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(71) Applicant: **MICROBIAL CHEMISTRY RESEARCH FOUNDATION**
14-23, Kamiosaki 3 Chome Shinagawa-ku
Tokyo 141(JP)

(72) Inventor: **Umezawa, Hamao, Prof.**
23 Toyotama-kita 4-chome
Nerima-ku Tokyo(JP)

(72) Inventor: **Takeuchi, Tomio**
1-11, Higashigotanda 5-chome
Shinagawa-ku Tokyo(JP)

(72) Inventor: **Ishizuka, Masaaki**
17, Denenchofu-honcho 3 chome
Ohta-ku Tokyo(JP)

(72) Inventor: **Abe, Fuminori**
29-15, Shimo 3-chome
Kita-ku Tokyo(JP)

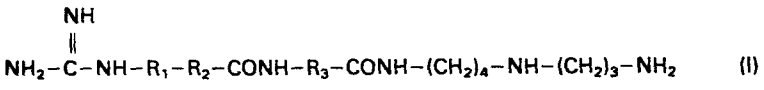
(72) Inventor: **Fujii, Akio**
8-13, Ofuna 4-chome
Kamakura-city Kanagawa Prefecture(JP)

(72) Inventor: **Nakamura, Teruya**
831, Nomura-cho
Kusatsu-city Shiga Prefecture(JP)

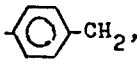
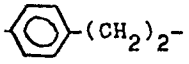
(74) Representative: **Becker, Heinrich Karl Engelbert, Dr. et al,**
HOECHST AKTIENGESELLSCHAFT Central Patent Department P.O. Box 80 03 20
D-6230 Frankfurt am Main 80(DE)

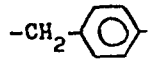
(54) Use of spergualin derivatives for the preparation of medicaments having immunosuppressive activity.

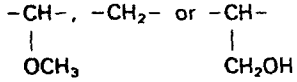
(57) The present invention relates to the use of compounds of the formula



(I)

wherein R_1 is $-(CH_2)_4-$, $-(CH_2)_6-$,  , 

or  ; R_2 is $-(CH_2)_2-$ or $-CH=CH-$; and R_3 is 

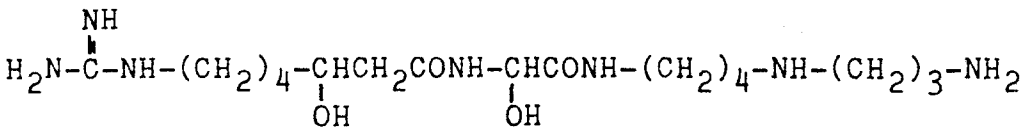


or pharmacologically acceptable salts thereof, for the preparation of medicaments having immunosuppressive activity.

The present invention relates to immunosuppressants containing Spergualin compounds as an active ingredient.

A number of drugs with immunosuppressive actions are already known. They include alkylating agents, antimetabolites, antibiotics, steroids, folic acid antagonists and plant alkaloids.

Spergualin is a compound that was isolated by Umezawa and others from the filtrate of a culture broth of Spergualin-producing microorganism of the genus Bacillus. The structural formula of Spergualin is shown below:



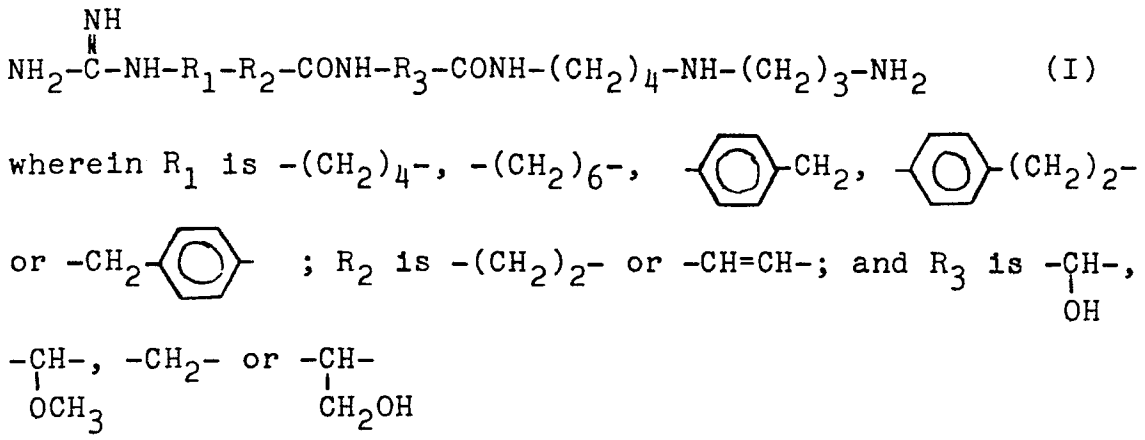
Spergualin is not only effective against mouse leukemia L-1210, mouse leukemia EL-4 , Ehrlich carcinoma and sarcoma 180 bus also exhibits promising activity in controlling malignant tumors (see Japanese Unexamined Published Patent Application No. 48957/1982).

Umezawa et al. continued their studies on Spergualin compounds and have synthesized numerous Spergualin compounds which are more stable and have a stronger antitumor activity (see Japanese Unexamined Published Patent Application Nos. 62152/1983, 42356/1984 and 76046/1984). Among these compounds are those used in the present invention.

The immunosuppressive effects of steroids are considered to be accomplished principally through the anti-inflammatory action and the lysis of lymphocytes. However, as is well known, steroids have diversified pharmacological effects and cause many side effects. The other immunosuppressants are classified as "cytotoxic" substances and their action is directed, among other things, to the pathways of nucleic acid synthesis and may often cause serious side effects on hematopoietic organs. It is therefore desired to develop immunosuppressive drugs that act

selectively on lymphocytes and other cells of immunological importance while causing minimum side effects.

The present invention relates to immunosuppressants containing as an active ingredient the Spergualin compounds of formula (I) shown below (such compounds are hereinafter simply referred to as the compounds of the present invention):



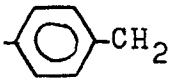
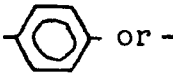
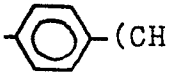
(I)

wherein R_1 is $-(CH_2)_4-$, $-(CH_2)_6-$, , , or ; R_2 is $-(CH_2)_2-$ or $-CH=CH-$; and R_3 is $-\underset{\underset{OH}{|}}{CH}-$, $-\underset{\underset{OCH_3}{|}}{CH}-$, $-CH_2-$ or $-\underset{\underset{CH_2OH}{|}}{CH}-$

or pharamcologically acceptable salts thereof.

Preferred compounds are those wherein R_1 is $-(CH_2)_4-$ or $-(CH_2)_6-$; R_2 is $-(CH_2)_2-$;

and R_3 is $-\overset{(S)}{\underset{\underset{OH}{|}}{CH}}-$, $-\underset{\underset{OCH_3}{|}}{CH_2}-$ or $-\overset{(S)}{\underset{\underset{CH_2OH}{|}}{CH}}-$;

those wherein R_1 is  ,  , or  ; R_2 is $-(CH_2)_2-$; and R_3 is $-CH_2-$ or $-\overset{(S)}{\underset{\underset{CH_2OH}{|}}{CH}}-$

and those wherein R_1 is $-(CH_2)_4-$ or $-(CH_2)_6-$; R_2 is $-CH=CH-$ (trans) and R_3 is $-\underset{\underset{OH}{|}}{CH}-$ or $-\underset{\underset{OCH_3}{|}}{CH}-$.

Specific examples of the compounds usable as immunosuppressive agents in accordance with the present invention are listed below:

(1) N-[4-(3-aminopropyl)aminobutyl]-2-(7-guanidinoheptaneamido)-2-hydroxyethaneamide;

(2) N-[4-(3-aminopropyl)aminobutyl]-2-(7-guanidinoheptaneamino)-2-methoxyethaneamide;

(3) N-[4-(3-aminopropyl)aminobutyl]-2-(9-guanidinononaneamido)-2-hydroxyethaneamide;

(4) N-[4-(3-aminopropyl)aminobutyl]-2-(7-guanidinoheptaneamido)-ethaneamide;

(5) N-[4-(3-aminopropyl)aminobutyl]-2-(7-guanidinoheptaneamido)-(S)-2-hydroxymethylethaneamide;

(6) N-[4-(3-aminopropyl)aminobutyl]-2-[4-(p-guanidinophenyl)butaneamido]ethaneamide;

(7) N-[4-(3-aminopropyl)aminobutyl]-2-[4-(p-guanidinophenyl)-butaneamido]-(S)-2-hydroxymethylethaneamide;

(8) N-[4-(3-aminopropyl)aminobutyl]-2-[3-(p-guanidinomethylphenyl)propaneamido]-(S)-2-hydroxymethylethaneamide;

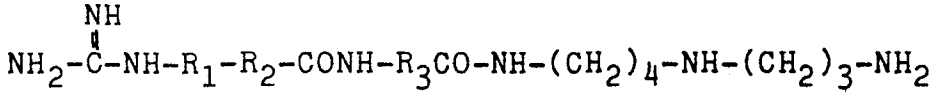
(9) N-[4-(3-aminopropyl)aminobutyl]-2-[5-(p-guanidinophenyl)-pentaneamido]-(S)-2-hydroxymethylethaneamide;

(10) N-[4-(3-aminopropyl)aminobutyl]-2-[7-guanidinohepta-2-enamido]-2-methoxyethaneamide; and

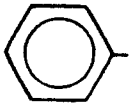
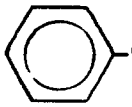
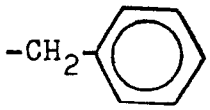
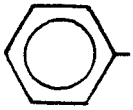
(11) N-[4-(3-aminopropyl)aminobutyl]-2-[7-guanidinohepta-2-enamido]-2-hydroxyethaneamide.

These compounds have the structures shown in Table 1.

Table 1 Chemicals Structures of Typical Examples of the Compounds of the Present Invention



Compound No.	R_1	R_2	R_3
(1)	$-(CH_2)_4-$	$-(CH_2)_2-$	$-\underset{\displaystyle OH}{\overset{\displaystyle \vert}{CH}}-$
(2)	$-(CH_2)_4-$	$-(CH_2)_2-$	$-\underset{\displaystyle OCH_3}{\overset{\displaystyle \vert}{CH}}-$

Compound No.	R_1	R_2	R_3
(3)	$-(CH_2)_6-$	$-(CH_2)_2-$	$-\underset{\displaystyle OH}{\underset{\vert}{CH}}-$
(4)	$-(CH_2)_4-$	$-(CH_2)_2-$	$-CH_2-$
(5)	$-(CH_2)_4-$	$-(CH_2)_2-$	$-\overset{(S)}{\underset{\displaystyle CH_2OH}{\underset{\vert}{CH}}}-$
(6)		$-(CH_2)_2-$	$-CH_2-$
(7)		$-(CH_2)_2-$	$-\overset{(S)}{\underset{\displaystyle CH_2OH}{\underset{\vert}{CH}}}-$
(8)		$-(CH_2)_2-$	$-\overset{(S)}{\underset{\displaystyle CH_2OH}{\underset{\vert}{CH}}}-$
(9)		$-(CH_2)_2-$	$-\overset{(S)}{\underset{\displaystyle CH_2OH}{\underset{\vert}{CH}}}-$
(10)	$-(CH_2)_4-$	$-CH=CH-$ (trans)	$-\underset{\displaystyle OH}{\underset{\vert}{CH}}-$
(11)	$-(CH_2)_6-$	$-CH=CH-$ (trans)	$-\underset{\displaystyle OH}{\underset{\vert}{CH}}-$

The compounds of formula (I) may form salts with acids. Salt-forming acids may be inorganic or organic if they are physiologically accpetable. Preferred inorganic acids are hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid; preferred organic acids include acetic acid, propionic acid, succinic acid, fumaric acid, maleic acid, malic acid, tartaric acid, glutaric acid, ci-

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