CROATICA CHEMICA ACTA CCACAA 54 (2) 225—232 (1981)

CCA-1278

YU ISSN 0011-1643
UCD 547.78
Original Scientific Paper

Imidazoles II. Synthesis and Some Pharmacological Properties of Nitroimidazol-1-yl-ethylsulphonamides[1]

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Received May 12, 1980

Starting from 1-aminoethyl-5-nitroimidazoles *9—12*, and their 4-nitro isomers *13—16*, sulphonamido derivatives *17—40* and *45—68* were prepared by condensation with various arylsulfonylchlorides. *Para*-amino derivatives *41—44* and *69—72* were obtained by acidic hydrolysis of the intermediary *para*-acetamido derivatives *22, 28, 34, 40, 50, 56, 62,* and *68*. Compounds *2* and *24—26* exhibited antitrichomonal activity comparable to that of metronidazole, while the bacteriostatic activity of compounds *2, 6, 10, 23—28, 42, 55, 56,* and *70* was comparable to that of sulfaphenazole.

INTRODUCTION

The well-established antitrichomonal activity of 1-substituted-5-nitroimidazoles[2,3] on one hand, and the broad spectrum of bacteriostatic activities of sulphonamides[4] on the other, prompted us to prepare a series of 4- and 5-nitroimidazol-l'-yl-ethylsulphonamides *17—72* and to test them for both types of biological activity. This paper briefly reports the synthesis, spectral characteristics, and some pharmacological properties of these compounds.

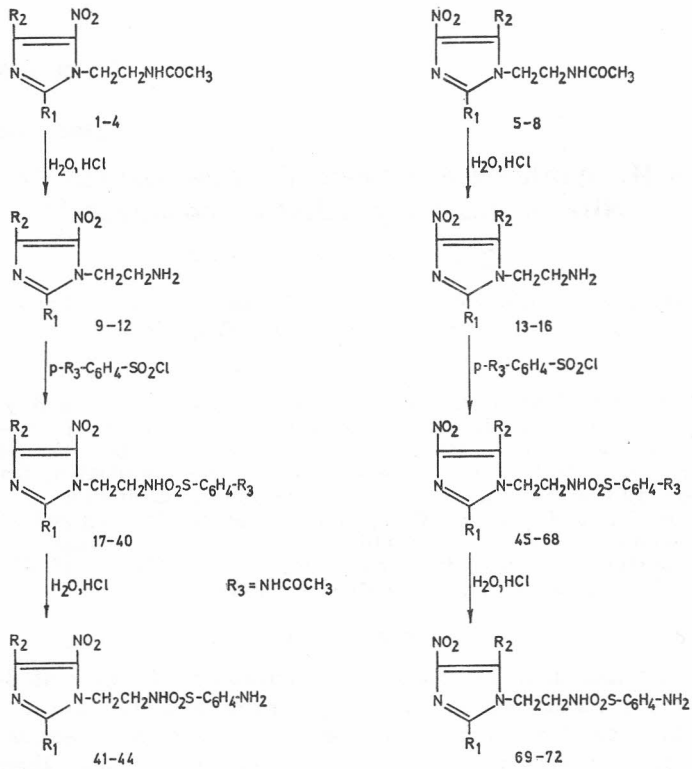
RESULTS AND DISCUSSION

Chemistry. Starting N^1-β-aminoethyl nitroimidazoles *9—16* were prepared by hydrolysis of the corresponding *N*-acetylamino derivatives *1—8*, recently described by us[5,6] (Scheme 1).

They, in turn, were condensed with a number of *para*-substituted benzenesulfonylchlorides affording sulphonamides *17—40* and 45—68. *Para*-amino derivatives *41—44* and *69—72* were obtained on subsequent hydrolysis of the intermediate acetamido derivatives *22, 28, 34, 40, 50, 56, 62,* and *68*.

Infrared spectra of all prepared compounds exhibited characteristic frequencies at 1520—1560 cm^{-1} (μ_{as}N—O, s) and at 1330—1370 cm^{-1} (μ_sN—O, vs)[7]. Sulphonamide groups regularly exhibited characteristic bands at 1300—1320 cm^{-1} (μ_{as}S—O, vs) and at 1145—1155 cm^{-1} (μ_sS—O, vs)[8]. The UV spectra of the 4-nitro isomers showed the maxima in the region 283—310 nm, while the 5-nitro isomers have shown the same at 295—316 nm. It is characteristic that of two isomeric compounds, the absorption maximum of 5-nitro isomer is shifted approximately 6—10 nm towards the longer wave length[9].

SCHEME I



1, 5, 9, 13, 17—22, 41, 45—50, 69 $R_1 = R_2 = H$
2, 6, 10, 14, 23—28, 42, 51—56, 70 $R_1 = CH_3$, $R_2 = H$
3, 7, 11, 15, 29—34, 43, 57—62, 71 $R_1 = H$, $R_2 = CH_3$
4, 8, 12, 16, 35—40, 44, 63—68, 72 $R_1 = R_2 = CH_3$
R_3 = H, CH_3, Cl, Br, NO_2, $NHCOCH_3$

In addition, each of the compounds *17—72* exhibited an additional characteristic maximum in the region of 221—276 nm.

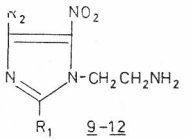
Other characteristic spectral and analytical data are given in the Tables I, II, and III.

Pharmacology. In Table IV the results of *in vitro* investigations of trichomonal[10] and bacteriostatic activity[11] of 1-substituted-2-methyl-5-nitro- and 4-nitroimidazoles are presented. Preliminary investigations revealed that derivatives of 5-nitroimidazoles *2* and *24—26* posses comparable antitrichomonal activity to that of the metronidazole [1-(2'-hydroxyethyl)-2-methyl-5-nitroimidazole], a well-known antitrichomonal agent[2].

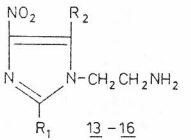
Bacteriostatic activities were determined on the species Streptococcus haemolyticus, Escherichia coli, Staphylococcus pyogenes aureus, Pseudomonas pyocinea, Klebsiella, Shigella Sonnei, and Bac. proteus mirabillis. The activities of the compounds *2, 6, 10, 23—28, 42, 55, 56,* and *70* were found to be

TABLE I

Some Characteristic Data for 5-Nitro-4-R_2- and 4-Nitro-5-R_2-1-(2'-aminoethyl)-2-R_1-imidazoles



9–12



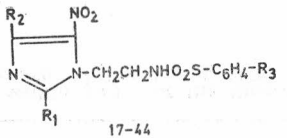
13–16

No.	R_1	R_2	Mp/°C	Yield	Formula[a]	M. w.	^{1}H-NMR (δ)			UV		IR (cm^{-1})	
							α-CH_2	β-CH_2	NH_3^+	nm	log ε	μ_{as} NO	μ_s NO
9	H	H	201—203	81.3	$C_5H_8N_4O_2 \cdot HCl$[b]	192.61	4.86	3.30	8.54	295	3.933	1565	1360
10	CH_3	H	210—212	82.6	$C_6H_{10}N_4O_2 \cdot HCl$[c]	206.64	4.65	3.28	8.66	312	3.948	1545	1365
11	H	CH_3	225—227	84.4	$C_6H_{10}N_4O_2 \cdot HCl$	206.64	4.70	3.30	8.60	304	3.959	1530	1360
12	CH_3	CH_3	198—200	76.7	$C_7H_{12}N_4O_2 \cdot 2HCl \cdot H_2O$	275.14	4.70	3.27	8.72	313	4.013	1555	1360
13	H	H	234—236	89.5	$C_5H_8N_4O_2 \cdot HCl$	192.61	4.47	3.30	8.58	283	3.858	1555	1355
14	CH_3	H	275—276	88.0	$C_6H_{10}N_4O_2 \cdot HCl$	206.64	4.32	3.28	8.66	297	3.806	1540	1355
15	H	CH_3	238—239	91.0	$C_6H_{10}N_4O_2 \cdot HCl$	206.64	4.48	3.30	8.64	295	3.853	1570	1350
16	CH_3	CH_3	178—180	94.2	$C_7H_{12}N_4O_2 \cdot HCl$	220.66	4.34	3.27	8.72	307	3.676	1560	1350

[a] Analytical results obtained for C, H, N, and Cl were within ±0.3% of the theoretical values unless otherwise. [b] Anal. for ionic Cl: calc'd, 18.42%; found, 18.10%. [c] Anal. for ionic Cl: calc'd, 17.14%; found, 17.50%.

TABLE II

Some Characteristic Data for 5-Nitro-4-R_2-1-(2'-p-R_3-benzenesulfonylaminoethyl)-2-R_1-imidazoles



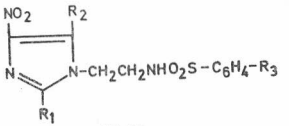
17–44

No.	R_1	R_2	R_3	Mp/°C	Yield	Formula[a]	M. w.	UV	IR (cm^{-1})			
								λ_{max}/nm	μ_{as} NO	μ_s NO	μ_{as} SO	μ_s SO
17	H	H	H	172—174	69.5	$C_{11}H_{12}N_4O_4S$	296.24	221 296	1530	1360	1320	1145
18	H	H	CH_3	132—134	78.3	$C_{12}H_{14}N_4O_4S$	310.26	227 296	1540	1350	1305	1150
19	H	H	Cl	168—170	77.7	$C_{11}H_{11}N_4O_4SCl$	330.74	232 296	1555	1350	1310	1150
20	H	H	Br	170—172	71.8	$C_{11}H_{11}N_4O_4SBr$	375.20	235 296	1545	1365	1305	1145
21	H	H	NO_2	193—195	71.6	$C_{11}H_{11}N_5O_6S$	341.24	264 300	1550	1355b	1310	1150
22	H	H	NHAc	193—194	76.0	$C_{13}H_{15}N_5O_5S$	353.29	262 300	1550b	1320b	1370	1150
23	CH_3	H	H	165—167	90.0	$C_{12}H_{14}N_4O_4S$	310.26	221 312	1545	1345	1310	1150
24	CH_3	H	CH_3	164—165	82.5	$C_{13}H_{16}N_4O_4S$	324.29	230 312	1550	1345	1320	1150
25	CH_3	H	Cl	171—172	80.7	$C_{12}H_{13}N_4O_4SCl$	344.77	232 312	1540	1350	1305	1145
26	CH_3	H	Br	188—189	77,4	$C_{12}H_{13}N_4O_4SBr$	389.23	237 312	1545	1345	1310	1150
27	CH_3	H	NO_2	210—212	66,2	$C_{12}H_{13}N_5O_6S$	355.26	268 312	1550	1355b	1310	1150
28	CH_3	H	NHAc	195—197	82.3	$C_{14}H_{17}N_5O_5S$	367.32	262 312	1550b	1365b	1315	1150
29	H	CH_3	H	165—166	78,7	$C_{12}H_{14}N_4O_4S$	310.26	221 305	1550	1355	1305	1150
30	H	CH_3	CH_3	163—165	89.5	$C_{13}H_{16}N_4O_4S$	324.29	227 305	1545	1345	1305	1150
31	H	CH_3	Cl	176—178	74.8	$C_{12}H_{13}N_4O_4SCl$	344.77	232 305	1540	1345b	1300	1150
32	H	CH_3	Br	193—195	73.2	$C_{12}H_{13}N_4O_4SBr$	389.23	235 305	1545	1340	1300	1150
33	H	CH_3	NO_2	248—250	79.5	$C_{12}H_{13}N_5O_6S$	355.26	264 305	1545b	1340	1305	1150
34	H	CH_3	NHAc	184—186	84,5	$C_{14}H_{17}N_5O_5S$	367.32	262 305	1540b	1355	1310	1150
35	CH_3	CH_3	H	179—180	72,2	$C_{13}H_{16}N_4O_4S$	324.29	221 316	1560	1355	1310	1155
36	CH_3	CH_3	CH_3	179—181	92,5	$C_{14}H_{18}N_4O_4S$	338.32	227 316	1545	1350	1300	1145
37	CH_3	CH_3	Cl	190—192	83,6	$C_{13}H_{15}N_4O_4SCl$	358.79	232 316	1550	1350	1310	1150
38	CH_3	CH_3	Br	214—217	69,8	$C_{13}H_{15}N_4O_4SBr$	403.25	235 316	1550	1350	1305b	1150
39	CH_3	CH_3	NO_2	206—209	89,0	$C_{13}H_{15}N_5O_6S$	369.29	264 316	1530	1340	1310b	1150
40	CH_3	CH_3	NHAc	218—220	74.5	$C_{15}H_{19}N_5O_5S$	381.34	262 316	1555	1345	1310	1150
41	H	H	NH_2	154—156	77.5	$C_{11}H_{13}N_5O_4S \cdot H_2O$	329.27	276 300	1530	1365	1310	1145
42	CH_3	H	NH_2	173—175	94.0	$C_{12}H_{15}N_5O_4S$	325.29	267 312	1540	1360	1315	1145
43	H	CH_3	NH_2	218—220	82.2	$C_{12}H_{15}N_5O_4S$	325.29	276 305	1540	1350	1300	1150
44	CH_3	CH_3	NH_2	223—226	73.2	$C_{13}H_{17}N_5O_4S$	339.31	276 316	1555	1355	1300	1145

[a] Analytical results obtained for C, H, N, Cl, and Br were within ±0.3% of the theoretical values.

TABLE III

Some Characteristic Data for 4-Nitro-5-R_2-1-(2'-p-R_3-benzenesulfonylaminoethyl)-2-R_1-imidazoles



45-72

No.				Mp/°C	Yield	Formula[a]	M. w.	UV	IR (cm^{-1})			
								λ_{max}/nm	μ_{as} NO	μ_s NO	μ_{as} SO	μ_s SO
45	H	H	H	176—177	92.3	$C_{11}H_{12}N_4O_4S$	296.24	221 286	1540	1350	1305	1145
46	H	H	CH_3	162—163	63.5	$C_{12}H_{14}N_4O_4S$	310.26	227 286	1540	1330	1300	1150
47	H	H	Cl	197—198	85,5	$C_{11}H_{11}N_4O_4SCl$	330.74	232 286	1540b	1350	1315	1150
48	H	H	Br	213—215	82.5	$C_{11}H_{11}N_4O_4SBr$	375.20	235 286	1545b	1365	1305b	1145
49	H	H	NO_2	227—229	83.0	$C_{11}H_{11}N_5O_6S$	341.24	264 286	1545b	1345b	1315	1150
50	H	H	NHAc	196—197	81.3	$C_{13}H_{15}N_5O_5S \cdot H_2O$	371.31	262 286	1530	1370	1310	1150
51	CH_3	H	H	203—204	71.0	$C_{12}H_{14}N_4O_4S$	310.26	229 300	1540	1350	1315	1150
52	CH_3	H	CH_3	230—232	72.0	$C_{13}H_{16}N_4O_4S$	324.29	230 302	1545	1345	1305	1150
53	CH_3	H	Cl	225—227	75.8	$C_{12}H_{13}N_4O_4SCl$	344.77	233 298	1555	1355	1315	1150
54	CH_3	H	Br	215—217	70.2	$C_{12}H_{13}N_4O_4SBr$	389.23	237 298	1550	1370	1310	1145
55	CH_3	H	NO_2	225—227	72.1	$C_{12}H_{13}N_5O_6S$	355.26	268 312	1555	1360b	1315	1150
56	CH_3	H	NHAc	251—253	71.4	$C_{14}H_{17}N_5O_5S$	367.32	262 298	1555b	1365b	1315	1150
57	H	CH_3	H	222—224	87.5	$C_{12}H_{14}N_4O_4S$	310.26	221 297	1565	1355	1315	1155
58	H	CH_3	CH_3	223—225	86.5	$C_{13}H_{16}N_4O_4S$	324.29	227 297	1555	1350	1310	1150
59	H	CH_3	Cl	263—265	71.5	$C_{12}H_{13}N_4O_4SCl$	344.77	232 297	1555	1355b	1315	1150
60	H	CH_3	Br	270—273	78.6	$C_{12}H_{13}N_4O_4SBr$	389.23	235 297	1555	1365	1305	1150
61	H	CH_3	NO_2	270—272	85.7	$C_{12}H_{13}N_5O_6S$	355.26	264 297	1550b	1350	1310	1150
62	H	CH_3	NHAc	140—145	78.6	$C_{14}H_{17}N_5O_5S \cdot H_2O$	385.44	262 297	1555	1345	1315	1145
63	CH_3	CH_3	H	213—214	76.5	$C_{13}H_{16}N_4O_4S$	324.29	221 310	1545	1360	1320	1155
64	CH_3	CH_3	CH_3	239—241	74.5	$C_{14}H_{18}N_4O_4S$	338.32	227 310	1560	1365	1315	1150
65	CH_3	CH_3	Cl	269—271	74.4	$C_{13}H_{15}N_4O_4SCl$	358.79	232 310	1540	1365	1310	1150
66	CH_3	CH_3	Br	281—283	73.1	$C_{13}H_{15}N_4O_4SBr$	403.25	235 310	1550	1360	1310	1150
67	CH_3	CH_3	NO_2	284—286	83.5	$C_{13}H_{15}N_5O_6S$	369.29	264 310	1555b	1365	1315	1150
68	CH_3	CH_3	NHAc	293—295	69.5	$C_{15}H_{19}N_5O_5S$	381.34	262 310	1570b	1360	1305	1150
69	H	H	NH_2	214—215	83.4	$C_{11}H_{13}N_5O_4S$	311.25	276 286	1540	1370	1315	1150
70	CH_3	H	NH_2	232—233	88.0	$C_{12}H_{15}N_5O_4S$	325.29	267 298	1540	1360	1310	1145
71	H	CH_3	NH_2	263—266	87.2	$C_{12}H_{15}N_5O_4S$	325.28	276 297	1565	1340	1305	1145
72	CH_3	CH_3	NH_2	232—234	79.4	$C_{13}H_{17}N_5O_4S$	339.31	276 310	1550	1350	1315	1150

[a] Analytical results obtained for C, H, N, Cl, and Br were within ±0.3% of the theoretical values.

TABLE IV

Trichomonacidal and Bactericidal Concentrations[a] of 1-Substituted-2-methyl-5-nitro- and -4-nitroimidazoles

Compd. Microorg. used	Mi[b]	Sph[c]	*2*	*6*	*10*	*14*	*23*	*24*	*25*	*26*	*27*	*28*	*42*	*51*	*52*	*53*	*54*	*55*	*56*	*70*
I[d]	5		5	⟨100	100	⟨100	10	5	5	5	50	⟨100	50	⟨100	⟨100	⟨100	⟨100	⟨100	⟨100	⟨100
II		5	125	125	125	250	125	125	125	125	125	125	125	125	250	250	125	125	125	125
III		250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
IV		250	250	250	250	250	250	250	250	250	125	250	250	250	250	250	250	250	250	250
V		125	125	125	125	125	125	125	125	125	125	125	125	125	125	125	125	125	125	125
VI		250		250		⟨250								⟨250	⟨250	250	⟨250	250	250	250
VII		250		250		250								250	250	250	250	250	250	250
VIII		250		250		250								250	250	250	250	250	250	250

[a] Concentrations used for trichomonacidal activity were: 1, 5, 10, 50, and 100 μg/ml nutrient, and for bactericidal activity were: 5, 10, 125, and 250 μg/ml nutrient. [b] Mi — Metronidazole. [c] Sph — Sulfaphenazole. [d] Inoculum — 8000 μg/ml nutrient; I — Trichomonas vaginalis, II — Streptococcus haemolyticus, III — Escherichia coli, IV — Staphylococcus pyogenes aurus, V — Pseudomonas pyocinea, VI — Klebsiella, VII — Shigella Sonnei, and VIII — Bac. proteus mirabillis.

comparable, except that they exhibited lower activity against Streptococcus haemolyticus, to that of sulfaphenazole taken as the standard with a well-know bacteriostatic properties[12].

EXPERIMENTAL

Melting points are determined on Fisher-Johns melting point apparatus, and are uncorrected. The IR-spectra were recorded with a Model 257 G Perkin-Elmer spectrometer. The UV-spectra were recorded with an SP 800 Unicam spectrometer in ethanol 96%. The ^{1}H-NMR spectra were run on the A-60 Varian instrument in DMSO-d_6, with TMS as an internal standard. TLC was performed on silica gel plates (Merck, Kieselgel HF_{254}) using chloroform-methanol (9 : 1) as the eluent.

General Procedure for the Preparation of 5-Nitro-4-R_2-, and 4-Nitro-5-R_2-1-(2'-aminoethyl)-2-R_1-imidazoles (9—12 and 13—16)

A solution of 5-nitro-4-R_2- or 4-nitro-5-R_2-1-(2-acetylaminoethyl)-2-R_1-imidazole [1.98 g of *1, 5,* 2.12 g of *2, 3, 6, 7,* 2.26 g of *4.8;* 10.0 mmol each] in hydrochloric acid 25% (20 ml) was heated under reflux for 4 h. The solvent was evaporated to dryness, a mixture of ethanol-ether (1 : 1) was added, and the product was filtered and recrystallized from ethanol 96% to give compounds *9—16* listed in Table I.

General Procedure for the Preparation of 5-Nitro-4-R_2-, and 4-Nitro-5-R_2-1-(2'-p-R_3-benzenesulfonylaminoethyl)-2-R_1-imidazoles (17—40 and 45—68)

To an ice-water cooled solution of hydrochloride of 5-nitro-4-R_2- or 4-nitro-5-R_2-1-(2'-aminoethyl)-2-R_1-imidazole (1.92 g of *9, 13;* 2.06 g of *10, 11, 14, 15;* 2.75 g of *12;* 2.20 g of *16;* 5.0 mmol each), and sodium bicarbonate (2.95 g, 35.0 mmol) in water (30 ml) was added the solution of arylsulfonylchloride (0.97 g of benzenesulfonylchloride, 1.05 g of tolylsulfonylchloride, 1.18 g of *p*-chlorobenzenesulfonylchloride, 1.41 g of *p*-bromobenzenesulfonylchloride, 1.22 g of *p*-nitrobenzenesulfonylchloride, 1.28 g of *p*-acetylaminobenzenesulfonylchloride; 5.5 mmol each) in methylethyl ketone (15 ml) over a period of 30 min, and the mixture was stirred at room temperature for next 3 hrs. Separated crystals were filtered, dissolved in diluted sodium hydroxide, and acidified to pH 6. Crude product was collected on a filter, washed with water, and recrystallized from ethanol 96% to give pure compounds *17—40,* and *45—68* listed in Tables II and III.

General Procedure for the Preparation of 5-Nitro-4-R_2-, and 4-Nitro-5-R_2-1-(2'-p-aminobenzenesulfonylaminoethyl)-2-R_1-imidazoles (41—44 and 69—72)

A mixture of 5-nitro-4-R_2- or 4-nitro-5-R_2-1-(2'-p-acetylaminobenzenesulfonylaminoethyl)-2-R_1-imidazole (1.77 g of *22, 50;* 1.85 g of *28, 34, 56, 62;* 1.91 g of *40, 68;* 5.0 mmol each), hydrochloric acid 15% (12 ml), and ethanol (10 ml) was refluxed under stirring for 30 min. Thereafter solvent was evaporated in vacuo, the residue dissolved in water, and filtered. The filtrate was adjusted to pH 6,5—7, the precipitate was collected on a filter, and recrystallized from ethanol 90% to give pure compounds *41—44,* and *69—72* listed in Tables II and III.

Acknowledgement. — The autors thank to the members of the Physical Chemistry Department of Pliva for all spectroscopic and microanalytical data.

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SAŽETAK

Imidazoli II. Priprava i neka farmakološka svojstva nitroimidazol-1'-il--etilsulfonamida

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Polazeći od 1-aminoetil-5-nitroimidazola *9—12* i njihovih 4-nitroizomera *13—16*, koje smo pripravili hidrolizom odgovarajućih acetamido derivata *1—8*, pripravljeni su sulfonamidi *17—40* i *45—68* kondenzacijom s raznim arilsulfokloridima. *Para*-amino derivati *41—44* i *69—72* su dobiveni hidrolizom u kiselom intermedijernih *para*-acetamido derivata *22, 28, 34, 40, 50, 56, 62* i *68*. Spojevi *2* i *24—26* pokazali su antitrihomonalno djelovanje usporedivo s onim od metronidazola, dok se *in vitro* bakteriostatska aktivnost spojeva *2, 6, 10, 23—28, 42, 55, 56* i *70* pokazala uporedivom s onom od sulfafenazola, izuzev niže aktivnosti na Streptococcus haemolyticus.

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Prispjelo 12. studenoga 1980.