REPORTS

Synthesis and Antimicrobial Activity of New Furan Derivatives

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Abstract: 5-Nitrofuran derivatives were synthesized and their antibacterial activity was investigated using standard bacterial strains and clinical isolates. The compounds showed inhibitory effects on both Gram-positive and Gram-negative organisms.

Since the work of Stillman et al. (1) and Dodd and Stillman (2) on the remarkable increase in antibacterial activity that results from a 5-nitrosubstituent in a series of 2-substituted furans, an interest in nitrofurans was evoked (3), and over 3500 5-nitrofurans have been synthesized and evaluated as antibacterial and antiprotozoal agents. Among those that found clinical applications are nifuroxazide (4, 5) and nitrofurantoin.

In this study closely related analogs of nifuroxazide were synthesized in the hope of obtaining new antimicrobial agents with a broader spectrum. The new compounds, being closely related to nifuroxazide, are expected to have low toxicity due to decreased systemic absorption. The antibacterial activity of these analogs on standard strains and clinical isolates was compared with that of nifuroxazide and nitrofurantoin.

Materials and Methods

Chemicals

Nitrofurantoin was obtained from Sigma Chemical Company, St. Louis, MO., U.S.A.; all other chemicals were purchased from Aldrich Chemical Co., Milwaukee, Wisconsin, U.S.A. Melting points were determined using Mettler FP5 melting point apparatus and are uncorrected. Analysis of compounds for C, H and N were done by Galbraith Laboratories Inc., Knoxville, Tennessee, U.S.A. and were in good agreement with the theoretical values. The IR and NMR spectra were consistent with the assigned structures.

Stock solutions (10 mg/ml) of the compounds tested were prepared in a mixture (1:1) of dimethyl sulfoxide and water. Dilutions were made in sterile distilled water to give the working solutions.

Organisms and Media

The standard strains used in this work were obtained from the National Collection of Type Cultures, Public Health Laboratory, London, United Kingdom.

The 101 clinical isolates were obtained from King Abdul Aziz University Hospital, Riyadh, Saudi Arabia.

For all bacterial strains brain-heart infusion broth was used for subculture, and Mueller-Hinton agar was used for both growth inhibition studies and the determination of the minimum inhibitory concentrations (MICs).

Synthesis

Nifuroxazide and compounds **1–4** were synthesized by dissolving the appropriate hydrazide (0.01 mol) in a mixture of water, conc. H_2SO_4, acetic acid and ethanol (8:7:8:20) and heating to 90 °C in a water bath. 5-Nitrofurfural diacetate (0.01 mol) was added and the mixture heated for an additional hour and left to cool at room temperature. The crude product was filtered and crystallized twice from a mixture of dimethylformamide and alcohol. Structures, m.p.s. and yields are shown in Table I.

Measurements of MICs

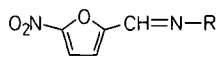
The MICs were determined by the two-fold agar dilution method (6).

Results and Discussion

Nifuroxazide [*N*-(5-nitrofurfurylidene)-4-hydroxybenzhydrazide] possesses an excellent antibacterial activity against both Gram-positive and Gram-negative organisms (4, 5, 7). The drug being virtually insoluble in water is not absorbed in the gastrointestinal tract and is therefore practically nontoxic. These properties of nifuroxazide led us to synthesize four closely related furan derivatives (Table I).

These derivatives were screened against different micro-organisms to determine their growth inhibitory effect.

Table I. Structure and Physical Constants of the Furan Derivatives.



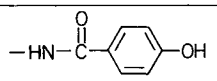
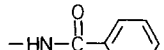
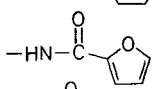
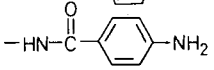
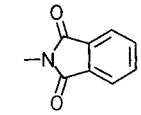
Compound No.	R	mp(°C)	Yield (%)
Nifuroxazide		299 [Reported –298 (8)]	58
1		220	68
2		238	63
3		283	74
4		292	56

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Table II. MICs of Compounds **1–4,** Nifuroxazide and Nitrofurantoin Against Standard Organisms.

Compounds Organisms (NCTC NO)	**1**	**2**	**3**	**4**	Nifurox-azide	Nitro-furantoin
Staph. aureus (6571, Oxford Hospital).	1.6	3.1	12.5	1.6	1.6	3.1
Strept. faecalis (775) (Enterococcus gp. D)	6.2	50	25	3.1	0.8	12.5
E. coli (10418)	12.5	12.5	25	25	0.8	25
Prot. vulgaris (4635)	50	50	100>200	100	>200	
Prot. rettgeri (7475)	100	>200	100	>200	100	200
Prot. mirabilis (3177)	200	>200	>200	>200	200	>200
Pseud. aeruginosa (10662)	>200	>200	>200	>200	>200	>200

Table III. MICs Inhibiting Cumulative Percentages of Isolates.

Organisms (No. of Isolates)	Compound	MIC (μg/ml) to inhibit Range	 90 %
Staph. aureus (37)	Nitrofurantoin	0.2–0.8	0.4
	Nifuroxazide	0.1– 0.8	0.4
	1	0.8–>200	>200
	2	0.4–200	200
	3	0.8–>200	>200
	4	6.2–12.5	12.5
Escherichica coli (40)	Nitrofurantoin	0.2–25	1.6
	Nifuroxazide	0.4–100	100
	1	25 –200	200
	2	25 –>200	>200
	3	6.2–>200	>200
	4	6.2>200	>200
Klebsiella sp. (247	Nitrofurantoin	3.1–100	100
	Nifuroxazide	50 –>200	>200
	1	>200	>200
	2	>200	>200
	3	>200	>200
	4	6.2–>200	>200

The choice of these different bacterial strains was made in order to investigate the effective spectrum presented by the new furan derivatives. Compounds **1–4** were found to be active against most of the organisms tested. Table II shows the MICs of these compounds, nifuroxazide and nitrofurantoin against standard organisms.

The growth inhibitory effect of the new compounds on clinical isolates was also compared with that of nifuroxazide and nitrofurantoin and the results are presented in Table III.

Compounds **1–4** were active against the standard organisms that are susceptible to nifuroxazide and nitrofurantoin (Table II). The Gram-positive cocci, *S. aureus* and *Strep. faecalis,* were the most susceptible often showing MICs less than or equal to those shown by nifuroxazide or nitrofurantoin. Among the Gram-negative organisms, compounds **1** and **2** showed significant activity against *E. coli.* The activity of **3** and **4** was similar to that of nitrofurantoin. On the other hand, *P. aeruginosa* and the three *Proteus* strains showed resistance to all compounds.

The clinical isolates varied in their susceptibilities to all compounds including nitrofurantoin and nifuroxazide (Table III). The activity of nifuroxazide against *Staph. aureus* isolates was identical to that of nitrofurantoin with an MIC for 90 % inhibition of 0.4 μg/ml. Compound **4** was also active, 90 % of the isolates being inhibited by 12.5 μg/ml, whereas compounds **1, 2** and **3** showed only low activity. Their respective MICs for 90 % inhibition were > 200, 200 and > 200 μg/ml, respectively.

Nitrofurantoin, nifuroxazide and compounds **1–4** showed low activity against *E. coli* and *Klebsiella* isolates with MIC's varying from 100 to > 200 μg/ml.

In conclusion, the synthesis of furan derivatives with close structural analogy to nifuroxazide has been achieved. The new compounds have shown antibacterial activity against standard Gram-positive and Gram-negative organisms. The activity of compound **4** against the clinical isolates is promising.

References

(1) Stillman, W. B., Scott, A. B., Clampit, J. M. (1943) United States Patent No. 2, 319, 481.

(2) Dodd, M. C., Stillman, W. B. (1944) J. Pharmacol. Exp. Ther. 82, 11–18.

(3) Chamberlain, R. E. (1976) J. Antibiol. Chemother. 2, 325–336.

(4) Société Anon. des Laboratories Robert et Carriere, Fr. Patent (1963) 1, 327, 840.

(5) Carron et al. (1963) Ann. Pharm. Fr. 21, 287. Through reference no. 8.

(6) Steers, E., Folz, E. L., Graves, B. S. (1959) Antibiot. Chemother. 9, 307–311.

(7) Thabaut, A., Durosoir, J. L. (1978) Gaz. Med. Fr. 85, 4516–18.

(8) Merck Index (1976) ninth edition, Merck and Co. Inc., Rahway, N. J., U.S.A. 6360.