Title	Structure-activity study of griseofulvin and its derivatives for the in vitro inhibition of microtubule polymerization and the in vitro depolymerization of microtubule
Sub Title	
Author	佐藤, 良博(Sato, Yoshihiro) 斎藤, 裕子(Saito, Yuko) 白鳥, 順子(Shiratori, Yoriko) 正田, 佐代子(Shoda, Sayoko) 細井, 純(Hosoi, Jun)
Publisher	共立薬科大学
Publication year	1981
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.26 (1981.) ,p.82- 83
JaLC DOI	
Abstract	
Notes	抄録
Genre	Technical Report
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000026-0082

No. 26 (1981)

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

Yoshihiro Sato, Yuko Saito, Yoriko Shiratori
Sayoko Shoda and Jun Hosoi

佐藤良博，斎藤裕子，白鳥順子，正田佐代子，細井　純**

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 (+)-grieofulvin [**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。
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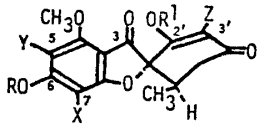
Table I. Inhibition of *in vitro* microtubule polymerization and *in vitro* depolymerization of microtubule by griseofu vin and its derivatives

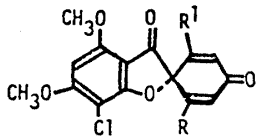
Compd.	R	R^1	X	Y	Z	DPM[a]	IMP[b]
[*1*]	CH_3	CH_3	Cl	H	H	100	100
[*2*]	CH_3	CH_3	H	H	H	38	54
[*3*]	CH_3	CH_3	Br	H	H	78	91
[*4*]	CH_3	CH_3	H	Br	H	20	22
[*5*]	CH_3	CH_3	Cl	H	Br	173	132
[*6*]	CH_3	C_3H_7	Cl	H	H	111	105
[*7*]	C_2H_5	CH_3	Cl	H	H	110	101
[*8*]	C_3H_7	CH_3	Cl	H	H	104	96
[*9*]	C_4H_9	CH_3	Cl	H	H	71	72
[*10*]	—	—	—	—	—	39	46
[*11*]	CH_3	—	H	—	—	65	102
[*12*]	C_2H_5	—	H	—	—	58	76
[*13*]	C_3H_7	—	H	—	—	51	76
[*14*]	CH_3	—	Br	—	—	41	48
[*15*]	CH_3	CH_3O	—	—	—	39	55
[*16*]	CH_3O	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]



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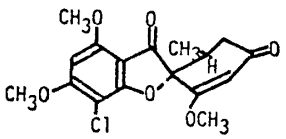

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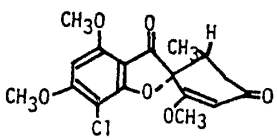

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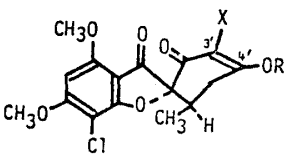

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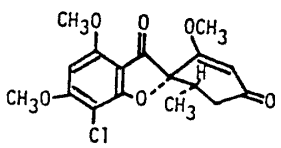

[18]