trasts markedly with the in vivo results. Thus, in an additional series of experiments, the addition of 10% (v/v) saline homogenates of liver and spleen cells from normal mice had no significant effect on the MIC of either antibiotic (Table II).

The results of these experiments confirm the marked difference between the in vitro and in vivo susceptibility of *E. coli* to cyclacillin. Whereas there was little difference between the effects of cyclacillin and ampicillin in vivo, there was a marked difference in the MIC tests. The reason for these differences is not clear.

Further studies, now in progress, on the in vitro effect of tissue homogenates from normal and antibiotic-treated mice should provide relevant information concerning the comparative efficacy of cyclacillin and other semisynthetic penicillins. The in vivo vs in vitro paradox is also being investigated by determining the effects of cyclacillin on RE cell funtion, antibody formation and nonspecific resistance.

Résumé. Chez la souris, l'effet de la cyclacilline diffère peu de celui de l'ampicilline, en ce qui concerne la concentration ou localisation de *E. coli* dans le sang, la rate et la foie. Une différence importante est cependant notée dans les concentrations minima inhibitrices (MIC) de ces deux antibiotiques pour les bactéries gram-négatives.

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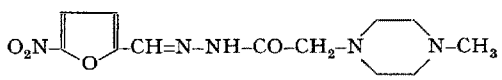
Nifurpipone, a New Nitrofuran with a Large Antimicrobial Spectrum

Since the low water solubility of nitrofurans is a limiting factor for pharmaceutical formulation and for some therapeutic uses, we synthesized a series of 5-nitro-2-furaldehyde aminoacethydrazones to obtain new nitrofurans with a better water solubility. Among these the 5-nitro-2-furaldehyde N'-methyl-N-piperazinoacethydrazone (Rec 15-0122 nifurpipone) showed a very good antimicrobial activity in vitro and in vivo, and also a high urinary excretion, so that this compound appears as a potential drug for urinary tract infections[1-4].



nifurpipone

Nifurpipone is a microcrystalline yellow powder with m.p. 167–168° (dec.). Its UV-spectrum in water shows 2 absorption maxima at 360 and 252 nm. ($E^{1\%}_{1cm}$ = 582 at 360 nm). The substance is very soluble in methanol, and chloroform, soluble in ethanol, acetone, and benzene, slightly soluble in water (0.2%). Its salts are very soluble in water. The monoacetate and the dihydrochloride are microcrystalline powders with m.p. at 126–129° and at 250 respectively.

The in vitro antimicrobial activity was tested by conventional methods and the results are reported in Table I. Nitrofurantoin was investigated for comparison.

[1] D. Nardi, E. Massarani, S. Rossi, A. Tajana and L. Degen, J. med. Chem. *14*, 635 (1971).
[2] E. Massarani, D. Nardi, A. Tajana and L. Degen, J. med. chem., *14*, 633 (1971).
[3] L. Degen, M. Salvaterra and S. Vella, Chemotherapy, in press (1971).
[4] L. Degen, M. Salvaterra, S. Vella, D. Nardi and E. Massarani, Chemotherapy, in press (1971).

Table I. Antimicrobial activity in vitro

Compound	Minimal inhibitory concentrations (μg/ml)												
	Escherichia coli 100	*Salmonella breslau* 1090	*Salmonella typhymurium* 1086	*Klebsiella*	*Pseudomonas aeruginosa* H2	*Proteus Vulgaris* OX	*Staphylococcus aureus* SG 511	*Streptococcus pyogenes humanus* A88	*Bacillus subtilis* ATCC 9466	*Chlostridium novyi*	*Mycobacterium tuberculosis* H37 Ra	*Tricophyton mentagrophytes* 1236	*Candida albicans* 28
Nifurpipone	20 10[a]	40	20 10[a]	160 160[a]	160	160 80[a]	10 10[a]	5 2.5[a]	20	160	>160	>160	>160
Nitrofurantoin	10 10[a]	40	20 20[a]	80 >160[a]	160	80 80[a]	10 10[a]	2.5 2.5[a]	10	160	160	>160	>160

[a] With 10% bovine serum.

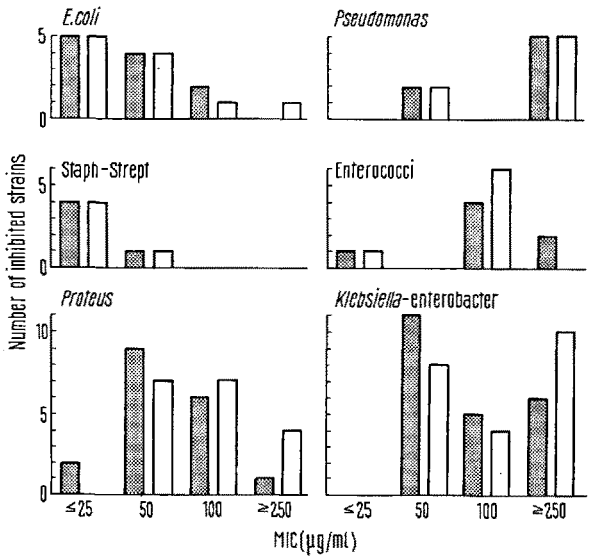


Fig. 1. Susceptibility of various bacterial species to increasing concentrations of nifurpipone (full columns) and to nitro-furantoin (empty columns).

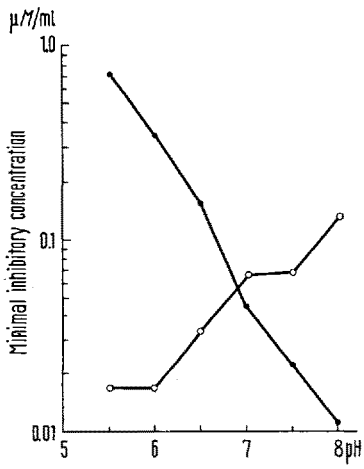


Fig. 2. Effect of pH on the antimicrobial activity of nifurpipone (full dots) and nitrofurantoin (circles) against *St. aureus* SG 511.

The results of experiments on possible development of resistance against 4 bacterial strains are summarized in Table II.

The in vitro activity against 70 bacterial strains isolated from infected human urines is reported in Figure 1.

In vivo nifurpipone exhibited some activity in systemic infection of mice with *Streptococcus pyogenes* C 203 and with *Salmonella typhimurium* 1086 and in intramuscular infection of mice with *Staphilococcus aureus* 742. In experimental urinary tract infections of rats with *Proteus vulgaris* 2 G/4, nifurpipone prevented the ascending infection and bladderstone formation. In bladder infection of rabbits with *Staphilococcus aureus* 742, nifurpipone lowered viable bacterial count after oral administration.

After single oral administration of 20 mg/kg to rats, of 20–100 mg/kg to rabbits, and of 5–10 mg/kg to dogs, the urinary excretion of nifurpipone was about 20, 10 and 10% respectively. Urinary excretion of nifurpipone was also studied in men. After single oral administration of

Table II. Development of resistance to nifurpipone and to nitrofurantoin

Strains	Nifurpipone		Nitrofurantoin	
	0[a]	10[a]	0[a]	10[a]
St. aureus SG 511	2.5	10	5	10
E. coli 100	20	40	10	> 20
Proteus morganii	40	>80	80	9 160
S. typhimurium 1086	20	40	20	40

Minimal inhibitory concentrations (µg/ml). [a] Number of transfers.

Table III. Acute toxicities of nifurpipone and nitrofurantoin

Animal species	Route	LD_{50} mg/kg	
		Nifurpipone	Nitrofurantoin
Mouse	Oral	1125	370
Mouse	i.p.	252	96
Rat	Oral	960	2500
Rabbit	Oral	400	
			VD_{50}[a]
Dog	Oral	6.9	1.6

[a] Vomiting dose in 50% of the animals.

100–150 mg, about 27% was excreted in the first 6 h and the concentration was always above chemoterapeutically active levels (>50 µg/ml).

After rectal administration of 20 mg/rats to rats, about 18% of the dose was eliminated in urine.

The effect of pH on antimicrobial activity differ for nifurpipone and for nitrofurantoine (Figure 2).

Table III shows that, in acute toxicity experiments, nifurpipone seems usually better tolerated than nitrofurantoin.

In chronic toxicity studies nifurpipone was well tolerated up to oral doses of 50 mg/kg/day for 130 days in rats and of 12 mg/kg/day for 242 days on dogs (vomiting being in the latter the limiting factor for dosing). Furthermore the drug was found without teratogenic properties up to 50 mg/kg/day orally in rats and rabbits.

Besides vomiting nifurpipone does not develope significant pharmacodynamic actions.

In conclusion the antimicrobial and the pharmacokinetic properties of nifurpipone and the absence of important pharmacodynamic effects outline the drug as a potential new therapeutic agent for the treatment of urinary tract infections. Its water solubility, the better gastric tolerance and the possibility of rectal administration may represent advantages over the commonly used nitrofurans. Clinical trials are in progress and are confirming these conclusions.

Riassunto. Il nifurpipone (5-nitro-2-furaldeide N'-metil-N-piperazino-acetidrazone) è un nuovo nitrofuranico a largo spettro antibatterico, escreto con le urine e quindi potenzialmente indicato nelle infezioni delle vie urinarie.

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