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D 1071-1 WO

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SD/EN/ie

THE PHARMACOLOGICAL USE OF CERTAIN CYSTINE DERIVATIVES

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D 1071-1

91-05-17

THE PHARMACOLOGICAL USE OF CERTAIN CYSTINE DERIVATIVES5 Field of the Invention

The present invention relates to a new medical use of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N, N'-dicaprylylcystine, N,N'-
10 diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester and N,N'-diisovalerylcystine dimethyl ester in racemic forms or in the form of optical D or L isomers.

In particular the invention relates to the use of the
15 abovementioned compounds for the preparation of medicaments with immunomodulating action, particularly immunostimulating action.

Background of the Invention

20

N-Acetyl-L-cysteine is a compound widely used for treating chronic obstructive airway diseases/chronic bronchitis (for further references see Multicentre Study Group. Long-term oral acetylcysteine in chronic bronchitis. A
25 double-blind controlled study. Eur. J. Respir. Dis. 1980, 61 (suppl. 111), 93-108; Boman, G., Bäckér, U., Larsson, S., Melander, B., and Wåhlander, L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis. Report of a trial organized by the Swedish Society for Pulmonary
30 Disease. Eur. J. Respir. Dis. 1983, 64, 405-415; and British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airway obstruction. Thorax 1985, 40, 832-835). The mechanism of action of the
35 compound is not disclosed; its effect has been attributed to mucolytic properties (see Multicentre Study Group.

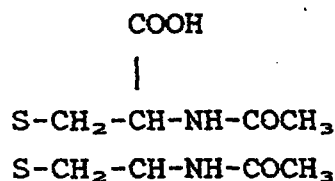


Long-term oral acetylcysteine in chronic bronchitis. A double-blind controlled study. Eur. J. Respir. Dis. 1980, 61 (suppl. 111), 93-108; Boman, G., Bäcker, U., Larsson, S., Melander, B., and Wåhlander, L. Oral acetylcysteine
 5 reduces exacerbation rate in chronic bronchitis. Report of a trial organized by the Swedish Society for Pulmonary Disease. Eur. J. Respir. Dis. 1983, 64, 405-415; and British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with
 10 chronic bronchitis and severe airway obstruction. Thorax 1985, 40, 832-835), antioxidant properties (see Aruoma, O.I., Halliwell, B., Hoey, B.M., and Butler, J. Free Radical Biol. Med. 1989, 6, 593-597), and also immunomodulating properties (see Bergstrand, H., Björnson, A., Eklund, A., Hernbrand, R., Eklund, A., Larsson, K.,
 15 Linden M., and Nilsson, A. Stimuli-induced superoxide radical generation in vitro by human alveolar macrophages from smokers: Modulation by N-Acetylcysteine treatment in vivo. J. Free Radicals Biol. & Med. 2, 1986, 119-127).

20

The present invention deals with the disulfide of N-acetylcysteine, that is N,N'-diacetylcystine (in the following referred to as DiNAC), i.e. the compound of the formula:

25



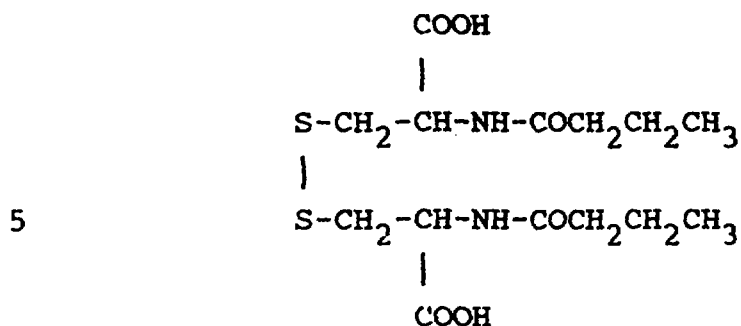
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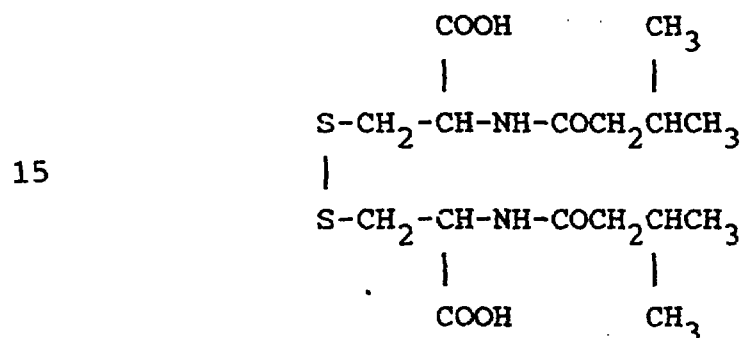
N,N' - dibutyrylcystine (in the following referred to as diBUT), i.e. the compound of the formula:

35

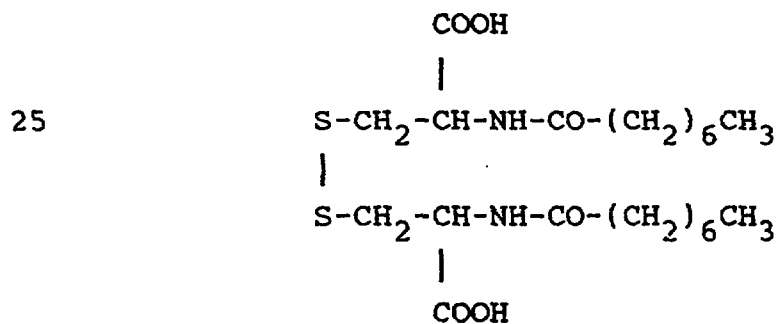




N,N'-diisovalerylcystine (in the following referred to as
10 diVAL), i.e. the compound of the formula

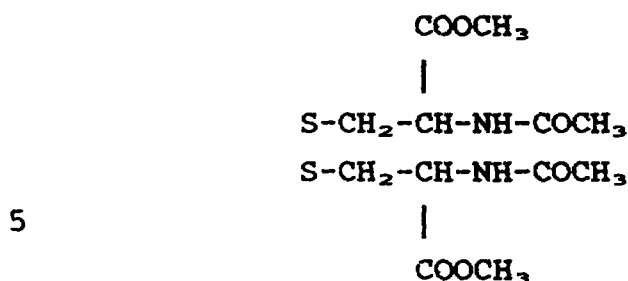


20 N,N'-dicaprylylcystine (in the following referred to as
diCAP), i.e. the compound of the formula

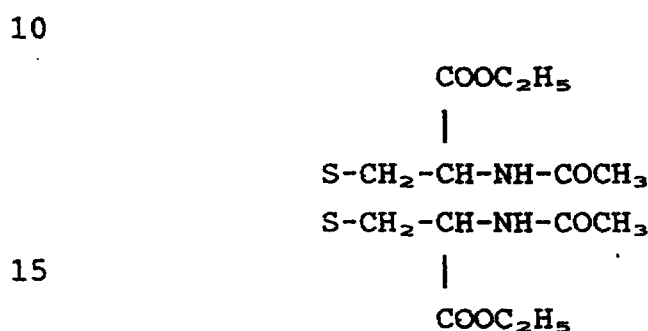


30 N,N'-diacetylcystine dimethyl ester (in the following
referred to as diMeNAC), i.e. the compound of the formula:

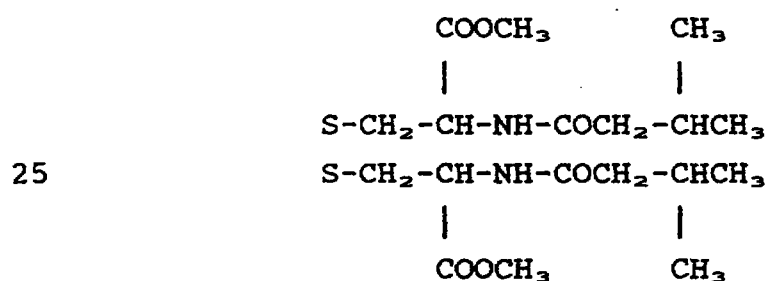




N,N'-diacetylcystine diethyl ester (in the following referred to as diEtNAC), i.e. the compound of the formula:



and N,N'-diisovalerylcystine dimethyl ester (in the following referred to as diMeVAL), i.e. the compound of the formula:



The invention deals with the above mentioned compounds in racemic form as well as the isomeric D and L forms of the compounds. Of particular interest are the compounds having the L configuration, particularly interesting is N,N'-diacetyl-L-cystine.

The invention also deals with the compounds in the form of their physiologically acceptable salts such as the salts



of sodium, potassium, ammonium, calcium or magnesium. Also included are salts of the compounds diNAC, diBUT, diVAL and diCAP with pharmaceutically acceptable organic bases.

5

The above mentioned compounds have previously been described in the patent literature as well as in the scientific literature. DiNAC in the following publications: US 4827016; EP 300100; US 4724239; US 10 4708965; DE 2326444; Wilson, I.D., and Nicholson, J.K. Analysis of thiols and disulfides in Sulphur-containing drugs and related organic compounds. Chemistry, Biochemistry and Toxicology (ed L.A. Damani) Vol. 2A. Analytical, biochemical and toxicological aspects of 15 sulphur xenobiochemistry. Ellis Horwood Series in Biochemical Pharmacology (Halsted Press: a division of John Wiley & Sons) Chichester 1989, p. 45; and Sjödin K., Nilsson E., Hallberg, A., and Tunek, A. Metabolism of N-Acetyl-L-cysteine. Some structural requirements for the 20 deacetylation and consequences for the oral bioavailability. Biochem. Pharmacol. 1989, 38, 3981-3985). In US 4827016 the compound is claimed to be effective for topical treatment of dermal inflammations which are induced and propagated by leukotrienes.

25

The remaining compounds have also been described in the literature. (See for instance, for diMeNAC: Bowman, W.R. Richardson, G.D. Tetrahedron Lett. 1981, 22, 1551-1554; for diEtNAC: Damico, R.A. Boggs, R.W. US 3952115 (1976); 30 for diVAL, diMeVAL: Martin, T.A. J. Med. Chem 1969, 12, 950-953), for diCAP: FR 8205 M, for diBUT: FR 2503151).

Nothing is reported or generally known concerning the pharmacological and/or therapeutic properties of these 35 compounds with respect to immunological systems or inflammatory diseases of the lung such as chronic



bronchitis.

Disclosure of the Invention

5 It has unexpectedly been found that the hereinbefore
mentioned compounds diNAC, diBUT, diVAL, diCAP, diMeNAC,
diEtNAC and diMeVAL in an experimental animal model for
assessing a T-cell reactivity in vivo, i.e. the delayed
10 type hypersensitivity (DTH) reaction in the mouse ear, are
highly potent and efficient immunostimulating agents, some
being in the order of 100-1000 times more effective than
the thiol NAC. Thus, in this model the compounds are
highly effective immunostimulators with a potency and
efficacy superior or equal to known immunostimulants such
15 as diethyl dithiocarbamate (DTC) or hydroxyethyl disulfide
(HEDS; see St Georgiev, V. New synthetic immunomodulating
agents. Trends in Pharmacological Science 1988, 446-451).

Therefore, the compounds DiNAC, diBUT, diVAL, diCAP,
20 diMeNAC, diEtNAC, diMeVAL and their D and L optical
isomers may be used for treatment of diseases where a
defect in the immune system and/or an ineffective host
defence is at hand or can be suspected.

25 Examples of such diseases are chronic bronchitis and other
inflammatory diseases of the airways such as asthma and
rhinitis but also certain forms of autoimmune diseases
like diabetes and rheumatoid arthritis and/or various
malignant diseases. HIV infection or AIDS may be treated
30 with the compounds. Also atherosclerotic disease may be
treated with the compounds.

Effective amounts of the compounds diNAC, diBUT, diVAL,
diCAP, diMeNAC, diEtNAC, diMeVAL and their D and L optical
35 isomers for use in the treatment of the above mentioned



diseases are in the range 0.5-500 mg, preferably 5-50 mg, daily dose.

Synthesis of compounds

- 5 The compounds diNAC, diBUT, diVAL and diCAP may be prepared, for example, from L-cystine via acylation (see US 4827016; EP 300100; US 4724239; US 4708965; DE 2326444; Marshall, R., Winitz, M., Birnbaum, S.M. and Greenstein, J.P. J. Am. Chem. Soc. 1957, 79, 4538-4544; and Cecil, R. McPhee, J.B. Biochem. J. 1957, 66, 538-543) or through oxidative dimerization of the appropriate acylcysteines (see Snow, J.T., Finley, J.W. Friedman, M. Biochem. Biophys. Res. Commun. 1975, 64, 441-447).
- 10
- 15 The esters diMeNAC, diEtNAC and diMeVAL may be synthesized analogously, i.e. by acylation of the cystine methyl or ethyl esters as appropriate or by oxidative dimerisation of the respective N-acetyl cystine methyl or ethyl esters or N-isovalerylcysteine methyl ester. For examples of preparations, see Bonnett, R., Nicolaidow, P. J. Chem. Soc. Perkin Trans. I 1979, 1069-1077. Schaad, L.J., Werner, R.M., Dillon, L., Field, L., Tate, C.E. J. Med. Chem. 1975, 18, 344-351, and Martin, T.A. J. Med. Chem. 1969, 12, 950-953.
- 20
- 25

Effects of compounds in a model of delayed type hypersensitivity in the mouse

- 30 The property of the compounds diNAC, diBUT, diVAL, diCAP, diMeNAC, diEtNAC and diMeVAL to stimulate immune responses is illustrated by their efficacy in a model of the delayed type hypersensitivity (DTH) reaction in the mouse.
- 35 Both male and female Balb/c mice obtained from Bomholtsgaard (Denmark) and Charlie Rivers (England), were



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used at the weight of 18-20 gram. 4-ethoxymethylene-2-phenyloxazolone (OXA) was purchased from BDH (England) and served as an antigen in this test.

5 The mice were sensitized, Day 0, by epicutaneous application of 150 μ l absolute ethanol-acetone (3:1) solution containing 3% OXA on the shaved thorax and abdomen. Treatment with the L-form of diNAC, diMeNAC, diEtNAC, diMeVAL, or vehicle (phosphate buffer, pH 7.0) was initiated by oral feeding immediately after sensitization and continued once daily to Day 6. Seven days (Day 6) after the sensitization both ears of all mice were challenged on both sides by topical application of 20 μ l 1% OXA dissolved in peanut oil. Ear thickness was measured prior to and 24 or 48 hours after challenge using an Oditest spring calliper. Challenges and measurements were performed under light pentobarbital anesthesia. The intensity of the DTH reactions was expressed according to the formula: $T_{t_{24/48}} - T_{t_0}$ μ m units, where t_0 , t_{24} and t_{48} represent the ear thickness before and 24 or 48 hours after challenge, respectively, in an individual test (T). The results were expressed as the mean $\pm$ S.E.M. The level of significance between means of the groups was obtained by Student's two-tailed t-test. Tables 1 and 2 show the results from 24 and 48 hours measurements, respectively, from a representative experiment with the L-form of diNAC. The results show that L-diNAC, after oral administration, caused a significant increase of the ear thickness in a concentration-response manner.

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Table 1

Ear thickness 24 hours after challenge of animals treated with the indicated doses of L-diNAC or vehicle.

5

	Conc. $\mu\text{mol/kg}$	N	Diff. $T_{t24}-T_{t0}$	S.E.M.	Sign.
10	Buffer	13	7.85	0.32	
	NaCl	10	7.90	0.30	n.s.
	0.03	10	13.75	0.47	***
	0.30	10	15.70	0.48	***
15	3.0	10	18.30	1.02	***
	30.0	15	20.67	0.67	***

***: $p < 0.001$

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Table 2

5

Ear thickness 48 hours after challenge of animals treated with the indicated doses of L-diNAC or vehicle.

10	Conc. $\mu\text{mol/kg}$	N	Diff $T_{t48}-T_{t0}$	S.E.M.	Sign.
	Buffer	14	9.64	0.35	
15	NaCl	10	9.85	0.54	n.s.
	0.03	10	11.65	0.27	***
	0.30	10	12.65	0.48	***
	3.0	10	14.95	0.55	***
	30.0	15	13.63	0.30	***
20					

***: $p < 0.001$

25 Table 3 gives the corresponding figures for ear thickness 24 and 48 hours after challenge of animals treated with diMeNAC and diEtNAC.

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Table 3

5 Ear thickness 24 and 48 hours after challenge of animals treated with the L-forms of diMeNAC and diEtNAC.

10		Conc $\mu\text{mol/kg}$	N	Diff $T_{t24}-T_{t0}$	S.E.M.	Sign.
		24 h				
15	Buffer		10	8.70	0.34	-
	diMeNAC	0.03	10	18.00	0.84	***
		3.0	10	12.55	0.88	**
20	diEtNAC	0.03	10	11.75	0.62	***
		3.0	10	13.05	0.59	***

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(...table 3)

5		Conc $\mu\text{mol/kg}$	N	Diff $T_{t48}-T_{t0}$	S.E.M.	Sign.
		48 h				
10	diMeNAC	0.03	10	12.85	0.67	**
		3.0	10	13.35	0.67	***
	diEtNAC	0.03	10	13.15	0.53	***
		3.0	10	13.20	0.66	***
15						

** : $p < 0.01$

20 *** : $p < 0.001$

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Pharmaceutical formulations

The described active substances can be included in
5 different dosage forms e.g. tablets, coated tablets,
gelatin capsules, solutions and aerosols.

For the preparation of tablets, coated tablets and gelatin
capsules the active substances can be combined with
10 pharmaceutically acceptable materials, e.g. lactose,
starch, dicalcium phosphate, microcrystalline cellulose,
polyvinylpyrrolidone, gelatin, cellulose derivatives,
colloidal silicone dioxide, talc and stearic acid or its
salts.

15 For the preparation of oral solutions suitable excipients
are water, saccharose, glucose, sorbitol, fructose and
xylitol.

20 The dosage forms can besides mentioned excipients contain
preservatives, stabilizers, viscosity regulating agents,
emulsifiers, sweetening agents, colouring agents,
flavouring agents, tonicity regulating agents, buffers or
antioxidants. They can also contain other therapeutically
25 valuable substances.

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Example 1

Tablet containing 10 mg of active substance per tablet:

5	Active substance	10 mg
	Lactose	100 mg
	Potato starch	50 mg
	Polyvinylpyrrolidone	5 mg
10	Microcrystalline cellulose	15 mg
	Magnesium stearate	1 mg

Example 2

15 Direct compression tablet containing 5 mg of active substance per tablet:

	Active substance	5 mg
	Lactose, anhydrous	150 mg
20	Microcrystalline cellulose	50 mg
	Colloidal silicon dioxide	1 mg
	Magnesium stearate	2 mg

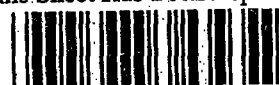
If desired, the obtained tablets can be film coated with
25 e.g. hydroxypropyl methylcellulose, hydroxypropyl cellulose or dimethylaminoethyl methacrylate methacrylic acid ester copolymer.

Example 3

30

Solution for injection containing active substance 1 mg/ml

	Active substance	1.0 mg
	Sodium chloride	8.8 mg
35	Water for injection	to 1 ml



Example 4

Oral solution containing active substance 1 mg/ml

5	Active substance	1.0 mg
	Sorbitol	150 mg
	Glycerin	100 mg
	Disodium edetate	0.5 mg
	Preservative	q.s.
10	Flavour	q.s.
	Water, purified	to 1 ml

Example 5

15 Powder aerosol giving 1 mg per dose

The micronized active substance can be filled into a powder inhaler device e.g. Turbuhaler^R giving 1 mg/dose.



CLAIMS

1. The use of racemic N,N'-diacetylcystine, N,N'-
dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-
5 dicaprylylcystine, N,N'-diacetylcystine dimethyl
ester, N,N'-diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
10 immunomodulating action.
2. The use of the L optical isomers of N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
15 diacetylcystine dimethyl ester, N,N'-diacetylcystine
diethyl ester, N,N'-diisovalerylcystine dimethyl
ester, or a physiologically acceptable salt thereof
for the preparation of medicaments with
immunomodulating action.
- 20 3. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
25 diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
effect against chronic bronchitis.
- 30 4. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-diacetylcystine
35 diethyl ester, N,N'-diisovalerylcystine dimethyl
ester, or a physiologically acceptable salt thereof





for the preparation of medicaments with effect against chronic bronchitis.

5. The use according to claim 1 of racemic N,N'-
5 diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
10 diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
effect against asthma.
6. The use according to claim 2 of the L optical isomers
15 of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
20 physiologically acceptable salt thereof for the
preparation of medicaments with effect against
asthma.
7. The use according to claim 1 of racemic N,N'-
25 diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
30 isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
effect against rhinitis.
8. The use according to claim 2 of the L optical isomers
35 of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-





- diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
5 preparation of medicaments with effect against
rhinitis.
9. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
10 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
15 thereof for the preparation of medicaments with
effect against diabetes.
10. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
20 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
25 preparation of medicaments with effect against
diabetes.
11. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
30 diisovalerylcystine, N,N'-dicaprylylcystine,
N,N'-diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L
optical isomers thereof or a physiologically
35 acceptable salt thereof for the preparation of
medicaments with effect against rheumatoid





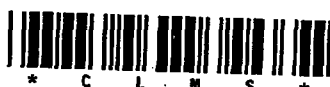
arthritis.

12. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
5 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
10 preparation of medicaments with effect against
rheumatoid arthritis.
13. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
15 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
20 thereof for the preparation of medicaments with
effect against malignant diseases.
14. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
25 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
30 preparation of medicaments with effect against
malignant diseases.
15. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
35 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-





- 5 diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
effect against HIV infections/AIDS.
- 10 16. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
preparation of medicaments with effect against HIV
15 infections/AIDS.
- 20 17. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
25 effect against atherosclerotic disease.
- 30 18. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
preparation of medicaments with effect against
35 atherosclerotic disease.





19. The use according to claim 2 of N,N'-
diacetyl-L-cystine.
- 5 20. A pharmaceutical preparation for use in the
treatment of diseases where an immunomodulating
substance is effective comprising as active
ingredient a compound as defined in claim 1.
- 10 21. A pharmaceutical preparation according to claim
20 in dosage unit form.
- 15 22. A pharmaceutical preparation according to claims
20-21 comprising the active ingredient in
association with a pharmaceutically acceptable
carrier.
- 20 23. A pharmaceutical preparation according to claims
20-22 comprising as active ingredient N,N'-
diacetyl-L-cystine.
- 25 24. A method for the treatment of diseases due to
defects in the immune system, particulary
chronic bronchitis, asthma, rhinitis, diabetes,
rheumatoid arthritis, malignant diseases, HIV
infection/AIDS and atherosclerotic disease, in
mammals including man, characterized by the
administration to a host in need of such
treatment of an effective amount of racemic
N,N'-diacetylcystine, N,N'-dibutyrylcystine,
30 N,N'-diisovalerylcystine, N,N'-
dicaprylylcystine, N,N'-diacetylcystine
dimethylester, N,N'-diacetylcystine
diethylester, N,N'-diisovalerylcystin dimethyl
ester, D and L optical isomers thereof or a



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physiologically acceptable salt thereof, optionally
together with a pharmaceutically acceptable carrier.

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