

Low molecular weight inhibitors of complement proteases

- The present invention relates to peptide substances, their
 5 preparation and their use as complement inhibitors. In particular, these are substances having a guanidine or amidine radical as terminal group. In particular, the present invention relates to inhibitors of the complement proteases C1s and C1r.
- 10 The activation of the complement system leads, via a cascade of about 30 proteins, finally to, inter alia, the lysis of cells. At the same time, molecules which, like, for example, C5a, can lead to an inflammatory reaction are liberated. Under physiological conditions, the complement system provides defense against
 15 foreign bodies, e.g. viruses, fungi, bacteria and cancer cells. The activation by the various routes takes place initially via proteases. Activation enables these proteases to activate other molecules of the complement system, which in turn may be inactive proteases. Under physiological conditions, this system -
 20 similarly to blood coagulation - is under the control of regulator proteins which counteract excessive activation of the complement system. In these cases, intervention to inhibit the complement system is not advantageous.
- 25 In some cases, however, the complement system overreacts and this contributes to the pathophysiology of disorders. In these cases, therapeutic intervention in the complement system by inhibition or modulation of the overshooting reaction is desirable. Inhibition of the complement system is possible at various levels
 30 in the complement system and by inhibition of various effectors. The literature contains examples of the inhibition of the serine proteases at the C1 level with the aid of the C1-esterase inhibitor as well as inhibition at the level of the C3- and C5-convertases with the aid of soluble complement receptor CR1
 35 (sCR1), inhibition at the C5 level with the aid of antibodies and inhibition at the C5a level with the aid of antibodies or antagonists. The tools used for achieving the inhibition in the abovementioned examples are proteins. The present invention describes low molecular weight substances which are used for
 40 inhibiting the complement system.

In general activation of the complement system is to be expected in every inflammatory disorder which is associated with intrusion of neutrophilic blood cells. It is therefore expected that an
 45 improvement in pathophysiological status will be achieved in all these disorders by inhibiting parts of the complement system.

The activation of the complement is associated with the following disorders or pathophysiological conditions (Liszewski, M.K.; Atkinson, J.P.: Exp. Opin. Invest. Drugs 7(3) (1998): 324-332; Morgan, B.P.: Biochemical Society Transactions 24; (1996), 224-9; Morgan, B.P.: Critical Review in Clinical Laboratory Sciences 32 (3); (1995), 265-298; Hagmann, W.K.; Sindelar, R.D.: Annual reports in medicinal chemistry 27, (1992), 199 et seq.; Lucchesi, B.R.; Kilgore, K.S.: Immunopharmacology 38 (1997), 27-42; Makrides, S.C.: Pharmacological Reviews 50(1)(1998), 59-85)

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- Reperfusion injuries after ischemias; ischemic conditions, during, for example, operations with the aid of heart-lung machines; operations in which blood vessels are clamped off generally for avoiding major hemorrhages; myocardial infarction; thromboembolic cerebral infarction; pulmonary thrombosis, etc.;
- Hyperacute organ rejection; especially in xenotransplantations;
- Organ failure, e.g. multiple organ failure or ARDS (adult respiratory distress syndrome);
- Disorders due to trauma (cranial trauma) or multiple injury, e.g. thermal injury (burns);
- Anaphylactic shock;
- Sepsis; "vascular leak syndrome": in the case of sepsis and after treatment with biological agents, such as interleukin-2 or after transplantation;
- Alzheimer's disease and other inflammatory neurological disorders, such as myasthenia graevis, multiple sclerosis, cerebral lupus, Guillain-Barre syndrome; meningitis; encephalitis;
- Systemic lupus erythematosus (SLE);
- Rheumatoid arthritis and other inflammatory disorders of the rheumatoid disorder group, e.g. Behcet's Syndrome; Juvenile rheumatoid arthritis;
- Renal inflammations of various origin, e.g. Glomerulonephritis, Lupus nephriti;
- Pancreatitis;
- Asthma; chronic bronchitis;
- Complications during dialysis in the case of kidney failure;
- Vasculitis; thyroiditis;
- Ulcerative colitis and other inflammatory disorders of the gastrointestinal tract;
- Autoimmune diseases.
- It is possible that complement plays a role in spontaneous abortions, based on immunological rejection reactions (Giacomucci E., Bulletti C., Polli V., Prefetto RA., Flamigni C., Immunologically mediated abortion (IMA). Journal

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of Steroid Biochemistry & Molecular Biology, 49(2-3) (1994), 107-21). Here, it is possible that modulation of the immunological rejection reaction is achieved by inhibition of the complement system and hence the rate of abortions is correspondingly reduced.

- Complement activation plays a role in the case of side effects of drugs. Liposome-based therapies which are used, for example, in cancer treatment may be mentioned as an example here. Hypersensitive reactions have been observed in patients who have been treated with drug formulations based on liposomes (Transfusion 37 (1997) 150). Activation of the complement system has also been demonstrated for other excipients used in drug formulations, e.g. Cremophor EL (Szebeni, J. et al. Journal of the National Cancer Institute 90 (4); 1998). The complement activation may therefore be responsible for the anaphylactoid reactions observed in some cases. Inhibition of the complement system, for example by the CIs inhibitors mentioned here, should therefore alleviate the side effects of medicaments based on activation of the complement system and reduce resulting hypersensitivity reactions.

In the abovementioned disorders, activation of the complement system has been demonstrated.

The synthesis of complement proteins in special diseased tissues or organs indicate [sic] participation of the complement system in the pathophysiology of these disorders. Thus, in the case of myocardial infarction, vigorous further synthesis of many complement proteins in the myocardium was detected (Yasojima, K.; Schwab, C.; McGeer, E.G.; McGeer, P.L.; Circulation Research 83 (1998), 860-869). This was also detected in inflammatory disorders of the brain, e.g. multiple sclerosis and bacterial meningitis, and in colitis.

Evidence that complement activation has taken place can be provided by detecting the cell lysis complex in the tissue and by detecting soluble SC5b-9 or other activation products of complement, e.g. factor Bb, C3a; C4a, C5a; C3b, C3d; etc., in the plasma. By corresponding tests, it was possible to demonstrate, inter alia, participation of the complement system in the atherosclerosis as well as to show a relationship with myocardial infarction, unstable angina pectoris and organ transplantations, to mention but a few examples.

Raised blood levels of complement proteins, such as C3 or C4, are correlated with various cardiovascular disorders, e.g. heart failure, as well as diabetes. A similar relationship has been demonstrated for an increase in TNF in the case of heart failure.

- 5 Initial studies on the treatment of heart failure with TNF inhibitors (soluble TNF receptor, antibodies) were rated positively. TNF is secreted, for example, after stimulation by complement factor C5a. It has been possible to show that inhibition of the C5a action prevents release of TNF (XVII
10 International Complement Workshop, P. Ward, Abstract 324 in Molecular Immunology 35 (411 6-7), 1998). Accordingly, a treatment of disorders, in which raised levels of complement proteins are present, with the inhibitors described in this publication is possible, as the treatment of disorders in which
15 raised levels of TNF are present.

- Furthermore, the participation of complement has been demonstrated in the case of (Atherosclerosis 132 (1997); 131-138. Particular complications due to rapid atherosclerotic processes
20 occur, for example, in organs after transplantations. These processes are the most frequent reason for the chronic failure of the transplanted organs in clinical medicine. In future, apart from transplantations of human organs (allotransplantations) uses of transplants from other species (xenotransplants) has also been
25 considered.

- Accordingly, the treatment of the abovementioned disorders or pathophysiological conditions with complement inhibitors is desirable, in particular the treatment with low molecular weight
30 inhibitors.

- FUT and FUT derivatives are amidinophenolic esters and amidinonaphthol esters and are described as complement inhibitors (e.g. Immunology 49(4) (1983), 685-91).
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- Serine proteases are present in the complement system in the three different activation routes: the traditional, alternative and MBL route (Arlaud, G.J. et al. Advances in Immunology 69; (1998) 249 et seq.). In their respective routes, they play a
40 decisive role at the beginning of the cascade.

- Inhibitors of the corresponding serine proteases can intervene here both in a completely inhibitory manner and in a modulating manner (partial inhibition) if the complement has been
45 pathophysiologically activated.

- Some proteases of the various activation routes are particularly suitable for inhibiting the complement system. From the class of the thrombin-like serine proteases these are the complement proteases C1r and C1s in the traditional route, factor D and factor B in the alternative route and MASP I and MASP II in the MBL route. Inhibition of these proteases then leads to restoration of physiological control of the complement system in the abovementioned disorders or pathophysiological conditions.
- 10 The traditional route of the complement system is usually activated by means of antibodies which have bound to an antigen. In physiological conditions this route of the complement system helps in the defense against foreign bodies which are recognized by antibodies. However, an overreaction leads to injuries in the
- 15 tissue and the body. These injuries can be prevented by inhibiting of the traditional route. According to present knowledge, activation of the complement system via antibodies is experienced during hyperacute organ rejection and especially in the case of xenotransplantations; in the case of reperfusion
- 20 injuries after ischemias (possibly via IgM antibodies and a neoepitope; Literature: Journal of Exp. Med. 183, (1996), 2343-8; Carroll, XVII International Complement Workshop, Rhodes 1998), for example in the case of myocardial infarction, other thrombotic disorders or long-term vascular occlusions, as are
- 25 usual, for example, during operations; in the case of anaphylactic shock; in the case of sepsis; in the case of SLE; in the case of disorders in the area of rheumatoid arthritis, renal inflammations of various origins; vasculitis, all autoimmune diseases and allergies. In general, injuries in various organs
- 30 due to activation of the complement system are to be expected in the case of every disorder in which circulating immune complexes are present. A part of the invention is to prevent these injuries by the C1-inhibitors described.
- 35 Activation of the complement system by the traditional route takes place under pathophysiological conditions partly with circumvention of antibodies. Examples of this are Alzheimer's disease, and the unspecified activation of this route by other proteases, as occur, for example, in the lysis therapy following
- 40 myocardial infarction. In these cases, too, limitation of the injury to be achieved with the C1 inhibitors described.

The activation of the classical route has been demonstrated, for example, by the detection of the activated proteins, for example

45 C1q in the affected tissue (e.g. Circulation Research 83; (1998) 860). However, the pathophysiological participation of the complement system is more substantial if inhibitors which inhibit

only the traditional route in the complement system are used. A physiological inhibitor for this purpose is the C1-esterase inhibitor (protein is described in The Complement System, Rother, Till, Hänsch eds.; Springer; 1998; pages 353 et seq.). With the aid of this inhibitor, participation of the traditional route and the possibility of therapeutic intervention have been demonstrated in experiments. Some references are given in more detail below:

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Rescue therapy with C1-esterase inhibitor concentrate after emergency coronary surgery for failed PTCA.
Intensive Care Medicine. 24(6): (1998), 635-8.
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Effects of C1-esterase inhibitor in three models of acute pancreatitis.
International Journal of Pancreatology. 17(2): (1995) 189-96.
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Prevention of complement-mediated activation of xenogeneic endothelial cells in an in vitro model of xenograft
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C1-esterase inhibitor prevents early pulmonary dysfunction
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cardiac function and reduces myocardial necrosis in an
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complement-mediated cytotoxicity by the human
complement regulators CD59, C1 inhibitor, and soluble
complement receptor type 1. Analysis in a pig-to-human in
vitro model relevant to hyperacute xenograft rejection.
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Effects of C1-esterase inhibitor in three models of acute
pancreatitis.
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189-96.
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Cardioprotective effects of a C1 esterase inhibitor in
myocardial ischemia and reperfusion circulation. 91(2):
45 (1995), 393-402.

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15 Endotoxin-induced pulmonary dysfunction is prevented by C1-esterase inhibitor.
Journal of Clinical Investigation. 91(6): (June 1993), 2754-60.
- 20 Inhibitors which inhibit C1s and/or C1r but not factor D are desirable. Preferably, MASP-I and lysis enzymes, such as t-PA and plasmin, should not be inhibited.

A hereditary disease, hereditary angioneurotic edema, which is
25 due to a deficiency of C1-esterase inhibitor is usually treated by administering C1-esterase inhibitor. Treatment with the C1 inhibitors described here, under certain circumstances as additional medication, is likewise an application of this invention.

30 Substances which effectively inhibit C1s and C1r are particularly preferred.

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Pharmacological examples

Example A

5 Color substrate test for Clr inhibition

Reagents: Clr from human plasma, activated, two-chain form
(purity: about. 95% according to SDS gel).
No foreign protease activity detectable.
Substrate: Cbz-Gly-Arg-S-Bzl, product
10 No.: WBASO12, (from PolyPeptide, D-38304
Wolfenbüttel, Germany) Color reagent:
DTNB (5,5'-dinitro [sic] bis-2-nitrobenzoic acid)
(No. 43760, Fluka, CH-9470 Buchs, Switzerland)
Buffer: 150 mM Tris/HCl pH = 7.50

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Color substrate test for Clr inhibition

Test procedure: The color substrate test for determining the Cls
activity is carried out in 96-well microtiter
plates.
20 10 µl of the inhibitor solution in 20% strength
DMSO (DMSO diluted with 15 millimolar Tris/HCl
pH = 7.50) are added to 140 µl of test buffer,
which contains Cls in a final concentration of
0.013 U/ml and DTNB with with [sic] a final
25 concentration of 0.27 mM/l. Incubation is carried
out for 10 minutes at 20 to 25°C.
The test is started by adding 50 µl of
1.5 millimolar substrate solution in 30% strength
DMSO (final concentration 0.375 mmol/l).
After an incubation time of 30 minutes at from
30 20 to 25°C, the absorbance of each well at 405 nm
is measured in a two-beam microtiter plate
photometer against a blank value (without
enzyme).

35 Measurement criteria: IC₅₀: required inhibitor concentration to reduce
the amidolytic Clr activity to 50%.

Statistical evaluation: The dependence of absorbance on the inhibitor
concentration serves as a basis for the
calculation.

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Example B

Material and methods: Color substrate test for CIs inhibition

- 5 Reagents: CIs from human plasma, activated, two-chain form (purity: about 95% according to SDS gel).
No foreign protease activity detectable.
Substrate: Cbz-Gly-Arg-S-Bzl, product
No.: WBAS012, (from PolyPeptide, D-38304
10 Wolfenbüttel, Germany) Color reagent: DTNB
(5,5'-dinitrobis-2-nitrobenzoic acid)
(No. 43760, Fluka, CH-9470 Buchs, Switzerland)
Buffer: 150 mM Tris/HCl pH = 7.50
- 15 Test procedure: The color substrate test for determining the CIs-activity is carried out in 96-well microtiter plates.
10 µl of the inhibitor solution in 20% strength DMSO (DMSO diluted with 15 millimolar Tris/HCl pH = 7.50) are added to 140 µl of test buffer, which contains CIs in a final concentration of
20 0.013 U/ml and DTNB with a final concentration of 0.27 mM/l. Incubation is carried out for 10 minutes at from 20 to 25°C. The test is started by adding 50 µl of 1.5 millimolar substrate solution in 30% strength DMSO (final concentration 0.375 mmol/l). After an incubation
25 time of 30 minutes at from 20 to 25°C, the absorbance of each well at 405 nm is measured in a two-beam microtiter plate photometer against a blank value (without enzyme).
- 30 Measurement criterion: IC₅₀: required inhibitor concentration to reduce the amidolytic CIs activity to 50%.
- Statistical evaluation: The dependence of the absorbance on the inhibitor concentration serves as a basis for calculation.

35 Example C

Detection of inhibition of complement in the traditional route by the hemolytic test

- 40 The measurement of potential complement inhibitors is carried out, on the basis of diagnostic tests, using a test for measuring the traditional route (literature: Complement, A practical Approach; Oxford University Press; 1997; page 20 et seq.). For this purpose, human serum is used as a source of complement. However, a test of the same type is also carried out using
45 various sera of other species in analogous manner. Erythrocytes from sheep are used as an indicator system. The antibody-dependent lysis of these cells and the hemoglobin which

consequently emerges are a measurement of the complement activity.

Reagents, biochemicals:

5	Veronal	from Merck	#2760500
	Na Veronal	from Merck	#500538
	NaCl	from Merck	#1.06404
	MgCl ₂ x6H ₂ O	from Baker	#0162
	CaCl ₂ x6H ₂ O	from Riedel de Haen	#31307
10	Gelatin	from Merck	#1.04078.0500
	EDTA	from Roth	#8043.2
	Alsever's solution	from Gibco	#15190-044
	Penicillin	from Grünenthal	#P1507 10Mega
	Amboceptor	from Behring	#ORLC

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Stock solutions:

	VBS stock solution:	2.875 g/l of Veronal; 1.875 g/l Na Veronal; 42.5 g/l NaCl
	Ca/Mg stock solution:	0.15 M Ca++, 1 M Mg++
20	EDTA stock solution:	0.1 M pH 7.5
	Buffer:	
	GVBS buffer:	dilute VBS stock solution 1:5 with Fin Aqua; dissolve 1 g/L of gelatin with a little buffer at elevated temperatures
25		
	GVBS++ buffer:	dilute Ca/Mg stock solution 1:1000 in GVBS buffer
	GVBS/EDTA buffer:	dilute EDTA stock solution 1:10 in GVBS buffer
30		

Biogenic components:

- Sheeps' erythrocytes (SRBC): sheep's blood was mixed 1+1 (v/v) with an Alsevers solution and filtered through glass wool and 1/10 of the volume of EDTA stock solution +1 pinch of penicillin were added. Human serum: after removal of the coagulated fractions by centrifuging at 4°C, the supernatant was stored in aliquots at -70°C. All measurements were carried out with one batch. No substantial deviations compared with serum of other test subjects were found.

Procedure:

- 45 1. Sensitization of the erythrocytes

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- SRBC were washed three times with GVBS buffer. The cell count was then set at $5.00E+08$ cells/ml in GVBS/EDTA buffer. Amboceptor was added in a dilution of 1:600, and the SRBC was sensitized with antibodies by incubation for 30 minutes at 37°C with agitation. The cells were then washed three times with GVBS buffer at 4°C , then taken up in GVBS++ buffer and adjusted to a cell count of 5×10^8 .

2. Lysis experiment:

- Inhibitors were preincubated in various concentrations with human serum or serum of other species in suitable dilution (e.g. 1:80 for human serum; a suitable dilution is one at which about 80% maximum lysis which can be achieved by serum is achieved) in GVBS++ for 10 minutes at 37°C in a volume of 100 μl . 50 μl of sensitized SRBC in GVBS++ were then added. After incubation for 1 hour at 37°C with agitation, the SRBC were separated off by centrifuging (5 minutes; 2500 rpm 4°C). 130 μl of the cell-free supernatant were transferred to a 96-well plate. The evaluation was carried out by measurement at 540 nm against GVBS++ buffer.

The absorbencies at 540 nm are used for the evaluation.

- (1) : Background; cells without serum
(3) : 100% Lysis, cells with serum
(x) : measured values with test substance

Calculation:

$$\% \text{ Lysis} = \frac{(X) - (1) \times 100\%}{(3) - (1)}$$

Example D

Testing of inhibitors for inhibition of the protease factor D

- In the alternative route of the complement system, factor D performs a central function. Owing to the low plasma concentration of factor D, the enzymatic step involving the cleavage of factor B by factor D constitutes the rate-determining step in the alternative route of complement activation. Owing to the limiting role which this enzyme plays in the alternative route, factor D is a target for the inhibition of the complement system.

- The commercial substrate Z-Lys-SBzl*HCl is converted by the enzyme factor D (literature: Kam, C.M. et al., J. Biol. Chem. 262, 1987, 3444-3451). The detection of the cleaved substrate is

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effected by reaction with Ellmann's reagent. The product formed is detected spectrophotometrically. The reaction can be monitored online. This permits measurements of enzyme kinetics.

5 Material:

Chemicals:

	Factor D	Calbiochem	341273
	Ellmann's reagent	SIGMA	D 8130
10	Z-Lys-SBzl*HCl (=substrate)	Bachem	M 1300 50 mg/ml (MeOH)
	NaCl	Riedel-De-Häen	13423
	Triton-X-100	Aldrich	23,472-9
15	Tris(hydroxymethyl)-aminomethane	MERCK	
	Dimethylformamide (DMF)		

Buffer:

	50 mM	Tris
20	150 mM	NaCl
	0.01%	Triton - X - 100
	pH 7.6	

Stock solutions:

25	Substrate	20 mM (8.46 mg/ml = 16.92 μ l (50 mg/ml) + 83.1 μ l H ₂ O)
	Ellmann's reagent	10 mM (3.963 mg/ml) in DMF
	Factor D	0.1 mg/ml
	Samples (inhibitors)	10 ⁻² M in DMSO

30

Procedure:

Batches:

	Blank value:	140 μ l of buffer + 4.5 μ l of substrate (0.6 mM) + 4.5 μ l of Ellmann's reagent (0.3 mM)
35	Positive control:	140 μ l of buffer + 4.5 μ l of substrate (0.6 mM) + 4.5 μ l of Ellmann's reagent (0.3 mM) + 5 μ l of Factor D
	Sample measurement:	140 μ l of buffer + 4.5 μ l of substrate (0.6 mM) + 4.5 μ l of Ellmann's reagent (0.3 mM) + 1.5 μ l of samples (10 ⁻⁴ M) + 5 μ l of Factor D
40		

The batches are pipetted together into microtiter plates.
45 After mixing of buffer, substrate and Ellmann's reagent
(possibly inhibitors), the enzyme reaction is started by

adding in each case 5 µl of factor D. Incubation takes place at room temperature for 60 minutes.

Measurement:

- 5 Measurement at 405 nm for 1 hour at 3 minute intervals

Evaluation:

- 10 The result is plotted graphically. The change in the absorbence per minute (delta OD per minute; slope) is relevant for the comparison of inhibitors so it is possible to determine K_i values of inhibitors therefrom.
In this test the serine protease inhibitor FUT-175; Futhan; from Torii; Japan, was also run as an effective inhibitor.

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Example E

Detection of the inhibition of complement in the alternative route by the hemolytic test (Literature: Complement, A practical
20 Approach; Oxford University Press; 1997, page 20 et seq.)

The test is carried out similarly to clinical tests. The test can be modified by additional activation by means of, for example, Zymosan or Cobra Venom Factor.

25 Material:

EGTA (ethylenebis(oxyethylenenitrilo)-tetracetic acid [sic]

Boehringer Mannheim 1093053

MgCl₂ * 6 H₂O

MERCK 5833.0250

NaCl

MERCK 1.06404.1000

30 D-Glucose

Cerestar

Veronal

MERCK 2760500

Na Veronal

MERCK 500538

VBS stock solution (5x)

Gelatin Veronal buffer

PD Dr. Kirschfink; University
of Heidelberg, Inst. for

35

Immunology;

Gelatin

MERCK 1.04078.0500

Tris(hydroxymethyl)amino-
methane

MERCK 1.08382.0100

40 CaCl₂

MERCK Art. 2382

Human serum was either bought from various suppliers (e.g. Sigma) or obtained from test subjects in the BASF Süd casualty department.

Guinea pigs' blood was obtained and diluted 2:8 in citrate

- 45 solution. Several batches without obvious differences were used.

Stock solutions:

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VBS stock solution: 2.875 g/l of Veronal
 1.875 g/l of Na Veronal
 42.5 g/l of NaCl

5 GVBS: dilute VBS stock solution 1:5 with water
 (Finn Aqua) + 0.1% of gelatin
 heat till gelatin has dissolved and cool

10 100 mM EGTA: slowly bring 38.04 mg of EGTA in 500 ml of
 Finn Aqua and [sic] to pH 7.5 with 10 M NaOH
 till dissolved and then make up to 1 l

Mg - EGTA : 5 ml or 100 mM EGTA
 3.5 ml or 100 mM MgCl₂
 15 10.4 ml of GVBS
 31.1 ml of 5% glucose solution

Saline: 0.9% of NaCl in water (Finn Aqua)

20 GTB: 0.15 mM CaCl₂
 141 mM NaCl
 0.5 mM MgCl₂* 6 H₂O
 10 mM Tris
 0.1% of gelatin
 25 pH 7.2 - 7.3

Procedure:

1. Cell preparation:

30 The erythrocytes from the guinea pig blood washed several
 times by centrifuging (5 minutes; 1000 rpm) with GTB until
 the supernatant was clear. The cell count was adjusted to
 2×10^9 cells/ml.

2. Procedure: the individual batches were incubated for 30
 minutes at 37°C with agitation. The incubation was then
 35 stopped for 480 µl of ice-cold physiological saline solution
 and the cells were separated off by centrifuging for 5
 minutes at 5000 rpm. 200 µl of supernatant were measured at
 405 nm by transfer to a microtiter plate and evaluation in a
 microtiter plate photometer.

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Pipetting scheme (stated amounts in μ l)

	Back-ground (- serum)	100% Lysis	100% Lysis + factor D	Background + Factor D (- serum)	Max. lysis (water)
5					
	20	20	20	20	20
		20	20		
10	480	480	480	480	
			0.5 μ g	0.5 μ g	
	480	480	480	480	
					980

15 Evaluation:

The OD - values are used for the evaluation.

- (1): Background; cells without serum
 (3): 100% lysis + Factor D; cells with serum
 (x): measured values with test substances

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Calculation:
$$\% \text{ Lysis} = \frac{(X) - (1) * 100}{(3) - (1)}$$

25 The present invention relates to peptide and peptidomimetic substances, their preparation and their use as complement inhibitors. In particular, these are substances having an amidine or guanidine radical as a terminal group.

30 The present invention also relates to the use of known amidine-containing substances for the preparation of complement inhibitors, specifically of inhibitors of C1s and C1r.

35 The present invention relates to the use of known and novel substances having an amidine or guanidine terminal group for the preparation of complement inhibitors, specially of inhibitors of C1s and C1r.

40 The present invention relates in particular to the use of chemically stable substances of the formula I, their tautomers, pharmacologically tolerated salts and prodrugs for the preparation of drugs for the treatment and prophylaxis of disorders which are alleviated or cured by partial or complete inhibition, in particular selective inhibition, of C1s and/or C1r. Formula I has the structure

45

where

A is

- 5 H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, RA¹OCO (where RA¹ is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₁₋₃-alkyl-C₃₋₈-cycloalkyl or C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H-, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl; RA²-RA³ together may also form a ring of 3 to 7
10 carbon atoms), RA⁴OCO₂ (where RA⁴ is C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA⁴OCNRA², NO₂, RA⁴CONRA², RA¹O, RA²RA³N, RA¹S, HO-SO₂, RA²RA³N-SO₂, Cl, phenoxy, Br, F, tetrazolyl, H₂O₃P, RA¹-N(OH)-CO, RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different radicals from
15 the group consisting of F, Cl, Br, OCH₃, CF₃, CH₃ and NO₂;

B is



20

1^B is 0, 1, 2 or 3;

m^B is 0, 1, 2, 3, 4 or 5;

25

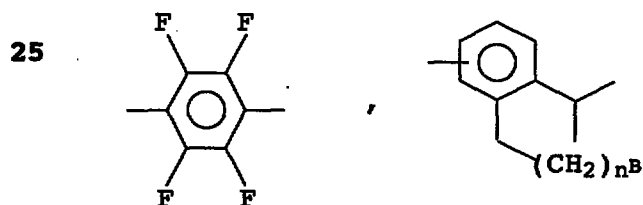
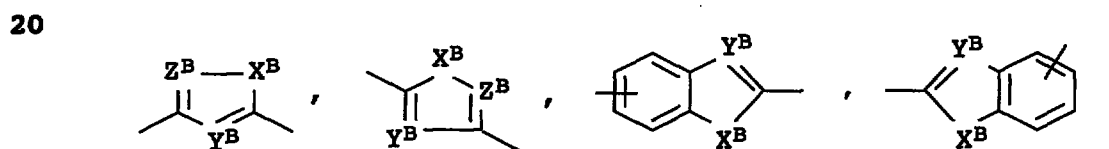
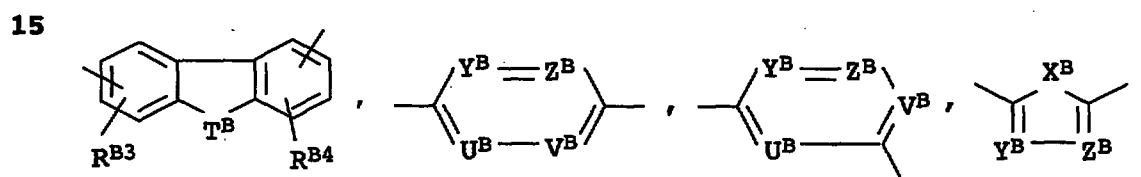
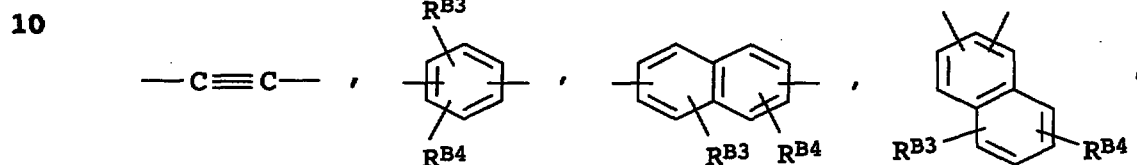
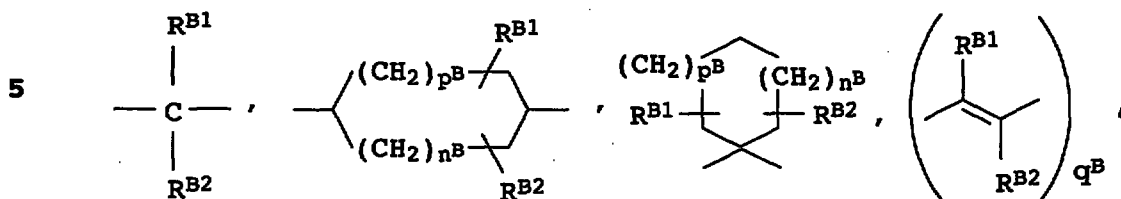
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35

40

45

L^B is



30

where, in each of the abovementioned ring systems, a phenyl ring may be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH_3 , CF_3 , Br, Cl and F or may be substituted by R^8OOC- (where R^8 is H or C_{1-3} -alkyl);

where

n^B is 0, 1 or 2,

p^B is 0, 1 or 2,

q^B is 1, 2 or 3,

40

RB^1 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

RB^2 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

45

19

R^{B3} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, $R^{B5}OCO$ (where R^{B5} is H, C_{1-6} -alkyl or C_{1-3} -alkylaryl), $R^{B6}-O$ (where R^{B6} is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

5

R^{B4} is H, C_{1-6} -alkyl, $R^{B6}-O$, Cl, Br, F or CF_3 ;

R^{B1} and R^{B2} may also be bonded together;

10

T^B is CH_2 , O, S, NH or N- C_{1-6} -alkyl;

X^B is O, S, NH or N- C_{1-6} -alkyl;

15

Y^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

Z^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

U^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl;

20

V^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl. [sic]

B is furthermore

$-(CH_2)_{1^B}-L^B-M^B-L^B-(CH_2)_{m^B}$, where

25

1^B and m^B have the abovementioned meanings and the two groups L^B , independently of one another, are identical or different radicals from among the stated radicals;

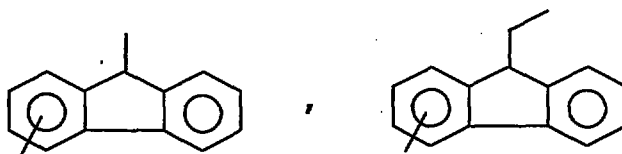
30

M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CO, SO_2 , $CH=CH$ or $C\equiv C$;

B may furthermore be

-1-adamantyl-, -2-adamantyl-, -1-adamantyl- CH_2- ,
-2-adamantyl- CH_2- ,

35



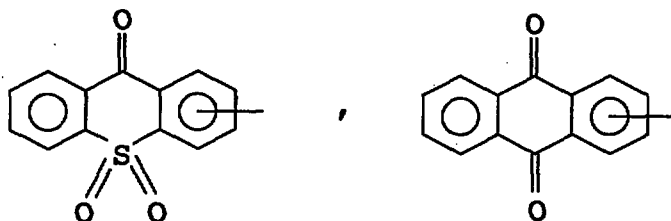
40

A-B may furthermore be

45

20

5

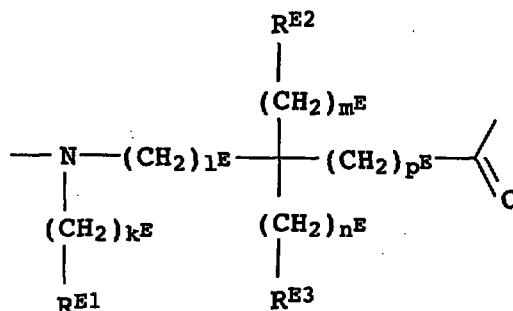


D is a single bond or
CO, OCO, NR^{D1}-CO (where R^{D1} is H, C₁₋₄-alkyl or
10 C₀₋₃-alkylaryl), SO₂ or NR^{D1}SO₂;

E is a single bond or

15

20



where

25

k^E is 0, 1 or 2;
l^E is 0, 1 or 2;
m^E is 0, 1, 2 or 3;
n^E is 0, 1 or 2;
30 p^E is 0, 1 or 2;

RE¹ is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, aryl (in particular
phenyl or naphthyl), heteroaryl (in particular pyridyl,
thienyl, imidazolyl or indolyl) or C₃₋₈-cycloalkyl having
35 a fused-on phenyl ring, it being possible for the
abovementioned radicals to carry up to three identical or
different substituents from the group consisting of
C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, F, Cl and Br;

40 RE¹ is furthermore RE⁴OCO-CH₂- (where RE⁴ is H, C₁₋₁₂-alkyl or
C₁₋₃-alkylaryl);

45 RE² is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, aryl (in particular
phenyl or naphthyl), heteroaryl (in particular pyridyl,
furyl, thienyl, imidazolyl or indolyl),
tetrahydropyranyl, tetrahydrothiopyranyl, C₃₋₈-cycloalkyl
having a fused-on phenyl ring, it being possible for the

abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, F, Cl and Br, or is CH(CH₃)OH, CH(CF₃)₂;

5

RE³ is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, aryl (in particular phenyl or naphthyl), heteroaryl (in particular pyridyl, thienyl, imidazolyl or indolyl) or C₃₋₈-cycloalkyl having a fused-on phenyl ring, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, F, Cl and Br;

10

RE² and RE¹ may together furthermore form a bridge having (CH₂)₀₋₄, CH=CH, CH₂-CH=CH or CH=CH-CH₂ groups;

15

the groups stated under RE¹ and RE³ may be linked to one another via a bond; the groups stated under RE² and RE³ may also be linked to one another via a bond;

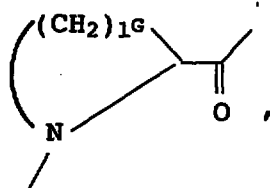
20

RE² is furthermore COR^{E5} (where RE⁵ is OH, O-C₁₋₆-alkyl or OC₁₋₃-alkylaryl), CONR^{E6}RE⁷ (where RE⁶ and RE⁷ are H, C₁₋₆-alkyl or C₀₋₃-alkylaryl);

25 E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;

G is

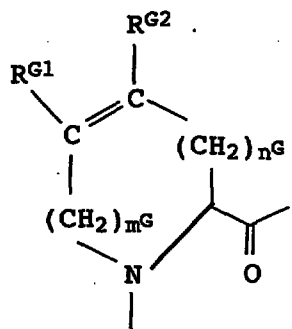
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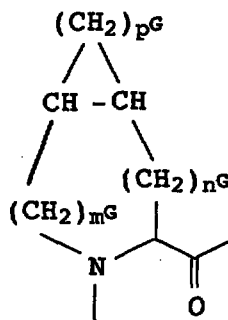
where 1^G is 2, 3, 4 and 5, where a CH₂ group of the ring may be replaced by O, S, NH, NC₁₋₃-alkyl, CHOH, CHOC₁₋₃-alkyl, C(C₁₋₃-alkyl)₂, CH(C₁₋₃-alkyl), CHF, CHCl or CF₂;

35

40



or



45

where

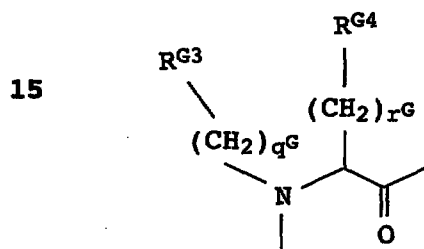
m^G is 0, 1 or 2;
 n^G is 0, 1 or 2;
 p^G is 1, 2, 3 or 4;

5 RG^1 is H, C_1 - C_6 -alkyl or aryl;

RG^2 is H, C_1 - C_6 -alkyl or aryl;

10 RG^1 and RG^2 together may furthermore form a $-CH=CH-CH=CH$ chain;

G is furthermore



where

q^G is 0, 1 or 2;
 r^G is 0, 1 or 2;

25 RG^3 is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or aryl;

RG^4 is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or aryl (in particular phenyl or naphthyl);

30 K is

$NH-(CH_2)_{n^K}-Q^K$ where

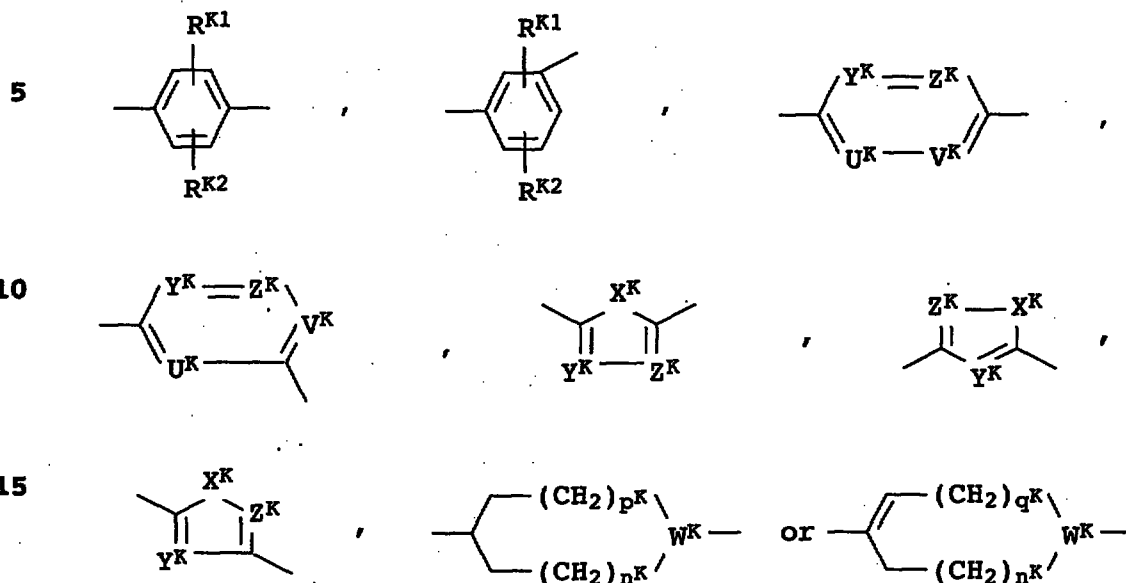
35 n^K is 0, 1, 2 or 3;

Q^K is C_{2-6} -alkyl, it being possible for the chain to be straight-chain or branched and up to two CH_2 groups can be replaced by O or S;

40

45

Q^K is



where

R^{K1} is H, C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl, F, Cl or Br;

R^{K2} is H, C_{1-3} -alkyl, O- C_{1-3} -alkyl, F, Cl or Br;

X^K is O, S, NH or N- C_{1-6} -alkyl;

Y^K is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

Z^K is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

U^K is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl;

V^K is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl;

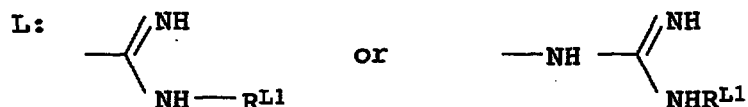
W^K is $\begin{array}{c} \diagup \\ CH \\ \diagdown \end{array}$ or $\begin{array}{c} \diagup \\ N \\ \diagdown \end{array}$, where, in the latter case, L may not be a guanidine group;

n^K is 0, 1 or 2;

p^K is 0, 1 or 2;

q^K is 1 or 2;

24



5

where

RL^1 is H, OH, O- C_{1-6} -alkyl, O-(CH_2) $_{0-3}$ -phenyl, CO- C_{1-6} -alkyl, CO_2 - C_{1-6} -alkyl or CO_2 - C_{1-3} -alkylaryl.

10

The term C_{1-x} -alkyl includes all straight-chain and branched alkyl chain of up to x -carbon atoms.

The term C_{3-8} -cycloalkyl refers to carbocyclic saturated radicals of 3 to 8 carbon atoms.

The term aryl refers to carbocyclic aromatics of 6 to 14 carbon atoms, in particular phenyl, 1-naphthyl or 2-naphthyl.

20 The term heteroaryl refers to aromatics having a five- or six-membered ring and at least one heteroatom N, O or S, in particular pyridyl, thienyl, furyl, thiazolyl or imidazolyl; furthermore, two aromatic rings may be fused, e.g. indole, N- C_{1-3} -alkylindole, benzothiophene, benzothiazole, benzimidazole, 25 quinoline or isoquinoline.

The term C_{x-y} -alkylaryl refers to carbocyclic aromatics which are linked to the skeleton via an alkyl group of x [sic], $x+1$, ... $y-1$ or y carbon atoms.

30

The present invention furthermore relates to compounds which contain the structural element



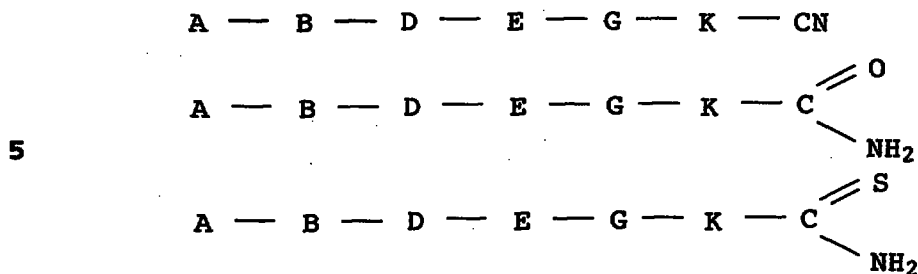
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where G, K and L have the abovementioned meanings. Preferably, G-K-L has the meaning of the novel compounds stated below. The structural fragment is valuable as part of complement inhibitors and in particular C_{18} - and/or C_{17} -inhibitors.

40

The present invention furthermore relates to the intermediates of the following formulae

45



10 where A, B, D, E, G and K have the meanings of the following novel compounds of the formula I.

The novel intermediates are used for the preparation of the compounds I and are valuable building blocks for the synthesis of
15 serine protease inhibitors.

The compounds of the formula I may be present as such or in the form of their salts with physiologically tolerated acids. Examples of such acids are: hydrochloric acid, citric acid,
20 tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid, succinic acid, hydroxysuccinic acid, sulfuric acid, glutaric acid, aspartic acid, pyruvic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid and acetylglycine.

25 The novel compounds of the formula I are competitive inhibitors of the complement system, in particular of C_{1s}, and furthermore C_{1r}.

30 The novel compounds can be administered orally or parentally (subcutaneously, intravenously, intramuscularly, intraperitoneally or rectally) in the usual manner. The application can also be effected by means of vapors or sprays through the nasopharyngeal space.

35 The dosage depends on the age, condition and weight of the patient and on the method of application. As a rule, the daily dose of active compound per person is from about 10 to 2000 mg in the case of oral administration and from about 1 to 200 mg in the
40 case of parental administration. This dose can be given in from 2 to 4 single doses once a day as a sustained-release form.

The compounds can be used in the conventional solid or liquid pharmaceutical application forms, for example as tablets,
45 film-coated tablets, capsules, powders, granules, coated tablets, suppositories, solutions, ointments, creams or sprays. These are prepared in a conventional manner. The active compounds can be

processed with the conventional pharmaceutical excipients, such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, diffusion coatings, antioxidants and/or
 5 propellants (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). The application forms thus obtained usually contain the active compound in an amount of 0.1 to 99% by weight.

10 Prodrugs are understood as meaning compounds which are converted in vivo (e.g. first pass metabolism [sic]) into the pharmacologically active compounds of the formula I.

The present invention also relates to the following novel
 15 compounds A-B-D-E-G-K-L and drugs which contain these compounds. Furthermore, these compounds are suitable as particularly good complement inhibitors.

Here:

20 A is
 H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, RA¹OCO (where RA¹ is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₃-alkyl or C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H-, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H, C₁₋₆-alkyl or
 25 C₀₋₃-alkylaryl); RA⁴OCNRA² (where RA⁴ is C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA⁴CONRA², RA¹O, RA²RA³N, HO-SO₂-, phenoxy, RA²RA³N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P-, NO₂, RA¹-N(OH)-CO- or RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different radicals from the group
 30 consisting of F, Cl, Br, CF₃, CH₃, OCH₃ and NO₂;

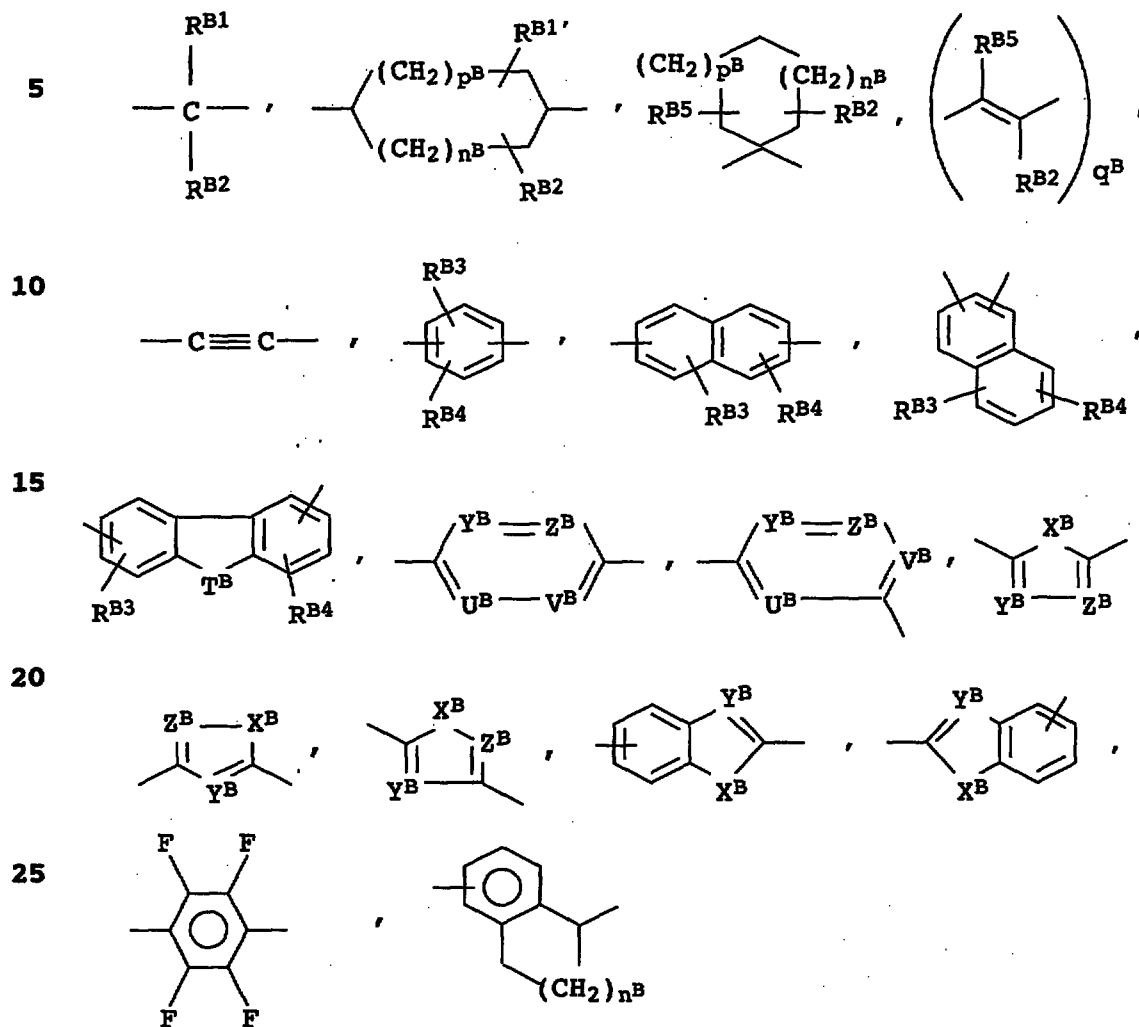
B is

-(CH₂)_{l^B}-L^B-(CH₂)_{m^B}- where
 35 l^B is 0, 1, 2 or 3;
 m^B is 0, 1 or 2;

40

45

L^B is



where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

where

40 n^B is 0, 1 or 2;
p^B is 0, 1 or 2;
q^B is 1, 2 or 3;

RB¹ is C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, C₀₋₃-alkyl-C₃₋₈-cycloalkyl, OH or OCH₃;

45 RB² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl;

28

R^{B3} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl [sic] or C_{0-3} -alkylheteroaryl;
 $R^{B5}OCO$ (where R^{B5} is H, C_{1-6} -alkyl or C_{1-3} -alkylaryl), $R^{B6}-O$
 (where R^{B6} is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

5 R^{B4} is H, C_{1-6} -alkyl, $R^{B6}-O$, Cl, Br, F or CF_3 ;

R^{B5} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

T^B is CH_2 , O, S, NH or N- C_{1-6} -alkyl;

10

$R^{B1'}$ is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl or
 C_{0-3} -alkyl- C_{3-8} -cycloalkyl;

R^{B1} and R^{B2} may also be bonded together;

15

X^B is O, S, NH or N- C_{1-6} -alkyl;

Y^B is $=CH-$, $=N-$ or $=C-Cl$;

20

Z^B is $=CH-$, $=N-$ or $=C-Cl$;

U^B is $=CH-$ or $=N-$;

25 V^B is $=CH-$ or $=N-$;

B is furthermore

$-(CH_2)_{1^B}-L^B-M^B-L^B-(CH_2)_{m^B}$, where

1^B and m^B have the abovementioned meanings and the two groups

30 L^B , independently of one another, are the radicals stated
 under L^B ;

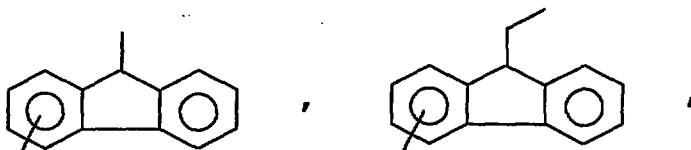
M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S ,
 $S-CH_2$, CO, SO_2 , $CH=CH$ or $C\equiv C$;

35

B is furthermore

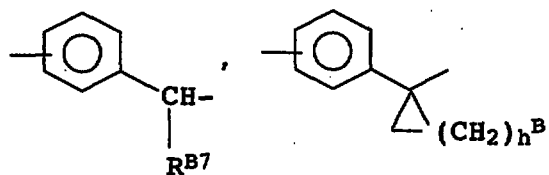
-1-adamantyl- CH_2- , -2-adamantyl- CH_2- , -1-adamantyl-,
 -2-adamantyl-,

40



45 B may furthermore be

29

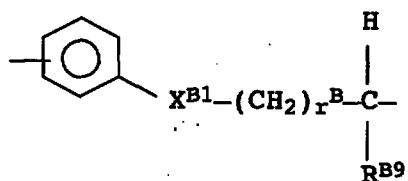
where h^B is 1, 2, 3 or 4

5

(RB⁷ is C₁₋₆-alkyl or C₃₋₈-cycloalkyl)

B may furthermore be

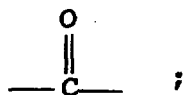
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15

where X^{B1} is a bond, O, S, or

20

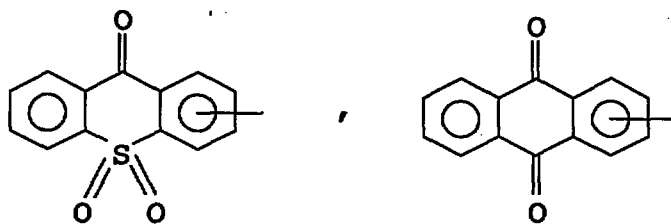
where r^B is 0, 1, 2 or 3;

25

and RB⁹ is H or C₁₋₃-alkyl;

A-B may be

30



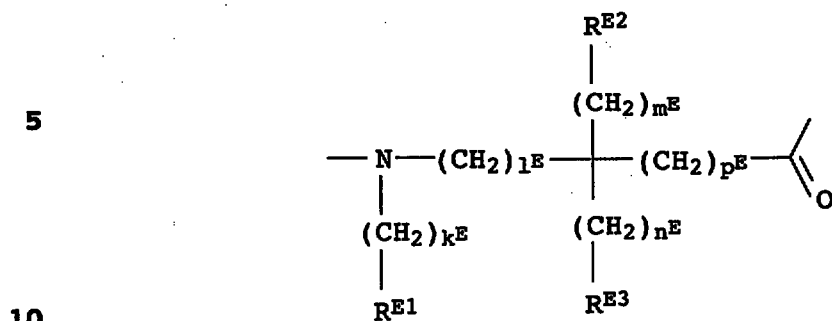
35

D is a single bond or
 CO, OCO, NR^{D1}-CO (where RD¹ is H, C₁₋₄-alkyl or
 C₀₋₃-alkylaryl), SO₂ or NR^{D1}SO₂;

40

45

E is a single bond or



where

- k^E is 0, 1 or 2;
 15 l^E is 0, 1 or 2;
 m^E is 0, 1, 2 or 3;
 n^E is 0, 1 or 2;
 p^E is 0, 1 or 2;

- 20 RE^1 is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, aryl (in particular phenyl or naphthyl), pyridyl, thienyl or C₃₋₈-cycloalkyl having a fused-on phenyl ring, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of
 25 C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br;

RE^1 is furthermore $\text{RE}^4\text{OCO-CH}_2$ (where RE^4 is H, C₁₋₁₂-alkyl or C₁₋₃-alkylaryl);

- 30 RE^2 is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, phenyl, pyridyl, furyl, thienyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of
 35 C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br, or is CH(CH₃)OH or CH(CF₃)₂;

- 40 RE^3 is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or phenyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br;

RE^2 and RE^1 may together furthermore form a bridge having (CH₂)₀₋₄, CH=CH, CH₂-CH=CH or CH=CH-CH₂ groups;

31

the groups stated under R^{E1} and R^{E3} may be linked to one another via a bond; the groups stated under R^{E2} and R^{E3} may also be linked to one another via a bond;

5 R^{E2} is furthermore $CORE^E$ (where R^E is OH, O-C₁₋₆-alkyl or O-C₁₋₃-alkylaryl);

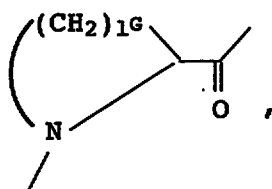
if it is asymmetrically substituted, the building block E is preferably present in the R configuration;

10

E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap, D-Arg;

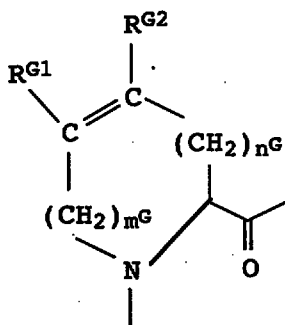
G is

15



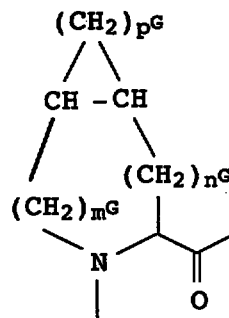
where 1^G is 2, 3, 4 and 5,
where a CH_2 group of the ring may be replaced by O, S, NH, CF_2 , CHF or $CH(C_{1-3}\text{-alkyl})$;

20



25

or



30 where

m^G is 0, 1 or 2;

n^G is 0, 1 or 2;

p^G is 1 or 3;

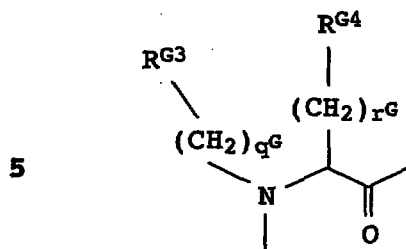
35

R^{G1} and R^{G2} are each H;

R^{G1} and R^{G2} together may furthermore form a $CH=CH-CH=CH$ chain;

40 G is furthermore

45



where

10

q^G is 0, 1 or 2;

r^G is 0, 1 or 2;

15 R^{G3} is H, C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl;

R^{G4} is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or phenyl;

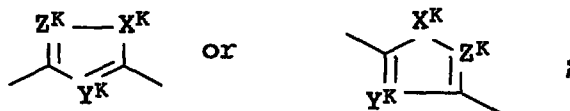
K is

20

$NH-(CH_2)_{n^K}-Q^K$ where

n^K is 1 or 2;

25 Q^K is



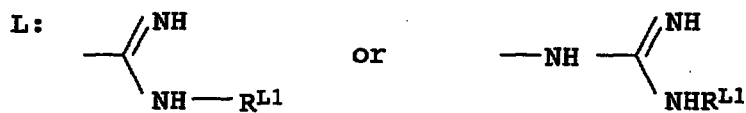
X^K is O, S, NH or N- C_1 - C_6 -alkyl;

30

Y^K is $=CH-$, $=C-C_1$ - C_3 -alkyl, $=N-$ or $=C-Cl$;

Z^K is $=CH-$, $=C-C_1$ - C_3 -alkyl, $=N-$ or $=C-Cl$;

35



40 where

R^{L1} is H, OH, O- C_1 - C_6 -alkyl, O- $(CH_2)_{0-3}$ -phenyl, CO- C_1 - C_6 -alkyl, CO $_2$ - C_1 - C_6 -alkyl or CO $_2$ - C_1 - C_3 -alkylaryl.

45

33

The present invention also relates to the following novel compounds, their tautomers, physiologically tolerable salts and prodrugs of the formula A-B-D-E-G-K-L and drugs which contain these compounds. These compounds are furthermore suitable as particularly good complement inhibitors.

Here:

A is

H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, R^{A1}OCO (where R^{A1} is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₁₋₃-alkyl-C₃₋₈-cycloalkyl or C₁₋₃-alkylaryl), R^{A2}R^{A3}NCO (where R^{A2} is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; R^{A3} is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl), R^{A4}OCONR^{A2}, R^{A4}CONR^{A2} (where R^{A4} is C₁₋₆-alkyl or C₁₋₃-alkylaryl), R^{A1}O, phenoxy, R^{A2}R^{A3}N, HO-SO₂, R^{A2}R^{A3}N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P, NO₂, R^{A1}-N(OH)-CO or R^{A1}R^{A2}NCONR^{A3}, where aryl in each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, OCH₃, CH₃, CF₃ and NO₂;

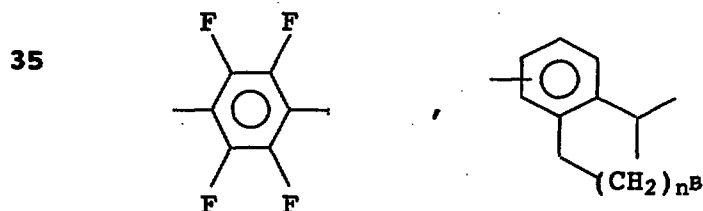
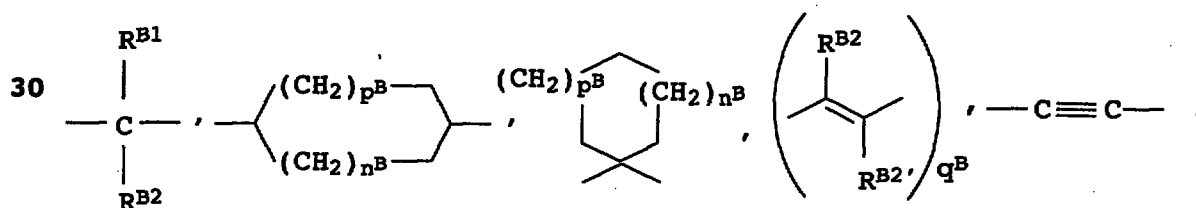
B is



1^B is 0, 1, 2 or 3;

m^B is 0, 1, 2 or 3;

L^B is



where, in each of the abovementioned ring systems, a phenyl ring may be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

where

- 5 n^B is 0, 1 or 2;
 p^B is 0, 1 or 2;
 q^B is 1, 2 or 3;

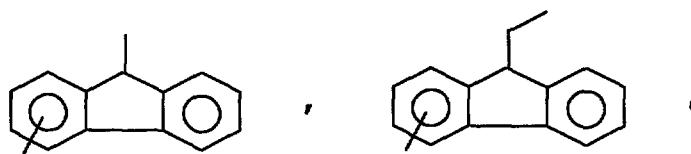
R^{B1} is C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl-
 C_{3-8} -cycloalkyl, OH or OCH_3 ;

- 10 R^{B2} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl.
[sic]

R^{B1} and R^{B2} may also be bonded together;

- 15 $R^{B2'}$ is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl or
 C_{0-3} -alkyl- C_{3-8} -cycloalkyl;

B is furthermore -1-adamantyl-, -1-adamantyl- CH_2 -,
-2-adamantyl- or -2-adamantyl- CH_2 -,



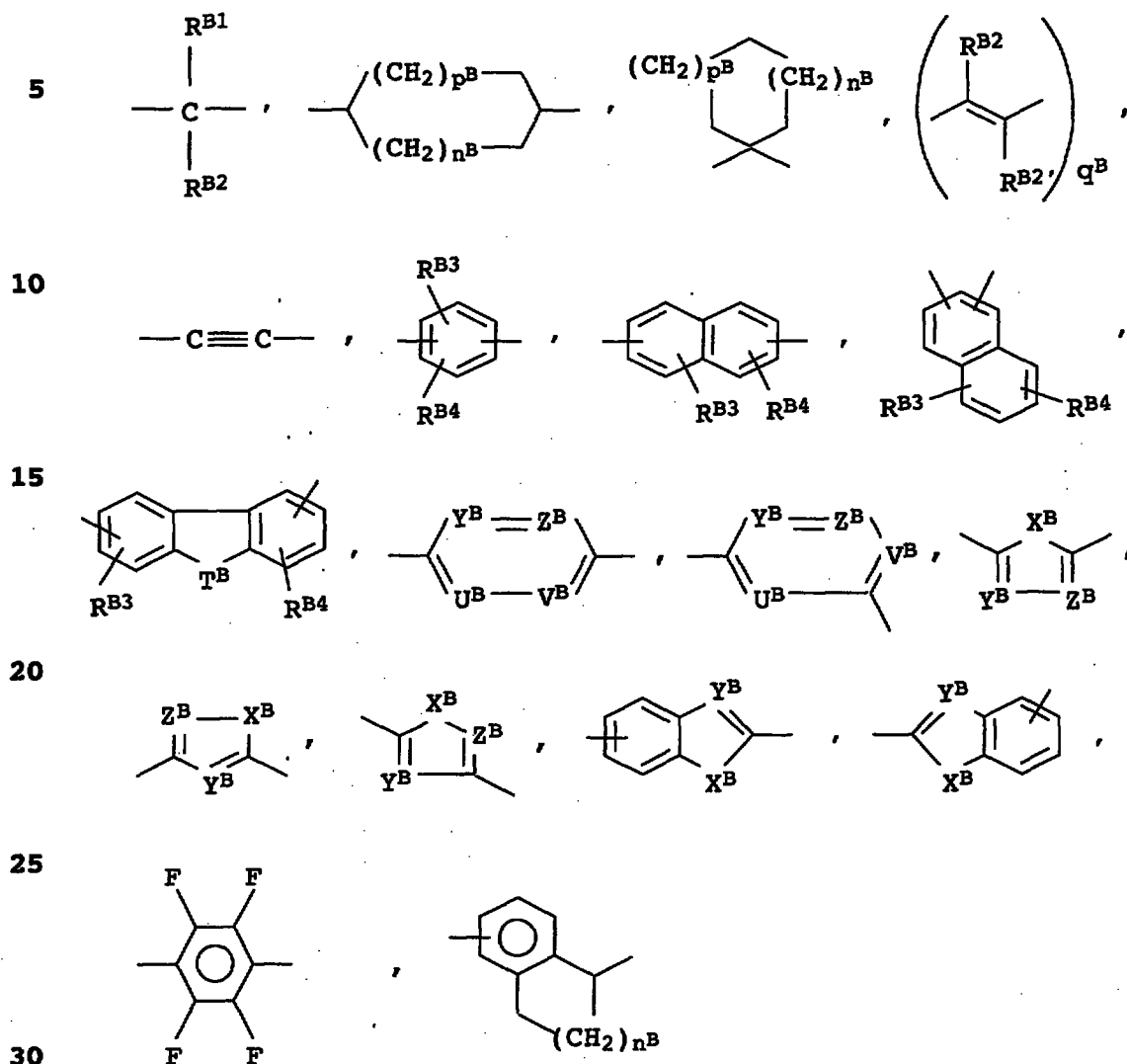
B is furthermore $-(CH_2)_{l^B}-L^{B1}-M^B-L^{B2}-(CH_2)_{m^B}-$, where l^B and m^B
have the abovementioned meanings and the two groups L^{B1} and
 L^{B2} , independently of one another, are the following radical:

30

35

40

45



where, in each of the abovementioned ring systems, a phenyl ring may be fused on;

35

where

- 40
- n^B is 0, 1 or 2;
 - p^B is 0, 1 or 2;
 - q^B is 1, 2 or 3;

$RB1$ is H (only for LB^2), C_{1-6} -alkyl (only for LB^2), C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

45

$RB2$ is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

36

$R^{B2'}$ is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl or C_{0-3} -alkyl- C_{3-8} -cycloalkyl;

5 R^{B3} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, $R^{B5}OCO$ (where R^{B5} is H, C_{1-6} -alkyl or C_{1-3} -alkylaryl), $R^{B6}-O$ (where R^{B6} is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

10 R^{B4} is H, C_{1-6} -alkyl, $R^{B6}-O$, Cl, Br, F or CF_3 ;

T^B is CH_2 , O, S, NH or N- C_{1-6} -alkyl;

X^B is O, S, NH or N- C_{1-6} -alkyl;

15 Y^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

Z^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

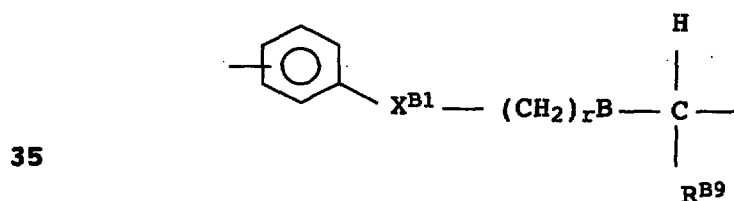
20 U^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl;

V^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl.

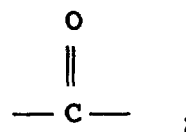
25 R^{B1} and R^{B2} may also be bonded together;

M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CO, SO_2 , $CH=CH$ or $C\equiv C$;

30 B may furthermore be



where X^{B1} is a bond, O, S or



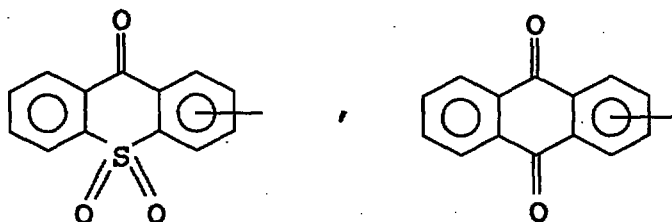
40 r^B is 0, 1, 2 or 3;

R^{B9} is H or C_{1-3} -alkyl;

45 A-B may be

37

5

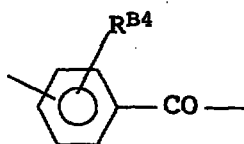


D is a single bond or

CO, OCO, $\text{NR}^{\text{D}1}\text{-CO}$ (where $\text{R}^{\text{D}1}$ is H, C_{1-4} -alkyl or C_{0-3} -alkylaryl), SO_2 or $\text{NR}^{\text{D}1}\text{SO}_2$;

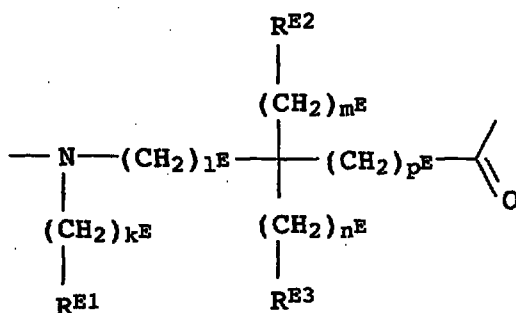
B-D may be

15



20 E is a single bond or

25



30

k^E is 0, 1 or 2;

l^E is 0, 1 or 2;

m^E is 0, 1, 2 or 3;

n^E is 0, 1 or 2;

35

p^E is 0, 1 or 2;

$\text{R}^{\text{E}1}$ is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, naphthyl, pyridyl, thienyl, C_{3-8} -cycloalkyl having a fused-on phenyl ring, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C_{1-6} -alkyl, O-C_{1-6} -alkyl, F, Cl and Br;

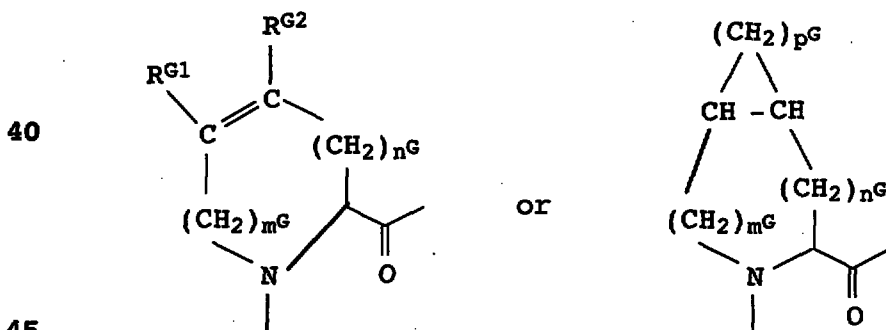
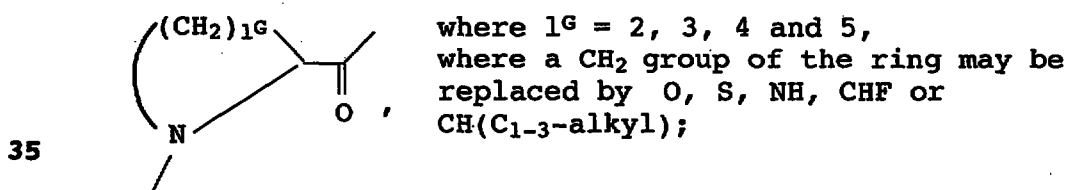
40

$\text{R}^{\text{E}1}$ is furthermore $\text{R}^{\text{E}4}\text{OCO-CH}_2$ (where $\text{R}^{\text{E}4}$ is H, C_{1-12} -alkyl or C_{1-3} -alkylaryl [lacuna]);

45

- R^{E2} is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C_{1-6} -alkyl, OH, O- C_{1-6} -alkyl, F, Cl and Br, or is $CH(CH_3)OH$ or $CH(CF_3)_2$;
- R^{E3} is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or phenyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C_{1-6} -alkyl, O- C_{1-6} -alkyl, F, Cl and Br;
- R^{E2} and R^{E1} together may furthermore form a bridge having $(CH_2)_{0-4}$, $CH=CH$, $CH_2-CH=CH$ or $CH=CH-CH_2$ groups;
- the groups stated under R^{E1} and R^{E3} may be linked to one another via a bond; the groups stated under R^{E2} and R^{E3} may also be linked to one another via a bond;
- R^{E2} is furthermore $CORE^5$ (where R^{E5} is OH, O- C_{1-6} -alkyl or O- C_{1-3} -alkylaryl);
- if it is asymmetrically substituted, the building block E is preferably present in the R configuration;
- E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap, D-Arg;

30 G is



45

where
 m^G is 0, 1 or 2;

n^G is 0, 1 or 2;

p^G is 1 or 3;

R^{G1} is H;

R^{G2} is H;

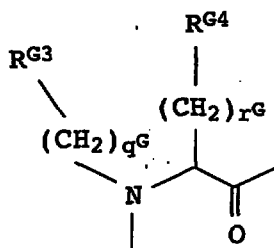
5

R^{G1} and R^{G2} together may also be a $\text{CH}=\text{CH}-\text{CH}=\text{CH}$ chain;

G is furthermore

10

15



where

20 q^G is 0, 1 or 2;

r^G is 0, 1 or 2;

R^{G3} is H, $\text{C}_1\text{-C}_6\text{-alkyl}$ or $\text{C}_3\text{-}_8\text{-cycloalkyl}$;

25 R^{G4} is H, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_3\text{-}_8\text{-cycloalkyl}$ or phenyl;

K is

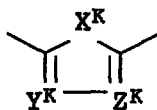
$\text{NH}-(\text{CH}_2)_{n^K}-\text{Q}^K$ where

30

n^K is 1 or 2;

Q^K is

35



X^K is O, S, NH or $\text{N-C}_1\text{-}_6\text{-alkyl}$;

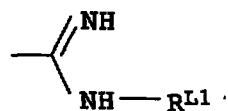
40

Y^K is $=\text{CH}-$, $=\text{C-C}_1\text{-}_3\text{-alkyl}$, $=\text{N}-$ or $=\text{C-Cl}$;

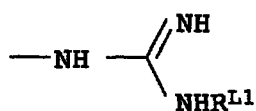
Z^K is $=\text{CH}-$, $=\text{C-C}_1\text{-}_3\text{-alkyl}$, $=\text{N}-$ or $=\text{C-Cl}$;

L:

45



or



where

RL¹ is H, OH, O-C₁₋₆-alkyl, O-(CH₂)₀₋₃-phenyl, CO-C₁₋₆-alkyl, CO₂-C₁₋₆-alkyl or CO₂-C₁₋₅-alkylaryl.

5

The present invention also relates to the following novel compounds, their tautomers, physiologically tolerable salts and prodrugs of the formula A-B-D-E-G-K-L and drugs which contain these compounds. These compounds are furthermore suitable as particularly good complement inhibitors.

Here,

A is

H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, RA¹OCO (where RA¹ is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₁₋₃-alkyl-C₃₋₈-cycloalkyl or C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl), RA⁴OCNRA², RA⁴CONRA² (where RA⁴ is C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA¹O, phenoxy, RA²RA³N, HO-SO₂, RA²RA³N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P, NO₂, RA¹-N(OH)-CO- or RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different substituents from the group consisting of F, Cl, Br, CH₃, CF₃, OCH₃ and NO₂;

25 B is

$-(CH_2)_{1B}-L^B-(CH_2)_{mB}-$ where

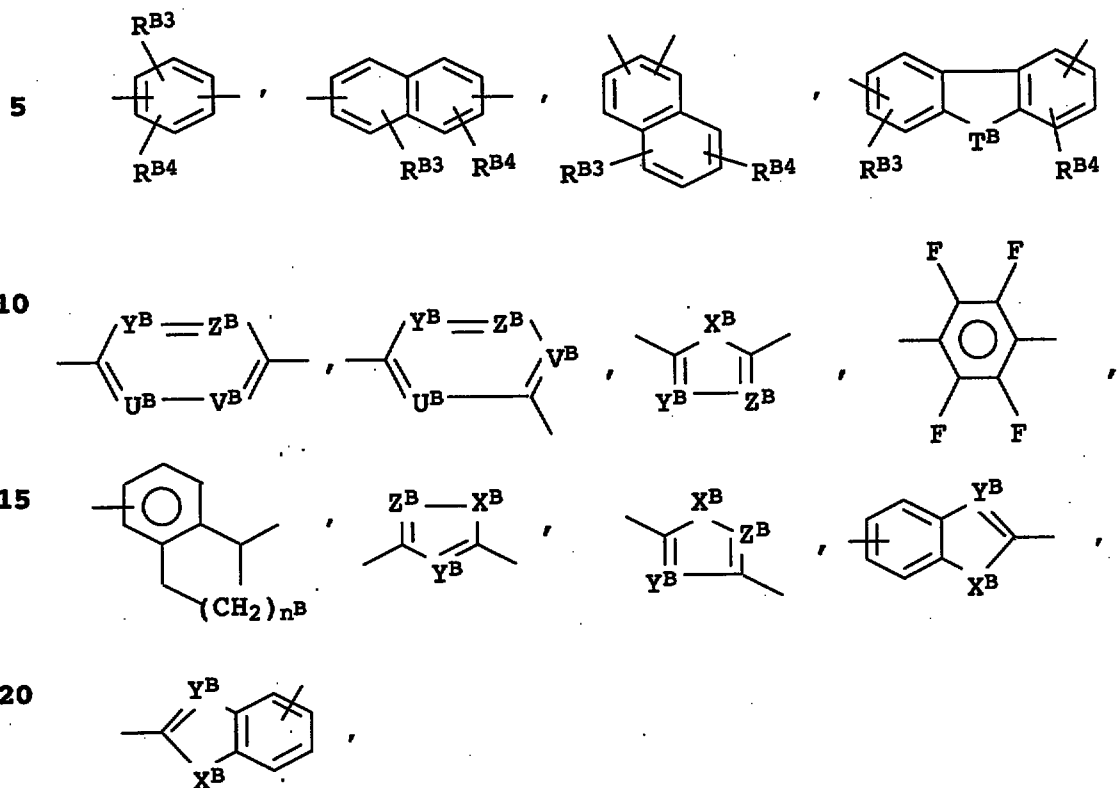
1^B is 0, 1, 2 or 3;
30 m^B is 0, 1, 2, 3, 4 or 5;

35

40

45

L^B is



where, in each of the abovementioned ring systems, a phenyl ring
 25 may be fused on, which phenyl ring may be substituted by up to 2
 identical or different radicals from the group consisting of CH₃,
 CF₃, F, Cl and Br or may be substituted by R⁸OOC- (where R⁸ is H
 or C₁₋₃-alkyl);

30 R^{B3} is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, R^{B5}OCO
 (where R^{B5} is H, C₁₋₆-alkyl or C₁₋₃-alkylaryl), R^{B6}-O (where R^{B6}
 is H or C₁₋₆-alkyl), F, Cl, Br, NO₂ or CF₃;

R^{B4} is H, C₁₋₆-alkyl, R^{B6}-O, Cl, Br, F or CF₃;

35

T^B is CH₂, O, S, NH or N-C₁₋₆-alkyl;

X^B is O, S, NH or N-C₁₋₆-alkyl;

40

Y^B is =CH-, =N- or =C-Cl;

Z^B is =CH-, =N- or =C-Cl;

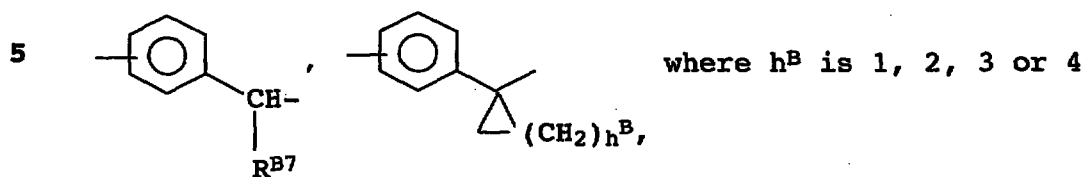
45

U^B is =CH- or =N-;

42

V^B is $=CH-$ or $=N-$;

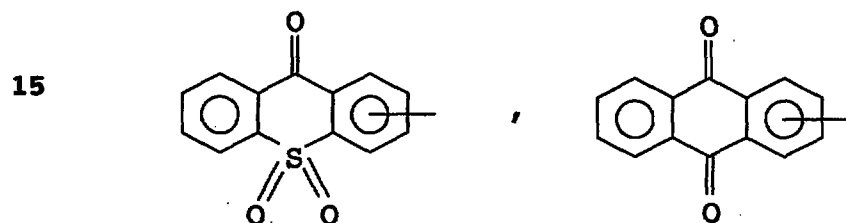
B may furthermore be



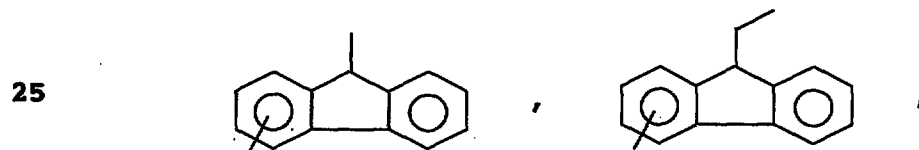
(R^{B7} is C_{1-6} -alkyl or C_{3-8} -cycloalkyl)

10

A-B may be

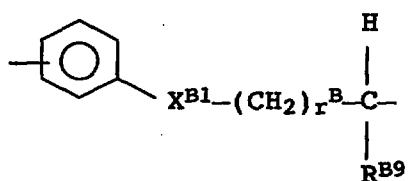


20 B may furthermore be
-1-adamantyl-, -2-adamantyl-, -1-adamantyl- CH_2 -,
-2-adamantyl- CH_2 ,



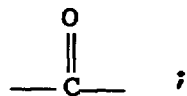
B may furthermore be

30



where X^{B1} is a bond, O, S, or

40



r^B is 0, 1, 2 or 3;

45 R^{B9} is H or C_{1-3} -alkyl;

D is a single bond or

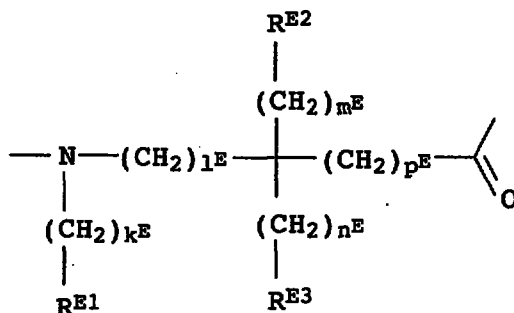
43

-NR^{D1}-CO (where R^{D1} is H, C₁₋₄-alkyl or C₀₋₃-alkylaryl) or
-NR^{D1}SO₂;

E is a single bond or

5

10



15

where

k^E is 0, 1 or 2;

l^E is 0, 1 or 2;

m^E is 0, 1, 2 or 3;

n^E is 0, 1 or 2;

20

p^E is 0, 1 or 2;

25

R^{E1} is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, aryl (in particular phenyl or naphthyl), pyridyl, thienyl, C₃₋₈-cycloalkyl having a fused-on phenyl ring, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br;

30

R^{E1} is furthermore RE⁴OCO-CH₂ (where RE⁴ is H, C₁₋₁₂-alkyl or C₁₋₃-alkylaryl);

35

R^{E2} is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, phenyl, pyridyl, furyl, thienyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br, or is CH(CH₃)OH or CH(CF₃)₂;

40

R^{E3} is H, C₁₋₆-alkyl or C₃₋₈-cycloalkyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br;

45

R^{E2} and R^{B1} together may furthermore form a bridge having (CH₂)₀₋₄, CH=CH, CH₂-CH=CH or CH=CH-CH₂ groups;

44

the groups stated under R^{E1} and R^{E3} may be linked to one another via a bond; the groups stated under R^{E2} and R^{E3} may also be linked to one another via a bond;

5 R^{E2} is furthermore $CORE^E$ (where R^E is OH, O- C_{1-6} -alkyl or OC_{1-3} -alkylaryl);

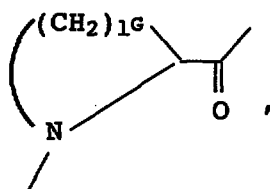
if it is asymmetrically substituted, the building block E is preferably present in the R configuration;

10

E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;

G is

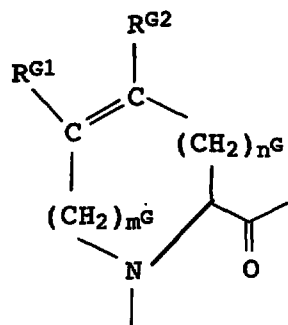
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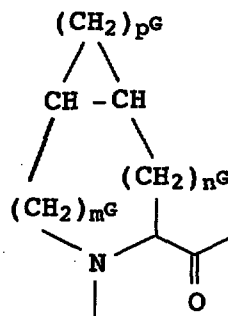
where $l^G = 2, 3, 4$ and 5 ,
where a CH_2 group of the ring may be replaced by O, S, NH, CHF, CF_2 or $CH(C_{1-3}\text{-alkyl})$;

20

25



or



30

where

m^G is 0, 1 or 2;

n^G is 0, 1 or 2;

35 p^G is 1 or 3;

R^{G1} is H;

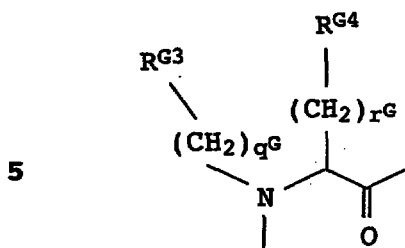
R^{G2} is H;

40

R^{G1} and R^{G2} together may furthermore form a $CH=CH-CH=CH$ chain;

G is furthermore

45



where

10

q^G is 0, 1 or 2;

r^G is 0, 1 or 2;

R^{G3} is H, C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl;

15

R^{G4} is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or phenyl;

K is

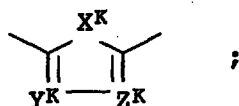
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$NH-(CH_2)_{n^K}-Q^K$ where

n^K is 1 or 2;

25

Q^K is



X^K is O, S, NH or $N-C_1$ - C_6 -alkyl;

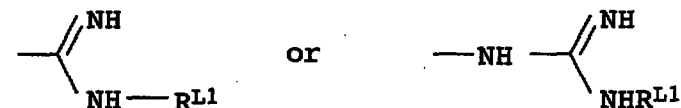
30

Y^K is $=CH-$, $=C-C_1$ - C_6 -alkyl, $=N-$ or $=C-Cl$;

Z^K is $=CH-$, $=C-C_1$ - C_6 -alkyl, $=N-$ or $=C-Cl$;

35

L:



40

where

R^{L1} is $-H$, $-OH$, $-O-C_1$ - C_6 -alkyl, $-O-(CH_2)_{0-3}$ -phenyl,
45 $-CO-C_1$ - C_6 -alkyl, $-CO_2-C_1$ - C_6 -alkyl or CO_2-C_1 - C_3 -alkylaryl.

46

The present invention also relates to the following novel preferred compounds, their tautomers, physiologically tolerable salts and prodrugs of the formula A-B-D-E-G-K-L and drugs which contain these compounds. Furthermore, these compounds are
5 suitable as particularly good complement inhibitors.

Here:

A is

10 H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, RA¹OCO (where RA¹ is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₃-alkyl or C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H-, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl); RA⁴CONRA² (where RA⁴ is C₁₋₆-alkyl or
15 C₁₋₃-alkylaryl), RA⁴CONRA², RA¹O, RA²RA³N, HO-SO₂-, phenoxy, RA²RA³N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P-, NO₂, RA¹-N(OH)-CO- or RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, CF₃, CH₃, OCH₃ and NO₂;
20

B is



25 1^B is 0, 1, 2 or 3;
 m^B is 0, 1 or 2;

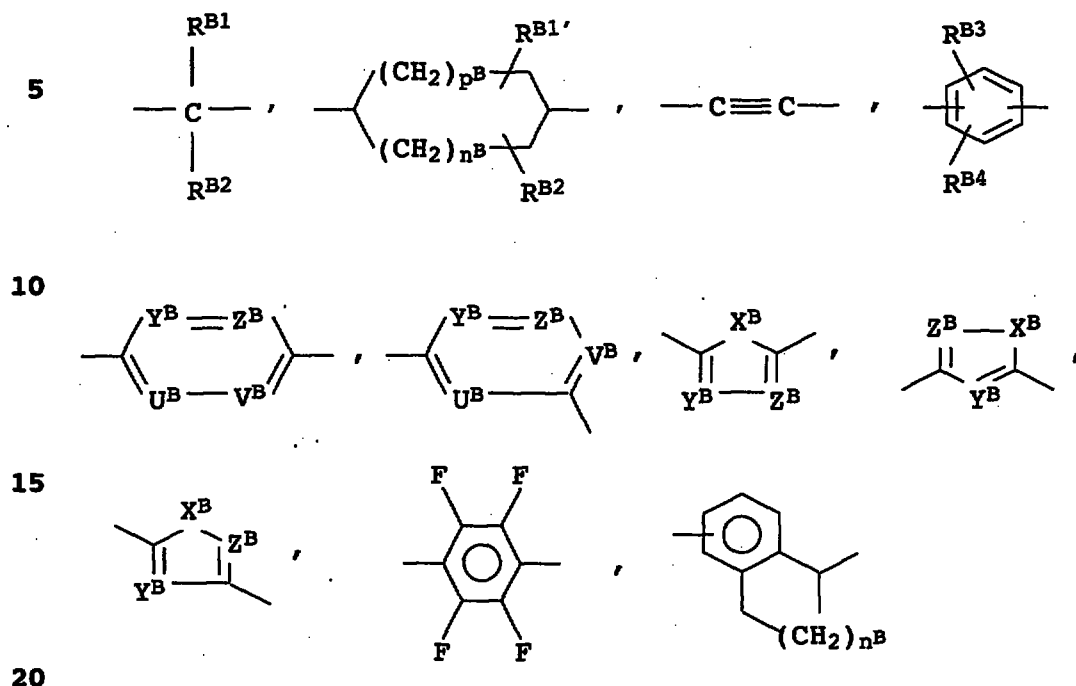
30

35

40

45

L^B is



where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃,
25 CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

where

30 n^B is 0, 1 or 2;
 p^B is 0, 1 or 2;

RB¹ is C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, C₀₋₃-alkyl-C₃₋₈-cycloalkyl, OH or OCH₃;

35 RB² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl;

RB³ is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl;
RB⁵OCO (where RB⁵ is H, C₁₋₆-alkyl or C₁₋₃-alkylaryl), RB⁶-O
40 (where RB⁶ is H or C₁₋₆-alkyl), F, Cl, Br, NO₂ or CF₃;

RB⁴ is H, C₁₋₆-alkyl, RB⁶-O, Cl, Br, F or CF₃;

RB^{1'} is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl or
45 C₀₋₃-alkyl-C₃₋₈-cycloalkyl;

48

R^{B1} and R^{B2} may also be bonded together;

X^B is O, S, NH or N-C₁₋₆-alkyl;

5

Y^B is =CH- or =N-;

Z^B is =CH- or =N-;

10

U^B is =CH- or =N-;

V^B is =CH- or =N-;

B is furthermore

15

$-(CH_2)_{1B}-L^B-M^B-L^B-(CH_2)_{mB}$, where

1^B and m^B have the abovementioned meanings and the two groups L^B , independently of one another, are the radicals stated under L^B ;

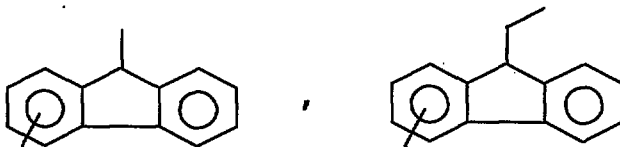
20

M^B is a single bond, O, S, CH₂, CH₂-CH₂, CH₂-O, O-CH₂, CH₂-S, S-CH₂, CO, SO₂, CH=CH or C≡C;

B is furthermore

25

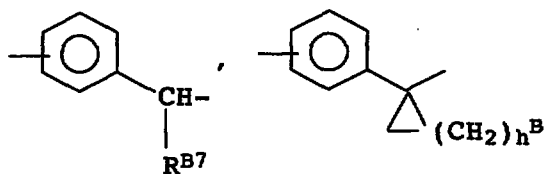
-1-adamantyl-CH₂-, -2-adamantyl-CH₂-, -1-adamantyl-,
-2-adamantyl-,



30

B may furthermore be

35



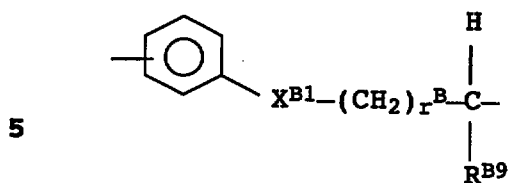
where h^B is 1, 2, 3 or 4

(R^{B7} is C₁₋₆-alkyl or C₃₋₈-cycloalkyl)

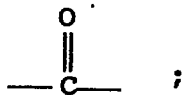
40

B may furthermore be

45



10 where XB^1 is a bond, O, S, or

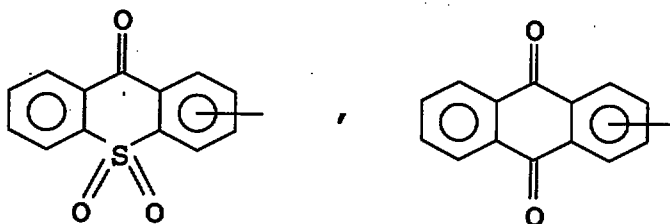


15 r^B is 0, 1, 2 or 3;

RB^9 is H or C_{1-3} -alkyl;

A-B may be

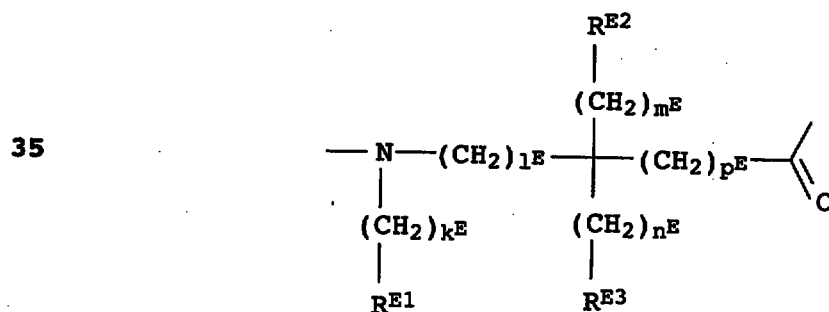
20



25

D is a single bond or CO, OCO or $\text{NR}^{\text{D}1}-\text{CO}$ (where $\text{R}^{\text{D}1}$ is H, C_{1-4} -alkyl or C_{0-3} -alkylaryl), SO_2 or $\text{NR}^{\text{D}1}\text{SO}_2$;

30 E is



40

where

45 k^E is 0 or 1;
 l^E is 0 or 1;
 m^E is 0 or 1;
 n^E is 0 or 1;

p^E is 0 or 1;

5 RE^1 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, aryl (in particular phenyl or naphthyl), pyridyl, thienyl or C_{3-8} -cycloalkyl having a fused-on phenyl ring;

RE^1 is furthermore $RE^4OCO-CH_2$ (where RE^4 is H, C_{1-12} -alkyl or C_{1-3} -alkylaryl);

10 RE^2 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, pyridyl, furyl, thienyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, where the abovementioned radicals may carry up to three identical or different substituents from the group consisting of C_{1-6} -alkyl, $O-C_{1-6}$ -alkyl, F, Cl and Br, or is $CH(CH_3)OH$ or $CH(CF_3)_2$;

RE^3 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or phenyl;

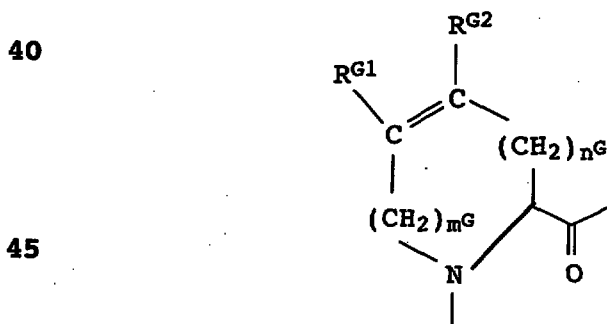
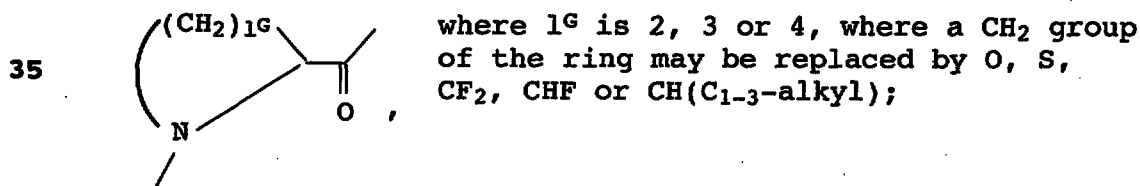
20 RE^2 and RE^1 together may also form a bridge with $(CH_2)_{0-4}$, $CH=CH$, $CH_2-CH=CH$ or $CH=CH-CH_2$ groups;

the groups stated under RE^1 and RE^2 may be linked to one another via a bond; the groups stated under RE^2 and RE^3 may also be linked to one another via a bond;

25 if it is asymmetrically substituted, the building block E is preferably present in the R configuration;

30 E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;

G is



where

m^G is 0, 1 or 2;

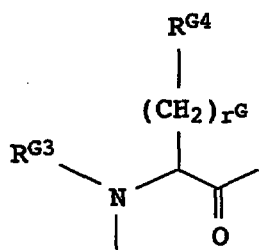
n^G is 0, 1 or 2;

5

R^{G1} and R^{G2} are each H;

G is furthermore

10



15

where r^G is 0 or 1;

R^{G3} is H, C_1 - C_6 -alkyl or C_3 -8-cycloalkyl;

20

R^{G4} is H, C_1 - C_6 -alkyl, C_3 -8-cycloalkyl or phenyl;

K is

25

$NH-(CH_2)_{n^K}-Q^K$, where

n^K is 1 or 2;

30

Q^K is



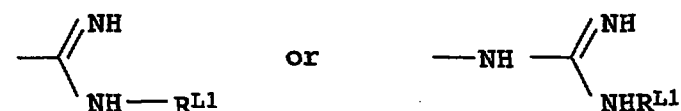
X^K is O or S;

35

Y^K is $=CH-$, $=C-C_{1-3}$ -alkyl or $=N-$;

Z^K is $=CH-$, $=C-C_{1-3}$ -alkyl or $=N-$;

40 L:



where

45

R^{L1} is H, OH, O-C₁₋₆-alkyl, O-(CH₂)₀₋₃-phenyl, CO-C₁₋₆-alkyl, CO₂-C₁₋₆-alkyl or CO₂-C₁₋₃-alkylaryl.

The present invention also relates to the following particularly preferred novel compounds, their tautomers, physiologically tolerable salts and prodrugs of the formula A-B-D-E-G-K-L and drugs which contain these compounds. Furthermore, these compounds are suitable as particularly good complement inhibitors.

10 Here:

A is

H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂ or $R^{A1}OCO$ (where R^{A1} is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₃-alkyl or C₁₋₃-alkylaryl), $R^{A2}R^{A3}NCO$ (where R^{A2} is H-, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; R^{A3} is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl); $R^{A4}OCONR^{A2}$ (where R^{A4} is C₁₋₆-alkyl or C₁₋₃-alkylaryl), $R^{A4}CONR^{A2}$, $R^{A1}O$, $R^{A2}R^{A3}N$, HO-SO₂-, phenoxy, $R^{A2}R^{A3}N-SO_2$, Cl, Br, F, tetrazolyl, H₂O₃P-, NO₂, $R^{A1}-N(OH)-CO-$ or $R^{A1}R^{A2}NCONR^{A3}$, where aryl in each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, CF₃, CH₃, OCH₃ and NO₂;

B is

25

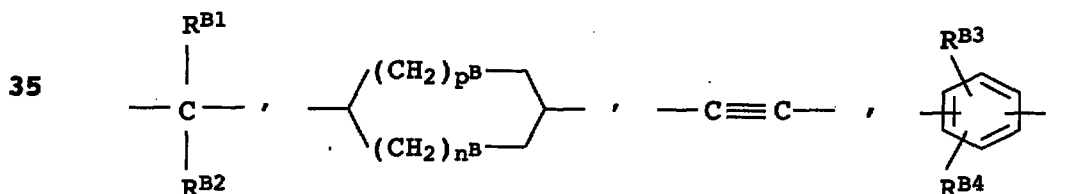


1^B is 0, 1 or 2;

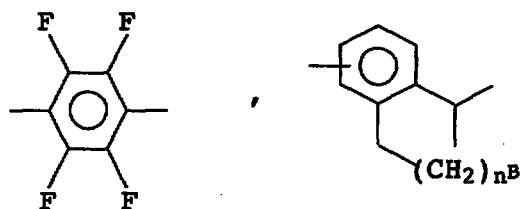
m^B is 0, 1 or 2;

30

L^B is



40



45

53

where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH_3 , CF_3 , Br, Cl and F or may be substituted by $\text{R}^8\text{OOC-}$ (where R^8 is H or C_{1-3} -alkyl);

where

n^B is 0 or 1;
 p^B is 0 or 1;

R^{B1} is C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

R^{B2} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

R^{B3} is H, C_{1-6} -alkyl;
 R^{B5}OCO (where R^{B5} is H, C_{1-6} -alkyl), $\text{R}^{B6}\text{-O}$ (where R^{B6} is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

R^{B4} is H, C_{1-6} -alkyl, $\text{R}^{B6}\text{-O}$, Cl, Br, F or CF_3 ;

R^{B1} and R^{B2} may also be bonded together;

B is furthermore $-(\text{CH}_2)_{1^B}\text{-L}^B\text{-M}^B\text{-L}^B\text{-(CH}_2)_{m^B}$, where 1^B and m^B have the abovementioned meanings and the two groups L^B , independently of one another, are the radicals stated under L^B ;

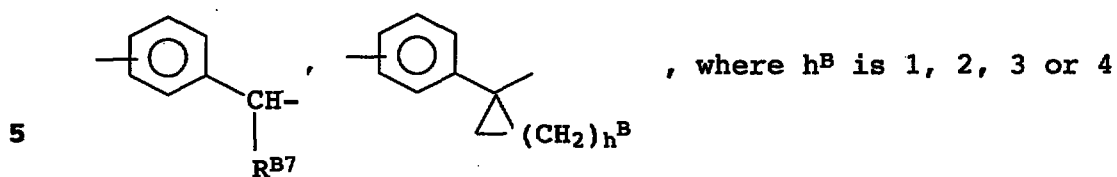
M^B is a single bond, O, S, CH_2 , $\text{CH}_2\text{-CH}_2$, $\text{CH}_2\text{-O}$, O-CH_2 , $\text{CH}_2\text{-S}$, S-CH_2 , CH=CH or $\text{C}\equiv\text{C}$;

B is furthermore -1-adamantyl- $\text{CH}_2\text{-}$, -2-adamantyl- $\text{CH}_2\text{-}$,



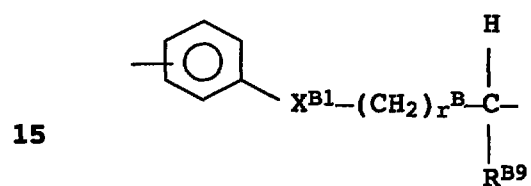
54

B may furthermore be



(RB^7 is C_{1-6} -alkyl or C_{3-8} -cycloalkyl)

10 B may furthermore be



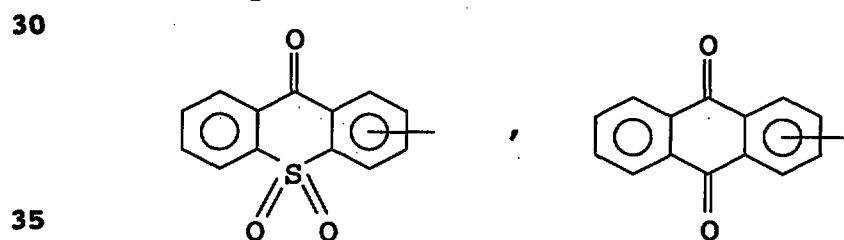
where XB^1 is a bond, O, S or



25 r^B is 0, 1, 2 or 3;

RB^9 is H or C_{1-3} -alkyl;

A-B may be



D is a single bond or
CO, OCO or NR^{D1} -CO (where R^{D1} is H, C_{1-4} -alkyl or
C₀₋₃-alkylaryl), SO₂ or $NR^{D1}SO_2$;

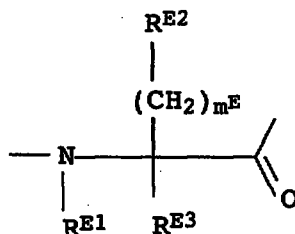
40

E is

45

55

5



10 where

 m^E is 0 or 1;

15

 RE^1 is H or C_{1-6} -alkyl;

RE^2 is H, C_{1-6} -alkyl or C_{3-8} -cycloalkyl, where the abovementioned radical may carry up to three substituents from the group consisting of C_{1-6} -alkyl and F, or is $CH(CH_3)OH$ or $CH(CF_3)_2$;

20

 RE^3 is H;

the groups stated under RE^1 and RE^2 may be linked to one another via a bond;

25

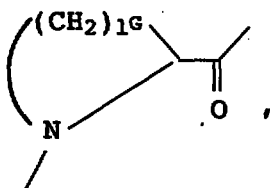
if it is asymmetrically substituted, the building block E is preferably present in the R configuration;

E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;

30

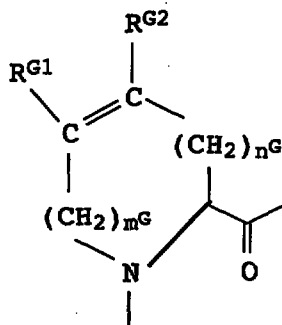
G is

35



where 1^G is 2 or 3, where a CH_2 group of the ring may be replaced by S or $CHCH_3$;

40



45

where

m^G is 1;

n^G is 0;

5

R^{G1} and R^{G2} are each H;

K is

10

$NH-(CH_2)_{n^K}-Q^K$, where

n^K is 1;

15 Q^K is



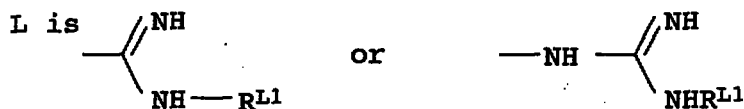
X^K is S;

20

Y^K is $=CH-$ or $=N-$;

Z^K is $=CH-$ or $=N-$;

25



where

30

R^{L1} is H, OH, $CO-C_{1-6}$ -alkyl, CO_2-C_{1-6} -alkyl or CO_2-C_{1-3} -alkylaryl.

The present invention also relates to the following very particularly preferred novel compounds, their tautomers, physiologically tolerable salts and prodrugs of the formula A-B-D-E-G-K-L and drugs which contain these compounds.

Furthermore, these compounds are suitable as particularly good complement inhibitors.

40

Here:

A is

H, C_{1-6} -alkyl, C_{1-6} -alkyl- SO_2 or RA^1OCO (where RA^1 is H, C_{1-12} -alkyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-3} -alkyl or C_{1-3} -alkylaryl), RA^2RA^3NCO (where RA^2 is H-, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl; RA^3 is H, C_{1-6} -alkyl or

57

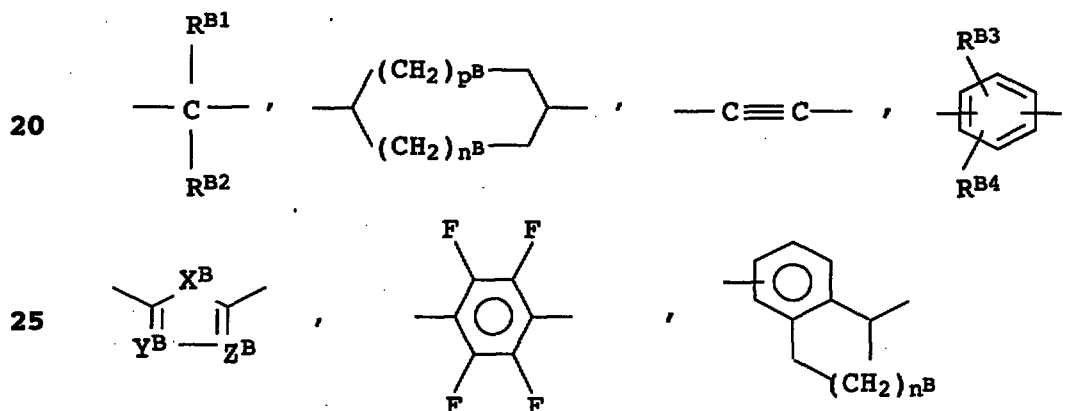
- 5 C₀₋₃-alkylaryl); RA⁴OCONRA² (where RA⁴ is C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA⁴CONRA², RA¹O, RA²RA³N, HO-SO₂-, phenoxy, RA²RA³N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P-, NO₂, RA¹-N(OH)-CO- or RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, CF₃, CH₃, OCH₃ and NO₂;

B is

- 10 $-(CH_2)_{l^B}-L^B-(CH_2)_{m^B}-$ where

l^B is 0 or 1;
 m^B is 0, 1 or 2;

- 15 L^B is



- 30 where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

- 35 where

n^B is 0 or 1;
 p^B is 0 or 1;

- 40 RB¹ is C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, C₀₋₃-alkyl-C₃₋₈-cycloalkyl, OH or OCH₃;

RB² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl;

- 45 RB³ is H, C₁₋₆-alkyl;

58

RB^5OCO (where RB^5 is H or C_{1-6} -alkyl), $\text{RB}^6\text{-O}$ (where RB^6 is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

RB^4 is H, C_{1-6} -alkyl, $\text{RB}^6\text{-O}$, Cl, Br, F or CF_3 ;

5

RB^1 and RB^2 may also be bonded together;

X^B is O or S;

10

Y^B is $=\text{CH-}$ or $=\text{N-}$;

Z^B is $=\text{CH-}$ or $=\text{N-}$;

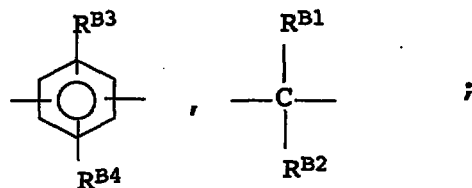
15

B is furthermore

$-(\text{CH}_2)_{1^B}\text{-L}^B\text{-M}^B\text{-L}^B\text{-(CH}_2)_{m^B}$, where

1^B and m^B have the abovementioned meanings and the two groups L^B , independently of one another, are the radicals $-\text{C}\equiv\text{C-}$ stated under L^B ,

20

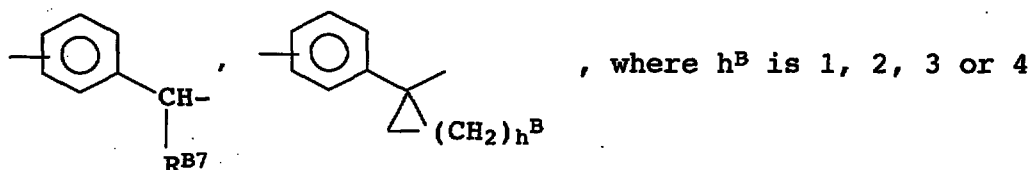


25

M^B is a single bond, O, $\text{CH}_2\text{-S}$, S-CH_2 , CO, SO_2 or $\text{CH}_2\text{-O}$;

B may furthermore be

30



(RB^7 is C_{1-6} -alkyl or C_{3-8} -cycloalkyl)

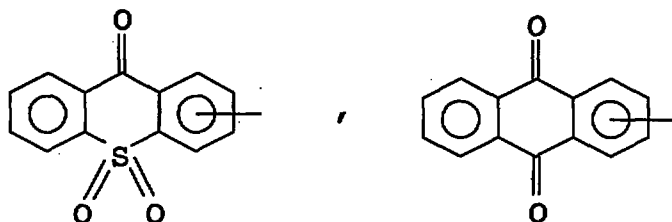
35

B may furthermore be 1-fluorenyl-, 1-adamantyl- or 1-adamantyl- $\text{CH}_2\text{-}$,

40

A-B may be 2-pyridyl- $\text{CH}_2\text{-}$, 2-benzothienyl-, 3-benzothienyl-,

45

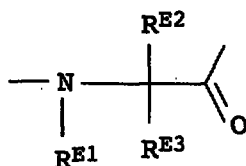


59

D is a single bond or CO or SO₂;

E is

5



10

where

RE¹ is H or CH₃;

15

RE² is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, thienyl, CH(CH₃)OH or CH(CF₃)₂;

RE³ is H;

20

the groups stated under RE¹ and RE² may be linked to one another via a bond; the groups stated under RE² and RE³ may also be linked to one another via a bond;

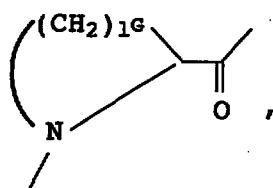
25

if it is asymmetrically substituted, the building block E is preferably present in the R configuration;

E may also be D-Lys, D-Orn, D-Dab, D-Dap or D-Arg;

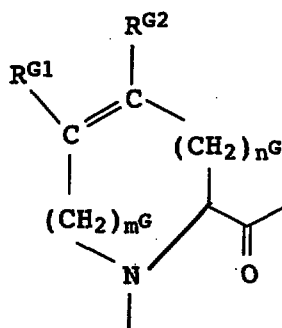
G is

30



where l^G is 2 or 3, where a CH₂ group of the ring may be replaced by CHCH₃;

35



40

45

where

m^G is 1;

n^G is 0;

R^{G1} and R^{G2} are each H;

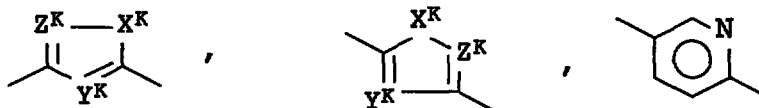
5 K is

$NH-(CH_2)_{n^K}-Q^K$, where

n^K is 1;

10

Q^K is



15

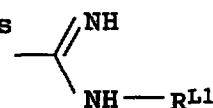
X^K is S;

Y^K is $=CH-$ or $=N-$;

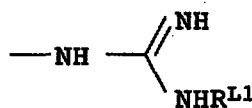
20

Z^K is $=CH-$ or $=N-$;

L is



or



25

where

R^{L1} is H or OH.

30 The present invention also relates to the following preferred novel compounds, their tautomers, physiologically tolerable salts and prodrugs of the formula A-B-D-E-G-K-L and drugs which contain these compounds. Furthermore, these compounds are suitable as particularly good complement inhibitors.

35 Here:

A is

H, C_{1-6} -alkyl, C_{1-6} -alkyl- SO_2 or RA^1OCO (where RA^1 is H, C_{1-12} -alkyl, C_{3-8} -cycloalkyl, C_{1-3} -alkyl- C_{3-8} -cycloalkyl or C_{1-3} -alkylaryl), RA^2RA^3NCO (where RA^2 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl; RA^3 is H, C_{1-6} -alkyl or C_{0-3} -alkylaryl), $RA^4OCONRA^2$, RA^4CONRA^2 (where RA^4 is C_{1-6} -alkyl or C_{1-3} -alkylaryl), RA^1O , phenoxy, RA^2RA^3N , $HO-SO_2$, $RA^2RA^3N-SO_2$, Cl, Br, F, tetrazolyl, H_2O_3P , NO_2 , $RA^1-N(OH)-CO$ or $RA^1RA^2NCONRA^3$, where aryl in each case may be substituted by

61

up to 2 identical or different radicals from the group consisting of F, Cl, Br, OCH₃, CH₃, CF₃ and NO₂;

B is

5

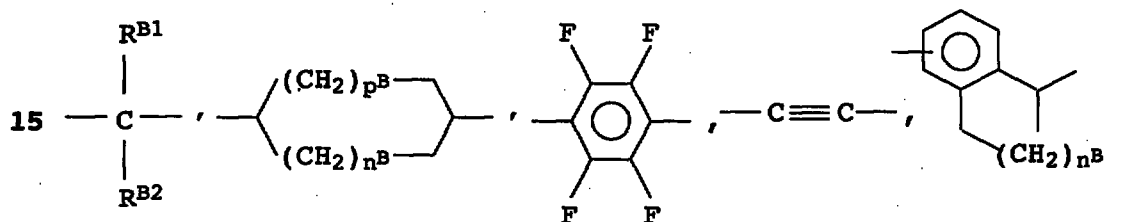
-(CH₂)_{l^B}-L^B-(CH₂)_{m^B}-, where

l^B is 0, 1 or 2;

m^B is 0, 1 or 2;

10

L^B is



20

where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

25

where

n^B is 0, 1 or 2;

p^B is 0, 1 or 2;

30

RB¹ is C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, C₀₋₃-alkyl-C₃₋₈-cycloalkyl, OH or OCH₃;

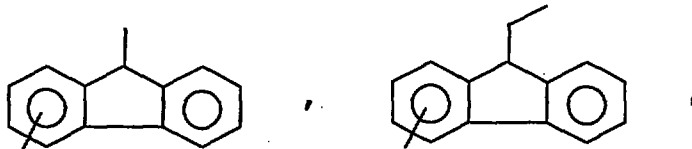
RB² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl;

35

RB¹ and RB² may also be bonded together;

B is furthermore -1-adamantyl-CH₂-, -2-adamantyl-CH₂-,

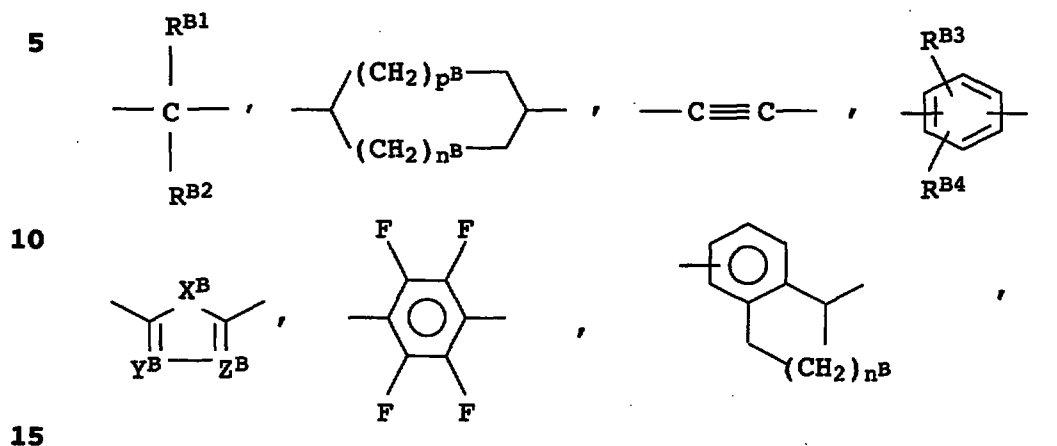
40



45

62

B is furthermore $-(CH_2)_{1B}-L^{B1}-M^B-L^{B2}-(CH_2)_{mB}-$, where 1^B and m^B have the abovementioned meanings and the two groups L^{B1} and L^{B2} , independently of one another, are the following radicals:



where, in each of the abovementioned ring systems, a phenyl ring can be fused on;

where

20 n^B is 0, 1 or 2;
 p^B is 0, 1 or 2;

25 RB^1 is H (only for L^{B2}), C_{1-6} -alkyl (only for L^{B2}), C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

RB^2 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

30 RB^3 is H, C_{1-6} -alkyl, aryl, heteroaryl, RB^5OCO (where RB^5 is H or C_{1-6} -alkyl), RB^6-O (where RB^6 is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

RB^4 is H, C_{1-6} -alkyl, RB^6-O , Cl, Br, F or CF_3 ;

35 XB is O or S;
 YB is $=CH-$ or $=N-$;

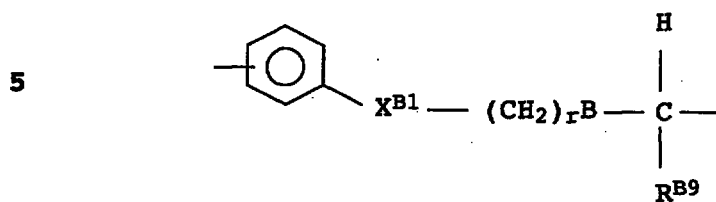
ZB is $=CH-$ or $=N-$;

40 RB^1 and RB^2 may also be bonded together;

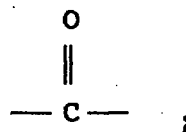
45 M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CO, SO_2 , $CH=CH$ or $C\equiv C$;

63

B may furthermore be



10 where XB1 is a bond, O, S or

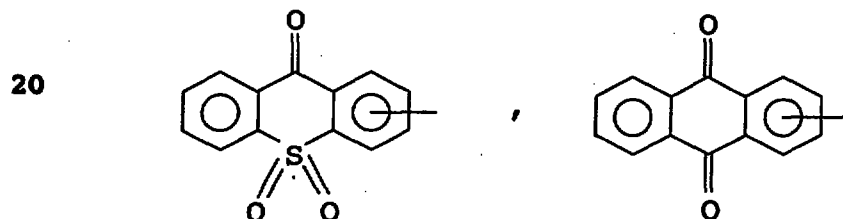


r^B is 0, 1, 2 or 3;

RB^9 is H or C_{1-3} -alkyl;

15

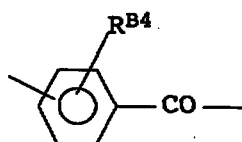
A-B may be



25 D is a single bond or
CO, OCO, $\text{NR}^{\text{D1}}\text{---CO}$ (where RD^1 is H, C_{1-4} -alkyl or
 C_{0-3} -alkylaryl), SO_2 or $\text{NR}^{\text{D1}}\text{SO}_2$;

B-D may be

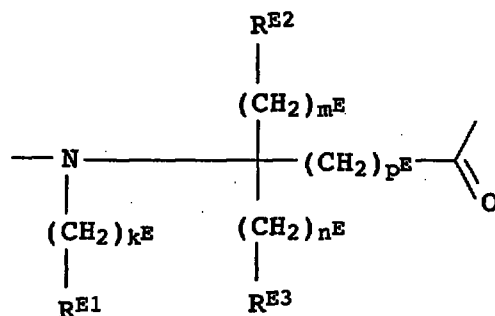
30



35

E is

40



45

k^E is 0 or 1;

m^E is 0 or 1;

n^E is 0 or 1;

p^E is 0 or 1;

5 RE^1 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, naphthyl, pyridyl, thienyl or C_{3-8} -cycloalkyl having a fused-on phenyl ring;

10 RE^2 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, $CH(CH_3)OH$ or $CH(CF_3)_2$;

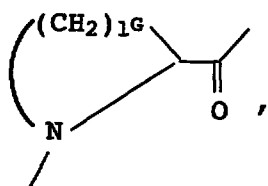
RE^3 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or phenyl;

15 the groups stated under RE^1 and RE^2 may be linked to one another via a bond; the groups stated under RE^2 and RE^3 may also be linked to one another via a bond;

20 if it is asymmetrically substituted, the building block E is preferably present in the R configuration;

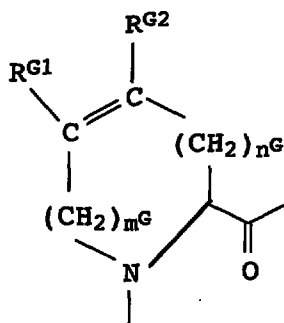
E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;

25 G is



where 1^G is 2, 3 or 4, where a CH_2 group of the ring may be replaced by $CHCH_3$;

30



35

40

where

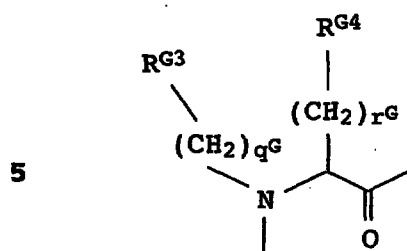
m^G is 1;

n^G is 0 or 1;

RG^1 is H;

45 RG^2 is H;

G is furthermore



where

10

q^G is 0 or 1;

r^G is 0 or 1;

RG^3 is H, C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl;

15

RG^4 is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or phenyl;

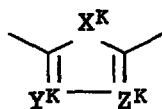
K is

20

$NH-(CH_2)_{n^K}-Q^K$, where

n^K is 1;

25 Q^K is



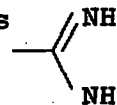
X^K is O or S;

30

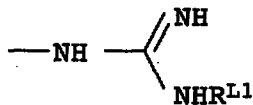
Y^K is $=CH-$ or $=N-$;

Z^K is $=CH-$ or $=N-$;

35 L is



or



where

40

RL^1 is H, OH, CO - C_{1-6} -alkyl, CO_2 - C_{1-6} -alkyl or CO_2 - C_{1-5} -alkylaryl.

The present invention also relates to the following particularly
 45 preferred novel compounds, their tautomers, physiologically
 tolerable salts and prodrugs of the formula A-B-D-E-G-K-L and
 drugs which contain these compounds. Furthermore, these compounds

66

are suitable as particularly good complement inhibitors.

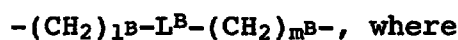
Here:

A is

- 5 H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, RA¹OCO (where RA¹ is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₁₋₃-alkyl-C₃₋₈-cycloalkyl or C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl), RA⁴OCNRA², RA⁴CONRA² (where RA⁴ is C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA¹O, phenoxy, RA²RA³N, HO-SO₂, RA²RA³N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P, NO₂, RA¹-N(OH)-CO or RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, OCH₃, CH₃, CF₃ and NO₂;

15

B is



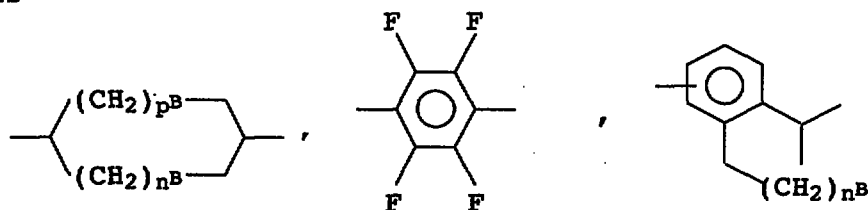
20

1^B is 0 or 1;

m^B is 0, 1 or 2;

L^B is

25



30

where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

35

where

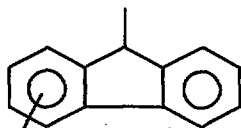
n^B is 0 or 1;

40

p^B is 0 or 1;

B is furthermore -1-adamantyl-CH₂-, -2-adamantyl-CH₂-,

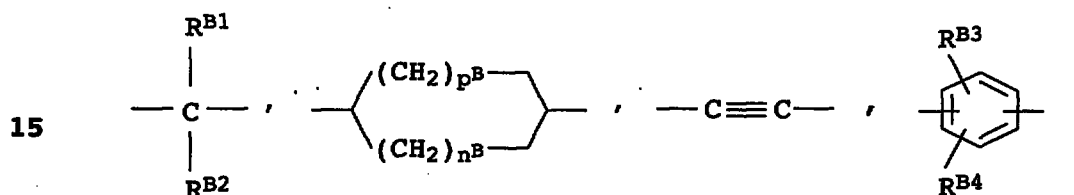
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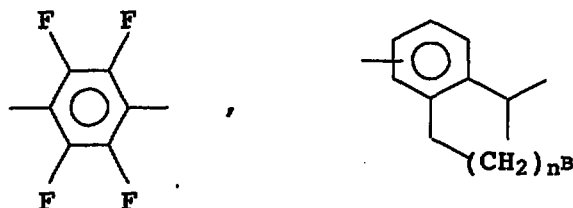
B is furthermore $-(CH_2)_{1^B}-L^{B1}-M^B-L^{B2}-(CH_2)_{m^B}-$, where 1^B and m^B have the abovementioned meanings and the two groups L^{B1} and L^{B2} , independently of one another, are the following radicals:

10



15

20



25 where, in each of the abovementioned ring systems, a phenyl ring can be fused on;

where

n^B is 1;
 p^B is 0 or 1;

30

$RB1$ is H (only for L^{B2}), C_{1-6} -alkyl (only for L^{B2}), C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

35

$RB2$ is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

$RB3$ is H, C_{1-6} -alkyl, RB^6-O (where RB^6 is H, C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

40

$RB4$ is H, C_{1-6} -alkyl, RB^6-O , Cl, Br, F or CF_3 ;

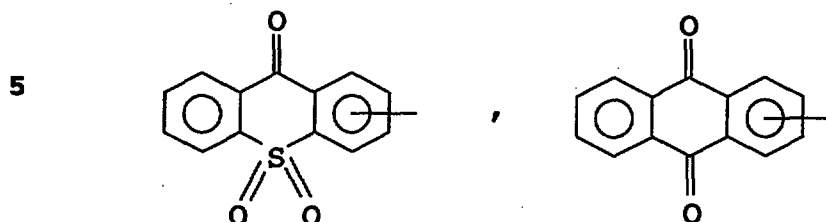
$RB1$ and $RB2$ may also be bonded together;

45

M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CO or SO_2 ;

68

A-B may be 2-pyridyl-CH₂-, 2-benzothienyl-,

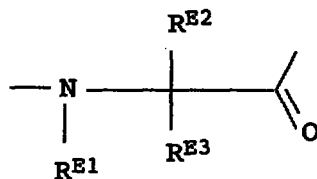


10 D is a single bond or CO or SO₂;

B-D may be



E is
20



25

R^{E1} is H;

30 R^{E2} is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, CH(CH₃)OH or CH(CF₃)₂;

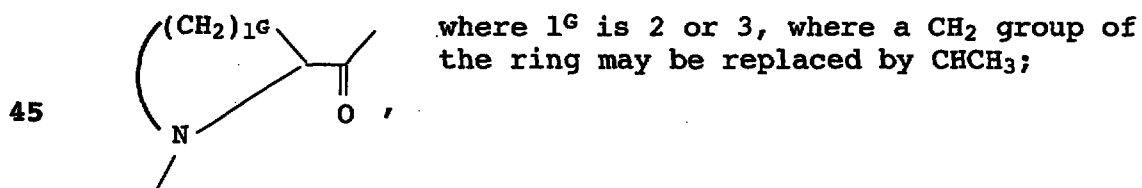
R^{E3} is H;

35

the groups stated under R^{E1} and R^{E2} may be linked to one another via a bond;

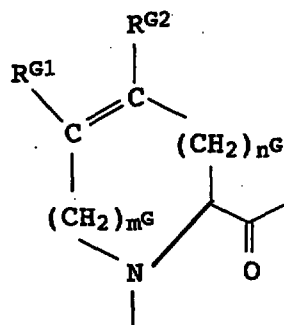
E may also be D-Lys, D-Orn, D-Dab, D-Dap or D-Arg;
40

G is



69

5



10

where

 m^G is 1; n^G is 0; $RG1$ is H; $RG2$ is H;

15

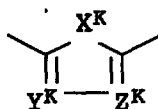
K is

 $NH-(CH_2)_{n^K}-Q^K$, where

20

 n^K is 1; Q^K is

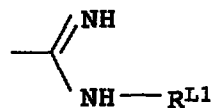
25

 X^K is S; Y^K is $=CH-$ or $=N-$;

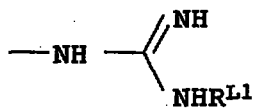
30

 Z^K is $=CH-$ or $=N-$;

L:



or



35

where

 R^{L1} is H or OH.

40

The present invention also relates to the following preferred novel compounds, their tautomers, physiologically tolerable salts and prodrugs of the formula A-B-D-E-G-K-L and drugs which contain these compounds. Furthermore, these compounds are suitable as particularly good complement inhibitors.

45

Here:

A is

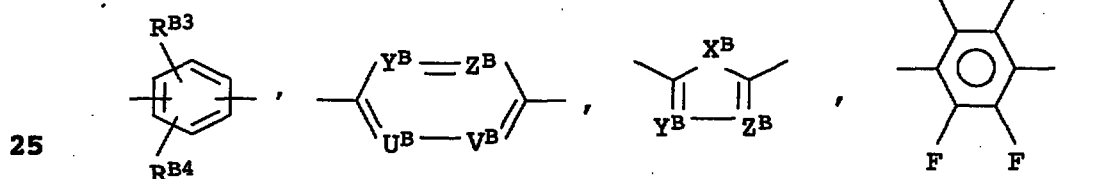
- H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, R^{A1}OCO (where R^{A1} is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₁₋₃-alkyl-C₃₋₈-cycloalkyl or C₁₋₃-alkylaryl), R^{A2}R^{A3}NCO (where R^{A2} is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; R^{A3} is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl), R^{A4}OCOR^{A2}, R^{A4}CONR^{A2} (where R^{A4} is C₁₋₆-alkyl or C₁₋₃-alkylaryl), R^{A1}O, phenoxy, R^{A2}R^{A3}N, HO-SO₂, R^{A2}R^{A3}N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P, NO₂, R^{A1}-N(OH)-CO- or R^{A1}R^{A2}NCONR^{A3}, where aryl in each case may be substituted by up to 2 identical or different substituents from the group consisting of F, Cl, Br, CH₃, CF₃, OCH₃ and NO₂;

B is

- (CH₂)_{1^B}-L^B-(CH₂)_{m^B}-, where

1^B is 0 or 1;
m^B is 0, 1 or 2;

- 20 L^B is



where, in each of the abovementioned ring systems, a phenyl ring can be fused on;

30

R^{B3} is H, C₁₋₆-alkyl, aryl, R^{B5}OCO (where R^{B5} is H, C₁₋₆-alkyl or C₁₋₃-alkylaryl), R^{B6}-O (where R^{B6} is H or C₁₋₆-alkyl), F, Cl, Br, NO₂ or CF₃;

- 35 R^{B4} is H, C₁₋₆-alkyl, R^{B6}-O, Cl, Br, F or CF₃;

X^B is O or S;

- 40 Y^B is =CH- or =N-;

Z^B is =CH- or =N-;

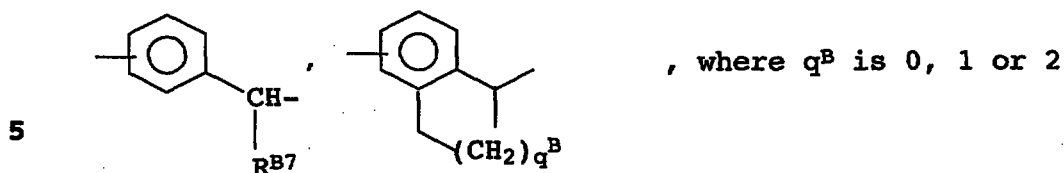
U^B is =CH- or =N-;

45

V^B is =CH- or =N-;

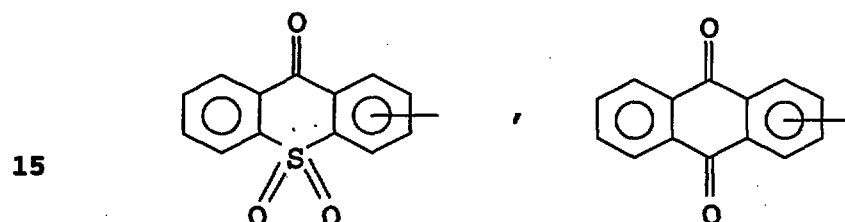
71

B may furthermore be



(R^{B7} is C_{1-6} -alkyl or C_{3-8} -cycloalkyl)

10 A-B may be



D is a single bond;

20 E is



where

30 R^{E1} is H;

35 R^{E2} is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, pyridyl, furyl, thienyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, where the abovementioned radicals may carry up to three identical or different substituents from the group consisting of $O-C_{1-6}$ -alkyl and F, or is $CH(CH_3)OH$ or $CH(CF_3)_2$;

40 R^{E3} is H;

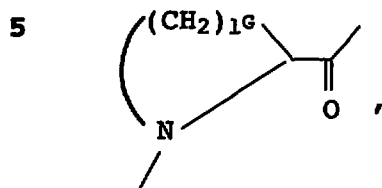
the groups stated under R^{E1} and R^{E2} may be linked to one another via a bond;

45 if it is asymmetrically substituted, the building block E is preferably present in the R configuration;

72

E may also be D-Lys, D-Orn, D-Dab, D-Dap or D-Arg;

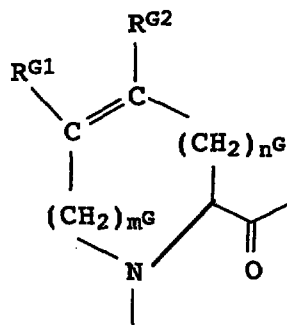
G is



where 1^G is 2 or 3, where a CH_2 group of the ring may be replaced by CHCH_3 ;

10

15



20 where

m^G is 1;

n^G is 0;

25 $RG1$ is H;

$RG2$ is H;

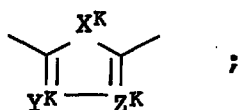
K is

30

$\text{NH}-(\text{CH}_2)_{n^K}-Q^K$, where

n^K is 1;

35 Q^K is



40 X^K is O or S;

Y^K is $=\text{CH}-$ or $=\text{N}-$;

45 Z^K is $=\text{CH}-$ or $=\text{N}-$;

73



5

where

 R^{L1} is -H or -OH.

- 10 If R^{L1} is not hydrogen in the compounds of the formula I, these substances are prodrugs from which the free amidine/guanidine compounds form under in vivo conditions. If the compounds of the formula I contain ester functions, these compounds can act in vivo as prodrugs from which the corresponding carboxylic acids
- 15 form.

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In addition to the substances stated in the examples, the following compounds are very particularly preferred and can be prepared by the stated preparation methods:

5	1.	$C_6H_5-C\equiv C-CO-(D)Cpg-Pyr-NH-CH_2-5-(3-am)-thioph$
	2.	$C_6H_5-C\equiv C-CO-(D)Ile-Pyr-NH-CH_2-5-(3-am)-thioph$
	3.	$C_6H_5-C\equiv C-CO-(D)allo-Ile-Pyr-NH-CH_2-5-(3-am)-thioph$
10	4.	$C_6H_5-C\equiv C-CO-(D)Pro-Pyr-NH-CH_2-5-(3-am)-thioph$
	5.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Thienyl))gly-Pyr-NH-CH_2-5-(3-am)-thioph$
	6.	$C_6H_5-C\equiv C-CO-(D)(2-(3-Thienyl))gly-Pyr-NH-CH_2-5-(3-am)-thioph$
15	7.	$C_6H_5-C\equiv C-CO-(D)Phg-Pyr-NH-CH_2-5-(3-am)-thioph$
	8.	$C_6H_5-C\equiv C-CO-(D)(2-Me)Chg-Pyr-NH-CH_2-5-(3-am)-thioph$
	9.	$C_6H_5-C\equiv C-CO-Aib-Pyr-NH-CH_2-5-(3-am)-thioph$
	10.	$C_6H_5-C\equiv C-CO-Acpc-Pyr-NH-CH_2-5-(3-am)-thioph$
20	11.	$C_6H_5-C\equiv C-CO-Achc-Pyr-NH-CH_2-5-(3-am)-thioph$
	12.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Furanyl))gly-Pyr-NH-CH_2-5-(3-am)-thioph$
	13.	$C_6H_5-C\equiv C-CO-(D)(N-Me)Val-Pyr-NH-CH_2-5-(3-am)-thioph$
	14.	$C_6H_5-C\equiv C-CO-(D)Nva-Pyr-NH-CH_2-5-(3-am)-thioph$
25	15.	$C_6H_5-C\equiv C-CO-(D)Thr-Pyr-NH-CH_2-5-(3-am)-thioph$
	16.	$C_6H_5-C\equiv C-CO-(D)(Tetrahydro-4-thiopyranyl)gly-Pyr-NH-CH_2-5-(3-am)-thioph$
	17.	$4-HOOC-C_6H_4-CH_2-(D)Cpg-Pyr-NH-CH_2-5-(3-am)-thioph$
30	18.	$4-HOOC-C_6H_4-CH_2-(D)2-(2-Thienyl)gly-Pyr-NH-CH_2-5-(3-am)-thioph$
	19.	$4-HOOC-C_6H_4-CH_2-(D)2-(3-Thienyl)gly-Pyr-NH-CH_2-5-(3-am)-thioph$
	20.	$4-HOOC-C_6H_4-CH_2-(D)Phg-Pyr-NH-CH_2-5-(3-am)-thioph$
	21.	$4-HOOC-C_6H_4-CH_2-(D)(2-Me)Chg-Pyr-NH-CH_2-5-(3-am)-thioph$
35	22.	$4-HOOC-C_6H_4-CH_2-Aib-Pyr-NH-CH_2-5-(3-am)-thioph$
	23.	$4-HOOC-C_6H_4-CH_2-Achc-Pyr-NH-CH_2-5-(3-am)-thioph$
	24.	$4-HOOC-C_6H_4-CH_2-(D)(2-(2-Furanyl))gly-Pyr-NH-CH_2-5-(3-am)-thioph$
40	25.	$4-HOOC-C_6H_4-CH_2-(D)Thr-Pyr-NH-CH_2-5-(3-am)-thioph$
	26.	$4-HOOC-C_6H_4-CH_2-(D)(Tetrahydro-4-thiopyranyl)gly-Pyr-NH-CH_2-5-(3-am)-thioph$
	27.	$C_6H_5-C\equiv C-CO-(D)Cpg-Pro-NH-CH_2-5-(3-am)-thioph$
	28.	$C_6H_5-C\equiv C-CO-(D)Ile-Pro-NH-CH_2-5-(3-am)-thioph$
45	29.	$C_6H_5-C\equiv C-CO-(D)allo-Ile-Pro-NH-CH_2-5-(3-am)-thioph$
	30.	$C_6H_5-C\equiv C-CO-(D)Pro-Pro-NH-CH_2-5-(3-am)-thioph$

5	31.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Thienyl))gly-Pro-NH-CH_2-5-(3-am)-thioph$
	32.	$C_6H_5-C\equiv C-CO-(D)(2-(3-Thienyl))gly-Pro-NH-CH_2-5-(3-am)-thioph$
	33.	$C_6H_5-C\equiv C-CO-(D)Phg-Pro-NH-CH_2-5-(3-am)-thioph$
	34.	$C_6H_5-C\equiv C-CO-(D)(2-Me)Chg-Pro-NH-CH_2-5-(3-am)-thioph$
	35.	$C_6H_5-C\equiv C-CO-Aib-Pro-NH-CH_2-5-(3-am)-thioph$
10	36.	$C_6H_5-C\equiv C-CO-Acpc-Pro-NH-CH_2-5-(3-am)-thioph$
	37.	$C_6H_5-C\equiv C-CO-Achc-Pro-NH-CH_2-5-(3-am)-thioph$
	38.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Furanyl))gly-Pro-NH-CH_2-5-(3-am)-thioph$
	39.	$C_6H_5-C\equiv C-CO-(D)(N-Me)Val-Pro-NH-CH_2-5-(3-am)-thioph$
	40.	$C_6H_5-C\equiv C-CO-(D)Abu-Pro-NH-CH_2-5-(3-am)-thioph$
15	41.	$C_6H_5-C\equiv C-CO-(D)Nva-Pro-NH-CH_2-5-(3-am)-thioph$
	42.	$C_6H_5-C\equiv C-CO-(D)Thr-Pro-NH-CH_2-5-(3-am)-thioph$
	43.	$C_6H_5-C\equiv C-CO-(D)(Tetrahydro-4-thiopyranyl)gly-Pro-NH-CH_2-5-(3-am)-thioph$
	44.	$C_6H_5-C\equiv C-CO-(D)Cpg-(3S)-3-MePro-NH-CH_2-5-(3-am)-thioph$
	45.	$C_6H_5-C\equiv C-CO-(D)Ile-L-(3S)-3-MePro-NH-CH_2-5-(3-am)-thioph$
20	46.	$C_6H_5-C\equiv C-CO-(D)2-(2-Thienyl)gly-((3S)-3-Me)Pro-NH-CH_2-5-(3-am)-thioph$
	47.	$C_6H_5-C\equiv C-CO-(D)2-(3-Thienyl)gly-((3S)-3-Me)Pro-NH-CH_2-5-(3-am)-thioph$
	48.	$C_6H_5-C\equiv C-CO-(D)Chg-((3S)-3-Me)Pro-NH-CH_2-5-(3-am)-thioph$
	49.	$C_6H_5-C\equiv C-CO-(D)(Tetrahydro-4-thiopyranyl)gly-((3S)-3-Me)-Pro-NH-CH_2-5-(3-am)-thioph$
	50.	$C_6H_5-C\equiv C-CO-(D)Cpg-(trans-4-F)Pro-NH-CH_2-5-(3-am)-thioph$
30	51.	$C_6H_5-C\equiv C-CO-(D)Val-(trans-4-F)Pro-NH-CH_2-5-(3-am)-thioph$
	52.	$C_6H_5-C\equiv C-CO-(D)2-(2-Thienyl)gly-(trans-4-F)Pro-NH-CH_2-5-(3-am)-thioph$
	53.	$C_6H_5-C\equiv C-CO-(D)2-(3-Thienyl)gly-(trans-4-F)Pro-NH-CH_2-5-(3-am)-thioph$
	54.	$C_6H_5-C\equiv C-CO-(D)Chg-(trans-4-F)Pro-NH-CH_2-5-(3-am)-thioph$
	55.	$C_6H_5-C\equiv C-CO-(D)Cpg-(cis-4-F)-Pro-NH-CH_2-5-(3-am)-thioph$
35	56.	$C_6H_5-C\equiv C-CO-(D)Val-(cis-4-F)Pro-NH-CH_2-5-(3-am)-thioph$
	57.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Thienyl))gly-(cis-4-F)Pro-NH-CH_2-5-(3-am)-thioph$
	58.	$C_6H_5-C\equiv C-CO-(D)(2-(3-Thienyl))gly-(cis-4-F)Pro-NH-CH_2-5-(3-am)-thioph$
	59.	$C_6H_5-C\equiv C-CO-(D)Chg-(cis-4-F)Pro-NH-CH_2-5-(3-am)-thioph$
	60.	$C_6H_5-C\equiv C-CO-(D)Cpg-(5-Me)Pro-NH-CH_2-5-(3-am)-thioph$
40	61.	$C_6H_5-C\equiv C-CO-(D)Val-(5-Me)Pro-NH-CH_2-5-(3-am)-thioph$
	62.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Thienyl))gly-(5-Me)Pro-NH-CH_2-5-(3-am)-thioph$

5	63.	$C_6H_5-C\equiv C-CO-(D)(2-(3-Thienyl))gly-(5-Me)Pro-NH-CH_2-5-(3-am)-thioph$
	64.	$C_6H_5-C\equiv C-CO-(D)Chg-(5-Me)Pro-NH-CH_2-5-(3-am)-thioph$
	65.	$C_6H_5-C\equiv C-CO-(D)Cpg-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
	66.	$C_6H_5-C\equiv C-CO-(D)Val-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
	67.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Thienyl))gly-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
10	68.	$C_6H_5-C\equiv C-CO-(D)(2-(3-Thienyl))gly-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
	69.	$C_6H_5-C\equiv C-CO-(D)Chg-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
	70.	$C_6H_5-C\equiv C-CO-(D)Cpg-Ohi-2-CO-NH-CH_2-5-(3-am)-thioph$
	71.	$C_6H_5-C\equiv C-CO-(D)Val-Ohi-2-CO-NH-CH_2-5-(3-am)-thioph$
15	72.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Thienyl))gly-Ohi-2-CO-NH-CH_2-5-(3-am)-thioph$
	73.	$C_6H_5-C\equiv C-CO-(D)(2-(3-Thienyl))gly-Ohi-2-CO-NH-CH_2-5-(3-am)-thioph$
	74.	$C_6H_5-C\equiv C-CO-(D)Chg-Ohi-2-CO-NH-CH_2-5-(3-am)-thioph$
	75.	$C_6H_5-C\equiv C-CO-(D)Cpg-Ind-2-CO-NH-CH_2-5-(3-am)-thioph$
20	76.	$C_6H_5-C\equiv C-CO-(D)Val-Ind-2-CO-NH-CH_2-5-(3-am)-thioph$
	77.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Thienyl))gly-Ind-2-CO-NH-CH_2-5-(3-am)-thioph$
	78.	$C_6H_5-C\equiv C-CO-(D)(2-(3-Thienyl))gly-Ind-2-CO-NH-CH_2-5-(3-am)-thioph$
25	79.	$C_6H_5-C\equiv C-CO-(D)Chg-Ind-2-CO-NH-CH_2-5-(3-am)-thioph$
	80.	$C_6H_5-C\equiv C-CO-(D)Cpg-Dhi-1-CO-NH-CH_2-5-(3-am)-thioph$
	81.	$C_6H_5-C\equiv C-CO-(D)Val-Dhi-1-CO-NH-CH_2-5-(3-am)-thioph$
30	82.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Thienyl))gly-Dhi-1-CO-NH-CH_2-5-(3-am)-thioph$
	83.	$C_6H_5-C\equiv C-CO-(D)(2-(3-Thienyl))gly-Dhi-1-CO-NH-CH_2-5-(3-am)-thioph$
	84.	$C_6H_5-C\equiv C-CO-(D)Chg-Dhi-1-CO-NH-CH_2-5-(3-am)-thioph$
35	85.	$C_6H_5-C\equiv C-CO-(D)Cpg-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
	86.	$C_6H_5-C\equiv C-CO-(D)Val-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
	87.	$C_6H_5-C\equiv C-CO-(D)(2-(2-Thienyl))gly-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
40	88.	$C_6H_5-C\equiv C-CO-(D)(2-(3-Thienyl))gly-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
	89.	$C_6H_5-C\equiv C-CO-(D)Chg-Ohi-1-CO-NH-CH_2-5-(3-am)-thioph$
	90.	$(D)HOOC-CH(CH_2-C_6H_5)-Gly-Pyr-NH-CH_2-5-(3-am)-thioph$
	91.	$HOOC-CH(CH_2-C_6H_5)-Gly-Pyr-NH-CH_2-5-(3-am)-thioph$
45	92.	$(D)HOOC-CH(CH_2-C_6H_5)-(D)Val-Pyr-NH-CH_2-5-(3-am)-thioph$
	93.	$HOOC-CH(CH_2-C_6H_5)-(D)Val-Pyr-NH-CH_2-5-(3-am)-thioph$
	94.	$(D)HOOC-CH(CH_2-C_6H_{10})-Gly-Pyr-NH-CH_2-5-(3-am)-thioph$
	95.	$HOOC-CH(CH_2-C_6H_{10})-Gly-Pyr-NH-CH_2-5-(3-am)-thioph$

5	96.	(D)HOOC-CH(CH ₂ -C ₆ H ₁₀)-(D)Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	97.	HOOC-CH(CH ₂ -C ₆ H ₁₀)-(D)Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	98.	(D)HOOC-CH(CH ₂ -C ₆ H ₅)-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	99.	HOOC-CH(CH ₂ -C ₆ H ₅)-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	100.	(D)HOOC-CH(CH ₂ -C ₆ H ₅)-(D)Val-Pro-NH-CH ₂ -5-(3-am)-thioph
10	101.	HOOC-CH(CH ₂ -C ₆ H ₅)-(D)Val-Pro-NH-CH ₂ -5-(3-am)-thioph
	102.	(D)HOOC-CH(CH ₂ -C ₆ H ₁₀)-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	103.	HOOC-CH(CH ₂ -C ₆ H ₁₀)-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	104.	(D)HOOC-CH(CH ₂ -C ₆ H ₁₀)-(D)Val-Pro-NH-CH ₂ -5-(3-am)-thioph
	105.	HOOC-CH(CH ₂ -C ₆ H ₁₀)-(D)Val-Pro-NH-CH ₂ -5-(3-am)-thioph
15	106.	(D)HOOC-CH(C ₆ H ₅)-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	107.	HOOC-CH(C ₆ H ₅)-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	108.	(D)HOOC-CH(C ₆ H ₁₀)-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	109.	HOOC-CH(C ₆ H ₁₀)-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	110.	(D)HOOC-CH(C ₆ H ₁₀)-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
20	111.	HOOC-CH(C ₆ H ₁₀)-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	112.	HOOC-(CH ₂) ₅ -(N-CH ₂ -C ₆ H ₅)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	113.	HOOC-(CH ₂) ₅ -(N-CH ₂ -C ₆ H ₁₀)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	114.	HOOC-(CH ₂) ₄ -(N-CH ₂ -C ₆ H ₅)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	115.	HOOC-(CH ₂) ₄ -(N-CH ₂ -C ₆ H ₁₀)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	116.	HOOC-(CH ₂) ₅ -(N-C ₆ H ₅)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	117.	HOOC-(CH ₂) ₅ -(N-C ₆ H ₁₀)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	118.	HOOC-(CH ₂) ₄ -(N-C ₆ H ₅)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	119.	HOOC-(CH ₂) ₄ -(N-C ₆ H ₁₀)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	120.	HOOC-(CH ₂) ₄ -SO ₂ -(N-CH ₂ -C ₆ H ₅)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	121.	HOOC-(CH ₂) ₄ -SO ₂ -(N-CH ₂ -C ₆ H ₁₀)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	122.	HOOC-(CH ₂) ₃ -SO ₂ -(N-CH ₂ -C ₆ H ₅)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	123.	HOOC-(CH ₂) ₃ -SO ₂ -(N-CH ₂ -C ₆ H ₁₀)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	124.	4-HOOC-C ₆ H ₄ -SO ₂ -Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	125.	3-HOOC-C ₆ H ₄ -SO ₂ -Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	126.	4-HOOC-C ₆ H ₄ -SO ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	127.	3-HOOC-C ₆ H ₄ -SO ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	128.	4-HOOC-C ₆ H ₄ -SO ₂ -Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	129.	3-HOOC-C ₆ H ₄ -SO ₂ -Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	130.	4-HOOC-C ₆ H ₄ -SO ₂ -D-Val-Pro-NH-CH ₂ -5-(3-am)-thioph
40	131.	3-HOOC-C ₆ H ₄ -SO ₂ -D-Val-Pro-NH-CH ₂ -5-(3-am)-thioph
	132.	MeHNOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	133.	H ₂ NO ₂ S-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	134.	BzHNO ₂ S-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	135.	5-Tetrazolyl-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph

	136.	HO-CH ₂ -p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	137.	HOOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(4-Me-3-am)-thioph
	138.	HOOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-Me-2-am)-thioph
5	139.	HOOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-3-(6-am)-pico
	140.	HOOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	141.	HOOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-fur
	142.	HOOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -2-(4-am)-thiaz
10	143.	HOOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am-4-Cl)-thioph
	144.	HOOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(2-am-3-Cl)-thioph
	145.	HOOC-p-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-fur
	146.	HOOC-m-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	147.	HOOC-m-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	148.	HOOC-m-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-3-(6-am)-pico
	149.	MeOOC-m-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	150.	H ₂ NCO-m-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	151.	HO ₃ S-m-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	152.	H ₂ NO ₂ S-m-C ₆ H ₄ CH ₂ -(D)Cha-Pyr-NH-CH ₂ -5-(2-am)-thioph
	153.	HO ₃ S-m-C ₆ H ₄ CH ₂ -(D)Cha-Pyr-NH-CH ₂ -5-(2-am)-thioph
	154.	(5-Tetrazolyl)-m-C ₆ H ₄ CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	155.	trans-(4-HOOC-C ₆ H ₁₀ CH ₂)-(D)Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	156.	HOOC-o-C ₆ H ₄ CH ₂ -Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	157.	4-Benzoyloxyphenyl-NH-C(O)-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	158.	4-Phenoxyphenyl-NH-C(O)-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	159.	4-(6'-Methyl-2'-benzothiazolyl)-phenyl-NH-C(O)-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	160.	MeOC(O)-(CH ₂) ₅ -NHC(O)-(D)-Ala-Pyr-5-(3-am)-thioph
	161.	4-Benzoyloxyphenyl-NH-C(O)-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	162.	4-Phenoxyphenyl-NH-C(O)-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	163.	4-(6'-Methyl-2'-benzothiazolyl)-phenyl-NH-C(O)-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	164.	MeOC(O)-(CH ₂) ₅ -NHC(O)-Gly-Pyr-5-(3-am)-thioph
	165.	4-Carboxybenzenesulfonyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	166.	3-Carboxybenzenesulfonyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	167.	4-Methyloxycarbonylbenzenesulfonyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	168.	3-Methyloxycarbonylbenzenesulfonyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	169.	4-Acetamidobenzenesulfonyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph

5	170.	3-Acetamidobenzenesulfonyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	171.	4-Phenylbenzenesulfonyl-(D)-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	172.	4-Carboxybenzenesulfonyl-(D)-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	173.	3-Carboxybenzenesulfonyl-(D)-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	174.	4-Methyloxycarbonylbenzenesulfonyl-(D)-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
10	175.	3-Methyloxycarbonylbenzenesulfonyl-(D)-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	176.	4-Acetamidobenzenesulfonyl-(D)-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	177.	3-Acetamidobenzenesulfonyl-(D)-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
15	178.	4-Carboxybenzenesulfonyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	179.	3-Carboxybenzenesulfonyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	180.	4-Methyloxycarbonylbenzenesulfonyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	181.	3-Methyloxycarbonylbenzenesulfonyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	182.	4-Acetamidobenzenesulfonyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	183.	3-Acetamidobenzenesulfonyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	184.	4-Phenylbenzenesulfonyl-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	185.	4-Carboxybenzenesulfonyl-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	186.	3-Carboxybenzenesulfonyl-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	187.	4-Methyloxycarbonylbenzenesulfonyl-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	188.	3-Methyloxycarbonylbenzenesulfonyl-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
30	189.	4-Acetamidobenzenesulfonyl-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	190.	3-Acetamidobenzenesulfonyl-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	191.	3-Benzoylbenzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	192.	4-Phenylbenzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	193.	4-Phenylphenylacetyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	194.	2-(Benzylthio)-benzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	195.	3-Phenylpropionyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	196.	4-Phenylbutyryl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	197.	5-Phenylvaleryl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	198.	(3-Phenyl)-acryloyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	199.	3-Benzoyloxycarbonylpropionyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	200.	3-(4-Methoxycarbonyl(-phenyl)-acryloyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	201.	4-Methoxycarbonylbenzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph

5	202.	6-(Acetylamino)-pyridyl-3-carbonyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	203.	3-(3'-Pyridyl)-acryloyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	204.	HOOC-p-C ₆ H ₄ -C≡C-CO-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	205.	HOOC-m-C ₆ H ₄ -C≡C-CO-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	206.	4-(4'-Aminophenoxy)-benzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
10	207.	3-(4'-Aminophenoxy)-benzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	208.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	209.	5-Phenylethynyl-nicotinoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	210.	4-Phenylethynyl-benzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	211.	3-Phenylethynyl-benzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	212.	3-Benzoylbenzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	213.	4-Benzoylbenzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	214.	4-Phenylbenzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	215.	4-Phenylphenylacetyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	216.	2-(Benzylthio)-benzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	217.	3-Phenylpropionyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	218.	4-Phenylbutyryl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	219.	5-Phenylvaleryl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	220.	Cinnamoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	221.	C ₆ H ₅ -C≡C-CO-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	222.	3-Benzoyloxycarbonylpropionyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	223.	4-Methoxycarbonylcinnamoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	224.	4-Methoxycarbonylbenzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	225.	6-(Acetylamino)-pyridyl-3-carbonyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	226.	3-(3'-Pyridyl)-acryloyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	227.	HOOC-p-C ₆ H ₄ -C≡C-CO-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	228.	HOOC-m-C ₆ H ₄ -C≡C-CO-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	229.	4-(4'-Aminophenoxy)-benzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	230.	3-(4'-Aminophenoxy)-benzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	231.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	232.	5-Phenylethynyl-nicotinoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	233.	4-Phenylethynyl-benzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	234.	3-Phenylethynyl-benzoyl-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	235.	3-Benzoylbenzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph

	236.	4-Phenylbenzoyl-(D)-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
	237.	4-Phenylphenylacetyl-(D)-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
	238.	4-Phenylphenylacetyl-(D)-Ala-Pro-NH-CH ₂ -5-(2-am)-thioph
5	239.	3-Benzoylbenzoyl-(D)-Ala-Pro-NH-CH ₂ -5-(2-am)-thioph
	240.	4-Benzoylbenzoyl-(D)-Ala-Pro-NH-CH ₂ -5-(2-am)-thioph
	241.	4-Phenylbenzoyl-(D)-Ala-Pro-NH-CH ₂ -5-(2-am)-thioph
	242.	3-Benzoylbenzoyl-(D)-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
10	243.	4-Phenylbenzoyl-(D)-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
	244.	4-Phenylphenylacetyl-(D)-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
	245.	3-(3'-Pyridyl)-acryloyl-(D)-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
	246.	4-(4'-Aminophenoxy)-benzoyl-(D)-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	247.	3-(4'-Aminophenoxy)-benzoyl-(D)-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
	248.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-(D)-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
	249.	3-Benzoylbenzoyl-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	250.	4-Benzoylbenzoyl-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
	251.	4-Phenylbenzoyl-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
	252.	4-Phenylphenylacetyl-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
	253.	C ₆ H ₅ -C≡C-CO-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	254.	3-Benzoylbenzoyl-(D)-Ala-Pyr-NH-3-(6-am)-pico
	255.	4-Benzoylbenzoyl-(D)-Ala-Pyr-NH-3-(6-am)-pico
	256.	4-Phenylbenzoyl-(D)-Ala-Pyr-NH-3-(6-am)-pico
	257.	4-Phenylphenylacetyl-(D)-Ala-Pyr-NH-3-(6-am)-pico
	258.	C ₆ H ₅ -C≡C-CO-(D)-Ala-Pyr-NH-3-(6-am)-pico
30	259.	3-Benzoylbenzoyl-(D)-Arg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	260.	4-Phenylphenylacetyl-(D)-Arg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	261.	3-Benzoylbenzoyl-Arg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	262.	4-Benzoylbenzoyl-Arg-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	263.	4-Phenylbenzoyl-Arg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	264.	4-Phenylphenylacetyl-Arg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	265.	C ₆ H ₅ -C≡C-CO-Arg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	266.	3-Benzoylbenzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	267.	4-Phenylbenzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	268.	4-Phenylphenylacetyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	269.	2-(Benzylthio)-benzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	270.	3-Phenylpropionyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	271.	4-Phenylbutyryl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	272.	5-Phenylvaleryl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	273.	Cinnamoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph

	274.	3-Benzoyloxycarbonylpropionyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	275.	4-Methoxycarbonylcinnamoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
5	276.	4-Methoxycarbonylbenzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	277.	6-(Acetylamino)-pyridyl-3-carbonyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	278.	3-(3'-Pyridyl)-acryloyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
10	279.	HOOC-p-C ₆ H ₄ -C≡C-CO-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	280.	HOOC-m-C ₆ H ₄ -C≡C-CO-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	281.	4-(4'-Aminophenoxy)-benzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	282.	3-(4'-Aminophenoxy)-benzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	283.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	284.	5-Phenylethynyl-nicotinoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	285.	4-Phenylethynyl-benzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	286.	3-Phenylethynyl-benzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	287.	3-Benzoylbenzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
	288.	4-Phenylbenzoyl-(D)-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
25	289.	4-Phenylphenylacetyl-(D)-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
	290.	4-Phenylphenylacetyl-(D)-Val-Pro-NH-CH ₂ -5-(2-am)-thioph
	291.	3-Benzoylbenzoyl-(D)-Val-Pro-NH-CH ₂ -5-(2-am)-thioph
	292.	4-Benzoylbenzoyl-(D)-Val-Pro-NH-CH ₂ -5-(2-am)-thioph
	293.	4-Phenylbenzoyl-(D)-Val-Pro-NH-CH ₂ -5-(2-am)-thioph
30	294.	C ₆ H ₅ -C≡C-CO-(D)-Lys-Pyr-NH-CH ₂ -5-(2-am)-thioph
	295.	3-Benzoylbenzoyl-(D)-Lys-Pyr-NH-CH ₂ -5-(3-am)-thioph
	296.	4-Phenylbenzoyl-(D)-Lys-Pyr-NH-CH ₂ -5-(3-am)-thioph
	297.	4-Phenylphenylacetyl-(D)-Lys-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	298.	3-(3'-Pyridyl)-acryloyl-(D)-Lys-Pyr-NH-CH ₂ -5-(3-am)-thioph
	299.	4-(4'-Aminophenoxy)-benzoyl-(D)-Lys-Pyr-NH-CH ₂ -5-(3-am)-thioph
	300.	3-(4'-Aminophenoxy)-benzoyl-(D)-Lys-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	301.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-(D)-Lys-Pyr-NH-CH ₂ -5-(3-am)-thioph
	302.	3-Benzoylbenzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	303.	4-Phenylbenzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	304.	4-Phenylphenylacetyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	305.	2-(Benzylthio)-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	306.	3-Phenylpropionyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph

	307.	4-Phenylbutyryl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	308.	5-Phenylvaleryl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	309.	(3-Phenyl)-acryloyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
5	310.	3-Benzoyloxycarbonylpropionyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	311.	3-(4-Methoxycarbonyl-phenyl)-acryloyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	312.	4-Methoxycarbonylbenzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
10	313.	6-(Acetylamino)-pyridyl-3-carbonyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	314.	3-(3'-Pyridyl)-acryloyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	315.	HOOC-p-C ₆ H ₄ -C≡C-CO-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	316.	HOOC-m-C ₆ H ₄ -C≡C-CO-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	317.	4-(4'-Aminophenoxy)-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	318.	3-(4'-Aminophenoxy)-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	319.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	320.	5-Phenylethynyl-nicotinoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	321.	4-Phenylethynyl-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	322.	3-Phenylethynyl-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	323.	HOOC-p-C ₆ H ₄ -C≡C-CO-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	324.	HOOC-m-C ₆ H ₄ -C≡C-CO-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
25	325.	5-Phenylethynyl-nicotinoyl-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	326.	4-Phenylethynyl-benzoyl-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	327.	3-Phenylethynyl-benzoyl-Gly-Pro-NH-CH ₂ -5-(3-am)-thioph
	328.	3-Benzoylbenzoyl-(D)-Val-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	329.	4-Benzoylbenzoyl-(D)-Val-Pyr-NH-CH ₂ -2-(4-am)-thiaz
30	330.	4-Phenylbenzoyl-(D)-Val-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	331.	4-Phenylphenylacetyl-(D)-Val-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	332.	3-Benzoylbenzoyl-(D)-Ala-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	333.	4-Benzoylbenzoyl-(D)-Ala-Pyr-NH-CH ₂ -2-(4-am)-thiaz
35	334.	4-Phenylbenzoyl-(D)-Ala-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	335.	4-Phenylphenylacetyl-(D)-Ala-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	336.	3-Benzoylbenzoyl-Gly-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	337.	4-Benzoylbenzoyl-Gly-Pyr-NH-CH ₂ -2-(4-am)-thiaz
40	338.	4-Phenylbenzoyl-Gly-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	339.	4-Phenylphenylacetyl-Gly-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	340.	3-Benzoylbenzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	341.	4-Benzoylbenzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	342.	4-Phenylbenzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	343.	4-Phenylphenylacetyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	344.	2-(Benzylthio)-benzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph

	345.	3-Phenylpropionyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	346.	4-Phenylbutyryl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	347.	5-Phenylvaleryl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
5	348.	(3-Phenyl)-acryloyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	349.	C ₆ H ₅ -C≡C-CO-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	350.	3-Benzoyloxycarbonylpropionyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	351.	3-(4-Methoxycarbonyl-phenyl)-acryloyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
10	352.	4-Methoxycarbonylbenzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	353.	6-(Acetylamino)-pyridine-3-carbonyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	354.	3-(3'-Pyridyl)-acryloyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	355.	HOOC-p-C ₆ H ₄ -C≡C-CO-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	356.	HOOC-m-C ₆ H ₄ -C≡C-CO-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	357.	4-(4'-Aminophenoxy)-benzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	358.	3-(4'-Aminophenoxy)-benzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	359.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	360.	5-Phenylethynyl-nicotinoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	361.	4-Phenylethynyl-benzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	362.	3-Phenylethynyl-benzoyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	363.	3-Benzoylbenzoyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
	364.	4-Phenylbenzoyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
	365.	4-Phenylphenylacetyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
	366.	3-Phenylpropionyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	367.	4-Phenylbutyryl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
	368.	5-Phenylvaleryl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
	369.	3-Benzoyloxycarbonylpropionyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
	370.	6-(Acetylamino)-pyridyl-3-carbonyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	371.	3-(3'-Pyridyl)-acryloyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
	372.	4-(4'-Aminophenoxy)-benzoyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
	373.	3-(4'-Aminophenoxy)-benzoyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
	374.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	375.	3-Benzoylbenzoyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
	376.	4-Benzoylbenzoyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
	377.	4-Phenylbenzoyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
	378.	4-Phenylphenylacetyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
45	379.	3-Phenylpropionyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
	380.	4-Phenylbutyryl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
	381.	5-Phenylvaleryl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph

	382.	$C_6H_5-C\equiv C-CO-Sar-Pro-NH-CH_2-5-(3-am)-thioph$
	383.	3-Benzylloxycarbonylpropionyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
5	384.	6-(Acetylamino)-pyridine-3-carbonyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
	385.	3-(3'-Pyridyl)-acryloyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
	386.	4-(4'-Aminophenoxy)-benzoyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
	387.	3-(4'-Aminophenoxy)-benzoyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
10	388.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-Sar-Pro-NH-CH ₂ -5-(3-am)-thioph
	389.	3-Benzoylbenzoyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	390.	4-Benzoylbenzoyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	391.	4-Phenylbenzoyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	392.	4-Phenylphenylacetyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	393.	3-Phenylpropionyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	394.	4-Phenylbutyryl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	395.	5-Phenylvaleryl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	396.	$C_6H_5-C\equiv C-CO-(D)-(N-Me)Ala-Pyr-NH-CH_2-5-(3-am)-thioph$
	397.	3-Benzylloxycarbonylpropionyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	398.	6-(Acetylamino)-pyridyl-3-carbonyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	399.	3-(3'-Pyridyl)-acryloyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	400.	4-(4'-Aminophenoxy)-benzoyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	401.	3-(4'-Aminophenoxy)-benzoyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	402.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-(D)-(N-Me)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	403.	3-Benzoylbenzoyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	404.	4-Benzoylbenzoyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
35	405.	4-Phenylbenzoyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	406.	4-Phenylphenylacetyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	407.	3-Phenylpropionyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
40	408.	4-Phenylbutyryl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	409.	5-Phenylvaleryl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	410.	$C_6H_5-C\equiv C-CO-(D)-(N-Me)Ala-Pro-NH-CH_2-5-(3-am)-thioph$
	411.	3-Benzylloxycarbonylpropionyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
45	412.	6-(Acetylamino)-pyridyl-3-carbonyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph

5	413.	3-(3'-Pyridyl)-acryloyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	414.	4-(4'-Aminophenoxy)-benzoyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	415.	3-(4'-Aminophenoxy)-benzoyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	416.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-(D)-(N-Me)Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
10	417.	3-Benzoylbenzoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	418.	Cinnamoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	419.	C ₆ H ₅ -C≡C-CO-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	420.	3-Benzoyloxycarbonylpropionyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
15	421.	4-Methoxycarbonylcinnamoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	422.	4-Methoxycarbonylbenzoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	423.	6-(Acetylamino)-pyridyl-3-carbonyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	424.	3-(3'-Pyridyl)-acryloyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
20	425.	HOOC-p-C ₆ H ₄ -C≡C-CO-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	426.	HOOC-m-C ₆ H ₄ -C≡C-CO-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	427.	4-(4'-Aminophenoxy)-benzoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	428.	3-(4'-Aminophenoxy)-benzoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
25	429.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	430.	5-Phenylethynyl-nicotinoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	431.	4-Phenylethynyl-benzoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
	432.	3-Phenylethynyl-benzoyl-β-Ala-Pro-NH-CH ₂ -5-(3-am)-thioph
30	433.	3-Benzoylbenzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	434.	4-Phenylbenzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	435.	4-Phenylphenylacetyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	436.	2-(Benzylthio)-benzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	437.	3-Phenylpropionyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	438.	4-Phenylbutyryl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	439.	5-Phenylvaleryl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	440.	3-Benzoyloxycarbonylpropionyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	441.	4-Methoxycarbonylcinnamoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	442.	4-Methoxycarbonylbenzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	443.	6-(Acetylamino)-pyridyl-3-carbonyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	444.	3-(3'-Pyridyl)-acryloyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	445.	HOOC-p-C ₆ H ₄ -C≡C-CO-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph

	446.	HOOC-m-C ₆ H ₄ -C≡C-CO-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	447.	4-(4'-Aminophenoxy)-benzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
5	448.	3-(4'-Aminophenoxy)-benzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	449.	4-(2'-Chloro-4'-aminophenoxy)-benzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	450.	5-Phenylethynyl-nicotinoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
10	451.	4-Phenylethynyl-benzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	452.	3-Phenylethynyl-benzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	453.	4-HOOC-C ₆ H ₄ -CH ₂ -(D)Cpg-Dhi-1-CO-NH-CH ₂ -5-(3-am)-thioph
	454.	4-HOOC-C ₆ H ₄ -CH ₂ -(D)Cpg-Ohi-1-CO-NH-CH ₂ -5-(3-am)-thioph
15	455.	4-HOOC-C ₆ H ₄ -CH ₂ -(D)Cpg-(5-Me)Pro-NH-CH ₂ -5-(3-am)-thioph
	456.	4-HOOC-C ₆ H ₄ -CH ₂ -(D)Cpg-cis-(4-F)Pro-NH-CH ₂ -5-(3-am)-thioph
	457.	4-HOOC-C ₆ H ₄ -CH ₂ -(D)Cpg-trans-(4-F)Pro-NH-CH ₂ -5-(3-am)-thioph
	458.	4-HOOC-C ₆ H ₄ -CH ₂ -(D)Cpg-(3S)(3-Me)Pro-NH-CH ₂ -5-(3-am)-thioph
20	459.	4-HOOC-C ₆ H ₄ -CH ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	460.	4-HOOC-C ₆ H ₄ -CH(CH ₃)-(D)Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	461.	4-HOOC-C ₆ H ₄ -CO-(D)Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	462.	4-HOOC-C ₆ H ₄ -CH(CH ₃)-(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	463.	4-HOOC-C ₆ H ₄ -CH ₂ -(N-Me)(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	464.	4-HOOC-C ₆ H ₄ -C(CH ₃) ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	465.	4-HOOC-3-Me-C ₆ H ₄ -CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	466.	4-HOOC-2-Me-C ₆ H ₄ -CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	467.	4-HOOC-CH ₂ -C ₆ H ₄ -CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	468.	3-HOOC-CH ₂ -C ₆ H ₄ -CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	469.	4-HOOC-C ₆ H ₄ -CH(CH ₃)-(D)Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	470.	4-HOOC-C ₆ H ₄ -CH ₂ -(N-Me)(D)Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	471.	4-HOOC-C ₆ H ₄ -C(CH ₃) ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	472.	4-HOOC-3-Me-C ₆ H ₄ -CH ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	473.	4-HOOC-2-Me-C ₆ H ₄ -CH ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	474.	4-HOOC-CH ₂ -C ₆ H ₄ -CH ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	475.	3-HOOC-CH ₂ -C ₆ H ₄ -CH ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	476.	4-HOOC-C ₆ H ₄ -CH(CH ₃)-(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	477.	4-HOOC-C ₆ H ₄ -CH ₂ -(N-Me)(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	478.	4-HOOC-C ₆ H ₄ -C(CH ₃) ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	479.	4-HOOC-3-Me-C ₆ H ₄ -CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	480.	4-HOOC-2-Me-C ₆ H ₄ -CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-thioph
45	481.	4-HOOC-CH ₂ -C ₆ H ₄ -CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	482.	3-HOOC-CH ₂ -C ₆ H ₄ -CH ₂ -(D)Chg-Pyr-NH-CH ₂ -5-(2-am)-thioph

	483.	4-HOOC-C ₆ H ₄ -CH(CH ₃)-(D)Cpg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	484.	4-HOOC-C ₆ H ₄ -CH ₂ -(N-Me)(D)Cpg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	485.	4-HOOC-C ₆ H ₄ -C(CH ₃) ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(2-am)-thioph
5	486.	4-HOOC-3-Me-C ₆ H ₄ -CH ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	487.	4-HOOC-2-Me-C ₆ H ₄ -CH ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	488.	4-HOOC-CH ₂ -C ₆ H ₄ -CH ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(2-am)-thioph
	489.	3-HOOC-CH ₂ -C ₆ H ₄ -CH ₂ -(D)Cpg-Pyr-NH-CH ₂ -5-(2-am)-thioph
10	490.	HOOC-p-C ₆ H ₄ -CH(CH ₃)-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	491.	HOOC-p-C ₆ H ₄ -(CH ₂) ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	492.	HOOC-p-CH ₂ -C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	493.	p-Carboxy-tetrafluorobenzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	494.	p-Carboxy-2'-F-benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	495.	p-Carboxy-2'-methoxy-benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	496.	p-Carboxy-3'-methoxy-benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	497.	H ₂ O ₃ P-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	498.	5-COOH-Indan-1-yl-D-Val-Pyr-NH-5-(3-am)-thioph
	499.	6-COOH-Indan-1-yl-D-Val-Pyr-NH-5-(3-am)-thioph
	500.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-4-amb
25	501.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
	502.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -4-(2-am)-thioph
	503.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-3-(6-am)pico
	504.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(2-am)-fur
	505.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-am-4-Cl)-thioph
	506.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(2-am-3-Cl)-thioph
30	507.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	508.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -2-(5-am)-thiaz
	509.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(2-am)-thiaz
	510.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -4-(2-am)-thiaz
	511.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-am-4-Me)-thioph
35	512.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(2-am-4-Me)-thioph
	513.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -2-(4-guan)-thiaz
	514.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -2-(5-guan)-thiaz
	515.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-guan)-thioph
	516.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(2-guan)-thioph
	517.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-(4-guan)benzyl
40	518.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-(CH ₂) ₄ -am
	519.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-(CH ₂) ₅ -am
	520.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-(CH ₂) ₃ -am
	521.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-(CH ₂) ₄ -guan
	522.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-(CH ₂) ₅ -guan
45	523.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-(CH ₂) ₃ -guan
	524.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-3-amb
	525.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-C(NHCH ₃)=NCH ₃)-thioph
	526.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-C(NH ₂)=NCH ₃)-thioph

	527.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Pic-NH-CH ₂ -5-(3-am)-thioph
	528.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Aze-NH-CH ₂ -5-(3-am)-thioph
	529.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-N-Me-Ala-NH-CH ₂ -5-(3-am)-thioph
	530.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-4,4-difluoro-Pro-NH-CH ₂ -5-(3-am)-thioph
5	531.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Val-Thz-4-CO-NH-CH ₂ -5-(3-am)-thioph
	532.	HOOC-p-C ₆ H ₄ -CH ₂ -D-(2-CF ₃)Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
	533.	HOOC-p-C ₆ H ₄ -CH ₂ -D-(3-CF ₃)Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	534.	HOOC-p-C ₆ H ₄ -CH ₂ -D-3,3-(CF ₃) ₂ -Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	535.	HOOC-p-C ₆ H ₄ -CH ₂ -D-2-Methyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	536.	(p-CH ₃)-Benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
10	537.	(p-Ethyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	538.	(p-Propyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	539.	(p-Butyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	540.	(p-Isopropyl)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	541.	(p-tBu)Benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	542.	(p-Pentyl)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	543.	(p-Hexyl)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	544.	(p-Trifluoromethyl)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	545.	(o-Methyl)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	546.	(o-Trifluoromethyl)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	547.	(o-Methoxy)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	548.	(o-Dimethyl)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	549.	(o-Dimethoxy)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	550.	(p-Methoxy)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	551.	(p-Ethoxy)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	552.	(p-Propoxy)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	553.	(p-Isopropoxy)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	554.	(p-Butyloxy)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	555.	(p-tert-Butoxy)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	556.	(p-Aminomethyl)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	557.	2,6-Dichlorophenyl-CH ₂ CO-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	558.	2,6-Dichlorophenyl-CH ₂ CO-D-Ile-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	559.	2,6-Dichlorophenyl-CH ₂ CO-D-allo-Ile-Pyr-NH-CH ₂ -5-(3-am)-thioph
	560.	2,6-Dichlorophenyl-CH ₂ CO-D-tLeu-Pyr-NH-CH ₂ -5-(3-am)-thioph
	561.	2,6-Dichlorophenyl-CH ₂ CO-D-hexafluoro-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	562.	2,6-Dichlorophenyl-CH ₂ CO-D-Thr-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	563.	2,6-Dichlorophenyl-CH ₂ CO-D-Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	564.	2,6-Dichlorophenyl-CH ₂ CO-D-2-methyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	565.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-4-amb
	566.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
40	567.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-3-(6-am)pico
	568.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(2-am)-fur
	569.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am-4-Cl)-thioph
	570.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(2-am-3-Cl)-thioph
45	571.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -2-(4-am)-thiaz
	572.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -2-(5-am)-thiaz
	573.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thiaz

	574.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -4-(2-am)-thiaz
	575.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -2-(4-guan)-thiaz
	576.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -2-(5-guan)-thiaz
	577.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-guan)-thioph
5	578.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(2-guan)-thioph
	579.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -4-(2-am)-thioph
	580.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-(4-guan)benzyl
	581.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-(CH ₂) ₄ -am
	582.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-(CH ₂) ₅ -am
	583.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-(CH ₂) ₃ -am
10	584.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-(CH ₂) ₄ -guan
	585.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-(CH ₂) ₅ -guan
	586.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-(CH ₂) ₃ -guan
	587.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-3-amb
	588.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-C(NHCH ₃)=NCH ₃)-thioph
15	589.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-C(NH ₂)=NCH ₃)-thioph
	590.	1R-Indanyl-D-Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	591.	1R-Indanyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	592.	1R-Indanyl-D-Thr-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	593.	1R-Indanyl-D-allo-Ile-Pyr-NH-CH ₂ -5-(3-am)-thioph
	594.	1R-Indanyl-D-tLeu-Pyr-NH-CH ₂ -5-(3-am)-thioph
	595.	1R-Indanyl-D-hexafluoro-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	596.	1R-Indanyl-D-2-methyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	597.	1R-Indanyl-CO-D-Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	598.	1R-Indanyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	599.	1R-Indanyl-CO-D-allo-Ile-Pyr-NH-CH ₂ -5-(3-am)-thioph
	600.	1R-Indanyl-CO-D-tLeu-Pyr-NH-CH ₂ -5-(3-am)-thioph
	601.	1S-Indanyl-D-Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	602.	1S-Indanyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	603.	1S-Indanyl-D-Thr-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	604.	1S-Indanyl-D-allo-Ile-Pyr-NH-CH ₂ -5-(3-am)-thioph
	605.	1S-Indanyl-D-tLeu-Pyr-NH-CH ₂ -5-(3-am)-thioph
	606.	1S-Indanyl-D-hexafluoro-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	607.	1S-Indanyl-D-2-methyl-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	608.	1S-Indanyl-CO-D-Cpg-Pyr-NH-CH ₂ -5-(3-am)-thioph
	609.	1S-Indanyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	610.	1S-Indanyl-CO-D-allo-Ile-Pyr-NH-CH ₂ -5-(3-am)-thioph
	611.	1S-Indanyl-CO-D-tLeu-Pyr-NH-CH ₂ -5-(3-am)-thioph
	612.	(5,6-Dimethyl)-1-indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	613.	(5,7-Dimethyl)-1-indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	614.	(p-Aminomethyl)-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	615.	(o-Carboxy)-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	616.	(m-Carboxy)-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	617.	(p-Carboxy)-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	618.	(p-Carboxy-methyl)-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	619.	Indanyl(2)-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	620.	(2,4,6-Trimethoxy)-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	621.	Tetrahydronaphthyl(1S)-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	622.	Tetrahydronaphthyl(1R)-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	623.	2,6-Dibromophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph

	624.	2,6-Ditrifluoromethyl-phenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	625.	3-Indolyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	626.	N-methyl-3-indolyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
5	627.	3-Benzothienyl- CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	628.	(5-Carboxy)-1R-indanyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	629.	(6-Carboxy)-1R-indanyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	630.	(4-Carboxy-2,6-dichloro)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	631.	(5-Carboxy)-1S-indanyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
10	632.	(6-Carboxy)-1S-indanyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	633.	(5-Carboxy)-1R-indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	634.	(6-Carboxy)-1R-indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	635.	(5-Carboxy)-1S-indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	636.	(6-Carboxy)-1S-indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	637.	(p-CH ₃)-Benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	638.	(p-Ethyl)-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	639.	(p-Propyl)-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	640.	(p-Butyl)-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	641.	(p-Isopropyl)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	642.	(p-tBu)Benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	643.	(p-Pentyl)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	644.	(p-Hexyl)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	645.	(p-Trifluoromethyl)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	646.	(o-Methyl)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	647.	(o-Trifluoromethyl)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	648.	(o-Methoxy)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	649.	(o-Dimethyl)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	650.	(o-Dimethoxy)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	651.	(p-Methoxy)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	652.	(p-Ethoxy)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	653.	(p-Propoxy)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	654.	(p-Isopropoxy)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	655.	(p-Butoxy)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	656.	(p-tert-Butoxy)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	657.	(p-CN)-Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	658.	(p-Dimethylamino)-benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	659.	(p-Methoxy)-benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	660.	(p-Ethoxy)-benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	661.	(p-Propyloxy)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	662.	(p-Isopropyloxy)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	663.	(p-Butoxy)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	664.	(p-tert-Butoxy)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	665.	(p-Pentoxy)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	666.	(p-Trifluoromethyl)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	667.	(p-Ethyl)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	668.	(p-Propyl)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	669.	(p-Butyl)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	670.	(p-tert-Butyl)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	671.	(p-Pentyl)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	672.	(p-Hexyl)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	673.	(p-MeSO ₂)Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph

	674.	(p-Nitro)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	675.	(p-Carboxy)benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	676.	(p-Carboxy)benzyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	677.	(p-Carboxy)benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
5	678.	(p-Carboxy)benzyl-D-Nva-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	679.	(p-Carboxy)benzyl-D-tLeu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	680.	(p-Carboxy)benzyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	681.	(p-Carboxy)benzyl-D-allo-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	682.	(p-Carboxy)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	683.	(p-Carboxy)benzyl-D-Cpg-Pyr-NH-CH ₂ -5-(3-ham)-thioph
10	684.	2,6-Dichlorobenzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	685.	2,6-Dichlorobenzyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	686.	2,6-Dichlorobenzyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	687.	2,6-Dichlorobenzyl-CO-D-Nva-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	688.	2,6-Dichlorobenzyl-CO-D-tLeu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
15	689.	2,6-Dichlorobenzyl-CO-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	690.	2,6-Dichlorobenzyl-CO-D-allo-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	691.	2,6-Dichlorobenzyl-CO-D-Cpg-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	692.	p-Benzoyl-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	693.	(p-Phenyl-NH-CO-NH)benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	694.	2,4,6-Trimethyl-benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
20	695.	Benzhydryl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	696.	(p-Carboxy)benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	697.	(p-COOMe)Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	698.	(p-COOEt)Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	699.	(p-COOPr)Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
25	700.	(p-COOiPr)Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	701.	(p-COOtBu)Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	702.	(p-COOCyclohexyl)Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	703.	(p-COOCyclopentyl)Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	704.	(p-COOMe)Benzyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	705.	(p-COOEt)Benzyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
30	706.	(p-COOPr)Benzyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	707.	(p-COOiPr)Benzyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	708.	(p-COOtBu)Benzyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	709.	(p-COOCyclohexyl)benzyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	710.	(p-COOCyclopentyl)benzyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
35	711.	(p-COOMe)Benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	712.	(p-COOEt)Benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	713.	(p-COOPr)Benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	714.	(p-COOiPr)Benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	715.	(p-COOtBu)Benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	716.	(p-COOCyclohexyl)benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
40	717.	(p-COOCyclopentyl)benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	718.	(p-COOMe)Benzyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	719.	(p-COOEt)Benzyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	720.	(p-COOPr)Benzyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	721.	(p-COOiPr)Benzyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
45	722.	(p-COOtBu)Benzyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	723.	(p-COOCyclohexyl)benzyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	724.	(p-COOCyclopentyl)benzyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	725.	(p-COOMe)Benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph

	726.	(p-COOEt) Benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	727.	(p-COOPr) Benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	728.	(p-COOiPr) Benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	729.	(p-COOtBu) Benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
5	730.	(p-COOCyclohexyl) benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	731.	(p-COOCyclopentyl) benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	732.	(p-COOMe) Benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	733.	(p-COOEt) Benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	734.	(p-COOPr) Benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	735.	(p-COOiPr) Benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
10	736.	(p-COOtBu) Benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	737.	(p-COOCyclohexyl) benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	738.	(p-COOCyclopentyl) benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	739.	(p-COOMe) Benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	740.	(p-COOEt) Benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
15	741.	(p-COOPr) Benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	742.	(p-COOiPr) Benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	743.	(p-COOtBu) Benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	744.	(p-COOCyclohexyl) benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	745.	(p-COOCyclopentyl) benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	746.	(p-COOMe) Benzoyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
20	747.	(p-COOEt) Benzoyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	748.	(p-COOPr) Benzoyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	749.	(p-COOiPr) Benzoyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	750.	(p-COOtBu) Benzoyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	751.	(p-COOCyclohexyl) benzoyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
25	752.	(p-COOCyclopentyl) benzoyl-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	753.	(p-COOMe) Benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	754.	(p-COOEt) Benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	755.	(p-COOPr) Benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	756.	(p-COOiPr) Benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	757.	(p-COOtBu) Benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
30	758.	(p-COOCyclohexyl) benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	759.	(p-COOCyclopentyl) benzyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	760.	(p-COOMe) Benzyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	761.	(p-COOEt) Benzyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	762.	(p-COOPr) Benzyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
35	763.	(p-COOiPr) Benzyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	764.	(p-COOtBu) Benzyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	765.	(p-COOCyclohexyl) benzyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	766.	(p-COOCyclopentyl) benzyl-CO-D-Ala-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	767.	(p-COOMe) Benzyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	768.	(p-COOEt) Benzyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
40	769.	(p-COOPr) Benzyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	770.	(p-COOiPr) Benzyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	771.	(p-COOtBu) Benzyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	772.	(p-COOCyclohexyl) benzyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	773.	(p-COOCyclopentyl) benzyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-ham)-thioph
45	774.	(p-COOMe) Benzyl-CO-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	775.	(p-COOEt) Benzyl-CO-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph

	776.	(p-COOPr)Benzyl-CO-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	777.	(p-COOiPr)Benzyl-CO-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	778.	(p-COOtBu)Benzyl-CO-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	779.	(p-COOCyclohexyl)benzyl-CO-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
5	780.	(p-COOCyclopentyl)benzyl-CO-D-Ile-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	781.	5-EtOOC-1R-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	782.	6-EtOOC-1R-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	783.	5-EtOOC-1R-Indanyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	784.	6-EtOOC-1R-Indanyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
10	785.	5-EtOOC-1S-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	786.	6-EtOOC-1S-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	787.	5-EtOOC-1S-Indanyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	788.	6-EtOOC-1S-Indanyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph
	789.	4-(Benzylamino-methyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	790.	4-(Cyclohexylmethylamino-methyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	791.	4-(Isobutylamino-methyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	792.	4-(Isopropylamino-methyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	793.	4-(Benzylamino-methyl)-benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	794.	4-(Cyclohexylmethylamino-methyl)-benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	795.	4-(Isobutylamino-methyl)-benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	796.	4-(Isopropylamino-methyl)-benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	797.	4-(Cyclohexylmethylamino-methyl)-benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
	798.	4-(Benzylamino-methyl)-benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	799.	3-(Benzylamino-methyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	800.	3-(Cyclohexylmethylamino-methyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	801.	3-(Isobutylamino-methyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	802.	3-(Isopropylamino-methyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	803.	3-(Benzylamino-methyl)-benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	804.	3-(Cyclohexylmethylamino-methyl)-benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	805.	3-(Isobutylamino-methyl)-benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	806.	3-(Isopropylamino-methyl)-benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	807.	4-(Benzylamino-methyl)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
45	808.	4-(Cyclohexylmethylamino-methyl)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
	809.	4-(Isobutylamino-methyl)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph

5	810.	4-(Isopropylamino-methyl)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
	811.	4-(Benzylamino-methyl)-phenylacetyl-D-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
	812.	4-(Cyclohexylmethylamino-methyl)-phenylacetyl-D-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
	813.	4-(Isobutylamino-methyl)-phenylacetyl-D-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
	814.	4-(Isopropylamino-methyl)-phenylacetyl-D-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
10	815.	4-(Benzylamino-methyl)-phenylacetyl-D-Abu-Pyr-NH-CH ₂ -5-(2-am)-thioph
	816.	4-(Cyclohexylmethylamino-methyl)-phenylacetyl-D-Abu-Pyr-NH-CH ₂ -5-(2-am)-thioph
	817.	4-(Benzylamino-methyl)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
15	818.	4-(Cyclohexylmethylamino-methyl)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	819.	4-(Isobutylamino-methyl)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	820.	4-(Isopropylamino-methyl)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
20	821.	4-(Benzylamino-methyl)-phenylacetyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	822.	4-(Cyclohexylmethylamino-methyl)-phenylacetyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	823.	4-(Isobutylamino-methyl)-phenylacetyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
25	824.	4-(Isopropylamino-methyl)-phenylacetyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	825.	4-(Benzylamino-methyl)-phenylacetyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
	826.	4-(Cyclohexylmethylamino-methyl)-phenylacetyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
30	827.	3-[4-(Benzylamino-methyl)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	828.	3-[4-(Cyclohexylmethylamino-methyl)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	829.	3-[4-(Isobutylamino-methyl)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
35	830.	3-[4-(Isopropylamino-methyl)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
	831.	3-[4-(Benzylamino-methyl)-phenyl]-propionyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	832.	3-[4-(Cyclohexylmethylamino-methyl)-phenyl]-propionyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
40	833.	3-[4-(Isobutylamino-methyl)-phenyl]-propionyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	834.	3-[4-(Isopropylamino-methyl)-phenyl]-propionyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
	835.	3-[4-(Benzylamino-methyl)-phenyl]-propionyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
45	836.	3-[4-(Isopropylamino-methyl)-phenyl]-propionyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
	837.	3-[4-(Cyclohexylmethylamino-methyl)-phenyl]-propionyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph

5	838.	3-[4-(Benzylamino-methyl)-phenyl]-propionyl-D-Abu-Pyr-NH-CH ₂ -5-(2-am)-thioph
	839.	3-[4-(Isopropylamino-methyl)-phenyl]-propionyl-D-Abu-Pyr-NH-CH ₂ -5-(2-am)-thioph
	840.	3-[4-(Cyclohexylmethylamino-methyl)-phenyl]-propionyl-D-Abu-Pyr-NH-CH ₂ -5-(2-am)-thioph
	841.	3-[4-(Benzylamino-methyl)-phenyl]-propionyl-D-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
	842.	3-[4-(Isopropylamino-methyl)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph

10 List of abbreviations:

	Abu:	2-Aminobutyric acid
	AIBN:	Azobisisobutyronitrile
	Ac:	Acetyl
15	Acpc:	1-Aminocyclopentane-1-carboxylic acid
	Achc:	1-Aminocyclohexane-1-carboxylic acid
	Aib:	2-Aminoisobutyric acid
	Ala:	Alanine
	β-Ala:	β-Alanine(3-Aminopropionic acid)
20	am:	Amidino
	amb:	Amidinobenzyl
	4-amb:	4-Amidinobenzyl (p-amidinobenzyl)
	Arg:	Arginine
	Asp:	Aspartic acid
25	Aze:	Azetidine-2-carboxylic acid
	Bn:	Benzyl
	Boc:	tert-Butoxycarbonyl
	Bu:	Butyl
	Cbz:	Benzyloxycarbonyl
30	Cha:	Cyclohexylalanine
	Chea:	Cycloheptylalanine
	Cheg:	Cycloheptylglycine
	Chg:	Cyclohexylglycine
	Cpa:	Cyclopentylalanine
35	Cpg:	Cyclopentylglycine
	d:	Doublet
	Dab:	2,4-diaminobutyric acid
	Dap:	2,3-diaminopropionic acid
	TLC:	Thin-layer chromatography
40	DCC:	Dicyclohexylcarbodiimide
	Dcha:	Dicyclohexylamine
	DCM:	Dichloromethane
	Dhi-1-COOH:	2,3-Dihydro-1H-isoindole-1-carboxylic acid
	DMF:	Dimethylformamide
45	DIPEA:	Diisopropylethylamine
	EDC:	N'-(3-Dimethylaminopropyl)-N-ethylcarbodiimide
	Et:	Ethyl

Eq:	Equivalents
Gly:	Glycine
Glu:	Glutamic acid
fur:	Furan
5 guan:	Guanidino
ham:	Hydroxyamidino
HCha	Homocyclohexylalanine, 2-amino-4-cyclohexylbutyric acid
His:	Histidine
10 HOBT:	Hydroxybenzotriazole
HOSucc:	Hydroxysuccinimide
HPLC:	High-performance liquid chromatography
Hyp:	Hydroxyproline
Ind-2-COOH:	Indoline-2-carboxylic acid
15 iPr:	Isopropyl
Leu:	Leucine
Soln:	Solution
Lys:	Lysine
m:	Multiplet
20 Me:	Methyl
MPLC:	Medium-pressure liquid chromatography
MTBE:	Methyl-tert-butyl-ether
NBS:	N-Bromosuccinimide
Nva:	Norvaline
25 Ohi-2-COOH:	Octahydroindole-2-carboxylic acid
Ohii-1-COOH:	Octahydroisoindole-1-carboxylic acid
Orn:	Ornithine
Oxaz:	Oxazole
p-amb:	p-Amidinobenzyl
30 Ph:	Phenyl
Phe:	Phenylalanine
Phg:	Phenylglycine
Pic:	Pipecolinic acid
pico:	Picolyl
35 PPA:	Propylphosphonic anhydride
Pro:	Proline
Py:	Pyridine
Pyr:	3,4-Dehydroproline
q:	Quartet
40 RT:	Room temperature
RP-18	Reversed Phase C-18
s:	Singlet
Sar:	Sarcosine (N-methylglycine)
sb:	Singlet broad
45 t:	Triplet
t:	Tertiary
tBu:	tertiary-Butyl

tert:	Tertiary
TBAB:	Tetrabutylammonium bromide
TEA:	Triethylamine
TFA:	Trifluoroacetic acid
5 TFFA:	Trifluoroacetic anhydride
thiaz:	Thiazole
Thz-2-COOH:	1,3-Thiazolidine-2-carboxylic acid
Thz-4-COOH:	1,3-Thiazolidine-4-carboxylic acid
thioph:	Thiophene
10 1-Tic:	1-Tetrahydroisoquinolinecarboxylic acid
3-Tic:	3-Tetrahydroisoquinolinecarboxylic acid
TOTU:	O-(Cyano-ethoxycarbonylmethylene)-amino]- N,N,N',N'-tetramethyluronium tetrafluoroborate [sic]
Z:	Benzyloxycarbonyl

15

Experimental section

The compounds of the formula I can be prepared according to schemes I-III.

20

The building blocks A-B-D, E, G and K are preferably synthesized separately and used in suitably protected form (cf. Schemes I-III, is in each case of orthogonal protective groups compatible with the synthesis method used (P or P*)).

25

Scheme I

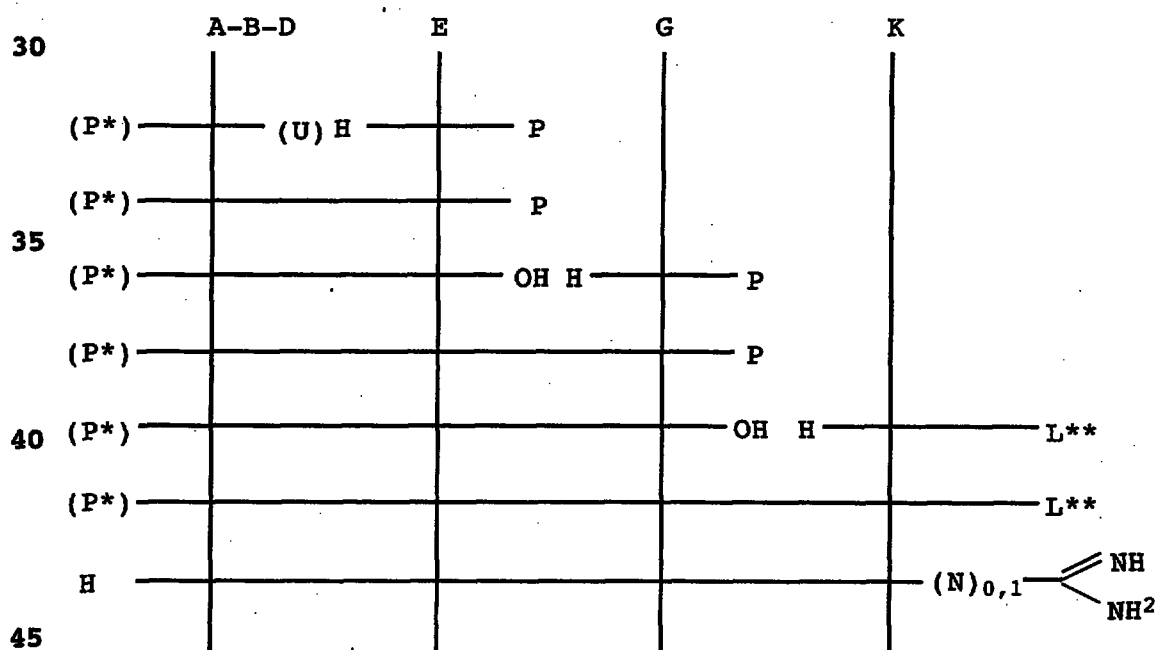
	A-B-D	E	G	K
30				P — L*
			P — OH H —	L*
			P —	L*
35		P — OH H —		L*
		P —		L*
	(P) — (U) H —			L*
40	(P) —			L*
	H —			NH NH ₂

45

(P = protective group, (P) = protective group or H)

- Scheme I describes the linear synthesis of the molecule I by eliminating the protective group from P-K-L* (where L* is CONH₂, CSNH₂, CN or C(=NH)NH-COOR*; and R* is a protective group or polymeric carrier with a spacer (solid-phase synthesis)),
- 5 coupling the amine H-K-L* to the N-protected amino acid P-G-OH to give P-G-K-L*, eliminating the N-terminal protective group to give H-G-K-L*, coupling to the N-protected amino acid P-E-OH to give P-E-G-K-L*, eliminating the protective group P to give H-E-G-K-L*, then coupling or alkylating with the unprotected or
 - 10 protected (P)-A-B-D-U building block (where U is a leaving group) or reductive alkylation with (P)-A-B-D'-U (where U is an aldehyde or ketone) or Michael-Addition with a suitable (P)-A-B-D"-C=C derivative to give (P)-A-B-D-E-G-K-L*. If L* is an amide function, it can be converted at the respective protected stages
 - 15 by dehydration with trifluoroacetic anhydride into the corresponding nitrile function. Amidine syntheses for the benzamidine, picolylamidine, thienylamidine, furylamidine and thiazolylamidine compounds of the structure type I starting from the corresponding carboxamides, nitriles, carboxylic acid
 - 20 thioamides and hydroxyamidines are described in a number of patent applications (cf. for example WO 95/35309, WO 96/178860, WO 96/24609, WO 96/25426, WO 98/06741 and WO 98/09950). Any protective groups still present are then eliminated. If L* is a C(=NH)NH-spacer-polymeric carrier, these compounds are cleaved
 - 25 from the polymeric carrier in the final step and the active substance thus liberated.

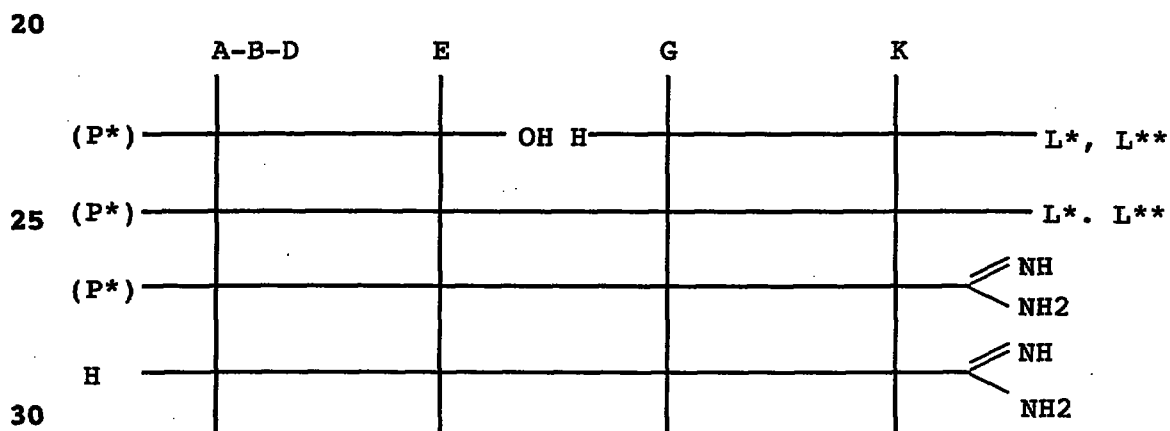
Scheme II



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Scheme II describes the linear synthesis of the molecule I by coupling, alkylation, reductive amination or Michael-Addition of H-E-P with suitable unprotected or protected (P*)-A-B-D building blocks [(P*)-A-B-D-U (where U is a leaving group) or (P*)-A-B-D'-U (where U is an aldehyde, ketone) or (P*)-A-B-D"-C=C derivative] to give (P*)-A-B-D-E-P. This is followed by elimination of the C-terminal protective group to give (P*)-A-B-D-E-OH, coupling with H-G-P to give (P*)-A-B-D-E-G-P, further elimination of the C-terminal protective group to give (P*)-A-B-D-E-G-OH and coupling with H-K-L** (where L** is CONH2 [sic], CSNH2 [sic], CN, NH-C(=NH)NH₂, C(=NH)NH-R** and R** is a hydrogen atom or protective group) to give (P*)-A-B-D-E-G-K-L**. The conversion of this intermediate into the end product is carried out analogously to scheme I. The synthesis sequence according to scheme II is also suitable for solid-phase synthesis if the A-B-D building block has a corresponding anchor function, e.g. a carboxyl or amino function.

Scheme III



Scheme III describes a very efficient route for preparing the compounds I by a convergent synthesis. The appropriately protected building blocks (P*)-A-B-D-E-OH and H-G-K-L* or H-G-K-L** are coupled to one another and the resulting intermediate (P*)-A-B-D-E-G-K-L* and (P*)-A-B-D-E-G-K-L** respectively, are reacted [lacuna] scheme I to give the end product.

40 The N-terminal protective groups used are Boc, Cbz or Fmoc, and C-terminal protective groups are methyl, tert-butyl and benzyl esters. Amidine protective groups are preferably BOC [sic], Cbz and groups derived therefrom, for the solid-phase synthesis. If the intermediates contain olefinic double bonds, protective groups which are eliminated hydrogenolytically are unsuitable.

101

The required coupling reactions and the customary reactions for introducing and eliminating protective groups are carried out according to standard conditions of peptide chemistry (cf. M. Bodanszky, A. Bodanszky "The Practice of Peptide Synthesis", 2nd edition, Springer Verlag Heidelberg, 1994).

Boc-protective groups are eliminated by means of dioxane/HCl or TFA/DCM, Cbz-protective groups are eliminated hydrogenolytically or with HF, and Fmoc protective groups are eliminated with piperidine. The hydrolysis of ester functions is effected with LiOH in an alcoholic solvent or in dioxane/water. t-Butylester are cleaved using TFA or dioxane/HCl.

The reactions were monitored by TLC, the following were mobile phases usually being used:

A.	DCM/MeOH	95:5
B.	DCM/MeOH	9:1
C.	DCM/MeOH	8:2
20 D.	DCM/MeOH/50% strength HOAc	40:10:5
E.	DCM/MeOH/50% strength HOAc	35:15:5

Where separation by means of column chromatography are mentioned, these were separations over silica gel, for which the abovementioned mobile phases were used.

Reversed-phase HPLC separation were carried out using acetonitrile/water and HOAc buffer.

The starting compounds can be prepared by the following methods:

A-B-D building blocks:

The compounds suitable as A-B-D building blocks are for the most part commercially available, e.g. tert-butyl α -bromoacetate, methylsulfonyl chloride, benzenesulfonyl chloride, 4-chlorosulfonylbenzoic acid, cinnamic acid, hydrocinnamic acid, 5-bromovaleric acid, phenylpropionic acid, 4-phenylbutyric acid, 5-phenylvaleric acid, 4-phenylbenzoic acid, 4-biphenyl acetic acid, etc. Where these compounds have a plurality of functional groups, protective groups are introduced at the required sites. If necessary, functional groups are converted into reactive or leaving groups (e.g. active esters, mixed anhydrides, sulfonyl chlorides, etc.), in order to permit appropriate chemical linkage with the other building blocks.

The synthesis of the E building blocks was carried out as follows:

The compounds used as E building blocks, i.e. glycine, (D)- and
5 (L)-alanine, (D)- and (L)-valine, (D)-phenylalanine,
(D)-cyclohexylalanine, (D)-cycloheptylglycine, etc., are
commercially available either as free amino acids, as
Boc-protected compounds or as corresponding methyl esters.

- 10 The preparation of cycloheptylglycine and cyclopentylglycine was
carried out by reacting cycloheptanone and cyclopentanone,
respectively, with ethyl isonitriloacetate by known methods
(H.-J. Prätorius, J. Flossdorf, M.Kula, Chem. Ber. 108, 1985,
3079 or U. Schöllkopf and R. Meyer, Liebigs Ann. Chem. (1977),
15 1174).

Said amino acids were provided, as required, with either an
N-terminal or a C-terminal protective groups.

- 20 The synthesis of the G building blocks was carried out as
follows:

- The compounds used as G building blocks, i.e. (L)-proline,
(L)-4,4-difluoroproline, (L)-3-methylproline, (L)-5-methyl-
25 proline, (L)-3,4-dehydroproline, (L)-octahydroindole-2-carboxylic
acid, (L)-thiazolidine-4-carboxylic acid and
(L)-azetidinecarboxylic acid, are commercially available either
as free amino acids, as Boc-protective compounds or as
corresponding methyl esters. Methyl
30 (-)-thiazolidine-2-carboxylate was prepared according to R.L.
Johnson, E.E. Smisson, J. Med. Chem. 21, (1978) 165.

The synthesis of K building blocks was carried as follows:

- 35 p-cyanobenzylamine

This building block was prepared as described in WO 95/35309.

3-(6-Cyano)-picolylamine

- This building block was prepared as described in WO 96/25426 or
40 WO 96/24609.

5-Aminomethyl-2-cyanothiophene

This building block was prepared as described in WO 95/23609.

- 45 5-Aminomethyl-3-cyanothiophene

This building block was prepared as described in WO 96/17860.

2-Aminomethyl-thiazole-4-thiocarboxamide

The preparation was carried out according to G. Videnov, D. Kaier, C. Kempter and G. Jung, *Angew. Chemie* **108** (1996), 1604, the protective group being eliminated from the N-Boc-protected
5 compound described there by means of ethereal hydrochloric acid in methylene chloride.

5-Aminomethyl-2-cyanofuran

This building block was prepared as described in WO 96/17860.

10

5-Aminomethyl-3-cyanofuran

This building block was prepared as described in WO 96/17860.

5-Aminomethyl-3-methylthiophene-2-carbonitrile

15

a) 5-Formyl-3-methylthiophene-2-carbonitrile:

112 ml (179 mmol) of a 1.6 molar solution of n-butyllithium in n-hexane were added in the course of 20 minutes to a
20 solution, cooled to -78°C, of 25.1 ml (179 mmol) of diisopropylamine in 400 ml of tetrahydrofuran. The solution was allowed to reach -35°C and was cooled again to -78°C, and a solution of 20.0 g (162 mmol) of 2-cyano-3-methylthiophene in 80 ml of tetrahydrofuran was slowly added dropwise at this
25 temperature. The solution acquired a dark red color. Stirring was continued for 45 minutes, 63 ml (811 mmol) of dimethylformamide were slowly added dropwise and stirring was carried out for a further 30 minutes. For working up, a solution of 27 g of citric acid and 160 ml of water was added
30 at -70°C. Evaporating down was carried out in a rotary evaporator, 540 ml of saturated sodium chloride solution were added and extraction was effected with three times 250 ml of diethyl ether. The combined organic extracts were dried over magnesium sulfate. After the drying agent had been filtered
35 off, the solvent was distilled off under reduced pressure from a water jet pump and the residue was purified by column chromatography (mobile phase: 4/1 hexane/ethyl acetate). 23 g (94%) of the title compound were obtained.
40 ¹H-NMR (270 MHz, DMSO-d₆): δ = 2.4 (s, 3H), 8.0 (s, 1H), 9.8 (s, 1H).

b) 5-Hydroxymethyl-3-methylthiophene-2-carbonitrile:

5.75 g (152 mmol) of sodium borohydride were added a little
45 at a time at room temperature to a solution of 23 g (152 mmol) of 5-formyl-3-methylthiophene-2-carbonitrile. Stirring was carried out for 5 minutes, the reaction mixture

was evaporated down under reduced pressure from a waterjet pump, the residue was taken up in ethyl acetate, extraction was carried out with 5% strength citric acid solution and with saturated sodium chloride solution, the organic phase was dried over magnesium sulfate, the drying agent was filtered off and the solvent was distilled off under reduced pressure from a waterjet pump at room temperature. This gave 24 g of the title compound as a dark red oil which still contains solvent and was used in the following reactions without further purification.

$^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 2.4 (s, 3H), 4.7 (m, 2H), 5.9 (m, 1H), 7.0 (s, 1H).

c) 5-Bromomethyl-3-methylthiophene-2-carbonitrile:

44 g (167 mmol) of triphenylphosphine were added to a solution of 24 g (152 mmol) of 5-hydroxymethyl-3-methylthiophene-2-carbonitrile in 180 ml of tetrahydrofuran. A solution of 55 g (167 mmol) of tetrabromomethane in 100 ml of tetrahydrofuran was then added. Stirring was carried out for 90 minutes at room temperature. The reaction mixture was evaporated down in a rotary evaporator under reduced pressure from a waterjet pump and the residue was purified by column chromatography (mobile phase: 8:2 hexane, ethyl acetate). 34 g of the title compound, which still contained a little solvent, were obtained.

$^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 2.4 (s, 3H), 5.0 (s, 2H), 7.3 (s, 1H).

d) 5-N,N-bis(tert-Butoxycarbonyl)aminomethyl-3-methylthiophene-2-carbonitrile:

5.0 g (167 mmol) of sodium hydride (80% strength suspension in mineral oil) were added a little at a time to a solution, cooled to 0°C, of 33.8 g (152 mmol) of 5-bromomethyl-3-methylthiophene-2-carbonitrile in 255 ml of tetrahydrofuran. A solution of 36.4 g (167 mmol) of di-tert-butyl iminodicarboxylate in 255 ml of tetrahydrofuran was then added dropwise, the temperature not exceeding 5°C. The mixture was allowed to reach room temperature and was stirred overnight. Heating was carried out for a further three hours at 35°C to complete the reaction, after which the mixture was allowed to cool to room temperature and 510 ml of a saturated ammonium chloride solution was slowly added. The solvent was distilled off under reduced pressure from a waterjet pump, the residue was extracted several times with

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ethyl acetate and the combined organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated down in a rotary evaporator. 57.6 g of an oily residue which still contained di-tert-butyl

5 iminodicarboxylate were obtained and said residue was used as a crude product in the following reaction.

$^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 1.45 (s, 18H), 2.35 (s, 3H), 4.85 (s, 2H), 7.05 (s, 1H).

10 e) 5-Aminomethyl-3-methylthiophene-2-carbonitrile hydrochloride:

52.6 g of 5-N,N-bis(tert-butoxycarbonyl)aminomethyl-3-methylthiophene-2-carbonitrile (crude product from d), not more than 139 mmol) were dissolved in 950 ml of ethyl acetate and cooled to 0°C. The solution was saturated with hydrogen chloride gas, white precipitate separating out after 10 minutes. Stirring was carried out for two hours at room temperature and for one hour at 30°C, the resulting suspension was then evaporated down in a rotary evaporator, the residue was stirred with diethyl ether and filtered off from the solvent and the solid residue was dried at room temperature under reduced pressure. 24.7 g (94%) of the title compound were obtained as a white powder.

25 $^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 2.4 (s, 3H), 4.25 (s, 2H), 7.3 (s, 1H), 8.8-9.0 (bs, 3H).

$^{13}\text{C-NMR}$ (DMSO-d_6): 15.0 (CH_3), 36.4 (CH_2), 104.8 (C-2), 113.8 (CN), 131.5 (C-4), 142.8 (C-5), 149.6 (C-3).

5-Aminomethyl-3-chlorothiophene-2-carbonitrile hydrochloride

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This compound was prepared analogously to 5-aminomethyl-3-methylthiophene-2-carbonitrile, the 3-chloro-2-cyanothiophene used having been prepared by dehydrating 3-chlorothiophene-2-carboxamide (substances commercially available) with trifluoroacetic anhydride.

5-Aminomethyl-4-methylthiophene-3-thiocarboxamide

a) Ethyl 2-amino-3-cyano-4-methylthiophene-5-carboxylate

40

Ethyl 2-amino-3-cyano-4-methylthiophene-5-carboxylate was prepared according to "Organikum", 19th edition, Dt. Verlag der Wissenschaften, Leipzig, Heidelberg, Berlin, 1993, Chapter 6, pages 374-375, starting from 130 g (1.0 mol) of ethyl acetoacetate, 66 g (1.0 mol) of malonodinitrile, 32 g (1.0 mol) of sulfur and 80 g (0.92 mol) of morpholine.

45

¹H-NMR (270 MHz, DMSO-d₆): δ = 1.25 (t, 3H), 2.3 (s, 3H), 4.2 (q, 2H), 7.9 (bs, 2H).

b) Ethyl-4-cyano-3-methylthiophene-2-carboxylate

5

A solution of 20.5 g (97.5 mmol) of ethyl 2-amino-3-cyano-4-methylthiophene-5-carboxylate in 600 ml of a 1:1 mixture of acetonitrile and dimethylformamide was cooled to 5°C, and 15.7 g (146 mmol) of tert-butyl nitrite were added dropwise, the reaction mixture heating up and vigorous gas evolution beginning. Stirring was carried out for seven hours at room temperature, the mixture was evaporated down in a rotary evaporator and under greatly reduced pressure, the residue was purified by column chromatography (mobile phase: dichloromethane) and 9.1 g (48 %) of the desired compound were obtained as a yellow oil. ¹H-NMR (270 MHz, DMSO-d₆): δ = 1.3 (t, 3H), 2.55 (s, 3H), 4.3 (q, 2H), 8.8 (s, 1H).

20 c) 5-Hydroxymethyl-4-methylthiophene-3-carbonitrile:

2.44 g (64 mmol) of lithium aluminum hydride were added a little at a time at 0°C to a solution of 25.1 g (129 mmol) of ethyl 3-cyano-4-methylthiophene-5-carboxylate in 400 ml of tetrahydrofuran. Stirring was carried out for five hours at room temperature, excess reducing agent was destroyed by adding 0.5 n [sic] hydrochloric acid, and the reaction mixture was evaporated down under reduced pressure from a waterjet pump, diluted with water and extracted three times with ethyl acetate. The combined organic phases were then washed once with 0.5 n [sic] hydrochloric acid and once with saturated sodium chloride solution. The organic phase was dried over magnesium sulfate, the drying agent was filtered off and the solvent was distilled off under reduced pressure from a waterjet pump at room temperature. The residue was purified by column chromatography (mobile phase: 95:5 dichloromethane/methanol) and 16.1 g (83%) of the desired compound were obtained as light yellow oil. ¹H-NMR (270 MHz, DMSO-d₆): δ = 2.2 (s, 3H), 4.6 (d, 2H), 5.7 (m, 1H), 8.35 (s, 1H).

d) 5-Bromomethyl-4-methylthiophene-3-carbonitrile:

30 g (115 mmol) of triphenylphosphine were added at 5°C to a solution of 16 g (104 mmol) of 5-hydroxymethyl-4-methylthiophene-3-carbonitrile in 300 ml of tetrahydrofuran. A solution of 38 g (115 mmol) of

tetrabromomethane in 100 ml of tetrahydrofuran was then added. Stirring was carried out overnight at room temperature. The reaction mixture was evaporated down in a rotary evaporator under reduced pressure from a waterjet pump and the residue was purified by column chromatography (mobile phase: 1:1 petroleum ether: dichloromethane). 17 g (76%) of the title compound were obtained as a yellow oil.
 $^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 2.25 (s, 3H), 5.0 (s, 2H), 8.5 (s, 1H).

- 10 e) 5-N,N-bis(tert-Butoxycarbonyl)aminomethyl-4-methylthiophene-3-carbonitrile:

3.5 g (103 mmol) of sodium hydride (oil-free) were added a little at a time to a solution, cooled to 0°C , of 17.2 g (79.5 mmol) of 5-bromomethyl-4-methylthiophene-3-carbonitrile in 250 ml of tetrahydrofuran. A solution of 22.5 g (103 mmol) of di-tert-butyl iminodicarboxylate in 100 ml of tetrahydrofuran was then added dropwise, the temperature not exceeding 5°C . The mixture was allowed to warm up to room temperature and was stirred for two hours. 400 ml of a saturated ammonium chloride solution was slowly added. The solvent was distilled off under reduced pressure from a waterjet pump and the residue was diluted with a little water and extracted three times with ethyl acetate. The combined organic phases were washed with saturated ammonium dichloride solution and with saturated sodium chloride solution, dried over magnesium sulfate and evaporated down in a rotary evaporator. 28 g of an oil which still contained di-tert-butyl iminodicarboxylate were obtained and said oil was used as a crude product in the following reaction.
 $^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 1.4 (s, 9H), 1.45 (s, 9H), 2.3 (s, 3H), 4.8 (s, 2H), 8.4 (s, 1H).

- 35 f) 5-N,N-bis(tert-Butoxycarbonyl)aminomethyl-4-methylthiophene-3-thiocarboxamide

The crude product (max. 79 mmol) obtained from e) was dissolved in 280 ml of pyridine and 140 ml of triethylamine and saturated with hydrogen sulfide at room temperature. The previously yellow solution became green. Stirring was carried out overnight at room temperature. To complete the reaction, hydrogen sulfide was passed in for a further 15 minutes and stirring was carried out for a further two hours at room temperature. Excess hydrogen sulfide was expelled with the aid of a stream of nitrogen via a scrubbing tower. Thereafter, the reaction mixture was evaporated down in a

rotary evaporator, taken up in ethyl acetate, washed several times with a 20% strength sodium bisulfate solution, dried over magnesium sulfate and evaporated down in a rotary evaporator. 27 g of a light yellow firm foam were obtained, and said foam was used without further purification in the following reaction.

$^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 1.4 (s, 18H), 2.15 (s, 3H), 4.8 (s, 2H), 7.5 (s, 1H), 9.3 (bs, 1H), 9.75 (bs, 1H).

10 g) 5-Aminomethyl-4-methylthiophene-3-thiocarboxamide hydrochloride

27 g of 5-N,N-bis(tert-butoxycarbonyl)aminomethyl-4-methylthiophene-3-thiocarboxamide (crude product from f), not more than 70 mmol) were dissolved in 400 ml of ethyl acetate and cooled to 0°C. The solution was saturated with hydrogen chloride gas, a white precipitate separating out after 10 minutes. Stirring was carried out after two hours at room temperature, the precipitate was filtered off and washed with ethyl acetate and the solid residue was dried at room temperature under reduced pressure. 13.6 g (87%) of the title compound were obtained as a white powder.

EI-MS: M^+ = 186.

25 5-Aminomethyl-4-chlorothiophene-3-thiocarboxamide

a) 5-Formyl-4-chlorothiophene-3-carbonitrile:

35 g (325 mmol) of tert-butyl nitrite were added dropwise at room temperature to a solution of 53.0 g (250 mmol) of 2-amino-4-chloro-5-formylthiophene-3-carbonitrile (the preparation of this compound is described in the patent DB 3738910) in 600 ml of a 1:1 mixture of acetonitrile and dimethylformamide, the reaction mixture warming up from 20°C to 37°C and vigorous gas evolution beginning. The mixture was cooled to 25°C and stirred for seven hours at room temperature, the black solution was evaporated down in a rotary evaporator and under greatly reduced pressure, the residue was purified by column chromatography (mobile phase: dichloromethane) and 29 g (68%) of the desired compound were obtained as a yellow oil.

$^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 9.1 (s, 1H), 10.0 (s, 1H).

b) 5-Hydroxymethyl-4-chlorothiophene-3-carbonitrile:

6.3 g (166 mmol) of sodium borohydride were added a little at a time at 5°C to a solution of 28.5 g (166 mmol) of 5-formyl-4-chlorothiophene-3-carbonitrile in 400 ml of absolute methanol. The reaction mixture warmed up slightly and acquired a dark red color. Vigorous gas evolution was observed. After ten minutes, the reaction mixture was evaporated down under reduced pressure from a waterjet pump, the residue was taken up in 200 ml of ethyl acetate and the solution was extracted with 200 ml of 1 M [sic] hydrochloric acid and the organic phase was washed with twice 250 ml of water and with saturated sodium chloride solution and dried over magnesium sulfate, the drying agent was filtered off and the solvent was distilled off under reduced pressure from a waterjet pump at room temperature. 22 g (76%) of the title compound were obtained as a dark red oil, which was used without further purification in the following reactions.

¹H-NMR (270 MHz, DMSO-d₆): δ = 4.65 (bs, 1H), 5.95 (t, 2H), 8.6 (s, 1H).

20 c) 5-Bromomethyl-4-chlorothiophene-3-carbonitrile:

36.1 g (137 mmol) of triphenylphosphine were added at 5°C to a solution of 21.7 g (125 mmol) of 5-hydroxymethyl-4-chlorothiophene-3-carbonitrile in 250 ml of tetrahydrofuran. A solution of 45.6 g (137 mmol) of tetrabromomethane in 100 ml of tetrahydrofuran was then added. Stirring was carried overnight at room temperature. The precipitate was filtered off, the filtrate was evaporated down in a rotary evaporator under reduced pressure from a waterjet pump and the residue was purified by column chromatography (mobile phase: 1:1 petroleum ether: dichloromethane). 26.0 g (88%) of the title compound were obtained as an oil.

¹H-NMR (270 MHz, DMSO-d₆): δ = 4.95 (s, 2H), 8.8 (s, 1H).

35 d) 5-N,N-bis(tert-Butoxycarbonyl)aminomethyl-4-chlorothiophene-3-carbonitrile:

6.9 g (159 mmol) of sodium hydride (oil-free) were added a little at a time to a solution, cooled to 0°C, of 25.0 g (106 mmol) of 5-bromomethyl-4-chlorothiophene-3-carbonitrile in 300 ml of tetrahydrofuran. A solution of 34.4 g (159 mmol) of di-tert-butyl iminodicarboxylate in 100 ml of tetrahydrofuran was then added dropwise, the temperature not exceeding 5°C. The mixture was allowed to warm up to room temperature and was stirred for two hours. 300 ml of saturated ammonium chloride solution was slowly added. The

solvent was distilled off under reduced pressure from a waterjet pump and the residue was diluted with a little water and extracted three times with ethyl acetate. The combined organic phases were washed with saturated ammonium chloride solution and with saturated sodium chloride solution, dried over magnesium sulfate and evaporated down in a rotary evaporator. 51.3 g of an oil which still contained di-tert-butyl iminodicarboxylate and solvent residues were obtained, and said oil was used as a crude product in the following reaction.

$^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 1.4 (s, 9H), 1.45 (s, 9H), 4.8 (s, 2H), 8.65 (s, 1H).

e) 5-N,N-bis(tert-Butoxycarbonyl)aminomethyl-4-methylthiophene-3-thiocarboxamide

A part of the crude product (39.4 g, max. 106 mmol) obtained from d) was dissolved in 400 ml of pyridine and 40 ml of triethylamine and saturated with hydrogen sulfide at room temperature. The previously yellow solution acquired a green color. Stirring was carried out overnight at room temperature. Excess hydrogen sulfide was expelled with the aid of a stream of nitrogen via a scrubbing tower. Thereafter the reaction mixture was poured into ice-cooled, 20% strength sodium bisulfate solution and extracted three times with ethyl acetate. The organic phase was then washed several times with 20% strength sodium bisulfate solution, dried over magnesium sulfate and evaporated down in a rotary evaporator. 49.0 g of a solvent-containing residue were obtained, and said residue was used without further purification in the following reaction.

$^1\text{H-NMR}$ (270 MHz, DMSO-d_6): δ = 1.4, 1.45 (s, 18H), 4.8 (s, 2H), 7.75 (s, 1H), 9.4 (bs, 1H), 10.0 (bs, 1H).

f) 5-Aminomethyl-4-chlorothiophene-3-thiocarboxamide hydrochloride

38.0 g of the crude product from e), not more than 93 mmol, were dissolved in 400 ml of ethyl acetate and cooled to 0°C. The solution was saturated with hydrogen chloride gas, white precipitate separating out after 10 minutes. Since the reaction was not yet complete, 200 ml of ethyl acetate were added, the solution was saturated again with hydrogen chloride gas and stirring was carried out overnight at room temperature. The precipitate was filtered off, washed with petroleum ether and dried at room temperature under reduced pressure. 21.1 g of the title compound were obtained as a

white powder which contained ammonium chloride as an impurity.

EI-MS: M^+ = 206.

5 5-Aminomethyl-2-guanidinothiazole bishydrochloride

a) N-Phthaloyl-5-aminomethyl-2-guanidinothiazole

A solution of 31 g (130 mmol) of
10 N-phthaloyl-3-amino-2-chloropropionaldehyde (S. Marchais et al., Tetrahedron Letters 39 (1998), 8085-8088) and 15.4 g (130 mmol) of amidinothiourea in 200 ml of butanol was heated at 110°C for 75 minutes under a nitrogen atmosphere, after which the reaction mixture was evaporated down under reduced
15 pressure (1 mbar, bath temperature up to 50°C) and methylene chloride and concentrated ammonia were added to the residue. A part of the product was precipitated from water. This was purified, together with the part obtained from the methylene chloride phase after drying and evaporating down, by column
20 chromatography (silica gel; mobile phase: methylene chloride with a methanol content increasing from 0 to 5%). The predominantly pure fractions were then crystallized from acetone, 12.3 g of the title compound being obtained.

25 b) 5-Aminomethyl-2-guanidinothiazole bishydrochloride

A solution of 5 g (16.6 mmol) of N-phthaloyl-5-aminomethyl-2-guanidinothiazole and 4.15 g (83 mmol) of hydrazine hydrate in 100 ml of methanol were [sic] stirred under a nitrogen
30 atmosphere for one hour at room temperature, after which the reaction mixture was evaporated down under reduced pressure (1 mbar, bath temperature to 50°C) and 70 ml of water and 20% strength hydrochloric acid were added to the residue until the pH reached 1, phthalylhydrazide being precipitated and
35 then filtered off. The filtrate was evaporated down under reduced pressure and the residue was codistilled three times with methanol, dried at 50°C under reduced pressure and then recrystallized from ethanol. 3.7 g of the title compound were obtained.

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5-Amino-3-amidino-thiophene bishydrochloride

The synthesis of this compound was carried out starting from 5-aminomethyl-3-cyanothiophene (WO 96/17860) by reaction with
45 (Boc)₂O to give 5-tert-butoxycarbonylaminoethyl-3-cyanothiophene, conversion of the nitrile function into the corresponding thioamide by addition of hydrogen sulfide, methylation of the

thioamide function with methyl iodide, reaction with ammonium acetate to give the corresponding amidine and subsequent elimination of the protective group with hydrochloric acid and isopropanol to give 5-aminomethyl-3-amidinothiophene bishydrochloride.

3-Amidino-5-[N-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl]-aminomethylthiophene hydrochloride

- 10 3-Amidino-5-aminomethylthiophene bishydrochloride (1.3 g, 5.7 mmol) in DMF (15 ml) was initially taken and N,N-diisopropylethylamine (0.884 g, 6.84 mmol) was added. Stirring was carried out for 5 minutes at room temperature, after which 2-acetyldimedone (1.25 g, 6.84 mmol) and trimethyl
- 15 orthoformate (3.02 g, 28.49 mmol) were added. Stirring was carried out for 2.5 hours at room temperature, after which the DMF was removed under greatly reduced pressure and the residue was stirred thoroughly with DCM (5 ml) and petroleum ether (20 ml). The solvent was decanted from slightly yellowish product,
- 20 and the solid was dried under reduced pressure at 40°C. Yield: 1.84 g (5.2 mmol, 91%).
- ¹H-NMR (400 MHz, [D₆]DMSO, 25°C, TMS): δ = 0.97 (s, 6H); 2.30 (s, 4H); 2.60 (s, 4H); 4.96 (d, J = 7 Hz, 2H); 7.63 (s, 1H); 8.60 (s, 1H); 9.07 (sbr, 2H); 9.37 (sbr, 1H).

25

Syntheses of building blocks:

A-B-D-E-OH (in appropriately protected form):

- The E building blocks were partly converted into the
- 30 corresponding benzyl esters (or methyl esters) and linked to the appropriately protected A-B-D-U building blocks (U is a leaving group). In the case of compounds still having a free N-H-function, this was then protected with a Boc-group, the benzyl ester group was eliminated by hydrogenolysis (or the
- 35 corresponding methyl ester group was hydrolyzed) and the building block A-B-D-E-OH was purified by crystallization, salt precipitation or column chromatography. This route is described by way of example for tBuOOC-CH₂-(Boc)(D)Cha-OH in WO 98/06741.

- 40 A-B-D-E-G-OH (in appropriately protected form):

The preparation of the A-B-D-E-G-OH building blocks in appropriately protected form is described by way of example for N-Boc-N-(tert-butoxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroproline in WO 98/06741.

45

H-G-K-CN:

113

The preparation of the H-G-K-CN building block is described by way of example for prolyl-4-cyanobenzylamide in WO 95/35309, for 3,4-dehydroprolyl-4-cyanobenzylamide in WO 98/06740 and for 3,4-dehydroprolyl-5-(2-cyano)-thienylmethylethylamide in WO 98/06741.

5

In the examples which follow, complement inhibitors are mentioned:

Example 1

10 $\text{CF}_3\text{-CH}_2\text{-SO}_2\text{-(D)Phe-Pro-NH-p-amb-CH}_3\text{COOH}$ (WO 96/17860 Example 13)

Example 2

n-Octyl-SO₂-(D)Phe-Pro-NH-p-amb-CH₃COOH (WO 96/17860 Example 14)

15 Example 3

3-Py-SO₂-(D)Phe-Pro-NH-p-amb-CH₃COOH (WO 96/17860 Example 4)

Example 4

CH₃-SO₂-(D)Cha-Pyr-NH-p-amb-CH₃COOH

20 (Preparation analogous to WO 96/17860 Example 1) FAB-MS: (M+H⁺) = 476

Example 5

H-(D)Val-Pro-NH-p-amb-2HCl (WO 95/35309 Example 151)

25

Example 6

Boc-(D)Asp(OBn)-Pro-NH-p-amb-CH₃COOH (WO 95/35309, intermediate of Example 179) FAB-MS: (M+H⁺) = 552

30 Example 7

2-C₆H₁₀-CH₂-Gly-Pro-NH-p-amb-2HCl

(Preparation analogous to WO 95/35309 Example 166) FAB-MS: (M+H⁺) = 444

35 Example 8

C₆H₅-CH₂-CH₂-CO-Gly-Pro-NH-p-amb-HI

(Preparation analogous to WO 95/35309 Example 6) FAB-MS: (M+H⁺) = 436

40 Example 9

C₆H₅-(CH₂)₃-CO-Gly-Pro-NH-p-amb-HI

(Preparation analogous to WO 95/35309 Example 6) FAB-MS: (M+H⁺) = 450

45 Example 10

114

(D)(4-Me)Pic-Pro-NH-p-amb·2CH₃COOH(Preparation analogous to WO 95/35309 Example 112) FAB-MS: (M+H⁺) = 372

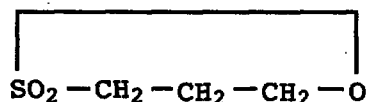
5 Example 11

H-(D)3-Tic-Pro-NH-p-amb·2CH₃COOH (WO 95/35309 Example 112)

Example 12

HO₃S-(CH₂)₃-(D)Phe-Pro-NH-p-amb·HCl

- 10 (The preparation of this compound was carried out by alkylating H-(D)Phe-Pro-NH-CH₂-pC₆H₄-CN with



15

The nitrile function was converted into the amidino group by hydrogenating the hydroxyamidino intermediate.) FAB-MS: (M+H⁺) = 516

20 Example 13

CH₃-SO₂-(D)Cha-Pyr-NH-3-(6-am)-pico·CH₃COOH
(WO 96/24609 Example 8)

Example 14

- 25 CH₃-SO₂-(D)Chg-Pro-NH-3-(6-am)-pico·CH₃COOH
(WO 96/24609 Example 6)

Example 15

C₆H₅-CH₂-SO₂-(D)Cha-Pyr-NH-3-(6-am)-pico·CH₃COOH

- 30 (Preparation analogous to WO 96/24609 Example 8) FAB-MS: (M+H⁺) = 553

Example 16

HOOC-CH₂-SO₂-(D)Chg-Pro-NH-3-(6-am)-pico·CH₃COOH

- 35 (WO 96/24609 Example 10)

Example 17

CH₃OOCH₂-SO₂-(D)Chg-Pro-NH-3-(6-am)-pico·CH₃COOH

(WO 96/24609, intermediate in the preparation of Example 10)

- 40 FAB-MS: (M+H⁺) = 523

Example 18

HOOC-CH₂-(D)Chg-Pyr-NH-3-(6-am)-pico·CH₃COOH

(Preparation analogous to WO 96/25426 Example 93; described as a

- 45 byproduct in the synthesis of Example 95 (WO 96/25426))

FAB-MS: (M+H⁺) = 443

Example 19

HOOC-CH₂-HCha-Pyr-NH-3-(6-am)-pico

(Preparation analogous to WO 96/25426 Example 93) FAB-MS: (M+H⁺) = 471

5

Example 20

Boc-NH-p-C₆H₄CH₂-SO₂-(D)Cha-Pyr-NH-3-(6-am)-pico-CH₃COOH

a) Methyl N-(4-nitrobenzylsulfonyl)-(D)-cyclohexylalanine

10

2.6 g (25 mmol) of triethylamine, 2.6 g (25 mmol) of N-methylmorpholine and a solution of 5.9 g (25 mmol) of p-nitrobenzylsulfonyl chloride (J.E. Macor et al., THL 33 (1992), 8011) in 50 ml of methylene chloride were added dropwise at 0°C, while stirring, to a solution of 5.53 g (25 mmol) of methyl (D)-cyclohexylalanine hydrochloride in 150 ml of methylene chloride and 10 ml of acetonitrile. Stirring was carried out for a further 30 minutes, after which the yellow reaction solution was washed with water, 5% strength citric acid solution, 5% strength NaHCO₃-solution and again with water and was dried over Na₂SO₄ and the solvent was distilled off under reduced pressure. 10 g of slightly yellowish oil remained.

25 b) Methyl N-(4-aminobenzylsulfonyl)-(D)-cyclohexylalanine

The above oil was dissolved in 250 ml of methanol, 1.5 g of 10% strength Pd/C were added and hydrogenation was carried out at room temperature with hydrogen. After the catalyst had been filtered off with suction, the methanol was distilled off under reduced pressure, crystallization beginning toward the end. The methanol-moist residue was substantially free from methanol by dissolving in methylene chloride and evaporating down again and, after dispersing with 1:4 toluene/n-hexane, was filtered off with suction. 8 g of the title compound (90% of theory) [sic], based on methyl D-cyclohexylalanine hydrochloride) were isolated as slightly yellowish crystals, m.p. 134-136°C, TLC: (9:1)CH₂Cl₂/acetone.

40 c) Methyl N-(4-tert-butoxycarbonylamino benzylsulfonyl)-(D)-cyclohexylalanine

A solution of 7.95 g (22.45 mmol) of the above compound and 5.4 g (24.7 mmol) of Boc₂O in 80 ml of THF was refluxed for 10 hours under nitrogen. The dark brown residue remaining after the solvent had been stripped off was purified over a silica gel column (eluent: 50:2.5 CH₂Cl₂/acetone). 8.85 g of

the title compound (86.7% of theory) were isolated as white crystals (m.p. 143-144°C, TLC: 47:3 CH₂Cl₂/acetone) from the uniform fractions after treatment with n-hexane.

5 d) N-(4-tert-Butoxycarbonylaminobenzylsulfonyl)-(D)-cyclohexyl-alanine

40 ml of 1 n LiOH were added dropwise at 5°C, while stirring, to a solution of 8.85 g (19.5 mmol) of the above ester in 70 ml of dioxane, and stirring was continued for 20 hours at room temperature. According to TLC (9:1 CH₂Cl₂/acetone) traces of ester were still detectable. After the dropwise addition of 1 N HCl the pH was brought to 8, the dioxane was substantially distilled off and the residue was diluted with 1 liter of water. The aqueous phase was brought to pH 2 by adding KHSO₄ solution, covered with a layer of 500 ml of ethyl acetate and stirred for 2 hours. The organic phase was separated off, washed with water and dried over Na₂SO₄. The residue obtained after the solvent had been distilled off was digested at elevated temperature of 1,2-dichloroethane to remove traces of ester. After filtration with suction and washing with n-hexane, 7.1 g of the title compound were isolated as white crystals (m.p. 186-187°C (decomposition), TLC: 20:5:1 CH₂Cl₂/acetone/acetic acid).

e) BocNH-p-C₆H₄CH₂-SO₂-(D)Cha-Pyr-NH-3-(6-CN)-pico

5.8 g of diisopropylamine followed by 11 ml (15 mmol) of a 50% strength solution of propanephosphoric anhydride in ethyl acetate were added dropwise at 0°C to a suspension of 4.4 g (10 mmol) of N-(4-tert-butoxycarbonylaminobenzylsulfonyl)-(D)-cyclohexylalanine and 2.7 g (10 mmol) of 3,4-dehydroprolyl-(3-(6-cyano)picolyl)amide (prepared from Boc-3,4-dehydroprolyl(3-(6-carboxamido)picolyl)amide (WO 96/25426) by dehydration by means of trifluoroacetic anhydride and subsequent elimination of the Boc group) in 70 ml of methylene chloride, and stirring was carried out for 3 hours at 0°C.

The organic phase was washed with water, 5% strength NaHCO₃ solution and 5% strength citric acid solution, dried over Na₂SO₄ and evaporated to dryness. The remaining oily residue was purified by column chromatography (eluent: 45:5:4 CH₂Cl₂/acetone/methanol). The residue remaining after the eluent had been stripped off was converted into 5 g of white

powder, m.p. 175-180°C (decomposition), by treatment with ether.

f) Boc-NH-p-C₆H₄CH₂-SO₂-(D)Cha-Pyr-NH-3-(6-am)-pico·CH₃COOH

5

A solution of 3.12 g (4.8 mmol) are Boc-NH-p-C₆H₄-CH₂-SO₂-(D)Cha-Pyr-NH-3-(6-CN)-pico and 0.94 g (5.8 mmol) of L-acetylcysteine in 6 ml of methanol was heated at 50°C for 4 hours while passing in ammonia.

10

To remove the ammonia, the methanol was distilled off and the residue was taken up again in 50 ml of methanol and converted into the acetate by means of an ion exchanger (acetate on polymeric carrier, Fluka 00402). After the methanol had been stripped off, the residue was purified by column chromatography (eluent: 43:7:1.5 CH₂Cl₂/methanol/50% strength acetic acid). 2.25 g of the title compound were obtained as the slightly yellowish powder by treating the pure acetate with ethyl acetate. FAB-MS: 668 (M+H⁺).

20

Example 21

H₂N-p-C₆H₄CH₂-SO₂-(D)Cha-Pyr-NH-3-(6-am)-pico-HCl

1.7 g (2.3 mmol) of the compound of Example 20 were dissolved in 10 ml of isopropanol and 4.5 ml of 4 N hydrochloric acid and heated at 50°C for 3 hours. After the solvent had been stripped off, the residue was treated with ether and the precipitated amorphous hydrochloride was filtered off with suction. This was dissolved in 200 ml of isopropanol with the addition of a little water at elevated temperatures, active carbon was added and the solution was filtered and was evaporated down to a volume of about 40 ml. The precipitated hydrochloride of the compound was filtered off with suction, 1.65 g of slightly yellowish crystals being obtained; TLC: 43:7:2 CH₂Cl₂/methanol/50% strength of acetic acid; FAB-MS: (M+H⁺) = 568.

Example 22

Boc-NH-p-C₆H₄-CH₂-SO₂-(D)Chg-Pyr-NH-3-(6-am)-pico·CH₃COOH (The preparation was carried out analogously to Example 20) FAB-MS (M+H⁺) = 654

Example 23

H₂N-p-C₆H₄-CH₂-SO₂-(D)Chg-Pyr-NH-CH₂-3-(6-am)-pico·HCl (The preparation was carried out starting from Example 22, analogously to Example 21) FAB-MS: (M+H⁺) = 554

Example 24

HOOC-(CH₂)₅-(D)Chg-Pro-NH-3-(6-am)-pico·CH₃COOH

(The preparation was carried out analogously to WO 95/35309

Example 221) FAB-MS: (M+H⁺) = 501

5

Example 25

C₂H₅OOC-(CH₂)₅-(D)Chg-Pro-NH-3-(6-am)-pico·CH₃COOH

(Preparation analogous to WO 95/35309 Example 221) FAB-MS: (M+H⁺) = 529

10

Example 26

HOOC-(CH₂)₄-(D)Chg-Pro-NH-3-(6-am)-pico·CH₃COOH

(Preparation analogous to WO 95/35309 Example 221) FAB-MS: (M+H⁺) = 487

15

Example 27

t-BuOOC-(CH₂)₃-(D)Chg-Pro-NH-3-(6-am)-pico·CH₃COOH

(Preparation analogous to WO 95/35309 Example 221 stage c)

FAB-MS: (M+H⁺) = 529

20

Example 28

(C₆H₅-CH₂)₂-Gly-Pyr-NH-3-(6-am)-pico·CH₃COOH

(Preparation analogous to WO 96/25426 Example 33 from

(C₆H₅-CH₂)₂-Gly-OH and H-Pyr-NH-CH₂-3-(6-CN-pico) FAB-MS: (M+H⁺) =

25 483

Example 29

HOOC-CH₂-(D)Chg-Pyr-NH-CH₂-5-(2-am)-thioph·CH₃COOH

(WO 98/06741 Example 3)

30

Example 30

HOOC-CH₂-CH₂-(D)Cha-Pro-NH-CH₂-5-(2-am)-thioph·CH₃COOH

(Preparation analogous to WO 98/06741 Example 1) FAB-MS: (M+H⁺) = 479

35

Example 31

HOOC-CH₂-(D)Chg-Aze-NH-CH₂-5-(2-am)-thioph

(Preparation analogous to WO 98/06741 Example 3) FAB-MS: (M+H⁺) = 436

40

Example 32

HOOC-CH₂-(D)Cha-Pyr-NH-CH₂-5-(2-am)-thioph·CH₃COOH

(WO 98/06741 Example 1)

45 Example 33

HOOC-CH₂-(D)Cha-Thz-4-CO-NH-CH₂-5-(2-am)-thioph·2HCl

119

(Preparation analogous to WO 98/06741 Example 1) FAB-MS: (M+H⁺) = 482

Example 34

5 HOOC-CH₂-(D)Cha-Pro-NH-CH₂-5-(3-am)-fur·CH₃COOH

(Preparation analogous to WO 98/06741 Example 10) FAB-MS: (M+H⁺) = 448

Example 35

10 HOOC-CH₂-(D)Chg-Pyr-NH-CH₂-2-(4-am)-thiaz·2HCl

(WO 98/06741 Example 22)

Example 36

HOOC-CH₂-(D)Chg-Pyr-NH-CH₂-5-(2-am-3-Cl)-thioph·2HCl

15 (Preparation analogous to WO 98/06741 Example 3) FAB-MS: (M+H⁺) = 482

Example 37

HOOC-CH₂-(D)Cha-Pyr-NH-CH₂-5-(2-am-3-Cl)-thioph·2HCl

20 (Preparation analogous to WO 98/06741 Example 1) FAB-MS: (M+H⁺) = 496

Example 38

HOOC-CH₂-(D)Cha-Pyr-NH-CH₂-5-(3-am)-thioph·CH₃COOH

25 (WO 98/06741 Example 5)

Example 39

HOOC-CH₂-(D)Chg-Aze-NH-CH₂-5-(3-am)-thioph

(Preparation analogous to WO 98/06741 Example 8) FAB-MS: (M+H⁺) = 30 436

Example 40

HOOC-CH₂(D)Chg-Pyr-NH-CH₂-5-(3-am)-thioph·CH₃COOH (WO 98/06741

Example 8)

35

Example 41

HOOC-CH₂-Chg-Pyr-NH-CH₂-5-(3-am)-thioph·CH₃COOH

(Preparation analogous to WO 98/06741 Example 8) FAB-MS: (M+H⁺) = 462

40

Example 42

HOOC-CH₂-Cpg-Pyr-NH-CH₂-5-(3-am)-thioph·CH₃COOH

(Preparation analogous to WO 98/06741 Example 8) FAB-MS: (M+H⁺) = 434

45

Example 43

HOOC-CH₂-(D)Chg-Pro-NH-CH₂-5-(3-am).thioph·2HCl

120

(Preparation analogous to WO 98/06741 Example 8) FAB-MS: (M+H⁺) = 450

Example 44

- 5 HOOC-CH₂-(D)Cha-Pyr-NH-CH₂-5-(3-am)-fur·CH₃COOH (WO 98/0671 Example 13)

Example 45

HOOC-CH₂-(D)Chg-Thz-2-CO-NH-CH₂-5-(3-am)-thioph

- 10 (Preparation analogous to WO 98/06741 Example 5) FAB-MS: (M+H⁺) = 468

Example 46

HOOC-CH₂-(D)Cha-Thz-2-CO-NH-CH₂-5-(3-am)-thioph·2HCl

- 15 (Preparation analogous to WO 98/06741 Example 8) FAB-MS: (M+H⁺) = 482

Example 47

HOOC-CH₂-(D)Cha-(L)Ohi-2-CO-NH-CH₂-5-(3-am)-thioph·HCl

- 20 (Preparation analogous to WO 98/06741 Example 8) FAB-MS: (M+H⁺) = 518

Example 48

HOOC-CH₂-(D)Chg-(L)Ohi-2-CO-NH-CH₂-5-(3-am)-thioph·HCl

- 25 (Preparation analogous to WO 98/06741 Example 5) FAB-MS: (M+H⁺) = 504

Example 49

HOOC-CH₂-(D)Chg-Pyr-NH-CH₂-5-(4-Cl-3-am)-thioph·CH₃COOH

- 30 (Preparation analogous to WO 98/06741 Example 5) FAB-MS: (M+H⁺) = 482

Example 50

HOOC-CH₂-(D)Cha-Pyr-NH-CH₂-5-(4-Cl-3-am)-thioph·CH₃COOH

- 35 (Preparation analogous to WO 98/06741 Example 8) FAB-MS: (M+H⁺) = 496

Example 51

HOOC-CH₂-(D)Chg-Pyr-NH-CH₂-5-(4-Me-3-am)-thioph·CH₃COOH

- 40 (Preparation analogous to WO 98/06741 Example 5) FAB-MS: (M+H⁺) = 462

Example 52

HOOC-CH₂-(D,L)Cpg-Pyr-NH-CH₂-5-(3-Me-3-am)-thioph·CH₃COOH

- 45 (Preparation analogous to WO 98/06741 Example 5) FAB-MS: (M+H⁺) = 448

Example 53

HOOC-CH₂-(D)Cha-Pyr-NH-CH₂-5-(3-Me-2-am)-thioph-CH₃COOH

(Preparation analogous to WO 98/06741 Example 8) FAB-MS: (M+H⁺) = 462

5

Example 54

N-(Hydroxycarbonyl-methylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-[5-(2-guanidino)thiazolylmethyl]amide bishydrochloride:

- 10 a) N-(tert-butoxycarbonyl-methylene)-(N-Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-[5-(2-guanidino)-thiazolylmethyl]-amide

- 15 7.28 g (15.15 mmol) of N-(t-BuO₂C-CH₂)-(N-Boc)-(D)-Cha-Pyr-OH, 3.7 g (15.15 mmol) of 5-aminomethyl-2-guanidinethiazole bishydrochloride and 7.8 g (10.3 ml of 60.6 mmol) of diisopropylethylamine in 90 ml of dichloromethane and 6 ml of DMF were initially taken and 6.46 g (19.7 mmol) of TOTU were added a little at a time, the temperature being kept at 20°C.
- 20 After 90 minutes, (the TLC check indicated complete conversion), the reaction mixture was evaporated down under gentle conditions under a reduced pressure, and the residue was taken up in ethyl acetate, the solution was extracted in succession with water, dilute hydrochloric acid (pH 1.5) and
- 25 saturated to sodium chloride solution (three times) and the organic phase was dried over magnesium sulfate and was evaporated down under reduced pressure. The crude product (9.3 g) was purified by column chromatography (silica gel; mobile phase, methylene chloride with a methanol content
- 30 increasing from 0 to 5%). The virtually pure fractions (3.2 g) were further purified by crystallization from a hexane-ether mixture, 2.7 g of the title compound being obtained.

- 35 b) N-(Hydroxycarbonyl-methylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-[5-(2-guanidino)thiazolylmethyl]amide bishydrochloride

- 40 2.7 g (4.03 mmol) of N-(tert-butoxycarbonyl-methylene)-(N-Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-[5-(2-guanidino)-thiazolylmethyl]-amide were stirred in 190 ml of dichloromethane and 50 ml of 5 M solution of hydrochloric acid in ether for 17 hours at room temperature, a precipitate separating out. The reaction
- 45 mixture was evaporated down under reduced pressure, codistilled several times with dichloromethane and finally thoroughly stirred from [sic] 1:1 ether/dichloromethane, 2.2

g of the title compound being obtained.

FAB-MS ($M+H^+$): 478.

Example 55

5 HOOC-p-C₆H₄CH₂-(D)Cha-Pyr-NH-CH₂-5-(3-am)-thioph

The compound was prepared analogously to Example 56, starting from methyl D-cyclohexylalanine hydrochloride.

White, amorphous powder, FAB-MS ($M-H^+$) = 538.

- 10 The intermediate N-(tert-butoxycarbonyl)-N-(4-tert-butoxycarbonylbenzyl)-D-cyclohexylamine was obtained in crystalline form, m.p. 119°C.

Example 56

15 HOOC-p-C₆H₄-CH₂-(D)Chg-Pyr-NH-CH₂-5-(3-am)-thioph

a) Methyl N-(4-tert-butoxycarbonylbenzyl)-D-cyclohexylglycine

- 20 A solution of 10 g (48.2 mmol) of methyl D-cyclohexylglycine hydrochloride, 13.1 g (38.3 mmol) of tert-butyl 4-bromomethyl-benzoate (A. Rosowsky et al. J. Med. Chem. 32 (1989), 709) and 15.6 g (121 mmol) of diisopropylethylamine in 50 ml of dimethylformamide were stirred for 16 hours at room temperature.

- 25 After the addition of 300 ml of water, extraction was carried out with methyl-tert-butylether (MTBE) and the organic phase was washed with 5% strength citric acid solution and water, dried over MgSO₄ and evaporated to dryness. The oily residue
- 30 was purified by column chromatography (eluent: 50:1 CH₂Cl₂/MTBE) and gave 11.5 g (66% of theory) of the title compound as a colorless oil.

- b) Methyl N-(tert-butoxycarbonyl)-N-(4-tert-butoxycarbonylbenzyl)-D-cyclohexylglycine
- 35

- 40 A solution of 11.5 g (31.8 mmol) of the above compound, 10.4 g (47.7 mmol) of di-tert-butyl dicarbonate and 1.5 ml of diisopropylethylamine were [sic] stirred for 40 hours at room temperature under nitrogen. The acetonitrile was distilled off, the residue was taken up in MTBE and the solution was washed with 5% strength citric acid solution and water, dried over MgSO₄ and evaporated to dryness. After purification by column chromatography (eluent: 99:2 CH₂Cl₂/acetone), the
- 45 residue gave 14 g (95% of theory) of the title compound as a colorless oil.

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c) N-(tert-Butoxycarbonyl)-N-(4-tert-butoxycarbonylbenzyl)-D-cyclohexylglycine

60 ml of 1 N sodium hydroxide solution were added dropwise at 10°C to a solution of 14 g (30.3 mmol) of the above compound in 100 ml of dioxane and stirring was carried out for 20 hours at 40°C. The pH of the reaction solution was brought to about 8 by adding citric acid, the dioxane was distilled off and aqueous phase was extracted with MTBE, acidified by further addition of citric acid and extracted several times with MTBE. The combined MTBE extract were dried over MgSO₄, the solvent was distilled off and the residue was crystallized by treatment with water-saturated n-hexane. Yield: 7.2 g of the title compound (53% of theory), m.p. 154°C, R_f 0,39 (95:5 CH₂Cl₂/methanol).

d) N-(tert-Butoxycarbonyl)-N-(4-tert-butoxycarbonylbenzyl)-D-cyclohexylglycyl-3,4-dehydroproline

5.3 g (40.5 mmol) of diisopropylethylamine, followed by 10 ml of a 50% strength solution of propane phosphonic anhydride in ethyl acetate, were added dropwise at 0°C to a suspension of 4.1 g (9 mmol) of the above compound and 1.5 g (9 mmol) of methyl 3,4-dehydroproline hydrochloride in 40 ml of CH₂Cl₂, and stirring was carried out for 2 hours at 0°C and for 12 hours at room temperature. The working up was carried out analogously to Example 20, stage e). After purification by column chromatography (eluent: 50:5 CH₂Cl₂/ether), 2.1 g (41.2 % of theory) of a slightly yellowish, amorphous powder were isolated. The hydrolysis to the acid was carried out analogously to stage c), a reaction time of 3 hours and a reaction temperature of 10°C being sufficient. 1.8 g of the title compound were isolated as a white amorphous powder, TLC 50:1 ether/acetic acid.

e) N-Boc-N-(t-BuOOC-p-C₆H₄CH₂)-(D)Chg-Pyr-NH-CH₂-5-(3-am)-thio-phacetate

0.68 g (6.6 mmol) of N-methylmorpholine was added at 0°C, under nitrogen, to a suspension of 1.8 g (3.3 mmol) of the above acid and 0.75 g (3.3 mmol) of 5-aminomethyl-3-amidino-thiophene dihydrochloride. Addition of 1.9 g (5.8 mmol) of O-[cyano(ethoxycarbonyl)methyleneamino]-N,N,N',N'-tetramethyl-uronium tetrafluoroborate (TOTU) a little at a time gave a clear solution, which was stirred for 3 hours. The yellow

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reaction solution was evaporated down under reduced pressure at from 35 to 40°C and the residue was digested three times with diisopropyl ether and, after dissolution in methanol, was converted into the acetate by means of an ion exchanger (acetate on polymeric carrier, Fluka 00402). After the eluent had been evaporated down, the crude acetate was purified by column chromatography (eluent: 40:10:0.5 CH₂Cl₂/methanol/50% strength acetic acid). 1.8 g of the title compound were isolated as a white amorphous powder, FAB-MS (M-H⁺) = 580.

10 f) HOOC-p-C₆H₄CH₂-(D)Chg-Pyr-NH-CH₂-5-(3-am)-thioph

1.8 g of the above amidine compound were dissolved in 12 ml of glacial acetic acid, 12 ml of 4 N HCl in dioxane and 0.5 ml of water were added and the mixture was left to stand for 2.5 hours at room temperature.

After the solvent had been stripped off, the residue was treated with acetonitrile, the dihydrochloride separating out. This was dissolved in water for conversion into a monohydrochloride and was brought to a pH of 4.5 with a weakly basic ion exchanger (3-X4 Resin, BioRad). The aqueous solution was lyophilized after treatment with active carbon. 1.0 g of the title compound was obtained as lyophilized product, which was converted into a crystalline state by treatment with isopropanol, m.p. 230-233°C (decomposition), FAB-MS (M+H⁺) = 524.

Example 57

30 MeOOC-p-C₆H₄CH₂-(D)Chg-Pyr-NH-CH₂-5-(3-am)-thioph·HCl

0.75 g (20 mmol) of hydrogen chloride was passed into a solution of 1.1 g (2 mmol) of the compound described in Example 56 in 70 ml of methanol and refluxing was then carried out for 8 hours.

35 The cooled solution was brought to pH 6 with a weakly basic ion exchanger (3-X4 Resin, BioRad), the methanol was distilled off and the viscous, oily residue was converted, by treatment with acetonitrile, into a slightly yellowish monohydrochloride which 40 could be filtered off with suction. By dissolution in methanol, treatment with active carbon and removal of the methanol by distillation, finally with the addition of acetonitrile, 1.9 g of the title compound were isolated as white crystals, m.p. 215-220°C (decomposition), FAB-MS (M+H⁺) = 538; TLC: 20:5:1 45 CH₂Cl₂/methanol/50% strength acetic acid.

Example 58

$\text{H}_2\text{N}-\text{CO}-\text{p}-\text{C}_6\text{H}_4\text{CH}_2-(\text{D})\text{Chg}-\text{Pyr}-\text{NH}-\text{CH}_2-5-(3\text{-am})\text{-thioph}\cdot\text{HCl}$

0.6 g of the above compound (Example 57) was dissolved in 40 ml
 5 of methanol and the solution was heated at about 45°C for 4 days
 while passing in ammonia. After the solvent had been stripped
 off, purification was carried out by column chromatography
 (eluent: 35:15:2.5 CH_2Cl_2 /methanol/50% strength acetic acid). The
 residue was dissolved in water, the solution was brought to pH 2
 10 with 1 N hydrochloric acid and was evaporated to dryness and the
 residue was again taken up in water, brought to pH 6 with a
 weakly basic ion exchanger and, after treatment with an active
 carbon, lyophilized. 0.28 g of the title compound was obtained as
 white, amorphous powder, FAB-MS ($\text{M}-\text{H}^+$) = 523.

15

Example 59

$\text{HOOC}-\text{m}-\text{C}_6\text{H}_4\text{CH}_2-\text{D}(\text{Chg})-\text{Pyr}-\text{NH}-\text{CH}_2-5-(3\text{-am})\text{-thioph}$

The title compound was obtained analogously to Example 56,
 20 starting from tert-butyl 3-bromomethylbenzoate (N. Shirai et al.,
 J. Org. Chem. 55, (1990), 2767). White, amorphous powder, FAB-MS
 ($\text{M}+\text{H}^+$) = 524.

Example 60

25 $\text{HOOC}-\text{p}-\text{C}_6\text{H}_4\text{CH}_2-(\text{D})\text{Cha}-\text{Pyr}-\text{NH}-3-(6\text{-am})\text{-pico}\cdot\text{HCl}$

The preparation was carried out by reacting
 N-(tert-butoxycarbonyl)-N-(4-tert-butoxycarbonylbenzyl)-D-cyclo-
 hexylalanine (Example 55) with
 30 3,4-dehydroprolyl-(3-(6-cyano)picolyl)amide (Example 20, stage
 e), then forming the amidine (Example 20, stage f) and
 eliminating the protective groups (Example 56, stage f).
 Colorless, amorphous powder, FAB-MS ($\text{M}+\text{H}^+$) = 533.

35 Example 61

$\text{HOOC}-\text{p}-\text{C}_6\text{H}_4\text{CH}_2-(\text{D})\text{Chg}-\text{Pyr}-\text{NH}-3-(6\text{-am})\text{-pico}\cdot\text{HCl}$

The preparation was carried out analogously to Example 60. The
 starting material
 40 N-(tert-butoxycarbonyl)-N-(tert-butoxycarbonylbenzyl)-D-cyclo-
 hexylglycine is described in Example 56, stages a) to c).
 Colorless, amorphous powder, FAB-MS ($\text{M}+\text{H}^+$) = 519.

Example 62

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N-(4-Hydroxycarbonyl-phenylsulfonyl)-(D)-cyclohexylglycyl-3,4-
 dehydroprolyl-[5-(3-amidino)thienylmethyl]amide:

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- This compound is prepared by coupling (PPA, dichloromethane) H-Pyr-NH-CH₂-5-(3-CN)-thioph with Boc(D)Chg-OH to give Boc(D)Chg-Pyr-NH-CH₂-5-(3-CN)-thioph, eliminating the protective group (HCl in isopropanol) and then reacting (dichloromethane, 5 DIPEA) with 4-HOOC-C₆H₄-SO₂Cl to give 4-HOOC-C₆H₄-SO₂-(D)Chg-Pyr-NH-CH₂-5-(3-CN)-thioph. After conversion of the nitrile function into the amidine function and purification by MPL chromatography, the title compound was obtained as a white amorphous powder.
- 10 FAB-MS (M+H⁺): 574.

Example 63

- N-(3-Hydroxycarbonyl-phenylsulfonyl)-(D)-cyclohexylglycyl-3,4-15 dehydroprolyl-[5-(3-amidino)thienylmethyl]amide:
This compound is prepared by coupling (PPA, dichloromethane) H-Pyr-NH-CH₂-5-(3-CN)-thioph with BOC(D)Chg-OH [sic] to give BOC(D)Chg-Pyr-NH-CH₂-5-(3-CN)-thioph [sic], eliminating the protective group (HCl in isopropanol) and then reacting 20 (dichloromethane, DIPEA) with 3-HOOC-C₆H₄-SO₂Cl to give 3-HOOC-C₆H₄-SO₂-(D)Chg-Pyr-NH-CH₂-5-(3-CN)-thioph. After conversion of the nitrile function into the amidine function and purification by MPL chromatography, the title compound was obtained as a white amorphous powder.
- 25 FAB-MS (M+H⁺): 574

Example 64

- t-BuOOC-p-C₆H₄CH₂-(D)Chg-Pyr-NH-CH₂-5-(3-am)-thiop acetate
- 30 a) N-(4-tert-Butoxycarbonylbenzyl)-D-cyclohexylglycine
- 96.3 ml (96.3 mmol) of 1 N sodium hydroxide solution were added dropwise at 10°C to a solution of 29 g (80 mmol) of 35 methyl N-(4-tert-butoxycarbonylbenzyl)-D-cyclohexylglycine (Example 56, stage a) and stirring was carried out for 48 hours at room temperature. After the addition of a further 0.3 equivalent of 1 N NaOH, stirring was carried out for a further 10 hours at 50°C. By adding 5% strength citric acid 40 solution, the pH of the solution was brought to about 8, the dioxane was distilled off and the aqueous phase was extracted with MTBE and acidified by further addition of citric acid. The precipitated acid was taken up in ethyl acetate, the aqueous phase was extracted several times with ethyl acetate, 45 the combined ethyl acetate extracts were dried with MgSO₄ and the solvent was then distilled off, the acid crystallizing

out toward the end. Yield: 17.5 g of white crystals (63% of theory), m.p. > 225°C (decomposition).

- 5 b) N-(tert-Butoxycarbonyl)-3,4-dehydroprolyl-[2-(4-hydroxy-amidino)thienylmethyl]amide

8 g of concentrated ammonia were added to a suspension of 15.6 g (224.5 mmol) of hydroxylamine hydrochloride in 300 ml of ethanol, stirring was carried out for 30 minutes, the precipitated NH_4Cl was filtered off with suction, 30 g (90 mmol) of N-(tert-butoxycarbonyl)-3,4-dehydroprolyl-[2-(4-cyano)thienylmethyl]amide (WO 98/06741, Examples 1 and 5) were then added and stirring was carried out overnight at room temperature. Thereafter, no starting material was detectable (TLC, mobile phase: $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9/1 or $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{concentrated ammonia}$, 4.5/5/0.3).

20 After the solvent had been distilled off, the residue was taken up in 300 ml of methylene chloride, and the solution was washed with water and aqueous NaHCO_3 solution and dried over Na_2SO_4 . After evaporating down, 31.5 g (95.5% of theory) of amorphous residue remained, RF 0.32 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$), FAB-MS: 366 (M^+).

- 25 c) N-(tert-Butoxycarbonyl)-3,4-dehydroprolyl-[2-(4-hydroxy-amidino)thienylmethyl]amide

31.5 g (86 mmol) of the above hydroxyamidine compound were dissolved in 300 ml of glacial acetic acid under nitrogen, 17 g of zinc dust (<10 μm) were added a little at a time at from 40 to 50°C and stirring was carried out for 6 hours at 40°C. Thereafter, no starting material was detectable (TLC, mobile phase: $\text{CH}_2\text{Cl}_2/\text{methanol}$, 9/1).

35 After removal of the solids by filtration with suction and washing with glacial acetic acid, the acetic acid was substantially distilled off, with addition of toluene toward the end. The residue was taken up in 350 ml of water, brought to pH 7 with 1 N sodium hydroxide solution and extracted once with 180 ml of MTBE. After addition of 200 ml of CH_2Cl_2 , the aqueous phase was brought to pH 12, the CH_2Cl_2 phase was separated off and then extraction was carried out again and the combined CH_2Cl_2 phases were dried over Na_2SO_4 . After distillation, 28.4 g (94% of theory) of amorphous residue remained, RF 0.35 ($\text{CH}_2\text{Cl}_2/\text{MeOH}/50\%$ strength acetic acid, 12/3/1), FAB-MS: 350 (M^+).

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- c) 3,4-Dehydroprolyl-[2-(4-amidino)thienylmethyl]amide dihydrochloride

28.4 g (81 mmol) of the above amidine were suspended in 450 ml of isopropanol, and 1215 ml of 4 N HCl in dioxane were added with stirring, a clear solution resulted in a short time, from which the dihydrochloride was slowly precipitated. The reaction mixture was stirred for 3 hours at room temperature and the crystals were filtered off with suction and washed thoroughly with cold isopropanol and finally with MTBE. After drying, 19.5 g (74.4% of theory) of the hygroscopic dihydrochloride remained, RF 0.53 (CH₂Cl₂/MeOH/H₂O/CF₃COOH, 24/9/1/0.5), FAB-MS: 250 (M⁺), m.p. 220-223°C (decomposition).

- d) t-BuOOC-p-C₆H₄CH₂-(D)Chg-Pyr-NH-CH₂-5-(3-am)-thioph acetate

N-(4-t-Butoxycarbonylbenzyl)-D-cyclohexylglycine (stage a) and 3,4-dehydroprolyl-[2-(4-amidino)thienylmethyl]amide dihydrochloride were coupled analogously to Example 56, stage e, to give the end product. White amorphous powder, FAB-MS: 579 (M⁺).

Example 65

- HOOC-p-C₆H₄CH₂-(D)Val-Pyr-NH-CH₂-5-(3-am)-thioph HCl

- a) Methyl N-(4-tert-butoxycarbonylbenzyl)-D-valine

Prepared by reaction of methyl D-valine hydrochloride and tert-butyl 4-bromomethylbenzoate analogously to Example 56, stage a. The compound was obtained in 74% yield after chromatographic purification, FAB-MS: 321 (M⁺).

- b) N-(4-tert-Butoxycarbonylbenzyl)-D-valine

The hydrolysis was carried out analogously to Example 64, stage a. White crystals, m.p. 224-226°C (decomposition), FAB-MS: 307 (M⁺).

- c) t-BuOOC-p-C₆H₄CH₂-(D)Val-Pyr-NH-CH₂-5-(3-am)-thioph acetate

N-(4-t-Butoxycarbonylbenzyl)-D-valine and 3,4-dehydroprolyl-[2-(4-amidino)thienylmethyl]amide dihydrochloride (Example 64, stage c) were coupled analogously to Example 56, stage e. After purification by

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column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}/50\%$ strength CH_3COOH , 20/5/1), 3.1 g of white amorphous powder were isolated, FAB-MS: 539 (M^+).

5 d) $\text{HOOC-p-C}_6\text{H}_4\text{CH}_2\text{-(D)Val-Pyr-NH-CH}_2\text{-5-(3-am)-thioph HCl}$

The hydrolysis of the tert-butyl ester was carried out analogously to Example 56, stage f. After freeze-drying, 1.6 g of lyophilized product were isolated, FAB-MS: 483 (M^+).

10

The following compounds were obtained analogously to Examples 56 and 64:

Example 66

15

$\text{HOOC-m-C}_6\text{H}_4\text{CH}_2\text{-(D)Val-Pyr-NH-CH}_2\text{-5-(3-am)-thioph HCl}$
White amorphous powder, FAB-MS: 483 (M^+).

Example 67

20

$\text{HOOC-p-C}_6\text{H}_4\text{CH}_2\text{-(D)tBu-Ala-Pyr-NH-CH}_2\text{-5-(3-am)-thioph acetate}$
White amorphous powder, FAB-MS: 511 (M^+).

Example 68

25

$\text{HOOC-p-C}_6\text{H}_4\text{CH}_2\text{-(D)tBu-Gly-Pyr-NH-CH}_2\text{-5-(3-am)-thioph HCl}$
White amorphous powder, FAB-MS: 497 (M^+).

Example 69

30

$\text{HOOC-p-C}_6\text{H}_4\text{CH}_2\text{-Pyr-NH-CH}_2\text{-5-(3-am)-thioph HCl}$
White amorphous powder, FAB-MS: 441 (M^+).

Example 70

35

$\text{HOOC-m-C}_6\text{H}_4\text{CH}_2\text{-Gly-Pyr-NH-CH}_2\text{-5-(3-am)-thioph HCl}$
White amorphous powder, FAB-MS: 441 (M^+).

Example 71

40

$\text{H}_2\text{N-p-C}_6\text{H}_4\text{CH}_2\text{-SO}_2\text{-(D)CHa-Pyr-NH-CH}_2\text{-(3-am)-thioph HCl}$

N-(4-tert-Butoxycarbonylamino benzylsulfonyl)-D-cyclohexylalanine
(preparation: Example 20, stage d) and

45 3,4-dehydroprolyl-[2-(4-amidino)thienylmethyl]amide
dihydrochloride (Example 64, stage c) were coupled analogously to
Example 56, stage c, and the tert-butoxycarbonyl protective group

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was then eliminated analogously to Example 21. White, amorphous powder, FAB-MS: 572 (M^+).

Example 72

5

$H_2N-p-C_6H_4CH_2-SO_2-(D)Chg-Pyr-NH-CH_2-(3-am)-thioph\ HCl$

Preparation analogous to Examples 20 and 21. The intermediates methyl N-(4-nitrobenzylsulfonyl)- and

- 10 N-(4-aminobenzylsulfonyl)-(D)-cyclohexylglycine were obtained as slightly yellowish crystals, m.p. 137°C and 181°C, respectively. White, amorphous powder, FAB-MS: 558 (M^+).

Example 73

- 15 $H_2N-p-C_6H_4CH_2-(D)Val-Pyr-NH-CH_2-5-(3-am)-thioph\ 2HCl$

The preparation was carried out analogously to Examples 20 and 21.

Intermediates:

- 20 methyl N-(4-nitrobenzylsulfonyl)-(D)-valine, slightly yellowish crystals, m.p. 98-100°C, FAB-MS: 330 (M^+);
methyl N-(4-aminobenzylsulfonyl)-(D)-valine, slightly yellowish crystals, m.p. 96-98°C, FAB-MS: 300 (M^+);
methyl N-(4-tert-butoxycarbonylamino benzylsulfonyl)-D-valine, white crystals, m.p. 150-152°C, (i-propanol);
25 N-(4-tert-butoxycarbonylamino benzylsulfonyl)-D-valine, colorless crystals, m.p. 177-180°C (decomposition), FAB-MS: 386 (M^+).
The end product was isolated as lyophilized product, FAB-MS: 558 (M^+).

30 Example 74

$H_2N-SO_2-p-C_6H_4CH_2-(D)Chg-Pyr-NH-CH_2-5-(3-am)-thioph\ HCl$

- a) Methyl N-(4-sulfonamidobenzyl)-D-cyclohexylglycine

35

- 7.3 g of diisopropylethylamine were added dropwise at room temperature to a solution of 5.2 g (25 mmol) of methyl D-cyclohexylglycine hydrochloride and 5.5 g (22 mmol) of 4-bromomethylbenzenesulfonamide (F. Amer. Chem. Soc. 79
40 (1957), 4232) in 30 ml of DMF, the temperature increasing to 26°C. The colorless solution remained standing overnight at room temperature. Thereafter, no starting material was detectable. (TLC, CH_2Cl_2 /ether, 5/2).

- 45 After dilution with 100 ml of ice water, the white precipitate which separated out was filtered off with suction, washed with water and dissolved in ethyl acetate. The ethyl acetate phase was washed several times with sodium

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chloride solution and dried over Na_2SO_4 , and the solvent was distilled off. The residue was recrystallized from 50 ml of isopropanol. 4.8 g (64% of theory) of white crystals were obtained, m.p. 113-114°C, FAB-MS: 340 (M^+).

5

b) N-(4-Sulfonamidobenzyl)-D-cyclohexylglycine

4.0 g (11.8 mmol) of the above ester were suspended in 50 ml of water, brought into solution by adding 35 ml of 1 N NaOH and allowed to stand overnight at room temperature. A pH of 5 was established by dropwise addition of 10% strength hydrochloric acid, a fine precipitate separating out. A structure which could be readily filtered off with suction was obtained by brief heating to 80°, slow cooling to room temperature and stirring for 30 minutes while cooling in an ice bath. After being filtered off with suction, the precipitate was washed chloride-free with cold water, then digested with 50 ml of acetone, filtered off with suction again and then washed several times with an acetone/ether mixture and dried. 3.6 g (93.5% of theory) of white powder remained, said powder being extremely sparingly soluble.

c) $\text{H}_2\text{N}-\text{SO}_2-\text{p}-\text{C}_6\text{H}_4\text{CH}_2-(\text{D})\text{Chg-Pyr-NH-CH}_2-5-(3\text{-am})\text{-thioph HCl}$

Coupling to give the end product was carried out analogously to Example 56, stage e. 1 g of a lyophilized product was obtained, FAB MS: 558 (M^+).

Example 75

30

$\text{HO}_3\text{S-p-C}_6\text{H}_4\text{CH}_2-(\text{D})\text{Chg-Pyr-NH-CH}_2-5-(3\text{-am})\text{-thioph}$
4-Bromomethylbenzenesulfonic acid (F. Med. Chem. 33 (1990), 2437) was reacted with methyl D-cyclohexylglycine hydrochloride analogously to Example 74 and the reaction product was hydrolyzed and was then coupled with 3,4-dehydropyrol-2-(4-amidino)thienylmethyl]amide dihydrochloride.

White amorphous powder, FAB-MS: 559 (M^+).

40 Example 76

$\text{HO-p-C}_6\text{H}_4\text{CH}_2-(\text{D})\text{Chg-Pyr-NH-CH}_2-5-(3\text{-am})\text{-thioph 2HCl}$

a) Methyl N-(4-tert-butoxybenzyl)-D-cyclohexylglycine

45

5.2 g (25 mmol) of methyl D-cyclohexylglycine hydrochloride were dissolved in 200 ml of toluene with gentle heating,

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2.6 g (25.7 mmol) of triethylamine were added and stirring was carried out for 1 hour. The triethylamine hydrochloride was filtered off with suction and washed with toluene, after which the filtrate was evaporated down to 70 ml, 4.5 g (25 mmol) of p-tert-butoxybenzaldehyde and 0.1 ml of glacial acetic acid were added and refluxing was carried out for 2.5 hours under a water separator. The toluene was distilled off under reduced pressure, the residue was dissolved in 50 ml of methanol, 1.5 g (25 mmol) of glacial acetic acid were added and 0.9 g of sodium cyanoborohydride was introduced a little at a time at 5°C (TLC check: CH₂Cl₂/E₂O, 25/1). The methanol was distilled off, excess 5% strength NaHCO₃ was added to the residue and extraction was carried out with ether. After washing the ether phase with sodium chloride solution, drying over Na₂SO₄ and distilling off the ether, the oily residue was purified by column chromatography (eluent: CH₂Cl₂/E₂O, 25/1).
Yield: 4.3 g (51% of theory), colorless oil;
FAB-MS: 333 (M⁺).

Analogously to Example 74, the above ester was hydrolyzed and was coupled with 3,4-dehydroprolyl-[2-(4-amidino)thienylmethyl]amide dihydrochloride, and the tert-butyl group was eliminated by means of hydrochloric acid. Amorphous, white powder, FAB-MS: 495 (M⁺).

Example 77

HO-p-C₆H₄CH₂-(D)Val-Pyr-NH-CH₂-5-(3-am)-thioph 2HCl

The preparation was carried out analogously to Example 76. White, amorphous powder, FAB-MS: 455 (M⁺).

Example 78

HOCH₂-p-C₆H₄CH₂-(D)Val-Pyr-NH-CH₂-5-(3-am)-thioph HCl

The preparation was carried out starting from 4-(hydroxymethyl)benzyl chloride (J. Org. Chem. 61 (1996), 449), analogously to Example 76.
White, amorphous powder, FAB-MS: 469 (M⁺).

Example 79

O₂N-p-C₆H₄CH₂-(D)Val-Pyr-NH-CH₂-5-(3-am)-thioph HCl

133

The preparation was carried out analogously to Example 76. Slightly yellowish, amorphous powder, FAB-MS: 484 (M^+).

Example 80

5

HOOC-p-C₆H₄CH₂-(D)Val-Pyr-NH-CH₂-5-(3-am)-thioph HCl

4-(tert-Butoxycarbonyl)benzylsulfonyl chloride

- 10 A suspension of 15 g (55 mol) of tert-butyl 4-bromomethylbenzoate and 6.95 g (55 mol) of sodium sulfite in 28.5 ml of water and 13.5 ml of DMF was heated at 80-90°C for 4 hours while stirring, after addition of 0.4 g of Adogen®. After cooling to room temperature, 100 ml of water were added, extraction was effected
- 15 with twice 100 ml of MTBE, 250 ml of MeOH were added to the aqueous phase, the precipitated salts were filtered off with suction and the filtrate was evaporated down, under reduced pressure from an oil pump toward the end. The residue was digested with 200 ml of MeOH, insoluble solid components were
- 20 filtered off with suction and the methanol was distilled off, after repeated addition of ethanol/toluene toward the end. The residue (16.1 g) was suspended in 200 ml of CH₂Cl₂, 0.8 g of tetraethylbenzylammonium chloride was added, 15 g of oxalyl dichloride were added dropwise at 0°C and refluxing was carried
- 25 out for 30 minutes. Undissolved matter was filtered off with suction and the CH₂Cl₂ phase was washed with 5% strength NaHCO₃ solution, dried over Na₂SO₄ and distilled off. By treatment with n-hexane, 6.6 g of virtually white crystals were isolated, m.p. 82-83°C (decomposition).
- 30 Analogously to Example 76, reaction was carried out with methyl D-valine hydrochloride, hydrolysis was effected to give the acid, coupling was carried out with 3,4-dehydroprolyl-[2-(4-amidino)thienylmethyl]amide dihydrochloride and the tert-butyl
- 35 ester group was eliminated.

White, amorphous powder, FAB-MS: 547 (M^+).

Example 81

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HOOC-p-C₆H₄CH₂-SO₂-(D)Chg-Pyr-NH-CH₂-5-(3-am)-thioph HCl

The preparation was carried out analogously to Examples 80 and 76.

- 45 White, amorphous powder, FAB-MS: 587 (M^+).

Example 82

trans-HOOC-4-Cyclohexylmethyl-Gly-Pyr-NH-CH₂-5-(3-am)-thioph 2HCl

- 5 a) trans-4-[N-(o-Nitrophenylsulfonyl)]aminomethylcyclohexane carboxylic acid

10 A solution of 29.9 g (0.135 mol) of o-nitrobenzenesulfonyl chloride in 150 ml of dioxane and 150 ml of 1 N NaOH was added simultaneously and dropwise at 4°C (ice bath) to a solution of 14.13 g (0.09 mol) of

15 trans-4-(aminomethyl)cyclohexanecarboxylic acid in a two-phase system comprising 90 ml of 1 N NaOH and 90 ml of dioxane. After the slightly exothermic reaction had died down, stirring was carried out for 30 minutes at room

20 temperature, the precipitate which separated out was filtered off with suction and washed with a little ice water and the filtrate was evaporated down under reduced pressure, further precipitation of salt occurring. The combined amounts of salt were digested with ether, suspended in water, acidified with 1 M KHSO₄ solution and extracted with ethyl acetate. The ethyl acetate phase was washed with sodium chloride solution, dried over Na₂SO₄ and evaporated down under reduced pressure. The residue was recrystallized from acetonitrile. Yield:

25 27.4 g (89% of theory), m.p. 179°C.

- b) tert-Butyl trans-4-[N-(o-nitrophenylsulfonyl)]aminomethyl-cyclohexane carboxylate

30 11.3 g (90 mmol) of oxalyl dichloride were added dropwise at 0° to a solution of 20.4 g (60 mmol) of the above compound and 0.1 ml of DMF in 350 ml of CH₂Cl₂, and the mixture was then heated until the gas evolution had ended. After the methylene chloride had been distilled off - with the addition

35 of toluene toward the end - the residue was dissolved in 20 ml of methylene chloride and was added dropwise to a solution of 6.1 g (83 mmol) of tert-butanol and 9.4 g (119 mmol) of pyridine in 60 ml of CH₂Cl₂ while cooling with ice. The reaction mixture remained standing at room

40 temperature for 24 hours and was then washed with 1 N KHSO₄ solution, water and NaHCO₃ solution and dried over Na₂SO₄, and the solvent was distilled off. The residue was recrystallized from cyclohexane/ethyl acetate (95/5) and gave 9.3 g of slightly yellowish crystals, m.p. 114°C.

45

135

- c) tert-Butyl trans-4-[N-(o-nitrophenylsulfonyl)-N-(methoxycarbonylmethyl)]aminomethylcyclohexanecarboxylate

5 A solution of 2.68 g (6.7 mmol) of the above compound and 1.23 g (7.6 mmol) of methyl bromoacetate in 50 ml of DMF was stirred overnight at room temperature with the addition of 1.85 g (13.4 mmol) of K₂CO₃ powder (TLC: ethyl acetate/n-hexane, 1/1). 100 ml of water were added to the reaction mixture, extraction was effected several times with 10 ethyl acetate, the combined ethyl acetate extracts were washed with sodium chloride solution and dried over Na₂SO₄ and the solvent was distilled off. After purification by column chromatography (eluent: ethyl acetate/n-hexane, 1/1) and crystallization from ether/n-hexane, 2.6 g (82.3% of theory) 15 of yellowish crystals were obtained, m.p. 123-124°C.

- d) tert-Butyl trans-4-[N-(o-nitrophenylsulfonyl)-N-(hydroxycarbonylmethyl)]aminomethylcyclohexanecarboxylate

20 The methyl ester group of the above compound was hydrolyzed analogously to Example 20, stage d. Viscous yellow oil, FAB-MS: 456 (M⁺), TLC: ethyl acetate/n-hexane/glacial acetic acid, 34/15/1.5.

- 25 e) trans-t-BuOOC-4-cyclohexylmethyl-(o-NO₂-C₆H₄SO₂)Gly-Pyr-NH-CH₂-5-(3-CN)-thioph

30 The above acid was coupled with 3,4-dehydroprolyl-[2-(4-cyano)thienylmethyl]amide hydrochloride analogously to Example 20, stage e. Amorphous, yellowish residue, FAB-MS: 671 (M⁺), TLC: CH₂Cl₂/acetone/methanol, 45/5/1.

- f) trans-t-BuOOC-4-cyclohexylmethyl-Gly-Pyr-NH-CH₂-5-(3-N)-thioph

35 A solution of 3.5 g (5.5 mmol) of the above compound and 0.7 g (6.35 mmol) of thiophenol in 10 ml of DMF was stirred overnight at room temperature with the addition of 2.5 g (18.1 mmol) of K₂CO₃ powder. 100 ml of ice water were added to 40 the yellow reaction mixture, extraction was effected with 4 x 35 ml of ethyl acetate, the ethyl acetate extracts were washed with sodium chloride solution and dried over Na₂SO₄ and the viscous yellow oil obtained after distilling off the solvent was purified by column chromatography (eluent: 45 CH₂Cl₂/methanol, 50/4). 2.3 g of yellowish amorphous residue were obtained, FAB-MS: 486 (M⁺).

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- g) trans-HOOC-4-Cyclohexylmethyl-Gly-Pyr-NH-5-(3-am)-thioph
2HCl

- 5 The amidine formation was carried out analogously to Example 64, stages b and c. The hydrolysis of the tert-butyl ester was carried out with 4 N hydrochloric acid in dioxane. 1.1 g of lyophilized product were obtained, FAB-MS: 447 (M^+), TLC: CH_2Cl_2 /MeOH/50% strength glacial acetic acid, 35/15/6.

10 Example 83

trans-HOOC-4-Cyclohexylmethyl-(D)Chg-Pyr-NH-CH₂-5-(3-am)-thioph
2HCl

- 15 1.9 ml (11 mmol) of trifluoromethanesulfonic anhydride and then 1.2 g (11 mmol) of 2,6-lutidine were added dropwise at -8°C to a solution of 1.72 g (10 mmol) of methyl S-hexahydromandelate while stirring. After stirring for 20 minutes at 0°C (TLC: Et₂O/n-hexane, 3/2), a solution of 5.3 g (24.9 mmol) of tert-butyl
20 trans-4-(aminomethyl)cyclohexane carboxylate and 2.6 g (20 mmol) of diisopropylethylamine in 20 ml of CH_2Cl_2 was added dropwise and stirring was carried out for a further 2 hours at 0°C and overnight at room temperature (TLC: CH_2Cl_2 /ether, 25/3).
- 25 The reaction solution was washed with water, with twice 10 ml 1 N hydrochloric acid and with 5% strength $NaHCO_3$ solution and dried over Na_2SO_4 , the solvent was distilled off and the residue was purified by column chromatography (eluent: CH_2Cl_2 /ether, 10/1). 2.7 g of a slightly yellowish oil were isolated, which oil was
30 hydrolyzed analogously to Example 56, stage c, to give the acid and then coupled analogously to stage e with 3,4-dehydroprolyl[2-(4-amidino)thienylmethyl]amide dihydrochloride. After hydrolysis of the tert-butyl ester group with 4 N hydrochloric acid in dioxane, the residue was freeze-dried to give a slightly
35 yellowish amorphous powder, FAB-MS: 529 (M^+), TLC: CH_2Cl_2 /MeOH/50% strength acetic acid, 35/15/3.

Example 84

4-Benzoylbenzoyl-Ala-Pro-5-(3-am)-thioph

40

- a) 3 g (1.62 mmol) p-nitrophenyl carbonate Wang resin (Novabiochem, substitution 0.54 mmol/g) were suspended in 20 ml of DMF and shaken with 1.15 g (3.24 mmol) of 4-amidino-2-[N-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl]aminomethylthiophene hydrochloride and 4.48 ml (32.4 mmol) of triethylamine for 4 days at room temperature. The solid was filtered off with suction and was

- washed with DMF, CH_2Cl_2 , methanol and CH_2Cl_2 . The resin was then treated with 0.5 M NH_4OAc solution in methanol (3x10 min), washed with methanol, DMF and CH_2Cl_2 and dried under reduced pressure at room temperature. To eliminate the Dde protective group, the resin was treated with 20 ml of a 2% strength solution of hydrazine hydrate in DMF at room temperature for 5 minutes. The solid was filtered off with suction and was washed with DMF. The elimination was repeated twice. Thereafter, the residue was washed with DMF, CH_2Cl_2 , methanol and CH_2Cl_2 and was dried under reduced pressure at room temperature (weight obtained: 2.84 g).
- b) A solution of 0.088 mmol of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate in 0.5 ml of dimethylformamide was added at room temperature to 0.044 mmol of a resin from a), 0.088 mmol of Fmoc-Pro-OH and 0.088 mmol of N,N-diisopropylethylamine in 1.5 ml of dimethylformamide and stirring was carried out for 2 hours at room temperature. The solid was then filtered off with suction and was washed with dimethylformamide, CH_2Cl_2 , methanol and CH_2Cl_2 . The elimination of the Fmoc-protective group was carried out with 2 ml of a solution of 10% of (1,8-diazabicyclo-[5.4.0.]undec-7-ene), 2% of piperidine and 88% of dimethylformamide (3 min). Thereafter, the resin was filtered off with suction and was washed with dimethylformamide, CH_2Cl_2 , methanol and CH_2Cl_2 .
- c) The resin from b) was suspended in a solution of 0.088 mmol of Fmoc-Ala-OH and 0.088 mmol of N,N-diisopropylethylamine in 1.5 ml of dimethylformamide, a solution of 0.088 mmol of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate in 0.5 ml of dimethylformamide was added and stirring was carried out for 2 hours at room temperature. Thereafter, the solid was filtered off with suction and was washed with dimethylformamide, CH_2Cl_2 , methanol and CH_2Cl_2 . The elimination of the Fmoc protective group was carried out with 2 ml of a solution of 10% of (1,8-diazabicyclo[5.4.0.]undec-7-ene), 2% of piperidine and 88% of dimethylformamide (3 min). Thereafter, the resin was filtered off with suction and was washed with dimethylformamide, CH_2Cl_2 , methanol and CH_2Cl_2 .
- d) The resin from c) was suspended in a solution of 0.088 mmol of 4-benzoylbenzoic acid acid [sic] in 1 ml of CH_2Cl_2 , and 0.088 mmol of diisopropylcarbodiimide in 0.5 ml of CH_2Cl_2 was added. Stirring was carried out for 2 hours at room temperature, after which the solid was filtered off with

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suction and was washed with dimethylformamide, CH_2Cl_2 , methanol and CH_2Cl_2 . The elimination of the product from the carrier was carried out by treatment with 95:5 trifluoroacetic acid/water

5 (1 h/room temperature).

Yield: 13 mg. HPLC-MS: $\text{M}+\text{H}^+$ 532 (calculated: 532).

The following examples were prepared analogously to Example 84, where, for example, reductive aminations of the resin can be
10 carried out with, for example, 4-carboxybenzaldehyde or other aldehydes under standard conditions with sodium cyanoborohydride in 1% AcOH/DMF instead of the final coupling.

Example 85

15 3-Benzoylbenzoyl-Gly-Pro-NH- CH_2 -5-(3-am)-thioph
ESI-MS $[\text{M}+\text{H}]^+$ 518

Example 86

4-Benzoylbenzoyl-Gly-Pro-NH- CH_2 -5-(3-am)-thioph
20 ESI-MS $[\text{M}+\text{H}]^+$ 518

Example 87

4-Phenylbenzoyl-Gly-Pro-NH- CH_2 -5-(3-am)-thioph
ESI-MS $[\text{M}+\text{H}]^+$ 490
25

Example 88

4-Phenylphenylacetyl-Gly-Pro-NH- CH_2 -5-(3-am)-thioph
ESI-MS $[\text{M}+\text{H}]^+$ 504

30 Example 89

2-(Benzylthio)-benzoyl-Gly-Pro-NH- CH_2 -5-(3-am)-thioph
ESI-MS $[\text{M}+\text{H}]^+$ 536

Example 90

35 3-Phenylpropionyl-Gly-Pro-NH- CH_2 -5-(3-am)-thioph
ESI-MS $[\text{M}+\text{H}]^+$ 442

Example 91

4-Phenylbutyryl-Gly-Pro-NH- CH_2 -5-(3-am)-thioph
40 ESI-MS $[\text{M}+\text{H}]^+$ 456

Example 92

5-Phenylvaleryl-Gly-Pro-NH- CH_2 -5-(3-am)-thioph
ESI-MS $[\text{M}+\text{H}]^+$ 470
45

Example 93

Cinnamoyl-Gly-Pro-NH- CH_2 -5-(3-am)-thioph

ESI-MS [M+H]⁺ 440

Example 94

C₆H₅-C≡C-CO-Gly-Pro-NH-CH₂-5-(3-am)-thioph

5 ESI-MS [M+H]⁺ 438

Example 95

9-Fluorenone-4-carbonyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 516

10

Example 96

3-Benzylloxycarbonylpropionyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 500

15 Example 97

4-Methoxycarbonylcinnamoyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 498

Example 98

20 4-Methoxycarbonylbenzoyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 472

Example 99

2-(4'-Chloro-3'-nitrobenzoyl)-benzoyl-Gly-Pro-NH-CH₂-5-(3-am)-

25 thioph

ESI-MS [M+H]⁺ 597

Example 100

6-(Acetylamino)-pyridyl-3-carbonyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

30 ESI-MS [M+H]⁺ 472

Example 101

3-(3'-Pyridyl)-acryloyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 441

35

Example 102

4-Acetylamino benzoyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 471

40 Example 103

4-(4'-Aminophenoxy)-benzoyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 521

Example 104

45 4-(2'-Chloro-4'-aminophenoxy)-benzoyl-Gly-Pro-NH-CH₂-5-(3-am)-
thioph

ESI-MS [M+H]⁺ 555

Example 105

4-Aminobenzoyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

5 ESI-MS [M+H]⁺ 486

Example 106

(4-Aminophenyl)acetyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 443

10

Example 107

(4-Aminophenylthio)-acetyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 475

15 Example 108

2-(Pyrid-3-yl)-acetyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 429

Example 109

20 3-(4'-Aminobenzoyl)-butyryl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 499

Example 110

4-Benzoylbenzoyl-(D)-Val-Pro-NH-CH₂-5-(3-am)-thioph

25 ESI-MS [M+H]⁺ 560

Example 111

4-Phenylphenylacetyl-(D)-Val-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 546

30

Example 112

4-Phenylphenylacetyl-(D)-Ala-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 518

35 Example 113

4-Benzoylbenzoyl-β-Ala-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 532

Example 114

40 4-Benzoylbenzoyl-(D)-Ala-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 532

Example 115

2-(Benzylthio)-benzoyl-(D)-Ala-Pro-NH-CH₂-5-(3-am)-thioph

45 ESI-MS [M+H]⁺ 550

Example 116

5-Phenylvaleryl-(D)-Val-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 512

5 Example 117

5-Phenylvaleryl-(D)-Ala-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 484

Example 118

10 5-Phenylvaleryl-Ala-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 484

Example 119

3-Phenylpropionyl-(D)-Val-Pro-NH-CH₂-5-(3-am)-thioph15 ESI-MS [M+H]⁺ 484

Example 120

4-Phenylbutyryl-(D)-Val-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 498

20

Example 121

4-Phenylbutyryl-(D)-Ala-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 470

25 Example 122

4-Phenylbenzoyl-(D)-Val-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 532

Example 123

30 4-Phenylbenzoyl-Ala-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 504

Example 124

4-Phenylbenzoyl-Val-Pro-NH-CH₂-5-(3-am)-thioph35 ESI-MS [M+H]⁺ 532

Example 125

3-Phenylpropionyl-(D)-Ala-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 456

40

Example 126

2-(Benzylthio)-benzoyl-(D)-Val-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 578

45 Example 127

5-Phenylvaleryl-Val-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 512

Example 128

4-Phenylphenylacetyl- β -Ala-Pro-NH-CH₂-5-(3-am)-thioph

5 ESI-MS [M+H]⁺ 518

Example 129

4-Phenylbenzoyl-(D)-Ala-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 504

10

Example 130

4-Phenylphenylacetyl-Val-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 546

15 Example 131

4-Phenylphenylacetyl-Ala-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 518

Example 132

20 3-Phenylpropionyl-Ala-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 456

Example 133

3-Phenylpropionyl- β -Ala-Pro-NH-CH₂-5-(3-am)-thioph

25 ESI-MS [M+H]⁺ 456

Example 134

4-Phenylbutyryl- β -Ala-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 470

30

Example 135

5-Phenylvaleryl- β -Ala-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 484

35 Example 136

4-Benzoylbenzoyl-Val-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 560

Example 137

40 4-Phenylbenzoyl- β -Ala-Pro-NH-CH₂-5-(3-am)-thioph

ESI-MS [M+H]⁺ 504

Example 138

3-Phenylpropionyl-Val-Pro-NH-CH₂-5-(3-am)-thioph

45 ESI-MS [M+H]⁺ 484

Example 139

4-Phenylbutyryl-Val-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 498

5 Example 140

2-(Benzylthio)-benzoyl-Val-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 578

Example 141

10 2-(Benzylthio)-benzoyl-Ala-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 550

Example 142

4-Benzoylbenzoyl-(D)-Ala-Pyr-NH-CH₂-5-(3-am)-thioph15 ESI-MS [M+H]⁺ 530

Example 143

4-Benzoylbenzoyl-(D)-Val-Pyr-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 558

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Example 144

4-Benzoylbenzoyl-Sar-Pyr-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 530

25 Example 145

C₆H₅-C≡C-CO-Gly-Pyr-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 436

Example 146

30 C₆H₅-C≡C-CO-Sar-Pyr-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 450

Example 147

C₆H₅-C≡C-CO-(D)-Val-Pyr-NH-CH₂-5-(3-am)-thioph35 ESI-MS [M+H]⁺ 478

Example 148

C₆H₅-C≡C-CO-(D)-Ala-Pyr-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 450

40

Example 149

4-Phenylbutyryl-Ala-Pro-NH-CH₂-5-(3-am)-thiophESI-MS [M+H]⁺ 470

45 Example 150

MeOC(O)-(CH₂)₅-NHC(O)-Gly-Pro-NH-CH₂-5-(3-am)-thioph

144

- a) 0.044 mmol of resin from Example 64/section b), were [sic] suspended in a solution of 0.088 mmol of Fmoc-Gly-OH and 0.088 mmol of N,N,-diisopropylethylamine in 1.5 ml of dimethylformamide, 0.088 mmol of
- 5 2(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate in 0.5 ml of dimethylformamide was added and stirring was carried out for 2 hours at room temperature. The resin was then filtered off with suction and was washed with dimethylformamide, CH₂Cl₂, methanol and CH₂Cl₂. The
- 10 elimination of the Fmoc protective group was carried out with 2 ml of a solution of 10% of (1,8-diazabicyclo[5.4.0]undec-7-ene), 2% of piperidine and 88% of dimethylformamide (3 min). Thereafter, the resin was filtered off with suction and was washed with
- 15 dimethylformamide, CH₂Cl₂, methanol and CH₂Cl₂.
- b) The resin was suspended in 1 ml of CH₂Cl₂, and 0.088 mmol of methyl 6-isocyanatocaproate in 0.5 ml of CH₂Cl₂ was added. Stirring was carried out for 2 hours at room temperature,
- 20 after which the solid was filtered off with suction and was washed with dimethylformamide, CH₂Cl₂, methanol and CH₂Cl₂. The elimination of the product from the carrier was carried out by treatment with 95:5 trifluoroacetic acid/water (1 h/room temperature).
- 25 Yield: 18 mg. HPLC-MS: M+H⁺ 481 (calculated: 481).

Example 151

Phenylsulfonyl-Gly-Pro-NH-CH₂-5-(3-am)-thioph

- 30 0.01 mmol of resin from Example 150/section a) were [sic] suspended in 0.2 ml of 1:1 CH₂Cl₂/DMF, and 10.4 µl (0.06 mmol) of N,N,-diisopropylethylamine and then a solution of 2.5 µl (0.02 mmol) of benzenesulfonyl chloride in 200 µl of 1:1 CH₂Cl₂/DMF were added. Stirring was carried out for 2 hours at
- 35 room temperature after which the solid was filtered off with suction and was washed with dimethylformamide, CH₂Cl₂, methanol and CH₂Cl₂. The elimination of the product from the carrier was carried out by treatment with 95:5 trifluoroacetic acid/water (1 h/room temperature).
- 40 Yield: 4.6 mg. HPLC-MS: M+H⁺ 450 (calculated: 450).

Example 152

3-[4-(2,5-Dichlorobenzyloxy)phenyl]propionyl(-D-Val-Pyr-NH-CH₂-5-(3-am)-thioph

145

- a) 0.2 mmol of 2-chlorotrityl 3-(4-hydroxyphenyl)propionic acid resin was suspended in a solution of 262 mg (1 mmol) of triphenylphosphine in 2 ml of THF. After the addition of a solution of 2 mmol of 2,5-dichlorobenzyl alcohol in 2 ml of THF, a solution of 408 μ l (2 mmol) of diisopropyl azodicarboxylate in 200 μ l of THF was added a little at a time in the course of 30 minutes while stirring. After incubation for 20 hours, the resin was filtered off with suction and washed with THF. Step a) was then repeated.
- b) For working up, the resin was filtered off with suction and washed with THF and then with methanol and dichloromethane. The product was cleaved from the substrate with trifluoroethanol, acetic acid and dichloromethane (1:1:3) over 45 minutes. After evaporating down under reduced pressure, the residue was dissolved in acetic acid and freeze-dried. Yield: 31 mg.

Reference:

- 20 Krchnak, V., Flegelova, Z., Weichsel, A.S., and Lebl, M. (1995). Tetrahedron Lett., 36, 6193.

- c) The acid component was coupled with TBTU on polymer-bound H-D-Val-Pyr-NH-CH₂-5-(3-am)-thioph, as described for Example 84. After elimination with TFA-water (95:5) (1 h at room temperature), the product was obtained (ESI-MS [M+H]⁺656).

The following compounds were prepared analogously to the above examples:

30	153.	4-(2,5-Dichloro-benzyloxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 628
35	154.	4-(2-Chloro-benzyloxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 594
	155.	3-[4-(2-Chloro-benzyloxy)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 622
40	156.	3-[4-(4-Nitro-benzyloxy)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 633
	157.	3-[4-(4-Methoxycarbonyl-benzyloxy)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 646
45	158.	3-[4-(4-Fluoro-3-trifluoromethyl-benzyloxy)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 674

	159.	3-[4-(2-Chloro-3-isopropyl-benzyloxy)-phenyl]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 664
5	160.	4-(2,5-Dichloro-benzyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 642
	161.	4-(4-Chloro-3-nitro-benzyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 653
10	162.	4-(4-Nitro-benzyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 619
	163.	4-(4-Methoxycarbonyl-benzyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 632
15	164.	4-(4-Fluoro-3-trifluoromethyl-benzyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 660
	165.	4-(2-Chloro-3-isopropyl-benzyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 650
20	166.	4-(4-Chloro-benzyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 608
	167.	5-[4-(2,5-Dichloro-benzyloxy)-phenyl]-5-oxo-pentanoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 698
25	168.	5-[4-(4-Chloro-3-nitro-benzyloxy)-phenyl]-5-oxo-pentanoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 709
	169.	5-[4-(4-Nitro-benzyloxy)-phenyl]-5-oxo-pentanoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 675
30	170.	5-[4-(4-Methoxycarbonyl-benzyloxy)-phenyl]-5-oxo-pentanoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 688
	171.	5-[4-(4-Fluoro-3-trifluoromethyl-benzyloxy)-phenyl]-5-oxo-pentanoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 715
35	172.	5-[4-(2-Chloro-3-isopropyl-benzyloxy)-phenyl]-5-oxo-pentanoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 706
40	173.	5-(4-Benzyloxy-phenyl)-5-oxo-pentanoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 630
	174.	5-[4-(4-Chloro-benzyloxy)-phenyl]-5-oxo-pentanoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 664
45		

	175.	2-[4-(2,5-Dichloro-benzyloxy)-phenoxy]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 672
5	176.	2-[4-(4-Chloro-3-nitro-benzyloxy)-phenoxy]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 683
	177.	2-[4-(2-Chloro-benzyloxy)-phenoxy]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 638
10	178.	2-[4-(4-Nitro-benzyloxy)-phenoxy]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 649
	179.	2-[4-(4-Methoxycarbonyl-benzyloxy)-phenoxy]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 662
15	180.	2-[4-(4-Fluoro-3-trifluoromethyl-benzyloxy)-phenoxy]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 690
	181.	2-[4-(2-Chloro-3-isopropyl-benzyloxy)-phenoxy]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 680
20	182.	2-(4-Benzyloxy-phenoxy)-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 604
	183.	2-[4-(4-Chloro-benzyloxy)-phenoxy]-propionyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 638
25	184.	2-[4-(2,5-Dichloro-benzyloxy)-phenyl]-3-methyl-butyryl-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 585
	185.	2-[4-(2,5-Dichloro-benzyloxy)-phenyl]-3-methyl-butyryl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 684
30	186.	2-[4-(4-Chloro-3-nitro-benzyloxy)-phenyl]-3-methyl-butyryl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 695
	187.	2-[4-(4-Nitro-benzyloxy)-phenyl]-3-methyl-butyryl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 661
35	188.	2-[4-(4-Methoxycarbonyl-benzyloxy)-phenyl]-3-methyl-butyryl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 674
	189.	2-[4-(4-Fluoro-3-trifluoromethyl-benzyloxy)-phenyl]-3-methyl-butyryl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 702
40	190.	2-(4-Benzyloxy-phenyl)-3-methyl-butyryl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 616
45		

	191.	2-[4-(4-Chloro-benzyloxy)-phenyl]-3-methyl-butyryl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 650
5	192.	2-[4-(2,5-Dichloro-benzyloxy)-phenoxy]-propionyl-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 573
	193.	2-[4-(4-Nitro-benzyloxy)-phenoxy]-propionyl-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 550
10	194.	2-[4-(4-Methoxycarbonyl-benzyloxy)-phenoxy]-propionyl-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 563
	195.	2-[4-(2-Chloro-3-isopropyl-benzyloxy)-phenoxy]-propionyl-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 581
15	196.	2-(4-Benzyloxy-phenoxy)-propionyl-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 505
	197.	2-[4-(4-Chloro-benzyloxy)-phenoxy]-propionyl-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 539
20	198.	2-[4-(4-Chloro-3-nitro-benzyloxy)-phenoxy]-propionyl-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 596
	199.	3-(2,5-Dichloro-benzyloxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 628
25	200.	3-(4-Chloro-3-nitro-benzyloxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 639
	201.	3-(2-Naphthylmethoxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 610
30	202.	3-(4-Methyl-3-nitro-benzyloxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 619
	203.	3-(4-Nitro-benzyloxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 605
35	204.	3-(4-Fluoro-3-trifluoromethyl)-benzyloxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 646
40	205.	3-(2-Chloro-3-isopropyl-benzyloxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 636
	206.	3-Benzyloxybenzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 560
45		

5	207.	3-(4-Chlorobenzoyloxy)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 594
	208.	3-(2,5-Dichloro-benzoyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 642
	209.	3-(4-Chloro-3-nitro-benzoyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 653
10	210.	3-(4-Methyl-3-nitro-benzoyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 633
	211.	3-(4-Nitro-benzoyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 619
15	212.	3-(4-Fluoro-3-trifluoromethyl-benzoyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 660
	213.	3-(2-Chloro-3-isopropyl-benzoyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 650
20	214.	3-Benzoyloxy-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 574
	215.	3-(4-Chloro-benzoyloxy)-phenylacetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 608
25	216.	3-[3-(2,5-Dichloro-benzoyloxy)-phenyl]-acryloyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 654
	217.	3-[3-(4-Chloro-3-nitro-benzoyloxy)-phenyl]-acryloyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 665
30	218.	3-[3-(4-Methyl-3-nitro-benzoyloxy)-phenyl]-acryloyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 645
	219.	3-[3-(4-Nitro-benzoyloxy)-phenyl]-acryloyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 631
35	220.	3-[3-(4-Fluoro-3-trifluoromethyl-benzoyloxy)-phenyl]-acryloyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 672
	221.	3-[3-(2-Chloro-3-isopropyl-benzoyloxy)-phenyl]-acryloyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 662
40	222.	3-(3-Benzoyloxy-phenyl)-acryloyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 586
	223.	4-Phenylbenzenesulfonyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 538

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	224.	4-Phenylbenzenesulfonyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 538
	225.	4-Phenylbenzenesulfonyl-Sar-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 538
5	226.	4-Phenylbenzenesulfonyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 524
	227.	C ₆ H ₅ -C≡C-CO-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 450
	228.	C ₆ H ₅ -C≡C-CO-D-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
10		ESI-MS [M+H] ⁺ 494
	229.	C ₆ H ₅ -C≡C-CO-D-Arg-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 535
	230.	4-Benzoylbenzoyl-β-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 530
15	231.	4-Benzoylbenzoyl-D-Asp-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 574
	232.	4-Benzoylbenzoyl-D-Arg-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 615
	233.	C ₆ H ₅ -C≡C-CO-Gly-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 436
20	234.	C ₆ H ₅ -C≡C-CO-β-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 450
	235.	C ₆ H ₅ -C≡C-CO-D-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 450
	236.	C ₆ H ₅ -C≡C-CO-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
25		ESI-MS [M+H] ⁺ 478
	237.	4-Benzoylbenzoyl-Gly-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 516
	238.	4-Benzoylbenzoyl-β-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 530
30	239.	4-Benzoylbenzoyl-D-Ala-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 530
	240.	4-Benzoylbenzoyl-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 558
	241.	4-Benzoylbenzoyl-D-Lys-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 587
35	242.	4-Benzoylbenzoyl-D-Orn-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 573
	243.	4-Benzoylbenzoyl-D-His-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 596
	244.	4-Benzoylbenzoyl-D-Dab-Pyr-NH-CH ₂ -5-(3-am)-thioph
40		ESI-MS [M+H] ⁺ 559
	245.	4-Benzoylbenzoyl-D-Dap-Pyr-NH-CH ₂ -5-(3-am)-thioph
		ESI-MS [M+H] ⁺ 545
	246.	4-Benzoylbenzoyl-D-Arg-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 615
45	247.	4-Benzoylbenzoyl-D-Lys-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 587
	248.	4-Benzoylbenzoyl-D-Orn-Pyr-NH-CH ₂ -5-(2-am)-thioph
		ESI-MS [M+H] ⁺ 573

	249.	4-Benzoylbenzoyl-D-His-Pyr-NH-CH ₂ -5-(2-am)-thioph ESI-MS [M+H] ⁺ 596
	250.	4-Benzoylbenzoyl-D-Dab-Pyr-NH-CH ₂ -5-(2-am)-thioph ESI-MS [M+H] ⁺ 559
5	251.	4-Benzoylbenzoyl-D-Dap-Pyr-NH-CH ₂ -5-(2-am)-thioph ESI-MS [M+H] ⁺ 545
	252.	9,10,10-Trioxo-9,10-dihydro-10I ⁶ -thioxanthene-3-carbonyl- D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 592
10	253.	9,10,10-Trioxo-9,10-dihydro-10I ⁶ -thioxanthene-3-carbonyl- Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 578
	254.	9,10,10-Trioxo-9,10-dihydro-10I ⁶ -thioxanthene-3-carbonyl- D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 620
15	255.	9,10-Dioxo-9,10-dihydro-anthracene-2-carbonyl-D-Ala-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 556
20	256.	9,10-Dioxo-9,10-dihydro-anthracene-2-carbonyl-Gly-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 542
	257.	9,10-Dioxo-9,10-dihydro-anthracene-2-carbonyl-D-Val-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 584
25	258.	4-Benzoylbenzoyl-D-Ser-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 546
	259.	4-Aminobenzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 441
	260.	4-Methylaminobenzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 455
30	261.	4-Aminobenzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 469
	262.	4-Methylaminobenzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 483
	263.	3-Aminobenzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 469
35	264.	4-(4-HOOC-Benzoyl)-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 602
	265.	4-(3-Phenyl-ureido)-benzoyl-D-Ala-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 560
40	266.	3-(3-Benzyl-ureido)-benzoyl-D-Ala-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 574
	267.	3-(3-Phenyl-ureido)-benzoyl-D-Ala-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 560
45	268.	4-(3-Phenyl-ureido)-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 546

	269.	3-(3-Benzyl-ureido)-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 560
	270.	3-(3-Phenyl-ureido)-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 546
5	271.	3-(3-Benzoyl-ureido)-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 574
	272.	4-(3-Phenyl-ureido)-benzoyl-D-Val-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 588
10	273.	3-(3-Phenyl-ureido)-benzoyl-D-Val-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 588
	274.	3-[3-(3-Acetyl-phenyl)-ureido)-benzoyl-D-Val-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 630
15	275.	4-Benzyloxy-benzoyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 532
	276.	4-(4-Chloro-benzyloxy)-benzoyl-D-Ala-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 566
20	277.	3-(4-Benzyloxy-phenyl)-propionyl-D-Ala-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 560
	278.	3-[4-(4-Chloro-benzyloxy)-phenyl]-propionyl-D-Ala-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 594
25	279.	4-Benzyloxy-benzoyl-Gly-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 518
	280.	4-(4-Chloro-benzyloxy)-benzoyl-Gly-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 552
30	281.	3-(4-Benzyloxy-phenyl)-propionyl-Gly-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 546
	282.	3-[4-(4-Chloro-benzyloxy)-phenyl]-propionyl-Gly-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 580
35	283.	4-Benzyloxy-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 560
	284.	4-(4-Chloro-benzyloxy)-benzoyl-D-Val-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 594
40	285.	3-(4-Benzyloxy-phenyl)-propionyl-D-Val-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 588
45	286.	3-[4-(4-Chloro-benzyloxy)-phenyl]-propionyl-D-Val-Pyr-NH- CH ₂ -5-(3-am)-thioph ESI-MS [M+H] ⁺ 622

	287.	Phenyl-C≡C-CO-D-Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 518
	288.	Phenyl-C≡C-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 466
5	289.	4-Benzoylbenzoyl-D-Abu-Pro-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 546
	290.	4-Benzoylbenzoyl-D-Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 598
10	291.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Pro-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 482
	292.	HOOC-p-C ₆ H ₄ -CH ₂ -D,L-Thienyl(3)glycine-Pyr-NH- CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 524
	293.	p-COOH-Benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 470
15	294.	4-Benzoyl-benzoyl-Acpc-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 570
	295.	4-Benzoyl-benzoyl-N-Me-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 572
20	296.	p-Carboxy-benzyl-D-Ile-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 498
	297.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Nva-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 484
	298.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Leu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 498
25	299.	4-Benzoylbenzoyl-D-Nva-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 558
	300.	p-Carboxy-benzyl-D-Ala-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 456
	301.	p-Carboxy-benzyl-Acpc-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 496
30	302.	HOOC-p-C ₆ H ₄ -CH ₂ -N-Me-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 498
	303.	p-Benzoyl-benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 530
35	304.	2-Carboxy-benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 470
	305.	(4-COOH-CH=CH)-Benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 496
	306.	4-Carboxy-benzyl-D-Abu-3-Me-Pro-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 486
40	307.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Abu-5-Me-Pro-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 486
	308.	2-(Carboxymethyloxy)-benzyl-D-Abu-Pyr-NH- CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 500
45	309.	Benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 426

	310.	4-(Carboxymethyloxy)-benzyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 500
5	311.	Benzenesulfonyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 490
	312.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Abu-Pyr-NH-CH ₂ -5-(2-am)-thioph MS [M+H] ⁺ 470
	313.	4-Benzoyl-benzoyl-D-Pro-Pyr-NH-CH ₂ -5-(2-am)-thioph MS [M+H] ⁺ 556
10	314.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Pro-Pyr-NH-CH ₂ -5-(2-am)-thioph MS [M+H] ⁺ 482
	315.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Pip-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 473
	316.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Abu-Pro-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 472
15	317.	4-Carboxy-benzyl-D-allo-Ile-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 498
	318.	2-HOOC-thienyl(5)-CH ₂ -D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 476
20	319.	2-COOH-furanyl(5)-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 460
	320.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Nle-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 498
	321.	Benzoyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 440
25	322.	4-MeSO ₂ -C ₆ H ₄ -CH ₂ -D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 504
	323.	Phenylsulfonyl-D-Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 530
	324.	Phenylacetyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 454
30	325.	Phenylsulfonyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 476
	326.	1-Naphthyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 504
	327.	2-Naphthyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 504
35	328.	1-Indanyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 480
	329.	Benzhydryl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 530
40	330.	2-Cl-Phenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 488
	331.	2,6-Dichlorophenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 524
	332.	2-Methyl-phenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 468
45	333.	Biphenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 530

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	334.	p-Methyl-phenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 468
	335.	3-Methyl-phenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 468
5	336.	2-Nitro-phenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 499
	337.	Fluoroenyl(1)-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 542
	338.	2-Br-Phenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 534
10	339.	2-Fluoro-phenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 472
	340.	2-Phenyl-isobutyryl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 482
15	341.	p-Benzyloxy-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 560
	342.	2,6-Dichlorophenyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(2-am)-thioph	MS [M+H] ⁺ 524
	343.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 538
20	344.	2,6-Dichloro-phenyl-CH ₂ CO-D-Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 578
	345.	1-Naphthyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 490
	346.	Cyclopentyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 446
25	347.	1-Adamantyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 498
	348.	Cyclohexyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 460
30	349.	2-Thienyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 460
	350.	2-Naphthyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 490
	351.	1-Naphthyl-CH ₂ -D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 476
35	352.	2-Naphthyl-CH ₂ -D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 476
	353.	Benzyloxycarbonyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 470
	354.	4-MeOOC-Benzyl-D-Val-Pyr-NH-CH ₂ -5-(3-ham)-thioph	MS [M+H] ⁺ 514
40	355.	2-Phenyl-2-hydroxy-acetyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 470
	356.	2-Phenyl-2-methoxy-acetyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 484
45	357.	2-(p-Isobutyl-phenyl)propionyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph	MS [M+H] ⁺ 524

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	358.	(S)-2-Phenyl-propionyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 468
	359.	(R)-2-Phenyl-propionyl-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 468
5	360.	3-Pyridyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 455
	361.	Phenyl-O-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 470
	362.	1-Adamantyl-CH ₂ CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
10		MS [M+H] ⁺ 512
	363.	2,4,6-Trimethylphenyl-CH ₂ CO-D-Abu-Pyr-NH-
		CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 496
	364.	p-Pentoxy-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 540
15	365.	p-Benzyloxy-phenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 574
	366.	1-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 494
	367.	2,6-Dichlorophenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph
20		MS [M+H] ⁺ 538
	368.	2-Benzothienyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 496
	369.	HOOC-p-C ₆ H ₄ -CH ₂ -D-Nva-Pyr-NH-3-(6-am)-pico
		MS [M+H] ⁺ 465
25	370.	2-Tetrahydronaphthyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 494
	371.	1-Indanyl-CO-D-Ile-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 508
	372.	1-Benzocyclobutane-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 466
30	373.	1-Benzocyclobutane-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 480
	374.	2,4,6-Trimethylphenyl-CH ₂ CO-D-Val-Pyr-NH-
		CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 510
35	375.	1-Indanyl-CO-D-Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 534
	376.	1-Indanyl-CO-D-Leu-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 508
	377.	1-Indanyl-CO-D-Phe-Pyr-NH-CH ₂ -5-(3-am)-thioph
40		MS [M+H] ⁺ 542
	378.	1-Anthracenyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 540
	379.	Benzenesulfonyl-D-Cha-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 558
45	380.	p-Hexyloxy-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph
		MS [M+H] ⁺ 554

	381.	2-(p-(Phenyloxy)phenyl)-acetyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 560
5	382.	(R)-1-Indanyl-CO-D-Abu-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 480
	383.	1-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph MS [M+H] ⁺ 494
	384.	(S)-1-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 494
10	385.	Butylsulfonyl-D-Phe-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 518
	386.	(3,5-Bistrifluoromethyl)phenyl(1)-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 604
15	387.	(3-Trifluoromethyl)phenyl(1)-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 536
	388.	1-Phenyl-cyclopropyl(1)-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 494
20	389.	(S)-1-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 494
	390.	p-Isopropyl-phenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 510
	391.	p-Butoxyphenyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 540
25	392.	Phenyl-CH(iPr)-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 510
	393.	1-(4-Cl-Phenyl)-cyclobut-1-ylCO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 542
30	394.	2-Carboxy-thien-5-yl-CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 490
	395.	1-Phenyl-cyclopent-1-yl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 522
	396.	1-Adamantyl-CH ₂ CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 526
35	397.	1-Fluorenyl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 542
	398.	Benzhydryl-CO-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 544
40	399.	(R)-1-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph MS [M+H] ⁺ 494
	400.	(S)-1-Indanyl-CO-D-Val-Pyr-NH-CH ₂ -5-(2-am)-thioph MS [M+H] ⁺ 494
	401.	p-COOH-Benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 498
45	402.	2-Carboxy-5-furyl-CH ₂ -D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 474
	403.	p-COOMe-benzoyl-D-Val-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 512

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404.	m-COOH-Phenyl-SO ₂ -D-Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 574
405.	p-COOH-Phenyl-SO ₂ -D-Chg-Pyr-NH-CH ₂ -5-(3-am)-thioph MS [M+H] ⁺ 574

5

The C_{1S} and C_{1R} inhibition values for some novel compounds are shown in the table below.

Table

10

Example No.	C _{1S} IC ₅₀ [μmol/l] according to Example B	C _{1R} IC ₅₀ [μmol/l] according to Example A
29	0.6	0.9
15 22	0.6	0.9
23	0.8	0.5
24	0.8	>100
42	1	0.7
20 49	1	1
21	1	4
20	2	0.6
35	2	2
41	2	2
25 15	2	3
26	2	>100
50	3	20
4	3	30
30 44	3	40
51	3	40
52	4	10
17	4	40
35 7	4	>100
38	5	10
30	5	>100
6	6	
40 25	6	50
1	6	>100
8	6	>100
18	7	10
54	8	
45 5	10	

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		C _{1S} IC ₅₀ [μ mol/l] according to Example B	C _{1R} IC ₅₀ [μ mol/l] according to Example A
5	39	10	2
	31	10	3
	43	10	6
	13	10	30
10	45	20	6
	53	20	8
	27	20	10
	46	20	40
15	2	20	50
	34	20	70
	9	20	>100
	28	20	>100
20	16	20	>100
	10	20	>100
	14	20	>100
	32	30	10
25	19	30	30
	48	30	50
	3	30	>100
	11	30	>100
30	12	30	>100
	35	40	20
	33	40	40
	47	50	10

35

40

45



We claim:-

1. The use of a compound of the formula I, their tautomers,
 5 pharmacologically tolerated salts or prodrugs for the
 preparation of drugs for the treatment or prophylaxis of
 disorders which are alleviated or cured by partial or
 complete inhibition of C_{1s} or C_{1r}, formula I having the
 following structure:

10

A-B-D-E-G-K-L

(I)

where

A is

- 15 H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, RA¹OCO (where RA¹ is H,
 C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₁₋₃-alkyl-C₃₋₈-cycloalkyl or
 C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H-, C₁₋₆-alkyl,
 C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H,
 C₁₋₆-alkyl or C₀₋₃-alkylaryl; RA²-RA³ together may also
 20 form a ring of 3 to 7 carbon atoms), RA⁴OCO₂ (where RA⁴ is
 C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA⁴CONRA², NO₂, RA⁴CONRA²,
 RA¹O, RA²RA³N, RA¹S, HO-SO₂, RA²RA³N-SO₂, Cl, phenoxy,
 Br, F, tetrazolyl, H₂O₃P, RA¹-N(OH)-CO or RA¹RA²NCONRA³,
 where aryl in each case may be substituted by up to 2
 25 identical or different radicals from the group consisting
 of F, Cl, Br, OCH₃, CF₃, CH₃ and NO₂;

B is

-(CH₂)_{1B}-L^B-(CH₂)_{mB}- where

30

1^B is 0, 1, 2 or 3;

m^B is 0, 1, 2, 3, 4 or 5;

35

40

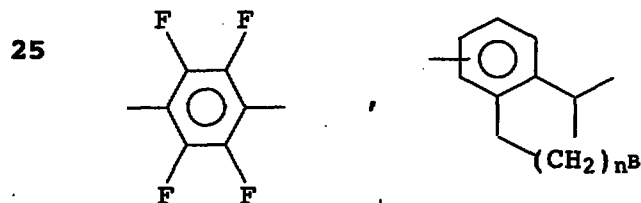
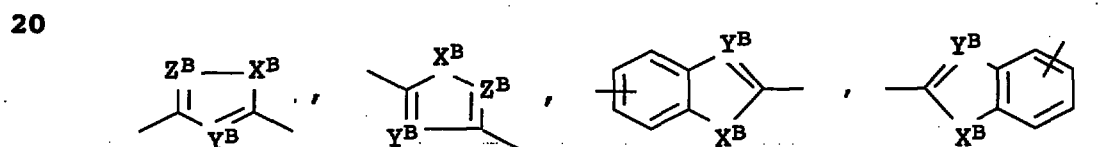
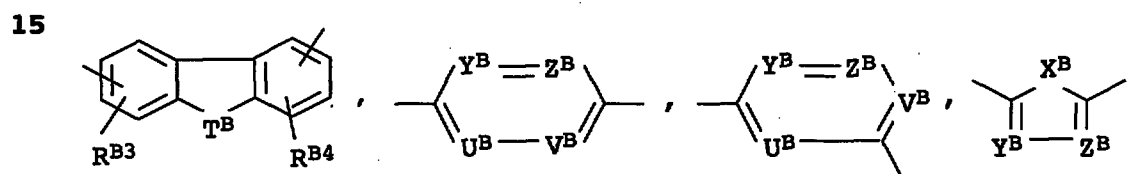
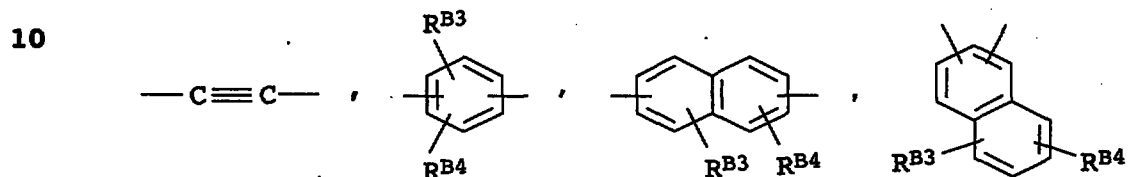
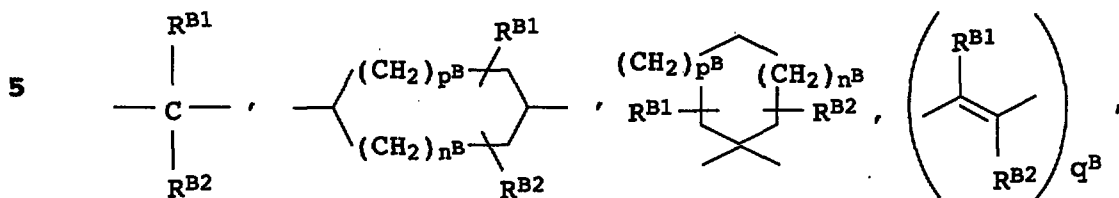
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L^B is



30 where, in each of the abovementioned ring systems, a phenyl ring may be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH_3 , CF_3 , Br, Cl and F or may be substituted by $\text{R}^8\text{OOC}-$ (where R^8 is H or C_{1-3} -alkyl);

35 where

n^B is 0, 1 or 2,

p^B is 0, 1 or 2,

q^B is 1, 2 or 3,

40

RB1 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

45

RB2 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

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R^{B3} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, $R^{B5}OCO$ (where R^{B5} is H, C_{1-6} -alkyl or C_{1-3} -alkylaryl), $R^{B6}-O$ (where R^{B6} is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

5

R^{B4} is H, C_{1-6} -alkyl, $R^{B6}-O$, Cl, Br, F or CF_3 ;

R^{B1} and R^{B2} may also be bonded together;

10

T^B is CH_2 , O, S, NH or N- C_{1-6} -alkyl;

X^B is O, S, NH or N- C_{1-6} -alkyl;

15

Y^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

Z^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

U^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl;

20

V^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl. [sic]

B is furthermore

$-(CH_2)_{l^B}-L^B-M^B-L^B-(CH_2)_{m^B}$, where

25

l^B and m^B have the abovementioned meanings and the two groups L^B , independently of one another, are identical or different radicals from among the stated radicals;

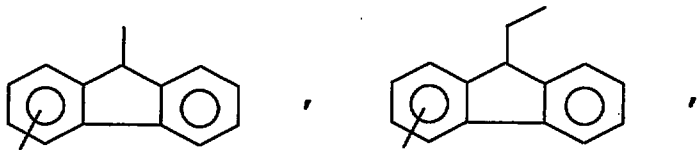
30

M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CO, SO_2 , $CH=CH$ or $C\equiv C$;

B may furthermore be

-1-adamantyl-, -2-adamantyl-, -1-adamantyl- CH_2- ,
-2-adamantyl- CH_2- ,

35



40

A-B may furthermore be

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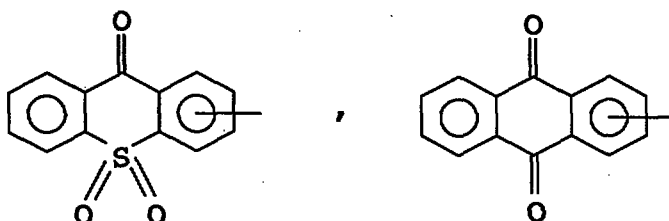
45



* C L M S *

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5

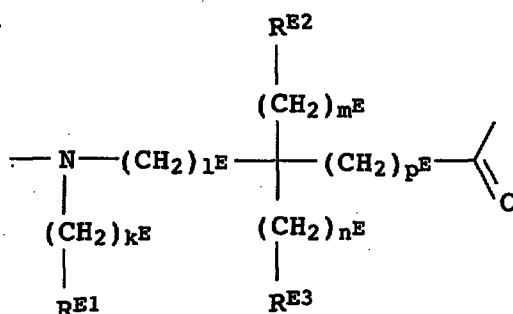


D is a single bond or
CO, OCO, NR^{D1}-CO (where R^{D1} is H, C₁₋₄-alkyl or
10 C₀₋₃-alkylaryl), SO₂ or NR^{D1}SO₂;

E is a single bond or

15

20



where

25

k^E is 0, 1 or 2;
l^E is 0, 1 or 2;
m^E is 0, 1, 2 or 3;
n^E is 0, 1 or 2;
30 p^E is 0, 1 or 2;

35

RE¹ is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, aryl, heteroaryl or
C₃₋₈-cycloalkyl having a fused-on phenyl ring, it being
possible for the abovementioned radicals to carry up to
three identical or different substituents from the group
consisting of C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, F, Cl and Br;

40

RE¹ is furthermore RE⁴OCO-CH₂- (where RE⁴ is H, C₁₋₁₂-alkyl or
C₁₋₃-alkylaryl);

45

RE² is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, aryl, heteroaryl,
tetrahydropyranyl, tetrahydrothiopyranyl, C₃₋₈-cycloalkyl
having a fused-on phenyl ring, it being possible for the
abovementioned radicals to carry up to three identical or
different substituents from the group consisting of

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* C L M S *

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C_{1-6} -alkyl, OH, O- C_{1-6} -alkyl, F, Cl, Br, $CH(CH_3)OH$ or $CH(CF_3)_2$;

5 RE^3 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, aryl, heteroaryl or C_{3-8} -cycloalkyl having a fused-on phenyl ring, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C_{1-6} -alkyl, OH, O- C_{1-6} -alkyl, F, Cl and Br;

10 RE^2 and RE^1 may together furthermore form a bridge having $(CH_2)_{0-4}$, $CH=CH$, $CH_2-CH=CH$ or $CH=CH-CH_2$ groups;

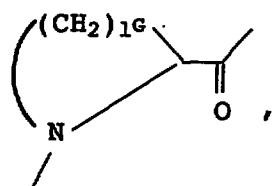
15 the groups stated under RE^1 and RE^3 may be linked to one another via a bond; the groups stated under RE^2 and RE^3 may also be linked to one another via a bond;

20 RE^2 is furthermore COR^{E5} (where RE^5 is OH, O- C_{1-6} -alkyl or OC_{1-3} -alkylaryl), $CONR^{E6}R^{E7}$ (where RE^6 and RE^7 are H, C_{1-6} -alkyl or C_{0-3} -alkylaryl);

E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;

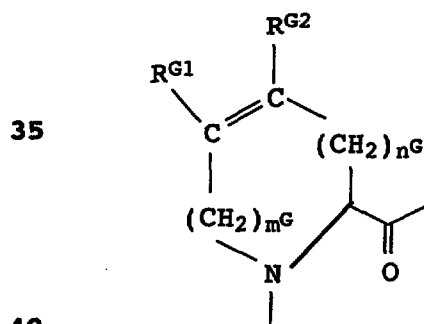
G is

25

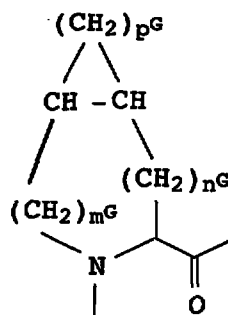


where 1^G is 2, 3, 4 and 5,
where a CH_2 group of the ring may be replaced by O, S, NH, NC_{1-3} -alkyl, $CHOH$, $CHOC_{1-3}$ -alkyl, $C(C_{1-3}\text{-alkyl})_2$, $CH(C_{1-3}\text{-alkyl})$, CHF , $CHCl$ or CF_2 ;

30



or



40

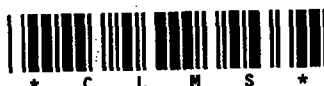
where

m^G is 0, 1 or 2;

45 n^G is 0, 1 or 2;

p^G is 1, 2, 3 or 4;

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* C L M S *

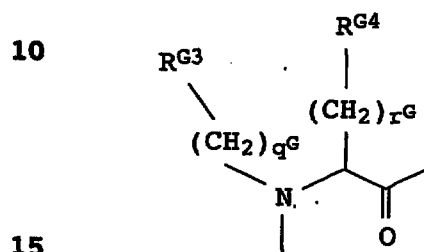
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R^{G1} is H, C_1 - C_6 -alkyl or aryl;

R^{G2} is H, C_1 - C_6 -alkyl or aryl;

5 R^{G1} and R^{G2} together may furthermore form a $-CH=CH-CH=CH$ chain;

G is furthermore



where

20 q^G is 0, 1 or 2;

r^G is 0, 1 or 2;

R^{G3} is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or aryl;

25 R^{G4} is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or aryl (in particular phenyl or naphthyl);

K is

30 $NH-(CH_2)_{n^K}-Q^K$ where

n^K is 0, 1, 2 or 3;

35 Q^K is C_{2-6} -alkyl, it being possible for the chain to be straight-chain or branched and up to two CH_2 groups can be replaced by O or S;

40

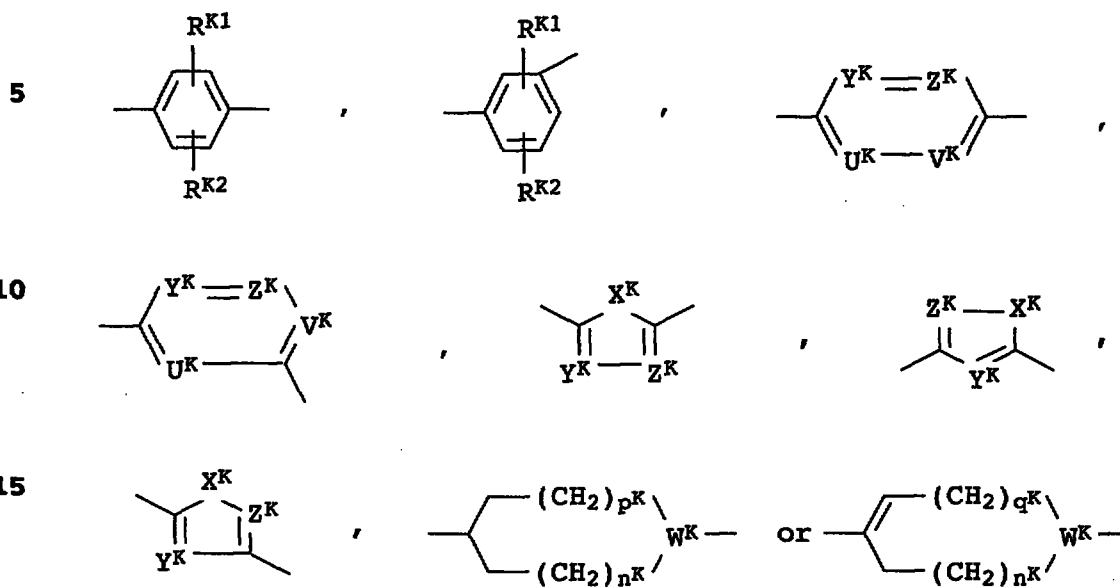
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* C L M S *

Q^K is

20 where

R^{K1} is H, C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, F, Cl or Br;R^{K2} is H, C₁₋₃-alkyl, O-C₁₋₃-alkyl, F, Cl or Br;

25

X^K is O, S, NH or N-C₁₋₆-alkyl;Y^K is =CH-, =C-C₁₋₆-alkyl, =N- or =C-Cl;

30

Z^K is =CH-, =C-C₁₋₆-alkyl, =N- or =C-Cl;U^K is =CH-, =C-C₁₋₆-alkyl, =N- or =C-O-C₁₋₃-alkyl;

35

V^K is =CH-, =C-C₁₋₆-alkyl, =N- or =C-O-C₁₋₃-alkyl;

W^K is or , where, in the latter

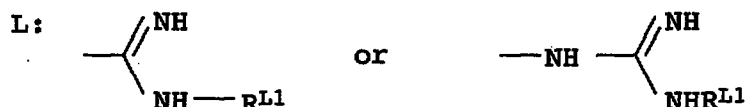
40 case, L may not be a guanidine group;

n^K is 0, 1 or 2;p^K is 0, 1 or 2;

45

q^K is 1 or 2;

167



5

where

R^{L1} is H, OH, O-C₁₋₆-alkyl, O-(CH₂)₀₋₃-phenyl, CO-C₁₋₆-alkyl, CO₂-C₁₋₆-alkyl or CO₂-C₁₋₃-alkylaryl.

10

2. The use of a compound of the formula I as claimed in claim 1 for the preparation of drugs for the treatment or prophylaxis of

15

- Reperfusion injuries after ischemias; ischemic conditions, during, for example, operations with the aid of heart-lung machines; operations in which blood vessels are clamped off generally for avoiding major hemorrhages; myocardial infarction; thromboembolic cerebral

20

- infarction; pulmonary thrombosis, etc.;
- Hyperacute organ rejection; especially in xenotransplantations;
- Organ failure, e.g. multiple organ failure or ARDS (adult respiratory distress syndrome);

25

- Disorders due to trauma (cranial trauma) or multiple injury, e.g. thermal injury (burns);
- Anaphylactic shock;

30

- Sepsis; "vascular leak syndrome": in the case of sepsis and after treatment with biological agents, such as interleukin-2 or after transplantation;

- Alzheimer's disease and other inflammatory neurological disorders, such as myasthenia graevis, multiple sclerosis, cerebral lupus, Guillain-Barre syndrome; meningitis; encephalitis;

35

- Systemic lupus erythematosus (SLE);
- Rheumatoid arthritis and other inflammatory disorders of the rheumatoid disorder group, e.g. Behcet's Syndrome; Juvenile rheumatoid arthritis;

40

- Renal inflammations of various origin, e.g. Glomerulonephritis, Lupus nephriti;
- Pancreatitis;
- Asthma; chronic bronchitis;
- Complications during dialysis in the case of kidney failure;

45

- Vasculitis; thyroiditis;
- Ulcerative colitis and other inflammatory disorders of the gastrointestinal tract;



* C L M S *

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- Autoimmune diseases;
- Spontaneous abortions.

3. The compound of the formula I, its tautomers,
5 pharmacologically tolerable salts and prodrugs, where:

A is

10 H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, RA¹OCO (where RA¹ is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₃-alkyl or C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H-, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl); RA⁴OCONRA² (where RA⁴ is C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA⁴CONRA², RA¹O, RA²RA³N, HO-SO₂-, phenoxy, RA²RA³N-SO₂, Cl, Br, F, tetrazolyl,
15 H₂O₃P-, NO₂, RA¹-N(OH)-CO- or RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, CF₃, CH₃, OCH₃ and NO₂;

20 B is

$-(CH_2)_{1B}-L^B-(CH_2)_{mB}-$ where

25 1^B is 0, 1, 2 or 3;
 m^B is 0, 1 or 2;

30

35

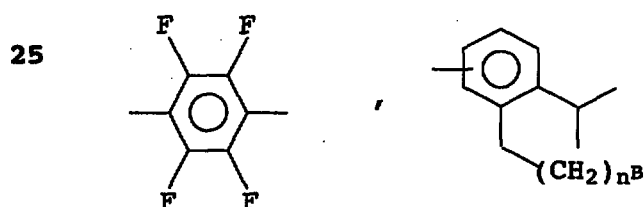
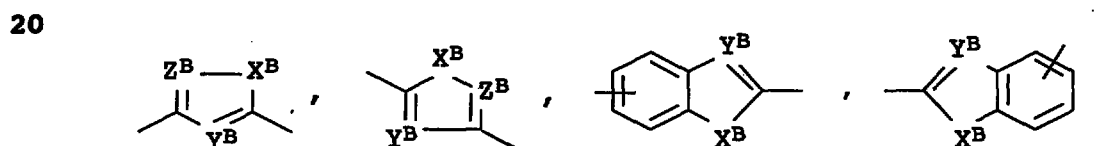
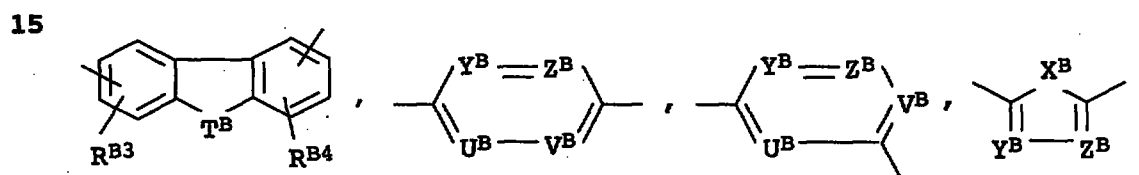
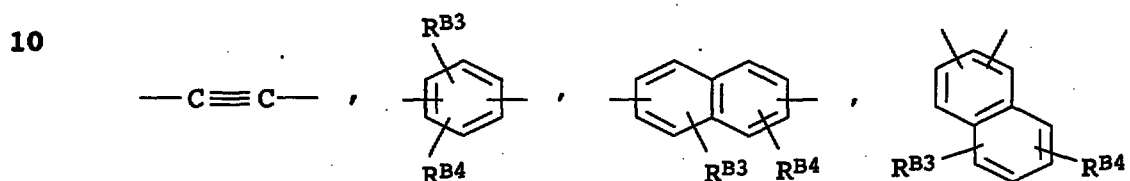
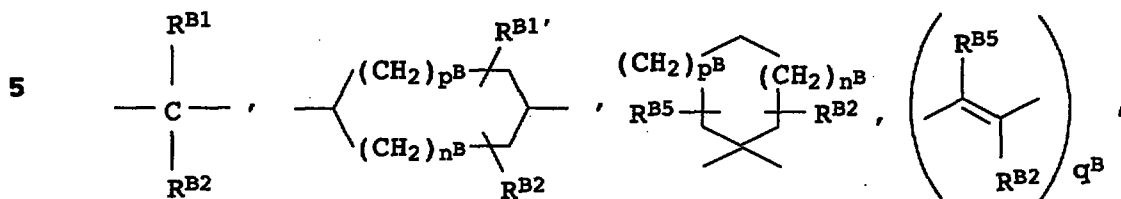
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L^B is

30

where, in each of the abovementioned ring systems, a phenyl ring may be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

35

where

40

n^B is 0, 1 or 2;
 p^B is 0, 1 or 2;
 q^B is 1, 2 or 3;

RB¹ is C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl,
 C₀₋₃-alkyl-C₃₋₈-cycloalkyl, OH or OCH₃;

45

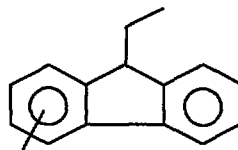
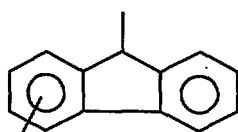
RB² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl;





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- R^{B3} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl [sic] or C_{0-3} -alkylheteroaryl
 $R^{B5}OCO$ (where R^{B5} is H, C_{1-6} -alkyl or C_{1-3} -alkylaryl),
 $R^{B6}-O$ (where R^{B6} is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;
 R^{B4} is H, C_{1-6} -alkyl, $R^{B6}-O$, Cl, Br, F or CF_3 ;
 R^{B5} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;
 T^B is CH_2 , O, S, NH or N- C_{1-6} -alkyl;
 $R^{B1'}$ is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl or C_{0-3} -alkyl- C_{3-8} -cycloalkyl;
 R^{B1} and R^{B2} may also be bonded together;
 X^B is O, S, NH or N- C_{1-6} -alkyl;
 Y^B is $=CH-$, $=N-$ or $=C-Cl$;
 Z^B is $=CH-$, $=N-$ or $=C-Cl$;
 U^B is $=CH-$ or $=N-$;
 V^B is $=CH-$ or $=N-$;
 B is furthermore
 $-(CH_2)_{1B}-L^B-M^B-L^B-(CH_2)_{mB}$, where
 1^B and m^B have the abovementioned meanings and the two
groups L^B , independently of one another, are the radicals
stated under L^B ;
 M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S ,
 $S-CH_2$, CO, SO_2 , $CH=CH$ or $C\equiv C$;
 B is furthermore
-1-adamantyl- CH_2- , -2-adamantyl- CH_2- , -1-adamantyl-,
-2-adamantyl-,

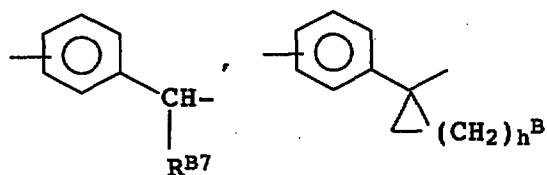


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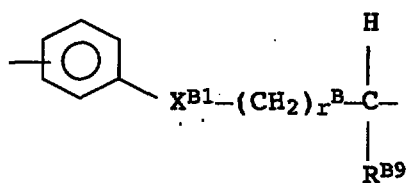
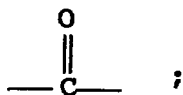
B may furthermore be



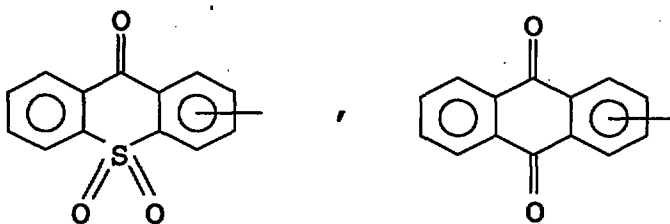
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where h^B is 1, 2, 3 or 4(RB⁷ is C₁₋₆-alkyl or C₃₋₈-cycloalkyl)

B may furthermore be

where X^{B1} is a bond, O, S, or r^B is 0, 1, 2 or 3;RB⁹ is H or C₁₋₃-alkyl;

A-B may be



D is a single bond or
CO, OCO, NR^{D1}-CO (where R^{D1} is H, C₁₋₄-alkyl or
C₀₋₃-alkylaryl), SO₂ or NR^{D1}SO₂;

E is a single bond or



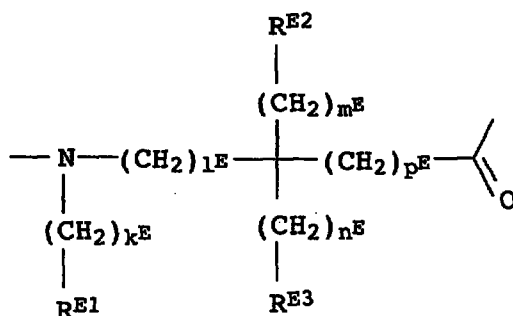
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5



10

where

- k^E is 0, 1 or 2;
 l^E is 0, 1 or 2;
 m^E is 0, 1, 2 or 3;
 n^E is 0, 1 or 2;
 p^E is 0, 1 or 2;

20

RE^1 is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, aryl, pyridyl, thienyl or C₃₋₈-cycloalkyl having a fused-on phenyl ring, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br;

25

RE^1 is furthermore $\text{RE}^4\text{OCO-CH}_2$ (where RE^4 is H, C₁₋₁₂-alkyl or C₁₋₃-alkylaryl);

30

RE^2 is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, phenyl, pyridyl, furyl, thienyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br, or is CH(CH₃)OH or CH(CF₃)₂;

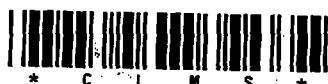
35

40

RE^3 is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or phenyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br;

RE^2 and RE^1 may together furthermore form a bridge having (CH₂)₀₋₄, CH=CH, CH₂-CH=CH or CH=CH-CH₂ groups

45



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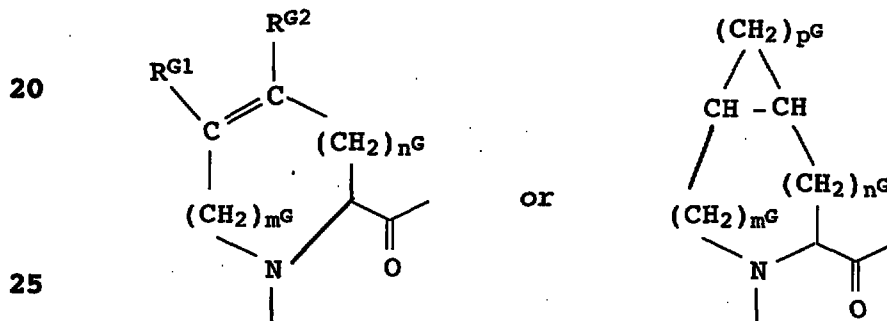
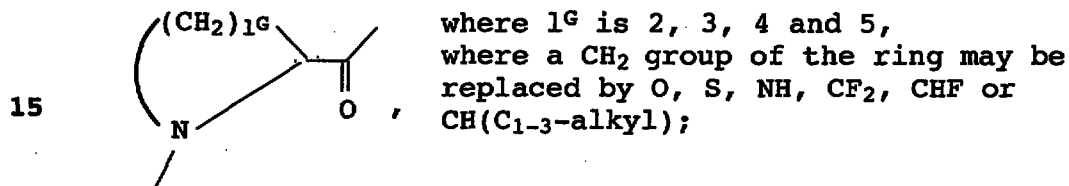
the groups stated under R^{E1} and R^{E3} may be linked to one another via a bond; the groups stated under R^{E2} and R^{E3} may also be linked to one another via a bond;

5 R^{E2} is furthermore COR^{E5} (where R^{E5} is OH, O-C₁₋₆-alkyl or O-C₁₋₃-alkylaryl);

E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;

10

G is



25

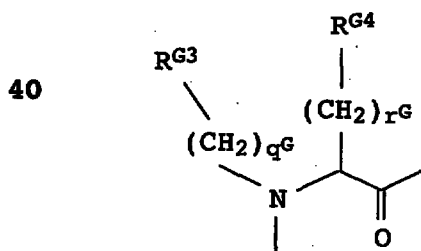
where

30 m^G is 0, 1 or 2;
 n^G is 0, 1 or 2;
 p^G is 1 or 3;

R^{G1} and R^{G2} are each H;

35 R^{G1} and R^{G2} together may furthermore form a $CH=CH-CH=CH$ chain

G is furthermore



45

This Sheet Has Been Replaced



* C L M S *



where

q^G is 0, 1 or 2;

r^G is 0, 1 or 2;

5

R^{G3} is H, C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl;

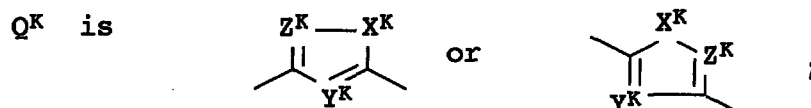
R^{G4} is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or phenyl;

10 K is

$NH-(CH_2)_{n^K}-Q^K$ where

n^K is 1 or 2;

15

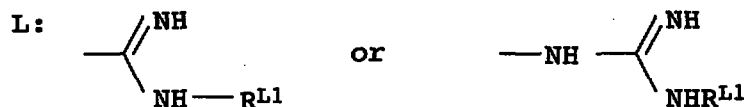


20 X^K is O, S, NH or N- C_1 - C_6 -alkyl;

Y^K is $=CH-$, $=C-C_1$ - C_3 -alkyl, $=N-$ or $=C-Cl$;

25

Z^K is $=CH-$, $=C-C_1$ - C_3 -alkyl, $=N-$ or $=C-Cl$;



30

where

R^{L1} is H, OH, O- C_1 - C_6 -alkyl, O- $(CH_2)_{0-3}$ -phenyl, CO- C_1 - C_6 -alkyl, CO $_2$ - C_1 - C_6 -alkyl or CO $_2$ - C_1 - C_3 -alkylaryl.

35

4. A compound of the formula I, its tautomers, pharmacologically tolerable salts and prodrugs, where:

40 A is

H, C_1 - C_6 -alkyl, C_1 - C_6 -alkyl-SO $_2$, RA^1OCO (where RA^1 is H, C_1 - C_{12} -alkyl, C_3 - C_8 -cycloalkyl, C_1 - C_3 -alkyl- C_3 - C_8 -cycloalkyl or C_1 - C_3 -alkylaryl), RA^2RA^3NCO (where RA^2 is H, C_1 - C_6 -alkyl, C_0 - C_3 -alkylaryl or C_0 - C_3 -alkylheteroaryl; RA^3 is H, C_1 - C_6 -alkyl or C_0 - C_3 -alkylaryl), $RA^4OCONRA^2$, RA^4CONRA^2 (where RA^4 is C_1 - C_6 -alkyl or C_1 - C_3 -alkylaryl), RA^1O , phenoxy, RA^2RA^3N , HO-SO $_2$, $RA^2RA^3N-SO_2$, Cl, Br, F, tetrazolyl, H $_2$ O $_3$ P, NO $_2$, $RA^1-N(OH)-CO$ or $RA^1RA^2NCONRA^3$, where aryl in each case



175

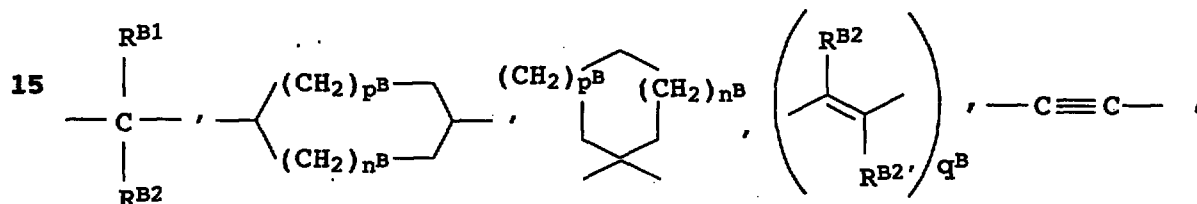
may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, OCH₃, CH₃, CF₃ and NO₂;

5 B is

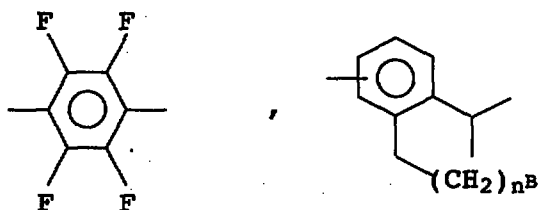


10 l^B is 0, 1, 2 or 3;
 m^B is 0, 1, 2 or 3;

L^B is



20



25

where, in each of the abovementioned ring systems, a phenyl ring may be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

30

where

35 n^B is 0, 1 or 2;
 p^B is 0, 1 or 2;
 q^B is 1, 2 or 3;

40 $RB1$ is C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, C₀₋₃-alkyl-C₃₋₈-cycloalkyl, OH or OCH₃;

$RB2$ is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl. [sic]

45 $RB1$ and $RB2$ may also be bonded together;



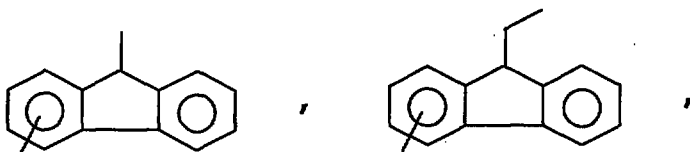
* C L M S *

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$R^{B2'}$ is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl
or C_{0-3} -alkyl- C_{3-8} -cycloalkyl;

5 B is furthermore -1-adamantyl-, -1-adamantyl- CH_2 -,
-2-adamantyl- or -2-adamantyl- CH_2 -,

10



15

B is furthermore $-(CH_2)_{1^B}-L^{B1}-M^B-L^{B2}-(CH_2)_{m^B}-$, where 1^B and m^B
have the abovementioned meanings and the two groups
 L^{B1} and L^{B2} , independently of one another, are the
following radical:

20

25

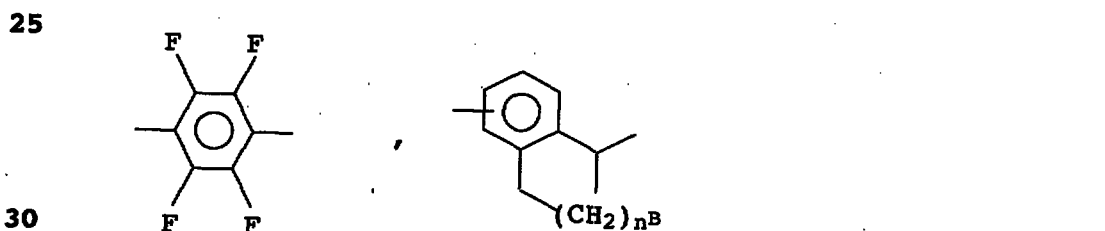
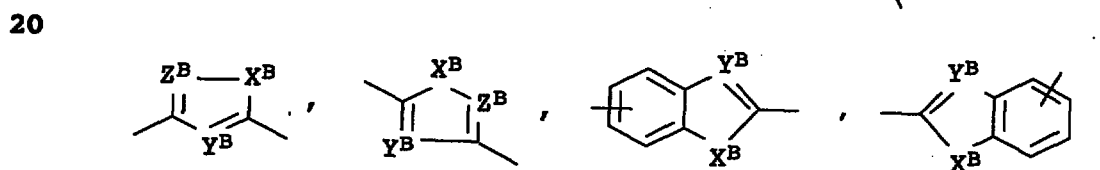
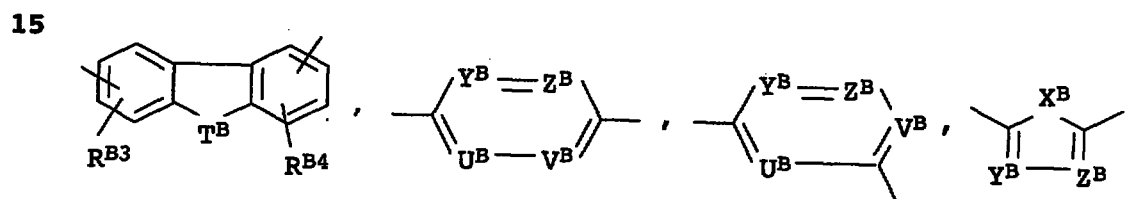
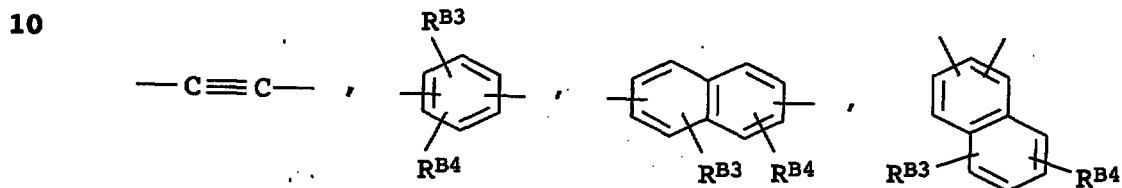
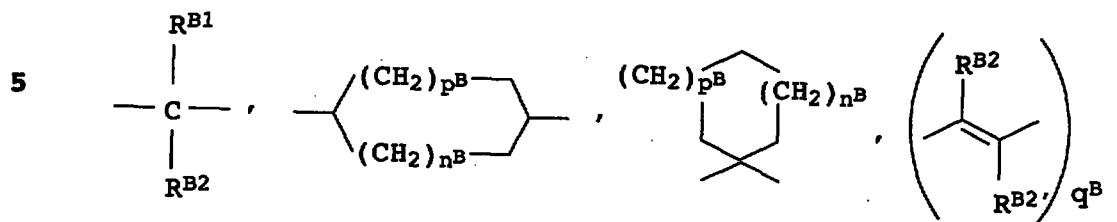
30

35

40

45





where, in each of the abovementioned ring systems, a phenyl ring may be fused on;

35 where

n^B is 0, 1 or 2;

p^B is 0, 1 or 2;

q^B is 1, 2 or 3;

40 $RB1$ is H (only for LB^2), C_{1-6} -alkyl (only for LB^2), C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

45 $RB2$ is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;



178

$R^{B2'}$ is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl or C_{0-3} -alkyl- C_{3-8} -cycloalkyl;

5 R^{B3} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, $R^{B5}OCO$ (where R^{B5} is H, C_{1-6} -alkyl or C_{1-3} -alkylaryl), $R^{B6}-O$ (where R^{B6} is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

10 R^{B4} is H, C_{1-6} -alkyl, $R^{B6}-O$, Cl, Br, F or CF_3 ;

T^B is CH_2 , O, S, NH or N- C_{1-6} -alkyl;

X^B is O, S, NH or N- C_{1-6} -alkyl;

15 Y^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

Z^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-Cl$;

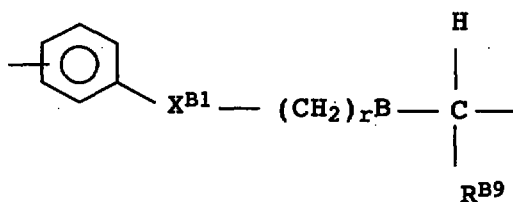
20 U^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl;

V^B is $=CH-$, $=C-C_{1-6}$ -alkyl, $=N-$ or $=C-O-C_{1-3}$ -alkyl.

25 R^{B1} and R^{B2} may also be bonded together;

M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CO, SO_2 , $CH=CH$ or $C\equiv C$;

30 B may furthermore be



35 where X^{B1} is a bond, O, S or $\begin{array}{c} O \\ || \\ -C- \end{array}$;

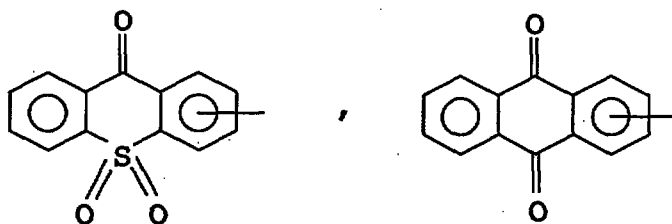
40 r^B is 0, 1, 2 or 3;

R^{B9} is H or C_{1-3} -alkyl;

45 A-B may be



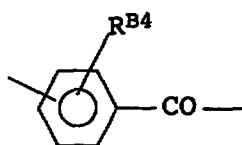
5



D is a single bond or
CO, OCO, NR^{D1}-CO (where R^{D1} is H, C₁₋₄-alkyl or
10 C₀₋₃-alkylaryl), SO₂ or NR^{D1}SO₂;

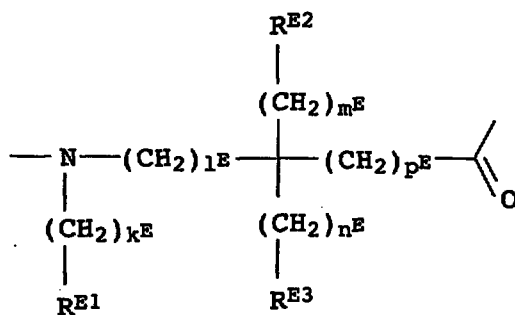
B-D may be

15



20 E is a single bond or

25



30

k^E is 0, 1 or 2;
l^E is 0, 1 or 2;
m^E is 0, 1, 2 or 3;
n^E is 0, 1 or 2;
35 p^E is 0, 1 or 2;

40

RE¹ is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, phenyl, naphthyl,
pyridyl, thienyl or C₃₋₈-cycloalkyl having a fused-on
phenyl ring, it being possible for the abovementioned
radicals to carry up to three identical or different
substituents from the group consisting of C₁₋₆-alkyl,
O-C₁₋₆-alkyl, F, Cl and, Br;

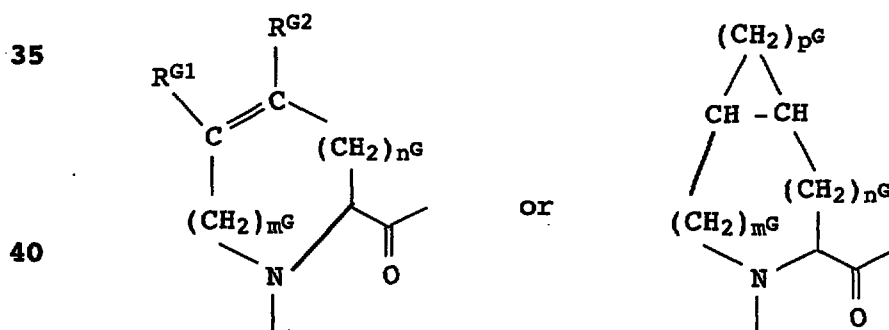
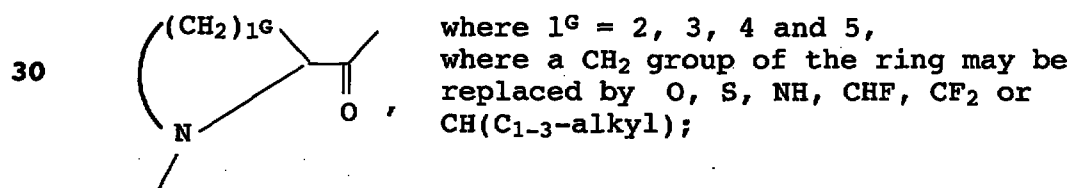
45

RE¹ is furthermore RE⁴OCO-CH₂ (where RE⁴ is H, C₁₋₁₂-alkyl or
C₁₋₃-alkylaryl);



180

- 5 R^{E2} is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C_{1-6} -alkyl, OH, O- C_{1-6} -Alkyl, F, Cl and Br, or is $CH(CH_3)OH$ or $CH(CF_3)_2$;
- 10 R^{E3} is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or phenyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C_{1-6} -alkyl, O- C_{1-6} -alkyl, F, Cl and Br;
- 15 R^{E2} and R^{B1} together may furthermore form a bridge having $(CH_2)_{0-4}$, $CH=CH$, $CH_2-CH=CH$ or $CH=CH-CH_2$ groups;
- 20 the groups stated under R^{E1} and R^{E3} may be linked to one another via a bond; the groups stated under R^{E2} and R^{E3} may also be linked to one another via a bond;
- 25 R^{E2} is furthermore COR^{E5} (where R^{E5} is OH, O- C_{1-6} -alkyl or O- C_{1-3} -alkylaryl);
- E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;
- G is



where

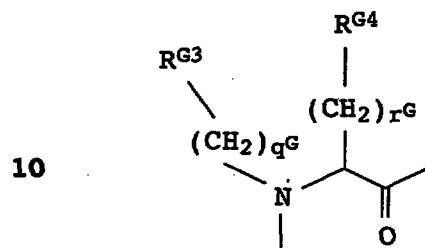
- 45 m^G is 0, 1 or 2;
 n^G is 0, 1 or 2;
 p^G is 1 or 3;
 $RG1$ is H;



R^{G2} is H;

R^{G1} and R^{G2} together may furthermore form a $CH=CH-CH=CH$ chain;

5 G is furthermore



where

15

q^G is 0, 1 or 2;

r^G is 0, 1 or 2;

R^{G3} is H, C_1-C_6 -alkyl or C_3-8 -cycloalkyl;

20

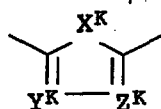
R^{G4} is H, C_1-C_6 -alkyl, C_3-8 -cycloalkyl or phenyl;

K is

25 $NH-(CH_2)_{n^K}-Q^K$ where

n^K is 1 or 2;

30 Q^K is



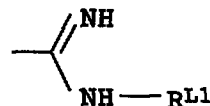
X^K is O, S, NH or $N-C_{1-6}$ -alkyl;

35

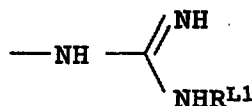
Y^K is $=CH-$, $=C-C_{1-3}$ -alkyl, $=N-$ or $=C-Cl$;

Z^K is $=CH-$, $=C-C_{1-3}$ -alkyl, $=N-$ or $=C-Cl$;

40 L:



or



where

45



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R^{L1} is H, OH, O-C₁₋₆-alkyl, O-(CH₂)₀₋₃-phenyl, CO-C₁₋₆-alkyl, CO₂-C₁₋₆-alkyl or CO₂-C₁₋₅-alkylaryl.

5. A compound of the formula I, its tautomers, pharmacologically tolerable salts and prodrugs, where:

A is

H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, R^{A1}OCO (where R^{A1} is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₁₋₃-alkyl-C₃₋₈-cycloalkyl or C₁₋₃-alkylaryl), R^{A2}R^{A3}NCO (where R^{A2} is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; R^{A3} is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl), R^{A4}OCONR^{A2}, R^{A4}CONR^{A2} (where R^{A4} is C₁₋₆-alkyl or C₁₋₃-alkylaryl), R^{A1}O, phenoxy, R^{A2}R^{A3}N, HO-SO₂, R^{A2}R^{A3}N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P, NO₂, R^{A1}-N(OH)-CO- or R^{A1}R^{A2}NCONR^{A3}, where aryl in each case may be substituted by up to 2 identical or different substituents from the group consisting of F, Cl, Br, CH₃, CF₃, OCH₃ and NO₂;

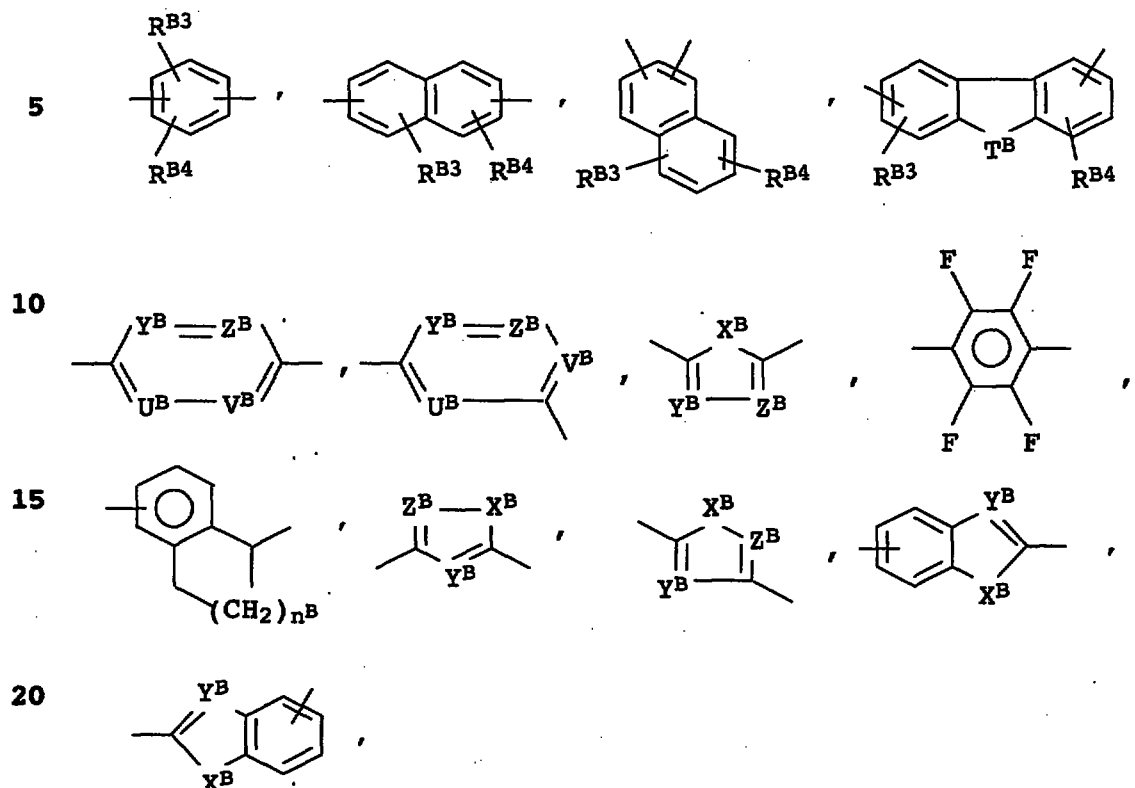
B is

-(CH₂)_{1^B}-L^B-(CH₂)_{m^B}- where

1^B is 0, 1, 2 or 3;

m^B is 0, 1, 2, 3, 4 or 5;



L^B is

25 where, in each of the abovementioned ring systems, a phenyl ring may be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, F, Cl and Br or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

30 R^{B3} is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, R^{B5}OCO (where R^{B5} is H, C₁₋₆-alkyl or C₁₋₃-alkylaryl), R^{B6}-O (where R^{B6} is H or C₁₋₆-alkyl), F, Cl, Br, NO₂ or CF₃;

35 R^{B4} is H, C₁₋₆-alkyl, R^{B6}-O, Cl, Br, F or CF₃;

T^B is CH₂, O, S, NH or N-C₁₋₆-alkyl;

X^B is O, S, NH or N-C₁₋₆-alkyl;

40

Y^B is =CH-, =N- or =C-Cl;

Z^B is =CH-, =N- or =C-Cl;

45

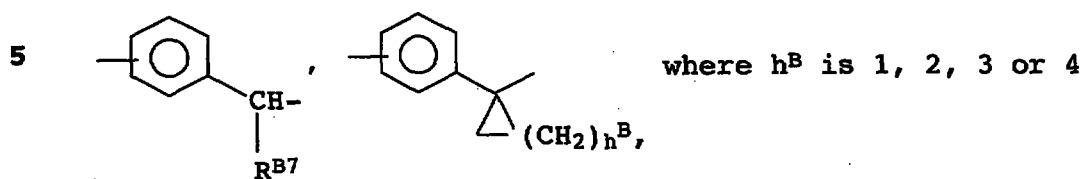
U^B is =CH- or =N-;



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v^B is $=CH-$ or $=N-$;

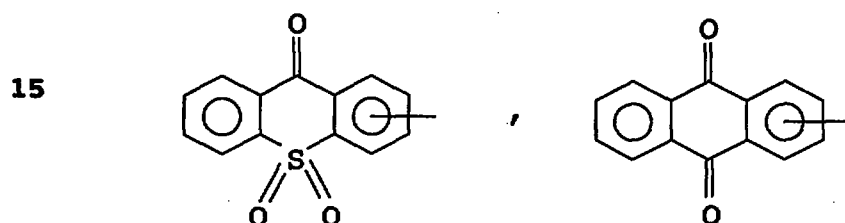
B may furthermore be



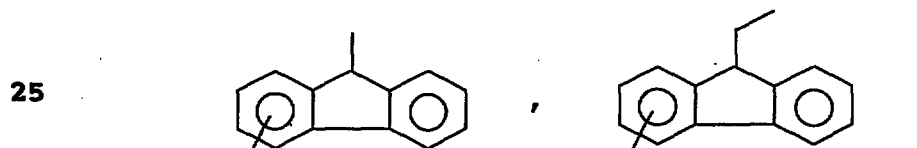
(RB^7 is C_{1-6} -alkyl or C_{3-8} -cycloalkyl)

10

A-B may be

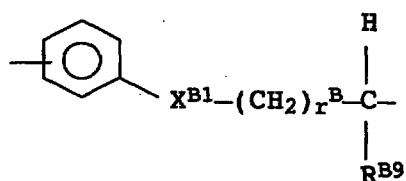


20 B may furthermore be
-1-adamantyl-, -2-adamantyl-, -1-adamantyl- CH_2- ,
-2-adamantyl- CH_2- ,



B may furthermore be

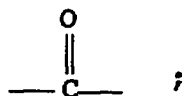
30



35

where XB^1 is a bond, O, S, or

40



45 r^B is 0, 1, 2 or 3;
 RB^9 is H or C_{1-3} -alkyl;

D is a single bond or



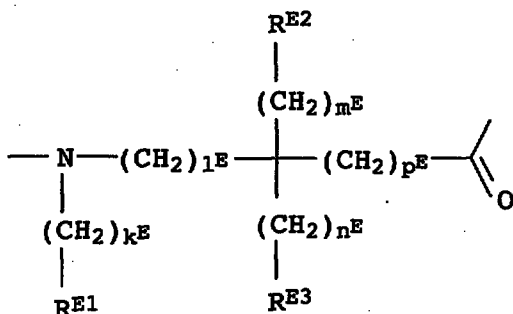
185

-NR^{D1}-CO (where R^{D1} is H, C₁₋₄-alkyl or C₀₋₃-alkylaryl) or
-NR^{D1}SO₂;

E is a single bond or

5

10



15

where

k^E is 0, 1 or 2;

l^E is 0, 1 or 2;

m^E is 0, 1, 2 or 3;

n^E is 0, 1 or 2;

20

p^E is 0, 1 or 2;

25

RE¹ is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, aryl, pyridyl, thienyl, C₃₋₈-cycloalkyl having a fused-on phenyl ring, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br;

30

RE¹ is furthermore RE⁴OCO-CH₂ (where RE⁴ is H, C₁₋₁₂-alkyl or C₁₋₃-alkylaryl);

35

RE² is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, phenyl, pyridyl, furyl, thienyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br, or is CH(CH₃)OH or CH(CF₃)₂;

40

RE³ is H, C₁₋₆-alkyl or C₃₋₈-cycloalkyl, it being possible for the abovementioned radicals to carry up to three identical or different substituents from the group consisting of C₁₋₆-alkyl, O-C₁₋₆-alkyl, F, Cl and Br;

45

RE² and RE³ together may furthermore form a bridge having (CH₂)₀₋₄, CH=CH, CH₂-CH=CH or CH=CH-CH₂ groups;



* C L M S *

186

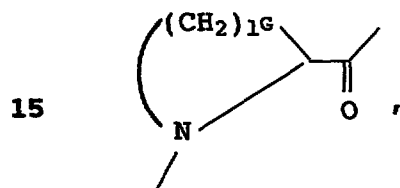
the groups stated under R^{E1} and R^{E3} may be linked to one another via a bond; the groups stated under R^{E2} and R^{E3} may also be linked to one another via a bond;

5 R^{E2} is furthermore COR^{E5} (where R^{E5} is OH, O-C₁₋₆-alkyl or OC₁₋₃-alkylaryl);

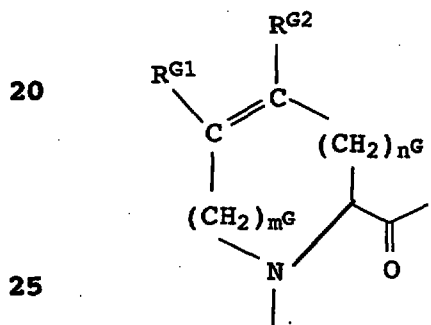
E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;

10

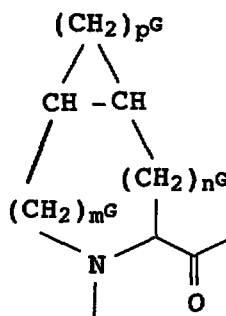
G is



where $1^G = 2, 3, 4$ and 5 ,
where a CH_2 group of the ring may be replaced by O, S, NH, CHF, CF₂ or CH(C₁₋₃-alkyl);



or



where

30 m^G is 0, 1 or 2;
 n^G is 0, 1 or 2;
 p^G is 1 or 3;

$RG1$ is H;

35

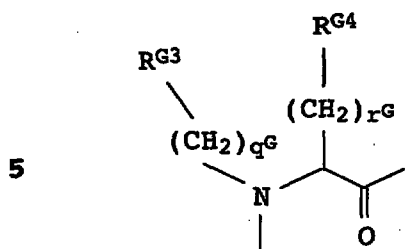
$RG2$ is H;

$RG1$ and $RG2$ together may furthermore form a $CH=CH-CH=CH$ chain;

40 G is furthermore

45





where

10

q^G is 0, 1 or 2;

r^G is 0, 1 or 2;

R^{G3} is H, C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl;

15

R^{G4} is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or phenyl;

K is

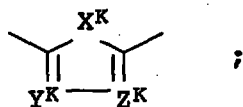
20

$NH-(CH_2)_{n^K}-Q^K$ where

$n^K = 1$ or 2 ;

25

Q^K is



X^K is O, S, NH or N- C_1 - C_6 -alkyl;

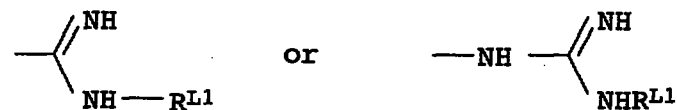
30

Y^K is $=CH-$, $=C-C_1$ - C_6 -alkyl, $=N-$ or $=C-Cl$;

Z^K is $=CH-$, $=C-C_1$ - C_6 -alkyl, $=N-$ or $=C-Cl$;

35

L:



40

where

RL^1 is $-H$, $-OH$, $-O-C_1$ - C_6 -alkyl, $-O-(CH_2)_{0-3}$ -phenyl,
45 $-CO-C_1$ - C_6 -alkyl, $-CO_2-C_1$ - C_6 -alkyl or CO_2-C_1 - C_3 -alkylaryl.



6. A compound of the formula I, its tautomers, pharmacologically tolerable salts and prodrugs, where

A is

- 5 H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, R^{A1}OCO (where R^{A1} is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₃-alkyl or C₁₋₃-alkylaryl), R^{A2}R^{A3}NCO (where R^{A2} is H-, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; R^{A3} is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl); R^{A4}OCONR^{A2} (where R^{A4} is C₁₋₆-alkyl or C₁₋₃-alkylaryl), R^{A4}CONR^{A2}, R^{A1}O, R^{A2}R^{A3}N, HO-SO₂-, phenoxy, R^{A2}R^{A3}N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P-, NO₂, R^{A1}-N(OH)-CO- or R^{A1}R^{A2}NCONR^{A3}, where aryl in
10 each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, CF₃, CH₃, OCH₃ and NO₂;

B is

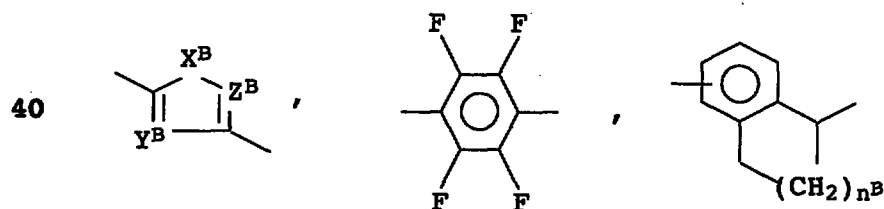
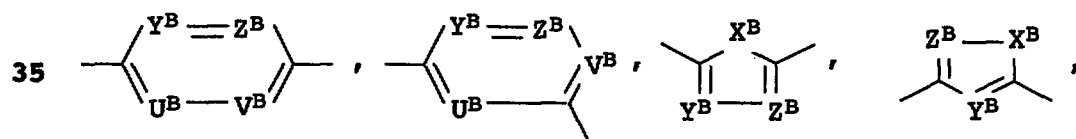
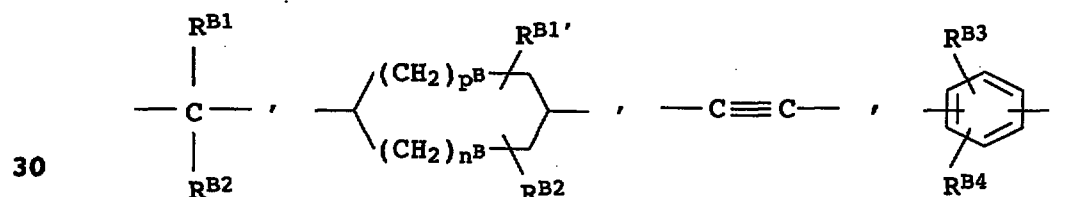


20

1^B is 0, 1, 2 or 3;

m^B is 0, 1 or 2;

25 L^B is



- 45 where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group



consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

where

5

n^B is 0, 1 or 2;

p^B is 0, 1 or 2;

10

RB¹ is C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, C₀₋₃-alkyl-C₃₋₈-cycloalkyl, OH or OCH₃;

RB² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl;

15

RB³ is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl;
RB⁵OCO (where RB⁵ is H, C₁₋₆-alkyl or C₁₋₃-alkylaryl),
RB⁶-O (where RB⁶ is H or C₁₋₆-alkyl), F, Cl, Br, NO₂ or CF₃;

20

RB⁴ is H, C₁₋₆-alkyl, RB⁶-O, Cl, Br, F or CF₃;

RB^{1'} is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl or C₀₋₃-alkyl-C₃₋₈-cycloalkyl;

25

RB¹ and RB² may also be bonded together;

XB is O, S, NH or N-C₁₋₆-alkyl;

30

Y^B is =CH- or =N-;

Z^B is =CH- or =N-;

U^B is =CH- or =N-;

35

V^B is =CH- or =N-;

40

B is furthermore
-(CH₂)_{1B}-L^B-M^B-L^B-(CH₂)_{m^B}, where
l^B and m^B have the abovementioned meanings and the two
groups L^B, independently of one another, are the radicals
stated under L^B;

45

M^B is a single bond, O, S, CH₂, CH₂-CH₂, CH₂-O, O-CH₂, CH₂-S,
S-CH₂, CO, SO₂, CH=CH or C≡C;

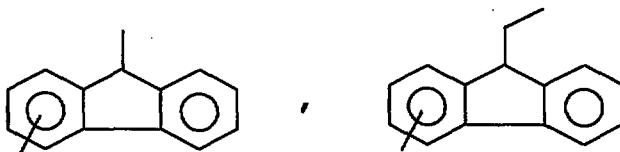


* C L M S *

190

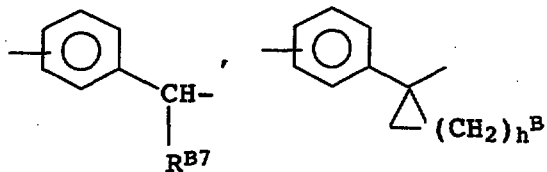
B is furthermore
 -1-adamantyl-CH₂-, -2-adamantyl-CH₂-, -1-adamantyl-,
 -2-adamantyl-,

5



10

B may furthermore be



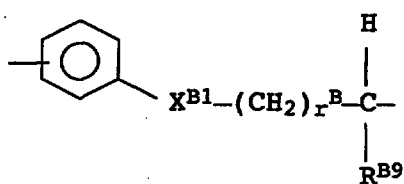
where h^B is 1, 2, 3 or 4

15

(RB⁷ is C₁₋₆-alkyl or C₃₋₈-cycloalkyl)

20

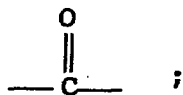
B may furthermore be



25

where XB¹ is a bond, O, S or

30



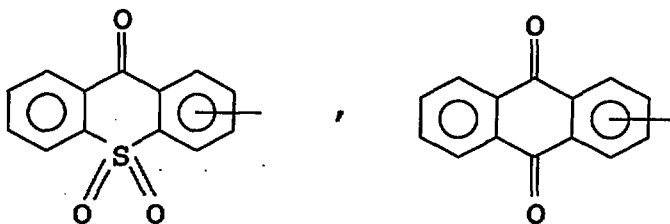
r^B is 0, 1, 2 or 3;

35

RB⁹ is H or C₁₋₃-alkyl;

A-B may be

40



45



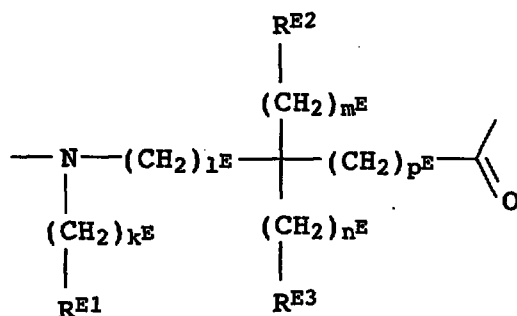
191

D is a single bond or CO, OCO or $\text{NR}^{\text{D1}}\text{-CO}$ (where R^{D1} is H, $\text{C}_{1-4}\text{-alkyl}$ or $\text{C}_{0-3}\text{-alkylaryl}$), SO_2 or $\text{NR}^{\text{D1}}\text{SO}_2$;

E is

5

10



15

where

20

k^{E} is 0 or 1;

l^{E} is 0 or 1;

m^{E} is 0 or 1;

n^{E} is 0 or 1;

p^{E} is 0 or 1;

25

RE1 is H, $\text{C}_{1-6}\text{-alkyl}$, $\text{C}_{3-8}\text{-cycloalkyl}$, aryl, pyridyl, thienyl or $\text{C}_{3-8}\text{-cycloalkyl}$ having a fused-on phenyl ring;

30

RE1 is furthermore RE4OCO-CH_2 (where RE4 is H, $\text{C}_{1-12}\text{-alkyl}$ or $\text{C}_{1-3}\text{-alkylaryl}$);

RE2 is H, $\text{C}_{1-6}\text{-alkyl}$, $\text{C}_{3-8}\text{-cycloalkyl}$, phenyl, pyridyl, furyl, thienyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, where the abovementioned radicals may carry up to three identical or different substituents from the group consisting of $\text{C}_{1-6}\text{-alkyl}$, $\text{O-C}_{1-6}\text{-alkyl}$, F, Cl and Br, or is $\text{CH}(\text{CH}_3)\text{OH}$ or $\text{CH}(\text{CF}_3)_2$;

35

RE3 is H, $\text{C}_{1-6}\text{-alkyl}$, $\text{C}_{3-8}\text{-cycloalkyl}$ or phenyl;

40

RE2 and RE1 together may also form a bridge with $(\text{CH}_2)_{0-4}$, CH=CH , $\text{CH}_2\text{-CH=CH}$ or CH=CH-CH_2 groups;

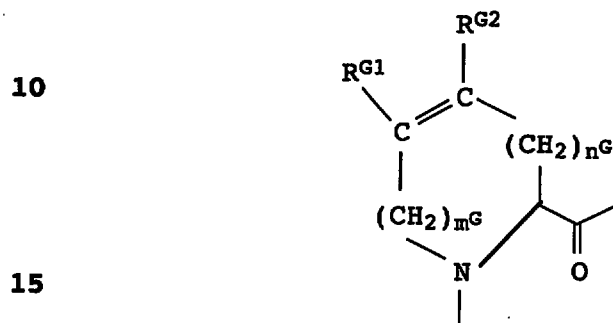
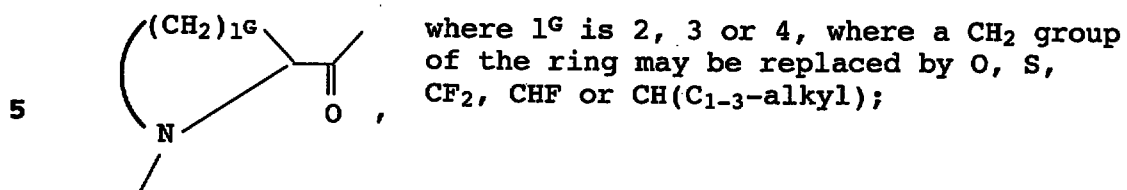
45

E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;



* C L M S *

G is

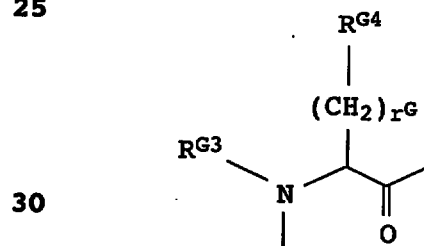


where

20 m^G is 0, 1 or 2;
 n^G is 0, 1 or 2;

RG^1 and RG^2 are each H;

25 G is furthermore



where r^G is 0 or 1;

35 RG^3 is H, $\text{C}_1\text{-C}_6\text{-alkyl}$ or $\text{C}_3\text{-8-cycloalkyl}$;

RG^4 is H, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_3\text{-8-cycloalkyl}$ or phenyl;

40 K is

$\text{NH}-(\text{CH}_2)_{n^K}\text{-Q}^K$, where

n^K is 1 or 2;

45



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Q^K is5 X^K is O or S;Y^K is =CH-, =C-C₁₋₃-alkyl or =N-;10 Z^K is =CH-, =C-C₁₋₃-alkyl or =N-;

L:



15

where

R^{L1} is H, OH, O-C₁₋₆-alkyl, O-(CH₂)₀₋₃-phenyl, CO-C₁₋₆-alkyl, CO₂-C₁₋₆-alkyl or CO₂-C₁₋₃-alkylaryl.

20

7. A compound of the formula I, its tautomers, pharmacologically tolerable salts and prodrugs, where

A is

25 H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂ or R^{A1}OCO (where R^{A1} is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₃-alkyl or C₁₋₃-alkylaryl), R^{A2}R^{A3}NCO (where R^{A2} is H-, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; R^{A3} is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl); R^{A4}ONRA^{A2} (where R^{A4} is C₁₋₆-alkyl or C₁₋₃-alkylaryl), R^{A4}CONRA^{A2}, R^{A1}O, R^{A2}R^{A3}N, HO-SO₂-, phenoxy, R^{A2}R^{A3}N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P-, NO₂, R^{A1}-N(OH)-CO- or R^{A1}R^{A2}NCONRA^{A3}, where aryl in

30 each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, CF₃, CH₃, OCH₃ and NO₂;

35 B is

-(CH₂)_{1B}-L^B-(CH₂)_{mB}- where

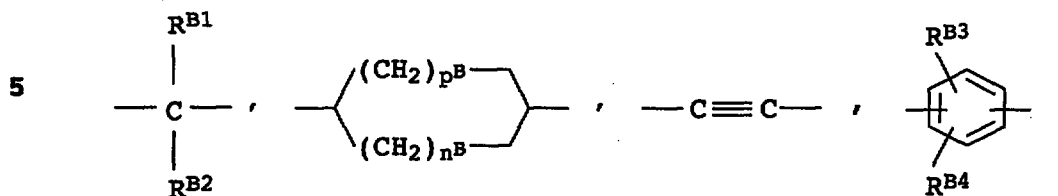
40

1^B is 0, 1 or 2;m^B is 0, 1 or 2;

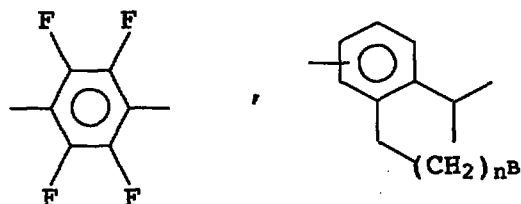
45



L^B is



10



15

where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH_3 , CF_3 , Br, Cl and F or may be substituted by $\text{R}^8\text{OOC-}$ (where R^8 is H or C_{1-3} -alkyl);

20

where

25 n^B is 0 or 1;
 p^B is 0 or 1;

RB^1 is C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

30 RB^2 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

RB^3 is H, C_{1-6} -alkyl;
 RB^5OCO (where RB^5 is H, C_{1-6} -alkyl), $\text{RB}^6\text{-O}$ (where RB^6 is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

35

RB^4 is H, C_{1-6} -alkyl, $\text{RB}^6\text{-O}$, Cl, Br, F or CF_3 ;

RB^1 and RB^2 may also be bonded together;

40

B is furthermore
 $\text{---}(\text{CH}_2)_{1^B}\text{---L}^B\text{---M}^B\text{---L}^B\text{---}(\text{CH}_2)_{m^B}$, where
 1^B and m^B have the abovementioned meanings and the two groups L^B , independently of one another, are the radicals stated under L^B ;

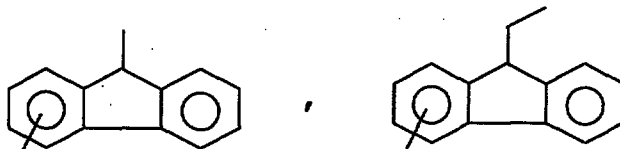
45



195

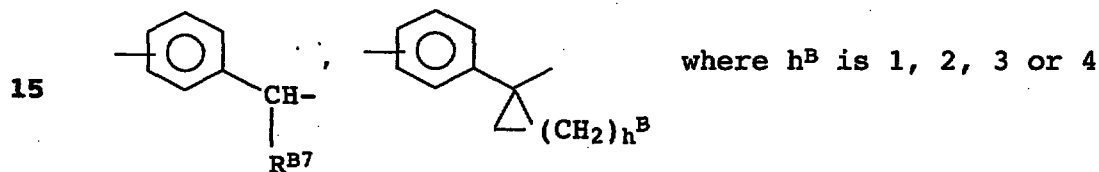
M^B is a single bond, O, S, CH₂, CH₂-CH₂, CH₂-O, O-CH₂, CH₂-S, S-CH₂, CH=CH or C≡C;

5 B is furthermore
-1-adamantyl-CH₂-, -2-adamantyl-CH₂-,



10

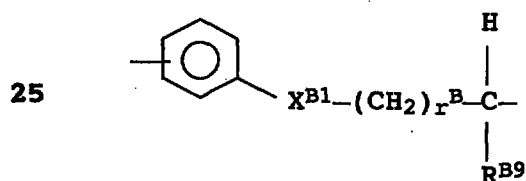
B may furthermore be



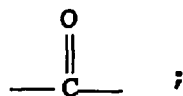
(R^{B7} is C₁₋₆-alkyl or C₃₋₈-cycloalkyl)

20

B may furthermore be



30 where X^{B1} is a bond, O, S or

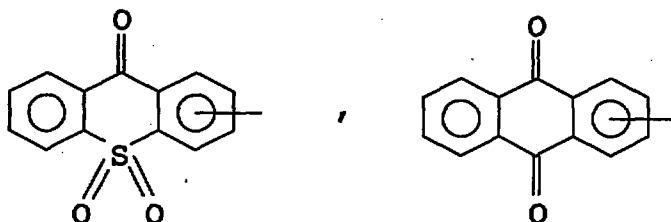


35

r^B is 0, 1, 2 or 3;

R^{B9} is H or C₁₋₃-alkyl;

40 A-B may be



196

D is a single bond or
CO, OCO or $\text{NR}^{\text{D1}}\text{-CO}$ (where R^{D1} is H, $\text{C}_{1-4}\text{-alkyl}$ or
 $\text{C}_{0-3}\text{-alkylaryl}$), SO_2 or $\text{NR}^{\text{D1}}\text{SO}_2$;

5 E is



15 where

m^E is 0, 1, 2 or 3;

RE^1 is H or $\text{C}_{1-6}\text{-alkyl}$;

20

RE^2 is H, $\text{C}_{1-6}\text{-alkyl}$ or $\text{C}_{3-8}\text{-cycloalkyl}$, where the
abovementioned radicals may carry up to three
substituents from the group consisting of $\text{C}_{1-6}\text{-alkyl}$ and
F, or is $\text{CH}(\text{CH}_3)\text{OH}$ or $\text{CH}(\text{CF}_3)_2$;

25

RE^3 is H;

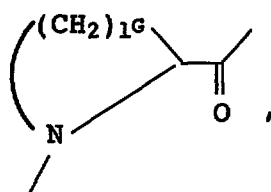
the groups stated under RE^1 and RE^2 may be linked to one
another via a bond;

30

E may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap
or D-Arg;

G is

35



where l^G is 2 or 3, where a CH_2 group of
the ring may be replaced by S or CHCH_3 ;

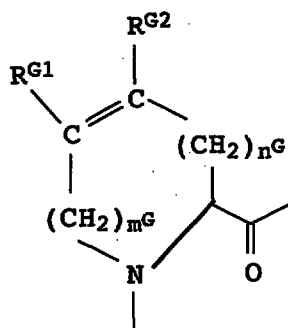
40

45



197

5



10 where

 m^G is 1; n^G is 0;15 R^{G1} and R^{G2} are each H;

K is

 $NH-(CH_2)_{n^K}-Q^K$, where

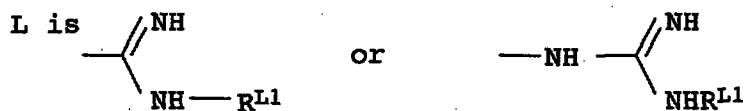
20

 n^K is 1; Q^K is

25

 X^K is S;30 Y^K is $=CH-$ or $=N-$; Z^K is $=CH-$ or $=N-$;

35



where

40 R^{L1} is H, OH, $CO-C_{1-6}$ -alkyl, CO_2-C_{1-6} -alkyl or CO_2-C_{1-3} -alkylaryl.

8. A compound of the formula I, its tautomers, pharmacologically tolerable salts and prodrugs, where

45

A is



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H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂ or RA¹OCO (where RA¹ is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₃-alkyl or C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H-, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl); RA⁴OCNRA² (where RA⁴ is C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA⁴CONRA², RA¹O, RA²RA³N, HO-SO₂-, phenoxy, RA²RA³N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P-, NO₂, RA¹-N(OH)-CO- or RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, CF₃, CH₃, OCH₃ and NO₂;

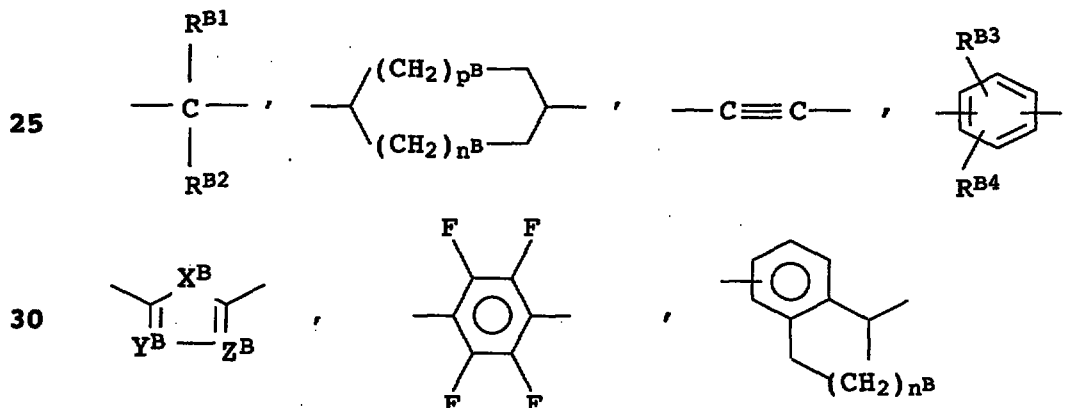
B is

15 $-(CH_2)_{1^B}-L^B-(CH_2)_{m^B}-$ where

1^B is 0 or 1;

m^B is 0, 1 or 2;

20 L^B is



35 where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

40 where

n^B is 0 or 1;

p^B is 0 or 1;

45 RB¹ is C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, C₀₋₃-alkyl-C₃₋₈-cycloalkyl, OH or OCH₃;



199

RB^2 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

RB^3 is H, C_{1-6} -alkyl;

5 RB^5OCO (where RB^5 is H or C_{1-6} -alkyl), RB^6-O (where RB^6 is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

RB^4 is H, C_{1-6} -alkyl, RB^6-O , Cl, Br, F or CF_3 ;

10 RB^1 and RB^2 may also be bonded together;

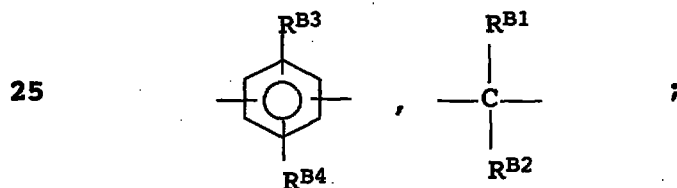
X^B is O or S;

15 Y^B is $=CH-$ or $=N-$;

Z^B is $=CH-$ or $=N-$;

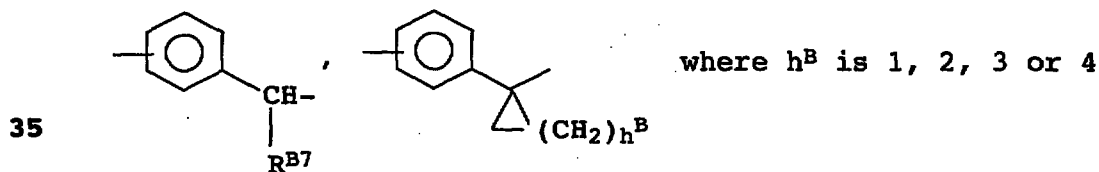
B is furthermore

20 $-(CH_2)_{1^B}-L^B-M^B-L^B-(CH_2)_{m^B}$, where 1^B and m^B have the abovementioned meanings and the two groups L^B , independently of one another, are the radicals $-C\equiv C-$ stated under L^B ,



30 M^B is a single bond, O, CH_2-S , $S-CH_2$, CO, SO_2 or CH_2-O ;

B may furthermore be



(RB^7 is C_{1-6} -alkyl or C_{3-8} -cycloalkyl)

40 B may furthermore be 1-fluorenyl-, 1-adamantyl- or 1-adamantyl- CH_2- ,

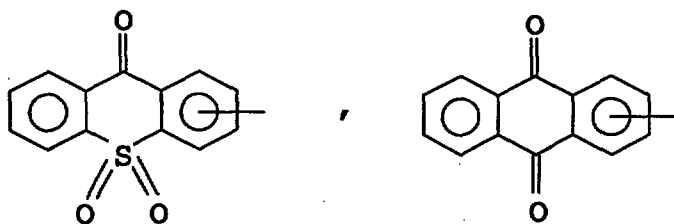
A-B may be 2-pyridyl- CH_2- , 2-benzothienyl-, 3-benzothienyl-,

45



200

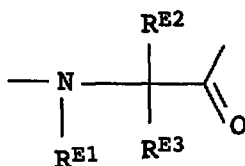
5



D is a single bond or CO or SO₂;

10 E is

15



where

20 RE¹ is H or CH₃;

RE² is H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, thienyl, CH(CH₃)OH or CH(CF₃)₂;

25 RE³ is H;

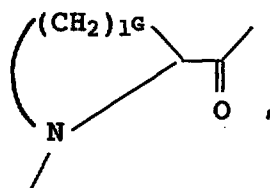
the groups stated under RE¹ and RE² may be linked to one another via a bond; the groups stated under RE² and RE³ may also be linked to one another via a bond;

30

E may also be D-Lys, D-Orn, D-Dab, D-Dap or D-Arg;

G is

35



where 1^G is 2 or 3, where a CH₂ group of the ring may be replaced by CHCH₃;

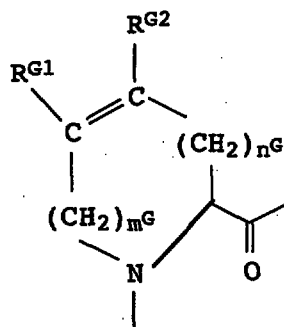
40

45



201

5



10

where

 m^G is 1; n^G is 0;

15

 R^{G1} and R^{G2} are each H;

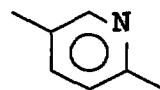
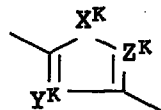
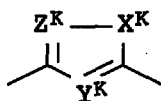
K is

 $NH-(CH_2)_{n^K}-Q^K$, where

20

 n^K is 1; Q^K is

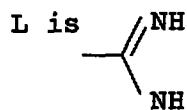
25

 X^K is S;

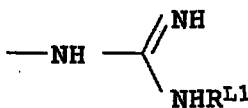
30

 Y^K is $=CH-$ or $=N-$; Z^K is $=CH-$ or $=N-$;

35



or



where

40

 R^{L1} is H or OH.

9. A compound of the formula I, its tautomers, pharmacologically tolerable salts and prodrugs, where

45

A is



* C L M S *

202

H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂ or RA¹OCO (where RA¹ is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₁₋₃-alkyl-C₃₋₈-cycloalkyl or C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl), RA⁴OCONRA², RA⁴CONRA² (where RA⁴ is C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA¹O, phenoxy, RA²RA³N, HO-SO₂, RA²RA³N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P, NO₂, RA¹-N(OH)-CO or RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, OCH₃, CH₃, CF₃ and NO₂;

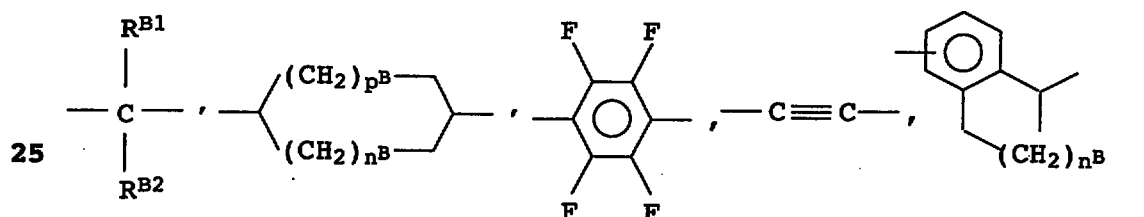
B is

-(CH₂)_{l^B}-L^B-(CH₂)_{m^B}-, where

l^B is 0, 1 or 2;

m^B is 0, 1 or 2;

20 L^B is



where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH₃, CF₃, Br, Cl and F or may be substituted by R⁸OOC- (where R⁸ is H or C₁₋₃-alkyl);

35

where

n^B is 0, 1 or 2;

p^B is 0, 1 or 2;

40

RB¹ is C₀₋₃-alkylaryl, C₀₋₃-alkylheteroaryl, C₀₋₃-alkyl-C₃₋₈-cycloalkyl, OH or OCH₃;

RB² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl;

45

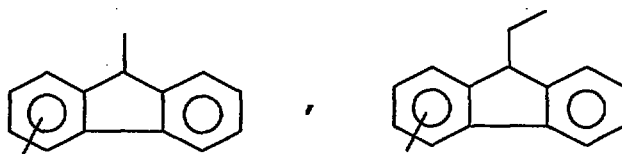


203

RB^1 and RB^2 may also be bonded together;

B is furthermore -1-adamantyl- CH_2 -, -2-adamantyl- CH_2 -,

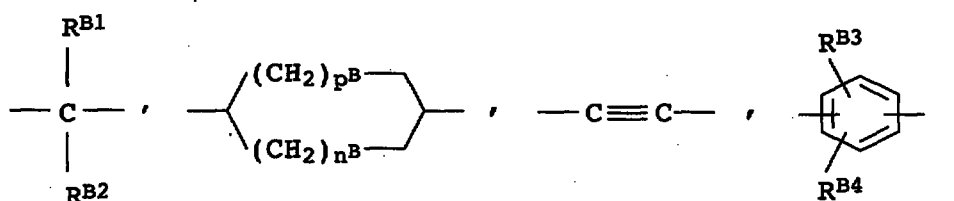
5



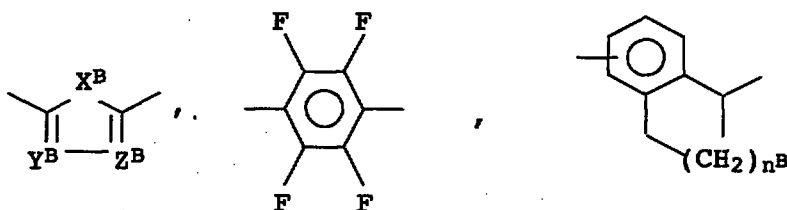
10

B is furthermore $-(CH_2)_{l^B}-L^{B1}-M^B-L^{B2}-(CH_2)_{m^B}-$, where l^B and m^B have the abovementioned meanings and the two groups L^{B1} and L^{B2} , independently of one another, are the following radicals:

15



20



25

where, in each of the abovementioned ring systems, a phenyl ring can be fused on;

where

30

n^B is 0, 1 or 2;

p^B is 0, 1 or 2;

35

RB^1 is H (only for L^{B2}), C_{1-6} -alkyl (only for L^{B2}), C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

40

RB^2 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

RB^3 is H, C_{1-6} -alkyl, aryl, heteroaryl, RB^5OCO (where RB^5 is H or C_{1-6} -alkyl), RB^6-O (where RB^6 is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

45

RB^4 is H, C_{1-6} -alkyl, RB^6-O , Cl, Br, F or CF_3 ;

X^B is O or S;



204

Y^B is $=CH-$ or $=N-$;

Z^B is $=CH-$ or $=N-$;

5

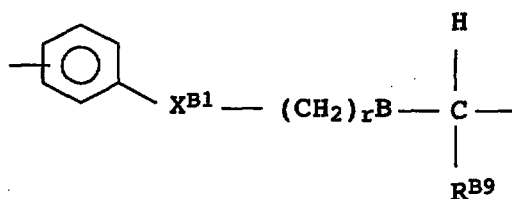
RB^1 and RB^2 may also be bonded together;

M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CO, SO_2 , $CH=CH$ or $C\equiv C$;

10

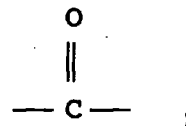
B may furthermore be

15



20

where XB^1 is a bond, O, S or



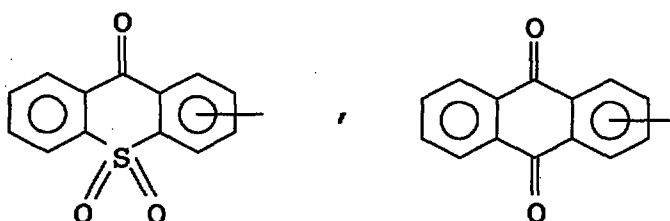
r^B is 0, 1, 2 or 3;

RB^9 is H or C_{1-3} -alkyl;

25

A-B may be

30

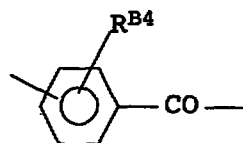


35

D is a single bond or CO, OCO, $NR^{D1}-CO$ (where R^{D1} is H, C_{1-4} -alkyl or C_{0-3} -alkylaryl), SO_2 or $NR^{D1}SO_2$;

40

B-D may be



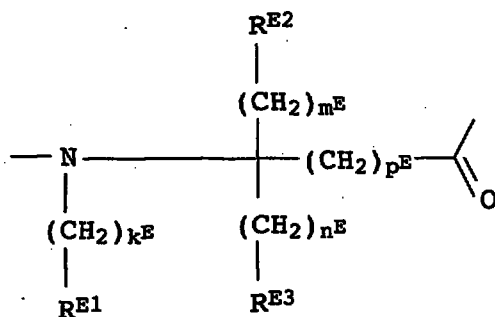
45

E is



205

5



10

 k^E is 0 or 1; m^E is 0 or 1; n^E is 0 or 1; p^E is 0 or 1;

15

RE^1 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, naphthyl, pyridyl, thienyl or C_{3-8} -cycloalkyl having a fused-on phenyl ring;

20

RE^2 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, $\text{CH}(\text{CH}_3)\text{OH}$ or $\text{CH}(\text{CF}_3)_2$;

RE^3 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or phenyl;

25

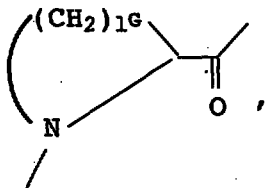
the groups stated under RE^1 and RE^2 may be linked to one another via a bond; the groups stated under RE^2 and RE^3 may also be linked to one another via a bond;

30 E

may also be D-Asp, D-Glu, D-Lys, D-Orn, D-His, D-Dab, D-Dap or D-Arg;

G is

35



where 1^G is 2, 3 or 4, where a CH_2 group of the ring may be replaced by CHCH_3 ;

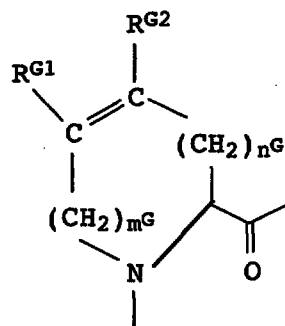
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206

5



10

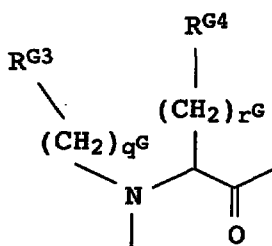
where

 m^G is 1; n^G is 0 or 1; $RG1$ is H; $RG2$ is H;

15

G is furthermore

20



25

where

 q^G is 0 or 1; r^G is 0 or 1;

30

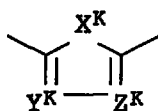
 $RG3$ is H, C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl; $RG4$ is H, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl or phenyl;

K is

35

 $NH-(CH_2)_{n^K}-Q^K$, where n^K is 1;

40

 Q^K is X^K is 0 or S;

45

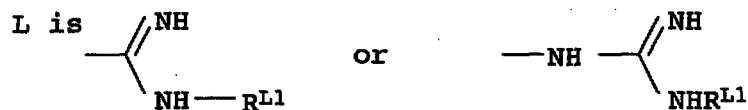


* C L M S *

Y^K is $=CH-$ or $=N-$;

Z^K is $=CH-$ or $=N-$;

5



10

where

R^{L1} is H, OH, CO-C₁₋₆-alkyl, CO₂-C₁₋₆-alkyl or CO₂-C₁₋₅-alkylaryl.

15

10. A compound of the formula I, its tautomers, pharmacologically tolerable salts and prodrugs, where

A is

20

H, C₁₋₆-alkyl, C₁₋₆-alkyl-SO₂, RA¹OCO (where RA¹ is H, C₁₋₁₂-alkyl, C₃₋₈-cycloalkyl, C₁₋₃-alkyl-C₃₋₈-cycloalkyl or C₁₋₃-alkylaryl), RA²RA³NCO (where RA² is H, C₁₋₆-alkyl, C₀₋₃-alkylaryl or C₀₋₃-alkylheteroaryl; RA³ is H, C₁₋₆-alkyl or C₀₋₃-alkylaryl), RA⁴CONRA², RA⁴CONRA² (where RA⁴ is C₁₋₆-alkyl or C₁₋₃-alkylaryl), RA¹O, phenoxy, RA²RA³N, HO-SO₂, RA²RA³N-SO₂, Cl, Br, F, tetrazolyl, H₂O₃P, NO₂, RA¹-N(OH)-CO or RA¹RA²NCONRA³, where aryl in each case may be substituted by up to 2 identical or different radicals from the group consisting of F, Cl, Br, OCH₃, CH₃, CF₃ and NO₂;

30

B is

$-(CH_2)_{1^B}-L^B-(CH_2)_{m^B}-$, where

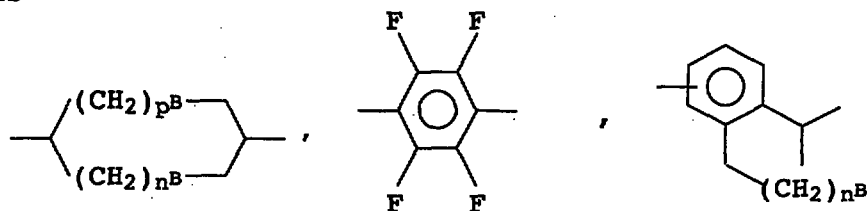
35

1^B is 0 or 1;

m^B is 0, 1 or 2;

L^B is

40



45



208

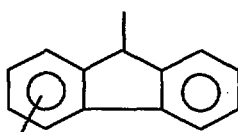
where, in each of the abovementioned ring systems, a phenyl ring can be fused on, which phenyl ring may be substituted by up to 2 identical or different radicals from the group consisting of CH_3 , CF_3 , Br, Cl and F or may be substituted by $\text{R}^8\text{OOC}-$ (where R^8 is H or $\text{C}_{1-3}\text{-alkyl}$);

where

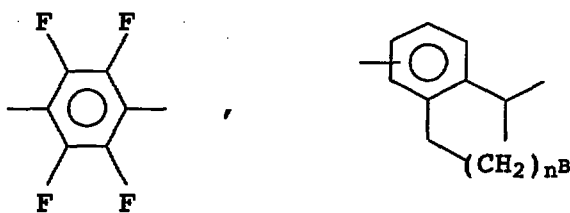
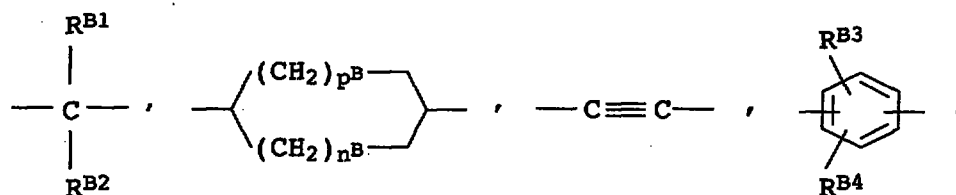
n^B is 0 or 1;

p^B is 0 or 1;

B is furthermore -1-adamantyl- CH_2- , -2-adamantyl- CH_2- ,



B is furthermore $-(\text{CH}_2)_{1^B}-\text{L}^{B1}-\text{M}^B-\text{L}^{B2}-(\text{CH}_2)_{m^B}-$, where 1^B and m^B have the abovementioned meanings and the two groups L^{B1} and L^{B2} , independently of one another, are the following radicals:



where, in each of the abovementioned ring systems, a phenyl ring can be fused on;

where

n^B is 1;

p^B is 0 or 1;



209

R^{B1} is H (only for L^{B2}), C_{1-6} -alkyl (only for L^{B2}), C_{0-3} -alkylaryl, C_{0-3} -alkylheteroaryl, C_{0-3} -alkyl- C_{3-8} -cycloalkyl, OH or OCH_3 ;

5 R^{B2} is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl;

R^{B3} is H, C_{1-6} -alkyl, R^{B6} -O (where R^{B6} is H, C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

10

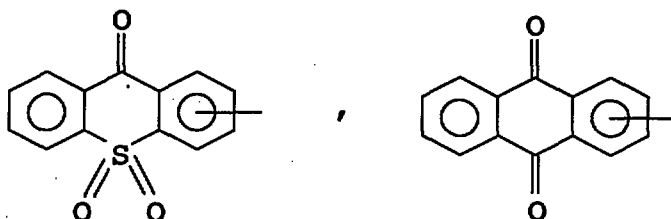
R^{B4} is H, C_{1-6} -alkyl, R^{B6} -O, Cl, Br, F or CF_3 ;

R^{B1} and R^{B2} may also be bonded together;

15 M^B is a single bond, O, S, CH_2 , CH_2-CH_2 , CH_2-O , $O-CH_2$, CH_2-S , $S-CH_2$, CO or SO_2 ;

A-B may be 2-pyridyl- CH_2 -, 2-benzothienyl-,

20

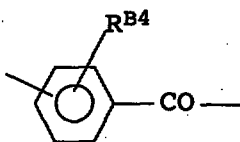


25

D is a single bond or CO or SO_2 ;

B-D may be

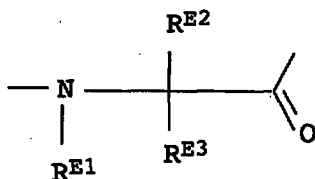
30



35

E is

40



45

R^{E1} is H;



210

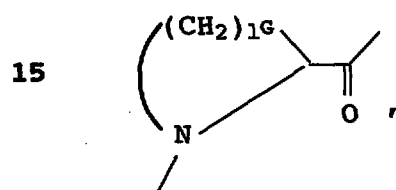
R^{E2} is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, $CH(CH_3)OH$ or $CH(CF_3)_2$;

5 R^{E3} is H;

the groups stated under R^{E1} and R^{E2} may be linked to one another via a bond;

10 E may also be D-Lys, D-Orn, D-Dab, D-Dap or D-Arg;

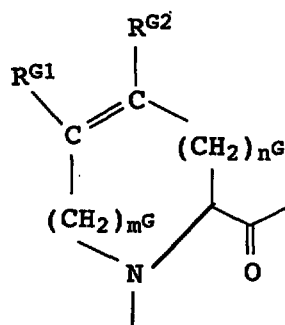
G is



where l^G is 2 or 3, where a CH_2 group of the ring may be replaced by $CHCH_3$;

20

25



where

m^G is 1;

30 n^G is 0;

$RG1$ is H;

$RG2$ is H;

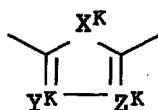
K is

35

$NH-(CH_2)_{n^K}-Q^K$, where

n^K is 1;

40 Q^K is



X^K is S;

45



Y^K is $=CH-$ or $=N-$;

5 Z^K is $=CH-$ or $=N-$;



where

RL^1 is H or OH.

15 11. A compound of the formula I, its tautomers, pharmacologically tolerable salts and prodrugs, where

A is

20 H, C_{1-6} -alkyl, C_{1-6} -alkyl- SO_2 , RA^1OCO (where RA^1 is H, C_{1-12} -alkyl, C_{3-8} -cycloalkyl, C_{1-3} -alkyl- C_{3-8} -cycloalkyl or C_{1-3} -alkylaryl), RA^2RA^3NCO (where RA^2 is H, C_{1-6} -alkyl, C_{0-3} -alkylaryl or C_{0-3} -alkylheteroaryl; RA^3 is H, C_{1-6} -alkyl or C_{0-3} -alkylaryl), $RA^4OCONRA^2$, RA^4CONRA^2 (where RA^4 is C_{1-6} -alkyl or C_{1-3} -alkylaryl), RA^1O , phenoxy,
25 RA^2RA^3N , $HO-SO_2$, $RA^2RA^3N-SO_2$, Cl, Br, F, tetrazolyl, H_2O_3P , NO_2 , $RA^1-N(OH)-CO-$ or $RA^1RA^2NCONRA^3$, where aryl in each case may be substituted by up to 2 identical or different substituents from the group consisting of F, Cl, Br, CH_3 , CF_3 , OCH_3 and NO_2 ;

30

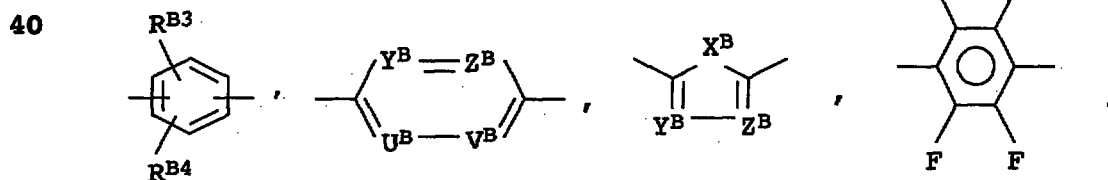
B is

$-(CH_2)_{1B}-L^B-(CH_2)_{mB}-$, where

35 1^B is 0 or 1;

m^B is 0, 1 or 2;

L^B is



45



where, in each of the abovementioned ring systems, a phenyl ring can be fused on;

5 R^{B3} is H, C_{1-6} -alkyl, aryl, $R^{B5}OCO$ (where R^{B5} is H, C_{1-6} -alkyl or C_{1-3} -alkylaryl), $R^{B6}-O$ (where R^{B6} is H or C_{1-6} -alkyl), F, Cl, Br, NO_2 or CF_3 ;

R^{B4} is H, C_{1-6} -alkyl, $R^{B6}-O$, Cl, Br, F or CF_3 ;

10 X^B is O or S;

Y^B is $=CH-$ or $=N-$;

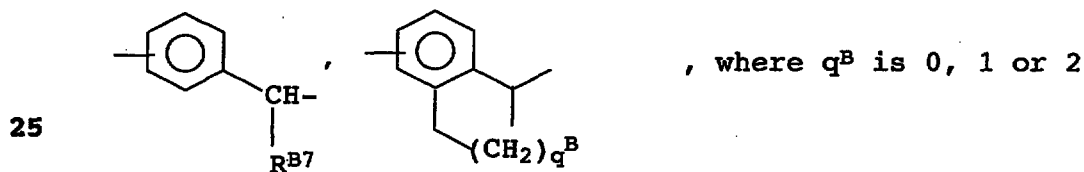
15 Z^B is $=CH-$ or $=N-$;

U^B is $=CH-$ or $=N-$;

V^B is $=CH-$ or $=N-$;

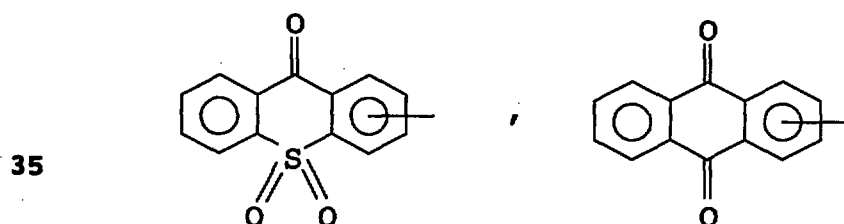
20

B may furthermore be



(R^{B7} is C_{1-6} -alkyl or C_{3-8} -cycloalkyl)

30 A-B may be



D is a single bond;

40 E is



where

RE^1 is H;

5 RE^2 is H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl, pyridyl, furyl, thienyl, imidazolyl, tetrahydropyranyl or tetrahydrothiopyranyl, where the abovementioned radicals may carry up to three identical or different substituents from the group consisting of O- C_{1-6} -alkyl and F, or is
10 $CH(CH_3)OH$ or $CH(CF_3)_2$;

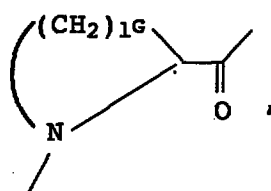
RE^3 is H;

15 the groups stated under RE^1 and RE^2 may be linked to one another via a bond;

E may also be D-Lys, D-Orn, D-Dab, D-Dap or D-Arg;

G is

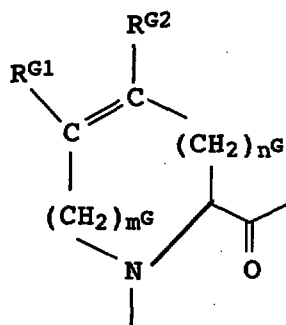
20



where 1^G is 2 or 3, where a CH_2 group of the ring may be replaced by $CHCH_3$;

25

30



35

where

m^G is 1;

n^G is 0;

40

RG^1 is H;

RG^2 is H;

45



K is

$\text{NH}-(\text{CH}_2)_{n^K}-\text{Q}^K$, where

5 n^K is 1;

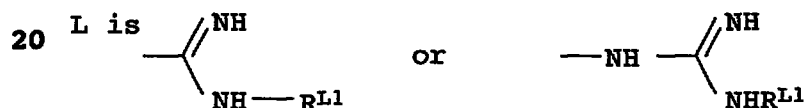
Q^K is



X^K is O or S;

15 Y^K is $=\text{CH}-$ or $=\text{N}-$;

Z^K is $=\text{CH}-$ or $=\text{N}-$;



where

25 R^{L1} is $-\text{H}$ or $-\text{OH}$.

12. A drug containing a compound of the formula I as claimed in
any of claims 3 to 11 in addition to conventional carriers
30 and excipients.

13. The use of a compound of the formula I as claimed in any of
claims 3 to 11 for the preparation of drugs for the treatment
of disorders which are alleviated or cured by partial or
35 complete inhibition of C_{1s} or C_{1r} .

14. The use of a compound of the formula I as claimed in any of
claims 3 to 11 for the preparation of drugs for the treatment
or prophylaxis of

40 • Reperfusion injuries after ischemias; ischemic
conditions, during, for example, operations with the aid
of heart-lung machines; operations in which blood vessels
are clamped off generally for avoiding major hemorrhages;
45 myocardial infarction; thromboembolic cerebral
infarction; pulmonary thrombosis, etc.;



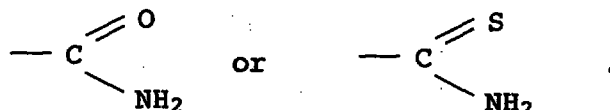
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- Hyperacute organ rejection; especially in xenotransplantations;
- Organ failure, e.g. multiple organ failure or ARDS (adult respiratory distress syndrome);
- 5 • Disorders due to trauma (cranial trauma) or multiple injury, e.g. thermal injury (burns);
- Anaphylactic shock;
- Sepsis; "vascular leak syndrome": in the case of sepsis and after treatment with biological agents, such as
- 10 interleukin-2 or after transplantation;
- Alzheimer's disease and other inflammatory neurological disorders, such as myasthenia graevis, multiple sclerosis, cerebral lupus, Guillain-Barre syndrome; meningitis; encephalitis;
- 15 • Systemic lupus erythematosus (SLE);
- Rheumatoid arthritis and other inflammatory disorders of the rheumatoid disorder group, e.g. Behcet's Syndrome; Juvenile rheumatoid arthritis;
- Renal inflammations of various origin, e.g.
- 20 Glomerulonephritis, Lupus nephriti;
- Pancreatitis;
- Asthma; chronic bronchitis;
- Complications during dialysis in the case of kidney failure;
- 25 • Vasculitis; thyroiditis;
- Ulcerative colitis and other inflammatory disorders of the gastrointestinal tract;
- Autoimmune diseases;
- Spontaneous premature births.

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15. A compound of the formula I as claimed in any of claims 3 to 11, where L is -CN,

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16. The use of a compound which has the structural element -G-K-L, where G, K and L have the meanings stated in any of claims 3 to 11, for the preparation of drugs which partially or completely inhibit C_{1s} or C_{1r}.

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