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**Structure-Activity Study of Griseofulvin and Its Derivatives for
the *in vitro* Inhibition of Microtubule Polymerization and
the *in vitro* Depolymerization of Microtubule***

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The seventeen derivatives of (+)-griseofulvin [1] were prepared in order to determine the activity of inhibition of microtubule polymerization and the depolymerization activity of microtubule. [1] was chemically transformed to afford its eleven derivatives: [5], [6], and [10] to [18]. Three 6-alkoxy derivatives: [7], [8] and [9], were prepared by the alkylation of 6-demethylgriseofulvin, which was obtained as a metabolite in the urine of rabbits following the administration of [1]. [2] was obtained from the broth of *Penicillium urticae* fermentation in the presence of potassium bromide. [3] and [4] were prepared from [2] by bromination. The partially purified microtubule proteins from pig brain were used for viscometric analyses. The activities of the test samples were shown as the percentage for the activity of [1], which was expressed as the decreasing ratio of the specific viscosity as compared with that of the control, in both experiments. The correlation between the structure and activity was proved and the order of the activities was almost same in both experimental systems, except for isogriseofulvin [11] (Table 1). (—)-Griseofulvin [10], the enantiomer of natural (+)-griseofulvin [1], showed the very low activities in both the inhibition of microtubule polymerization and the depolymerization of microtubule. The activities of [1] were also confirmed by electron microscopy, in which samples were negatively stained with uranyl acetate. Of eighteen samples tested, 3'-bromogriseofulvin [5] showed the highest activities. Accordingly, the aggregate-formation activity of [5] was compared with that of [1], whose activities are thoroughly examined. It was proved that [5] has weaker activity than that of [1] in the formation of aggregate of microtubule proteins at 4°C.

* 本報告は日本化学会誌, 1981 (5), 746—754 に発表。

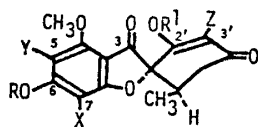
** 日本電子株式会社

Table I. Inhibition of *in vitro* microtubule polymerization and *in vitro* depolymerization of microtubule by griseofulvin and its derivatives

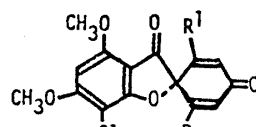
Compd.	R	R ¹	X	Y	Z	DPM ^{a)}	IMP ^{b)}
[1]	CH ₃	CH ₃	Cl	H	H	100	100
[2]	CH ₃	CH ₃	H	H	H	38	54
[3]	CH ₃	CH ₃	Br	H	H	78	91
[4]	CH ₃	CH ₃	H	Br	H	20	22
[5]	CH ₃	CH ₃	Cl	H	Br	173	132
[6]	CH ₃	C ₃ H ₇	Cl	H	H	111	105
[7]	C ₂ H ₅	CH ₃	Cl	H	H	110	101
[8]	C ₃ H ₇	CH ₃	Cl	H	H	104	96
[9]	C ₄ H ₉	CH ₃	Cl	H	H	71	72
[10]	—	—	—	—	—	39	46
[11]	CH ₃	—	H	—	—	65	102
[12]	C ₂ H ₅	—	H	—	—	58	76
[13]	C ₃ H ₇	—	H	—	—	51	76
[14]	CH ₃	—	Br	—	—	41	48
[15]	CH ₃	CH ₃ O	—	—	—	39	55
[16]	CH ₃ O	CH ₃	—	—	—	48	70
[17]	—	—	—	—	—	20	18
[18]	—	—	—	—	—	22	38

a) DPM indicates % for the activity of [1] on depolymerization of microtubule.

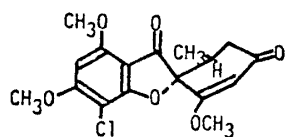
b) IMP indicates % for the activity of [1] on inhibition of microtubule polymerization.



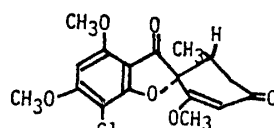
[1]~[9]



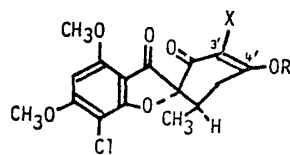
[15], [16]



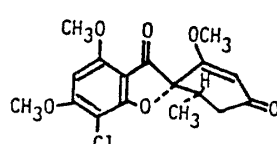
[10]



[17]



[11]~[14]



[18]