1-(β-Phenethyl)-2,3,6-triphenyl-4-benzylaminopiperidine (XXVII). To a solution of 4.5 g (8.6 mmoles) of imine XXVI in 60 ml of ethanol was added in portions with stirring 3.27 g (86 mmoles) of $NaBH_4$. The reaction mixture was stirred for 3 h, then poured into water. The resulting precipitate was filtered off and recrystallized from a mixture of ethanol and hexane (1:1) to give 3.21 g of compound XXVII.

1-(β-Phenethyl)-2,3,6-triphenyl-4-(N-benzyl-N-propionylamino)piperidine (XXVIII). A mixture of 1.0 g (1.9 mmoles) of benzylaminopiperidine XXVII and 2.5 g (19 mmoles) of $(EtCO)_2O$ in 5 ml of pyridine was heated for 1 h. The pyridine and excess anhydride were distilled and the residue was treated with 20% salt solution, extracted with ether, and dried with $MgSO_4$. Removal of the ether gave 0.51 g of compound XXVIII as yellow crystals. Mass spectrum m/z (%): 578 (1), 487 (57), 325 (45), 91 (100).

1-Methyl-4-(2'-phenyl-3',4',5',6'-tetramethoxycarbonyl-1',2'-dihydropyridin-1'-yl)-2,3,6-triphenylpiperidine (XXX). A solution of 0.75 g (1.7 mmoles) of imine XXIX, prepared from 1-methyl-2,3,6-triphenylpiperidin-4-one analogously to the synthesis of imine XXVI, and 1.01 g (3.5 mmoles) of dimethyl acetylene dicarboxylate in 20 ml of absolute toluene was boiled for 8 h. The solvent was evaporated and the residue (1.76 g) was chromatographed on silica gel (eluent = 1:5 ethyl acetate/pentane) to give 0.3 g of compound XXX as pale yellow crystals.

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BENZIMIDAZOLYLALKYLSULFONIC ACIDS: SYNTHESIS AND ANTIVIRAL PROPERTIES

Yu. V. Badeev, O. K. Pozdeev,
V. B. Ivanov, V. D. Korobkova,
S. V. Andreev, E. A. Egorova,
and É. S. Bat'yeva

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Viral diseases are recognized as causing intense harm to the health of people with considerable damage to the national economy, which makes the question of chemotherapy of viral infections one of the most urgent topics of modern virusology [1].

As well as viral influenza infections, other contagious diseases of the respiratory tract, induced by RNA-containing viruses, also occupy a leading place with respect to frequency of occurrence and their epidemic proportions. For a long time the arsenal of specific influenza prophylaxis was filled by various vaccines. However, because of the antigenic mutability of the influenza virus, the use of vaccines appears to be only slightly effective in the dynamics of the epidemic process. This gives a special importance and definite attractiveness to the production of chemotherapeutic agents against influenza infection. To achieve this it is very important to study the manifestations of antiviral properties among various classes of chemical compounds with prospects of further directed search for effective antiviral preparations [3].

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan' Branch, Academy of Sciences of the USSR.

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TABLE 1. Physicochemical Properties of Benzimidazolylalkylsulfonic Acid Derivatives

Compound	Yield,%	Mp, °C	Empirical formula
I	58	73	$C_{10}H_{12}N_2O_3S$
II	33	65	$C_{14}H_{20}N_2O_3S$
III	48	58	$C_{11}H_{14}N_2O_3S$
IV	36	96	$C_{14}H_{12}N_2O_3S$
V	86	54	$C_{10}H_{10}N_2O_3S$
VI	73	62	$C_{13}H_{16}N_2O_3S$

In the present work the results are given of the investigation of antiviral properties of derivatives of α-aminoalkylsulfonic acid – benzimidazolylalkylsulfonic acids – in relation to the influenza virus A(H_3N_2). The in vitro antiviral activity of the compounds was evaluated from their ability to inhibit the reproduction of the virus A/Leningrad 34/72 (H_3N_2) in surviving fragments of chorionallantoic membrane of chicken embryo (CAM). The in vivo investigations were carried out on a model of an experimental influenza infection of nonpedigree white mice infected with an influenza virus A/Aichi 2/68 (H_3N_2) adapted to lung tissue of mice.

Benzimidazolylalkylsulfonic acids I-VI were obtained from benzimidazole, a carbonyl compound and SO_2.

$$R{-}C(R'R''){-}SO_2OH$$
I–VI

R = 1-benzimidazolyl;
R′=H(IV,V), Me(I,III,VI), Et(II);
R″=Me(I), Et(III), n-Bu(II), Ph(IV);
$CH{=}CH_2$(V), $CH{=}C(CH_3)_2$(IV).

Derivatives of α-aminoalkylsulfonic acid II

EXPERIMENTAL (CHEMICAL)

General Method for Preparation of Compounds I-VI. Sulfur dioxide was bubbled through a solution of an amine (0.10 mole) in ether (25 ml), which contained a small excess of water (0.11 mole). The bubbling through of SO_2 was continued up to the beginning of separation of crystals from the yellow colored homogeneous solution. This bisulfite solution was added to an excess of a carbonyl compound (0.20 mole). The solution at once became decolorized, the reaction mixture warmed up slightly and soon crystallized. It was found that the use of ethanol for the preparation of the β-naphthylphenylaminomethane-bisulfite addition compound was preferable to that of ether. In all cases the filtered products were washed with ether before their recrystallization from an ether–absolute ethanol or an ethanol–water mixture. The data of the elemental analysis corresponded to the calculated values. The yield and physicochemical properties of the compounds obtained are given in Table 1.

EXPERIMENTAL (BIOLOGICAL)

Practically all the compounds studied were slightly toxic towards CAM cells. The minimal toxic dose (MTD) of compounds I and II was equal to 2000 μg/ml, for compound III – 1000 μg/ml, while for compounds IV and V it was 500 μg/ml. Only compound VI was more toxic for the CAM cells. The MTD of compound VI was 31.7 μg/ml.

Analysis of the antiviral activity of the compounds in vitro showed that they practically do not influence the reproduction of the influenza virus A/Leningrad 34/72 (H_3N_2) in a culture of the CAM cells.

The development of experimental influenza infection was effected by infecting nonpedigree white mice of both sexes weighing 16-18 g each with an adapted A/Aichi 2/68 (H_3N_2) virus. The infection of the experimental animals was effected by an intranasal administration in a dose of 50 μliters, under light ether anesthesia of the allantoic virus, which underwent one passage over 10-11-day-old chicken embryos. The LD_{50} of the virus for white mice was a 10^{-5} dilution in a cooled (4°C) Hanks solution. The hemagglutinin titer of the virus

TABLE 2. Antiviral Activity of Benzimidazolylalkylsulfonic Acid Derivatives under Experimental Influenza Infection Conditions

Compound	MTD, mg/kg	Dose, mg/kg		Lethality, %	Survival, %	Protection, %	Protection index, %	Prolongation of life span of animals	
		one-time dose	course dose					days	%
I	600	60	300	27,6±8,6	72,4	22,4	48,8 (++)	0,5	3,5
II	500	50	250	32,1±9,0	67,9	17,9	35,8 (+)	1,5	10,7
III	500	50	250	30,0±8,5	70,0	20,0	40,0 (++)	0,1	0,7
IV	550	55	275	30,0±8,5	70,0	20,0	40,0 (++)	0,1	0,7
V	1150	115	575	46,7±9,26	3,7	11,9	20,0	2,1	15,0
VI	500	50	250	26,7±8,2	73,3	23,3	46,6 (++)	1,0	0,7

TABLE 3. Immunomodulating Activity of Compound I in Norm and under Infection Immunopathology Conditions

Group	Dose, mg/kg	Weight of spleen, mg	Number of splenocytes, mln/org	Number of AFC (.10^6 cells)	Stimulation coefficient
Infected animals	—	201,6±42,07	254,5±21,32	83,7±10,7	—
Infected animals receiving the preparation	600	224,3±37,16	301,4±30,6	203,3±15,8	2,3
Healthy animals	—	234,14±51,6	297,9±14,5	198,7±21,3	—
Healthy animals receiving the preparation	600	237,28±13,6	301,8±29,4	260,5±37,2	1,8

was equal to 1:2048. The antiviral properties of the compounds under the experimental influenza infection conditions were determined by a generally accepted method by introducing the compounds according to a therapeutically prophylactic scheme [2].

The toxicity of the benzimidazolylalkylsulfonic acid derivatives for warm-blooded animals varied between 500 and 1150 mg/kg. Compounds I-V had a protective effect under the influenza infection conditions. The protection indexes of the active compounds were 35.8-48.8%. The mean life span of the experimental animals increased by 0.7-15% (Table 2).

The manifestation of antiviral activity in vivo by the benzimidazolylalkylsulfonic acid derivatives in combination with the absence of a direct antiviral action in vitro can be due to the ability to act on the functional activity of the nonspecific resistance factors of the organism to infection with increase and acceleration of the development of the immune response to the infecting agent.

To verify this we studied the influence of a derivative of benzimidazolylalkylsulfonic acids (compound I) on the development of a primary humoral immune response to sheep erythrocytes in healthy animals and those infected by the influenza virus. In the investigation we used the method of local hemolysis in a gel [4], which was used to determine the number of antibody-forming cells (AFC) in the spleen of mice. The immunization by the antigen was carried out by intraperitoneal administration of 10^7 sheep erythrocytes in 0.5 ml of a sterile Hanks solution simultaneously with the fourth administration of the compound. By applying such an immunization scheme, it is possible to obtain a matching of the peak of the development of the primary immune response (5 days) with the maximum development of pneumonia resulting from the influenza (7-8 days).

Administration of compound I caused a 2.3-fold increase in the number of the antibody-forming cells (AFC) in the group of infected animals and 1.8-fold increase in their number in the group of intact animals (Table 3).

Our investigations showed that certain derivatives of benzimidazolylalkylsulfonic acids have the capability of protecting mice from death under the conditions of an experimental influenza infection. This effect can be explained by the decided influence on the rate and magnitude of development of immunological reactions in response to penetration of the infecting agent, since the compounds themselves do not have the ability of inhibiting the reproduction of the influenza virus in the sensitive cells of the organism.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF DERIVATIVES OF 2-METHYL-3-ETHOXYCARBONYL-5-(5-NITROPYRIMID-4-YL)OXYINDOLE

N. I. Mikerova, E. K. Panisheva,
I. S. Nikolaeva, T. V. Pushkina,
A. N. Fomina, and V. G. Granik

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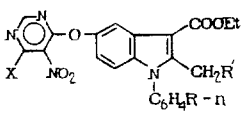
In continuation of our research on the synthesis and investigation of the antiviral activity of derivatives of 5-hetaryloxyindoles [6, 8], compounds were obtained in the present work in which a substituted 5-nitropyrimidyl grouping is present as the hetaryl fragment. The impetus for the synthesis and investigation of this type of compounds in addition to the above-mentioned papers [6, 8] also included [10], in which the antiviral activity of hetaryl aryl ethers was attributed to the presence of one electron-deficient ring which is capable of reacting with the nucleophilic part of viral proteins.

Transition from a substituted cyanopyridyl fragment [6] to a nitropyrimidyl fragment substantially increases the electron deficiency in the heteroaromatic ring, and it therefore was of interest to study the antiviral action of these new compounds.

The first stage in the synthesis of the desired dihetaryl oxides was carried out by reacting 1-phenyl-, 1-p-methoxyphenyl- and 1-p-bromophenyl-2-methyl-3-ethoxycarbonyl-5-hydroxyindoles (Ia-c) with 5-nitro-6-methoxy (IIa)- and 5-nitro-6-piperidino (IIb)-4-chloropyrimidines [11, 12]. The reaction of hydroxyindoles I with chloropyrimidines II proceeds under considerably milder conditions (DMFA, potassium carbonate, 20°C) than with the 2-chloropyridine derivatives [1, 6, 7, 11] due to the considerably higher activation of the chlorine atom in the former compounds, and the desired end products (IIIa-e) were obtained in satisfactory yields.



a-e

R=H (IIIa, a, IV), OMe (IIIb c) Bd (IIIe); R'=H (IIIa-e), Cl (IV); X=OMe (IIIa, d, IV), $N(CH_2)_5$ (IIIb, c, e).

We proposed to carry out the subsequent chlorination of III by the method in [8] to obtain chloromethyl derivatives, from which it was planned to obtain 2-dialkylaminomethyl-5-hydroxyindole derivatives. This possibility was studied using the example of compound IIIa. The chlorination of IIIa by SO_2Cl_2 proceeds smoothly, but further reaction of 1-phenyl-2-chloromethyl-3-ethoxycarbonyl-5-(5'-nitro-6"-methoxypyrimid-4'-yl)oxyindole (IV) with amines proceeds ambiguously and the corresponding dialkyl methyl derivatives could not be isolated in a pure state.

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