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Inhibition of Guanine Deaminase with Derivatives of Imidazole

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Antitumor activity of 8-azaguanine was enhanced by simultaneous administration of 5-amino-4-imidazolecarboxamide (AICA).[2] This effect was suggested to be due to the inhibition of guanine deaminase (3.5.4.3) by AICA.[2,3] 1-β-D-Ribofuranosyl- and 5-formamide derivatives of AICA were not inhibitory.[4] In continuation of a previous report,[4] inhibitory compounds for guanine deaminase more potent than AICA were searched among derivatives of imidazole. 4-Imidazolecarboxamide was thus found as a potent inhibitor.

Material and Method

Assay of Guanine Deaminase Activity——Guanine deaminase of rat liver[5] and photometric procedure[6] were used as reported previously.[4] The reaction mixture was incubated with shaking in a water-bath at 37° for 30 min in air atmosphere. The concentration for 50% inhibition was obtained by plotting V_0/V_I against the concentration of inhibitor [I], where V_0 is the velocity without inhibitor and V_I is the velocity with inhibitor. Further, the ratio of concentration of inhibitor to substrate giving 50% inhibition, $([I]/[S])_{0.5}$, was determined.[4,7]

Materials——The following nine compounds were used: 5-Amino-4-imidazolecarboxamide (I), 5-iodo-4-imidazolecarboxamide (II), 5-bromo-4-imidazolecarboxamide (III), 5-chloro-4-imidazolecarboxamide (IV), 4-imidazolecarboxamide (V), imidazole (VI), 4-amino-5-carbethoxyimidazole (VII), imidazole-4,5-dicarboxylic acid (VIII), and 5-chloro-4-imidazolecarboxamidoxime (IX). Their chemical formulate are shown in Table I.

Result and Discussion

As shown in Fig. 1, the inhibitory activity against guanine deaminase of the derivatives of 5-amino-4-imidazolecarboxamide (AICA) was determined. Chloro derivative (IV) was the most inhibitory among the halogeno derivatives but it was less effective than the parent compound (I). Amino group at position 5 of I had been considered to be essential for the inhibition of the enzyme,[4] but amino group was not the only thing which inhibited the guanine deaminase. Therefore 4-imidazolecarboxamide (V) was unexpected but powerful inhibitor than I.

Furthermore, the imidazole itself (VI) was a weak inhibitor (Fig. 2). Ethylester of carboxylic acid (VII) and carboxamidoxime (IX) of I were less effective. Dicarboxylic acid of imidazole (VIII) was almost non effective.

4-Imidazolecarboxamide was found to be the most potent inhibitor among the imidazole derivatives tested for guanine deaminase, and carboxamide group and hydrogen for the sub-

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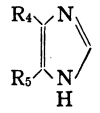
TABLE I. Inhibition of Guanine Deaminase by Imidazole Derivatives



Compound	R_4	R_5	$([I]/[S])_{0.5}$ [a]
I (AICA)	$-\overset{O}{\overset{\|}{C}}-NH_2$	$-NH_2$	1.9
II	$-\overset{O}{\overset{\|}{C}}-NH_2$	-I	over 100
III	$-\overset{O}{\overset{\|}{C}}-NH_2$	-Br	10.3
IV	$-\overset{O}{\overset{\|}{C}}-NH_2$	-Cl	4.7
V	$-\overset{O}{\overset{\|}{C}}-NH_2$	-H	0.90
VI	-H	-H	10.3
VII	$-\overset{O}{\overset{\|}{C}}-OC_2H_5$	$-NH_2$	4.0
VIII	$-\overset{O}{\overset{\|}{C}}-OH$	$-\overset{O}{\overset{\|}{C}}-OH$	over 100
IX	$-\overset{NOH}{\overset{\|}{C}}-NH_2$	-Cl	16.3

a) Ratio of concentration of inhibitor to substrate giving 50% inhibition.

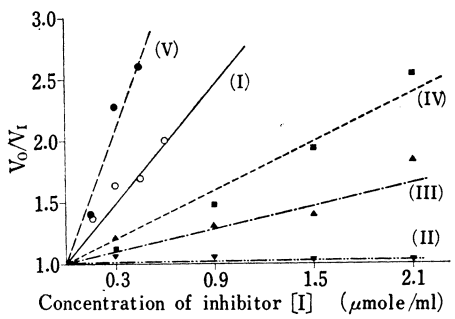


Fig. 1. Effect of the Compounds on Guanine Deaminase (1)

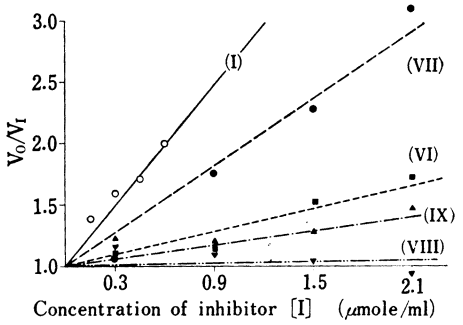


Fig. 2. Effect of the Compounds on Guanine Deaminase (2)

stituent at positions 4 and 5 of I were the most suitable groups for the inhibition of guanine deaminase.

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