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Activity of Derivatives and Analogs of Dapsone Against *Mycobacterium leprae*

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Of 25 dapsone derivatives and analogs screened for activity against *Mycobacterium leprae* in the mouse footpad system, only 7 were active. All seven were metabolized to or contaminated with dapsone.

To investigate the mechanism of the antimicrobial action of dapsone (4,4'-diaminodiphenylsulfone) against *Mycobacterium leprae,* dapsone and 25 analogs and derivatives were screened for activity in the mouse footpad system by Shepard's kinetic method (15, 17). Locally bred male BALB/c mice were inoculated, each hind footpad receiving 5,000 *M. leprae* of a single strain. In a series of 10 experiments, the compounds were administered incorporated into the mouse chow, each to a group of infected mice for periods of about 90 days, beginning 60 or 75 days after inoculation. Compounds were screened at a dietary concentration equimolar to 0.01 g of dapsone per 100 g of diet, except when the quantity available was insufficient. Groups of untreated mice served as controls. Harvests of *M. leprae,* usually from a pool of four footpads, were performed at intervals by established methods (14, 18); from the results of the harvests, bacterial growth curves were constructed. Activity of the compounds is expressed in terms of the "delay" of bacterial multiplication in treated mice compared with that in appropriate untreated control mice (15, 17); a delay of 30 days or longer is considered significant.

The results are summarized in Table 1. In addition to dapsone (compound no. 1 in Table 1), only seven compounds were found to be active. Compounds no. 2 and 15 have been shown to be metabolized to dapsone (3, 8). Compounds no. 3, 16, and 17 were probably metabolized to dapsone (1). Compounds no. 12 and 20 were contaminated with dapsone.

Only a few additional sulfones and sulfonamides have been screened for activity against *M. leprae* in the mouse footpad system. Both 4,4'-diacetamidodiphenylsulfone and 4,4'-diformamidodiphenylsulfone are active against *M. leprae* in the mouse footpad system (16, 17) and are metabolized to dapsone in mice (6, 9). Sulfadimethoxine is active at a concentration of 0.01 g/100 g, and sulfadoxine is active at a concentration of 0.04 g/100 g of mouse chow (5, 13). The minimal inhibitory concentration of dapsone for *M. leprae* is smaller than 5 ng/ml (12), approximately 100 times smaller than that for the most susceptible cultivable mycobacterial strains studied thus far (7, 10, 11). The administration of dapsone to mice in a concentration of 0.01 g/100 g of chow produces a plasma concentration of about 1 μg/ml in the mouse (9). The minimal inhibitory concentrations of sulfadimethoxine and sulfadoxine against *M. leprae* lie in the range 20 to 35 μg/ml (4). Therefore, some of the dapsone derivatives and analogs found inactive in this study might have been active had they been administered in a larger concentration, but with minimal inhibitory concentrations at least 200-fold that of dapsone.

These data suggest an antimicrobial effect of dapsone on *M. leprae* that is qualitatively different from the effect of dapsone and related compounds on other mycobacteria. Not only may the structure of the target enzyme differ importantly from species to species, but the very identity of the target enzyme may differ among mycobacterial species. Therefore, the results of studies of structure-action relationships of dapsone and its analogs and derivatives in cultivable mycobacteria (2) may not be directly applicable to *M. leprae.*

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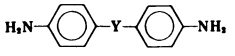
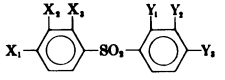
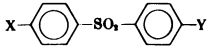
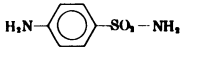
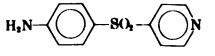
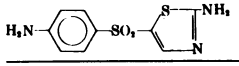
TABLE 1. *Results of screening*

Structure	Compound[a] No.	X	X_1	X_2	X_3	Y	Y_1	Y_2	Y_3	Concn (g/100 g)	Delay (days)
	1					SO_2				0.0001[b]	>91
	2					SO				0.0045[c]	90
	3					S				0.0087	68
	4					SO_2-SO_2				0.014	25
	5					S-S				0.01	15
	6					NH_2				0.008	<10
	7					CO				0.0085	<10
	8					CH_2				0.008	<10
	9					O				0.0081	<10
	10		H	NH_2	H		H	NH_2	H	0.01	15
	11		H	H	NH_2		H	H	NH_2	0.01	<10
	12		H	NH_2	H		H	H	NH_2	0.01[d]	60
	13		NH_2	H	SO_2		SO_2	H	NH_2	0.013	26
	14		NH_2	H	OH		OH	H	NH_2	0.0013	18
	15	NH_2				$NHCOCH_3$				0.003[e]	133
	16	NH_2				$NHCH_2CH_3$				0.011	126
	17	NH_2				NO_2				0.012	85
	18	NH_2				OCH_3				0.0086	<10
	19	NH_2				Br				0.013	<10
	20	NH_2				OH				0.01[f]	>58
	21	NH_2				H				0.0086	<10
	22	H				H				0.009	<10
	23	OH				OH				0.01	12
	24									0.0069	<10
	25									0.009	<10
	26									0.01	26

[a] Compound no. 2 was supplied by G. A. Ellard, Postgraduate Medical School, London, England; compound no. 4 was supplied by M. W. Cronyn, Reed College, Portland, Oreg.; compounds no. 12 and 20 were supplied by W. T. Colwell, SRI International, Menlo Park, Calif.; compound no. 15 was supplied by A. J. Glazko, Parke, Davis & Co., Ann Arbor, Mich.; compound 16 was supplied by H. P. Burchfield, Gulf South Research Institute, New Iberia, La.

[b] Active when administered in a concentration of 0.00003 g%, but not in a concentration of 0.00001 g%.

[c] Inactive when administered in a concentration of 0.0003 g%.

[d] Contaminated with dapsone (3%); inactive when administered in a concentration of 0.0003 g%.

[e] Active when administered in concentrations of 0.0003 and 0.00003 g%.

[f] Contaminated with dapsone (6%); active when administered in a concentration of 0.001 g%, but not in a concentration of 0.0001 g%.

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