

## Neue Carbonsäurederivate, ihre Herstellung und Verwendung

## Beschreibung

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Die vorliegende Erfindung betrifft neue Carbonsäurederivate, deren Herstellung und Verwendung.

Endothelin ist ein aus 21 Aminosäuren aufgebautes Peptid, das von vaskulärem Endothel synthetisiert und freigesetzt wird. Endothelin existiert in drei Isoformen, ET-1, ET-2 und ET-3. Im Folgenden bezeichnet "Endothelin" oder "ET" eine oder alle Isoformen von Endothelin. Endothelin ist ein potenter Vasokonstriktor und hat einen starken Effekt auf den Gefäßtonus. Es ist bekannt, daß diese Vasokonstriktion von der Bindung von Endothelin an seinen Rezeptor verursacht wird (Nature, 332, 411-415, 1988; FEBS Letters, 231, 440-444, 1988 und Biochem. Biophys. Res. Commun., 154, 868-875, 1988).

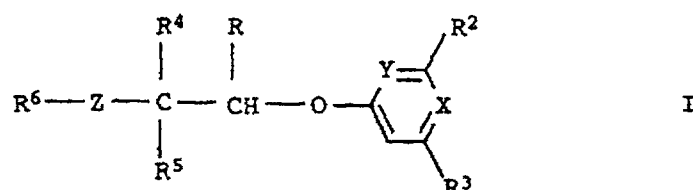
Erhöhte oder abnormale Freisetzung von Endothelin verursacht eine anhaltende Gefäßkontraktion in peripheren, renalen und zerebralen Blutgefäßen, die zu Krankheiten führen kann. Wie in der Literatur berichtet, wurden erhöhte Plasmaspiegel von Endothelin gefunden bei Patienten mit Hypertonie, akutem Myokardinfarkt, pulmonärer Hypertonie, Raynaud-Syndrom, Atherosklerose und in den Atemwegen von Asthmatikern (Japan J. Hypertension, 12, 79 (1989), J. Vascular Med. Biology 2, 207 (1990), J. Am. Med. Association 264, 2868 (1990)).

Demnach sollten Substanzen, die spezifisch die Bindung von Endothelin an den Rezeptor inhibieren, auch die obengenannten verschiedenen physiologischen Effekte von Endothelin antagonisieren und daher wertvolle Pharmaka darstellen.

Es wurde nun gefunden, daß bestimmte Carbonsäurederivate gute Hemmstoffe für Endothelinrezeptoren sind.

Gegenstand der Erfindung sind Carbonsäurederivate der Formel I

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in der R Tetrazol, Nitril, eine Gruppe COOH oder einen zu COOH hydrolysierbaren Rest bedeutet und die übrigen Substituenten folgende Bedeutung haben:

- 5 R<sup>2</sup> Wasserstoff, Hydroxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>4</sub>-Alkyl), N(C<sub>1</sub>-C<sub>4</sub>-Alkyl)<sub>2</sub>, Halogen, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy oder C<sub>1</sub>-C<sub>4</sub>-Alkylthio, oder CR<sup>12</sup> ist mit CR<sup>12</sup> wie unten angegeben zu einem 5- oder 6-gliedrigen Ring verknüpft;
- 10 X Stickstoff oder CR<sup>12</sup>, worin R<sup>12</sup> Wasserstoff oder C<sub>1-5</sub>-Alkyl bedeutet oder CR<sup>12</sup> zusammen mit CR<sup>2</sup> oder CR<sup>3</sup> einen 5- oder 6-gliedrigen Alkylen- oder Alkenylenring bildet, der durch eine oder zwei C<sub>1-4</sub>-Alkylgruppen substituiert sein kann und
- 15 worin jeweils eine Methylengruppe durch Sauerstoff, Schwefel, -NH oder -NC<sub>1-4</sub>-Alkyl ersetzt sein kann;
- Y Stickstoff oder Methin;
- R<sup>3</sup> Wasserstoff, Hydroxy, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>4</sub>-Alkyl), N(C<sub>1</sub>-C<sub>4</sub>-Alkyl)<sub>2</sub>, Halogen, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, -NH-O-C<sub>1-4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Alkylthio; oder
- 20 CR<sup>3</sup> ist mit CR<sup>12</sup> wie oben angegeben zu einem 5- oder 6-gliedrigen Ring verknüpft;
- 25 R<sup>4</sup> und R<sup>5</sup> (die gleich oder verschieden sein können):
- Phenyl oder Naphthyl, die durch einen oder mehrere der folgenden Reste substituiert sein können: Halogen, Nitro, Cyano, Hydroxy, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy,
- 30 C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, Phenoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Amino, C<sub>1</sub>-C<sub>4</sub>-Alkylamino oder C<sub>1</sub>-C<sub>4</sub>-Dialkylamino; oder
- Phenyl oder Naphthyl, die orthoständig über eine direkte Bindung, eine Methylen-, Ethylen- oder Ethenylengruppe, ein Sauerstoff- oder Schwefelatom oder eine SO<sub>2</sub>-, NH- oder N-Alkyl-Gruppe miteinander verbunden sind oder C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl;
- 35
- R<sup>6</sup> Wasserstoff, C<sub>1</sub>-C<sub>8</sub>-Alkyl, C<sub>3</sub>-C<sub>6</sub>-Alkenyl, C<sub>3</sub>-C<sub>6</sub>-Alkinyl oder C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl, wobei diese Reste jeweils ein- oder mehrfach
- 40 substituiert sein können durch: Halogen, Hydroxy, Mercapto, Carboxy, Nitro, Cyano, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>3</sub>-C<sub>6</sub>-Alkenyloxy, C<sub>3</sub>-C<sub>6</sub>-Alkinyloxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxycarbonyl, C<sub>3-8</sub>-Alkylcarbonylalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkylamino,
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Di-C<sub>1</sub>-C<sub>4</sub>-alkylamino, Phenyl oder ein- oder mehrfach, z.B. ein- bis dreifach durch Halogen, Nitro, Cyano, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy oder C<sub>1</sub>-C<sub>4</sub>-Alkylthio substituiertes Phenyl oder Phenoxy;

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Phenyl oder Naphthyl, die jeweils durch einen oder mehrere der folgenden Reste substituiert sein können: Halogen, Nitro, Cyano, Hydroxy, Amino, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, Phenoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, C<sub>1</sub>-C<sub>4</sub>-Alkylamino, C<sub>1</sub>-C<sub>4</sub>-Dialkylamino, Dioxomethylen oder Dioxoethylen;

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ein fünf- oder sechsgliedriger Heteroaromat, enthaltend ein bis drei Stickstoffatome und/oder ein Schwefel- oder Sauerstoffatom, welcher ein bis vier Halogenatome und/oder einen bis zwei der folgenden Reste tragen kann: C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Phenyl, Phenoxy oder Phenylcarbonyl, wobei die Phenylreste ihrerseits ein bis fünf Halogenatome und/oder einen bis drei der folgenden Reste tragen können: C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy und/oder C<sub>1</sub>-C<sub>4</sub>-Alkylthio;

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Z Schwefel oder Sauerstoff.

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Die Verbindungen und auch die Zwischenprodukte zu ihrer Herstellung, wie z.B. II und IV, können ein oder mehrere asymmetrische substituierte Kohlenstoffatome besitzen. Solche Verbindungen können als reine Enantiomere bzw. reine Diastereomere oder als deren Mischung vorliegen. Bevorzugt ist die Verwendung einer enantiomerenreinen Verbindung als Wirkstoff.

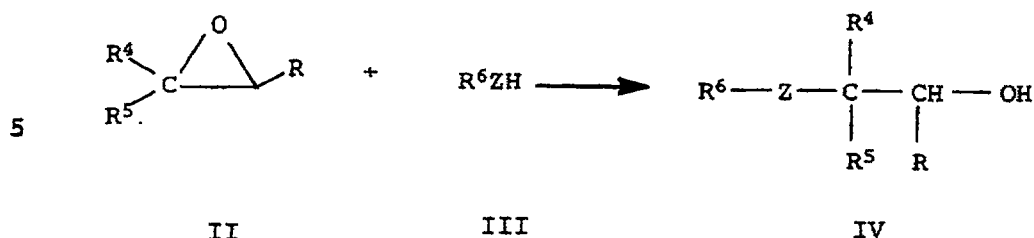
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Gegenstand der Erfindung ist weiter die Verwendung der oben genannten Carbonsäurederivate zur Herstellung von Arzneimitteln, insbesondere zur Herstellung von Hemmstoffen für Endothelinrezeptoren.

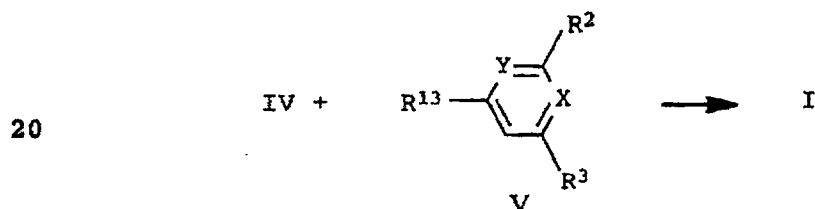
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Die Herstellung der Verbindungen mit der allgemeinen Formel IV, in denen Z Schwefel oder Sauerstoff ist, kann - auch in enantiomerenreiner Form - wie in P 44 36 851.8 beschrieben, erfolgen.

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10 Die erfindungsgemäßen Verbindungen, in denen die Substituenten die unter der allgemeinen Formel I angegebenen Bedeutung haben, können beispielsweise derart hergestellt werden, daß man die Carbonsäurederivate der allgemeinen Formel IV, in denen die Substituenten die angegebene Bedeutung haben, mit Verbindungen  
 15 der allgemeinen Formel V,



in der  $\text{R}^{13}$  Halogen oder  $\text{R}^{14}\text{-SO}_2\text{-}$  bedeutet, wobei  $\text{R}^{14}$   $\text{C}_1\text{-C}_4\text{-Alkyl}$ ,  $\text{C}_1\text{-C}_4\text{-Halogenalkyl}$  oder Phenyl sein kann, zur Reaktion bringt. Die  
 25 Reaktion findet bevorzugt in einem inerten Lösungs- oder Verdünnungsmittel unter Zusatz einer geeigneten Base, d.h. einer Base, die eine Deprotonierung des Zwischenproduktes IV bewirkt, in einem Temperaturbereich von Raumtemperatur bis zum Siedepunkt des Lösungsmittels statt.

30 Beispiele für solche Lösungsmittel beziehungsweise Verdünnungsmittel sind aliphatische, alicyclische und aromatische Kohlenwasserstoffe, die jeweils gegebenenfalls chloriert sein können, wie zum Beispiel Hexan, Cyclohexan, Petrolether, Ligroin, Benzol,  
 35 Toluol, Xylol, Methylenchlorid, Chloroform, Kohlenstofftetra-  
 chlorid, Ethylchlorid und Trichlorethylen, Ether, wie zum Beispiel Diisopropylether, Dibutylether, Methyl-tert.-Butylether, Propylenoxid, Dioxan und Tetrahydrofuran, Nitrile, wie zum Beispiel Acetonitril und Propionitril, Säureamide, wie zum Beispiel  
 40 Dimethylformamid, Dimethylacetamid und N-Methylpyrrolidon, Sulfoxide und Sulfone, wie zum Beispiel Dimethylsulfoxid und Sulfolan.

Verbindungen der Formel V sind bekannt, teilweise käuflich oder  
 45 können nach allgemein bekannter Weise hergestellt werden.

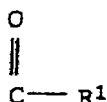
Als Base kann ein Alkali- oder Erdalkalimetallhydrid wie Natriumhydrid, Kaliumhydrid oder Calciumhydrid, ein Carbonat wie Alkalimetallcarbonat, z.B. Natrium- oder Kaliumcarbonat, ein Alkali- oder Erdalkalimetallhydroxid wie Natrium- oder Kaliumhydroxid, 5 eine metallorganische Verbindung wie Butyllithium oder ein Alkaliamid wie Lithiumdiisopropylamid dienen.

Verbindungen der Formel I können auch dadurch hergestellt werden, daß man von den entsprechenden Carbonsäuren, d. h. Verbindungen 10 der Formel I, in denen R COOH bedeutet, ausgeht und diese zunächst auf übliche Weise in eine aktivierte Form wie ein Säurehalogenid, ein Anhydrid oder Imidazolid überführt und dieses dann mit einer entsprechenden Hydroxylverbindung HOR<sup>8</sup> umsetzt. Diese Umsetzung läßt sich in den üblichen Lösungsmitteln durchführen 15 und erfordert oft die Zugabe einer Base, wobei die oben genannten in Betracht kommen. Diese beiden Schritte lassen sich beispielsweise auch dadurch vereinfachen, daß man die Carbonsäure in Gegenwart eines wasserabspaltenden Mittels wie eines Carbodiimids auf die Hydroxylverbindung einwirken läßt.

20 Außerdem können Verbindungen der Formel I auch dadurch hergestellt werden, daß man von den Salzen der entsprechenden Carbonsäuren ausgeht, d. h. von Verbindungen der Formel I, in denen R für eine Gruppe COR<sup>1</sup> und R<sup>1</sup> für OM stehen, wobei M ein Alkali- 25 metallkation oder das Äquivalent eines Erdalkalimetallkations sein kann. Diese Salze lassen sich mit vielen Verbindungen der Formel R<sup>1</sup>-A zur Reaktion bringen, wobei A eine übliche nucleofuge Abgangsgruppe bedeutet, beispielsweise Halogen wie Chlor, Brom, Iod oder gegebenenfalls durch Halogen, Alkyl oder Halogenalkyl 30 substituiertes Aryl- oder Alkylsulfonyl wie z.B. Toluolsulfonyl und Methylsulfonyl oder eine andere äquivalente Abgangsgruppe. Verbindungen der Formel R<sup>1</sup>-A mit einem reaktionsfähigen Substituenten A sind bekannt oder mit dem allgemeinen Fachwissen leicht zu erhalten. Diese Umsetzung läßt sich in den üblichen Lö- 35 sungsmitteln durchführen und wird vorteilhaft unter Zugabe einer Base, wobei die oben genannten in Betracht kommen, vorgenommen.

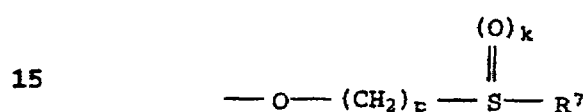
Der Rest R in Formel I ist breit variabel. Beispielsweise steht R für eine Gruppe

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45 in der R<sup>1</sup> die folgende Bedeutung hat:

- a) Wasserstoff;
- b) eine Succinylimidoxygruppe;
- 5 c) ein über ein Stickstoffatom verknüpfter 5-gliedriger Hetero-  
aromat wie Pyrrolyl, Pyrazolyl, Imidazolyl und Triazolyl,  
welcher ein bis zwei Halogenatome, oder eins bis zwei  
C<sub>1</sub>-C<sub>4</sub>-Alkyl oder eins bis zwei C<sub>1</sub>-C<sub>4</sub>-Alkoxygruppen tragen  
kann.
- 10 d) R<sup>1</sup> ferner eine Gruppe



in der k die Werte 0, 1 und 2, p die Werte 1, 2, 3 und 4 an-  
nehmen und R<sup>7</sup> für

- 20 C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, C<sub>3</sub>-C<sub>6</sub>-Alkenyl, C<sub>3</sub>-C<sub>6</sub>-Alkynyl  
oder gegebenenfalls substituiertes Phenyl steht, das durch  
einen oder mehrere, z.B. ein bis drei der folgenden Reste  
substituiert sein kann:

- 25 Halogen, Nitro, Cyano, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl,  
Hydroxy, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Mercapto, Amino,  
C<sub>1</sub>-C<sub>4</sub>-Alkylamino, C<sub>1</sub>-C<sub>4</sub>-Dialkylamino;

- e) R<sup>1</sup> ferner ein Rest OR<sup>8</sup>, worin R<sup>8</sup> bedeutet:

- 30 Wasserstoff, das Kation eines Alkalimetalls wie Lithium,  
Natrium, Kalium oder das Kation eines Erdalkalimetalls wie  
Calcium, Magnesium und Barium oder ein physiologisch verträg-  
liches organisches Ammoniumion wie tertiäres C<sub>1</sub>-C<sub>4</sub>-Alkyl-  
ammonium oder das Ammoniumion;

- 35 C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl, wie Cyclopropyl, Cyclobutyl, Cyclopentyl,  
Cyclohexyl und Cycloheptyl, Cyclooctyl,

- 40 C<sub>1</sub>-C<sub>8</sub>-Alkyl, insbesondere C<sub>1</sub>-C<sub>4</sub>-Alkyl wie Methyl, Ethyl,  
n-Propyl, iso-Propyl, n-Butyl, iso-Butyl, tert.-Butyl;

- CH<sub>2</sub>-Phenyl, das durch einen oder mehrere der folgenden Reste  
substituiert sein kann: Halogen, Nitro, Cyano, C<sub>1</sub>-C<sub>4</sub>-Alkyl,  
C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, Hydroxy, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, Mercapto,  
45 C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Amino, C<sub>1</sub>-C<sub>4</sub>-Alkylamino, C<sub>1</sub>-C<sub>4</sub>-Dialkylamino,

Eine C<sub>3</sub>-C<sub>6</sub>-Alkenyl - oder eine C<sub>3</sub>-C<sub>6</sub>-Alkynylgruppe, wobei diese Gruppe ihrerseits ein bis fünf Halogenatome tragen können;

- 5 R<sup>8</sup> kann weiterhin ein Phenylrest sein, welcher ein bis fünf Halogenatome und/oder ein bis drei der folgenden Reste tragen kann: Nitro, Cyano, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, Hydroxy, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, Mercapto, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Amino, C<sub>1</sub>-C<sub>4</sub>-Alkylamino, C<sub>1</sub>-C<sub>4</sub>-Dialkylamino;

- 10 ein über ein Stickstoffatom verknüpfter 5-gliedriger Heteroaromat, enthaltend ein bis drei Stickstoffatome, welcher ein bis zwei Halogenatome und/oder ein bis zwei der folgenden Reste tragen kann: C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, Phenyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy und/oder C<sub>1</sub>-C<sub>4</sub>-Alkylthio. Insbesondere seien genannt: 1-Pyrazolyl,

- 3-Methyl-1-pyrazolyl, 4-Methyl-1-pyrazolyl,  
3,5-Dimethyl-1-pyrazolyl, 3-Phenyl-1-pyrazolyl,  
20 4-Phenyl-1-pyrazolyl, 4-Chlor-1-pyrazolyl,  
4-Brom-1-pyrazolyl, 1-Imidazolyl, 1-Benzimidazolyl,  
1,2,4-Triazol-1-yl, 3-Methyl-1,2,4-triazol-1-yl,  
5-Methyl-1,2,4-triazol-1-yl,  
1-Benztriazolyl, 3,4-Dichlorimidazol-1-yl;

- 25 f) R<sup>1</sup> ferner ein Rest



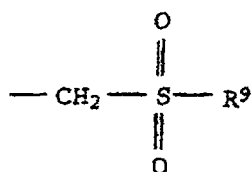
worin R<sup>9</sup> bedeutet:

- 35 C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>3</sub>-C<sub>6</sub>-Alkenyl, C<sub>3</sub>-C<sub>6</sub>-Alkynyl, C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl wie insbesondere vorstehend genannt, wobei diese Reste einen C<sub>1</sub>-C<sub>4</sub>-Alkoxy-, C<sub>1</sub>-C<sub>4</sub>-Alkylthio- und/oder einen Phenylrest wie oben genannt tragen können;

- 40 Phenyl, gegebenenfalls substituiert, insbesondere wie vorstehend genannt;

- g) R<sup>1</sup> ein Rest  
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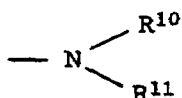


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worin  $\text{R}^9$  die oben genannte Bedeutung hat;

h) ferner kann  $\text{R}^1$  bedeuten

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wobei  $\text{R}^{10}$  und  $\text{R}^{11}$  gleich oder verschieden sein können und folgende Bedeutung haben:

20 Wasserstoff,  $\text{C}_1$ - $\text{C}_7$ -Alkyl,  $\text{C}_3$ - $\text{C}_7$ -Cycloalkyl,  $\text{C}_3$ - $\text{C}_7$ -Alkenyl,  $\text{C}_3$ - $\text{C}_7$ -Alkynyl, Benzyl, Phenyl, gegebenenfalls substituiert, wie oben beschrieben, oder  $\text{R}^{10}$  und  $\text{R}^{11}$  bilden gemeinsam eine zu einem Ring geschlossene, optionell substituierte, z.B. durch  $\text{C}_1$ - $\text{C}_4$ -Alkyl substituierte  $\text{C}_4$ - $\text{C}_7$ -Alkylenkette, die ein Heteroatom, z.B. Sauerstoff, Schwefel oder Stickstoff enthalten

25 kann wie  $-(\text{CH}_2)_4-$ ,  $-(\text{CH}_2)_5-$ ,  $-(\text{CH}_2)_6-$ ,  $-(\text{CH}_2)_7-$ ,  $-(\text{CH}_2)_2\text{-O-}(\text{CH}_2)_2-$ ,  $-\text{CH}_2\text{-S-}(\text{CH}_2)_2-$ ,  $-\text{CH}_2\text{-NH-}(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_2\text{-NH-}(\text{CH}_2)_2-$ .

30 Im Hinblick auf die biologische Wirkung sind Carbonsäurederivate der allgemeinen Formel I - sowohl als reine Enantiomere bzw. reine Diastereomere oder als deren Mischung - bevorzugt, in denen die Substituenten folgende Bedeutung haben:

35  $\text{R}^2$  Wasserstoff, Hydroxy,  $\text{N}(\text{C}_1\text{-C}_4\text{-Alkyl})_2$ , die bei  $\text{R}^1$  im einzelnen genannten  $\text{C}_1$ - $\text{C}_4$ -Alkyl-,  $\text{C}_1$ - $\text{C}_4$ -Halogenalkyl-,  $\text{C}_1$ - $\text{C}_4$ -Alkoxy-,  $\text{C}_1$ - $\text{C}_4$ -Halogenalkoxy-,  $\text{C}_1$ - $\text{C}_4$ -Alkylthiogruppen und Halogenatome, insbesondere Chlor, Methyl, Methoxy, Ethoxy, Difluormethoxy, Trifluormethoxy, oder  $\text{CR}^2$  ist mit  $\text{CR}^{12}$  wie unten angegeben zu

40 einem 5- oder 6-gliedrigen Ring verknüpft;

X Stickstoff oder  $\text{CR}^{12}$ , worin

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- R<sup>12</sup> Wasserstoff oder Alkyl bedeutet oder CR<sup>12</sup> zusammen mit CR<sup>2</sup> oder CR<sup>3</sup> einen 5- bis 6-gliedrigen Alkylen- oder Alkenylen-ring bildet, in der jeweils eine Methylengruppe durch Sauerstoff oder Schwefel ersetzt sein kann wie
- 5 -CH<sub>2</sub>-CH<sub>2</sub>-O-, -CH=CH-O-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-O-, -CH=CH-CH<sub>2</sub>O-, insbesondere Wasserstoff, -CH<sub>2</sub>-CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-CH(CH<sub>3</sub>)-O-, -C(CH<sub>3</sub>)=C(CH<sub>3</sub>)-O-, -CH=C(CH<sub>3</sub>)-O- oder -C(CH<sub>3</sub>)=C(CH<sub>3</sub>)-S;
- 10 Y Stickstoff oder Methin;
- R<sup>3</sup> Wasserstoff, Hydroxy, N(C<sub>1</sub>-C<sub>4</sub>-Alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>-Alkyl-, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl-, C<sub>1</sub>-C<sub>4</sub>-Alkoxy-, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy-, C<sub>1</sub>-C<sub>4</sub>-Alkylthiogruppen und Halogenatome, insbesondere Chlor,
- 15 Methyl, Methoxy, Ethoxy, Difluormethoxy, Trifluormethoxy oder C-R<sup>3</sup> ist mit C-R<sup>12</sup> wie oben genannt zu einem 5- oder 6-gliedrigen Ring verknüpft ist;
- R<sup>4</sup> und R<sup>5</sup> die gleich oder verschieden sein können, Phenyl oder
- 20 Naphthyl, die durch einen oder mehrere, z.B. einen bis drei der folgenden Reste substituiert sein können: Halogen, Nitro, Cyano, Hydroxy, Mercapto, Amino, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, C<sub>1</sub>-C<sub>4</sub>-Alkylamino, Di-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-Alkylcarbonyl,
- 25 C<sub>1</sub>-C<sub>4</sub>-Alkoxy carbonyl;
- Phenyl oder Naphthyl, die orthoständig über eine direkte Bindung, eine Methylen-, Ethylen- oder Ethenylengruppe, ein Sauerstoff- oder Schwefelatom oder eine SO<sub>2</sub>-, NH- oder N-Alkyl-
- 30 Gruppe miteinander verbunden sind oder C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl;
- R<sup>6</sup> C<sub>1</sub>-C<sub>8</sub>-Alkyl, C<sub>3</sub>-C<sub>6</sub>-Alkenyl, C<sub>3</sub>-C<sub>6</sub>-Alkinyl oder C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl wie insbesondere oben genannt, wobei diese Reste jeweils ein- oder mehrfach substituiert sein können durch: Halogen,
- 35 Hydroxy, Mercapto, Carboxy, Nitro, Cyano,
- C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>3</sub>-C<sub>5</sub>-Alkenyloxy, C<sub>3</sub>-C<sub>6</sub>-Alkinyloxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylcarbonyl, Hydroxycarbonyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy carbonyl, C<sub>1</sub>-C<sub>4</sub>-Alkylamino,
- 40 Di-C<sub>1</sub>-C<sub>4</sub>-alkylamino oder gegebenenfalls substituiertes Phenyl oder Phenoxy, wie insbesondere vorstehend genannt;
- Phenyl oder Naphthyl, das durch einen oder mehreren der folgenden Reste substituiert sein kann: Halogen, Nitro, Cyano,
- 45 Hydroxy, Amino, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl,

C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, Phenoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, C<sub>1</sub>-C<sub>4</sub>-Akylamino oder C<sub>1</sub>-C<sub>4</sub>-Dialkylamino;

- 5 ein fünf- oder sechsgliedriger Heteroaromat, enthaltend ein bis drei Stickstoffatome und/oder ein Schwefel- oder Sauerstoffatom, welcher ein bis vier Halogenatome und/oder einen bis zwei der folgenden Reste tragen kann: C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Phenyl, Phenoxy oder Phenylcarbonyl, wobei  
 10 die Phenylreste ihrerseits ein bis fünf Halogenatome und/oder einen bis drei der folgenden Reste tragen können: C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy und/oder C<sub>1</sub>-C<sub>4</sub>-Alkylthio, wie insbesondere bei R<sup>4</sup> genannt;

15 Z Schwefel oder Sauerstoff.

Besonders bevorzugt sind Verbindungen der Formel I - sowohl als reine Enantiomere bzw. reine Diastereomere oder als deren Mischung - in denen die Substituenten folgende Bedeutung haben:

- 20 R<sup>2</sup> C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Trifluormethyl oder mit R<sup>12</sup> wie unten genannt zu einem 5- oder 6-gliedrigen Ring verknüpft ist;

25 X Stickstoff oder CR<sup>12</sup>, worin

- R<sup>12</sup> Wasserstoff oder Alkyl bedeutet oder CR<sup>12</sup> zusammen mit CR<sup>2</sup> oder CR<sup>3</sup> einen 4- bis 5-gliedrigen Alkylen- oder Alkenylenring bildet wie z.B. -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, in der jeweils eine Methylengruppe durch Sauerstoff oder Schwefel ersetzt sein kann wie -CH<sub>2</sub>-CH<sub>2</sub>-O-, -CH=CH-O-,  
 30 -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-O-, -CH=CH-CH<sub>2</sub>O-, insbesondere Wasserstoff, -CH<sub>2</sub>-CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-CH(CH<sub>3</sub>)-O-, -C(CH<sub>3</sub>)=C(CH<sub>3</sub>)-O-,  
 35 -CH=C(CH<sub>3</sub>)-O- oder -C(CH<sub>3</sub>)=C(CH<sub>3</sub>)-S;

Y Stickstoff oder Methin;

- R<sup>3</sup> die bei R<sup>1</sup> genannten C<sub>1</sub>-C<sub>4</sub>-Alkyl-, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthiogruppen oder C-R<sup>3</sup> ist mit C-R<sup>12</sup> wie oben genannt zu einem  
 40 5- oder 6-gliedrigen Ring verknüpft;

- R<sup>4</sup> und R<sup>5</sup> Phenyl (gleich oder verschieden), die durch einen oder mehrere, z.B. einen bis drei der folgenden Reste substituiert  
 45 sein können: Halogen, Nitro, Hydroxy, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio oder

- R<sup>4</sup> und R<sup>5</sup> sind Phenylgruppen, die orthoständig über eine direkte Bindung, eine Methylen-, Ethylen- oder Ethenylengruppe, ein Sauerstoff- oder Schwefelatom oder eine SO<sub>2</sub>-, NH- oder N-Alkyl-Gruppe miteinander verbunden sind; oder
- 5 R<sup>4</sup> und R<sup>5</sup> sind C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl;
- R<sup>6</sup> C<sub>1</sub>-C<sub>8</sub>-Alkyl, C<sub>3</sub>-C<sub>6</sub>-Alkenyl oder C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl, wobei diese Reste jeweils ein-oder mehrfach substituiert sein können
- 10 durch: Halogen, Mercapto, Carboxy, Hydroxy, Nitro, Cyano, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>3</sub>-C<sub>6</sub>-Alkenyloxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio;
- 15 Phenyl oder Naphthyl, das durch einen oder mehreren der folgenden Reste substituiert sein kann: Halogen, Nitro, Cyano, Hydroxy, Amino, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, Phenoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, C<sub>1</sub>-C<sub>4</sub>-Alkylamino oder C<sub>1</sub>-C<sub>4</sub>-Dialkylamino;
- 20 ein fünf- oder sechsgliedriger Heteroaromat, enthaltend ein Stickstoffatom und/oder ein Schwefel- oder Sauerstoffatom, welcher ein bis vier Halogenatome und/oder einen bis zwei der folgenden Reste tragen kann: C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Phenyl, Phenoxy oder Phenyl-
- 25 carbonyl, wobei die Phenylreste ihrerseits ein bis fünf Halogenatome und/oder einen bis drei der folgenden Reste tragen können: C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy und/oder C<sub>1</sub>-C<sub>4</sub>-Alkylthio;
- 30 Z Schwefel oder Sauerstoff.

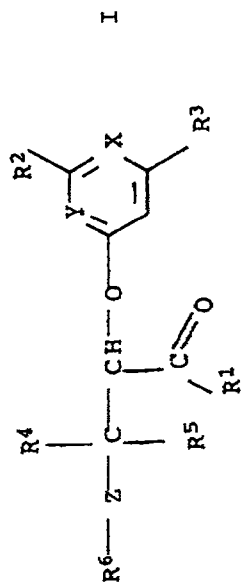
Beispiele für bevorzugte Verbindungen sind in der folgenden Tabelle aufgeführt.

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Tabelle I



| Nr.  | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup> | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|------|----------------|---------------------------------|----------------|----------------|-----------------|---|---|---|
| I-1  | OH             | Phenyl                          | Methyl         | OMe            | OMe             | N | N | O |
| I-2  | OH             | Phenyl                          | Methyl         | OMe            | Me              | N | N | O |
| I-3  | OH             | Phenyl                          | Methyl         | Me             | OMe             | N | N | O |
| I-4  | OH             | Phenyl                          | Methyl         | Ethyl          | Me              | N | N | O |
| I-5  | OH             | Phenyl                          | Methyl         | Me             | Ethyl           | N | N | O |
| I-6  | OH             | Phenyl                          | Methyl         | Me             | Me              | N | N | O |
| I-7  | OH             | Phenyl                          | Methyl         | OMe            | SMe             | N | N | O |
| I-8  | OH             | Phenyl                          | Methyl         | OMe            | CF <sub>3</sub> | N | N | O |
| I-9  | OH             | Phenyl                          | Methyl         | OMe            | OMe             | N | N | S |
| I-10 | OH             | Phenyl                          | Methyl         | OMe            | Me              | N | N | S |
| I-11 | OH             | Phenyl                          | Methyl         | Me             | OMe             | N | N | S |
| I-12 | OH             | Phenyl                          | Methyl         | Ethyl          | Me              | N | N | S |

| Nr.  | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                                      | R <sup>3</sup> | R <sup>2</sup> | X | Y | Z |
|------|----------------|---------------------------------|-----------------------------------------------------|----------------|----------------|---|---|---|
| I-13 | OH             | Phenyl                          | Ethyl                                               | OMe            | OMe            | N | N | O |
| I-14 | OH             | Phenyl                          | Ethyl                                               | OMe            | Me             | N | N | O |
| I-15 | OH             | Phenyl                          | Ethyl                                               | Me             | OMe            | N | N | O |
| I-16 | OH             | Phenyl                          | Ethyl                                               | Ethyl          | Me             | N | N | O |
| I-17 | OH             | Phenyl                          | Ethyl                                               | Me             | Ethyl          | N | N | O |
| I-18 | OH             | Phenyl                          | Ethyl                                               | OMe            | OMe            | N | N | O |
| I-19 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | OMe            | Me             | N | N | O |
| I-20 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | OMe            | OMe            | N | N | O |
| I-21 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | Me             | OMe            | N | N | O |
| I-22 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | Ethyl          | Me             | N | N | O |
| I-23 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | Me             | Ethyl          | N | N | O |
| I-24 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | Me             | Me             | N | N | O |
| I-25 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | OMe            | SMe            | N | N | O |
| I-26 | OH             | Phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | OMe            | OMe            | N | N | O |
| I-27 | OH             | Phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | OMe            | Me             | N | N | O |
| I-28 | OH             | Phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | Me             | OMe            | N | N | O |
| I-29 | OH             | Phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | Ethyl          | Me             | N | N | O |
| I-30 | OH             | Phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | Me             | Ethyl          | N | N | O |
| I-31 | OH             | Phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | Me             | Me             | N | N | O |
| I-32 | OH             | Phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | OMe            | SMe            | N | N | O |
| I-33 | OH             | Phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | OMe            | OMe            | N | N | O |
| I-34 | OH             | Phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | OMe            | Me             | N | N | O |
| I-35 | OH             | Phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | Me             | OMe            | N | N | O |
| I-36 | OH             | Phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | Ethyl          | Me             | N | N | O |
| I-37 | OH             | Phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | Me             | Ethyl          | N | N | O |
|      |                |                                 |                                                     | Me             | Me             | N | N | O |

| Nr.  | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                                | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|------|----------------|---------------------------------|-----------------------------------------------|----------------|-----------------|---|---|---|
| I-38 | OH             | Phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -           | OMe            | SMe             | N | N | O |
| I-39 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | OMe             | N | N | O |
| I-40 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | Me              | N | N | O |
| I-41 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | OMe             | N | N | O |
| I-42 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Ethyl          | Me              | N | N | O |
| I-43 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | Ethyl           | N | N | O |
| I-44 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | Me              | N | N | O |
| I-45 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | SMe             | N | N | O |
| I-46 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | CF <sub>3</sub> | N | N | O |
| I-47 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | OMe             | N | N | S |
| I-48 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | Me              | N | N | S |
| I-49 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | OMe             | N | N | S |
| I-50 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Ethyl          | Me              | N | N | S |
| I-51 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | OMe            | OMe             | N | N | S |
| I-52 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | OMe            | Me              | N | N | S |
| I-53 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Me             | OMe             | N | N | S |
| I-54 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Ethyl          | Me              | N | N | S |
| I-55 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | OMe            | OMe             | N | N | O |
| I-56 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | OMe            | Me              | N | N | O |
| I-57 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | Me             | OMe             | N | N | O |
| I-58 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | Ethyl          | Me              | N | N | O |
| I-59 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | Me             | Ethyl           | N | N | O |
| I-60 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | Me             | Me              | N | N | O |
| I-61 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | OMe            | SMe             | N | N | O |
| I-62 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | OMe            | CF <sub>3</sub> | N | N | O |

| Nr.  | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                       | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|------|----------------|---------------------------------|--------------------------------------|----------------|-----------------|---|---|---|
| 1-63 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> - | OMe            | OMe             | N | N | S |
| 1-64 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> - | OMe            | Me              | N | N | S |
| 1-65 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> - | Me             | OMe             | N | N | S |
| 1-66 | OH             | Phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> - | Ethyl          | Me              | N | N | S |
| 1-67 | OH             | Phenyl                          | n-Propyl                             | OMe            | OMe             | N | N | O |
| 1-68 | OH             | Phenyl                          | n-Propyl                             | OMe            | Me              | N | N | O |
| 1-69 | OH             | Phenyl                          | n-Propyl                             | Me             | OMe             | N | N | O |
| 1-70 | OH             | Phenyl                          | n-Propyl                             | Ethyl          | Me              | N | N | O |
| 1-71 | OH             | Phenyl                          | n-Propyl                             | Me             | Ethyl           | N | N | O |
| 1-72 | OH             | Phenyl                          | n-Propyl                             | Me             | Me              | N | N | O |
| 1-73 | OH             | Phenyl                          | n-Propyl                             | OMe            | SMe             | N | N | O |
| 1-74 | OH             | Phenyl                          | n-Propyl                             | OMe            | CF <sub>3</sub> | N | N | O |
| 1-75 | OH             | Phenyl                          | n-Propyl                             | OMe            | OMe             | N | N | S |
| 1-76 | OH             | Phenyl                          | n-Propyl                             | OMe            | Me              | N | N | S |
| 1-77 | OH             | Phenyl                          | n-Propyl                             | Me             | OMe             | N | N | S |
| 1-78 | OH             | Phenyl                          | n-Propyl                             | Ethyl          | Me              | N | N | S |
| 1-79 | OH             | Phenyl                          | iso-Propyl                           | OMe            | OMe             | N | N | O |
| 1-80 | OH             | Phenyl                          | iso-Propyl                           | OMe            | Me              | N | N | O |
| 1-81 | OH             | Phenyl                          | iso-Propyl                           | Me             | OMe             | N | N | O |
| 1-82 | OH             | Phenyl                          | iso-Propyl                           | Ethyl          | Me              | N | N | O |
| 1-83 | OH             | Phenyl                          | iso-Propyl                           | Me             | Ethyl           | N | N | O |
| 1-84 | OH             | Phenyl                          | iso-Propyl                           | Me             | Me              | N | N | O |
| 1-85 | OH             | Phenyl                          | iso-Propyl                           | OMe            | SMe             | N | N | O |
| 1-86 | OH             | Phenyl                          | iso-Propyl                           | OMe            | CF <sub>3</sub> | N | N | O |
| 1-87 | OH             | Phenyl                          | iso-Propyl                           | OMe            | OMe             | N | N | S |

| Nr.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup> | R <sup>3</sup>  | R <sup>2</sup>  | X | Y | Z |
|-------|----------------|---------------------------------|----------------|-----------------|-----------------|---|---|---|
| I-88  | OH             | Phenyl                          | iso-Propyl     | OMe             | Me              | N | N | S |
| I-89  | OH             | Phenyl                          | iso-Propyl     | Me              | OMe             | N | N | S |
| I-90  | OH             | Phenyl                          | iso-Propyl     | Ethyl           | Me              | N | N | S |
| I-91  | OH             | Phenyl                          | Methyl         | CF <sub>3</sub> | tert.-Butyl     | N | N | O |
| I-92  | OH             | Phenyl                          | Methyl         | CF <sub>3</sub> | OMe             | N | N | O |
| I-93  | OH             | Phenyl                          | Methyl         | OMe             | OMe             | N | N | O |
| I-94  | OH             | Phenyl                          | Methyl         | CF <sub>3</sub> | Me              | N | N | O |
| I-95  | OH             | Phenyl                          | Methyl         | Me              | CF <sub>3</sub> | N | N | O |
| I-96  | OH             | Phenyl                          | Methyl         | OMe             | Me              | N | N | O |
| I-97  | OH             | Phenyl                          | Benzyl         | Me              | OMe             | N | N | O |
| I-98  | OH             | Phenyl                          | Benzyl         | Ethyl           | Me              | N | N | O |
| I-99  | OH             | Phenyl                          | Benzyl         | Me              | Ethyl           | N | N | O |
| I-100 | OH             | Phenyl                          | Benzyl         | Me              | Me              | N | N | O |
| I-101 | OH             | Phenyl                          | Benzyl         | OMe             | OMe             | N | N | O |
| I-102 | OH             | Phenyl                          | Phenyl         | OMe             | Me              | N | N | O |
| I-103 | OH             | Phenyl                          | Phenyl         | Me              | OMe             | N | N | O |
| I-104 | OH             | Phenyl                          | Phenyl         | Ethyl           | Me              | N | N | O |
| I-105 | OH             | Phenyl                          | Phenyl         | Me              | Ethyl           | N | N | O |
| I-106 | OH             | Phenyl                          | Phenyl         | Me              | Me              | N | N | O |
| I-107 | OH             | Phenyl                          | Phenyl         | OMe             | OMe             | N | N | O |
| I-108 | OH             | Phenyl                          | 4-OMe-Benzyl   | OMe             | Me              | N | N | O |
| I-109 | OH             | Phenyl                          | 4-OMe-Benzyl   | Me              | OMe             | N | N | O |
| I-110 | OH             | Phenyl                          | 4-OMe-Benzyl   | Ethyl           | Me              | N | N | O |
| I-111 | OH             | Phenyl                          | 4-OMe-Benzyl   | Me              | Ethyl           | N | N | O |
| I-112 | OH             | Phenyl                          | 4-OMe-Benzyl   | Me              | Me              | N | N | O |

| Nr.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                        | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|-------|----------------|---------------------------------|---------------------------------------|----------------|-----------------|---|---|---|
| I-113 | OH             | Phenyl                          | 4-OMe-Benzyl                          | OMe            | OMe             | N | N | O |
| I-114 | OH             | Phenyl                          | 4-Cl-Benzyl                           | OMe            | Me              | N | N | O |
| I-115 | OH             | Phenyl                          | 4-Cl-Benzyl                           | Me             | OMe             | N | N | O |
| I-116 | OH             | Phenyl                          | 4-Cl-Benzyl                           | Ethyl          | Me              | N | N | O |
| I-117 | OH             | Phenyl                          | 4-Cl-Benzyl                           | Me             | Ethyl           | N | N | O |
| I-118 | OH             | Phenyl                          | 4-Cl-Benzyl                           | Me             | Me              | N | N | O |
| I-119 | OH             | Phenyl                          | 4-Cl-Benzyl                           | OMe            | OMe             | N | N | O |
| I-120 | OH             | Cyclohexyl                      | Methyl                                | OMe            | OMe             | N | N | O |
| I-121 | OH             | Cyclohexyl                      | Methyl                                | OMe            | Me              | N | N | O |
| I-122 | OH             | Cyclohexyl                      | Methyl                                | Me             | OMe             | N | N | O |
| I-123 | OH             | Cyclohexyl                      | Methyl                                | Ethyl          | Me              | N | N | O |
| I-124 | OH             | Cyclohexyl                      | Methyl                                | Me             | Ethyl           | N | N | O |
| I-125 | OH             | Cyclohexyl                      | Methyl                                | Me             | CF <sub>3</sub> | N | N | O |
| I-126 | OH             | Cyclohexyl                      | Ethyl                                 | OMe            | Me              | N | N | O |
| I-127 | OH             | Cyclohexyl                      | Ethyl                                 | Me             | OMe             | N | N | O |
| I-128 | OH             | Cyclohexyl                      | Ethyl                                 | Ethyl          | Me              | N | N | O |
| I-129 | OH             | Cyclohexyl                      | Ethyl                                 | OMe            | Ethyl           | N | N | O |
| I-130 | OH             | Cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me              | N | N | O |
| I-131 | OH             | Cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | OMe             | N | N | O |
| I-132 | OH             | Cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Ethyl          | Me              | N | N | O |
| I-133 | OH             | Cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Ethyl           | N | N | O |
| I-134 | OH             | Cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Me              | N | N | O |
| I-135 | OH             | 4-Fluorophenyl                  | Methyl                                | OMe            | OMe             | N | N | O |
| I-136 | OH             | 4-Fluorophenyl                  | Methyl                                | OMe            | Me              | N | N | O |
| I-137 | OH             | 4-Fluorophenyl                  | Methyl                                | Me             | OMe             | N | N | O |

| Nr.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                        | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|-------|----------------|---------------------------------|---------------------------------------|----------------|-----------------|---|---|---|
| I-138 | OH             | 4-Fluorophenyl                  | Methyl                                | Ethyl          | Me              | N | N | O |
| I-139 | OH             | 4-Fluorophenyl                  | Methyl                                | Me             | Ethyl           | N | N | O |
| I-140 | OH             | 4-Fluorophenyl                  | Methyl                                | Me             | CF <sub>3</sub> | N | N | O |
| I-141 | OH             | 4-Fluorophenyl                  | Ethyl                                 | OMe            | Me              | N | N | O |
| I-142 | OH             | 4-Fluorophenyl                  | Ethyl                                 | Me             | OMe             | N | N | O |
| I-143 | OH             | 4-Fluorophenyl                  | Ethyl                                 | Me             | Et              | N | N | O |
| I-144 | OH             | 4-Fluorophenyl                  | Ethyl                                 | OMe            | Ethyl           | N | N | O |
| I-145 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me              | N | N | O |
| I-146 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | OMe             | N | N | O |
| I-147 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Ethyl          | Me              | N | N | O |
| I-148 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Ethyl           | N | N | O |
| I-149 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Me              | N | N | O |
| I-150 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | OMe             | N | N | O |
| I-151 | OH             | 4-Chlorophenyl                  | Methyl                                | OMe            | Me              | N | N | O |
| I-152 | OH             | 4-Chlorophenyl                  | Methyl                                | Me             | OMe             | N | N | O |
| I-153 | OH             | 4-Chlorophenyl                  | Methyl                                | Ethyl          | Me              | N | N | O |
| I-154 | OH             | 4-Chlorophenyl                  | Methyl                                | Me             | Ethyl           | N | N | O |
| I-155 | OH             | 4-Chlorophenyl                  | Methyl                                | Me             | CF <sub>3</sub> | N | N | O |
| I-156 | OH             | 4-Chlorophenyl                  | Ethyl                                 | OMe            | Me              | N | N | O |
| I-157 | OH             | 4-Chlorophenyl                  | Ethyl                                 | Me             | OMe             | N | N | O |
| I-158 | OH             | 4-Chlorophenyl                  | Ethyl                                 | Me             | Et              | N | N | O |
| I-159 | OH             | 4-Chlorophenyl                  | Ethyl                                 | OMe            | Ethyl           | N | N | O |
| I-160 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me              | N | N | O |
| I-161 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | OMe             | N | N | O |
| I-162 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Ethyl          | Me              | N | N | O |

| Nr.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                        | R <sup>3</sup>  | R <sup>2</sup>                                       | X  | Y | Z |
|-------|----------------|---------------------------------|---------------------------------------|-----------------|------------------------------------------------------|----|---|---|
| I-163 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | Ethyl                                                | N  | N | O |
| I-164 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | Me                                                   | N  | N | O |
| I-165 | OH             | 4-Methylphenyl                  | Methyl                                | Me              | Me                                                   | N  | N | O |
| I-166 | OH             | Phenyl                          | Methyl                                | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-167 | OH             | Phenyl                          | Methyl                                | H               | CH=CH-CH=CH-C                                        |    | N | O |
| I-168 | OH             | Phenyl                          | Methyl                                | Me              | Me                                                   | CH | N | O |
| I-169 | OH             | Phenyl                          | Methyl                                | Me              | Ethyl                                                | CH | N | O |
| I-170 | OH             | Phenyl                          | Methyl                                | Ethyl           | Me                                                   | CH | N | O |
| I-171 | OH             | Phenyl                          | Methyl                                | OMe             | Me                                                   | CH | N | O |
| I-172 | OH             | Phenyl                          | Methyl                                | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-173 | OH             | Phenyl                          | Methyl                                | Ethyl           | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-174 | OH             | Phenyl                          | Methyl                                | CF <sub>3</sub> | Me                                                   | CH | N | O |
| I-175 | OH             | Phenyl                          | Methyl                                | CF <sub>3</sub> | Ethyl                                                | CH | N | O |
| I-176 | OH             | Phenyl                          | Ethyl                                 | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-177 | OH             | Phenyl                          | Ethyl                                 | H               | CH=CH-CH=CH-C                                        |    | N | O |
| I-178 | OH             | Phenyl                          | Ethyl                                 | Me              | Me                                                   | CH | N | O |
| I-179 | OH             | Phenyl                          | Ethyl                                 | Me              | Ethyl                                                | CH | N | O |
| I-180 | OH             | Phenyl                          | Ethyl                                 | Ethyl           | Me                                                   | CH | N | O |
| I-181 | OH             | Phenyl                          | Ethyl                                 | OMe             | Me                                                   | CH | N | O |
| I-182 | OH             | Phenyl                          | Ethyl                                 | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-183 | OH             | Phenyl                          | Ethyl                                 | Ethyl           | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-184 | OH             | Phenyl                          | Ethyl                                 | CF <sub>3</sub> | Me                                                   | CH | N | O |
| I-185 | OH             | Phenyl                          | Ethyl                                 | CF <sub>3</sub> | Ethyl                                                | CH | N | O |
| I-186 | OH             | Phenyl                          | n-Propyl                              | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-187 | OH             | Phenyl                          | n-Propyl                              | H               | CH=CH-CH=CH-C                                        |    | N | O |

| Nr.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                          | R <sup>3</sup>  | R <sup>2</sup>                                       | X  | Y | Z |
|-------|----------------|---------------------------------|-----------------------------------------|-----------------|------------------------------------------------------|----|---|---|
| I-188 | OH             | Phenyl                          | n-Propyl                                | Me              | Me                                                   | CH | N | O |
| I-189 | OH             | Phenyl                          | n-Propyl                                | Me              | Ethyl                                                | CH | N | O |
| I-190 | OH             | Phenyl                          | n-Propyl                                | Ethyl           | Me                                                   | CH | N | O |
| I-191 | OH             | Phenyl                          | n-Propyl                                | OMe             | Me                                                   | CH | N | O |
| I-192 | OH             | Phenyl                          | n-Propyl                                | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-193 | OH             | Phenyl                          | n-Propyl                                | Ethyl           | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-194 | OH             | Phenyl                          | n-Propyl                                | CF <sub>3</sub> | Me                                                   | CH | N | O |
| I-195 | OH             | Phenyl                          | n-Propyl                                | CF <sub>3</sub> | Ethyl                                                | CH | N | O |
| I-196 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-197 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | H               | CH=CH-CH=CH-C                                        |    | N | O |
| I-198 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | Me              | CH                                                   |    | N | O |
| I-199 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | Me              | Ethyl                                                | CH | N | O |
| I-200 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | Ethyl           | Me                                                   | CH | N | O |
| I-201 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | OMe             | Me                                                   | CH | N | O |
| I-202 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-203 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | Ethyl           | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-204 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | CF <sub>3</sub> | Me                                                   | CH | N | O |
| I-205 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | CF <sub>3</sub> | Ethyl                                                | CH | N | O |
| I-206 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-207 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | H               | CH=CH-CH=CH-C                                        |    | N | O |
| I-208 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | CH                                                   |    | N | O |
| I-209 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | Ethyl                                                | CH | N | O |
| I-210 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | Ethyl           | Me                                                   | CH | N | O |
| I-211 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | OMe             | Me                                                   | CH | N | O |
| I-212 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |

| Nr.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                                | R <sup>3</sup>  | R <sup>2</sup> | X                                                    | Y | Z |
|-------|----------------|---------------------------------|-----------------------------------------------|-----------------|----------------|------------------------------------------------------|---|---|
| I-213 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | Ethyl           |                | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C | N | O |
| I-214 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | CF <sub>3</sub> | Me             | CH                                                   | N | O |
| I-215 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | CF <sub>3</sub> | Ethyl          | CH                                                   | N | O |
| I-216 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me              | Me             | CH                                                   | N | O |
| I-217 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me              | Ethyl          | CH                                                   | N | O |
| I-218 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Ethyl           | Me             | CH                                                   | N | O |
| I-219 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe             | Me             | CH                                                   | N | O |
| I-220 | OH             | Phenyl                          | iso-Propyl                                    | Me              | Me             | CH                                                   | N | O |
| I-221 | OH             | Phenyl                          | iso-Propyl                                    | Me              | Ethyl          | CH                                                   | N | O |
| I-222 | OH             | Phenyl                          | iso-Propyl                                    | Ethyl           | Me             | CH                                                   | N | O |
| I-223 | OH             | Phenyl                          | iso-Propyl                                    | OMe             | Me             | CH                                                   | N | O |
| I-224 | OH             | Phenyl                          | Methyl                                        | Me              | Me             | CH                                                   | N | S |
| I-225 | OH             | Phenyl                          | Methyl                                        | Me              | Ethyl          | CH                                                   | N | S |
| I-226 | OH             | Phenyl                          | Methyl                                        | Ethyl           | Me             | CH                                                   | N | S |
| I-227 | OH             | Phenyl                          | Methyl                                        | OMe             | Me             | CH                                                   | N | S |
| I-228 | OH             | 4-Fluorophenyl                  | Methyl                                        | Me              | Me             | CH                                                   | N | O |
| I-229 | OH             | 4-Fluorophenyl                  | Methyl                                        | Me              | Ethyl          | CH                                                   | N | O |
| I-230 | OH             | 4-Fluorophenyl                  | Methyl                                        | Ethyl           | Me             | CH                                                   | N | O |
| I-231 | OH             | 4-Fluorophenyl                  | Methyl                                        | OMe             | Me             | CH                                                   | N | O |
| I-232 | OH             | 4-Fluorophenyl                  | Methyl                                        | Me              | Me             | CH                                                   | N | O |
| I-233 | OH             | 4-Fluorophenyl                  | Methyl                                        | CF <sub>3</sub> | Me             | CH                                                   | N | O |
| I-234 | OH             | 4-Fluorophenyl                  | Methyl                                        | CF <sub>3</sub> | Ethyl          | CH                                                   | N | O |
| I-235 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Me              | Me             | CH                                                   | N | O |
| I-236 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Me              | Ethyl          | CH                                                   | N | O |
| I-237 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Ethyl           | Me             | CH                                                   | N | O |
|       |                |                                 |                                               | OMe             | Me             | CH                                                   | N | O |

| Nr.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                        | R <sup>3</sup>  | R <sup>2</sup>  | X  | Y  | Z |
|-------|----------------|---------------------------------|---------------------------------------|-----------------|-----------------|----|----|---|
| I-238 | OH             | 4-Chlorophenyl                  | Methyl                                | Me              | Me              | CH | N  | O |
| I-239 | OH             | 4-Chlorophenyl                  | Methyl                                | Me              | Ethyl           | CH | N  | O |
| I-240 | OH             | 4-Chlorophenyl                  | Methyl                                | Ethyl           | Me              | CH | N  | O |
| I-241 | OH             | 4-Chlorophenyl                  | Methyl                                | OMe             | Me              | CH | N  | O |
| I-242 | OH             | 4-Chlorophenyl                  | Methyl                                | CF <sub>3</sub> | Me              | CH | N  | O |
| I-243 | OH             | 4-Chlorophenyl                  | Methyl                                | CF <sub>3</sub> | Ethyl           | CH | N  | O |
| I-244 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | Me              | CH | N  | O |
| I-245 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | Ethyl           | CH | N  | O |
| I-246 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Ethyl           | Me              | CH | N  | O |
| I-247 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe             | Me              | CH | N  | O |
| I-248 | OH             | Phenyl                          | Ethyl                                 | Me              | Me              | N  | N  | O |
| I-249 | OH             | Phenyl                          | Ethyl                                 | OMe             | SMc             | N  | N  | O |
| I-250 | OH             | Phenyl                          | Ethyl                                 | OMe             | CF <sub>3</sub> | N  | N  | O |
| I-251 | OH             | Phenyl                          | Methyl                                | OMe             | OMe             | N  | CH | O |
| I-252 | OH             | Phenyl                          | Methyl                                | OMe             | Me              | N  | CH | O |
| I-253 | OH             | Phenyl                          | Methyl                                | Me              | Me              | N  | CH | O |
| I-254 | OH             | Phenyl                          | Methyl                                | Ethyl           | Me              | N  | CH | O |
| I-255 | OH             | Phenyl                          | Methyl                                | Ethyl           | Ethyl           | N  | CH | O |
| I-256 | OH             | Phenyl                          | Methyl                                | CF <sub>3</sub> | Me              | N  | CH | O |
| I-257 | OH             | Phenyl                          | Methyl                                | CF <sub>3</sub> | Ethyl           | N  | CH | O |
| I-258 | OH             | Phenyl                          | Methyl                                | OMe             | CF <sub>3</sub> | N  | CH | O |
| I-259 | OH             | Phenyl                          | Methyl                                | OMe             | OMe             | N  | CH | S |
| I-260 | OH             | Phenyl                          | Methyl                                | OMe             | Me              | N  | CH | S |
| I-261 | OH             | Phenyl                          | Methyl                                | Me              | Me              | N  | CH | S |
| I-262 | OH             | Phenyl                          | Methyl                                | Ethyl           | Me              | N  | CH | S |

| Nr.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                                | R <sup>3</sup> | R <sup>2</sup> | X | Y  | Z |
|-------|----------------|---------------------------------|-----------------------------------------------|----------------|----------------|---|----|---|
| 1-263 | OH             | Phenyl                          | Ethyl                                         | OMe            | OMe            | N | CH | O |
| 1-264 | OH             | Phenyl                          | Ethyl                                         | OMe            | Me             | N | CH | O |
| 1-265 | OH             | Phenyl                          | Ethyl                                         | Me             | Me             | N | CH | O |
| 1-266 | OH             | Phenyl                          | Ethyl                                         | Ethyl          | Me             | N | CH | O |
| 1-267 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | OMe            | OMe            | N | CH | O |
| 1-268 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | OMe            | Me             | N | CH | O |
| 1-269 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Me             | Me             | N | CH | O |
| 1-270 | OH             | Phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Ethyl          | Me             | N | CH | O |
| 1-271 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | OMe            | N | CH | O |
| 1-272 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | Me             | N | CH | O |
| 1-273 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | Me             | N | CH | O |
| 1-274 | OH             | Phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Ethyl          | Me             | N | CH | O |
| 1-275 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | OMe            | OMe            | N | CH | O |
| 1-276 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | OMe            | Me             | N | CH | O |
| 1-277 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | Me             | Me             | N | CH | O |
| 1-278 | OH             | Phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | Ethyl          | Me             | N | CH | O |
| 1-279 | OH             | Phenyl                          | Propyl                                        | OMe            | OMe            | N | CH | O |
| 1-280 | OH             | Phenyl                          | Propyl                                        | OMe            | Me             | N | CH | O |
| 1-281 | OH             | Phenyl                          | Propyl                                        | Me             | Me             | N | CH | O |
| 1-282 | OH             | Phenyl                          | Propyl                                        | Ethyl          | Me             | N | CH | O |
| 1-283 | OH             | Phenyl                          | 4-OMe-Benzyl                                  | OMe            | OMe            | N | CH | O |
| 1-284 | OH             | Phenyl                          | 4-OMe-Benzyl                                  | OMe            | Me             | N | CH | O |
| 1-285 | OH             | Phenyl                          | 4-OMe-Benzyl                                  | Me             | Me             | N | CH | O |
| 1-286 | OH             | Phenyl                          | 4-OMe-Benzyl                                  | Ethyl          | Me             | N | CH | O |
| 1-287 | OH             | 4-Fluorophenyl                  | Methyl                                        | OMe            | OMe            | N | CH | O |

| Nr.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                        | R <sup>3</sup> | R <sup>2</sup> | X | Y  | Z |
|-------|----------------|---------------------------------|---------------------------------------|----------------|----------------|---|----|---|
| I-288 | OH             | 4-Fluorophenyl                  | Methyl                                | OMe            | Me             | N | CH | O |
| I-289 | OH             | 4-Fluorophenyl                  | Methyl                                | Me             | Me             | N | CH | O |
| I-290 | OH             | 4-Fluorophenyl                  | Methyl                                | Ethyl          | Me             | N | CH | O |
| I-291 | OH             | 4-Fluorophenyl                  | Ethyl                                 | OMe            | OMe            | N | CH | O |
| I-292 | OH             | 4-Fluorophenyl                  | Ethyl                                 | OMe            | Me             | N | CH | O |
| I-293 | OH             | 4-Fluorophenyl                  | Ethyl                                 | Me             | Me             | N | CH | O |
| I-294 | OH             | 4-Fluorophenyl                  | Ethyl                                 | Ethyl          | Me             | N | CH | O |
| I-295 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | OMe            | N | CH | O |
| I-296 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me             | N | CH | O |
| I-297 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Me             | N | CH | O |
| I-298 | OH             | 4-Fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Ethyl          | Me             | N | CH | O |
| I-299 | OH             | 4-Chlorophenyl                  | Methyl                                | OMe            | OMe            | N | CH | O |
| I-300 | OH             | 4-Chlorophenyl                  | Methyl                                | OMe            | Me             | N | CH | O |
| I-301 | OH             | 4-Chlorophenyl                  | Methyl                                | Me             | Me             | N | CH | O |
| I-302 | OH             | 4-Chlorophenyl                  | Methyl                                | Ethyl          | Me             | N | CH | O |
| I-303 | OH             | 4-Chlorophenyl                  | Ethyl                                 | OMe            | OMe            | N | CH | O |
| I-304 | OH             | 4-Chlorophenyl                  | Ethyl                                 | OMe            | Me             | N | CH | O |
| I-305 | OH             | 4-Chlorophenyl                  | Ethyl                                 | Me             | Me             | N | CH | O |
| I-306 | OH             | 4-Chlorophenyl                  | Ethyl                                 | Ethyl          | Me             | N | CH | O |
| I-307 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | OMe            | N | CH | O |
| I-308 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me             | N | CH | O |
| I-309 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Me             | N | CH | O |
| I-310 | OH             | 4-Chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Ethyl          | Me             | N | CH | O |

Die Verbindungen der vorliegenden Erfindung bieten ein neues therapeutisches Potential für die Behandlung von Hypertonie, pulmonalem Hochdruck, Myokardinfarkt, Angina Pectoris, akutem Nierenversagen, Niereninsuffizienz, zerebralen Vasospasmen, zerebraler Ischämie, Subarachnoidalblutungen, Migräne, Asthma, Atherosklerose, endotoxischem Schock, Endotoxin-induziertem Organversagen, intravaskulärer Koagulation, Restenose nach Angioplastie, benigne Prostata-Hyperplasie, ischämisches und durch Intoxikation verursachtes Nierenversagen bzw. Hypertonie, sowie von Krebserkrankungen insbesondere von Prostatakrebs und Hautkrebs. Ein weiterer Gegenstand der Erfindung ist die Kombination von Verbindungen der Formel I mit Hemmstoffen des Renin-Angiotensin-Systems (RAS). RAS-Hemmstoffe sind beispielsweise aus EP 634 175 bekannt.

15

Die erfindungsgemäßen Kombinationen eignen sich zur Behandlung von solchen Krankheiten, für die auch die Verbindungen der Formel I allein Wirksamkeit zeigen, insbesondere zur Behandlung von Hypertonie und chronischer Herzinsuffizienz.

20

Die gute Wirkung der Verbindungen läßt sich in folgenden Versuchen zeigen:

#### 25 Rezeptorbindungsstudien

Für Bindungsstudien wurden klonierte humane  $ET_A$ -Rezeptor-exprimierende CHO-Zellen und Meerschweinchen-Kleinhirnmembranen mit  $> 60\%$   $ET_B$  im Vergleich zu  $ET_A$ -Rezeptoren eingesetzt.

30

#### Membranpräparation

Die  $ET_A$ -Rezeptor-exprimierenden CHO-Zellen wurden in  $F_{12}$ -Medium mit 10 % fötalem Kälberserum, 1 % Glutamin, 100 E/ml Penicillin und 0,2 % Streptomycin (Gibco BRL, Gaithersburg, MD, USA) vermehrt. Nach 48 h wurden die Zellen mit PBS gewaschen und mit 0,05 % trypsinhaltiger PBS 5 min inkubiert. Danach wurde mit  $F_{12}$ -Medium neutralisiert und die Zellen durch Zentrifugation bei 300 x g gesammelt. Zur Lyse der Zellen wurde kurz das Pellet mit Lysispuffer (5 mM Tris-HCl, pH 7,4 mit 10 % Glycerin) gewaschen und danach in einer Konzentration von  $10^7$ -Zellen/ml Lysispuffer 30 min bei 4°C inkubiert. Die Membranen wurden bei 20.000 x g 10 min zentrifugiert und das Pellet in flüssigem Stickstoff gelagert.

45

Meerschweinchenkleinhirne wurden im Potter-Elvehjem-Homogenisator homogenisiert und durch differentielle Zentrifugation 10 min bei 1.000 x g und wiederholte Zentrifugation des Überstandes 10 min bei 20.000 x g gewonnen.

5

#### Bindungstests

Für den  $ET_A$ - und  $ET_B$ -Rezeptorbindungstest wurden die Membranen in Inkubationspuffer (50 mM Tris-HCl, pH 7,4 mit 5 mM  $MnCl_2$ , 40  $\mu$ g/ml  
10 Bacitracin und 0,2 % BSA) in einer Konzentration von 50  $\mu$ g Protein pro Testansatz suspendiert und bei 25°C mit 25 pM [ $^{125}J$ ]- $ET_1$  ( $ET_A$ -Rezeptortest) oder 25 pM [ $^{125}J$ ]- $RZ_3$  ( $ET_B$ -Rezeptortest) in Anwesenheit und Abwesenheit von Testsubstanz inkubiert. Die unspezifische Bindung wurde mit  $10^{-7}$  M  $ET_1$  bestimmt. Nach 30 min  
15 wurde der freie und der gebundene Radioligand durch Filtration über GF/B Glasfaserfilter (Whatman, England) an einem Skatron-Zellsammler (Skatron, Lier, Norwegen) getrennt und die Filter mit eiskaltem Tris-HCl-Puffer, pH 7,4 mit 0,2 % BSA gewaschen. Die auf den Filtern gesammelte Radioaktivität wurde mit einem Packard  
20 2200 CA Flüssigkeitszintillationszähler quantifiziert.

Funktionelles in vitro-Testsystem für die Suche nach Endothelinrezeptor (Subtyp A)-Antagonisten

25 Dieses Testsystem ist ein funktioneller, auf Zellen basierender Test für Endothelinrezeptoren. Bestimmte Zellen zeigen, wenn sie mit Endothelin 1 ( $ET_1$ ) stimuliert werden, einen Anstieg der intrazellulären Calciumkonzentration. Dieser Anstieg kann in intakten Zellen, die mit Calcium-sensitiven Farbstoffen beladen wurden,  
30 den, gemessen werden.

Aus Ratten isolierte 1-Fibroblasten, bei denen ein endogener Endothelinrezeptor vom A-Subtyp nachgewiesen wurde, wurden mit dem Fluoreszenzfarbstoff Fura 2-am wie folgt beladen: Nach Trypsinierung wurden die Zellen in Puffer A (120 mM NaCl, 5 mM KCl,  
35 1,5 mM  $MgCl_2$ , 1 mM  $CaCl_2$ , 25 mM HEPES, 10 mM Glucose, pH 7,4) bis zu einer Dichte von  $2 \times 10^6$ /ml resuspendiert und in 30 min bei 37°C im Dunkeln mit Fura 2-am (2  $\mu$ M), Pluronic F-127 (0,04 %) und DMSO (0,2 %) inkubiert. Danach wurden die Zellen zweimal mit Puffer A gewaschen und zu  $2 \times 10^6$ /ml resuspendiert.  
40

Das Fluoreszenzsignal von  $2 \times 10^5$  Zellen pro ml bei Ex/Em 380/510 wurde bei 30°C kontinuierlich registriert. Zu den Zellen wurden die Testsubstanzen und nach einer Inkubationszeit von 3 min  $ET_1$  wurde  
45 die maximale Änderung der Fluoreszenz bestimmt. Die Antwort der

Zellen auf ET1 ohne vorherige Zugabe einer Testsubstanz diente als Kontrolle und wurde gleich 100 % gesetzt.

#### Testung der ET-Antagonisten *in vivo*

5

Männliche 250 - 300 g schwere SD-Ratten wurden mit Amobarbital narkotisiert, künstlich beatmet, vagotomisiert und despinalisiert. Die Arteria carotis und Vena jugularis wurden kathetisiert.

10

In Kontrolltieren führt die intravenöse Gabe von 1 µg/kg ET1 zu einem deutlichen Blutdruckanstieg, der über einen längeren Zeitraum anhält.

15 Den Testtieren wurde 5 min vor der ET1 Gabe die Testverbindungen i.v. injiziert (1 ml/kg). Zur Bestimmung der ET-antagonistischen Eigenschaften wurde der Blutdruckanstieg in den Testtieren mit dem in den Kontrolltieren verglichen.

#### 20 Endothelin-1 induzierter "sudden death" an Mäusen

Das Testprinzip besteht in der Hemmung des durch Endothelin verursachten plötzlichen Herztodes der Maus, der wahrscheinlich durch Verengung der Herzkranzgefäße bedingt ist, durch Vorbehand-

25 lung mit Endothelin-Rezeptorantagonisten. Nach intravenöser Injektion von 10 nmol/kg Endothelin im Volumen von 5 ml/kg Körpergewicht kommt es innerhalb weniger Minuten zum Tod der Tiere.

Die letale Endothelin-1 Dosis wird jeweils an einem kleinen Tierkollektiv überprüft. Wird die Prüfsubstanz intravenös appliziert, erfolgt meist 5 min danach die im Referenzkollektiv letale Endothelin-1 Injektion. Bei anderen Applikationsarten verlängern sich die Vorgabezeiten, gegebenenfalls bis zu mehreren Stunden.

35 Die Überlebensrate wird dokumentiert und effektive Dosen, die 50 % der Tiere 24 h oder länger gegen den Endothelin-Herztod schützen (ED 50) werden ermittelt.

#### Funktioneller Gefäßtest für Endothelin-Rezeptorantagonisten

40

An Aortensegmenten des Kaninchens wird nach einer Vorspannung von 2 g und einer Relaxationszeit von 1 h in Krebs-Henseleitlösung bei 37°C und einem pH-Wert zwischen 7,3 und 7,4 zunächst eine K<sup>+</sup>-Kontraktur ausgelöst. Nach Auswaschen wird eine Endothelin-Dosiswirkungskurve bis zum Maximum erstellt.

45

Potentielle Endothelin-Antagonisten werden an anderen Präparaten des gleichen Gefäßes 15 min vor Beginn der Endothelin-Dosiswirkungskurve appliziert. Die Effekte des Endothelins werden in % der K<sup>+</sup>-Kontraktur berechnet. Bei wirksamen Endothelin-Antagonisten kommt es zur Rechtsverschiebung der Endothelin-Dosiswirkungskurve.

Die erfindungsgemäßen Verbindungen können in üblicher Weise oral oder parenteral (subkutan, intravenös, intramuskulär, intraperitoneal) verabfolgt werden. Die Applikation kann auch mit Dämpfen oder Sprays durch den Nasen-Rachenraum erfolgen.

Die Dosierung hängt vom Alter, Zustand und Gewicht des Patienten sowie von der Applikationsart ab. In der Regel beträgt die tägliche Wirkstoffdosis zwischen etwa 0,5 und 50 mg/kg Körpergewicht bei oraler Gabe und zwischen etwa 0,1 und 10 mg/kg Körpergewicht bei parenteraler Gabe.

Die neuen Verbindungen können in den gebräuchlichen galenischen Applikationsformen fest oder flüssig angewendet werden, z.B. als Tabletten, Filmtabletten, Kapseln, Pulver, Granulate, Dragees, Suppositorien, Lösungen, Salben, Cremes oder Sprays. Diese werden in üblicher Weise hergestellt. Die Wirkstoffe können dabei mit den üblichen galenischen Hilfsmitteln wie Tablettenbindern, Füllstoffen, Konservierungsmitteln, Tablettensprengmitteln, Fließregulierungsmitteln, Weichmachern, Netzmitteln, Dispergiermitteln, Emulgatoren, Lösungsmitteln, Retardierungsmitteln, Antioxidantien und/oder Treibgasen verarbeitet werden (vgl. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). Die so erhaltenen Applikationsformen enthalten den Wirkstoff normalerweise in einer Menge von 0,1 bis 90 Gew.-%.

#### Synthesebeispiele

##### 35 Beispiel 1

2-Hydroxy-3-methoxy-3,3-diphenylpropionsäuremethylester

5 g (19,6 mmol) 3,3-Diphenyl-2,3-epoxypropionsäuremethylester wurden in 50 ml absolutem Methanol gelöst und bei 0°C mit 0,1 ml Bortrifluorid-Etherat versetzt. Man rührte 2 h bei 0°C und weitere 12 h bei Raumtemperatur. Das Lösungsmittel wurde abdestilliert, der Rückstand mit Essigester aufgenommen, mit Natriumhydrogencarbonat-Lösung und Wasser gewaschen und über Magnesiumsulfat getrocknet. Nach Abdestillieren des Lösungsmittels verblieben 5,5 g (88 %) eines schwach gelben Öls.

## Beispiel 2

2-(2,6-Dimethoxy-pyrimidin-4-yloxy)-3-methoxy-3,3-diphenyl-propionsäuremethylester

- 5 1.15 g (4 mmol) 2-Hydroxy-3-methoxy-3,3-diphenyl-propionsäuremethylester wurden in 10 ml Dimethylformamid gelöst und mit 276 mg (2 mmol) Kaliumcarbonat versetzt. Man gab dann 524 mg (3 mmol) 2,6-Dimethoxy-4-chlorpyrimidin zu und rührte 6 Stunden bei 100°C. Dann wurde vorsichtig mit 10 ml Wasser  
10 hydrolysiert, mit Citronensäure ein pH-Wert von 5 eingestellt, mit Essigester extrahiert, die organische Phase mit Wasser gewaschen, über Magnesiumsulfat getrocknet und das Lösungsmittel abdestilliert. Der ölige Rückstand (1.9 g) wurde an Kieselgel chromatographiert, wobei man 617 mg eines leicht verunreinigten  
15 Öls erhielt.

## Beispiel 3

2-(2,6-Dimethoxy-pyrimidin-4-yloxy)-3-methoxy-3,3-diphenyl-propionsäure

20

- 550 mg (1,3 mmol) 2-(2,6-Dimethoxy-pyrimidin-4-yloxy)-3-methoxy-3,3-diphenyl-propionsäuremethylester wurden in 5 ml Dioxan gelöst, mit 2.6 ml 1 n KOH-Lösung versetzt und 3 h bei 100°C gerührt. Die Lösung wurde mit 300 ml Wasser verdünnt und mit Essig-  
25 ester zur Entfernung von nicht umgesetztem Ester extrahiert. Anschließend stellte man die Wasserphase mit verdünnter Salzsäure auf pH 1-2 und extrahierte mit Essigester. Nach Trocknen über Magnesiumsulfat und Abdestillieren des Lösungsmittels wurde der schaumige Rückstand (425 mg) über MPLC gereinigt, wobei man  
30 205 mg (40%) eines schaumigen Produkts erhielt.

## Beispiel 4

2-(4-Methylchinolin-2-yloxy)-3-methoxy-3,3-diphenyl-propionsäuremethylester

35

- 5.7 g (20 mmol) 2-Hydroxy-3-methoxy-3,3-diphenyl-propionsäuremethylester wurden in 90 ml Dimethylformamid gelöst und mit 0,98 g (22 mmol) Natriumhydrid (55% in Öl) versetzt. Man rührte 15 Minuten und gab dann 3,9 g (22 mmol) 2-Chlor-4-methylchinolin zu. Die  
40 dunkelrote Lösung wurde über Nacht bei Raumtemperatur gerührt, dann vorsichtig mit 20 ml Wasser hydrolysiert, und anschließend mit Essigester extrahiert. Die organische Phase wurde mit Wasser gewaschen, über Magnesiumsulfat getrocknet und das Lösungsmittel abdestilliert. Der Rückstand (8.1 g) wurde dann an  
45 Kieselgel chromatographiert, wobei 2.6 g verunreinigtes Produkt als Öl erhalten wurden.

## Beispiel 5

2-(4-Methylchinolin-2-yloxy)-3-methoxy-3,3-diphenyl-propionsäure

1.8 g (4.2 mmol) 2-(4-Methylchinolin-2-yloxy)-3-methoxy-3,3-di-  
5 phenyl-propionsäuremethylester wurden in 25 ml Dioxan gelöst, mit  
8.4 ml 1 n KOH-Lösung versetzt und 20 Stunden bei 60°C gerührt.  
Die Lösung wurde mit 300 ml Wasser verdünnt und mit Essigester  
zur Entfernung von nicht umgesetztem Ester und Verunreinigungen  
extrahiert. Anschließend stellte man die Wasserphase mit verdünn-  
10 ter Salzsäure auf pH 1-2 und extrahierte mit Essigester. Nach  
Trocknen über Magnesiumsulfat und Abdestillieren des Lösungs-  
mittels wurden 1.0 g eines Schaumes erhalten. Dieser wurde in we-  
nig Essigester gelöst und über Nacht bei Raumtemperatur stehen  
gelassen. dabei fielen 265 mg des Produkts in Form von weißen  
15 Kristallen an. Die Wiederholung dieser Prozedur mit der Mutter-  
lauge erbrachten weitere 166 mg des Produkts.

Gesamtausbeute: 431 mg  $\hat{=}$  25%

Fp.: 131-133°C

20 MS:  $M^+ = 413$

## Beispiel 6

2-(2-tert-Butyl-6-trifluormethyl-pyrimidin-4-yloxy)-3-methoxy-  
3,3-diphenyl-propionsäurebenzylester

25 2.0 g (5.5 mmol) 2-Hydroxy-3-methoxy-3,3-diphenyl-propionsäure-  
benzylester (siehe P44 36 851.8) wurden in 20 ml Dimethylformamid  
gelöst und mit 0.76 g (5.5 mmol) Kaliumcarbonat versetzt. Man gab  
dann 1.32 g (5.5 mmol) 2-tert-Butyl-6-trifluormethyl-4-chlorpyri-  
30 midin zu, rührte über Nacht bei Raumtemperatur, dann 5 Stunden bei  
100°C. zur Vervollständigung der Reaktion wurden weitere 0.5 g des  
Pyrimidins sowie 0.5 g NaH zugegeben und nochmals 6 Stunden bei  
60°C gerührt. Schließlich wurde auf Eiswasser gegossen, mit Essig-  
ester extrahiert, die organische Phase mit ges. NaCl-Lösung  
35 gewaschen über Magnesiumsulfat getrocknet und das Lösungsmittel  
abdestilliert. Der ölige Rückstand (3.5 g) kristallisierte in  
n-Heptan/Essigester (5%). Der Niederschlag wurde abgesaugt und  
getrocknet.

40 Ausbeute: 1.6 g  $\hat{=}$  52%

MS:  $M^+ = 564$

## Beispiel 7

2-(2-tert-Butyl-6-trifluormethyl-pyrimidin-4-yloxy)-3-methoxy-3,3-diphenyl-propionsäure

5 2.0 g (5.5 mmol) 2-(2-tert-Butyl-6-trifluormethyl-pyrimidin-4-yloxy)-3-methoxy-3,3-diphenyl-propionsäurebenzylester wurden in 250 ml Methanol gelöst, mit 120 mg Palladium auf Aktivkohle (5%) versetzt und unter Wasserstoff bei Raumtemperatur 2 Stunden gerührt. Nach beendeter Wasserstoffaufnahme wurde der Katalysator über  
 10 Celite abfiltriert und das Lösungsmittel am Rotationsverdampfer abgezogen.

Ausbeute: 1.0 g  $\cong$  98%

<sup>1</sup>H-NMR (360 MHz, in CDCl<sub>3</sub>, Angabe in ppm):

15 1.35 (s, 9H); 3.3 (s, 3H); 6.3 (s, 1H); 6.8 (s, 1H);  
 7.15 - 7.45 (m, 10H)

Analog lassen sich die in Tabelle 1 aufgeführten Verbindungen herstellen.

20

## Beispiel 8

Gemäß dem oben beschriebenen Bindungstest wurden für die nachfolgend aufgeführten Verbindungen Rezeptorbindungsdaten gemessen.

25

Die Ergebnisse sind in Tabelle 2 dargestellt.

Tabelle 2

30 Rezeptorbindungsdaten (K<sub>i</sub>-Werte)

|    | Verbindung | ET <sub>A</sub> [μM] | ET <sub>B</sub> [μM] |
|----|------------|----------------------|----------------------|
|    |            |                      |                      |
| 35 | I-1        | 0.038                | 8                    |
|    | I-91       | 3.3                  | > 10                 |
|    | I-166      | 0.5                  | 4                    |
|    | I-167      | 3                    | > 7                  |

40

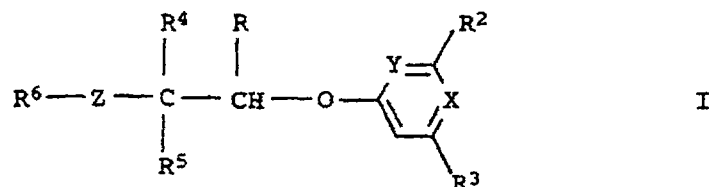
45

## Patentansprüche

## 1. Carbonsäurederivate der Formel I

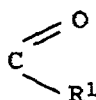
5

10



in der R ein Tetrazol, Nitril, eine Gruppe

15



bedeutet, in der R<sup>1</sup> folgende Bedeutung hat:

20

a) Wasserstoff;

b) eine Succinylimidoxygruppe;

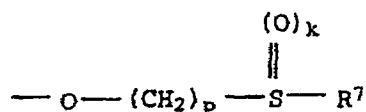
25

c) ein über ein Stickstoffatom verknüpfter 5-gliedriger Heteroaromat wie Pyrrolyl, Pyrazolyl, Imidazolyl und Triazolyl, welcher ein bis zwei Halogenatome, oder eins bis zwei C<sub>1</sub>-C<sub>4</sub>-Alkyl oder eins bis zwei C<sub>1</sub>-C<sub>4</sub>-Alkoxygruppen tragen kann.

30

d) R<sup>1</sup> ferner eine Gruppe

35



in der k die Werte 0, 1 und 2, p die Werte 1, 2, 3 und 4 annehmen und R<sup>7</sup> für

40

C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, C<sub>3</sub>-C<sub>6</sub>-Alkenyl, C<sub>3</sub>-C<sub>6</sub>-Alkynyl oder gegebenenfalls substituiertes Phenyl steht, das durch einen oder mehrere, z.B. ein bis drei der folgenden Reste substituiert sein kann:

45

Halogen, Nitro, Cyano, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, Hydroxy, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Mercapto, Amino, C<sub>1</sub>-C<sub>4</sub>-Alkylamino, C<sub>1</sub>-C<sub>4</sub>-Dialkylamino;



e)  $R^1$  ferner ein Rest  $OR^8$ , worin  $R^8$  bedeutet:

5 Wasserstoff, das Kation eines Alkalimetalls wie Lithium, Natrium, Kalium oder das Kation eines Erdalkalimetalls wie Calcium, Magnesium und Barium oder ein physiologisch verträgliches organisches Ammoniumion wie tertiäres  $C_1$ - $C_4$ -Alkylammonium oder das Ammoniumion;

10  $C_3$ - $C_8$ -Cycloalkyl, wie Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl und Cycloheptyl, Cyclooctyl,

15  $C_1$ - $C_8$ -Alkyl, insbesondere  $C_1$ - $C_4$ -Alkyl wie Methyl, Ethyl, n-Propyl, iso-Propyl, n-Butyl, iso-Butyl, tert.-Butyl;  $CH_2$ -Phenyl, das durch einen oder mehrere der folgenden Reste substituiert sein kann: Halogen, Nitro, Cyano,  $C_1$ - $C_4$ -Alkyl,  $C_1$ - $C_4$ -Halogenalkyl, Hydroxy,  $C_1$ - $C_4$ -Alkoxy, Mercapto,

$C_1$ - $C_4$ -Alkylthio, Amino,  $C_1$ - $C_4$ -Alkylamino,  $C_1$ - $C_4$ -Dialkylamino,

20 Eine  $C_3$ - $C_6$ -Alkenyl - oder eine  $C_3$ - $C_6$ -Alkynylgruppe, wobei diese Gruppe ihrerseits ein bis fünf Halogenatome tragen können;

25  $R^8$  kann weiterhin ein Phenylrest sein, welcher ein bis fünf Halogenatome und/oder ein bis drei der folgenden Reste tragen kann: Nitro, Cyano,  $C_1$ - $C_4$ -Alkyl,  $C_1$ - $C_4$ -Halogenalkyl, Hydroxy,  $C_1$ - $C_4$ -Alkoxy, Mercapto,  $C_1$ - $C_4$ -Alkylthio, Amino,

30  $C_1$ - $C_4$ -Alkylamino,  $C_1$ - $C_4$ -Dialkylamino;

ein über ein Stickstoffatom verknüpfter 5-gliedriger Heteroaromat, enthaltend ein bis drei Stickstoffatome, welcher ein bis zwei Halogenatome und/oder ein bis zwei der folgenden Reste tragen kann:  $C_1$ - $C_4$ -Alkyl,

35  $C_1$ - $C_4$ -Halogenalkyl,  $C_1$ - $C_4$ -Alkoxy, Phenyl,  $C_1$ - $C_4$ -Halogenalkoxy und/oder  $C_1$ - $C_4$ -Alkylthio. Insbesondere seien genannt: 1-Pyrazolyl,

40 3-Methyl-1-pyrazolyl, 4-Methyl-1-pyrazolyl, 3,5-Dimethyl-1-pyrazolyl, 3-Phenyl-1-pyrazolyl, 4-Phenyl-1-pyrazolyl, 4-Chlor-1-pyrazolyl, 4-Brom-1-pyrazolyl, 1-Imidazolyl, 1-Benzimidazolyl, 1,2,4-Triazol-1-yl, 3-Methyl-1,2,4-triazol-1-yl, 5-Methyl-1,2,4-triazol-1-yl, 1-Benztriazolyl, 3,4-Dichlorimidazol-1-yl;

45



f)  $R^1$  ferner ein Rest

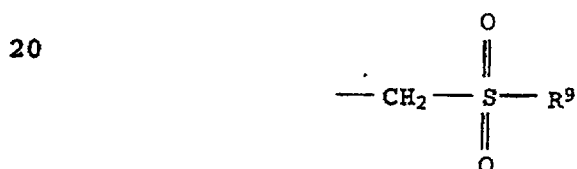


worin  $R^9$  bedeutet:

10  $C_1$ - $C_4$ -Alkyl,  $C_3$ - $C_6$ -Alkenyl,  $C_3$ - $C_6$ -Alkynyl,  $C_3$ - $C_8$ -Cycloalkyl wie insbesondere vorstehend genannt, wobei diese Reste einen  $C_1$ - $C_4$ -Alkoxy-,  $C_1$ - $C_4$ -Alkylthio- und/oder einen Phenylrest wie oben genannt tragen können;

15 Phenyl, gegebenenfalls substituiert, insbesondere wie vorstehend genannt.

g)  $R^1$  ein Rest



25 worin  $R^9$  die oben genannte Bedeutung hat.

h) ferner kann  $R^1$  bedeuten



35 wobei  $R^{10}$  und  $R^{11}$  gleich oder verschieden sein können und folgende Bedeutung haben:

Wasserstoff,  $C_1$ - $C_7$ -Alkyl,  $C_3$ - $C_7$ -Cycloalkyl,  $C_3$ - $C_7$ -Alkenyl,  $C_3$ - $C_7$ -Alkynyl, Benzyl, Phenyl, gegebenenfalls substituiert, wie oben beschrieben,  
 40 oder  $R^{10}$  und  $R^{11}$  bilden gemeinsam eine zu einem Ring geschlossene, optionell substituierte, z.B. durch  $C_1$ - $C_4$ -Alkyl substituierte  $C_4$ - $C_7$ -Alkylenkette, die ein Heteroatom, z.B. Sauerstoff, Schwefel oder Stickstoff enthalten kann wie  $-(CH_2)_4-$ ,  $-(CH_2)_5-$ ,  $-(CH_2)_6-$ ,  $-(CH_2)_7-$ ,  
 45  $-(CH_2)_2-O-(CH_2)_2-$ ,  $-(CH_2)_2-S-(CH_2)_2-$ ,  $-(CH_2)_2-NH-(CH_2)_2-$ ,  
 $-(CH_2)_2-N-(CH_2)_2-$ ;



die übrigen Substituenten haben die folgende Bedeutung:

- 5  $R^2$  Wasserstoff, Hydroxy,  $NH_2$ ,  $NH(C_1-C_4-Alkyl)$ ,  
 $N(C_1-C_4-Alkyl)_2$ , Halogen,  $C_1-C_4-Alkyl$ ,  $C_1-C_4-Halogenalkyl$ ,  
 $C_1-C_4-Alkoxy$ ,  $C_1-C_4-Halogenalkoxy$  oder  $C_1-C_4-Alkylthio$ ,  
oder  $CR^2$  ist mit  $CR^{12}$  wie unten angegeben zu einem 5- oder  
6-gliedrigen Ring verknüpft;
- 10 X Stickstoff oder  $CR^{12}$ , worin  $R^{12}$  Wasserstoff oder  
 $C_{1-5}-Alkyl$  bedeutet oder  $CR^{12}$  zusammen mit  $CR^2$  oder  $CR^3$   
einen 5- oder 6-gliedrigen Alkylen- oder Alkenylenring  
bildet, der durch eine oder zwei  $C_{1-4}-Alkyl$ gruppen sub-  
stituiert sein kann und worin jeweils eine Methylengruppe  
15 durch Sauerstoff, Schwefel,  $-NH$  oder  $-NC_{1-4}-Alkyl$  ersetzt  
sein kann;
- Y Stickstoff oder Methin;
- 20  $R^3$  Wasserstoff, Hydroxy,  $NH_2$ ,  $NH(C_1-C_4-Alkyl)$ ,  
 $N(C_1-C_4-Alkyl)_2$ , Halogen,  $C_1-C_4-Alkyl$ ,  $C_1-C_4-Halogenalkyl$ ,  
 $C_1-C_4-Alkoxy$ ,  $C_1-C_4-Halogenalkoxy$ ,  $-NH-O-C_{1-4}-Alkyl$ ,  
 $C_1-C_4-Alkylthio$ ; oder  $CR^3$  ist mit  $CR^{12}$  wie oben angegeben  
zu einem 5- oder 6-gliedrigen Ring verknüpft;
- 25  $R^4$  und  $R^5$  (die gleich oder verschieden sein können):
- 30 Phenyl oder Naphthyl, die durch einen oder mehrere der  
folgenden Reste substituiert sein können: Halogen, Nitro,  
Cyano, Hydroxy,  $C_1-C_4-Alkyl$ ,  $C_1-C_4-Halogenalkyl$ ,  
 $C_1-C_4-Alkoxy$ ,  $C_1-C_4-Halogenalkoxy$ , Phenoxy,  $C_1-C_4-Alkyl$ -  
thio, Amino,  $C_1-C_4-Alkylamino$  oder  $C_1-C_4-Dialkylamino$ ;  
oder
- 35 Phenyl oder Naphthyl, die orthoständig über eine direkte  
Bindung, eine Methylen-, Ethylen- oder Ethenylengruppe,  
ein Sauerstoff- oder Schwefelatom oder eine  $SO_2$ -,  $NH$ -  
oder N-Alkyl-Gruppe miteinander verbunden sind oder  
 $C_3-C_7-Cycloalkyl$ ;
- 40  $R^6$  Wasserstoff,  $C_1-C_8-Alkyl$ ,  $C_3-C_6-Alkenyl$ ,  $C_3-C_6-Alkynyl$   
oder  $C_3-C_8-Cycloalkyl$ , wobei diese Reste jeweils ein-  
oder mehrfach substituiert sein können durch: Halogen,  
Hydroxy, Mercapto, Carboxy, Nitro, Cyano,  $C_1-C_4-Alkoxy$ ,  
 $C_3-C_6-Alkenyloxy$ ,  $C_3-C_6-Alkynyloxy$ ,  $C_1-C_4-Alkylthio$ ,  
45  $C_1-C_4-Halogenalkoxy$ ,  $C_1-C_4-Alkylcarbonyl$ ,  $C_1-C_4-Alkoxy$ -  
carbonyl,



## 36

C<sub>3-8</sub>-Alkylcarbonylalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkylamino,  
 Di-C<sub>1</sub>-C<sub>4</sub>-alkylamino, Phenyl oder ein- oder mehrfach, z.B.  
 ein- bis dreifach durch Halogen, Nitro, Cyano,  
 C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy,  
 5 C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy oder C<sub>1</sub>-C<sub>4</sub>-Alkylthio substituiertes  
 Phenyl oder Phenoxy;

Phenyl oder Naphthyl, die jeweils durch einen oder meh-  
 rere der folgenden Reste substituiert sein können: Halo-  
 10 gen, Nitro, Cyano, Hydroxy, Amino, C<sub>1</sub>-C<sub>4</sub>-Alkyl,  
 C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy,  
 Phenoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, C<sub>1</sub>-C<sub>4</sub>-Alkylamino, C<sub>1</sub>-C<sub>4</sub>-Dialkyl-  
 amino, Dioxomethylen oder Dioxoethylen;

15 ein fünf- oder sechsgliedriger Heteroaromat, enthaltend  
 ein bis drei Stickstoffatome und/oder ein Schwefel- oder  
 Sauerstoffatom, welcher ein bis vier Halogenatome und/  
 oder einen bis zwei der folgenden Reste tragen kann:  
 C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy,  
 20 C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylthio, Phenyl, Phenoxy oder  
 Phenylcarbonyl, wobei die Phenylreste ihrerseits ein bis  
 fünf Halogenatome und/oder einen bis drei der folgenden  
 Reste tragen können: C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl,  
 C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy und/oder C<sub>1</sub>-C<sub>4</sub>-Alkyl-  
 25 thio;

Z Schwefel oder Sauerstoff.

2. Carbonsäurederivate nach Anspruch 1, dadurch gekennzeichnet,  
 30 daß R=COOH bedeutet.
3. Carbonsäurederivate nach einem der oben stehenden Ansprüche,  
 dadurch gekennzeichnet, daß mindestens einer der Reste R<sup>4</sup> und  
 R<sup>5</sup> Phenyl bedeutet.  
 35
4. Carbonsäurederivate nach Anspruch 3, dadurch gekennzeichnet,  
 daß R<sup>4</sup> und R<sup>5</sup> beide Phenyl bedeuten.
5. Carbonsäurederivate nach Anspruch 3, dadurch gekennzeichnet,  
 40 daß R<sup>6</sup> = C<sub>1</sub>-C<sub>8</sub>-Alkyl, gegebenenfalls substituiert durch OH  
 oder C<sub>1</sub>-C<sub>4</sub>-Alkoxy und Z=O bedeuten.
6. Carbonsäurederivate nach einem der obenstehenden Ansprüche,  
 dadurch gekennzeichnet, daß X=CH bedeutet.  
 45



## 37

7. Carbonsäurederivate nach einem der obenstehenden Ansprüche, dadurch gekennzeichnet, daß mindestens einer der Reste X, Y Stickstoff (N) bedeutet.
- 5 8. Carbonsäurederivate nach einem der obenstehenden Ansprüche, dadurch gekennzeichnet, daß mindestens einer der Reste R<sup>2</sup>, R<sup>3</sup> C<sub>1</sub>-C<sub>4</sub>-Alkyl bedeutet.
9. Verwendung von Verbindungen gemäß Anspruch 1-8 zur Herstellung von Medikamenten zur Behandlung von Hypertonie, pulmonalem Hochdruck, akutem und chronischem Nierenversagen, chronischer Herzinsuffizienz, zerebraler Ischämie, Restenose nach Angioplastie, Prostatakrebs.
- 10 10. Verwendung einer Kombination einer Verbindung gemäß Anspruch 1-8 mit einem Inhibitor des Renin-Angiotensin-Systems (RAS).
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## Novel carboxylic acid derivatives, their preparation and use

The present invention relates to novel carboxylic acid  
 5 derivatives, to their preparation and to their use.

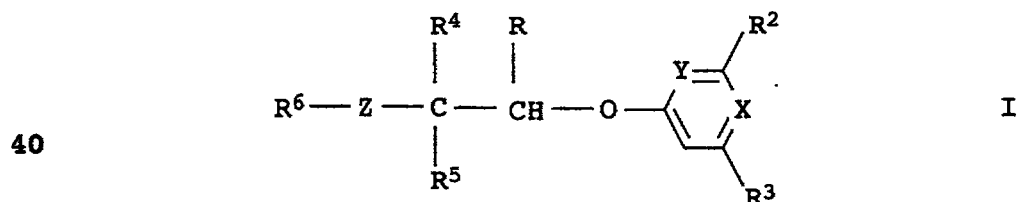
Endothelin is a peptide which is composed of 21 amino acids and is synthesized and released by the vascular endothelium. Endothelin exists in three isoforms, ET-1, ET-2 and ET-3. In the  
 10 following text, "Endothelin" or "ET" signifies one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a potent effect on vessel tone. It is known that this vasoconstriction is caused by binding of endothelin to its receptor (Nature, 332, 1988, 411-415; FEBS Letters, 231, 1988,  
 15 440-444 und Biochem. Biophys. Res. Commun., 154, 1988, 868-875).

Increased or abnormal release of endothelin causes persistent vasoconstriction in the peripheral, renal and cerebral blood vessels, which may lead to illnesses. It has been reported in the  
 20 literature that elevated plasma levels of endothelin were found in patients with hypertension, acute myocardial infarct, pulmonary hypertension, Raynaud's syndrome, atherosclerosis and in the airways of asthmatics (Japan J. Hypertension, 12, (1989), 79, J. Vascular Med. Biology 2, (1990) 207, J. Am. Med. Associa-  
 25 tion 264, (1990) 2868).

Accordingly, substances which specifically inhibit the binding of endothelin to the receptor ought also to antagonize the various  
 30 abovementioned physiological effects of endothelin and therefore be valuable drugs.

We have found that certain carboxylic acid derivatives are good inhibitors of endothelin receptors.

35 The invention relates to carboxylic derivatives of the formula I



where R is tetrazole [sic], nitrile [sic], a group COOH or a radical which can be hydrolyzed to COOH, and the other  
 45 substituents have the following meanings:

R<sup>2</sup> hydrogen, hydroxyl, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>4</sub>-alkyl), N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>,

## 2

halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy or C<sub>1</sub>-C<sub>4</sub>-alkylthio, or CR<sup>2</sup> is linked to CR<sup>12</sup> as indicated below to form a 5- or 6-membered ring;

- 5 X nitrogen or CR<sup>12</sup> where R<sup>12</sup> is hydrogen or C<sub>1-5</sub>-alkyl, or CR<sup>12</sup> forms together with CR<sup>2</sup> or CR<sup>3</sup> a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two C<sub>1-4</sub>-alkyl groups and in which in each case one methylene group can be replaced by oxygen, sulfur, -NH or -NC<sub>1-4</sub>-alkyl;
- 10 Y nitrogen or methine;
- R<sup>3</sup> hydrogen, hydroxyl, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>4</sub>-alkyl), N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy,
- 15 C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, -NH-O-C<sub>1-4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylthio; or CR<sup>3</sup> is linked to CR<sup>12</sup> as indicated above to form a 5- or 6-membered ring;
- R<sup>4</sup> and R<sup>5</sup> (which can be identical or different):
- 20 phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, amino,
- 25 C<sub>1</sub>-C<sub>4</sub>-alkylamino or C<sub>1</sub>-C<sub>4</sub>-dialkylamino; or
- phenyl or naphthyl, which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO<sub>2</sub>-, NH- or
- 30 N-alkyl group, or C<sub>3</sub>-C<sub>7</sub>-cycloalkyl;
- R<sup>6</sup> hydrogen, C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-alkenyl, C<sub>3</sub>-C<sub>6</sub>-alkynyl or C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, it being possible for each of these radicals to be substituted one or more times by: halogen, hydroxyl,
- 35 mercapto, carboxyl, nitro, cyano, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>6</sub>-alkenyloxy, C<sub>3</sub>-C<sub>6</sub>-alkynyloxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, C<sub>3-8</sub>-alkylcarbonylalkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino, di-C<sub>1</sub>-C<sub>4</sub>-alkylamino, phenyl or phenoxy or phenyl, substituted
- 40 one or more times, e.g. once to three times, by halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy or C<sub>1</sub>-C<sub>4</sub>-alkylthio;
- phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano,
- 45 hydroxyl, amino, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, C<sub>1</sub>-C<sub>4</sub>-alkylamino,

## 3

C<sub>1</sub>-C<sub>4</sub>-dialkylamino, dioxomethylene [sic] or dioxoethylene [sic];

- 5 a five- or six-membered heteroaromatic system which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the following radicals: C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy and/or C<sub>1</sub>-C<sub>4</sub>-alkylthio;
- 10
- 15 Z sulfur or oxygen.

The compounds, and the intermediates for preparing them, such as II and IV, may have one or more asymmetrically substituted carbon atoms. Such compounds may be in the form of the pure enantiomers or pure diastereomers or a mixture thereof. The use of an enantiomerically pure compound as active substance is preferred.

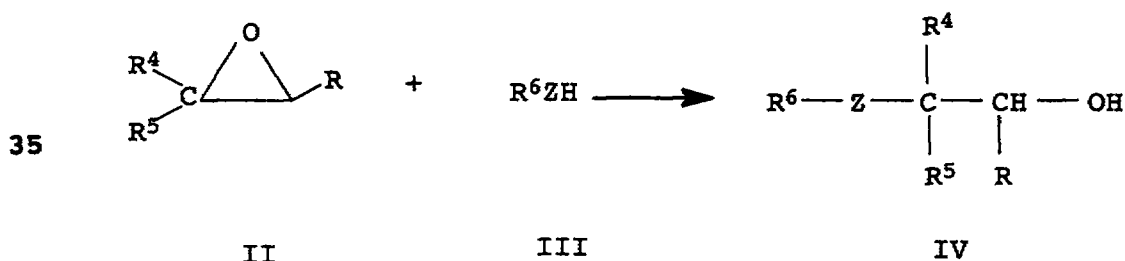
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The invention furthermore relates to the use of the abovementioned carboxylic acid derivatives for producing drugs, in particular for producing endothelin receptor inhibitors.

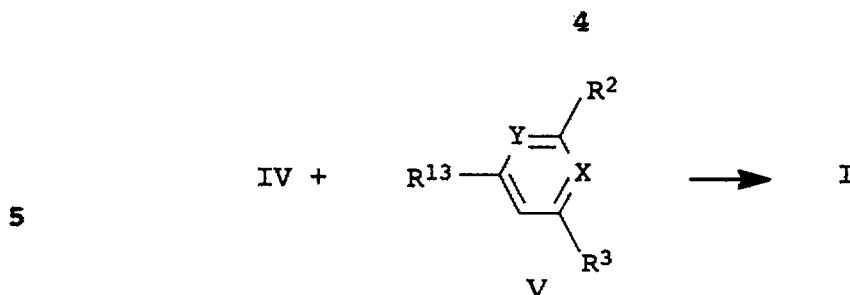
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Compounds of the general formula IV where Z is sulfur or oxygen can be prepared, also in enantiomerically pure form, as described in P 44 36 851.8.

30



- 40 Compounds according to the invention in which the substituents have the meanings stated under the general formula I can be prepared, for example, by reacting the carboxylic acid derivatives of the general formula IV in which the substituents have the stated meanings with compounds of the general formula V,
- 45



where  $\text{R}^{13}$  is halogen or  $\text{R}^{14}\text{-SO}_2\text{-}$ , where  $\text{R}^{14}$  can be  $\text{C}_1\text{-C}_4\text{-alkyl}$ ,  $\text{C}_1\text{-C}_4\text{-haloalkyl}$  or phenyl. The reaction preferably takes place in  
 10 an inert solvent or diluent with the addition of a suitable base, i.e. a base which deprotonates the intermediate IV, at a temperature in the range from room temperature to the boiling point of the solvent.

15 Examples of such solvents or diluents are aliphatic, alicyclic and aromatic hydrocarbons, each of which may be chlorinated, such as hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride, chloroform, carbon tetrachloride, ethyl chloride and trichloroethylene, ethers such  
 20 as diisopropyl ether, dibutyl ether, methyl tert-butyl ether, propylene oxide, dioxane and tetrahydrofuran, nitriles, such as acetonitrile and propionitrile, acid amides such as dimethylformamide, dimethylacetamide and N-methylpyrrolidone, sulfoxides and sulfones, such as dimethyl sulfoxide and  
 25 sulfolane.

Compounds of the formula V are known, and some of them can be bought, or they can be prepared in a conventional manner.

30 The base which can be used is an alkali metal or alkaline earth metal hydride such as sodium hydride, potassium hydride or calcium hydride, a carbonate such as an alkali metal carbonate, e.g. sodium or potassium carbonate, an alkali metal or alkaline earth metal hydroxide such as sodium or potassium hydroxide, an  
 35 organometallic compound such as butyllithium, or an alkali metal amide such as lithium diisopropylamide.

Compounds of the formula I can also be prepared by starting from the corresponding carboxylic acids, i.e. compounds of the formula  
 40 I where R is  $\text{COOH}$ , and first converting the latter in a conventional way into an activated form, such as an acid halide, an anhydride or imidazolidine, and then reacting the latter with an appropriate hydroxyl compound  $\text{HOR}^8$ . This reaction can be carried out in conventional solvents and often requires the addition of a  
 45 base, in which case the abovementioned are suitable. These two steps can also be simplified, for example, by allowing the

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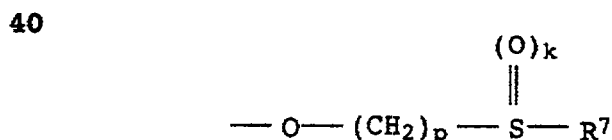
carboxylic acid to act on the hydroxyl compound in the presence of a dehydrating agent such as a carbodiimide.

- Moreover, compounds of the formula I can also be prepared by
- 5 starting from salts of the corresponding carboxylic acids, i.e. from compounds of the formula I where R is a group  $\text{COR}^1$  and  $\text{R}^1$  is OM, where M can be an alkali metal cation or the equivalent of an alkaline earth metal cation. These salts can be reacted with many compounds of the formula  $\text{R}^1\text{-A}$  where A is a conventional
- 10 nucleofugic leaving group, for example halogen such as chlorine, bromine, iodine or unsubstituted or halogen-, alkyl- or haloalkyl-substituted aryl- or alkylsulfonyl, such as toluenesulfonyl and methylsulfonyl, or another equivalent leaving group. Compounds of the formula  $\text{R}^1\text{-A}$  with a reactive substituent A
- 15 are known or can easily be obtained with general expert knowledge. This reaction can be carried out in conventional solvents and advantageously takes place with the addition of a base, in which case the abovementioned are suitable.
- 20 The radical R in formula I can be varied widely. R is, for example, a group



where  $\text{R}^1$  has the following meanings:

- a) hydrogen;
- 30 b) a succinylimidoxy [sic] group;
- c) a 5-membered heteroaromatic system linked via a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl,
- 35 which may then carry one or two halogen atoms or one or two  $\text{C}_1\text{-C}_4\text{-alkyl}$  or one or two  $\text{C}_1\text{-C}_4\text{-alkoxy}$  groups.
- d)  $\text{R}^1$  is furthermore a group



- where k can assume the values 0, 1 and 2, p can assume the
- 45 values 1, 2, 3 and 4, and  $\text{R}^7$  is

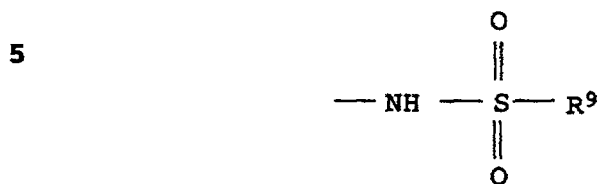
- C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>6</sub>-alkenyl, C<sub>3</sub>-C<sub>6</sub>-alkynyl or unsubstituted or substituted phenyl which can be substituted by one or more, e.g. one to three, of the following radicals: halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, hydroxyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, mercapto, amino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-dialkylamino;

e) R<sup>1</sup> is furthermore a radical OR<sup>8</sup> where R<sup>8</sup> is:

- hydrogen, the cation of an alkali metal such as lithium, sodium, potassium, or the cation of an alkaline earth metal such as calcium, magnesium and barium or a physiologically tolerated organic ammonium ion such as tertiary C<sub>1</sub>-C<sub>4</sub>-alkylammonium or the ammonium ion;
- C<sub>3</sub>-C<sub>8</sub>-cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and [sic] cycloheptyl, cyclooctyl,
- C<sub>1</sub>-C<sub>8</sub>-alkyl, in particular C<sub>1</sub>-C<sub>4</sub>-alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl;
- CH<sub>2</sub>-phenyl, which may be substituted by one or more of the following radicals: halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, hydroxyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, mercapto, C<sub>1</sub>-C<sub>4</sub>-alkylthio, amino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-dialkylamino, a C<sub>3</sub>-C<sub>6</sub>-alkenyl or C<sub>3</sub>-C<sub>6</sub>-alkynyl group, it being possible for this group in turn to carry one to five halogen atoms;
- R<sup>8</sup> can furthermore be a phenyl radical which can carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, hydroxyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, mercapto, C<sub>1</sub>-C<sub>4</sub>-alkylthio, amino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-dialkylamino;
- a 5-membered heteroaromatic system which is linked via a nitrogen atom and contains one to three nitrogen atoms and which can carry one or two halogen atoms and/or one or two of the following radicals: C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, phenyl, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy and/or C<sub>1</sub>-C<sub>4</sub>-alkylthio. Particular mention may be made of 1-pyrazolyl,
- 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl,

1-benzotriazolyl, 3,4-dichloro-1-imidazolyl;

f)  $R^1$  is furthermore a radical



10 where  $R^9$  is:

$C_1$ - $C_4$ -alkyl,  $C_3$ - $C_6$ -alkenyl,  $C_3$ - $C_6$ -alkynyl,  $C_3$ - $C_8$ -cycloalkyl as mentioned above in particular, it being possible for these radicals to carry a  $C_1$ - $C_4$ -alkoxy,  $C_1$ - $C_4$ -alkylthio and/or a

15 phenyl radical as mentioned above;

phenyl, unsubstituted or substituted, in particular as mentioned above;

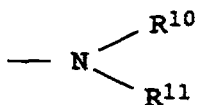
20 g)  $R^1$  is a radical



where  $R^9$  has the abovementioned meaning;

h)  $R^1$  can furthermore be

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where  $R^{10}$  and  $R^{11}$  can be identical or different and have the following meanings:

40 hydrogen,  $C_1$ - $C_7$ -alkyl,  $C_3$ - $C_7$ -cycloalkyl [sic],  $C_3$ - $C_7$ -alkenyl,  $C_3$ - $C_7$ -alkynyl, benzyl, phenyl, unsubstituted or substituted, as described above,

or  $R^{10}$  and  $R^{11}$  together form a  $C_4$ - $C_7$ -alkylene chain which is closed to form a ring, is unsubstituted or substituted, e.g. substituted by  $C_1$ - $C_4$ -alkyl, and may contain a heteroatom, e.g.

45 oxygen, sulfur or nitrogen, such as  $-(CH_2)_4-$ ,  $-(CH_2)_5-$ ,

$-(\text{CH}_2)_6-$ ,  $-(\text{CH}_2)_7-$ ,  $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ ,  $-\text{CH}_2-\text{S}-(\text{CH}_2)_2-$ ,  
 $-\text{CH}_2-\text{NH}-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_2-\text{N}-(\text{CH}_2)_2-$ .

With a view to the biological effect, preferred carboxylic acid  
 5 derivatives of the general formula I, both as pure enantiomers  
 and pure diastereomers or as mixtures thereof, are those where  
 the substituents have the following meanings:

10  $\text{R}^2$  hydrogen, hydroxyl,  $\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$ , the  $\text{C}_1\text{-C}_4\text{-alkyl}$ ,  
 $\text{C}_1\text{-C}_4\text{-haloalkyl}$ ,  $\text{C}_1\text{-C}_4\text{-alkoxy}$ ,  $\text{C}_1\text{-C}_4\text{-haloalkoxy}$ ,  
 $\text{C}_1\text{-C}_4\text{-alkylthio}$  groups and halogen atoms specifically  
 mentioned for  $\text{R}^1$ , in particular chlorine, methyl, methoxy,  
 ethoxy, difluoromethoxy and trifluoromethoxy, or  $\text{CR}^2$  is  
 15 linked to  $\text{CR}^{12}$  as indicated below to form a 5- or 6-membered  
 ring;

X nitrogen or or  $\text{CR}^{12}$ , where

20  $\text{R}^{12}$  is hydrogen or alkyl, or  $\text{CR}^{12}$  forms together with  $\text{CR}^2$  or  $\text{CR}^3$  a  
 5- to 6-membered alkylene or alkenylene ring in which, in  
 each case, a methylene group can be replaced by oxygen or  
 sulfur, such as

25  $-\text{CH}_2-\text{CH}_2-\text{O}-$ ,  $-\text{CH}=\text{CH}-\text{O}-$ ,  $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-$ ,  $-\text{CH}=\text{CH}-\text{CH}_2\text{O}-$ , in  
 particular hydrogen,  $-\text{CH}_2-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{CH}(\text{CH}_3)-\text{O}-$ ,  
 $-\text{C}(\text{CH}_3)=\text{C}(\text{CH}_3)-\text{O}-$ ,  $-\text{CH}=\text{C}(\text{CH}_3)-\text{O}-$  or  $-\text{C}(\text{CH}_3)=\text{C}(\text{CH}_3)-\text{S}$ ;

Y nitrogen or methine;

30  $\text{R}^3$  hydrogen, hydroxyl,  $\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$ ,  $\text{C}_1\text{-C}_4\text{-alkyl}$ ,  
 $\text{C}_1\text{-C}_4\text{-haloalkyl}$ ,  $\text{C}_1\text{-C}_4\text{-alkoxy}$ ,  $\text{C}_1\text{-C}_4\text{-haloalkoxy}$ ,  
 $\text{C}_1\text{-C}_4\text{-alkylthio}$  groups and halogen atoms, in particular  
 chlorine, methyl, methoxy, ethoxy, difluoromethoxy and  
 trifluoromethoxy, or  $\text{C}-\text{R}^3$  is linked to  $\text{C}-\text{R}^{12}$  as mentioned  
 35 above to form a 5- or 6-membered ring;

40  $\text{R}^4$  and  $\text{R}^5$ , which may be identical or different, phenyl or  
 naphthyl, each of which may be substituted by one or more,  
 e.g. one to three, of the following radicals: halogen, nitro,  
 cyano, hydroxyl, mercapto, amino,  $\text{C}_1\text{-C}_4\text{-alkyl}$ ,  
 $\text{C}_1\text{-C}_4\text{-haloalkyl}$ ,  $\text{C}_1\text{-C}_4\text{-alkoxy}$ ,  $\text{C}_1\text{-C}_4\text{-haloalkoxy}$ ,  
 $\text{C}_1\text{-C}_4\text{-alkylthio}$ ,  $\text{C}_1\text{-C}_4\text{-alkylamino}$ , di- $\text{C}_1\text{-C}_4\text{-alkylamino}$ ,  
 $\text{C}_1\text{-C}_4\text{-alkylcarbonyl}$ ,  $\text{C}_1\text{-C}_4\text{-alkoxycarbonyl}$ ;

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phenyl or naphthyl, which may be connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO<sub>2</sub>, NH or N-alkyl group, or C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

5

R<sup>6</sup> C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-alkenyl, C<sub>3</sub>-C<sub>6</sub>-alkynyl or C<sub>3</sub>-C<sub>8</sub>-cycloalkyl as mentioned above in particular, it being possible for each of these radicals to be substituted one or more times by: halogen, hydroxyl, mercapto, carboxyl, nitro, cyano,

10

C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>6</sub>-alkenyloxy, C<sub>3</sub>-C<sub>6</sub>-alkynyloxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl, hydroxycarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino, di-C<sub>1</sub>-C<sub>4</sub>-alkylamino or unsubstituted or substituted phenyl or phenoxy, as mentioned above in particular;

15

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy,

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C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, C<sub>1</sub>-C<sub>4</sub>-alkylamino or C<sub>1</sub>-C<sub>4</sub>-dialkylamino;

a five- or six-membered heteroaromatic system which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the following radicals: C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy and/or C<sub>1</sub>-C<sub>4</sub>-alkylthio, as mentioned for R<sup>4</sup> in particular;

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Z sulfur or oxygen.

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Particularly preferred compounds of the formula I, both as pure enantiomers and pure diastereomers or as mixture thereof, are those in which the substituents have the following meanings:

40 R<sup>2</sup> C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, trifluoromethyl or is linked to R<sup>12</sup> as mentioned below to form a 5- or 6-membered ring;

X nitrogen or CR<sup>12</sup>, where

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## 10

- $R^{12}$  is hydrogen or alkyl, or  $CR^{12}$  forms together with  $CR^2$  or  $CR^3$  a 4- to 5-membered alkylene or alkenylene ring, e.g.  $-CH_2-CH_2-CH_2-$  or  $-CH=CH-CH_2-$ , in which, in each case, one methylene group can be replaced by oxygen or sulfur, such as  
 5  $-CH_2-CH_2-O-$ ,  $-CH=CH-O-$ ,  
 $-CH_2-CH_2-CH_2-O-$ ,  $-CH=CH-CH_2O-$ , in particular hydrogen,  $-CH_2-CH_2-O-$ ,  $-CH(CH_3)-CH(CH_3)-O-$ ,  $-C(CH_3)=C(CH_3)-O-$ ,  $-CH=C(CH_3)-O-$  or  $-C(CH_3)=C(CH_3)-S$ ;  
 10  
 $Y$  nitrogen or methine;  
 $R^3$  the  $C_1-C_4$ -alkyl,  $C_1-C_4$ -alkoxy,  $C_1-C_4$ -alkylthio groups mentioned for  $R^1$  or  $C-R^3$  is linked to  $C-R^{12}$  as mentioned above  
 15 to form a 5- or 6-membered ring;  
 $R^4$  and  $R^5$  phenyl (identical or different), which may be substituted by one or more, e.g. one to three, of the following radicals: halogen, nitro, hydroxyl,  $C_1-C_4$ -alkyl,  
 20  $C_1-C_4$ -alkoxy,  $C_1-C_4$ -alkylthio or  
 $R^4$  and  $R^5$  are phenyl groups which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an  $SO_2$ ,  $NH$  or  
 25  $N$ -alkyl group; or  
 $R^4$  and  $R^5$  are  $C_3-C_7$ -cycloalkyl;  
 $R^6$   $C_1-C_8$ -alkyl,  $C_3-C_6$ -alkenyl or  $C_3-C_8$ -cycloalkyl, it being  
 30 possible for each of these radicals to be substituted one or more times by: halogen, mercapto, caboxyl [sic], hydroxyl, nitro, cyano,  
 $C_1-C_4$ -alkoxy,  $C_3-C_6$ -alkenyloxy,  $C_1-C_4$ -alkylthio;  
 35 phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino,  $C_1-C_4$ -alkyl,  $C_1-C_4$ -haloalkyl,  $C_1-C_4$ -alkoxy,  $C_1-C_4$ -haloalkoxy, phenoxy,  $C_1-C_4$ -alkylthio,  $C_1-C_4$ -akylamino  
 40 [sic] or  $C_1-C_4$ -dialkylamino;  
 a five- or six-membered heteroaromatic system which contains a nitrogen atom and/or a sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the  
 45 following radicals:  $C_1-C_4$ -alkyl,  $C_1-C_4$ -haloalkyl,  $C_1-C_4$ -alkoxy,  $C_1-C_4$ -alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five

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halogen atoms and/or one to three of the following radicals:  
C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy and/or  
C<sub>1</sub>-C<sub>4</sub>-alkylthio;

5 Z sulfur or oxygen.

Examples of preferred compounds are listed in the following  
table.

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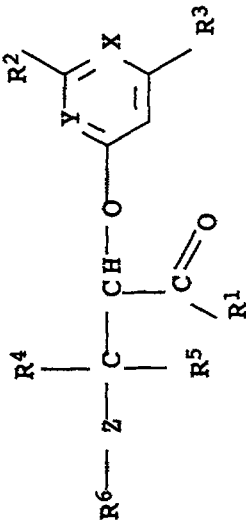
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Table I [sic]



| No.  | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup> | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|------|----------------|---------------------------------|----------------|----------------|-----------------|---|---|---|
| I-1  | OH             | phenyl                          | methyl         | OMe            | OMe             | N | N | O |
| I-2  | OH             | phenyl                          | methyl         | OMe            | Me              | N | N | O |
| I-3  | OH             | phenyl                          | methyl         | Me             | OMe             | N | N | O |
| I-4  | OH             | phenyl                          | methyl         | ethyl          | Me              | N | N | O |
| I-5  | OH             | phenyl                          | methyl         | Me             | ethyl           | N | N | O |
| I-6  | OH             | phenyl                          | methyl         | Me             | Me              | N | N | O |
| I-7  | OH             | phenyl                          | methyl         | OMe            | SMe             | N | N | O |
| I-8  | OH             | phenyl                          | methyl         | OMe            | CF <sub>3</sub> | N | N | O |
| I-9  | OH             | phenyl                          | methyl         | OMe            | OMe             | N | N | S |
| I-10 | OH             | phenyl                          | methyl         | OMe            | Me              | N | N | S |
| I-11 | OH             | phenyl                          | methyl         | Me             | OMe             | N | N | S |
| I-12 | OH             | phenyl                          | methyl         | ethyl          | Me              | N | N | S |

| No.  | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                                      | R <sup>3</sup> | R <sup>2</sup> | X | Y | Z |
|------|----------------|---------------------------------|-----------------------------------------------------|----------------|----------------|---|---|---|
| I-13 | OH             | phenyl                          | ethyl                                               | OMe            | OMe            | N | N | O |
| I-14 | OH             | phenyl                          | ethyl                                               | OMe            | Me             | N | N | O |
| I-15 | OH             | phenyl                          | ethyl                                               | Me             | OMe            | N | N | O |
| I-16 | OH             | phenyl                          | ethyl                                               | ethyl          | Me             | N | N | O |
| I-17 | OH             | phenyl                          | ethyl                                               | Me             | ethyl          | N | N | O |
| I-18 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | OMe            | OMe            | N | N | O |
| I-19 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | OMe            | Me             | N | N | O |
| I-20 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | Me             | OMe            | N | N | O |
| I-21 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | ethyl          | Me             | N | N | O |
| I-22 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | Me             | ethyl          | N | N | O |
| I-23 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | Me             | Me             | N | N | O |
| I-24 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -               | OMe            | SMe            | N | N | O |
| I-25 | OH             | phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | OMe            | OMe            | N | N | O |
| I-26 | OH             | phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | OMe            | Me             | N | N | O |
| I-27 | OH             | phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | Me             | OMe            | N | N | O |
| I-28 | OH             | phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | ethyl          | Me             | N | N | O |
| I-29 | OH             | phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | Me             | ethyl          | N | N | O |
| I-30 | OH             | phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | Me             | Me             | N | N | O |
| I-31 | OH             | phenyl                          | HO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>2</sub> - | OMe            | SMe            | N | N | O |
| I-32 | OH             | phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | OMe            | OMe            | N | N | O |
| I-33 | OH             | phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | OMe            | Me             | N | N | O |
| I-34 | OH             | phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | Me             | OMe            | N | N | O |
| I-35 | OH             | phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | ethyl          | Me             | N | N | O |
| I-36 | OH             | phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | Me             | ethyl          | N | N | O |
| I-37 | OH             | phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -                 | Me             | Me             | N | N | O |

| No.  | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                                | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|------|----------------|---------------------------------|-----------------------------------------------|----------------|-----------------|---|---|---|
| 1-38 | OH             | phenyl                          | HO <sub>2</sub> C-CH <sub>2</sub> -           | OMe            | SMe             | N | N | O |
| 1-39 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | OMe             | N | N | O |
| 1-40 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | Me              | N | N | O |
| 1-41 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | OMe             | N | N | O |
| 1-42 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | ethyl          | Me              | N | N | O |
| 1-43 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | ethyl           | N | N | O |
| 1-44 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | Me              | N | N | O |
| 1-45 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | SMe             | N | N | O |
| 1-46 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | CF <sub>3</sub> | N | N | O |
| 1-47 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | OMe             | N | N | S |
| 1-48 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | Me              | N | N | S |
| 1-49 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | OMe             | N | N | S |
| 1-50 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | ethyl          | Me              | N | N | S |
| 1-51 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | OMe            | OMe             | N | N | S |
| 1-52 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | OMe            | Me              | N | N | S |
| 1-53 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Me             | OMe             | N | N | S |
| 1-54 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | ethyl          | Me              | N | N | S |
| 1-55 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | OMe            | OMe             | N | N | O |
| 1-56 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | OMe            | Me              | N | N | O |
| 1-57 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | Me             | OMe             | N | N | O |
| 1-58 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | ethyl          | Me              | N | N | O |
| 1-59 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | Me             | ethyl           | N | N | O |
| 1-60 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | Me             | Me              | N | N | O |
| 1-61 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | OMe            | SMe             | N | N | O |
| 1-62 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> -          | OMe            | CF <sub>3</sub> | N | N | O |

| No.  | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                       | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|------|----------------|---------------------------------|--------------------------------------|----------------|-----------------|---|---|---|
| I-63 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> - | OMe            | OMe             | N | N | S |
| I-64 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> - | OMe            | Me              | N | N | S |
| I-65 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> - | Me             | OMe             | N | N | S |
| I-66 | OH             | phenyl                          | HO-(CH <sub>2</sub> ) <sub>3</sub> - | ethyl          | Me              | N | N | S |
| I-67 | OH             | phenyl                          | n-propyl                             | OMe            | OMe             | N | N | O |
| I-68 | OH             | phenyl                          | n-propyl                             | OMe            | Me              | N | N | O |
| I-69 | OH             | phenyl                          | n-propyl                             | Me             | OMe             | N | N | O |
| I-70 | OH             | phenyl                          | n-propyl                             | ethyl          | Me              | N | N | O |
| I-71 | OH             | phenyl                          | n-propyl                             | Me             | ethyl           | N | N | O |
| I-72 | OH             | phenyl                          | n-propyl                             | Me             | Me              | N | N | O |
| I-73 | OH             | phenyl                          | n-propyl                             | OMe            | SMe             | N | N | O |
| I-74 | OH             | phenyl                          | n-propyl                             | OMe            | CF <sub>3</sub> | N | N | O |
| I-75 | OH             | phenyl                          | n-propyl                             | OMe            | OMe             | N | N | S |
| I-76 | OH             | phenyl                          | n-propyl                             | OMe            | Me              | N | N | S |
| I-77 | OH             | phenyl                          | n-propyl                             | Me             | OMe             | N | N | S |
| I-78 | OH             | phenyl                          | n-propyl                             | ethyl          | Me              | N | N | S |
| I-79 | OH             | phenyl                          | iso-propyl                           | OMe            | OMe             | N | N | O |
| I-80 | OH             | phenyl                          | iso-propyl                           | OMe            | Me              | N | N | O |
| I-81 | OH             | phenyl                          | iso-propyl                           | Me             | OMe             | N | N | O |
| I-82 | OH             | phenyl                          | iso-propyl                           | ethyl          | Me              | N | N | O |
| I-83 | OH             | phenyl                          | iso-propyl                           | Me             | ethyl           | N | N | O |
| I-84 | OH             | phenyl                          | iso-propyl                           | Me             | Me              | N | N | O |
| I-85 | OH             | phenyl                          | iso-propyl                           | OMe            | SMe             | N | N | O |
| I-86 | OH             | phenyl                          | iso-propyl                           | OMe            | CF <sub>3</sub> | N | N | O |
| I-87 | OH             | phenyl                          | iso-propyl                           | OMe            | OMe             | N | N | S |

| No.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup> | R <sup>3</sup>  | R <sup>2</sup>  | X | Y | Z |
|-------|----------------|---------------------------------|----------------|-----------------|-----------------|---|---|---|
| I-88  | OH             | phenyl                          | iso-propyl     | OMe             | Me              | N | N | S |
| I-89  | OH             | phenyl                          | iso-propyl     | Me              | OMe             | N | N | S |
| I-90  | OH             | phenyl                          | iso-propyl     | ethyl           | Me              | N | N | S |
| I-91  | OH             | phenyl                          | methyl         | CF <sub>3</sub> | tert-Butyl      | N | N | O |
| I-92  | OH             | phenyl                          | methyl         | CF <sub>3</sub> | OMe             | N | N | O |
| I-93  | OH             | phenyl                          | methyl         | OMe             | OMe             | N | N | O |
| I-94  | OH             | phenyl                          | methyl         | CF <sub>3</sub> | Me              | N | N | O |
| I-95  | OH             | phenyl                          | methyl         | Me              | CF <sub>3</sub> | N | N | O |
| I-96  | OH             | phenyl                          | benzyl         | OMe             | Me              | N | N | O |
| I-97  | OH             | phenyl                          | benzyl         | Me              | OMe             | N | N | O |
| I-98  | OH             | phenyl                          | benzyl         | ethyl           | Me              | N | N | O |
| I-99  | OH             | phenyl                          | benzyl         | Me              | ethyl           | N | N | O |
| I-100 | OH             | phenyl                          | benzyl         | Me              | Me              | N | N | O |
| I-101 | OH             | phenyl                          | benzyl         | OMe             | OMe             | N | N | O |
| I-102 | OH             | phenyl                          | phenyl         | OMe             | Me              | N | N | O |
| I-103 | OH             | phenyl                          | phenyl         | Me              | OMe             | N | N | O |
| I-104 | OH             | phenyl                          | phenyl         | ethyl           | Me              | N | N | O |
| I-105 | OH             | phenyl                          | phenyl         | Me              | ethyl           | N | N | O |
| I-106 | OH             | phenyl                          | phenyl         | Me              | Me              | N | N | O |
| I-107 | OH             | phenyl                          | phenyl         | OMe             | OMe             | N | N | O |
| I-108 | OH             | phenyl                          | 4-OMe-benzyl   | OMe             | Me              | N | N | O |
| I-109 | OH             | phenyl                          | 4-OMe-benzyl   | Me              | OMe             | N | N | O |
| I-110 | OH             | phenyl                          | 4-OMe-benzyl   | ethyl           | Me              | N | N | O |
| I-111 | OH             | phenyl                          | 4-OMe-benzyl   | Me              | ethyl           | N | N | O |
| I-112 | OH             | phenyl                          | 4-OMe-benzyl   | Me              | Me              | N | N | O |

| No.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                        | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|-------|----------------|---------------------------------|---------------------------------------|----------------|-----------------|---|---|---|
| I-113 | OH             | phenyl                          | 4-OMe-benzyl                          | OMe            | OMe             | N | N | O |
| I-114 | OH             | phenyl                          | 4-Cl-benzyl                           | OMe            | Me              | N | N | O |
| I-115 | OH             | phenyl                          | 4-Cl-benzyl                           | Me             | OMe             | N | N | O |
| I-116 | OH             | phenyl                          | 4-Cl-benzyl                           | ethyl          | Me              | N | N | O |
| I-117 | OH             | phenyl                          | 4-Cl-benzyl                           | Me             | ethyl           | N | N | O |
| I-118 | OH             | phenyl                          | 4-Cl-benzyl                           | Me             | Me              | N | N | O |
| I-119 | OH             | phenyl                          | 4-Cl-benzyl                           | OMe            | OMe             | N | N | O |
| I-120 | OH             | cyclohexyl                      | methyl                                | OMe            | OMe             | N | N | O |
| I-121 | OH             | cyclohexyl                      | methyl                                | OMe            | Me              | N | N | O |
| I-122 | OH             | cyclohexyl                      | methyl                                | Me             | OMe             | N | N | O |
| I-123 | OH             | cyclohexyl                      | methyl                                | ethyl          | Me              | N | N | O |
| I-124 | OH             | cyclohexyl                      | methyl                                | Me             | ethyl           | N | N | O |
| I-125 | OH             | cyclohexyl                      | methyl                                | Me             | CF <sub>3</sub> | N | N | O |
| I-126 | OH             | cyclohexyl                      | ethyl                                 | OMe            | Me              | N | N | O |
| I-127 | OH             | cyclohexyl                      | ethyl                                 | Me             | OMe             | N | N | O |
| I-128 | OH             | cyclohexyl                      | ethyl                                 | ethyl          | Me              | N | N | O |
| I-129 | OH             | cyclohexyl                      | ethyl                                 | OMe            | ethyl           | N | N | O |
| I-130 | OH             | cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me              | N | N | O |
| I-131 | OH             | cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | OMe             | N | N | O |
| I-132 | OH             | cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | ethyl          | Me              | N | N | O |
| I-133 | OH             | cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | ethyl           | N | N | O |
| I-134 | OH             | cyclohexyl                      | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Me              | N | N | O |
| I-135 | OH             | 4-fluorophenyl                  | methyl                                | OMe            | OMe             | N | N | O |
| I-136 | OH             | 4-fluorophenyl                  | methyl                                | OMe            | Me              | N | N | O |
| I-137 | OH             | 4-fluorophenyl                  | methyl                                | Me             | OMe             | N | N | O |

| No.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                        | R <sup>3</sup> | R <sup>2</sup>  | X | Y | Z |
|-------|----------------|---------------------------------|---------------------------------------|----------------|-----------------|---|---|---|
| I-138 | OH             | 4-fluorophenyl                  | methyl                                | ethyl          | Me              | N | N | O |
| I-139 | OH             | 4-fluorophenyl                  | methyl                                | Me             | ethyl           | N | N | O |
| I-140 | OH             | 4-fluorophenyl                  | methyl                                | Me             | CF <sub>3</sub> | N | N | O |
| I-141 | OH             | 4-fluorophenyl                  | ethyl                                 | OMe            | Me              | N | N | O |
| I-142 | OH             | 4-fluorophenyl                  | ethyl                                 | Me             | OMe             | N | N | O |
| I-143 | OH             | 4-fluorophenyl                  | ethyl                                 | Me             | Et              | N | N | O |
| I-144 | OH             | 4-fluorophenyl                  | ethyl                                 | OMe            | ethyl           | N | N | O |
| I-145 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me              | N | N | O |
| I-146 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | OMe             | N | N | O |
| I-147 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | ethyl          | Me              | N | N | O |
| I-148 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | ethyl           | N | N | O |
| I-149 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Me              | N | N | O |
| I-150 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | OMe             | N | N | O |
| I-151 | OH             | 4-chlorophenyl                  | methyl                                | OMe            | Me              | N | N | O |
| I-152 | OH             | 4-chlorophenyl                  | methyl                                | Me             | OMe             | N | N | O |
| I-153 | OH             | 4-chlorophenyl                  | methyl                                | ethyl          | Me              | N | N | O |
| I-154 | OH             | 4-chlorophenyl                  | methyl                                | Me             | ethyl           | N | N | O |
| I-155 | OH             | 4-chlorophenyl                  | methyl                                | Me             | CF <sub>3</sub> | N | N | O |
| I-156 | OH             | 4-chlorophenyl                  | ethyl                                 | OMe            | Me              | N | N | O |
| I-157 | OH             | 4-chlorophenyl                  | ethyl                                 | Me             | OMe             | N | N | O |
| I-158 | OH             | 4-chlorophenyl                  | ethyl                                 | Me             | Et              | N | N | O |
| I-159 | OH             | 4-chlorophenyl                  | ethyl                                 | OMe            | ethyl           | N | N | O |
| I-160 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me              | N | N | O |
| I-161 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | OMe             | N | N | O |
| I-162 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | ethyl          | Me              | N | N | O |

| No.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                        | R <sup>3</sup>  | R <sup>2</sup>                                       | X  | Y | Z |
|-------|----------------|---------------------------------|---------------------------------------|-----------------|------------------------------------------------------|----|---|---|
| I-163 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | ethyl                                                | N  | N | O |
| I-164 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | Me                                                   | N  | N | O |
| I-165 | OH             | 4-methylphenyl                  | methyl                                | Me              | Me                                                   | N  | N | O |
| I-166 | OH             | phenyl                          | methyl                                | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-167 | OH             | phenyl                          | methyl                                | H               | CH=CH-CH=CH-C                                        |    | N | O |
| I-168 | OH             | phenyl                          | methyl                                | Me              | Me                                                   | CH | N | O |
| I-169 | OH             | phenyl                          | methyl                                | Me              | ethyl                                                | CH | N | O |
| I-170 | OH             | phenyl                          | methyl                                | ethyl           | Me                                                   | CH | N | O |
| I-171 | OH             | phenyl                          | methyl                                | OMe             | Me                                                   | CH | N | O |
| I-172 | OH             | phenyl                          | methyl                                | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-173 | OH             | phenyl                          | methyl                                | ethyl           | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-174 | OH             | phenyl                          | methyl                                | CF <sub>3</sub> | Me                                                   | CH | N | O |
| I-175 | OH             | phenyl                          | methyl                                | CF <sub>3</sub> | ethyl                                                | CH | N | O |
| I-176 | OH             | phenyl                          | ethyl                                 | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-177 | OH             | phenyl                          | ethyl                                 | H               | CH=CH-CH=CH-C                                        |    | N | O |
| I-178 | OH             | phenyl                          | ethyl                                 | Me              | Me                                                   | CH | N | O |
| I-179 | OH             | phenyl                          | ethyl                                 | Me              | ethyl                                                | CH | N | O |
| I-180 | OH             | phenyl                          | ethyl                                 | ethyl           | Me                                                   | CH | N | O |
| I-181 | OH             | phenyl                          | ethyl                                 | OMe             | Me                                                   | CH | N | O |
| I-182 | OH             | phenyl                          | ethyl                                 | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-183 | OH             | phenyl                          | ethyl                                 | ethyl           | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-184 | OH             | phenyl                          | ethyl                                 | CF <sub>3</sub> | Me                                                   | CH | N | O |
| I-185 | OH             | phenyl                          | ethyl                                 | CF <sub>3</sub> | ethyl                                                | CH | N | O |
| I-186 | OH             | phenyl                          | n-propyl                              | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-187 | OH             | phenyl                          | n-propyl                              | H               | CH=CH-CH=CH-C                                        |    | N | O |

| No.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                          | R <sup>3</sup>  | R <sup>2</sup>                                       | X  | Y | Z |
|-------|----------------|---------------------------------|-----------------------------------------|-----------------|------------------------------------------------------|----|---|---|
| I-188 | OH             | phenyl                          | n-propyl                                | Me              | Me                                                   | CH | N | O |
| I-189 | OH             | phenyl                          | n-propyl                                | Me              | ethyl                                                | CH | N | O |
| I-190 | OH             | phenyl                          | n-propyl                                | ethyl           | Me                                                   | CH | N | O |
| I-191 | OH             | phenyl                          | n-propyl                                | OMe             | Me                                                   | CH | N | O |
| I-192 | OH             | phenyl                          | n-propyl                                | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-193 | OH             | phenyl                          | n-propyl                                | ethyl           | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-194 | OH             | phenyl                          | n-propyl                                | CF <sub>3</sub> | Me                                                   | CH | N | O |
| I-195 | OH             | phenyl                          | n-propyl                                | Cl <sub>3</sub> | ethyl                                                | CH | N | O |
| I-196 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-197 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | H               | CH=CH-CH=CH-C                                        |    | N | O |
| I-198 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | Me              | Me                                                   | CH | N | O |
| I-199 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | Me              | ethyl                                                | CH | N | O |
| I-200 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | ethyl           | Me                                                   | CH | N | O |
| I-201 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | OMe             | Me                                                   | CH | N | O |
| I-202 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-203 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | ethyl           | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |
| I-204 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | CF <sub>3</sub> | Me                                                   | CH | N | O |
| I-205 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | CF <sub>3</sub> | ethyl                                                | CH | N | O |
| I-206 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | CH <sub>3</sub> | CH=CH-CH=CH-C                                        |    | N | O |
| I-207 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | H               | CH=CH-CH=CH-C                                        |    | N | O |
| I-208 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | Me                                                   | CH | N | O |
| I-209 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | ethyl                                                | CH | N | O |
| I-210 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | ethyl           | Me                                                   | CH | N | O |
| I-211 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | OMe             | Me                                                   | CH | N | O |
| I-212 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> - | Me              | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C |    | N | O |

| No.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                                | R <sup>3</sup>  | R <sup>2</sup> | X                                                    | Y | Z |
|-------|----------------|---------------------------------|-----------------------------------------------|-----------------|----------------|------------------------------------------------------|---|---|
| I-213 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | ethyl           |                | CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -C | N | O |
| I-214 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | CF <sub>3</sub> | Me             | CH                                                   | N | O |
| I-215 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | CF <sub>3</sub> | ethyl          | CH                                                   | N | O |
| I-216 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me              | Me             | CH                                                   | N | O |
| I-217 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me              | ethyl          | CH                                                   | N | O |
| I-218 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | ethyl           | Me             | CH                                                   | N | O |
| I-219 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe             | Me             | CH                                                   | N | O |
| I-220 | OH             | phenyl                          | iso-propyl                                    | Me              | Me             | CH                                                   | N | O |
| I-221 | OH             | phenyl                          | iso-propyl                                    | Me              | ethyl          | CH                                                   | N | O |
| I-222 | OH             | phenyl                          | iso-propyl                                    | ethyl           | Me             | CH                                                   | N | O |
| I-223 | OH             | phenyl                          | iso-propyl                                    | OMe             | Me             | CH                                                   | N | O |
| I-224 | OH             | phenyl                          | methyl                                        | Me              | Me             | CH                                                   | N | S |
| I-225 | OH             | phenyl                          | methyl                                        | Me              | ethyl          | CH                                                   | N | S |
| I-226 | OH             | phenyl                          | methyl                                        | ethyl           | Me             | CH                                                   | N | S |
| I-227 | OH             | phenyl                          | methyl                                        | OMe             | Me             | CH                                                   | N | S |
| I-228 | OH             | 4-fluorophenyl                  | methyl                                        | Me              | Me             | CH                                                   | N | O |
| I-229 | OH             | 4-fluorophenyl                  | methyl                                        | Me              | ethyl          | CH                                                   | N | O |
| I-230 | OH             | 4-fluorophenyl                  | methyl                                        | ethyl           | Me             | CH                                                   | N | O |
| I-231 | OH             | 4-fluorophenyl                  | methyl                                        | OMe             | Me             | CH                                                   | N | O |
| I-232 | OH             | 4-fluorophenyl                  | methyl                                        | CF <sub>3</sub> | Me             | CH                                                   | N | O |
| I-233 | OH             | 4-fluorophenyl                  | methyl                                        | CF <sub>3</sub> | ethyl          | CH                                                   | N | O |
| I-234 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Me              | Me             | CH                                                   | N | O |
| I-235 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Me              | ethyl          | CH                                                   | N | O |
| I-236 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | ethyl           | Me             | CH                                                   | N | O |
| I-237 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | OMe             | Me             | CH                                                   | N | O |

| No.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                          | R <sup>3</sup>  | R <sup>2</sup>  | X  | Y  | Z |
|-------|----------------|---------------------------------|-----------------------------------------|-----------------|-----------------|----|----|---|
| I-238 | OH             | 4-chlorophenyl                  | methyl                                  | Me              | Me              | CH | N  | O |
| I-239 | OH             | 4-chlorophenyl                  | methyl                                  | Me              | ethyl           | CH | N  | O |
| I-240 | OH             | 4-chlorophenyl                  | methyl                                  | ethyl           | Me              | CH | N  | O |
| I-241 | OH             | 4-chlorophenyl                  | methyl                                  | OMe             | Me              | CH | N  | O |
| I-242 | OH             | 4-chlorophenyl                  | methyl                                  | CF <sub>3</sub> | Me              | CH | N  | O |
| I-243 | OH             | 4-chlorophenyl                  | methyl                                  | CF <sub>3</sub> | ethyl           | CH | N  | O |
| I-244 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | Me              | Me              | CH | N  | O |
| I-245 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -Cl | Me              | ethyl           | CH | N  | O |
| I-246 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | ethyl           | Me              | CH | N  | O |
| I-247 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> -   | OMe             | Me              | CH | N  | O |
| I-248 | OH             | phenyl                          | ethyl                                   | Me              | Me              | N  | N  | O |
| I-249 | OH             | phenyl                          | ethyl                                   | OMe             | SMe             | N  | N  | O |
| I-250 | OH             | phenyl                          | ethyl                                   | OMe             | CF <sub>3</sub> | N  | N  | O |
| I-251 | OH             | phenyl                          | methyl                                  | OMe             | OMe             | N  | CH | O |
| I-252 | OH             | phenyl                          | methyl                                  | OMe             | Me              | N  | CH | O |
| I-253 | OH             | phenyl                          | methyl                                  | Me              | Me              | N  | CH | O |
| I-254 | OH             | phenyl                          | methyl                                  | ethyl           | Me              | N  | CH | O |
| I-255 | OH             | phenyl                          | methyl                                  | ethyl           | ethyl           | N  | CH | O |
| I-256 | OH             | phenyl                          | methyl                                  | CF <sub>3</sub> | Me              | N  | CH | O |
| I-257 | OH             | phenyl                          | methyl                                  | CF <sub>3</sub> | ethyl           | N  | CH | O |
| I-258 | OH             | phenyl                          | methyl                                  | OMe             | CF <sub>3</sub> | N  | CH | O |
| I-259 | OH             | phenyl                          | methyl                                  | OMe             | OMe             | N  | CH | S |
| I-260 | OH             | phenyl                          | methyl                                  | OMe             | Me              | N  | CH | S |
| I-261 | OH             | phenyl                          | methyl                                  | Me              | Me              | N  | CH | S |
| I-262 | OH             | phenyl                          | methyl                                  | ethyl           | Me              | N  | CH | S |

| No.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                                | R <sup>3</sup> | R <sup>2</sup> | X | Y  | Z |
|-------|----------------|---------------------------------|-----------------------------------------------|----------------|----------------|---|----|---|
| I-263 | OH             | phenyl                          | ethyl                                         | OMe            | OMe            | N | CH | O |
| I-264 | OH             | phenyl                          | ethyl                                         | OMe            | Me             | N | CH | O |
| I-265 | OH             | phenyl                          | ethyl                                         | Me             | Me             | N | CH | O |
| I-266 | OH             | phenyl                          | ethyl                                         | ethyl          | Me             | N | CH | O |
| I-267 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | OMe            | OMe            | N | CH | O |
| I-268 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | OMe            | Me             | N | CH | O |
| I-269 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | Me             | Me             | N | CH | O |
| I-270 | OH             | phenyl                          | HO-CH <sub>2</sub> -CH <sub>2</sub> -         | ethyl          | Me             | N | CH | O |
| I-271 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | OMe            | N | CH | O |
| I-272 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | OMe            | Me             | N | CH | O |
| I-273 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | Me             | Me             | N | CH | O |
| I-274 | OH             | phenyl                          | HO-CH <sub>2</sub> -(CH-OH)-CH <sub>2</sub> - | ethyl          | Me             | N | CH | O |
| I-275 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | OMe            | OMe            | N | CH | O |
| I-276 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | OMe            | Me             | N | CH | O |
| I-277 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | Me             | Me             | N | CH | O |
| I-278 | OH             | phenyl                          | HOOC-CH <sub>2</sub> -CH <sub>2</sub> -       | ethyl          | Me             | N | CH | O |
| I-279 | OH             | phenyl                          | propyl                                        | OMe            | OMe            | N | CH | O |
| I-280 | OH             | phenyl                          | propyl                                        | OMe            | Me             | N | CH | O |
| I-281 | OH             | phenyl                          | propyl                                        | Me             | Me             | N | CH | O |
| I-282 | OH             | phenyl                          | propyl                                        | ethyl          | Me             | N | CH | O |
| I-283 | OH             | phenyl                          | 4-OMe-benzyl                                  | OMe            | OMe            | N | CH | O |
| I-284 | OH             | phenyl                          | 4-OMe-benzyl                                  | OMe            | Me             | N | CH | O |
| I-285 | OH             | phenyl                          | 4-OMe-benzyl                                  | Me             | Me             | N | CH | O |
| I-286 | OH             | phenyl                          | 4-OMe-benzyl                                  | ethyl          | Me             | N | CH | O |
| I-287 | OH             | 4-fluorophenyl                  | methyl                                        | OMe            | OMe            | N | CH | O |

| No.   | R <sup>1</sup> | R <sup>4</sup> , R <sup>5</sup> | R <sup>6</sup>                        | R <sup>3</sup> | R <sup>2</sup> | X | Y  | Z |
|-------|----------------|---------------------------------|---------------------------------------|----------------|----------------|---|----|---|
| 1-288 | OH             | 4-fluorophenyl                  | methyl                                | OMe            | Me             | N | CH | O |
| 1-289 | OH             | 4-fluorophenyl                  | methyl                                | Me             | Me             | N | CH | O |
| 1-290 | OH             | 4-fluorophenyl                  | methyl                                | ethyl          | Me             | N | CH | O |
| 1-291 | OH             | 4-fluorophenyl                  | ethyl                                 | OMe            | OMe            | N | CH | O |
| 1-292 | OH             | 4-fluorophenyl                  | ethyl                                 | OMe            | Me             | N | CH | O |
| 1-293 | OH             | 4-fluorophenyl                  | ethyl                                 | Me             | Me             | N | CH | O |
| 1-294 | OH             | 4-fluorophenyl                  | ethyl                                 | ethyl          | Me             | N | CH | O |
| 1-295 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | OMe            | N | CH | O |
| 1-296 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me             | N | CH | O |
| 1-297 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Me             | N | CH | O |
| 1-298 | OH             | 4-fluorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | ethyl          | Me             | N | CH | O |
| 1-299 | OH             | 4-chlorophenyl                  | methyl                                | OMe            | OMe            | N | CH | O |
| 1-300 | OH             | 4-chlorophenyl                  | methyl                                | OMe            | Me             | N | CH | O |
| 1-301 | OH             | 4-chlorophenyl                  | methyl                                | Me             | Me             | N | CH | O |
| 1-302 | OH             | 4-chlorophenyl                  | methyl                                | ethyl          | Me             | N | CH | O |
| 1-303 | OH             | 4-chlorophenyl                  | ethyl                                 | OMe            | OMe            | N | CH | O |
| 1-304 | OH             | 4-chlorophenyl                  | ethyl                                 | OMe            | Me             | N | CH | O |
| 1-305 | OH             | 4-chlorophenyl                  | ethyl                                 | Me             | Me             | N | CH | O |
| 1-306 | OH             | 4-chlorophenyl                  | ethyl                                 | ethyl          | Me             | N | CH | O |
| 1-307 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | OMe            | N | CH | O |
| 1-308 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | OMe            | Me             | N | CH | O |
| 1-309 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | Me             | Me             | N | CH | O |
| 1-310 | OH             | 4-chlorophenyl                  | HO-CH <sub>2</sub> -CH <sub>2</sub> - | ethyl          | Me             | N | CH | O |

The compounds of the present invention provide a novel therapeutic potential for the treatment of hypertension, pulmonary hypertension, myocardial infarct, angina pectoris, acute kidney failure, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoidal hemorrhages, migraine, asthma, atherosclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty, benign prostate hyperplasia, or hypertension or kidney failure caused by ischemia or intoxication, and of cancers, especially prostate cancer and skin cancer. The invention further relates to the combination of compounds of the formula I with inhibitors of the renin-angiotensin system (RAS). RAS inhibitors are disclosed in, for example, EP 634 175.

The combinations according to the invention are suitable for treating disorders for which compounds of the formula I also shows efficacy on their own, especially for treating hypertension and chronic heart failure.

The good effect of the compounds can be shown in the following tests:

#### Receptor binding studies

Cloned human  $ET_A$  receptor-expressing CHO cells and guinea pig cerebellar membranes with  $> 60\%$   $ET_B$  compared with  $ET_A$  receptors were used for binding studies.

#### Membrane preparation

The  $ET_A$  receptor-expressing CHO cells were grown in  $F_{12}$  medium containing 10% fetal calf serum, 1% glutamine, 100 E/ml penicillin and 0.2% streptomycin (Gibco BRL, Gaithersburg, MD, USA). After 48 h, the cells were washed with PBS and incubated with 0.05% trypsin-containing PBS for 5 min. Neutralization was then carried out with  $F_{12}$  medium and the cells were collected by centrifugation at 300 x g. To lyse the cells, the pellet was briefly washed with lysis buffer (5 mM tris-HCl, pH 7.4 with 10% glycerol) and then incubated at a concentration of  $10^7$  cells/ml of lysis buffer at 4°C for 30 min. The membranes were centrifuged at 20,000 x g for 10 min, and the pellet was stored in liquid nitrogen.

Guinea pig cerebella were homogenized in a Potter-Elvehjem homogenizer and were obtained by differential centrifugation at 1,000 x g for 10 min and repeated centrifugation of the supernatant at 20,000 x g for 10 min.

5

#### Binding assays

For the  $ET_A$  and  $ET_B$  receptor binding assay, the membranes were suspended in incubation buffer (50 mM tris-HCl, pH 7.4 with 5 mM of  $MnCl_2$ , 40  $\mu$ g/ml bacitracin and 0.2% BSA) at a concentration of 50  $\mu$ g of protein per assay mixture and incubated with 25 pM [ $^{125}I$ ] [*sic*]- $ET_1$  ( $ET_A$  receptor assay) or 25 pM [ $^{125}I$ ] [*sic*]- $RZ_3$  ( $ET_B$  receptor assay) in the presence and absence of test substance. The nonspecific binding was determined with  $10^{-7}$  M  $ET_1$ . After 30 min, filtration was carried out through GF/B glass fiber filters (Whatman, England) in a Skatron cell collector (Skatron, Lier, Norway) to separate free and bound radioligands, and the filters were washed with ice-cold tris-HCl buffer, pH 7.4 with 0.2% BSA. The radioactivity collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

Functional in vitro assay system to look for endothelin receptor (subtype A) antagonists

25 This assay system is a functional, cell-based assay for endothelin receptors. When certain cells are stimulated with endothelin 1 ( $ET_1$ ) they show an increase in the intracellular calcium concentration. This increase can be measured in intact cells loaded with calcium-sensitive dyes.

30

1-Fibroblasts which had been isolated from rats and in which an endogenous endothelin receptor of the A subtype had been detected were loaded with the fluorescent dye Fura 2-am as follows: after trypsinization, the cells were resuspended in buffer A (120 mM NaCl, 5 mM KCl, 1.5 mM  $MgCl_2$ , 1 mM  $CaCl_2$ , 25 mM HEPES, 10 mM glucose, pH 7.4) to a density of  $2 \times 10^6$ /ml and incubated with Fura 2-am (2  $\mu$ M), Pluronic [*sic*] F-127 (0.04%) and DMSO (0.2%) at 37°C in the dark for 30 min. The cells were then washed twice with buffer A and resuspended at  $2 \times 10^6$ /ml.

40

The fluorescence signal from  $2 \times 10^5$  cells per ml with Ex/Em 380/510 was recorded continuously at 30°C. The test substances and, after an incubation time of 3 min,  $ET_1$  were [*lacuna*] to the cells, the maximum change in the fluorescence was determined. The response of the cells to  $ET_1$  without previous addition of a test substance was used as control and was set equal to 100%.

45

## Testing of ET antagonists in vivo

Male SD rats weighing 250-300 g were anesthetized with amobarbital, artificially ventilated, vagotomized and pithed. The 5 carotid artery and jugular vein were cathetized [sic].

In control animals, intravenous administration of 1  $\mu\text{g/kg}$  ET1 led to a distinct rise in blood pressure which persisted for a lengthy period.

10

The test animals received an i.v. injection of the test compounds (1 ml/kg) 5 min before administration of ET1. To determine the ET-antagonistic properties, the rise in blood pressure in the test animals was compared with that in the control animals.

15

Endothelin-1 induced "sudden death" in mice

The principle of the test is the inhibition of the sudden heart death caused in mice by endothelin, which is probably induced by 20 constriction of the coronary vessels, by pretreatment with endothelin receptor antagonists. Intravenous injection of 10 nmol/kg endothelin in a volume of 5 ml/kg of bodyweight results in death of the animals within a few minutes.

25 The lethal endothelin-1 dose is checked in each case on a small group of animals. If the test substance is administered intravenously, the endothelin-1 injection which was lethal in the reference group usually takes place 5 min thereafter. With other modes of administration, the times before administration are 30 extended, where appropriate up to several hours.

The survival rate is recorded, and effective doses which protect 50% of the animals (ED 50) from endothelin-induced heart death for 24 h or longer are determined.

35

Function test on vessels for endothelin receptor antagonists

Segments of rabbit aorta are, after an initial tension of 2 g and a relaxation time of 1 h in Krebs-Henseleit solution at 37°C and 40 pH 7.3-7.4, first induced to contract with  $\text{K}^+$ . After washing out, an endothelin dose-effect plot up to the maximum is constructed.

Potential endothelin antagonists are administered to other preparations of the same vessel 15 min before starting the 45 endothelin dose-effect plot. The effects of the endothelin are calculated as % of the  $\text{K}^+$ -induced contraction. Effective

endothelin antagonists result in a shift to the right in the endothelin dose-effect plot.

The compounds according to the invention can be administered  
5 orally or parenterally (subcutaneously, intravenously, intramuscularly, intraperitoneally [sic]) in a conventional way. Administration can also take place with vapors or sprays through the nasopharyngeal space.

10 The dosage depends on the age, condition and weight of the patient and on the mode of administration. The daily dose of active substance is, as a rule, about 0.5 to 50 mg/kg of bodyweight on oral administration and about 0.1-10 mg/kg of bodyweight on parenteral administration.

15 The novel compounds can be used in conventional solid or liquid pharmaceutical forms, e.g. as uncoated or (film-)coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The  
20 active substances can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, bulking agents, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellant gases (cf.  
25 H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The forms obtained in this way normally contain from 0.1 to 90% by weight of active substance.

#### Synthesis examples

30

##### Example 1

##### Methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate

5 g (19.6 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate were  
35 dissolved in 50 ml of absolute methanol, and, at 0°C, 0.1 ml of boron trifluoride etherate was added. The mixture was stirred at 0°C for 2 h and at room temperature for a further 12 h. The solvent was removed by distillation, the residue was taken up in ethyl acetate, and the solution was washed with sodium  
40 bicarbonate solution and water and dried over magnesium sulfate. After removal of the solvent by distillation, 5.5 g (88%) of a pale yellow oil remained.

##### Example 2

45 Methyl 2-(2,6-dimethoxy-4-pyrimidyloxy)-3-methoxy-3,3-diphenylpropionate

1.15 g (4 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate were dissolved in 10 ml of dimethylformamide, and 276 mg (2 mmol) of potassium carbonate were added. Then 524 mg (3 mmol) of 2,6-dimethoxy-4-chloropyrimidine were added, and the mixture was stirred at 100°C for 6 hours. It was then cautiously hydrolyzed with 10 ml of water, the pH was adjusted to 5 with citric acid and, after extraction with ethyl acetate, the organic phase was washed with water then dried over magnesium sulfate, and the solvent was removed by distillation. The oily residue (1.9 g) was chromatographed on silica gel, resulting in 617 mg of a slightly impure oil.

#### Example 3

2-(2,6-Dimethoxy-4-pyrimidinyl-oxy)-3-methoxy-3,3-diphenylpropionic acid

550 mg (1.3 mmol) of methyl 2-(2,6-dimethoxy-4-pyrimidinyl-oxy)-3-methoxy-3,3-diphenylpropionate were dissolved in 5 ml of dioxane, 2.6 ml of 1N KOH solution were added, and the mixture was stirred at 100°C for 3 h. The solution was diluted with 300 ml of water and extracted with ethyl acetate to remove unreacted ester. The aqueous phase was then adjusted to pH 1-2 with dilute hydrochloric acid and was extracted with ethyl acetate. After drying over magnesium sulfate and removal of the solvent by distillation, the residual foam (425 mg) was purified by MPLC, resulting in 205 mg (40%) of product as foam.

#### Example 4

Methyl 2-(4-methyl-2-quinolinyl-oxy)-3-methoxy-3,3-diphenylpropionate

5.7 g (20 mmol) of Methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate were dissolved in 90 ml of dimethylformamide, and 0.98 g (22 mmol) of sodium hydride (55% in oil) was added. After stirring for 15 minutes, 3.9 g (22 mmol) of 2-chloro-4-methylquinoline were added. The dark red solution was stirred at room temperature overnight, then cautiously hydrolyzed with 20 ml of water and subsequently extracted with ethyl acetate. The organic phase was washed with water, and dried over magnesium sulfate, and the solvent was removed by distillation. The residue (8.1 g) was then chromatographed on silica gel, resulting in 2.6 g of impure product as oil.

#### Example 5

2-(4-Methyl-2-quinolinyl-oxy)-3-methoxy-3,3-diphenylpropionic acid

## 30

1.8 g (4.2 mmol) of methyl 2-(4-methyl-2-quinolinyloxy)-3-methoxy-3,3-diphenylpropionate were dissolved in 25 ml of dioxane, 8.4 ml of 1N KOH solution were added, and the mixture was stirred at 60°C for 20 hours. The solution was diluted with 300 ml of water and extracted with ethyl acetate to remove unreacted ester and impurities. The aqueous phase was then adjusted to pH 1-2 with dilute hydrochloric acid and was extracted with ethyl acetate. Drying over magnesium sulfate and removal of the solvent by distillation resulted in 1.0 g of a foam. This was dissolved in a little ethyl acetate and left to stand at room temperature overnight, during which 265 mg of the product separated out as white crystals. Repetition of this procedure with the mother liquor afforded a further 166 mg of the product.

15 Total yield: 431 mg  $\approx$  25%  
Melting point: 131-133°C  
MS:  $M^+$  = 413

## Example 6

20 Benzyl 2-(2-tert-butyl-6-trifluoromethyl-4-pyrimidinyloxy)-3-methoxy-3,3-diphenylpropionate

2.0 g (5.5 mmol) of benzyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate (see P44 36 851.8) were dissolved in 20 ml of dimethylformamide, and 0.76 g (5.5 mmol) of potassium carbonate was added. Then 1.32 g (5.5 mmol) of 2-tert-butyl-6-trifluoromethyl-4-chloropyrimidine were added, and the mixture was stirred at room temperature overnight and then at 100°C for 5 hours. To complete the reaction, a further 0.5 g of the pyrimidine and 0.5 g of NaH were added, and the mixture was stirred at 60°C for a further 6 hours. Finally, it was poured into ice-water and extracted with ethyl acetate, the organic phase was washed with saturated NaCl solution and dried over magnesium sulfate, and the solvent was removed by distillation. The oily residue (3.5 g) crystallized in n-heptane/ethyl acetate (5%). The precipitate was filtered off with suction and dried.

Yield: 1.6 g  $\approx$  52%  
MS:  $M^+$  = 564

40

## Example 7

2-(2-tert-Butyl-6-trifluoromethyl-4-pyrimidinyloxy)-3-methoxy-3,3-diphenylpropionic acid

45 2.0 g (5.5 mmol) of benzyl 2-(2-tert-butyl-6-trifluoromethyl-4-pyrimidinyloxy)-3-methoxy-3,3-diphenylpropionate were dissolved in 250 ml of methanol, 120 mg of palladium on active

## 31

carbon (5%) were added, and the mixture was stirred under hydrogen at room temperature for 2 hours. After hydrogen uptake ceased, the catalyst was removed by filtration through celite, and the solvent was stripped off in a rotary evaporator.

5

Yield: 1.0 g  $\cong$  98%

<sup>1</sup>H-NMR (360 MHz, in CDCl<sub>3</sub>, data in ppm):

1.35 (s, 9H); 3.3 (s, 3H); 6.3 (s, 1H); 6.8 (s, 1H);

7.15 - 7.45 (m, 10H)

10

The compounds listed in Table 1 can be prepared in a similar way.

## Example 8

15 Receptor binding data were measured for the compounds listed below using the binding assay described above.

The results are shown in Table 2.

20 Table 2

Receptor binding data (K<sub>i</sub> values)

| 25 | Compound | ET <sub>A</sub> [μM] | ET <sub>B</sub> [μM] |
|----|----------|----------------------|----------------------|
|    | I-1      | 0.038                | 8                    |
|    | I-91     | 3.3                  | > 10                 |
|    | I-166    | 0.5                  | 4                    |
| 30 | I-167    | 3                    | > 7                  |

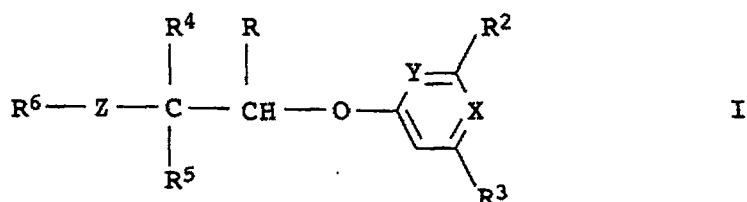
35

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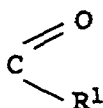
45

We claim:

1. A carboxylic acid derivative of the formula I

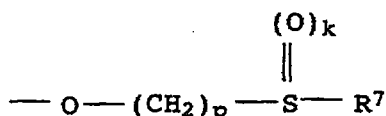


where R is a tetrazole [sic], nitrile [sic], or a group



where  $R^1$  has the following meanings:

- a) hydrogen;
- b) a succinylimidoxy [sic] group;
- c) a 5-membered heteroaromatic system linked via a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, which may carry one or two halogen atoms or one or two C<sub>1</sub>-C<sub>4</sub>-alkyl or one or two C<sub>1</sub>-C<sub>4</sub>-alkoxy groups.
- d) R<sup>1</sup> is furthermore a group



where  $k$  can assume the values 0, 1 and 2,  $p$  can assume the values 1, 2, 3 and 4, and  $R^7$  is

C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>6</sub>-alkenyl, C<sub>3</sub>-C<sub>6</sub>-alkynyl or unsubstituted or substituted phenyl which can be substituted by one or more, e.g. one to three, of the following radicals:

halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, hydroxyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, mercapto, amino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-dialkylamino;

- e)  $R^1$  is furthermore a radical  $OR^8$  where  $R^8$  is:



hydrogen, the cation of an alkali metal such as lithium, sodium, potassium, or the cation of an alkaline earth metal such as calcium, magnesium and barium or a physiologically tolerated organic ammonium ion such as tertiary C<sub>1</sub>-C<sub>4</sub>-alkylammonium or the ammonium ion;

C<sub>3</sub>-C<sub>8</sub>-cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and [sic] cycloheptyl, cyclooctyl,

C<sub>1</sub>-C<sub>8</sub>-alkyl, in particular C<sub>1</sub>-C<sub>4</sub>-alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl;

CH<sub>2</sub>-phenyl, which may be substituted by one or more of the following radicals: halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, hydroxyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, mercapto,

C<sub>1</sub>-C<sub>4</sub>-alkylthio, amino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-dialkylamino,

a C<sub>3</sub>-C<sub>6</sub>-alkenyl or C<sub>3</sub>-C<sub>6</sub>-alkynyl group, it being possible for this group in turn to carry one to five halogen atoms;

R<sup>8</sup> can furthermore be a phenyl radical which can carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, hydroxyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, mercapto, C<sub>1</sub>-C<sub>4</sub>-alkylthio, amino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-dialkylamino;

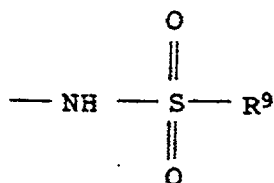
a 5-membered heteroaromatic system which is linked via a nitrogen atom and contains one to three nitrogen atoms and which can carry one or two halogen atoms and/or one or two of the following radicals: C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, phenyl, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy and/or C<sub>1</sub>-C<sub>4</sub>-alkylthio. Particular mention may be made of 1-pyrazolyl,

3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3,4-dichloro-1-imidazolyl;

f) R<sup>1</sup> is furthermore a radical



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where R<sup>9</sup> is:

10 C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-alkenyl, C<sub>3</sub>-C<sub>6</sub>-alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl as mentioned above in particular, it being possible for these radicals to carry a C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio and/or a phenyl radical as mentioned above;

15 phenyl, unsubstituted or substituted, in particular as mentioned above.

g) R<sup>1</sup> is a radical

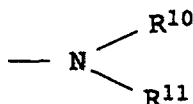


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where R<sup>9</sup> has the abovementioned meaning.

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h) R<sup>1</sup> can furthermore be



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where R<sup>10</sup> and R<sup>11</sup> can be identical or different and have the following meanings:

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hydrogen, C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl [sic], C<sub>3</sub>-C<sub>7</sub>-alkenyl, C<sub>3</sub>-C<sub>7</sub>-alkynyl, benzyl, phenyl, unsubstituted or substituted, as described above, or R<sup>10</sup> and R<sup>11</sup> together form a C<sub>4</sub>-C<sub>7</sub>-alkylene chain which is closed to form a ring, is unsubstituted or substituted, e.g. substituted by C<sub>1</sub>-C<sub>4</sub>-alkyl, and may contain a heteroatom, e.g. oxygen, sulfur or nitrogen, such as -(CH<sub>2</sub>)<sub>4</sub>-, -(CH<sub>2</sub>)<sub>5</sub>-, -(CH<sub>2</sub>)<sub>6</sub>-, -(CH<sub>2</sub>)<sub>7</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-O-(CH<sub>2</sub>)<sub>2</sub>-, -CH<sub>2</sub>-S-(CH<sub>2</sub>)<sub>2</sub>-, -CH<sub>2</sub>-NH-(CH<sub>2</sub>)<sub>2</sub>-,

40 -(CH<sub>2</sub>)<sub>2</sub>-N-(CH<sub>2</sub>)<sub>2</sub>-;

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the other substituents have the following meanings:

- 5  $R^2$  hydrogen, hydroxyl,  $NH_2$ ,  $NH(C_1-C_4-alkyl)$ ,  $N(C_1-C_4-alkyl)_2$ , halogen,  $C_1-C_4-alkyl$ ,  $C_1-C_4-haloalkyl$ ,  $C_1-C_4-alkoxy$ ,  $C_1-C_4-haloalkoxy$  or  $C_1-C_4-alkylthio$ , or  $CR^{12}$  is linked to  $CR^{12}$  as indicated below to form a 5- or 6-membered ring;
- 10  $X$  nitrogen or  $CR^{12}$  where  $R^{12}$  is hydrogen or  $C_{1-5}-alkyl$ , or  $CR^{12}$  forms together with  $CR^2$  or  $CR^3$  a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two  $C_{1-4}-alkyl$  groups and in which in each case one methylene group can be replaced by oxygen, sulfur,  $-NH$  or  $-NC_{1-4}-alkyl$ ;
- 15  $Y$  nitrogen or methine;
- 20  $R^3$  hydrogen, hydroxyl,  $NH_2$ ,  $NH(C_1-C_4-alkyl)$ ,  $N(C_1-C_4-alkyl)_2$ , halogen,  $C_1-C_4-alkyl$ ,  $C_1-C_4-haloalkyl$ ,  $C_1-C_4-alkoxy$ ,  $C_1-C_4-haloalkoxy$ ,  $-NH-O-C_{1-4}-alkyl$ ,  $C_1-C_4-alkylthio$ ; or  $CR^3$  is linked to  $CR^{12}$  as indicated above to form a 5- or 6-membered ring;
- 25  $R^4$  and  $R^5$  (which can be identical or different):
- 30 phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl,  $C_1-C_4-alkyl$ ,  $C_1-C_4-haloalkyl$ ,  $C_1-C_4-alkoxy$ ,  $C_1-C_4-haloalkoxy$ , phenoxy,  $C_1-C_4-alkylthio$ , amino,  $C_1-C_4-alkylamino$  or  $C_1-C_4-dialkylamino$ ; or
- 35 phenyl or naphthyl, which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an  $SO_2-$ ,  $NH-$  or  $N-alkyl$  group, or  $C_3-C_7-cycloalkyl$ ;
- 40  $R^6$  hydrogen,  $C_1-C_8-alkyl$ ,  $C_3-C_6-alkenyl$ ,  $C_3-C_6-alkynyl$  or  $C_3-C_8-cycloalkyl$ , it being possible for each of these radicals to be substituted one or more times by: halogen, hydroxyl, mercapto, carboxyl, nitro, cyano,  $C_1-C_4-alkoxy$ ,  $C_3-C_6-alkenyloxy$ ,  $C_3-C_6-alkynyloxy$ ,  $C_1-C_4-alkylthio$ ,  $C_1-C_4-haloalkoxy$ ,  $C_1-C_4-alkylcarbonyl$ ,  $C_1-C_4-alkoxycarbonyl$ ,
- 45  $C_{3-8}-alkylcarbonylalkyl$ ,  $C_1-C_4-alkylamino$ ,



\* C L M S \*

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di-C<sub>1</sub>-C<sub>4</sub>-alkylamino, phenyl or phenoxy or phenyl, substituted one or more times, e.g. once to three times, by halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy or C<sub>1</sub>-C<sub>4</sub>-alkylthio;

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phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-dialkylamino, dioxomethylene [sic] or dioxoethylene [sic];

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a five- or six-membered heteroaromatic system which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the following radicals: C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy and/or C<sub>1</sub>-C<sub>4</sub>-alkylthio;

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Z sulfur or oxygen.

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2. A carboxylic acid derivative as claimed in claim 1, wherein R is COOH.

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3. A carboxylic acid derivative as claimed in any of the preceding claims, wherein at least one of the radicals R<sup>4</sup> and R<sup>5</sup> is phenyl.

4. A carboxylic acid derivative as claimed in claim 3, wherein R<sup>4</sup> and R<sup>5</sup> are both phenyl.

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5. A carboxylic acid derivative as claimed in claim 3, wherein R<sup>6</sup> is C<sub>1</sub>-C<sub>8</sub>-alkyl, unsubstituted or substituted by OH or C<sub>1</sub>-C<sub>4</sub>-alkoxy, and Z is O.

40 6. A carboxylic acid derivative as claimed in any of the preceding claims, wherein X is CH.

7. A carboxylic acid derivative as claimed in any of the preceding claims, wherein at least one of the radicals X, Y is nitrogen (N).

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8. A carboxylic acid derivative as claimed in any of the preceding claims, wherein at least one of the radicals  $R^2$ ,  $R^3$  is  $C_1$ - $C_4$ -alkyl.

5 9. The use of compounds as claimed in any of claims 1 to 8 for producing medicines for treating hypertension, pulmonary hypertension, acute and chronic kidney failure, chronic heart failure, cerebral ischemia, restenosis after angioplasty, prostate cancer.

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10. The use of a combination of a compound as claimed in any of claims 1 to 8 with an inhibitor of the renin-angiotensin system (RAS).

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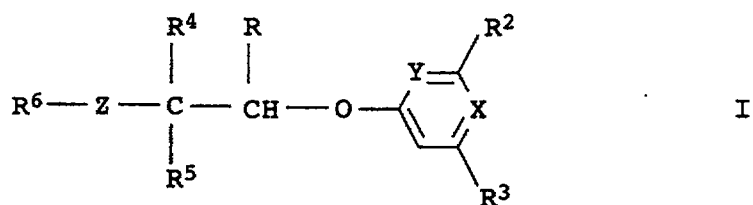


Novel carboxylic acid derivatives, their preparation and their use

## 5 Abstract

Carboxylic acid derivatives of the formula I

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where the radicals have the meanings stated in the description, and the preparation of these agreements [sic] and their use as drugs are described.

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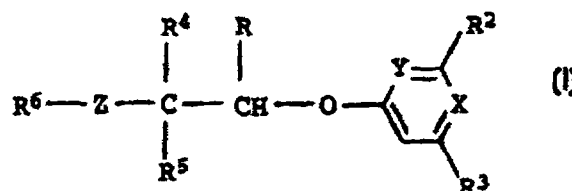
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(54) Title: **NOVEL CARBOXYLIC ACID DERIVATIVES, THEIR PRODUCTION AND USE**(54) Bezeichnung: **NEUE CARBONSÄUREDERIVATE, IHRE HERSTELLUNG UND VERWENDUNG**

(57) Abstract

The present invention relates to carboxylic acid derivatives of formula (I) in which the radicals have the meaning given in the description, and the production of these substances and their use as medicaments.



(57) Zusammenfassung

Die vorliegende Erfindung betrifft Carbonsäurederivate der Formel (I), wobei die Reste die in der Beschreibung angegebene Bedeutung besitzen, sowie die Herstellung dieser Verbindungen und ihre Verwendung als Arzneimittel.