



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/HU84/00016 (22) International Filing Date: 12 March 1984 (12.03.84) (31) Priority Application Number: 842/83 (32) Priority Date: 11 March 1983 (11.03.83) (33) Priority Country: HU (71) Applicants (for all designated States except US): BIO-GAL, Gyógyszergyár [HU/HU]; Pallagi u. 13., H-4042 Debrecen (HU). ALKALOIDA, Vegyészeti, Gyár [HU/HU]; H-4440 Tiszavasvári (HU). (72) Inventors; and (75) Inventors/Applicants (for US only) : MÁDI-SZABÓ, László [HU/HU]; MORVAI, Margit [HU/HU]; 20, Mátyáshegyi ut, H-1037 Budapest (HU). HORVÁTH, Éva [HU/HU]; 33, Naphegy u., H-1016 Budapest (HU). JANCsó, Sándor [HU/HU]; 28, Kardos u., H-Debrecen (HU). TAMÁSI, Piroska [HU/HU]; 24, Bem tér, H-Debrecen (HU). KOVÁCS, István [HU/HU]; 86, Csapó u., H-Debrecen (HU). KISS, Ilona, Mária née LOOS [HU/HU]; 12, Monostor u., H-Debrecen (HU). BACSA, György [HU/HU]; 90, Csapó u., H-Debrecen (HU). KUBALA, Mária née PAPP [HU/HU]; 4, Élmunkás u., H-Tiszavasvári (HU). BENE, Magdolna née HORVÁTH [HU/HU]; 23, Élmunkás u., H-Tiszavasvári (HU).		(74) Agent: PATENTBUREAU DANUBIA; P.O. Box 198, H-1368 Budapest (HU). (81) Designated States: AT (European patent), AU, BE (European patent), BR, CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), NO, RO, SE (European patent), SU, US. Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS OF ANTI-PANCREATIC INFLAMMATORY EFFECT (57) Abstract Pharmaceutical compositions comprising 3-dimethylamino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine and at least one of a factor of Vitamine P and/or (+)-2-(3,4-dihydroxyphenyl)-3,5,7-cromanetriole as active ingredients, a process for preparing the same and a method for treating pancreatic inflammations with the said composition. The pharmaceutical compositions according to the invention are useful for the treatment of pancreatic inflammations.		

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PHARMACEUTICAL COMPOSITIONS OF ANTI-PANCREATIC
INFLAMMATORY EFFECT

Technical field

5 The present invention relates to synergistic
pharmaceutical compositions of anti-pancreatic
inflammatory effect, a process for preparing the same
and a method for treating pancreatic inflammations.

 In particular, the invention is directed to
10 pharmaceutical compositions comprising one or more
active ingredients of antiphlogystic and vascular effect,
a process for preparing the same and a method for
treating pancreatic inflammations with the said compo-
sitions.

15 Background art

 In the last two decades the chronic inflammatory
diseases of pancreas appeared to cause increased
clinical problems. This phenomenon is accompanied on
one hand by the increased number of patients, on the
20 other hand by the increased number of diagnostic methods.
These facts are referred to in the following publication:
Marks, J.N., Bank, S., Louw, I.H.: Leber, Magen, Darm.
6 257, 1976.

 It is known in the art that the pancreatic
25 inflammatory processes show specific features (Papp, M.:



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Congress of the Hungarian Gastroent. Society, Keszthely, Hungary, 1981).

The inflammation is of either ductal or parenchymic feature, the deterioration of parenchyma, progressive histolysis, fibrotizing processes and cicatrization occur soon. The constant presence of the free digestive enzymes assuring the autoperpetuation is induced by the inflammatory mechanism, the oedematic processes and the trophic disorders to a high degree.

Besides the inflamed oedema the compression of the subcapsular lymphatics also diminishes the microcirculation. G. Kaiser's and G. Hommel's observation is also of great importance. According to their report the decreasing demand for blood supply of the pancreas mass under deterioration induces adaptive intima-fibrosis in the small blood-vessels. This process further reduces the blood amount rushing to the gland and it can be the basis of further atrophy. /Kaiser, G., Hommel, G.: Morphometrisch-statistische Analyse der Pankreasarterien bei chronischer Pankreatitis. Virchows Arch (Pathol. Anat.) 365 103 (1975)7.

In spite of the above theoretical considerations there are no available pharmaceutical compositions of satisfactory efficiency for the treatment of pancreatic inflammations till now. In order to relieve the patients of the unpleasant effect of the chronic inflammations



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the medical treatment is delimited to administering enzyme as substitution with simultaneous diet. Such enzyme preparations are e. g. Dipankrine, Cotasym Forte or Panpur.

5 Disclosure of the invention

The aim of our research work was to elaborate a pharmaceutical composition which is suitable for the efficient treatment of patients suffering from pancreatic inflammations and for the cure of pan-
10 creatitis. According to our observation from the group of antiinflammatory agents the steroids would rather induce recidiva while the prostaglandine antagonists are powerless.

Surprisingly we have found that the pharmaceutical
15 compositions containing 3-dimethylamino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine and at least one of the Vitamine P factors and/or (+)-2-(3,4-dihydroxyphenyl)-3,5,7-cromanetriole as active ingredients are effective against pancreatic inflamma-
20 tions.

As a factor of Vitamine P a water soluble rutine derivative, preferably 3',4',7-tris(β -hydroxyethyl)-rutoside, can be used.

The weight ratio of 3-dimethylamino-7-methyl-
25 1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine and a factor of Vitamine P is between 2 : 1 to 1 : 1



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in the compositions of the invention.

The weight ratio of 3-dimethylamino-7-methyl-
1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine
and (+)-2-(3,4-dihydroxyphenyl)-3,5,7-cromanetriole
5 varies within the range of 2 : 1 to 1 : 1 in the composi-
tions of the invention.

The compositions according to the invention
contain suitably 60 to 300 mg. of 3-dimethylamino-7-
methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzo-
10 triazine and altogether 60 to 300 mg. of a factor of
Vitamine P and/or (+)-2-(3,4-dihydroxyphenyl)-3,5,7-
cromanetriole per dosage unit.

The pharmaceutical compositions according to the
invention contain optionally one or more known anti-
15 biotics and/or trace elements and/or vitamins in
association with carrier(s), excipient(s) and diluent(s)
conventionally used in the preparation of pharmaceutical
compositions.

As antibiotics Penicillin V or Tobramycin are
20 preferred.

The compositions of the invention contain option-
ally as vitamins e. g. magnesium ascorbate, ascorbinic
acid or other conventionally used vitamins.

As carriers or diluents those conventionally used,
25 e.g. talc, calcium carbonate, magnesium stearate, starch,
dextrine, water, physiological saline solution or poly-



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ethylene glycols can be used.

The compositions according to the invention contain as excipients conventional excipients, for example emulsifying agents, disintegrating agents or sweeteners.

5 Preferred pharmaceutical forms of the present invention are solid forms such as tablets, pills, capsules, dragees, granules, or liquid forms, such as solutions, suspensions, emulsion, syrups, injections, infusion solutions.

10 These compositions are administered orally, by intravenous or subcutane injections or by infusions.

Clinical results obtained by the administration of 3-dimethylamino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine (Azapropazonum)

15 As it is well known from pharmacological and pharmaco-kinetical experiments, Azapropazonum can be well absorbed from the duodenum and well spreads in the extra-cellular space. In inflammed tissues it enriches to 3 to 8-fold amound calculated for the oedemic liquids.

20 It does not get decomposed in the organismus, it is not metabolised in liver and it evacuates with the urine. The ulcerogenic effect of the compound can be neglected, liver and medulla damaging effect is not observed, and it does not possess teratogenic and
25 carcinogenic effect. It does not influence detectably the function of the organs, does not effect the increase in



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the body weight, the composition of the urine and the blood. It has a slight influence on the anabolic function of the cells, does not change either the cell production or the specific synthesis thereof, thus it does not
5 embarrass the mucopolysaccharide production and therefore does not interfere with the reparation process. However, it restrains the catabolic anabolic processes by its effect on the mediators of the inflammation. It blocks the course of the inflammatory process on the level of
10 the deliberation or the function of the lysosomal enzymes.

The results of the treatments with Azapropazonum as active ingredients are enclosed by Table 1.

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Table 1

Number of patients	P a t o g r a p h y				
	cholecysto- pancreatitis (with stones)	cholangiopancr. (st.p.cholecyst- ectomiam)	Chol.pancr. + diabetes	Panc. chr. alc.	Panc. chr. alc. + ps.cysta
from 20 patients					
men: 7	-	1	1	4	1
women: 13	7	4	1	1	-
clinical effect					
insignificant	5	4	1	2	1
medium	2	1	-	3	-
excellent	-	-	-	-	-

Daily 3 x 300 mg. of Azapropazonum were administered orally.

The treatment was carried out for 12 weeks.

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Clinical results obtained by the administration of Hydroxyrutosidea or Catechin alone and combinations according to the invention

5 In order to increase the antiinflammatory effect, compounds of vascular effect were simultaneously tested.

Two compounds were choosen: 3',4',7-tris(β -hydroxyethyl)rutoside (referred to as Hydroxyrutosidea) and (+)-2-(3,4-dihydroxyphenyl)-3,5,7-cromanetriole
10 (referred to as Catechin).

Having demonstrated that the acut toxicity of Azapropazonum is not increased in the presence of Hydroxyrutosidea or Catechin, further experiments were carried out.

15 In the first step of these experiments Hydroxy-rutosidea or Catechin were administered to the patients alone. The results are shown in Tables 2 and 3.



Table 2

Number of patients	P a t h o g r a p h y						
	cholecysto- pancreatit- is (with stones)	cholangiopancr. (st.p. chole- cystectomy)	chol.pancr. + diabetes	chol. pancr. + ps.cysta	Panc. chr. alc.	Panc. chr. + ps.cysta	
men: 5	1	-	-	-	3	1	
women: 15	5	5	2	1	2	-	
clinical effect							
insignificant	2	2	-	1	-	1	

Daily 3 x 300 mg. of Hydroxyrutosidea were administered orally.

The treatment was carried out for 12 weeks.

Table 3

Number of patients		P a t h o g r a p h y					
from 20 patients	cholecysto-pancreatit- is (with stones)	cholangiopancr. (st.p.cholecyst- ectomiam)	chol.pancr. + diabetes	chol. pancr. + ps.cysta	Panc. chr. alc.	Panc. chr. + ps.cysta	
men: 7	2	1	-	-	3	1	
women: 13	5	4	1	1	2	1	
clinical effect							
insignificant	6	1	2	-	1	1	1

Daily 3 x 300 mg. of Catechin were administered orally to the patients.
The treatment was carried out for 12 weeks.

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As it is shown by the tables, the administration of Hydroxyrutosidea or Catechin alone resulted in an insignificant effect.

Surprisingly, the simultaneous administration
5 of Azapropazonum and Hydroxyrutosidea or Azapropazonum
and Catechin resulted in an unexpected effect. The
anti-pancreatic inflammatory effect of Azapropazonum
was highly synergized by the compounds of vascular
effect employed in the experiments. The results are
10 included into Table 4.



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Table 4

Number of patients		Combination of compounds applied		P a t h o g r a p h y									
				Azapropa- zomum + Hydroxy- rutosidea	Chole- cysto pancr. (with stones)	Chol. pancr. (st.p. chole- cysteco- miam)	Chol. angio pancr. + dia- betes	Chol- angio pancr. + ps. cysta	Pancr. chr. alc.	Pancr. chron. alc. + diabe- tes	Pancr. chron. alc. + ps. cysta		
from 50 patients													
men: 16		2		2		1		2		3		4	
women: 34		10		10		6		5		1		-	
clinical effect													
insufficient		-		-		-		-		-		-	
medium		18	7	3		4		-		2		1	
excellent		32	5	9		4		7		1		3	
men: 16		1		2		1		1		3		4	
woman: 36		10		11		6		5		1		-	
Catechin													
clinical effect													
insufficient		-		-		-		-		-		-	
medium		15	6	3		3		1		1		1	
excellent		35	6	8		5		3		8		2	

Daily 3 x 300 mg. of Azapropazonum and 3 x 300 mg. of Hydroxyrutosidea or 3 x 300 mg. of Cathechin were administered to the patients. The treatment was carried out for 12 weeks in the case of both combinations.

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Abbreviations applied in Tables 1 to 4:

cholangiopancr. = cholangiopancreatitis

st.p.cholecystectomy = status post cholecystectomy

chol.pancr.+diabetes = cholangiopancreatitis + diabetes

5 panc.chr.alc. = pancreatitis chronica alcoholica

panc.chr.alc.+ps.cysta = pancreatitis chronica alcoho-
lica + pancreas cysta

Modes of Carrying out the Invention

The invention is illustrated by the following,

10 non-limiting examples.

Example 1

Composition of a tablet:

Azapropazonum 300 mg.

Hydroxyrutosidea 300 mg.

15 Carrier q.s. for a tablet

Example 2

Composition of a tablet:

Azapropazonum 300 mg.

Hydroxyrutosidea 150 mg.

20 Catechin 150 mg.

Carrier q.s. for a tablet

Example 3

Composition of a tablet:

Azapropazonum 300 mg.

25 Hydroxyrutosidea 150 mg.

Ascorbinic acid 100 mg.

Carrier q.s. for a tablet



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Example 4

Composition for a tablet:

Azapropazonum 150 mg.

Catechin 150 mg.

5 Carrier q.s. for a tablet

Example 5

Composition of a dragée:

Azapropazonum 150 mg.

Hydroxyrutosidea 150 mg.

10 Magnesium ascorbate 150 mg.

Penicillin V 30 mg.

Tobramycin 40 mg.

Carrier q.s. for a dragée

Example 6

15 Composition of a capsule:

Azapropazonum 150 mg.

Hydroxyrutosidea 150 mg.

Carrier q.s. for a capsule

Example 7

20 Composition of a capsule:

Azapropazonum 150 mg.

Catechin 150 mg.

Sodium ascorbate 30 mg.

Carrier q.s. for a capsule



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Example 8

Composition of a drinkable liquid (drops):

	Azapropazonum	300 mg.
	Hydroxyrutosidea	300 mg.
5	Vitamine C	3 mg.
	Diluent	q.s. 100 ml.

Example 9

Composition of an infusion solution:

	Azapropazonum	3 g.
10	Folescutol	3 g.
	Vitamine C	3 g.

Solved in physiological saline solution,
filled into infusion glasses of 0.5 or
1.0 l. volume after filtration to

15	steryle	q.s. 1000 ml.
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Example 10

Composition of an injectable preparation:

	Azapropazonum	3 g.
	Hydroxyrutosidea	3 g.
20	Penicillin V	30 mg.

Solved in physiological saline solution,
filled into 2.0 to 5.0 ml. ampoules after
filtration to steryle q.s. 1000 ml.



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What we claim is:

1. Pharmaceutical compositions comprising 3-dimethylamino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine and at least one of a factor of Vitamine P and/or (+)-2-(3,4-dihydroxyphenyl)-3,5,7-cromanetriole as active ingredient.

2. Pharmaceutical compositions as claimed in Claim 1 comprising one or more antibiotics and/or trace elements and/or vitamines and carrier(s), diluent(s), excipient(s) generally used in the preparation of pharmaceutical compositions.

3. Pharmaceutical compositions as claimed in Claim 1 or 2 comprising a water soluble rutine derivative, preferably 3',4',7-tris(β -hydroxyethyl)rutoside, as a factor of Vitamine P.

4. Pharmaceutical compositions as claimed in Claims 1 to 3 comprising 60 to 300 mg. of 3-dimethylamino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine per dosage unit.

5. Pharmaceutical compositions as claimed in Claims 1 to 4 comprising 60 to 300 mg. of a factor of Vitamine P and/or (+)-2-(3,4-dihydroxyphenyl)-3,5,7-cromanetriole per dosage unit.

6. Pharmaceutical compositions as claimed in Claims 1 to 4 comprising 3-dimethylamino-7-methyl-



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1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine
and a factor of Vitamine P in a weight ratio of 2 : 1
to 1 : 1.

7. Pharmaceutical compositions as claimed in any
5 of Claims 1 to 4 comprising 3-dimethylamino-7-methyl-
-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine
and (+)-2-(3,4-dihydroxyphenyl)-3,5-7-cromanetriole in
a weight ratio of 2 : 1 to 1 : 1.

8. A process for the preparation of pharmaceu-
10 tical compositions which comprises admixing 3-dimethyl-
amino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-
1,2,4-benzotriazine and at least one of a factor of
Vitamine P and/or (+)-2-(3,4-dihydroxyphenyl)-3,5,7-
chromanetriole and optionally one or more antibiotics
15 and/or trace elements and/or vitamins to excipient(s),
carrier(s), diluent(s) conventionally used in the
preparation of pharmaceutical compositions and transfor-
ming the obtained mixture into a pharmaceutical composi-
tion in a known manner.

20 9. A process as claimed in Claim 8 which comprises
applying a water soluble rutine derivative, preferably
3',4',7-tris(β -hydroxyethyl)rutoside, as a factor of
Vitamine P.

10. A process as claimed in Claims 8 or 9 which
25 comprises applying 60 to 300 mg. of 3-dimethylamino-7-
methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzo-



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triazine per dosage unit.

11. A process as claimed in any of Claims 8 to 10 which comprises applying 60 to 300 mg. of a factor of Vitamine P and/or (+)-2-(3,4-dihydroxyphenyl)-
5 3,5,7-cromanetriole per dosage unit.

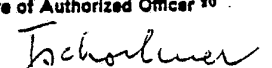
12. A process as claimed in any of Claims 8 to 11 which comprises applying 3-dimethylamino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine and a factor of Vitamine P in a weight ratio of 2 : 1
10 to 1 : 1.

13. A process as claimed in any of claims 8 to 12 which comprises applying 3-dimethylamino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine in a weight ratio of 2 : 1 to 1 : 1.
- 15 14. Method for treating pancreatic inflammations which comprises administering an effective amount of a pharmaceutical composition according to any of Claims 1 to 7.



INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 84/00016

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. ³ : A 61 K 31/53, 31/35, 31/535, 31/70, 31/37		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
Int.Cl. ³ :	A 61 K 31/53, 31/35, 31/37, 31/535, 31/70	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category ⁶	Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
Y	DE, B, 1 470 296 (SIEGFRIED AG), 20 June 1974 (20.06.74), see column 2, line 62 - column 4, line 26, example 6.	(1,4,8,10)
Y	EP, A1, 0 028 660 (SIEGFRIED AG), 20 May 1981 (20.05.81), see abstract; claim 1; page 5, lines 19-24.	(1,4,8,10)
Y	FR, M, 1 611 (M. WAHL), 17 December 1962 (17.12.62), see totality.	(1,2,5,8,11)
Y	GB, A, 1 595 351 (INVERNI DELLA BEFFA), 12 August 1981 (12.08.81), see claims 1-34, 37; page 6, lines 1-38; page 12.	(1,2,5,8,11)
Y	GB, A, 1 589 294 (INVERNI DELLA BEFFA), 13 May 1981 (13.05.81), see pages 1-3; page 7, line 47 - page 9, line 15.	(1,2,5,8,11)
Y	DE, B2, 2 206 570 (ZYMA S.A.), 16 October 1980 (16.10.80), see column 1, lines 1-60; column 2, line 30 - column 4, line 13.	(1,2,5,8,11)
¹⁵ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ⁹	Date of Mailing of this International Search Report ⁸	
21 May 1984 (21.05.84)	24 May 1984 (24.05.84)	
International Searching Authority ¹	Signature of Authorized Officer ¹⁰	
AUSTRIAN PATENT OFFICE		

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No ¹⁸
Y	DE, A1, 3 047 487 (CONTINENTAL PHARMA S.A.), 8 July 1982 (08.07.82), see claims 1,3,4; page 5, line 11 - page 6, line 22; page 8, lines 10-17; pages 10-12.	(1,2,5,8,11)
	M. Negwer, " Organisch-Chemische Arznei- mittel und ihre Synonyma" Volume I, published 1978, Akademie-Verlag (Berlin),	
Y	see page 565, reference 3117,	(1,4,8)
Y	see pages 447-448, references 2486, 2487,	(1,8)
Y	see page 496, references 2761, 2762.	(1,5,8)
	Volume II, published 1978, Akademie-Verlag (Berlin),	
Y	see page 1040, reference 5573 see page 1113, references 5897, 5898.	(1,8) (1-3,9)
A	FR, A, 2 437 838 (ROECAR HOLDINGS), 30 April 1980 (30.04.1980), see claims 1,5; page 3, line 31 - page 4, line 3; page 6, line 23.	(1,4,8,10)
A	EP, A1, 0 034 270 (AMERICAN CYANAMID COM- PANY), 26 August 1981 (26.08.81), see page 2, especially lines 1-4,11,12; pages 4-6; claim 1.	(1,2,4,8,10)
A	FR, M, 917 (CENTRE D'ETUDES POUR L'INDUSTRIE), 6 November 1961 (06.11.61), see claims 1,4; page 1, lines 1-19; page 2, formula; page 3, point IV.	
A	P.H. List, L. Hörhammer, "Hagers Handbuch der Pharmazeutischen Praxis", fourth edition, volumn 2, published 1969, Springer- Verlag (Berlin, Heidelberg, New York), see pages 714-717.	(1,2,8,10)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹⁰

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 14, because they relate to subject matter ¹³ not required to be searched by this Authority, namely:

method for treatment of the human or animal body by therapy - see Article 17(2)(a)(i) and Rule 39

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹³, specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ¹¹

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentedokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Annex to the International Search Report on International Patent Application No. PCT/HU 84/00016

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Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

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