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STRUCTURE-ACTIVITY RELATIONSHIPS OF NATURAL OCCURRING PLANT GROWTH-INHIBITING SUBSTANCE CAPROLACTAM AND ITS RELATED COMPOUNDS

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Abstract – The structure-activity relationships of naturally occurring plant growth-inhibiting substance caprolactam and its related lactams, and the corresponding open-chain amino carboxylic acids were studied for the inhibition of the growth of cress radicles. The lactams ranging from six- to nine-, and thirteen-membered rings showed significant growth inhibitory activity. Moreover, the activity was found to be enhanced by increasing the carbon number of lactams, except for 2-azacyclononanone. On the other hand, the open-chain amino carboxylic acids and the smallest ring lactam 2-pyrrolidinone did not inhibit the growth of cress radicles.

Chemical substances releasing from plant organs into neighboring environment as a biological information give stimulating or inhibiting onto development and/or growth of other plants: this chemical communication is called as an allelopathy.[1-3] We have hitherto studied on allelopathy during seed germination, which occurs in the very early stages of development. Lepidimoide as a stimulatory allelochemical was isolated and identified from the exudates of germinating cress (*Lepidium sativum* L.)[4] and *Arabidopsis thaliana*[5] seeds. Vanillic acid[6] and sundiversifolide[7] as an inhibitory allelochemical were isolated and identified from the exudates of germinating watermelon (*Citrullus vulgaris* Schrad.) and sunflower (*Helianthus annuus* L.) seeds, respectively. Recently, we isolated an inhibitory allelochemical from the exudates of germinating buckwheat (*Fagopyrum esculentum*) seeds and identified as caprolactam based on its ^{1}H and ^{13}C NMR spectra.[8] Caprolactam, a precursor in the fabrication of 6-nylon (perlon L),[9] had been already found in sunflower seedlings as a light-promoted growth inhibitor.[10] The

occurrence of caprolactam in the exudates from germinating seeds of various plant species was studied. Caprolactam was detected in the exudates from seeds of sunflower as well as buckwheat, but not in those from seeds of cress, rice, pea, lettuce and radish.[8] From the results, it was suggested that caprolactam may play not only as a light-promoted growth inhibitor but also a plant-selective inhibitory allelochemical.[8] Allelochemicals or their analogs could provide important new source of agricultural chemicals for the future. The direct or modified use of the allelochemicals as new herbicides is accomplished through their structure-activity relationships studies. In this paper, therefore, the structure-activity relationships of a series of lactams including caprolactam and the corresponding open-chain amino carboxylic acids were investigated to the chemical structure required for the inhibitory activity.

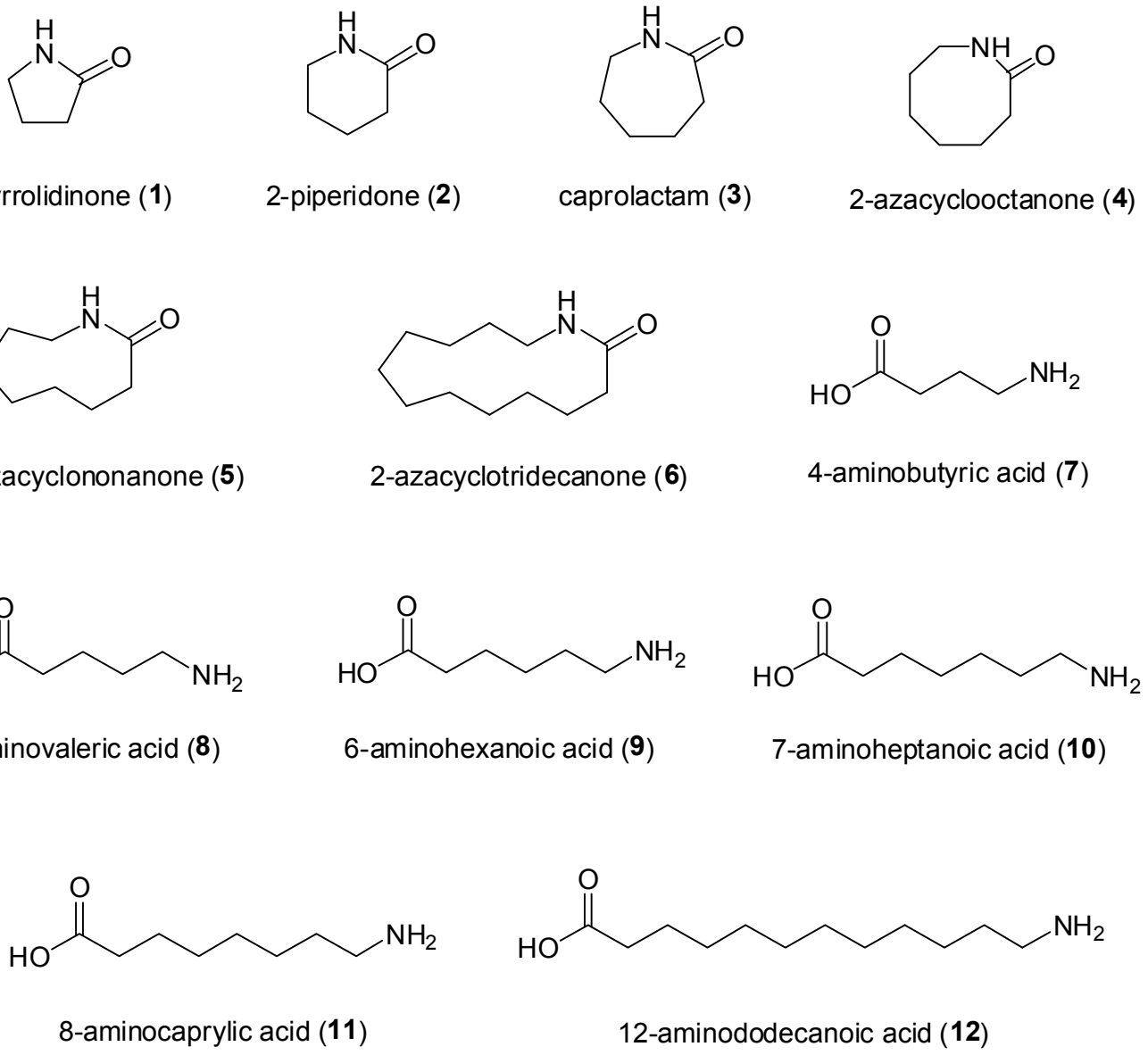

Figure 1. Caprolactam and its related compounds

Table 1. Inhibitory activity of the lactams and their corresponding open-chain amino carboxylic acids on the growth of cress radicles

Lactams	EC_{50}* /M	Amino carboxylic acids	EC_{50}*/M
2-pyrrolidinone (**1**)	-	4-aminobutyric acid (**7**)	-
2-piperidone (**2**)	6.2×10^{-3}	5-aminovaleric acid (**8**)	-
caprolactam (**3**)	1.3×10^{-3}	6-aminohexanoic acid (**9**)	-
2-azacyclooctanone (**4**)	5.6×10^{-4}	7-aminoheptanoic acid (**10**)	-
2-azacyclononanone (**5**)	1.7×10^{-4}	8-aminocaprylic acid (**11**)	-
2-azacyclotridecanone (**6**)	4.2×10^{-4}	12-aminododecanoic acid (**12**)	-
MBOA	5.1×10^{-4}		

*EC_{50} represents the concentration of samples, which cause 50% inhibition of the radicle growth of cress by testing each compound at five concentrations from 10^{-2} M to 10^{-4} M. – No activity. The activity of 6-methoxy-2-benzoxazolinone (MBOA) was added for comparison. Bioassay was performed in triplicate.

All chemicals used in this study are shown in Figure 1. 2-Pyrrolidinone (**1**), 2-piperidone (**2**), caprolactam (**3**), 4-aminobutyric acid (**7**), 5-amonovaleric acid (**8**), 6-aminohexanoic acid (**9**) and 7-aminoheptanoic acid (**10**) were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), and 2-azacyclooctanone (**4**), 2-azacyclononanone (**5**), 2-azacyclotridecanone (**6**), 8-aminocaprylic acid (**11**) and 12-aminododecanoic acid (**12**) from Aldrich Chemical Co. (Milwaukee, WI), respectively. The biological activities of lactams and amino carboxylic acids were determined using the cress (*L. sativum* L.) radicle growth test. Ten seeds of cress were placed on a filter paper moistened with 500 μl of test solution in a 2.7-cm Petri dish and kept for 24 hrs at 25 °C in the dark, after which the lengths of their radicles were measured. The structure-activity relationships of the lactams and other corresponding open-chain amino carboxylic acids were shown in Table 1.

The lactams ranging from six- to nine-membered rings (**2-5**) and thirteen-membered ring 2-azacyclotridecanine (**6**) exhibited significant inhibitory activity against the growth of cress radicles at 10^{-3} – 10^{-4} M concentration (EC_{50}). 2-Azacyclononanone (**5**) was the most potent of this series with an EC_{50} of 1.7×10^{-4} M. The ring size of the lactams influences the inhibitory activity. The increasing order activity in nine (**5**)- > thirteen (**6**)- > eight (**4**)- > seven (**3**)- > six (**2**)- membered rings. On the other hand, the smallest ring 2-pyrrolidinone (**1**) and the open-chain amino carboxylic acids (**7-12**) showed no activity. From these results, it was clarified that the presence of lactams and their ring size is crucial for the growth inhibitory activity.

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