BIOLOGICAL ACTIVITY OF FURAN DERIVATIVES (REVIEW)

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Information on the biological activity of furan derivatives for the period 1981-1991 is correlated. The promising character of the study of the biological properties of furan derivatives for the creation of new medicinals is demonstrated.

1. INTRODUCTION

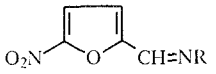
The broad spectrum of biological activity of furan derivatives continues to attract the attention of synthetic chemists to this class of compounds.

In the last decade interest in furan derivatives has remained quite high — new types of compounds have been synthesized, and new forms of activity for known types have been discovered. Since 1988, the furan derivative ranitidin, which is an antagonist of histamine H_2 receptors, has steadfastly remained in first place with respect to total sales of medicinals on the world market.

The existing reviews contain data on the biological activity of furan derivatives up to 1982 [1-8]. We have correlated information on the biological activity of furan derivatives for the period 1981-1991.

2. ANTIBACTERIAL ACTIVITY

Antibacterial agents that are products of condensation of the formyl group of 5-nitrofurfural with compounds that contain an amino (hydrazino) group — nitrofurantoin, furazolidone, nifurimide, etc. — are widely used in medical practice. The search for new antibacterial agents that have general formula I continues.



I

As shown in [9], I (R = 4-HOC_6H_4CONH, R = $PhCH_2NH$, R = 2-furylcarbonylamino, R = 4-$H_2NC_6H_4CONH$) inhibit the growth of both Gram-positive and Gram-negative microorganisms. Compound I with R = $PhCH_2$ also has bactericidal activity [10].

The condensation of 2-di(acetoxy)methyl-5-nitrofuran with derivatives of 4-amino-5-alkyl(or aryl)-2,4-dihydro-1,2,4-triazol-3-ones in the presence of HCl gave the corresponding 4-(5-nitro-2-furfurylideneamino) derivatives II [11] (see scheme 1 on the following page).

All of the investigated compounds displayed antibacterial activity only with respect to Gram-positive bacteria. The most pronounced activity with respect to *Staphylococcus aureus* was discovered when R^1 = an aromatic substituent and R^2 = $(CH_2)_2OH$. The antibacterial activity of the three best compounds was additionally investigated with respect to 36 strains of *S. aureus*. Compound II with R^1 = p-$MeOC_6H_4$ and R^2 = $(CH_2)_2OH$ has greater activity with respect to *S. aureus* than the commercial nitrofurantoin [minimum bacteriostatic concentration (MBC) = 4-8 μg/ml].

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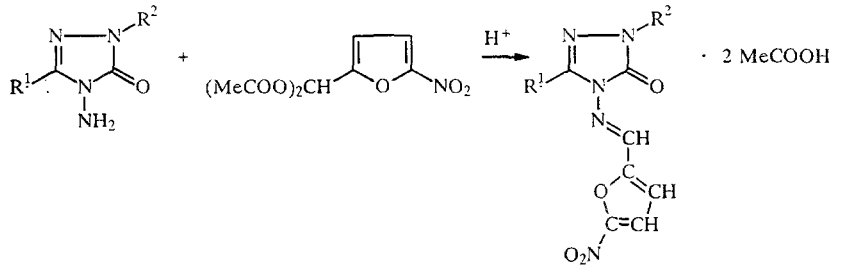
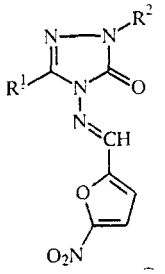
Scheme 1



II

R^1 = Me, R^1 = Et, R^1 = Ph, R^1 = *p*-$MeOC_6H_4$, R^1 = *p*-ClC_6H_4;
R^2 = CH_2CO_2Et, R^2 = CH_2CO_2Pr

Among the products of condensation III of 4-amino-3-alkyl(aryl)-1,2,4-triazol-3-ones with 5-nitrofuraldehyde [12], the most active with respect to *S. aureus* 209P were IIIe and IIIf (MBC = 1 and 0.25 μg/ml, respectively).

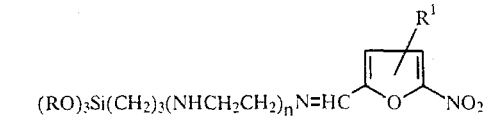


III

III: a-g a R^1 = R^2 = H; b R^1 = Me, R^2 = H; c R^1 = Et, R^2 = H; d R^1 = Ph, R^2 = H; e R^1 = Ph, R^2 = =$(CH_2)_2OH$; f R^1 = Ph, R^2 = $(CH_2)_6OH$; g R^1 = Ph, R^2 = $CH_2CH{=}CH_2$

Organosilicon derivatives IV of furan display antibacterial and fungicidal properties in a concentration of 1% [13].

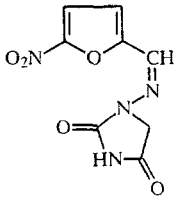
Compounds IV are easily attached to the surface of materials that have OH and other reactive groups (glasses, papers, wool), as a consequence of which they can be used as a means of sanitary treatment.



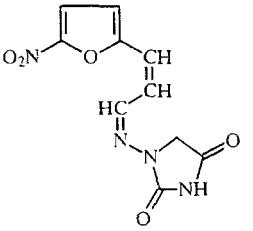
IV

IV R = alkyl R^1 = H, R^1 = halo R^1 = alkyl n = 0, 1, 2

An increase in the number of double bonds between the nitrofuran fragment and the nitrogen atom usually increases the antibacterial activity of the compound. Thus the activity of furagin is higher than the activity of nitrofurantoin.

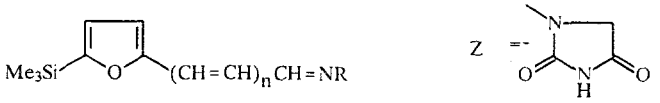


Nitrofurantoin



Furagin

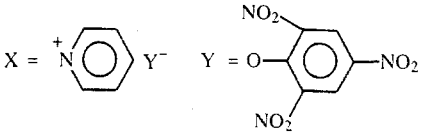
However, the antimicrobial activity of furan compounds V with respect to *S. aureus* 209P, *Escherichia coli* 675, and *Microsporum lanosum* was low (MBC of all of the compounds > 200 μg/ml). In the opinion of Lukevits and coworkers [14], the slight bacteriostatic activity of trimethylsilylfuran derivatives constitutes evidence for the decisive effect of the nitro group on the existence of antimicrobial activity in compounds of the furan series.



Va-g

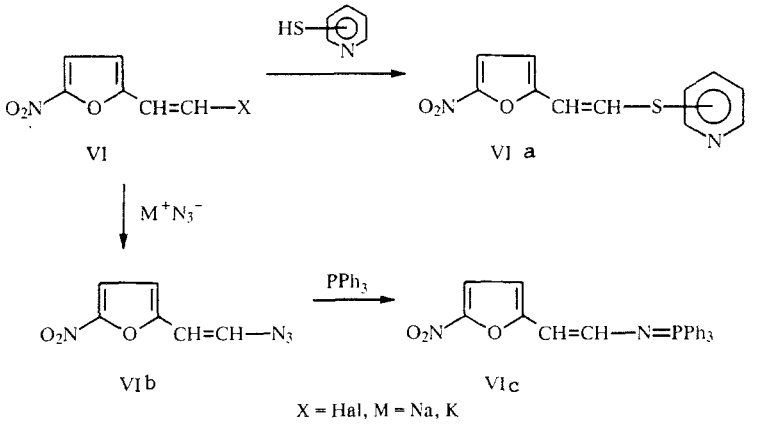
Va-g n = 0;a R = Z; b R = $NHCONH_2$; c R = $NHCSNH_2$; d R = $(CH_2COOH)CONH_2$; n = 1, e R = Z; f R = $NHCONH_2$; n = 2, g R = Z

The antibacterial properties of 2-(5-nitro-2-furyl)vinyl azide (VIb) were studied using the disk method for five forms of microorganisms (*Streptococcus pyogenes*, *Streptococcus faecalis*, *Bacillus subtilis*, *Proteus vulgaris*, *E. coli*) [15]. The compound has high inhibiting activity against Gram-negative and Gram-positive bacteria. Replacement of the N_3 group by $N{=}PPh_3$ (VIc) leads to a loss in activity with respect to Gram-positive bacteria, and the MBC with respect to Gram-negative bacteria (*E. coli*) is 50 μg/ml [16]. The antibacterial activity of VI with substituents



is very low (MBC = 0.4-25 mg/ml) [17]. The high bactericidal activity of thiopyridine derivatives VIa of 5-nitro-2-vinylfuran with respect to Gram-positive bacteria (for *S. aureus* and *B. subtilis*, MBC = 3.1 μg/ml; for *S. faecalis*, MBC = 12.5 μg/ml) and Gram-negative bacteria (for *P. vulgaris* and *Pseudomonas aeruginosa*, MBC = 3.1-3.5 μg/ml) does not depend on the position in which the pyridine ring is substituted [18].

Scheme 2



X = Hal, M = Na, K

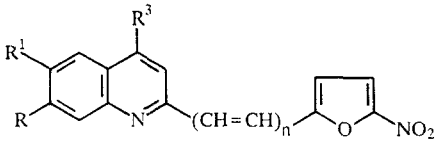
In the search for and the purposeful synthesis of effective biologically active substances in a series of a new type of nitrofuran compounds — nitrofurylvinyl(polyenyl)quinolines [19] — the biological activity of more than 150 compounds was predicted with a computer by means of the package of ORAKUL programs. The antimicrobial activity was predicted with the highest coefficient of confidence (K = 0.69). The nitrofuran ring and conjugation of the quinoline and nitrofuran components are characteristics of this activity. The results of the biological studies are presented in Table 1.

Compounds that have a hydroxy group in the 4 position have the lowest activity with respect to Gram-positive microorganisms. The introduction of additional conjugated bonds leads to a decrease in the activity [20-22]. The character of the substituent in the 4 position and the presence of a chlorine atom in the 7 position of the quinoline ring affect the antimicrobial activity.

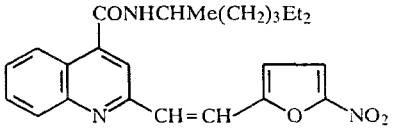
The original preparation khinifuril, created in the Institute of Organic Synthesis of the Latvian Academy of Sciences, was the result of this research.

Compound VII is particularly active with respect to Gram-positive coccal microflora with different degrees of pathogenicity, including those that are resistant to antibiotics, and, with respect to its activity, is significantly superior to nitrofuran preparations of the azomethine series — furatsilin, furazolidone, and furagin [23].

TABLE 1. Biological Properties of Some Nitrofurylvinyl(polyenyl)quinolines

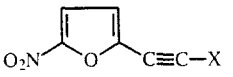


R	R^1	R^2	n	Minimum bacteriostatic concn.	
				S. aureus 209P	*B.mycoides* 537
H	H	H	1	0,21	0,21
H	H	H	2	6,6	0,8
H	H	H	3	16,6	16,6
H	H	H	4	33,3	33,3
H	H	OH	1	333,0	333,0
H	OCH_3	Cl	1	50,0	50,0
H	H	COOH	1	1,0	2,0
H	H	COOH	3	4,0	3,0
Cl	H	COONa	1	0,13	0,28
Cl	H	COOH	2	2,0	2,0
Cl	H	$NHCHMe(CH_2)_3NEt_2 \cdot 2H_3PO_4$	2	0,52	4,2
H	OCH_3	$NHCHMe(CH_2)_3NEt_2 \cdot 2H_3PO_4$	1	16,6	16,6
Cl	H	$NH(CH_2)_3OH \cdot 2H_3PO_4$	1	0,31	4,1
H	H	$CONHCHMe(CH_2)_3Et_2$	1	0,39	—
Furazolidone				2,0	0,4
Furagin				4,0	0,6

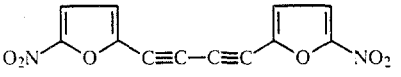


VII

In contrast to 5-nitro-2-furylethylenes, extremely little study has been devoted to the antibacterial activity of 5-nitro-2-furylacetylenes. Compounds VIIIa and VIIIb, which were obtained from 5-nitro-2-furylacetylene, as well as 1,4-bis(5-nitro-2-furyl)-1,3-butadiyne (IX), displayed high antimicrobial activity with respect to *B. subtilis* and *S. aureus* (both Gram-positive) and *E. coli* and *P. aeruginosa* (both Gram-negative) in concentrations of 1-10 μg/ml [24].



VIII



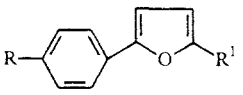
IX

VIII a X = I, b X = COOH

The study of the antimicrobial activity of arylfurans was continued. It was previously shown [25] that a significant number of 2-arylfuran derivatives that have a hydroxymethyl or amido group as a substituent in the 5 position of the furan ring display high tuberculostatic activity.

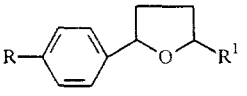
The activity of new arylfuran derivatives X with various substituents in the benzene and furan rings was studied for nine species of bacteria and five species of pathogenic fungi [26]. Almost all of the investigated compounds were found to be virtually inactive and did not suppress the growth of microorganisms at concentrations of 250-500 μg/ml. Only Xe had more pronounced activity with respect to Gram-positive and Gram-negative bacteria and pathogenic fungi (minimum suppressing concentration 31.2-250 μg/ml).

The tuberculostatic activity of Xa-e and XI in vitro was investigated (Table 2). *Mycobacterium tuberculosis* $H_{37}R_v$ and saprophytic mycobacteria of the ATCC-607 strain were used as test cultures.



Xa-e

X a-e a R = EtO_2C, R^1 = CH_2OH; b R = NH_2, R^1 = $CONH_2$; c R = NO_2, R^1 = $CONH_2$; d R = MeO, R^1 = $CONH_2$; e R = OH, R^1 = Me



XI

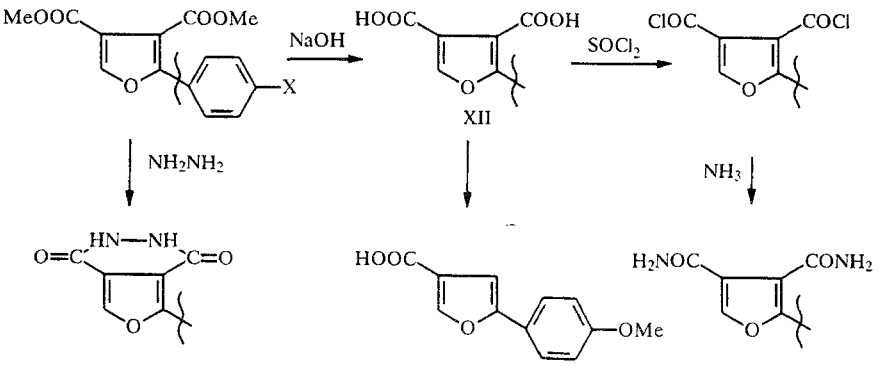
XI R = Br, R^1 = CH_2OH

TABLE 2. Minimum Inhibiting Concentration (μg/ml) of 2-Arylfurans Xa-e and XI

Compound	$H_{37}R_v$		ATCC-607
	without serum	with the addition of 10% serum	
Xa	2,0	250,0	1000
Xb	32,0	...	1000
Xc	0,5	16,0	1000
Xd	1,0	...	1000
Xe	4,0	...	32
XI	4,0	16,0	250

The antimicrobial activity of derivatives involving the carboxyl groups of 2-aryl-3,4-di(carboxy)furans XII was studied in experiments in vitro with respect to four species of Gram-positive bacteria, five species of Gram-negative bacteria, and five species of pathogenic fungi [27].

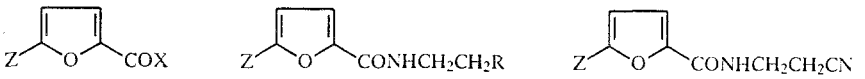
Scheme 3



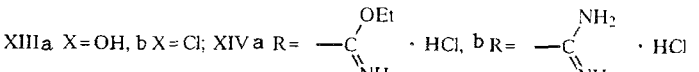
XII X = Me, X = OMe

The investigated compounds are virtually inactive. A comparison of the antimicrobial activity of the synthesized derivatives of XII and the previously investigated 2-aryl-5-carboxyfurans provides evidence for a sharp decrease in the activity of these compounds when the carboxyl substituent is moved from the α position to the β position of the furan ring.

The high antiviral activity of the antibiotics Novomycin, Mixoviromycin, and Distamycin-A, which contain an N-(2-amidinoethyl)carbamoyl fragment in their molecules, and the inhibiting activity displayed by N-(2-aminoethyl)benzamide and some of its analogs compelled Shridhar and Jogibhunta [28] to synthesize a number of 5-substituted N-(2-amidinoethyl)furan-2-carboxamides and investigate their bactericidal and fungicidal activity.



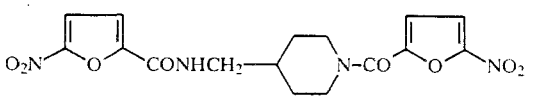
XIIIa, b XIVa, b XV



For all compounds,
Z = H, Z = Br, Z = NO_2

Not one of the compounds had activity against a number of pathogenic microorganisms.

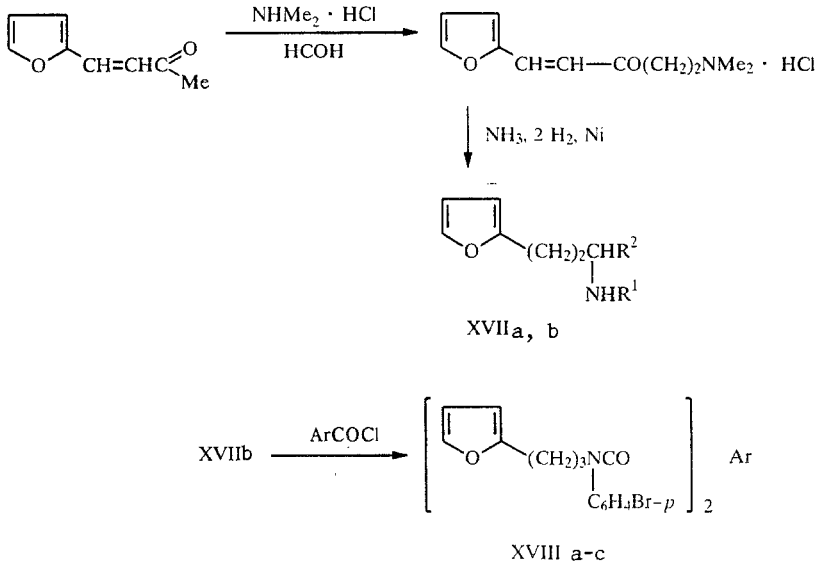
On the other hand, 5-nitro-2-furamides XVI have bacteriostatic activity [29].



XVI

The minimum bacteriostatic concentration of furan amines XVII and XVIII [30], which contain aminoalkyl and bromoaryl substituents (the latter were converted to amides) in their side chains, was 25-100 μg/ml in all cases.

Scheme 4

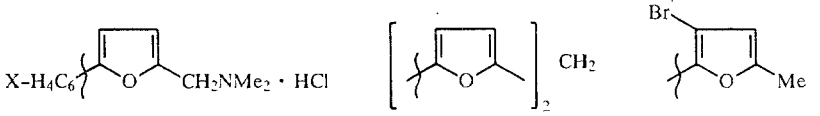


XVII a, b

XVIIb —ArCOCl→ XVIII a-c

XVII a,b R^1 = H; R^2 = $(CH_2)_2NMe_2$; b R^1 = C_6H_4Br-*p*, R^2 = H; XVIII a-c: a Ar=p-phenylene, b Ar= =2,3-dinitro-p-phenylene, c Ar = 2,4-dinitro-m-phenylene

A study of the antimicrobial activity of XIX-XXI with respect to three species of acid-resistant mycobacteria showed [31] that all of the investigated compounds have pronounced activity with respect to the mycobacteria of tuberculosis of the human type (the $H_{37}R_v$ strain). Compounds that contain a Cl atom in the benzene ring were found to be the most effective (Table 3).



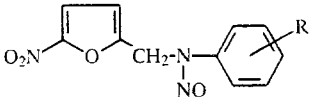
XIXa-f XXa-c XXI a,b

XIXa X = Cl, bX = Me, c X = OMed X = H, e X= NHCOMe, f X = NO_2

XX aX = Cl, b X = Me, c X = NO_2

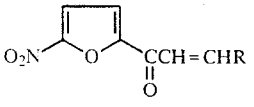
XXI aX = Br, b X = Cl

A comparison of the biological activity of compounds with the general formula XXII with 5-nitrofurfurylaniline with respect to *S. aureus*, *Staphylococcus epidermis*, *B. subtilis*, *E. coli*, and *Klebsiella pneumoniae* was made in [32]. The N-nitroso derivatives proved to be somewhat more active.



XXII

The condensation of 5-nitro-2-acetylfuran with RCHO (R = substituted Ph) gave furylpropenones XXIII. Compounds that contain alkyl, halo, and hydroxy substituents in the aryl residue displayed significant activity with respect to *Aerobacter aerogenes* and *E. coli* [33].

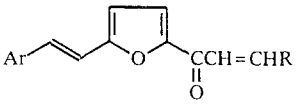


XXIII

The antimicrobial activity of phosphonium salts and imides of the 5-styryl-2-acetylfuran series and the α,β-unsaturated ketones XXIV obtained from them was investigated [34].

TABLE 3. Antituberculosis Activity (μg/ml) of 3- and 5-Substituted 2-Arylfurans

Compound	Strain of mycobacteria			
	$H_{37}R_V$		M. tuberculosis avium	acid-resistant saprophyte B_5
	without serum	with the addition of serum		
XIXa	2,0	10	62,5	62,5
XIXb	16,0	16	125,0	125,0
XIXc	31,2	—	500,0	500,0
XXa	2,0	1000	500,0	500,0
XXb	62,5	2	500,0	500,0
XXIa	32,0	—	—	—
XXIb	4,0	250	—	—



XXIV

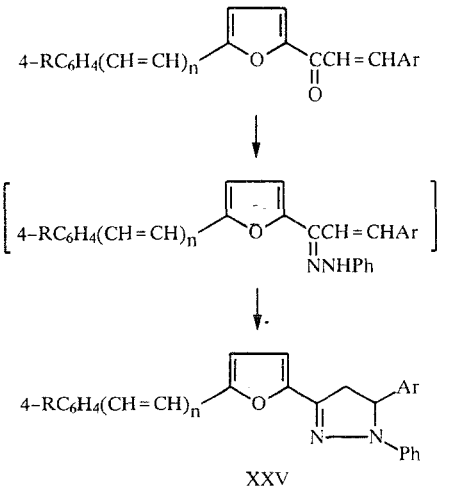
XXIV R = Ph, R = 2-furyl

The antibacterial activity of the synthesized compounds is expressed to a high degree with respect to Gram-positive bacteria. Complete furan analogs of chalcone that contain styryl substituents in the 5 position of the furan ring display, with respect to the Gram-positive bacteria *S. aureus* and *B. subtilis*, antimicrobial activity that is higher by a factor of 2-8 than that of chalcones that are partially substituted by a furan ring (the minimum suppressing concentrations are 62.5-125 μg/ml and 500 μg/ml, respectively).

The antibacterial activity of 5-styryl-2-furoylmethyltriphenylphosphonium imides with respect to Gram-positive microorganisms is lower by a factor of 2-4 than the activity of their phosphonium salts. Replacement of the styryl radical by an anthracenylethyl radical leads to an increase in the antimicrobial activity by a factor of 2-8 or more.

In the 1-[5-(methoxystyryl)-2-furoyl]-3-(p-R-phenyl)propenone series the antimicrobial activity with respect to *S. aureus*, *Serratia marcescens*, and *P. vulgaris* increases by a factor of two when the OCH_3 group is replaced by Cl or Br. In a continuation of these studies new furan derivatives — Δ^2-pyrazolines that contain styryl and phenylbutadienyl substituents in the 5 position of the furan ring — were synthesized, and their antimicrobial activity was studied [35]. The Δ^2-pyrazolines were synthesized by condensation of furan analogs of chalcone with phenylhydrazine and subsequent heterocyclization of the unstable hydrazones formed in the first step.

Scheme 5



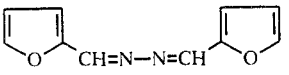
XXV

XXV R = H, R = Br, R = Cl, R = Me, R = Me_2N; Ar = Ph, Ar = 2-furyl

Thirteen standard strains belonging to 11 genera — *S. aureus* 209, *S. aureus* ATCC 25923, *E. coli* K-12, *B. subtilis*, *P. aeruginosa* 136, *S. marcescens* 1266, and *P. vulgaris* 410 — were used as test microbes. The investigated compounds display antimicrobial activity with respect to Gram-positive and Gram-negative bacteria. Replacement of the furan ring in the 5 position of the pyrazoline ring by a phenyl ring leads to an increase in the antimicrobial activity with respect to *Staphylococcus aureus* but decreases the activity with respect to the hay bacillus. The antimicrobial activity of the investigated compounds is not affected by H, Br, Cl, and MeO substituents in the 4 position of the styryl ring.

Information on the synthesis of furanthiocarboxyhydrazides and their complexes with transition metals has been presented as a confirmation of the prevailing hypothesis that the N—C=S group is one of the active links in compounds that have antibacterial activity [36]. All of the compounds exhibited activity. The complexes with Cu(II), Zn(II), and Ni(II) have higher activity with respect to Gram-positive bacteria than furan-2-thiocarboxyhydrazides and other complexes. The complex with Ag(I) is more active with respect to Gram-negative bacteria.

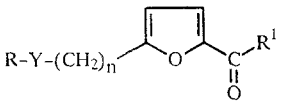
An investigation of the antimicrobial and antiphage activity of furaldazin (XXVI) and its Pt(II), Pd(II), W(V,0), and Mo(V) complexes showed that all of the complexes, like the starting ligand, have moderate antimicrobial activity [37]. The minimum bacteriostatic concentration for all of the test microbes used was 25-100 μg/ml. One may note only the somewhat higher activity of the platinum complex with respect to proteus (MBC = 12 μg/ml).



XXVI

3. ANTIVIRAL ACTIVITY

Furyl ketones XXVII with a long alkyl or alkenyl chain in the 5 position of the furan ring and attached to the furan ring through an ether (thioether) bridge or through a hydroxymethyl (thiomethyl) group have activity with respect to retrovirus infections, including the HSV-1 virus [38].

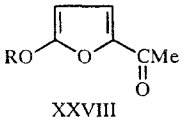


XXVII

XXVII R = C_{8-20} alkyl R = C_{8-20} alkyl with 1-4 double bonds, R^1 = C_{1-6} alkyl; Y = bond Y = O, Y = S; n = 0, 1

The antiviral properties of the compounds were determined from their ability to inhibit the growth and replication of the oncogenic retrovirus of leukemia in mice in vitro. The IC_{50} (the concentration that gives 50% inhibition of the virus) for the series of investigated compounds was 1-10 μg/ml. Methyl 5-tetradecylthiomethyl-2-furyl ketone (IC_{50} = 1 μg/ml) and methyl 5-tetradecyloxy-2-furyl ketone (IC_{50} = 4 μg/ml) were additionally investigated with respect to HIV. At a concentration of 30 μg/ml the inhibition was 100% in both cases; at a concentration of 15 μg/ml methyl 5-tetradecylthiomethyl-2-furyl ketone suppressed the virus by 90%, as compared with 34% in the case of methyl 5-tetradecyloxy-2-furyl ketone.

Furyl ketones XXVIII have antirhinovirus activity [39].



XXVIII

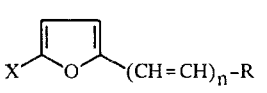
XXVIII R = C_{12-16} alkyl or alkenyl with 1-4 double bonds

Compounds XXVIII significantly inhibit the cytopathic effect of a virus. For example, when XXVIII in a concentration of 4 μg/ml was added to cell cultures along with rhinovirus 100 TC ID_{50}, the cytopathic effect of the virus decreased by 87% as compared with the control.

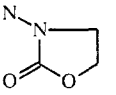
4. SEARCH FOR PESTICIDES AMONG FURAN DERIVATIVES

A study of the fungicidal properties of XXIX [40] demonstrated the expediency of searching for new fungicides among nitro derivatives of furan.

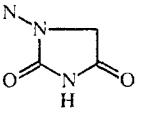
2-Nitrofuran and a large number of its derivatives in dilute solutions suppress the development of the mycelium of many pathogenic fungi:



XXIX



A



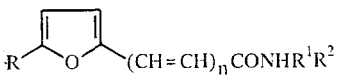
B

XXIX n = 0, 1; X = H, X = Me, X = NO_2; R = H, R = CHO, R = $CH(OEt)_2$, R = $CH(OCOMe)_2$, R = = COMe, R = CH=NOH, R = CH=N—$C_6H_4R^1$; R = CH = $NNHCOR^2$, R = COOH, R = $COOR^3$, R = = $CONR^4R^5$, R = CN, R = CF_3, R = NO_2, R = CH=$NN(CONH_2)CH_2COOH$, R = CH = A, R = CH = B, R^1 = 4-OEt, R^2 = H, R^2 = NH_2, R^2 = 4-NO_2-C_6H_4, R^2 = Ph, R^2 =5-nitro-2-furyl, R^2 = 2-furyl R^3 = Me, R^3 = Et; R^4 = H, R^4 = Me, R^4 = Et, R^4 = C_4H_9; R^5 = H, R^5 = Me, R^5 = Et, R^5 = C_4H_9

The presence of substituents in the 2 position of the furan ring changes the selectivity of the fungicidal activity of the compounds to a great degree. The nitrofuran molecule is activated by CH=CH, CN, C=O, CH=NOH, CON, CF_3, and other groupings. Most hydrazones of the furan series, including the known antibacterial preparations furatsilin, furadonine, and furazolidone, have little fungicidal activity.

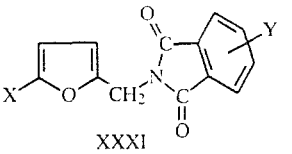
A number of 5-nitro-2-furylacrylic acid amides XXX with aliphatic and aromatic substituents in the amido group, a number of N,N-dimethyl-N′-phenylsulfamide derivatives containing a furan ring, and furfurylphthalimide derivatives XXXI with a halogen atom in the benzene ring were obtained and tested as fungicides on standard test objects [41].

Under laboratory conditions the greatest activity was exhibited by 5-nitro-2-furylacrylic acid N-furfurylamide, which, however, was inferior to the standard — tetramethylthiuram disulfide.



XXX

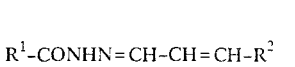
XXX R = H, R = NO_2; R^1 = Ph, R^1 = Et, R^1 = Me_2CHCH_2, R^1 = furfuryl , R^1 = Ph—CH_2; R^2 = H, R^2 = Et, R^2 = SO_2NMe_2



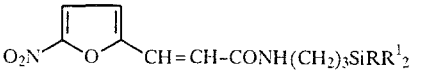
XXXI

XXXI X = H, X = NO_2; Y = H, Y = Cl, Y = I

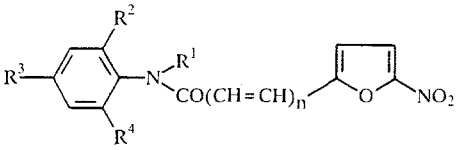
An attempt to establish a relationship between the chemical structure and the fungicidal activity was undertaken in [42] in the case of 40 derivatives of 5-nitrofuran acids. In addition to data on the previously described [40] furan acids and their esters and amides, data on the fungicidal activity of furancarboxylic acid hydrazides XXXII, silicon-containing amides XXXIII, and 5-nitrofurancarboxylic acid anilides XXXIV was presented.



XXXII



XXXIII



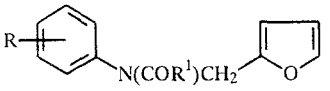
XXXIV

XXXII R^1 = 2-furyl, R^2 =5-nitro-2-furyl; XXXIII R = Me, R = Et, R = C_3H_7, R = C_4H_9, R = =C_7H_{15}, R = $C_{10}H_{21}$; R^1 = Me, R^1 = Et, R^1 = C_3H_7,; R^1 = C_4H_9, R^1 = C_6H_{13}; XXXIV R^1 = H, R^1 = =CHCOOMe, R^1 = Me, R^1 = CH_2CH_2COOMe, R^1 = CH_2COOEt, R^1 = CHCOOMe; R^2 = H, R^2 = Me; R^3 = H, R^3 = Me; R^4 = H, R^4 = Me

Silicon-containing 3-(5-nitro-2-furyl)acrylic acid amides exhibit the greatest activity with respect to phytophthorosis of tomatoes [XXXIII (R = R^1 = C_3H_7, C_4H_9; R = CH_3, R^1 = C_3H_7; R = CH_3, R^1 = C_6H_{13}; R = $C_{10}H_{21}$, R^1 = CH_3) suppress the growth by 67% as compared with Zineb] and botrytis rot of beans [XXXIII (R = CH_3, R^1 = C_4H_9; R = CH_3, R^1 = C_6H_{13}) suppress the growth by 75% as compared with Euparen].

Most of the investigated anilides displayed a moderate level of fungicidal activity with respect to phytophthorosis of tomatoes and botrytis rot of beans. The activity of one of the 5-nitrofurancarboxylic acid anilides (IOS-3358) with respect to phytophthorosis of potatoes was comparable to that of the standard — Metalaxyl.

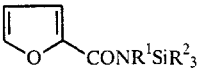
The fungicidal activity of N-furfurylanilides XXXV was studied [43]. Compound XXXV (R = 2,6-Me_2, R^1 = 2-furyl) has fungicidal activity that exceeds the activity of Kitazin P.



XXXV

XXXV R = H; R = 2,6-Me_2; R^1 = Et, R^1 = CH_2OMe, R^1 = 2-$MeOC_2H_4$; R^1 = 2,4-$Cl_2C_6H_3$, R^1 = 2-furyl, etc.

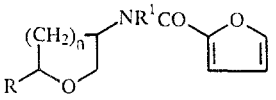
The fungicidal activity of organosilicon pyromucic acid amides XXXVI is comparable to the activity of carbendazole [44].



XXXVI

XXXVI R^1 = Pr, R^1 = Bu, R^1 = Me_2CHCH_2, R^1 = Ph, R^1 = 2-MeC_6H_4, R^1 = 4-MeC_6H_4, R^1 = 2-ClC_6H_4, R^1 = 2,4-$Cl_2C_6H_3$; R^2 = Me, R^2 = EtO

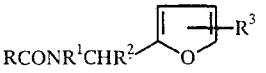
When the pesticide content is 0.8 g/kg of seeds, XXXVII ensures 90% protection of sugar beet seeds from *Pythium ultimum*.



XXXVII

XXXVII *n* = 1, R = H, R^1 = 2,6-$Me_2C_6H_3$ [45]

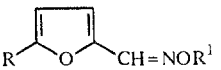
Amides XXXVIII and compositions that contain them are active with respect to *Plasmopara viticola*, *Venturia inaequalis*, and *Cercospora arachidicola*. A concentration of 100 μg/ml ensures protection of tomatoes from *Phytophthora infestans* [46].



XXXVIII

XXXVIII R = (un)substituted alkyl, R = aryl, R = heterocycle; R^1 = H, R^1 = (un)substituted alkyl; R^2 = cyano, R^2 = $CSNH_2$, R^2 = alkoxy, R^2 = carbonyl, R^2 = carbamoyl; R^3 = H, R^3 = Me, R^3 = Cl

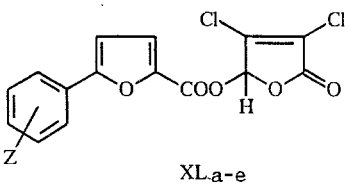
5-[(3,4-Dimethoxyphenyl) or (4-chlorophenyl)]furan-2-carboxaldehyde O-[(methylamino)carbonyl] oximes XXXIX exhibit fungicidal activity [47].



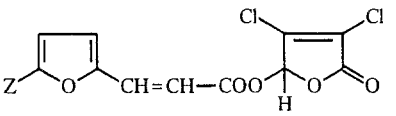
XXXIX

XXXIX R = 3,4-$(MeO)_2C_6H_3$, R^1 = CONHMe; R = 3,4-$Cl_2C_6H_3$, R^1 = H; R = 4-ClC_6H_4, R^1 = CONHMe

The synthesis of new fungicidally active 5-acyloxy-3,4-dichloro-5H-furan-2-ones XL and XLI was described in [48].



XLa-e

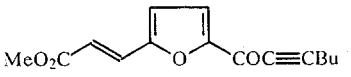


XLIa,b

XLa Z = H,b Z = NO_2, cZ = Cl,d Z = 3-NO_2, eZ = 3-CF_3; XLIa Z = H,b Z = NO_2

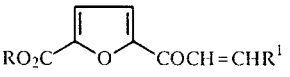
The investigated compounds exhibited fungicidal activity with respect to *Tilletia caries*, *Fusarium avenaceum*, *Botrytis cinerea*, *Alternaria alternata*, and *P. infestans* that is comparable to that of the standards Vitavax, Captan, and Dithan. Compounds XLa and XLIa had the highest activity.

Derivatives that are similar in structure to the natural compound dihydrovierone (XLII), which has fungicidal properties [49],



XLII

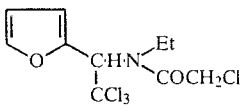
and 2-carboxyfuryl α,β-unsaturated ketones XLIII [50], which are also fungicides, were synthesized.



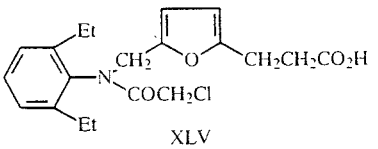
XLIII

XLIII R = Bu, R^1 = 4-, 3-, 2-$O_2NC_6H_4$, R^1 = 4-BrC_6H_4, R^1 = 4-ClC_6H_4, R^1 = 2-FC_6H_4, R^1 = Ph, R^1 = =4-$MeOC_6H_4$; R = H, R^1 = 3-BrC_6H_4, R^1 = Ph, R^1 = 4-MeC_6H_4; R^1 = 4-$MeOC_6H_4$ etc.

There have been reports of furan derivatives that are used as herbicides — N-substituted chloroacetamides XLIV [51], which exhibit activity at a concentration of 30 g/are, and heteroarylamides XLV [52], which are active herbicides.

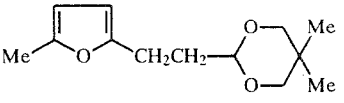


XLIV



XLV

Furans XXIX (for example, X = NO_2; n = 0, 1; R = CN, NO_2, CH=NOH, CF_3, CH=$NNHOC_6H_5$, etc.) exhibit herbicidal activity. Unsubstituted 2-nitrofuran has almost no effect on the development of plants [40]. 1-(5-Methyl-2-furyl)-2-(5,5-dimethyl-1,3-dioxan-2-yl)ethane (XLVI), on the other hand, has a stimulating effect on the growth of tomatoes [53].



XLVI

A study of the insecto-acaricidal activity showed that XXIX exhibit a certain degree of activity with respect to flies and rice weevil beetles in a concentration of 0.5% (for X = NO_2, n = 1, and R = CF_3, 83% as compared with the standard — Aldrin; for X = H, n = 1, and R = NO_2, 70%; for X = NO_2, n = 1, and R = CN, 90% as compared with the standard — Kelthane) [40].

Compounds XXX and XXXI exhibit weak insecto-acaricidal properties with respect to flies, arachnoid mites, and rice weevil beetles [41].

TABLE 4. Cytostatic and Antitumorigenic Activity of Uracil Derivatives of Furan*

Compound	EC_{50}, μg/ml	Strains of tumors			
		lympholeucosis P 388		Lewis lung carcinoma	
		OD/MTD, mg/kg	T/C, %	dose, mg/kg	T/C, %
XLVII a	1,0	320	85	180	95
XLVII b	1,0	320	100	180	95
XLVII c	10,0	320	88	180	95
XLVII d	32,0	320	83	100	95
XLVII e	10,0	1000	103	180	95
XLVII f	1,0	100	131	32	128
XLVII g	10,0	100	88	32	95
XLVIII	1,0	1000	125	320	135

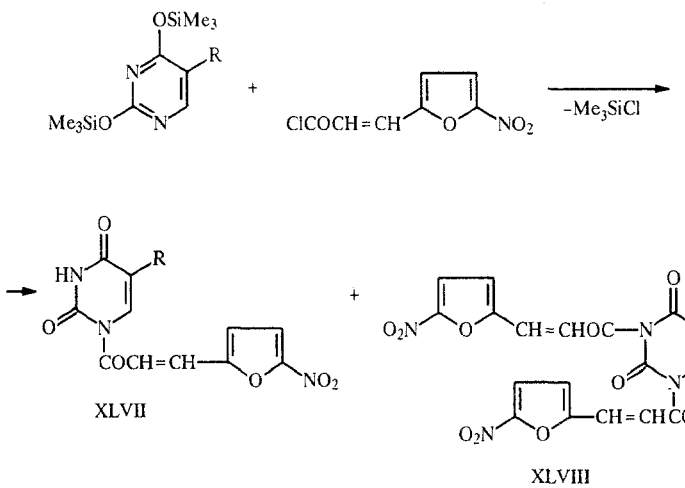
*EC_{50} is the concentration in micrograms per milliliter that suppresses the growth of melanoma B 16 by 50%; OD is the daily optimum dose, MTD is the maximally tolerable dose, and T/C is the ratio of the lifetimes in test (T) and control (C) groups.

5. CYTOSTATIC AND ANTITUMORIGENIC ACTIVITY

The antitumorigenic preparation ftorafur, the active source of which is 1-(2-tetrahydrofuryl)-5-fluorouracil, is widely known [54]. 5-Nitrofuran derivatives that contain azomethine and vinyl groups also have antitumorigenic activity [55].

Data from a study of the cytostatic and antitumorigenic activity of uracil derivatives of 3-(5-nitro-2-furyl)acrylic acid, which were synthesized via the following scheme, are presented in Table 4:

Scheme 6



XLVIIa R = H, bR = Me, cR = $GeMe_3$, d R = $SiMe_3$, e R = Br, f R = F, g R = NO_2

Thus, 5-fluorouracil derivatives of 3-(5-nitro-2-furyl)acrylic acid exhibited antitumorigenic activity with respect to lympholeucosis P 388 that is comparable to that of ftorafur [56].

Data from a study of the antitumorigenic activity of 5-trimethylsilylfuran derivatives with azomethine and vinyl groups attached to the ring (V) are presented in Table 5 [14].

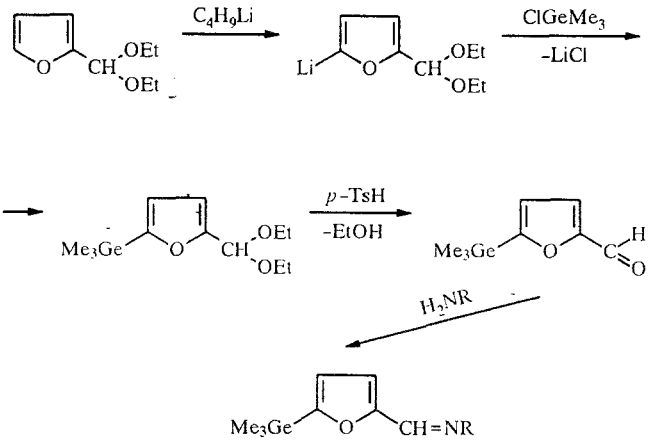
The most pronounced antitumorigenic activity was noted for Lewis lung carcinoma and melanoma B 16, the growth of which is retarded by 62% and 52%, respectively, when Vd is introduced. Erlich's ascitic tumor and sarcoma 37 are less sensitive to V. Compound Vd had no effect on leukemias L1210 and P 388.

5-Trimethylgermyl derivatives of furfural that are similar to V were synthesized in [57]:

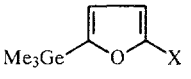
TABLE 5. Maximum Antitumorigenic Effect of 5-Trimethylsilylfuran Derivatives

Compound	Prolongation of life		Retardation of tumor growth, %		
	Erlich's ascitic tumor	sarcoma-37	Lewis lung carcinoma	melanoma B 16	adenocarcinoma 755
Va	—	45	23	45	—
Vb	22	28	52	40	18
Vc	0	0	33	40	—
Vd	26	—	62	52	15
Ve	0	26	45	32	—

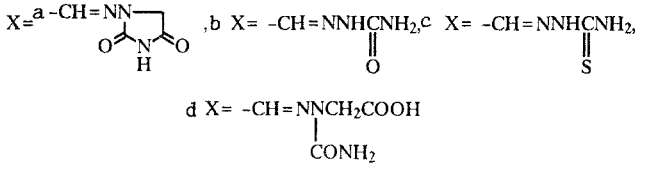
Scheme 7



The reaction of 5-trimethylgermylfurfural with aminohydantoin, semicarbazide, thiosemicarbazide, and semicarbazide-acetic acid gave XLIX.

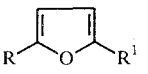


XLIX a-d



The most pronounced antitumorigenic activity among the investigated compounds was noted for Lewis lung carcinoma and melanoma B 16, the growth of which is retarded by 48% (XLIXc, d) and 43% (XLIXb). Erlich's ascitic tumor and sarcoma 37 proved to be insensitive to these compounds. Just as in the case of the silicon-containing derivatives, the investigated compounds had no effect on leukemias L1210 and P 388.

A number of mono- and disubstituted furan derivatives with general formula L were synthesized and investigated in a culture of melanoma B 16 cells [58-60].



L

L R = H, R = $SiMe_3$, R = Me_2EtSi, R = $PhSiMe_2$, R = Ph_2SiMe, R = $CN(CH_2)_3SiMe_2$, R = Me_3C, R = =MeS, R = BuS, R = $CH(OEt)_2$, R^1 = CHO, $CH(OEt)_2$, $HOCHSO_3Na$, $CHNCH_2CH(OMe)_2$, $CHNN(CH_2COOH)CONH_2$, $CH(OCH_2CH_2O)$, $CHNNHCONH_2$, $SiMe_3$

TABLE 6. Data from a Study of the Antitumorigenic Activity of N-Salicyloyl-N′-(2-furylthiocarbonyl)hydrazine and Its Complex with Cu in Mice with Transplanted Tumors

Form of tumor	Dose, mg/kg	T/C, %		No. of mice that survived for more than 6 months	
		LI a	LI b	LI a	LI b
Fibrosarcoma MFS_8	5	152	131	4 (50)	2 (25)
	5*	139	111		
	10	146	130	3 (50)	
	10*	137	146		
	25	143	132	5 (50)	3 (38)
	25*	158	135	6 (75)	6 (75)
	50	167	132	6 (75)	4 (40)
Dalton's lymphoma	5	128	104		
	10	157	130		
	25	195	165		

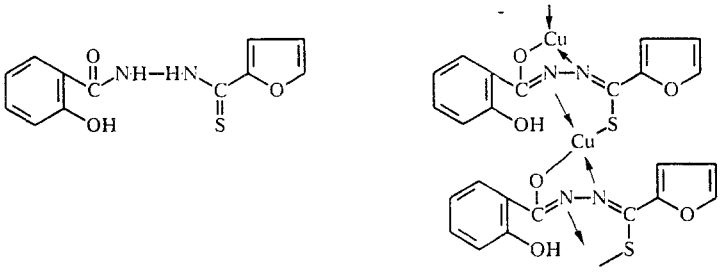
*Subcutaneously; the rest of the doses were administered intraperitoneally.

The cytotoxicity of the substances was determined as the concentration in micrograms per milliliter that suppresses the growth of the cells by 50% (EC_{50}). The functional thresholds of high and moderate cytotoxicity were 3.2 and 32 μg/ml, respectively. Furfural and its carbofunctional derivatives are noncytotoxic. A significant (by a factor of 3-10) increase in the cytotoxicity as compared with furfural is observed when various alkylsilyl and alkylthio substituents are introduced into the 5 position of the furan ring. The character of the substituents attached to silicon does not affect the cytotoxicity of the compounds.

The antitumorigenic activity of compounds that have cytotoxicity in oncogenic strains of mice — lympholeucosis P 388 and Lewis lung carcinoma — as compared with the known antitumorigenic preparations Natulan and hexamethylmelamine was investigated. Substances that in optimum doses increase the lifetime of mice with lympholeucosis P 388 by 28-36% and retard the growth of Lewis lung carcinoma by 55-68% were discovered.

In contrast to thiosemicarbazide derivatives, the cytotoxicity and antitumorigenic activity of which have been studied in sufficient detail over the last 30 yr, not much data on the antitumorigenic activity of thiohydrazide derivatives are available, despite their structural similarity to thiosemicarbazide.

Data from an investigation of the antitumorigenic activity of N-salicyloyl-N′-(2-furylthiocarbonyl)hydrazine (LIa) and its complex (LIb) with Cu in mice with transplanted tumors are presented in Table 6 [61].



LIa,b

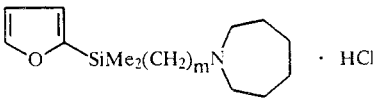
The results show that both compounds are active with respect to transplanted tumors, reducing them after a single injection. Proceeding from morphological studies, Agrawal and coworkers [61] assume that the compounds inhibit the mitotic activity of the tumor cells, since mitotic fragments were not observed in the treated tumors. This effect is apparently due to suppression of DNA reproduction. The development of lymphocytes and macrophages in the mass of the tumor after treatment with antitumorigenic compounds also constitutes evidence that the immune system is activated. The sharp decrease in the mass of the tumor at a dose of 50 mg/kg indicates that large doses are cytotoxic. A dose of 25 mg/kg is more effective, since it destroys the cells to a lesser extent. It was established that the complex of Cu formed in the organism from the free ligand and endogenous copper affects the tumor.

TABLE 7. Pharmacological Activity of Perhydroazepinoalkylsilane Hydrochlorides

m	LD_{50}, mg/kg	ED_{50}, mg/kg			
		"rotating rod" test	"tube" test	hypothermia	analgesia
1	78 (58—105)	9 (6—15)	9 (6—15)	26 (11—35)	26 (11—35)
2	72 (38—137)	6 (4—8)	6 (4—8)	23 (14—39)	28 (15—53)
3	70 (64—77)	14 (7—28)	13 (8—19)	23 (14—39)	38 (25—59)

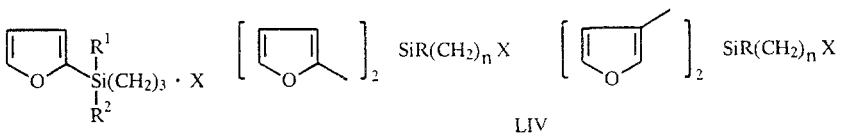
6. PSYCHOTROPIC ACTIVITY

It was previously established [62] that 3-aminopropylsilanes and their hydrochlorides with 2-furyl groups attached to silicon have neurotropic activity of the depressive type. A pharmacological investigation of furyl-containing perhydroazepinoalkylsilane hydrochlorides with the general formula LII [63], the results of which are presented in Table 7, was carried out to evaluate the psychotropic activity of aminoalkylsilanes as a function of the location of the amino group relative to the silicon atom.

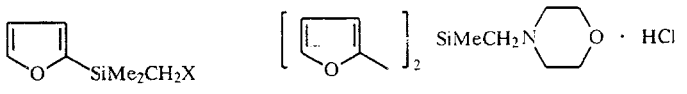


LII

A study [64] was devoted to the determination of the effect of the alkyl substituent attached to the silicon atom, the number of furyl groups, the location of the silyl substituent in the ring, and the number of methylene groups between the amino nitrogen atom and the silicon atom on the spectrum of pharmacological activity of hetarylaminoalkylsilane hydrochlorides LIII-LVI.



LIII LIV



LV LVI

LIII X = N-methylpiperazinyl·2HCl R^1 = Me, R^2 = Me, R^2 = Et, R^2 = Bu, R^2 = $C_{12}H_{25}$, R^1 = R^2 = Et; X = morpholyl·HCl, R^1 = Me, R^2 = Bu, R^2 = $C_{12}H_{25}$; R^1 = R^2 = Et. LIV n = 3, R = Me, X = pyrrolidyl·HCl, piperidyl·HCl, morpholyl·HCl; n = 3, R = Bu, X = N-methylpiperazinyl·2HCl morpholyl·HCl, LV X = pyrrolidyl· HCl, morpholyl·HCl,

All of the synthesized compounds are characterized by a moderate degree of neurotropic activity of the depressive type (ED_{50} 10-100 mg/kg). Similar principles between their chemical structure and pharmacological activity were discovered for 2-furyl-γ-morpholinopropylsilane and 2-furyl-γ-(N-methylpiperazino)propylsilane derivatives. Thus, the toxicity and neurotropic activity of 2-furylmorpholinopropylsilanes with mixed alkyl substituents are greater than for the dimethyl and diethyl derivatives; as in the piperazinopropylsilane series, the dodecyl derivative has the highest depressive activity.

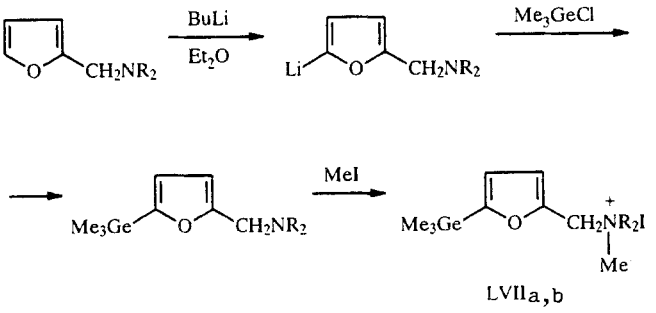
The morpholinopropylsilane derivatives are less toxic than the corresponding methylpiperazinopropylsilane derivatives. The introduction of a second furyl group into the N-methylpiperazinopropylsilane molecule leads to an increase in the acute toxicity as compared with the monofuryl derivative vis-à-vis a slight change in the neurotropic effect. A second furyl group in morpholinopropylsilane, on the other hand, leads to a decrease in the pharmacological activity.

Morpholinomethylsilane has greater psychotropic activity than the γ-morpholinopropyl derivative. The introduction of a second furyl group into the morpholinomethylsilane molecule is accompanied by an increase in the therapeutic index both due to a decrease in the toxicity of the compound and as a result of a decrease in the effective dose.

The neurotropic activity of di(3-furyl)-γ-morpholinopropylsilane is manifested only in doses close to the lethal amount.

The psychotropic activity of furan-containing germyl-substituted amines XLIXa-c and LVIIa, b was studied [65].

Scheme 8



LVIIa,b

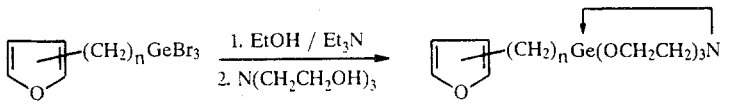
LVIIa R = Me, b R = Et

Methiodide LVIIb exhibited the highest depressive activity (the ED_{50} values in the "rotating rod" and "tube" tests were 4.1 and 2.6 mg/kg, respectively, and I = ED_{50}/LD_{50} = 19.9 and 31.3). Replacement of the diethyl group by a dimethyl group in the methiodide structure significantly decreases the depressive activity (I decreases by a factor of 6-10).

All of the investigated compounds exhibit antagonistic activity with respect to the pharmacological effects of Phenamine, as well as antihypoxic activity (by 21-64%) in doses of 5-50 mg/kg.

Furylgermatranes LVIII [66-69] have low toxicity; their LD_{50} = 1630-2050 mg/kg. When the germatranyl group is separated from the furan ring by one methylene group, the toxicity is even lower — 2960 mg/kg. The toxicities of all of the investigated germatranes are considerably lower than the toxicities of the corresponding silatranes (by one to two orders of magnitude).

Scheme 9



LVIII a-c

LVIII 2-furyl n = 0; 3-furyl n = 0; 2-furyl n = 1.

Data from a study of the psychotropic activity of LVIIIa-c are contained in Table 8.

The highest neurotropic activity among the furylgermatranes was noted for 2-furylgermatrane LVIIIc, the therapeutic indexes for which exceed the corresponding values for Aminazine by a factor of approximately three.

All of the furylgermatranes in doses of up to 50 mg/kg extend the duration of Hexenal narcosis by a factor of 1.5-2, which constitutes evidence for their pronounced sedative activity, and also exhibit antihypoxic activity.

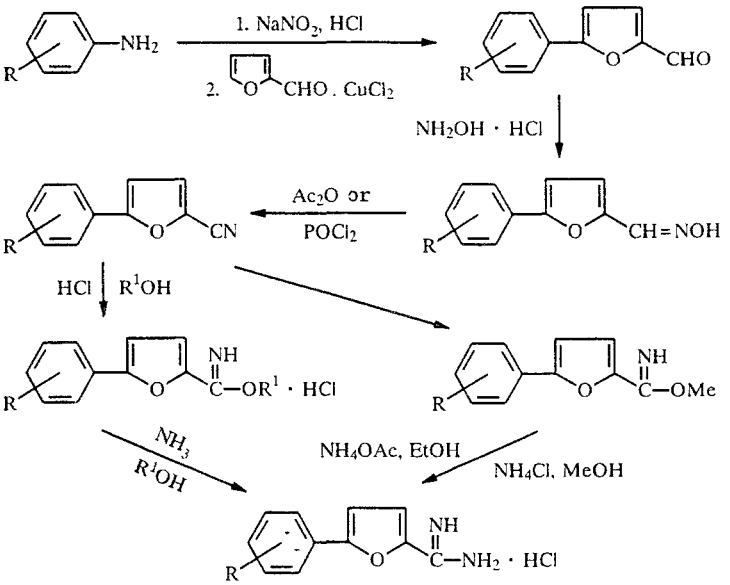
Thus, organosilicon and organogermanium derivatives of furan are a promising class of compounds for the search for new psychotropic medicinal preparations.

A chemical class of potential antidepressants was reported in [70]. A series of 5-phenyl-2-furamidines LIX was investigated as antidepressants.

TABLE 8. Neurotropic Activity of Furylgermatranes

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg (I = ED_{50}/LD_{50})				
		test				
		"rotating rod"	"tube"	pull up	hypo-thermia	analgesia
LVIII a	2050	41 (50)	41 (50)	35 (58,6)	45 (45,6)	71 (28,9)
LVIII b	1630	71 (22, 96)	82 (19,9)	82 (19,9)	51 (31,9)	100 (16,3)
LVIII c	2960	21 (141)	22 (134,5)	18 (164)	22 (134,5)	100 (29,6)

Scheme 10



LIX

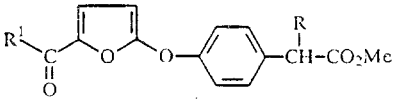
LIX R = H, R = 4-NO_2, R = 3-NO_2, R = 2-NO_2, R = 4-Cl, R = 2-Cl, R = 4-F, R = 2-F, R = 3-CF_3, R = 4-NH_2, R = 3-NH_2, R = 2-NH_2, R = 4-Br, R = 2-Br, R = 4-MeO, R = 4-MeCO, R = 4-OH, R = 4-MeS, R = 4-Me, R = 4-Me$(CH_2)_5$O, R = 4-$MeCH_2OCO$, R = 4-Me_2CH, R = 3-Cl

The presence of a nitro or amino group in the ortho position of the phenyl ring intensifies the antidepressant activity. The activity of these compounds is comparable to the activity of the tricyclic antidepressants used in clinical practice. However, these compounds do not give undesirable anticholinergic and antihistamine side effects and also do not have an unfavorable effect on the cardiovascular system.

7. ANTI-INFLAMMATORY PROPERTIES

Arylalkanoic acids constitute the basis for the widely used nonsteroidal anti-inflammatory agents Naproxen and buprofen. However, their prolonged use is harmful to the gastrointestinal tract.

Modification of phenylalkanoic acids gave a series of furanoxyphenylalkanoic acid esters LX, some of which have anti-inflammatory properties (see Table 9) [71].



LX a-h

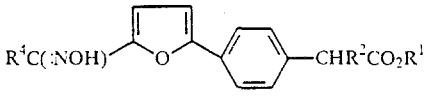
LXa R = R^1 = H; b R = H, R^1 = Me; c R = H, R^1 = Et; d R = Me, R^1 = H; e R = R^1 = Me; f R = Me, R^1 = Et; g R = Et, R^1 = H; h R = Et, R^1 = Me

TABLE 9. Results of an Initial Investigation of the Anti-inflammatory Properties of Furanoxyphenylalkanoic Acid Esters LX

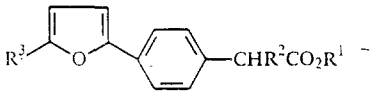
LX	Anti-inflammatory activity, % suppression of carrageenin-induced edema	LX	Anti-inflammatory activity, % suppression of carrageenin-induced edema
a	47,09	e	16,3
b	34,14	f	27,84
c	8,16	g	—
d	8,85	h	6,47

The LD_{50} value in mice for all of the compounds was 1000 mg/kg. All of the compounds except LXg exhibited activity ranging from moderate to good. The anti-inflammatory activity of LXa was studied in greater detail in a comparison with the standard medicinal agents Indomethacin and Phenylbutazone. As a result, LXa, with respect to its effect on carrageenin-induced edema, is almost equal to Phenylbutazone but is inferior to Indomethacin.

The synthesis of phenylalkanoic acid derivatives LXI and LXII, which have anti-inflammatory, analgesic, and antipyretic properties, has also been reported [72, 73].



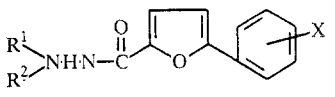
LXI



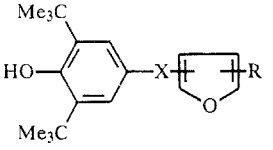
LXII

LXII R^1 = H, R^1 = alkyl; R^2 = H, R^2 = C_{1-4} alkyl R^3 = COH, R^3 = C_{1-4} alkyl R^3 = unsubstituted Ph, R^4 = H, R^4 = C_{1-4} alkyl R^4 = unsubstituted Ph

Anti-inflammatory properties were also observed for other arylfuran derivatives. Thus a method for obtaining LXIII and LXIV and the results of an investigation of their effect on carrageenin-induced edema were set forth in [74, 75].



LXIII

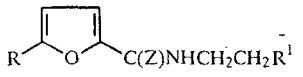


LXIV

LXIII R^1 = H, R^1 = Me, R^2 = Ac, R^2 = $CHMe_2$; R^1 = R^2 = CMe_2 4-pyridylmethylene ; X = 4-Cl, X = F, X = 3-CF_3, X = H; LXIV R = H, R = Cl, R = Br, R = I, R = Me; X = CO, bond

In the case of oral administration to rats in a dose of 300 mg/kg, LXIII decreases edema by 40-85% after 4 h and by 43-92% after 6 h. Compound LXIV in a dose of 100 mg/kg decreases edema by 54%.

Furan-2-carboxylic acid derivatives LXV [76] decrease the body temperature of mice in the case of intraperitoneal administration in a concentration of 0.02 mole/liter by 4-7°C in 30 min. The LD_{50} value of LXVa, b is 250 mg/kg, as compared with 3000 mg/kg for LXVc.

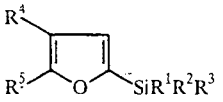


LXV

LXV a-c: a R = H, R^1 = Cl, Z = O; b R = H, R^1 = OH, Z = S; c R = Me, R^1 = OH, Z = O

Silylfurans LXVI have anti-inflammatory and analgesic activity vis-à-vis minimal side effects (see scheme on the following page).

Haber [77, 78] recommends them for the treatment of arthritic conditions. The compounds are more effective as analgesic agents than aspirin.



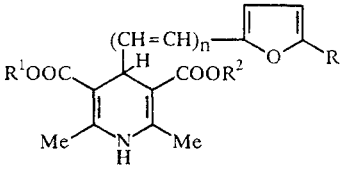
LXVI

LXVI $R^1 = R^2 = R^3 = H$, $R^1 = R^2 = R^3 =$ alkoxy, $R^1 = R^2 = R^3 = C_1$-C_2 haloalkyl or alkyl, $R^1 = R^2 = R^3 =$ alkenyl, $R^1 = R^2 = R^3 = Ph$, $R^1 = R^2 = R^3 = PhCH_2$; $R^4 = R^5 =$ pyridyl, $R^4 = R^5 = 4\text{-}R^6C_6H_4$, where $R^6 = H$, $R^6 = F$, $R^6 = Cl$, $R^6 = Br$, $R^6 = NR^7R^8$, $R^6 = R^7$, $R^6 = OR^7$, $R^6 = S(O)_nR^7$, $R^6 = NO_2$, where $R^7 = R^8 =$ alkyl $n = 0$-2

8. EFFECT ON THE CARDIOVASCULAR SYSTEM

Some 4-furyl-1,4-dihydropyridines are known as compounds that have a certain degree of hypotensive and coronary-dilating activity [79, 80]. However, the cardiovascular activity of these compounds is significantly lower than the activity of a well-known preparation of the 1,4-dihydropyridine series — Nifedipine.

The previously unknown 4-furyl-1,4-dihydropyridine derivatives LXVIIa-j, which contain substituted silicon atoms and $C(CH_3)_3$ and CH_3S groups attached to the furyl substituent, were synthesized in [81, 82].

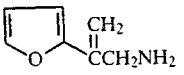


LXVII a-j

LXVII n = 0; j n = 1a, R = $SiMe_3$, $R^1 = R^2 = Me$; b R = $SiMe_3$, $R^1 = R^2 = Et$; c R = $SiMe_3$, $R^1 = Me$, $R^2 = Et$; d R = $SiMe_3$, $R^1 = R^2 = i\text{-}C_3H_7$; e R = $SiEtMe_2$, $R^1 = R^2 = Me$; f R = $SiMe_2(CH_2)_3CN$, $R^1 = R^2 = Me$; g R = SMe, $R^1 = R^2 = Me$; h R = $SiMe_3$, $R^1 = R^2 = Me$; i R = CMe_3, $R^1 = R^2 = Me$; j R = $SiMe_3$, $R^1 = R^2 = Me$

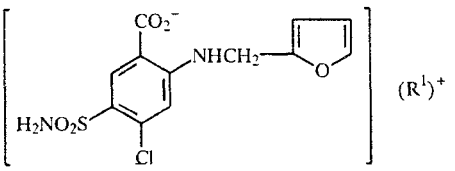
A pharmacological study of the compounds was carried out in a comparison with a cardiovascular preparation of the 1,4-dihydropyridine series — foridon — and 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-furyl-1,4-dihydropyridine. The effect of the investigated compounds on the cardiovascular system does not exceed the effect of foridon. Compounds LXVIId, e have the most pronounced hypotensive effect: the doses that decrease the arterial pressure by 30% (ED_{30}) are, respectively, 0.18 and 0.37 mg/kg, which is somewhat better than for 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-furyl-1,4-dihydropyridine. Compound LXVIId causes dilation of the femoral and carotid arteries only in small doses (0.01 mg/kg) and has little effect on the blood flow in the vessels of the heart. Compounds LXVIIa, f have virtually no effect on the arterial pressure. The introduction of a vinyl group into the molecule leads to an increase in the hypotensive activity (LXVIIj).

In the case of the administration to hypertensive rats in a dose of 10 mg/kg, LXVIII [83] decreases the blood pressure by 18%.



LXVIII

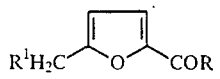
Quaternary ammonium salts LXIX have hypotensive activity [84].



LXIX

LXIX R^1 obtained from $N^+R^2R^3R^4R^5X^-$; $R^2 = R^3 = R^4 = R^5 =$ alkyl, $R^2 = R^3 = R^4 = R^5 =$ aryl or other group bonded through C with N I; X = OH, X = halo

The coronary-dilating activity of some amino amides of the furan series was investigated in [85].

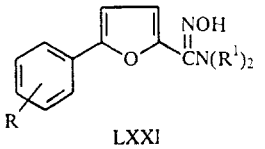


LXX

LXXa R, R^1 = NEt_2; b R,R^1 = piperidyl; c R, R^1 = pyrrolidyl; d R = NEt_2, R^1 = morpholyl; e R = NHPh, R^1 = morpholyl; f R = pyrrolidyl; R^1 = piperidyl; g R = pyrrolidyl, R^1 = morpholyl; h R = piperidyl, R^1 = morpholyl; i R = piperidyl, R^1 = cyclohexylamine; j R = piperidyl, R^1 = 2-pyridylamine; k R = 2-pyridylamine, R^1 = morpholyl

The investigations showed that LXXb (in the citrate form) in a dose of 0.01 mg/kg and LXXf, i, j (in the hydrochloride form) in a dose of 0.1 mg/kg increase the volume rate of coronary blood flow by 90%, 120%, 87%, and 76%, respectively. The coronary-dilating effect decreases appreciably when the indicated dose is increased.

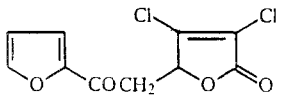
Just like 5-[(2-furylcarbonyl)methyl]-2(5H)-furanone LXXII [87], N-hydroxy-5-phenylfuran-2-carboximidamides LXXI [86] exhibit cardiotonic properties:



LXXI

LXX IR = H or 1–3-substituents (2-halo, 3-halo, 4-halo, 3-trifluoromethyl, 3-methyl, etc.); R^1 = H, R^1 = lower alkyl.

Compound LXXII in a concentration of 100 μg/ml in vitro increases the contractility of the heart muscle of guinea pigs by 62%.



LXXII

9. HYPOGLYCEMIC ACTIVITY

Many sulfonylurea derivatives that exhibit hypoglycemic activity are known.

A method for the synthesis of a number of sulfonylurea derivatives LXXIII and LXXIV is presented in scheme 11 [88]. Data from a study of the hypoglycemic activity of the synthesized compounds are presented in Table 10.

Among the investigated compounds, N-(5-isopropoxycarbonyl-2-furylsulfonyl)-N′-butylurea (LXXIVd) has pronounced hypoglycemic properties; in a dose of 250 mg/kg, it reliably decreases the glucose content in the blood by 18%. Alkyl 5-sulfamidofuran-2-carboxylates LXXIIIa-d have a somewhat weaker hypoglycemic effect (see scheme 11 on the following page).

10. ANTIFERTILITY ACTIVITY

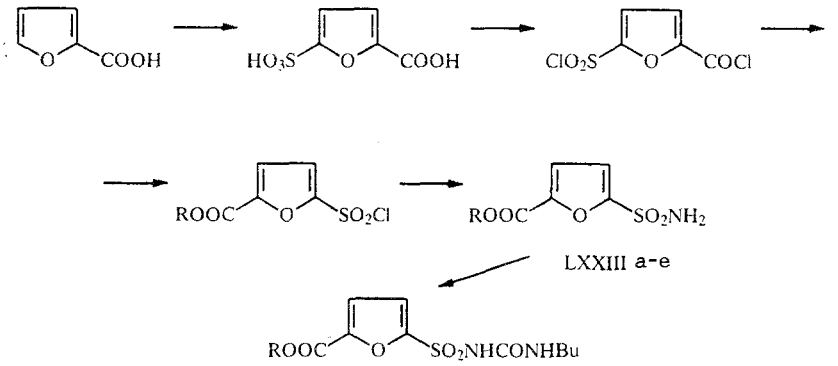
Considering the fact that metal complexes of heterocycles such as furan, benzofuran, and pyridine exhibit antiestrogen and antitesticular activity [89], as well as the fact that many silicon complexes cause atrophy of the testicles, the hypophyses of the testicles, and the prostate in mature male mice [90], Singh and coworkers [91] studied the antifertility activity of 2-acetylfuran thiosemicarbazone and its silicon complexes. Data from the investigation are presented in Table 11.

A significant decrease in the sperm motility from 79.33 ± 2.02% to 34.66 ± 2.60% was observed in the case of administration of the ligand to mice. The number of sperm in this case decreased from $(28.66 \pm 0.66) \cdot 10^6$ cm^{-3} to $(14.00 \pm 1.562) \cdot 10^6$ cm^{-3}. The antifertility effect was intensified when silicon complexes were administered to the mice.

TABLE 10. Hypoglycemic Activity of Sulfamidofuran-2-carboxylic Acid Derivatives

Compound	Glucose level in the blood, mg/100 ml		
	before administration of the preparation	after administration of the preparation	
		100	250
LXXIIIa	70 ± 4,0	76 ± 5,6	57 ± 2,2
LXXIIIb	79 ± 3,0	78 ± 4,1	68 ± 3,9
LXXIIIc	85 ± 1,0	94 ± 2,9	77 ± 2,8
LXXIIId	88 ± 1,0	80 ± 3,5	88 ± 1,0
LXXIIIe	85 ± 8,4	91 ± 4,6	81 ± 5,0
LXXIVa	81 ± 4,6	83 ± 4,3	75 ± 1,0
LXXIVb	82 ± 3,1	83 ± 3,5	76 ± 2,0
LXXIVc	79 ± 3,9	79 ± 3,9	71 ± 2,0
LXXIVd	83 ± 5,3	85 ± 5,4	68 ± 2,7
LXXIVe	83 ± 1,0	74 ± 5,3	80 ± 2,7

Scheme 11

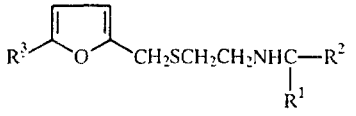


LXXIV a-e

LXXIV a R = Me, b R = Et, c R = Pr, d R = *i*-Pr, e R = Bu

11. ULCER-HEALING PROPERTIES

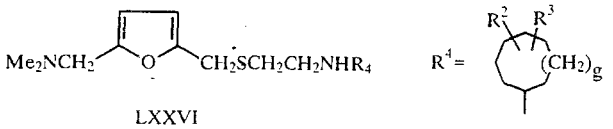
A number of researchers have described various methods for obtaining the well-known anti-ulcer preparation ranitidin [92-94] with the formula LXXVa and its analogs — LXXVb-f [95-99] and LXXVI [100].



LXXV a-f

LXXVa R^1 = CHNO2, R^2 = NHMe, R^3 = CH_2NMe_2; b R^1 = CHNO2, R^2 = piperidyl, R^3 = CH_2NMe_2 [95]; c R^1 = O, R^2 = C_6H_4R, R^3 = CH_2NMe [96]; d R^1 = CH_2NO_2, R^2 = HNHMe, R^3 = CH_2NMe_2 [97]; e R^1 = O, R^2 = NHCHMe2, R^3 = CH_2NEt_2 [98]; f methyl derivative LXXV with R^1 = NCN, R^1 = CHNO2, R^2 = NHMe, R^3 = CH_2NMe [99].

Compound LXXVI exhibits antihistamine activity and in a concentration of 1-2 μmole/kg gives rise to 75-90% inhibition of the secretion of gastric juice in rats.



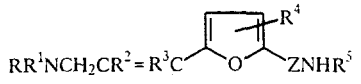
LXXVI

TABLE 11. Antifertility Activity of 2-Acetylfuran Thiosemicarbazone and Its Silicon(IV) Complexes

Compound	Sperm mobility, %	No. of sperm·10^{-6}, cm^{-3}
Control	79,33 ± 2,02	28,66 ± 0,66
Fur-CMeNNHCSNH$_2$ (L)	34,66 ± 2,60	14,00 ± 1,52
Me_2SiLCl	27,66 ± 4,17	14,33 ± 2,18
Me_2SiL_2	24,33 ± 2,33	10,00 ± 2,08

Replacement of the NHMe group in the ranitidin molecule by a piperidyl group leads to the development of anti-ulcer activity that exceeds the activity of ranitidin by a factor of 1.2-1.3 and the activity of Cimetidine by a factor of three [95]. The antihistamine activity of LXXVc [96] is characterized by ED_{50} = 0.63 μmole/kg.

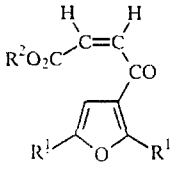
Compounds with the general formula LXXVII are active antisecretory agents in a concentration of 0.01-1 mg/kg in experiments on rats [101, 102].



LXXVII

LXXVII X = O, X = S; Z = $CH_2SCH_2CH_2$; R = R^1 = H, R = R^1 = alkyl, R = R^1 = alkenyl, R = R^1 = cycloalkyl, R = R^1 = aralkyl, R = R^1 = aryl; R^2 = R^3 = H, R^2 = R^3 = alkyl, R^2 = R^3 = aryl; R^4 = H, R^4 = halo, R^4 = alyl, R^4 = alkoxy; R^5 = H, R^5 = carbamoyl, R^5 = thiocarbamoyl.

β-Furoylacrylic acids and esters LXXVIII are also inhibitors of the secretion of gastric juice [103].



LXXIII

LXXVIII R^1 = H, R^1 = Me; R^2 = H, R^2 = alkyl

The examined data show that a continuation of the study of the biological properties of furan derivatives may lead to the creation of new medicinal agents. Although nitrofurans still remain under the scrutiny of researchers, the chemistry of heteroorganic furan derivatives that exhibit cytotoxic, antitumorigenic, psychotropic, anti-inflammatory, hypotensive, and other properties has undergone rapid development in recent years. The further multifaceted study of the biological activity of derivatives of arylfurans and furyl ketones is of interest, and, finally, the search for new analogs of the antihistamine preparation ranitidin is promising.

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