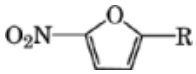
Kirk-Othmer Encyclopedia of Chemical Technology.

ANTIBACTERIAL AGENTS, NITROFURANS

The nitrofurans encompass a class of synthetic antibacterials characterized by the 5-nitro-2-furanyl group:



With relatively few exceptions, the R function contains the azomethine (—CH=N—) moiety. The most prominent exceptions contain the olefinic (—C=C—) moiety (Table 1).

The antimicrobial activity of this class of compounds was first reported in 1943 (1) and this finding was described independently four years later (2). After investigation of several derivatives, it was concluded that the 5-nitro function was responsible for the observed antimicrobial activity (3). These preliminary findings focused attention on this area of research and as a result, several thousand nitrofurans have been prepared, and thousands of articles have been prepared, and thousands of articles have been published describing the extensive efforts in these areas.

Several nitrofurans have been marketed either regionally or worldwide in the human and veterinary areas because of their broad spectrum of activity, relatively mild toxicity, and low tendency for resistance development. However, accurate total volumes or sales of these products on a global basis are not generally available. In the United States, nearly four million prescriptions were written in 1989 for products containing nitrofurazone or nitrofurantoin. U.S. sales during this period for these products approached $70 million; thus therapy with this class of compounds remains a significant therapeutic alternative.

1. Chemical Properties

Nitrofurans are generally stable, water-insoluble, crystalline solids, which decompose (darken) upon prolonged exposure to light or alkali. Their strong ultraviolet absorption provides the basis for analytical procedures for these materials. Chemical reduction of these nitro compounds gives rise to amino derivatives (4) as well as products of ring-opening (5, 6). Nucleophiles which have been shown to displace the nitro function include methoxy (7, 8), halogen (9), azido (10), alkylmercapto (10), and phenylsulfonyl (10). Photochemical hydroxylation of 5-nitro-2-furancarboxaldehyde gives rise to the 4-hydroxy derivative (11).

2. Biological Mechanism of Action

The mechanism of action of selected members of this class has been investigated. Nitrofurantoin is bactericidal at the concentrations achieved in the urinary tract and highly effective against the corresponding pathogens (12). Since its introduction for use in uncomplicated urinary tract infections, essentially no resistance development has occurred, unlike nearly all other antimicrobials. This is believed to be because of the ability of the

nitrofurans to affect multiple cytoplasmic targets such as citric acid cycloenzyme, bacterial DNA and RNA, and ribosomes essential for bacterial function. Both nitrofurazone (13) and nitrofurantoin (12) are metabolized to reactive intermediates that facilitate inhibitory processes at multiple sites such that a low probability of simultaneous resistance development exists. Potential intermediates have been postulated to be hydroxylamines, nitrosamines, and free radicals.

3. Mutagenic and Carcinogenic Activity

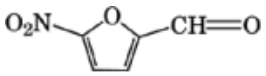
Although *in vitro* mutagenicity tests suggest that some nitrofurans in general provoke a positive response, use of *in vivo* mammalian systems has produced equivocal or negative results.

It is not appropriate to generalize the carcinogenicity of this class of compounds. Nitrofurazone appears to increase the incidence of benign mammary tumors in rats. The tumorigenic activity of furazolidone is expressed by an increase in the incidence of spontaneous tumors in both mice and rats. Bioassays of nitrofurantoin in several species of mice and rats failed to reveal any evidence of direct tumorigenic activity. Ovarian tumors have been reported in $B_6C_3F_1$ mice, but these are believed due to an indirect expression of toxicity (14, 15).

These three nitrofurans have been used therapeutically for over 30 years with no reports of human neoplasia and the relevance of the animal findings to short term therapy in humans has not been established.

4. Preparation

Most commercialized nitrofurans are derived from 5-nitro-2-furancarboxaldehyde [698-63-5] or the corresponding diacetate.



These precursors are prepared by reaction of fuming nitric acid in excess acetic anhydride at low temperatures with 2-furancarboxaldehyde [98-01-1] (furfural) or its diacetate (16) followed by treatment of an intermediate 2-acetoxy-2,5-dihydrofuran [63848-92-0] with pyridine (17). This process has been improved by the use of concentrated nitric acid (18, 19), as well as catalytic amounts of phosphorus pentoxide, trichloride, and oxychloride (20), and sulfuric acid (21). Orthophosphoric acid, *p*-toluenesulfonic acid, arsenic acid, boric acid, and stibonic acid, among others are useful additives for the nitration of furfural with acetyl nitrate. Hydrolysis of 5-nitro-2-furancarboxyaldehyde diacetate [92-55-7] with aqueous mineral acids provides the aldehyde which is suitable for use without additional purification.

An alternative route to 5-nitro-2-furancarboxaldehyde requires nitration of 2-furancarboxaldehyde oxime [1121-47-7] with mixed acid to give the nitrated oxime [555-15-7], and concomitant hydrolysis (22). Furthermore, 2-furan-carboxaldehyde derivatives with the R-substituent in place have been nitrated to the desired product (23).

4.1. Furium

N[4-(5-Nitro-2-furanyl)-2-thiazolyl]acetamide, has demonstrated activity against bacilli and pathogenic enterobacteria (24). The product, prepared from thiourea and 2-bromo-1-(5-nitro-2-furanyl)ethanone followed by acetylation of the intermediate aminothiazole with acetic anhydride in pyridine (25), is marketed in several countries for both human and veterinary use.

4.2. Furazolidone

3-[(5-Nitro-2-furanyl)methyleneamino]-2-oxazolidinone, is manufactured by the condensation of 5-nitro-2-furancarboxaldehyde with 3-amino-2-oxazolidinone (19, 26). The product is employed clinically for gastrointestinal and vaginal infections as well as an antibacterial and antiprotozoal agent in poultry and swine. Furazolidone has been shown to be metabolized to its 4-hydroxyfuryl derivative in rats (27) and to 3-(4-cyano-2-oxobutylideneamino)-2-oxazolidinone in several species (28).

Table 1. Structures of Representative Antibacterial Nitrofurans

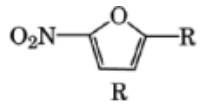
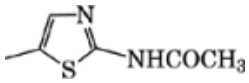
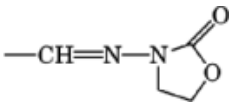
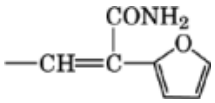
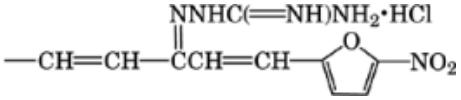
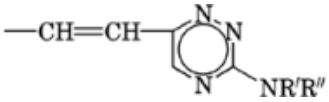
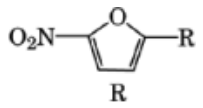
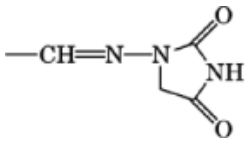
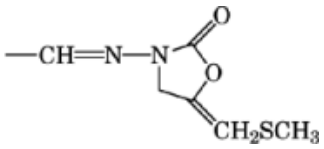
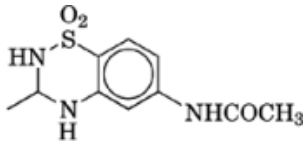
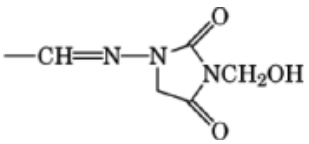
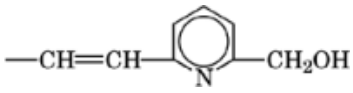
Name	CAS Registry Number	Molecular formula	 R
furium	[531-82-8]	$C_9H_7N_3O_4S$	
furazolidone	[67-45-8]	$C_8H_7N_3O_5$	
Z-furan	[710-25-8]	$C_7H_6N_2O_4$	—CH=CH—$CONH_2$
furylfuramide	[3688-53-7]	$C_{11}H_8N_2O_5$	
nitrovin	[2315-20-0]	$C_{14}H_{12}N_6O_6 \cdot HCl$	
furalazine[a]	[566-12-7]	$C_9H_7N_5O_3$	
acetylfuratrizine[b]	[1789-26-0]	$C_{11}H_9N_5O_4$	
panfuran-S[c]	[794-93-4]	$C_{11}H_{11}N_5O_5$	
nifuroxime	[6236-05-1]	$C_5H_4N_2O_4$	—CH=NOH (anti)
nitrofurazone	[59-87-0]	$C_6H_6N_4O_4$	—CH=N—$NHCONH_2$
nifuraldezone	[3270-71-1]	$C_7H_6N_4O_5$	—CH=N—$NHCOCONH_2$
nihydrazone	[67-28-7]	$C_7H_7N_3O_4$	—CH=N—$NHCOCH_3$

Table 1. ***Continued***

Name	CAS Registry Number	Molecular formula	
nitrofurantoin	[67-20-9]	$C_8H_6N_4O_5$	
nifuratel	[4936-47-4]	$C_{10}H_{11}N_3O_5S$	
nitrofurathiazide	[61143-06-4]	$C_{13}H_{12}N_4O_6S$	
nifurtoinol	[1088-92-2]	$C_9H_8N_4O_6$	
nifurprinol	[13411-16-0]	$C_{12}H_{10}N_2O_4$	

[a] $R' = R'' =$ H.
[b] $R' =$ H; $R'' = CH_3CO$—
[c] $R' = R'' =$ —CH_2OH.

4.3. Z-Furan

3-(5-Nitro-2-furanyl)-2-propenamide, is prepared by condensation of 5-nitro-2-furancarboxaldehyde diacetate with malonic ester followed by PCl_5 chlorination and amination (29). The product was marketed in Japan as a food preservative.

4.4. Furylfuramide

α[(5-Nitro-2-furanyl)-2-methylene]-2-furanacetamide, withdrawn from the market in Japan in 1974 because of mutagenicity, is prepared by condensation of 5-nitro-2-furancarboxaldehyde with 2-furanacetic acid followed by chlorination and amination (30). The isomerization of cis to trans form of furlyfuramide has been shown to occur in the presence of a variety of biological reducing agents (31).

4.5. Nitrovin

2-{3-(5-Nitro-2-furanyl)-1-[2-(5-nitro-2-furanyl)ethenyl]-2-propenylidene}hydrazinecarboximidamide hydrochloride has been marketed for both human and veterinary use as an antibacterial agent. The product, which has also seen use as a veterinary food additive (32), is prepared from 5-nitro-2-furan-carboxaldehyde and acetone followed by treatment of the resulting dione with aminoguanidine (33).

4.6. Furalazine, Acetylfuratrizine, Panfuran-S

Heating nitrovin in butanol or dimethylformamide at 100–130°C affords furalazine, 6-[2-(5-nitro-2-furanyl)ethenyl]-1,2,4-triazine-3-amine (34). An improved synthesis originates with 5-nitro-2-furancarboxaldehyde and acetone, proceeds through 4-(5-nitro-2-furanyl)-3-buten-2-one followed by a selenium dioxide oxidation to the pyruvaldehyde hydrate, and subsequent reaction with aminoguanidine (35). Furalazine, acetylfuratrizine (36), and the *N*-*N*-bis(hydroxymethyl) derivative, Panfuran-S, formed from the parent compound and formaldehyde (37), are systemic antibacterial agents.

4.7. Nifuroxime

The anti form of the oxime prepared from 5-nitro-2-furancarboxaldehyde and hydroxylamine, has been marketed for topical use as an antibacterial or an antifungal agent (1, 17).

4.8. Nitrofurazone

2-[5-Nitro-2-furanyl)methylene]hydrazinecarboximide, the first nitrofuran to be employed clinically, is prepared from 5-nitro-2-furancarboxaldehyde and semicarbazide (19). This product has seen clinical use topically as an antibacterial, for systemic application for bacterial infections in poultry and swine, and also has been employed as a food additive. In rats, nitrofurazone is hydroxylated at the 4 position of the furan moiety (27). The involvement of nitrenium ions has also been postulated in the mechanism of action of nitrofurazone (38).

4.9. Nifuraldezone

Aminooxoacetic acid [(5-nitro-2-furanyl)methylene]-hydrazide, nifuraldezone, is prepared by the reaction of 5-nitro-2-furancarboxaldehyde with semioxamazide. The product is useful in the treatment of dysentery in calves (39).

4.10. Nihydrazone

Acetic acid [5-nitro-2-furanyl)methylene]-hydrazide has seen use in veterinary medicine both as a coccidiostat and an antibacterial (39).

4.11. Nitrofurantoin

The urinary tract antibacterial, 1-[(5-nitro-2-furanyl)-methyleneamino]-2,4-imidazolidinedione, is prepared by reaction of 5-nitro-2-furancarboxaldehyde with 1-amino-2,4-imidazolidinedione (19, 40). Crystallization of the material from nitromethane provides a macrocrystalline form (41) which continues to be employed clinically.

In rats, the oxidative and reductive metabolism products have been identified as the 4-hydroxylated furan and [(3-cyano-1-oxopropyl)methyleneamino]-2-4-imidazolidinedione, respectively (27, 42). In addition, the ease of electron transfer as a mechanism of activity with nitrofurantoin and nitrofurazone has been studied (43).

4.12. Nifuratel

Nifuratel, 5-[(methylthio)methyl]-3-[5-nitro-2-furanyl)-methyleneamino]-2-oxazolidinone, is prepared by treatment of the appropriate methyl-thiohydrazinopropanol with diethylcarbonated followed by condensation with 5-nitro-2-furancarboxaldehyde diacetate (44). The product has been used in antibacterial, antifungal, and antiprotozoal applications.

4.13. Nitrofurathiazide

6-Acetylamino-3,-4-dihydro-3-(5-nitro-2-furanyl)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide, nitrofurathiazide, is synthesized from 4-acetylamino-2-aminobenzenesulfonamide with 5-nitro-2-furancarboxaldehyde (45). The product has been employed as an antibacterial agent for humans and, in combination with other drugs, has been used for acute or chronic otitis externa of dogs and cats.

4.14. Nifurtoinol

Treatment of nitrofurantoin with formaldehyde gives nifurtoinol, 3-hydroxymethyl-1-[5-nitro-2-furanyl)methyleneamino]-2,4-imidazolidinedione, a urinary tract antibacterial (46). The kinetics of decomposition of this drug and its potential as a prodrug of nitrofurantoin have been reported (47).

4.15. Nifurprinol

6-[2-(5-Nitro-2-furanyl)ethenyl]-2-pyridine methanol, is prepared from 5-nitro-2-furancarboxaldehyde and 6-methyl-2-pyridine methanol (48). The product has been used as an antibacterial in fish diseases.

Additional discussions are available in the General References concerning the properties of several nitrofurans. This includes further coverage of the chemotherapeutic and physical properties; antimicrobial activity; bacterial resistance; absorption, distribution, and excretion; clinical use; and safety studies, of this interesting class of antiinfective compounds.

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