FSTC-HT-23-242-69

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NEW SYNTHETIC ANTIMICROBIC PREPARATIONS

THE ANTIMICROBIC ACTIVITY OF SOME SALICYLANILIDE DERIVATIVES

COUNTRY: USSR

TECHNICAL TRANSLATION

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New Synthetic Antimicrobic Preparations. The Antimicrobic Activity of Some Salicylanilide Derivatives.

by

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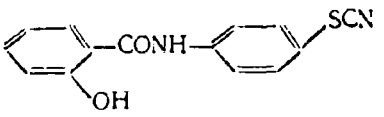
Source: MIKROBIOLOGICHNIYY ZHURNAL
(Microbiological Journal)
Vol 27, No. 2, pp 52-56, 1965
USSR

Translated for FSTC by Techtran Corporation

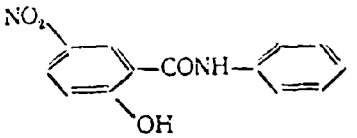
NEW SYNTHETIC ANTIMICROBIC PREPARATIONS

THE ANTIMICROBIC ACTIVITY OF SOME SALICYLANILIDE DERIVATIVES

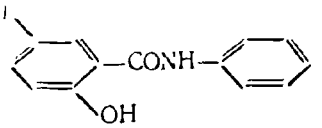
In the antibiotics laboratory of Kiev State University the antimicrobic and therapeutic properties of salicylanilide derivatives have been studied since 1956. During this time salicylanilide has been investigated as well as its chlorine and bromine derivatives, which possess good therapeutic properties; three preparations have already been approved by the Pharmacological Committee of the USSR Academy of Medical Sciences as new medical supplies and have been brought into production after clinical testing [1, 2]. In connection with this, there is no doubt in the conformity of a series of other cylanilide derivatives to the study. By this method we have also synthesized and studied the antimicrobial activity and toxicity of such derivatives as:



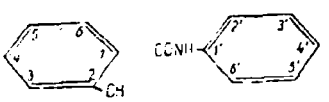
4'-rhodansalicylanilide



5-nitrosalicylanilide



5-iodosalicylanilide



Anilide salicylic acid (ASA)

4′-rhodansalicylanilide is the original compound; as regards 5-nitrosalicylanilide and 5-iodosalicylanilide only data on its synthesis are encountered in the literature; the antimicrobial properties of these compounds have not been discussed [3].

A broad spectrum of test-microbes were utilized for research on the microbial activity of these preparations, including bacteria, cocci, microbacteria Candida albicans, and also representatives of the pathogenic, phytopathogenic and saprophytic mycelial fungi. Research was carried out by the generally accepted method of serial dilution. The solvent was 0.1% alcohol.

4′-rhodansalicylanilide had the highest MBSC of all the salicylanilides that were tested in these experiments. ASA has already been recognized as an antifungus preparation from the class of salicylanilides, namely from its antimicrobic activity compared to other salicylanilides. The results of the experiments indicate that the minimal fungistatic concentration (MFSC) of 4′-rhodansalicylanilide is higher than the MFSC of ASA and for all fungi except Aspergillus niger (Table 1).

Table 1

Results of Research on the Antimicrobic Effect of Salicylanilide

Microorganisms	Minimal bacteriostatic (MBSC) and minimal fungastatic (MFSC) concentrations in γ/ml			
	4′-rhodansalicylanilide	5-nitrosalicylanilide	5-iodosalicylanilide	Anilide of Salicylic acid (ASA)
Staph. aureus, шт.[a] 209	0,1	200	10	100
Staph. aureus, шт. 5	3,3	100	3,3	100
Staph. aureus «Жаев»	0,3	100	3,3	100
Staph. albus	0,3	100	3,3	100
Staph. citreus	0,3	100	3,3	100
Micrococcus agilis	3,3	1000	1000	100
Sarcina flava	3,3	100	3,3	—
Bac. subtilis	0,3	100	330	100
Bac. mycoides	0,3	100	33	1000
Bact. pyacianeum	330	0	0	0
Bact. coli	0	0	0	0
Proteus vulgaris	0	0	0	0
Mycobact. В-5 [a]	0,5	5	0,5	1000
Mycobact. tuberculosis, шт. *hominis*, Академія 332	—	10	100	—
Trich. gypseum	0,6	5	10	10
Epidermoph K—W	0,1	2	10	10
Microsporum lanosum	3,3	2	100	100
Candida albicans	250	125	0	100
Penicillium cyclop	100	10	100	100
Trichoderma lignor	10	10	100	100
Aspergillus niger	330	33	100	100

Note. - Experiments were not performed.

a) strain

We utilized a broad spectrum of microorganisms (Table 2) for detailed study of 4′-rhodansalicylanilide. In all 28 tests, among which a majority of pathogenic fungi predominated, the preparation acted at significantly lower concentrations than salicylanilide (ASA).

Table 2

Antimicrobic Effect of 4-rhodansalicylanilide

Microorganisms	Minimal bacteriastatic concentration (MBSC) in γ/ml	Microorganisms	Minimal bacteriastatic concentration (MBSC) in γ/ml
Bact. malvacearum	10	*Trichophyton crateriforme*	2,5
Bact. Fridlendi	10	*Trichophyton roseum*	10
Bact. paratyphi A	10	*Trichophyton equinum*	0,1
Bact. prodigiosum	0	*Trichophyton violaceum*	0,1
Bac. mesentericus	10	*Microsp. audouini*	0,1
Bac. megaterium	10	*Microsp. equinum*	0,1
Staph. aureus C	100	*Rh. nigricans*	10
Micrococcus citreus	0,1	*Penicillium cinea*	10
Vibrio Metchnicovi	10	*Penicillium tardum*	10
Pseud. fluorescens	10	*Fusarium culmorum*	0,1
Achorion quinckeanum	0,1	*Fusarium avenaceum*	100
Achorion Schönleini	100	*Fusarium gibberilinum*	0,1
Achorion gypseum	0,1	*Fusarium gladioli*	10
Trichophyton cylinum	2,5	*Fusarium graminearum*	2,5

It should be noted that experiments investigating the antituberculosis effect of salicylanilides, which were carried out at the Institute of Tuberculosis and Chest Surgery of the World Health Organization of the URSR on pathogenic micobacteria (BK), showed that 5-nitrosalicylanilide displayed tuberculo-static activity in vitro at a concentration of 10 γ/ml. However, study of this preparation in a model of experimental tuberculosis in white mice did not reveal its chemotherapeutic activity.

Comparative study of the influence of serum on the activity of salicylanilide and its derivatives 4′-rhodan-, 5-iodo- and 5-nitrosalicylanilides showed that upon addition of 10% normal horse serum to MPB the antimicrobic effect of these substances decreased 10-100 times (Table 3). This is in agreement with literature data on the antimicrobic activity of salicylanilide derivative [4, 5].

Investigation of the toxicity of the salicylanilides which we studied showed that these compounds are not very toxic. Experiments were carried out in white mice by subcutaneous and peroral injections and in white rats by intraperitoneal injection. White mice tolerate 2 g per kg of live weight of 4′-rhodansalicylanilide and 5-iodosalicylanilide in castor oil by subcutaneous injection. Salicylanilide has significantly higher toxicity than its derivatives (Table 4).

Table 3

Effect of Normal Horse Serum on Bactericidal Effect of Salicylanilides in Relation to Mycobacterium B-5

Compound	Minimal bacteriostatic concentration (MBSC) in γ/ml	
	MTB	MTB+10% normal horse serum
4′-rhodansalicylanilide	10	1000
5-nitrosalicylanilide	2.5	25
5-iodosalicylanilide	2.5	25
Anilide of salicylic acid (ASA)	100	1000

Table 4

Toxicity of Salicylanilides

Compound	Injection of MTD(in mg/kg)			LD-50	LD-100
	subcutaneous (in mice)	per os (in mice)	intraperitoneally (in rats)	per os	
4′-rhodansalicylanilide	2000	500	2000	3000	-
5-nitrosalicylanilide	700	700	800	1400	2000
5-iodosalicylanilide	2000	1000	1000	2500	3000
Salicylanilide (ASA)	500	500	500	750	

Note. -dose was not established for the poorly soluble 4′-rhodansalicylanilide.

Thus, 4′-rhodansalicylanilide, 5-nitrosalicylanilide and 5-iodosalicylanilide are slightly toxic substances with high antimicrobic effect. Therefore, research on salicylanilide and, in particular, 4′-rhodansalicylanilide merits detailed laboratory and clinical study. There is reason to expect that deeper study of these compounds, especially 4′-rhodansalicylanilide, will permit their utilization as new antimicrobic therapeutic preparations.

Conclusions

1. We have synthesized and studied the antimicrobic effect of salicylanilide derivatives: 4′-rhodansalicylanilide, 5-nitrosalicylanilide and 5-iodosalicylanilide.

2. All three of the salicylanilide derivatives studied are characterized by significant antimicrobic effect on gram positive bacteria, pathogenic and saprophytic fungi. They have no effect on gram negative bacteria. Their antimicrobic effect was studied in comparison to anilide salicylic acid (ASA).

3. 5-nitrosalicylanilide possesses fair antimicrobic activity, MBSC is like that of ASA (100 γ/ml); its fungistatic activity, MFSC (2.0-10 γ/ml) is higher than that of ASA (100 γ/ml).

4. 5-iodosalicylanilide has a MFSC equal to that of ASA (from 10 to 100 γ/ml), its antibacterial activity, MBSC (from 0.5 to 33 γ/ml) is higher than that of ASA (100 γ/ml).

5. 4'-rhodansalicylanilide possesses the highest antimicrobic effect of all the compounds studied; it is as good or better than antibiotics. The MBSC for gram positive bacteria and the MFSC for pathogenic hyphal dermatophytes, from 0.1 to 3.3 γ/ml. For Candida albicans (250 γ/ml) and saprophytic fungi (100-330 γ/ml) this preparation is not effective.

6. Microbic activity of these compounds decreases 10-100 times upon addition of 10% normal horse serum.

7. The salicylanilides which we studied possess low toxicity; the maximal tolerable dose (MTD) varies in the range 700-2000 mg/kg of live weight with various methods of injection.

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UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY *(Corporate author)*
Foreign Science and Technology Center
US Army Materiel Command
Department of the Army

2a. REPORT SECURITY CLASSIFICATION
UNCLASSIFIED

2b. GROUP

3. REPORT TITLE

New Synthetic Antimicrobic Preparations. The Antimicrobic Activity of Some Salicylanilide Derivatives.

4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*
Translation

5. AUTHOR(S) *(First name, middle initial, last name)*

M. M. Rotmistrov, G. V. Kulik and O. S. Nevkipila

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
17 June 69	5	N/A

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
b. PROJECT NO. 8703017 03.00	FSTC-HT-23-242-69
c. 9223628 2301	9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)*
d. P. Cushing	ACSI Control Number (None)

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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
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13. ABSTRACT

The authors ~~have~~ synthesized three new derivatives of salicylanilide: 5-nitrosalicylanilide, 5-iodosalicylanilide and 4-rhodansalicylanilide. The antimicrobic activity of 5-nitro- and 5-iodosalicylanilide (40-100 γ/ml) was found to be somewhat higher than that of salicylanilide. 4-rhodan-salicylanilide has higher antimicrobic activity than salicylanilide: its MBSC and MFSC are 0.1-3.3 γ/ml. The salicylanilides investigated possess low toxicity. MTD varies from 700-2000 mg/kg of live weight for various methods of injection. The antimicrobic activity of the preparation is considerably lower upon addition of serum. Three other derivatives have already been approved by the pharmacological committee as new drugs.

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UNCLASSIFIED

Security Classification

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
antimicrobic preparations salicylanilide salicylanilide derivatives drugs						