

# PATENT SPECIFICATION

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## (54) 5-ACYLOXY-IMIDAZOLE-4-CARBOXAMIDES

(71) We, SUMITOMO CHEMICAL COMPANY, LIMITED, a Japanese Company, of 15, Kitahama 5-chome, Higashi-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

### 5 - Acyloxy - imidazole - 4 - carboxamides

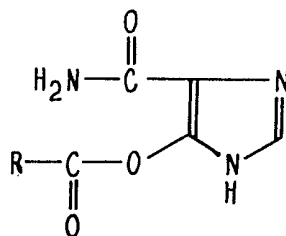
The present invention relates to novel imidazole-4-carboxamide derivatives and preparation thereof. More particularly, the present invention pertains to 5 - acyloxy - imidazole - 4 - carboxamide derivatives useful as antitumor agents and immunosuppressants, and to their preparation and use.

So far, it has been known that bredinin, 4 - carbamoyl - 1 -  $\beta$  - D - ribofuranosylimidazolium - 5 - olate, has immunosuppressive activity and weak antitumor activity against lymphatic leukemia L1210 (Kimio Mizuno et al. J. of Antibiotics, 27, 775 (1974)).

The aglycone of bredinin, 4 - carbamoylimidazolium - 5 - olate, was also known. (Edgar Shipper et al. J. Amer. Chem. Soc., 74, 350 (1952)). However, the pharmacological properties of 4-carbamoylimidazolium - 5 - olate were not known till quite recently.

It is reported that growth inhibitory effects on L5178Y cells and immunosuppressive effects are produced by administration of 4 - carbamoylimidazolium - 5 - olate. It is suggested, however, that these effects are not directly produced by it, but they are due to metabolic conversion of 4 - carbamoylimidazolium - 5 - olate to bredinin. (Kenzo Sakaguchi et al. J. of Antibiotics, 28, 798 (1975); T. Tsujino et al. Proceedings of the first intersectoral congress of IAMS Vol. 3, 441 (1974)).

5 - Acyloxy - imidazole - 4 - carboxamide derivatives provided by the present invention are representable by the formula:

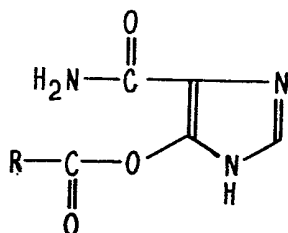


wherein R is a C<sub>1</sub>—C<sub>17</sub> alkyl group, an adamantyl group, or a phenyl group unsubstituted or substituted with a lower alkyl, lower alkoxy, lower alkylthio, nitro, cyano, methylenedioxy or acetamido group or a halogen atom.

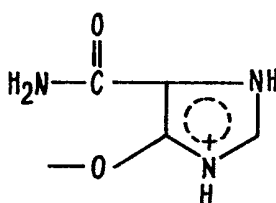
As used herein, the term "C<sub>1</sub>—C<sub>17</sub> alkyl" means a straight or branched alkyl having 1 to 17 carbon atoms (e.g. methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *t*-butyl,

isobutyl, *n*-pentadecyl, *n*-hexadecyl, *n*-heptadecyl). The term "lower alkyl" means a straight or branched alkyl having from 1 to 5 carbon atoms (e.g. methyl, ethyl, *n*-propyl, isopropyl). The term "lower alkoxy" means a straight or branched alkoxy having from 1 to 5 carbon atoms (e.g. methoxy, ethoxy, *n*-propoxy, *n*-butoxy, isobutoxy). The term "lower alkylthio" means a straight or branched alkylthio having from 1 to 5 carbon atoms (e.g. methylthio, ethylthio). The term "halogen" means fluorine, chlorine, bromine and iodine.

According to the present invention the 5 - acyloxyimidazole - 4 - carboxamide derivatives of the formula:



wherein R is as defined above, can be prepared by reacting 4 - carbamoylimidazolium - 5 - olate of the formula:



or its silylated derivative with a reactive derivative of a carboxylic acid of the formula:



wherein R is as defined above.

Examples of preferred reactive derivatives of carboxylic acids of the formula (III) are carboxylic acid anhydrides and halides, preferably chlorides.

The reaction can generally be effected by cooling a reaction mixture to a temperature from  $-10$  to  $30^\circ\text{C}$ ., preferably for 1 to 10 hours. The reaction of 4 - carbamoylimidazolium - 5 - olate with carboxylic acid halides can usually be carried out in an inert polar solvent or in a mixture of water and an inert organic solvent preferably in the presence of an inorganic or tertiary organic base. Typical examples of said inert polar solvents are pyridine, dimethylformamide, formamide, dimethylsulfoxide, hexamethylphosphoric triamide, and dimethylacetamide. Typical examples of said inert organic solvents are ethyl ether, benzene, toluene, chloroform, ethylacetate, *n*-hexane, and xylene. Examples of preferred inorganic base are sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate and potassium hydroxide. Examples of preferred tertiary organic base are triethylamine, *N,N*-dimethylaniline, and pyridine.

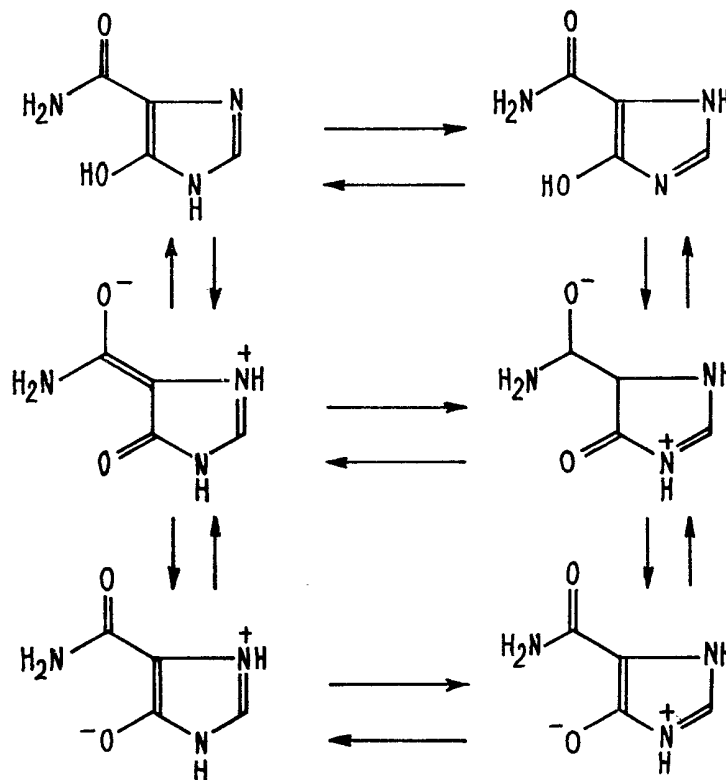
The reaction of 4 - carbamoylimidazolium - 5 - olate with carboxylic acid anhydrides can be carried out in the presence or absence of an inert organic solvent (e.g. methanol, ethanol, dimethylformamide, dimethylsulfoxide, formamide, hexamethylphosphoric triamide, dimethylacetamide, acetonitrile, acetone, nitromethane or ethyl acetate). In this case, the carboxylic acid anhydrides may be used as a solvent.

The compounds of the formula (1) can also be prepared by reacting a silylated derivative of 4 - carbamoylimidazolium - 5 - olate with aforesaid carboxylic acid halides in an inert organic solvent (e.g. benzene, toluene, xylene, ethylacetate, *n*-hexane, dichloroethane anhydrous ethyl ether, anhydrous dioxane or anhydrous tetrahydrofuran).

The reaction can be effected by cooling at a temperature  $-10$  to  $30^\circ\text{C}$ ., preferably for 1 to 10 hours.

The silylated derivatives of 4 - carbamoylimidazolium - 5 - olate are known and can be prepared by known methods. [Hayashi et al. Japanese Patent Kokai 50-

121276]. 4 - Carbamoylimidazolium - 5 - olate may exist in the form of tautomers as follows



so the position of acylation may be ambiguous.

We found out that the acylation occurs preferentially at the 5 position of 4 - carbamoylimidazolium - 5 - olate and completed this invention.

5 - Acyloxy imidazole - 4 - carboxamide derivatives of the formula (1) possess excellent immunosuppressive activity as well as potent antitumor activity.

For example, they exhibit much higher immunosuppressive activity than those of 6 - (1 - methyl - 4 - nitro - 5 - imidazolyl) mercaptopurine (Azathioprine) and 6-mercaptopurine.

The compounds (1) of the present invention have low toxicity. They do not show any toxic symptoms, when over 500 mg/kg of the compounds are orally administered to a mouse. Moreover, they do not show influences on decrease of peripheral leucocytes, which is one of the most serious side effects of immunosuppressants.

The immunosuppressive activities of the compounds of the present invention, Azathioprine and 6-mercaptopurine are given in the following table. After a sheep red blood cell preparation (SRBC) was injected in mice, the compounds were administered orally once a day on days 0 to 3. The plaque forming cell (PFC) number was measured on day 4 by Cunningham method. Cunningham A.J. et al. Immunol. 14 599 (1968).

TABLE

	Compounds	Dose mg/kg/day p.o	Effects PFC/spleen× 10 <sup>-4</sup>	Suppres- sion (%)	
5	5-Benzoyloxy-imida- zole-4-carboxamide	25 100	19.88±6.06 <sup>a</sup> 8.63±2.61 <sup>b</sup>	68.1 89.4	5
	5-Adamantoyloxy- imidazole-4- carboxamide	25 100	14.19±2.24 <sup>a</sup> 5.19±1.29 <sup>b</sup>	77.2 93.6	
10	5-Palmitoyloxy- imidazole-4- carboxamide	100	15.88±4.10 <sup>b</sup>	80.5	10
15	5-(p-Chlorobenzoyloxy)- imidazole-4- carboxamide	25	22.06±5.37 <sup>a</sup>	64.6	15
	6-Mercaptopurine	25	30.78±6.28	60.2	
	Azathioprine	100	26.73	81.6	
	Control <sup>a</sup>	62.25±11.73			
20	Control <sup>b</sup>	81.44± 6.56			20
	(a) These experiments were conducted at the same time on the same day.				
	(b) These experiments were conducted at the same time on a different day.				
25	The compounds of the present invention have also been found to possess potent antitumor activities against Sarcoma 180, Ehrlich carcinoma, MH 134 hepatoma, and P388 leukemia. They exhibit particularly excellent inhibitory effects against solid tumors.				25
	The compounds of the present invention also have anticandida and antiviral activities. Thus, the compounds of the present invention are useful particularly as immunosuppressants and antitumor agents.				
30	The compounds of the present invention can be administered orally or parenterally at a daily dose of 0.1 g to 1.0 g/adult person as an immunosuppressant, and 3 g to 10 g/adult person as an antitumor agent in a conventional dosage unit form. For the oral or parenteral administration, they are made up alone or together with a conventional pharmaceutical carrier or diluent to a conventional solid or liquid pharmaceutical preparation (e.g. powders, granules, tablets, capsules, suspensions, emulsions or solutions) using the conventional methods in the pharmaceutical field.				30
35	The following examples are given to illustrate the present invention more precisely but it is not intended to limit the present invention thereto.				35
40	Example 1				40
	To a suspension of 455 mg of 4 - carbamoyl - imidazolium - 5 - olate in 5 ml of dry pyridine was added 1.02 g of benzoyl chloride at a temperature below 5°C. After addition was over, the mixture was stirred under ice cooling for 2 hours. Then separated crystals were filtered off, washed with water and diethyl ether, dried to give 5 - benzoyloxy - imidazole - 4 - carboxamide, M.P. 204°C. (dec).				
45	$\begin{array}{c} \text{O} \\ \parallel \\ \text{OC}-\text{C}_6\text{H}_5 \end{array}$ $\nu_{\text{Nujol}}^{\text{Max.}}(\text{cm}^{-1}); 3450, 3170, 3100 (\text{NH}), 1740 (\text{OC}-\text{C}_6\text{H}_5)$ (Nujol is a Registered Trade Mark).				45
	Example 2				
50	To a suspension of 508 mg of 4 - carbamoylimidazolium - 5 - olate and 486 mg of triethylamine in 6 ml of anhydrous dimethylformamide was added 770 mg of p-chlorobenzoyl chloride in 3 ml of anhydrous dimethylformamide at a temperature below 5°C. The mixture was stirred under ice cooling for 4 hours. The insoluble crystals were filtered off, then the filtrate were concentrated to a residue under reduced pressure, and the resulting residue was dissolved in chloroform. The chloroform solution was washed with water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 5 - (p - chlorobenzoyloxy) - imidazole - 4 - carboxamide. The crude solid was washed with ethyl acetate to give 340 mg of pure product, M.P. 220°C. (charred).				50
55					55

The following compounds were obtained by substantially the same procedures as described above:

- 5 - Adamantoyloxy - imidazole - 4 - carboxamide M.P. 211°C. (dec.)  
 5 - (*p* - Nitrobenzoyloxy) - imidazole - 4 - carboxamide M.P. 177—184°C (dec.)  
 5 - (*p* - Fluorobenzoyloxy) - imidazole - 4 - carboxamide M.P. 214°C. (dec.)

#### Example 3

The mixture of 100 mg. of 4 - carbamoyl - imidazolium - 5 - olate and 1.1 g. of acetic anhydride in 50 ml of anhydrous ethanol was stirred at a temperature below 5°C. for one hour. Then 20 mg of insoluble crystals of 4 - carbamoylimidazolium - 5 - olate were recovered. The filtrate was allowed to stand in the refrigerator for 2 days.

The resulting solution was evaporated *in vacuo* to a residue, to which was added 10 ml of 50% toluene-ethanol solution. Further, the organic solvent was evaporated *in vacuo* to dryness and the resulting residue was washed with a small amount of ethyl acetate, and filtered off to give 5 - acetyloxy - imidazole - 4 - carboxamide, M.P. 190°C. (charred).

Infrared absorption spectra

$\nu_{\text{max}}^{\text{nujol}}(\text{cm}^{-1})$ : 3440 (NH), 1770, 1755, 1205 (OCOCH<sub>3</sub>)

Nuclear magnetic resonance spectra  
 $\delta_{\text{T.M.S.}}^{\text{CDCl}_3}$  (ppm): 2.3 (singlet, 3H, OCOCH<sub>3</sub>)  
 7.6 (singlet, 1H, C<sub>2</sub>-H)

The following compound was obtained in the same manner as described above.

- 5 - Butyryloxyimidazole - 4 - carboxamide M.P. 240°C. (charred)

#### Example 4

A mixture of hexamethyldisilazane (10 g), a catalytic amount of ammonium sulfate and 4 - carbamoyl - imidazolium - 5 - olate (745 mg) was refluxed for an hour and a half. The solution was condensed under reduced pressure to give silylated 4 - carbamoylimidazolium - 5 - olate derivative. The resulting solid (345 mg) was dissolved in dry benzene (30 ml). To the benzene solution was added 350 mg of *p*-chlorobenzoylchloride under ice cooling, then the mixture was stirred for 3 hours and for 6 hours at room temperature. The resulting solution was evaporated *in vacuo* to dryness and the resulting solid was washed with ethyl acetate to give 5 - (*p* - chlorobenzoyloxy) - imidazole - 4 - carboxamide, M.P. 220°C. (charred).

#### Example 5

To a mixture of 1.27 g of 4 - carbamoyl - imidazolium - 5 - olate in 42.4 g of 10% aqueous solution of sodium carbonate was added 7.38 g of 3,4 - methylenedioxybenzoylchloride in 20 ml of toluene at room temperature. After addition was over, the mixture was stirred for 4 hours. Then the separated crystals were filtered off, washed with water and toluene, dried *in vacuo* to give 5 - (3',4' - methylenedioxybenzoyloxy)imidazole - 4 - carboxamide, M.P. 206.5—208°C. (dec.).

And the following compounds were obtained by the manner similar to that described in Example 5.

- 5 - (*o* - Methoxybenzoyloxy) - imidazole - 4 - carboxamide M.P. 205°C. (charred).  
 5 - (*m* - Cyanobenzoyloxy) - imidazole - 4 - carboxamide M.P. 195°C. (dec.).  
 5 - (*p* - Methylbenzoyloxy) - imidazole - 4 - carboxamide M.P. 211°C. (dec.).

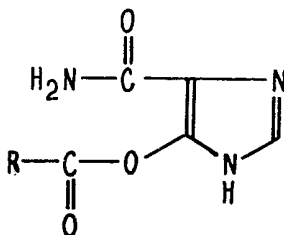
According to the processes of the present invention, there are obtained, for example, the following 5 - acyloxyimidazole - 4 - carboxamides.

- 5 - (*o* - Chlorobenzoyloxy) - imidazole - 4 - carboxamide  
 5 - (*m* - Chlorobenzoyloxy) - imidazole - 4 - carboxamide  
 5 - (*p* - Bromobenzoyloxy) - imidazole - 4 - carboxamide  
 5 - (*p* - Acetamidobenzoyloxy) - imidazole - 4 - carboxamide  
 5 - (*p* - Methylthiobenzoyloxy) - imidazole - 4 - carboxamide  
 5 - Propionyloxy - imidazole - 4 - carboxamide

5 - Isobutyryloxy - imidazole - 4 - carboxamide  
 5 - Palmitoyloxy - imidazole - 4 - carboxamide  
 5 - Stearoyloxy - imidazole - 4 - carboxamide  
 5 - Margaroyloxy - imidazole - 4 - carboxamide  
 5 - Pivaloyloxy - imidazole - 4 - carboxamide  
 5 - Isovaleryloxy - imidazole - 4 - carboxamide  
 5 - Valeryloxy - imidazole - 4 - carboxamide

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein R is an alkyl group having 1 to 17 carbon atoms, an adamantyl group, or a phenyl group unsubstituted or substituted with a lower alkyl, lower alkoxy, lower alkylthio, nitro, cyano, methylenedioxy or acetamido group or a halogen atom.

2. A compound according to Claim 1, wherein R is an alkyl group having 1 to 17 carbon atoms.

3. A compound according to Claim 1, wherein R is a phenyl group unsubstituted or substituted with a lower alkyl, lower alkoxy, lower alkylthio, nitro, cyano, methylenedioxy or acetamido group or a halogen atom.

4. A compound according to Claim 1, wherein R is an alkyl group having 1 to 17 carbon atoms, an adamantyl group, a phenyl group or a halogen atom-substituted phenyl group.

5. A compound according to Claim 1, wherein R is a phenyl group substituted with a lower alkyl, lower alkoxy, nitro, cyano, methylenedioxy, acetamido or lower alkylthio group.

6. 5 - Benzoyloxy - imidazole - 4 - carboxamide.

7. 5 - (*p* - Chlorobenzoyloxy) - imidazole - 4 - carboxamide.

8. 5 - Acetyloxy - imidazole - 4 - carboxamide.

9. 5 - (3',4' - Methylenedioxybenzoyloxy) - imidazole - 4 - carboxamide.

10. 5 - Adamantoyloxy - imidazole - 4 - carboxamide.

11. 5 - Palmitoyloxy - imidazole - 4 - carboxamide.

12. 5 - (*p* - Nitrobenzoyloxy) - imidazole - 4 - carboxamide.

13. 5 - (*p* - Fluorobenzoyloxy) - imidazole - 4 - carboxamide.

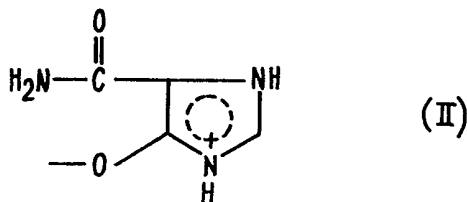
14. 5 - Butyryloxy - imidazole - 4 - carboxamide.

15. 5 - (*o* - Methoxybenzoyloxy) - imidazole - 4 - carboxamide.

16. 5 - (*m* - Cyanobenzoyloxy) - imidazole - 4 - carboxamide.

17. 5 - (*p* - Methylbenzoyloxy) - imidazole - 4 - carboxamide.

18. A process for producing a compound according to Claim 1, which comprises reacting 4 - carbamoylimidazolium - 4 - olate of the formula



or its silylated derivative with a reactive derivative of carboxylic acids of the formula,



wherein R is defined in Claim 1.

19. A process according to Claim 18, wherein the reactive derivative of a carboxylic acid of the formula (III) is carboxylic acid halide or anhydride.

20. A process according to Claim 19, wherein the reaction is carried out at a temperature from  $-10$  to  $30^{\circ}\text{C}$ . in the presence or absence of a solvent.

5      21. A pharmaceutical composition useful as antitumor agents and immunosuppressants, which comprises an effective amount of a compound of Claim 1 as an active ingredient and a pharmaceutically acceptable carrier or diluent.      5

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