survival of mice in the MES antagonism test to 67%. Increases in the dose of **1f** to 12.5 mg/kg decreased efficacy in terms of survival. In the case of compound **2a**, the plot of the survival-dose relationship was bell-shaped. Thus, compound **2a** at a dose of 5 mg/kg promoted elimination of tonic extension and led to survival of 25% of mice, while a dose of 20 mg/kg gave a survival rate of 63% and an increase in the dose of compound 2a to 40 mg/kg decreased efficacy to 50% in terms of survival (Table 2). Compound **2b** at a dose of 60 mg/kg decreased the proportion of animals with tonic extension and increased the proportion of surviving animals, as compared with controls, to 67%, while smaller doses (40, 20, and 5 mg/kg) did not produce this effect. Compounds **2g**, **2k** and **2l** at doses of 0.25 – 10 mg/kg increased

TABLE 1. Physiochemical Properties of 3- and 4-Benzoylpyridine O-R-Oximes (1a-i and 2a-l)

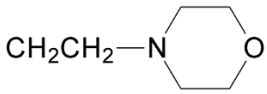
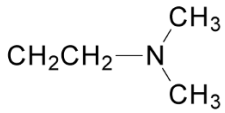
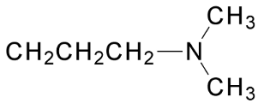
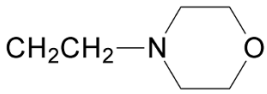
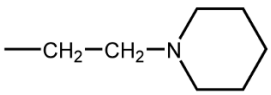
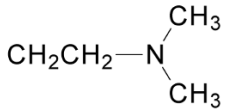
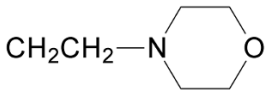
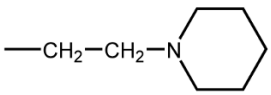
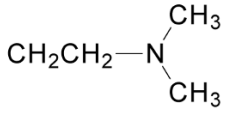
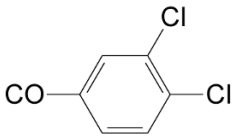
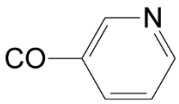
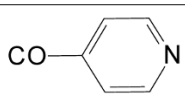
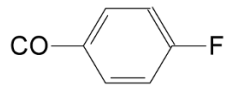
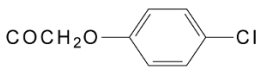
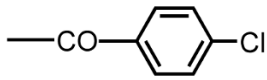
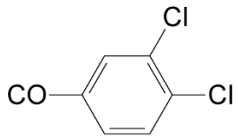
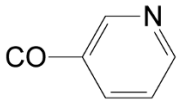
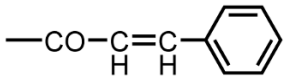
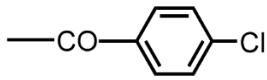
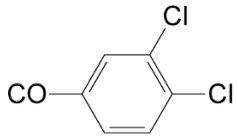
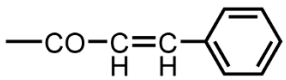
Compound	Z	R	Yield, %	T_m, °C, solvent	Molecular formula*	PMR spectra, DMSO-d_6, e, J/Hz
1a	H		75.0	154 – 155 (ethanol)	$C_{18}H_{21}N_3O_2 \cdot H_2C_2O_4$	2.83 (4H, m, -CH_2-N-CH_2-); 3.10 (2H, t, CH_2N, J = 6.0); 3.67 (4H, m, 4H, m, CH_2-O-CH_2); 4.39 (2H, t, CH_2O, J = 6.0); 7.35 (2H, m, 3- and 5-H Py); 7.37 – 7.51 (5H, m, ArH); 8.71 (2H, m, 2- and 6-H Py), 5.10 av.(HDO and$(COOH)_2$)
1b	H		63.7	164 – 165 (ethanol)	$C_{16}H_{19}N_3O \cdot 1.5H_2C_2O_4$	2.71 (6H, s, N$(CH_3)_2$), 3.42 (2H, t, CH_2N, J = 6.0); 4.48 (2H, n, OCH_2, J = 6.0); 7.37 and 7.45; 8.61 and 8.71 (4H, m, PyH), 7.39 and 7.52 (5H, m, ArH)
1c	H		76.3	152 – 153 (ethanol)	$C_{17}H_{21}N_3O \cdot H_2C_2O_4$	2.73 (6H, s, N$(CH_3)_2$); 2.08 (2H, m, CH_2[b]); 3.04 (2H, t, CH_2[c], J = 6.0); 4.18 (2H, t, CH_2[a], J = 6.0); 7.35 and 8.72 (4H, m, PyH), 7.42 (5H, m, ArH), 6.92 av. (HDO and $(COOH)_2$)
1ã	Cl		46.6	177 – 178 (ethanol)	$C_{20}H_{22}ClN_3O_6$	2.92 (4H, m, CH_2-N-CH_2), 3.21 (2H, m, CH_2), 3.70 (4H, m, CH_2-O-CH_2), 4.44 (2H, m, CH_2, under HDO), 7.40 – 7.79 (4H, m, ArH), 8.56 – 8.66 (4H, m, 2-H, 4-H, 5-H, 6-H (Py))
1d	Cl		88.6	125 – 127 (ethanol)	$C_{21}H_{24}ClN_3O_5$	1.45 (6H, m, $(CH_2)_3$ ring), 3.05 (4H, m, CH_2-N-CH_2-ring), 3.36 (2H, t, NCH_2, J = 6.0), 4.49 (2H, m, CH_2), 7.40 – 7.90 (7H, m, PyH, ArH), 8.50 – 8.70 (2H, m, 2-H, 6-H)
1e	Cl		78.0	154 – 155 (ethanol)	$C_{18}H_{20}ClN_3O_5$	2.71 and 2.73 (3H, s, N$(CH_3)_2$), 3.43 (2H, m, CH_2), 4.49 (2H, m, CH_2), 4.70 (av. HDO and COOH), 7.40 – 7.60 (5H, m, 5-H (Py), ArH), 7.76 – 7.82 (1H, m, 4-H (Py)), 8.52 – 8.70 (2H, m, 2-H, 6-H (Py))
1g	F		32.0	145 – 146 (ethanol)	$C_{20}H_{22}FN_3O_6$	3.18 (4H, m, CH_2-N-CH_2), 3.48 (2H, m, CH_2), 3.77 and 4.00 (4H, m, CH_2-O-CH_2), 4.49 (2H, m, CH_2), 7.25 – 7.65 (6H, m, ArH, PyH), 8.50 – 8.70 (2H, m, 2-H, 6-H)
1h	F		70.7	152 – 153 (ethanol)	$C_{21}H_{24}FN_3O_5$	1.47 (2H, m, CH_2), 1.65 (4H, m, CH_2-CH_2), 3.02 (4H, m, CH_2-N-CH_2), 3.32 (2H, m, CH_2N), 4.46 (2H, m, CH_2O), 7.20 – 7.85 (6H, m, 4-H, 5-H (Py), ArH), 8.55 – 8.66 (2H, m, 2-H, 6-H(Py))
1i	F		48.0	136 – 137 (ethanol)	$C_{18}H_{20}FN_3O_5$	2.73 and 2.75 (6H, s, N$(CH_3)_2$), 3.45 and 4.48 (4H, 2 m, CH_2-CH_2), 7.00 – 7.50 (5H, m, ArH, 5-H(Py)), 7.51 – 8.80 (3H, m, 2-H, 4-H, 6-H (Py))
2a	H		70.3	100 – 101 (ethanol)	$C_{19}H_{12}Cl_2N_2O_2$	7.45 – 7.60 and 7.62 – 7.85 (10H, m, 5-H ArH, Ar(Cl) and 3-H Py); 8.60 – 8.80 (2H, m, 2-H and 6-H (Py))
2b	H		55.5	142 – 144 (ethyl acetate)	$C_{18}H_{13}N_3O_2$	7.30 – 7.60 and 7.75 (9H, two m, ArH, 5-H and Py); 8.67 and 8.72 (2H, two m, 6-H from two Py); 8.72 – 8.84 (2H, m, 2-H from two Py)
2c	H		65.5	150 – 151 (ethyl acetate)	$C_{18}H_{13}N_3O_2$	7.20 – 7.45 and 7.45 – 7.80 (9H, two m, ArH, 5-H and Py); 8.60 – 8.85 (4H, two m, 2-H and 6-H)

TABLE 1. Continued

Compound	Z	R	Yield, %	T_m, °C, solvent	Molecular formula*	PMR spectra, DMSO-d_6, e, J/Hz
2ã	H		55.7	125 – 126 (ethanol)	$C_{18}H_{13}FN_2O_2$	7.3 – 7.8 (10H, m, ArH, PyH), 8.7 – 8.8 (3H, m, 2-H, 4-H, 6-H (Py))
2e	H		70.2	99 – 100 (ethanol)	$C_{19}H_{15}ClN_2O_3$	5.00 (2H, s, CH_2), 6.94 and 7.31 (4H, m, O-C_6H_4-Cl), 7.51 (5H, m, ArH), 7.39 and 8.74 (4H, two m, PyH)
2å	Cl		43.0	143 – 145 (ethyl acetate)	$C_{19}H_{12}Cl_2N_2O_2$	7.45 – 7.75 (9H, m, ArH, 5-H (Py)), 8.04 (1H, m, 4-H (Py)), 8.65 – 8.84 (2H, m, 2-H and 6-H (Py))
2g	Cl		50.5	129 – 130 (ethanol)	$C_{19}H_{11}Cl_3N_2O_2$	7.50 – 7.85 (8H, m, 2 ArH, 5-H (Py)), 7.90 – 8.02 (1H, m, 4-H (Py)), 8.70 – 8.82 (2H, m, 2-H and 6-H (Py))
2ç	Cl		34.0	142 – 143 (ethyl acetate)	$C_{18}H_{12}ClN_3O_2$	7.25 – 7.60 and 7.75 (8H, two m, ArH, 4-H and 5-H from two Py), 8.60 – 8.80 (3H, m, 2-H and 6-H from two Py), 8.80 – 8.90 (1H, m, 2-H (Py))
2i	Cl		52.5	141 – 142 (ethyl acetate)	$C_{21}H_{15}ClN_2O_2$	6.60 – 6.64 (1H, m, CH=), 7.36 – 7.77 (11H, m and 2 sec, 2 ArH, CH=, 5-H (Py)), 7.91 (1H, m, 4-H (Py)), 8.62 – 8.76 (2H, m, 2-H and 6-H (Py))
2j	F		34.0	137 – 139 (ethanol)	$C_{19}H_{12}FClN_2O_2$	7.30 – 8.01 (10H, m, ArH, 4-H, 5-H (Py)), 8.71 – 8.78 (2H, m, 2-H, 6-H (Py))
2k	F		77.1	125 – 127 (ethanol)	$C_{19}H_{11}FCl_2N_2O_2$	7.37 – 7.82 (8H, m, ArH, 5-H (Py)), 7.90 – 8.02 (1H, m, 4-H (Py)), 8.70 – 8.82 (2H, m, 2-H-6-H (Py))
2l	F		49.7	124 – 126 (ethanol)	$C_{21}H_{15}FN_2O_2$	6.82 (1H, m, CH=), 7.35 – 8.11 (11H, m and 2 sec, ArH and CH=), 7.90 (1H, m, 4-H (Py)), 8.62 – 8.79 (2H, m, 2-H and 6-H (Py))

* Compounds 1a-h were prepared as oxalates and compounds 2a-l as bases.

survival of the animals to 50% ($p < 0.12$). Reference agent Convulsofin (100 mg/kg) eliminated tonic extension of the limbs and death in 89% of animals in the MES antagonism test (Table 2).

Thus, compounds **1a**, **1c**, **1d**, and **1g** produced statistically significant protection of animals from developing tonic extension and dying as a result of MES with a linear dose-effect plot over the dose range 0.5 – 150 mg/kg. Compound **1f** was effective only at low doses (1.5 – 3 mg/kg). Compound 2a showed a bell-shaped dose-effect curve with peak efficacy at 20 mg/kg. The activities of compounds **1a**, **1c**, and **1d** in the MES antagonism test were comparable with the actions of the anticonvulsant agent Convulsofin, used as reference drug.

S.c. administration of corasol (100 mg/kg) produced first convulsive generalized seizures with a latent period of 32.8 sec and killed 100% of the mice. Studies using the corasol antagonism test showed that compound 1a at doses of 20 and 60 mg/kg produced statistically significant increases in the latent period of the first generalized seizure (LP) by 148 and 59 sec respectively, while compounds 1c (50 mg/kg) and **1d** (100 mg/kg) gave increases by 56 and 64 sec respectively as compared with the control group, but did not prevent the development of corasol-induced convulsions or death (Table 2). Compound **1f** at doses of 6 and 12.5 mg/kg and compound **2c** at doses of 12.5 and 50 mg/kg produced statistically significant increases in the latent period of the first convulsive seizure and protected 50 – 66.7% of animals from death (Table 2). Compounds **1e**, **2b**, **2f**, **2g**, **2k**, and **2l** had no effect on the development of convulsions or death among the animals at doses of 0.5 – 60 mg/kg (Table 2). Reference

TABLE 2. Anticonvulsant Activity of 3- and 4-Benzoylpyridine Oxime Derivatives in the MES Test and the Corasol-Induced Primary Generalized Convulsions Model

Compound	MES		Corasol		
	dose, mg/kg	% survivors	dose, mg/kg	LP 1-st seizure	% survivors
Control	–	10	–	32.8 ± 7.2	0
1a	0.5; 1.5	25	20	180.3 ± 37.4*	13
	10	50	60	91.4 ± 10.1*	20
	20; 40	67#	100		20
	60, 80, 100, 150	100#			
1b	25	0	13	21.3 ± 11.2	17
	50	33	5		0
	100	11	25	28.8 ± 10.6	0
			50	17.5 ± 8.7	0
1c	1	13	13		0
	3	38	25	40.5 ± 10.2	0
	5	63#	50	89.1 ± 7.8*	17
	20	75#			
	40	88#			
1d	2.5; 5	17	5	65 ± 29	0
	10	33	100	96 ± 18*	0
	100	75#			
	150	100#			
1e	12.5	0	12.5, 25, 50		0
	25, 50	33			
1f	1.5; 3	67#	6	49.0 ± 11.3*	40
	6.25	50	12.5	71.7 ± 16.5*	50#
	12.5	43	20	53.9 ± 17.1	10
1g	5	0	12.5		0
	10	17	20		17
	20, 40	67#			
1i			10, 20		33
2a	5	25	5	28.5 ± 11.5	0
	10	38	20	44.5 ± 14.3	33
	20	63#			
	40	50			
2b	5	33	5		0
	20	33	20		33
	40	0			
	60	67#			
2c	5	0	12.5	85.3 ± 28.3*	67#
	20	13	20	48.6 ± 15.3	33
	50	0	50	67.8 ± 17.6*	56#
2f	12.5	17	10		0
	25	33	25		17
	50	17	50		0
2g	0.5	37	12.5		0
	1.25; 2.5	50	25, 50		17
	5	38			
	10	25			
	50	25			

TABLE 2. Continued

Compound	MES		Corasol		
	dose, mg/kg	% survivors	dose, mg/kg	LP 1-st seizure	% survivors
2k	0.12	33	0.12 – 5		0
	0.25	50	25		17
	0.5, 5	17	50		0
	10, 30	13	100		17
2l	5	38	5		0
	10	50			
	20	25			
Valproic acid (Convulsofin)	100	89#	100	64.6 ± 14.7*	78#

Note: regime 500/300 V/mA: 144 mA, $t = 0.3$ secretary.
* Significance of differences from control group, $p \le 0.05$ (Mann-Whitney test); # significance of differences from control group, $p \le 0.05$ (Fisher's exact test).

agent Convulsofin (100 mg/kg) increased the latent period of onset of the first convulsive seizure and protected 78% of animals from death (Table 2).

Thus, studies using the corasol antagonism test showed that only compounds **1f** and **2c** produced effects in terms of survival. Compounds **1a**, **1c**, **1d**, and **1f** had moderate anticonvulsant effects in terms of increases in the latent period of the onset of corasol-induced convulsive seizures.

Acute toxicity (mice, i.p.) was studied for the most active compounds with efficacies comparable to that of Convulsofin in the MES antagonism test, i.e., **1a**, **1c**, **1d**, and **1f**, which were effective in both the MES antagonism test and the corasol test.

ED_{50} and LD_{50} vales were determined by probit analysis (Finney method). TI was calculated as $TI = LD_{50}/ED_{50}$.

Studies of the acute toxicity of compounds containing a morpholinoethyl group (**1a**, **1d**) showed that 10% of animals died by 24 h after administration of compound **1a** at a dose of 22 mg/kg (i.e., 1 in 10), with no change in survival during the subsequent two weeks. An increase in the dose of 420 mg/kg led to death of 100% of animals by 24 h. Administration of compound **1d** at a dose of 150 mg/kg did not cause death throughout the observation period, while a dose of 300 mg/kg produced death in 10% of animals at 24 h and 83% by 14 days. Compound **1c**, containing a dimethylaminopropyl group, produced death of 10% of the ani-

TABLE 3. Acute Toxicity of 3- and 4-Benzoylpyridine Oxime Derivatives in Mice (i.p.)

Compound	Dose, mg/kg	Survivors			
		24 h, abs.	24 h, %	14 days, abs.	14 days, %
1a	220	9/10	90	9/10	90
	300	6/10	60	6/10	60
	350	5/10	50	5/10	50
	420	0/10	0	0/10	0
1c	100	9/10	90	6/10	60
	150	7/10	70	2/10	20
	200	2/10	20	1/10	10
	400	1/10	10	0/10	0
1d	150	6/6	100	6/6	100
	200	6/6	100	4/6	67
	300	5/6	83	1/6	17
1f	50	6/6	100	6/6	100
	100	9/10	90	9/10	90
	200	4/6	67	4/6	67
	400	3/6	50	3/6	50

TABLE 4. Calculated LD_{50} and ED_{50} Values for 3- and 4-Benzoylpyridine Oxime Derivatives

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg	TI
1a	316	17	21
1c	115	7	16
1f	385	11	34
1g	242	59	4

mals by 24 h after a single dose of 100 mg/kg, lethality increasing to 40% by 14 days. An increase in the dose to 200 mg/kg led to death of 80% of the animals by 24 h and 90% by 14 days, while a dose of 400 mg/kg of compound **1d** led to death of 90% of animals by 24 h and 100% by the end of the experiment. Administration of compound **1f** at a dose of 100 mg/kg led to death of 10% of animals at 24 h, with no increase by two weeks of observation. Administration of compound **1f** at a dose of 400 mg/kg led to death of 50% of mice at 24 h, with no increase over the following two weeks (Table 3).

Calculation of lethal doses (LD) by probit analysis (Finney method) showed that the dose of compound **1a** killing 50% of mice (LD_{50}) was 115 mg/kg, while values for **1d** and **1f** were 242 and 385 mg/kg respectively (Table 4).

Thus, the 3- and 4-benzoylpyridine oxime derivatives studied here - **1a**, **1c**, and **1f** - are members of the class of moderately toxic substances; their therapeutic indexes were greater than 10.

Analysis of the structure-action interaction in the series of compounds obtained here provided evidence that substance activity was significantly dependent on structure. The most active compounds were those containing morpholinoethyl (**1a**, **1d**, **1g**), dimethylaminoethyl (**1f**), or dimethylaminopropyl (**1c**) groups, as well as the 3,4-dichlorobenzoyl (**2a**) group, which consists of a single spatial isomer. At the same time, there was no clear correlation between the position of the nitrogen atom in the pyridine heterocycle and the presence of absence of a halogen in the benzene ring and the activity of the compounds. Compounds **2l**, **2g**, and **2f**, with low anticonvulsant activity, had benzene radicals with two or one chlorine halogens, and substitution of the halogen Cl by F in the pyridine heterocycle did not increase efficacy. Anticonvulsant activity in the MES antagonism test of compounds with the morpholinoethyl radical was seen at intermediate and high doses (20 – 150 mg/kg) and was independent of substitutions between Cl, F, and H in the Z position of the pyridine heterocycle. The anticonvulsant activity of compounds with the aliphatic radical - **1c** and **1f** - was seen in the low dose range (1 – 5 mg/kg).

Thus, we present the synthesis of 3- and 4-benzoylpyridine oxime derivatives with potential anticonvulsant activity. The most active compound in the maximum electric shock test was O-2,4-benzoylpyridine morpholinoethyloxime (oxalate **1a**), which at i.p. doses of 60 and 150 mg/kg increased survival in mice to 100%. The best effect in the corasol antagonism test was obtained with 4-benzoylpyridine O-(isonicotinoyl)oxime (**2c**), which at an i.p. dose of 12.5 mg/kg increased the survival of mice to 67% and the latent period of onset of generalized tonic-clonic convulsions by 52 sec. Compound **1a** had low toxicity (LD_{50} 316 mg/kg, mice, i.p.) and a therapeutic index of 21.

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