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ALKYLATED PYRIMIDINES: RELATIONSHIP BETWEEN STRUCTURE AND FUNGISTATIC ACTIVITY

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In experiments in vitro 1,3,5-trisubstituted-6-chlorouracils act as inhibitors of the yeast alcoholdehydrogenase (1). The inhibitory activity does not depend upon the individual N-1, N-3 and C-5-substituent but is solely related to the total length of the carbon side chain. For the optimal activity an average chain length of 7 atoms is required. These 7-carbon atoms can either be attached as a single chain or may be distributed in any ratio on the mentioned three positions of the 6-chlorouracil ring. With the higher homologues a prolongation of the alkyl chain beyond 8 carbon atoms leads to a quick loss of the inhibiting activity (2).

Since in an orienting experiment in vitro we had found that the virostatic compound 1-allyl-3,5-diethyl-6-chlorouracil (3) exhibits an inhibitory effect upon four different dermatophyte strains (see Table 1), the question arose whether a structure activity relationship exists regarding the fungistatic activity in the group of alkyl uracils.

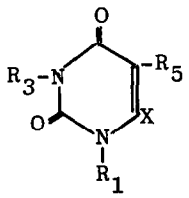
To examine this question we have studied the in vitro effect of eleven alkyl substituted uracil derivatives on four different dermatophyte strains.

The results are shown in Table 1. According to it only the 6-chloro substituted alkyluracils are active. The corresponding non-chlorinated compounds which carry a hydrogen atom at C-6 are ineffective against either of the investigated strains. Disregarding the fact that the substituent at the N-1 is an alkenyl or an alkyl group the maximum growth inhibition is exhibited by the compounds with a side chain of a total of 7 or 8 C-atoms (i.e. compounds 1 to 6). In general the 1-alkenyl compounds are less effective than the corresponding derivatives substituted with a saturated chain. With the higher homologues the activity decreases rapidly. The compound carrying 11 C-atoms is completely ineffective against three of the four investigated strains. Only in the case of Trichophyton rubrum it shows an activity that corresponds to about two thirds of the C-7 compound number 2.

The present results show that in the group of alkyl uracils the previously reported structure activity relationship confirmed for the alcoholdehydrogenase inhibition holds for the fungistatic activity as well. Although the simple in vitro test on the yeast-ADH seems to be a well-suited criterium for the prediction and design of new fungistatic pyrimidines, the inhibitory mechanism on the dermatophytes still remains to be clarified.

The association of the fungistatic properties with the specific C-chain length of an average of 7 atoms once again points out its particular significance in the biochemical and the biological activity of the heterocyclic compounds (2,4,5,6).

Table 1. RELATIONSHIP BETWEEN STRUCTURE AND FUNGISTATIC ACTIVITY IN THE GROUP OF ALKYL SUBSTITUTED URACIL DERIVATIVES



Serial No.	R_1	R_3	R_5	X	Total chain length (C-atoms)	Diameter of the inhibitory zone in mm at 0.005M against the strain: I	II	III	IV
1	allyl	ethyl	ethyl	Cl	7	48	54	48	54*
2	propyl	ethyl	ethyl	Cl	7	60	60	52	56
3	allyl	allyl	ethyl	Cl	8	36*	48*	45*	24*
4	allyl	allyl	ethyl	H	8	22	0	0	0
5	crotyl	ethyl	ethyl	Cl	8	38	34*	30*	48
6	butyl	ethyl	ethyl	Cl	8	54	52	48	44
7	pentyl	ethyl	ethyl	Cl	9	50	34	34	44
8	crotyl	crotyl	ethyl	Cl	10	28	16	28	32
9	crotyl	crotyl	ethyl	H	10	26*	0	0	22
10	hexyl	ethyl	ethyl	Cl	10	38	0	16	26
11	heptyl	ethyl	ethyl	Cl	11	40	0	0	16

I Trichophyton rubrum II Trichophyton mentagrophytes

III Mikrosporum gypseum IV Epidermophyton floccosum

* No total inhibition; only inhibition of the growth density

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