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DFW/aja
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BY FAX

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CONFIRMATION

Dear Sirs

RE: European Patent Application No 95915671.2-2101
American Home Products Corporation Case AHP-93171

I refer to the Communication pursuant to Article 96(2) and Rule 51(2) EPC dated 1 September 1999.

Dealing in turn with the points raised by the Examiner:

1. It is noted that the new claims filed on 10 October 1996 are based on the original disclosure.

2 and 3. The Examining Division considers the Documents D1 - D4 as relevant.

D1	=	US 4650803
D2	=	WO-A-9205179
D3	=	US 5233036
D4	=	Tetrahedron Letters 35(1994), 1019-1022

Novelty over D1 - D4 is acknowledged.

4.1 The Applicants point out that the problem solved by the present application is to provide hydroxyesters of rapamycin useful as immunosuppressants but also useful in the treatment of diseases including adult T-cell leukemia/lymphoma and solid tumors, see page 1 lines 7 and 8. See also page 2 where "anti-tumor" use is indicated. Further test data is available to illustrate anti-tumor use (*vide infra*). A compound claimed in this application is undergoing clinical trials as an anti-tumor agent.

4.2 It is noted that D2 is considered the closest prior art. The Examining Division also comments that D1 - D4 are all relevant because they appear to be prodrugs of rapamycin. This statement is disputed in so far as D2 - D4 are concerned since it implies that the side chain is lost during metabolism to give rapamycin which is the active entity responsible for the pharmacological effect. However no evidence is provided by the Examining Division to show whether or not the compounds of these references are prodrugs of rapamycin. It appears to be an assumption made by the

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Examining Division which insofar as the present compounds are concerned is incorrect. The Applicants consider that the activity in the present compounds resides in the compounds themselves and they do not require conversion to rapamycin to exert their biological activity.

4.3-5 The Examining Division comments that the compounds disclosed in D2-D4 all have qualitatively the same activity. This is not correct in that the compounds of the present application have an additional and important activity as anti tumor agents - see page 1 line 8 which is substantiated by data included hereinbelow.

The Examining Division appears to suggest that the presence of an inventive step could be acknowledged if it is made credible by test results that another problem has been solved. It appears also that we are required to provide a comparison with the closest prior art compound of D2, viz. rapamycin 42-mono-methylsuccinate.

It is pointed out firstly that none of the prior art documents D2-D4 teach anti-tumor activity. Secondly the Table below demonstrates highly significant anti tumor test data for the compound of Example 11 (rapamycin 42-ester with 2,2-bis-(hydroxymethyl)propionic acid). Since the closest prior art makes no reference to anti-tumor activity it is submitted that there is no need to make a comparison.

TABLE

Inhibition of growth of human tumor cell lines (in vitro) by compound of Example 11

Tumor type	Cell line	IC_{50} (μM)[a]
Breast Cancer	BT-474	0.0006
	SK-BR-3	0.0007
	MCF7	0.001
Prostate Cancer	PC-3	0.0005
	LNCaP	0.0007
	DU 145	0.001
Melanoma	LOX	0.001
Ovarian Cancer	A2780 S	0.004
	A2780 DDP	0.04
	HTB 161	0.07
Lung Cancer	A549	0.1
	LX-1	2.5
Colon Cancer	CaCo 2	0.004
	HCT-15	0.07
	SW 948	0.05
	MIP 101	0.08
	CX-1	4.4
	SW 620	4.4

	COLO 205	4.8
	LS 174T	4.9
	SW 480	5.9
Leukemia	CCRF-CEM	0.1
	HL-60	5.8

a: IC_{50} = concentration causing 50% growth inhibition.

Based on the teaching in the application as filed and the data provided herein it is submitted that the compounds of the present application do possess an inventive step over the prior art being indicated as anti-tumor agents.

4.6 The Examining Division has objected to the breadth of scope. Enclosed herewith are replacement claims which more narrowly define the invention and are based on the original specification as filed. In particular the features of claim 4 have been introduced into claim 1. 42,31-Bis compounds are removed.

The Examining Division has objected to Claim 1 for being unclear due to the presence of two provisos. Restriction of Claim 1 to the features of Claim 4 has resulted in one proviso being removed and the other being simplified. The use of the one proviso is regarded as clear and the meaning is readily comprehensible.

Claim 12 (new claim 11) has been amended to remove functional language. The term "reactive derivative" however has been retained since its meaning is readily clear from the description on page 5 lines 26 to 30. Those skilled in the art would be aware of how to perform an acylation reaction and what the term means.

5. The Applicants propose to bring the description into line once the claims have been agreed.

A new claim 3 has been added to the claims directed to first pharmaceutical use. A second medical use claim has been added as new claim 9 directed to anti tumor treatment.

These amendments are made without prejudice to reinstatement of the original wording during future prosecution of this application or any application derived therefrom, and without prejudice to filing of divisional applications.

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The Applicant requests Oral Proceedings (Article 116 EPC) before any notice of rejection may issue.

A form 1037 accompanies the confirmatory copy of the fax for acknowledging receipt.

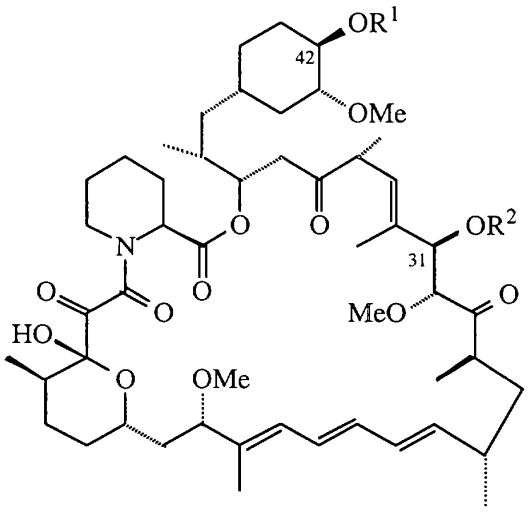
Yours faithfully

DFW

Dr D F Wileman
European Patent Attorney (GA 2141)

CLAIMS

1. A compound of the structure



(I)

wherein R^1 is $-COCR^7R^8R^9$ and R^2 is H;

R^7 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or $-CO_2R^{11}$;

R^8 and R^9 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, or-$(CR^3R^4)_fOR^{10}$; or R^8 and R^9 may be taken together to form X;

R^{10} is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silyl, tri-(alkyl of 1-6 carbon atoms)silylethyl, triphenylmethyl, benzyl, alkoxymethyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silylethoxymethyl, chloroethyl, or tetrahydropyranyl;

X is 5-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 5-(2-spiro(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 4-(2-spiro(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxalanyl, or 4-(2-spiro(cycloalkyl of 3-8 carbon atoms))[1,3]dioxalanyl;

R^3 and R^4 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, trifluoromethyl, or -F;

and

f = 0-6

with the proviso that R^1 contains at least one $-(CR^3R^4)_fOR^{10}$ or X group,

or a pharmaceutically acceptable salt thereof.

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