Industria y Comercio QF

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Delegatura de propiedad Industrial

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SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 05-116726

54 **TÍTULO** Derivados de bencimidazol como inhibidores del factor Xa

51 **CLASIFICACIÓN INTERNACIONAL** C07D 413/14 A61K 31/4184

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74 **APODERADO** Luis Patiño Leyva

22 **BOGOTÁ, D. C.,** 17 de noviembre 2005

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
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ENTRADA EN FASE NACIONAL

Dic- 19-2005

① **SOLICITUD DE :**

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capitulo I. ☒ Capitulo II.

② **SOLICITANTE (71)**	Nombre: **SANOFI-AVENTIS DEUTSCHLAND GmbH** Dirección: Brüningstrasse 50, 65929 Frankfurt am Main, Alemania Nacionalidad o Domicilio: Frankfurt am Main,Alemania Lugar de Constitución: Alemania Teléfono: Fax: E-mail:	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
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⑤ **PCT (86)**

Solicitud Internacional No. PCT/EP2004/004750 Fecha Mayo 5 de 2004

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⑥ **Título (54)** DERIVADOS DE BENCIMIDAZOL COMO INHIBIDORES DEL FACTOR Xa.

⑦ **Clasificación Internacional (51)** C07D 413/14

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Instrucciones para el diligenciamiento del presente formulario , ver reverso de esta página.

JJJ4

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [x] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de deposito del material biológico
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros Reporte de Búsqueda Internacional.

(11) FIGURA CARACTERISTICA

(12) Solicito la concesión de la patente,

NOMBRE: LUIS PATIÑO LEYVA

FIRMA:

C.C. 2.930.616 Bogotá T.P. 2698

Instrucciones para el diligenciamiento del presente formulario , ver reverso de esta página.

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RITTER Kurt	Gutzkowstrasse 2,	60594 Frankfurt am Main, Alemania

Otros anexos que se acompañan a la solicitud.

Copia formulario PCT/RO/101 correspondiente a la presentación de la solicitud internacional.

Copia formulario PCT/IB/304 correspondiente a la notificación relativa al envío o transmisión del documento de prioridad.

Reivindicaciones Modificadas.

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(75) Inventors/Applicants (*for US only*): NAZARE, Marc [DE/DE]; Felix-Lahnstein-Str. 4b, 65510 Idstein (DE). WAGNER, Michael [DE/DE]; Alte Bergstr. 42a, 64665 Alsbach (DE). WEHNER, Volkmar [DE/DE]; Lindenstrasse 1, 97657 Sandberg (DE). MATTER, Hans [DE/DE]; Feldbergring 37, 63505 Langenselbold (DE). URMANN, Matthias [DE/DE]; Im Sylvaner 4b, 65760 Eschborn (DE). RITTER, Kurt [DE/DE]; Gutzkowstrasse 2, 60594 Frankfurt am Main (DE).

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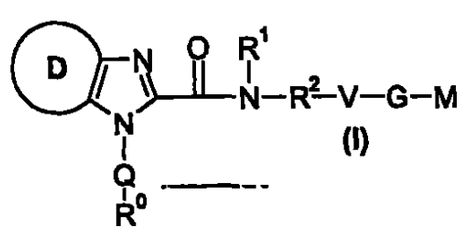
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(54) Title: BENZIMIDAZOLE-DERIVATIVES AS FACTOR Xa INHIBITORS



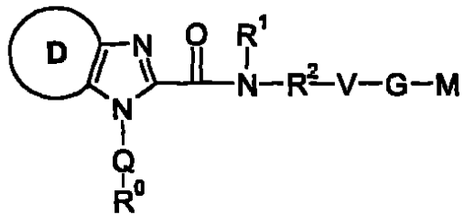
(I)

(57) Abstract: The present invention relates to compounds of the formula (I), wherein R^0, R^1 , R^2, Q, V, G and M have the meanings indicated in the claims. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

Description

Benzimidazole-derivatives as factor Xa inhibitors

The present invention relates to compounds of the formula I,



(I)

in which R^0 ; R^1 ; R^2 ; Q; V, G and M have the meanings indicated below. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong anti-thrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardio-vascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

Normal haemeostasis is the result of a complex balance between the processes of clot initiation, formation and clot dissolution. The complex interactions between blood cells, specific plasma proteins and the vascular surface, maintain the fluidity of blood unless injury and blood loss occurs (EP-A-987274). Many significant disease states are related to abnormal haemeostasis. For example, local thrombus formation due to rupture of athereoslerotic plaque a major cause of acute myocardial infarction and unstable angina. Treatment of an occlusive coronary thrombus by either thrombolytic therapy or percutaneous angioplasty may be accompanied by acute thrombolytic reclosure of the affected vessel.

There continues to be a need for safe and effective therapeutic anticoagulants to limit or prevent thrombus formation. It is most desirable to develop agents that inhibit coagulation without directly inhibiting thrombin but by inhibiting other steps in the coagulation cascade

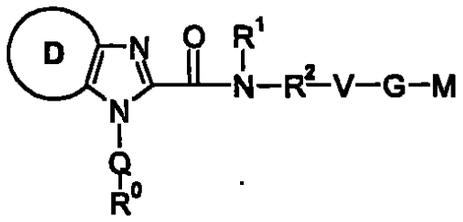
like factor Xa and/or factor VIIa activity. It is now believed that inhibitors of factor Xa carry a lower bleeding risk than thrombin inhibitors (A. E. P. Adang & J. B. M. Rewinkel, Drugs of the Future 2000, 25, 369-383).

Low molecular weight, factor Xa-specific blood clotting inhibitors that are effective but do not cause unwanted side effects have been described, for example, in WO-A-95/29189. However, besides being an effective factor Xa-specific blood clotting inhibitor, it is desirable that such inhibitors also have further advantageous properties, for instance stability in plasma and liver and selectivity versus other serine proteases whose inhibition is not intended, such as thrombin. There is an ongoing need for further low molecular weight factor Xa specific blood clotting inhibitors, which are effective and have the above advantages as well.

Specific inhibition of the factor VIIa/tissue factor catalytic complex using monoclonal antibodies (WO-A-92/06711) or a protein such as chloromethyl ketone inactivated factor VIIa (WO-A-96/12800, WO-A-97/47651) is an extremely effective means of controlling thrombus formation caused by acute arterial injury or the thrombotic complications related to bacterial septicemia. There is also experimental evidence suggesting that inhibition of factor VIIa/tissue factor activity inhibits restenosis following balloon angioplasty. Bleeding studies have been conducted in baboons and indicate that inhibition of the factor VIIa/tissue factor complex has the widest safety window with respect to therapeutic effectiveness and bleeding risk of any anticoagulant approach tested including thrombin, platelet and factor Xa inhibition. Certain inhibitors of factor VIIa have already been described. EP-A-987274, for example discloses compounds containing a tripeptide unit, which inhibit factor VIIa. However, the property profile of these compounds is still not ideal, and there is an ongoing need for further low molecular weight factor VIIa inhibitory blood clotting inhibitors

The present invention satisfies the above needs by providing novel compounds of the formula I, which exhibit better factor Xa and/or factor VIIa inhibitory activity and are favorable agents with high bioavailability.

Thus, the present invention relates to compounds of the formula I,

(I) 

wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a monocyclic or bicyclic 4- to 15-membered heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and
which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,

9) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

10) –O-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

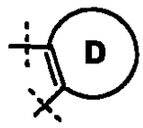
11) -SO_2-CH_3 or

12) –SO_2-CF_3,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are a monocyclic or bicyclic 6- to 14-membered aryl,

the substructure



in formulae I is a 4-to 8 membered saturated, partially unsaturated or aromatic cyclic group containing zero, 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen and is unsubstituted or substituted 1, 2, 3, 4, 5 or 6 times by R3 or substituted 1 or 2 times by =O,

Q is a direct bond, -(C_0 –C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, methylene, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -(C_2-C_3)-alkylene-O-(C_0-C_3)-alkylene-, -(C_2-C_3)-alkylene-S(O)-, -(C_2-C_3)-alkylene-$S(O)_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -(C_2-C_3)-alkylene-$S(O)_2$-NH-(R^{10})-, -(C_2-C_3)-alkylene-N(R^{10})- or -(C_0-C_3)-alkylene-C(O)-O-$(CH_2)_m$-,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -$(CH_2)_m$- or -$(CH_2)_n$- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH; or

–$(C_3$-$C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or –OH;

R^1 is a hydrogen atom, $-(C_1$-$C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; $-(C_1$-$C_3)$-alkylene-C(0)-NH-R^0, $-(C_1$-$C_3)$-alkylene-C(0)-O-R^{10}, a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above; a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen; $-(C_1$-$C_3)$-perfluoroalkylene, $-(C_1$-$C_3)$-alkylene-S(0)-$(C_1$-$C_4)$-alkyl, $-(C_1$-$C_3)$-alkylene-$S(0)_2$-$(C_1$-$C_3)$-alkyl, $-(C_1$-$C_3)$-alkylene-$S(0)_2$-N($R^{4'}$)-$R^{5'}$, $-(C_1$-$C_3)$-alkylene-O-$(C_1$-$C_4)$-alkyl, $-(C_0$-$C_3)$-alkylene-$(C_3$-$C_8)$-cycloalkyl, or $-(C_0$-$C_3)$-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or $-(C_1$-$C_4)$-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is halogen, -OH, =O, $-(C_1$-$C_8)$-alkyl, $-(C_1$-$C_4)$-alkoxy, $-NO_2$, -C(0)-OH, -CN, $-NH_2$, -C(0)-O-$(C_1$-$C_4)$-alkyl, $-(C_0$-$C_8)$-alkyl-SO_2-$(C_1$-$C_4)$-alkyl, $-(C_0$-$C_8)$-alkyl-SO_2-$(C_1$-$C_3)$-perfluoroalkyl, $-(C_0$-$C_8)$-alkyl-SO_2-N(R^{18})-R^{21}, -C(0)-NH-$(C_1$-$C_8)$-alkyl, -C(0)-N-$[(C_1$-$C_8)$-alkyl$]_2$, $-NR^{18}$-C(0)-NH-$(C_1$-$C_8)$-alkyl, -C(0)-NH_2, –S-R^{18}, or $–NR^{18}$-C(0)-NH-$[(C_1$-$C_8)$-alkyl$]_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, $-(C_1$-$C_3)$-perfluoroalkyl or $–(C_1$-$C_6)$-alkyl,

V is 1) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2) a heterocyclyl out of the group acridinyl, 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 1,4-diazepane, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, 1λ6-thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$,

$-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is
1) a hydrogen atom,
2) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
3) $-C(O)-N(R11)-R12$,
4) $-(CH_2)_m-NR^{10}$,
5) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
6) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
7) $-(C_3-C_8)$-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or
8) a 3- to 7-membered cyclic residue, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen; wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, wherein R14 is defined above,

R3 is
1) hydrogen atom,
2) halogen,
3) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
4) $-(C_1-C_3)$-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
6) $-(C_0-C_4)$-alkylene-O-R19, wherein R19 is
   a) hydrogen atom,
   b) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

7) $-NO_2$,

8) -CN,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) $-(C_0-C_4)$-alkylene-C(O)-R^{11},

12) $-(C_0-C_4)$-alkylene-C(O)-O-R^{11},

13) $-(C_0-C_4)$-alkylene-C(O)-$N(R^{11})-R^{12}$,

14) $-(C_0-C_4)$-alkylene-$N(R^{11})-R^{12}$,

15) $-NR^{10}-SO_2-R^{10}$,

16) $-S-R^{10}$,

17) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

20) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

21) $-(C_0-C_4)$-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13,

22) $-(C_0-C_4)$-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13

23) $-(C_0-C_4)$-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

24) $-(C_0-C_4)$-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

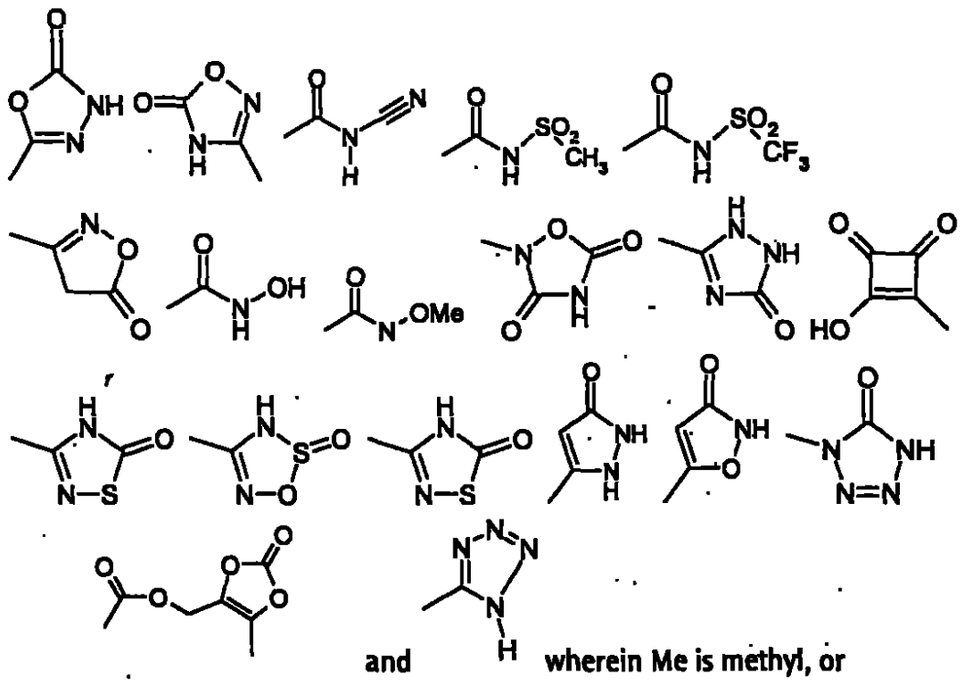
25) $-(C_0-C_4)$-alkylene-O-$CH_2-(C_1-C_3)$-perfluoroalkylene-CH_2-O-(C_0-C_4)-alkyl,

26) $-SO_w-N(R^{11})-R^{13}$, wherein w is 1 or 2,

27) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{13},

28) -(C_0-C_4)-alkylene-N(R^{11})-R^{13}, or

29) a residue from the following list



and wherein Me is methyl, or

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 5- or 6- membered ring, which is unsubstituted or substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_0-C_6)-alkyl-(C_3-C_8)-cycloalkyl,

4) -SO_t-R^{10}; wherein t is 1 or 2,

5) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,

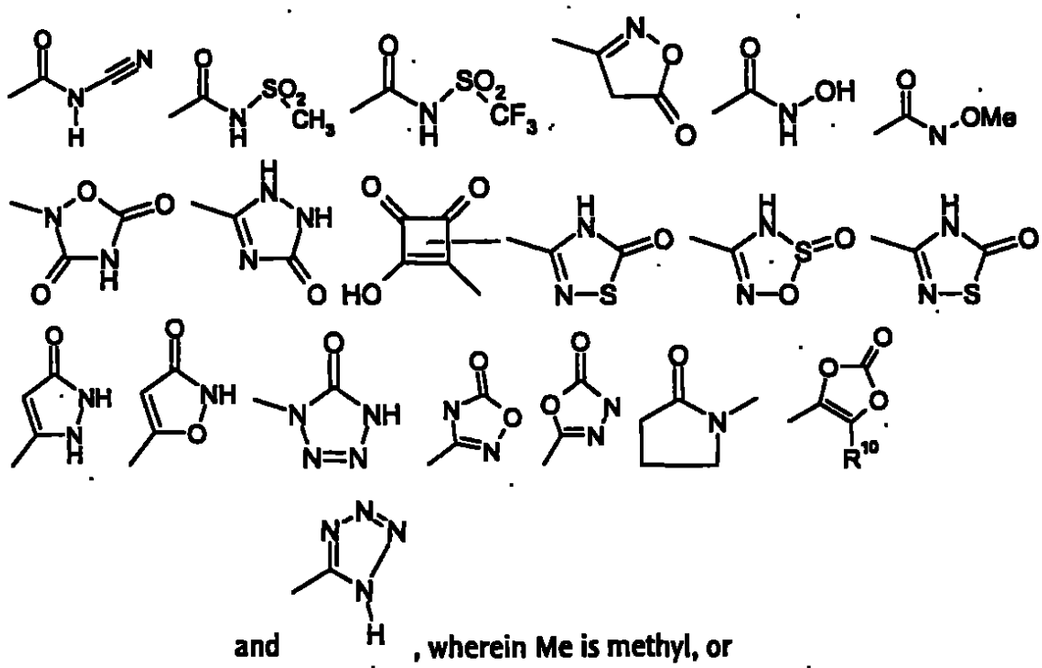
6) -(C_1-C_3)-perfluoroalkyl,

7) -O-R^{17}, or

8) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded can form a 4- to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, -(C_3-C_8)-cycloalkyl, -(C_0-C_3)-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_u-R^{10}$, wherein u is 1 or 2, $-S-R^{10}$, $-SO_r-R^{10}$, wherein r is 1 or 2, $-S(O)_v-N(R^{10})-R^{20}$, wherein v is 1 or 2, $-C(O)-R^{10}$, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, -(C_1-C_4)-alkoxy-phenyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -(C_1-C_3)-perfluoroalkyl, -O-R15, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, or a residue from the following list



and , wherein Me is methyl, or

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-akyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by R^{10}, and

R17 is-(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

2) Thus, the present invention relates to compounds of the formula I, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl, wherein heterocyclyl is selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-

isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and

which is additionally substituted by a heterocyclyl selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl,

phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above and wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,

9) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or

10) $-O-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

11) $-SO_2-CH_3$ or

12) $-SO_2-CF_3$,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above, provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are a monocyclic or bicyclic 6- to 14-membered aryl,

substructure D is a residue selected out of the group azetidine, azetine, azocane, azocane-2-one, cyclobutyl, cyclooctane, cyclooctene, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolan, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, [1,4]oxazocane, [1,3]oxazocan-2-one, oxetan, oxocane, oxocan-2-one, piperazine, piperidine, phenyl, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, 5,6,7,8-tetrahydro-1H-azocin-2-one, tetrahydrofuran, tetrahydropyran, tetrahydropyridine, tetrazine, thiadiazine, thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thietan, thiocane, thiocane-1,1-dioxide, thiocane-1-oxide, thiocan-2-one, thiomorpholine, thiophene, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole and is unsubstituted or substituted 1, 2, 3, 4, 5 or 6 times by R3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -(C_0 –C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, methylene, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -(C_2-C_3)-alkylene-O-(C_0-C_3)-alkylene-, -(C_2-C_3)-alkylene-S(O)-, -(C_2-C_3)-alkylene-$S(O)_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -(C_2-C_3)-alkylene-$S(O)_2$-NH-(R^{10})-, -(C_2-C_3)-alkylene-N(R^{10})- or -(C_0-C_3)-alkylene-C(O)-O-$(CH_2)_m$-,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -$(CH_2)_m$- or -$(CH_2)_n$- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH; or –(C_3-C_6)-cycloalkylen, wherein

cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or $-OH$;

R^1 is a hydrogen atom, $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; $-(C_1-C_3)$-alkylene-C(O)-NH-R^0, $-(C_1-C_3)$-alkylene-C(O)-O-R15, an aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above;
a monocyclic or bicyclic 4- to 15-membered heterocyclyl,which is as defined above;
$-(C_1-C_3)$-perfluoroalkylene, $-(C_1-C_3)$-alkylene-S(O)-(C_1-C_4)-alkyl, $-(C_1-C_3)$-alkylene-$S(O)_2$-(C_1-C_3)-alkyl, $-(C_1-C_3)$-alkylene-$S(O)_2$-$N(R^{4'})$-$R^{5'}$, $-(C_1-C_3)$-alkylene-O-(C_1-C_4)-alkyl, $-(C_0-C_3)$-alkylene-(C_3-C_8)-cycloalkyl, or $-(C_0-C_3)$-alkylene-het, wherein het is a residue selected out of the group azepine, azetidine, aziridine, azirine, 1,4-diazapane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,4-oxazepane, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or $-(C_1-C_4)$-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group selected out of the group azepine, azetidine, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazole,

piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, bromine, iodine, -OH, =O, -$(C_1$-$C_8)$-alkyl, -$(C_1$-$C_4)$-alkoxy, -NO_2,

-C(O)-OH, -CN, -NH_2, -C(O)-O-$(C_1$-$C_4)$-alkyl, -$(C_0$-$C_8)$-alkyl-SO_2-$(C_1$-$C_4)$-alkyl, -$(C_0$-$C_8)$-alkyl-SO_2-$(C_1$-$C_3)$-perfluoroalkyl, -$(C_0$-$C_8)$-alkyl-SO_2-$N(R^{18})$-R^{21}, -C(O)-NH-$(C_1$-$C_8)$-alkyl, -C(O)-N-$[(C_1$-$C_8)$-alkyl$]_2$, -NR^{18}-C(O)-NH-$(C_1$-$C_8)$-alkyl, -C(O)-NH_2, -S-R^{18}, or -NR^{18}-C(O)-NH-$[(C_1$-$C_8)$-alkyl$]_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -$(C_1$-$C_3)$-perfluoroalkyl or -$(C_1$-$C_6)$-alkyl,

V is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R14,

2) a heterocyclyl out of the group acridinyl, 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl; chromenyl, cinnolinyl, decahydrochinolinyl, 1,4-diazepane, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl,

oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, 1λ6-thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is
1) a hydrogen atom,
2) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
3) -C(O)-N(R11)-R12,
4) $-(CH_2)_m-NR^{10}$,
5) $-(C_6-C_{14})$-aryl, wherein aryl is as defined above and wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) -(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

7) -(C_3-C_8)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R3 is

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

7) $-NO_2$,

8) -CN,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) $-S-R^{10}$,

17) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

20) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

21) $-(C_0-C_4)$-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13,

22) $-(C_0-C_4)$-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13.

23) $-(C_0-C_4)$-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

24) $-(C_0-C_4)$-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

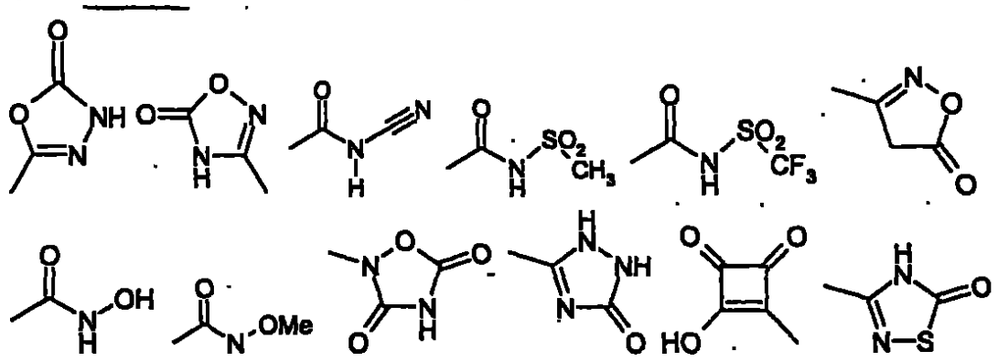
25) $-(C_0-C_3)$-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-O-(C_0-C_3)-alkyl,

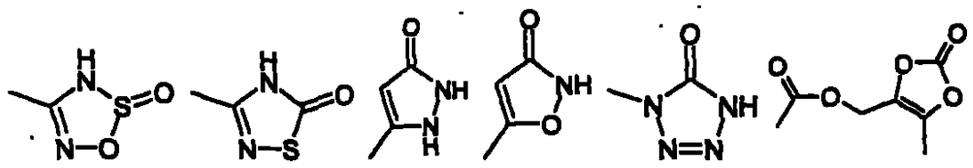
26) $-SO_w-N(R^{11})-R^{13}$, wherein w is 1 or 2,

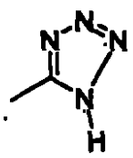
27) $-(C_0-C_4)$-alkylene-C(O)-$N(R^{11})-R^{13}$,

28) $-(C_0-C_4)$-alkylene-$N(R^{11})-R^{13}$, or

29) a residue from the following list







and , wherein Me is methyl, or

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

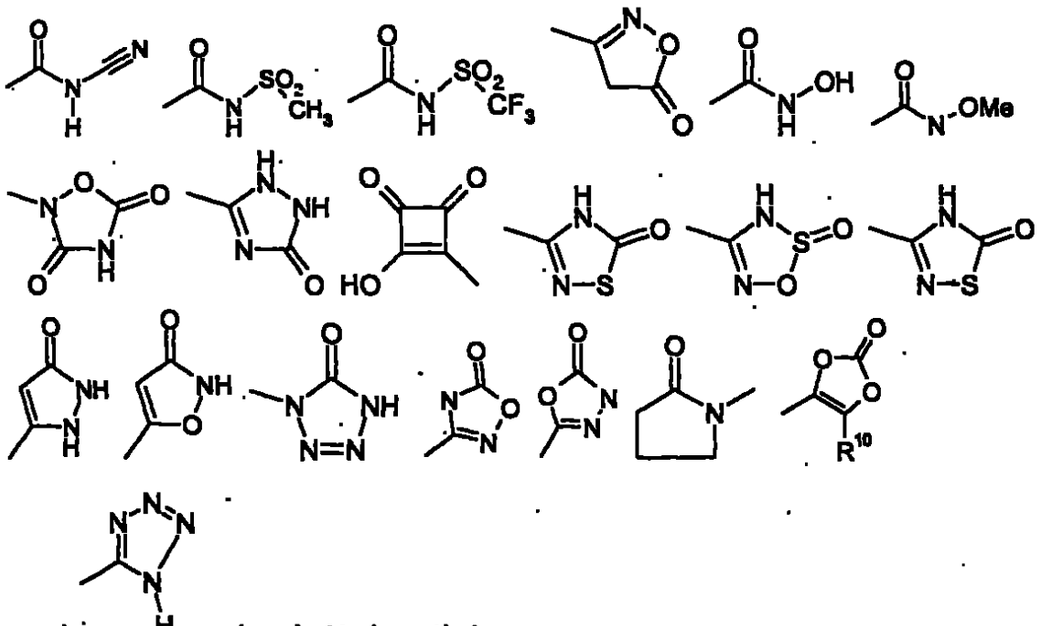
R11 and R12 are indepependently of one another identical or different and are

1) hydrogen atom,
2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
3) -(C_0-C_6)-alkyl-(C_3-C_8)-cycloalkyl,
4) -SO_t-R^{10}, wherein t is 1 or 2,
5) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,
6) -(C_1-C_3)-perfluoroalkyl,
7) -O-R^{17}, or
8) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl are as defined above and are independently from one another unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded form a heterocyclic ring out of the group azepine, azetidine, dioxazole, dioxazine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, thiophene,

1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_3-C_8)$-cycloalkyl, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_u-R^{10}$, wherein u is 1 or 2, $-S-R^{10}$, $-SO_r-R^{10}$, wherein r is 1 or 2, $-S(O)_v-N(R^{10})-R^{20}$, wherein v is 1 or 2, $-C(O)-R^{10}$, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, $-(C_1-C_4)$-alkoxy-phenyl, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, $-(C_1-C_3)$-perfluoroalkyl, -O-R15, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, or a residue from the following list



and , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, $-(C_0-C_4)$-alkyl-OH, $-(C_0-C_4)$-alkyl-O-(C_1-C_4)-akyl or $-(C_1-C_3)$-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is $-(C_1-C_6)$-alkyl, $-(C_1-C_6)$-alkyl-OH, $-(C_1-C_6)$-alkyl-O-(C_1-C_6)-alkyl, $-(C_3-C_8)$-cycloalkyl, $-(C_1-C_6)$-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, $-(C_1-C_6)$-alkyl-(C_3-C_8)-cycloalkyl,

wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by

–OH,

-O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts

3) The present invention also relates to the compounds of the formula I, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl out of the group azabenzimidazolyl, benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, 2-furyl, 3-furyl; imidazolyl, indolyl, indazolyl, isochromanyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidinyl, pyrrolyl; 2-pyrrolyl, 3-pyrrolyl, quinolinyl, quinazolinyl, quinoxalinyl, tetrazolyl, thiadiazolyl, thiazolyl, 2-thienyl or 3-thienyl,

which is additionally substituted by a heterocyclyl selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl; dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-

dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is
1. fluor, chlor or brom,
2. $-NO_2$,
3. -CN,
4. $-C(O)-NH_2$,
5. -OH,
6. $-NH_2$,
7. $-OCF_3$

8. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above and is mono-, di- or trisubstituted independently of one another by halogen or –O-(C_1-C_8)-alkyl,
9. -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or
10. –O-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,
11. $-SO_2CH_3$ or
12. $-SO_2CF_3$,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R0 is a aryl or a heterocyclyl, which are as defined above,

provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -(C_0 –C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, methylene or -(C_0-C_3)-alkylene-C(O)-O-(C_0-C_2)-alkylene ,

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R15, -(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-N($R^{4'}$)-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is a residue selected out of the group azepine, azetidine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline,

isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V form a 4- to 8-membered cyclic group selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,4-oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, bromine, iodine, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-perfluoroalkyl, -(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein $R^{18'}$ and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1) a het residue out of the group 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), azepine, azetidine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine,

1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine, thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine; 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, which is as defined above and wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) $-(CH_2)_m-NR^{10}$,

5) phenyl or naphthyl, wherein phenyl or naphthyl are unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from azepane, azepine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline,

ketomorpholine, ketopiperazine, morpholine, oxazole, [1,4]-oxazepane, piperazine, piperazinone, piperidine, piperidinone, pyrazine, pyridazine, pyridazinone, pyridine, pyridone, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, tetrazine, tetrazole, thiadiazole, thiazole, thiomorpholine, 1λ6-thiomorpholinyl, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

7) -(C_3-C_8)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R3 is

1) hydrogen atom,
2) halogen,
3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
4) -(C_1-C_3)-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is
   a) hydrogen atom,
   b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or
   c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
   d) $-CF_3$, or
   e) CHF_2,
7) -CN,
8) -(C_0-C_4)-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) $-(C_0-C_4)$-alkylene-C(O)-R^{11},

12) $-(C_0-C_4)$-alkylene-C(O)-O-R^{11},

13) $-(C_0-C_4)$-alkylene-C(O)-$N(R^{11})-R^{12}$,

14) $-(C_0-C_4)$-alkylene-$N(R^{11})-R^{12}$,

15) $-NR^{10}-SO_2-R^{10}$,

16) $-(C_0-C_4)$-alkylene-het, wherein het is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

17) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

20) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

21) $-(C_0-C_4)$-alkylene-(C_6-C_{14})-aryl, wherein aryl is as defined above and is mono-, di- or trisubstituted independently of one another by R13,

22) $-(C_0-C_4)$-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

23) $-(C_0-C_3)$-alkylene-O-$CH_2-CF_2-CH_2$-O-(C_0-C_3)-alkyl,

24) $-(C_0-C_3)$-alkylene-O-$CH_2-CF_2-CF_2-CH_2$-O-(C_0-C_3)-alkyl,

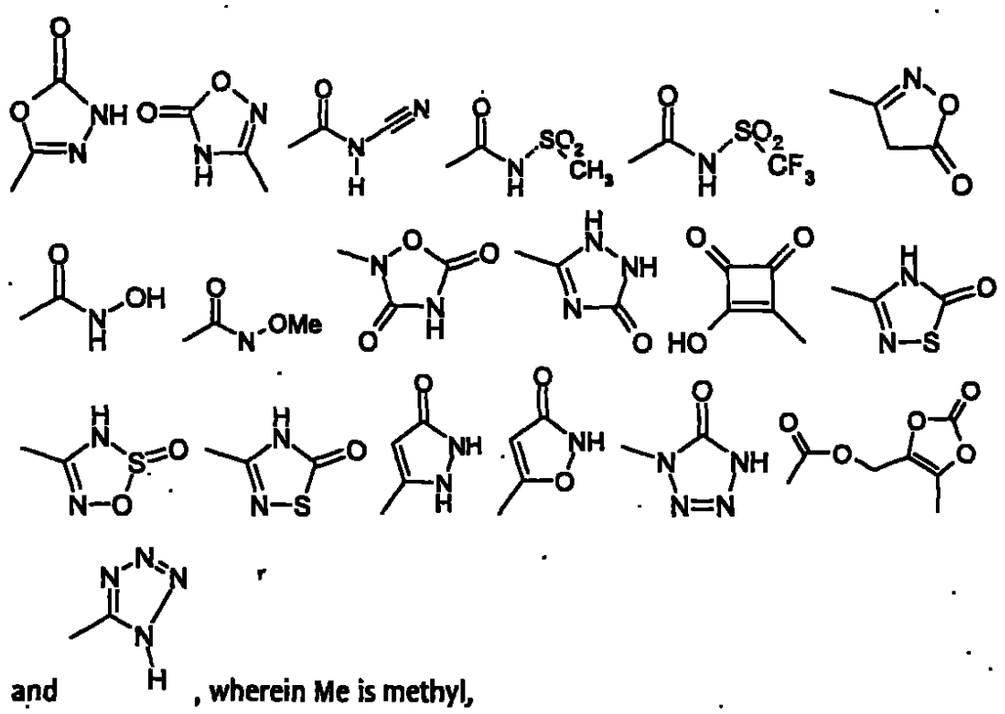
25) $-(C_0-C_3)$-alkylene-O-$CH_2-(C_1-C_3)$-perfluoroalkylene-CH_2-OH,

26) $-SO_w-N(R^{11})-R^{13}$, wherein w is 1 or 2,

27) $-(C_0-C_4)$-alkylene-C(O)-$N(R^{11})-R^{13}$,

28) $-(C_0-C_4)$-alkylene-$N(R^{11})-R^{13}$, or

29) a residue from the following list



and , wherein Me is methyl,

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein aryl is as defined above and wherein alkyl and aryl are independently from one another unsubstituted or mono-, di- or trisubstituted by R13,

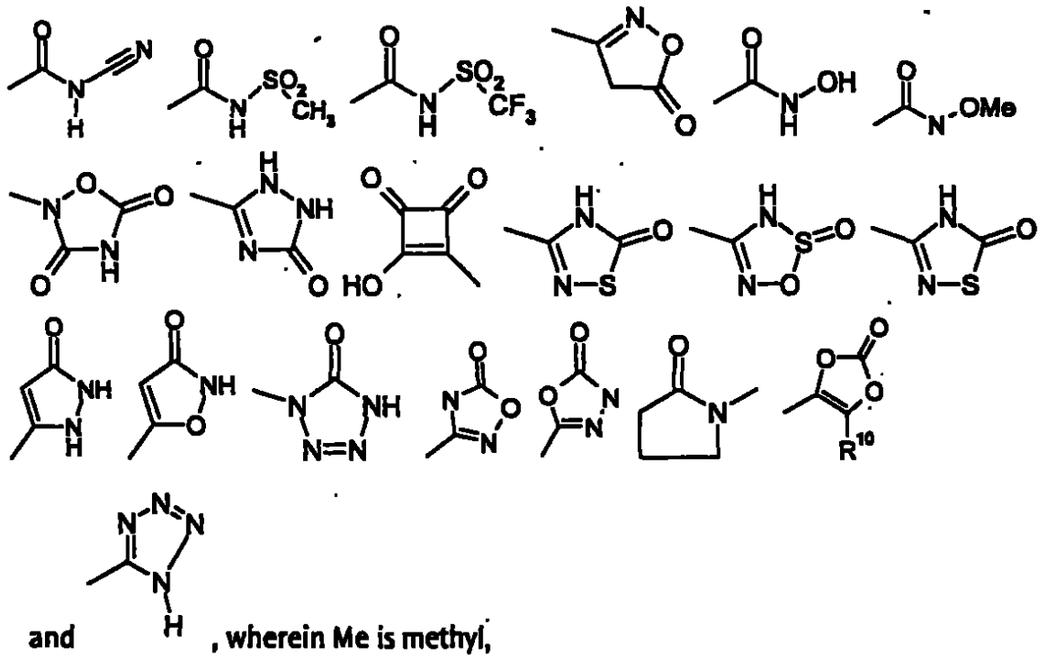
4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl is as defined above and independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline,

isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, which is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is fluorine, chlorine, bromine, iodine, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, $-(C_1-C_3)$-perfluoroalkyl, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, $-(C_1-C_4)$-alkoxy-phenyl, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -O-R15, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, or a residue from the following list



and , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, $-(C_0-C_4)$-alkyl-OH, $-(C_0-C_4)$-alkyl-O-(C_1-C_4)-alkyl or $-(C_1-C_3)$-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH,

-O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

4) The present invention also relates to the compounds of the formula I, wherein

R0 is 1) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

R8 is 1. F, Cl, Br or J,

2. -C(O)-NH_2,

3. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. –O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R0 is a aryl or a heterocyclyl, which are as defined above,

provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -C(O)-; -SO_2- , methylene, -(C_0–C_2)-alkylene-C(O)-NR^{10}- or -(C_0-C_3)-alkylene-C(O)-O-(C_0-C_2)-alkylene ,

R^1 is hydrogen atom, -(C_1-C_2)-alkyl, -(C_1-C_3)-alkylene-C(O)-NH-R0, -(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-C(O)-O-R^{15}, -(C_1-C_3)-alkylene-S(O)$_2$-(C_1-C_3)-alkyl or -(C_1-C_3)-alkylene-S(O)$_2$-N($R^{4'}$)-$R^{5'}$, wherein $R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 7- membered cyclic group out of the group azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, 1,4-oxazepane, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, -OH, =O, -(C_1-C_8)-alkyl, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -C(O)-NH_2 or –N(R^{18})-R^{21},

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_4)-alkyl,

V is 1. a cyclic residue out of the group containing compounds which are derived from 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), aziridine, azirine, azetidine, azetidinone, 1,4-diazepane, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, 1,4-oxazepane, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,3-dioxolane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiodiazole, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

G is a direct bond, -$(CH_2)_m$-, or -$(CH_2)_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

M is 1. a hydrogen atom,

2. heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from azepane, azepine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, oxazole, [1,4]-oxazepane, piperazine, piperazinone, piperidine, piperidinone, pyrazine, pyridazine, pyridazinone, pyridine, pyridone, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, tetrazine, tetrazole, thiadiazole, thiazole, thiomorpholine, 1λ6-thiomorpholinyl, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

4. (C_3-C_6)-cycloalkyl or

5. -C(O)-N(R^{11})-R^{12},

R3 is

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) -CF_3, or

e) CHF_2,

7) -CN,

8) -NR^{10}-SO_2-R^{10},

9) -SO_s-R^{11}, wherein s is 1 or 2,

10) -SO_t-N(R^{11})-R^{12}, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

15) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

19) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

20) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

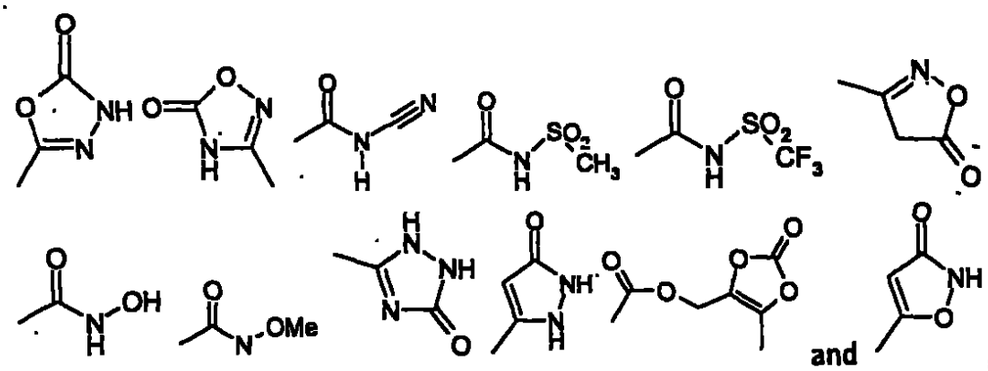
21) -(C_0-C_3)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-OH,

22) -SO_w-N(R^{11})-R^{13}, wherein w is 1 or 2,

23) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{13},

24) -(C_0-C_4)-alkylene-N(R^{11})-R^{13}, or

25) a residue from the following list



and , wherein

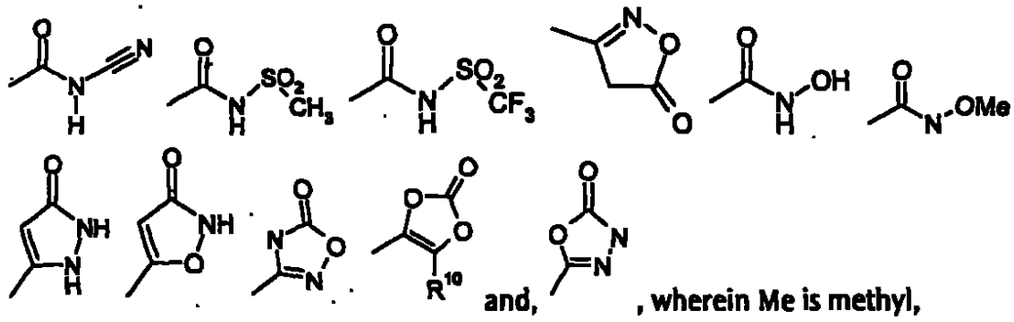
Me is methyl,

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a ring selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]-oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said

ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is fluorine, chlorine, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, $-(C_1-C_3)$-perfluoroalkyl, $-NH-C(O)-NH-R^{10}$, $-(C_0-C_4)$-alkyl-$C(O)-O-C(R15, R16)-O-C(O)-R17$, $-(C_1-C_4)$-alkoxy-phenyl, $-(C_0-C_4)$-alkyl-$C(O)-O-C(R15, R16)-O-C(O)-O-R17$, $-O-R15$, $-NH-C(O)-O-R^{10}$, or a residue from the following list



and, , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, $-(C_0-C_4)$-alkyl-OH, $-(C_0-C_4)$-alkyl-$O-(C_1-C_4)$-akyl or $-(C_1-C_3)$-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is $-(C_1-C_6)$-alkyl, $-(C_1-C_6)$-alkyl-OH, $-(C_1-C_6)$-alkyl-$O-(C_1-C_6)$-alkyl, $-(C_3-C_8)$-cycloalkyl, $-(C_1-C_6)$-alkyl-$O-(C_1-C_8)$-alkyl-(C_3-C_8)-cycloalkyl, $-(C_1-C_6)$-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, $-O-(C_1-C_4)$-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

5) The present invention also relates to the compounds of the formula I, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2. a heterocyclyl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyridyl, purinyl and pteridinyl,

wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

3. a heterocyclyl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

R8 is 1. is F, Cl, Br, J,

2. $-C(O)-NH_2$,

3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. $-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R0 is a aryl or a heterocyclyl, which are as defined above,

provided that R8 is not a $-O-(C_1-C_8)$-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R^3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -C(O)-; -SO_2-, -C(O)-O-methylene, methylene or -(C_0 –C_2)-alkylene-C(O)-NR^{10}-,

R^1 is hydrogen atom or -(C_1-C_2)-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 7-membered cyclic group out of the group piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, -(C_1-C_4)-alkyl or -NH_2,

V is 1. a cyclic residue out of the group containing compounds, which are derived from 8-aza-bicyclo[3.2.1]oct-3-yl, azaindolyl (1H-pyrrolopyridyl), azetidine, azepine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diazirine, 1,3-dioxolane, dioxazole, furan, imidazole, isoquinoline, isothiazole, isothiazolidine, isothiazoline, isoxazole, 2-isoxazoline, isoxazolidine, ketopiperazine, morpholine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, 1,2-oxathiolan, piperidine, pyran, pyrazine, pyrazole, pyridazine, piperazine, pyridine, pyridone, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, quinazoline, quinoline, tetrazine, tetrazole, thiadiazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thietan, thiomorpholine, thiophene, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -(CH_2)$_m$-, or -(CH_2)$_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

M is 1. a hydrogen atom,

2. heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from 1,4-diazepane, ketomorpholine, thiophene, pyridazone, piperidine,

piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, thiadiazole, 1λ6-thiomorpholinyl or thiomorpholine, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

4. (C_3-C_6)-cycloalkyl,

R3 is

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

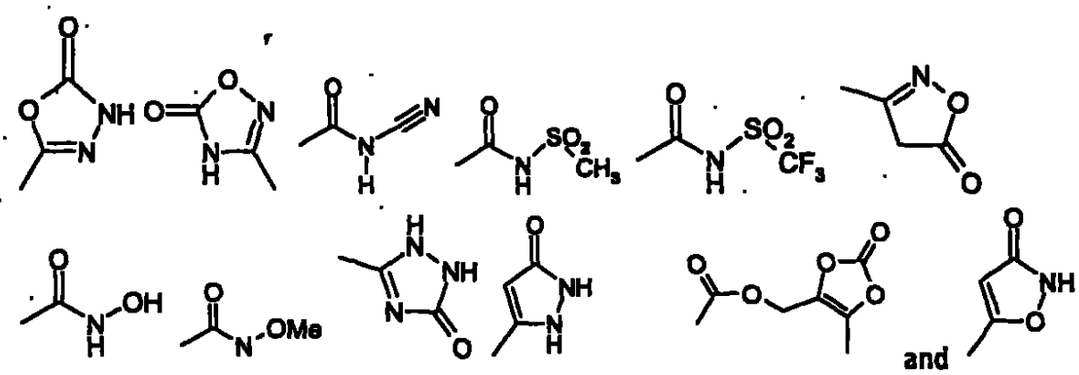
15) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17, or

19) a residue from the following list



and

wherein Me is methyl,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

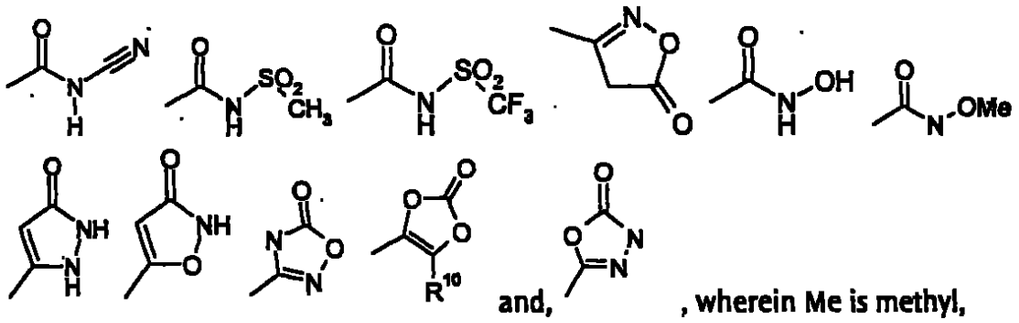
3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl,

4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13 and wherein heterocyclyl is selected out of the group azetidine, cyclopropyl, cyclobutyl, 4,5-dihydro-oxazole, imidazolidine, morpholine, (1,4)-oxazepane, oxazolidine, piperidine, piperazine, pyrrolidine, tetrahydrothiophene, thiazolidine or thiomorpholine, or

R11 and R12 together with the nitrogen atom to which they are bonded form a heterocyclic ring, which is selected out of the group azetidine, cyclopropyl, cyclobutyl, 4,5-dihydro-oxazole, imidazolidine, morpholine, (1,4)-oxazepane, oxazolidine, piperidine, piperazine, pyrrolidine, tetrahydrothiophene, thiazolidine or thiomorpholine, wherein said ring is unsubstituted or mono-, di- or trisubstituted by R13,

R13 is fluorine, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_3-C_6)$-cycloalkyl, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-S-R^{10}$, $-SO_2-R^{10}$, $-(C_1-C_3)$-perfluoroalkyl, or a residue from the following list



and, , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, $-(C_1-C_4)$-alkyl or $-(C_1-C_3)$-perfluoroalkyl,

R^{15} and R^{16} are independently of one another hydrogen, $-(C_1-C_4)$-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is $-(C_1-C_6)$-alkyl, $-(C_1-C_6)$-alkyl-OH, $-(C_1-C_6)$-alkyl-$O-(C_1-C_8)$-alkyl-(C_3-C_8)-cycloalkyl, $-(C_1-C_6)$-alkyl-$O-(C_1-C_6)$-alkyl or $-(C_0-C_6)$-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, $-O-(C_1-C_4)$-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

6) The present invention also relates to the compounds of the formula I, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R8,

2. pyridyl or 1H-indazolyl, wherein pyridyl and 1H-indazolyl are unsubstituted or mono- or disubstituted independently of one another by R8, or

3. a heterocyclyl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heterocyclyl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R8,

R8 is F, Cl, Br, -O-CH_3 or -C(O)-NH_2,

provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide, pyrrolyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl or pyrazinyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -C(O)-; -SO_2-, -C(O)-O-methylene, -CH_2-C(O)-NH- or methylene,

R^1 is hydrogen atom,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group out of the group azetidine, pyrrolidine, piperidine and piperazine,

R14 is fluorine, chlorine, methyl, ethyl, =O, -SO_2-CH_3 or -NH_2,

V is 1. a residue out of the group containing compounds which is derived from 8-aza-bicyclo[3.2.1]oct-3-yl, azaindolyl (1H-pyrrolopyridyl), azetidine, 1,4-diazepane, isoxazole, isoquinoline, piperazine, piperidine, pyrazine, pyridazine, pyrimidine, pyrrolidine, quinazoline, quinoline or tetrahydropyrane, wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R14,

G is a direct bond, -(CH_2)$_m$-, -C(O)- or -(CH_2)$_m$-NR^{10}-,

m is the integers zero, 1 or 2,

M is a hydrogen atom, (C_2-C_4)-alkyl, azepanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolyl, ketomorpholinyl, morpholinyl, [1,4]Oxazepanyl, piperazinyl, piperidinyl, piperidonyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolidinyl, 1λ6-

thiomorpholinyl, 1,4,5,6-tetrahydro-pyridazinyl, or tetrahydropyranyl, wherein the residues are unsubstituted or mono- or disubstituted independently of one another by R14

R3 is

1) hydrogen atom,

2) fluorine, chlorine,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_2)-alkylene-O-R19, wherein R19 is

   a) hydrogen atom,

   b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

   c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

   d) $-CF_3$, or

   e) $-CHF_2$,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

15) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) –(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl or

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17, or

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl,

4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13 and wherein heterocyclyl is selected out of the group azetidine, imidazolidine, morpholine, (1,4)-oxazepane or pyrrolidine or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring, which is selected out of the group azetidine, imidazolidine, morpholine, (1,4)-oxazepane piperazine, piperidine, pyrrolidine or thiomorpholine, wherein said ring is unsubstituted or mono-, di- or trisubstituted by R13,

R13 is fluorine, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_1-C_3)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -SO_2-NH, or -(C_1-C_3)-perfluoroalkyl,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_4)-alkyl or -(C_1-C_3)-perfluoroalkyl,

R^{15} and R^{16} are independently of one another hydrogen, -(C_1-C_4)-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl or -(C_0-C_4)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

7) The present invention also relates to the compounds of the formula I, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R8,

2. pyridyl or 1H-indazolyl, wherein pyridyl and 1H-indazolyl are unsubstituted or mono- or disubstituted independently of one another by R8, or

3. a heterocyclyl out of the group thiadiazolyl, isoxazolyl and thiazolyl, wherein said heterocyclyl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R8,

R8 is Cl or -O-CH_3,

provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, thienyl or pyrimidinyl, and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is -CH_2-C(O)-NH- or methylene,

R^1 is hydrogen atom,

R^2 is a direct bond,

R14 is fluorine or =O,

V is piperidinyl or phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R14,

G is a direct bond or -C(O)-,

M is a hydrogen atom, (C_2-C_4)-alkyl, isopropyl, cyclopropyl, morpholinyl, piperazinyl, piperidinyl, pyrazinyl, pyridyl, pyrimidyl, pyrrolidinyl or 1λ6-thiomorpholinyl, wherein the residues are unsubstituted or mono- or disubstituted independently of one another by R14

R3 is

1) hydrogen atom,

2) fluorine, chlorine,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_0-C_2)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) $-CF_3$,

5) $-SO_2-R^{11}$,

6) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

7) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12}

8) -(C_0-C_2)-alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl or

9) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring, which is selected out of the group azetidine, morpholine, (1,4)-oxazepane or piperidine, wherein said ring is unsubstituted or mono-, di- or trisubstituted by R13,

R13 is fluorine, =O, -OH, $-CF_3$, -C(O)-O-R^{10}, -(C_1-C_3)-alkyl, -(C_3-C_6)-cycloalkyl or -(C_0-C_3)-alkylene-O-R^{10},

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

R^{15} and R^{16} are independently of one another hydrogen atom or -(C_1-C_4)-alkyl, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH or -(C_0-C_4)-alkyl-(C_3-C_8)-cycloalkyl,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

8) The present invention also relates to the compounds of the formula I, which are 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(4-Chloro-phenylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1- isopropyl-piperidine-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-pyrimidine-4-yl-piperidine-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,

1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-5-carboxylic acid methyl ester,

3-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 3H-benzoimidazole-5-carboxylic acid methyl ester,

1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-5-carboxylic acid,

3-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 3H-benzoimidazole-5-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b] pyridine-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4- [(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4- [(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(3- oxo-morpholin-4-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- H-benzoimidazole-4-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide,

1-(3-Methoxy-benzyl)-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)- phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide,-

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-oxazolidin-3-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-oxazolidin-3-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-piperidin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1l6-thiomorpholin-4-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1l6-thiomorpholin-4-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2- oxo-2H-pyrazin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-piperazin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2- oxo-piperazin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- 1H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 2-hydroxy-ethyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid carboxymethyl ester,

1-(3-Methoxy-benzyl)-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(2-hydroxy-ethanesulfonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(2-hydroxy-ethanesulfonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid cyclopropylmethyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 2-methoxy-ethyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-hydroxymethyl-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxymethyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(morpholine-4-carbonyl)-1H-benzoimidazole- 2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-([1,4]oxazepane-4-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2,6-dimethyl-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(4,4-difluoro-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid carboxymethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-methoxy-azetidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-4- carboxylic acid,
2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-4- carboxylic acid,
1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 4-carboxylic acid,
3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 4-carboxylic acid,
4-(3-Hydroxy-azetidine-1-carbonyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-methoxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-5- carboxylic acid methyl ester,
2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-5- carboxylic acid methyl ester,
1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid methyl ester,
3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 5-carboxylic acid methyl ester,

1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid,

1-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

3-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid,

1-(5-Chloro-1H-indazol-3-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(4-hydroxy-piperidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

7-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1,3-dimethyl-2,6-dioxo-2,3,6,7- tetrahydro-1H-purine-8-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid methyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid cyclopropylmethyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-thieno[3,4-d]imidazole-2,6-dicarboxylic acid 6-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)- amide],

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-([1,4]oxazepane-4-carbonyl)-3H-thieno[3,4-d]imidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester,

1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid

1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-ethoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-hydroxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[2-fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-3H-benzoimidazole-5-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid or

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-5- (2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide.

In general, the meaning of any group, residue, heteroatom, number etc., which can occur more than once in the compounds of the formula I, is independent of the meaning of this group, residue, heteroatom, number etc. in any other occurrence. All groups, residues, heteroatoms, numbers etc., which can occur more than once in the compounds of the formula I can be identical or different.

As used herein, the term alkyl is to be understood in the broadest sense to mean hydrocarbon residues which can be linear, e.g. straight-chain, or branched and which can be acyclic or cyclic residues or comprise any combination of acyclic and cyclic subunits. Further, the term alkyl as used herein expressly includes saturated groups as well as unsaturated groups which latter groups contain one or more, for example one, two or three, double bonds and/or triple bonds, provided that the double bonds are not located within a cyclic alkyl group in such a manner that an aromatic system results. All these statements also apply if an alkyl group occurs as a substituent on another residue, for example in an alkyloxy residue, an alkyloxycarbonyl residue or an arylalkyl residue. Examples of „-(C_1-C_8)-alkyl" or „-(C_1-C_8)-alkylene" are alkyl residues containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms are methyl, methylene, ethyl, ethylene. propyl, propylene, butyl, butylene, pentyl, pentylene, hexyl, heptyl or octyl, the n-isomers of all these residues, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tBu, tert-pentyl, sec-butyl, tert-butyl or tert-pentyl. The term „-(C_0-C_6)-alkyl" or „-(C_0-C_8)-alkylene" is a hydrocarbon residues

containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms. The term „-C_0-alkyl" or „-C_0-alkylene" is a covalent bond.

Unsaturated alkyl residues are, for example, alkenyl residues such as vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl, or alkynyl residues such as ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butynyl. Alkyl residues can also be unsaturated when they are substituted.

Examples of -(C_3-C_8)-cycloalkyl cyclic alkyl residues are cycloalkyl residues containing 3, 4, 5, 6, 7 or 8 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyloheptyl or cyclooctyl, which can also be substituted and/or unsaturated. Unsaturated cyclic alkyl groups and unsaturated cycloalkyl groups like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom.

The terms "a monocyclic or bicyclic 6- to 14-membered aryl" or "-(C_6-C_{14})-aryl" are understood as meaning aromatic hydrocarbon radicals containing from 6 to 14 carbon atoms in the ring. Examples of -(C_6-C_{14})-aryl radicals are phenyl, naphthyl, for example 1-naphthyl and 2-naphthyl, biphenylyl, for example 2-biphenylyl, 3-biphenylyl and 4-biphenylyl, anthryl or fluorenyl. Biphenylyl radicals, naphthyl radicals and, in particular, phenyl radicals are preferred aryl radicals.

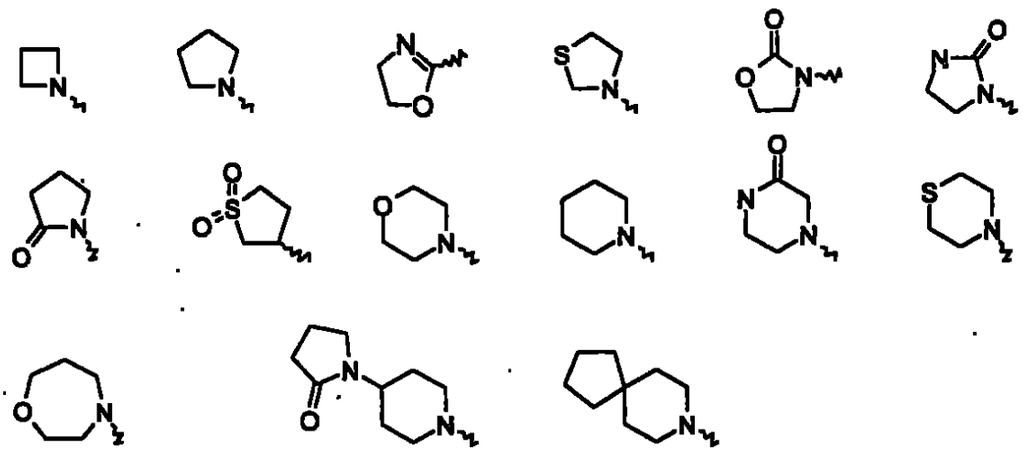
The terms "mono- or bicyclic 4- to 15-membered heterocyclyl" or "-(C_4-C_{15})-heterocyclyl" refer to heterocycles in which one or more of the 4 to 15 ring carbon atoms are replaced by heteroatoms such as nitrogen, oxygen or sulfur.

Examples are acridinyl, 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridinyl), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxazolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 3,3-dioxo[1,3,4]oxathiazinyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl,

ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, oxetanyl, oxocanyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

Preferred are heterocyclyls, such as benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, 2-furyl, 3-furyl; imidazolyl, indolyl, indazolyl, isochromanyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidinyl, pyrrolyl; 2-pyrrolyl, 3-pyrrolyl, quinolinyl, quinazolinyl; quinoxalinyl, tetrazolyl, thiazolyl, 2-thienyl and 3-thienyl.

Also preferred are:



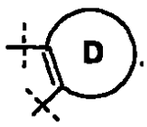
The terms "het" or "a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms" refer to structures of heterocycles which can be derived from compounds such as azepine, azetidine, aziridine, azirine, 1,4 diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxetan, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, -pyrrolidinone, pyrroline, tetrahydrofuran, tetrahydropyran, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole.

The term " R^1-N-R^2-V can form a 4- to 8-membered cyclic group " or "R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a 4- to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen" refer to structures of heterocycles which can be derived from compounds such as azepane, azepine, azetidine, dioxazole, dioxazine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 2,3 dihydroindole, imidazole, imidazoline, imidazolidine, indole, isothiazole,

isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole.

The term "R^{15} and R^{16} together with the carbon atom to which they are bonded can form a 3- to 6 membered carbocyclic ring" refer to structures, which can be derived from compounds such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "substructure



in formulae I" or the "substructure D" is a 4-to 8 membered saturated, partially unsaturated or aromatic cyclic group containing zero, 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen" refer to structures, which can be derived from compounds such as azepane, azetidine, azetine, azocane, azocane-2-one, cyclobutyl, cyclooctane, cyclooctene, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1,2-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,4-oxaazepane, 1,2-oxathiepane, 1,2-oxathiolan, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, [1,4]oxazocane, [1,3]oxazocan-2-one, oxetan, oxocane, oxocan-2-one, piperazine, piperidine, phenyl, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, 5,6,7,8-tetrahydro-1H-azocin-2-one, tetrahydrofuran, tetrahydropyran, tetrahydropyridine, tetrazine, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thietan, thiocane, thiocane-1,1-dioxide, thiocane-1-oxide, thiocan-2-one, thiomorpholine, thiophen, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole.

The term "substructure D" is a 5 to 6 membered saturated, partially unsaturated or aromatic cyclic group containing zero, 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen" refer to structures, which can be derived from compounds such as cyclopentyl, cyclohexyl, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, 1,2-oxathiolan, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, piperazine, piperidine, phenyl, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyrazine, pyrazinone, pyridazine, pyridazone, pyridine, pyridone, pyrimidine, pyrimidone, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydrofuran, tetrahydropyran, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thiomorpholine, thiophen, thiopyran, tetrazine, tetrazole, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole.

The term "R^1 and R^3 together with the atoms to which they are bonded can form a 6- to 8-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen" refers to structures of heterocycles which can be derived from compounds such as azocane, azocane-2-one, cyloheptyl cyclohexyl, cyclooctane, cyclooctene, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, dioxazine, [1,4]dioxocane, dioxole, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, [1,4]oxazocane, [1,3]oxazocan-2-one, oxocane, oxocan-2-one, phenyl, piperazine, piperidine, pyran, pyrazine, pyridazine, pyrimidine, 5,6,7,8-tetrahydro-1H-azocin-2-one or thiomorpholine.

The term "oxo-residue" or "=O" refers to residues such as carbonyl (-C(O)-) or nitroso (-N=O).

The fact that many of the before-listed names of heterocycles are the chemical names of unsaturated or aromatic ring systems does not imply that the, the 4-15 membered mono- or polycyclic group could only be derived from the respective unsaturated ring system. The names here only serve to describe the ring system with respect to ring size and the number of the heteroatoms and their relative positions. As explained above, the 4-15 membered mono- or polycyclic group can be saturated or partially unsaturated or aromatic, and can thus be derived not only from the before-listed heterocycles themselves but also from all their partially

or completely hydrogenated analogues and also from their more highly unsaturated analogues if applicable. As examples of completely or partially hydrogenated analogues of the before-listed heterocycles from which this group may be derived the following may be mentioned: pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, piperidine, 1,3-dioxolane, 2-imidazoline, imidazolidine, 4,5-dihydro-1,3-oxazol, 1,3-oxazolidine, 4,5-dihydro-1,3-thiazole, 1,3-thiazolidine, perhydro-1,4-dioxane, piperazine, perhydro-1,4-oxazine (= morpholine), perhydro-1,4-thiazine (= thiomorpholine), perhydroazepine, indoline, isoindoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, etc.

The term "-(C_1-C_3)-perfluoroalkyl" is a partial or totally fluorinated alkyl-residue, which can be derived from residues such as -CF_3, -CHF_2, -CH_2F, -CHF-CF_3, -CHF-CHF_2, -CHF-CH_2F, -CH_2-CF_3,

-CH_2-CHF_2, -CH_2-CH_2F, -CF_2-CF_3, -CF_2-CHF_2, -CF_2-CH_2F, -CH_2-CHF-CF_3, -CH_2-CHF-CHF_2, -CH_2-CHF-CH_2F, -CH_2-CH_2-CF_3, -CH_2-CH_2-CHF_2, -CH_2-CH_2-CH_2F, -CH_2-CF_2-CF_3, -CH_2-CF_2-CHF_2, -CH_2-CF_2-CH_2F; -CHF-CHF-CF_3, -CHF-CHF-CHF_2, -CHF-CHF-CH_2F, -CHF-CH_2-CF_3, -CHF-CH_2-CHF_2, -CHF-CH_2-CH_2F, -CHF-CF_2-CF_3, -CHF-CF_2-CHF_2, -CHF-CF_2-CH_2F, -CF_2-CHF-CF_3,

-CF_2-CHF-CHF_2, -CF_2-CHF-CH_2F, -CF_2-CH_2-CF_3, -CF_2-CH_2-CHF_2, -CF_2-CH_2-CH_2F, -CF_2-CF_2-CF_3, -CF_2-CF_2-CHF_2 or -CF_2-CF_2-CH_2F.

The term "-(C_1-C_3)-perfluoroalkylene" is a partial or totally fluorinated alkylene-residue, which can be derived from residues such as –CF_2-, -CHF-, -CHF-CHF_2-, -CHF-CHF-, -CH_2-CF_2-, -CH_2-CHF-, -CF_2-CF_2-, -CF_2-CHF-, -CH_2-CHF-CF_2-, -CH_2-CHF-CHF-, -CH_2-CH_2-CF_2-, -CH_2-CH_2-CHF, -CH_2-CF_2-CF_2-, -CH_2-CF_2-CHF-, -CHF-CHF-CF_2-, -CHF-CHF-CHF-, -CHF-CH_2-CF_2-, -CHF-CH_2-CHF-, -CHF-CF_2-CF_2-, -CHF-CF_2-CHF-, -CF_2-CHF-CF_2-, -CF_2-CHF-CHF-, -CF_2-CH_2-CF_2-, -CF_2-CH_2-CHF-, -CF_2-CF_2-CF_2-, or -CF_2-CF_2-CHF.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, particularly preferably chlorine or bromine.

Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure enantiomers or pure diastereomers or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I, and it comprises all ratios of the stereoisomers in the mixtures. In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers or trans isomers) the invention relates both to pure E isomers and pure Z isomers and to E/Z mixtures in all ratios. The invention also comprises all tautomeric forms of the compounds of the formula I.

Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases or by resolution, for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically uniform compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

Physiologically tolerable salts of the compounds of formula I are nontoxic salts that are physiologically acceptable, in particular pharmaceutically utilizable salts. Such salts of compounds of the formula I containing acidic groups, for example a carboxyl group COOH, are for example alkali metal salts or alkaline earth metal salts such as sodium salts, potassium salts, magnesium salts and calcium salts, and also salts with physiologically tolerable quaternary ammonium ions such as tetramethylammonium or tetraethylammonium, and acid addition salts with ammonia and physiologically tolerable organic amines, such as methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine. Basic groups contained in the compounds of the formula I, for example amino groups or guanidino groups, form acid addition salts, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid, or with organic carboxylic acids and sulfonic acids such as formic acid, acetic acid, oxalic acid, citric acid, lactic acid, malic acid, succinic acid, malonic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid.

Compounds of the formula I, which simultaneously contain a basic group and an acidic group, for example a guanidino group and a carboxyl group, can also be present as zwitterions (betaines) which are likewise included in the present invention.

Salts of compounds of the formula I can be obtained by customary methods known to those skilled in the art, for example by combining a compound of the formula I with an inorganic or organic acid or base in a solvent or dispersant, or from other salts by cation exchange or anion exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiologically tolerability, are not directly suitable for use in pharmaceuticals but are suitable, for example, as intermediates for carrying out further chemical modifications of the compounds of the formula I or as starting materials for the preparation of physiologically tolerable salts.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols.

The invention also includes derivatives and modifications of the compounds of the formula I, for example prodrugs, protected forms and other physiologically tolerable derivatives, as well as active metabolites of the compounds of the formula I. The invention relates in particular to prodrugs and protected forms of the compounds of the formula I, which can be converted into compounds of the formula I under physiological conditions. Suitable prodrugs for the compounds of the formula I, i. e. chemically modified derivatives of the compounds of the formula I having properties which are improved in a desired manner, for example with respect to solubility, bioavailability or duration of action, are known to those skilled in the art. More detailed information relating to prodrugs is found in standard literature like, for example, Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Fleisher et al., Advanced Drug Delivery Reviews 19 (1996) 115-130; or H. Bundgaard, Drugs of the Future 16 (1991) 443 which are all incorporated herein by reference. Suitable prodrugs for the compounds of the formula I are especially acyl prodrugs and carbamate prodrugs of acylatable nitrogen-containing groups such as amino groups and the guanidino group and also ester prodrugs and amide prodrugs of carboxylic acid groups which may be present in compounds of the formula I. In the acyl prodrugs and carbamate prodrugs one or more, for example one or two, hydrogen atoms on nitrogen atoms in such groups are replaced with an acyl group or a carbamate, preferably a -(C_1-C_6)-alkyloxycarbonyl group. Suitable acyl groups and carbamate groups for acyl prodrugs

and carbamate prodrugs are, for example, the groups R^{p1}-CO- and R^{p2}O-CO-, in which R^{p1} is hydrogen, (C_1-C_{18})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl-, (C_6-C_{14})-aryl, Het-, (C_6-C_{14})-aryl-(C_1-C_4)-alkyl- or Het-(C_1-C_4)-alkyl- and in which R^{p2} has the meanings indicated for R^{p1} with the exception of hydrogen.

Especially preferred compounds of the formula I are those wherein two or more residues are defined as indicated before for preferred compounds of the formula I, or residues can have one or some of the specific denotations of the residues given in their general definitions or in the definitions of preferred compounds before. All possible combinations of definitions given for preferred definitions and of specific denotations of residues explicitly are a subject of the present invention.

Also with respect to all preferred compounds of the formula I all their stereoisomeric forms and mixtures thereof in any ratio and their physiologically acceptable salts explicitly are a subject of the present invention, as well as are their prodrugs. Similarly, also in all preferred compounds of the formula I, all residues that are present more than one time in the molecule are independent of each other and can be identical or different.

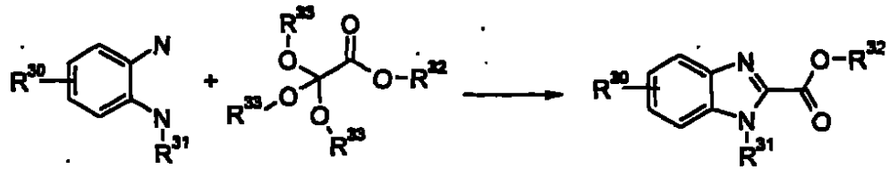
The compounds of the formula I can be prepared by utilising procedures and techniques, which per se are well known and appreciated by one of ordinary skill in the art. Starting materials or building blocks for use in the general synthetic procedures that can be applied in the preparation of the compounds of formula I are readily available to one of ordinary skill in the art. In many cases they are commercially available or have been described in the literature. Otherwise they can be prepared from readily available precursor compounds analogously to procedures described in the literature, or by procedures or analogously to procedures described in this application.

In general, compounds of the formula I can be prepared, for example in the course of a convergent synthesis, by linking two or more fragments which can be derived retrosynthetically from the formula I. More specifically, suitably substituted starting benzoimidazole derivatives are employed as building blocks in the preparation of the compounds of formula I. If not commercially available, such benzoimidazole derivatives can be prepared according to the well-known standard procedures for the formation of the benzoimidazole ring system. By

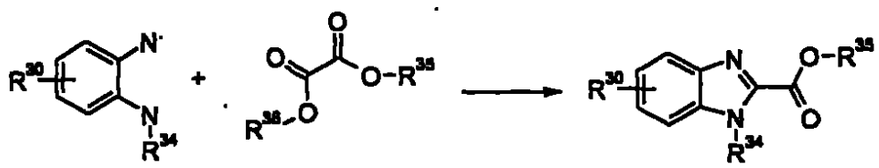
choosing suitable precursor molecules, these benzoimidazole syntheses allow the introduction of a variety of substituents into the various positions of the benzoimidazole system, which can be chemically modified in order to finally arrive at the molecule of the formula I having the desired substituent pattern. As one of the comprehensive reviews in which numerous details and literature references on the chemistry of benzoimidazole and on synthetic procedures for their preparation can be found, J. Backes, B. Heinz, W. G. Ried in Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany 1994, Vol. E8c Hetarene.

If starting benzoimidazole derivatives are not commercially available and have to be synthesized this can be done, for example, according to the well-known benzoimidazole syntheses mentioned above. In the following procedures of particuluar interest for the embodiment of this invention are listed and referenced briefly, however, they are standard procedures comprehensively discussed in the literature, and are well known to one skilled in the art. Although not always shown explicitly, in certain cases positional isomers will occur during the synthesis of the below mentioned reactions. Nevertheless such mixtures of positional isomers, can be separated by modern separation techniques like, for example, preparative HPLC.

1) J. H. Musser et al., Synth. Commun. 1984, 10, 947.



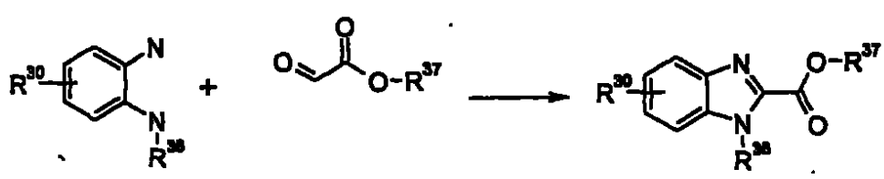
2) Reissert et al., Chem. Ber. 1905, 38, 93.



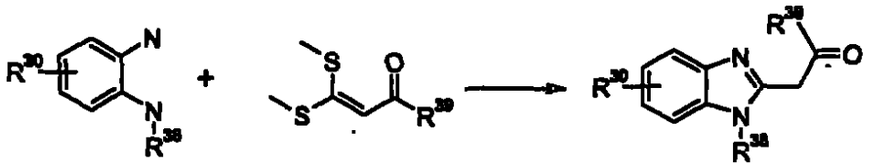
3) a) Usherwood et al., J. Chem. Soc. 1923, 123, 1082

b) J. R. Young et al., Bioorg. Med. Chem Lett. 2002, 12, 827.

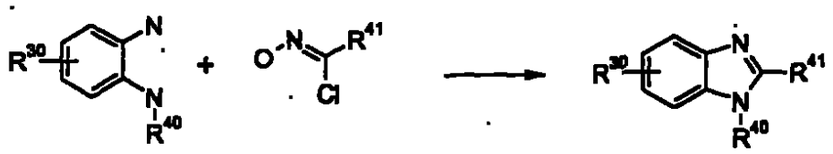
c) H. Yukawa et al., Bioorg. Med. Chem Lett. 1997, 10, 1267.



4) Z.-T. Huang et al., Tetrahedron 1992, 48, 2325.



5) A. O. Abdelhamid et al., J. Heterocycl. Chem. 1988, 25, 403.



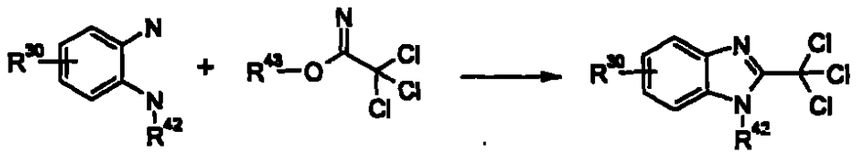
6) a) G. Holan et al., J. Chem. Soc. 1967, 20.

b) G. Crank et al., Aust. J. Chem. 1982, 35, 775.

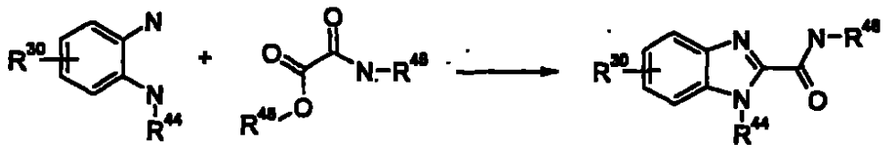
c) G. Dannhardt et al., Arch. Pharm. 2000, 333, 123.

d) P. Louvet et al., Eur. J. Med. Chem. 1993, 28, 71.

e) E. L. Samuel et al., J. Chem. Soc. C, 1967, 25.



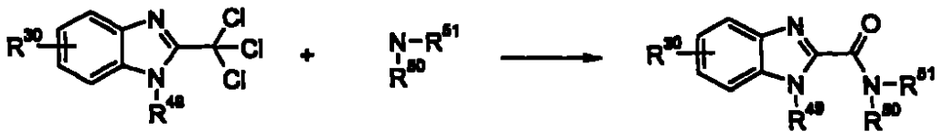
7) P. A. Petyunin et al., Khim. Geterosikl Soedin 19982, 5, 684.



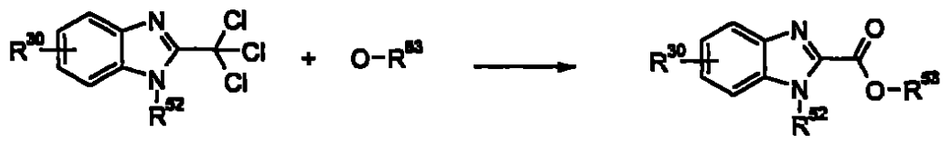
8) C. T. Brain et al.,Tetrahedron Lett., 2002, 43, 1893.



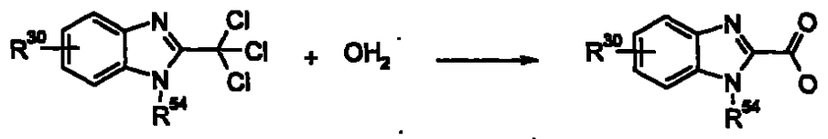
9) E. L. Samuel et al., J. Chem. Soc. C, 1967, 25.



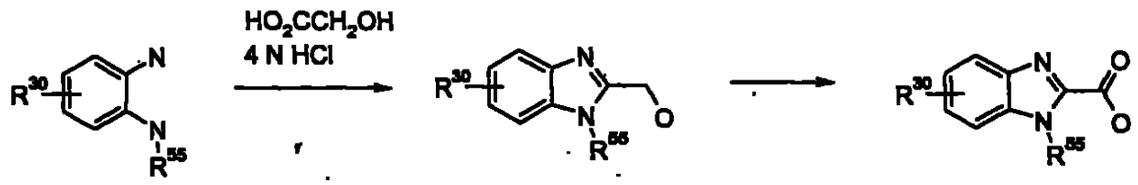
10) E. L. Samuel et al., J. Chem. Soc. C, 1967, 25.



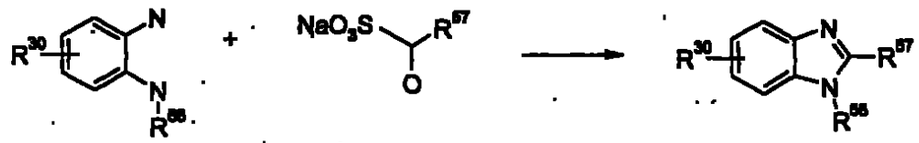
11) G. Dannhardt et al., Arch. Pharm. 2000, 333, 123.



12) A. Orjales et al., Eur. J. Med. Chem. 1999, 34, 415.

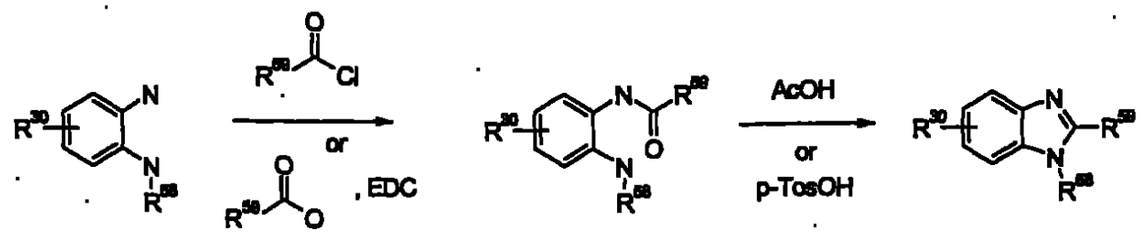


13) H. Göker et al., Arch. Pharm. Pharm. Med. Chem. 2001, 334, 148.

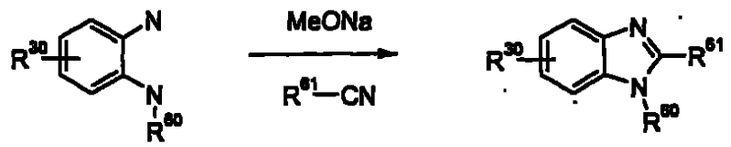


14) a) R. B. Baudy et al., J. Med. Chem. 2001, 44, 1516.

b) Y. K. Yun et al., Synlett 2002, No. 5, 739.



15) N. Nabulsi, R. Gandour, J. Org. Chem. 1991, 56, 2260.



Depending on the substituents in the starting materials, in certain benzoimidazole syntheses mixtures of positional isomers may be obtained, which, however, can be separated by modern separation techniques like, for example, preparative HPLC.

Further, in order to obtain the desired substituents at the benzoimidazole ring system in the formula I, the functional groups introduced into the ring system during the benzoimidazole synthesis can be chemically modified. Especially the groups present in the benzoimidazole ring system can be modified by a variety of reactions and thus the desired residues R^{30} be obtained. For example, a benzoimidazole carrying a hydrogen atom in the 2-position can also be obtained by saponification and subsequent decarboxylation of benzoimidazole carrying an ester group in the respective position. Carboxylic acid groups and acetic acid groups in the 2-position, the 4-position, 5-position, 6-position and the 7-position can be converted into their homologues by usual reactions for chain elongation of carboxylic acids. Halogen atoms can be introduced, for example according to procedures described in the literature like the following. For the fluorination of benzoimidazoles N-fluoro-2,4,6-trimethylpyridinium triflate is the reagent of choice (T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomita, J. Am. Chem. Soc. 1990, 112, 8563) but is not limited to this reagent. The chlorination, bromination, or iodination of benzoimidazoles can be accomplished by the reaction of the elemental halogens or by the use of NCS, NBS or NIS and many other reagents well known to those skilled in the art. These procedures are for example referred in Y. Shi et al., Synth. Commun. 1993, 23, 2623; H. Rapoport et al., Synthesis 1988, 767; R. Jones et al., J. Org. Chem. 1999, 64, 6575; J. Sessler et al., Chem. Eur. J. 2001, 7, 721. Depending on the reaction conditions, reagent, stochiometry and substitution pattern the halogen is introduced in the 2-position and/or 4-position and/or 5-position and/or 6-position and/or 7-position. By selective halogen/metal exchange or metalation by selective hydrogen/metal exchange and subsequent reaction with a wide range of electrophiles various substituents can be introduced at the heterocyclic nucleus. (R. Breslow et al., J. Am. Chem. Soc. 1983, 105, 5337; P. Knochel et al., J. Org. Chem. 2000, 65, 4618; S. Ohta et al., Chem. Pharm. Bull. 1996, 44, 1831). Halogens or hydroxy groups – via the triflate or nonaflate – or primary amines - via its diazonium salt – or after interconversion to the corresponding stannane, or boronic acid - present in the benzoimidazole structure can be converted into a variety of other functional groups like for example –CN, $-CF_3$, $-C_2F_5$, ethers, acids, amides, amines, alkyl- or aryl- groups mediated by means of transition metals, namely palladium or nickel catalysts or copper salts and reagents for example referred to below (F. Diederich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; or M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1996; J. Hartwig, Angew. Chem. 1998, 110, 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 1999, 576, 125; T.

Sakamoto, K. Ohsawa, J. Chem. Soc. Perkin Trans I, 1999, 2323; D. Nichols, S. Frescas, D. Marona-Lewicka, X. Huang, B. Roth, G. Gudelsky, J. Nash, J. Med. Chem, 1994, 37, 4347; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, Tetrahedron Lett., 1998, 39, 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 1998, 39, 2933; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994; F. Qing et al. J. Chem. Soc. Perkin Trans. I 1997, 3053; S. Buchwald et al. J. Am. Chem Soc. 2001, 123, 7727; S. Kang et al. Synlett 2002, 3, 427; S. Buchwald et al. Organic Lett. 2002, 4, 581; T. Fuchikami et al. Tetrahedron Lett. 1991, 32, 91; Q. Chen et al. Tetrahedron Lett. 1991, 32, 7689).

For example, nitro groups can be reduced to amino group with various reducing agents, such as sulfides, dithionites, complex hydrides or by catalytic hydrogenation. A reduction of a nitro group may also be carried out at a later stage of the synthesis of a compound of the formula I, and a reduction of a nitro group to an amino group may also occur simultaneously with a reaction performed on another functional group, for example when reacting a group like a cyano group with hydrogen sulfide or when hydrogenating a group. In order to introduce the residues R^{30}, amino groups can then be modified according to standard procedures for alkylation, for example by reaction with (substituted) alkyl halogenides or by reductive amination of carbonyl compounds, according to standard procedures for acylation, for example by reaction with activated carboxylic acid derivatives such as acid chlorides, anhydrides, activated esters or others or by reaction with carboxylic acids in the presence of an activating agent, or according to standard procedures for sulfonylation, for example by reaction with sulfonyl chlorides.

Ester groups present in the benzoimidazole nucleus can be hydrolyzed to the corresponding carboxylic acids, which after activation can then be reacted with amines or alcohols under standard conditions. Furthermore these ester or acid groups can be reduced to the corresponding alcohols by many standard procedures. Ether groups present at the benzoimidazole nucleus, for example benzyloxy groups or other easily cleavable ether groups, can be cleaved to give hydroxy groups which then can be reacted with a variety of agents, for example etherification agents or activating agents allowing replacement of the hydroxy group by other groups. Sulfur-containing groups can be reacted analogously.

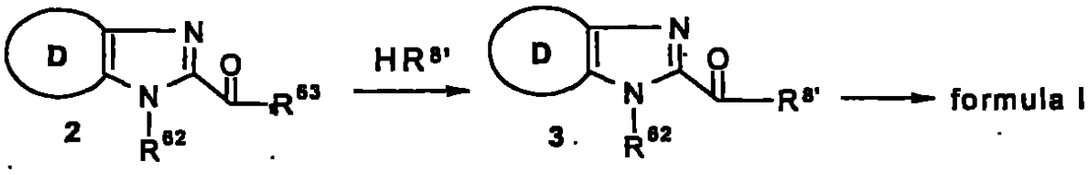
During the course of the synthesis in order to modify the groups R^{62} or R^{6} attached to the benzoimidazole ring system by application of parallel synthesis methodology, beside a variety

of reactions, palladium, nickel or copper catalysis can be extremely useful. Such reactions are described for example in F. Diederich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; or M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1996; J. Hartwig, Angew. Chem. 1998, 110, 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 1999, 576, 125; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, Tetrahedron Lett. 1998, 39, 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 1998, 39, 2933; J. Wolfe, H. Tomori, J. Sadight, J. Yin, S. Buchwald, J. Org. Chem. 2000, 65, 1158; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994; S. Buchwald et al., J. Am. Chem Soc. 2001, 123, 7727; S. Kang et al., Synlett 2002, 3, 427; S. Buchwald et al., Org. Lett. 2002, 4, 581.

The previously-mentioned reactions for the conversion of functional groups are furthermore, in general, extensively described in textbooks of organic chemistry like M. Smith, J. March, March's Advanced Organic Chemistry, Wiley-VCH, 2001 and in treatises like Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany, or "Organic Reactions", John Wiley & Sons, New York, or R. C. Larock, " Comprehensive Organic Transformations", Wiley-VCH, 2nd ed (1999), B. Trost, I. Fleming (eds.) Comprehensive Organic Synthesis, Pergamon,1991; A. Katritzky, C. Rees, E. Scriven Comprehensive Heterocyclic Chemistry II, Elsevier Science, 1996) in which details on the reactions and primary source literature can be found. Due to the fact that in the present case the functional groups are attached to a benzoimidazole ring it may in certain cases become necessary to specifically adapt reaction conditions or to choose specific reagents from a variety of reagents that can in principle be employed into a conversion reaction, or otherwise to take specific measures for achieving a desired conversion, for example to use protection group techniques. However, finding out suitable reaction variants and reaction conditions in such cases does not cause any problems for one skilled in the art.

The structural elements present in the residues in the 1-position of the benzoimidazole ring in the compounds of the formula I and in the COR^6 group present in the 2-position of the benzoimidazole ring can be introduced into the starting benzoimidazole derivative obtainable as outlined above by consecutive reaction steps using parallel synthesis methodologies like those outlined below using procedures which per se are well known to one skilled in the art.

The residues $R^{8'}$ that can be introduced in formula 2, for example, by condensing a corresponding carboxylic acid of the formula 2 with a compound of the formula $HR^{8'}$, i. e. with an amine of the formula $HN(R^{1'})R^{2'}$–V-G-M to give a compound of the formula 3. The compound of the formula 3 thus obtained can already contain the desired final groups, i. e. the groups $R^{8'}$ and R^{62} can be the groups $-N(R^1)-R^2$–V-G-M and R^0-Q- as defined in the formula I, or optionally in the compound of the formula 3 thus obtained subsequently the residue or the residues $R^{8'}$ and the residue R^{62} are converted into the residues $-N(R^1)-R^2$–V-G-M and R^0-Q-, respectively, to give the desired compound of the formula I.



Thus, the residues $R^{8'}$ and the residues $R^{1'}$ and $R^{2'}$–V-G-M contained therein can have the denotations of R^1 and R^2–V-G-M, respectively, given above or in addition in the residues $R^{1'}$ and $R^{2'}$–V-G-M functional groups can also be present in the form of groups that can subsequently be transformed into the final groups R^1 and R^2–V-G-M; i.e. functional groups can be present in the form of precursor groups or of derivatives, for example in protected form. In the course of the preparation of the compounds of the formula I it can generally be advantageous or necessary to introduce functional groups which reduce or prevent undesired reactions or side reactions in the respective synthesis step, in the form of precursor groups which are later converted into the desired functional groups, or to temporarily block functional groups by a protective group strategy suited to the synthesis problem. Such strategies are well known to those skilled in the art (see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, Wiley, 1991, or P. Kocienski, Protecting Groups, Thieme 1994). Examples of precursor groups are cyano groups and nitro groups. The cyano group can in a later step be transformed into carboxylic acid derivatives or by reduction into aminomethyl groups, or the nitro groups may be transformed by reduction like catalytic hydrogenation into amino groups. Protective groups can also have the meaning of a solid phase, and cleavage from the solid phase stands for the removal of the protective group. The use of such techniques is known to those skilled in the art (Burgess K (Ed.) Solid Phase Organic Synthesis, New York, Wiley, 2000). For example, a phenolic hydroxy group can be attached to a trityl-polystyrene resin, which serves as a

protecting group, and the molecule is cleaved from this resin by treatment with TFA at a later stage of the synthesis.

The residue R^{62} in the compounds of the formulae 2 and 3 can denote the group -Q-R^0 as defined above which finally is to be present in the desired target molecule of the formula I, or it can denote a group which can subsequently be transformed into the group -Q-R^0, for example a precursor group or a derivative of the group -Q-R^0 in which functional groups are present in protected form, or R^{62} can denote a hydrogen atom or a protective group for the nitrogen atom of the benzoimidazole ring. Similarly, the residues R^{30} have the corresponding definitions of R^3 in formula I as defined above, however, for the synthesis of the compounds of the formula I these residues, too, can in principle be present at the stage of the condensation of a compound of the formula 2 with a compound of the formula $HR^{8'}$ giving a compound of the formula 3 in the form of precursor groups or in protected form.

The residues R^{63} in the compounds of the formula 2 which can be identical or different, can be, for example, hydroxy or (C_1-C_4)-alkoxy, i. e., the groups COR^{63} present in the compounds of the formula 2 can be, for example, the free carboxylic acids or esters thereof like alkyl esters as can be the groups $COR^{8'}$ in the compounds of the formula I. The groups COR^{63} can also be any other activated derivative of a carboxylic acid which allows amide formation, ester formation or thioester formation with a compound of the formula $HR^{8'}$. The group COR^{63} can be, for example, an acid chloride, an activated ester like a substituted phenyl ester, an azolide like an imidazolide, an azide or a mixed anhydride, for example a mixed anhydride with a carbonic acid ester or with a sulfonic acid, which derivatives can all be prepared from the carboxylic acid by standard procedures and can be reacted with an amine, an alcohol or a mercaptan of the formula $HR^{8'}$ under standard conditions. A carboxylic acid group COOH representing COR^{63} in a compound of the formula 2 can be obtained, for example, from an ester group introduced into the benzoimidazole system during a benzoimidazole synthesis by standard hydrolysis procedures.

Compounds of the formula I in which a group $COR^{8'}$ is an ester group can also be prepared from compounds of the formula 2 in which COR^{63} is a carboxylic acid group by common esterification reactions like, for example, reacting the acid with an alcohol under acid catalysis, or alkylation of a salt of the carboxylic acid with an electrophile like an alkyl halogenide, or by

transesterification from another ester. Compounds of the formula I in which a group COR^6 is an amide group can be prepared from amines and compounds of the formula 2 in which COR^{63} is a carboxylic acid group or an ester thereof by common amination reactions. Especially for the preparation of amides the compounds of the formula 2 in which COR^{63} is a carboxylic acid group can be condensed under standard conditions with compounds of the formula HR^6 which are amines by means of common coupling reagents used in peptide synthesis. Such coupling reagents are, for example, carbodiimides like dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide, carbonyldiazoles like carbonyldiimidazole (CDI) and similar reagents, propylphosphonic anhydride, O-[(cyano-(ethoxycarbonyl)-methylene)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU), diethylphosphoryl cyanide (DEPC) or bis-(2-oxo-3-oxazolidinyl)-phosphoryl chloride (BOP-Cl) and many others.

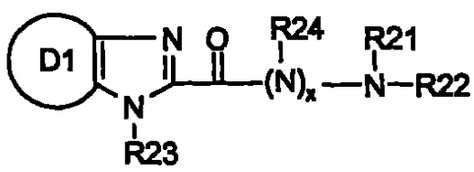
If the residue $-Q-R^0$ present in a benzoimidazole of the formula I or the residue R^{63} present in a benzoimidazole of the formula 2, or a residue in which functional groups within the residue $-Q-R^0$ or R^{63} are present in protected form or in the form of a precursor group, have not already been introduced during a preceding step, for example during a synthesis of the benzoimidazole nucleus, these residues can, for example, be introduced into the 1-position of the benzoimidazole system by conventional literature procedures well known to one skilled in the art for N-alkylation, reductive amination, N-arylation, N-acylation or N-sulfonylation of ring nitrogen atoms of heterocycles. The starting benzoimidazole derivative that is to be employed in such a reaction carries a hydrogen atom in the 1-position. N-Alkylation of a ring nitrogen atom can, for example, be performed under standard conditions, preferably in the presence of a base like K_2CO_3, Cs_2CO_3, NaH or KO^tBu, using an alkylating compound of the formula $LG-Q-R^0$ or of the formula $R^{62}-LG$, wherein the atom in the group Q or in the group R^{62} bonded to the group LG in this case is an aliphatic carbon atom of an alkyl moiety and LG is a leaving group, for example halogen like chlorine, bromine or iodine, or a sulfonyloxy group like tosyloxy, mesyloxy or trifluormethylsulfonyloxy. LG may, for example, also be a hydroxy group which, in order to achieve the alkylation reaction, is activated by a conventional activating agent. For the preparation of compounds in which A is a direct linkage and an aromatic group is directly bonded to the 1-position of the benzoimidazole system, conventional arylation procedures can be used. For example aryl fluorides like alkyl fluorobenzoates or 4-fluorophenyl methyl sulfones can be employed as arylating agents. Such processes are described, for example, by M. Yamada et al. J. Med. Chem. 1996, 39, 596; J.

Ohmori et al. J. Med. Chem. 1996, 39, 3971. Alternatively a wide variety of substituted aryl iodides, aryl bromides or aryl triflates can serve as arylating agents at the 1-position of the heterocyclic nitrogen in a copper salt or palladium mediated reaction according for example to P. Cozzi et al. Farmaco 1987, 42, 205; P. Unangst, D. Connor, R. Stabler, R. Weikert, J. Heterocycl. Chem. 1987, 24, 811; G. Tokmakov, I. Grandberg, Tetrahedron 1995, 51, 2091; D. Old, M. Harris, S. Buchwald, Org. Lett. 2000, 2, 1403, G. Mann, J. Hartwig, M. Driver, C. Fernandez-Rivas, J. Am. Chem. Soc. 1998, 120, 827; J. Hartwig, M. Kawatsura, S. Hauk, K. Shaughnessy, L. J. Org. Chem. 1999, 64, 5575; S. Buchwald et al., J. Am. Chem. Soc. 2001, 123, 7727. Moreover such arylations can also be accomplished by reaction of a wide range of substituted aryl boronic acids as demonstrated for example by W. Mederski, M. Lefort, M. Germann, D. Kux, Tetrahedron 1999, 55, 12757; J. Collman et al., J. Org. Chem. 2001, 66, 7892. During the above-mentioned transformations positional isomers may occur, nevertheless these mixtures of positional isomers can be separated by modern separation techniques like, for example, preparative HPLC.

The invention also relates to a process for preparing a compound of the formula IV.

A process for the preparation of benzoimidazole-anilide-derivatives is described in DE 3708292. Said compounds were prepared under strong acidic conditions and with yields of about 50%. Similar processes are also described in DE 4304650 or in the Journal of Medicinal Chemistry (1984, Vol. 27, No. 2, pages 121-125), wherein the compounds were prepared in the presence of sodium bicarbonate. These conditions gave the products in only low yields. Another object of the present invention is to find a process for the amination of the compounds of the formula V in high yields and purity.

The invention therefore relates to a process for producing the compound of formula IV,



(IV)

wherein

x is the integer zero or 1,

R21 and R24 are identical or different and are independent from each other

a) a hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,

c) -(C_1-C_3)-alkylene-C(O)-NH-R^0,

d) -(C_1-C_3)-alkylene-C(O)-O-R^{10},

e) -(C_0-C_4)-alkyl-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl and is mono-, di- or trisubstituted independently of one another by R8,

f) -(C_0-C_4)-alkyl-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, thre or four heteroatoms chosen from nitrogen, sulphur or oxygen and is mono-, di- or trisubstituted independently of one another by R8,

g) -(C_1-C_4)-alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

h) -(C_1-C_3)-perfluoroalkylene,

i) -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

j) -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl,

k) -(C_1-C_3)-alkylene-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

l) -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl,

m) -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl or

n) -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or

trisubstituted independently of one another by R14,

wherein R^0, $R^{4'}$, $R^{5'}$, R8, R^{10}, R^{13} and R^{14} are as defined in formula I,

R22 is a) a hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,

c) -(C_1-C_3)-alkylene-C(O)-NH-R^0,

d) -(C_1-C_3)-alkylene-C(O)-O-R^{10},

e) -(C_0-C_4)-alkyl-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl and is mono-, di- or trisubstituted independently of one another by R8,

f) -(C_0-C_4)-alkyl-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, thre or four heteroatoms chosen from nitrogen, sulphur or oxygen and is mono-, di- or trisubstituted independently of one another by R8,

g) -(C_0-C_4)-alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

h) -(C_1-C_3)-perfluoroalkylene,

i) -(C_0-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

j) -(C_0-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl,

k) -(C_0-C_3)-alkylene-$S(O)_2$-N($R^{4'}$)-$R^{5'}$,

l) -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl,

m) -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl,

n) -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue,

containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

o) R^2-V-G-M,

wherein R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, R14, V, G and M are as defined in formula I, or the substructure R21-N-R^2-V in formula IV can form a 4- to 8-membered cyclic group, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

wherein the residue R14 is as defined as in formula I ,

R23 is a) a hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,

c) -(C_1-C_3)-alkylene-C(O)-NH-R^0,

d) -(C_1-C_3)-alkylene-C(O)-O-R^{10},

e) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

f) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen,

g) -(C_1-C_3)-perfluoroalkylene,

h) -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

j) -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl,

k) -(C_1-C_3)-alkylene-$S(O)_2$-N($R^{4'}$)-$R^{5'}$,

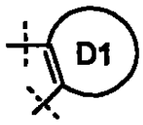
l) -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl,

m) -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl,

n) -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

o) -Q-R^0,

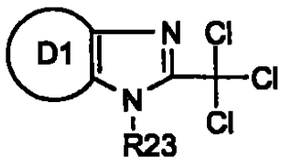
wherein R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, R14, Q, V, G and M are as defined in formula I, and



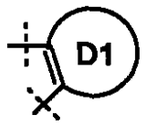
substructure in formula IV is

a 4-to 8 membered saturated, partially unsaturated or aromatic cyclic group containing zero, 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen and is unsubstituted or substituted 1, 2, 3, 4, 5 or 6 times by R3, wherein R3 is as defined in formula I,

which comprises reacting a compound of formula V



(V)



wherein R23 is as defined in formula IV and substructure in formula V is as defined in formula IV,

with a primary amine or a secondary amine

in the presence of water, at least one base and at least one water-miscible organic solvent.

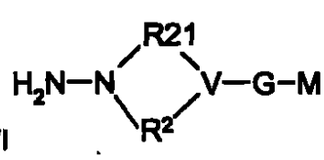
Another object of the present invention is a process for the preparation of a compound of formula IV,

wherein the primary amine is

a). NH_2-R21, wherein R21 is as defined in formula IV,

b) NH_2-R^2-V-G-M, wherein R^2, V, G and M are as defined in formula IV,

c) NH_2-N(R21)-R22, wherein R21 and R22 are as defined in formula IV or



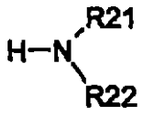
(VI)

d) a compound of formula VI

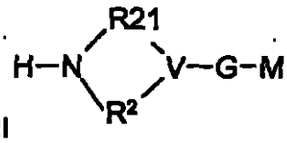
wherein R^2, R21, V, G and M are as defined as in formula IV.

Another object of the present invention is a process for the preparation of a compound of formula IV,

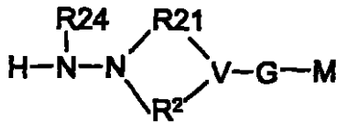
wherein the secondary amine is

a) 

wherein R21 and R22 are as defined in formula IV,

b) a compound of formula VII  (VII)

wherein R21, R^2, V, G and M are as defined in formula IV, or

c) a compound of formula VIII  (VIII)

wherein R^2, R21, R24, V, G and M are as defined in formula IV.

Introducing a primary or secondary amine into a mixture of water and a water miscible organic solvent starts the preparation of the compound of the formula IV. Then a base, particularly sodium bicarbonate, is added and the resulting solution or suspension is stirred or shaken at room temperature. Finally the compound of the formula V is added either in solid form or dissolved in an appropriate organic solvent. The resulting reaction mixture is then stirred or shaken under temperature control. After an appropriate reaction time the compound of the formula IV is isolated by precipitation, e.g. by removing the organic solvent by evaporation. Alternatively, the compound of the formula IV can be extracted using an organic solvent such as dichloromethane, ethyl acetate, toluene, tertiary-butyl methyl ether or diethyl ether.

The term "water-miscible organic solvent" is taken to mean, for example, organic solvents such as:

Tetrahydrofuran, acetonitrile, dimethylsulfoxide, dioxane, 1,2-dimethoxyethane, N,N-dimethylformamide, N-methylpyrrolidone, acetone or sulfolane.

The term "base" is taken to mean alkali metal carbonates, for example sodium bicarbonate or potassium bicarbonate, in solid form or in the form of solutions of differing concentrations. Basically all inorganic salts, particularly bicarbonates, which have a basicity comparable to sodium bicarbonate, can be used for the above described process. Also, the term "base" is taken to mean tertiary amines, such as triethylamine or diisopropylethylamine.

The term "primary amine" is taken to mean an amine, which is substituted by one residue at the nitrogen atom. The term "secondary amine" is taken to mean an amine, which is substituted by two residues at the nitrogen atom.

The term "$-(N)_x-$, wherein x is zero" in formula IV is a covalent bond and wherein x is 1 is a –N(R24)- residue.

Preferably, for the inventive reaction, 2 mol to 12 mol of a base are used per 1 mol of the compound of the formula V.

Preferably, for the inventive reaction, 1 mol to 1.5 mol of a primary amine or a secondary amine are used per 1 mol of the compound of the formula V.

The amount of water-miscible organic solvent used is generally from 5 g to 300 g per 1 g of the compound of the formula V, preferably from 10 g to 200 g.

The reaction time is generally between a few minutes and 24 hours, preferably 1 to 5 hours, depending on the composition of the mixture and the temperature range selected.

The reaction temperature is from 5 °C to 120 °C, preferably from 10 °C to 35°C, in particular 25 °C. In case of 1-substitued imidazole-derivatives (compounds wherein R23 is not a hydrogen atom) the reaction temperature is from 50 °C to 120 °C, preferably from 70 °C to 100 °C, in particular 90 °C.

The residual content of starting substrate of the compound of the formula V was reduced to a content, which is below 0.5 % in the isolated compound of formula IV.

Advantageous features in the inventive process are the very short reaction times, the omission of additional purification steps, the high yields and the high purity of the products prepared.

Further advantageous features in the inventive process are:

- easy accessibility of diversely substituted imidazole-2-carboxylic acid amides, particularly benzoimidazole-2-carboxylic acid amides. The preparation of these structural classes is difficult when using standard procedures such as coupling of benzoimidazole-2-carboxylic acids with amines. Very often the synthesis of substituted benzoimidazole-2-carboxylic acids is laborious. Furthermore, benzoimidazole-2-carboxylic acids, especially 1-substituted benzoimidazole-2-carboxylic acids, tend to decarboxylate during their synthesis but also under typical amide coupling conditions.
- easy accessibility of yet completely unknown structural classes, for example thieno-[3,4]-imidazole-2-carboxylic acid amides.

amines with a very low reactivity, for example amines which even do not react with the corresponding benzoimidazole-2-carboxylic acid chlorides, such as (4-amino-3-fluoro-phenyl)-pyrrolidin-1-yl-methanone (example 165) or 2-amino-3-nitro-benzoic acid methyl ester (example 167), react in a smooth way (under very mild conditions) allowing the construction of special imidazole-2-carboxylic acid anilides, which are difficult to synthesize by other existing methods. For example, the acylation of 2-amino-3-nitro-benzoic acid methyl ester with even a sterically not hindered acid chloride, for example acetyl chloride, requires a large excess of the corresponding acid chloride and elevated temperatures (100 °C, toluene as solvent).

Preferred methods include, but are not limited to those described in the examples.

The compounds of the present invention are serine protease inhibitors, which inhibit the activity of the blood coagulation enzyme factors Xa and/or factor VIIa. In particular, they are highly active inhibitors of factor Xa. They are specific serine protease inhibitors inasmuch as they do not substantially inhibit the activity of other proteases whose inhibition is not desired.

The activity of the compounds of the formula I can be determined, for example, in the assays described below or in other assays known to those skilled in the art. With respect to factor Xa inhibition, a preferred embodiment of the invention comprises compounds which have a Ki < 1 mM for factor Xa inhibition as determined in the assay described below, with or without concomitant factor VIIa inhibition, and which preferably do not substantially inhibit the activity of other proteases involved in coagulation and fibrinolysis whose inhibition is not desired (using the same concentration of the inhibitor). The compounds of the invention inhibit factor Xa catalytic activity either directly, within the prothrombinase complex or as a soluble subunit, or indirectly, by inhibiting the assembly of factor Xa into the prothrombinase complex.

As inhibitors of factor Xa and/or factor VIIa the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for the therapy and prophylaxis of conditions in which the activity of factor Xa and/or factor VIIa plays a role or has an undesired extent, or which can favorably be influenced by inhibiting factor Xa and/or factor VIIa or decreasing their activities, or for the prevention, alleviation or cure of which an inhibition of factor Xa and/or factor VIIa or a decrease in their activity is desired by the physician. As inhibition of factor Xa and/or factor VIIa influences blood coagulation and fibrinolysis, the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for reducing blood clotting, or for the therapy and prophylaxis of conditions in which the activity of the blood coagulation system plays a role or has an undesired extent, or which can favorably be influenced by reducing blood clotting, or for the prevention, alleviation or cure of which a decreased activity of the blood coagulation system is desired by the physician. A specific subject of the present invention thus are the reduction or inhibition of unwanted blood clotting, in particular in an individual, by administering an effective amount of a compound I or a physiologically tolerable salt or a prodrug thereof, as well as pharmaceutical preparations therefor.

The present invention also relates to the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation, inflammatory response or

fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for the production of pharmaceuticals for the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses. The invention also relates to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for use in the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses, and to methods of treatment aiming at such purposes including methods for said therapies and prophylaxis. The present invention also relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs in addition to a customary pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances or excipients and/or auxiliary substances or additives.

The invention also relates to the treatment of disease states such as abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication or bypass grafting of the coronary or peripheral arteries, vessel luminal narrowing, restenosis post coronary or venous angioplasty, maintenance of vascular access patency in long-term hemodialysis patients, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee or hip surgery, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulatopathy occurring in vascular systems during septic shock, certain viral infections or cancer.
The compounds of the present invention can also be used to reduce an inflammatory response. Examples of specific disorders for the treatment or prophylaxis of which the compounds of the formula I can be used are coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure and disseminated intravascular clotting disorder. Examples of related complications associated with surgery are thromboses like deep vein and proximal vein thrombosis, which can occur following surgery.

The compounds of the formula I and their physiologically tolerable salts and their prodrugs can be administered to animals, preferably to mammals, and in particular to humans as pharmaceuticals for therapy or prophylaxis. They can be administered on their own, or in mixtures with one another or in the form of pharmaceutical preparations, which permit enteral or parenteral administration.

The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatine capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carriers being used in addition to the compound(s) of the formula I and/or its (their) physiologically tolerable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatine capsules it is possible to use, for example, lactose, cornstarch or derivatives thereof, talc, stearic acid or its salts, etc. Carriers for soft gelatine capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 % to 90 % by weight of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. The amount of the active ingredient of the formula I and/or its physiologically tolerable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg.

In addition to the active ingredients of the formula I and/or their physiologically acceptable salts and/or prodrugs and to carrier substances, the pharmaceutical preparations can contain additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula I, and/or their physiologically tolerable salts and/or their prodrugs. In case a pharmaceutical preparation contains two or more compounds of the formula I, the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula I allows a great deal of control over the biological and physico-chemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula I and/or a physiologically tolerable salt and/or its prodrug, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

When using the compounds of the formula I the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for achieving the desired results in an adult weighing about 75 kg is from 0.01 mg/kg to 100 mg/kg, preferably from 0.1 mg/kg to 50 mg/kg, in particular from 0.1 mg/kg to 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behaviour it may be necessary to deviate upwards or downwards from the daily dose indicated.

A compound of the formula I can also advantageously be used as an anticoagulant outside an individual. For example, an effective amount of a compound of the invention can be contacted

with a freshly drawn blood sample to prevent coagulation of the blood sample. Further, a compound of the formula I or its salts can be used for diagnostic purposes, for example in in vitro diagnoses, and as an auxiliary in biochemical investigations. For example, a compound of the formula I can be used in an assay to identify the presence of factor Xa and/or factor VIIa or to isolate factor Xa and/or factor VIIa in a substantially purified form. A compound of the invention can be labelled with, for example, a radioisotope, and the labelled compound bound to factor Xa and/or factor VIIa is then detected using a routine method useful for detecting the particular label. Thus, a compound of the formula I or a salt thereof can be used as a probe to detect the location or amount of factor Xa and/or factor VIIa activity in vivo, in vitro or ex vivo.

Furthermore, the compounds of the formula I can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

The general synthetic sequences for preparing the compounds useful in the present invention our outlined in the examples given below. Both an explanation of, and the actual procedure for, the various aspects of the present invention are described where appropriate. The following examples are intended to be merely illustrative of the present invention, and not limiting thereof in either scope or spirit. Those with skill in the art will readily understand that known variations of the conditions and processes described in the examples can be used to synthesize the compounds of the present invention.

It is understood that changes that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Thus, the following examples are intended to illustrate but not limit the present invention.

Examples

When in the final step of the synthesis of a compound an acid such as trifluoroacetic acid or acetic acid was used, for example when trifluoroacetic acid was employed to remove a tBu group or when a compound was purified by chromatography using an eluent which contained

such an acid, in some cases, depending on the work-up procedure, for example the details of a freeze-drying process, the compound was obtained partially or completely in the form of a salt of the acid used, for example in the form of the acetic acid salt or trifluoroacetic acid salt or hydrochloric acid salt.

Abbreviations used:

tert-Butyl	tBu
2,2'-bis(diphenylphoshino-1,1'-binaphthyl	Binap
Bis-(oxo-3-oxazolidinyl)-phosphoryl chloride	BOP-Cl
dibenzylidenacetone	dba
Dichloromethane	DCM
Dicyclohexyl-carbodiimide	DCC
Diethylphosphoryl cyanide	DEPC
Diisopropylethyl amine	DIPEA
4-Dimethyaminopyridine	DMAP
N,N-Dimethylformamide	DMF
Dimethylsulfoxide	DMSO
1,1'-Bis(diphenylphosphino)ferrocene	DPPF
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate	HATU
N-Bromosuccinimide	NBS
N-Chlorosuccinimide	NCS
N-Iodosuccinimide	NIS
N-Ethylmorpholine	NEM
Methanol	MeOH
Room temperature 20 °C to 25 °C	RT
Saturated	sat.
Tetrahydrofuran	THF
Trifluoroacetic acid	TFA
O-((Ethoxycarbonyl)cyanomethyleneamino)-N,N,N',N'-tetramethyluronium tetrafluoroborate	TOTU

Example 1: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester

To a solution of 5.0 g Piperidin-4-yl-carbamic acid tert-butyl ester in 15 ml methanol, 7.34 ml acetone, 3.14 g $Na(CN)BH_3$ and 0.3 ml acetic acid were added. After stirring for 16h at room temperature the solvent was removed under reduced pressure and the residue was partitioned between 30 ml water and 30 ml ethyl acetate. The organic layer was washed with saturated Na_2CO_3 solution, water and then dried over Na_2SO_4. The solvent was removed under reduced pressure to give the product as a white solid. Yield: 4.8g MS (ES^+): m/e= 243.

(ii) 1-Isopropyl-piperidin-4-ylamine

To 4.8 g (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester in 15 ml methanol, 20 ml methanolic hydrochloric acid (8M) were added and the mixture was stirred for 16h. Removal of the solvent under reduced pressure, followed by removal of residual volatiles by twice coevaporating with toluene, gave the product. Yield: 5.42 g MS (ES^+): m/e= 143.

(iii) 1H-Benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 300 mg 1H-Benzoimidazole-2-carboxylic acid in 3 ml DMF and 1 ml NEt_3, 398 mg 1-Isopropyl-piperidin-4-ylamine hydrochloride and 470 mg BOP-Cl were added and the mixture was stirred for 3 h. Finally, 3 ml saturated $NaHCO_3$ solution were added and the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After removal of the solvent under reduced pressure the crude product was subjected to the next reaction step without further purification. Yield: 604 mg.

(iv) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 200 mg 1H-Benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide in 2 ml DMF, 227 mg Cs_2CO_3 and 194 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole [prepared by adopting a procedure described by Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B; PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] were added at RT and the mixture was stirred for 16 h. After addition of 5 ml water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse

phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt. Yield: 29 mg MS.(ES+): m/e= 484, chloro pattern.

Example 2: 1-[(4-Chloro-phenylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl- piperidin-4-yl)-amide

(i) 2-Bromo-N-(4-chloro-phenyl)-acetamide

To a solution of 5 g 4-Chloro-phenylamine and 1.5 ml pyridine in 30 ml toluene, 8 g bromo-acetyl bromide dissolved in 10 ml toluene were added dropwise under ice cooling. After 2 h the precipitate was isolated by filtration and recrystallized from toluene to yield a white solid. Yield: 10 g.

(ii) 1-[(4-Chloro-phenylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 200 mg 1H-Benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide in 2 ml DMF, 227 mg Cs_2CO_3 and 173 mg 2-Bromo-N-(4-chloro-phenyl)-acetamide were added at RT and the mixture was stirred for 16 h. After addition of 5 ml water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt. Yield: 63 mg MS (ES+): m/e= 454, chloro pattern.

Example 3: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide

(i) 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide

To a solution of 5 g 5-Chloro-pyridin-2-ylamine and 1.5 ml pyridine in 30 ml toluene, 8 g bromo-acetyl bromide dissolved in 10 ml toluene were added dropwise under ice cooling. After 2 h the precipitate was isolated by filtration and recrystallized from toluene to yield a white solid.

Yield: 12 g.

(ii) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

To a solution of 200 mg 1H-Benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide in 2 ml DMF, 227 mg Cs_2CO_3 and 174 mg 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide were added at RT and the mixture was stirred for 16 h. After addition of 5 ml water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt. Yield: 34 mg MS (ES^+): m/e= 455, chloro pattern.

Example 4: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-pyrimidin-4-yl-piperidin-4-yl)-amide

(i) (1-Pyrimidin-4-yl-piperidin-4-yl)-carbamic acid tert-butyl ester

To a solution of 395 mg [1-(2-Chloro-pyrimidin-4-yl)-piperidin-4-yl]-carbamic acid tert-butyl ester in 10 ml ethanol and 0.3 ml acetic acid, 20 mg Pd/C (10%) were added and the mixture purged with argon for 10 min. Then the mixture was stirred under a hydrogen atmosphere for 5 h at RT. After addition of 10 ml ethyl acetate the reaction mixture was filtered through a pad of celite. The solvent was evaporated under reduced pressure and the residue codistilled twice with toluene to give the product as a white solid. Yield: 468 mg.

(ii) 1-Pyrimidin-4-yl-piperidin-4-ylamine

To a solution of 468 mg (1-Pyrimidin-4-yl-piperidin-4-yl)-carbamic acid tert-butyl ester in 2 ml DCM, 2 ml TFA were added and the mixture was stirred for 2 h at RT. Then, 10 ml toluene were added and the solvents were removed under reduced pressure. The residue was codistilled twice with toluene to yield a yellow oil. The product was obtained as its trifluoroacetate salt. Yield: 703 mg.

(iii) 1H-Benzoimidazole-2-carboxylic acid (1-pyrimidin-4-yl-piperidin-4-yl)-amide

To a solution of 80 mg 1H-Benzoimidazole-2-carboxylic acid in 1 ml DMF and 0.2 ml NEt_3, 200 mg 1-Pyrimidin-4-yl-piperidin-4-ylamine trifluoroacetate and 125 mg BOP-Cl were added and the mixture was stirred for 3 h. Finally, 3 ml saturated $NaHCO_3$ solution were added and the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After removal of the solvent under reduced pressure the crude product was subjected to the next reaction step without further purification. Yield: 160 mg.

(iv) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-pyrimidin-4-yl-piperidin-4-yl)-amide

To a solution of 160 mg 1H-Benzoimidazole-2-carboxylic acid (1-pyrimidin-4-yl-piperidin-4-yl)-amide in 2 ml DMF, 161 mg Cs_2CO_3 and 138 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added at RT and the mixture was stirred for 16 h. After addition of 5 ml water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt. Yield: 114 mg MS (ES^+): m/e= 520, chloro pattern.

Example 5: a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester

(i) Methyl-2-trichloromethyl-1H-benzoimidazole-5-carboxylate

2.00 g (12.0 mmol) Methyl-3,4-diamino-benzoate were dissolved in 50 ml concentrated acetic acid. Then 2.09 ml (1.4 equiv.) methyl-2,2,2-trichloroacetimidate were added slowly and the resulting mixture was stirred at room temperature for 2 h. The mixture was diluted with 100 ml toluene and the solvent was removed under reduced pressure. The residue was taken up in dichloromethane and washed once with a saturated $NaHCO_3$-solution and once with brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give pure methyl-2-trichloromethyl-1H-benzoimidazole-5-carboxylate as a light brown amorphous solid. Yield: 3.64 g MS (ES^+): m/e = 293, chloro pattern.

(ii) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

500 mg (1.7 mmol) Methyl-2-trichloromethyl-1H-benzoimidazole-5-carboxylate were added to a mixture of 548 mg (1.8 equiv.) 1-isopropyl-piperidine-4-ylamine-dihydrochloride and 1.43 g (10 equiv.) $NaHCO_3$ in 15 ml THF and 7.5 ml H_2O and stirred vigorously for 4 h at room temperature. The reaction mixture was diluted with dichloromethane and washed with a saturated $NaHCO_3$-solution and brine. The organic layer was dried over $MgSO_4$ and

concentrated. Preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave pure 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester as a white solid.

Yield: 300 mg MS (ES^+): m/e = 345.

(iii) a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester

115 mg (0.33 mmol) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester were dissolved in 10 ml DMF. Subsequently 69.2 mg (1. 5 equiv.) K_2CO_3 and 111.6 mg (1.2 equiv.) 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added and the resulting mixture was stirred for 2 h at 80° C. The reaction mixture was diluted with toluene and washed twice with a saturated $NaHCO_3$-solution and once with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave a 6:4 mixture of both isomers described in the title. These isomers could be separated by NP-HPLC using a chiral stationary phase and a mixture of heptane, ethanol, methanol and diethyl amine as solvent. Structural assignment of both isomers was achieved by NOE-spectroscopy.

Yield of 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester: 52 mg; MS (ES^+): m/e =542, chloro pattern.

Yield of 3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester: 34 mg; MS (ES^+): m/e =542, chloro pattern.

Example 6: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid

To a suspension of 43.6 mg (0.080 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester in 4 ml MeOH 0.4 ml of a 1 M aqueous LiOH-solution were added and the resulting mixture was stirred at 60 °C for 5 h. The mixture was acidified by the addition of a 1 M HCl-solution (pH ≈ 2-3) and concentrated under reduced pressure. Final purification by preparative RP-HPLC

(CH_3CN/H_2O gradient + 0.05 % formic acid) gave pure 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid. The corresponding dihydrochloride was obtained by treatment of the product with a 0.1 M HCl-solution followed by lyophilization. Yield: 43 mg MS (ES^+): m/e =528, chloro pattern.

Example 7: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid was prepared as described in example 6 from 20 mg (0.037 mmol) 3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester.
Yield: 18 mg MS (ES^+): m/e =528, chloro pattern.

Example 8: a) 1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

b) 3-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester

To a solution of 80.0 mg (0.23 mmol) 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester in 5 ml DMF 9.3 mg sodium hydride (60% supension in mineral oil) were added. The mixture was stirred for 30 min at room temperature and subsequently 68.4 mg (0.23 mmol) 5-bromomethyl-2-(5-chloro-thiophen-2-yl)-thiazole [prepared by adopting a procedure described by Ewing, William R. et al.; PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] were added. After 1 h another 17.1 mg (0.25 equiv.) 5-bromomethyl-2-(5-chloro-thiophen-2-yl)-thiazole were added and the reaction mixture was stirred for further 2 h. The reaction was stopped by the careful addition of MeOH and water. The solvent was removed under reduced pressure and the residue was purified by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid). The two isomers were then separated using NP-HPLC on a chiral stationary phase with a mixture of heptane, ethanol, methanol and diethyl amine as solvent. Structural assignment of both isomers was achieved by NOE-spectroscopy.
Yield of 1-[2-(5-chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester: 40 mg; MS (ES^+): m/e =558, chloro pattern.

Yield of 3-[2-(5-chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester: 26 mg; MS (ES+): m/e =558, chloro pattern.

Example 9: 1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid

1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid was prepared by a procedure according to example 6 starting from 40 mg (0.072 mmol) 1-[2-(5-chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester. The title compound was obtained as its dihydrochloride. Yield: 23 mg MS (ES+): m/e =544, chloro pattern.

Example 10: 3-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid

3-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid was prepared by a procedure according to example 6 starting from 26 mg (0.047 mmol) 3-[2-(5-chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester. The title compound was obtained as its dihydrochloride. Yield: 19 mg MS (ES+): m/e =544, chloro pattern.

Example 11: a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid methyl ester

(i) Methyl-2,3-diamino-benzoate

3.0 g (15.3 mmol) Methyl-2-amino-3-nitro-benzoate were dissolved in 200 ml abs. MeOH. The solution was evacuated and rinsed with argon several times. 300 mg palladium on charcoal (10%) were added and again the mixture was evacuated and rinsed with argon a several times. Finally argon was exchanged by hydrogen (balloon filled with hydrogen) and the mixture was stirred for 4 h at room temperature. The reaction mixture was filtered over "Celite" and the filter residue was washed with 150 ml methanol. The filtrate was concentrated under reduced

pressure to give pure methyl-2,3-diamino-benzoate as a brown oil. Yield: 2.53 g MS (ES+): m/e = 167.

(ii) Methyl-2-trichloromethyl-1H-benzoimidazole-4-carboxylate

Methyl-2-trichloromethyl-1H-benzoimidazole-4-carboxylate was prepared similarly to methyl-2-trichloromethyl-1H-benzoimidazole-5-carboxylate as described in example 5 i) starting from 2.53 g (15.1 mmol) methyl-2,3-diamino-benzoate. Yield: 4.15 g MS (ES+): m/e =293, chloro pattern.

(iii) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester was prepared from 1.82 g (6.2 mmol) methyl-2-trichloromethyl-1H-benzoimidazole-4-carboxylate as described in example 5 ii). Yield: 1.10 g MS (ES+): m/e = 345.

(iv) a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid methyl ester

Both isomers were obtained by an analogous procedure as described for example 5 iii) starting from 150.0 mg (0.44 mmol) 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester and 145.6 mg (1.2 equiv.) 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. In this case the ratio of both isomers was 3:1. As described in example 5 iii) the isomers were separated by NP-HPLC using a chiral stationary phase and a mixture of heptane, ethanol, methanol and diethyl amine as solvent. Again structural assignment of both isomers was achieved by NOE-spectroscopy.

Yield of 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester: 105 mg; MS (ES+): m/e =542, chloro pattern.

Yield of 3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid methyl ester: 45 mg; MS (ES+): m/e =542, chloro pattern.

Example 12: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid was prepared from 60 mg (0.111 mmol) 1-[5-(5-chloro-

thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester as described in example 6. The title compound was obtained as its dihydrochloride. Yield: 34 mg MS (ES+): m/e = 528, chloro pattern.

Example 13: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid was prepared from 20 mg (0.037 mmol) 3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid methyl ester as described in example 6. The title compound was obtained as its dihydrochloride. Yield: 16 mg MS (ES+): m/e = 528, chloro pattern.

Example 14: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 3H-Imidazo[4,5-b]pyridine-2-carboxylic acid methyl ester

1.76 g (9.16 mmol) methyl-dichloro-methoxy-acetate were added to a solution of 1.00 g (9.16 mmol) 2,3-diamino-pyridine in 40 ml methanol and stirred at room temperature. 1.85 g (18.32 mmol) triethyl amine were added dropwise. After complete addition the reaction mixture was stirred for 15 h at 80°C. The reaction was not complete resulting in the additon of another 1.76 g methyl-dichloro-methoxy-acetate and 1.85 g triethyl amine. Again the reaction mixture was stirred for 8 h at 80°C. The mixture was concentrated under reduced pressure and the residue was digerated sequentially with diethyl ether and a saturated $NaHCO_3$-solution and then washed with water yielding almost pure 3H-imidazo[4,5-b]pyridine-2-carboxylic acid methyl ester.

Yield: 210 mg MS (ES+): m/e = 178.

(ii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-2- carboxylic acid methyl ester

100 mg (0.56 mmol) 3H-Imidazo[4,5-b]pyridine-2-carboxylic acid methyl ester were dissolved in 3 ml DMF. 22.6 mg (0.56 mmol) sodium hydride (60% in mineral oil) were added and the mixture was stirred 30 minutes at room temperature. 157.2 mg (0.56 mmol) 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added and the resulting mixture was stirred for 1 h at

80°C. The reaction mixture was cooled to room temperature and after the addition of a few drops of water concentrated under reduced pressure. HPLC-MS-analysis showed the presence of another isomer (ratio of isomers ≈ 7:1). Final purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave pure 3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-2- carboxylic acid methyl ester as a brown amorphous solid.

Yield: 203 mg MS (ES^+): m/e = 375; chloro pattern.

(iii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b] pyridine-2-carboxylic acid

175.0 mg (0.46 mmol) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-2- carboxylic acid methyl ester were added to a solution of 19.6 mg (0.82 mmol) LiOH in 6 ml THF and 2 ml H_2O. The reaction mixture was stirred for 2 h at 60°C, cooled to room temperature and acidified (pH= 2) by the addition of a half concentrated HCl-solution. The precipitate was filtered off and washed with water to give pure 3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b] pyridine-2-carboxylic acid as a brown crystalline solid.

Yield: 150 mg MS (ES^+): m/e = 361, chloro pattern.

(iv) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

150.0 mg (0.41 mmol) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b] pyridine-2-carboxylic acid were dissolved in 4 ml DMF. Sequentially 142 µl DIPEA and 151.8 mg (0.41 mmol) HATU were added and the mixture was stirred for 20 min at room temperature. 74.3 mg (0.41 mmol) 1-Isopropyl-piperidine-4-ylamine-hydrochloride and another 71 µl DIPEA were added and the resulting mixture was stirred 3 h at room temperature. Concentration under reduced pressure and final purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave pure 3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide as a light brown amorphous solid. The title compound was obtained as its hydroformiate.

Yield: 17 mg MS (ES^+): m/e = 485, chloro pattern.

Example 15: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester

100.8 mg (0.29 mmol) 2-(Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester were dissolved in 6 ml DMF. Subsequently 60.6 mg (0.44 mmol) K_2CO_3 and 87.5 mg (0.35 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl-)-acetamide were added and the resulting mixture was stirred for 3h at 80°C. The reaction mixture was diluted with 60 ml toluene and washed with a sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester as a white amorphous solid. The product was obtained as its hydroformiate. Yield: 106 mg MS (ES^+): m/e = 513, chloro pattern.

Example 16: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid

30 mg (0.058 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester were dissolved in 3 ml dichloromethane and cooled to 0°C. 234 µl of a 1 M BBr_3-solution (4 equiv.) in dichloromethane were carefully added and the resulting mixture was stirred at room temperature for 16 h. Under cooling 3 ml water were added dropwise followed by the addition of 0.7 ml of a 1 M NaOH-solution. The mixture was concentrated under reduced pressure. Purification by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave pure 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid. The corresponding dihydrochloride was obtained by treatment of the product with a 0.1 M HCl-solution and following lyophilization. Yield: 26 mg

MS (ES^+): m/e = 499, chloro pattern.

Example 17: a) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

b) 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester

102.3 mg (0.297 mmol) 2-(Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester were dissolved in 6 ml DMF. Subsequently 61.6 mg (0.446 mmol) K_2CO_3 and 88.9 mg (0.356 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl-)-acetamide were added and the

resulting mixture was stirred for 2h at 80°C. The reaction mixture was diluted with 60 ml toluene and washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give both isomers described in the title in a 1.3:1 ratio. Both isomers could be separated by NP-HPLC using a chiral stationary phase and a mixture of heptane, ethanol and methanol as solvent. Structural assignment of both isomers was achieved by NOE-spectroscopy. Both isomers were transformed into their dihydrochloride by treatment with a 0.1 M HCl-solution and following lyophilization.

Yield of 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester: 50 mg MS (ES^+): m/e = 513, chloro pattern.

Yield of 3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester: 51 mg MS (ES^+): m/e = 513, chloro pattern.

Example 18: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid was prepared by a procedure according to example 16 starting from 27.8 mg (0.047 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester. The title compound was obtained as its dihydrochloride. Yield: 15 mg MS (ES^+): m/e = 499, chloro pattern.

Example 19: 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid was prepared by a procedure according to example 16 starting from 28 mg (0.048 mmol) 3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester. The title compound was obtained as its dihydrochloride. Yield: 22 mg MS (ES^+): m/e = 499, chloro pattern.

Example 20: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester

50 mg (0.08 mmol) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid were dissolved in 3 ml DMF. Subsequently 27.6 mg (0.16 mmol) KI, 46 mg (0.33 mmol) K_2CO_3 and 45 µl (0.32 mmol) 1-chloroethyl-ethylcarbonate were added and the reaction mixture was stirred at 60°C for 4 h. The reaction mixture was concentrated and the resulting residue purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give pure 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester as a white amorphous solid. The corresponding dihydrochloride was obtained by treatment with a 0.1 M HCl-solution and following lyophilization.

Yield: 46 mg MS (ES^+): m/e = 644, chloro pattern.

Example 21: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester was prepared by adopting the procedure described for example 20 starting from 50 mg (0.08 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 61 µl (0.32 mmol) cyclohexyl-1-chloroethyl carbonate. The title compound was obtained as its dihydrochloride. Yield: 47 mg MS (ES^+): m/e = 698, chloro pattern.

Example 22: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide]

30 mg (0.057 mmol) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid were dissolved in 3 ml DMF. Subsequently 29 µl (0.171 mmol) DIPEA and 21.6 mg (0.057 mmol) HATU were added. After 30 minutes 3.5 µl (0.057 mmol) 2-amino-ethanol and 10 µl DIPEA were added and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and

the residue was purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid). The title compound was obtained as its hydroformiate in form of a white amorphous solid.
Yield: 29 mg MS (ES^+): m/e = 571, chloro pattern.

Example 23: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 50 mg (0.08 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 6.7 mg (0.09 mmol) 3-hydroxy-acetidine. The title compound was obtained as its hydroformiate in form of a white amorphous solid. Yield: 51 mg MS (ES^+): m/e = 583, chloro pattern.

Example 24: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide]
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] was prepared by a procedure according to example 22 starting from 40 mg (0.067 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 5.6 mg (0.075 mmol) N-methyl-2-aminoethanol. The title compound was obtained as its hydroformiate in form of a white amorphous solid.
Yield: 35 mg MS (ES^+): m/e = 585, chloro pattern.

Example 25: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide]
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] was prepared by a procedure according to example 22 starting from 50 mg (0.08 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 6.8 mg (0.09 mmol) N-methyl-2-aminoethanol. The title compound was obtained as its hydroformiate in form of a white amorphous solid.
Yield: 43 mg MS (ES^+): m/e = 585, chloro pattern.

Example 26: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 50 mg (0.08 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 6.7 mg (0.09 mmol) 3-hydroxy-acetidine. The title compound was obtained as its hydroformiate in form of a white amorphous solid. Yield: 37 mg MS (ES+): m/e = 583, chloro pattern.

Example 27: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester was prepared by adopting the procedure described for example 20 starting from 50 mg (0.08 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 45 µl (0.32 mmol) 1-chloroethyl-ethylcarbonate. The title compound was obtained as its dihydrochloride. Yield: 57 mg MS (ES+): m/e = 644, chloro pattern.

Example 28: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester was prepared by. adopting the procedure described for example 20 starting from 50 mg (0.08 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 61 µl (0.32 mmol) cyclohexyl-1-chloroethyl carbonate. The title compound was obtained as its dihydrochloride. Yield: 59 mg MS (ES+): m/e = 698, chloro pattern.

Example 29: a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxy-ethanesulfonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

b) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 2-(2-Trichloromethyl-1H-benzoimidazole-5-sulfonyl)-ethanol

500 mg (2.31 mmol) 3,4-diamino-benzene-sulfonylethan-2-ol were dissolved in 10 ml concentrated acetic acid. 0.4 ml (1.4 equiv.) methyl-2,2,2-trichloroacetimidate were added slowly and the resulting mixture was stirred at room temperature for 4 h. The mixture was diluted with 100 ml toluene and the solvent was removed under reduced pressure. The residue was rinsed with toluene, filtered and dried under vacuo to give a brown crystalline solid pure enough for all further reactions. Yield: 680 mg MS (ES^+): m/e = 345, chloro pattern.

(ii) 5-(2-Hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin- 4-yl)-amide

360 mg (1.05 mmol) 2-(2-Trichloromethyl-1H-benzoimidazole-5-sulfonyl)-ethanol were added to a mixture of 225.4 mg (1.05 equiv.) 1-isopropyl-piperidine-4-ylamine-dihydrochloride and 880 mg (10 equiv.) $NaHCO_3$ in 6 ml THF and 3 ml H_2O and stirred vigorously for 2 h at room temperature. The reaction mixture was diluted with dichloromethane and washed with a saturated $NaHCO_3$-solution and brine. The organic layer was dried over $MgSO_4$ and concentrated. The obtained product was pure enough for further reactions.

Yield: 207 mg MS (ES^+): m/e = 395.

(iii) a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

b) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

126.2 mg (0.32 mmol) 5-(2-Hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin- 4-yl)-amide were dissolved in 10 ml DMF. Subsequently 48.6 mg (1. 1 equiv.) K_2CO_3 and 89.0 mg (1.0 equiv.) 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added and the resulting mixture was stirred for 3 h at 55° C. The reaction mixture was diluted with toluene and washed twice with a saturated $NaHCO_3$-solution and once with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave a 6:4 mixture of both isomers described in the title. These isomers could be separated by NP-HPLC using a chiral stationary phase and a

mixture of heptane, ethanol, methanol and diethyl amine as solvent. Structural assignment of both isomers was achieved by NOE-spectroscopy.

Yield of 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxy-ethanesulfonyl)-1H-benzo-imidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide: 79 mg

MS (ES^+): m/e =591, chloro pattern.

Yield of 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzo-imidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide: 59 mg

MS (ES^+): m/e =591, chloro pattern.

Example 30: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4- [(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide]

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4- [(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] was prepared by a procedure according to example 22 starting from 40 mg (0.08 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 5.4 mg (0.088 mmol) 2-aminoethanol. The title compound was obtained as its hydroformiate in form of a white amorphous solid. Yield: 34 mg MS (ES^+): m/e = 542, chloro pattern.

Example 31: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4- [(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide]

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4- [(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] was prepared by a procedure according to example 22 starting from 50 mg (0.10 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 8.3 mg (0.11 mmol) N-methyl-2-amino-ethanol. The title compound was obtained as its hydroformiate in form of a white amorphous solid. Yield: 30 mg MS (ES^+): m/e = 556, chloro pattern.

Example 32: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 50 mg (0.10 mmol) 1-[(5-chloro-pyridin-2-

ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 8.1 mg (0.11 mmol) 3-hydroxy-acetidine. The title compound was obtained as its hydroformiate in form of a white amorphous solid. Yield: 28 mg . MS (ES+): m/e = 554, chloro pattern.

Example 33: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester was prepared by a procedure according to example 20 starting from 50 mg (0.10 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 61.2 mg (0.401 mmol) 1-chloroethyl-ethylcarbonate. The title compound was obtained as its hydroformiate in form of a white amorphous solid.
Yield: 38 mg MS (ES+): m/e = 615, chloro pattern.

Example 34: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester was prepared by a procedure according to example 20 starting from 50 mg (0.10 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 82.8 mg (0.401 mmol) cyclohexyl-1-chloroethyl carbonate. The title compound was obtained as its hydroformiate in form of a white amorphous solid.
Yield: 46 mg MS (ES+): m/e = 669, chloro pattern.

Example 35: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(3- oxo-morpholin-4-yl)-phenyl]-amide

(i) 4-(4-Nitro-phenyl)-morpholine

A mixture of 24.5 g morpholine and 13.3 g 1-Fluoro-4-nitro-benzene in 30 ml DMSO was heated to 100°C for 4 h. This solution was poured on to 300 ml of water and the resulting precipitate was collected by filtration to yield a bright yellow crystalline product, which was dried under reduced pressure. Yield: 19.7g.

(ii) 4-(4-Nitro-phenyl)-morpholin-3-one

To a solution of 10 g 4-(4-Nitro-phenyl)-morpholine in 200 ml DCM, 32 g Benzyl-triethyl-ammonium chloride and 22.7 g potassium permanganate (325 mesh) were cautiously added at RT. After stirring for 1 h at RT the reaction mixture was heated to reflux for 10 h. Then a solution of 95 g Na_2SO_3 in 450 ml water were added under ice cooling and vigourous stirring. The mixture was filtered trough a pad of celite and the filtrate was concentrated under reduced pressure. The yellow solid was stirred with 250 ml water and the precipitated product was collected by filtration. This crude product was purified by chromatography on silica gel eluting with a gradient of DCM/MeOH 100%->50%. The fractions containing the product were combined and the solvent evaporated under reduced pressure. Yield: 2.6 g.

(iii) 4-(4-Amino-phenyl)-morpholin-3-one

To a solution of 2.6 g 4-(4-Nitro-phenyl)-morpholin-3-one in 350 ml ethyl acetate and 17 ml ethanol, 13.2 g $SnCl_2$ dihydrate were added and the reaction mixture was heated to reflux for 2 h. Then, after cooling to RT the mixture was stirred for 16 h. The precipitated product was collected by filtration and was pure enough for the next reaction step. Yield: 2.07 g.

(iv) 1H-Benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide

To a solution of 100 mg 1H-Benzoimidazole-2-carboxylic acid and 118 mg 4-(4-Amino-phenyl)-morpholin-3-one in 2 ml DCM, 157 mg BOP-Cl and 0.3 ml NEt_3 were added and the mixture was stirred for 16 h at RT. Then, after the reaction mixture was diluted with 20 ml water, the precipitated product was collected by filtration. The crude product was subjected to the next reaction step without further purification. Yield: 122 mg.

(v) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide

To a solution of 50 mg 1H-Benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide in 2 ml DMF, 49 mg Cs_2CO_3 and 37 mg 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide were added at RT and the reaction mixture was stirred for 2 h. Then, additional 20 mg Cs_2CO_3 and 30 mg 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide were added at RT and the reaction mixture was stirred for additional 2 h. The reaction mixture was diluted with 20 ml water and the precipitated product was collected by filtration. The product was taken-up in 3 ml diluted HCl and lyophilized to yield a white solid. The product was obtained as its hydrochloride.

Yield: 128 mg MS (ES^+): m/e = 505, chloro pattern.

Example 36: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- 1H-benzoimidazole-4-carboxylic acid methyl ester

(i) 2-[4-(3-Oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester

A solution of 69.4 mg (0.236mmol) methyl-2-trichloromethyl-1H-benzoimidazole-4-carboxylate in 2 ml THF were slowly added to a mixture containing 50 mg (0.26 mmol) 4-(4-amino-phenyl)-morpholin-3-one, 220 mg (2.62 mmol) $NaHCO_3$, 8 ml THF and 3 ml H_2O. The mixture was stirred vigorously for 3 h at room temperature, diluted with 50 ml CH_2Cl_2 and washed with 30 ml of a saturated $NaHCO_3$-solution. The aqueous solution was extracted with 50 ml CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give a brown solid, which was pure enough for the following reactions.

Yield: 72 mg MS (ES+): m/e = 395.

(ii) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester

72.0 mg (0.183 mmol) 2-[4-(3-Oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester were dissolved in 7 ml DMF. Sequentially 37.8 mg (0.274 mmol) K_2CO_3 and 54.6 mg (0.219 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl-)-acetamide were added and the resulting mixture was stirred for 4h at 80°. The mixture was diluted with 200 ml toluene and washed with 50 ml of a saturated $NaHCO_3$-solution. The product was not completely soluble in toluene, so ethyl acetate had to be added. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- 1H-benzoimidazole-4-carboxylic acid methyl ester as a light brown amorphous solid.

Yield: 46 mg MS (ES+): m/e = 563, chloro pattern.

Example 37: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide

(i) 1-(4-Nitro-phenyl)-1H-pyridin-4-one

A mixture of 10.1 g Pyridin-4-ol and 10 g 1-Fluoro-4-nitro-benzene and 46.1 g Cs_2CO_3 in 30 ml DMF was stirred at RT for 2 h. This solution was poured on to 300 ml of water and the resulting precipitate was collected by filtration to yield a bright yellow crystalline product, which was dried under reduced pressure. Yield: 11.2 g.

(ii) 1-(4-Amino-phenyl)-1H-pyridin-4-one

To a solution of 10 g 1-(4-Nitro-phenyl)-1H-pyridin-4-one in 510 ml ethyl acetate and 26 ml ethanol, 52.1 g $SnCl_2$ dihydrate were added and the reaction mixture was heated to reflux for 6 h. Then, after cooling to RT the solvents were removed under reduced pressure. The residue was taken-up in 100 ml aqueous $NaHCO_3$ solution and 200 ml ethyl acetate were added. The inorganic precipitate was filtered off and the solids were washed with ethyl acetate. After separation of the organic layer, the aqueous layer of the filtrate was extracted with ethyl acetate (2x100 ml) and with DCM (3x150 ml). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The remaining product was pure enough for the next reaction step. Yield: 6 g.

(iii) 2-Trichloromethyl-1H-benzoimidazole

To a solution of 10 g Benzene-1,2-diamine in 250 ml acetic acid, 22.8 g 2,2,2-Trichloro-acetimidic acid methyl ester were added drop wise at RT. After 2 h 500 ml toluene were added and the solvents were removed under reduced pressure. The residue was codestilled additional two times with toluene. After drying under reduced pressure the product was pure enough for the next reaction step. Yield: 25 g.

(iv) 1H-Benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide

A solution of 769 mg 2-Trichloromethyl-1H-benzoimidazole in 10 ml THF were slowly added to a mixture containing 304 mg 1-(4-Amino-phenyl)-1H-pyridin-4-one, 1.3 g $NaHCO_3$, 40 ml THF and 15 ml H_2O. The mixture was stirred vigorously for 3 h at room temperature, diluted with 200 ml CH_2Cl_2 and washed with 40 ml of a saturated $NaHCO_3$-solution. The aqueous solution was extracted with CH_2Cl_2 (3x200 ml) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give a brown solid, which was pure enough for the following reactions. Yield: 598 mg.

(v) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide

To a solution of 192 mg 1H-Benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide in 10 ml DMF, 120 mg K_2CO_3 and 194 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added at RT and the mixture was heated for 2 h at 70°C. After addition of 30 ml of water the mixture was extracted with ethyl acetate (3x100 ml). After drying the combined organic phases over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 70 mg MS (ES+): m/e= 528, chloro pattern.

Example 38: 1-(3-Methoxy-benzyl)-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)- phenyl]-amide

The title compound was prepared analogously to example 37 with the difference that 1-Bromomethyl-3-methoxy-benzene was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole in the alkylation step. MS (ES+): m/e = 451.

Example 39: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide

The title compound was prepared analogously to example 37 with the difference that 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole in the alkylation step. MS (ES+): m/e = 499, chloro pattern.

Example 40: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amide

The title compound was prepared analogously to example 37 with the difference that 8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylamine hydrochloride was used instead of 1-(4-Amino-phenyl)-1H-pyridin-4-one in step (iv). MS (ES+): m/e = 482, chloro pattern.

Example 41: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-phenyl]-amide

(i) 1-(4-Nitro-phenyl)-1H-pyrimidine-2,4-dione

A mixture of 3.5 g 1H-Pyrimidine-2,4-dione and 3 g 1-Fluoro-4-nitro-benzene and 13.8 g Cs_2CO_3 in 60 ml DMF was heated to 80°C for 12 h. This solution was poured on to 200 ml of water and the resulting precipitate was collected by filtration to yield a bright yellow crystalline product, which was dried under reduced pressure. Yield: 2.6 g.

(ii) 1-(4-Amino-phenyl)-1H-pyrimidine-2,4-dione

To a solution of 1.4 g 1-(4-Nitro-phenyl)-1H-pyrimidine-2,4-dione in 120 ml MeOH, 15 g Raney Nickel (washed three times with MeOH) were introduced under a nitrogen atmosphere. Then 15 ml of a 7 M solution of NH_3 in MeOH were added. The nitrogen atmosphere was replaced by a hydrogen atmosphere and the mixture was hydrogenated under normal pressure at RT. After 2 h the reaction mixture was filtered through a pad of celite. The solvents were removed under

reduced pressure and the residue was subjected to the next reaction step without further purification. Yield: 502 mg.

(iii) 1H-Benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)- phenyl]-amide

The title compound was prepared analogously to example 37, step (iv) with the difference that 1-(4-Amino-phenyl)-1H-pyrimidine-2,4-dione was used instead of 1-(4-Amino-phenyl)-1H-pyridin-4-one. MS (ES^+): m/e = 348.

(iv) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-phenyl]-amide

The title compound was prepared analogously to example 37, step (iv) with the difference that 1H-Benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)- phenyl]-amide was used instead of 1H-Benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide. MS (ES^+): m/e = 545, chloro pattern.

Example 42: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-oxazolidin-3-yl)-phenyl]-amide

The title compound was prepared analogously to example 41 with the difference that Oxazolidin-2-one and was used instead of 1H-Pyrimidine-2,4-dione in step (i).

MS (ES^+): m/e = 520, chloro pattern.

Example 43: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2- oxo-oxazolidin-3-yl)-phenyl]-amide

The title compound was prepared analogously to example 41 with the difference that Oxazolidin-2-one and 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide was used instead of 1H-Pyrimidine-2,4-dione (step (i)) and 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole (step (iv)).

MS (ES^+): m/e = 490, chloro pattern.

Example 44: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2,4- dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-phenyl]-amide

The title compound was prepared analogously to example 41 with the difference that 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole in the alkylation step. MS (ES^+): m/e = 516, chloro pattern.

Example 45: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-piperidin-1-yl)-phenyl]-amide

The title compound was prepared analogously to example 41 with the difference that Piperidin-4-one hydrochloride was used instead of 1H-Pyrimidine-2,4-dione in step (i).

MS (ES^+): m/e = 532, chloro pattern.

Example 46: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-phenyl]-amide

(i) [4-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-phenyl]-carbamic acid tert-butyl ester

A solution of 408 mg (4-Amino-phenyl)-carbamic acid tert-butyl ester and 254 mg Ethenesulfonyl-ethene in 4 ml EtOH were heated for 30 min at 140°C under microwave irradiation (100 W, CEM Discover™ apparatus). Then, after cooling to RT the solvents were removed under reduced pressure and the residue was dried in vacuo. The crude product was subjected to the next reaction step. Yield: 0.64 g.

(ii) 4-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-phenylamine

A solution of 640 mg [4-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-phenyl]-carbamic acid tert-butyl ester in 30 ml DCM and 30 ml TFA were allowed to stand for 16 h at RT. Then, after addtion of 100 ml toluene the solvents were removed under reduced pressure and the residue was dried in vacuo. The product was obtained as its trifluoro acetate. Yield: 0.44 g.

(iii) 1H-Benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-phenyl]- amide

The title compound was prepared analogously to example 37, step (iv) with the difference that 14-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-phenylamine was used instead of 1-(4-Amino-phenyl)-1H-pyridin-4-one.

(iv) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-phenyl]-amide

The title compound was prepared analogously to example 37, step (v) with the difference that 1H-Benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-phenyl]- amide was used instead of 1H-Benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide.

MS (ES^+): m/e = 568, chloro pattern.

Example 47: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(1,1- dioxo-1λ6-thiomorpholin-4-yl)-phenyl]-amide

The title compound was prepared analogously to example 46 with the difference that 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole (step (iv)). MS (ES+): m/e = 500, chloro pattern.

Example 48: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide

(i) 1-(4-Nitro-phenyl)-1H-pyrazin-2-one

A mixture of 632 mg Sodium pyrazin-2-olate and 720 mg 1-Fluoro-4-nitro-benzene and 3.3 g Cs_2CO_3 in 13 ml DMF was heated to 35°C for 6 h. This solution was poured on to 300 ml of water and the resulting precipitate was collected by filtration to yield a bright yellow crystalline product, which was dried under reduced pressure. Yield: 545 mg.

(ii) 1-(4-Amino-phenyl)-1H-pyrazin-2-one

To a solution of 520 mg 1-(4-Nitro-phenyl)-1H-pyrazin-2-one in 26 ml ethyl acetate and 1.3 ml ethanol, 2.7 g $SnCl_2$ dihydrate were added and the reaction mixture was heated to reflux for 6 h. Then, after cooling to RT the mixture was stirred for 16 h. The precipitated product was collected by filtration and was pure enough for the next reaction step. Yield: 450 mg.

(iii) 1H-Benzoimidazole-2-carboxylic acid [4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide

The title compound was prepared analogously to example 37, step (iv) with the difference that 1-(4-Amino-phenyl)-1H-pyrazin-2-one was used instead of 1-(4-Amino-phenyl)-1H-pyridin-4-one.

Yield: 513 mg.

(iv) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide

The title compound was prepared analogously to example 37, step (v) with the difference that 1H-Benzoimidazole-2-carboxylic acid [4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide was used instead of 1H-Benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide.

MS (ES+): m/e = 529, chloro pattern.

Example 49: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2- oxo-2H-pyrazin-1-yl)-phenyl]-amide

The title compound was prepared analogously to example 48 with the difference that 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. MS (ES+): m/e = 500, chloro pattern.

Example 50: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-piperazin-1-yl)-phenyl]-amide

(i) 1-(4-Amino-phenyl)-piperazin-2-one

To a solution of 670 mg 1-(4-Nitro-phenyl)-1H-pyrazin-2-one in 100 ml MeOH, 8 g Raney Nickel (washed three times with MeOH) were introduced under a nitrogen atmosphere. Then 10 ml of a 7 M solution of NH_3 in MeOH were added. The nitrogen atmosphere was replaced by a hydrogen atmosphere and the mixture was hydrogenated under normal pressure at RT. After 2 h the reaction mixture was filtered through a pad of celite. The solvents were removed under reduced pressure and the residue was subjected to the next reaction step without further purification.

Yield: 464 mg.

(ii) 4-(4-Amino-phenyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 464 mg 1-(4-Amino-phenyl)-piperazin-2-one and 30 mg DMAP in 15 ml acetonitrile, 794 mg Di-tert-butyldicarbonate were added at RT. After 2 h the solvents were removed under reduced pressure and the residue was taken-up in 200 ml ethyl acetate. The organic phase was washed with water and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Yield: 547 mg.

(iii) 4-{4-[(1H-Benzoimidazole-2-carbonyl)-amino]-phenyl}-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared analogously to example 37, step (iv) with the difference that 4-(4-Amino-phenyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester was used instead of 1-(4-Amino-phenyl)-1H-pyridin-4-one. Yield: 160 mg.

(iv) 4-[4-({1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carbonyl}-amino)-phenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared analogously to example 37, step (v) with the difference that 4-{4-[(1H-Benzoimidazole-2-carbonyl)-amino]-phenyl}-3-oxo-piperazine-1-carboxylic acid tert-butyl ester was used instead of 1H-Benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide. MS (ES+): m/e = 633, chloro pattern.

(v) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-piperazin-1-yl)-phenyl]-amide

A solution of 150 mg 4-[4-({1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carbonyl}- amino)-phenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester in 30 ml DCM and 10 ml TFA were allowed to stand for 16 h at RT. Then, after addtion of 100 ml toluene the solvents were removed under reduced pressure and the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt. Yield: 84 mg MS (ES^+): m/e= 533, chloro pattern.

Example 51: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2- oxo-piperazin-1-yl)-phenyl]-amide

The title compound was prepared analogously to example 50 with the difference that 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. MS (ES^+): m/e = 504, chloro pattern.

Example 52: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2- carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide

(i) 2-(2-Methoxy-ethoxy)-6-nitro-phenylamine

A solution of 5 g 2-Amino-3-nitro-phenol, 4.5 g 1-Bromo-2-methoxy-ethane, 4.4 g K_2CO_3 in 50 ml DMF were heated to 60°C for 16 h. Then 50 ml of water were added and the mixture was extracted with ethyl acetate (3x100 ml). The combined organic layers were dried over $MgSO_4$, and the solvents were removed under reduced pressure. The remaining product was pure enough for the next reaction step. Yield: 5.8 g.

(ii) 3-(2-Methoxy-ethoxy)-benzene-1,2-diamine

To a solution of 1 g 2-(2-Methoxy-ethoxy)-6-nitro-phenylamine in 10 ml ethyl acetate and 3 ml ethanol, 4.4 g $SnCl_2$ dihydrate were added and the reaction mixture was heated to reflux for 6 h. Then, after cooling 50 ml 2 M NaOH were added and the inorganic precipitate was filtered and washed extensivley with ethyl acetate. The filtrate was extracted with exthyl acetate (3x100 ml), the combined organic layers were dried over $MgSO_4$, and the solvents were removed under reduced pressure. The remaining product was pure enough for the next reaction step. Yield: 640 mg.

(iii) 4-(2-Methoxy-ethoxy)-2-trichloromethyl-1H-benzoimidazole

The title compound was prepared analogously to example 37, step (iii) with the difference that 3-(2-Methoxy-ethoxy)-benzene-1,2-diamine was used instead of Benzene-1,2-diamine.

(iv) 4-(2-Methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide

The title compound was prepared analogously to example 37, step (iv) with the difference that 4-(2-Methoxy-ethoxy)-2-trichloromethyl-1H-benzoimidazole was used instead of 2-Trichloromethyl-1H-benzoimidazole. MS (ES^+): m/e = 411.

(v) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide

The title compound was prepared analogously to example 35, step (v) with the difference that 4-(2-Methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)- phenyl]-amide was used instead of 1H-Benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide. MS (ES^+): m/e = 579, chloro pattern.

Example 53: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- 1H-benzoimidazole-4-carboxylic acid

127 mg (0.20 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- 1H-benzoimidazole-4-carboxylic acid methyl ester were dissolved in 15 ml CH_2Cl_2. At 0°C 1.8 ml (1.8 mmol) of a 1 M BBr_3-solution were added. The reaction mixture was stirred for 24 h at room temperature. Because of incomplete conversion further 0.9 ml (0.9 mmol) of a 1 M BBr_3-solution were added. After stirring for 24 h at room temperature the reaction mixture was concentrated and purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid). 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- 1H-benzoimidazole-4-carboxylic acid was obtained as a light brown, amorphous solid. Yield: 73 mg MS (ES^+): m/e = 549, chloro pattern.

Example 54: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 50 mg (0.10 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic

acid and 8.1 mg (0.11 mmol) 3-hydroxy-acetidine. The title compound was obtained as its formiate in form of a white amorphous solid. Yield: 10 mg MS (ES+): m/e = 552, chloro pattern.

Example 55: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(3-hydroxy-azetidine-1-carbonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 50 mg (0.10 mmol) 3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid and 8.1 mg (0.11 mmol) 3-hydroxy-acetidine. The title compound was obtained as its formiate in form of a white amorphous solid. Yield: 27 mg MS (ES+): m/e = 552, chloro pattern.

Example 56: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide]
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] was prepared by a procedure according to example 22 starting from 50 mg (0.10 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 6.8 mg (0.11 mmol) 2-amino-ethanol. The title compound was obtained as its formiate in form of a white amorphous solid. Yield: 4 mg MS (ES+): m/e = 542, chloro pattern.

Example 57: 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide]
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] was prepared by a procedure according to example 22 starting from 50 mg (0.10 mmol) 3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid and 6.7 mg (0.11 mmol) 2-amino-ethanol. The title compound was obtained as its formiate in form of a white amorphous solid. Yield: 18 mg MS (ES+): m/e = 542, chloro pattern.

Example 58: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] was prepared by a procedure according to example 22 starting from 50 mg (0.10 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 8.3 mg (0.11 mmol) N-methyl-2-aminoethanol. The title compound was obtained as its formiate in form of a white amorphous solid. Yield: 23 mg MS (ES^+): m/e = 556, chloro pattern.

Example 59: 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide] was prepared by a procedure according to example 22 starting from 50 mg (0.10 mmol) 3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid and 8.3 mg (0.11 mmol) N-methyl-2-aminoethanol. The title compound was obtained as its formiate in form of a white amorphous solid. Yield: 32 mg MS (ES^+): m/e = 556, chloro pattern.

Example 60: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester was prepared by a procedure according to example 20 starting from 50 mg (0.10 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 82.8 mg (0.40 mmol) cyclohexyl-1-chloroethyl carbonate. The title compound was obtained as its dihydrochloride in form of a white amorphous solid.
Yield: 27 mg MS (ES^+): m/e = 669, chloro pattern.

Example 61: 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H- benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester was prepared by a procedure according to example 20 starting from 50 mg (0.10 mmol) 3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid and 82.8 mg (0.40 mmol) cyclohexyl-1-chloroethyl carbonate. The title compound was obtained as its dihydrochloride in form of a white amorphous solid.

Yield: 49 mg MS (ES+): m/e = 669, chloro pattern.

Example 62: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester was prepared by a procedure according to example 20 starting from 50 mg (0.10 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 61.2 mg (0.40 mmol) 1-chloroethyl ethylcarbonate. The title compound was obtained as its dihydrochloride in form of a white amorphous solid.

Yield: 21 mg MS (ES+): m/e = 615, chloro pattern.

Example 63: 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H- benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester was prepared by a procedure according to example 20 starting from 50 mg (0.10 mmol) 3-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]- 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid and 61.2 mg (0.40 mmol) 1-chloroethyl ethylcarbonate. The title compound was obtained as its dihydrochloride in form of a white amorphous solid.

Yield: 42 mg MS (ES+): m/e = 615, chloro pattern.

Example 64: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 2-hydroxy-ethyl ester
50 mg (0.08 mmol) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid were dissolved in 4 ml DMF. Subsequently 20 mg DMAP, 34.3 mg (0.16 mmol) DCC and 46 µl (0.83 mmol) ethylene glycol

were added. The resulting mixture was stirred for 8 h at 60°C and then concentrated under removed pressure. The remaining residue was purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give pure 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 2-hydroxy-ethyl ester as a white amorphous solid. The corresponding dihydrochloride was obtained by treatment with a 0.1 M HCl-solution and following lyophilization. Yield: 22 mg MS (ES^+): m/e = 572, chloro pattern.

Example 65: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester

50 mg (0.08 mmol) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid were dissolved in 10 ml CH_2Cl_2. Subsequently 3 mg DMAP, 23 mg (0.11 mmol) DCC and 46 µl (0.83 mmol) ethylene glycol were added. The resulting mixture was stirred at room temperature for 16 h and then concentrated under removed pressure. The remaining residue was purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give pure 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester as a white amorphous solid. The corresponding dihydrochloride was obtained by treatment with a 0.1 M HCl-solution and following lyophilization.

Yield: 44 mg MS (ES^+): m/e = 572, chloro pattern.

Example 66: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid carboxymethyl ester

50 mg (0.08 mmol) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid were dissolved in 6 ml DMF. Subsequently 27.6 mg KI, 126.5 mg (0.88 mmol) K_2CO_3 and 62.8 mg (0.64 mmol) chloro-acetic acid were added. The resulting mixture was stirred for 8 h at 60°C. Further 92 mg K_2CO_3 and 62.8 mg (0.64 mmol) chloro-acetic acid were added. After further 8 h at 60°C the reaction mixture was concentrated under removed pressure. The remaining residue was purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give pure 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid carboxymethyl ester

as a white amorphous solid. The corresponding dihydrochloride was obtained by treatment with a 0.1 M HCl-solution and following lyophilization.

Yield: 21 mg MS (ES+): m/e = 586, chloro pattern.

Example 67: 1-(3-Methoxy-benzyl)-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4- carboxylic acid

(i) 1-(3-Methoxy-benzyl)-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester

366.5.0 mg (0.929 mmol) 2-[4-(3-Oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester were dissolved in 15 ml DMF. Sequentially 192.6 mg (1.394 mmol) K_2CO_3 and 156.1 µl (1.394 mmol) 1-bromomethyl-3-methoxy-benzene were added and the resulting mixture was stirfed for 4h at 80°. The mixture was diluted with 300 ml toluene and washed with 50 ml of a saturated $NaHCO_3$-solution. The product was not completely soluble in toluene, so ethyl acetate had to be added. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) (separation of isomers) to give 1-(3-Methoxy-benzyl)-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester as a light brown amorphous solid.

Yield: 150 mg MS (ES+): m/e = 515.

(ii) 1-(3-Methoxy-benzyl)-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid

20 mg (0.04 mmol) 1-(3-Methoxy-benzyl)-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4- carboxylic acid methyl ester were suspended in 5 ml MeOH. 194 µl (0.19 mmol) of an aqueous 1 M LiOH-solution were added and the resulting mixture was stirred for for 8 h at 60°C. After acidification with a 1 M HCL-solution the mixture was concentrated. The resulting residue was purified by preparative HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give pure 1-(3-Methoxy-benzyl)-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4- carboxylic acid as a colorless amorphous solid. Yield: 44 mg MS (ES+): m/e = 501.

Example 68: a) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

b) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(2-hydroxy-ethanesulfonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide and 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(2-hydroxy-ethanesulfonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide were prepared by a procedure according to example 29 starting from 1g (2.5 mmol) crude 5-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin- 4-yl)-amide and 758.9 mg (3.04 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl)-acetamide. Preparative RP-HPLC (CH_3CN/H_2O gradient.+ 0.05 % formic acid) gave a 1:1 mixture of both isomers described in the title. These isomers could be separated by NP-HPLC using a chiral stationary phase and a mixture of heptane, ethanol, methanol and diethyl amine as solvent. Structural assignment of both isomers was achieved by NOE-spectroscopy.
Yield of 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide: 79 mg
MS (ES^+): m/e =563, chloro pattern.
Yield of 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide is 44 mg
MS (ES^+): m/e =563, chloro pattern.

Example 69: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid cyclopropylmethyl ester
325.1 mg (0.57 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid were dissolved in 20 ml CH_2Cl_2. Subsequently 470 µl (5.7 mmol) cyclopropyl-methanol, 152.2 mg (0.74 mmol) DCC and 6.9 mg DMAP were added. The resulting mixture was stirred at room temperature for 16 h. The next day further 100 µl (2.28 mmol) cyclopropyl-methanol, 58.6 mg (0.29 mmol) DCC and 20 mg DMAP were added and the reaction mixture was stirred for 48 h. The solvent was removed under vacuo. Final purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid cyclopropylmethyl ester as a white amorphous solid. The corresponding acetate was obtained by the following procedure: The above described material was dissolved in CH_2Cl_2 and washed with a saturated $NaHCO_3$-solution. The organic layer was

dried over anhydrous $MgSO_4$ and concentrated. The resulting residue was diluted in 20 ml water containing 4 equiv. AcOH and lyophilized. Yield: 231 mg MS (ES^+): m/e = 553, chloro pattern.

Example 70: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid 2-methoxy-ethyl ester
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 2-methoxy-ethyl ester was prepared by a procedure according to example 69 starting from 112 mg (0.22 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid and 177 µl (2.2 mmol) 2-methoxy-ethanol. The title compound was obtained as its dihydrochloride in form of a white amorphous solid. Yield: 66 mg MS (ES^+): m/e = 557, chloro pattern.

Example 71: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-hydroxymethyl-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
85.0 mg (0.166 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid methyl ester were dissolved in 3 ml abs. THF. Under argon 0.25 ml (0.497 mmol) of a 2 M $LiBH_4$-solution in THF were added. After stirring for 1.5 h at room temperature 0.5 ml water were added and the reaction mixture was concentrated. The residue was purified by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-hydroxymethyl-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide as a white amorphous solid. The title compound was obtained as its formiate. Yield: 20 mg MS (ES^+): m/e = 485, chloro pattern.

Example 72: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxymethyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
81.6 mg (0.065 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-hydroxymethyl-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide were dissolved in 5 ml abs. DMF. At 0 °C 21.9 mg (0.195 mmol) potassium tert.butylate were added. After 5 min 12 µl (0.13 mmol) 1-bromo-2-methoxy-ethane were added and the reaction mixture was allowed to

come to room temperature. After 3 h further 12 µl (0.13 mmol) 1-bromo-2-methoxy-ethane were added and the reaction mixture was stirred for 16 h. The solvent was distilled off and the resulting residue was purified by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxymethyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide as a light brown amorphous solid. The title compound was obtained as its formiate. Yield: 12 mg MS (ES^+): m/e = 543, chloro pattern.

Example 73: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(morpholine-4-carbonyl)-1H-benzoimidazole- 2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(morpholine-4-carbonyl)-1H-benzoimidazole- 2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 450 mg (0.90 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid and 87 µl (2.70 mmol) morpholine. The title compound was obtained as its formiate . Subsequent transformation to the corresponding acetate gave a white amorphous solid.
Yield: 456 mg MS (ES^+): m/e = 568, chloro pattern.

Example 74: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-([1,4]oxazepane-4-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-([1,4]oxazepane-4-carbonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 423 mg (0.85 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid and 128.3 mg (0.94 mmol) homomorpholine-hydrochloride. The title compound was obtained as its formiate . Subsequent transformation to the corresponding acetate gave a white amorphous solid.
Yield: 370 mg MS (ES^+): m/e = 582, chloro pattern.

Example 75: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2,6-dimethyl-piperidine-1-carbonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2,6-dimethyl-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a

procedure according to example 22 starting from 100 mg (0.20 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid and 50.0 µl (0.40 mmol) 2,6-dimethyl-piperidine. The title compound was obtained as its formiate in form of a white amorphous solid. Yield: 72 mg MS (ES+): m/e = 594, chloro pattern.

Example 76: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(4,4-difluoro-piperidine-1-carbonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(4,4-difluoro-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 870 mg (1.70 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid and 302.3 mg (1.87 mmol) 4,4-difluoro-piperidine-hydrochloride. The title compound was obtained as its formiate. Subsequent transformation to the corresponding acetate gave a white amorphous solid. Yield: 700 mg MS (ES+): m/e = 602, chloro pattern.

Example 77: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H- benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 147.8 mg (0.296 mmol) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-5-carboxylic acid and 44.8 mg (0.326 mmol) homomorpholine-hydrochloride. The title compound was obtained as its formiate. Subsequent transformation to the corresponding acetate gave a white amorphous solid.

Yield: 113 mg MS (ES+): m/e = 582, chloro pattern.

Example 78: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester was prepared by a procedure according to example 65 starting from 100 mg (0.17 mmol) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-

ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 93 µl (1.7 mmol) ethylene glycol. The title compound was obtained as its dihydrochloride in form of a white amorphous solid. Yield: 86 mg MS (ES+): m/e = 572, chloro pattern.

Example 79: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid carboxymethyl ester
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid carboxymethyl ester was prepared by a procedure according to example 66 starting from 100 mg (0.17 mmol) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 62.9 mg (0.68 mmol) chloro-acetic acid. The title compound was obtained as its dihydrochloride in form of a white amorphous solid. Yield: 44 mg MS (ES+): m/e = 586, chloro pattern.

Example 80: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-methoxy-azetidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-methoxy-azetidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 205 mg (0.34 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 46.6 mg (0.37 mmol) 3-methoxy-azetidine-hydrochloride. The title compound was obtained as its formiate . Subsequent transformation to the corresponding acetate gave a white amorphous solid. Yield: 190 mg MS (ES+): m/e = 597, chloro pattern.

Example 81: a) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-4- carboxylic acid
b) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-4-carboxylic acid

1.45 g (4.21 mmol) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester were dissolved in 45 ml DMF. Subsequently 698.2 mg (5.05 mmol) K_2CO_3 and 888.8 mg (4.42 mmol) 1-bromomethyl-3-methoxy-benzene were added and the resulting

mixture was stirred for 2 h at 60°C. The solvent was distilled off. The residue was taken up in 300 ml ethyl acetate and washed once with a saturated $NaHCO_3$-solution and with brine. The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography on silica gel using an ethyl acetate – methanol mixture as eluent to give 1.19 g of a 4:1 – mixture of 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-4- carboxylic acid methyl ester and 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-4- carboxylic acid methyl ester. That mixture of isomers was dissolved in 100 ml MeOH. 12.8 ml (12.8 mmol) of a 1 M aqueous LiOH-solution were added and the resulting suspension was stirred for 3 h at 60°C. The mixture was acidified by the addition of a 1 M HCl-solution and concentrated under reduced pressure. Final purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave both isomers a) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-4- carboxylic acid and b) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-4- carboxylic acid as white amorphous solids. Both isomers were transformed to the corresponding dihydrochlorides.

Yield of 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-4-carboxylic acid: 890 mg MS (ES^+): m/e = 451.

Yield of 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-4-carboxylic acid: 250 mg MS (ES^+): m/e = 451.

Example 82: a) 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 4-carboxylic acid

b) 3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 4-carboxylic acid

1.45 g (4.21 mmol) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester were dissolved in 45 ml DMF. Subsequently 989.1 mg (7.16 mmol) K_2CO_3 and 1.11 g (6.32 mmol) 1-chloro-4-(2-chloro-ethyl)-benzene were added and the resulting mixture was stirred for 24 h at 80°C. The solvent was distilled off. The residue was taken up in 300 ml ethyl acetate and washed once with a saturated $NaHCO_3$-solution and with brine. The organic layer was dried over anhydrous $MgSO_4$, concentrated and purified by flash chromatography using an ethyl acetate – methanol mixture as eluent to give 1.30 g of a 3:1 – mixture of 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 4-carboxylic acid methyl ester and 3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-

ylcarbamoyl)-3H-benzoimidazole- 4-carboxylic acid methyl ester. That mixture of isomers was dissolved in 100 ml MeOH. 16.2 ml (16.2 mmol) of a 1 M aqueous LiOH-solution were added and the resulting suspension was stirred for 3 h at 60°C. The mixture was acidified by the addition of a 1 M HCl-solution and concentrated under reduced pressure. Final purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave both isomers a) 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 4-carboxylic acid and b) 3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 4-carboxylic acid as white amorphous solids. Both isomers were isolated as their formiates.

Yield of 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 4-carboxylic acid: 800 mg MS (ES^+): m/e = 468, chloro pattern.
Yield of 3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 4-carboxylic acid: 250 mg MS (ES^+): m/e = 468, chloro pattern.

Example 83: 4-(3-Hydroxy-azetidine-1-carbonyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
4-(3-Hydroxy-azetidine-1-carbonyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 150 mg (0.287 mmol) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-4- carboxylic acid and 23.0 mg (0.315 mmol) 3-hydroxy-azetidine. The title compound was obtained as its formiate in form a white amorphous solid.
Yield: 62 mg MS (ES^+): m/e = 506.

Example 84: 1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 150 mg (0.29 mmol) 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 4-carboxylic acid and 23.4 mg (0.32 mmol) 3-hydroxy-azetidine. The title compound was obtained as its formiate in form a white amorphous solid.
Yield: 62 mg MS (ES^+): m/e = 524, chloro pattern.

Example 85: 1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-methoxy-azetidine-1-carbonyl)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-methoxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 50 mg (0.097 mmol) 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 4-carboxylic acid and 13.5 mg (0.015 mmol) 3-methoxy-azetidine. The title compound was obtained as its formiate in form a white amorphous solid.

Yield: 35 mg MS (ES^+): m/e = 538, chloro pattern.

Example 86: a) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-5- carboxylic acid methyl ester

b) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-5-carboxylic acid methyl ester

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-5- carboxylic acid methyl ester and 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-5- carboxylic acid methyl ester were prepared by a procedure according to example 5 iii) starting from 300 mg (0.87 mmol) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester and 210.2 mg (1.04 mmol) 1-bromomethyl-3-methoxy-benzene. Preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave a 1:1 mixture of both isomers described in the title. These isomers could be separated by NP-HPLC using a chiral stationary phase and a mixture of heptane, ethanol, methanol and diethyl amine as solvent. Structural assignment of both isomers was achieved by NOE-spectroscopy.

Yield of 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-5-carboxylic acid methyl ester: 65 mg MS (ES^+): m/e =465.

Yield of 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-5-carboxylic acid methyl ester: 70 mg MS (ES^+): m/e =465.

Example 87: a) 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid methyl ester

b) 3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 5-carboxylic acid methyl ester

1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid methyl ester and 3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 5-carboxylic acid methyl ester were prepared by a procedure according to example 5 iii) starting from 300 mg (0.87 mmol) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester and 365.9 mg (2.09 mmol) 1-chloro-4-(2-chloro-ethyl)-benzene. Since 1-chloro-4-(2-chloro-ethyl)-benzene is less reactive the reaction time had to be extended to 10 h. Preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave a 4:3 mixture of both isomers described in the title. These isomers could be separated by NP-HPLC using a chiral stationary phase and a mixture of heptane, ethanol and methanol as solvent. Structural assignment of both isomers was achieved by NOE-spectroscopy. Yield of 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid methyl ester: 102 mg MS (ES^+): m/e =483, chloro pattern. Yield of 3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 5-carboxylic acid methyl ester: 74 mg MS (ES^+): m/e =483, chloro pattern.

Example 88: 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid

1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid was prepared by a procedure according to example 6 starting from 100 mg (0.21 mmol) 1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid methyl ester and 1.04 ml (1.04 mmol) of a 1 M LiOH-solution. The title compound was obtained as its dihydrochloride in form a white amorphous solid.

Yield: 54 mg MS (ES^+): m/e = 469, chloro pattern.

Example 89: a) 1-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H- benzoimidazole-4-carboxylic acid

b) 3-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid

1-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 3-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H- benzoimidazole-4-carboxylic acid were prepared by a

procedure according to example 81 starting from 200 mg (0.58 mmol) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester and 151.9 mg (0.58 mmol) 2-bromomethyl-5-chloro-benzo[b]thiophene. Hydrolysis of the resulting esters and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compounds as their formiates in form of white amorphous solids.

Yield of 1-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid: 134 mg MS (ES^+): m/e = 511, chloro pattern.

Yield of 3-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid: 49 mg MS (ES^+): m/e = 511, chloro pattern.

Example 90: 1-(5-Chloro-1H-indazol-3-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid

1-(5-Chloro-1H-indazol-3-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid was prepared by a procedure according to example 81 starting from 200 mg (0.58 mmol) 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester and 116.8 mg (0.58 mmol) 5-chloro-3-chloromethyl-1H-indazole. Hydrolysis of the resulting ester and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compound as its formiate in form of a white amorphous solid.

Yield: 20 mg MS (ES^+): m/e = 495, chloro pattern.

Example 91: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(4-hydroxy-piperidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(4-hydroxy-piperidine-1-carbonyl)- 1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 670 mg (1.10 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 124.0 mg (1.21 mmol) piperidin-4-ol. The title compound was obtained as its formiate . Subsequent transformation to the corresponding acetate gave a white amorphous solid.

Yield: 538 mg MS (ES^+): m/e = 611, chloro pattern.

Example 92: 7-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 1,3-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid

5.00 g (24.0 mmol) 8-Hydroxymethyl-1,3-dimethyl-3,7-dihydro-purine-2,6-dione were suspended in 15 ml water. 16.8 ml (33.6 mmol) of a 2 N NaOH-solution were added. The resulting mixture was cooled to 5°C . At that temperature a solution of 5.05 g (32.2 mmol) $KMnO_4$ in 86 ml water was added. After stirring at room temperature for 4 h the reaction mixture was filtered over Celite. After addition of activated carbon the filtrate was again filtered over Celite. The filtrate was concentrated to a volume of 200 ml and 5 ml of conc. HCl-solution were added. After standing at 4 °C for 16 h the crystaline product was filtered off , washed twice with cold water and acetone and dried under reduced pressure at 40°C.

Yield: 5.18 g MS (ES^+): m/e = 225.

(ii) 1,3-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

100 mg (0.45 mmol) 1,3-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid were dissolved in 5 ml DMF. Subsequently 227 µl (1.35 mmol) DIPEA and 186.5 mg (0.495 mmol) HATU were added. After 1 h 105.6 mg (0.495 mmol) 1-isopropyl-piperidine-4-ylamine-dihydrochloride and 227 µl (1.35 mmol) DIPEA were added and the resulting mixture ws stirred at room temperature for 4 h. The reaction mixture was concentrated and purified by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give 1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid (1-isopropyl- piperidin-4-yl)-amide as its formiate.

(iii) 7-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

155 mg (0.45 mmol) 1,3-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid (1-isopropyl- piperidin-4-yl)-amide were dissolved in 5 ml DMF. Subsequently 184.4 mg (1.35 mmol) K_2CO_3 and 111.5 mg (0.405 mmol) 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added and the resulting mixture was stirred at 80°C for 1h. The mixture was concentrated and purified by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give 7-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide. The corresponding

dihydrochloride was obtained by treatment of the product with a 0.1 M HCl-solution and following lyophilization.

Yield: 55 mg MS (ES+): m/e = 546, chloro pattern.

Example 93: a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester

(i) (1-Cyclopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester

To a solution of 14.0 g (0.0699 mol) piperidin-4-yl-carbamic acid tert-butyl ester in 500 ml abs. MeOH 250 g of dried molecular sieves 3 Å were added. Under argon 39.9 ml (0.699 mol) acetic acid and 52.5 ml (0.262 mol) (1-ethoxy-cyclopropoxy)-trimethyl-silane were added. Finally 314.5 ml (0.3145 mol) of a 1 M $NaCNBH_3$-solution in THF were added dropwise. After 20 min at room temperature the reaction mixture was stirred for 6 h at 60° C. The mixture was filtered over "Celite". The filtrate was concentrated under reduced pressure. The resulting residue was taken up in 700 ml ethyl acetate and washed with 250 ml of a 1 M NaOH-solution. The aqueous layer was extracted with 300 ml ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuo to give crude (1-cyclopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester as a colorless solid.

Yield: 23.0 g MS (ES+): m/e= 241.

(ii) 1-Cyclopropyl-piperidin-4-ylamine dihydrochloride

23.0 g of above described crude (1-cyclopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester were dissolved in 350 ml TFA and stirred for 45 minutes at room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in water. After addition of 23.1 ml of a conc. HCl-solution the mixture was lyophilized to yield a white amorphous solid. That solid was suspended in 300 ml ethyl acetate and treated for 45 minutes under ultrasonic conditions. That procedure was repeated twice. Finally, the filtered crystalline solid was dried at 45° C under reduced pressure.

Yield: 15.9 g MS (ES+): m/e= 141.

(iii) 2-Trichloromethyl-1H-benzoimidazole-5-carboxylic acid methyl ester

To a solution of 10.0 g (0.060 mol) 3,4-diaminobenzoic acid methyl ester in 260 ml acetic acid 10.47 ml (0.084 mol) 2,2,2-trichloro-acetimidic acid methyl ester were added. After stirring for 2 h at room temperature the acetic acid was evaporated. The residue was dissolved in CH_2Cl_2,

washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give crude 2-Trichloromethyl-1H-benzoimidazole-5-carboxylic acid methyl ester as a brown rubbery material.

Yield: 20.5 g MS (ES^+): m/e= 293, chloro pattern.

(iv) 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

To a mixture of 7.53 g (35.3 mmol) 1-cyclopropyl-piperidin-4-ylamine-dihydrochloride and 32.39 g (0.386 mol) $NaHCO_3$ in 1300 ml THF and 370 ml water was added a solution of 11.79 g (32.1 mmol) 2-trichloromethyl-1H-benzoimidazole-5-carboxylic acid methyl ester in 360 ml THF. The reaction mixture was stirred vigorously for 2 h at room temperature. The THF was evaporated. The precipitate was filtered off and treated twice with approx. 300 ml of a saturated $NaHCO_3$-solution under ultrasonic conditions. After filtration the resulting solid was washed twice with 150 ml water and dried under vacuo at 45 °C to give pure 2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic methyl ester in form of a light brown crystalline material. Yield: 9.9 g MS.(ES^+): m/e= 343.

(v) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

17.3 g (50.52 mmol) 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester were dissolved in 800 ml DMF. Subsequently 10.47 g (75.8 mmol) K_2CO_3 and 14.84 g (50.52 mmol) methanesulfonic acid 5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl ester were added and the resulting mixture was stirred for 2 h at 80°C. The mixture was concentrated under reduced pressure. The residue was suspended in 800 ml ethyl acetate. The next day the resulting precipitate was filtered off and washed with 100 ml ethyl acetate to give 3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester. The filtrate was concentrated to a volume of approx. 100 ml . Again the formed precipitate was filtered off. That procedure was repeated once again. The remaining filtrate was concentrated under reduced pressure and finally purified by flash-chromatography on silica gel using ethyl acetate as eluent. The product containing fractions were concentrated under vacuo to give pure (> 98%) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester as a light brown crystalline solid.

Yield: 7.9 g MS (ES^+): m/e = 540, chloro pattern.

(vi) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester

1.0 g of crude 3-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester was recrystallized from ethyl acetate.

Yield: 500 mg MS (ES^+): m/e = 540, chloro pattern.

Example 94: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid

7.84 g (14.52 mmol) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester were dissolved in 400 ml MeOH. 72.59 ml (72.59 mmol) of a 1 M aqueous LiOH-solution were added and the resulting mixture was stirred for 7 h at 60 °C. The solution was concentrated to a volume of approx. 200 ml and acidified by the addition of a 4 M aqueous HCl-solution until pH ≈ 1 was reached. After 30 minutes the resulting precipitate was filtered off and washed several times with cold MeOH. Recrystallization from MeOH gave pure 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid in form of a colorless, crystalline solid. The title compound was obtained as its monohydrochloride.

Yield: 7.3 g MS (ES^+): m/e = 526, chloro pattern.

4.0 g (7.11 mmol) of the above described product were transformed into its sodium salt by suspension in 10 ml water, additon of 100.15 ml of a 0.2 M aqueous NaOH-solution and following extraction with 100 ml n-butanol (2x). The combined butanol layers were reextracted with 20 ml water (3x) and co-distilled with 200 ml water (3x). The resulting solution was lyophilized to give the title compound as its sodium salt in form of a white amorphous material.

Yield: 3.49 g

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid was also prepared by a selective synthesis:

(i) C-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-yl]-methylamine

1.00 g (3.59 mmol) 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole and 503.3 mg (3.59 mmol) urotropin were dissolved in 40 ml EtOH. The reaction mixture was stirred at room

temperature for 16 h. The next day 3 ml of a conc. HCl-solution were added and the resulting mixture was refluxed for 45 minutes. After cooling the precipitate was filtered off and washed with water. The white crystalline material was dried under reduced pressure at 40 °C.
Yield: 806 mg

(ii) 4-{[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-amino}-3-nitro-benzoic acid methyl ester

To a solution of 634.4 mg (3.19 mmol) 4-Fluoro-3-nitro-benzoic acid methyl ester in 12 ml DMF were added 800.0 mg (3.19 mmol) C-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-yl]-methylamine and 0.88 ml (6.37 mmol) triethylamine. The reaction mixture was stirred at room temperature for 16 h. 12 ml water was added .The precipitate was filtered off and washed with water. The yellow crystalline material was dried under reduced pressure at 40°C.
Yield: 1.03 g MS (ES+): m/e = 394, chloro pattern.

(iii) 3-Amino-4-{[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-amino}-benzoic acid methyl ester

97.1 mg (0.41 mmol) $NiCl_2 \cdot 6H_2O$ were dissolved in 10 ml MeOH and treated under ultrasonic conditions. 46.4 mg (1.24 mmol) $NaBH_4$ were added. After 15 minutes a solution of 214.0 mg (0.54 mmol) 4-{[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-amino}-3-nitro-benzoic acid methyl ester in 20 ml CH_2Cl_2 was added. After further 15 minutes 55.6 mg (1.48 mmol) $NaBH_4$ were added in three portions. The reaction mixture was treated under ultrasonic conditions for 2 h. Addition of $NaBH_4$ (55.6 mg each time) and treatment under ultrasonic conditions had to be repeated three times to achieve complete conversion. The reaction mixture was filtered over "Celite" and the filtrate was concentrated under reduced pressure. The residue was suspended in 30 ml MeOH. After filtration the filtrate was concentrated under vacuo and the residue was taken up in 100 ml CH_2Cl_2. The organic layer was washed four times with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford crude 3-Amino-4-{[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-amino}-benzoic acid methyl ester as a brown oil.
Yield: 83 mg MS (ES+): m/e = 364, chloro pattern.

(iv) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-trichloromethyl-1H-benzoimidazole- 5-carboxylic acid methyl ester

36.0 mg (0.098 mmol) 3-Amino-4-{[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-amino}-benzoic acid methyl ester were dissolved in 3 ml acetic acid: 17.4 µl (0.14 mmol) 2,2,2-

trichloro-acetimidic acid methyl ester were added and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was co-distilled twice with 15 ml toluene to give crude 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-trichloromethyl-1H-benzoimidazole- 5-carboxylic acid methyl ester as a brown solid. Yield: 49 mg MS (ES+): m/e = 491, chloro pattern.

(v) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid

21.0 mg (0.098 mmol) (1-Cyclopropyl-piperidin-4-ylamine-dihydrochloride were dissolved in 3 ml CH_3CN and 3 ml water. 82.3 mg (0.98 mmol, 10 equiv.) $NaHCO_3$ were added. Finally, a solution of 48.1 mg (0.098 mmol) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-trichloromethyl-1H-benzoimidazole- 5-carboxylic acid methyl ester in 2 ml CH_3CN was added and the resulting mixture was stirred vigorously for 3 h under reflux. The mixture was concentrated under reduced pressure. The residue was purified by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) to give pure 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid in form of a colorless amorphous solid.

Yield: 26 mg (50 %) MS (ES+): m/e = 526, chloro pattern.

(Under the described conditions the methyl ester was hydrolyzed simultaneously)

Example 95: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid was prepared by a procedure according to example 94 starting from 250.0 mg (0.46 mmol) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester. The title compound was isolated as its monohydrochloride in form of a colorless crystalline material.

Yield: 135 mg MS (ES+): m/e = 526, chloro pattern.

Example 96: a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid

(i) 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester was prepared by a procedure according to example 93 (iv) starting from 1.62 g (5.52 mmol) 2-trichloromethyl-1H-benzoimidazole-4-carboxylic acid methyl ester and 1.29 g (6.07 mmol) 1-cyclopropyl-piperidin-4-ylamine dihydrochloride.

Yield: 1.62 g MS (ES^+): m/e= 343.

(ii) a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid and 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid were prepared by a procedure according to example 81 starting from 248.0 mg (0.72 mmol) 2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester and 221.9 mg (0.79 mmol) 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. Hydrolysis of the resulting esters and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compounds as their formiates in form of white amorphous solids. The corresponding hydrochlorides were obtained by treatment of both products with a 0.1 M HCl-solution and following lyophilization.

Yield of 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid: 119 mg MS (ES^+): m/e = 526, chloro pattern.

Yield of 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid: 39 mg MS (ES^+): m/e = 526, chloro pattern.

Example 97: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid methyl ester

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid methyl ester was prepared by a procedure according to example 15 starting from 1.40 g (4.09 mmol) 2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-

benzoimidazole-4-carboxylic acid methyl ester and 1.02 g (4.09 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl)-acetamide.

Yield: 1.90 g MS (ES+): m/e= 511, chloro pattern.

Example 98: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid methyl ester was prepared by a procedure according to example 16 starting from 1.89 g (3.70 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid methyl ester.

Yield: 1.90 g MS (ES+): m/e= 497, chloro pattern.

Example 99: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid cyclopropylmethyl ester

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid cyclopropylmethyl ester was prepared by a procedure according to example 69 starting from 589.0 mg (1.19 mmol) 1-[(5-chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-4-carboxylic acid and 1.92 ml (23.8 mmol) cyclopropyl-methanol.

Yield: 362 mg MS (ES+): m/e= 551, chloro pattern.

Example 100: a) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid

(i) 2-Trichloromethyl-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester

To a solution of 2.00 g (11.6 mmol) 3,4-diamino-thiophene-2-carboxylic acid methyl ester in 50 ml acetic acid 2.06 ml (16.24 mmol) 2,2,2-trichloro-acetimidic acid methyl ester were added. After stirring for 2 h at 95 °C the mixture was concentrated and co-distilled twice with 100 ml toluene.

The residue was dried under vacuo to afford a brown rubbery material.

Yield: 4.2 g MS (ES+): m/e= 300, chloro pattern.

(ii) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester was prepared by a procedure according to example 93 (iv) starting from 3.48 g (11.6 mmol) 2-trichloromethyl-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester and 2.50 g (11.6 mmol) 1-isopropyl-piperidin-4-ylamine-dihydrochloride.

Yield: 3.7 g MS (ES+): m/e= 351.

(iii) a) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid and 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid were prepared by a procedure according to example 81 starting from 500 mg (1.40 mmol) 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester and 397.4 mg (1.40 mmol) 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. Hydrolysis of the resulting esters and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compounds as their formiates in form of white amorphous solids. Structural assignment of both isomers was achieved by NOE-spectroscopy.

Yield of 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid: 113 mgMS (ES+): m/e = 534, chloro pattern.

Yield of 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid: 146 mgMS (ES+): m/e = 534, chloro pattern.

Example 101: a) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid

(i) 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester

2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester was prepared by a procedure according to example 93 (iv) starting from 203.7 mg (0.68 mmol) 2-trichloromethyl-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester and 158.7 mg (0.75 mmol) 1-cyclopropyl-piperidin-4-ylamine -dihydrochloride.

Yield: 309 mg MS (ES+): m/e= 349.

(ii) a) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid and 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid were prepared by a procedure according to example 81 starting from 236.0 mg (0.68 mmol) 2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester and 188.7 mg (0.68 mmol) 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. Hydrolysis of the resulting esters and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compounds as their formiates in form of white amorphous solids. Structural assignment of both isomers was achieved by NOE-spectroscopy.

Yield of 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid: 46 mg MS (ES+): m/e = 531, chloro pattern.

Yield of 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid is 78 mg; MS (ES+): m/e = 531, chloro pattern.

Example 102: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-thieno[3,4-d]imidazole-2,6- dicarboxylic acid 6-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)- amide]

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-thieno[3,4-d]imidazole-2,6- dicarboxylic acid 6-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)- amide] was prepared by a procedure according to example 22 starting from 96 mg (0.18 mmol) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-thieno[3,4-d]imidazole-

6-carboxylic acid and 11.0 µl (0.18 mmol) 2-amino-ethanol. The title compound was obtained as its formiate in form of a white amorphous solid.
Yield: 55 mg MS (ES+): m/e = 577, chloro pattern.

Example 103: a) 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H- thieno[3,4-d]imidazole-6-carboxylic acid
b) 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid and 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H- thieno[3,4-d]imidazole-4-carboxylic acid were prepared by a procedure according to example 81 starting from 500 mg (1.40 mmol) 2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester and 356.0 mg (1.40 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl)-acetamide. Hydrolysis of the resulting esters by treatment with BBr_3 according to example 16 and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compounds as their formiates in form of white amorphous solids. Structural assignment of both isomers was achieved by NOE-spectroscopy.
Yield of 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H- thieno[3,4-d]imidazole-6-carboxylic acid: 142 mg MS (ES+): m/e = 505, chloro pattern.
Yield of 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H- thieno[3,4-d]imidazole-4-carboxylic acid: 58 mg MS (ES+): m/e = 505, chloro pattern.

Example 104: 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-([1,4]oxazepane-4-carbonyl)-3H-thieno[3,4- d]imidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-([1,4]oxazepane-4-carbonyl)-3H-thieno[3,4-d]imidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 22 starting from 80 mg (0.158 mmol) 3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H- thieno[3,4-d]imidazole-6-

carboxylic acid and 21.8 mg (0.158 mmol) homomorpholine-hydrochloride. The title compound was obtained as its formiate in form of a white amorphous solid.
Yield: 70 mg MS (ES+): m/e = 588, chloro pattern.

Example 105: 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester

(i) 2-Trichloromethyl-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester

2-Trichloromethyl-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester was prepared by a procedure according to example 100 (i) from 500 mg (1.85 mmol) 3,4-diamino-5-(2,2,2-trifluoro-ethoxy)-thiophene-2-carboxylic acid methyl ester and 328.0 µl (2.59 mmol) 2,2,2-trichloro-acetimidic acid methyl ester.
Yield: 735 mg MS (ES+): m/e = 397, chloro pattern.

(ii) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4- d]imidazole-4-carboxylic acid methyl ester was prepared by a procedure according to example 93 (iv) starting from 735.0 mg (1.85 mmol) 2-trichloromethyl-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester and 397.8 mg (1.85 mmol) 1-isopropyl-piperidin-4-ylamine -dihydrochloride. Yield: 71 mg MS (ES+): m/e= 449.

(iii) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester was prepared by a procedure according to example 81 starting from 68.0 mg (0.15 mmol) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4- d]imidazole-4-carboxylic acid methyl ester and 42.2 mg (0.15 mmol) 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. Purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compound as its formiate in form of a white amorphous solid. Structural assignment was achieved by NOE-spectroscopy. Yield: 19 mg MS (ES+): m/e = 646, chloro pattern.

Example 106 : a) 1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid

b) 3-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid

1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 3-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid were prepared by a procedure according to example 81 starting from 240 mg (0.70 mmol) 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester and 201.3 mg (0.70 mmol) 5-bromomethyl-3-(5-chloro-thiophen-2-yl)-isoxazole. Hydrolysis of the resulting esters and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compounds as their formiates in form of white amorphous solids. Structural assignment of both isomers was achieved by NOE-spectroscopy.

Yield of 1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid: 93 mg MS (ES^+): m/e = 526, chloro pattern.

Yield of 3-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4- yl-carbamoyl)-3H-benzoimidazole-5-carboxylic acid is 60 mg; MS (ES^+): m/e = 526, chloro pattern.

Example 107 : a) 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid

b) 3-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid

1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid and 3-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid were prepared by a procedure according to example 81 starting from 200 mg (0.58 mmol) 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester and 181.8 mg (0.58 mmol) 2-bromomethyl-5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazole. Hydrolysis of the resulting esters and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compounds as their formiates in form

of white amorphous solids. Structural assignment of both isomers was achieved by NOE-spectroscopy.

Yield of 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-yl-carbamoyl)-1H-benzoimidazole-5-carboxylic acid is 18 mg; MS (ES^+): m/e = 543, chloro pattern.

Yield of 3-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-yl-carbamoyl)-3H-benzoimidazole-5-carboxylic acid is 6 mg; MS (ES^+): m/e = 543, chloro pattern.

Example 108: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 1-(2-Methoxy-ethoxy)-2,3-dinitro-benzene

1.50 g (8.15 mmol) 2,3-Dinitro-phenol were dissolved in 75 ml acetone. Subsequently 1.69 g (12.22 mol) K_2CO_3, 135.3 mg KI (0.81 mmol) and 0.93 ml (9.77 mmol) 1-bromo-2-methoxy-ethane were added. The reaction mixture was refluxed for 8 h. After that time further 1.69 g (12.22 mol) K_2CO_3, 400 mg KI and 0.93 ml (9.77 mmol) 1-bromo-2-methoxy-ethane were added. The resulting mixture was refluxed for 16 h and then concentrated under reduced pressure. The residue was dissolved in warm ethyl acetate and purified by flash-chromatography on silica gel using an ethyl acetate / heptane-mixture as eluent to afford 1-(2-Methoxy-ethoxy)-2,3-dinitro-benzene as an orange crystalline material. Yield: 1.35 g MS (ES^+): m/e = 243.

(ii) 3-(2-Methoxy-ethoxy)-benzene-1,2-diamine

1.80 g (7.43 mmol) 1-(2-Methoxy-ethoxy)-2,3-dinitro-benzene were dissolved in 250 ml MeOH. The solution was evacuated and rinsed with argon several times. 250 mg palladium on charcoal (10%) were added and again the mixture was evacuated and rinsed with argon several times. Finally argon was exchanged by hydrogen (balloon filled with hydrogen) and the mixture was stirred for 2 h at room temperature. The reaction mixture was filtered over "Celite" and the filter residue was washed with 100 ml MeOH. The filtrate was concentrated under vacuo to give pure 3-(2-Methoxy-ethoxy)-benzene-1,2-diamine as a brown oil. Yield: 1.33 g MS (ES^+): m/e = 183.

(iii) 4-(2-Methoxy-ethoxy)-2-trichloromethyl-1H-benzoimidazole

1.33 g (7.30 mmol) 3-(2-Methoxy-ethoxy)-benzene-1,2-diamine were dissolved in 35 ml acetic acid. 1.25 ml (10.22 mmol) 2,2,2-trichloro-acetimidic acid methyl ester were added and the resulting mixture was stirred for 2 h at room temperature. The mixture was concentrated

under reduced pressure and the residue was co-distilled twice with 20 ml toluene to give crude 4-(2-Methoxy-ethoxy)-2-trichloromethyl-1H-benzoimidazole as a brown solid.
Yield: 2.25 g MS (ES+): m/e = 309, chloro pattern.

(iv) 4-(2-Methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

4-(2-Methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide was prepared by a procedure according to example 5 (ii) starting from 1.91 g (6.18 mmol) 4-(2-Methoxy-ethoxy)-2-trichloromethyl-1H-benzoimidazole and 1.46 g (6.79 mmol) 1-isopropyl-piperidin-4-ylamine-dihydrochloride. Final purification was achieved by flash-chromatography on silica gel using an ethyl acetate /MeOH – mixture as eluent. Yield: 660 mg MS (ES+): m/e= 361.

(v) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 5 (iii) starting from 650.0 mg (1.80 mmol) 4-(2-Methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide and 449.9 mg (1.80 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl)-acetamide. Purification by flash-chromatography on silica gel using a ethyl acetate / heptane - mixture as eluent gave a 9:1 mixture of 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide and 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-7-(2-methoxy-ethoxy)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide. These isomers were separated by NP-HPLC using a chiral stationary phase and a mixture of heptane, ethanol, methanol and diethyl amine as solvent. The title compound was transformed into its acetate affording a colorless amorphous material.
Yield of 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide is 500 mg; MS (ES+): m/e= 529, chloro pattern.

Example 109: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-ethoxy-ethoxy)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 1-(2-Ethoxy-ethoxy)-2,3-dinitro-benzene

1-(2-Ethoxy-ethoxy)-2,3-dinitro-benzene was prepared by a procedure according to example 108 (i) starting from 500 mg (2.72 mmol) 2,3-dinitro-phenol and 0.72 ml (6.52 mmol) 1-chloro-2-ethoxy-ethane. Yield: 450 mg MS (ES+): m/e = 257.

(ii) 3-(2-Ethoxy-ethoxy)-benzene-1,2-diamine

3-(2-Ethoxy-ethoxy)-benzene-1,2-diamine was prepared by a procedure according to example 108 (ii) starting from 450 mg (1.76 mmol) 1-(2-Ethoxy-ethoxy)-2,3-dinitro-benzene. Yield: 345 mg MS (ES+): m/e = 197.

(iii) 4-(2-Ethoxy-ethoxy)-2-trichloromethyl-1H-benzoimidazole

4-(2-Ethoxy-ethoxy)-2-trichloromethyl-1H-benzoimidazole was prepared by a procedure according to example 108 (iii) starting from 345 mg (1.76 mmol) 3-(2-Ethoxy-ethoxy)-benzene-1,2-diamine and 0.30 ml (2.46 mmol) 2,2,2-trichloro-acetimidic acid methyl ester. Yield: 568 mg MS (ES+): m/e = 323, chloro pattern.

(iv) 4-(2-Ethoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

4-(2-Ethoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide was prepared by a procedure according to example 108 (iv) starting from 569.6 mg (1.76 mmol) 4-(2-Ethoxy-ethoxy)-2-trichloromethyl-1H-benzoimidazole and 454.4 mg (2.11 mmol) 1-isopropyl-piperidin-4-ylamine-dihydrochloride. Yield: 540 mg MS (ES+): m/e= 375.

(v) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-ethoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-ethoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 108 (v) starting from 540.0 mg (1.44 mmol) 4-(2-Ethoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide and 359.8 mg (1.44 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl)-acetamide. The title compound was transformed into its acetate affording a colorless amorphous material.

Yield of 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-ethoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide: 201 mg MS (ES+): m/e= 543, chloro pattern.

Example 110: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-hydroxy-ethoxy)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) tert-Butyl-[2-(2,3-dinitro-phenoxy)-ethoxy]-dimethyl-silane

tert-Butyl-[2-(2,3-dinitro-phenoxy)-ethoxy]-dimethyl-silane was prepared by a procedure according to example 108 (i) starting from 500 mg (2.72 mmol) 2,3-dinitro-phenol and 1.00 g (4.18 mmol) (2-Bromo-ethoxy)-tert-butyl-dimethyl-silane.
Yield: 610 mg MS (ES+): m/e = 343.

(ii) 3-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzene-1,2-diamine
3-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzene-1,2-diamine was prepared by a procedure according to example 108 (ii) starting from 610 mg (1.78 mmol) tert-Butyl-[2-(2,3-dinitro-phenoxy)-ethoxy]-dimethyl-silane. Yield: 503 mg MS (ES+): m/e = 283.

(iii) 4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-2-trichloromethyl-1H- benzoimidazole
4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-2-trichloromethyl-1H- benzoimidazole was prepared by a procedure according to example 108 (iii) starting from 503 mg (1.78 mmol) 3-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzene-1,2-diamine and 0.31 ml (2.49 mmol) 2,2,2-trichloro-acetimidic acid methyl ester. Yield: 680 mg MS (ES+): m/e = 409, chloro pattern.

(iv) 4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-1H-benzoimidazole-2-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 108 (iv) starting from 680.0 mg (1.66 mmol) 4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-2-trichloromethyl-1H-benzoimidazole and 428.4 mg (1.99 mmol) 1-isopropyl-piperidin-4-ylamine-dihydrochloride.
Yield: 670 mg MS (ES+): m/e= 461.

(v) 4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-1-[(5-chloro-pyridin-2-ylcarbamoyl)- methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-1-[(5-chloro-pyridin-2-ylcarbamoyl)- methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide was prepared by a procedure according to example 108 (v) starting from 670.0 mg (1.45 mmol) 4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-1H-benzoimidazole-2-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide and 362.8 mg (1.45 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl)-acetamide. Final purification by flash-chromatography on silica gel using ethyl acetate as eluent gave the title compound as a brown oil. Yield: 350 mg MS (ES+): m/e= 629, chloro pattern.

(vi) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-hydroxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

250 mg (0.40 mmol) 4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-1-[(5-chloro-pyridin-2-ylcarbamoyl)- methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide were dissolved in 15 ml THF. 435 µl of a 1 M TBAF-solution in THF and 26 µl acetic acid were added. The resulting mixture was stirred for 48 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was taken up in 50 ml CH_2Cl_2 and washed once with a saturated $NaHCO_3$-solution and five times with water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuo. Final purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave pure 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-hydroxy-ethoxy)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide as its formiate in form of a colorless amorphous material. The title compound was transformed into its acetate. Yield: 132 mg MS (ES^+): m/e= 515, chloro pattern.

Example 111: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[2-fluoro-4-(pyrrolidine-1-carbonyl)- phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester

(i) (3-Fluoro-4-nitro-phenyl)-pyrrolidin-1-yl-methanone

1.00 g (5.40 mmol) 3-Fluoro-4-nitro-benzoic acid were suspended in 55 ml benzene. 1 ml Thionyl chloride and 7 drops DMF were added. The resulting mixture was stirred of 5 h at 70 °C and then concentrated under reduced pressure. The residue was dissolved in 40 ml CH_2Cl_2. Subsequently 0.75 ml (5.40 mmol) triethylamine and 0.45 ml (5.40 mmol) pyrrolidine were added and the resulting solution was stirred for 1 h at room temperature. The mixture was diluted with CH_2Cl_2 and washed subsequently with a 0.1 N HCl-solution, with a saturated $NaHCO_3$-solution and with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuo to give crude (3-Fluoro-4-nitro-phenyl)-pyrrolidin-1-yl-methanone as an orange solid.

Yield: 1.35 g MS (ES^+): m/e= 239.

(ii) (4-Amino-3-fluoro-phenyl)-pyrrolidin-1-yl-methanone

515.0 mg (2.16 mmol) (3-Fluoro-4-nitro-phenyl)-pyrrolidin-1-yl-methanone were dissolved in 20 ml MeOH. The solution was evacuated and rinsed with argon several times. 150 mg palladium on charcoal (10%) were added and again the mixture was evacuated and rinsed with argon several times. Finally argon was exchanged by hydrogen (balloon filled with hydrogen) and the mixture was stirred for 2 h at room temperature. The reaction mixture was filtered over

"Celite" and the filter residue was washed with 30 ml MeOH. The filtrate was concentrated under vacuo to give pure (4-Amino-3-fluoro-phenyl)-pyrrolidin-1-yl-methanone as a colorless oil.

Yield: 448 mg MS (ES+): m/e = 209.

(iii) 2-[2-Fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester

59.0 mg (0.28 mmol) (4-Amino-3-fluoro-phenyl)-pyrrolidin-1-yl-methanone were dissolved in 6 ml THF and 3 ml water. 238.0 mg (2.83 mmol) $NaHCO_3$ were added. Finally 75.6 mg (0.26 mmol) 2-Trichloromethyl-1H-benzoimidazole-4-carboxylic acid methyl ester were added and the resulting mixture was stirred vigorously for 3 h at room temperature. The mixture was diluted with CH_2Cl_2 and washed with a saturated $NaHCO_3$-solution and with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Final purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave pure 2-[2-Fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester in form of a colorless amorphous solid. Yield: 69 mg MS (ES+): m/e = 411.

(iv) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[2-fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[2-fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester was prepared by a procedure according to example 36 (ii) starting from 40.0 mg (0.10 mmol) 2-[2-Fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester and 29.2 mg (0.12 mmol) 2-bromo-N-(5-chloro-pyridin-2-yl)-acetamide. Final purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave pure 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[2-fluoro-4-(pyrrolidine-1-carbonyl)- phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester as a colorless amorphous solid.

Yield: 13 mg MS (ES+): m/e = 579, chloro pattern.

Example 112 : a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-methyl-3H-benzoimidazole-5-carboxylic acid

(i) 4-Amino-3-methyl-5-nitro-benzoic acid

4-Amino-3-methyl-5-nitro-benzoic acid was prepared as desribed by Bolhofer et al. in US3691166.

(ii) 4-Amino-3-methyl-5-nitro-benzoic acid methyl ester

500 mg (2.50 mmol) 4-Amino-3-methyl-5-nitro-benzoic acid were dissolved in a mixture of 8 ml CH_2Cl_2 and 2 ml MeOH. At 0 °C 1.3 ml of a 2 M trimethylsilyldiazomethane-solution in hexane were added. After 1 h at 0 °C the reaction mixture was allowed to warm to room temperature. The next day further 1.3 ml of a 2 M trimethylsilyldiazomethane-solution in hexane were added. After stirring for 3 h at room temperature a solution of 0.22 ml acetic acid in 1.8 ml CH_2Cl_2 was added dropwise to destroy excess trimethylsilyldiazomethane. The reaction mixture was concentrated under reduced pressure. The residue was digerated with heptane and the crystalline material was filtered off to give pure 4-Amino-3-methyl-5-nitro-benzoic acid methyl ester. Yield: 496 mg MS (ES^+): m/e = 211.

(iii) 3,4-Diamino-5-methyl-benzoic acid methyl ester

3,4-Diamino-5-methyl-benzoic acid methyl ester was prepared by a procedure according to example 11 (i) starting from 495.0 mg (2.36 mmol) 4-Amino-3-methyl-5-nitro-benzoic acid methyl ester. Yield: 404 mg MS (ES^+): m/e= 181.

(iv) 7-Methyl-2-trichloromethyl-1H-benzoimidazole-5-carboxylic acid methyl ester

7-Methyl-2-trichloromethyl-1H-benzoimidazole-5-carboxylic acid methyl ester was prepared by a procedure according to example 5 (i) starting from 404.0 mg (2.20 mmol) 3,4-Diamino-5-methyl-benzoic acid methyl ester and 0.39 ml (3.08 mmol) 2,2,2-trichloro-acetimidic acid methyl ester.

Yield: 869 mg MS (ES^+): m/e= 307, chloro pattern.

(v) 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid methyl ester

2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid methyl ester was prepared by a procedure according to example 93 (iv) starting from 685.0 mg (2.20 mmol) 7-Methyl-2-trichloromethyl-1H-benzoimidazole-5-carboxylic acid methyl ester and 474.4 mg (2.20 mmol) 1-cyclopropyl-piperidin-4-ylamine -dihydrochloride.

Yield: 730 mg MS (ES^+): m/e= 357.

(vi) a) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid

b) 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-methyl-3H-benzoimidazole-5-carboxylic acid

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid and 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-methyl-3H-benzoimidazole-5-carboxylic acid were prepared by a procedure according to example 81 starting from 200 mg (0.56 mmol) 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid methyl ester and 164.8 mg (0.56 mmol) methanesulfonic acid 5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl ester. Hydrolysis of the resulting esters by treatment with LiOH and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compounds as their formiates in form of white amorphous solids. Structural assignment of both isomers was achieved by NOE-spectroscopy.

Yield of 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid is 7 mg; MS (ES^+): m/e = 540, chloro pattern.

Yield of 3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-3H-benzoimidazole-5-carboxylic acid is 111 mg; MS (ES^+): m/e = 540, chloro pattern.

Example 113: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid

(i) 2,3-Diamino-6-fluoro-benzoic acid ethyl ester

2,3-Diamino-6-fluoro-benzoic acid ethyl ester was prepared by a procedure according to example 11 (i) starting from 200.0 mg (0.88 mmol) 2-Amino-6-fluoro-3-nitro-benzoic acid ethyl ester.

Yield: 157 mg MS (ES^+): m/e= 229.

(ii) 5-Fluoro-2-trichloromethyl-1H-benzoimidazole-4-carboxylic acid ethyl ester

5-Fluoro-2-trichloromethyl-1H-benzoimidazole-4-carboxylic acid ethyl ester was prepared by a procedure according to example 5 (i) starting from 150.0 mg (0.76 mmol) 2,3-Diamino-6-fluoro-benzoic acid ethyl ester and 133 µl (1.06 mmol) 2,2,2-trichloro-acetimidic acid methyl ester.

Yield: 280 mg MS (ES^+): m/e= 325, chloro pattern.

(iii) 5-Fluoro-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid ethyl ester

5-Fluoro-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid ethyl ester was prepared by a procedure according to example 93 (iv) starting from 240.0 mg (0.74 mmol) 5-Fluoro-2-trichloromethyl-1H-benzoimidazole-4-carboxylic acid ethyl ester and 158.6 mg (0.74 mmol) 1-Isopropyl-piperidin-4-ylamine-dihydrochloride.

Yield: 232 mg MS (ES+): m/e= 377.

(iv) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid was prepared by a procedure according to example 81 starting from 230 mg (0.60 mmol) 5-Fluoro-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid ethyl ester and 179.5 mg (0.60 mmol) methanesulfonic acid 5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl ester. Hydrolysis of the resulting ethyl ester by treatment with LiOH and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compound as its formiate in form of a white amorphous solid.

Yield: 87 mg MS (ES+): m/e= 546, chloro pattern.

Example 114: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid

(i) 2-Amino-3-nitro-6-(2,2,2-trifluoro-ethoxy)-benzoic acid ethyl ester

420 mg NaH (60% suspension in oil) were added to a solution of 2.16 ml (29.8 mmol) 2,2,2-trifluoro-ethanol in 5 ml THF. When the gas evolution ceased, 1.0 g (4.38 mmol) 2-Amino-6-fluoro-3-nitro-benzoic acid ethyl ester was added. The resulting mixture was stirred at 0 °C for 30 minutes and at room temperature for further 30 minutes. To this mixture were added 2 ml of a 6 M aqueous HCl-solution, and most of the solvent was removed under reduced pressure. The residue was mixed with 20 ml water and the resulting solid was collected and washed with water and then hexane. The obtained yellow crystalline material was dried under reduced pressure at 35 °C. Yield: 1.22 g.

(ii) 2,3-Diamino-6-(2,2,2-trifluoro-ethoxy)-benzoic acid ethyl ester

2,3-Diamino-6-(2,2,2-trifluoro-ethoxy)-benzoic acid ethyl ester was prepared by a procedure according to example 11 (i) starting from 1.22 g (3.96 mmol) 2-Amino-3-nitro-6-(2,2,2-trifluoro-ethoxy)-benzoic acid ethyl ester. Yield: 1.07 g MS (ES+): m/e= 279.

(iii) 2-Trichloromethyl-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid ethyl ester

2-Trichloromethyl-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid ethyl ester was prepared by a procedure according to example 5 (i) starting from 200.0 mg (0.72 mmol) 2,3-Diamino-6-fluoro-benzoic acid ethyl ester and 128 µl (1.01 mmol) 2,2,2-trichloro-acetimidic acid methyl ester. Yield: 340 mg MS (ES+): m/e= 405, chloro pattern.

(iv) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid ethyl ester

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid ethyl ester was prepared by a procedure according to example 93 (iv) starting from 290.0 mg (0.72 mmol) 2-Trichloromethyl-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid ethyl ester and 153.8 mg (0.72 mmol) 1-Isopropyl-piperidin-4-ylamine-dihydrochloride. Yield: 299 mg MS (ES+): m/e= 457.

(v) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid was prepared by a procedure according to example 81 starting from 299.0 mg (0.66 mmol) 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4- carboxylic acid ethyl ester and 192.4 mg (0.66 mmol) methanesulfonic acid 5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl ester. Hydrolysis of the resulting ethyl ester by treatment with LiOH in MeOH and purification by preparative RP-HPLC (CH_3CN/H_2O gradient + 0.05 % formic acid) gave the title compound as its formiate in form of a white amorphous solid. Yield: 90 mg MS (ES+): m/e= 626, chloro pattern.

Example 115: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-5- (2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4- yl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-5- (2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4- yl)-amide was prepared by a procedure according to example 22 starting from 50.0 mg (0.08 mmol) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4- ylcarbamoyl)-5-(2,2,2-

trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid and 8.7 mg (0.12 mmol) azetidin-3-ol. The title compound was obtained as its formiate in form of a white amorphous solid. Yield: 18 mg MS (ES+): m/e = 681, chloro pattern.

Example 116: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-fluoro-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 117: 7-Chloro-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 118: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-7-cyclopropyl-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 119: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-ethyl-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 120: 1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 121: 1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-fluoro-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 122: 7-Chloro-1-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 123: 1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-7-cyclopropyl-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 124: 1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-ethyl-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 125: 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 126: 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-fluoro-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 127: 7-Chloro-1-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl- piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 128: 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-ethyl-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 129: 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-7-cyclopropyl-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 130: 1-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7- methyl-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 131: 7-Chloro-1-(6-chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 132: 1-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7- fluoro-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 133: 1-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-7-cyclopropyl-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 134: 1-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7- ethyl-1H-benzoimidazole-5-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 135: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-4-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 136: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-fluoro-1H-benzoimidazole-4-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 137: 7-Chloro-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 138: 1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-4-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 139: 1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-fluoro-1H-benzoimidazole-4-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 140: 7-Chloro-1-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 141: 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-methyl-1H-benzoimidazole-4-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 142: 7-Chloro-1-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl- piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 143: 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4- ylcarbamoyl)-7-fluoro-1H-benzoimidazole-4-carboxylic acid
The title compound can be prepared by adapting the methodology described above.

Example 144: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-4-(3-hydroxy-azetidine-1- carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-cyclopropyl-piperidin-4-yl)-amide
The title compound can be prepared by adapting the methodology described above.

Example 145: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-1H-benzoimidazole-2,4- dicarboxylic acid 4-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)- amide]
The title compound can be prepared by adapting the methodology described above.

Example 146: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-2,4-dicarboxylic acid 4-amide 2-[(1-isopropyl-piperidin-4-yl)- amide]
The title compound can be prepared by adapting the methodology described above.

Example 147: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl- piperidin-4-yl)-amide]

The title compound can be prepared by adapting the methodology described above.

Example 148: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-2,4-dicarboxylic acid 4-dimethylamide 2-[(1-isopropyl-piperidin-4-yl)- amide]

The title compound can be prepared by adapting the methodology described above.

Example 149: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-2,4-dicarboxylic acid 2-[(1-isopropyl-piperidin-4-yl)-amide] 4-(methyl- propyl-amide)

The title compound can be prepared by adapting the methodology described above.

Example 150: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-7-methyl-1H-benzoimidazole- 2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)- amide]

The title compound can be prepared by adapting the methodology described above.

Example 151: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-4-(3-hydroxy-azetidine-1- carbonyl)-7-methyl-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

The title compound can be prepared by adapting the methodology described above.

Example 152: 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-5-fluoro-7-methyl-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide]

The title compound can be prepared by adapting the methodology described above.

Example 153: 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-5-fluoro-4-(3-hydroxy-azetidine-1-carbonyl)-7-methyl-1H-benzoimidazole-2-carboxylic acid (1-isopropyl- piperidin-4-yl)-amide

The title compound can be prepared by adapting the methodology described above.

Example 154: 1-[2-(4-Chloro-phenyl)-ethyl]-4-(2-hydroxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound can be prepared by adapting the methodology described above.

Example 155: 1-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-4-(2-hydroxy-ethoxy)-1H-benzoimidazole-2- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound can be prepared by adapting the methodology described above.

Example 156: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)- 1H-thieno[3,4-d]imidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

The title compound can be prepared by adapting the methodology described above.

Example 157: 5-Chloro-1H-benzoimidazole-2-carboxylic acid benzylamide

A solution of 120.0 mg (0.45 mmol) 5-chloro-2-trichloromethyl-1H-benzoimidazole in 2 ml tetrahydrofuran (THF) was added slowly to a mixture of 53.5 µl (0.49 mmol) benzylamine and 373.8 mg (4.45 mmol, 10 equiv.) $NaHCO_3$ in 8 ml THF and 4 ml water. The reaction mixture was stirred for 2 h at room temperature (20 °C to 25 °C in the following RT). The suspension was filtered and the filtrate was concentrated under reduced pressure. After purification by preparative RP-HPLC (CH_3CN/H_2O gradient and 0.05 % formic acid) pure 5-Chloro-1H-benzoimidazole-2-carboxylic acid benzylamide was obtained as a white amorphous solid.

Yield: 84 mg MS (ES^+): m/e : 286, chloro pattern.

Example 158: 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester

A solution of 3.99 g (13.6 mmol) 2-trichloromethyl-1H-benzoimidazole-4-carboxylic acid methyl ester in 40 ml THF was added slowly to a mixture of 2.9 g (13.6 mmol) 1-isopropyl-piperidin-4-ylamine-dihydrochloride and 13.7 g (0.163 mol, 12 equivalents) $NaHCO_3$ in 200 ml THF and 120 ml water. The reaction mixture was stirred for 2 h at RT. The THF was distilled off. The resulting aqueous suspension was diluted with 200 ml CH_2Cl_2 and extracted twice with 150 ml water. The organic layer was concentrated under reduced pressure and the resulting residue

was purified by flash-chromatography on silica gel using an ethyl acetate / methanol-(4:1)-mixture as eluent. The title compound was obtained as a light brown crystalline material.

Yield: 3.20 g MS (ES^+): m/e : 345.

Example 159: 2-(1-Cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

To a mixture of 7.53 g (35.3 mmol) 1-cyclopropyl-piperidin-4-ylamine dihydrochloride and 32.39 g (0.386 mol) $NaHCO_3$ in 1300 ml THF and 370 ml water a solution of 11.79 g (32.1 mmol) 2-trichloromethyl-1H-benzoimidazole-5-carboxylic acid methyl ester in 360 ml THF was added. The reaction mixture was stirred vigorously for 2 h at RT. The THF was evaporated. The precipitate was filtered off and treated twice with about 300 ml of a saturated $NaHCO_3$-solution under ultrasonic conditions. After filtration the resulting solid was washed twice with 150 ml water and dried under reduced pressure at 45 °C to give pure 2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic methyl ester in form of a light brown crystalline material.

Yield: 9.9 g (90 %) MS (ES^+): m/e= 343.

Example 160: 5-Chloro-1H-benzoimidazole-2-carboxylic acid diisopropylamide

A solution of 500.0 mg (1.85 mmol) 5-Chloro-2-trichloromethyl-1H-benzoimidazole in 20 ml THF was added slowly to a mixture of 286 µl (2.04 mmol) diisopropyl-amine and 1.55 g (18.5 mmol, 10 equivalents) $NaHCO_3$ in 70 ml THF and 20 ml water. The reaction mixture was stirred for 2 h at RT. The organic solvent was evaporated. The formed crystalline material was filtered off and treated once with about 50 ml of a saturated $NaHCO_3$-solution under ultrasonic conditions. The crystalline residue was filtered off again and washed twice with 20 ml water. Drying under reduced pressure at 35 °C gave pure 5-Chloro-1H-benzoimidazole-2-carboxylic acid diisopropylamide in form of a light brown crystalline solid.

Yield: 321 mg MS (ES^+): m/e : 280, chloro pattern.

Example 161: (5-Chloro-1H-benzoimidazol-2-yl)-morpholin-4-yl-methanone

(5-Chloro-1H-benzoimidazol-2-yl)-morpholin-4-yl-methanone was prepared by a procedure according to example 157 starting from 120.0 mg (0.45 mmol) 5-Chloro-2-trichloromethyl-1H-benzoimidazole and 42.6 µl (0.49 mmol) morpholine. The title compound was isolated as a

colorless amorphous solid. Yield: 95 mg (80 %) MS (ES^+): m/e : 266, chloro pattern.

Example 162: 5-Chloro-1H-benzoimidazole-2-carboxylic acid (4-methyl-piperazin-1-yl)-amide

5-Chloro-1H-benzoimidazole-2-carboxylic acid (4-methyl-piperazin-1-yl)-amide was prepared by a procedure according to example 157 starting from 120.0 mg (0.45 mmol) 5-Chloro-2-trichloromethyl-1H-benzoimidazole and 58.9 µl (0.49 mmol) 4-Methyl-piperazin-1-ylamine. The title compound was isolated as a colorless amorphous solid.

Yield: 89 mg MS (ES^+): m/e : 294, chloro pattern.

Example 163: 5-Chloro-1H-benzoimidazole-2-carboxylic acid (4-cyano-phenyl)-amide

5-Chloro-1H-benzoimidazole-2-carboxylic acid (4-cyano-phenyl)-amide was prepared by a procedure according to example 160 starting from 500.0 mg (1.85 mmol) 5-Chloro-2-trichloromethyl-1H-benzoimidazole and 229.8 mg (1.95 mmol) 4-amino-benzonitrile. The title compound was isolated as a light brown crystalline solid.

Yield: 475 mg (86 %) MS (ES^+): m/e : 297, chloro pattern.

Example 164: 2-[4-(3-Oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester

2-[4-(3-Oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester was prepared by a procedure according to example 160 starting from 1.32 g (4.49 mmol) 2-trichloromethyl-1H-benzoimidazole-4-carboxylic acid methyl ester and 950.0 mg (4.94 mmol) 4-(4-Amino-phenyl)-morpholin-3-one. The title compound was isolated as a light brown crystalline solid. Yield: 1.44 g (81 %) MS (ES^+): m/e : 395.

Example 165: 2-[2-Fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzo-imidazole-4-carboxylic acid methyl ester

59.0 mg (0.28 mmol) (4-Amino-3-fluoro-phenyl)-pyrrolidin-1-yl-methanone was dissolved in 6 ml THF and 3 ml water. 238.0 mg (2.83 mmol) $NaHCO_3$ were added. Finally 75.6 mg (0.26 mmol) 2-Trichloromethyl-1H-benzoimidazole-4-carboxylic acid methyl ester were added and the resulting mixture was stirred vigorously for 3 h at RT. The mixture was diluted with 25 ml CH_2Cl_2 and washed with a saturated $NaHCO_3$-solution and with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification by

preparative RP-HPLC (CH_3CN/H_2O gradient and 0.05 % formic acid) pure 2-[2-Fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester was obtained in form of a colorless amorphous solid. Yield: 69 mg (65 %) MS (ES^+): m/e = 411.

Example 166: 5-Chloro-1H-benzoimidazole-2-carboxylic acid isoquinolin-4-ylamide

5-Chloro-1H-benzoimidazole-2-carboxylic acid isoquinolin-4-ylamide was prepared by a procedure according to example 160 starting from 100.0 mg (0.37 mmol) 5-chloro-2-trichloromethyl-1H-benzoimidazole and 56.1 mg (0.39 mmol) isoquinolin-4-ylamine. The title compound was isolated as a light brown crystalline solid.

Yield: 113 mg (94 %) MS (ES^+): m/e : 323, chloro pattern.

Example 167: 2-[(5-Chloro-1H-benzoimidazole-2-carbonyl)-amino]-3-nitro-benzoic acid methyl ester

2-[(5-Chloro-1H-benzoimidazole-2-carbonyl)-amino]-3-nitro-benzoic acid methyl ester was prepared by a procedure according to example 160 starting from 200.0 mg (0.74 mmol) 5-chloro-2-trichloromethyl-1H-benzoimidazole and 152.6 mg (0.78 mmol) 2-amino-3-nitro-benzoic acid methyl ester. The title compound was isolated as a yellow crystalline solid.

Yield: 218 mg (79 %)

Example 168: 2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester was prepared by a procedure according to example 158 starting from 1.74 g (5.80 mmol) 2-trichloromethyl-3H-thieno[3,4-d]imidazole-6-carboxylic acid methyl ester and 1.25 g (5.80 mmol) 1-isopropyl-piperidin-4-ylamine-dihydrochloride. The title compound was isolated as a light brown crystalline solid. Yield: 1.75 g (86 %) MS (ES^+): m/e : 351.

Example 169: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid

21.0 mg (0.098 mmol) (1-Cyclopropyl-piperidin-4-ylamine-dihydrochloride were dissolved in 3 ml CH_3CN and 3 ml water: 82.3 mg (0.98 mmol, 10 equivalents) $NaHCO_3$ were added. Then, a

solution of 48.1 mg (0.098 mmol) 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-trichloromethyl-1H-benzoimidazole-5-carboxylic acid methyl ester in 2 ml CH_3CN was added and the resulting mixture was stirred vigorously for 3 h under reflux. The mixture was concentrated under reduced pressure. The residue was purified by preparative RP-HPLC (CH_3CN/H_2O gradient and 0.05 % formic acid) to give pure 1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid in form of a colorless amorphous solid. (Under these conditions the methyl ester was hydrolyzed simultaneously!)

Yield: 26 mg (50 %) MS (ES^+): m/e = 526, chloro pattern.

Pharmacological testing

The ability of the compounds of the formula I to inhibit factor Xa or factor VIIa or other enzymes like thrombin, plasmin, or trypsin can be assessed by determining the concentration of the compound of the formula I that inhibits enzyme activity by 50 %, i. e. the IC50 value, which was related to the inhibition constant Ki. Purified enzymes were used in chromogenic assays. The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis was determined by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the concentration of the compound of formula I. For calculating the inhibition constant Ki, the IC50 value was corrected for competition with substrate using the formula

$$Ki = IC50 / \{1 + (\text{substrate concentration} / Km)\}$$

wherein Km is the Michaelis-Menten constant (Chen and Prusoff, Biochem. Pharmacol. 22 (1973) 3099-3108; I. H. Segal, Enzyme Kinetics, 1975, John Wiley & Sons, New York, 100-125; which were incorporated herein by reference).

a) Factor Xa Assay

In the assay for determining the inhibition of factor Xa activity TBS-PEG buffer (50 mM Tris-HCl, pH 7.8, 200 mM NaCl, 0.05 % (w/v) PEG-8000, 0.02 % (w/v) NaN3) was used. The IC50 was determined by combining in appropriate wells of a Costar half-area microtiter plate 25 µl human factor Xa (Enzyme Research Laboratories, Inc.; South Bend, Indiana) in TBS-PEG; 40 µl 10 % (v/v) DMSO in TBS-PEG (uninhibited control) or various concentrations of the compound to

be tested diluted in 10 % (v/v) DMSO in TBS-PEG; and substrate S-2765 (N(α)-benzyloxycarbonyl-D-Arg-Gly-L-Arg-p-nitroanilide; Kabi Pharmacia, Inc.; Franklin, Ohio) in TBS-PEG.

The assay was performed by pre-incubating the compound of formula I plus enzyme for 10 min. Then the assay was initiated by adding substrate to obtain a final volume of 100 µl. The initial velocity of chromogenic substrate hydrolysis was measured by the change in absorbance at 405 nm using a Bio-tek Instruments kinetic plate reader (Ceres UV900HDi) at 25 °C during the linear portion of the time course (usually 1.5 min after addition of substrate). The enzyme concentration was 0.5 nM and substrate concentration was 140 µM.

b) Factor VIIa Assay

The inhibitory activity towards factor VIIa/tissue factor activity was determined using a chromogenic assay essentially as described previously (J. A. Ostrem et al., Biochemistry 37 (1998) 1053-1059 which was incorporated herein by reference). Kinetic assays were conducted at 25 °C in half-area microtiter plates (Costar Corp., Cambridge, Massachusetts) using a kinetic plate reader (Molecular Devices Spectramax 250). A typical assay consisted of 25 µl human factor VIIa and TF (5 nM and 10 nM, respective final concentration) combined with 40 µl of inhibitor dilutions in 10% DMSO/TBS-PEG buffer (50 mM Tris, 15 mM NaCl, 5 mM $CaCl_2$, 0.05 % PEG 8000, pH 8.15). Following a 15 minutes preincubation period, the assay was initiated by the addition of 35 µl of the chromogenic substrate S-2288 (D-Ile-Pro-Arg-p-nitroanilide, Pharmacia Hepar Inc., 500 µM final concentration). The results (inhibition constants Ki (FXa) for inhibition of factor Xa) are shown in Table 1.

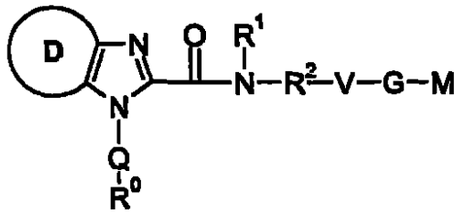
Table1:

Example	Ki(FXa) [µM]	Example	Ki(FXa) [µM]	Example	Ki(FXa) [µM]
1	0,0007	29b	0,0115	68 a)	0,070
2	0,0031	30	0,0090	68 b)	0,226
3	0,0014	31	0,0155	69	0,015
4	0,0592	32	0,0105	70	0,015
5a	0,0025	33	0,0125	71	0,007
5b	0,1750	34	0,0195	72	0,0125
6	0,0030	35	0,041	73	0,019
7	0,0165	36	0,0315	74	0,0105
9	0,0940	37	0,012	75	0,0026

10	1,357	39	0,047	76	0,0085
11a	0,004	40	0,020	77	0,0525
11b	0,001	41	0,006	78	0,0035
12	0,0030	42	0,462	79	0,001
13	0,2990	43	0,840	80	0,007
14	2,3900	44	0,028	81 a)	0,558
15	0,0115	45	0,210	82 a)	0,064
16	0,0110	48	0,002	91	0,021
17a	0,0195	49	0,015	92	0,0225
17b	0,3710	50	0,141	94	0,0245
18	0,0225	51	0,510	96 a)	0,0305
19	0,0235	52	0,014	100 a)	0,005
20	0,0085	53	0,040	102	0,0025
21	0,0310	54	0,031	103 a)	0,022
22	0,0007	55	1.30 µM	103 b)	0,088.5
23	0,0080	57	0,585	104	0,020
24	0,0260	60	0,035	105	0,054.5
25	0,0650	61	0,867	106 a)	0,022
26	0,0185	62	0,019	106 b)	0,188
27	0,0125	63	0,687	108	0,0065
28	0,0480	64	0,002	109	0,0035
29a	0,0255	65	0,121	110	0,004
		66	0,003	112 a)	0,0008

Patent Claims

1. A compound of the formula I

(I) 

, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) –O-CF_3

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or –O-(C_1-C_8)-alkyl,

9) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

10) –O-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

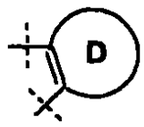
11) -SO_2-CH_3 or

12) –SO_2-CF_3,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are a monocyclic or bicyclic 6- to 14-membered aryl,

the substructure



in formulae I is a 4-to 8 membered saturated, partially unsaturated or aromatic cyclic group containing zero, 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen and is unsubstituted or substituted 1, 2, 3, 4, 5 or 6 times by R3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -(C_0 –C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, methylene, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -(C_2-C_3)-alkylene-O-(C_0-C_3)-alkylene-, -(C_2-C_3)-alkylene-

S(O)-, -(C_2-C_3)-alkylene-S(O)$_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -(C_2-C_3)-alkylene-S(O)$_2$-NH-(R^{10})-,

-(C_2-C_3)-alkylene-N(R^{10})- or -(C_0-C_3)-alkylene-C(O)-O-$(CH_2)_m$- ,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -$(CH_2)_m$- or -$(CH_2)_n$- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH; or –(C_3-C_6)-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH;

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R^{10}, a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above; a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen; -(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-S(O)$_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-S(O)$_2$-N($R^{4'}$)-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is halogen, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-

perfluoroalkyl,

-(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$,

-NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, -S-R^{18}, or -NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or -(C_1-C_6)-alkyl,

V is 1) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2) a heterocyclyl out of the group acridinyl, 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 1,4-diazepane, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-

thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, 1λ6-thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) $-(CH_2)_m-NR^{10}$,

5) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

7) $-(C_3-C_8)$-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

8) a 3- to 7-membered cyclic residue, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, wherein R14 is defined above,

R3 is 1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) -CF_3, or

e) -CHF_2,

7) -NO_2,

8) -CN,

9) -SO_s-R^{11}, wherein s is 1 or 2,

10) -SO_t-$N(R^{11})$-R^{12}, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-$N(R^{11})$-R^{12},

14) -(C_0-C_4)-alkylene-$N(R^{11})$-R^{12},

15) -NR^{10}-SO_2-R^{10},

16) -S-R^{10},

17) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

20) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

21) -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13,

22) -(C_0-C_4)-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13

23) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

24) -(C_0-C_4)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

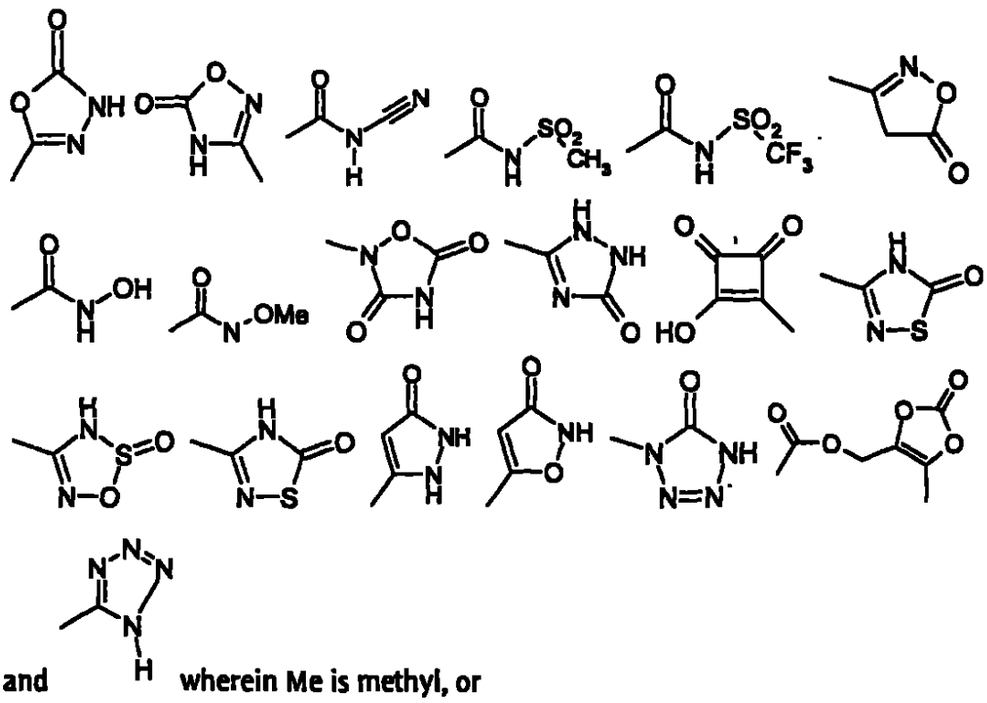
25) -(C_0-C_4)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-O-(C_0-C_4)-alkyl,

26) -SO_w-N(R^{11})-R^{13}, wherein w is 1 or 2,

27) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{13},

28) -(C_0-C_4)-alkylene-N(R^{11})-R^{13}, or

29) a residue from the following list



and wherein Me is methyl, or

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 5- or 6- membered ring, which is unsubstituted or substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_0-C_6)-alkyl-(C_3-C_8)-cycloalkyl,

4) -SO_t-R^{10}, wherein t is 1 or 2,

5) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,

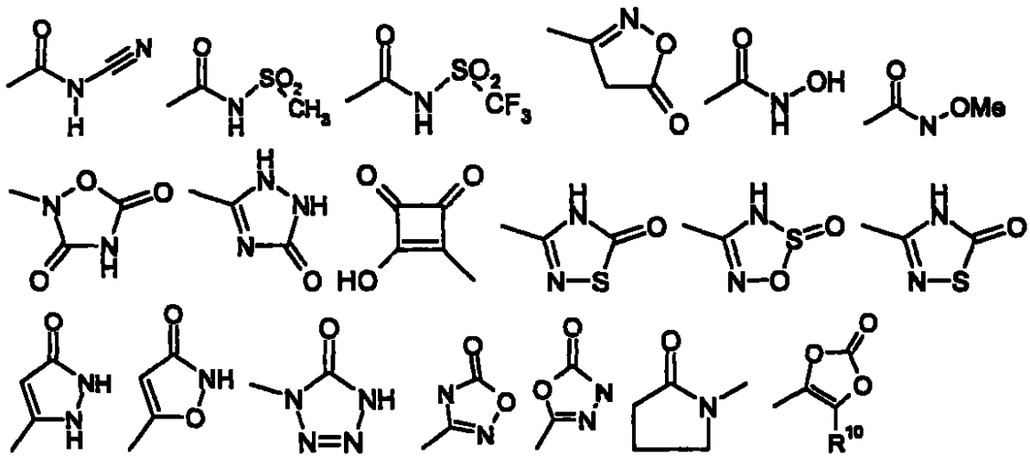
6) -(C_1-C_3)-perfluoroalkyl,

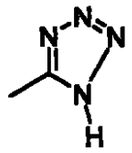
7) -O-R^{17}, or

8) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded can form a 4- to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, -NO_2, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_3-C_8)-cycloalkyl, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -N(R^{10})-S(O)$_u$-R^{10}, wherein u is 1 or 2, -S-R^{10}, -SO_r-R^{10}, wherein r is 1 or 2, -S(O)$_v$-N(R^{10})-R^{20}, wherein v is 1 or 2, -C(O)-R^{10}, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, phenyl, phenyloxy-, -O-CF_3, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, -(C_1-C_4)-alkoxy-phenyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -(C_1-C_3)-perfluoroalkyl, -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, or a residue from the following list





and , wherein Me is methyl, or

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-akyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

2. A compound of formula I as claimed in claim 1, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl, wherein heterocyclyl is selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl,

thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and

which is additionally substituted by a heterocyclyl selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl,

thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above and wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,

9) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

10) $-O-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

11) $-SO_2-CH_3$ or

12) $-SO_2-CF_3$,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a

provided that R8 is not a $-O-(C_1-C_8)$-alkyl residue, if R^0 and V are phenyl,

monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above,

substructure D is a residue selected out of the group azetidine, azetine, azocane, azocane-2-one, cyclobutyl, cyclooctane, cyclooctene, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine,

isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolan, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, [1,4]oxazocane, [1,3]oxazocan-2-one, oxetan, oxocane, oxocan-2-one, piperazine, piperidine, phenyl, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, 5,6,7,8-tetrahydro-1H-azocin-2-one, tetrahydrofuran, tetrahydropyran, tetrahydropyridine, tetrazine, thiadiazine, thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thietan, thiocane, thiocane-1,1-dioxide, thiocane-1-oxide, thiocan-2-one, thiomorpholine, thiophene, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole and is unsubstituted or substituted 1, 2, 3, 4, 5 or 6 times by R3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -(C_0-C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, methylene, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -(C_2-C_3)-alkylene-O-(C_0-C_3)-alkylene-, -(C_2-C_3)-alkylene-S(O)-, -(C_2-C_3)-alkylene-$S(O)_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -(C_2-C_3)-alkylene-$S(O)_2$-NH-(R^{10})-, -(C_2-C_3)-alkylene-N(R^{10})- or -(C_0-C_3)-alkylene-C(O)-O-$(CH_2)_m$-,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -$(CH_2)_m$- or -$(CH_2)_n$- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH; or –(C_3-C_6)-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH;

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R15,

an aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above;

a monocyclic or bicyclic 4- to 15-membered heterocyclyl,which is as defined above;

-(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

-(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

-(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl, or

-(C_0-C_3)-alkylene-het, wherein het is a residue selected out of the group azepine, azetidine, aziridine, azirine, 1,4-diazapane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,4-oxazepane, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group selected out of the group azepine, azetidine, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said

cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, bromine, iodine, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2,

-C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-perfluoroalkyl, -(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, -S-R^{18}, or -NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or -(C_1-C_6)-alkyl,

V is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R14,

2) a heterocyclyl out of the group acridinyl, 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 1,4-diazepane, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl,

pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, 1λ6-thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) $-(CH_2)_m-NR^{10}$,

5) $-(C_6-C_{14})$-aryl, wherein aryl is as defined above and wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) -(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

7) -(C_3-C_8)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R3 is

1) hydrogen atom,
2) halogen,
3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
4) -(C_1-C_3)-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is
   a) hydrogen atom,
   b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or
   c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
   d) -CF_3,
   e) -CHF_2,
7) -NO_2,
8) -CN,
9) -SO_s-R^{11}, wherein s is 1 or 2,
10) -SO_t-N(R^{11})-R^{12}, wherein t is 1 or 2,
11) -(C_0-C_4)-alkylene-C(O)-R^{11},
12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},
13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},
14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) $-S-R^{10}$,

17) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

20) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

21) $-(C_0-C_4)$-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13,

22) $-(C_0-C_4)$-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13

23) $-(C_0-C_4)$-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

24) $-(C_0-C_4)$-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

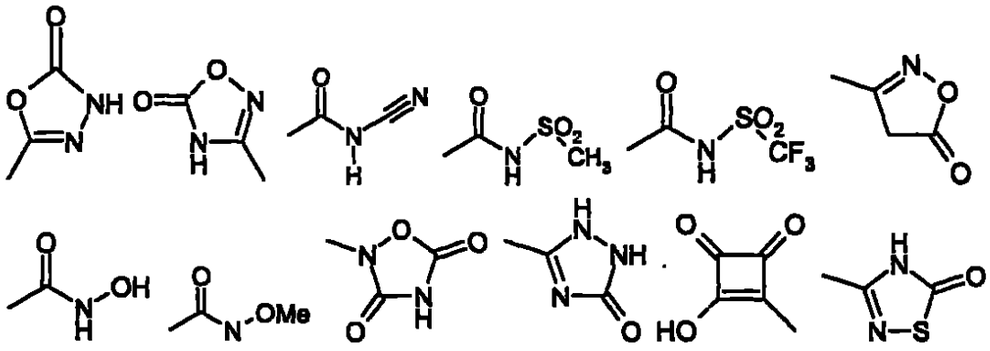
25) $-(C_0-C_3)$-alkylene-O-$CH_2-(C_1-C_3)$-perfluoroalkylene-CH_2-O-(C_0-C_3)-alkyl,

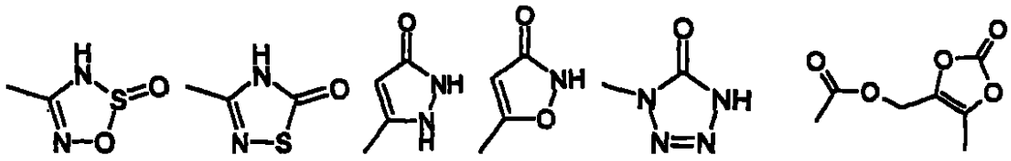
26) $-SO_w-N(R^{11})-R^{13}$, wherein w is 1 or 2,

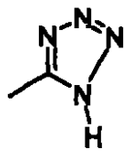
27) $-(C_0-C_4)$-alkylene-C(O)-$N(R^{11})-R^{13}$,

28) $-(C_0-C_4)$-alkylene-$N(R^{11})-R^{13}$, or

29) a residue from the following list







and , wherein Me is methyl, or

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_0-C_6)-alkyl-(C_3-C_8)-cycloalkyl,

4) -SO_t-R^{10}, wherein t is 1 or 2,

5) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,

6) -(C_1-C_3)-perfluoroalkyl,

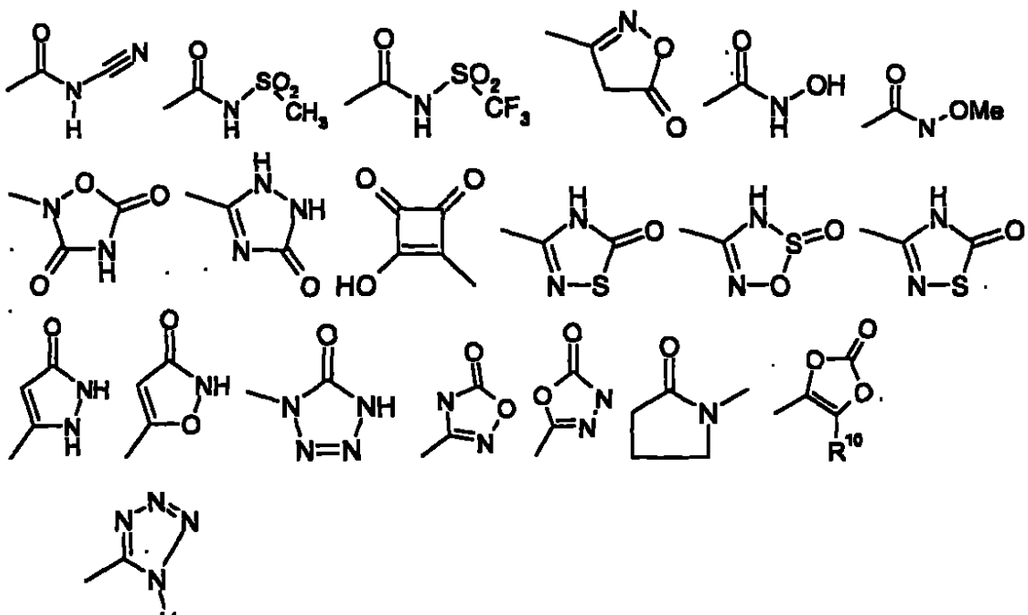
7) -O-R^{17}, or

8) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl are as defined above and are independently from one another unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded form a heterocyclic ring out of the group azepine, azetidine, dioxazole, dioxazine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine,

thiazoline, thiomorpholine, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_3-C_8)$-cycloalkyl, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_u-R^{10}$, wherein u is 1 or 2, $-S-R^{10}$, $-SO_r-R^{10}$, wherein r is 1 or 2, $-S(O)_v-N(R^{10})-R^{20}$, wherein v is 1 or 2, $-C(O)-R^{10}$, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, $-(C_1-C_4)$-alkoxy-phenyl, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, $-(C_1-C_3)$-perfluoroalkyl, -O-R15, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, or a residue from the following list



and , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, $-(C_0-C_4)$-alkyl-OH, $-(C_0-C_4)$-alkyl-O-(C_1-C_4)-akyl or $-(C_1-C_3)$-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

3. A compound of formula I as claimed in claims 1 to 2, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl out of the group azabenzimidazolyl, benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, 2-furyl, 3-furyl; imidazolyl, indolyl, indazolyl, isochromanyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidinyl, pyrrolyl; 2-pyrrolyl, 3-pyrrolyl, quinolinyl, quinazolinyl, quinoxalinyl, tetrazolyl, thiadiazolyl, thiazolyl, 2-thienyl or 3-thienyl, which is additionally substituted by a heterocyclyl selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl,

benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is
1. fluorine, chlor or brom,
2. $-NO_2$,
3. -CN,
4. $-C(O)-NH_2$,
5. -OH,

6. $-NH_2$,
7. $-OCF_3$
8. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above and is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,
9. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or
10. $-O-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,
11. $-SO_2CH_3$ or
12. $-SO_2CF_3$,

provided that R8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R0 is a aryl or a heterocyclyl, which are as defined above,

provided that R8 is not a $-O-(C_1-C_8)$-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl or thiophenyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is a direct bond, $-(C_0-C_2)$-alkylene-$C(O)-NR^{10}$-, $-NR^{10}-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$-, methylene or $-(C_0-C_3)$-alkylene-$C(O)-O-(C_0-C_2)$-alkylene,

R^1 is a hydrogen atom, $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; $-(C_1-C_3)$-alkylene-$C(O)-NH-R^0$, $-(C_1-C_3)$-alkylene-C(O)-O-R15, $-(C_1-C_3)$-perfluoroalkylene, $-(C_1-C_3)$-alkylene-$S(O)-(C_1-C_4)$-alkyl, $-(C_1-C_3)$-alkylene-$S(O)_2-(C_1-C_3)$-alkyl, $-(C_1-C_3)$-alkylene-$S(O)_2-N(R^{4'})-R^{5'}$, $-(C_1-C_3)$-alkylene-$O-(C_1-C_4)$-alkyl, $-(C_0-C_3)$-alkylene-(C_3-C_8)-cycloalkyl, or $-(C_0-C_3)$-alkylene-het, wherein het is a residue selected out of the group azepine,

azetidine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V form a 4- to 8-membered cyclic group selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,4-oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, bromine, iodine, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2,

-C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-perfluoroalkyl, -(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, -S-R^{18}, or -NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or -(C_1-C_6)-alkyl,

V is 1) a het residue out of the group 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), azepine, azetidine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine, thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, which is as defined above and wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$-, -(CH_2)-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -(CH_2)-S-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$- or -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) $-(CH_2)_m-NR^{10}$,

5) phenyl or naphthyl, wherein phenyl or naphthyl are unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from azepane, azepine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, oxazole, [1,4]-oxazepane, piperazine, piperazinone, piperidine, piperidinone, pyrazine, pyridazine, pyridazinone, pyridine, pyridone, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, tetrazine, tetrazole, thiadiazole, thiazole, thiophene, thiomorpholine, 1λ6-thiomorpholinyl, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

7) $-(C_3-C_8)$-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R3 is

1) hydrogen atom,

2) halogen,

3) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) $-(C_1-C_3)$-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) $-(C_0-C_4)$-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) CHF_2,

7) -CN,

8) -(C_0-C_4)-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) -(C_0-C_4)-alkylene-het, wherein het is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

17) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) —(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

20) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

21) -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, wherein aryl is as defined above and is mono-, di- or trisubstituted independently of one another by R13,

22) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

23) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

24) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

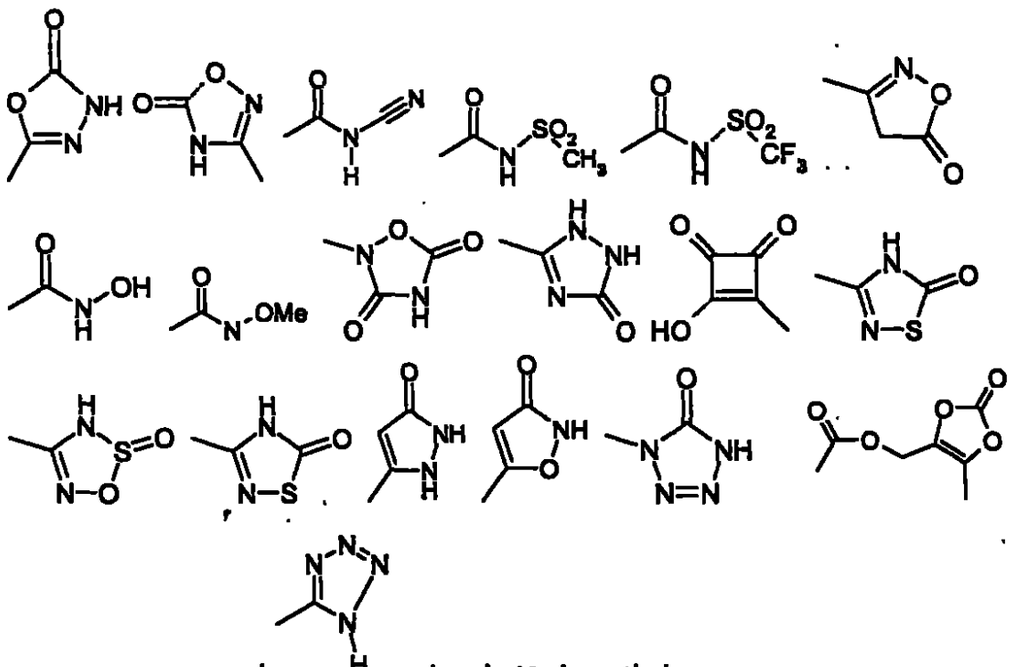
25) -(C_0-C_3)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-OH,

26) $-SO_w-N(R^{11})-R^{13}$, wherein w is 1 or 2,

27) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{13},

28) -(C_0-C_4)-alkylene-N(R^{11})-R^{13}, or

29) a residue from the following list



and , wherein Me is methyl,

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein aryl is as defined above and wherein alkyl and aryl are independently from one another unsubstituted or mono-, di- or trisubstituted by R13,

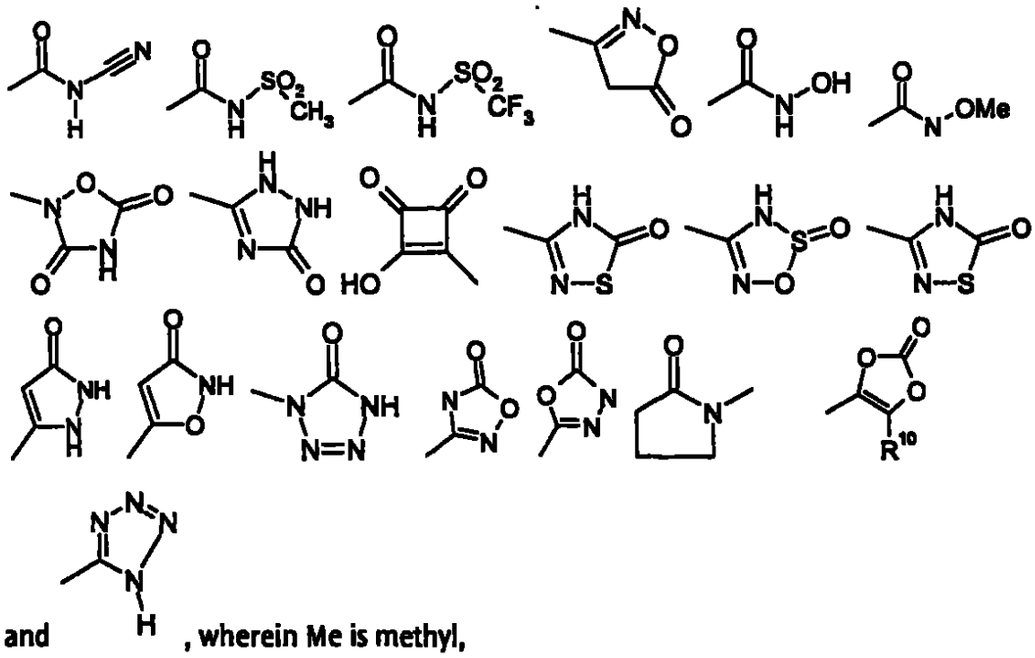
4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl is as defined above and independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline,

imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, which is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is fluorine, chlorine, bromine, iodine, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, $-(C_1-C_3)$-perfluoroalkyl, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, $-(C_1-C_4)$-alkoxy-phenyl, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -O-R15, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, or a residue from the following list



and , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, $-(C_0-C_4)$-alkyl-OH, $-(C_0-C_4)$-alkyl-O-(C_1-C_4)-akyl or $-(C_1-C_3)$-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

4. A compound of formula I as claimed in claims 1 to 3, wherein

R0 is 1) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein

said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

R8 is 1. F, Cl, Br or J,

2. -C(O)-NH_2,

3. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. –O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R0 is a aryl or a heterocyclyl, which are as defined above,

provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl or thiophenyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -C(O)-; -SO_2-, methylene, -(C_0–C_2)-alkylene-C(O)-NR^{10}- or -(C_0-C_3)-alkylene-C(O)-O-(C_0-C_2)-alkylene ,

R^1 is hydrogen atom, -(C_1-C_2)-alkyl, -(C_1-C_3)-alkylene-C(O)-NH-R0,

-(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-C(O)-O-R^{15},

-(C_1-C_3)-alkylene-S(O)$_2$-(C_1-C_3)-alkyl or -(C_1-C_3)-alkylene-S(O)$_2$-N($R^{4'}$)-$R^{5'}$,

wherein $R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 7- membered cyclic group out of the group azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, 1,4-oxazepane, oxazole, isoxazole, isoxazolidine, 2-isoxazoline,

morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, -OH, =O, -(C_1-C_8)-alkyl, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -C(O)-NH_2 or –N(R^{18})-R^{21},

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_4)-alkyl,

V is 1. a cyclic residue out of the group containing compounds which are derived from 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), aziridine, azirine, azetidine, azetidinone, 1,4-diazepane, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, 1,4-oxazepane, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,3-dioxolane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiodiazole, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,
wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or
2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

G is a direct bond, -(CH_2)$_m$-, or -(CH_2)$_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

M is 1. a hydrogen atom,
2. heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from azepane, azepine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, oxazole, [1,4]-

oxazepane, piperazine, piperazinone, piperidine, piperidinone, pyrazine, pyridazine, pyridazinone, pyridine, pyridone, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, tetrazine, tetrazole, thiadiazole, thiazole, thiomorpholine, 1λ6-thiomorpholinyl, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

4. (C_3-C_6)-cycloalkyl, or

5. -C(O)-N(R^{11})-R^{12},

R3 is

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is

   a) hydrogen atom,

   b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

   c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

   d) -CF_3, or

   e) CHF_2,

7) -CN,

8) -NR^{10}-SO_2-R^{10},

9) -SO_s-R^{11}, wherein s is 1 or 2,

10) -SO_t-N(R^{11})-R^{12}, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

15) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

19) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

20) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

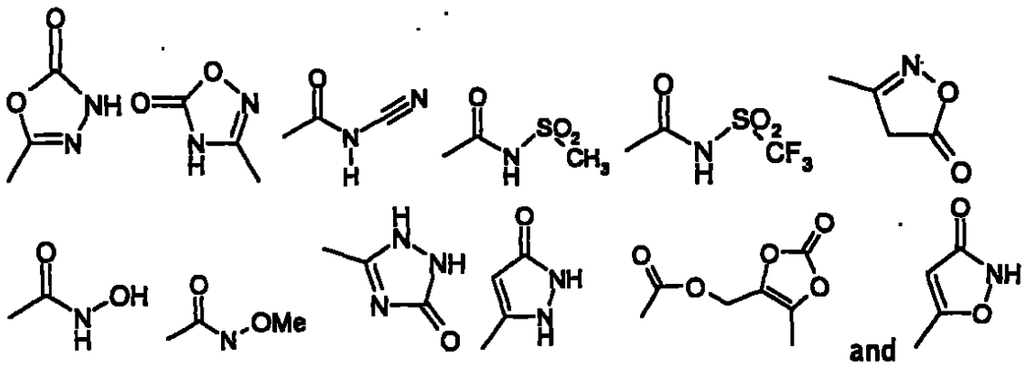
21) -(C_0-C_3)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-OH,

22) -SO_w-N(R^{11})-R^{13}, wherein w is 1 or 2,

23) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{13},

24) -(C_0-C_4)-alkylene-N(R^{11})-R^{13}, or

25) a residue from the following list



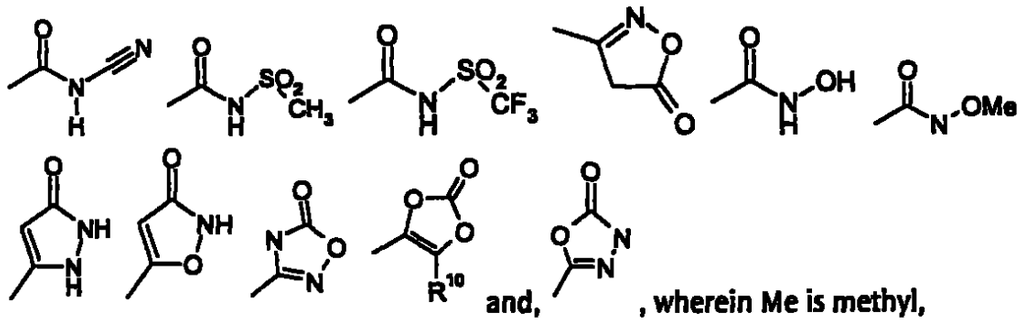
and

wherein Me is methyl,

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a ring selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]-oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is fluorine, chlorine, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, $-(C_1-C_3)$-perfluoroalkyl, $-NH-C(O)-NH-R^{10}$, $-(C_0-C_4)$-alkyl-$C(O)-O-C(R15, R16)-O-C(O)-R17$, $-(C_1-C_4)$-alkoxy-phenyl, $-(C_0-C_4)$-alkyl-$C(O)-O-C(R15, R16)-O-C(O)-O-R17$, $-O-R15$, $-NH-C(O)-O-R^{10}$, or a residue from the following list



and, , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, $-(C_0-C_4)$-alkyl-OH, $-(C_0-C_4)$-alkyl-$O-(C_1-C_4)$-akyl or $-(C_1-C_3)$-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, $-(C_1-C_6)$-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

5. A compound of formula I as claimed in claims 1 to 4, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2. a heterocyclyl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyridyl, purinyl and pteridinyl,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

3. a heterocyclyl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,
and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

R8 is 1. is F, Cl, Br, J,

2. -C(O)-NH_2,

3. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4. –O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R8 is at least one halogen, -C(O)-NH_2 or –O-(C_1-C_8)-alkyl residue, if R0 is a aryl or a heterocyclyl, which are as defined above,

provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl or thiophenyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R^3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -C(O)-; -SO_2- , methylene or -(C_0 –C_2)-alkylene-C(O)-NR^{10}-,

R^1 is hydrogen atom or -(C_1-C_2)-alkyl,

R^2 is a direct bond or -(C_1-C_2)-alkylen, or

R^1-N-R^2-V can form a 4- to 7- membered cyclic group out of the group piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluoro, chlorine, -(C_1-C_4)-alkyl or -NH_2,

V is 1. a cyclic residue out of the group containing compounds, which are derived from 8-aza-bicyclo[3.2.1]oct-3-yl, azaindolyl (1H-pyrrolopyridyl), azetidine, azepine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diazirine, 1,3-dioxolane, dioxazole, furan, imidazole, isoquinoline, isothiazole, isothiazolidine, isothiazoline, isoxazole, 2-isoxazoline, isoxazolidine, ketopiperazine, morpholine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, 1,2-oxathiolan, piperidine, pyran, pyrazine, pyrazole, pyridazine, piperazine, pyridine, pyridone, pyrimidine, pyrrole, pyrrolidine,

pyrrolidinone, quinazoline, quinoline, tetrazine, tetrazole, thiadiazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thietan, thiomorpholine, thiophene, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -$(CH_2)_m$-, or -$(CH_2)_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

M is 1. a hydrogen atom,

2. heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from 1,4-diazepane, ketomorpholine, thiophene, pyridazone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, 1λ6-thiomorpholinyl, thiadiazole or thiomorpholine, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

4. (C_3-C_6)-cycloalkyl,

R3 is

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

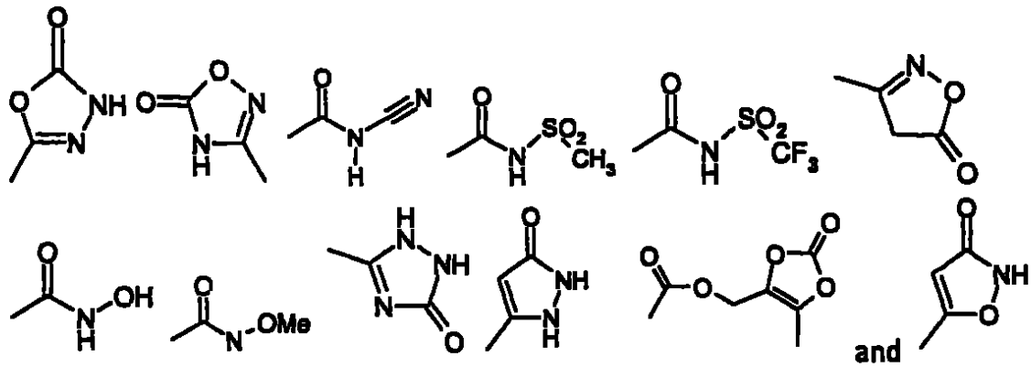
15) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17, or

19) a residue from the following list



and

wherein Me is methyl,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

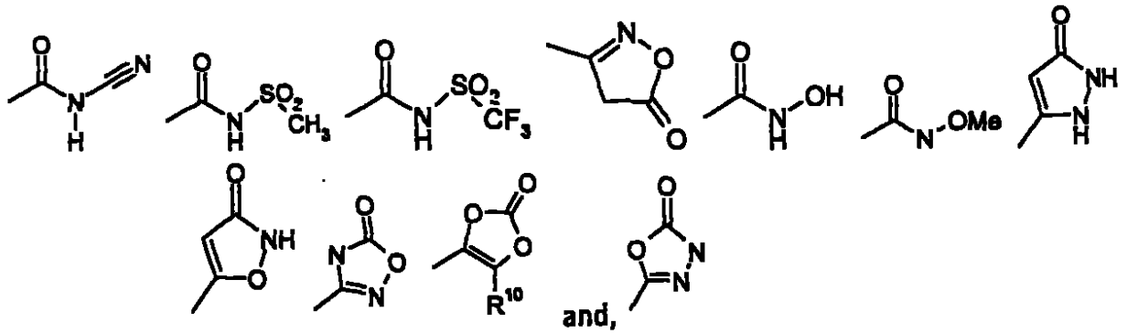
3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl,

4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13 and wherein heterocyclyl is selected out of the group azetidine, cyclopropyl, cyclobutyl, 4,5-dihydro-oxazole, imidazolidine, morpholine, (1,4)-oxazepane, oxazolidine, piperidine, piperazine, pyrrolidine, tetrahydrothiophene, thiazolidine or thiomorpholine, or

R11 and R12 together with the nitrogen atom to which they are bonded form a heterocyclic ring, which is selected out of the group azetidine, cyclopropyl, cyclobutyl, 4,5-dihydro-oxazole, imidazolidine, morpholine, (1,4)-oxazepane, oxazolidine, piperidine, piperazine, pyrrolidine, tetrahydrothiophene, thiazolidine or thiomorpholine, wherein said ring is unsubstituted or mono-, di- or trisubstituted by R13,

R13 is fluorine, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_3-C_6)-cycloalkyl, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -(C_1-C_3)-perfluoroalkyl, or a residue from the following list



and,

wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_4)-alkyl or -(C_1-C_3)-perfluoroalkyl,

R^{15} and R^{16} are independently of one another hydrogen, -(C_1-C_4)-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl or -(C_0-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

6. A compound of formula I as claimed in claims 1 to 5, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R8,

2. pyridyl, wherein pyridyl is unsubstituted or mono- or disubstituted independently of one another by R8, or

3. a heterocyclyl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heterocyclyl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R8,

R8 is F, Cl, Br, -OCH_3 or -C(O)-NH_2,

provided that R8 is not a –O-(C_1-C_8)-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide, pyrrolyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thiophen, pyrimidinyl, pyridazinyl or pyrazinyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is a direct bond, -C(O)-; -SO_2-, -C(O)-O-methylene, -CH_2-C(O)-NH- or methylene,

R^1 is hydrogen atom,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group out of the group azetidine, pyrrolidine, piperidine and piperazine,

R14 is fluorine, chlorine, methyl, ethyl, =O, $-SO_2-CH_3$ or $-NH_2$,

V is 1. a residue out of the group containing compounds which is derived from 8-aza-bicyclo[3.2.1]oct-3-yl, azaindolyl (1H-pyrrolopyridyl), azetidine, 1,4-diazepane, isoxazole, isoquinoline, piperazine, piperidine, pyrazine, pyridazine, pyrimidine, pyrrolidine, quinazoline, quinoline or tetrahydropyrane, wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-$, -C(O)- or $-(CH_2)_m-NR^{10}-$,

m is the integers zero, 1 or 2,

M is a hydrogen atom, (C_2-C_4)-alkyl, azepanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolyl, ketomorpholinyl, morpholinyl, [1,4]Oxazepanyl, piperazinyl, piperidinyl, piperidonyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolidinyl, 1,4,5,6-tetrahydro-pyridazinyl, 1λ6-thiomorpholinyl or tetrahydropyranyl, wherein the residues are unsubstituted or mono- or disubstituted independently of one another by R14

R3 is

1) hydrogen atom,
2) fluorine, chlorine,
3) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
4) $-(C_1-C_3)$-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
6) $-(C_0-C_2)$-alkylene-O-R19, wherein R19 is
   a) hydrogen atom,
   b) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) $-(C_0-C_4)$-alkylene-C(O)-R^{11},

12) $-(C_0-C_4)$-alkylene-C(O)-O-R^{11},

13) $-(C_0-C_4)$-alkylene-C(O)-$N(R^{11})-R^{12}$,

14) $-(C_0-C_4)$-alkylene-$N(R^{11})-R^{12}$,

15) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl or

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) $-(C_0-C_6)$-alkyl-(C_3-C_6)-cycloalkyl,

4) $-O-R^{17}$, or

5) $-(C_0-C_6)$-alkyl-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13 and wherein heterocyclyl is selected out of the group azetidine, imidazolidine, morpholine, (1,4)-oxazepane or pyrrolidine or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring, which is selected out of the group azetidine, imidazolidine, morpholine, (1,4)-

oxazepane piperazine, piperidine, pyrrolidine or thiomorpholine, wherein said ring is unsubstituted or mono-, di- or trisubstituted by R13,

R13 is fluorine, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_1-C_3)$-alkyl, $-(C_3-C_6)$-cycloalkyl, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-S-R^{10}$, $-SO_2-R^{10}$, $-SO_2-NH$, or $-(C_1-C_3)$-perfluoroalkyl,

R^{10} and R^{20} are independently of one another hydrogen, $-(C_1-C_4)$-alkyl or $-(C_1-C_3)$-perfluoroalkyl,

R^{15} and R^{16} are independently of one another hydrogen, $-(C_1-C_4)$-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is $-(C_1-C_6)$-alkyl, $-(C_1-C_6)$-alkyl-OH, $-(C_1-C_6)$-alkyl-$O-(C_1-C_8)$-alkyl-(C_3-C_8)-cycloalkyl, $-(C_1-C_6)$-alkyl-$O-(C_1-C_6)$-alkyl or $-(C_0-C_4)$-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, $-O-(C_1-C_4)$-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

7. A compound of formula I as claimed in one or more of claims 1 to 6, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R8,

2. pyridyl, wherein pyridyl is unsubstituted or mono- or disubstituted independently of one another by R8, or

3. a heterocyclyl out of the group thiadiazolyl, isoxazolyl and thiazolyl, wherein said heterocyclyl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R8,

R8 is Cl or $-O-CH_3$,

provided that R8 is not a $-O-(C_1-C_8)$-alkyl residue, if R^0 and V are phenyl,

substructure D is a residue selected out of the group phenyl, pyridyl, thiophenyl, thienyl or pyrimidinyl, and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is $-CH_2-C(O)-NH-$ or methylene,

R^1 is hydrogen atom,

R^2 is a direct bond,

R14 is fluorine or =O,

V is piperidinyl or phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R14,

G is a direct bond or -C(O)-,

M is a hydrogen atom, (C_2-C_4)-alkyl, isopropyl, cyclopropyl, morpholinyl, piperazinyl, piperidinyl, pyrazinyl, pyridyl, pyrimidyl, pyrrolidinyl or 1λ6-thiomorpholinyl, wherein the residues are unsubstituted or mono- or disubstituted independently of one another by R14

R3 is 1) hydrogen atom,

2) fluorine, chlorine,

3) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) $-(C_0-C_2)$-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) $-CF_3$,

5) $-SO_2-R^{11}$,

6) $-(C_0-C_4)$-alkylene-C(O)-O-R^{11},

7) $-(C_0-C_4)$-alkylene-C(O)-N(R^{11})-R^{12},

8) $-(C_0-C_2)$-alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl or

9) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring, which is selected out of the group azetidine, morpholine, (1,4)-oxazepane or piperidine, wherein said ring is unsubstituted or mono-, di- or trisubstituted by R13,

R13 is fluorine, =O, -OH, -CF_3, -C(O)-O-R^{10}, -(C_1-C_3)-alkyl, -(C_3-C_6)-cycloalkyl or -(C_0-C_3)-alkylene-O-R^{10},

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

R^{15} and R^{16} are independently of one another hydrogen atom or -(C_1-C_4)-alkyl, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH or -(C_0-C_4)-alkyl-(C_3-C_8)-cycloalkyl.

8. A compound of formula I as claimed in one or more of claims 1 to 7, wherein the compound of formula I is

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

Example 2: 1-[(4-Chloro-phenylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl- piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidine-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-pyrimidine-4-yl-piperidine-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,
1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-5-carboxylic acid methyl ester,
3-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 3H-benzoimidazole-5-carboxylic acid methyl ester,
1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-5-carboxylic acid,
3-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 3H-benzoimidazole-5-carboxylic acid,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid methyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b] pyridine-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

Example 35: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(3- oxo-morpholin-4-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- H-benzoimidazole-4-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide,

1-(3-Methoxy-benzyl)-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-oxazolidin-3-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-oxazolidin-3-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-piperidin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1l6-thiomorpholin-4-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1l6-thiomorpholin-4-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-piperazin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-piperazin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- 1H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 2-hydroxy-ethyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid carboxymethyl ester,
1-(3-Methoxy-benzyl)-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4- carboxylic acid,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid cyclopropylmethyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 2-methoxy-ethyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-hydroxymethyl-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxymethyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(morpholine-4-carbonyl)-1H-benzoimidazole- 2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-([1,4]oxazepane-4-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2,6-dimethyl-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(4,4-difluoro-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid carboxymethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-methoxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-4-carboxylic acid,

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-4-carboxylic acid,

1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 4-carboxylic acid,

3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 4-carboxylic acid,

4-(3-Hydroxy-azetidine-1-carbonyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-methoxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,

1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid methyl ester,

3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 5-carboxylic acid methyl ester,

1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid,

1-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

3-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid,

1-(5-Chloro-1H-indazol-3-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(4-hydroxy-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

7-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid cyclopropylmethyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-thieno[3,4-d]imidazole-2,6-dicarboxylic acid 6-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)- amide],

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid,
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-([1,4]oxazepane-4-carbonyl)-3H-thieno[3,4- d]imidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester,
1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,
3-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid
1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,
3-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-ethoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-hydroxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[2-fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-3H-benzoimidazole-5-carboxylic acid,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid or

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide.

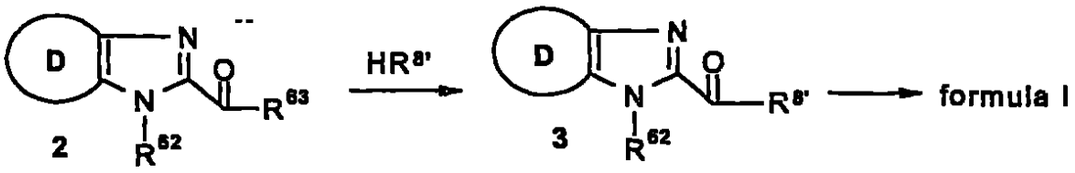
9. A pharmaceutical preparation, comprising at least one compound of the formula I as claimed in one or more of claims 1 to 8 in all its stereoisomeric forms and mixtures thereof in any ratio and/or its physiologically tolerable salts and a pharmaceutically acceptable carrier.

10. The use of a compound of the formula I as claimed in one or more of claims 1 to 8 in all its stereoisomeric forms and mixtures thereof in any ratio and/or their physiologically tolerable salts for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis.

11. The use as claimed in claim10 for abnormal thrombus formation, acute myocardial infarction, cardiovascular disorders, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication, bypass grafting of the coronary or peripheral arteries, vessel luminal narrowing, restenosis post coronary or venous angioplasty, maintenance of vascular access patency in long-term hemodialysis patients, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee or hip surgery, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulatopathy occurring in vascular systems during septic shock, viral infections or cancer, or reducing an inflammatory response, fibrinolysis, or treatment of coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure and disseminated intravascular clotting disorder, deep vein or proximal vein thrombosis, which can occur following surgery.

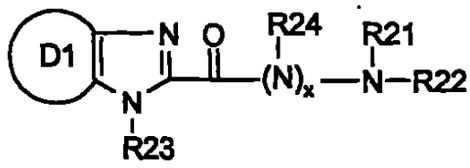
12. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 8, which comprises condensing a compound of the formula 2 with a

compound of the formula $HR^{8'}$ to give a compound of the formula 3 and optionally converting the compound of the formula 3 into a compound of the formula I,



wherein the residue $R^{8'}$ has the donation of $-N(R^1)-R^2-V-G-M$ as indicated in claims 1 to 8, but where in $R^{8'}$ functional groups can also be present in the form of groups that are subsequently transformed into the final functional groups present in $-N(R^1)-R^2-V-G-M$, and where the residue R^{62} denotes the group $-Q-R^0$ or can denote a group which is subsequently transformed into the group $-Q-R^0$, and where the group $-C(O)-R^{63}$ can be a carboxylic acid group or derivatives thereof, as defined in claims 1 to 8, wherein said functional groups can also be present in protected form or in the form of precursor groups.

13. A process for the preparation of a compound of formula IV,



(IV)

wherein

x is the integer zero or 1,

R21 and R24 are identical or different and are independent from each other

a) a hydrogen atom,

b) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,

c) $-(C_1-C_3)$-alkylene-C(O)-NH-R^0,

d) $-(C_1-C_3)$-alkylene-C(O)-O-R^{10},

e) $-(C_0-C_4)$-alkyl-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl and is mono-, di- or trisubstituted independently of one another by R8,

f) $-(C_0-C_4)$-alkyl-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, thre or four heteroatoms chosen

from nitrogen, sulphur or oxygen and is mono-, di- or trisubstituted independently of one another by R8,

g) -(C_1-C_4)-alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

h) -(C_1-C_3)-perfluoroalkylene,

i) -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

j) -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl,

k) -(C_1-C_3)-alkylene-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

l) -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl,

m) -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl or

n) -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

wherein R^0, $R^{4'}$, $R^{5'}$, R8, R^{10}, R^{13} and R^{14} are as defined in claim 1 for the compound of formula I,

R22 is a) a hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13 ,

c) -(C_1-C_3)-alkylene-C(O)-NH-R^0,

d) -(C_1-C_3)-alkylene-C(O)-O-R^{10},

e) -(C_0-C_4)-alkyl-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl and is mono-, di- or trisubstituted independently of one

another by R8,

f) -(C_0-C_4)-alkyl-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, thre or four heteroatoms chosen from nitrogen, sulphur or oxygen and is mono-, di- or trisubstituted independently of one another by R8,

g) -(C_0-C_4)-alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

h) -(C_1-C_3)-perfluoroalkylene,

i) -(C_0-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

j) -(C_0-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl,

k) -(C_0-C_3)-alkylene-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

l) -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl,

m) -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl,

n) -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

o) R^2-V-G-M,

wherein R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, R14, V, G and M are as defined in claim 1 for the compound of formula I, or

the substructure R21-N-R^2-V in formula IV can form a 4- to 8-membered cyclic group, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one

another by R14, wherein the residue R14 is as defined as in claim 1 for the compound of formula I ,

R23 is

a) a hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,

c) -(C_1-C_3)-alkylene-C(O)-NH-R^0,

d) -(C_1-C_3)-alkylene-C(O)-O-R^{10},

e) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

f) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen,

g) -(C_1-C_3)-perfluoroalkylene,

h) -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

j) -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl,

k) -(C_1-C_3)-alkylene-$S(O)_2$-N($R^{4'}$)-$R^{5'}$,

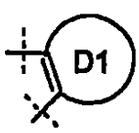
l) -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl,

m) -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl,

n) -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

o) -Q-R^0,

wherein R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, R14, Q, V, G and M are as defined as in claim 1 for the compound of formula I, and

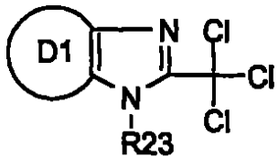


substructure in formula IV is

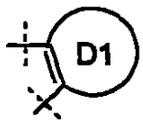
a 4-to 8 membered saturated, partially unsaturated or aromatic cyclic group containing zero, 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen

and is unsubstituted or substituted 1, 2, 3, 4, 5 or 6 times by R3, wherein R3 is as defined in claim 1 for the compound of formula I,

which comprises reacting a compound of formula V



(V)



wherein R23 is as defined in formula IV and substructure in formula V is as defined in formula IV,

with a primary amine or a secondary amine

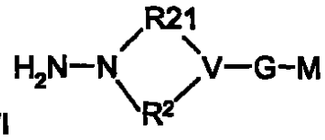
in the presence of water, at least one base and at least one water-miscible organic solvent.

14. A process for the preparation of a compound of formula IV as claimed in claim 13, wherein the primary amine is

a) NH_2-R21, wherein R21 is as defined in formula IV,

b) NH_2-R^2-V-G-M, wherein R^2, V, G and M are as defined in formula IV,

c) NH_2-N(R21)-R22, wherein R21 and R22 are as defined in formula IV or

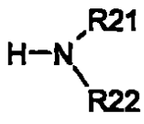


(VI)

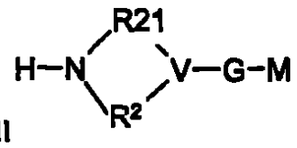
d) a compound of formula VI

wherein R^2, R21, V, G and M are as defined as in formula IV.

15. A process for the preparation of a compound of formula IV as claimed in claim 13, wherein the secondary amine is

a) 

wherein R21 and R22 are as defined in formula IV,

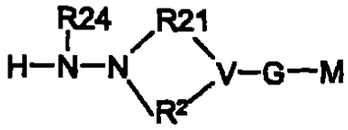


(VII)

b) a compound of formula VII

wherein R21, R^2, V, G and M are as defined in formula IV, or

c) a compound of formula VIII



(VIII)

wherein R^2, R21, R24, V, G and M are as defined in formula IV.

16. A process for the preparation of a compound of formula IV as claimed in claims 13 or 15, wherein the water-miscible organic solvent is Tetrahydrofuran, acetonitrile, 1,2-dimethoxyethane, dimethylsulfoxide, dioxane, N,N-dimethylformamide, N-methylpyrrolidone, acetone or sulfolane and the base is an alkali metal carbonate, sodium bicarbonate, potassium bicarbonate, an tertiary amine, triethylamine or diisopropylethylamine.

17. A process for the preparation of a compound of formula IV as claimed in claims 13 or 15, wherein the amount of water-miscible organic solvent used is from 5 g to 300 g per 1 g of the compound of the formula V, preferably from 10 g to 200 g.

18. A process for the preparation of a compound of formula IV as claimed in claims 13 or 15, wherein the reaction temperature is from 5 °C to 120 °C, preferably from 10 °C to 35°C, in particular 25 °C.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/14 C07D401/14 C07D417/14 C07D471/04 A61K31/4184
A61P7/02 C07D413/14 C07D401/12 C07D451/06 C07D401/14
C07D417/14 C07D413/12 C07D409/14 C07D473/08 C07D495/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 562 828 B1 (HAYASHI MIKIO ET AL) 13 May 2003 (2003-05-13) page 4 - column 6 example 114; table 8	1-12
A	MATTER, HANS ET AL: "Design and Quantitative Structure-Activity Relationship of 3-Amidinobenzyl-1H-indole-2-carboxamides as Potent, Nonchiral, and Selective Inhibitors of Blood Coagulation Factor Xa" JOURNAL OF MEDICINAL CHEMISTRY (2002), 45(13), 2749-2769 CODEN: JMCMAR; ISSN: 0022-2623, 2002, XP0002256632 the whole document	1-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2004	14. 10. 04

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kollmannsberger, M

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004750

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 03, 31 March 1997 (1997-03-31) & JP 8 295667 A (TAKEDA CHEM IND LTD), 12 November 1996 (1996-11-12) abstract	1-7,9-12
X	EP 0 254 322 A (NISSHIN FLOUR MILLING CO) 27 January 1988 (1988-01-27) claim 1	1-7,9-12
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A	DE 38 28 537 A (BASF AG) 1 March 1990 (1990-03-01) example 17	1-7,10
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A	DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2003, XP002256742 order numbers: 7215720016, 7215720017 & "Otava chemical collection" 21 April 2003 (2003-04-21), OTAVA , KYIV, UKRAINE	1-7

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004750

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICES, COLUMBUS, OHIO, US; 2003, XP002256743 order numbers STOCK2S-06321, t0311-0063, t0311-0061, t011-0059, t0311-0057 & "Ambinter: Exploratory library" 30 April 2003 (2003-04-30), AMBINTER , PARIS, FRANCE	1-7
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X	US 4 269 846 A (HUANG FU C ET AL) 26 May 1981 (1981-05-26) example 3	13-18
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/004750

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

International Application No. PCT/EP2004 /004750

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-12

   Compounds of structure (I), their uses and methods for their preparation

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2. claims: 13-18

   A process for the preparation of compounds (IV)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/004750

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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57574 123

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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PCT

(10) International Publication Number
WO 2004/101553 A1

(51) International Patent Classification[7]: C07D 413/14, 401/14, 417/14, 471/04, A61K 31/4184, A61P 7/02, C07D 413/14, 401/12, 451/06, 401/14, 417/14, 413/12, 409/14, 473/08, 495/04

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(25) Filing Language: English

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(30) Priority Data:
03011305.4 19 May 2003 (19.05.2003) EP

(71) Applicant (*for all designated States except US*): AVENTIS PHARMA DEUTSCHLAND GMBH [DE/DE]; Brüningstrasse 50, 65929 Frankfurt (DE).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): NAZARE, Marc [DE/DE]; Felix-Lahnstein-Str. 4b, 65510 Idstein (DE). WAGNER, Michael [DE/DE]; Alte Bergstr. 42a, 64665 Alsbach (DE). WEHNER, Volkmar [DE/DE]; Lindenstrasse 1, 97657 Sandberg (DE). MATTER, Hans [DE/DE]; Feldbergring 37, 63505 Langenselbold (DE). URMANN, Matthias [DE/DE]; Im Sylvaner 4b, 65760 Eschborn (DE). RITTER, Kurt [DE/DE]; Gutzkowstrasse 2, 60594 Frankfurt am Main (DE).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

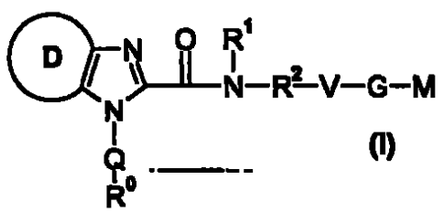
Published:
— *with international search report*
— *with amended claims*

Date of publication of the amended claims: 3 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/101553 A1

(54) Title: BENZIMIDAZOLE-DERIVATIVES AS FACTOR Xa INHIBITORS



(I)

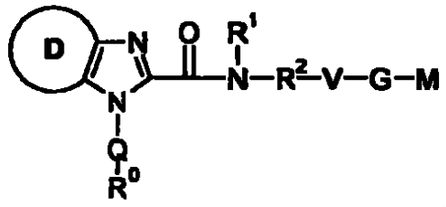
(57) Abstract: The present invention relates to compounds of the formula (I), wherein R^a, R^1, R^2, Q, V, G and M have the meanings indicated in the claims. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

AMENDED CLAIMS

[Received by the International Bureau on 14 December 2004 (14.12.2004):
original claims 1-18 replaced by amended claims 1-20 (60 pages)]

Patent Claims

1. A compound of the formula I



(I)

, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,

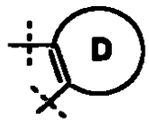
9) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

10) $-SO_2-CH_3$ or

11) $-SO_2-CF_3$,

provided that R8 is at least one halogen or $-C(O)-NH_2$ residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

the substructure



in formulae I is a 4-to 8 membered saturated, partially unsaturated or aromatic cyclic group containing zero, 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen and is unsubstituted or substituted 1, 2, 3, 4, 5 or 6 times by R3 or is substituted 1 or 2 times by =O,

Q is $-(C_0-C_2)$-alkylene-$C(O)-NR^{10}-$, $-NR^{10}-C(O)-NR^{10}-$, $-NR^{10}-C(O)-$, $-SO_2-$, methylene, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-S-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$, $-(C_2-C_3)$-alkylene-$O-(C_0-C_3)$-alkylene-, $-(C_2-C_3)$-alkylene-$S(O)-$, $-(C_2-C_3)$-alkylene-$S(O)_2-$, $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$, $-(C_2-C_3)$-alkylene-$S(O)_2-NH-(R^{10})-$, $-(C_2-C_3)$-alkylene-$N(R^{10})-$ or $-(C_0-C_3)$-alkylene-$C(O)-O-(CH_2)_m-$,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by $-(CH_2)_m-$ or $-(CH_2)_n-$ are unsubstituted or mono-,

di- or trisubstituted independently of one another by halogen, -NH_2 or –OH; or –$(C_3$-$C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH;

R^1 is a hydrogen atom, -$(C_1$-$C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -$(C_1$-$C_3)$-alkylene-C(O)-NH-R^0, -$(C_1$-$C_3)$-alkylene-C(O)-O-R^{10}, a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above; a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen; -$(C_1$-$C_3)$-perfluoroalkylene, -$(C_1$-$C_3)$-alkylene-S(O)-$(C_1$-$C_4)$-alkyl, -$(C_1$-$C_3)$-alkylene-$S(O)_2$-$(C_1$-$C_3)$-alkyl, -$(C_1$-$C_3)$-alkylene-$S(O)_2$-N($R^{4'}$)-$R^{5'}$, -$(C_1$-$C_3)$-alkylene-O-$(C_1$-$C_4)$-alkyl, -$(C_0$-$C_3)$-alkylene-$(C_3$-$C_8)$-cycloalkyl, or -$(C_0$-$C_3)$-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -$(C_1$-$C_4)$-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is halogen, -OH, =O, -$(C_1$-$C_8)$-alkyl, -$(C_1$-$C_4)$-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-$(C_1$-$C_4)$-alkyl, -$(C_0$-$C_8)$-alkyl-SO_2-$(C_1$-$C_4)$-alkyl, -$(C_0$-$C_8)$-alkyl-SO_2-$(C_1$-$C_3)$-perfluoroalkyl,

-$(C_0$-$C_8)$-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-$(C_1$-$C_8)$-alkyl, -C(O)-N-[$(C_1$-$C_8)$-alkyl]$_2$, -NR^{18}-C(O)-NH-$(C_1$-$C_8)$-alkyl, -C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[$(C_1$-$C_8)$-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -$(C_1$-$C_3)$-perfluoroalkyl or –$(C_1$-$C_6)$-alkyl,

V is 1) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2) a heterocyclyl out of the group acridinyl, 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 1,4-diazepane, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, 1λ6-thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10} -$(CH_2)_n$-, -(CH_2)-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -(CH_2)-S-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$- or -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) -$(CH_2)_m$-NR^{10},

5) a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

7) -(C_3-C_8)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

8) a 3- to 7-membered cyclic residue, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, wherein R14 is defined above,

R3 is 1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

7) $-NO_2$,

8) -CN,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) $-S-R^{10}$,

17) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

20) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

21) -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13,

22) -(C_0-C_4)-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13

23) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

24) -(C_0-C_4)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

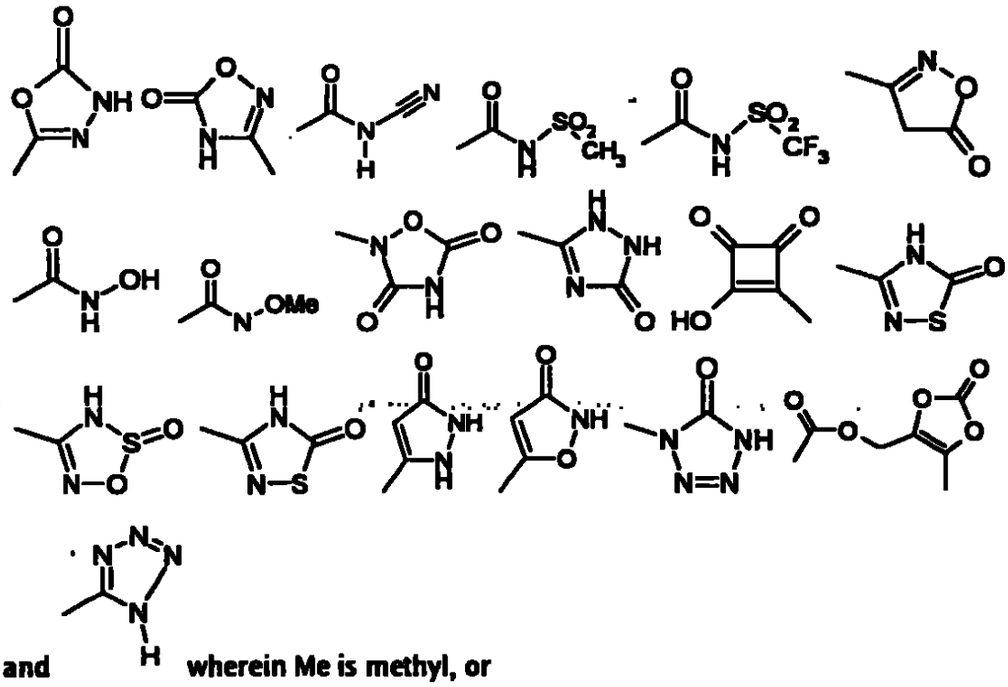
25) -(C_0-C_4)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-O-(C_0-C_4)-alkyl,

26) -SO_w-N(R^{11})-R^{13}, wherein w is 1 or 2,

27) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{13},

28) -(C_0-C_4)-alkylene-N(R^{11})-R^{13}, or

29) a residue from the following list



and wherein Me is methyl, or

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 5- or 6- membered ring, which is unsubstituted or substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_0-C_6)-alkyl-(C_3-C_8)-cycloalkyl,

4) $-SO_t-R^{10}$, wherein t is 1 or 2,

5) $-(C_0-C_6)$-alkyl-(C_6-C_{14})-aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,

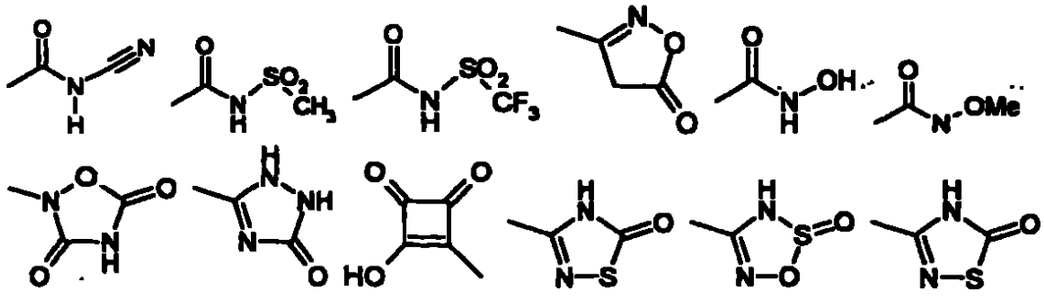
6) $-(C_1-C_3)$-perfluoroalkyl,

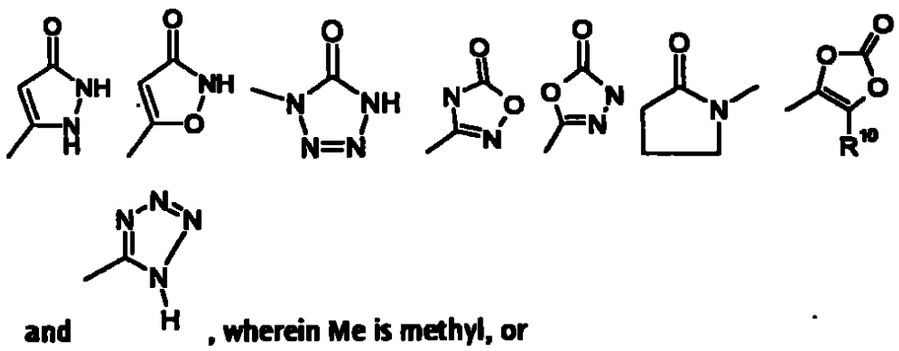
7) $-O-R^{17}$, or

8) $-(C_0-C_6)$-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded can form a 4- to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_3-C_8)$-cycloalkyl, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_u-R^{10}$, wherein u is 1 or 2, $-S-R^{10}$, $-SO_r-R^{10}$, wherein r is 1 or 2, $-S(O)_v-N(R^{10})-R^{20}$, wherein v is 1 or 2, $-C(O)-R^{10}$, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, $-(C_1-C_4)$-alkoxy-phenyl, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, $-(C_1-C_3)$-perfluoroalkyl, -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, or a residue from the following list





and , wherein Me is methyl, or

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-akyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

2. A compound of formula I as claimed in claim 1, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is

unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl, wherein heterocyclyl is selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and

which is additionally substituted by a heterocyclyl selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is 1) halogen,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above and wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,

9) $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

10) $-SO_2-CH_3$ or

11) $-SO_2-CF_3$,

provided that R8 is at least one halogen or $-C(O)-NH_2$ residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above,

substructure D is a residue selected out of the group azetidine, azetine, azocane, azocane-2-one, cyclobutyl, cyclooctane, cyclooctene, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, [1,4]diazocane, [1,2]diazocan-3-one, [1,3]diazocan-2-one, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolan, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, [1,4]oxazocane, [1,3]oxazocan-2-one, oxetan, oxocane, oxocan-2-one, piperazine, piperidine, phenyl, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, 5,6,7,8-tetrahydro-1H-azocin-2-one, tetrahydrofuran, tetrahydropyran, tetrahydropyridine, tetrazine, thiadiazine, thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thietan, thiocane, thiocane-1,1-dioxide, thiocane-1-oxide, thiocan-2-one, thiomorpholine, thiophene, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-

triazole and is unsubstituted or substituted 1, 2, 3, 4, 5 or 6 times by R3 or is substituted 1 or 2 times by =O,

Q is -(C_0 –C_2)-alkylene-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, methylene, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -(C_2-C_3)-alkylene-O-(C_0-C_3)-alkylene-, -(C_2-C_3)-alkylene-S(O)-, -(C_2-C_3)-alkylene-$S(O)_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -(C_2-C_3)-alkylene-$S(O)_2$-NH-(R^{10})-, -(C_2-C_3)-alkylene-N(R^{10})- or -(C_0-C_3)-alkylene-C(O)-O-$(CH_2)_m$- ,

wherein R^{10} is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -$(CH_2)_m$- or -$(CH_2)_n$- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH; or –(C_3-C_6)-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH_2 or –OH;

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R15, an aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above;
a monocyclic or bicyclic 4- to 15-membered heterocyclyl,which is as defined above;
-(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-N($R^{4'}$)-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is a residue selected out of the group azepine, azetidine, aziridine, azirine, 1,4-diazapane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,4-

oxazepane, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group selected out of the group azepine, azetidine, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, bromine, iodine, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-perfluoroalkyl, -(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenylyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R14,

2) a heterocyclyl out of the group acridinyl, 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 1,4-diazepane, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, 1λ6-thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$-, -(CH_2)-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -(CH_2)-S-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$- or -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) -$(C_1$-$C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) -$(CH_2)_m$-NR^{10},

5) -$(C_6$-$C_{14})$-aryl, wherein aryl is as defined above and wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) -$(C_4$-$C_{15})$-heterocyclyl, wherein heterocyclyl is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

7) -$(C_3$-$C_8)$-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R3 is

1) hydrogen atom,

2) halogen,

3) -$(C_1$-$C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -$(C_1$-$C_3)$-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -$(C_0$-$C_4)$-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) -CF_3,

e) -CHF_2,

7) -NO_2,

8) -CN,

9) -SO_s-R^{11}, wherein s is 1 or 2,

10) -SO_t-$N(R^{11})$-R^{12}, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-$N(R^{11})$-R^{12},

14) -(C_0-C_4)-alkylene-$N(R^{11})$-R^{12},

15) -NR^{10}-SO_2-R^{10},

16) -S-R^{10},

17) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) –(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

20) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

21) -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13,

22) -(C_0-C_4)-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13

23) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

24) -(C_0-C_4)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

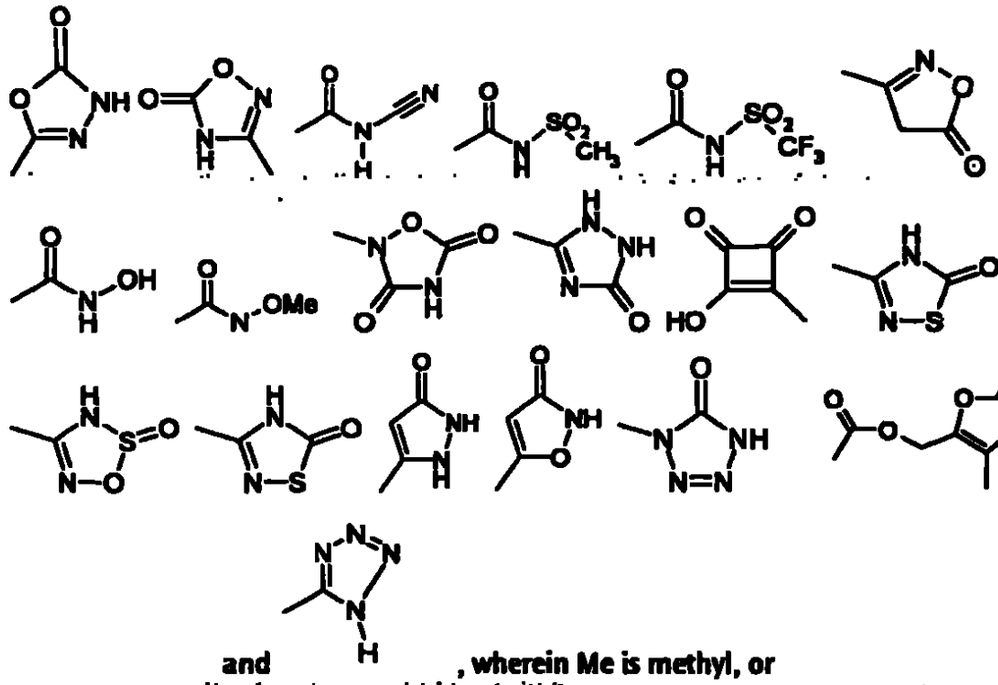
25) -(C_0-C_3)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-O-(C_0-C_3)-alkyl,

26) $-SO_w-N(R^{11})-R^{13}$, wherein w is 1 or 2,

27) $-(C_0-C_4)$-alkylene-C(O)-$N(R^{11})-R^{13}$,

28) $-(C_0-C_4)$-alkylene-$N(R^{11})-R^{13}$, or

29) a residue from the following list



and , wherein Me is methyl, or

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) $-(C_0-C_6)$-alkyl-(C_3-C_8)-cycloalkyl,

4) $-SO_t-R^{10}$, wherein t is 1 or 2,

5) $-(C_0-C_6)$-alkyl-(C_6-C_{14})-aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,

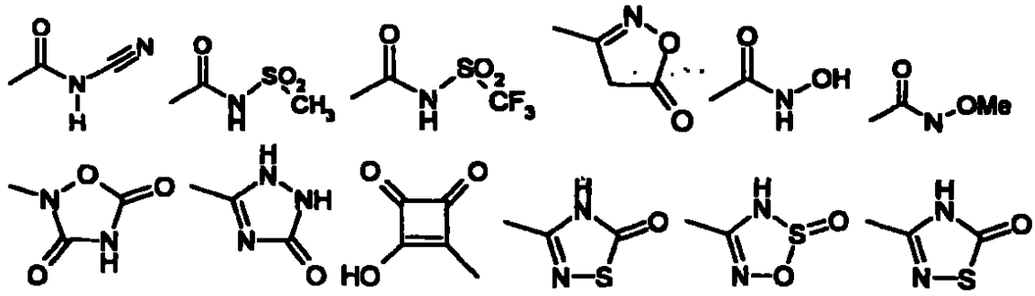
6) $-(C_1-C_3)$-perfluoroalkyl,

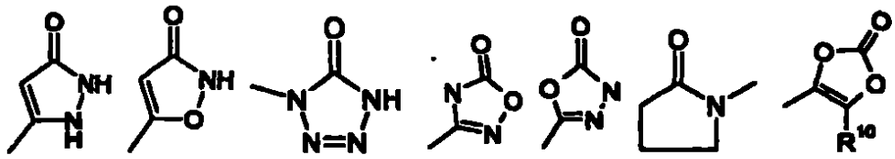
7) $-O-R^{17}$, or

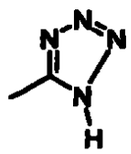
8) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl are as defined above and are independently from one another unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded form a heterocyclic ring out of the group azepine, azetidine, dioxazole, dioxazine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is halogen, -NO_2, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_3-C_8)-cycloalkyl, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -N(R^{10})-S(O)$_u$-R^{10}, wherein u is 1 or 2, -S-R^{10}, -SO_r-R^{10}, wherein r is 1 or 2, -S(O)$_v$-N(R^{10})-R^{20}, wherein v is 1 or 2, -C(O)-R^{10}, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, phenyl, phenyloxy-, -O-CF_3, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, -(C_1-C_4)-alkoxy-phenyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -(C_1-C_3)-perfluoroalkyl, -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, or a residue from the following list







and , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-alkyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

3. A compound of formula I as claimed in claims 1 to 2, wherein

R^0 is 1) a monocyclic or bicyclic 6- to 14-membered aryl out of the group phenyl, naphthyl, biphenyl, anthryl or fluorenyl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl out of the group azabenzimidazolyl, benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, 2-furyl, 3-furyl; imidazolyl, indolyl, indazolyl, isochromanyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidinyl, pyrrolyl; 2-pyrrolyl, 3-pyrrolyl, quinolinyl, quinazolinyl, quinoxalinyl, tetrazolyl, thiadiazolyl, thiazolyl, 2-thienyl or 3-thienyl, which is additionally substituted by a heterocyclyl selected out of the group acridinyl, azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxa-zolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolinyl, tetrahydrochinolinyl, 1,4,5,6-tetrahydro-pyridazinyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl,

1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thietanyl, thiomorpholinyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl,

wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

R8 is
1. fluorine, chlor or brom,
2. $-NO_2$,
3. -CN,
4. $-C(O)-NH_2$,
5. -OH,
6. $-NH_2$,
7. $-OCF_3$
8. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is as defined above and is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,
9. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or
10. $-SO_2CH_3$ or
11. $-SO_2CF_3$,

provided that R8 is at least one halogen or $-C(O)-NH_2$, if R0 is a aryl or a heterocyclyl, which are as defined above,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl or thiophenyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is $-(C_0-C_2)$-alkylene-$C(O)-NR^{10}-$, $-NR^{10}-C(O)-NR^{10}-$, $-NR^{10}-C(O)-$, $-SO_2-$, methylene or $-(C_0-C_3)$-alkylene-$C(O)-O-(C_0-C_2)$-alkylene,

R^1 is a hydrogen atom, -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13; -(C_1-C_3)-alkylene-C(O)-NH-R^0, -(C_1-C_3)-alkylene-C(O)-O-R15, -(C_1-C_3)-perfluoroalkylene, -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl, -(C_1-C_3)-alkylene-$S(O)_2$-$N(R^{4'})$-$R^{5'}$, -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl, -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl, or -(C_0-C_3)-alkylene-het, wherein het is a residue selected out of the group azepine, azetidine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

$R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or -(C_1-C_4)-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V form a 4- to 8-membered cyclic group selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,4-oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, bromine, iodine, -OH, =O, -(C_1-C_8)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_4)-alkyl, -(C_0-C_8)-alkyl-SO_2-(C_1-C_3)-perfluoroalkyl, -(C_0-C_8)-alkyl-SO_2-N(R^{18})-R^{21}, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -NR^{18}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, –S-R^{18}, or –NR^{18}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or –(C_1-C_6)-alkyl,

V is 1) a het residue out of the group 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), azepine, azetidine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diaziridine, diazirine, dioxazole, dioxazine, dioxole, 1,3-dioxolene, 1,3-dioxolane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, 1,2-oxa-thiepane, 1,2-oxathiolane, 1,4-oxazepane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, oxaziridine, oxirane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiadiazine, thiadiazole, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thiazole, thiazolidine, thiazoline, thienyl, thietan, thiomorpholine, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, which is as defined above and wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -(CH_2)$_m$-NR^{10}-SO_2-NR^{10}-(CH_2)$_n$-, -(CH_2)$_m$-CH(OH)-(CH_2)$_n$-, -(CH_2)$_m$-, -(CH_2)$_m$-O-(CH_2)$_n$-, -(CH_2)$_m$-C(O)-NR^{10}-(CH_2)$_n$-, -(CH_2)-SO_2-(CH_2)$_n$-, -(CH_2)$_m$-NR^{10}-C(O)-NR^{10}-(CH_2)$_n$-, -(CH_2)$_m$-NR^{10}-C(O)-(CH_2)$_n$-, -(CH_2)$_m$-C(O)-(CH_2)$_n$-, -(CH_2)-S-(CH_2)$_n$-, -(CH_2)$_m$-SO_2-NR^{10}-(CH_2)$_n$-, -(CH_2)$_m$-NR^{10}-SO_2-(CH_2)$_n$-, -(CH_2)$_m$-NR^{10}-, -(CH_2)$_m$-O-C(O)-NR^{10}-(CH_2)$_n$- or –(CH_2)$_m$-NR^{10}-C(O)-O-(CH_2)$_n$-,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

M is 1) a hydrogen atom,

2) -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R11)-R12,

4) -$(CH_2)_m$-NR^{10},

5) phenyl or naphthyl, wherein phenyl or naphthyl are unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from azepane, azepine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, oxazole, [1,4]-oxazepane, piperazine, piperazinone, piperidine, piperidinone, pyrazine, pyridazine, pyridazinone, pyridine, pyridone, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, tetrazine, tetrazole, thiadiazole, thiazole, thiophene, thiomorpholine, 1λ6-thiomorpholinyl, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

7) -(C_3-C_8)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R3 is

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) CHF_2,

7) -CN,

8) -(C_0-C_4)-alkylene-(C_4-C_{15})-heterocyclyl, wherein heterocyclyl is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) -(C_0-C_4)-alkylene-het, wherein het is as defined above and is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

17) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

20) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

21) -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, wherein aryl is as defined above and is mono-, di- or trisubstituted independently of one another by R13,

22) -(C_0-C_4)-alkylene-(C_3-C_8)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

23) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

24) -(C_0-C_3)-alkylene-O-CH_2-CF_2-CF_2-CH_2-O-(C_0-C_3)-alkyl,

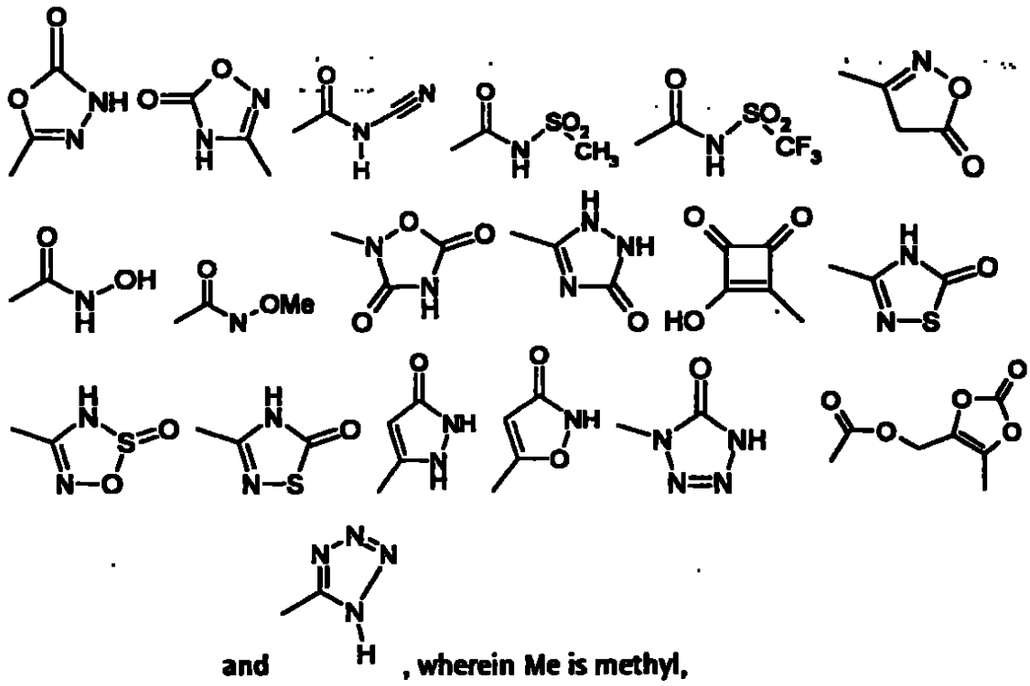
25) -(C_0-C_3)-alkylene-O-CH_2-(C_1-C_3)-perfluoroalkylene-CH_2-OH,

26) -SO_w-N(R^{11})-R^{13}, wherein w is 1 or 2,

27) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{13},

28) -(C_0-C_4)-alkylene-N(R^{11})-R^{13}, or

29) a residue from the following list



and , wherein Me is methyl,

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

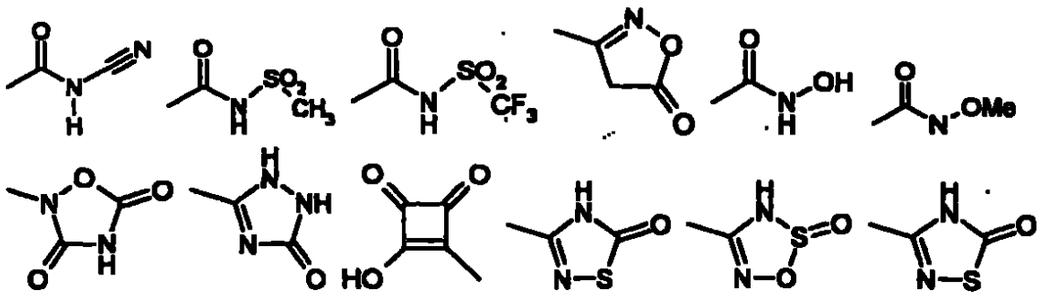
3) -(C_0-C_6)-alkyl-(C_6-C_{14})-aryl, wherein aryl is as defined above and wherein alkyl and aryl are independently from one another unsubstituted or mono-, di- or trisubstituted by R13,

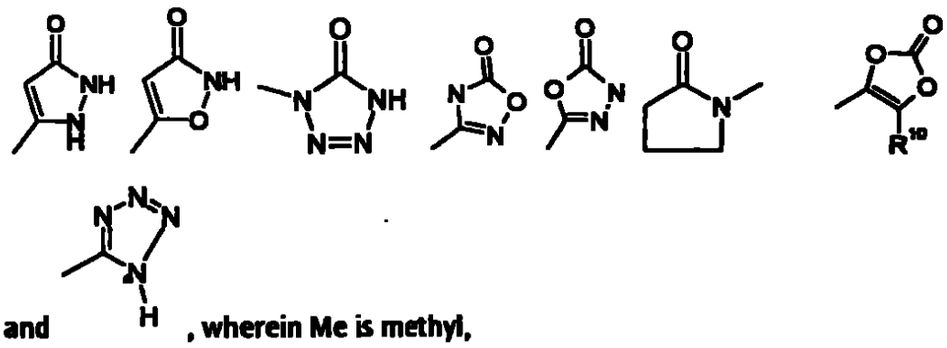
4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl is as defined above and independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, which is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

R13 is fluorine, chlorine, bromine, iodine, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, -(C_0-C_3)-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, -(C_1-C_8)-alkyl, -(C_1-C_8)-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, -(C_1-C_3)-perfluoroalkyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, -(C_1-C_4)-alkoxy-phenyl, -(C_0-C_4)-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -O-R15, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, or a residue from the following list





and , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-akyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

4. A compound of formula I as claimed in claims 1 to 3, wherein

R0 is 1) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2) a heterocyclyl out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, chromanyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, phenylpyridyl, phthalazinyl, pteridinyl, purinyl, pyridyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyrimidinyl, quinazolinyl, quinolyl, quinoxalinyl or 1,4,5,6-tetrahydro-pyridazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, or

3) a heterocyclyl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl; thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

R8 is 1. F, Cl, Br or J,

2. $-C(O)-NH_2$, or

3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue,

provided that R8 is at least one halogen or $-C(O)-NH_2$, if R0 is a aryl or a heterocyclyl, which are as defined above,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl or thiophenyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is $-C(O)-$; $-SO_2-$, methylene, $-(C_0-C_2)$-alkylene-$C(O)-NR^{10}-$ or $-(C_0-C_3)$-alkylene-$C(O)-O-(C_0-C_2)$-alkylene ,

R^1 is hydrogen atom, $-(C_1-C_2)$-alkyl, $-(C_1-C_3)$-alkylene-C(O)-NH-R0, $-(C_1-C_3)$-perfluoroalkylene, $-(C_1-C_3)$-alkylene-$C(O)-O-R^{15}$, $-(C_1-C_3)$-alkylene-$S(O)_2-(C_1-C_3)$-alkyl or $-(C_1-C_3)$-alkylene-$S(O)_2-N(R^{4'})-R^{5'}$,

wherein $R^{4'}$ and $R^{5'}$ are independent of one another are identical or different and are hydrogen atom or $-(C_1-C_4)$-alkyl,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 7- membered cyclic group out of the group azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, 1,4-oxazepane, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluorine, chlorine, -OH, =O, -(C_1-C_8)-alkyl, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-N-[(C_1-C_8)-alkyl]$_2$, -C(O)-NH_2 or -N(R^{18})-R^{21},

wherein R^{18} and R^{21} are independently from each other hydrogen atom, -(C_1-C_3)-perfluoroalkyl or -(C_1-C_4)-alkyl,

V is 1. a cyclic residue out of the group containing compounds which are derived from 8-aza-bicyclo[3.2.1]oct-3-yl, azaindole (1H-pyrrolopyridine), aziridine, azirine, azetidine, azetidinone, 1,4-diazepane, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, 1,4-oxazepane, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,3-dioxolane, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiodiazole, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,
wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

G is a direct bond, -$(CH_2)_m$-, or -$(CH_2)_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

M is
1. a hydrogen atom,
2. heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from azepane, azepine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketomorpholine, ketopiperazine, morpholine, oxazole, [1,4]-oxazepane, piperazine, piperazinone, piperidine, piperidinone, pyrazine, pyridazine, pyridazinone, pyridine, pyridone, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, tetrazine, tetrazole, thiadiazole, thiazole, thiomorpholine, 1λ6-thiomorpholinyl, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
3. -$(C_1$-$C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
4. $(C_3$-$C_6)$-cycloalkyl, or
5. -C(O)-N(R^{11})-R^{12},

R3 is
1) hydrogen atom,
2) halogen,
3) -$(C_1$-$C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
4) -$(C_1$-$C_3)$-perfluoroalkyl,
5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
6) -$(C_0$-$C_4)$-alkylene-O-R19, wherein R19 is
   a) hydrogen atom,
   b) -$(C_1$-$C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) CHF_2,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) $-(C_0-C_4)$-alkylene-C(O)-R^{11},

12) $-(C_0-C_4)$-alkylene-C(O)-O-R^{11},

13) $-(C_0-C_4)$-alkylene-C(O)-$N(R^{11})-R^{12}$,

14) $-(C_0-C_4)$-alkylene-$N(R^{11})-R^{12}$,

15) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) $-(C_0-C_2)$alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

19) $-(C_0-C_3)$-alkylene-O-$CH_2-CF_2-CH_2$-O-(C_0-C_3)-alkyl,

20) $-(C_0-C_3)$-alkylene-O-$CH_2-CF_2-CF_2-CH_2$-O-(C_0-C_3)-alkyl,

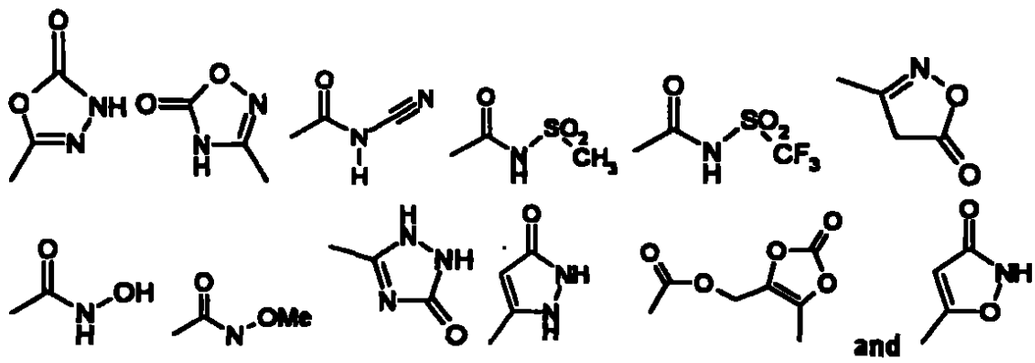
21) $-(C_0-C_3)$-alkylene-O-$CH_2-(C_1-C_3)$-perfluoroalkylene-CH_2-OH,

22) $-SO_w-N(R^{11})-R^{13}$, wherein w is 1 or 2,

23) $-(C_0-C_4)$-alkylene-C(O)-$N(R^{11})-R^{13}$,

24) $-(C_0-C_4)$-alkylene-$N(R^{11})-R^{13}$, or

25) a residue from the following list



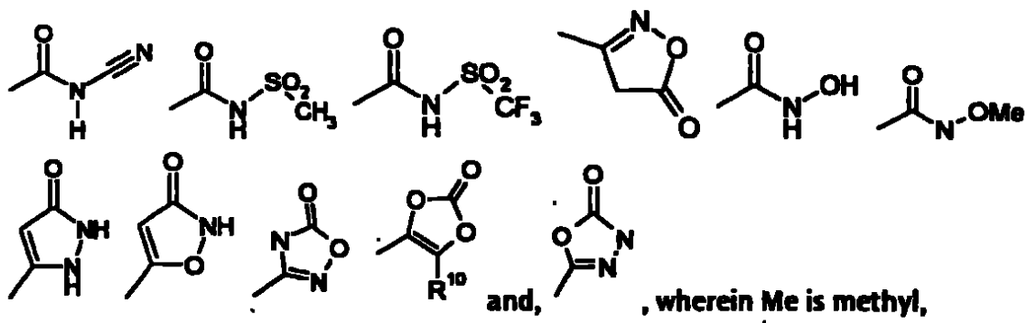
and

wherein Me is methyl,

if two -OR19 residues are attached to adjacent atoms they can form together with the atoms which they are attached to a 1,3-dioxole ring or a 2,3-dihydro-[1,4]dioxine ring, which is substituted one, two, three or four times by R13,

R^{11} and R^{12} together with the nitrogen atom to which they are bonded can form a ring selected out of the group azepine, azetidine, 1,4-diazepane, dioxazole, dioxazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, imidazole, imidazoline, imidazolidine, isothiazole, isothiazolidine, isothiazoline, isoxazole, isoxazoline, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, [1,4]-oxazepane, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, pyrroline, tetrahydropyridine, tetrazine, tetrazole, thiazole, thiadiazole, thiazolidine, thiazoline, thiomorpholine, thiophene, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said ring is unsubstituted or *mono-, di- or trisubstituted independently of one another* by R13,

R13 is fluorine, chlorine, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, $-(C_0-C_3)$-alkylene-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkoxy, phenyl, phenyloxy-, $-O-CF_3$, $-(C_1-C_3)$-perfluoroalkyl, $-NH-C(O)-NH-R^{10}$, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-R17, $-(C_1-C_4)$-alkoxy-phenyl, $-(C_0-C_4)$-alkyl-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -O-R15, $-NH-C(O)-O-R^{10}$, or a residue from the following list



and, , wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_6)-alkyl, -(C_0-C_4)-alkyl-OH, -(C_0-C_4)-alkyl-O-(C_1-C_4)-akyl or -(C_1-C_3)-perfluoroalkyl,

R15 and R16 are independently of one another hydrogen, -(C_1-C_6)-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, -(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

5. A compound of formula I as claimed in claims 1 to 4, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

2. a heterocyclyl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyridyl, purinyl and pteridinyl,
wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

3. a heterocyclyl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl,

triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R8

R8 is 1. is F, Cl, Br, J,

2. $-C(O)-NH_2$, or

3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue,

provided that R8 is at least one halogen or $-C(O)-NH_2$, if R0 is a aryl or a heterocyclyl, which are as defined above,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl or thiophenyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R^3 or is substituted 1 or 2 times by =O,

Q is -C(O)-; $-SO_2-$, methylene or $-(C_0-C_2)$-alkylene-$C(O)-NR^{10}$-,

R^1 is hydrogen atom or $-(C_1-C_2)$-alkyl,

R^2 is a direct bond or $-(C_1-C_2)$-alkylen, or

R^1-N-R^2-V can form a 4- to 7- membered cyclic group out of the group-piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is fluoro, chlorine, $-(C_1-C_4)$-alkyl or $-NH_2$,

V is 1. a cyclic residue out of the group containing compounds, which are derived from 8-aza-bicyclo[3.2.1]oct-3-yl, azaindolyl (1H-pyrrolopyridyl), azetidine, azepine, aziridine, azirine, 1,4-diazepane, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, diazirine, 1,3-dioxolane, dioxazole, furan, imidazole, isoquinoline, isothiazole, isothiazolidine, isothiazoline, isoxazole, 2-isoxazoline, isoxazolidine, ketopiperazine, morpholine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxazole, 1,2-oxathiolan, piperidine, pyran, pyrazine, pyrazole, pyridazine, piperazine, pyridine, pyridone, pyrimidine, pyrrole, pyrrolidine, pyrrolidinone, quinazoline, quinoline, tetrazine, tetrazole, thiadiazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,3-thiazole, thietan, thiomorpholine, thiophene, thiopyran, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole,
wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -$(CH_2)_m$-, or -$(CH_2)_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

M is 1. a hydrogen atom,

2. heterocyclyl, wherein heterocyclyl is a residue out of the group which can be derived from 1,4-diazepane, ketomorpholine, thiophene, pyridazone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, 1,4,5,6-tetrahydro-pyridazinyl, 1λ6-thiomorpholinyl, thiadiazole or thiomorpholine, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

4. (C_3-C_6)-cycloalkyl,

R3 is

1) hydrogen atom,

2) halogen,

3) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_4)-alkylene-O-R19, wherein R19 is

   a) hydrogen atom,

   b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

   c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

   d) $-CF_3$, or

   e) $-CHF_2$,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

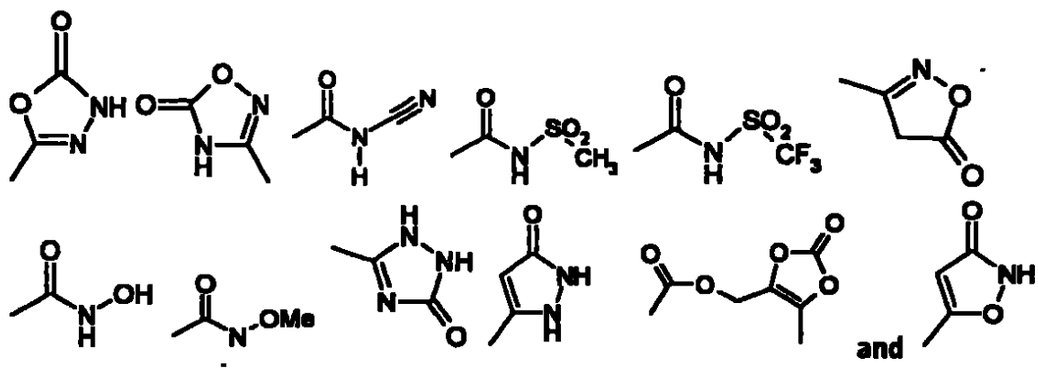
15) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) –(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl,

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17, or

19) a residue from the following list



and

wherein Me is methyl,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

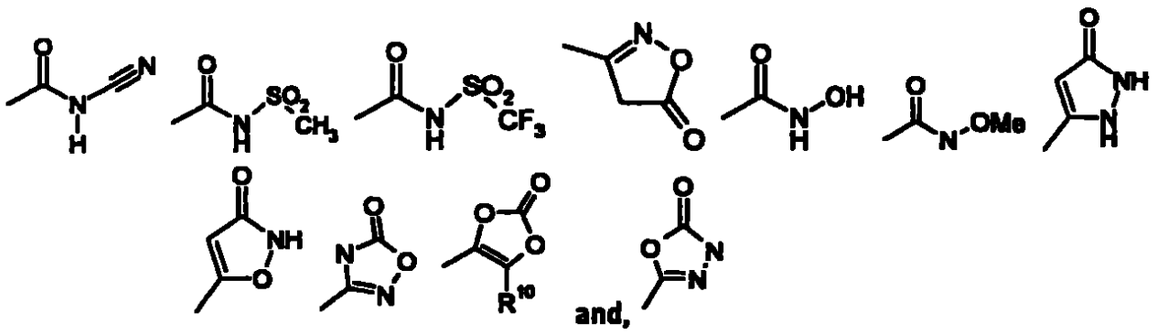
3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl,

4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-(C_4-C_{15})-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13 and wherein heterocyclyl is selected out of the group azetidine, cyclopropyl, cyclobutyl, 4,5-dihydro-oxazole, imidazolidine, morpholine, (1,4)-oxazepane, oxazolidine, piperidine, piperazine, pyrrolidine, tetrahydrothiophene, thiazolidine or thiomorpholine, or

R11 and R12 together with the nitrogen atom to which they are bonded form a heterocyclic ring, which is selected out of the group azetidine, cyclopropyl, cyclobutyl, 4,5-dihydro-oxazole, imidazolidine, morpholine, (1,4)-oxazepane, oxazolidine, piperidine, piperazine, pyrrolidine, tetrahydrothiophene, thiazolidine or thiomorpholine, wherein said ring is unsubstituted or mono-, di- or trisubstituted by R13,

R13 is fluorine, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_3-C_6)-cycloalkyl, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -(C_1-C_3)-perfluoroalkyl, or a residue from the following list



and,

wherein Me is methyl,

R^{10} and R^{20} are independently of one another hydrogen, -$(C_1$-$C_4)$-alkyl or -$(C_1$-$C_3)$-perfluoroalkyl,

R^{15} and R^{16} are independently of one another hydrogen, -$(C_1$-$C_4)$-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -$(C_1$-$C_6)$-alkyl, -$(C_1$-$C_6)$-alkyl-OH, -$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_8)$-alkyl-$(C_3$-$C_8)$-cycloalkyl, -$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_6)$-alkyl or -$(C_0$-$C_6)$-alkyl-$(C_3$-$C_8)$-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-$(C_1$-$C_4)$-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

6. A compound of formula I as claimed in claims 1 to 5, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R8,

2. pyridyl, wherein pyridyl is unsubstituted or mono- or disubstituted independently of one another by R8, or

3. a heterocyclyl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heterocyclyl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R8,

R8 is F, Cl, Br or -C(O)-NH_2,

substructure D is a residue selected out of the group phenyl, pyridyl, pyridyl-N-oxide, pyrrolyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thiophen, pyrimidinyl, pyridazinyl or pyrazinyl and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is -C(O)-; $-SO_2-$, -C(O)-O-methylene, $-CH_2$-C(O)-NH- or methylene,

R^1 is hydrogen atom,

R^2 is a direct bond,

R^1-N-R^2-V can form a 4- to 8-membered cyclic group out of the group azetidine, pyrrolidine, piperidine and piperazine,

R14 is fluorine, chlorine, methyl, ethyl, =O, $-SO_2-CH_3$ or $-NH_2$,

V is 1. a residue out of the group containing compounds which is derived from 8-aza-bicyclo[3.2.1]oct-3-yl, azaindolyl (1H-pyrrolopyridyl), azetidine, 1,4-diazepane, isoxazole, isoquinoline, piperazine, piperidine, pyrazine, pyridazine, pyrimidine, pyrrolidine, quinazoline, quinoline or tetrahydropyrane,
wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by R14, or

2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R14,

G is a direct bond, $-(CH_2)_m-$, -C(O)- or $-(CH_2)_m-NR^{10}-$,

m is the integers zero, 1 or 2,

M is a hydrogen atom, (C_2-C_4)-alkyl, azepanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolyl, ketomorpholinyl, morpholinyl, [1,4]Oxazepanyl, piperazinyl, piperidinyl, piperidonyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolidinyl, 1,4,5,6-tetrahydro-pyridazinyl, 1λ6-thiomorpholinyl or tetrahydropyranyl, wherein the residues are unsubstituted or mono- or disubstituted independently of one another by R14

R3 is

1) hydrogen atom,

2) fluorine, chlorine,

3) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) -(C_1-C_3)-perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

6) -(C_0-C_2)-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

d) $-CF_3$, or

e) $-CHF_2$,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, wherein s is 1 or 2,

10) $-SO_t-N(R^{11})-R^{12}$, wherein t is 1 or 2,

11) -(C_0-C_4)-alkylene-C(O)-R^{11},

12) -(C_0-C_4)-alkylene-C(O)-O-R^{11},

13) -(C_0-C_4)-alkylene-C(O)-N(R^{11})-R^{12},

14) -(C_0-C_4)-alkylene-N(R^{11})-R^{12},

15) -(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-(C_1-C_4)-alkyl,

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) –(C_0-C_2)alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl or

18) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl,

4) -O-R^{17}, or

5) -(C_0-C_6)-alkyl-heterocyclyl, wherein alkyl and heterocyclyl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13 and wherein heterocyclyl is selected out of the group azetidine, imidazolidine, morpholine, (1,4)-oxazepane or pyrrolidine or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring, which is selected out of the group azetidine, imidazolidine, morpholine, (1,4)-oxazepane piperazine, piperidine, pyrrolidine or thiomorpholine, wherein said ring is unsubstituted or mono-, di- or trisubstituted by R13,

R13 is fluorine, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -(C_1-C_3)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_3)-alkylene-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -SO_2-NH, or -(C_1-C_3)-perfluoroalkyl,

R^{10} and R^{20} are independently of one another hydrogen, -(C_1-C_4)-alkyl or -(C_1-C_3)-perfluoroalkyl,

R^{15} and R^{16} are independently of one another hydrogen, -(C_1-C_4)-alkyl, or together form a ring out of the group cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein each ring is unsubstituted or substituted one to three times by R^{10}, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH, -(C_1-C_6)-alkyl-O-(C_1-C_8)-alkyl-(C_3-C_8)-cycloalkyl, -(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl or -(C_0-C_4)-alkyl-(C_3-C_8)-cycloalkyl, wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by –OH, -O-(C_1-C_4)-alkyl or R^{10},

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

7. A compound of formula I as claimed in one or more of claims 1 to 6, wherein

R0 is 1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R8,

2. pyridyl, wherein pyridyl is unsubstituted or mono- or disubstituted independently of one another by R8, or

3. a heterocyclyl out of the group thiadiazolyl, isoxazolyl and thiazolyl, wherein said heterocyclyl is substituted by a residue selected out of the group thienyl, 2-thienyl

and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R8,

R8 is Cl,

substructure D is a residue selected out of the group phenyl, pyridyl, thiophenyl, thienyl or pyrimidinyl, and is unsubstituted or substituted 1, 2, 3 or 4 times by R3 or is substituted 1 or 2 times by =O,

Q is $-CH_2-C(O)-NH-$ or methylene,

R^1 is hydrogen atom,

R^2 is a direct bond,

R14 is fluorine or =O,

V is piperidinyl or phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R14,

G is a direct bond or -C(O)-,

M is a hydrogen atom, (C_2-C_4)-alkyl, isopropyl, cyclopropyl, morpholinyl, piperazinyl, piperidinyl, pyrazinyl, pyridyl, pyrimidyl, pyrrolidinyl or 1λ6-thiomorpholinyl, wherein the residues are unsubstituted or mono- or disubstituted independently of one another by R14

R3 is 1) hydrogen atom,

2) fluorine, chlorine,

3) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

4) $-(C_0-C_2)$-alkylene-O-R19, wherein R19 is

a) hydrogen atom,

b) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

c) $-CF_3$,

5) $-SO_2-R^{11}$,

6) $-(C_0-C_4)$-alkylene-C(O)-O-R^{11},

7) $-(C_0-C_4)$-alkylene-C(O)-N(R^{11})-R^{12},

8) $-(C_0-C_2)$-alkylene-C(O)-O-(C_2-C_4)-alkylene-O-C(O)-O-(C_1-C_6)-alkyl or

9) -C(O)-O- C(R15, R16)-O-C(O)-O-R17,

R11 and R12 are independently of one another identical or different and are

1) hydrogen atom,

2) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

3) -(C_0-C_6)-alkyl-(C_3-C_6)-cycloalkyl or

R11 and R12 together with the nitrogen atom to which they are bonded can form a ring, which is selected out of the group azetidine, morpholine, (1,4)-oxazepane or piperidine, wherein said ring is unsubstituted or mono-, di- or trisubstituted by R13,

R13 is fluorine, =O, -OH, $-CF_3$, -C(O)-O-R^{10}, -(C_1-C_3)-alkyl, -(C_3-C_6)-cycloalkyl or -(C_0-C_3)-alkylene-O-R^{10},

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

R^{15} and R^{16} are independently of one another hydrogen atom or -(C_1-C_4)-alkyl, and

R17 is -(C_1-C_6)-alkyl, -(C_1-C_6)-alkyl-OH or -(C_0-C_4)-alkyl-(C_3-C_8)-cycloalkyl.

8. A compound of formula I as claimed in one or more of claims 1 to 7, wherein the compound of formula I is

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

Example 2: 1-[(4-Chloro-phenylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl- piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidine-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (1-pyrimidine-4-yl-piperidine-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,
1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-5-carboxylic acid methyl ester,
3-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 3H-benzoimidazole-5-carboxylic acid methyl ester,
1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 1H-benzoimidazole-5-carboxylic acid,
3-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)- 3H-benzoimidazole-5-carboxylic acid,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid methyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid,
3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-imidazo[4,5-b] pyridine-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,
3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,4-dicarboxylic acid 4-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,
Example 35: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(3- oxo-morpholin-4-yl)-phenyl]-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- H-benzoimidazole-4-carboxylic acid methyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide,
1-(3-Methoxy-benzyl)-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-4H-pyridin-1-yl)-phenyl]-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid (8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-phenyl]-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-oxazolidin-3-yl)-phenyl]-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-oxazolidin-3-yl)-phenyl]-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-phenyl]-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(4-oxo-piperidin-1-yl)-phenyl]-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1l6-thiomorpholin-4-yl)-phenyl]-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(1,1-dioxo-1l6-thiomorpholin-4-yl)-phenyl]-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-2H-pyrazin-1-yl)-phenyl]-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-piperazin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2-carboxylic acid [4-(2-oxo-piperazin-1-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-phenyl]-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]- 1H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(6-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-3H-benzoimidazole-2,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 2-[(1-isopropyl-piperidin-4-yl)-amide],

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 1-cyclohexyloxycarbonyloxy-ethyl ester,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 1-ethoxycarbonyloxy-ethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 2-hydroxy-ethyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid carboxymethyl ester,
1-(3-Methoxy-benzyl)-2-[4-(3-oxo-morpholin-4-yl)-phenylcarbamoyl]-1H-benzoimidazole-4- carboxylic acid,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-(2-hydroxy-ethanesulfonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid cyclopropylmethyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid 2-methoxy-ethyl ester,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-hydroxymethyl-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxymethyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(morpholine-4-carbonyl)-1H-benzoimidazole- 2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-([1,4]oxazepane-4-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2,6-dimethyl-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(4,4-difluoro-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-([1,4]oxazepane-4-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid 2-hydroxy-ethyl ester,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid carboxymethyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-methoxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-4-carboxylic acid,

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-4-carboxylic acid,

1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 4-carboxylic acid,

3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 4-carboxylic acid,

4-(3-Hydroxy-azetidine-1-carbonyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[2-(4-Chloro-phenyl)-ethyl]-4-(3-methoxy-azetidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-1-(3-methoxy-benzyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,

2-(1-Isopropyl-piperidin-4-ylcarbamoyl)-3-(3-methoxy-benzyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,

1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid methyl ester,

3-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole- 5-carboxylic acid methyl ester,

1-[2-(4-Chloro-phenyl)-ethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole- 5-carboxylic acid,

1-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

3-(5-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid,

1-(5-Chloro-1H-indazol-3-ylmethyl)-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(4-hydroxy-piperidine-1-carbonyl)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

7-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid methyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid methyl ester,

1-[(6-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid cyclopropylmethyl ester,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3H-thieno[3,4-d]imidazole-2,6-dicarboxylic acid 6-[(2-hydroxy-ethyl)-amide] 2-[(1-isopropyl-piperidin-4-yl)- amide],

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-6-carboxylic acid,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-3H-thieno[3,4-d]imidazole-4-carboxylic acid,

3-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-6-([1,4]oxazepane-4-carbonyl)-3H-thieno[3,4- d]imidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-6-(2,2,2-trifluoro-ethoxy)-3H-thieno[3,4-d]imidazole-4-carboxylic acid methyl ester,

1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid

1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-5-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-3H-benzoimidazole-5-carboxylic acid,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-methoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-ethoxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-4-(2-hydroxy-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-2-[2-fluoro-4-(pyrrolidine-1-carbonyl)-phenylcarbamoyl]-1H-benzoimidazole-4-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-1H-benzoimidazole-5-carboxylic acid,

3-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-cyclopropyl-piperidin-4-ylcarbamoyl)-7-methyl-3H-benzoimidazole-5-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-fluoro-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-benzoimidazole-4-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1-isopropyl-piperidin-4-ylcarbamoyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-4-carboxylic acid or

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(3-hydroxy-azetidine-1-carbonyl)-5-(2,2,2-trifluoro-ethoxy)-1H-benzoimidazole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide.

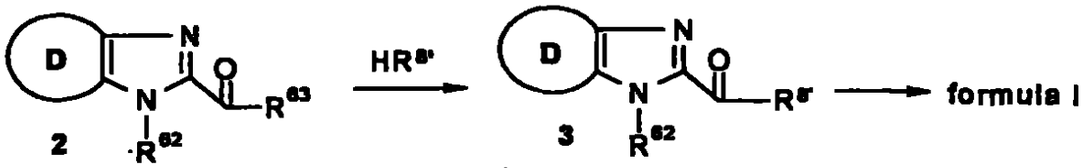
9. A pharmaceutical preparation, comprising at least one compound of the formula I as claimed in one or more of claims 1 to 8 in all its stereoisomeric forms and mixtures thereof in any ratio and/or its physiologically tolerable salts and a pharmaceutically acceptable carrier.

10. The use of a compound of the formula I as claimed in one or more of claims 1 to 8 in all its stereoisomeric forms and mixtures thereof in any ratio and/or their physiologically tolerable salts for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis.

11. The use as claimed in claim 10 for abnormal thrombus formation, acute myocardial infarction, cardiovascular disorders, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication, bypass grafting of the coronary or peripheral arteries, vessel luminal narrowing, restenosis post coronary or venous angioplasty, maintenance of vascular access patency in long-term hemodialysis patients, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee or hip surgery, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulatopathy occurring in vascular systems during septic shock, viral infections or cancer, or reducing an inflammatory response, fibrinolysis, or treatment of coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure and disseminated intravascular clotting disorder, deep vein or proximal vein thrombosis, which can occur following surgery.

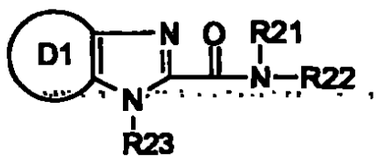
12. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 8, which comprises condensing a compound of the formula 2 with a

compound of the formula $HR^{8'}$ to give a compound of the formula 3 and optionally converting the compound of the formula 3 into a compound of the formula I,



wherein the residue $R^{8'}$ has the donation of $-N(R^1)-R^2-V-G-M$ as indicated in claims 1 to 8, but where in $R^{8'}$ functional groups can also be present in the form of groups that are subsequently transformed into the final functional groups present in $-N(R^1)-R^2-V-G-M$, and where the residue R^{62} denotes the group $-Q-R^0$ or can denote a group which is subsequently transformed into the group $-Q-R^0$, and where the group $-C(O)-R^{63}$ can be a carboxylic acid group or derivatives thereof, as defined in claims 1 to 8, wherein said functional groups can also be present in protected form or in the form of precursor groups.

13. A process for the preparation of a compound of formula IV,



(IV)

wherein

R21 is

a) a hydrogen atom,

b) $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,

c) $-(C_1-C_3)$-alkylene-C(O)-NH-R^0,

d) $-(C_1-C_3)$-alkylene-C(O)-O-R^{10},

e) $-(C_0-C_4)$-alkyl-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl and is mono-, di- or trisubstituted independently of one another by R8,

f) $-(C_0-C_4)$-alkyl-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, thre or four heteroatoms chosen from nitrogen, sulphur or oxygen and is mono-, di- or trisubstituted

independently of one another by R8,

g) -(C_1-C_4)-alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

h) -(C_1-C_3)-perfluoroalkylene,

i) -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

j) -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl,

k) -(C_1-C_3)-alkylene-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

l) -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl,

m) -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl or

n) -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

wherein R^0, $R^{4'}$, $R^{5'}$, R8, R^{10}, R^{13} and R^{14} are as defined in claim 1 for the compound of formula I,

R22 is a) a hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13 ,

c) -(C_1-C_3)-alkylene-C(O)-NH-R^0,

d) -(C_1-C_3)-alkylene-C(O)-O-R^{10},

e) -(C_0-C_4)-alkyl-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl and is mono-, di- or trisubstituted independently of one another by R8,

f) -(C_0-C_4)-alkyl-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, thre or four heteroatoms chosen from nitrogen, sulphur or oxygen and is mono-, di- or trisubstituted independently of one another by R8,

g) -(C_0-C_4)-alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen,
wherein heterocyclyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R8,

h) -(C_1-C_3)-perfluoroalkylene,

i) -(C_0-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

j) -(C_0-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl,

k) -(C_0-C_3)-alkylene-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

l) -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl,

m) -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl,

n) -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

o) R^2-V-G-M,

wherein R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, R14, V, G and M are as defined in claim 1 for the compound of formula I, or

the substructure R21-N-R^2-V in formula IV can form a 4- to 8-membered cyclic group, containing 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, wherein the residue R14 is as defined as in claim 1 for the compound

of formula I ,

R23 is

a) a hydrogen atom,

b) -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R13,

c) -(C_1-C_3)-alkylene-C(O)-NH-R^0,

d) -(C_1-C_3)-alkylene-C(O)-O-R^{10},

e) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8,

f) a monocyclic or bicyclic 4- to 15-membered heterocyclyl, containing one, two, three or four heteroatoms chosen from nitrogen, sulphur or oxygen,

g) -(C_1-C_3)-perfluoroalkylene,

h) -(C_1-C_3)-alkylene-S(O)-(C_1-C_4)-alkyl,

j) -(C_1-C_3)-alkylene-$S(O)_2$-(C_1-C_3)-alkyl,

k) -(C_1-C_3)-alkylene-$S(O)_2$-N($R^{4'}$)-$R^{5'}$,

l) -(C_1-C_3)-alkylene-O-(C_1-C_4)-alkyl,

m) -(C_0-C_3)-alkylene-(C_3-C_8)-cycloalkyl,

n) -(C_0-C_3)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

o) -Q-R^0,

wherein R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, R14, Q, V, G and M are as defined as in claim 1 for the compound of formula I, and

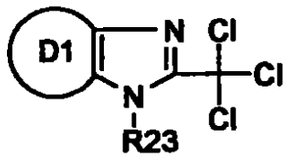
substructure 

in formula IV is

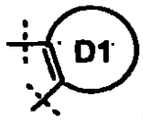
a 4-to 8 membered saturated, partially unsaturated or aromatic cyclic group containing zero, 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulphur or oxygen

and is unsubstituted or substituted 1, 2, 3, 4, 5 or 6 times by R3, wherein R3 is as defined in claim 1 for the compound of formula I,

which comprises reacting a compound of formula V



(V)

wherein R23 is as defined in formula IV and substructure 

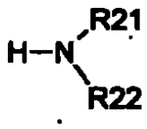
in formula V is as defined in formula IV,

with a primary amine, wherein the primary amine is selected out of the group

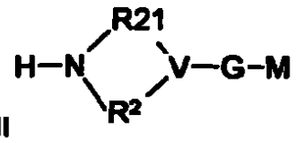
a) NH_2-R21, wherein R21 is as defined in formula IV, or

b) NH_2-R^2-V-G-M, wherein R^2, V, G and M are as defined in formula IV,

or a secondary amine, wherein the secondary amine is selected out of the group

a) 

wherein R21 and R22 are as defined in formula IV, or

b) a compound of formula VII 

(VII)

wherein R21, R^2, V, G and M are as defined in formula IV,

provided that R21 is not 8-aza-bicyclo[3.2.1]octane or
provided that R21-N-R2-V do not form a piperazine or [1,4]diazepane residue,

in the presence of water, at least one base and at least one water-miscible organic solvent, wherein the water-miscible organic solvent is selected out of the group tetrahydrofuran, acetonitrile, 1,2-dimethoxyethane, dimethylsulfoxide, dioxane, N,N-dimethylformamide, N-methylpyrrolidone, acetone or sulfolane.

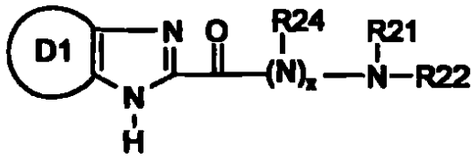
AMENDED SHEET (ARTICLE 19)

14. A process for the preparation of a compound of formula IV as claimed in claim 13, wherein the base is an alkali metal carbonate, sodium bicarbonate, potassium bicarbonate, an tertiary amine, triethylamine or diisopropylethylamine.

15. A process for the preparation of a compound of formula IV as claimed in claim 13, wherein the amount of water-miscible organic solvent used is from 5 g to 300 g per 1 g of the compound of the formula V, preferably from 10 g to 200 g.

16. A process for the preparation of a compound of formula IV as claimed in claim 13, wherein the reaction temperature is from 5 °C to 120 °C, preferably from 10 °C to 35 °C, in particular 25 °C.

17. A process for the preparation of a compound of formula IX,



(IX)

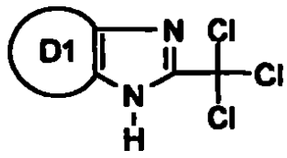
wherein

x is the integer 1,

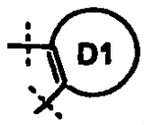
R24 is identical with R21, which is as defined in formula IV in claim 13, and

R22 is as defined in formula IV,

which comprises reacting a compound of formula X



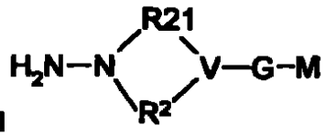
(X)



wherein the substructure in formula X is as defined in formula IV,

with a primary amine, wherein the primary amine is selected out of the group

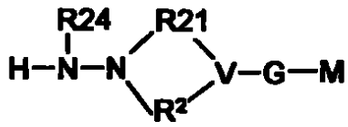
a) NH_2-N(R21)-R22, wherein R21 and R22 are as defined in formula IV or



b) a compound of formula VI (VI)

wherein R^2, R21, V, G and M are as defined as in formula IV or

a secondary amine, wherein the secondary amine is a compound of formula VIII



(VIII)

wherein R^2, R21, R24, V, G and M are as defined in formula IV,

in the presence of water, at least one base and at least one water-miscible organic solvent, wherein the water-miscible organic solvent is selected out of the group tetrahydrofuran, acetonitrile, 1,2-dimethoxyethane, dimethylsulfoxide, dioxane, N,N-dimethylformamide, N-methylpyrrolidone, acetone or sulfolane.

18. A process for the preparation of a compound of formula IX as claimed in claim 17, wherein the base is an alkali metal carbonate, sodium bicarbonate, potassium bicarbonate, a tertiary amine, triethylamine or diisopropylethylamine.

19. A process for the preparation of a compound of formula IX as claimed in claim 17, wherein the amount of water-miscible organic solvent used is from 5 g to 300 g per 1 g of the compound of the formula V, preferably from 10 g to 200 g.

20. A process for the preparation of a compound of formula IX as claimed in claim 17, wherein the reaction temperature is from 5 °C to 120 °C, preferably from 10 °C to 35°C, in particular 25 °C.

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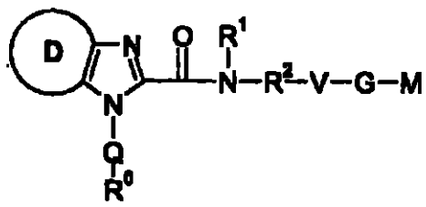
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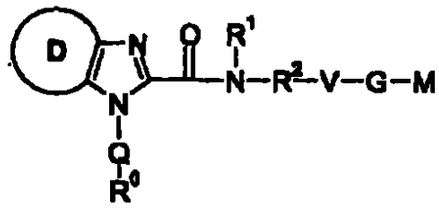
(54) Título: DERIVADOS DE BENCIMIDAZOL COMO INHIBIDORES DEL FACTOR Xa

(I) 

(57) Extracto: La presente invención se relaciona con compuestos de la fórmula (I) donde R^0, R^1, R^2, Q, V, G y M tienen los significados indicados a continuación. Los compuestos de la fórmula I son compuestos farmacológicamente activos valiosos. Muestran un fuerte efecto antitrombótico y son adecuados, por ejemplo, para la terapia y profilaxis de trastornos cardiovasculares tales como enfermedades tromboembólicas o reestenosis. Son inhibidores reversibles de las enzimas de la coagulación sanguínea factor Xa (FXa) y/o factor VIIa (FVIIa) y, en general, pueden aplicarse en situaciones en las que está presente una actividad indeseada del factor Xa y/o del factor VIIa o en situaciones para cuya curación o prevención se desea la inhibición del factor Xa y/o del factor VIIa. Además, la invención se refiere a procesos para la preparación de compuestos de la fórmula I, a su uso, en particular como ingredientes activos en productos farmacéuticos, y a preparaciones farmacéuticas que los contienen.

Derivados de bencimidazol como inhibidores del factor Xa

La presente invención se refiere a compuestos de la fórmula I,



(I)

en la que R^0; R^1; R^2; Q; V, G y M tienen los significados indicados a continuación. Los compuestos de la fórmula I son compuestos farmacológicamente activos valiosos. Muestran un fuerte efecto antitrombótico y son adecuados, por ejemplo, para la terapia y profilaxis de trastornos cardiovasculares tales como enfermedades tromboembólicas o reestenosis. Son inhibidores reversibles de las enzimas de la coagulación sanguínea factor Xa (FXa) y/o factor VIIa (FVIIa) y, en general, pueden aplicarse en situaciones en las que está presente una actividad indeseada del factor Xa y/o del factor VIIa o en situaciones para cuya curación o prevención se desea la inhibición del factor Xa y/o del factor VIIa. Además, la invención se refiere a procesos para la preparación de compuestos de la fórmula I, a su uso, en particular como ingredientes activos en productos farmacéuticos, y a preparaciones farmacéuticas que los contienen.

La homeostasis normal es el resultado de un equilibrio complejo entre los procesos de inicio del coágulo, formación del coágulo y disolución del coágulo. Las interacciones complejas entre células sanguíneas, proteínas plasmáticas específicas y la superficie vascular mantienen la fluidez de la sangre a menos que exista una lesión y se produzca una pérdida de sangre (documento EP-A-987274). Muchos estados de enfermedad significativos están relacionados con una homeostasis anormal. Por ejemplo, la formación de trombos locales debida a la ruptura de una placa aterosclerótica es una causa importante de infarto de miocardio agudo y de angina inestable. El tratamiento de un trombo coronario oclusivo mediante terapia trombolítica o angioplastia percutánea puede ir acompañado de una reoclusión trombolítica del vaso afectado.

Sigue existiendo la necesidad de anticoagulantes terapéuticos seguros y eficaces para limitar o prevenir la formación de trombos. Lo más deseable es crear agentes que inhiban la coagulación sin inhibir directamente la trombina pero inhibiendo otras etapas de la cascada de la coagulación tales como la actividad del

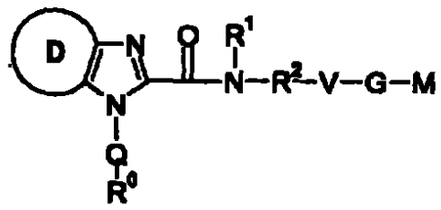
factor Xa y/o del factor VIIa. Actualmente se cree que los inhibidores del factor Xa llevan asociado un menor riesgo de hemorragia que los inhibidores de trombina (A. E. P. Adang y J. B. M. Rewinkel, Drugs of the Future 2000, 25, 369-383).

En el documento WO-A-95/29189, por ejemplo, se han descrito inhibidores de la coagulación sanguínea específicos del factor Xa, de bajo peso molecular, que son eficaces pero no producen efectos secundarios indeseados. Sin embargo, además de ser inhibidores eficaces de la coagulación sanguínea específicos del factor Xa, es deseable que tales inhibidores también tengan otras propiedades ventajosas, por ejemplo estabilidad en plasma e hígado y selectividad frente a otras proteasas de serina cuya inhibición no se desea, tales como la trombina. Actualmente existe la necesidad de otros inhibidores de la coagulación sanguínea específicos del factor Xa de bajo peso molecular que sean eficaces y que también tengan las ventajas anteriores.

La inhibición específica del complejo catalítico factor VIIa/factor tisular usando anticuerpos monoclonales (documento WO-A-92/06711) o una proteína tal como el factor VIIa inactivado por clorometil cetona (documentos WO-A-96/12800 y WO-A-97/47651) es un medio extremadamente eficaz para controlar la formación de trombos debida a una lesión arterial aguda o de las complicaciones trombóticas relacionadas con la septicemia bacteriana. También existen indicios experimentales que sugieren que la inhibición de la actividad del factor VIIa/factor tisular inhibe la reestenosis que sigue a una angioplastia de balón. Se han realizado estudios de hemorragia en babuinos e indican que la inhibición del complejo factor VIIa/factor tisular tiene la mayor ventana de seguridad con respecto a la eficacia terapéutica y al riesgo de hemorragia de cualquier estrategia con anticoagulantes que se haya ensayado, incluyendo la inhibición de la trombina, de las plaquetas y del factor Xa. Ya se han descrito ciertos inhibidores del factor VIIa. Por ejemplo, el documento EP-A-987274 describe compuestos que contienen una unidad tripeptídica que inhiben el factor VIIa. Sin embargo, el perfil de propiedades de estos compuestos aún no es ideal, y sigue existiendo la necesidad de más inhibidores de la coagulación sanguínea de bajo peso molecular que inhiban el factor VIIa.

La presente invención satisface las necesidades anteriores proporcionando nuevos compuestos de la fórmula I que muestran una mejor actividad inhibidora del factor Xa y/o del factor VIIa y que son agentes favorables con una alta biodisponibilidad.

De esta manera, la presente invención se refiere a compuestos de la fórmula I,

(I) 

, en la que

R^0 es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y
que está adicionalmente sustituido con un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno,
donde el heterociclilo está sin sustituir, mono-, di- o trisustituido independientemente entre sí con R8,

R8 es 1) halógeno,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con halógeno o -O-alquilo (C_1-C_8),

9) alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o

trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

10) -O-alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

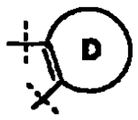
11) $-SO_2CH_3$ o

12) $-SO_2-CF_3$,

con la condición de que R8 sea al menos un halógeno, $-C(O)-NH_2$ o un resto -O-alquilo (C_1-C_8), si R^0 es un arilo de 6 a 14 miembros monocíclico o bicíclico,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R^0 y V son un arilo de 6 a 14 miembros monocíclico o bicíclico,

la subestructura



en la fórmula I es un grupo cíclico saturado, parcialmente insaturado o aromático de 4 a 8 miembros que contiene cero, 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está sin sustituir o sustituido 1, 2, 3, 4, 5 ó 6 veces con R3 o sustituido 1 ó 2 veces con =0,

Q es un enlace directo, -alquileno (C_0-C_2)-$C(O)-NR^{10}$-, $-NR^{10}-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$-, metileno, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$-, $-(CH_2)_m-S-(CH_2)_n$-, $-(CH_2)_m-C(O)-(CH_2)_n$-, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-CH(OH)-(CH_2)_n$-, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$-, -alquileno ($C_2$-$C_3$)-O-alquileno ($C_0$-$C_3$), -alquileno ($C_2$-$C_3$)-S(O)-, -alquileno ($C_2$-$C_3$)-$S(O)_2$-, $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n$-, -alquileno ($C_2$-$C_3$)-$S(O)_2-NH-(R^{10})$-, -alquileno ($C_2$-$C_3$)-$N(R^{10})$- o -alquileno ($C_0$-$C_3$)-C(O)-O-$(CH_2)_m$-,

donde R^{10} es como se define a continuación, y donde n y m son independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6 donde los restos alquileno que se forman por $-(CH_2)_m$- o -$(CH_2)_n$- están sin sustituir o mono-, di- o trisustituidos independientemente entre sí con halógeno, $-NH_2$ o -OH; o -cicloalquileno (C_3-C_8), donde el cicloalquileno está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, $-NH_2$ o -OH;

R^1 es un átomo de hidrógeno, -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13; -alquileno (C_1-C_3)-$C(O)-NH-R^0$, -alquileno (C_1-C_3)-$C(O)-O-R^{10}$, un arilo de 6 a 14 miembros monocíclico o

bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8, donde R8 es como se ha definido anteriormente; un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno; -perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4), -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3), -alquileno (C_1-C_3)-$S(O)_2$-$N(R^{4'})$-$R^{5'}$, -alquileno (C_1-C_3)-O-alquilo (C_1-C_4), -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8) o alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

$R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros que contiene 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R^{14} es halógeno, -OH, =O, -alquilo (C_1-C_8), -alcoxi (C_1-C_4), $-NO_2$, -C(O)-OH, -CN, $-NH_2$, -C(O)-O-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-perfluoroalquilo (C_1-C_3), -alquil (C_0-C_8)-SO_2-$N(R^{18})$-R^{21}, -C(O)-NH-alquilo (C_1-C_8), -C(O)-N[alquilo (C_1-C_8)]$_2$, -NR^{18}-C(O)-NH-alquilo (C_1-C_8), -C(O)-NH_2, -S-R^{18} o -NR^{18}-C(O)-NH-[alquilo (C_1-C_8)]$_2$, donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o alquilo (C_1-C_8),

V es 1) un arilo de 6 a 14 miembros, donde el arilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14, o

2) un heterociclilo del grupo compuesto por acridinilo, 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol-(1H-pirrolopiridina), azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 1,4-diazepano, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo,

1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, *quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo,* 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,

G es un enlace directo, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ o $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6,

M es
1) un átomo de hidrógeno,
2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,
3) -C(O)-N(R11)-R12,
4) $-(CH_2)_m-NR^{10}$,
5) un arilo de 6 a 14 miembros, donde el arilo está sin sustituir o mono-,

di- o trisustituido, independientemente entre sí, con R14,

6) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, donde el heterociclilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,

7) -cicloalquilo (C_3-C_8), donde dicho cicloalquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14, o

8) un resto cíclico de 3 a 7 miembros que contiene 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14, donde R14 es como se ha definido anteriormente,

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

d) -CF_3, o

e) -CHF_2,

7) -NO_2,

8) -CN,

9) -SO_s-R^{11}, donde s es 1 ó 2,

10) -SO_t-$N(R^{11})$-R^{12}, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})$-R^{12},

14) -alquileno (C_0-C_4)-$N(R^{11})$-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) $-S-R^{10}$,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_8),

20) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

21) -alquileno (C_0-C_4)-arilo (C_6-C_{14}), donde el arilo está mono-, di- o trisustituido, independientemente entre sí, con R13,

22) -alquileno (C_0-C_4)-heterociclilo (C_4-C_{15}), donde el heterociclilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

23) -alquileno (C_0-C_4)-cicloalquilo (C_3-C_8), donde el cicloalquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

24) alquileno (C_0-C_4)het, donde het está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

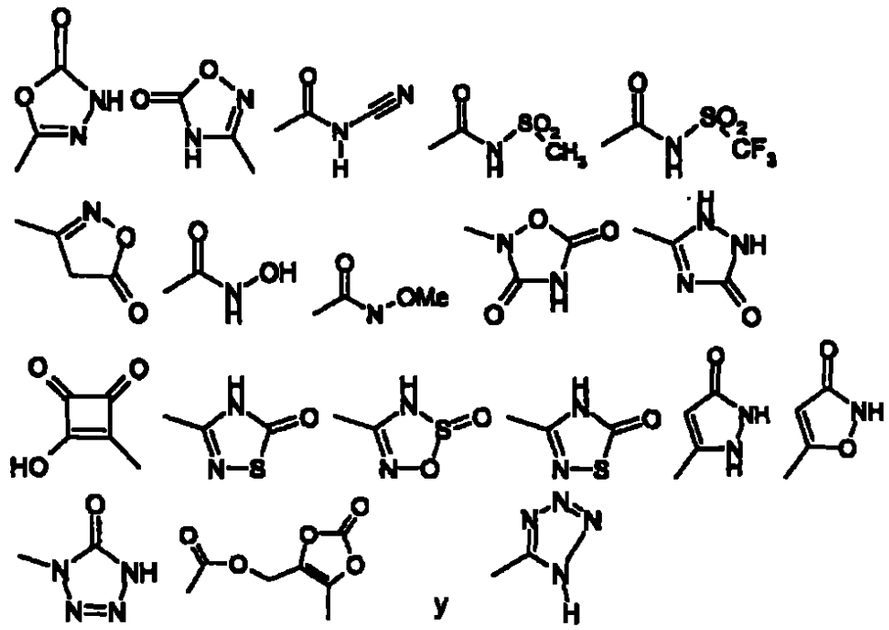
25) -alquileno (C_0-C_4)-O-CH_2-perfluoroalquileno (C_1-C_3)-CH_2-O-alquilo (C_0-C_4),

26) $-SO_w-N(R^{11})-R^{13}$, donde w es 1 ó 2,

27) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{13}$, o

28) -alquileno (C_0-C_4)-$N(R^{11})-R^{13}$, o

29) un resto de la siguiente lista



y

donde Me es metilo o, si dos restos -OR19 están unidos a átomos adyacentes, pueden formar junto con los átomos a los que están unidos un anillo de 5 ó 6 miembros que está sin sustituir o sustituido una, dos, tres o cuatro veces con R^{13},

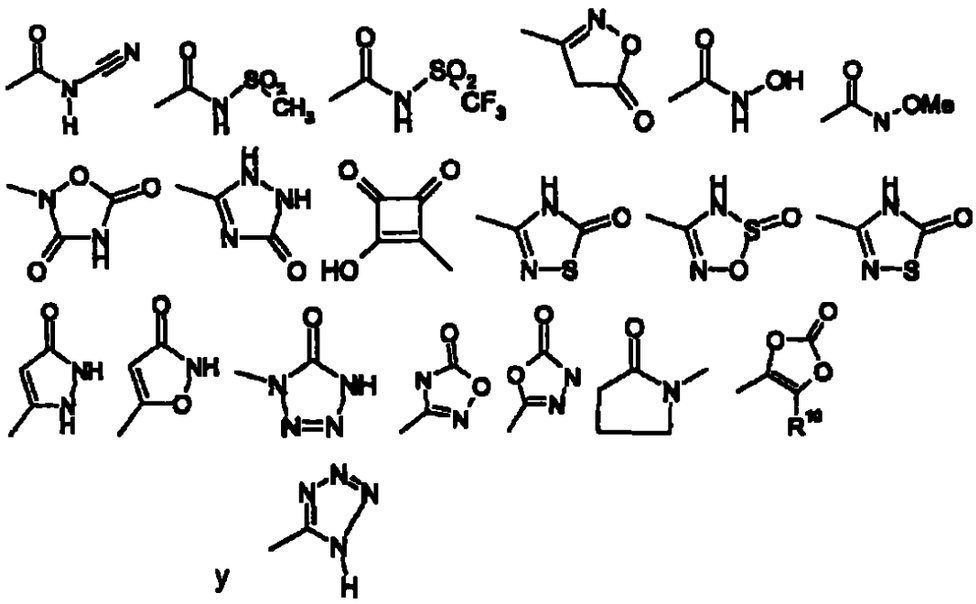
R^{11} y R^{12} son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,
2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
3) -alquil (C_0-C_8)-cicloalquilo (C_3-C_8),
4) -SO_t-R^{10}, donde t es 1 ó 2,
5) -alquil (C_0-C_8)-arilo (C_6-C_{14}), donde el alquilo y el arilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13,
6) -perfluoroalquilo (C_1-C_3),
7) -O-R^{17}, o
8) -alquil (C_0-C_8)-heterociclilo (C_4-C_{14}), donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo heterocíclico monocíclico de 4 a 8 miembros que además del átomo de

nitrógeno puede contener uno o dos heteroátomos en el anillo iguales o diferentes seleccionados entre oxígeno, azufre y nitrógeno; donde dicho anillo heterocíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es halógeno, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, - cicloalquilo (C_3-C_8), -alquileno (C_0-C_3)-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_u-R^{10}$, donde u es 1 ó 2, $-S-R^{10}$, $-SO_r-R^{10}$, donde r es 1 ó 2, $-S(O)_v-N(R^{10})-R^{20}$, donde v es 1 ó 2, $-C(O)-R^{10}$, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, feniloxi-, $-O-CF_3$, -alquil (C_0-C_4)-C(O)-O-C(R15,R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -perfluoroalquilo (C_1-C_3), -O-R15, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, o un resto de la siguiente lista



y

donde Me es metilo, o

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), o junto con el átomo de carbono al que están unidos pueden formar un anillo carbocíclico de 3 a 6 miembros que está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_8), -alquil (C_1-C_8)-OH, -alquil (C_1-C_8)-O-alquilo (C_1-C_8), -cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-O-alquil (C_1-C_8)-cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquil (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

2) De esta manera, la presente invención se refiere a compuestos de la fórmula I, en la que

R^0 es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico del grupo de fenilo, naftilo, bifenililo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo, donde el heterociclilo se selecciona entre el grupo de acridinilo, azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo,

1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y

que además está sustituido con un heterociclilo seleccionado entre el grupo de acridinilo, azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo,

tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

R8 es 1) halógeno,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con halógeno o -O-alquilo (C_1-C_8),

9) alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi, o

10) -O-alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

11) $-SO_2CH_3$ o

12) $-SO_2-CF_3$,

con la condición de que R8 sea al menos un halógeno, $-C(O)-NH_2$ o un resto -O-alquilo (C_1-C_8), si R^0 es un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo es como se ha definido anteriormente,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R^0 y V son un arilo de 6 a 14 miembros monocíclico o bicíclico,

la subestructura D es un resto seleccionado entre el grupo azetidina, azetina, azocano, azocano-2-ona, ciclobutilo, ciclooctano, cicloocteno, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, [1,4]diazocano, [1,2]diazocan-3-ona, [1,3]diazocan-2-ona, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,2-oxa-tiepano, 1,2-oxatiolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, [1,4]oxazocano, [1,3]oxazocan-2-ona, oxetano, oxocano, oxocan-

2-ona, piperazina, piperidina, fenilo, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, 5,6,7,8-tetrahidro-1H-azocin-2-ona, tetrahidrofurano, tetrahidropirano, tetrahidropiridina, tetrazina, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tietano, tiocano, tiocano-1,1-dióxido, tiocano-1-óxido, tiocan-2-ona, tiomorfolina, tifeno, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol y está sin sustituir o sustituido 1, 2, 3, 4, 5 ó 6 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -alquileno (C_0-C_2)-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C(O)-, -SO_2-, metileno, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$C(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -alquileno (C_2-C_3)-O-alquileno (C_0-C_3), -alquileno (C_2-C_3)-S(O)-, -alquileno (C_2-C_3)-$S(O)_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -alquileno (C_2-C_3)-$S(O)_2$-NH-(R^{10})-, -alquileno (C_2-C_3)-N(R^{10})- o -alquileno (C_0-C_3)-C(O)-O-$(CH_2)_m$-,

donde R^{10} es como se define más adelante, y donde n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6, donde los restos alquileno que se forman con -$(CH_2)_m$- o -$(CH_2)_n$- están sin sustituir o mono-, di- o trisustituidos independientemente entre sí con halógeno, -NH_2 o -OH; o -cicloalquileno (C_3-C_6), donde el cicloalquileno está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, -NH_2 o -OH;

R^1 es un átomo de hidrógeno, -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13; -alquileno (C_1-C_3)-C(O)-NH-R^0, -alquileno (C_1-C_3)-C(O)-O-R15, un arilo del grupo de fenilo, naftilo, bifenililo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8, donde R8 es como se ha definido anteriormente;

un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, que es como se ha definido anteriormente;

-perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4), -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3), -alquileno (C_1-C_3)-$S(O)_2$-N($R^{4'}$)-$R^{5'}$, -alquileno (C_1-C_3)-O-alquilo (C_1-C_4), -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8) o alquileno (C_0-C_3)-het, donde het es un resto seleccionado entre el grupo de azepina, azetidina, aziridina, azirina, 1,4-diazapano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diaziridina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano,

furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,4-oxazepano, 1,2-oxa-tiepano, 1,2-oxatiolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

$R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros seleccionado entre el grupo de azepina, azetidina, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, bromo, yodo, -OH, =O, alquilo (C_1-C_8), -alcoxi (C_1-C_4), -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-perfluoroalquilo (C_1-C_3), -alquil (C_0-C_8)-SO_2-N(R^{18})-R^{21}, -C(O)-NH-alquilo (C_1-C_8), -C(O)-N-[alquilo (C_1-C_8)]$_2$, -NR^{18}-C(O)-NH-alquilo (C_1-C_8), -C(O)-NH_2-, -S-R^{18} o -NR^{18}-C(O)-NH-[alquilo (C_1-C_8)]$_2$,

donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o -alquilo (C_1-C_8),

V es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico del grupo de fenilo, naftilo, bifenililo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R14,

2) un heterociclilo del grupo de acridinilo, 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol-(1H-pirrolopiridina), azabencimidazolilo, azaespirodecanilo, azepinilo,

azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 1,4-diazepano, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopirazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

G es un enlace directo, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$ o $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6,

M es 1) un átomo de hidrógeno,

2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

3) -C(O)-N(R11)-R12,

4) -$(CH_2)_m$-NR^{10},

5) -arilo (C_6-C_{14}), donde el arilo es como se ha definido anteriormente y donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

6) -heterociclilo (C_4-C_{15}), donde el heterociclilo es como se ha definido anteriormente y está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

7) -cicloalquilo (C_3-C_8), donde dicho cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está no sustituido o mono-, di- o trisustituido independientemente entre sí con R13,

d) -CF_3, o

e) -CHF_2,

7) -NO_2,

8) -CN,

9) -SO_s-R^{11}, donde s es 1 ó 2,

10) -SO_t-$N(R^{11})$-R^{12}, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})$-R^{12},

14) -alquileno (C_0-C_4)-N(R^{11})-R^{12},

15) -NR^{10}-SO_2-R^{10},

16) -S-R^{10},

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

20) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

21) -alquileno (C_0-C_4)-arilo (C_6-C_{14}), donde el arilo está mono-, di- o trisustituido independientemente entre sí con R13,

22) -alquileno (C_0-C_4)-heterociclilo (C_4-C_{15}), donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

23) -alquileno (C_0-C_4)-cicloalquilo (C_3-C_6), donde el cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

24) alquileno (C_0-C_4)-het, donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

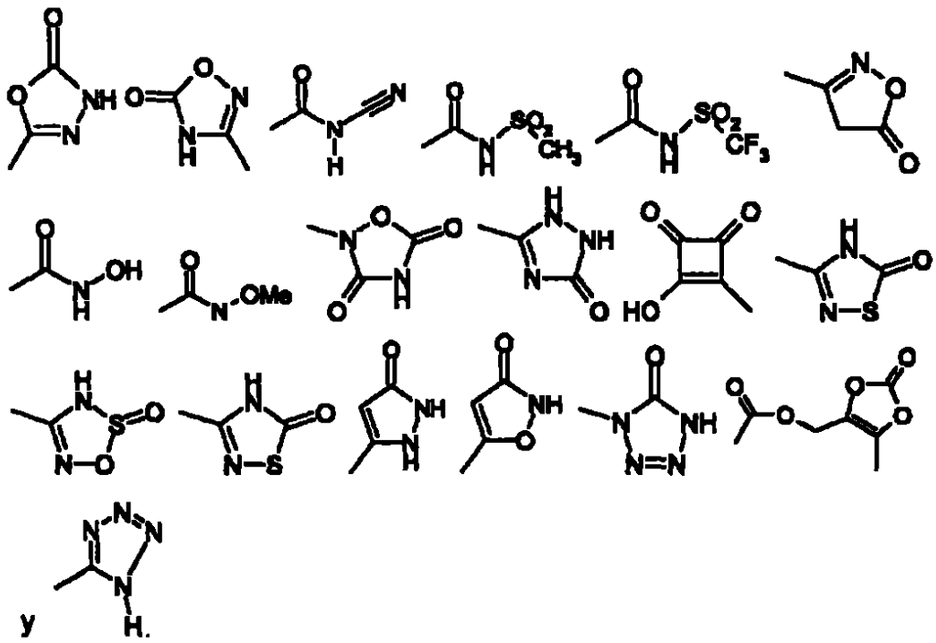
25) -alquileno (C_0-C_4)-O-CH_2-perfluoroalquileno (C_1-C_3)-CH_2-O-alquilo (C_0-C_4),

26) -SO_w-N(R^{11})-R^{13}, donde w es 1 ó 2,

27) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{13}, o

28) -alquileno (C_0-C_4)-N(R^{11})-R^{13}, o

29) un resto de la siguiente lista



y

donde Me es metilo o,

si dos restos -OR19 están unidos a átomos adyacentes pueden formar junto con los átomos a los que están unidos un anillo 1,3-dioxol o un anillo 2,3-dihidro-[1,4]dioxina, que está sustituido una, dos, tres o cuatro veces con R13,

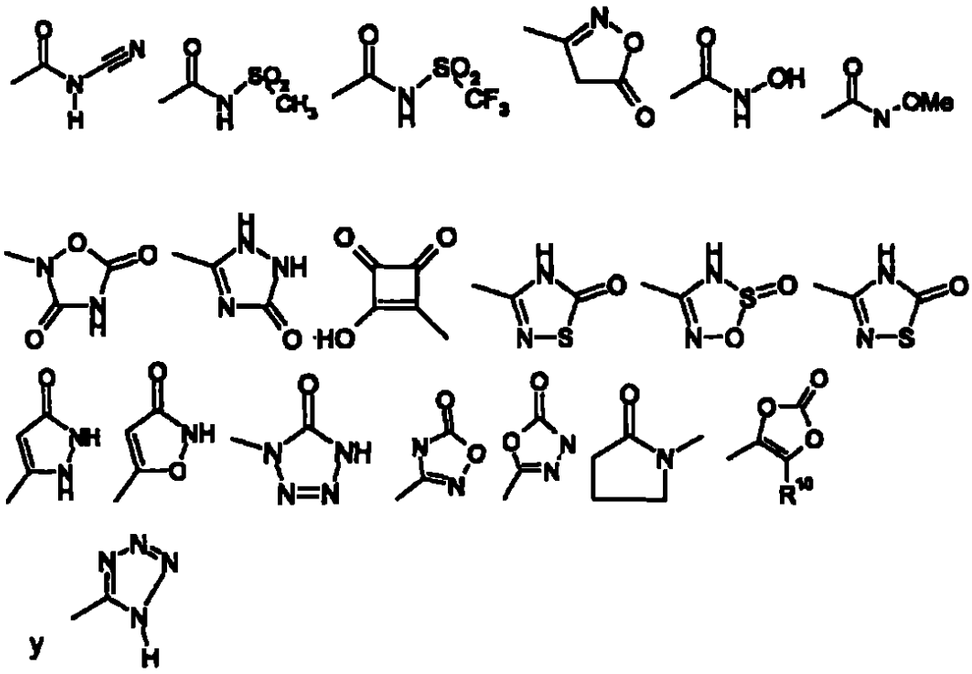
R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,
2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
3) -alquil (C_0-C_8)-cicloalquilo (C_3-C_8),
4) -SO_t-R^{10}, donde t es 1 ó 2,
5) -alquil (C_0-C_8)-arilo (C_6-C_{14}), donde el alquilo y el arilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13,
6) -perfluoroalquilo (C_1-C_3),
7) -O-R^{17}, o
8) -alquil (C_0-C_8)-heterociclilo (C_4-C_{14}), donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo heterocíclico del grupo de azepina, azetidina, dioxazol, dioxazina, 1,4-diazepano, 1,2-diazepina, 1,4-diazepina, 1,4-diazepina, imidazol, imidazolina,

imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho anillo heterocíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es halógeno, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})R^{20}$, -cicloalquilo (C_3-C_8), -alquileno (C_0-C_3)-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_u-R^{10}$, donde u es 1 ó 2, $-S-R^{10}$, $-SO_r-R^{10}$, donde r es 1 ó 2, $-S(O)_v-N(R^{10})-R^{20}$, donde v es 1 ó 2, $-C(O)-R^{10}$, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, feniloxi-, $-O-CF_3$, -alquil (C_0-C_4)-C(O)-O-C(R15,R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15,R16)-O-C(O)-R17, -perfluoroalquilo (C_1-C_3), $-O-R15$, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, o un resto de la siguiente lista



donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o

sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_8), -alquil (C_1-C_8)-OH, -alquil (C_1-C_8)-O-alquilo (C_1-C_8), -cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-O-alquil (C_1-C_8)-cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

3) La presente invención también se refiere a los compuestos de fórmula I, en la que

R^0 es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico del grupo de fenilo, naftilo, bifenilo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo del grupo de azabencimidazolilo, bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzotiazolilo, benzotiofenilo, benzoxazolilo, cromanilo, cinolinilo, 2-furilo, 3-furilo; imidazolilo, indolilo, indazolilo, isocromanilo, isoindolilo, isoquinolinilo, isotiazolilo, isoxazolilo, oxazolilo, ftalazinilo, pteridinilo, purinilo, pirazinilo, pirazolilo, piridazinilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, 2-piridilo, 3-piridilo, 4-piridilo, pirimidinilo, pirrolilo; 2-pirrolilo, 3-pirrolilo, quinolinilo, quinazolinilo, quinoxalinilo, tetrazolilo, tiadiazolilo, tiazolilo, 2-tienilo o 3-tienilo, que además está sustituido con un heterociclilo seleccionado entre el grupo acridinilo, azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo,

1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo(bencimidazolilo), isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridinilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo,

donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

R8 es
1. flúor, cloro o bromo,
2. $-NO_2$,
3. -CN,
4. $-C(O)-NH_2$,
5. -OH,
6. $-NH_2$,
7. $-OCF_3$
8. un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo es como se ha definido anteriormente y está mono-, di- o trisustituido independientemente entre sí con halógeno o -O-alquilo (C_1-C_8),
9. -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un

resto metoxi, o

10. -O-alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

11. $-SO_2CH_3$ o

12. $-SO_2CF_3$,

con la condición de que R8 sea al menos un halógeno, $-C(O)-NH_2$ o un resto -O-alquilo (C_1-C_8), si R0 es un arilo o un heterociclilo, que son como se han definido anteriormente,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R^0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido piridilo, pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo, pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -alquileno (C_0-C_2)-$C(O)-NR^{10}$, $-NR^{10}-C(O)-NR^{10}-$, $-NR^{10}-C(O)-$, $-SO_2-$, metileno o -alquileno (C_0-C_3)-C(O)-O-alquileno (C_0-C_2),

R^1 es un átomo de hidrógeno, -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13; -alquileno (C_1-C_3)-$C(O)-NH-R^0$, -alquileno (C_1-C_3)-C(O)-O-R15, -perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4), -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3), -alquileno (C_1-C_3)-$S(O)_2-N(R^{4'})-R^{5'}$, -alquileno (C_1-C_3)-O-alquilo (C_1-C_4), -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8), o -alquileno (C_0-C_3)-het, donde het es un resto seleccionado entre el grupo de azepina, azetidina, aziridina, azirina, 1,4-diazapano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diazirina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,2-oxatiepano, 1,2-oxatiolano, 1,4-oxazepano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-

triazol o 1,2,4-triazol, donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

$R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V forma un grupo cíclico de 4 a 8 miembros seleccionado entre el grupo de azepina, azetidina, 1,4-diazepano, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,4-oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, bromo, yodo, -OH, =O, alquilo (C_1-C_8), -alcoxi (C_1-C_4), -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-perfluoroalquilo (C_1-C_3), -alquil (C_0-C_8)-SO_2-N(R^{18})-R^{21}, -C(O)-NH-alquilo (C_1-C_8), -C(O)-N-[alquilo (C_1-C_8)]$_2$, -NR^{18}-C(O)-NH-alquilo (C_1-C_8), -C(O)-NH_2, -S-R^{18} o -NR^{18}-C(O)-NH-[alquilo (C_1-C_8)]$_2$,

donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o -alquilo (C_1-C_8).

V es 1) un resto het del grupo de 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol(1H-pirrolopiridina), azepina, azetidina, aziridina, azirina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diazirina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,2-oxa-tiepano, 1,2-oxatiolano, 1,4-oxazepano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, que es como se ha definido anteriormente y donde het está sin

sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

2) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

G es un enlace directo, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$ o $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6,

M es 1) un átomo de hidrógeno,

2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

3) $-C(O)-N(R11)-R12$,

4) $-(CH_2)_m-NR^{10}$,

5) fenilo o naftilo, donde el fenilo o el naftilo están sin sustituir o mono-, di- o trisustituidos, independientemente entre sí, con R14,

6) heterociclilo, donde el heterociclilo es un resto del grupo que puede derivarse de azepano, azepina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, isotiazol, isoxazol, isoxazolidina, 2-isoxazolina, cetomorfolina, cetopiperazina, morfolina, oxazol, [1,4]-oxazepano, piperazina, piperazinona, piperidina, piperidinona, pirazina, piridazina, piridazinona, piridina, piridona, pirimidina, pirrolidina, pirrolidinona, tetrahidropirano, 1,4,5,6-tetrahidro-piridazinilo, tetrazina, tetrazol, tiadiazol, tiazol, tiomorfolina, 1λ6-tiomorfolinilo, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

7) -cicloalquilo (C_3-C_8), donde dicho cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) $-CHF_2$,

7) -CN,

8) -alquileno (C_0-C_4)-heterociclilo (C_4-C_{16}), donde el heterociclilo es como se ha definido anteriormente y está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{12},

14) -alquileno (C_0-C_4)-N(R^{11})-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) -alquileno (C_0-C_4)-het, donde het es como se ha definido anteriormente y está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_8),

20) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

21) -alquileno (C_0-C_4)-arilo (C_6-C_{14}), donde el arilo es como se ha definido anteriormente y está mono-, di- o trisustituido independientemente entre sí con R13,

22) -alquileno (C_0-C_4)-cicloalquilo (C_3-C_8), donde el cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

23) -alquileno (C_0-C_3)-O-CH_2-CF_2-CH_2-O-alquilo (C_0-C_3),

24) -alquileno (C_0-C_3)-O-CH_2-CF_2-CF_2-CH_2-O-alquilo (C_0-C_3),

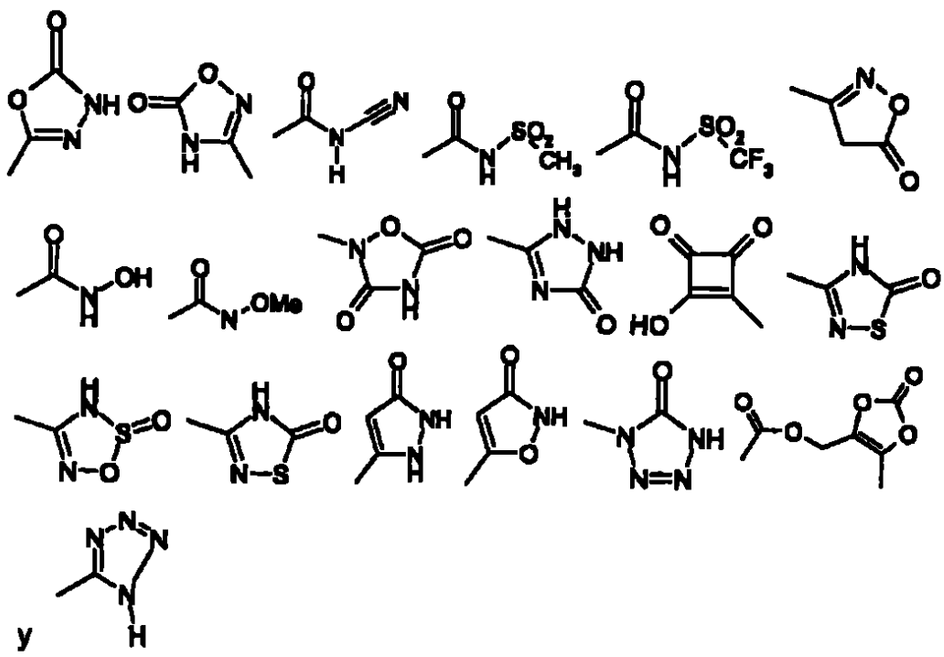
25) -alquileno (C_0-C_3)-O-CH_2-perfluoroalquileno (C_1-C_3)-CH_2-OH,

26) -SO_w-N(R^{11})-R^{13}, donde w es 1 ó 2,

27) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{13},

28) -alquileno (C_0-C_4)-N(R^{11})-R^{13}, o

29) un resto de la siguiente lista



y

donde Me es metilo,

si dos restos -OR19 están unidos a átomos adyacentes pueden formar junto con los átomos a los que están unidos un anillo 1,3-dioxol o un anillo 2,3-dihidro-[1,4]dioxina que está sustituido una, dos, tres o cuatro veces con R13,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_6), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

3) -alquil (C_0-C_6)-arilo (C_6-C_{14}), donde el arilo es como se ha definido anteriormente y donde el alquilo y el arilo están, independientemente entre sí, sin sustituir o mono-, di- o trisustituidos con R13,

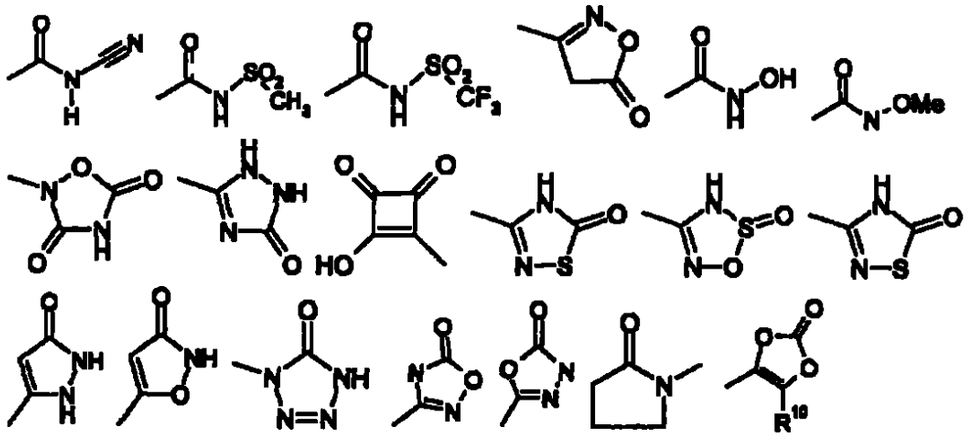
4) -O-R^{17}, o

5) -alquilo (C_0-C_6)-heterociclilo (C_4-C_{15}), donde el alquilo y el heterociclilo

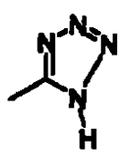
son como se han definido anteriormente y están, independientemente entre sí, sin sustituir o mono-, di- o trisustituidos con R13, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo seleccionado entre el grupo de azepina, azetidina, 1,4-diazepano, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]-oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, que está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, cloro, bromo, yodo, $-NO_2$, -CN, =O, -OH, $-CF_3$, $C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, -alquileno (C_0-C_3)-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, feniloxi-, $-O-CF_3$, -perfluoroalquilo (C_1-C_3), -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, o un resto de la siguiente lista



y



donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R10, y

R17 es -alquilo (C_1-C_8), -alquil (C_1-C_8)-OH, -alquil (C_1-C_8)-O-alquilo (C_1-C_8), -cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-O-alquil (C_1-C_8)-cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

4) La presente invención también se refiere a los compuestos de la fórmula I, en la que

R0 es 1) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo del grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y además está sustituido con un resto seleccionado entre el grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho resto está sin sustituir o mono-, di- o trisustituido

independientemente entre sí con R8

R8 es 1. F, Cl Br o I,

2. $-C(O)-NH_2$,

3. -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, -OH o un resto metoxi, o

4. -O-alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno o un resto metoxi, con la condición de que R8 sea al menos un halógeno, $-C(O)-NH_2$ o un resto -O-alquilo (C_1-C_6), si R0 es un arilo o un heterociclilo, que son como se han definido anteriormente,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_6), si R0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido, pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo, pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -C(O)-; $-SO_2-$, metileno, -alquileno (C_0-C_2)-C(O)-NR^{10}- o -alquileno (C_0-C_3)-C(O)-O-alquileno (C_0-C_2),

R^1 es un átomo de halógeno, -alquilo (C_1-C_2), -alquileno (C_1-C_3)-C(O)-NH-R0, -perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-C(O)-O-R^{15}, -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3) o -alquileno (C_1-C_3)-$S(O)_2$-$N(R^{4'})$-$R^{5'}$, donde $R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 7 miembros del grupo de azetidina, azetidinona, piperidina, piperazina, piridina, pirimidina, pirrolidina, pirrolidinona, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol, 1,2,4-triazol, tetrazina, tetrazol, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, azepina, cetopiperidina, 1,4-oxazepano, oxazol, isoxazol, isoxazolidina, 2-isoxazolina, morfolina, tiazol, isotiazol, tiadiazol o tiomorfolina, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, -OH, =O, -alquilo (C_1-C_6), -C(O)-OH, -CN, $-NH_2$, -C(O)-O-alquilo (C_1-C_4), -C(O)-NH-alquilo (C_1-C_6), -C(O)-N-[alquilo (C_1-C_6)]$_2$, $-C(O)-NH_2$ o -

$N(R^{18})$-R^{21}, donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o -alquilo (C_1-C_4),

V es 1. un resto cíclico del grupo que contiene compuestos que se derivan de 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol(1H-pirrolopiridina), aziridina, azirina, azetidina, azetidinona, 1,4-diazepano, pirrol, pirrolidina, piridonilo, imidazol, pirazol, 1,2,3-triazol, 1,2,4-triazol, tetrazol, piridina, pirimidina, pirazina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, tetrazina, tetrazol, azepina, diazirina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, piridazina, piperidina, piperazina, pirrolidinona, cetopiperazina, furano, pirano, dioxol, 1,4-oxazepano, oxazol, isoxazol, 2-isoxazolina, isoxazolidina, morfolina, oxirano, oxaziridina, 1,3-dioxoleno, 1,3-dioxolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxaziridina, tiofeno, tiopirano, tietano, tiazol, isotiazol, isotiazolina, isotiazolidina, 1,2-oxatiolano, tiodiazol, tiopirano, 1,2-tiazina, 1,3-tiazol, 1,3-tiazina, 1,4-tiazina, tiadiazina o tiomorfolina, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

2. fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

G es un enlace directo, -$(CH_2)_m$- o -$(CH_2)_m$-NR^{10}-,

m son los números enteros cero, 1, 2, 3 ó 4,

M es 1. un átomo de hidrógeno,

2. heterociclilo, donde el heterociclilo es un resto del grupo que puede derivarse de azepano, azepina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, isotiazol, isoxazol, isoxazolidina, 2-isoxazolina, cetomorfolina, cetopiperazina, morfolina, oxazol, [1,4]-oxazepano, piperazina, piperazinona, piperidina, piperidinona, pirazina, piridazina, piridazinona, piridina, piridona, pirimidina, pirrolidina, pirrolidinona, tetrahidropirano, 1,4,5,6-tetrahidro-piridazinilo, tetrazina, tetrazol, tiadiazol, tiazol, tiomorfolina, 1λ6-tiomorfolinilo, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

3. -alquilo (C_1-C_6), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

4. -cicloalquilo (C_3-C_6) o

5. -C(O)-$N(R^{11})$-R^{12},

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) CHF_2,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{12}$,

14) -alquileno (C_0-C_4)-$N(R^{11})-R^{12}$,

15) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

18) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

19) -alquileno (C_0-C_3)-O-CH_2-CF_2-CH_2-O-alquilo (C_0-C_3),

20) -alquileno (C_0-C_3)-O-CH_2-CF_2-CF_2-CH_2-O-alquilo (C_0-C_3),

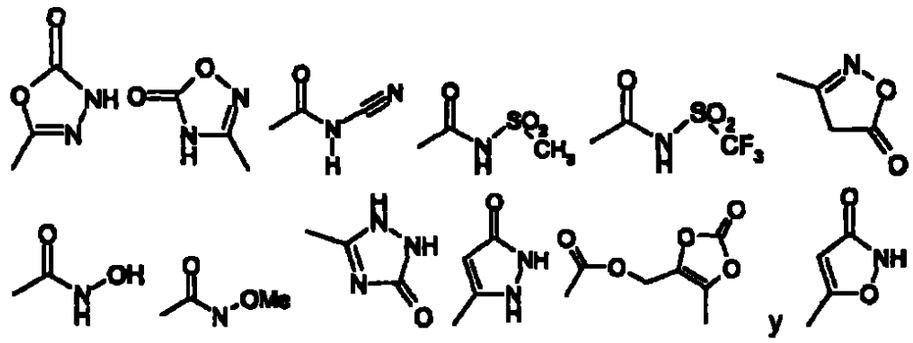
21) -alquileno (C_0-C_3)-O-CH_2-perfluoroalquilo (C_1-C_3)-CH_2-OH,

22) $-SO_w-N(R^{11})-R^{13}$, donde w es 1 ó 2,

23) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{13}$,

24) -alquileno (C_0-C_4)-$N(R^{11})-R^{13}$, o

25) un resto de la siguiente lista



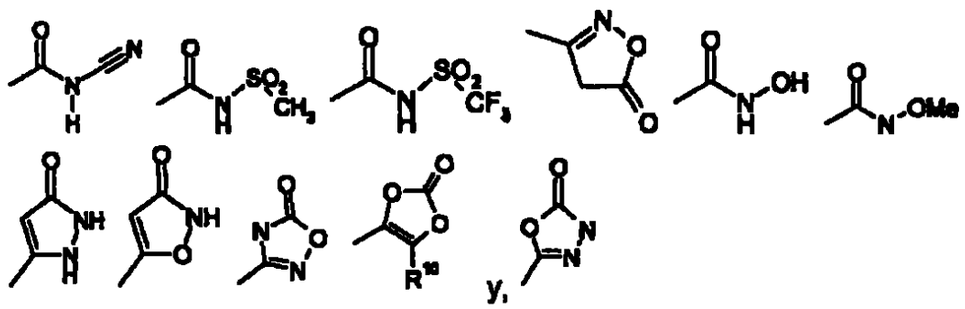
y

donde Me es metilo,

si dos restos -OR19 están unidos a átomos adyacentes pueden formar junto con los átomos a los que están unidos un anillo 1,3-dioxol o un anillo 2,3-dihidro-[1,4]dioxina, que está sustituido una, dos, tres o cuatro veces con R13,

R^{11} y R^{12} junto con el átomo de nitrógeno al que están unidos pueden formar un anillo seleccionado entre el grupo de azepina, azetidina, 1,4-diazepano, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]-oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho anillo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, cloro, $-NO_2$, -CN, =O, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, -alquileno (C_0-C_3)-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, -alquilo (C_1-C_6), -alcoxi (C_1-C_6), fenilo, feniloxi, $-O-CF_3$, -perfluoroalquilo (C_1-C_3), $-NH-C(O)-NH-R^{10}$, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -O-R15, $-NH-C(O)-O-R^{10}$, o un resto de la siguiente lista



y,

donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_6), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_6) o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10} y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH, -alquil (C_1-C_6)-O-alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-O-alquil (C_1-C_6)-cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-cicloalquilo (C_3-C_6), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquil (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

5) La presente invención también se refiere a los compuestos de fórmula I, en la que

R0 es 1. fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

2. un heterociclilo seleccionado entre el grupo de indolilo, isoindolilo, benzofuranilo, benzotiofenilo, 1,3-benzodioxolilo, indazolilo, bencimidazolilo, benzoxazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, cromanilo, isocromanilo, cinolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, piridilo, purinilo y pteridinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

3. un heterociclilo del grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y

además está sustituido con un resto seleccionado entre el grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho resto está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8

R8 es 1. F, Cl Br o I,

2. -C(O)-NH_2,

3. -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, -OH o un resto metoxi, o

4. -O-alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno o un resto metoxi,

con la condición de que R8 sea al menos un halógeno, -C(O)-NH_2 o un resto -O-alquilo (C_1-C_8), si R0 es un arilo o un heterociclilo, que son como se han definido anteriormente,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido, pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo, pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -C(O)-; -SO_2-, -C(O)-O-metileno, metileno o -alquileno (C_0-C_2)-C(O)-NR^{10},

R^1 es un átomo de hidrógeno o -alquilo (C_1-C_2),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 7 miembros del grupo de piperidina, piperazina, piridina, pirimidina, pirrolidina, pirrolidinona, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol, 1,2,4-triazol, tetrazina, tetrazol, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, azepina, cetopiperazina, oxazol, isoxazol, isoxazolidina, 2-isoxazolina, morfolina, tiazol, isotiazol, tiadiazol o tiomorfolina, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, -alquilo (C_1-C_4) o -NH_2,

V es 1. un resto cíclico del grupo que contiene compuestos que se derivan de 8-aza-biciclo[3.2.1]oct-3-ilo, azaindolil(1H-pirrolopiridilo), azetidina, azepina, aziridina, azirina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diazirina, 1,3-dioxolano, dioxazol, furano, imidazol, isoquinolina, isotiazol, isotiazolidina, isotiazolina, isoxazol, 2-isoxazolina, isoxazolidina, cetopiperazina, morfolina, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, 1,2-oxatiolano, piperidina, pirano, pirazina, pirazol, piridazina, piperazina, piridina, piridona, pirimidina, pirrol, pirrolidina, pirrolidinona, quinazolina, quinolina, tetrazina, tetrazol, tiadiazina, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tietano, tiomorfolina, tiofeno, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

2. fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

G es un enlace directo, $-(CH_2)_m-$ o $-(CH_2)_m-NR^{10}-$,

m son los números enteros cero, 1, 2, 3 ó 4,

M es 1. un átomo de hidrógeno,

2. heterociclilo, donde el heterociclilo es un resto del grupo que puede derivarse de 1,4-diazepano, cetomorfolina, tiofeno, piridazona, piperidina, piperazina, piridina, pirimidina, pirrolidina, pirrolidinona, piridonilo, imidazol, piridazina, pirazina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol, 1,2,4-triazol, tetrazina, tetrazol, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, azepina, cetopiperazina, oxazol, isoxazol, isoxazolidina, 2-isoxazolina, morfolina, tiazol, isotiazol, tetrahidropirano, 1,4,5,6-tetrahidro-pirazinilo, tiadiazol, 1λ6-tiomorfolinilo o tiomorfolina, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

3. -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

4. -cicloalquilo (C_3-C_8),

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido

independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) CHF_2,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{12}$,

14) -alquileno (C_0-C_4)-$N(R^{11})-R^{12}$,

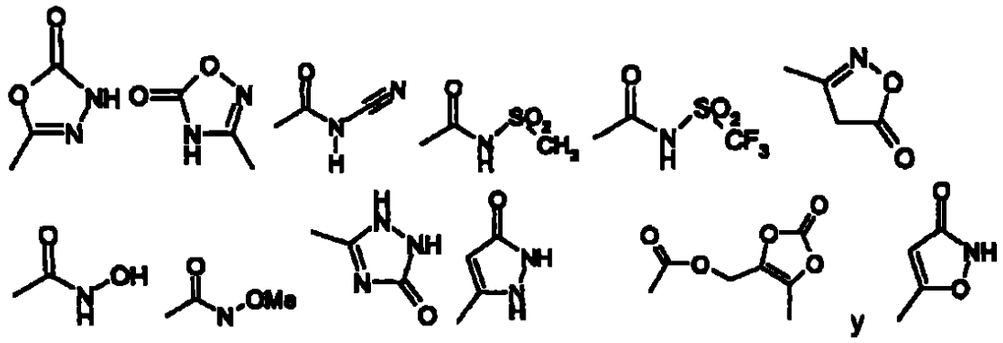
15) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

18) -C(O)-O-C(R15, R16)-O-C(O)-O-R17, o

19) un resto de la siguiente lista



y

donde Me es metilo,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o

trisustituido independientemente entre sí con R13,

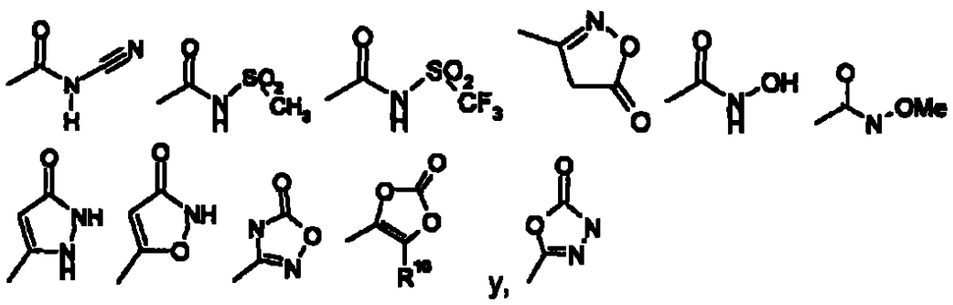
3) -alquil (C_0-C_6)-cicloalquilo (C_3-C_8),

4) -O-R^{17}, o

5) -alquil (C_0-C_6)-heterociclilo (C_4-C_{15}), donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13 y donde el heterociclilo se selecciona entre el grupo de azetidina, ciclopropilo, ciclobutilo, 4,5-dihidro-oxazol, imidazolidina, morfolina, (1,4)-oxazepano, oxazolidina, piperidina, piperazina, pirrolidina, tetrahidrotiofeno, tiazolidina o tiomorfolina, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico que se selecciona entre el grupo de azetidina, ciclopropilo, ciclobutilo, 4,5-dihidrooxazol, imidazolidina, morfolina, (1,4)-oxazepano, oxazolidina, piperidina, piperazina, pirrolidina, tetrahidrotiofeno, tiazolidina o tiomorfolina, donde dicho anillo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -cicloalquilo (C_3-C_8), -alquileno (C_0-C_3)-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -perfluoroalquilo (C_1-C_3) o un resto de la siguiente lista



y,

donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R^{15} y R^{16} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH, -alquil (C_1-C_6)-O-alquil (C_1-C_6)-cicloalquilo (C_3-C_8), -alquil (C_1-C_6)-O-alquilo (C_1-C_6) o -alquil (C_0-C_6)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

6) La presente invención también se refiere a los compuestos de la fórmula I, en la que

R0 es 1. fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R8,

2. piridilo o 1H-indazolilo, donde el piridilo y el 1H-indazolilo están sin sustituir o mono- o disustituidos independientemente entre sí con R8, o

3. un heterociclilo del grupo de tienilo, tiadiazolilo, isoxazolilo y tiazolilo, donde dicho heterociclilo está sustituido con un resto seleccionado entre el grupo de tienilo, 2-tienilo y 3-tienilo, donde dicho resto está sin sustituir o mono- o disustituido independientemente entre sí con R8,

R8 es F, Cl, Br, -O-CH_3 o -C(O)-NH_2,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R^0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido, pirrolilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo o pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -C(O)-; -SO_2-, -C(O)-O-metileno, -CH_2-C(O)-NH- o metileno,

R^1 es un átomo de hidrógeno,

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros del grupo de azetidina, pirrolidina, piperidina y piperazina,

R14 es flúor, cloro, metilo, etilo, =O, -SO_2-CH_3 o -NH_2,

V es 1. un resto del grupo que contiene los compuestos que se derivan de 8-aza-biciclo[3.2.1]oct-3-ilo, azaindolil(1H-pirrolopiridilo), azetidina, 1,4-diazepano, isoxazol, isoquinolina, piperazina, piperidina, pirazina, piridazina, pirimidina, pirrolidina, quinazolina, quinolina o tetrahidropirano, donde dicho resto cíclico está sin sustituir o mono- o disustituido independientemente entre sí con R14, o

2. fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R14,

G es un enlace directo, -$(CH_2)_m$, -C(O)- o -$(CH_2)_m$-NR^{10}-,

m son los números enteros cero, 1 ó 2,

M es un átomo de hidrógeno, alquilo (C_2-C_4), azepanilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, imidazolilo, cetomorfolinilo, morfolinilo, [1,4]Oxazepanilo, piperazinilo, piperidinilo, piperidonilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidilo, pirrolidinilo, 1λ6-tiomorfolinilo, 1,4,5,6-tetrahidro-piridazinilo o tetrahidropiranilo, donde los restos están sin sustituir o mono- o disustituidos independientemente entre sí con R14

R3 es 1) un átomo de hidrógeno,

2) flúor, cloro,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_2)-O-R19, donde R19 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) $-CHF_2$,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{12}$,

14) -alquileno (C_0-C_4)-$N(R^{11})-R^{12}$,

15) -alquileno (C_0-C_4)-C(O)-O-alquileno (C_2-C_4)-C(O)-alquilo (C_1-C_4),

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_8) o

18) -C(O)-O-C(R15, R16)-O-C(O)-O-R17, o

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

3) -alquil (C_0-C_6)-cicloalquilo (C_3-C_6),

4) -O-R^{17}, o

5) -alquil (C_0-C_6)-heterociclilo, donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos independientemente entre sí con R13 y donde el heterociclilo se selecciona entre el grupo de azetidina, imidazolidina, morfolina, (1,4)-oxazepano o pirrolidina o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo que se selecciona entre el grupo de azetidina, imidazolidina, morfolina, (1,4)-oxazepano, piperazina, piperidina, pirrolidina o tiomorfolina, donde dicho anillo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, -CN, =O, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -alquilo (C_1-C_3), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_3)-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -SO_2-NH o -perfluoroalquilo (C_1-C_3),

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R^{15} y R^{16} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH, -alquil (C_1-C_6)-O-alquil (C_1-C_6)-cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-O-alquilo (C_1-C_6) o -alquil (C_0-C_6)-cicloalquilo (C_3-C_6), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

7) La presente invención también se refiere a los compuestos de la fórmula I, en la que

R0 es 1. fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R8,

2. piridilo o 1H-indazolilo, donde el piridilo y el 1H-indazolilo están sin

sustituir o mono- o disustituidos independientemente entre sí con R8, o

3. un heterociclilo del grupo tiadiazolilo, isoxazolilo y tiazolilo, donde dicho heterociclilo está sustituido con un resto seleccionado entre el grupo de tienilo, 2-tienilo y 3-tienilo, donde dicho resto está sin sustituir o mono- o disustituido independientemente entre sí con R8,

R8 es Cl o -O-CH_3,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R^0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, tienilo o pirimidinilo, y está sustituido o sin sustituir 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es -CH_2-C(O)-NH- o metileno,

R^1 es un átomo de hidrógeno,

R^2 es un enlace directo,

R14 es flúor o =O,

V es piperidinilo o fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R14,

G es un enlace directo o -C(O)-

M es un átomo de hidrógeno, -alquilo (C_2-C_4), isopropilo, ciclopropilo, morfolinilo, piperazinilo, piperidinilo, pirazinilo, piridilo, pirimidilo, pirrolidinilo o 1λ6-tiomorfolinilo, donde los restos están sin sustituir o mono- o disustituidos independientemente entre sí con R14,

R3 es 1) un átomo de hidrógeno,

2) flúor, cloro,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -alquileno (C_0-C_2)-O-R19, donde R19 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) -CF_3,

5) -SO_2-R^{11},

6) -alquileno (C_0-C_4)-C(O)-O-R^{11},

7) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{12},

8) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_6) o

9) -C(O)-O-C(R15, R16)-O-C(O)-R17,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

3) -alquil (C_0-C_6)-cicloalquilo (C_3-C_6) o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo que se selecciona entre el grupo de azetidina, morfolina, (1,4)-oxazepano o piperidina, donde dicho anillo está sin sustituir o mono-, di- o trisustituido con R13,

R13 es flúor, =O, -OH, -CF_3, -C(O)-O-R^{10}, -alquilo (C_1-C_3), -cicloalquilo (C_3-C_6) o -alquileno (C_0-C_3)-O-R^{10},

R^{10} es un átomo de hidrógeno o -alquilo (C_1-C_4),

R^{15} y R^{16} son, independientemente entre sí, un átomo de hidrógeno o -alquilo (C_1-C_4), y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH o -alquil (C_0-C_4)-cicloalquilo (C_3-C_6),

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

8) La presente invención también se refiere a los compuestos de la fórmula I, que son

(1-Isopropil-piperidin-4-il)-amida del ácido 1[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(4-cloro-fenilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

(1-Pirimidin-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

éster metílico del ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]piridina-2-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofeno-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofeno-2-il)-isoxazol-3-

ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,
2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,4-dicarboxílico,
(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,
2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,4-dicarboxílico,
2-[(1-Isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,5-dicarboxílico,
(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(3-hidroxd-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,
1-Etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,
1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,
(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,
(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,
2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico,
2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico,
(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,
1-Etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,
1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,
[4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,
Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil)-H-benzoimidazol-4-carboxílico,
[4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-(3-metoxi-bencil)-1H-benzoimidazol-2-carboxílico,

[4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

(8-Metil-8-aza-biciclo[3.2.1]oct-3-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-oxazolidin-3-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-oxazolidin-3-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(4-Oxo-piperidin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(1,1-Dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(1,1-Dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-il]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-piperazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-piperazin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico,

Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(3-

hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,
2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico,
2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-3H-benzoimidazol-2,5-dicarboxílico,
2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico,
2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-metil-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-3H-benzoimidazol-2,5-dicarboxílico,
1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,
1-Ciclohexiloxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,
1-Etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,
1-Etoxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,
2-Hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,
2-Hidroxi-etil éster del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,
Carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,
Ácido 1-(3-metoxi-bencil)-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico,
(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,
(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,
Ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,
2-Metoxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,
(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-hidroximetil-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoximetil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(morfolina-4-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2,6-dimetil-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(4,4-difluoro-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico,

2-Hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

Ácido 2-(1-Isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-4-carboxílico,

Ácido 2-(1-Isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-4-carboxílico,

Ácido 1-[2-(4-cloro-fenil)(-etil]-2-1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 4-(3-hidroxi-azetidina-1-carbonil)-1-(3-metoxi-bencil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-1H-

benzoimidazol-5-carboxílico,

Éster metílico del ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 1-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

Ácido 1-(5-cloro-1H-indazol-3-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(4-hidroxi-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 7-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico,

Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 6-[(2-hidroxi-etil)-amida] del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-tieno[3,4-d]imidazol-2,6-dicarboxílico,

Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico,

Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-([1,4]oxazepano-4-carbonil)-3H-tieno[3,4-d]imidazol-2-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico,

Ácido 1-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-ilcarbamoil)-metil]-4-(2-etoxi-etoxi)(-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-hidroxi-etoxi)-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-

ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-trifluoroetoxi)-1H-benzoimidazol-4-carboxílico, o

(1-isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-2-carboxílico.

En general, el significado de cualquier grupo, resto, heteroátomo, número, etc., que puede aparecer más de una vez en los compuestos de la fórmula I, es *independiente del significado de este grupo, resto, heteroátomo, número, etc., en* cualquier otra aparición. Todos los grupos, restos, heteroátomos, números, etc. que pueden aparecer más de una vez en los compuestos de la fórmula I pueden ser iguales o diferentes.

Como se usa en este documento, el término alquilo se entiende en su sentido más amplio y hace referencia a restos de hidrocarburo que pueden ser lineales, por ejemplo, de cadena lineal o ramificada, y que pueden ser restos acíclicos o cíclicos o comprender cualquier combinación de subunidades acíclicas y cíclicas. Además, el término alquilo como se usa en este documento incluye expresamente grupos saturados así como grupos insaturados, conteniendo estos últimos grupos uno o más, por ejemplo uno, dos o tres dobles enlaces y/o triples enlaces, siempre que los dobles enlaces no estén localizados dentro de un grupo alquilo cíclico, de tal manera que se obtenga un sistema aromático. Todas estas afirmaciones también se aplican si un grupo alquilo aparece como un sustituyente sobre otro resto, por ejemplo en un resto alquiloxi, un resto alquiloxicarbonilo o un resto arilalquilo. Son ejemplos de "-alquilo (C_1-C_8)" o "-alquileno (C_1-C_8)" restos alquilo que contienen 1, 2, 3, 4, 5, 6, 7 u 8 átomos de carbono que son metilo, metileno, etilo, etileno, propilo, propileno, butilo, butileno, pentilo, pentileno, hexilo, heptilo u octilo, los n-isómeros de todos estos restos, isopropilo, isobutilo, 1-metilbutilo, isopentilo, neopentilo, 2,2-dimetilbutilo, 2-metilpentilo, 3-metilpentilo, isohexilo, sec-butilo, tBu, terc-pentilo, sec-butilo, terc-butilo o terc-pentilo. La expresión "alquilo (C_0-C_8)" o "-alquileno (C_0-C_8)" se refiere a restos de hidrocarburo que contienen 1, 2, 3, 4, 5, 6, 7 u 8 átomos de carbono. La expresión "-alquilo C_0" o "-alquileno C_0" es un enlace covalente. Son restos alquilo insaturados, por ejemplo, restos alquenilo tales como vinilo, 1-propenilo, 2-propenilo (= alilo), 2-

butenilo, 3-butenilo, 2-metil-2-butenilo, 3-metil-2-butenilo, 5-hexenilo o 1,3-pentadienilo, o restos alquinilo tales como etinilo, 1-propinilo, 2-propinilo (= propargilo) o 2-butinilo. Los restos alquilo también pueden ser insaturados cuando están sustituidos. Son ejemplos de restos alquilo cíclicos -cicloalquilo (C_3-C_8) restos cicloalquilo que contienen 3, 4, 5, 6, 7 u 8 átomos de carbono en el anillo, tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo o ciclooctilo, que también pueden estar sustituidos y/o insaturados. Los grupos alquilo cíclicos insaturados y los grupos cicloalquilo insaturados tales como, por ejemplo, ciclopentenilo o ciclohexenilo pueden unirse a través de cualquier átomo de carbono.

Se entiende que las expresiones "un arilo de 6 a 14 miembros monocíclico o bicíclico" o "-arilo (C_6-C_{14})" hacen referencia a radicales hidrocarburo aromáticos que contienen de 6 a 14 átomos de carbono en el anillo. Son ejemplos de radicales -arilo (C_6-C_{14}) fenilo, naftilo, por ejemplo 1-naftilo y 2-naftilo, bifenililo, por ejemplo 2-bifenililo, 3-bifenililo y 4-bifenililo, antrilo o fluorenilo. Son radicales arilo preferidos los radicales bifenililo, los radicales naftilo y, en particular, los radicales fenilo.

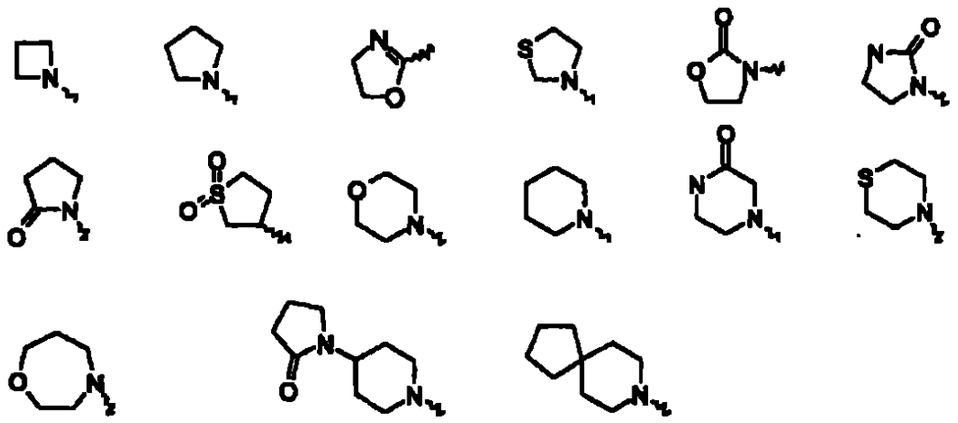
Las expresiones "heterociclilo de 4 a 15 miembros mono- o bicíclico" o "-heterociclilo (C_4-C_{15})" se refieren a heterociclos en los que uno o más de los de 4 a 15 átomos de carbono del anillo se han reemplazado por heteroátomos tales como nitrógeno, oxígeno o azufre.

Son ejemplos acridinilo, 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol (1H-pirrolopiridinilo), azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 3,3-dioxo[1.3.4]oxatiazinilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo (bencimidazolilo), isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, oxetanilo, oxocanilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo,

ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridinilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, tetrahidrofuranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, tiofenolilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,4-triazinilo, 1,3,5-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo.

Se prefieren heterociclilos tales como bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzotiazolilo, benzotiofenilo, benzoxazolilo, cromanilo, cinolinilo, 2-furilo, 3-furilo; imidazolilo, indolilo, indazolilo, isocromanilo, isoindolilo, isoquinolinilo, isotiazolilo, isoxazolilo, oxazolilo, ftalazinilo, pteridinilo, purinilo, pirazinilo, pirazolilo, piridazinilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, 2-piridilo, 3-piridilo, 4-piridilo, pirimidinilo, pirrolilo; 2-pirrolilo, 3-pirrolilo, quinolinilo, quinazolinilo, quinoxalinilo, tetrazolilo, tiazolilo, 2-tienilo y 3-tienilo.

También se prefieren:



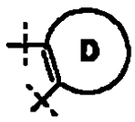
Las expresiones "het" o "un resto cíclico de 3 a 7 miembros, que contiene hasta 1, 2, 3 ó 4 heteroátomos" se refieren a estructuras de heterociclos que pueden derivar de compuestos tales como azepina, azetidina, aziridina, azirina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diazirina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina,

cetomorfolina, cetopiperazina, morfolina, 1,2-oxatiepano, 1,2-oxatiolano, 1,4-oxazepano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxetano, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidrofurano, tetrahidropirano, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol.

La expresión "R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros" o "R^{11} y R^{12} junto con el átomo de nitrógeno al que están unidos pueden formar un anillo heterocíclico monocíclico de 4 a 8 miembros que además del átomo de nitrógeno puede contener uno o dos heteroátomos en el anillo idénticos o diferentes seleccionados entre oxígeno, azufre y nitrógeno" se refiere a estructuras de heterociclos que pueden derivar de compuestos tales como azepano, azepina, azetidina, dioxazol, dioxazina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, 2,3-dihidroindol, imidazol, imidazolina, imidazolidina, indol, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol.

La expresión "R^{15} y R^{16} junto con el átomo de carbono al que están unidos pueden formar un anillo carbocíclico de 3 a 6 miembros" se refiere a estructuras que pueden derivar de compuestos tales como ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

La expresión "subestructura



en la fórmula I" o "la subestructura D es un grupo cíclico saturado, parcialmente insaturado o aromático de 4 a 8 miembros que contiene cero, 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno" se refiere a estructuras que pueden derivar de compuestos tales como azepano, azetidina, azetina, azocano, azocan-2-ona, ciclobutilo, ciclooctano, ciclooctено, ciclopentilo,

ciclohexilo, cicloheptilo, ciclooctilo, 1,2-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, [1,4]diazocano, [1,2]diazocan-3-ona, [1,3]diazocan-2-ona, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,4-oxazepano, 1,2-oxatiepano, 1,2-oxatiolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, [1,4]oxazocano, [1,3]oxazocan-2-ona, oxetano, oxocano, oxocan-2-ona, piperazina, piperidina, fenilo, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, 5,6,7,8-tetrahidro-1H-azocin-2-ona, tetrahidrofurano, tetrahidropirano, tetrahidropiridina, tetrazina, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tietano, tiocano, tiocano-1,1-dióxido, tiocano-1-óxido, tiocan-2-ona, tiomorfolina, tiofeno, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol.

La expresión "la subestructura D es un grupo cíclico saturado, parcialmente insaturado o aromático de 5 a 6 miembros que contiene cero, 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno" se refiere a estructuras que pueden derivar de compuestos tales como ciclopentilo, ciclohexilo, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetomorfolina, cetopiperazina, morfolina, 1,2-oxatiolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, piperazina, piperidina, fenilo, pirano, pirazina, pirazol, pirazolina, pirazolidina, pirazina, pirazinona, piridazina, piridazona, piridina, piridona, pirimidina, pirimidona, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidrofurano, tetrahidropirano, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tiomorfolina, tiofeno, tiopirano, tetrazina, tetrazol, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol.

La expresión "R^1 y R^3 junto con los átomos a los que están unidos pueden formar un grupo cíclico de 6 a 8 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno" se refiere a estructuras de heterociclos que pueden derivar de compuestos tales como azocano, azocan-2-ona, cicloheptilo, ciclohexilo, ciclooctano, ciclooctano, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, [1,4]diazocano, [1,2]diazocan-3-ona, [1,3]diazocan-2-ona, dioxazina, [1,4]dioxocano, dioxol, cetopiperazina, morfolina, 1,2-oxa-tiepano, 1,4-oxazepano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, [1,4]oxazocano, [1,3]oxazocan-2-ona, oxocano, oxocan-2-ona, fenilo, piperazina, piperidina, pirano,

pirazina, piridazina, pirimidina, 5,6,7,8-tetrahidro-1H-azocin-2-ona o tiomorfolina.

La expresión "resto oxo" o "=O" se refiere a restos tales como carbonilo (-C(O)-) o nitroso (-N=O).

El hecho de que muchos de los nombres de heterociclos indicados anteriormente sean los nombres químicos de sistemas de anillos insaturados o aromáticos no implica que el grupo mono- o policíclico de 4-15 miembros pueda derivar únicamente del sistema de anillos insaturados respectivo. Los nombres indicados en este documento sólo sirven para describir el sistema de anillos con respecto al tamaño del anillo y el número de los heteroátomos y sus posiciones relativas. Como se ha explicado anteriormente, el grupo mono- o policíclico de 4-15 miembros puede estar saturado o parcialmente insaturado o aromático y, de esta manera, puede derivar no sólo de los propios heterociclos indicados anteriormente, sino también de todos sus análogos parcial o completamente hidrogenados y también de sus análogos más insaturados si esto es aplicable. Como ejemplos de análogos completa o parcialmente hidrogenados de los heterociclos indicados anteriormente de los que puede derivar este grupo pueden mencionarse los siguientes: pirrolina, pirrolidina, tetrahidrofurano, tetrahidrotiofeno, dihidropiridina, tetrahidropiridina, piperidina, 1,3-dioxolano, 2-imidazolina, imidazolidina, 4,5-dihidro-1,3-oxazol, 1,3-oxazolidina, 4,5-dihidro-1,3-tiazol, 1,3-tiazolidina, perhidro-1,4-dioxano, piperazina, perhidro-1,4-oxazina (= morfolina), perhidro-1,4-tiazina (= tiomorfolina), perhidroazepina, indolina, isoindolina, 1,2,3,4-tetrahidroquinolina, 1,2,4-tetrahidroisoquinolina, etc.

La expresión "-perfluoroalquilo (C_1-C_3)" es un resto alquilo parcial o totalmente fluorado que puede derivar de restos tales como $-CF_3$, $-CHF_2$, $-CH_2F$, $-CHF-CF_3$, $-CHF-CHF_2$, $-CHF-CH_2F$, $-CH_2-CF_3$, $-CH_2-CHF_2$, $-CH_2-CH_2F$, $-CF_2-CF_3$, $-CF_2-CHF_2$, $-CF_2-CH_2F$, $-CH_2-CHF-CF_3$, $-CH_2-CHF-CHF_2$, $-CH_2-CHF-CH_2F$, $-CH_2-CH_2-CF_3$, $-CH_2-CH_2-CHF_2$, $-CH_2-CH_2-CH_2-F$, $-CH_2-CF_2-CF_3$, $-CH_2-CF_2-CHF_2$, $-CH_2-CF_2-CH_2F$, $-CHF-CHF-CF_3$, $-CHF-CHF-CHF_2$, $-CHF-CHF-CH_2F$, $-CHF-CH_2-CF_3$, $-CHF-CH_2-CHF_2$, $-CHF-CH_2-CH_2F$, $-CHF-CF_2-CF_3$, $-CHF-CF_2-CHF_2$, $-CHF-CF_2-CH_2F$, $-CF_2-CHF-CF_3$, $-CF_2-CHF-CHF_2$, $-CF_2-CHF-CH_2F$, $-CF_2-CH_2-CF_3$, $-CF_2-CH_2-CHF_2$, $-CF_2-CH_2-CH_2F$, $-CF_2-CF_2-CF_3$, $-CF_2-CF_2-CHF_2$ o $-CF_2-CF_2-CH_2F$.

La expresión "-perfluoroalquileno (C_1-C_3)" es un resto alquileno parcial o totalmente fluorado que puede derivar de restos tales como $-CF_2-$, -CHF-, $-CHF-CHF_2-$, -CHF-CHF-, $-CH_2-CF_2-$, $-CH_2-CHF-$, $-CF_2-CF_2-$, $-CF_2-CHF-$, $-CH_2-CHF-CF_2-$, $-CH_2-CHF-CHF-$, $-CH_2-CH_2-CF_2-$, $-CH_2-CH_2-CHF$, $-CH_2-CF_2-CF_2-$, CH_2-CF_2-CHF-, -CHF-

CHF-CF_2-, -CHF-CHF-CHF-, -CHF-CH_2-CF_2, -CHF-CH_2-CHF-, -CHF-CF_2-CF_2-, -CHF-CF_2-CHF-, -CF_2-CHF-CF_2-, -CF_2-CHF-CHF-, -CF_2-CH_2-CF_2, -CF_2-CH_2-CHF-, -CF_2-CF_2-CF_2- o -CF_2-CF_2-CHF.

Halógeno es flúor, cloro, bromo o yodo, preferiblemente flúor, cloro o bromo, de una forma particularmente preferida cloro o bromo.

Los átomos de carbono ópticamente activos presentes en los compuestos de la fórmula I pueden tener, independientemente entre sí, la configuración R o la configuración S. Los compuestos de la fórmula I pueden estar presentes en forma de enantiómeros puros o diastereómeros puros o en forma de mezclas de enantiómeros y/o diastereómeros, por ejemplo en forma de racematos. La presente invención se refiere a enantiómeros puros y a mezclas de enantiómeros así como a diastereómeros puros y a mezclas de diastereómeros. La invención comprende mezclas de dos o más de dos estereoisómeros de la fórmula I y comprende todas las relaciones de los estereoisómeros en las mezclas. En caso de que los compuestos de la fórmula I puedan estar presentes como isómeros E o isómeros Z (o isómeros cis o isómeros trans), la invención se refiere a los isómeros E puros, a los isómeros Z puros y a las mezclas E/Z en cualquier relación. La invención también comprende todas las formas tautoméricas de los compuestos de la fórmula I.

Los diastereómeros, incluyendo los isómeros E/Z, pueden separarse en los isómeros individuales, por ejemplo, por cromatografía. Los racematos pueden separarse en los dos enantiómeros por métodos habituales, por ejemplo por cromatografía en fases quirales o por resolución, por ejemplo, por cristalización de sales diastereoméricas obtenidas con ácidos o bases ópticamente activos. Los compuestos estereoquímicamente uniformes de la fórmula I también pueden obtenerse empleando materiales de partida estereoquímicamente uniformes o usando reacciones estereoselectivas.

Las sales fisiológicamente tolerables de los compuestos de fórmula I son sales no tóxicas que son fisiológicamente aceptables, en particular sales farmacéuticamente utilizables. Tales sales de compuestos de la fórmula I que contienen grupos ácidos, por ejemplo un grupo carboxilo COOH, son, por ejemplo, sales de metales alcalinos o sales de metales alcalinotérreos tales como sales de sodio, sales de potasio, sales de magnesio y sales de calcio, y también sales con iones amonio cuaternario fisiológicamente tolerables tales como tetrametilamonio o tetraetilamonio, y sales de adición de ácidos con amoniaco y aminas orgánicas fisiológicamente tolerables, tales como metilamina, dimetilamina, trimetilamina, etilamina, trietilamina, etanolamina o

tris-(2-hidroxietil)amina. Los grupos básicos contenidos en los compuestos de la fórmula I, por ejemplo grupos amino o grupos guanidino, forman sales de adición de ácidos, por ejemplo con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico o ácido fosfórico, o con ácidos carboxílicos y ácidos sulfónicos orgánicos tales como ácido fórmico, ácido acético, ácido oxálico, ácido cítrico, ácido láctico, ácido málico, ácido succínico, ácido malónico, ácido benzoico, ácido maleico, ácido fumárico, ácido tartárico, ácido metanosulfónico o ácido p-toluenosulfónico. Los compuestos de la fórmula I que contienen simultáneamente un grupo básico y un grupo ácido, por ejemplo un grupo guanidino y un grupo carboxilo, también pueden estar presentes como zwitteriones (betaínas) que de igual forma se incluyen en la presente invención.

Las sales de los compuestos de la fórmula I pueden obtenerse por métodos habituales conocidos por los especialistas en la técnica, por ejemplo combinando un compuesto de la fórmula I con un ácido o base inorgánica u orgánica en un disolvente o dispersante, o a partir de otras sales por intercambio catiónico o intercambio aniónico. La presente invención también incluye todas las sales de los compuestos de la fórmula I que, debido a su baja tolerancia fisiológica, no son directamente adecuadas para uso en productos farmacéuticos pero son adecuadas, por ejemplo, como intermedios para realizar modificaciones químicas adicionales de los compuestos de la fórmula I o como materiales de partida para la preparación de sales fisiológicamente tolerables.

La presente invención también incluye todos los solvatos de los compuestos de la fórmula I, por ejemplo hidratos o aductos con alcoholes.

La invención también incluye derivados y modificaciones de los compuestos de la fórmula I, por ejemplo profármacos, formas protegidas y otros derivados fisiológicamente tolerables, así como metabolitos activos de los compuestos de la fórmula I. La invención se refiere en particular a profármacos y a formas protegidas de los compuestos de la fórmula I, que pueden convertirse en compuestos de la fórmula I en condiciones fisiológicas. Los especialistas en la técnica conocerán profármacos adecuados para los compuestos de la fórmula I, es decir, derivados modificados químicamente de los compuestos de la fórmula I que tienen propiedades que están mejoradas de una manera deseada, por ejemplo con respecto a la solubilidad, biodisponibilidad o duración de la acción. Puede encontrarse una información más detallada en relación con los profármacos en la bibliografía convencional tal como, por ejemplo, Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Fleisher et al.,

Advanced Drug Delivery Reviews 19 (1996) 115-130; o H. Bundgaard, Drugs of the Future 16 (1991) 443 que se incorporan en este documento en su totalidad como referencia. Los profármacos adecuados para los compuestos de la fórmula I son especialmente profármacos de acilo y profármacos de carbamato de grupos que contienen nitrógeno aciables tales como grupos amino y el grupo guanidino y también profármacos de éster y profármacos de amida de grupos de ácido carboxílico que pueden estar presentes en los compuestos de la fórmula I. En los profármacos de acilo y los profármacos de carbamato, uno o más, por ejemplo uno o dos, átomos de hidrógeno en átomos de nitrógeno de tales grupos se han reemplazado por un grupo acilo o un carbamato, preferiblemente un grupo -alquiloxicarbonilo (C_1-C_8). Son grupos acilo y grupos carbamato adecuados para los profármacos de acilo y profármacos de carbamato, por ejemplo, los grupos R^{p1}-CO- y R^{p2}O-CO-, en los que R^{p1} es hidrógeno, -alquilo (C_1-C_{18}), -cicloalquilo (C_3-C_8), -cicloalquil (C_3-C_8)-alquilo (C_1-C_4), arilo (C_6-C_{14})-, Het-, aril (C_6-C_{14})-alquilo (C_1-C_4)- o Het-alquilo (C_1-C_4)-, y en los que R^{p2} tiene los significados indicados para R^{p1} con la excepción de hidrógeno.

Son compuestos especialmente preferidos de la fórmula I aquellos en los que dos o más restos se definen como se ha indicado anteriormente para los compuestos preferidos de la fórmula I, o restos que pueden tener una o más de las denotaciones específicas de los restos dadas en sus definiciones generales o en las definiciones de compuestos preferidos proporcionadas anteriormente. Todas las combinaciones posibles de definiciones dadas para definiciones preferidas y de denotaciones específicas de restos son explícitamente un objeto de la presente invención.

También con respecto a todos los compuestos preferidos de la fórmula I, todas sus formas estereoisoméricas y mezclas de los mismos en cualquier relación y sus sales fisiológicamente aceptables son explícitamente un objeto de la presente invención, así como sus profármacos. De forma similar, también en todos los compuestos preferidos de la fórmula I, todos los restos que están presentes más de una vez en la molécula son independientes entre sí y pueden ser idénticos o diferentes.

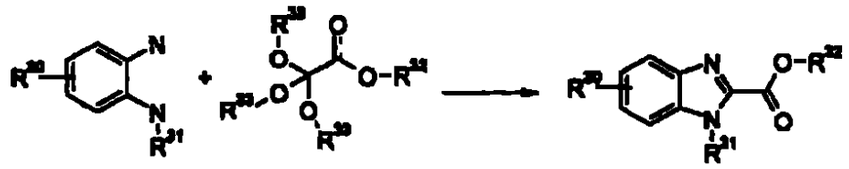
Los compuestos de la fórmula I pueden prepararse utilizando procedimientos y técnicas que per se son bien conocidas y apreciadas por un especialista habitual en la técnica. Los materiales de partida o los bloques de construcción para uso en los procedimientos de síntesis generales que pueden aplicarse en la preparación de los compuestos de fórmula I se pueden adquirir fácilmente por un especialista habitual en la técnica. En muchos casos, están disponibles en el mercado o se han descrito en la

bibliografía. En caso contrario, pueden prepararse a partir de compuestos precursores que se pueden adquirir fácilmente de forma análoga a los procedimientos descritos en la bibliografía, o mediante procedimientos o de forma análoga a los procedimientos descritos en esta solicitud.

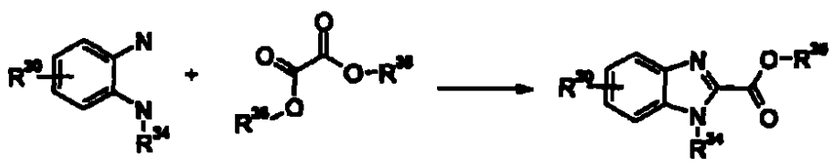
En general, los compuestos de la fórmula I pueden prepararse, por ejemplo, en el transcurso de una síntesis convergente, uniendo dos o más fragmentos que pueden derivar retrosintéticamente de la fórmula I. Más específicamente, en la preparación de los compuestos de fórmula I se emplean derivados de benzoimidazol de partida convenientemente sustituidos como bloques de construcción. Si no están disponibles en el mercado, tales derivados de benzoimidazol pueden prepararse de acuerdo con los procedimientos convencionales bien conocidos para la formación del sistema de anillos de benzoimidazol. Por medio de la selección de las moléculas precursoras adecuadas, estas síntesis de benzoimidazoles permiten la introducción de una diversidad de sustituyentes en las diversas posiciones del sistema de benzoimidazol, que pueden modificarse químicamente para llegar finalmente a la molécula de la fórmula I que tiene el modelo de sustituyentes deseado. Como una de las revisiones exhaustivas en la que pueden encontrarse numerosos detalles y referencias bibliográficas sobre la química del benzoimidazol y sobre los procedimientos sintéticos para su preparación, véase J. Backes, B. Heinz, W. G. Ried en Houben-Weyl, "Methoden de Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Alemania 1994, Vol. E8c Hetarene.

Si los derivados de benzoimidazol de partida no están disponibles en el mercado y tienen que sintetizarse, esto puede hacerse, por ejemplo, de acuerdo con las síntesis de benzoimidazol bien conocidas mencionadas anteriormente. A continuación se indican y mencionan procedimientos de particular interés para la realización de esta invención, sin embargo, son procedimientos convencionales discutidos de forma exhaustiva en la bibliografía, y son bien conocidos para un especialista en la técnica. Aunque no siempre se muestra explícitamente, en ciertos casos se producirán isómeros posicionales durante la síntesis de las reacciones mencionadas más adelante. Sin embargo, tales mezclas de isómeros posicionales pueden separarse por técnicas de separación modernas tales como, por ejemplo, HPLC preparativa.

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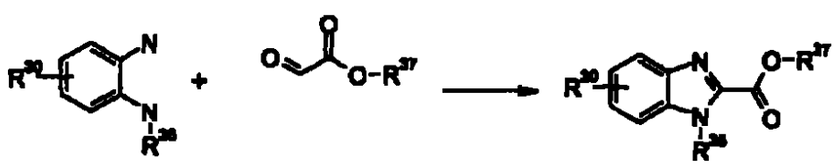
2) Reissert et al., Chem. Ber. 1905, 38, 93



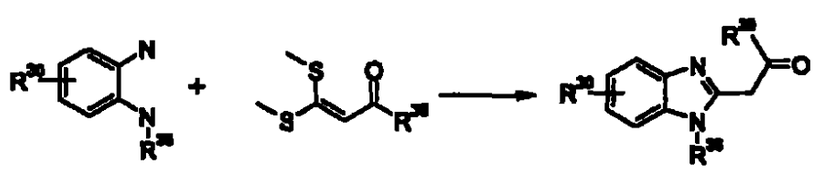
3) a) Usherwood et al., J. Chem. Soc. 1923, 123, 1082

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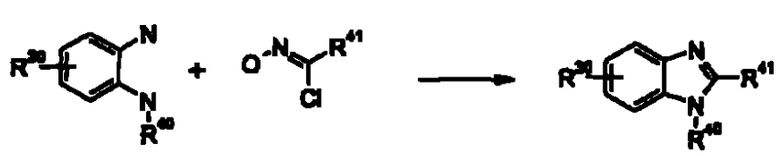
c) H. Yukawa et al., Bioorg. Med. Chem Lett. 1997, 10, 1267.



4) Z. -T. Huang et al., Tetrahedron 1992, 48, 2325.



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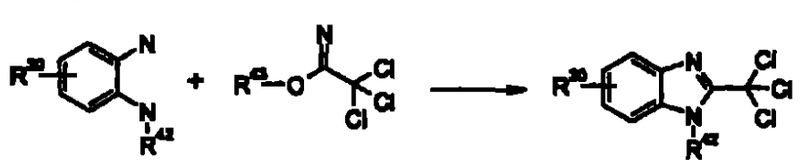
6) a) G. Holan et al., J. Chem. Soc. 1967, 20.

b) G. Crank et al., Aust. J. Chem. 1982, 35, 775,

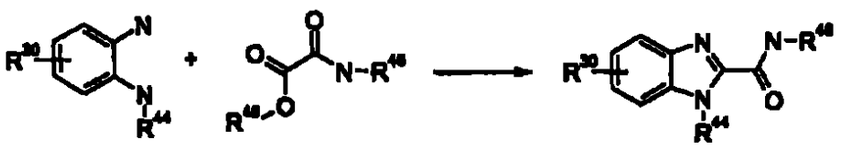
c) G. Dannhardt et al., Arch. Pharm. 2000, 333, 123.

d) P. Louvet et al., Eur. J. Med. Chem. 1993, 28, 71.

e) E. L. Samuel et al., J. Chem. Soc. C, 1967, 25.



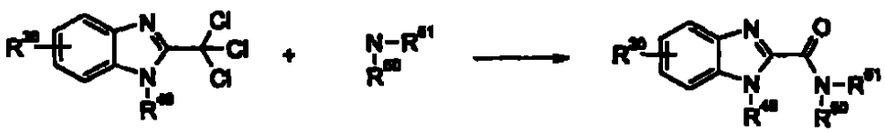
7) P. A. Petyunin et al., Khim. Geterosikl Soedin 19982, 5, 684.



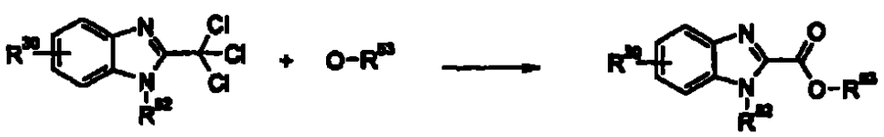
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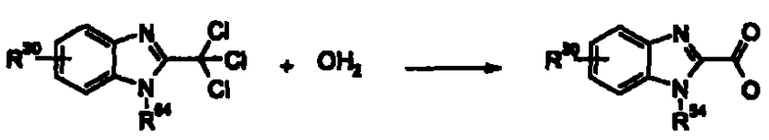
9) E. L. Samuel et al., J. Chem. Soc. C, 1967, 25.



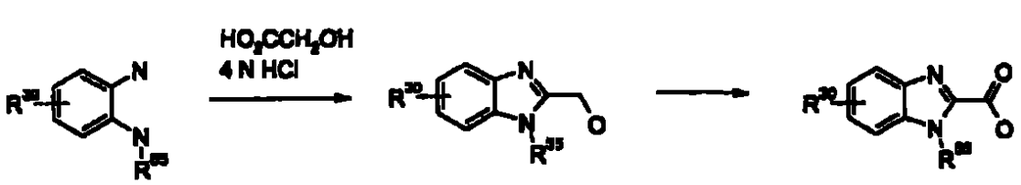
10) E. L Samuel et al., J. Chem. Soc. C, 1967, 25.



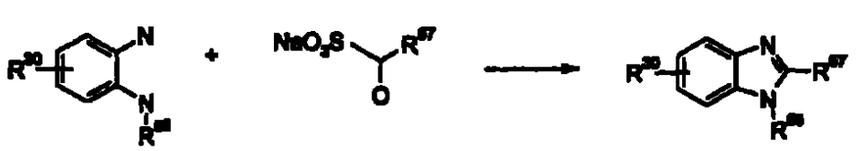
11) G. Dannhardt et al., Arch. Pharm. 2000, 333, 123.



12) A. Orjales et al., Eur. J. Med. Chem. 1999, 34, 415.

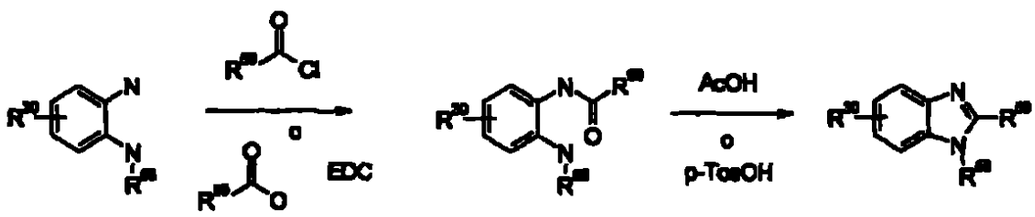


13) H. Göker et al., Arch. Pharm. Pharm. Med. Chem. 2001, 334, 148.

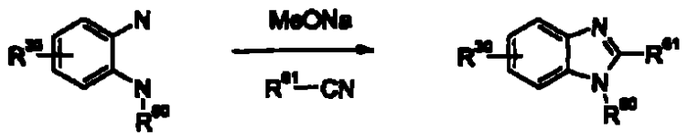


14) a) R. B. Baudy et al., J. Med. Chem. 2001, 44, 1516.

b) Y. K. Yun et al., Synlett 2002, Nº 5, 739.



15) N. Nabulsi, R. Gandour, J. Org. Chem. 1991, 56, 2260.



Dependiendo de los sustituyentes en los materiales de partida, en ciertas síntesis de benzoimidazol pueden obtenerse mezclas de isómeros posicionales que, sin embargo, pueden separarse por técnicas de separación modernas tales como, por ejemplo, HPLC preparativa.

Además, para obtener los sustituyentes deseados en el sistema de anillos de benzoimidazol en la fórmula I, los grupos funcionales introducidos en el sistema de anillos durante la síntesis de benzoimidazol pueden modificarse químicamente. Especialmente, los grupos presentes en el sistema de anillos de benzoimidazol pueden modificarse por una diversidad de reacciones y de esta manera pueden obtenerse los restos R^{30} deseados. Por ejemplo, un benzoimidazol que lleva un átomo de hidrógeno en la posición 2 también puede obtenerse por saponificación y posterior descarboxilación del benzoimidazol que lleva un grupo éster en la posición respectiva. Los grupos de ácido carboxílico y los grupos de ácido acético en la posición 2, posición 4, posición 5, posición 6 y posición 7 pueden convertirse en sus homólogos por reacciones habituales para alargar la cadena de los ácidos carboxílicos. Pueden introducirse átomos de halógeno, por ejemplo de acuerdo con procedimientos descritos en la bibliografía tales como el siguiente. Para la fluoración de benzoimidazoles, el reactivo elegido es triflato de N-fluoro-2,4,6-trimetilpiridinio (T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomita, J. Am. Chem. Soc. 1990, 112, 8563) pero no se limita a este reactivo. La cloración, bromación o yodación de benzoimidazoles puede realizarse por la reacción de los halógenos elementales o mediante el uso de NCS, NBS o NIS y muchos otros reactivos bien conocidos por los especialistas en la técnica. Estos procedimientos se mencionan por ejemplo en Y. Shi et al., Synth. Commun. 1993, 23, 2623; H. Rapoport

et al., Synthesis 1988, 767; R. Jones et al., J. Org. Chem. 1994, 64, 6575; J. Sessler et al., Chem. Eur. J. 2001, 7, 721. Dependiendo de las condiciones de reacción, los reactivos, la estequiometría y el patrón de sustitución, el halógeno se introduce en la posición 2 y/o en la posición 4 y/o en la posición 5 y/o en la posición 6 y/o en la posición 7. Por medio del intercambio selectivo de halógeno/metal o metalación por intercambio selectivo de hidrógeno/metal y la posterior reacción con una amplia serie de electrófilos pueden introducirse diversos sustituyentes en el núcleo heterocíclico. (R. Breslow et al., J. Am. Chem. Soc. 1983, 105, 5337; P. Knochel et al., J. Org. Chem. 2000, 65, 4618; S. Ohta et al., Chem. Pharm. Bull. 1996, 44, 1831).

Los halógenos o grupos hidroxi - a través del triflato o nonaflato - o las aminas primarias - a través de su sal de diazonio - o después de la interconversión en el correspondiente estannano, o ácido borónico - presente en la estructura de benzoimidazol, pueden convertirse en una diversidad de grupos funcionales distintos tales como por ejemplo -CN, $-CF_3$, $-C_2F_5$, éteres, ácidos, amidas, aminas, grupos alquilo o arilo por medio de metales de transición, particularmente catalizadores de paladio o níquel o sales de cobre y reactivos, por ejemplo, los mencionados más adelante (F. Diederich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; o M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1996; J. Hartwig, Angew. Chem. 1998, 110, 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 1999, 576, 15; T. Sakamoto, K. Ohsawa, J. Chem. Soc. Perkin Trans I, 1999, 2323; D. Nichols, S. Frescas, D. Marona-Lewicka, X. Huang, B. Roth, G. Gudelsky, J. Nash, J. Med. Chem, 1994, 37, 4347; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan., A. Combs, Tetrahedron Lett., 1998, 39, 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 1998, 39, 2933; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994; F. Qing et al. J. Chem. Soc. Perkin Trans. I 1997, 3053; S. Buchwald et al. J. Am. Chem Soc. 2001, 123, 7727; S. Kang et al. Synlett 2002, 3, 427; S. Buchwald et al. Organic Lett. 2002, 4, 581; T. Fuchikami et al. Tetrahedron Lett. 1991, 32, 91; Q. Chen et al. Tetrahedron Lett. 1991, 32, 7689).

Por ejemplo, los grupos nitro pueden reducirse a grupos amino con diversos agentes reductores tales como sulfuros, ditionitas, hidruros complejos o por hidrogenación catalítica. La reducción de un grupo nitro también puede realizarse en una etapa posterior de la síntesis de un compuesto de la fórmula I y la reducción de un grupo nitro a un grupo amino también puede realizarse simultáneamente con una reacción realizada sobre otro grupo funcional, por ejemplo cuando se hace reaccionar

un grupo tal como un grupo ciano con sulfuro de hidrógeno o cuando se hidrogena un grupo. Para introducir los restos R^{30}, los grupos amino después pueden modificarse de acuerdo con procedimientos convencionales para alquilación, por ejemplo por reducción con halogenuros de alquilo (sustituidos) o por aminación reductora de compuestos carbonílicos, de acuerdo con procedimientos de acilación convencionales, por ejemplo por reacción con derivados activados de ácido carboxílico tales como cloruros de ácido, anhídridos, ésteres activados u otros o por reacción con ácidos carboxílicos en presencia de un agente de activación, o de acuerdo con procedimientos convencionales para sulfonilación, por ejemplo por reacción con cloruros de sulfonilo.

Los grupos éster presentes en el núcleo de benzoimidazol pueden hidrolizarse a los ácidos carboxílicos correspondientes, que tras la activación pueden hacerse reaccionar con aminas o alcoholes en condiciones convencionales. Además, estos grupos éster o ácido pueden reducirse para dar los correspondientes alcoholes por muchos procedimientos convencionales. Los grupos éter presentes en el núcleo de benzoimidazol, por ejemplo grupos benciloxi u otros grupos éter fácilmente escindibles, pueden escindirse para dar grupos hidroxi que después pueden hacerse reaccionar con una diversidad de agentes, por ejemplo agentes de eterificación o agentes de activación que permiten reemplazar el grupo hidroxi por otros grupos. Los grupos que contienen azufre pueden hacerse reaccionar de forma análoga.

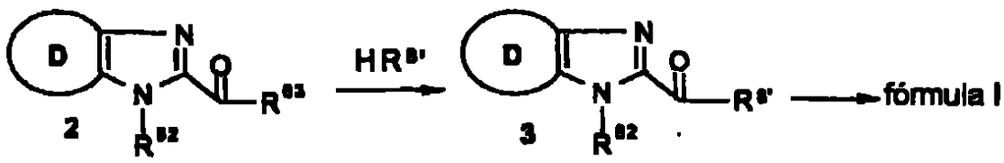
Durante el transcurso de la síntesis y con el fin de modificar los grupos R^{62} o $R^{6'}$ unidos al sistema de anillos de benzoimidazol mediante la aplicación de la metodología de síntesis paralela, también pueden ser extremadamente útiles una diversidad de reacciones catalizadas por paladio, níquel o cobre. Tales reacciones se describen, por ejemplo, en F. Diedrich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; o M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysis, Wiley, 1998; J. Hartwig, Angew. Chem. 1998, 110, 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 1999, 576, 125; P. Lam. C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan. A. Combs, Tetrahedron Lett. 1998, 39, 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 1998, 39, 2933; J. Wolfe, H. Tomori, J. Sadight, J. Yin, S. Buchwald, J. Org. Chem. 2000, 65, 1158; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994; S. Buchwald et al., J. Am. Chem Soc. 2001, 123, 7727; S. Kang et al., Synlett 2002, 3, 427; S. Buchwald et al., Org. Lett. 2002, 4, 581.

Las reacciones mencionadas anteriormente para la conversión de grupos

funcionales se describen además, en general, ampliamente en libros de texto de química orgánica tales como M. Smith, J. March, March's Advanced Organic Chemistry, Wiley-VCH, 2001 y en tratados tales como Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Alemania, o ("Organic Reactions", John Wiley & Sons, Nueva York, o R. C. Larock, "Comprehensive Organic Transformations", Wiley-VCH, 2ª ed (1999), B. Trost, I. Fleming (eds.) Comprehensive Organic Synthesis, Pergamon, 1991; A. Katritzky, C. Rees, E. Scriven, Comprehensive Heterocyclic Chemistry II, Elsevier Science, 1996), donde pueden encontrarse detalles sobre las reacciones y bibliografías de fuentes primarias. Debido al hecho de que en el presente caso los grupos funcionales están unidos a un anillo de benzoimidazol, en ciertos casos puede ser necesario adaptar de forma específica las condiciones de reacción o seleccionar reactivos específicos entre una diversidad de reactivos que pueden emplearse en principio en una reacción de conversión, o tomar medidas específicas de otra forma para conseguir una conversión deseada, por ejemplo usar técnicas de grupos de protección. Sin embargo, el descubrimiento de las variantes de reacción y de las condiciones de reacción adecuadas en tales casos no supone ningún problema para un especialista en la técnica.

Los elementos estructurales presentes en los restos en la posición 1 del anillo de benzoimidazol en los compuestos de la fórmula I y en el grupo $COR^{6'}$ presente en la posición 2 del anillo de benzoimidazol pueden introducirse en el derivado de benzoimidazol de partida que se puede obtener como se ha indicado anteriormente mediante etapas de reacción consecutivas usando metodologías de síntesis paralela como las descritas más adelante usando procedimientos que per se son bien conocidos para un especialista en la técnica.

Los restos $R^{6'}$ que pueden introducirse en la fórmula 2, por ejemplo, condensando un ácido carboxílico correspondiente de la fórmula 2 con un compuesto de la fórmula $HR^{6'}$, es decir, con una amina de la fórmula $HN(R^{1'})R^{2'}$-V-G-M para dar un compuesto de la fórmula 3. El compuesto de la fórmula 3 obtenido de esta manera puede contener ya los grupos finales deseados, es decir, los grupos $R^{6'}$ y R^{62} pueden ser los grupos $-N(R^1)-R^2$-V-G-M y R^0-Q- como se han definido en la fórmula I, u opcionalmente, en el compuesto de la fórmula 3 obtenido de esta manera posteriormente el resto o los restos $R^{6'}$ y el resto R^{62} se convierten en los restos $-N(R^1)-R^2$-V-G-M y R^0-Q-, respectivamente, para dar el compuesto deseado de la fórmula I.



De esta manera, los restos $R^{8'}$ y los restos $R^{1'}$ y $R^{2'}$-V-G-M contenidos en este documento pueden tener las denotaciones de R^1 y R^2-V-G-M, respectivamente, proporcionadas anteriormente o, además, en los restos los grupos funcionales $R^{1'}$ y $R^{2'}$-V-G-M también pueden estar presentes en forma de grupos que posteriormente pueden transformarse en los grupos finales R^1 y R^2-V-G-M, es decir, pueden estar presentes grupos funcionales en forma de grupos precursores o de derivados, por ejemplo en forma protegida. En el transcurso de la preparación de los compuestos de la fórmula I, generalmente puede ser ventajoso o necesario introducir grupos funcionales que reduzcan o prevengan reacciones indeseadas o reacciones secundarias en la etapa de síntesis respectiva, en forma de grupos precursores que posteriormente se convierten en los grupos funcionales deseados, o bloquear temporalmente grupos funcionales por una estrategia de grupos protectores adecuada para el problema de la síntesis. Tales estrategias se conocen bien por los especialistas en la técnica (véase, por ejemplo, Greene y Wuts, Protective Groups in Organic Synthesis, Wiley, 1991, o P. Kocienski, Protecting Groups, Thieme 1994). Son ejemplos de grupos precursores grupos ciano y grupos nitro. El grupo ciano puede transformarse en una etapa posterior en derivados de ácido carboxílico o por reducción en grupos aminometilo, o los grupos nitro pueden transformarse por reducción, tal como hidrogenación catalítica, en grupos amino. Los grupos protectores también pueden tener el significado de una fase sólida, y la escisión de la fase sólida significa la retirada del grupo protector.

El uso de tales técnicas se conoce por los especialistas en la técnica (Burgess K (Ed.) Solid Phase Organic Synthesis, Nueva York, Wiley, 2000). Por ejemplo, un grupo hidroxi fenólico puede unirse a una resina de tritil-poliestireno, que sirve como grupo protector, y la molécula se escinde de esta resina por tratamiento con TFA en una etapa posterior de la síntesis.

El resto R^{82} en los compuestos de las fórmulas 2 y 3 puede denotar el grupo -Q-R^0 como se ha definido anteriormente, que finalmente estará presente en la molécula diana deseada de la fórmula I, o puede denotar un grupo que posteriormente puede transformarse en el grupo -Q-R^0, por ejemplo un grupo precursor o un derivado del grupo -Q-R^0 en el que los grupos funcionales están presentes en forma protegida,

o R^{62} puede denotar un átomo de hidrógeno o un grupo protector para el átomo de nitrógeno del anillo de benzoimidazol. De forma similar, los restos R^{30} tienen las correspondientes definiciones de R^3 en la fórmula I como se ha definido anteriormente, sin embargo, para la síntesis de los compuestos de la fórmula I, estos restos, además, pueden estar presentes en principio en la etapa de la condensación de un compuesto de la fórmula 2 con un compuesto de la fórmula $HR^{8'}$ dando un compuesto de la fórmula 3 en forma de grupos precursores o en forma protegida.

Los restos R^{63} en los compuestos de la fórmula 2, que pueden ser idénticos o diferentes, pueden ser, por ejemplo, hidroxi o alcoxi (C_1-C_4), es decir, los grupos COR^{63} presentes en los compuestos de la fórmula 2 pueden ser, por ejemplo, los ácidos carboxílicos libres o ésteres de los mismos tales como alquil ésteres que pueden ser los grupos $COR^{8'}$ en los compuestos de la fórmula I. Los grupos COR^{63} también pueden ser cualquier otro derivado activado de un ácido carboxílico que permita la formación de amida, formación de éster o formación de tioéster con un compuesto de la fórmula $HR^{8'}$. El grupo COR^{63} puede ser, por ejemplo, un cloruro de ácido, un éster activado tal como un fenil éster sustituido, una azolida tal como una imidazolida, una azida o un anhídrido mixto, por ejemplo un anhídrido mixto con un éster de ácido carbónico o con un ácido sulfónico, pudiendo prepararse todos estos derivados a partir del ácido carboxílico por procedimientos convencionales y pudiendo hacerse reaccionar con una amina, un alcohol o un mercaptano de la fórmula $HR^{8'}$ en condiciones convencionales. Un grupo de ácido carboxílico COOH que representa COR^{63} en un compuesto de la fórmula 2 puede obtenerse, por ejemplo, a partir de un grupo éster introducido en el sistema de benzoimidazol durante una síntesis de benzoimidazol por procedimientos de hidrólisis convencionales.

También pueden prepararse compuestos de la fórmula I en la que un grupo $COR^{8'}$ es un grupo éster a partir de compuestos de la fórmula 2 en la que COR^{63} es un grupo de ácido carboxílico por reacciones de esterificación comunes tales como, por ejemplo, la reacción del ácido con un alcohol en catálisis ácida, o alquilación de una sal del ácido carboxílico con un electrófilo tal como un halogenuro de alquilo, o por transesterificación a partir de otro éster. Los compuestos de la fórmula I en la que un grupo $COR^{8'}$ es un grupo amida pueden prepararse a partir de aminas y compuestos de la fórmula 2 en la que COR^{63} es un grupo de ácido carboxílico o un éster del mismo por reacciones de aminación comunes. Especialmente para la preparación de amidas, los compuestos de la fórmula 2 en la que COR^{63} es un grupo de ácido carboxílico pueden condensarse en condiciones convencionales con compuestos de la fórmula

$HR^{6'}$ que son aminas por medio de reactivos de acoplamiento comunes usados en la síntesis de péptidos. Tales reactivos de acoplamiento son, por ejemplo, carbodiimidas tales como diciclohexilcarbodiimida (DCC) o diisopropilcarbodiimida, carbonildiazoles tales como carbonildiimidazol (CDI) y reactivos similares, anhídrido propilfosfónico, tetrafluoroborato de O-((ciano-(etoxicarbonil)-metileno)amino)-N,N,N',N'-tetrametiluronio (TOTU), cianuro de dietilfosforilo (DEPC) o cloruro de bis-(2-oxo-3-oxazolidinil)-fosforilo (BOP-Cl) y muchos otros.

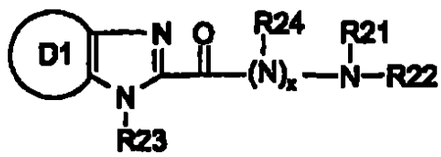
Si el resto $-Q-R^0$ presente en un benzoimidazol de la fórmula I o el resto R^{63} presente en un benzoimidazol de la fórmula 2, o un resto en el que los grupos funcionales dentro del resto $-Q-R^0$ o R^{63} están presentes en forma protegida o en forma de un grupo precursor, aún no se ha introducido durante una etapa precedente, por ejemplo durante una síntesis del núcleo de benzoimidazol, estos restos pueden introducirse, por ejemplo, en la posición 1 del sistema de benzoimidazol mediante procedimientos bibliográficos convencionales bien conocidos para un especialista en la técnica para N-alquilación, aminación reductora, N-arilación, N-acilación o N-sulfonilación de átomos de nitrógeno del anillo de heterociclos. El derivado de benzoimidazol de partida a emplear en tal reacción lleva un átomo de hidrógeno en la posición 1. La N-alquilación de un átomo de nitrógeno del anillo puede realizarse, por ejemplo, en condiciones convencionales, preferiblemente en presencia de una base tal como K_2CO_3, Cs_2CO_3, NaH o KO^tBu, usando un compuesto de alquilación de la fórmula $LG-Q-R^0$ o de la fórmula $R^{62}-LG$, donde el átomo del grupo Q o del grupo R^{62} unido al grupo LG en este caso es un átomo de carbono alifático de un resto alquilo y LG es un grupo saliente, por ejemplo halógeno, tal como cloro, bromo o yodo, o un grupo sulfoniloxi tal como tosiloxi, mesiloxi o trifluorometilsulfoniloxi. LG también puede ser, por ejemplo, un grupo hidroxi que, para conseguir la reacción de alquilación, se activa por un reactivo de activación convencional. Para la preparación de compuestos en los que A es un enlace directo y un grupo aromático está unido directamente a la posición 1 del sistema de benzoimidazol, pueden usarse procedimientos de arilación convencionales. Por ejemplo, como agentes de arilación pueden emplearse fluoruros de arilo tales como fluorobenzoatos de alquilo o 4-fluorofenil metil sulfonas. Tales procesos se describen, por ejemplo, por M. Yamada et al. J. Med. Chem. 1996, 39, 596; J. Ohmori et al. J. Med. Chem. 1996, 39, 3971. Como alternativa, una gran diversidad de yoduros de arilo sustituidos, bromuros de arilo o triflatos de arilo pueden servir como agentes de arilación en la posición 1 del nitrógeno heterocíclico en una reacción mediada por sal de cobre o por paladio de acuerdo, por ejemplo, con P.

Cozzi et al. Farmaco 1987, 42, 205; P. Unangst, D. Connor, R. Stabler, R. Weikert, J. Heterocycl. Chem. 1987, 24, 811; G. Tokmakov, I. Grandberg, Tetrahedron 1995, 51, 2091; D. Old, M. Harris, S. Buchwald, Org. Lett. 2000, 2, 1403, G. Mann, J. Hartwig, M. Driver, C. Fernandez-Rivas, J. Am. Chem. Soc. 1998, 120, 827; J. Hartwig, M. Kawatsura, S. Hauk, K. Shaughnessy, L. J. Org. Chem. 1999, 64, 5575; S. Buchwald, et al., J. Am. Chem. Soc. 2001, 123, 7727. Además, tales arilaciones también pueden realizarse por reacción de una amplia serie de ácidos aril borónicos sustituidos como se demuestra, por ejemplo, por W. Mederski, M. Lefort, M. Germann, D. Kux, Tetrahedron 1999, 55, 12757; J. Collman et al., J. Org. Chem. 2001, 66, 7892. Durante las transformaciones mencionadas anteriormente pueden existir isómeros posicionales, sin embargo, estas mezclas de isómeros posicionales pueden separarse por técnicas de separación modernas tales como, por ejemplo, HPLC preparativa.

La invención también se refiere a un proceso para preparar un compuesto de la fórmula IV.

En el documento DE 3708292 se describe un proceso para la preparación de derivados de benzoimidazol-anilida. Dichos compuestos se prepararon en condiciones ácidas fuertes y con rendimientos de aproximadamente 50%. También se describen procedimientos similares en el documento DE 4304650 o en el Journal of Medicinal Chemistry (1984, vol. 27, Nº 2, páginas 121-125), donde los compuestos se prepararon en presencia de bicarbonato sódico. Estas condiciones dieron los productos sólo con bajos rendimientos. Otro objeto de la presente invención es encontrar un proceso para la aminación de los compuestos de la fórmula V con altos rendimientos y pureza.

Por lo tanto, la invención se refiere a un proceso para producir el compuesto de fórmula IV,



(IV)

en la que

x es el número entero cero o 1,

R21 y R24 son idénticos o diferentes y son, independientemente entre sí

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13,

c) -alquileno (C_1-C_3)-C(O)-NH-R^0,

d) -alquileno (C_1-C_3)-C(O)-O-R^{10},

e) -alquil (C_0-C_4)-arilo, donde el arilo es un arilo de 6 a 14 miembros monocíclico o bicíclico y está mono-, di- o trisustituido independientemente entre sí con R8,

f) -alquil (C_0-C_4)-heteroarilo, donde el heteroarilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está mono-, di- o trisustituido independientemente entre sí con R8,

g) -alquil (C_1-C_4)-heterociclilo, donde el heterociclilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y que está adicionalmente sustituido con un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

h) -perfluoroalquileno (C_1-C_3),

i) -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4),

j) -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3),

k) -alquileno (C_1-C_3)-$S(O)_2$-N($R^{4'}$)-$R^{8'}$,

l) -alquileno (C_1-C_3)-O-alquilo (C_1-C_4),

m) -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8) o

n) -alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

donde R^0, $R^{4'}$, $R^{8'}$, R8, R^{10}, R^{13} y R^{14} son como se han definido en la fórmula I,

R22 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13,

c) -alquileno (C_1-C_3)-C(O)-NH-R^0,

d) -alquileno (C_1-C_3)-C(O)-O-R^{10},

e) -alquil (C_0-C_4)-arilo, donde el arilo es un arilo de 6 a 14 miembros monocíclico o bicíclico y está mono-, di- o trisustituido independientemente entre sí con R8,

f) -alquil (C_0-C_4)-heteroarilo, donde el heteroarilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está mono-, di- o trisustituido independientemente entre sí con R8,

g) -alquil (C_1-C_4)-heterociclilo, donde el heterociclilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y que está adicionalmente sustituido con un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

h) -perfluoroalquileno (C_1-C_3),

i) -alquileno (C_0-C_3)-S(O)-alquilo (C_1-C_4),

j) -alquileno (C_0-C_3)-$S(O)_2$-alquilo (C_1-C_3),

k) -alquileno (C_0-C_3)-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

l) -alquileno (C_1-C_3)-O-alquilo (C_1-C_4),

m) -alquileno (C_0-C_3)-cicloalquilo (C_3-C_5),

n) -alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

o) R^2-V-G-M,

donde R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, $R14^4$, V, G y M son como se han definido en la fórmula I, o la subestructura R21-N-R^2-V en la fórmula IV puede formar un grupo cíclico de 4 a 8 miembros que contiene 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, donde el resto R14 es como se ha definido en la fórmula I,

R23 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13,

c) -alquileno (C_1-C_3)-C(O)-NH-R^0,

d) -alquileno (C_1-C_3)-C(O)-O-R^{10},

e) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

f) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno,

g) -perfluoroalquileno (C_1-C_3),

h) -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4),

j) -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3),

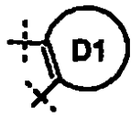
k) -alquileno (C_1-C_3)-$S(O)_2$-N($R^{4'}$)-$R^{5'}$,

l) -alquileno (C_1-C_3)-O-alquilo (C_1-C_4),

m) -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8),

n) -alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

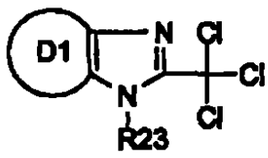
o) -Q-R^0,

donde R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, R14, Q, V, G y M son como se han definido en la fórmula I, y la subestructura 

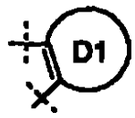
en la fórmula IV es

un grupo cíclico saturado, parcialmente insaturado o aromático de 4 a 8 miembros que contiene cero, 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está sin sustituir o sustituido 1, 2, 3, 4, 5 ó 6 veces con R3, donde R3 es como se ha definido en la fórmula I,

que comprende hacer reaccionar un compuesto de la fórmula V



(V)



en la que R23 es como se ha definido en la fórmula IV y la subestructura

en la fórmula V es como se ha definido en la fórmula IV,

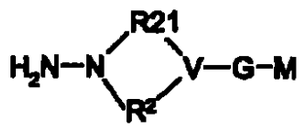
con una amina primaria o con una amina secundaria en presencia de agua, al menos una base y al menos un disolvente orgánico miscible con agua.

Otro objeto de la presente invención es un proceso para la preparación de un compuesto de la fórmula IV, donde la amina primaria es

a) NH_2-R21, donde R21 es como se ha definido en la fórmula IV,

b) NH_2-R^2-V-G-M, donde R^2, V, G y M son como se han definido en la fórmula IV,

c) -NH_2-N(R21)-R22, donde R21 y R22 son como se han definido en la fórmula IV o

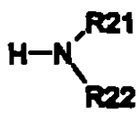


(VI)

d) un compuesto de fórmula VI

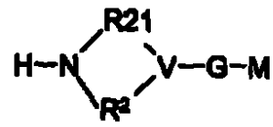
en la que R^2, R21, V, G y M son como se han definido en la fórmula IV.

Otro objeto de la presente invención es un proceso para la preparación de un compuesto de fórmula IV, donde la amina secundaria es



a)

donde R21 y R22 son como se han definido en la fórmula IV,



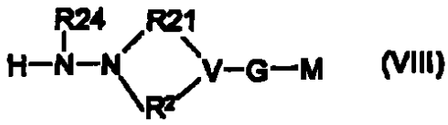
(VII)

b) un compuesto de la fórmula VII

en la que R21, R^2, V, G y M son como se han definido en la fórmula IV,

o

c) un compuesto de fórmula VIII



(VIII)

en la que R^2, R21, R24, V, G y M son como se han definido en la fórmula IV.

Introduciendo una amina primaria o secundaria en una mezcla de agua y un disolvente orgánico miscible en agua comienza la preparación del compuesto de la fórmula IV. Después se añade una base, particularmente bicarbonato sódico, y la solución o suspensión resultante se agita o remueve a temperatura ambiente. Finalmente se añade el compuesto de la fórmula V en forma sólida o disuelto en un disolvente orgánico apropiado. Después, la mezcla de reacción resultante se agita o remueve a temperatura controlada. Después de un tiempo de reacción apropiado, el compuesto de la fórmula IV se aísla por precipitación, por ejemplo, retirando el disolvente orgánico por evaporación. Como alternativa, el compuesto de la fórmula IV puede extraerse usando un disolvente orgánico tal como diclorometano, acetato de etilo, tolueno, terc-butil metil éter o éter dietílico.

La expresión "disolvente orgánico miscible en agua" se utiliza para hacer referencia, por ejemplo, a disolventes orgánicos tales como:

Tetrahidrofurano, acetonitrilo, dimetilsulfóxido, dioxano, 1,2-dimetoxietano, N,N-dimetilformamida, N-metilpirrolidona, acetona o sulfolano.

El término "base" se utiliza para hacer referencia a carbonatos de metales alcalinos, por ejemplo bicarbonato sódico o bicarbonato potásico, en forma sólida o en forma de soluciones de diferentes concentraciones. Básicamente todas las sales inorgánicas, particularmente los bicarbonatos, que tienen una basicidad comparable a la del bicarbonato sódico, pueden usarse para el proceso descrito anteriormente. Además, el término "base" se utiliza para hacer referencia a aminas terciarias, tales como trietilamina o diisopropiletilamina.

La expresión "amina primaria" se utiliza para hacer referencia a una amina, que está sustituida con un resto en el átomo de nitrógeno. La expresión "amina secundaria" se utiliza para hacer referencia a una amina que está sustituida con dos restos en el átomo de nitrógeno.

El término  donde x es cero" en la fórmula IV es un enlace covalente y cuando x es 1 es un resto -N(R24)-.

Preferiblemente, para la reacción de la invención, se usan de 2 moles a 12 moles de una base por 1 mol del compuesto de la fórmula V.

Preferiblemente, para la reacción de la invención, se usan de 1 mol a 1,5 moles de una amina primaria o de una amina secundaria por 1 mol del compuesto de la fórmula V.

La cantidad de disolvente orgánico miscible con agua usada generalmente es de 5 g a 300 g por 1 g del compuesto de la fórmula V, preferiblemente de 10 g a 200 g.

El tiempo de reacción generalmente está comprendido entre algunos minutos y 24 horas, preferiblemente de 1 a 5 horas, dependiendo de la composición de la mezcla y del intervalo de temperaturas seleccionado.

La temperatura de reacción es de 5°C a 120°C, preferiblemente de 10°C a 35°C, en particular 25°C. En el caso de derivados de imidazol 1-sustituidos (compuestos en los que R23 no es un átomo de hidrógeno), la temperatura de reacción es de 50°C a 120°C, preferiblemente de 70°C a 100°C y en particular 90°C.

El contenido residual del sustrato de partida del compuesto de la fórmula V se redujo a un contenido que está por debajo de 0,5% en el compuesto aislado de fórmula IV.

Son características ventajosas en el proceso de la invención tiempos de reacción muy cortos, la omisión de etapas de purificación adicionales, los altos rendimientos y la alta pureza de los productos preparados.

Otras características ventajosas en el proceso de la invención son:

- la fácil accesibilidad de amidas de ácido imidazol-2-carboxílico sustituidas de forma diversa, particularmente amidas de ácido benzoimidazol-2-carboxílico. La preparación de estas clases estructurales es difícil cuando se usan procedimientos convencionales tales como el acoplamiento de ácidos benzoimidazol-2-carboxílicos con aminas. Con mucha frecuencia, la síntesis de ácidos benzoimidazol-2-carboxílicos sustituidos es laboriosa. Además, los ácidos benzoimidazol-2-carboxílicos, especialmente los ácidos benzoimidazol-2-carboxílicos 1-sustituidos, tienden a descarboxilarse durante su síntesis pero también en condiciones de acoplamiento de amida típicas,

- la fácil accesibilidad de clases estructurales que aún son completamente desconocidas, por ejemplo amidas del ácido tieno-[3,4]-imidazol-2-carboxílico,

ciertas aminas con una reactividad muy baja, por ejemplo aminas que incluso no reaccionan con los cloruros de ácido benzoimidazol-2-carboxílico correspondientes, tales como (4-amino-3-fluoro-fenil)-pirrolidin-1-il-metanona (ejemplo 165) o el éster metílico del ácido 2-amino-3-nitro-benzoico (ejemplo 167), reaccionan de una manera muy fluida (en condiciones muy suaves) permitiendo la construcción de anilidas de ácido imidazol-2-carboxílico especiales, que son difíciles de sintetizar por otros métodos existentes. Por ejemplo, la acilación del éster metílico del ácido 2-amino-3-nitro-benzoico con un cloruro de ácido no impedido estéricamente, por ejemplo cloruro de acetilo, requiere un gran exceso del cloruro de ácido correspondiente y temperaturas elevadas (100ºC, tolueno como disolvente).

Los métodos preferidos incluyen, pero sin limitación, los descritos en los ejemplos.

Los compuestos de la presente invención son inhibidores de proteasas de serina que inhiben la actividad de las enzimas de la coagulación sanguínea factor Xa y/o factor VIIa. En particular, son inhibidores muy selectivos del factor Xa. Son inhibidores de proteasas de serina específicos puesto que no inhiben sustancialmente la actividad de otras proteasas cuya inhibición no se desea. La actividad de los compuestos de la fórmula I puede determinarse, por ejemplo, en los ensayos descritos más adelante o en otros ensayos conocidos por los especialistas en la técnica. Con respecto a la inhibición del factor Xa, una realización preferida de la invención comprende compuestos que tienen una Ki < 1 mM para la inhibición del factor Xa, determinada en el ensayo descrito más adelante, con o sin la inhibición conjunta del factor VIIa, y que preferiblemente no inhiben sustancialmente la actividad de otras proteasas implicadas en la coagulación y en la fibrinolisis cuya inhibición no se desea (usando la misma concentración del inhibidor). Los compuestos de la invención inhiben la actividad catalítica del factor Xa directamente, dentro del complejo protrombinasa o como una subunidad soluble, o indirectamente, inhibiendo la unión del factor Xa al complejo protrombinasa.

Como inhibidores del factor Xa y/o del factor VIIa, los compuestos de la fórmula I, sus sales fisiológicamente tolerables y sus profármacos generalmente son

adecuados para la terapia y profilaxis de afecciones en las que la actividad del factor Xa y/o del factor VIIa juega un papel o tiene una medida indeseada, o que pueden verse influenciadas favorablemente por la inhibición del factor Xa y/o del factor VIIa o por la reducción de sus actividades, o para cuya prevención, alivio o curación el médico desea una inhibición del factor Xa y/o del factor VIIa o una reducción de sus actividades. Como la inhibición del factor Xa y/o del factor VIIa influye sobre la coagulación sanguínea y la fibrinolisis, los compuestos de la fórmula I y sus sales fisiológicamente tolerables y sus profármacos generalmente son adecuados para reducir la coagulación sanguínea, o para la terapia y profilaxis de afecciones en las que la actividad del sistema de coagulación sanguínea juega un papel o tiene una medida indeseada, o que pueden verse influenciadas favorablemente por la reducción de la coagulación sanguínea, o para cuya prevención, alivio o curación el médico desea una actividad reducida del sistema de coagulación sanguínea. De esta manera, un objeto específico de la presente invención es la reducción o inhibición de la coagulación sanguínea indeseada, en particular en un individuo, por medio de la administración de una cantidad eficaz de un compuesto I, una sal fisiológicamente tolerable o un profármaco del mismo, así como preparaciones farmacéuticas de los mismos.

La presente invención también se refiere a los compuestos de la fórmula I y/o sus sales fisiológicamente tolerables y/o sus profármacos para uso como productos farmacéuticos (o medicamentos), al uso de los compuestos de la fórmula I y/o sus sales fisiológicamente tolerables y/o sus profármacos para la producción de productos farmacéuticos para la inhibición del factor Xa y/o del factor VIIa o para influir sobre la coagulación sanguínea, la respuesta inflamatoria o la fibrinolisis o para la terapia o profilaxis de las enfermedades mencionadas anteriormente o más adelante, por ejemplo para la producción de productos farmacéuticos para la terapia y profilaxis de trastornos cardiovasculares, enfermedades tromboembólicas o reestenosis. La invención también se refiere al uso de los compuestos de la fórmula I y/o sus sales fisiológicamente tolerables y/o sus profármacos para la inhibición del factor Xa y/o del factor VIIa o para influir sobre la coagulación sanguínea o la fibrinólisis o para la terapia o profilaxis de las enfermedades mencionadas anteriormente o más adelante, por ejemplo para uso en la terapia y profilaxis de trastornos cardiovasculares, enfermedades tromboembólicas o reestenosis, y a métodos de tratamiento dirigidos a tales propósitos, incluyendo métodos para dichas terapias y profilaxis. La presente invención también se refiere a preparaciones farmacéuticas (o composiciones

farmacéuticas) que contienen una cantidad eficaz de al menos un compuesto de la fórmula I y/o sus sales fisiológicamente tolerables y/o sus profármacos además de un vehículo farmacéuticamente aceptable habitual, es decir, una o más sustancias de vehículo o excipientes farmacéuticamente aceptables y/o sustancias auxiliares o aditivos.

La invención también se refiere al tratamiento de estados de enfermedad tales como una formación anormal de trombos, infarto de miocardio agudo, angina inestable, tromboembolia, cierre de vasos agudo asociado con una terapia trombolítica o angioplastia coronaria transluminal percutánea (PTCA), ataques isquémicos transitorios, apoplejía, claudicación intermitente o injerto de bypass de las arterias coronarias o periféricas, estrechamiento del lumen de vasos, reestenosis después de una angioplastia coronaria o venosa, mantenimiento de la patencia de acceso vascular en pacientes con hemodiálisis a largo plazo, formación patológica de trombos que tiene lugar en las venas de las extremidades inferiores después de una cirugía abdominal, de rodilla o de cadera, riesgo de tromboembolia pulmonar o coagulopatía intravascular sistémica diseminada que se produce en sistemas vasculares durante el choque séptico, ciertas infecciones víricas o cáncer.

Los compuestos de la presente invención también pueden usarse para reducir una respuesta inflamatoria. Son ejemplos de trastornos específicos para cuyo tratamiento o profilaxis pueden usarse los compuestos de la fórmula I enfermedad cardiaca coronaria, infarto de miocardio, angina de pecho, reestenosis vascular, por ejemplo reestenosis posterior a una angioplastia tal como PTCA, síndrome de distrés respiratorio en adultos, insuficiencia de múltiples órganos y trastorno de coagulación intravascular diseminada. Son ejemplos de complicaciones relacionadas asociadas con la cirugía trombosis tales como trombosis de venas profundas y de venas proximales, que pueden producirse después de una cirugía.

Los compuestos de la fórmula I, sus sales fisiológicamente tolerables y sus profármacos pueden administrarse a animales, preferiblemente a mamíferos, y en particular a seres humanos como productos farmacéuticos para terapia o profilaxis. Pueden administrarse solos, en mezclas con otros compuestos o en forma de preparaciones farmacéuticas que permitan la administración entérica o parenteral.

Los productos farmacéuticos pueden administrarse por vía oral, por ejemplo en forma de píldoras, comprimidos, comprimidos laqueados, comprimidos recubiertos, gránulos, cápsulas de gelatina duras y blandas, soluciones, jarabes, emulsiones, suspensiones o mezclas de aerosoles. Sin embargo, la administración también puede

realizarse por vía rectal, por ejemplo en forma de supositorios, o por vía parenteral, por ejemplo por vía intravenosa, intramuscular o subcutánea, en forma de soluciones de inyección o soluciones de infusión, microcápsulas, implantes o varillas, o por vía percutánea o tópica, por ejemplo en forma de pomadas, soluciones o tinturas, o en otras formas, por ejemplo en forma de aerosoles o pulverizaciones nasales.

Las preparaciones farmacéuticas de acuerdo con la invención se preparan de una manera conocida per se y con la que están familiarizados los especialistas en la técnica, usándose vehículos inorgánicos y/u orgánicos inertes farmacéuticamente aceptables además del compuesto o los compuestos de la fórmula I y/o sus sales fisiológicamente tolerables y/o sus profármacos. Para la producción de píldoras, comprimidos, comprimidos recubiertos y cápsulas de gelatina duras es posible usar, por ejemplo, lactosa, almidón de maíz o derivados del mismo, talco, ácido esteárico o sus sales, etc. Son vehículos para las cápsulas de gelatina blandas y los supositorios, por ejemplo, grasas, ceras, polioles semisólidos y líquidos, aceites naturales o hidrogenados, etc. Son vehículos adecuados para la producción de soluciones, por ejemplo soluciones de inyección, o de emulsiones o jarabes, por ejemplo, agua, solución salina, alcoholes, glicerol, polioles, sacarosa, azúcar invertido, glucosa, aceites vegetales, etc. Son vehículos adecuados para las microcápsulas, implantes o varillas, por ejemplo, copolímeros de ácido glicólico y de ácido láctico. Las preparaciones farmacéuticas normalmente contienen de aproximadamente 0,5% a 90% en peso de los compuestos de la fórmula I y/o sus sales fisiológicamente tolerables y/o sus profármacos. La cantidad del ingrediente activo de la fórmula I y/o de sus sales fisiológicamente tolerables y/o de sus profármacos en las preparaciones farmacéuticas normalmente es de aproximadamente 0,5 mg a aproximadamente 1000 mg, preferiblemente de aproximadamente 1 mg a aproximadamente 500 mg.

Además de los ingredientes activos de la fórmula I y/o sus sales fisiológicamente aceptables y/o profármacos y de las sustancias de vehículo, las preparaciones farmacéuticas pueden contener aditivos tales como, por ejemplo, cargas, disgregantes, aglutinantes, lubricantes, agentes humectantes, estabilizantes, emulsionantes, conservantes, edulcorantes, colorantes, saborizantes, aromatizantes, espesantes, diluyentes, sustancias tamponantes, disolventes, solubilizantes, agentes para conseguir un efecto de depósito, sales para alterar la presión osmótica, agentes de recubrimiento o antioxidantes. También pueden contener dos o más compuestos de la fórmula I, y/o sus sales fisiológicamente tolerables y/o sus profármacos. En caso de que una preparación farmacéutica contenga dos o más compuestos de la fórmula I,

la selección de los compuestos individuales puede tener como objetivo un perfil farmacológico global específico de la preparación farmacéutica. Por ejemplo, un compuesto muy potente con una duración de acción corta puede combinarse con un compuesto de actuación prolongada de menor potencia. La flexibilidad permitida con respecto a la selección de los sustituyentes en los compuestos de la fórmula I permite un elevado grado de control sobre las propiedades biológicas y físico-químicas de los compuestos y de esta manera permite la selección de tales compuestos deseados. Además, a parte de al menos un compuesto de la fórmula I y/o una sal fisiológicamente tolerable y/o su profármaco, las preparaciones farmacéuticas también pueden contener uno o más ingredientes terapéutica o profilácticamente activos.

Cuando se usan los compuestos de la fórmula I, la dosis puede variar dentro de amplios límites y, como es habitual y conocido por el médico, debe ser adecuada para las condiciones individuales en cada caso individual. La dosis depende, por ejemplo, del compuesto específico empleado, de la naturaleza y gravedad de la enfermedad a tratar, del modo y programa de administración o de si se trata una afección aguda o crónica o de si se realiza profilaxis. Una dosificación apropiada puede establecerse usando estrategias clínicas bien conocidas en la técnica médica. En general, la dosis diaria para conseguir los resultados deseados en un adulto que pesa aproximadamente 75 kg es de 0,01 mg/kg a 100 mg/kg, preferiblemente de 0,1 mg/kg a 50 mg/kg, en particular de 0,1 mg/kg a 10 mg/kg, (en cada caso en mg por kg de peso corporal). La dosis diaria puede dividirse, en particular en el caso de la administración de cantidades relativamente grandes, en varias, por ejemplo 2, 3 ó 4, administraciones separadas. Como es habitual, dependiendo del comportamiento individual puede ser necesario variar hacia arriba o hacia abajo la dosis diaria indicada.

Un compuesto de la fórmula I también puede usarse ventajosamente como un anticoagulante fuera de un individuo. Por ejemplo, una cantidad eficaz de un compuesto de la invención puede ponerse en contacto con una muestra de sangre recién extraída para prevenir la coagulación de la muestra de sangre. Además, un compuesto de la fórmula I o sus sales pueden usarse para fines de diagnóstico, por ejemplo en diagnósticos in vitro, y como auxiliares en investigaciones bioquímicas. Por ejemplo, un compuesto de la fórmula I puede usarse en un ensayo para identificar la presencia del factor Xa y/o del factor VIIa o para aislar el factor Xa y/o el factor VIIa en una forma sustancialmente purificada. Un compuesto de la invención puede marcarse, por ejemplo, con un radioisótopo, y entonces el compuesto marcado unido al factor Xa

y/o al factor VIIa se detecta usando un método rutinario útil para detectar el marcador particular. De esta manera, un compuesto de la fórmula I o una sal del mismo pueden usarse como sonda para detectar la localización o la cantidad de actividad del factor Xa y/o del factor VIIa in vivo, in vitro o ex vivo.

Además, los compuestos de la fórmula I también pueden usarse como intermedios de síntesis para la preparación de otros compuestos, en particular de otros ingredientes farmacéuticos activos, que pueden obtenerse a partir de los compuestos de la fórmula I, por ejemplo, mediante la introducción de sustituyentes o mediante la modificación de grupos funcionales.

Las secuencias de síntesis generales para preparar los compuestos útiles en la presente invención se resumen en los ejemplos proporcionados a continuación. En los sitios apropiados se describe tanto una explicación como el procedimiento real para los diversos aspectos de la presente invención. Los siguientes ejemplos pretenden ser simplemente ilustrativos de la presente invención y no limitantes de la misma en su alcance o espíritu. Los especialistas en la técnica entenderán fácilmente que pueden usarse variaciones conocidas de las condiciones y procesos descritos en los ejemplos para sintetizar los compuestos de la presente invención.

Se entenderá que dentro de la invención descrita en este documento se incluyen cambios que no afectan sustancialmente a la actividad de las diversas realizaciones de esta invención. De esta manera, los siguientes ejemplos pretenden ilustrar pero no limitar la presente invención.

Ejemplos

Cuando en la etapa final de la síntesis de un compuesto se usó un ácido tal como ácido trifluoroacético o ácido acético, por ejemplo cuando se empleó ácido trifluoroacético para retirar un grupo tBu o cuando se purificó un compuesto por cromatografía usando un eluyente que contenía tal ácido, en algunos casos, dependiendo del procedimiento de tratamiento, por ejemplo los detalles de un proceso de liofilización, el compuesto se obtuvo parcial o completamente en forma de una sal del ácido usado, por ejemplo en forma de la sal de ácido acético, de la sal de ácido trifluoroacético o de la sal de ácido clorhídrico.

Abreviaturas usadas:

terc-Butilo	tBu
2,2'-bis(difenilfosfino-1,1'-binaftilo	Binap
Cloruro de bis-(oxo-3-oxazolidinil)-fosforilo	BOP-Cl
dibencilidenoacetona	dba

Diclorometano	DCM
Diciclohexil-carbodiimida	DCC
Cianuro de dietilfosforilo	DEPC
Diisopropiletil amina	DIPEA
4-Dimetilaminopiridina	DMAP
N,N-Dimetilformamida	DMF
Dimetilsulfóxido	DMSO
1,1'-Bis(difenilfosfino)ferroceno	DPPF
Hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio	HATU
N-Bromosuccinimida	NBS
N-Clorosuccinimida	NCS
N-Yodosuccinimida	NIS
N-Etilmorfolina	NEM
Metanol	MeOH
Temperatura ambiente, de 20°C a 25°C	TA
Saturado	sat.
Tetrahidrofurano	THF
Ácido trifluoroacético	TFA
Tetrafluoroborato de O-((etoxicarbonil)cianometilenoamino)-N,N,N',N'-tetrametiluronio	TOTU

Ejemplo 1: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

(i) Éster terc-butílico del ácido (1-isopropil-piperidin-4-il)-carbámico

A una solución de 5,0 g de éster terc-butílico del ácido piperidin-4-il-carbámico en 15 ml de metanol se le añadieron 7,34 ml de acetona, 3,14 g de $Na(CN)BH_3$ y 0,3 ml de ácido acético. Después de agitar durante 16 h a temperatura ambiente, el disolvente se retiró a presión reducida y el residuo se repartió entre 30 ml de agua y 30 ml de acetato de etilo. La capa orgánica se lavó con una solución saturada de Na_2SO_3 y agua y después se secó sobre Na_2SO_4. El disolvente se retiró a presión reducida para dar el producto en forma de un sólido blanco. Rendimiento: 4,8 g, MS (ES^+): m/e = 243.

(ii) (1-Isopropil-piperidin-4-il)-amida

A 4,8 g de éster terc-butílico del ácido (1-isopropil-piperidin-4-il)-carbámico en

15 ml de metanol se le añadieron 20 ml de ácido clorhídrico metanólico (8 M) y la mezcla se agitó durante 16 h. La retirada del disolvente a presión reducida seguido de la retirada de los componentes volátiles residuales mediante la coevaporación dos veces con tolueno produjo el producto. Rendimiento: 5,42 g, MS (ES^+): m/e = 143.

(iii) (1-Isopropil-piperidin-4-il)-amida del ácido 1H-benzoimidazol-2-carboxílico

A una solución de 300 mg de ácido 1H-benzoimidazol-2-carboxílico en 3 ml de DMF y 1 ml de NEt_3 se le añadieron 398 mg de clorhidrato de (1-isopropil-piperidin-4-il)-amida y 470 mg de BOP-Cl y la mezcla se agitó durante 3 h. Finalmente, se añadieron 3 ml de una solución saturada de $NaHCO_3$ y la mezcla se filtró a través de un cartucho chem elut® por elución con acetato de etilo. Después de la retirada del disolvente a presión reducida, el producto bruto se sometió a la siguiente etapa de reacción sin purificación adicional. Rendimiento: 604 mg.

(iv) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

A una solución de 200 mg de (1-isopropil-piperidin-4-il)-amida del ácido 1H-benzoimidazol-2-carboxílico en 2 ml de DMF se le añadieron 227 mg de Cs_2CO_3 y 194 mg de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol [preparado adoptando un procedimiento descrito por Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Alwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B; Solicitud Int. PCT (2001), pág 460, documento WO 0107436 A2] a TA y la mezcla se agitó durante 16 h. Después de la adición de 5 ml de agua, la mezcla se filtró a través de un cartucho chem elut® por elución con acetato de etilo. Después de la retirada del disolvente a presión reducida, el residuo se purificó por HPLC preparativa (columna de fase inversa C18, elución con un gradiente de H_2O/MeCN con TFA al 0,1%). Las fracciones que contenían el producto se evaporaron y se liofilizaron para producir un sólido blanco. El producto se obtuvo en forma de su sal trifluoroacetato. Rendimiento: 29 mg, MS (ES^+): m/e = 484, patrón de cloro.

Ejemplo 2: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(4-cloro-fenilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

(i) 2-Bromo-N-(4-cloro-fenil)-acetamida

A una solución de 5 g de 4-cloro-fenilamina y 1,5 ml de piridina en 30 ml de tolueno se le añadieron gota a gota 8 g de bromuro de bromoacetilo disuelto en 10 ml de tolueno con refrigeración con hielo. Después de 2 h, el precipitado se aisló por

filtración y se recristalizó en tolueno para producir un sólido blanco. Rendimiento: 10 g.

(ii) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(4-cloro-fenilcarbamoil)metil]-1H-benzoimidazol-2-carboxílico

A una solución de 200 mg de (1-isopropil-piperidin-4-il)-amida del ácido 1H-benzoimidazol-2-carboxílico en 2 ml de DMF se le añadieron 227 mg de Cs_2CO_3 y 173 mg de 2-bromo-N-(4-cloro-fenil)-acetamida a TA y la mezcla se agitó durante 16 h. Después de la adición de 5 ml de agua, la mezcla se filtró a través de un cartucho chem elut® por elución con acetato de etilo. Después de la retirada del disolvente a presión reducida, el residuo se purificó por HPLC preparativa (columna de fase inversa C18, elución con un gradiente de H_2O/MeCN con TFA al 0,1%). Las fracciones que contenían el producto se evaporaron y se liofilizaron para producir un sólido blanco. El producto se obtuvo en forma de su sal trifluoroacetato. Rendimiento: 83 mg, MS (ES^+): m/e = 454, patrón de cloro.

Ejemplo 3. (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

(i) 2-Bromo-N-(5-cloro-piridin-2-il)-acetamida

A una solución de 5 g de 5-cloro-piridin-2-ilamina y 1,5 ml de piridina en 30 ml de tolueno se le añadieron gota a gota 8 mg de bromuro de bromoacetilo disuelto en 10 ml de tolueno con refrigeración con hielo. Después de 2 h, el precipitado se aisló por filtración y se recristalizó en tolueno para producir un sólido blanco. Rendimiento: 12 g.

(ii) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

A una solución de 200 mg de (1-isopropil-piperidin-4-il)-amida del ácido 1H-benzoimidazol-2-carboxílico en 2 ml de DMF se le añadieron 227 mg de Cs_2CO_3 y 174 mg de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida a TA y la mezcla se agitó durante 16 h. Después de la adición de 5 ml de agua, la mezcla se filtró a través de un cartucho chem elut® por elución con acetato de etilo. Después de la retirada del disolvente a presión reducida, el residuo se purificó por HPLC preparativa (columna de fase inversa C18, elución con un gradiente de H_2O/MeCN con TFA al 0,1%). Las fracciones que contenían el producto se evaporaron y se liofilizaron para producir un sólido blanco. El producto se obtuvo en forma de su sal trifluoroacetato. Rendimiento: 34 mg, (ES^+): m/e = 455, patrón de cloro.

Ejemplo 4: (1-Pirimidin-4-il-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

(i) Éster terc-butílico del ácido (1-pirimidin-4-il-piperidin-4-il)-carbámico

A una solución de 395 mg de éster terc-butílico del ácido [1-(2-cloro-pirimidin-4-il)-piperidin-4-il]-carbámico en 10 ml de etanol y 0,3 ml de ácido acético se le añadieron 20 mg de Pd/C (10%) y la mezcla se purgó con argón durante 10 min. Después, la mezcla se agitó en una atmósfera de hidrógeno durante 5 h a TA. Después de la adición de 10 ml de acetato de etilo, la mezcla de reacción se filtró a través de una capa de celite. El disolvente se evaporó a presión reducida y el residuo se codestiló dos veces con tolueno para dar el producto en forma de un sólido blanco. Rendimiento: 468 mg.

(ii) 1-Pirimidin-4-il-piperidin-4-ilamina

A una solución de 468 mg de éster terc-butílico del ácido (1-pirimidin-4-il-piperidin-4-il)-carbámico en 2 ml de DCM se le añadieron 2 ml de TFA y la mezcla se agitó durante 2 h a TA. Después, se añadieron 10 ml de tolueno y los disolventes se retiraron a presión reducida. El residuo se codestiló dos veces con tolueno para producir un aceite amarillo. El producto se obtuvo en forma de su sal trifluoroacetato. Rendimiento: 703 mg.

(iii) (1-Pirimidin-4-il-piperidin-4-il)-amida del ácido 1H-benzoimidazol-2-carboxílico

A una solución de 80 mg de ácido 1H-benzoimidazol-2-carboxílico en 1 ml de DMF y 0,2 ml de NEt_3 se le añadieron 200 mg de trifluoroacetato de 1-pirimidin-4-il-piperidin-4-ilamina y 125 mg de BOP-Cl y la mezcla se agitó durante 3 h. Finalmente, se añadieron 3 ml de una solución saturada de $NaHCO_3$ y la mezcla se filtró a través de un cartucho chem elut® por elución con acetato de etilo. Después de la retirada del disolvente a presión reducida, el residuo se sometió a la siguiente etapa de reacción sin purificación adicional. Rendimiento: 160 mg.

(iv) (1-Pirimidin-4-il-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

A una solución de 160 mg de (1-pirimidin-4-il-piperidin-4-il)-amida del ácido 1H-benzoimidazol-2-carboxílico en 2 ml de DMF se le añadieron 161 mg de Cs_2CO_3 y 138 mg de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol a TA y la mezcla se agitó durante 16 h. Después de la adición de 5 ml de agua, la mezcla se filtró a través de un cartucho chem elut® por elución con acetato de etilo. Después de la retirada del disolvente a presión reducida, el residuo se purificó por HPLC preparativa (columna de fase inversa C18, elución con un gradiente de H_2O/MeCN con TFA al 0,1%). Las fracciones que contenían el producto se evaporaron y se liofilizaron para producir un sólido blanco. El producto se obtuvo en su forma de sal trifluoroacetato. Rendimiento:

114 mg, (ES^+): m/e = 520, patrón de cloro.

Ejemplo 5: a) Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

b) Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

(i) 2-Triclorometil-1H-benzoimidazol-5-carboxilato de metilo

Se disolvieron 2,00 g (12,0 mmol) de 3,4-diamino-benzoato de metilo en 50 ml de ácido acético concentrado. Después, se añadieron lentamente 2,09 ml (1,4 equiv.) de 2,2,2-tricloroacetamidato de metilo y la mezcla resultante se agitó a temperatura ambiente durante 2 h. La mezcla se diluyó con 100 ml de tolueno y el disolvente se retiró a presión reducida. El residuo se recogió en diclorometano y se lavó una vez con una solución saturada de $NaHCO_3$ y una vez con salmuera. La capa orgánica se secó sobre $MgSO_4$ y el disolvente se retiró a presión reducida para dar 2-triclorometil-1H-benzoimidazol-5-carboxilato de metilo puro en forma de un sólido amorfo pardo claro. Rendimiento: 3,64 g, (ES^+): m/e = 293, patrón de cloro.

(ii) Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

Se añadieron 500 mg (1,7 mmol) de 2-triclorometil-1H-benzoimidazol-5-carboxilato de metilo a una mezcla de 548 mg (1,8 equiv.) de diclorhidrato de 1-isopropil-piperidina-4-ilamina y 1,43 g (10 equiv.) de $NaHCO_3$ en 15 ml de THF y 7,5 ml de H_2O y se agitó vigorosamente durante 4 h a temperatura ambiente. La mezcla de reacción se diluyó con diclorometano y se lavó con una solución saturada de $NaHCO_3$ y salmuera. La capa orgánica se secó sobre $MgSO_4$ y se concentró. La HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio el éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico puro en forma de un sólido blanco. Rendimiento: 300 mg, (ES^+): m/e = 345.

(iii) a) Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

b) Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

Se disolvieron 115 mg (0,33 mmol) de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico en 10 ml de DMF. Posteriormente, se añadieron 69,2 mg (1,5 equiv.) de K_2CO_3 y 111,6 mg (1,2 equiv.) de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol y la mezcla resultante se agitó durante 2 h a 80°C. La mezcla de reacción se diluyó con tolueno y se lavó dos veces con una

solución saturada de $NaHCO_3$ y una vez con salmuera, se secó sobre $MgSO_4$ anhidro y se concentró a presión reducida. La RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio una mezcla 6:4 de los dos isómeros descritos en el título. Estos isómeros podrían separarse por RP-HPLC usando una fase quiral estacionaria y una mezcla de heptano, etanol, metanol y dietilamina como disolvente. La asignación estructural de los dos isómeros se consiguió mediante espectroscopía NOE.

Rendimiento del éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico: 52 mg; (ES^+): m/e = 542, patrón de cloro.

Rendimiento del éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico: 34 mg; (ES^+): m/e = 542, patrón de cloro.

Ejemplo 6: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

A una suspensión de 43,6 mg (0,080 mmol) de éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico en 4 ml de MeOH se le añadieron 0,4 ml de una solución acuosa 1 M de LiOH y la mezcla resultante se agitó a 60ºC durante 5 h. La mezcla se acidificó mediante la adición de una solución 1 M de HCl (pH ≈ 2-3) y se concentró a presión reducida. La purificación final por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio el ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico puro. El correspondiente diclorhidrato se obtuvo por tratamiento del producto con una solución 0,1 M de HCl seguido de liofilización. Rendimiento: 43 mg, MS (ES^+): m/e = 528, patrón de cloro.

Ejemplo 7: Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

El ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico se preparó como se ha descrito en el ejemplo 6 a partir de 20 mg (0,037 mmol) de éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico. Rendimiento: 18 mg, MS (ES^+): m/e = 528, patrón de cloro.

Ejemplo 8: a) Éster metílico del ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

b) Éster metílico del ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

A una solución de 80,0 mg (0,23 mmol) de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico en 5 ml de DMF se le añadieron 9,3 mg de hidruro sódico (suspensión al 60% en aceite mineral). La mezcla se agitó durante 30 min a temperatura ambiente y posteriormente se le añadieron 68,4 mg (0,23 mmol) de 5-bromometil-2-(5-cloro-tiofen-2-il)-tiazol [preparado adoptando un procedimiento descrito por Ewing, William R. et al.; Solicitud Int. PCT (2001), pág 460, documento WO 0107436 A2]. Después de 1 h, se añadieron 17,1 mg (0,25 equiv.) más de 5-bromometil-2-(5-cloro-tiofen-2-il)-tiazol y la mezcla de reacción se agitó durante 2 h más. La reacción se interrumpió mediante la adición cuidadosa de MeOH y agua. El disolvente se retiró a presión reducida y el residuo se purificó por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%). Después, los dos isómeros se separaron usando NP-HPLC sobre una fase estacionaria quiral con una mezcla de heptano, etanol, metanol y dietilamina como disolvente. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento del éster metílico del ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico: 40 mg; MS (ES^+): m/e = 558, patrón de cloro.

Rendimiento del éster metílico del ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico: 26 mg; MS (ES^+): m/e = 558, patrón de cloro.

Ejemplo 9: Ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 6 partiendo de 40 mg (0,072 mmol) de éster metílico del ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico. El compuesto del título se obtuvo en forma de su diclorhidrato. Rendimiento: 23 mg, MS (ES^+): m/e = 544, patrón de cloro.

Ejemplo 10: Ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

El ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 6 partiendo de 40 mg (0,072 mmol) de éster metílico del ácido

3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico. El compuesto del título se obtuvo en forma de su diclorhidrato. Rendimiento: 19 mg, MS (ES^+): m/e = 544, patrón de cloro.

Ejemplo 11: a) Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

b) Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico

(i) 2,3-Diamino-benzoato de metilo

Se disolvieron 3,0 g (15,3 mmol) de 2-amino-3-nitro-benzoato de metilo en 200 ml de MeOH absoluto. La solución se evacuó y se aclaró varias veces con argón. Se añadieron 300 mg de paladio sobre carbono (10%) y la mezcla se evacuó de nuevo y se aclaró varias veces con argón. Finalmente, el argón se cambió por hidrógeno (globo cargado con hidrógeno) y la mezcla se agitó durante 4 h a temperatura ambiente. La mezcla de reacción se filtró sobre "Celite" y el residuo del filtro se lavó con 150 ml de metanol. El filtrado se concentró a presión reducida para dar 2,3-diamino-benzoato de metilo puro en forma de un aceite pardo. Rendimiento: 2,53 g, MS (ES^+): m/e = 167.

(ii) 2-Triclorometil-1H-benzoimidazol-4-carboxilato de metilo

Se preparó 2-triclorometil-1H-benzoimidazol-4-carboxilato de metilo de forma similar a 2-triclorometil-1H-benzoimidazol-5-carboxilato de metilo como se ha descrito en el ejemplo 5 i) partiendo de 2,53 g (15,1 mmol) de 2,3-diamino-benzoato de metilo. Rendimiento: 4,15 g, MS (ES^+): m/e = 293, patrón de cloro.

(iii) Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

Se preparó el éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico a partir de 1,82 g (6,2 mmol) de 2-triclorometil-1H-benzoimidazol-4-carboxilato de metilo como se ha descrito en el ejemplo 5 ii). Rendimiento: 1,10 g, MS (ES^+): m/e = 345.

(iv) a) Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

b) Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico

Ambos isómeros se obtuvieron mediante un procedimiento análogo al descrito en el ejemplo 5 iii) partiendo de 150,0 mg (0,44 mmol) de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 145,6 mg (1,2

metoxi-acetato de metilo y 1,85 g de trietilamina. De nuevo, la reacción se agitó durante 8 h a 80°C. La mezcla se concentró a presión reducida y el residuo se digirió secuencialmente con éter dietílico y una solución saturada de $NaHCO_3$ y después se lavó con agua, produciendo el éster metílico del ácido 3H-imidazo[4,5-b]piridina-2-carboxílico casi puro. Rendimiento: 210 mg, MS (ES^+): m/e = 178.

(ii) Éter metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]piridina-2-carboxílico

Se disolvieron 100 mg (0,56 mmol) de éster metílico del ácido 3H-imidazo[4,5-b]piridina-2-carboxílico en 3 ml de DMF. Se añadieron 22,6 mg (0,56 mmol) de hidruro sódico (al 60% en aceite mineral) y la mezcla se agitó durante 30 minutos a temperatura ambiente. Se añadieron 157,2 mg (0,56 mmol) de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol y la mezcla resultante se agitó durante 1 h a 80°C. La mezcla de reacción se enfrió a temperatura ambiente y después de la adición de unas gotas de agua se concentró a presión reducida. El análisis por HPLC-MS mostró la presencia de otro isómero (relación de isómeros ≈ 7:1). La purificación final por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio el éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]piridina-2-carboxílico puro en forma de un sólido amorfo pardo. Rendimiento: 203 mg, MS (ES^+): m/e = 375, patrón de cloro.

(iii) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]pirimidin-2-carboxílico

Se añadieron 175,0 mg (0,46 mmol) de éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]piridina-2-carboxílico a una solución de 19,6 mg (0,82 mmol) de LiOH en 6 ml de THF y 2 ml de H_2O. La mezcla de reacción se agitó durante 2 h a 60°C, se enfrió a temperatura ambiente y se acidificó (pH = 2) mediante la adición de una solución semi-concentrada de HCl. El precipitado se retiró por filtración y se lavó con agua para dar el ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]pirimidin-2-carboxílico puro en forma de un sólido cristalino pardo. Rendimiento: 150 mg, MS (ES^+): m/e = 361, patrón de cloro.

(iv) (1-Isopropil-piperidin-4-il)-amida del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]piridina-2-carboxílico

Se disolvieron 150,0 mg (0,41 mmol) de ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]piridina-2-carboxílico en 4 ml de DMF. Posteriormente, se añadieron 142 µl de DIPEA y 151,8 mg (0,41 mmol) de HATU y la mezcla se agitó durante 20 min a temperatura ambiente. Se añadieron 74,3 mg (0,41 mmol) de

clorhidrato de 1-isopropil-piperidina-4-ilamina y otros 71 µl de DIPEA y la mezcla resultante se agitó durante 3 h a temperatura ambiente. La concentración a presión reducida y la purificación final por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron la (1-isopropil-piperidin-4-il)-amida del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]piridina-2-carboxílico pura en forma de un sólido amorfo pardo claro. El compuesto del título se obtuvo en forma de su hidroformiato. Rendimiento: 17 mg, MS (ES^+): m/e = 485, patrón de cloro.

Ejemplo 15: Éter metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

Se disolvieron 100,8 mg (0,29 mmol) de éster metílico del ácido 2-(isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 6 ml de DMF. Posteriormente, se añadieron 60,6 mg (0,44 mmol) de K_2CO_3 y 87,5 mg (0,35 mmol) de 2-bromo-*N*-(5-cloro-piridin-2-il)-acetamida y la mezcla resultante se agitó durante 3 h a 80ºC. La mezcla de reacción se diluyó con 60 ml de tolueno y se lavó con una solución saturada de $NaHCO_3$ y salmuera. La capa orgánica se secó sobre $MgSO_4$ y el disolvente se retiró a presión reducida. El residuo se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar el éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico puro en forma de un sólido amorfo blanco. El producto se obtuvo en forma de su hidroformiato. Rendimiento: 106 mg, MS (ES^+): m/e = 513, patrón de cloro.

Ejemplo 16: Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

Se disolvieron 30 mg (0,058 mmol) de éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 3 ml de diclorometano y se enfrió a 0ºC. Se añadieron cuidadosamente 234 µl de una solución 1 M de BBr_3 (4 equiv.) en diclorometano y la mezcla resultante se agitó a temperatura ambiente durante 16 h. Con refrigeración, se añadieron gota a gota 3 ml de agua seguido de la adición de 0,7 ml de una solución 1 M de NaOH. La mezcla se concentró a presión reducida. La purificación por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio el ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico puro. El diclorhidrato correspondiente se obtuvo por tratamiento del producto con una solución 0,1 M de HCl y después por liofilización. Rendimiento: 26 mg, MS (ES^+): m/e = 499, patrón de cloro.

Ejemplo 17: a) Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

b) Éster metílico del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

Se disolvieron 102,3 mg (0,297 mmol) de éster metílico del ácido 2-(isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico en 6 ml de DMF. Posteriormente, se añadieron 61,6 mg (0,446 mmol) de K_2CO_3 y 88,9 mg (0,356 mmol) de 2-bromo-*N*-(5-cloro-piridin-2-il)-acetamida y la mezcla resultante se agitó durante 2 h a 80°C. La mezcla de reacción se diluyó con 60 ml de tolueno y se lavó con una solución sat. de $NaHCO_3$ y salmuera. La capa orgánica se secó sobre $MgSO_4$ y el disolvente se retiró a presión reducida. El residuo se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar los dos isómeros descritos en el título en una relación de 1,3:1. Ambos isómeros podrían separarse por NP-HPLC usando una fase estacionaria quiral y una mezcla de heptano, etanol y metanol como disolvente. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE. Ambos isómeros se transformaron en sus diclorhidratos por tratamiento con una solución 0,1 M de HCl y después por liofilización.

Rendimiento del éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico: 50 mg, MS (ES^+): m/e = 513, patrón de cloro.

Rendimiento del éster metílico del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico: 51 mg, MS (ES^+): m/e = 513, patrón de cloro.

Ejemplo 18: Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

Se preparó ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico mediante un procedimiento de acuerdo con el ejemplo 16 partiendo de 27,8 mg (0,047 mmol) de éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico. El compuesto del título se obtuvo en forma de su diclorhidrato. Rendimiento: 15 mg, MS (ES^+): m/e = 499, patrón de cloro.

Ejemplo 19: Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

Se preparó ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico mediante un procedimiento de acuerdo

con el ejemplo 16 partiendo de 28 mg (0,048 mmol) de éster metílico del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico. El compuesto del título se obtuvo en forma de su diclorhidrato. Rendimiento: 22 mg, MS (ES^+): m/e = 499, patrón de cloro.

Ejemplo 20: 1-Etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

Se disolvieron 50 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 3 ml de DMF. Posteriormente, se añadieron 27,6 mg (0,16 mmol) de KI, 46 mg (0,33 mmol) de K_2CO_3 y 45 µl (0,32 mmol) de etilcarbonato de 1-cloroetilo y la mezcla de reacción se agitó a 60°C durante 4 h. La mezcla de reacción se concentró y el residuo resultante se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar el 1-etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico puro en forma de un sólido amorfo blanco. El diclorhidrato correspondiente se obtuvo por tratamiento con una solución 0,1 M de HCl y después por liofilización. Rendimiento: 46 mg, MS (ES^+): m/e = 644, patrón de cloro.

Ejemplo 21: 1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El 1-ciclohexiloxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó adoptando el procedimiento descrito en el ejemplo 20 partiendo de 50 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 61 µl (0,32 mmol) de carbonato de ciclohexil-1-cloroetilo. El compuesto del título se obtuvo en forma de su diclorhidrato. Rendimiento: 47 mg, MS (ES^+): m/e = 698, patrón de cloro.

Ejemplo 22: 2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,4-dicarboxílico

Se disolvieron 30 mg (0,057 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 3 ml de DMF. Posteriormente, se añadieron 29 µl (0,171 mmol) de DIPEA y 21,6 mg (0,057 mmol) de HATU. Después de 30 min, se añadieron 3,5 µl (0,057 mmol) de 2-amino-etanol y 10 µl de DIPEA y la mezcla resultante se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se concentró y el residuo se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%). El compuesto del

título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 29 mg, MS (ES^+): m/e = 571, patrón de cloro.

Ejemplo 23: (1-isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 6,7 mg (0,09 mmol) de 3-hidroxi-azetidina. El compuesto del título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 51 mg, MS (ES^+): m/e = 583, patrón de cloro.

Ejemplo 24: 2-[(1-isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,4-dicarboxílico

La 2-[(1-isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,4-dicarboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 40 mg (0,067 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 5,6 mg (0,075 mmol) de *N*-metil-2-aminoetanol. El compuesto del título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 35 mg, MS (ES^+): m/e = 585, patrón de cloro.

Ejemplo 25: 2-[(1-isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,5-dicarboxílico

La 2-[(1-isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,5-dicarboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 6,8 mg (0,09 mmol) de *N*-metil-2-aminoetanol. El compuesto del título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 43 mg, MS (ES^+): m/e = 585, patrón de cloro.

Ejemplo 26: (1-isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó

mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol y 6,7 mg (0,09 mmol) de 3-hidroxi-azetidina. El compuesto del título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 37 mg, MS (ES^+): m/e = 583, patrón de cloro.

Ejemplo 27: 1-Etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El 1-Etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico se preparó adoptando el procedimiento descrito para el ejemplo 20 partiendo de 50 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 45 µl (0,32 mmol) de etilcarbonato de 1-cloroetilo. El compuesto del título se obtuvo en forma de su diclorhidrato. Rendimiento: 57 mg, MS (ES^+): m/e = 644, patrón de cloro.

Ejemplo 28: 1-Ciclohexilcarboniloxi-etiléter del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El 1-ciclohexilcarboniloxi-etiléter del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico se preparó adoptando el procedimiento descrito para el ejemplo 20 partiendo de 50 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 61 µl (0,32 mmol) de carbonato de ciclohexil-1-cloroetilo. El compuesto del título se obtuvo en forma de su diclorhidrato. Rendimiento: 59 mg, MS (ES^+): m/e = 698, patrón de cloro.

Ejemplo 29: a) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico

b) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico

(I) 2-(2-Triclorometil-1H-benzoimidazol-5-sulfonil)-etanol

Se disolvieron 500 mg (2,31 mmol) de 3,4-diamino-benceno-sulfoniletan-2-ol en 10 ml de ácido acético concentrado. Se añadieron lentamente 0,4 ml (1,4 equiv.) de 2,2,2-tricloroacetamidato de metilo y la mezcla resultante se agitó a temperatura ambiente durante 4 h. La mezcla se diluyó con 100 ml de tolueno y el disolvente se retiró a presión reducida. El residuo se aclaró con tolueno, se filtró y se secó al vacío para dar un sólido cristalino pardo suficientemente puro para todas las reacciones posteriores. Rendimiento: 680 mg, MS (ES^+): m/e = 345, patrón de cloro.

(li) (1-Isopropil-piperidin-4-il)-amida del ácido 5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico

Se añadieron 360 mg (1,05 mmol) de 2-(2-triclorometil-1H-benzoimidazol-5-sulfonil)-etanol a una mezcla de 225,4 mg (1,05 equiv.) de diclorhidrato de 1-isopropil-piperidina-4-ilamina y 880 mg (10 equiv.) de $NaHCO_3$ en 6 ml de THF y 3 ml de H_2O y se agitó vigorosamente durante 2 h a temperatura ambiente. La mezcla de reacción se diluyó con diclorometano y se lavó con una solución saturada de $NaHCO_3$ y salmuera. La capa orgánica se secó sobre $MgSO_4$ y se concentró. El producto obtenido fue lo suficientemente puro para las reacciones posteriores. Rendimiento: 207 mg, MS (ES^+): m/e = 395.

(lii) a) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico

b) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico

Se disolvieron 126,2 mg (0,32 mmol) de (1-Isopropil-piperidin-4-il)-amida del ácido 5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico en 10 ml de DMF. Posteriormente, se añadieron 48,6 mg (1,1 equiv.) de K_2CO_3 y 89,0 mg (1,0 equiv.) de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol y la mezcla resultante se agitó durante 3 h a 55ºC. La mezcla de reacción se diluyó con tolueno y se lavó dos veces con una solución saturada de $NaHCO_3$ y una vez con salmuera, se secó sobre $MgSO_4$ anhidro y se concentró a presión reducida. La RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio una mezcla 6:4 de los dos isómeros descritos en el título. Estos isómeros podrían separarse por NP-HPLC usando una fase estacionaria quiral y una mezcla de heptano, etanol, metanol y dietilamina como disolvente. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento de la (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico: 79 mg, MS (ES^+): m/e = 591, patrón de cloro.

Rendimiento de la (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico: 59 mg, MS (ES^+): m/e = 591, patrón de cloro.

Ejemplo 30: 2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico

La 2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico se preparó

mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 40 mg (0,08 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 5,4 mg (0,088 mmol) de 2-aminoetanol. El compuesto del título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 34 mg, MS (ES^+): m/e = 542, patrón de cloro.

Ejemplo 31: 2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico

La 2-[(1-isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,10 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 8,3 mg (0,11 mmol) de *N*-metil-2-amino-etanol. El compuesto del título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 30 mg, MS (ES^+): m/e = 556, patrón de cloro.

Ejemplo 32: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,10 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 8,1 mg (0,11 mmol) de 3-hidroxi-azetidina. El compuesto del título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 28 mg, MS (ES^+): m/e = 554, patrón de cloro.

Ejemplo 33: 1-Etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El 1-etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 20 partiendo de 50 mg (0,10 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 61,2 mg (0,401 mmol) de etilcarbonato de 1-cloroetilo. El compuesto del título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 38 mg, MS (ES^+): m/e = 615, patrón de cloro.

Ejemplo 34: 1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-

carboxílico

El 1-ciclohexiloxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 20 partiendo de 50 mg (0,10 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 82,8 mg (0,401 mmol) de carbonato de ciclohexil-1-cloroetilo. El compuesto del título se obtuvo en forma de su hidroformiato en forma de un sólido amorfo blanco. Rendimiento: 46 mg, MS (ES^+): m/e = 669, patrón de cloro.

Ejemplo 35: [4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

(i) 4-(4-Nitro-fenil)-morfolina

Una mezcla de 24,5 g de morfolina y 13,3 g de 1-fluoro-4-nitro-benceno en 30 ml de DMSO se calentó a 100°C durante 4 h. Esta solución se vertió en 300 ml de agua y el precipitado resultante se recogió por filtración para producir un producto cristalino amarillo brillante que se secó a presión reducida. Rendimiento: 19,7 g.

(ii) 4-(4-Nitro-fenil)-morfolin-3-ona

A una solución de 10 g de 4-(4-nitro-fenil)-morfolina en 200 ml de DCM se le añadieron cuidadosamente 23 g de cloruro de bencil-trietil-amonio y 22,7 g de permanganato potásico (malla 325) a TA. Después de agitar durante 1 h a TA, la mezcla de reacción se calentó a reflujo durante 10 h. Después, se añadió una solución de 95 g de Na_2SO_3 en 450 ml de agua con refrigeración y agitación vigorosa. La mezcla se filtró a través de una capa de celite y el filtrado se concentró a presión reducida. El sólido amarillo se agitó con 250 ml de agua y el producto precipitado se recogió por filtración. Este producto bruto se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente de DCM/MeOH al 100% -> 50%. Las fracciones que contenían el producto se combinaron y el disolvente se evaporó a presión reducida. Rendimiento: 2,6 g.

(iii) 4-(4-Amino-fenil)-morfolin-3-ona

A una solución de 2,6 g de 4-(4-nitro-fenil)-morfolin-3-ona en 350 ml de acetato de etilo y 17 ml de etanol se le añadieron 13,2 g de $SnCl_2$ dihidrato y la mezcla de reacción se calentó a reflujo durante 2 h. Después de enfriar a TA, la mezcla se agitó durante 16 h. El producto precipitado se recogió por filtración y fue lo suficientemente puro para la siguiente etapa de reacción. Rendimiento: 2,07 g.

(iv) [4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico

A una solución de 100 mg de ácido 1H-benzoimidazol-2-carboxílico y 118 mg de 4-(4-amino-fenil)-morfolin-3-ona en 2 ml de DCM se le añadieron 157 mg de BOP-Cl y 0,3 ml de NEt_3 y la mezcla se agitó durante 16 h a TA. Después de que la mezcla de reacción se diluyera con 20 ml de agua, el producto precipitado se recogió por filtración. El producto bruto se sometió a la siguiente etapa de reacción sin purificación adicional. Rendimiento: 122 mg.

(v) [4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

A una solución de 50 mg de [4-(3-oxo-morfolin-4-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico en 2 ml de DMF se le añadieron 49 mg de Cs_2CO_3 y 37 mg de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida a TA y la mezcla de reacción se agitó durante 2 h. Después, se añadieron 209 mg más de Cs_2CO_3 y 30 mg de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida a TA y la mezcla de reacción se agitó durante 2 h más. La mezcla de reacción se diluyó con 20 ml de agua y el producto precipitado se recogió por filtración. El producto se recogió en 3 ml de HCl diluido y se liofilizó para producir un sólido blanco. El producto se obtuvo en forma de su clorhidrato. Rendimiento: 128 mg, MS (ES^+): m/e = 505, patrón de cloro.

Ejemplo 36: Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

(i) Éster metílico del ácido 2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

Una solución de 69,4 mg (0,236 mol) de 2-triclorometil-1H-benzoimidazol-4-carboxilato de metilo en 2 ml de THF se añadió lentamente a una mezcla que contenía 50 mg (0,26 mmol) de 4-(4-amino-fenil)-morfolin-3-ona, 220 mg (2,62 mmol) de $NaHCO_3$, 8 ml de THF y 3 ml de H_2O. La mezcla se agitó vigorosamente durante 3 h a temperatura ambiente, se diluyó con 50 ml de CH_2Cl_2 y se lavó con 30 ml de una solución saturada de $NaHCO_3$. La solución acuosa se extrajo con 50 ml de CH_2Cl_2 y las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron a presión reducida para dar un sólido pardo que fue lo suficientemente puro para las siguientes reacciones. Rendimiento: 72 mg, MS (ES^+): m/e = 395.

(ii) Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

Se disolvieron 72,0 mg (0,183 mmol) de éster metílico del ácido 2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico en 7 ml de DMF. Se añadieron secuencialmente 37,8 mg (0,274 mmol) de K_2CO_3 y 54,6 mg (0,219 mmol)

de 2-bromo-*N*-(5-cloro-piridin-2-il)-acetamida y la mezcla resultante se agitó durante 4 h a 80ºC. La mezcla se diluyó con 200 ml de tolueno y se lavó con 50 ml de una solución saturada de $NaHCO_3$. El producto no fue completamente soluble en tolueno, por lo que hubo que añadir acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ anhidro y se concentró a presión reducida. El residuo se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar el éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico en forma de un sólido amorfo pardo claro. Rendimiento: 46 mg, MS (ES^+): m/e = 563, patrón de cloro.

Ejemplo 37: [4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

(*i*) 1-(4-Nitro-fenil)-1H-piridin-4-ona

Una mezcla de 10,1 g de piridin-4-ol y 10 g de 1-fluoro-4-nitro-benceno y 46,1 g de Cs_2CO_3 en 30 ml de DMF se agitó a TA durante 2 h. Esta solución se vertió en 300 ml de agua y el precipitado resultante se recogió por filtración para producir un producto cristalino amarillo brillante que se secó a presión reducida. Rendimiento: 11,2 g.

(ii) 1-(4-Amino-fenil)-1H-piridin-4-ona

A una solución de 10 g de 1-(4-nitro-fenil)-1H-piridin-4-ona en 510 ml de acetato de etilo y 26 ml de etanol se le añadieron 52,1 g de $SnCl_2$ dihidrato y la mezcla de reacción se calentó a reflujo durante 6 h. Después de enfriar a TA, los disolventes se retiraron a presión reducida. El residuo se recogió en 100 ml de una solución acuosa de $NaHCO_3$ y se le añadieron 200 ml de acetato de etilo. El precipitado inorgánico se retiró por filtración y los sólidos se lavaron con acetato de etilo. Después de la separación de la capa orgánica, la capa acuosa del filtrado se extrajo con acetato de etilo (2 x 100 ml) y con DCM (3 x 150 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y los disolventes se retiraron a presión reducida. El producto restante fue lo suficientemente puro para la siguiente etapa de reacción. Rendimiento: 6 g.

(iii) 2-Triclorometil-1H-benzoimidazol

A una solución de 10 g de benceno-1,2-diamina en 250 ml de ácido acético se le añadieron gota a gota 22,8 g de éster metílico del ácido 2,2,2-tricloro-acetimídico a TA. Después de 2 h, se añadieron 500 ml de tolueno y los disolventes se retiraron a presión reducida. El residuo se codestiló dos veces más con tolueno. Después de secar a presión reducida, el producto fue lo suficientemente puro para la siguiente

etapa de reacción. Rendimiento: 25 g.

(iv) [4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico

Una solución de 769 mg de 2-Triclorometil-1H-benzoimidazol en 10 ml de THF se añadió lentamente a una mezcla que contenía 304 mg de 1-(4-amino-fenil)-1H-piridin-4-ona, 1,3 g de $NaHCO_3$, 40 ml de THF y 15 ml de H_2O. La mezcla se agitó vigorosamente durante 3 h a temperatura ambiente, se diluyó con 200 ml de CH_2Cl_2 y se lavó con 40 ml de una solución saturada de $NaHCO_3$. La solución acuosa se extrajo con CH_2Cl_2 (3 x 200 ml) y las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron a presión reducida para dar un sólido pardo que fue lo suficientemente puro para las siguientes reacciones. Rendimiento: 598 mg.

(v) [4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

A una solución de 192 mg de [4-(4-oxo-4H-piridin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico en 10 ml de DMF se le añadieron 120 mg de K_2CO_3 y 194 mg de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol a TA y la mezcla se calentó durante 2 h a 70°C. Después de la adición de 30 ml de agua, la mezcla se extrajo con acetato de etilo (3 x 100 ml). Después de secar las fases orgánicas combinadas sobre Na_2SO_4, el disolvente se retiró a presión reducida y el residuo se purificó por HPLC preparativa (columna de fase inversa C18, elución con un gradiente de H_2O/MeCN con TFA al 0,1%). Las fracciones que contenían el producto se evaporaron y se liofilizaron para producir un sólido blanco. El producto se obtuvo en forma de su sal trifluoroacetato. Rendimiento: 70 mg, MS (ES^+): m/e = 528, patrón de cloro.

Ejemplo 38: [4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-(3-metoxi-bencil)-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37 con la diferencia de que se usó 1-bromometil-3-metoxi-benceno en lugar de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol en la etapa de alquilación. MS (ES^+): m/e = 451.

Ejemplo 39: [4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37 con la diferencia de que se usó 2-bromo-N-(5-cloro-piridin-2-il)-acetamida en lugar de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol en la etapa de alquilación. MS (ES^+): m/e = 499, patrón de cloro.

Ejemplo 40: (8-Metil-8-aza-biciclo[3.2.1]oct-3-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37 con la diferencia de que se usó clorhidrato de 8-Metil-8-aza-biciclo[3.2.1]oct-3-ilamina en lugar de 1-(4-Amino-fenil)-1H-piridin-4-ona en la etapa (iv). MS (ES^+): m/e = 482, patrón de cloro.

Ejemplo 41: [4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

(i) 1-(4-Nitro-fenil)-1H-pirimidin-2,4-diona

Una mezcla de 3,5 g de 1H-pirimidin-2,4-diona, 3 g de 1-fluoro-4-nitro-benceno y 13,8 g de Cs_2CO_3 en 60 ml de DMF se calentó a 80°C durante 12 h. Esta solución se vertió en 200 ml de agua y el precipitado resultante se recogió por filtración para producir un producto cristalino amarillo claro que se secó a presión reducida. Rendimiento: 2,6 g.

(ii) 1-(4-Amino-fenil)-1H-pirimidin-2,4-diona

En una solución de 1,4 g de 1-(4-Nitro-fenil)-1H-pirimidin-2,4-diona en 120 ml de MeOH se introdujeron 15 g de níquel Raney (lavado tres veces con MeOH) en una atmósfera de nitrógeno. Después, se añadieron 15 ml de una solución 7 M de NH_3 en MeOH. La atmósfera de nitrógeno se reemplazó por una atmósfera de hidrógeno y la mezcla se hidrogenó a presión normal y a TA. Después de 2 h, la mezcla de reacción se filtró a través de una capa de celite. Los disolventes se retiraron a presión reducida y el residuo se sometió a la siguiente etapa de reacción sin purificación adicional. Rendimiento: 502 mg.

(iii) [4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (iv) con la diferencia de que se usó 1-(4-amino-fenil)-1H-pirimidin-2,4-diona en lugar de 1-(4-amino-fenil)-1H-piridin-4-ona. MS (ES^+): m/e = 348.

(iv) [4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (iv) con la diferencia de que se usó [4-(2,4-dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico en lugar de [4-(4-oxo-4H-piridin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico. MS (ES^+): m/e = 545, patrón de cloro.

Ejemplo 42: [4-(2-Oxo-oxazolidin-3-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 41 con al

diferencia de que se usó oxazolidin-2-ona en lugar de 1H-pirimidin-2,4-diona en la etapa (i).

MS (ES^+): m/e = 520, patrón de cloro.

Ejemplo 43: [4-(2-Oxo-oxazolidin-3-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 41 con la diferencia de que se usaron oxazolidin-2-ona y 2-bromo-N-(5-cloro-piridin-2-il)-acetamida en lugar de 1H-pirimidin-2,4-diona (etapa (i)) y 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol (etapa (iv)). MS (ES^+): m/e = 490, patrón de cloro.

Ejemplo 44: [4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 41 con la diferencia de que se usó 2-bromo-N-(5-cloro-piridin-2-il)-acetamida en lugar de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol en la etapa de alquilación. MS (ES^+): m/e = 516, patrón de cloro.

Ejemplo 45: [4-(4-Oxo-piperidin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 41 con la diferencia de que se usó clorhidrato de Piperidin-4-ona en lugar de 1H-pirimidin-2,4-diona en la etapa (i). MS (ES^+): m/e = 532, patrón de cloro.

Ejemplo 46: [4-(1,1-Dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

(i) Éster terc-butílico del ácido [4-(1,1-dioxo-1λ6-tiomorfolin-4-il)-fenil]-carbámico

Una solución de 408 mg de éster terc-butílico del ácido (4-amino-fenil)-carbámico y 254 mg de etilsulfonileteno en 4 ml de EtOH se calentó durante 30 min a 140°C bajo irradiación de microondas (100 W, aparato CEM Discover™). Después de la refrigeración a TA, los disolventes se retiraron a presión reducida y el residuo se secó al vacío. El producto bruto se sometió a la siguiente etapa de reacción. Rendimiento: 0,64 g.

(ii) 4-(1,1-Dioxo-1λ6-tiomorfolin-4-il)-fenilamina

Una solución de 640 mg de éster terc-butílico del ácido [4-(1,1-dioxo-1λ6-tiomorfolin-4-il)-fenil]-carbámico en 30 ml de DCM y 30 ml de TFA se dejó en reposo durante 16 h a TA. Después de la adición de 100 ml de tolueno, los disolventes se retiraron a presión reducida y el residuo se secó al vacío. El producto se obtuvo en forma de su trifluoroacetato. Rendimiento: 0,44 g.

(iii) [4-(1,1-Dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (iv) con la diferencia de que se usó [4-(1,1-dioxo-1λ6-tiomorfolin-4-il)-fenilamina en lugar de 1-(4-amino-fenil)-1H-piridin-4-ona.

(iv) [4-(1,1-dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (v) con la diferencia de que se usó [4-1,1-dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico en lugar de [4-(4-oxo-4H-piridin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico. MS (ES^+): m/e = 568, patrón de cloro.

Ejemplo 47: [4-(1,1-dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 46 con la diferencia de que se usó 2-bromo-N-(5-cloro-piridin-2-il)-acetamida en lugar de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol (etapa (iv)). MS (ES^+): m/e = 500, patrón de cloro.

Ejemplo 48: [4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

(i) 1-(4-Nitro-fenil)-1H-pirazin-2-ona

Una mezcla de 632 mg de pirazin-2-olato sódico, 720 mg de 1-fluoro-4-nitro-benceno y 3,3 g de Cs_2CO_3 en 13 ml de DMF se calentó a 35°C durante 6 h. Esta solución se vertió en 300 ml de agua y el precipitado resultante se recogió por filtración para producir un producto cristalino amarillo brillante que se secó a presión reducida. Rendimiento: 545 mg.

(ii) 1-(4-Amino-fenil)-1H-pirazin-2-ona

A una solución de 520 mg de 1-(4-nitro-fenil)-1H-pirazin-2-ona en 26 ml de acetato de etilo y 1,3 ml de etanol se le añadieron 2,7 g de $SnCl_2$ dihidrato y la mezcla de reacción se calentó a reflujo durante 6 h. Después de enfriar a TA, la mezcla se agitó durante 16 h. El producto precipitado se recogió por filtración y fue lo suficientemente puro para la siguiente etapa de reacción. Rendimiento: 450 mg.

(iii) [4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (iv) con la diferencia de que se usó 1-(4-amino-fenil)-1H-pirazin-2-ona en lugar de 1-(4-amino-fenil)-1H-piridin-4-ona. Rendimiento: 513 mg.

(iv) [4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (v) con la diferencia de que se usó [4-(2-oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico en lugar de [4-(4-oxo-4H-piridin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico MS (ES^+): m/e = 529, patrón de cloro.

Ejemplo 49: [4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 48 con la diferencia de que se usó 2-bromo-N-(5-cloro-piridin-2-il)-acetamida en lugar de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol. MS (ES^+): m/e = 500, patrón de cloro.

Ejemplo 50: [4-(2-Oxo-piperazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

(i) 1-(4-Amino-fenil)-piperazin-2-ona

En una solución de 670 mg de 1-(4-nitro-fenil)-1H-pirazin-2-ona en 100 ml de MeOH se introdujeron 8 g de níquel Raney (lavado tres veces con MeOH) en una atmósfera de nitrógeno. Después, se añadieron 10 ml de una solución 7 M de NH_3 en MeOH. La atmósfera de nitrógeno se reemplazó por una atmósfera de hidrógeno y la mezcla se hidrogenó a presión normal a TA. Después de 2 h, la mezcla de reacción se filtró a través de una capa de celite. Los disolventes se retiraron a presión reducida y el residuo se sometió a la siguiente etapa de reacción sin purificación adicional. Rendimiento: 464 mg.

(ii) Éster terc-butílico del ácido 4-(4-amino-fenil)-3-oxo-piperazin-1-carboxílico

A una solución de 464 mg de 1-(4-amino-fenil)-piperazin-2-ona y 30 mg de DMAP en 15 ml de acetonitrilo se le añadieron 794 mg de carbonato de di-terc-butilo a TA. Después de 2 h, los disolventes se retiraron a presión reducida y el residuo se recogió en 200 ml de acetato de etilo. La fase orgánica se lavó con agua y salmuera, se secó sobre Na_2SO_4 y el disolvente se retiró a presión reducida. Rendimiento: 547 mg.

(iii) Éster terc-butílico del ácido 4-{4-[(1H-benzoimidazol-2-carbonil)-amino]-fenil}-3-oxo-piperazin-1-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (iv) con la diferencia de que se usó éster terc-butílico del ácido 4-(4-amino-fenil)-3-oxo-piperazin-1-carboxílico en lugar de 1-(4-amino-fenil)-1H-piridin-4-ona. Rendimiento: 160 mg.

(iv) Éster terc-butílico del ácido 4-[4-({4-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carbonil}-amino)-fenil]-3-oxo-piperazin-1-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (v) con la diferencia de que se usó éster terc-butílico del ácido 4-{4-[(1H-benzoimidazol-2-carbonil)-amino]-fenil}-3-oxo-piperazin-1-carboxílico en lugar de [4-(4-oxo-4H-piridin-1-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico. MS (ES^+): m/e = 633, patrón de cloro.

(v) [4-(2-Oxo-piperazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico

Una solución de 150 mg de éster terc-butílico del ácido 4-[4-({4-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carbonil}-amino)-fenil]-3-oxo-piperazin-1-carboxílico en 30 ml de DCM y 10 ml de TFA se dejó en reposo durante 16 h a TA. Después de la adición de 100 ml de tolueno, los disolventes se retiraron a presión reducida y el residuo se purificó por HPLC preparativa (columna de fase inversa C18, elución con un gradiente de H_2O/MeCN con TFA al 0,1%). Las fracciones que contenían el producto se evaporaron y se liofilizaron para producir un sólido blanco. El producto se obtuvo en forma de su sal trifluoroacetato. Rendimiento: 84 mg, MS (ES^+): m/e = 533, patrón de cloro.

Ejemplo 51: [4-(2-Oxo-piperazin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 50 con la diferencia de que se usó 2-bromo-N-(5-cloro-piridin-2-il)-acetamida en lugar de 3-bromo-5-(5-cloro-tiofen-2-il)-isoxazol. MS (ES^+): m/e = 504, patrón de cloro.

Ejemplo 52: [4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico

(i) 2-(2-Metoxi-etoxi)-6-nitro-fenilamina

Una solución de 5 g de 2-amino-3-nitro-fenol, 4,5 g de 1-bromo-2-metoxi-etano y 4,4 g de K_2CO_3 en 50 ml de DMF se calentó a 60°C durante 16 h. Después, se añadieron 50 ml de agua y la mezcla se extrajo con acetato de etilo (3 x 100 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y los disolventes se retiraron a presión reducida. El producto restante fue lo suficientemente puro para la siguiente etapa de reacción. Rendimiento: 5,8 g.

(ii) 3-(2-Metoxi-etoxi)-benceno-1,2-diamida

A una solución de 1 g de 2-(2-metoxi-etoxi)-6-nitro-fenilamina en 10 ml de acetato de etilo y 3 ml de etanol se le añadieron 4,4 g de $SnCl_2$ dihidrato y la mezcla

de reacción se calentó a reflujo durante 6 h. Después de enfriar, se añadieron 50 ml de NaOH 2 M y el precipitado inorgánico se filtró y se lavó abundantemente con acetato de etilo. El filtrado se extrajo con acetato de etilo (3 x 100 ml), las capas orgánicas combinadas se secaron sobre $MgSO_4$ y los disolventes se retiraron a presión reducida. El producto restante fue lo suficientemente puro para la siguiente etapa de reacción. Rendimiento: 640 mg.

(iii) 4-(2-Metoxi-etoxi)-2-triclorometil-1H-benzoimidazol

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (iii) con la diferencia de que se usó 3-(2-metoxi-etoxi)-benceno-1,2-diamina en lugar de benceno-1,2-diamina.

(iv) [4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 37, etapa (iv) con la diferencia de que se usó 4-(2-metoxi-etoxi)-2-triclorometil-1H-benzoimidazol en lugar de 2-triclorometil-1H-benzoimidazol. MS (ES^+): m/e = 411.

(v) [4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico

El compuesto del título se preparó de forma análoga al ejemplo 35, etapa (v) con la diferencia de que se usó [4-(3-oxo-morfolin-4-il)-fenil]-amida del ácido 4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico en lugar de [4-(3-oxo-morfolin-4-il)-fenil]-amida del ácido 1H-benzoimidazol-2-carboxílico. MS (ES^+): m/e = 579, patrón de cloro.

Ejemplo 53: Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

Se disolvieron 127 mg (0,20 mol) de éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico en 15 ml de CH_2Cl_2. A 0°C, se añadieron 1,8 ml (1,8 mmol) de una solución 1 M de BBr_3. La mezcla de reacción se agitó durante 24 h a temperatura ambiente. debido a la incompleta conversión, se añadieron 0,9 ml más (0,9 mmol) de una solución 1 M de BBr_3. Después de agitar durante 24 h a temperatura ambiente, la mezcla de reacción se concentró y se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%). El ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico se obtuvo en forma de un sólido amorfo pardo claro. Rendimiento: 73 mg, MS (ES^+): m/e = 549, patrón de cloro.

Ejemplo 54: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-

ilcarbamoil)-metil]-5-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,10 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 8,1 mg (0,11 mmol) de 3-hidroxi-azetidina. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 10 mg, MS (ES^+): m/e = 552, patrón de cloro.

Ejemplo 55: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,10 mmol) de ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico y 8,1 mg (0,11 mmol) de 3-hidroxi-azetidina. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 27 mg, MS (ES^+): m/e = 552, patrón de cloro.

Ejemplo 56: 2-[(1-Isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico

La 2-[(1-isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico se preparó mediante un procedimiento análogo al ejemplo 22 partiendo de 50 mg (0,10 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 6,8 mg (0,11 mmol) de 2-amino-etanol. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 4 mg, MS (ES^+): m/e = 542, patrón de cloro.

Ejemplo 57: 2-[(1-Isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-3H-benzoimidazol-2,5-dicarboxílico

La 2-[(1-isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-3H-benzoimidazol-2,5-dicarboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,10 mmol) de ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico y 6,7 mg (0,11 mmol) de 2-amino-etanol. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 18 mg, MS (ES^+): m/e = 542, patrón de cloro.

Ejemplo 58: 2-[(1-Isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico

La 2-[(1-isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,10 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 8,3 mg (0,11 mmol) de N-metil-2-aminoetanol. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 23 mg, MS (ES^+): m/e = 556, patrón de cloro.

Ejemplo 59: 2-[(1-Isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-metil-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-3H-benzoimidazol-2,5-dicarboxílico

La 2-[(1-isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-metil-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-3H-benzoimidazol-2,5-dicarboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,10 mmol) de ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico y 8,3 mg (0,11 mmol) de N-metil-2-aminoetanol. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 32 mg, MS (ES^+): m/e = 556, patrón de cloro.

Ejemplo 60: 1-Ciclohexiloxicarboniloxi-etil-éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El 1-ciclohexiloxicarboniloxi-etil-éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 20 partiendo de 50 mg (0,10 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 82,8 mg (0,40 mmol) de carbonato de ciclohexil-1-cloroetilo. El compuesto del título se obtuvo en forma de su diclorhidrato en forma de un sólido amorfo blanco. Rendimiento: 27 mg, MS (ES^+): m/e = 669, patrón de cloro.

Ejemplo 61: 1-Ciclohexiloxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

El 1-ciclohexiloxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 20 partiendo de 50 mg (0,10

mmol) de ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico y 82,8 mg (0,40 mmol) de carbonato de ciclohexil-1-cloroetilo. El compuesto del título se obtuvo en forma de su diclorhidrato en forma de un sólido amorfo blanco. Rendimiento: 49 mg, MS (ES^+): m/e = 669, patrón de cloro.

Ejemplo 62: 1-Etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El 1-etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 20 partiendo de 50 mg (0,10 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 61,2 mg (0,40 mmol) de etilcarbonato de 1-cloroetilo. El compuesto del título se obtuvo en forma de su diclorhidrato en forma de un sólido amorfo blanco.

Rendimiento: 21 mg MS (ES^+): m/e = 615, patrón de cloro.

Ejemplo 63: 1-Etoxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

El 1-etoxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 20 partiendo de 50 mg (0,10 mmol) de ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico y 61,2 mg (0,40 mmol) de etilcarbonato de 1-cloroetil. El compuesto del título se obtuvo en forma de su clorhidrato en forma de un sólido amorfo blanco.

Rendimiento 42 mg MS (ES^+): m/e = 615, patrón de cloro.

Ejemplo 64: 2-Hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

Se disolvieron 50 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 4 ml de DMF. Posteriormente, se añadieron 20 mg de DMAP, 34,3 mg (0,16 mmol) de DCC y 46 µl (0,83 mmol) de etilenglicol. El residuo restante se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar el 2-hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico puro en forma de un sólido amorfo blanco. El diclorhidrato correspondiente se obtuvo por tratamiento con una solución 0,1 M de

HCl y por liofilización. Rendimiento: 22 mg, MS (ES^+): m/e = 572, patrón de cloro.

Ejemplo 65: 2-Hidroxi-etil éster del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

Se disolvieron 50 mg (0,08 mmol) de ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico en 10 ml de CH_2Cl_2. Posteriormente, se añadieron 3 mg de DMAP, 23 mg (0,11 mmol) de DCC y 46 µl (0,83 mmol) de etilenglicol. La mezcla resultante se agitó a temperatura ambiente durante 16 h y después se concentró a presión reducida. El residuo restante se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar el 2-hidroxi-etil éster del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico puro en forma de un sólido amorfo blanco. El diclorhidrato correspondiente se obtuvo por tratamiento con una solución 0,1 M de HCl y por liofilización. Rendimiento: 44 mg, MS (ES^+): m/e = 572, patrón de cloro.

Ejemplo 66: Carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

Se disolvieron 50 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 6 ml de DMF. Posteriormente, se añadieron 27,6 mg de KI, 126,5 mg (0,88 mmol) de K_2CO_3 y 62,8 mg (0,64 mmol) de ácido cloro-acético. La mezcla resultante se agitó durante 8 h a 60°C. Se añadieron 92 mg más de K_2CO_3 y 62,8 mg (0,64 mmol) de ácido cloro-acético. Después de 8 h más a 60°C, la mezcla de reacción se concentró a presión reducida. El residuo restante se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar el carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico puro en forma de un sólido amorfo blanco. El correspondiente diclorhidrato se obtuvo por tratamiento con una solución 0,1 M de HCl y por liofilización. Rendimiento: 21 mg, MS (ES^+): m/e = 586, patrón de cloro.

Ejemplo 67: Ácido 1-(3-metoxi-bencil)-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

(i) Éster metílico del ácido 1-(3-metoxi-bencil)-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

Se disolvieron 366,50 mg (0,929 mmol) de éster metílico del ácido 2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico en 15 ml de DMF. Se añadieron secuencialmente 192,6 mg (1,394 mmol) de K_2CO_3 y 156,1 µl (1,394 mmol)

de 1-bromometil-3-metoxi-benceno y la mezcla resultante se agitó durante 4 h a 80°C. La mezcla se diluyó con 300 ml de tolueno y se lavó con 50 ml de una solución saturada de $NaHCO_3$. El producto no era completamente soluble en tolueno, por lo que hubo que añadir acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ anhidro y se concentró a presión reducida. El residuo se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) (separación de isómeros) para dar el éster metílico del ácido 1-(3-metoxi-bencil)-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico en forma de un sólido amorfo pardo claro.

Rendimiento: 150 mg MS (ES^+): m/e = 515.

(ii) Ácido 1-(3-metoxi-bencil)-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

Se suspendieron 20 mg (0,04 mmol) de éster metílico del ácido 1-(3-metoxi-bencil)-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico en 5 ml de MeOH. Se añadieron 194 µl (0,19 mmol) de una solución acuosa 1 M de LiOH y la mezcla resultante se agitó durante 8 h a 60°C. Después de la acidificación con una solución 1 M de HCl, la mezcla se concentró. El residuo resultante se purificó por HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar el ácido 1-(3-metoxi-bencil)-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico puro en forma de un sólido amorfo incoloro. Rendimiento: 44 mg, MS (ES^+): m/e = 501.

Ejemplo 68: a) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbonil)-metil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico

b) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico

Se prepararon (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbonil)-metil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico y (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico mediante un procedimiento de acuerdo con el ejemplo 29 partiendo de 1 g (2,5 mmol) de (1-isopropil-piperidin-4-il)-amida del ácido 5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico bruta y 758,9 mg (3,04 mmol) de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida. La RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio una mezcla 1:1 de los dos isómeros descritos en el título. Estos isómeros podrían separarse por NP-HPLC usando una fase estacionaria quiral y una mezcla de heptano, etanol, metanol y

dietilamina como disolvente. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento de la (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbonil)-metil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico: 79 mg, MS (ES^+): m/e = 563, patrón de cloro.

Rendimiento de la (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico: 44 mg, MS (ES^+): m/e = 563, patrón de cloro.

Ejemplo 69: Ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

Se disolvieron 325,1 mg (0,57 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 20 ml de CH_2Cl_2. Posteriormente, se añadieron 470 µl (5,7 mmol) de ciclopropil-metanol, 152,2 mg (0,74 mmol) de DCC y 6,9 mg de DMAP. La mezcla resultante se agitó a temperatura ambiente durante 16 h. Al día siguiente se añadieron 100 µl más (2,28 mmol) de ciclopropil-metanol, 58,6 mg (0,29 mmol) de DCC y 20 mg de DMAP y la mezcla de reacción se agitó durante 48 h. El disolvente se retiró al vacío. La purificación final por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio el ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en forma de un sólido amorfo blanco. El acetato correspondiente se obtuvo mediante el siguiente procedimiento: El material descrito anteriormente se disolvió en CH_2Cl_2 y se lavó con una solución saturada de $NaHCO_3$. La capa orgánica se secó sobre $MgSO_4$ anhidro y se concentró. El residuo resultante se diluyó con 20 ml de agua que contenía 4 equiv. de AcOH y se liofilizó. Rendimiento: 231 mg, MS (ES^+): m/e = 553, patrón de cloro.

Ejemplo 70: 2-Metoxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El 2-metoxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 69 partiendo de 112 mg (0,22 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 177 µl (2,2 mmol) de 2-metoxi-etanol. El compuesto del título se obtuvo en forma de su diclorhidrato en forma de un sólido amorfo blanco. Rendimiento: 66 mg, MS (ES^+): m/e =557, patrón de cloro.

Ejemplo 71: (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-

ilcarbamoil)-metil]-4-hidroximetil-1H-benzoimidazol-2-carboxílico

Se disolvieron 85,0 mg (0,166 mmol) de éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 3 ml de THF abs. En una atmósfera de argón, se añadieron 0,25 ml (0,497 mmol) de una solución 2 M de $LiBH_4$ en THF. Después de agitar durante 1,5 h a temperatura ambiente, se añadieron 0,5 ml de agua y la mezcla de reacción se concentró. El residuo se purificó por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar la (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-hidroximetil-1H-benzoimidazol-2-carboxílico en forma de un sólido amorfo blanco. El compuesto del título se obtuvo en forma de su formiato. Rendimiento: 20 mg, MS (ES^+): m/e = 485, patrón de cloro.

Ejemplo 72: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoximetil)-1H-benzoimidazol-2-carboxílico

Se disolvieron 81,6 mg (0,065 mmol) de (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-hidroximetil-1H-benzoimidazol-2-carboxílico en 5 ml de DMF abs. A 0°C, se añadieron 21,9 mg (0,195 mmol) de terc-butilato potásico. Después de 5 min, se añadieron 12 µl (0,13 mmol) de 1-bromo-2-metoxi-etano y se dejó que la mezcla de reacción volviera a la temperatura ambiente. Después de 3 h, se añadieron 12 µl más (0,13 mmol) de 1-bromo-2-metoxi-etano y la mezcla de reacción se agitó durante 16 h. El disolvente se retiró por destilación y el residuo resultante se purificó por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar la (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoximetil)-1H-benzoimidazol-2-carboxílico en forma de un sólido amorfo pardo claro. El compuesto del título se obtuvo en forma de su formiato. Rendimiento: 12 mg, MS (ES^+): m/e = 543, patrón de cloro.

Ejemplo 73: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(morfolina-4-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(morfolina-4-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 450 mg (0,90 mmol) de ácido 1-[(5-cloro-piridin-2-carbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 87 µl (2,70 mmol) de morfolina. El compuesto del título se obtuvo en forma de su formiato. La posterior transformación en el correspondiente acetato dio un sólido amorfo blanco. Rendimiento: 476 mg, MS (ES^+): m/e = 568,

patrón de cloro.

Ejemplo 74: (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 423 mg (0,85 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 128,3 mg (0,94 mmol) de clorhidrato de homomorfolina. El compuesto del título se obtuvo en forma de su formiato. La posterior transformación en el acetato correspondiente dio un sólido amorfo blanco. Rendimiento: 370 mg, MS (ES^+): m/e = 582, patrón de cloro.

Ejemplo 75: (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2,6-dimetil-piperidina-1-carbamoil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2,6-dimetil-piperidina-1-carbamoil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 100 mg (0,20 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 50,0 µl (0,40 mmol) de 2,6-dimetil-piperidina. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 72 mg, MS (ES^+): m/e = 594, patrón de cloro.

Ejemplo 76: (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(4,4-difluoro-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(4,4-difluoro-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 870 mg (1,70 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 302,3 mg (1,87 mmol) de clorhidrato de 4,4-difluoro-piridina. El compuesto del título se obtuvo en forma de su formiato. La posterior transformación en el acetato correspondiente dio un sólido amorfo blanco. Rendimiento: 700 mg, MS (ES^+): m/e = 602, patrón de cloro.

Ejemplo 77: (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico se preparó

mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 147,8 mg (0,296 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 44,8 mg (0,326 mmol) de clorhidrato de homomorfolina. El compuesto del título se obtuvo en forma de su formiato. La posterior transformación en el correspondiente acetato dio un sólido amorfo blanco. Rendimiento: 113 mg, MS (ES^+): m/e = 582, patrón de cloro.

Ejemplo 78: 2-Hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El 2-Hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 65 partiendo de 100 mg (0,17 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 93 µl (1,7 mmol) de etilenglicol. El compuesto del título se obtuvo en forma de su diclorhidrato en forma de un sólido amorfo blanco. Rendimiento: 86 mg, MS (ES^+): m/e = 572, patrón de cloro.

Ejemplo 79: Carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 66 partiendo de 100 mg (0,17 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 62,9 mg (0,68 mmol) de ácido cloro-acético. El compuesto del título se obtuvo en forma de su diclorhidrato en forma de un sólido amorfo blanco. Rendimiento: 44 mg, MS (ES^+): m/e = 586, patrón de cloro.

Ejemplo 80: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 205 mg (0,34 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 46,6 mg (0,37 mmol) de clorhidrato de 3-metoxi-azetidina. El compuesto del título se obtuvo en forma de su formiato. La posterior transformación en el correspondiente acetato dio un sólido amorfo blanco. Rendimiento: 190 mg, MS (ES^+): m/e = 597, patrón de cloro.

Ejemplo 81: a) Ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-

benzoimidazol-4-carboxílico

b) Ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-4-carboxílico

Se disolvieron 1,45 g (4,21 mmol) de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 45 ml de DMF. Posteriormente, se añadieron 698,2 mg (5,05 mmol) de K_2CO_3 y 888,8 mg (4,42 mmol) de 1-bromometil-3-metoxi-benceno y la mezcla resultante se agitó durante 2 h a 60°C. El disolvente se retiró por destilación. El residuo se recogió en 300 ml de acetato de etilo y se lavó una vez con una solución saturada de $NaHCO_3$ y con salmuera. La capa orgánica se secó sobre $MgSO_4$ anhidro, se concentró a presión reducida y se purificó por cromatografía sobre gel de sílice usando una mezcla de acetato de etilo-metanol como eluyente para dar 1,19 g de una mezcla 4:1 de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-4-carboxílico y éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-4-carboxílico. Esa mezcla de isómeros se disolvió en 100 ml de MeOH. Se añadieron 12,8 ml (12,8 mmol) de una solución acuosa 1 M de LiOH y la suspensión resultante se agitó durante 3 h a 60°C. La mezcla se acidificó mediante la adición de una solución 1 M de HCl y se concentró a presión reducida. La purificación final por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio los dos isómeros a) ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-4-carboxílico y b) ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-4-carboxílico en forma de sólidos amorfos blancos. Los dos isómeros se transformaron en los correspondientes diclorhidratos.

Rendimiento del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-4-carboxílico: 890 mg, MS (ES^+): m/e = 451.

Rendimiento del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-4-carboxílico: 250 mg, MS (ES^+): m/e = 451.

Ejemplo 82: a) Ácido 1-[2-(4-cloro-fenil)-etil-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

b) Ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico

Se disolvieron 1,45 g (4,21 mmol) de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico en 45 ml de DMF. Posteriormente, se añadieron 989,1 mg (7,16 mmol) de K_2CO_3 y 1,11 g (6,32 mmol)

de 1-cloro-4-(2-cloro-etil)-benceno y la mezcla resultante se agitó durante 24 h a 80°C. El disolvente se retiró por destilación. El residuo se recogió en 300 ml de acetato de etilo y se lavó una vez con una solución saturada de $NaHCO_3$ y con salmuera. La capa orgánica se secó sobre $MgSO_4$ anhidro, se concentró y se purificó por cromatografía ultrarrápida usando una mezcla de acetato de etilo-metanol como eluyente para dar 1,30 g de una mezcla 3:1 de éster metílico del ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y éster metílico del ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico. Esa mezcla de isómeros se disolvió en 100 ml de MeOH. Se añadieron 16,2 ml (16,2 mmol) de una solución acuosa 1 M de LiOH y la suspensión resultante se agitó durante 3 h a 60°C. La mezcla se acidificó mediante la adición de una solución 1 M de HCl y se concentró a presión reducida. La purificación final por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio los dos isómeros a) ácido 1-[2-(4-cloro-fenil)-etil-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y b) ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico en forma de sólidos amorfos blancos. Los dos isómeros se aislaron en forma de sus formiatos.

Rendimiento del ácido 1-[2-(4-cloro-fenil)-etil-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico: 800 mg, MS (ES^+): m/e = 468, patrón de cloro.

Rendimiento del ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico: 250 mg, MS (ES^+): m/e = 468, patrón de cloro.

Ejemplo 83: (1-isopropil-piperidin-4-il)-amida del ácido 4-(3-hidroxi-azetidina-1-carbonil)-1-(3-metoxi-bencil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 4-(3-hidroxi-azetidina-1-carbonil)-1-(3-metoxi-bencil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 150 mg (0,287 mol) de ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-4-carboxílico y 23,0 mg (0,315 mmol) de 3-hidroxi-azetidina. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 62 mg, MS (ES^+): m/e = 506.

Ejemplo 84: (1-isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-

hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 150 mg (0,29 mmol) de ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 23,4 mg (0,32 mmol) de 3-hidroxi-azetidina. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 62 mg, MS (ES^+): m/e = 524, patrón de cloro.

Ejemplo 85: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50 mg (0,097 mmol) de ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 13,5 mg (0,015 mmol) de 3-metoxi-azetidina. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 35 mg, MS (ES^+): m/e = 538, patrón de cloro.

Ejemplo 86: a) Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-5-carboxílico

b) Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-5-carboxílico

El éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-5-carboxílico y el éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-5-carboxílico se prepararon mediante un procedimiento de acuerdo con el ejemplo 5 iil) partiendo de 300 mg (0,87 mmol) de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 210,2 mg (1,04 mmol) de 1-bromometil-3-metoxi-benceno. La RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio una mezcla 1:1 de los dos isómeros descritos en el título. Estos isómeros podrían separarse por NP-HPLC usando una fase estacionaria quiral y una mezcla de heptano, etanol, metanol y dietilamina como disolvente. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento del éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-5-carboxílico: 65 mg, MS (ES^+): m/e = 465.

Rendimiento del éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-5-carboxílico: 70 mg, MS (ES^+): m/e = 465.

Ejemplo 87: a) Éster metílico del ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-

piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

b) Éster metílico del ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

El éster metílico del ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y el éster metílico del ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico se prepararon mediante un procedimiento de acuerdo con el ejemplo 5 iii) partiendo de 300 mg (0,87 mmol) de ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 365,9 mg (2,09 mmol) de 1-cloro-4-(2-cloro-etil)-benceno. Como el 1-cloro-4-(2-cloro-etil)-benceno es menos reactivo, el tiempo de reacción tuvo que ampliarse a 10 h. La RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio una mezcla 4:3 de los dos isómeros descritos en el título. Estos isómeros podrían separarse por NP-HPLC usando una fase estacionaria quiral y una mezcla de heptano, etanol y metanol como disolvente. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento del éster metílico del ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico: 102 mg, MS (ES^+): m/e = 483, patrón de cloro.

Rendimiento del éster metílico del ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico: 74 mg, MS (ES^+): m/e = 483, patrón de cloro.

Ejemplo 88: Ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 6 partiendo de 100 mg (0,21 mmol) de éster metílico del ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 1,04 ml (1,04 mmol) de una solución 1 M de LiOH. El compuesto del título se obtuvo en forma de su diclorhidrato en forma de un sólido amorfo blanco. Rendimiento: 54 mg, MS (ES^+): m/e = 469, patrón de cloro.

Ejemplo 89: a) Ácido 1-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

b) Ácido 3-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico

El ácido 1-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-

ilcarbamoil)-1H-benzoimidazol-4-carboxílico y el ácido 3-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico se prepararon mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 200 mg (0,58 mmol) de ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 151,9 mg (0,58 mmol) de 2-bromoetil-5-cloro-benzo[b]tiofeno. La hidrólisis de los ésteres resultantes y la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron los compuestos del título en forma de sus formiatos en forma de sólidos amorfos blancos.

Rendimiento del ácido 1-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico: 134 mg, MS (ES^+): m/e = 511, patrón de cloro.

Rendimiento del ácido 3-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico: 49 mg, MS (ES^+): m/e = 511, patrón de cloro.

Ejemplo 90: Ácido 1-(5-cloro-1H-indazol-3-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El ácido 1-(5-cloro-1H-indazol-3-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 200 mg (0,58 mmol) de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 116,8 mg (0,58 mmol) de 5-cloro-3-clorometil-1H-indazol. La hidrólisis del éster resultante y la purificación por RP-HPLC (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron el compuesto del título en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 20 mg, MS (ES^+): m/e = 495, patrón de cloro.

Ejemplo 91: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(4-hidroxi-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(4-hidroxi-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 670 mg (1,10 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 124,0 mg (1,21 mmol) de piperidin-4-ol. El compuesto del título se obtuvo en forma de su formiato. La posterior transformación en el correspondiente acetato dio un sólido amorfo blanco. Rendimiento: 538 mg, MS (ES^+): m/e = 611, patrón de cloro.

Ejemplo 92: (1-Isopropil-piperidin-4-il)-amida del ácido 7-[5-(5-cloro-tiofen-2-il)-

isoxazol-3-ilmetil]-1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico

(i) Ácido 1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico

Se suspendieron 5,00 g (24,0 mmol) de 8-hidroximetil-1,3-dimetil-3,7-dihidro-purina-2,6-diona en 15 ml de agua. Se añadieron 16,8 ml (33,6 mmol) de una solución 2 N de NaOH. La mezcla resultante se enfrió a 5°C. A esa temperatura, se añadió una solución de 5,05 g (32,2 mmol) de $KMnO_4$ en 86 ml de agua. Después de agitar a temperatura ambiente durante 4 h, la mezcla de reacción se filtró sobre Celite. Después de la adición de carbono activado, el filtrado se filtró de nuevo sobre Celite. El filtrado se concentró hasta un volumen de 200 ml y se le añadieron 5 ml de una solución conc. de HCl. Después de dejar en reposo a 4°C durante 16 h, el producto cristalino se retiró por filtración, se lavó dos veces con agua fría y acetona y se secó a presión reducida a 40°C. Rendimiento: 5,18 g, MS (ES^+): m/e = 225.

(ii) (1-Isopropil-piperidin-4-il)-amida del ácido 1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico

Se disolvieron 100 mg (0,45 mmol) de ácido 1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico en 5 ml de DMF. Posteriormente, se añadieron 227 µl (1,35 mmol) de DIPEA y 186,5 mg (0,495 mmol) de HATU. Después de 1 h, se añadieron 105,6 mg (0,495 mmol) de diclorhidrato de 1-isopropil-piperidina-4-ilamina y 227 µl (1,35 mmol) de DIPEA y la mezcla resultante se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se concentró y se purificó por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar la (1-isopropil-piperidin-4-il)-amida del ácido 1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico en forma de su formiato.

(iii) (1-Isopropil-piperidin-4-il)-amida del ácido 7-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico

Se disolvieron 155 mg (0,45 mmol) de ácido 1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico en 5 ml de DMF. Posteriormente, se añadieron 184,4 mg (1,35 mmol) de K_2CO_3 y 111,5 mg (0,405 mmol) de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol y la mezcla resultante se agitó a 80°C durante 1 h. La mezcla se concentró y se purificó por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar la (1-isopropil-piperidin-4-il)-amida del ácido 7-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico. El diclorhidrato correspondiente se obtuvo por tratamiento del producto con una solución 0,1 M de HCl y por liofilización. Rendimiento: 55 mg, MS (ES^+): m/e = 546, patrón de cloro.

Ejemplo 93: a) Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

b) Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico

(i) Éster terc-butílico del ácido (1-ciclopropil-piperidin-4-il)-carbámico

A una solución de 14,0 g (0,0699 mol) de éster terc-butílico del ácido piperidin-4-il-carbámico en 500 ml de MeOH abs. se le añadieron 250 mg de tamices moleculares 3 Å secos. En una atmósfera de argón, se añadieron 39,9 ml (0,699 mol) de ácido acético y 52,5 ml (0,262 mol) de (1-etoxi-ciclopropoxi)-trimetil-silano. La capa acuosa se extrajo con 300 ml de acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ y se concentraron al vacío para dar el éster terc-butílico del ácido (1-ciclopropil-piperidin-4-il)-carbámico bruto en forma de un sólido incoloro. Rendimiento: 23,0 g, MS (ES^+): m/e = 241.

(ii) Diclorhidrato 1-ciclopropil-piperidin-4-ilamina

Se disolvieron 23,0 g del éster terc-butílico del ácido (1-ciclopropil-piperidin-4-il)-carbámico descrito anteriormente en 35 0 ml de TFA y se agitaron durante 45 minutos a temperatura ambiente. La mezcla de reacción se concentró a presión reducida y el residuo resultante se disolvió en agua. Después de la adición de 23,1 ml de una solución conc. de HCl, la mezcla se liofilizó para producir un sólido amorfo blanco. El sólido se suspendió en 300 ml de acetato de etilo y se trató durante 45 minutos en condiciones ultrasónicas. Ese procedimiento se repitió dos veces. Finalmente, el sólido cristalino filtrado se secó a 45°C a presión reducida. Rendimiento: 15,9 g, MS (ES^+): m/e = 141.

(iii) Éster metílico del ácido 2-triclorometil-1H-benzoimidazol-5-carboxílico

A una solución de 10,0 g (0,060 mol) de éster metílico del ácido 3,4-diaminobenzoico en 260 ml de ácido acético se le añadieron 10,47 ml (0,084 mol) de éster metílico del ácido 2,2,2-tricloro-acetimídico. Después de agitar durante 2 h a temperatura ambiente, el ácido acético se evaporó. El residuo se disolvió en CH_2Cl_2, se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró a presión reducida para dar el éster metílico del ácido 2-triclorometil-1H-benzoimidazol-5-carboxílico bruto en forma de un material gomoso de color pardo. Rendimiento: 20,5 g, MS (ES^+): m/e = 293, patrón de cloro.

(iv) Éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

A una mezcla de 7,53 g (35,3 mmol) de diclorhidrato de 1-ciclopropil-piperidin-

4-ilamina y 32,39 g (0,386 mol) de $NaHCO_3$ en 1300 ml de THF y 370 ml de agua se le añadió una solución de 11,79 g (32,1 mmol) de éster metílico del ácido 2-triclorometil-1H-benzoimidazol-5-carboxílico en 370 ml de THF. La mezcla de reacción se agitó vigorosamente durante 2 h a temperatura ambiente. El THF se evaporó. El precipitado se retiró por filtración y se lavó dos veces con aprox. 300 ml de una solución saturada de $NaHCO_3$ en condiciones ultrasónicas. Después de la filtración, el sólido resultante se lavó dos veces con 150 ml de agua y se secó al vacío a 45°C para dar el éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico puro en forma de un material cristalino pardo claro. Rendimiento: 9,9 g, MS (ES^+): m/e = 343.

(v) Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

Se disolvieron 17,3 g (50,52 mmol) del éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico en 800 ml de DMF. Posteriormente, se añadieron 10,47 g (75,8 mmol) de K_2CO_3 y 14,84 g (50,52 mmol) 5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil éster del ácido metanosulfónico y la mezcla resultante se agitó durante 2 h a 80°C. La mezcla se concentró a presión reducida. El residuo se suspendió en 800 ml de acetato de etilo. Al día siguiente el precipitado resultante se retiró por filtración y se lavó con 100 ml de acetato de etilo para dar el éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico. El filtrado se concentró hasta un volumen de aprox. de 100 ml. De nuevo el precipitado formado se retiró por filtración. Ese procedimiento se repitió una vez más. El filtrado resultante se concentró a presión reducida y finalmente se purificó por cromatografía ultrarrápida sobre gel de sílice usando acetato de etilo como eluyente. Las fracciones que contenían el producto se concentraron al vacío para dar el éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico puro (>98%) en forma de un sólido cristalino pardo claro. Rendimiento: 7,9 g, MS (ES^+): m/e = 540, patrón de cloro.

(vi) Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

Se recristalizó 1,0 g del éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico en acetato de etilo. Rendimiento: 500 mg, MS (ES^+): m/e = 540, patrón de cloro.

Ejemplo 94: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-

4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

Se disolvieron 7,84 g (14,52 mmol) de éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico en 400 ml de MeOH. Se añadieron 72,59 ml (72,59 mmol) de una solución acuosa 1 M de LiOH y la mezcla resultante se agitó durante 7 h a 60ºC. La solución se concentró hasta un volumen de aprox. 200 ml y se acidificó mediante la adición de una solución acuosa 4 M de HCl hasta que se alcanzó un pH ≈ 1. Después de 30 minutos, el precipitado resultante se retiró por filtración y se lavó varias veces con MeOH frío. La recristalización en MeOH dio el ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico puro en forma de un sólido cristalino incoloro. El compuesto del título se obtuvo en forma de su monoclorhidrato. Rendimiento: 7,3 g, MS (ES^+): m/e = 526, patrón de cloro.

Se transformaron 4,0 g (7,11 mmol) del producto descrito anteriormente en su sal sódica por suspensión en 10 ml de agua, adición de 100,15 ml de una solución acuosa 0,2 M de NaOH y posterior extracción con 100 ml de n-butanol (2 x). Las capas de butanol combinadas se extrajeron de nuevo con 20 ml de agua (3 x) y se codestilaron con 200 ml de agua (3 x). La solución resultante se liofilizó para dar el compuesto del título en forma de su sal sódica en forma de un material amorfo blanco. Rendimiento: 3,49 g.

El ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico también se preparó mediante una síntesis selectiva:

(i) C-[5-(5-cloro-tiofen-2-il)-isoxazol-3-il]-metilamina

Se disolvieron 1,00 g (3,59 mmol) de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol y 503,3 mg (3,59 mmol) de urotropina en 40 ml de EtOH. La mezcla de reacción se agitó a temperatura ambiente durante 16 h. Al día siguiente, se añadieron 3 ml de una solución conc. de HCl y la mezcla resultante se calentó a reflujo durante 45 minutos. Después de enfriar, el precipitado se retiró por filtración y se lavó con agua. El material blanco cristalino se secó a presión reducida a 40ºC. Rendimiento: 806 mg.

(ii) Éster metílico del ácido 4-{[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-amino}-3-nitro-benzoico

A una solución de 634,4 mg (3,19 mmol) de éster metílico del ácido 4-fluoro-3-nitro-benzoico en 12 ml de DMF se le añadieron 800,0 mg (3,19 mmol) de C-[5-(5-

cloro-tiofen-2-il)-isoxazol-3-il]-metilamina y 0,88 ml (6,37 mmol) de trietilamina. La mezcla de reacción se agitó a temperatura ambiente durante 16 h y se le añadieron 12 ml de agua. El precipitado se retiró por filtración y se lavó con agua. El material cristalino amarillo se secó a presión reducida a 40ºC. Rendimiento: 1,03 g, MS (ES^+): m/e = 394, patrón de cloro.

(iii) Éster metílico del ácido 3-amino-4-{[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-amino}-benzoico

Se disolvieron 97,1 mg (0,41 mmol) de $NiCl_3 \cdot 6H_2O$ en 10 ml de MeOH y se trataron en condiciones ultrasónicas. Se añadieron 46,4 mg (1,24 mmol) de $NaBH_4$. Después de 15 minutos, se añadió una solución de 214,0 g (0,54 mmol) de éster metílico del ácido 4-{[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-amino}-3-nitro-benzoico en 20 ml de CH_2Cl_2. Después de 15 minutos, se añadieron en tres porciones 55,6 mg (1,48 mmol) de $NaBH_4$. La mezcla de reacción se trató en condiciones ultrasónicas durante 2 h. La adición de $NaBH_4$ (55,6 mg cada vez) y el tratamiento en condiciones ultrasónicas tuvo que repetirse tres veces para conseguir la completa conversión. La mezcla de reacción se filtró sobre "Celite" y el filtrado se concentró a presión reducida. El residuo se suspendió en 30 ml de MeOH. Después de la filtración, el filtrado se concentró al vacío y el residuo se recogió en 100 ml de CH_2Cl_2. La capa orgánica se lavó cuatro veces con agua, se secó sobre $MgSO_4$ anhidro y se concentró a presión reducida para producir el éster metílico del ácido 3-amino-4-{[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-amino}-benzoico bruto en forma de un aceite pardo. Rendimiento: 83 mg, MS (ES^+): m/e = 364, patrón de cloro.

(iv) Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-triclorometil-1H-benzoimidazol-5-carboxílico

Se disolvieron 36,0 mg (0,098 mmol) de éster metílico del ácido 3-amino-4-{[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-amino}-benzoico en 3 ml de ácido acético. Se añadieron 17,4 µl (0,14 mmol) de éster metílico del ácido 2,2,2-tricloro-acetimídico y la mezcla resultante se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró a presión reducida y el residuo se codestiló dos veces con 15 ml de tolueno para dar el éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-triclorometil-1H-benzoimidazol-5-carboxílico bruto en forma de un sólido pardo. Rendimiento: 49 mg, MS (ES^+): m/e = 491, patrón de cloro.

(v) Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

Se disolvieron 21,0 mg (0,098 mmol) de diclorhidrato de 1-ciclopropil-piperidin-

4-ilamina en 3 ml de CH_3CN y 3 ml de agua. Se añadieron 82,3 mg (0,98 mmol, 10 equiv.) de $NaHCO_3$. Finalmente, se añadió una solución de 48,1 mg (0,098 mmol) de éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico en 2 ml de CH_3CN y la mezcla resultante se agitó vigorosamente durante 3 h a temperatura de reflujo. La mezcla se concentró a presión reducida. El residuo se purificó por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar el ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico puro en forma de un sólido amorfo incoloro. Rendimiento: 26 mg (50%), MS (ES^+): m/e = 526, patrón de cloro.

(Simultáneamente, se hidrolizó el éster metílico en las condiciones descritas).

Ejemplo 95: Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

El ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 94 partiendo de 250,0 mg (0,46 mmol) de éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico. El compuesto del título se aisló en forma de su monoclorhidrato en forma de un material cristalino incoloro. Rendimiento: 135 mg, MS (ES^+): m/e = 526, patrón de cloro.

Ejemplo 96: a) Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

b) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico

(i) Éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El Éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 93 (iv) partiendo de 1,62 g (5,52 mmol) de éster metílico del ácido 2-triclorometil-1H-benzoimidazol-4-carboxílico y 1,29 g (6,07 mmol) de diclorhidrato de 1-ciclopropil-piperidin-4-ilamina. Rendimiento: 1,62 g, MS (ES^+): m/e = 343.

(ii) a) Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

b) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico

El ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y el ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico se prepararon mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 248,0 mg (0,72 mmol) de éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 221,9 mg (0,79 mmol) de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol. La hidrólisis de los ésteres resultantes y la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron los compuestos del título y sus formiatos en forma de sólidos amorfos blancos. Los correspondientes clorhidratos se obtuvieron por tratamiento de ambos productos con una solución 0,1 M de HCl y por liofilización.

Rendimiento del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico: 119 mg, MS (ES^+): m/e = 526, patrón de cloro.

Rendimiento del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico: 39 mg, MS (ES^+): m/e = 526, patrón de cloro.

Ejemplo 97: Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 15 partiendo de 1,40 g (4,09 mmol) de ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 1,02 g (4,09 mmol) de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida. Rendimiento: 1,90 g, MS (ES^+): m/e = 511, patrón de cloro.

Ejemplo 98: Ácido 1-[(5-cloro-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El ácido 1-[(5-cloro-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 16 partiendo de 1,89 g (3,70 mmol) de éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico. Rendimiento: 1,90 g, MS (ES^+): m/e = 497, patrón de cloro.

Ejemplo 99: Ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante

un procedimiento de acuerdo con el ejemplo 69 partiendo de 589,0 (1,19 mmol) de ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico y 1,92 ml (23,8 mmol) de ciclopropil-metanol. Rendimiento: 362 mg, MS (ES^+): m/e = 551, patrón de cloro.

Ejemplo 100: a) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico

b) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico

(i) Éster metílico del ácido 2-triclorometil-3H-tieno[3,4-d]imidazol-6-carboxílico

A una solución de 2,00 g (11,6 mmol) de éster metílico del ácido 3,4-diamino-tiofeno-2-carboxílico en 50 ml de ácido acético se le añadieron 2,06 ml (16,24 mmol) de éster metílico del ácido 2,2,2-tricloro-acetimídico. Después de agitar durante 2 h a 95°C, la mezcla se concentró y se codestiló dos veces con 100 ml de tolueno.

El residuo se secó al vacío para producir un material gomoso pardo. Rendimiento: 4,2 g, MS (ES^+): m/e = 351.

(iii) a) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico

b) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico

El ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico y el ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico se prepararon mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 500 mg (1,40 mmol) de ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico y 397,4 mg (1,40 mmol) de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol. La hidrólisis de los ésteres resultantes y la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio los compuestos del título en forma de sus formiatos en forma de sólidos amorfos blancos. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico: 113 mg, MS (ES^+): m/e = 534, patrón de cloro.

Rendimiento del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico: 146 mg, MS (ES^+): m/e = 534, patrón de cloro.

Ejemplo 101: a) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico

b) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico

El éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 93 (iv) partiendo de 203,7 mg (0,68 mmol) de éster metílico del ácido 2-triclorometil-3H-tieno[3,4-d]imidazol-6-carboxílico y 158,7 mg (0,75 mmol) de diclorhidrato de 1-ciclopropil-piperidin-4-ilamina. Rendimiento: 309 mg, MS (ES^+): m/e = 349.

(ii) a) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico

b) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico

El ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico y el ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico se prepararon mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 236,0 mg (0,68 mmol) de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico y 188,7 mg (0,68 mmol) de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol. La hidrólisis de los ésteres resultantes y la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron los compuestos del título en forma de sus formiatos en forma de sólidos amorfos blancos. La asignación estructural se realizó por espectroscopía NOE.

Rendimiento del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico: 46 mg, MS (ES^+): m/e = 531, patrón de cloro.

Rendimiento del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico: 78 mg, MS (ES^+): m/e = 531, patrón de cloro.

Ejemplo 102: 2-[(1-isopropil-piperidin-4-il)-amida] de 6-[(2-hidroxi-etil)-amida] del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-tieno[3,4-d]imidazol-2,6-dicarboxílico

La 2-[(1-isopropil-piperidin-4-il)-amida] de 6-[(2-hidroxi-etil)-amida] del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-tieno[3,4-d]imidazol-2,6-dicarboxílico se

preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 96 mg (0,18 mmol) de ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico y 11,0 µl (0,18 mmol) de 2-amino-etanol. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 55 mg, MS (ES^+): m/e = 577, patrón de cloro.

Ejemplo 103: a) Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico

b) Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico

El ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico y el ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico se prepararon mediante un procedimiento análogo al ejemplo 81 partiendo de 500 mg (1,40 mmol) de ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico y 356,0 mg (1,40 mmol) de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida. La hidrólisis de los ésteres resultantes por tratamiento con BBr_3 de acuerdo con el ejemplo 16 y la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron los compuestos del título en forma de sus formiatos en forma de sólidos amorfos blancos. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico: 142 mg, MS (ES^+): m/e = 505, patrón de cloro.

Rendimiento del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico: 58 mg, MS (ES^+): m/e = 505, patrón de cloro.

Ejemplo 104: (1-Isopropil-piperidin-4-il)-amida del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-([1,4]oxazepano-4-carbonil)-3H-tieno[3,4-d]imidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-([1,4]oxazepano-4-carbonil)-3H-tieno[3,4-d]imidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 80 mg (0,158 mmol) de ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico y 21,8 mg (0,158 mmol) de clorhidrato de homomorfolina. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 70 mg, MS (ES^+): m/e =

588, patrón de cloro.

Ejemplo 105: Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico

(i) Éster metílico del ácido 2-triclorometil-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico

El Éster metílico del ácido 2-triclorometil-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 100 (i) partiendo de 500 mg (1,85 mmol) de éster metílico del ácido 3,4-diamino-5-(2,2,2-trifluoro-etoxi)-tiofeno-2-carboxílico y 328,0 µl (2,59 mmol) de éster metílico del ácido 2,2,2-tricloro-acetimídico.

(ii) Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico

El Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 93 (iv) partiendo de 735,0 mg (1,85 mmol) de éster metílico del ácido 2-triclorometil-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico y 397,8 mg (1,85 mmol) de diclorhidrato de 1-isopropil-piperidin-4-ilamina. Rendimiento: 71 mg, MS (ES^+): m/e = 449.

(iii) Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico

El Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 68,0 mg (0,15 mmol) de éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico y 42,2 mg (0,15 mmol) de 3-bromometil-5-(5-cloro-tiofen-2-il)-isoxazol. La purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio el compuesto del título en forma de su formiato en forma de un sólido amorfo blanco. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE. Rendimiento: 19 mg, MS (ES^+): m/e = 646, patrón de cloro.

Ejemplo 106: a) Ácido 1-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

b) Ácido 3-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

El ácido 1-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y el ácido 3-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico se prepararon mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 240 mg (0,70 mmol) de éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 201,3 mg (0,70 mmol) de 5-bromometil-3-(3-cloro-tiofen-2-il)-isoxazol. La hidrólisis de los ésteres resultantes y la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron los compuestos del título en forma de sus formiatos en forma de sólidos amorfos blancos. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento del ácido 1-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico: 93 mg, MS (ES^+): m/e = 526, patrón de cloro.

Rendimiento del ácido 3-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico: 60 mg, MS (ES^+): m/e = 526, patrón de cloro.

Ejemplo 107: a) Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

b) Ácido 3-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico

El ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y el ácido 3-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico se prepararon mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 200 mg (0,58 mmol) de éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico y 181,8 mg (0,58 mmol) de 2-bromometil-5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol. La hidrólisis de los ésteres resultantes y la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron los compuestos del título en forma de sus formiatos en forma de sólidos amorfos blancos. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento del ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico: 18 mg, MS (ES^+): m/e = 543, patrón de cloro.

Rendimiento del ácido 3-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-

isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico: 6 mg, MS (ES^+): m/e = 543, patrón de cloro.

Ejemplo 108: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico

(i) 1-(2-Metoxi-etoxi)-2,3-dinitro-benceno

Se disolvieron 1,50 g (8,15 mmol) de 2,3-dinitro-fenol en 75 ml de acetona. Posteriormente, se añadieron 1,69 g (12,22 mol) de K_2CO_3, 135,3 mg (0,81 mmol) de KI y 0,93 ml (9,77 mmol) de 1-bromo-2-metoxi-etano. La mezcla de reacción se calentó a reflujo durante 8 h. Después de ese tiempo, se añadieron 1,69 g más (12,22 mol) de K_2CO_3, 400 mg de KI y 0,93 ml (9,77 mmol) de 1-bromo-2-metoxi-etano. La mezcla resultante se calentó a reflujo durante 16 h y después se concentró a presión reducida. El residuo se disolvió en acetato de etilo caliente y se purificó por cromatografía ultrarrápida sobre gel de sílice usando una mezcla de acetato de etilo/heptano como eluyente para producir 1-(2-metoxi-etoxi)-2,3-dinitro-benceno en forma de un material cristalino naranja. Rendimiento: 1,35 g, MS (ES^+): m/e = 243.

(ii) 3-(2-Metoxi-etoxi)-benceno-1,2-diamina

Se disolvieron 1,80 g (7,43 mmol) de 1-(2-metoxi-etoxi)-2,3-dinitro-benceno en 250 ml de MeOH. La solución se evacuó y se aclaró varias veces con argón. Se añadieron 250 mg de paladio sobre carbono (10%) y la mezcla se evacuó de nuevo y se aclaró varias veces con argón. Finalmente, el argón se cambió por hidrógeno (globo cargado con hidrógeno) y la mezcla se agitó durante 2 h a temperatura ambiente. La mezcla de reacción se filtró sobre "Celite" y el residuo del filtro se lavó con 100 ml de MeOH. El filtrado se concentró al vacío para dar la 3-(2-metoxi-etoxi)-benceno-1,2-diamina pura en forma de un aceite pardo. Rendimiento: 1,33 g, MS (ES^+): m/e = 183.

(iii) 4-(2-Metoxi-etoxi)-2-triclorometil-1H-benzoimidazol

Se disolvieron 1,33 g (7,30 mmol) de 3-(2-metoxi-etoxi)-benceno-1,2-diamina en 35 ml de ácido acético. Se añadieron 1,25 ml (10,22 mmol) de éster metílico del ácido 2,22,-tricloro-acetimídico y la mezcla resultante se agitó durante 2 h a temperatura ambiente. La mezcla se concentró a presión reducida y el residuo se codestiló dos veces con 20 ml de tolueno para dar el 4-(2-metoxi-etoxi)-2-triclorometil-1H-benzoimidazol bruto en forma de un sólido pardo. Rendimiento: 2,25 g, MS (ES^+): m/e = 309, patrón de cloro.

(iv) (1-Isopropil-piperidin-4-il)-amida del ácido 4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 5 (ii) partiendo de 1,91 g (6,18 mmol) de 4-(2-metoxi-etoxi)-2-triclorometil-1H-benzoimidazol y 1,46 g (6,79 mmol) de diclorhidrato de 1-isopropil-piperidin-4-ilamina. La purificación final se consiguió por cromatografía ultrarrápida sobre gel de sílice usando una mezcla de acetato de etilo/MeOH como eluyente. Rendimiento: 660 mg, MS (ES^+): m/e = 361.

(v) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 5 (iii) partiendo de 650,0 mg (1,80 mmol) de (1-isopropil-piperidin-4-il)-amida del ácido 4-(2-metoxi-etoxi)(-1H-benzoimidazol-2-carboxílico y 449,9 mg (1,80 mmol) de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida. La purificación por cromatografía ultrarrápida sobre gel de sílice usando una mezcla de acetato de etilo/heptano como eluyente dio una mezcla 9:1 de (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico y (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-7-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico. Estos isómeros se separaron por NP-HPLC usando una fase estacionaria quiral y una mezcla de heptano, etanol, metanol y dietilamina como disolvente. El compuesto del título se transformó en su acetato produciendo un material amorfo incoloro.

El rendimiento del (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico fue de 500 mg; MS (ES^+): m/e = 529, patrón de cloro.

Ejemplo 109: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-etoxi-etoxi)-1H-benzoimidazol-2-carboxílico

(i) 1-(2-Etoxi-etoxi)-2,3-dinitro-benceno

El 1-(2-etoxi-etoxi)-2,3-dinitro-benceno se preparó mediante un procedimiento de acuerdo con el ejemplo 108 (i) partiendo de 500 mg (2,72 mmol) de 2,3-dinitro-fenol y 0,72 ml (6,52 mmol) de 1-cloro-2-etoxi-etano. Rendimiento: 450 mg, MS (ES^+): m/e = 257.

(ii) 3-(2-Etoxi-etoxi)-benceno-1,2-diamina

La 3-(2-etoxi-etoxi)-benceno-1,2-diamina se preparó mediante un procedimiento de acuerdo con el ejemplo 108 (ii) partiendo de 450 mg (1,76 mmol) de

1-(2-etoxi-etoxi)-2,3-dinitro-benceno. Rendimiento: 345 mg, MS (ES^+): m/e = 197.

(iii) 4-(2-etoxi-etoxi)-2-triclorometil)-1H-benzoimidazol

El 4-(2-etoxi-etoxi)-2-triclorometil)-1H-benzoimidazol se preparó mediante un procedimiento de acuerdo con el ejemplo 108 (iii) partiendo de 345 mg (1,76 mmol) de 3-(2-etoxi-etoxi)-benceno-1,2-diamina y 0,30 ml (2,46 mmol) de éster metílico del ácido 2,2,2-tricloro-acetimídico. Rendimiento: 568 mg, MS (ES^+): m/e = 323, patrón de cloro.

(iv) (1-Isopropil-piperidin-4-il)-amida del ácido 4-(2-etoxi-etoxi)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 4-(2-etoxi-etoxi)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 108 (iv) partiendo de 569,6 mg (1,76 mmol) de 4-(2-etoxi-etoxi)-2-triclorometil-1H-benzoimidazol y 454,4 mg (2,11 mmol) de diclorhidrato de 1-isopropil-piperidin-4-ilamina. Rendimiento: 540 mg, MS (ES^+): m/e = 375.

(v) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-etoxi-etoxi)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-etoxi-etoxi)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 108 (v) partiendo de 540,0 mg (1,44 mmol) de (1-isopropil-piperidin-4-il)-amida del ácido 4-(2-etoxi-etoxi)-1H-benzoimidazol-2-carboxílico y 359,8 mg (1,44 mmol) de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida. El compuesto del título se transformó en su acetato produciendo un material amorfo incoloro.

Rendimiento de la (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-etoxi-etoxi)-1H-benzoimidazol-2-carboxílico: 201 mg, MS (ES^+): m/e = 543, patrón de cloro.

Ejemplo 110: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-hidroxi-etoxi)-1H-benzoimidazol-2-carboxílico

(i) terc-Butil-[2-(2,3-dinitro-fenoxi)-etoxi]-dimetil-silano

El terc-butil-[2-(2,3-dinitro-fenoxi)-etoxi]-dimetil-silano se preparó mediante un procedimiento de acuerdo con el ejemplo 108 (i) partiendo de 500 mg (2,72 mmol) de 2,3-dinitro-fenol y 1,00 g (4,18 mmol) de (2-bromo-etoxi)-terc-butil-dimetil-silano. Rendimiento: 810 mg, MS (ES^+): m/e = 343.

(ii) 3-[2-(terc-Butil-dimetil-silaniloxi)-etoxi]-benceno-1,2-diamina

La 3-[2-(terc-butil-dimetil-silaniloxi)-etoxi]-benceno-1,2-diamina se preparó

mediante un procedimiento de acuerdo con el ejemplo 108 (ii) partiendo de 610 mg (1,78 mmol) de terc-butil-[2-(2,3-dinitro-fenoxi)-etoxi]-dimetil-silano. Rendimiento: 503 mg, MS (ES^+): m/e = 283.

(iii) 4-[2-(terc-Butil-dimetil-silaniloxi)-etoxi]-2-triclorometil-1H-benzoimidazol

El 4-[2-(terc-butil-dimetil-silaniloxi)-etoxi]-2-triclorometil-1H-benzoimidazol se preparó mediante un procedimiento de acuerdo con el ejemplo 108 (iii) partiendo de 503 mg (1,78 mmol) de 3-[2-(terc-butil-dimetil-silaniloxi)-etoxi]-benceno-1,2-diamina y 0,31 ml (2,49 mmol) de éster metílico del ácido 2,2,2-tricloro-acetimídico. Rendimiento: 680 mg, MS (ES^+): m/e = 409, patrón de cloro.

(iv) (1-Isopropil-piperidin-4-il)-amida del ácido 4-[2-(terc-butil-dimetil-silaniloxi)-etoxi]-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 4-[2-(terc-butil-dimetil-silaniloxi)-etoxi]-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 108 (iv) partiendo de 680,0 mg (1,66 mmol) de 4-[2-(terc-Butil-dimetil-silaniloxi)-etoxi]-2-triclorometil-1H-benzoimidazol y 428,4 mg (1,99 mmol) de diclorhidrato de 1-isopropil-piperidin-4-ilamina. Rendimiento: 670 mg, MS (ES^+): m/e = 461.

(v) (1-Isopropil-piperidin-4-il)-amida del ácido 4-[2-(terc-butil-dimetil-silaniloxi)-etoxi]-1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 4-[2-(terc-butil-dimetil-silaniloxi)-etoxi]-1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 108 (v) partiendo de 670,0 mg (1,45 mmol) de (1-isopropil-piperidin-4-il)-amida del ácido 4-[2-(terc-butil-dimetil-silaniloxi)-etoxi]-1H-benzoimidazol-2-carboxílico y 362,8 mg (1,45 mmol) de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida. La purificación final por cromatografía ultrarrápida sobre gel de sílice usando acetato de etilo como eluyente dio el compuesto del título en forma de un aceite pardo. Rendimiento: 350 mg, MS (ES^+): m/e = 629, patrón de cloro.

(vi) (1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-hidroxi-etoxi)-1H-benzoimidazol-2-carboxílico

Se disolvieron 250 mg (0,40 mmol) de (1-isopropil-piperidin-4-il)-amida del ácido 4-[2-(terc-butil-dimetil-silaniloxi)-etoxi]-1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico en 15 ml de THF. Se añadieron 435 µl de una solución 1 M de TBAF en THF y 26 µl de ácido acético. La mezcla resultante se agitó durante 48 h a temperatura ambiente. La mezcla de reacción se concentró a presión reducida. El

residuo se recogió en 50 ml de CH_2Cl_2 y se lavó una vez con una solución saturada de $NaHCO_3$ y cinco veces con agua. La capa orgánica se secó sobre $MgSO_4$ anhidro y se concentró al vacío. La purificación final por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio la (1-isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-hidroxi-etoxi)-1H-benzoimidazol-2-carboxílico pura en forma de su formiato en forma de un material amorfo incoloro. El compuesto del título se transformó en su acetato. Rendimiento: 132 mg, MS (ES^+): *m/e* = 515, patrón de cloro.

Ejemplo 111: Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[2-fluoro-4-(pirrolidina-1-carbonil)(-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

(i) (3-Fluoro-4-nitro-fenil)-pirrolidin-1-il-metanona

Se suspendió 1,00 g (5,40 mmol) de ácido 3-fluoro-4-nitro-benzoico en 55 ml de benceno. Se añadieron 1 ml de cloruro de tionilo y 7 gotas de DMF. La mezcla resultante se agitó durante 5 h a 70°C y después se concentró a presión reducida. El residuo se disolvió en 40 ml de CH_2Cl_2. Posteriormente, se añadieron 0,75 ml (5,40 mmol) de trietilamina y 0,45 ml (5,40 mmol) de pirrolidina y la solución resultante se agitó durante 1 h a temperatura ambiente. La mezcla se diluyó con CH_2Cl_2 y posteriormente se lavó con una solución 0,1 N de HCl, con una solución saturada de $NaHCO_3$ y con salmuera. La capa orgánica se secó sobre $MgSO_4$ anhidro y se concentró al vacío para dar la (3-fluoro-4-nitro-fenil)-pirrolidin-1-il-metanona bruta en forma de un sólido naranja. Rendimiento: 1,35 g, MS (ES^+): m/e = 239.

(ii) (4-Amino-3-fluoro-fenil)-pirrolidin-1-il-metanona

Se disolvieron 515,0 mg (2,16 mmol) de (3-fluoro-4-nitro-fenil)-pirrolidin-1-il-metanona en 20 ml de MeOH. La solución se evacuó y se aclaró varias veces con argón. Se añadieron 150 mg de paladio sobre carbono (10%) y la mezcla se evacuó de nuevo y se aclaró varias veces con argón. Finalmente, el argón se cambió por hidrógeno (globo cargado con hidrógeno) y la mezcla se agitó durante 2 h a temperatura ambiente. La mezcla de reacción se filtró sobre de "Celite" y el residuo del filtro se lavó con 30 ml de MeOH: El filtrado se concentró al vacío para dar la (4-amino-3-fluoro-fenil)-pirrolidin-1-il-metanona pura en forma de un aceite incoloro. Rendimiento: 448 mg, MS (ES^+): m/e = 209.

(iii) Éster metílico del ácido 2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

Se disolvieron 59,0 mg (0,28 mmol) de (4-Amino-3-fluoro-fenil)-pirrolidin-1-il-metanona en 6 ml de THF y 3 ml de agua. Se añadieron 238,0 mg (2,83 mmol) de

$NaHCO_3$. Finalmente, se añadieron 75,6 mg (0,26 mmol) de éster metílico del ácido 2-triclorometil-1H-benzoimidazol-4-carboxílico y la mezcla resultante se agitó vigorosamente durante 3 h a temperatura ambiente. La mezcla se diluyó con CH_2Cl_2 y se lavó con una solución saturada de $NaHCO_3$ y con salmuera. La capa orgánica se secó sobre $MgSO_4$ anhidro y se concentró a presión reducida. La purificación final por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio el éster metílico del ácido 2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico puro en forma de un sólido amorfo incoloro. Rendimiento: 69 mg, MS (ES^+): m/e = 411.

(iv) Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

El éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 36 (ii) partiendo de 40,0 mg (0,10 mmol) de éster metílico del ácido 2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico y 29,2 mg (0,12 mmol) de 2-bromo-N-(5-cloro-piridin-2-il)-acetamida. La purificación final por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dio el éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico puro en forma de un sólido amorfo incoloro. Rendimiento: 13 mg, MS (ES^+): m/e = 579, patrón de cloro.

Ejemplo 112: a) Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico

b) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-3H-benzoimidazol-5-carboxílico

(i) Ácido 4-amino-3-metil-5-nitro-benzoico

El ácido 4-amino-3-metil-5-nitro-benzoico se preparó como se describe por Bolhofer et al. en el documento US369166.

(ii) Éster metílico del ácido 4-amino-3-metil-5-nitro-benzoico

Se disolvieron 500 mg (2,50 mmol) de ácido 4-amino-3-metil-5-nitro-benzoico en una mezcla de 8 ml de CH_2Cl_2 y 2 ml de MeOH. A 0°C, se añadieron 1,3 ml de una solución 2 M de trimetilsilildiazometano en hexano. Después de 1 h a 0°C, la mezcla de reacción se dejó calentar a temperatura ambiente. Al día siguiente, se añadieron 1,3 ml más de una solución 2 M de trimetilsilildiazometano en hexano. Después de agitar durante 3 h a temperatura ambiente, se añadió gota a gota una solución de 0,22

ml de ácido acético en 1,8 ml de CH_2Cl_2 para destruir el exceso de trimetilsilildiazometano. La mezcla de reacción se concentró a presión reducida. El residuo se digirió con heptano y el material cristalino se retiró por filtración para dar el éster metílico del ácido 4-amino-3-metil-5-nitro-benzoico puro. Rendimiento: 496 mg, MS (ES^+): m/e = 211.

(iii) Éster metílico del ácido 3,4-diamino-5-metil-benzoico

El Éster metílico del ácido 3,4-diamino-5-metil-benzoico se preparó mediante un procedimiento de acuerdo con el ejemplo 11 (i) partiendo de 495,0 mg (2,36 mmol) de éster metílico del ácido 4-amino-3-metil-5-nitro-benzoico. Rendimiento: 404 mg, MS (ES^+): m/e = 181.

(iv) Éster metílico del ácido 7-metil-2-triclorometil-1H-benzoimidazol-5-carboxílico

El éster metílico del ácido 7-metil-2-triclorometil-1H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 5 (l) partiendo de 404,4 mg (2,20 mmol) de éster metílico del ácido 3,4-diamino-5-metil-benzoico y 0,39 ml (3,08 mmol) de éster metílico de 2,2,2-tricloro-acetimídico. Rendimiento: 869 mg, MS (ES^+): m/e = 307, patrón de cloro.

(v) Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico

El Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 93 (iv) partiendo de 685,0 mg (2,20 mmol) de éster metílico del ácido 7-metil-2-triclorometil-1H-benzoimidazol-5-carboxílico y 474,4 mg (2,20 mmol) de diclorhidrato de 1-ciclopropil-piperidin-4-ilamina. Rendimiento: 730 mg, MS (ES^+): m/e = 357.

(vi) a) Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico

b) Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-3H-benzoimidazol-5-carboxílico

El ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico y el ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-3H-benzoimidazol-5-carboxílico se prepararon mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 200 mg (0,56 mmol) de éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico y 164,8 mg (0,56 mmol) de 5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil éster del ácido metanosulfónico. La hidrólisis de los ésteres resultantes por tratamiento con LiOH y la purificación por RP-HPLC

preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron los compuestos del título en forma de sus formiatos en forma de sólidos amorfos blancos. La asignación estructural de los dos isómeros se realizó por espectroscopía NOE.

Rendimiento del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico: 7 mg, MS (ES^+): m/e = 540, patrón de cloro.

Rendimiento del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-7-metil-3H-benzoimidazol-5-carboxílico: 111 mg, MS (ES^+): m/e = 540, patrón de cloro.

Ejemplo 113: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

(i) Éster etílico de ácido 2,3-diamino-6-fluoro-benzoico

El Éster etílico de ácido 2,3-diamino-6-fluoro-benzoico se preparó mediante un procedimiento de acuerdo con el ejemplo 11 (i) partiendo de 20,0 mg (0,88 mmol) de éster etílico del ácido 2-amino-6-fluoro-3-nitro-benzoico. Rendimiento: 157 mg, MS (ES^+): m/e = 229.

(ii) Éster etílico del ácido 5-fluoro-2-triclorometil-1H-benzoimidazol-4-carboxílico

El éster etílico del ácido 5-fluoro-2-triclorometil-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 5 (i) partiendo de 150,0 mg (0,76 mmol) de éster etílico del ácido 2,3-diamino-6-fluoro-benzoico y 133 µl (1,06 mmol) de éster metílico del ácido 2,2,2-tricloro-acetimídico. Rendimiento: 280 mg, MS (ES^+): m/e = 325, patrón de cloro.

(iii) Éster etílico del ácido 5-fluoro-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El Éster etílico del ácido 5-fluoro-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 93 (iv) partiendo de 240,0 mg (0,74 mmol) de éster etílico del ácido 5-fluoro-2-triclorometil-1H-benzoimidazol-4-carboxílico y 158,6 mg (0,74 mmol) de diclorhidrato de 1-isopropil-piperidin-4-ilamina. Rendimiento: 232 mg, MS (ES^+): m/e = 377.

(iv) Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 230 mg (0,60 mmol) de éster etílico del ácido 5-fluoro-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-

4-carboxílico y 179,5 mg (0,60 mmol) de 5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil éster del ácido metanosulfónico. La hidrólisis del éster etílico resultante por tratamiento con LiOH y la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron el compuesto del título en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 87 mg, MS (ES^+): m/e = 546, patrón de cloro.

Ejemplo 114: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-4-carboxílico

(i) Éster etílico del ácido 2-amino-3-nitro-6-(2,2,2-trifluoro-etoxi)(-benzoico

Se añadieron 420 mg de NaH (suspensión al 60% en aceite) a una solución de 2,16 ml (29,8 mmol) de 2,2,2-trifluoro-etanol en 5 ml de THF. Cuando cesó el desprendimiento de gas, se añadió 1,0 g (4,38 mmol) de éster etílico del ácido 2-amino-6-fluoro-3-nitro-benzoico. La mezcla resultante se agitó a 0°C durante 30 minutos y a temperatura ambiente durante 30 minutos más. A esta mezcla se le añadieron 2 ml de una solución acuosa 6 M de HCl y la mayor parte del disolvente se retiró a presión reducida. El residuo se mezcló con 20 ml de agua y el sólido resultante se recogió y se lavó con agua y después con hexano. El material cristalino amarillo obtenido se secó a presión reducida a 35°C. Rendimiento: 1,22 g.

(ii) Éster etílico del ácido 2,3-diamino-6-(2,2,2-trifluoro-etoxi)-benzoico

El Éster etílico del ácido 2,3-diamino-6-(2,2,2-trifluoro-etoxi)-benzoico se preparó mediante un procedimiento de acuerdo con el ejemplo 11 (i) partiendo de 1,22 g (3,96 mmol) de éster etílico del ácido 2-amino-3-nitro-6-(2,2,2-trifluoro-etoxi)-benzoico. Rendimiento: 1,07 g, MS (ES^+): m/e = 279.

(iii) Éster etílico del ácido 2-triclorometil-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-4-carboxílico

El Éster etílico del ácido 2-triclorometil-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 5 (i) partiendo de 200,0 mg (0,72 mmol) de éster etílico del ácido 2,3-diamino-6-fluoro-benzoico y 128 µl (1,01 mmol) de éster metílico del ácido 2,2,2-tricloro-acetimídico. Rendimiento: 340 mg, MS (ES^+): m/e = 405, patrón de cloro.

(iv) Éster etílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-4-carboxílico

El éster etílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 93 (iv) partiendo de 290,0 mg (0,72 mmol) de éster etílico del ácido 2-triclorometil-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-4-carboxílico y 153,8 mg

(0,72 mmol) de diclorhidrato de 1-isopropil-piperidin-4-ilamina. Rendimiento: 299 mg, MS (ES^+): m/e = 457.

(v) Ácido 1-[5-(5-cloro-tiofen-2-il)(-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-fluoro-etoxi)-1H-benzoimidazol-4-carboxílico

El ácido 1-[5-(5-cloro-tiofen-2-il)(-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-fluoro-etoxi)-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 81 partiendo de 299,0 mg (0,66 mmol) de éster etílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-4-carboxílico y 192,4 mg (0,66 mmol) de 5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil éster del ácido metanosulfónico. La hidrólisis del éster etílico resultante por tratamiento con LiOH en MeOH y la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) dieron el compuesto del título en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 90 mg, MS (ES^+): m/e = 626, patrón de cloro.

Ejemplo 115: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-2-carboxílico

La (1-isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 22 partiendo de 50,0 mg (0,08 mmol) de ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-1-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-4-carboxílico y 8,7 mg (0,12 mmol) de azetidin-3-ol. El compuesto del título se obtuvo en forma de su formiato en forma de un sólido amorfo blanco. Rendimiento: 18 mg, MS (ES^+): m/e = 681, patrón de cloro.

Ejemplo 116: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-fluoro-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 117: Ácido 7-cloro-1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 118: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-7-ciclopropil-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 119: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-etil-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 120: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 121: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-fluoro-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 122: Ácido 7-cloro-1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 123: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-7-ciclopropil-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 124: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-etil-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 125: Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 126: Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-fluoro-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 127: Ácido 7-cloro-1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-

ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 128: Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-etil-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 129: Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-7-ciclopropil-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 130: Ácido 1-(6-cloro-benzo[b]tiofen-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 131: Ácido 7-cloro-1-(6-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 132: Ácido 1-(6-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-fluoro-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 133: Ácido 1-(6-cloro-benzo[b]tiofen-2-ilmetil)-7-ciclopropil-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 134: Ácido 1-(6-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-etil-1H-benzoimidazol-5-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 135: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-4-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 136: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-fluoro-1H-benzoimidazol-4-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 137: Ácido 7-cloro-1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 138: Ácido 1-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-4-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 139: Ácido 1-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-fluoro-1H-benzoimidazol-4-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 140: Ácido 7-cloro-1-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 141: Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-4-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 142: Ácido 7-cloro-1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 143: Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-fluoro-1H-benzoimidazol-4-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 144: (1-Ciclopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 145: 2-[(1-isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-1H-benzoimidazol-2,4-dicarboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 146: 2-[(1-isopropil-piperidin-4-il)-amida] de 4-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-2,4-dicarboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 147: 2-[(1-isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-2,4-dicarboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 148: 2-[(1-isopropil-piperidin-4-il)-amida] de 4-dimetilamida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-2,4-dicarboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 149: 4-(Metil-propil-amida) de 2-[(1-isopropil-piperidin-4-il)-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-2,4-dicarboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 150: 2-[(1-isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-7-metil-1H-benzoimidazol-2,4-dicarboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 151: (1-isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-4-(3-hidroxi-azetidina-1-carbonil)-7-metil-1H-benzoimidazol-2-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 152: 2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-5-fluoro-7-metil-1H-benzoimidazol-2,4-dicarboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 153: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-5-fluoro-4-(3-hidroxi-azetidina-1-carbonil)-7-metil-1H-benzoimidazol-2-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 154: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(2-hidroxi-etoxi)-1H-benzoimidazol-2-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 155: (1-Isopropil-piperidin-4-il)-amida del ácido 1-(6-cloro-benzo[b]tiofen-2-ilmetil)-4-(2-hidroxi-etoxi)-1H-benzoimidazol-2-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 156: (1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-tieno[3,4-d]imidazol-2-carboxílico

El compuesto del título puede prepararse adaptando la metodología descrita anteriormente.

Ejemplo 157: Bencilamina del ácido 5-cloro-1H-benzoimidazol-2-carboxílico

Una solución de 120,0 mg (0,45 mmol) de 5-cloro-triclorometil-1H-benzoimidazol en 2 ml de tetrahidrofurano (THF) se añadió lentamente a una mezcla de 53,5 µl (0,49 mmol) de bencilamina y 373,8 mg (4,45 mmol, 10 equiv.) de $NaHCO_3$ en 8 ml de THF y 4 ml de agua. La mezcla de reacción se agitó durante 2 h a temperatura ambiente (de 20°C a 25°C, en lo sucesivo TA). La suspensión se filtró y el filtrado se concentró a presión reducida. Después de la purificación por RP-HPLC (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) se obtuvo bencilamina del ácido 5-cloro-1H-benzoimidazol-2-carboxílico en forma de un sólido amorfo blanco. Rendimiento: 84 mg, MS (ES^+): m/e = 286, patrón de cloro.

Ejemplo 158: Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico

Una solución de 3,99 g (13,6 mmol) de éster metílico del ácido 2-triclorometil-1H-benzoimidazol-4-carboxílico en 40 ml de THF se añadió lentamente a una mezcla de 2,9 g (13,6 mmol) de diclorhidrato de 1-isopropil-piperidin-4-ilamina y 13,7 g (0,163 mol, 12 equivalentes) de $NaHCO_3$ en 200 ml de THF y 120 ml de agua. La mezcla de reacción se agitó durante 2 h a TA. El THF se retiró por destilación. La suspensión acuosa resultante se diluyó con 200 ml de CH_2Cl_2 y se extrajo dos veces con 150 ml de agua. La capa orgánica se concentró a presión reducida y el residuo resultante se purificó por cromatografía ultrarrápida sobre gel de sílice usando una mezcla 4:1 de acetato de etilo/metanol como eluyente. El compuesto del título se obtuvo en forma de un material cristalino pardo claro. Rendimiento: 3,20 g, MS (ES^+): m/e = 345.

Ejemplo 159: Éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

A una mezcla de 7,53 g (35,3 mmol) de diclorhidrato de 1-ciclopropil-piperidin-4-ilamina y 32,39 g (0,386 mol) de $NaHCO_3$ en 1300 ml de THF y 370 ml de agua se le añadió una solución de 11,79 g (32,1 mmol) de éster metílico del ácido 2-triclorometil-1H-benzoimidazol-5-carboxílico en 360 ml de THF. La mezcla de reacción se agitó vigorosamente durante 2 h a TA. El THF se evaporó. El precipitado se retiró por filtración y se trató dos veces con aproximadamente 300 ml de una solución saturada de $NaHCO_3$ en condiciones ultrasónicas. Después de la filtración, el sólido resultante se lavó dos veces con 150 ml de agua y se secó a presión reducida a 45°C para dar el éster metílico del ácido 2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico puro en forma de un material cristalino pardo claro. Rendimiento: 9,9 g (90%), MS (ES^+): m/e = 343.

Ejemplo 160: Diisopropilamida del ácido 5-cloro-1H-benzoimidazol-2-carboxílico

Una solución de 500,0 mg (1,85 mmol) de 5-cloro-2-triclorometil-1H-benzoimidazol en 20 ml de THF se añadió lentamente a una mezcla de 286 µl (2,04 mmol) de diisopropil-amina y 1,55 g (18,5 mmol, 10 equivalentes) de $NaHCO_3$ en 70 ml de THF y 20 ml de agua. La mezcla de reacción se agitó durante 2 h a TA. El disolvente orgánico se evaporó. El material cristalino formado se retiró por filtración y se trató una vez con aproximadamente 50 ml de una solución saturada de $NaHCO_3$ en condiciones ultrasónicas. El residuo cristalino se retiró de nuevo por filtración y se lavó dos veces con 20 ml de agua. El secado a presión reducida a 35°C dio la diisopropilamida del ácido 5-cloro-1H-benzoimidazol-2-carboxílico pura en forma de un

sólido cristalino pardo claro. Rendimiento: 321 mg, MS (ES^+): m/e = 280, patrón de cloro.

Ejemplo 161: (5-Cloro-1H-benzoimidazol-2-il)-morfolin-4-il-metanona

La (5-cloro-1H-benzoimidazol-2-il)-morfolin-4-il-metanona se preparó mediante un procedimiento de acuerdo con el ejemplo 157 partiendo de 120,0 mg (0,45 mmol) de 5-cloro-2-triclorometil-1H-benzoimidazol y 42,6 µl (0,49 mmol) de morfolina. El compuesto del título se aisló en forma de un sólido amorfo incoloro. Rendimiento: 95 mg (80%), MS (ES^+): m/e = 266, patrón de cloro.

Ejemplo 162: (4-metil-piperazin-1-il)-amida del ácido 5-cloro-1H-benzoimidazol-2-carboxílico

La (4-metil-piperazin-1-il)-amida del ácido 5-cloro-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 157 partiendo de 120,0 mg (0,45 mmol) de 5-cloro-2-triclorometil-1H-benzoimidazol y 58,9 µl (0,49 mmol) de 4-metil-piperazin-1-ilamina. El compuesto del título se aisló en forma de un sólido amorfo incoloro.

Rendimiento: 89 mg MS (ES^+): m/e: 294, patrón de cloro

Ejemplo 163: (4-Ciano-fenil)-amida del ácido 5-cloro-1H-benzoimidazol-2-carboxílico

La (4-ciano-fenil)-amida del ácido 5-cloro-1H-benzoimidazol-2-carboxílico se preparó por un procedimiento de acuerdo con el ejemplo 160 partiendo de 500,0 mg (1,85 mmol) de 5-cloro-2-triclorometil-1H-benzoimidazol y 229,8 mg (1,95 mmol) de 4-amino-benzonitrilo. El compuesto del título se aisló en forma de un sólido cristalino pardo claro.

Rendimiento: 475 mg (86%) MS (ES^+): m/e = 297, patrón de cloro.

Ejemplo 164: Éster metílico del ácido 2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico

El Éster metílico del ácido 2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 160 partiendo de 1,32 g (4,49 mmol) de éster metílico del ácido 2-triclorometil-1H-benzoimidazol-4-carboxílico y 950,0 mg (4,94 mmol) de 4-(4-Amino-fenil)-morfolin-3-ona. El compuesto del título se aisló en forma de un sólido cristalino pardo claro.

Rendimiento: 1,44 g (81%) MS (ES^+): m/e = 395.

Ejemplo 165: Éster metílico del ácido 2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzo-imidazol-4-carboxílico

Se disolvieron 59,0 mg (0,28 mmol) de (4-amino-3-fluoro-fenil)-pirrolidin-1-il-metanona en 6 ml de THF y 3 ml de agua. Se añadieron 238,0 mg (2,83 mmol) de

$NaHCO_3$ Finalmente, se añadieron 75,6 mg (0,26 mmol) de éster metílico del ácido 2-triclorometil-1H-benzoimidazol-4-carboxílico y la mezcla resultante se agitó vigorosamente durante 3 h a TA. La mezcla se diluyó con 25 ml de CH_2Cl_2 y se lavó con una solución saturada de $NaHCO_3$ y con salmuera. La capa orgánica se secó sobre $MgSO_4$ anhidro y se concentró a presión reducida. Después de la purificación por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) se obtuvo el éster metílico del ácido 2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzo-imidazol-4-carboxílico puro en forma de un sólido amorfo incoloro. Rendimiento: 69 mg, MS (ES^+): m/e = 411.

Ejemplo 166: Isoquinolin-4-ilamida del ácido 5-cloro-1H-benzoimidazol-2-carboxílico

La isoquinolin-4-ilamida del ácido 5-cloro-1H-benzoimidazol-2-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 160 partiendo de 100,0 mg (0,37 mmol) de 5-cloro-2-triclorometil-1H-benzoimidazol y 56,1 mg (0,39 mmol) de isoquinolin-4-ilamina. El compuesto del título se aisló en forma de un sólido cristalino de color pardo claro.

Rendimiento: 113 mg (94%) MS (ES^+): m/e: 323, patrón de cloro

Ejemplo 167: Éster metílico del ácido 2-[(5-cloro-1H-benzoimidazol-2-carbonil)-amino]-3-nitro-benzoico.

El éster metílico del ácido 2-[(5-cloro-1H-benzoimidazol-2-carbonil)-amino]-3-nitro-benzoico se preparó por un procedimiento de acuerdo con el Ejemplo 160 partiendo de 200,0 mg (0,74 mmol) de 5-cloro-2-triclorometil-1H-benzoimidazol y 152,6 mg (0,78 mmol) de éster metílico del ácido 2-amino-3-nitro-benzoico. El compuesto del título se aisló en forma de un sólido cristalino amarillo.

Rendimiento: 218 mg (79%).

Ejemplo 168: Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-tieno[3,4-d]imidazol-4-carboxílico

El Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-tieno[3,4-d]imidazol-4-carboxílico se preparó mediante un procedimiento de acuerdo con el ejemplo 158 partiendo de 1,74 g (5,80 mmol) de éster metílico del ácido 2-triclorometil-3H-tieno[3,4-d]imidazol-6-carboxílico y 1,25 g (5,80 mmol) de diclorhidrato de 1-isopropil-piperidin-4-ilamina. El compuesto del título se aisló en forma de un sólido cristalino de color pardo claro. Rendimiento: 1,75 g (86%), MS (ES^+): m/e = 351.

Ejemplo 169: Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico

Se disolvieron 21,0 mg (0,098 mmol) de diclorhidrato de (1-ciclopropil-piperidin-

4-ilamina en 3 ml de CH_3CN y 3 ml de agua. Se añadieron 82,3 mg (0,98 mmol, 10 equivalentes) de $NaHCO_3$. Después, se añadió una solución de 48,1 mg (0,098 mmol) de éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico en 2 ml de CH_3CN y la mezcla resultante se agitó vigorosamente durante 3 h a la temperatura de reflujo. La mezcla se concentró a presión reducida. El residuo se purificó por RP-HPLC preparativa (gradiente de CH_3CN/H_2O + ácido fórmico al 0,05%) para dar el ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico puro en forma de un sólido amorfo incoloro. (Simultáneamente, se hidrolizó el éster metílico en estas condiciones).

Rendimiento: 26 mg (50%), MS (ES^+): m/e = 526, patrón de cloro.

Ensayo farmacológico

La capacidad de los compuestos de la fórmula I para inhibir el factor Xa o el factor VIIa u otras enzimas tales como la trombina, plasmina o tripsina puede evaluarse determinando la concentración del compuesto de la fórmula I que inhibe la actividad enzimática en un 50%, es decir, el valor de CI50, que está relacionado con la constante de inhibición Ki. En los ensayos cromogénicos se usaron enzimas purificadas. La concentración de inhibidor que produce una reducción de 50% en la velocidad de hidrólisis del sustrato se determinó por regresión lineal después de representar las velocidades de hidrólisis relativas (comparadas con el control no inhibido) frente al logaritmo de la concentración del compuesto de fórmula I. Para calcular la constante de inhibición Ki, el valor de CI50 se corrigió con respecto a la competición con el sustrato usando la fórmula

$$Ki = CI50 / \{1 + (\text{concentración de sustrato}/Km)\}$$

donde Km es la constante de Michaelis-Menten (Chen y Prusoff, Biochem. Pharmacol. 22 (1973) 3099-3108; I. H. Segal, Enzyme Kinetics, 1975, John Wiley & Sons, Nueva York, 100-125; que se incorporaron en este documento como referencia).

a) Ensayo del Factor Xa

En el ensayo para determinar la inhibición de la actividad del factor Xa, se usó tampón TBS-PEG (Tris-HCl 50 mM, pH 7,6, NaCl 200 mM, PEG-8000 al 0,05% (p/v), NaN3 al 0,02% (p/v)). El valor de CI50 se determinó combinando en pocillos apropiados de una placa de microtitulación de semiárea Costar de 25 µl el factor Xa humano (Enzyme Research Laboratories, Inc.; South Bend, Indiana) en TBS-PEG; 40 µl de DMSO al 10% (v/v) en TBS-PEG (control no inhibido) o diversas concentraciones del compuesto a ensayar diluido en DMSO al 10% (v/v) en TBS-PEG; y sustrato S-

2765 (N(α)-benciloxicarbonil-D-Arg-Gly-L-Arg-p-nitroanilida; Kabi Pharmacia, Inc.; Franklin, Ohio) en TBS-PEG.

El ensayo se realizó preincubando el compuesto de fórmula I más la enzima durante 10 min. Después, el ensayo se inició añadiendo sustrato para obtener un volumen final de 100 µl. La velocidad inicial de la hidrólisis del sustrato cromogénico se midió por el cambio de absorbancia a 405 nm usando un lector de placas cinético de Bio-tek Instruments (Ceres UV900HDI) a 25°C durante la porción lineal del transcurso de tiempo (normalmente 1,5 min después de la adición del sustrato). La concentración enzimática fue de 0,5 nM y la concentración de sustrato fue de 140 µM.

b) Ensayo del Factor VIIa

La actividad inhibidora hacia la actividad del factor VIIa/factor tisular se determinó usando un ensayo cromogénico esencialmente como se ha descrito previamente (J. A. Ostrem et al., Biochemistry 37 (1998) 1053-1059 que se incorporó en este documento como referencia). Los ensayos cinéticos se realizaron a 25°C en placas de microtitulación de semiárea (Costar Corp., Cambridge, Massachusetts) usando un lector de placas cinético (Molecular Devices Spectramax 250). Un ensayo típico constaba de 25 µl de factor VIIa humano y TF (5 nM y 10 nM, concentración final respectiva) combinados con 40 µl de diluciones de inhibidor en DMSO al 10%/tampón TBS-PEG (Tris 50 mM, NaCl 15 mM, $CaCl_2$ 5 mM, PEG 8000 al 0,05%, pH 8,15). Después de un periodo de incubación de 15 minutos, el ensayo se inició mediante la adición de 35 µl del sustrato cromogénico S-2288 (D-Ile-Pro-Arg-p-nitroanilida, Pharmacia Hepar Inc., concentración final 500 µM). Los resultados (constantes de inhibición Ki (FXa) para la inhibición del factor Xa) se muestran en la Tabla 1.

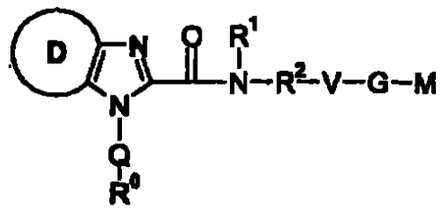
Tabla 1:

Ejemplo	Ki (FXa) [µM]	Ejemplo	Ki (FXa) [µM]	Ejemplo	Ki (FXa) [µM]
1	0,0007	29b	0,0115	68 a)	0,070
2	0,0031	30	0,0090	68 b)	0,226
3	0,0014	31	0,0155	69	0,015
4	0,0592	32	0,0105	70	0,015
5a	0,0025	33	0,0125	71	0,007
5b	0,1750	34	0,0195	72	0,0125
6	0,0030	35	0,041	73	0,019
7	0,0165	36	0,0315	74	0,0105

9	0,0940	37	0,012	75	0,0026
10	1,357	39	0,047	76	0,0085
11a	0,004	40	0,020	77	0,0525
11b	0,001	41	0,006	78	0,0035
12	0,0030	42	0,462	79	0,001
13	0,2990	43	0,840	80	0,007
14	2,3900	44	0,028	81 a)	0,558
15	0,0115	45	0,210	82 a)	0,064
16	0,0110	48	0,002	91	0,021
17a	0,0195	49	0,015	92	0,0225
17b	0,3710	50	0,141	94	0,0245
18	0,0225	51	0,510	96 a)	0,0305
19	0,0235	52	0,014	100 a)	0,005
20	0,0085	53	0,040	102	0,0025
21	0,0310	54	0,031	103 a)	0,022
22	0,0007	55	1,30 μM	103 b)	0,088.5
23	0,0080	57	0,585	104	0,020
24	0,0260	60	0,035	105	0,054.5
25	0,0650	61	0,867	106 a)	0,022
26	0,0185	62	0,019	106 b)	0,188
27	0,0125	63	0,687	108	0,0065
28	0,0480	64	0,002	109	0,0035
29a	0,0255	65	0,121	110	0,004
		66	0,003	112 a)	0,0008

REIVINDICACIONES

1. Un compuesto de la fórmula I,



(I)

, en la que

R^0 es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo,

donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y que está adicionalmente sustituido con un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno,

donde el heterociclilo está sin sustituir, mono-, di- o trisustituido independientemente entre sí con R8,

R8 es 1) halógeno,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está

mono-, di- o trisustituido independientemente entre sí con halógeno o -O-alquilo (C_1-C_6),

9) alquilo (C_1-C_6), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

10) -O-alquilo (C_1-C_6), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

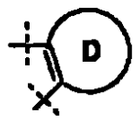
11) $-SO_2CH_3$ o

12) $-SO_2-CF_3$,

con la condición de que R8 sea al menos un halógeno, $-C(O)-NH_2$ o un resto -O-alquilo (C_1-C_6), si R^0 es un arilo de 6 a 14 miembros monocíclico o bicíclico,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_6), si R^0 y V son un arilo de 6 a 14 miembros monocíclico o bicíclico,

la subestructura



en la fórmula I es un grupo cíclico saturado, parcialmente insaturado o aromático de 4 a 8 miembros que contiene cero, 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está sin sustituir o sustituido 1, 2, 3, 4, 5 ó 6 veces con R3 o sustituido 1 ó 2 veces con =0,

Q es un enlace directo, -alquileno (C_0-C_2)-$C(O)-NR^{10}$-, $-NR^{10}-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$-, metileno, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$-, $-(CH_2)_m-S-(CH_2)_n$-, $-(CH_2)_m-C(O)-(CH_2)_n$-, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-CH(OH)-(CH_2)_n$-, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$-, -alquileno ($C_2$-$C_3$)-O-alquileno ($C_0$-$C_3$), -alquileno ($C_2$-$C_3$)-S(O)-, -alquileno ($C_2$-$C_3$)-$S(O)_2$-, $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n$-, -alquileno ($C_2$-$C_3$)-$S(O)_2$-NH-($R^{10}$)-, -alquileno ($C_2$-$C_3$)-N($R^{10}$)- o -alquileno ($C_0$-$C_3$)-C(O)-O-$(CH_2)_m$-,

donde R^{10} es como se define a continuación, y donde n y m son independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6 donde los restos alquileno que se forman por $-(CH_2)_m$- o $-(CH_2)_n$- están sin sustituir o mono-, di- o trisustituidos independientemente entre sí con halógeno, $-NH_2$ o -OH; o

-cicloalquileno (C_3-C_6), donde el cicloalquileno está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, $-NH_2$ o -OH;

R^1 es un átomo de hidrógeno, -alquilo (C_1-C_4), donde el alquilo está sin sustituir o

sustituido de una a tres veces con R13; -alquileno (C_1-C_3)-C(O)-NH-R^0, -alquileno (C_1-C_3)-C(O)-O-R^{10}, un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8, donde R8 es como se ha definido anteriormente; un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno; -perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4), -alquileno (C_1-C_3)-S(O)$_2$-alquilo (C_1-C_3), -alquileno (C_1-C_3)-S(O)$_2$-N($R^{4'}$)-$R^{5'}$, -alquileno (C_1-C_3)-O-alquilo (C_1-C_4), -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8) o alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

$R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros que contiene 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es halógeno, -OH, =O, -alquilo (C_1-C_8), -alcoxi (C_1-C_4), -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-perfluoroalquilo (C_1-C_3), -alquil (C_0-C_8)-SO_2-N(R^{18})-R^{21}, -C(O)-NH-alquilo (C_1-C_8), -C(O)-N[alquilo (C_1-C_8)]$_2$, -NR^{18}-C(O)-NH-alquilo (C_1-C_8), -C(O)-NH_2, -S-R^{18} o -NR^{18}-C(O)-NH-[alquilo (C_1-C_8)]$_2$,

donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o alquilo (C_1-C_8),

V es 1) un arilo de 6 a 14 miembros, donde el arilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14, o

2) un heterociclilo del grupo compuesto por acridinilo, 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol-(1H-pirrolopiridina), azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 1,4-diazepano, 4,5-dihidrooxazolinilo, dioxazolilo,

dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,

G es un enlace directo, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ o $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6,

M es 1) un átomo de hidrógeno,

2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,

3) -C(O)-N(R11)-R12,

4) $-(CH_2)_m-NR^{10}$,

5) un arilo de 6 a 14 miembros, donde el arilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,

6) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, donde el heterociclilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,

7) -cicloalquilo (C_3-C_8), donde dicho cicloalquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14, o

8) un resto cíclico de 3 a 7 miembros que contiene 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14, donde R14 es como se ha definido anteriormente,

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

d) $-CF_3$, o

e) $-CHF_2$,

7) $-NO_2$,

8) -CN,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-$C(O)-R^{11}$,

12) -alquileno (C_0-C_4)-$C(O)-O-R^{11}$,

13) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{12},

14) -alquileno (C_0-C_4)-N(R^{11})-R^{12},

15) -NR^{10}-SO_2-R^{10},

16) -S-R^{10},

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

20) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

21) -alquileno (C_0-C_4)-arilo (C_6-C_{14}), donde el arilo está mono-, di- o trisustituido, independientemente entre sí, con R13,

22) -alquileno (C_0-C_4)-heterociclilo (C_4-C_{15}), donde el heterociclilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

23) -alquileno (C_0-C_4)-cicloalquilo (C_3-C_8), donde el cicloalquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

24) alquileno (C_0-C_4)het, donde het está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

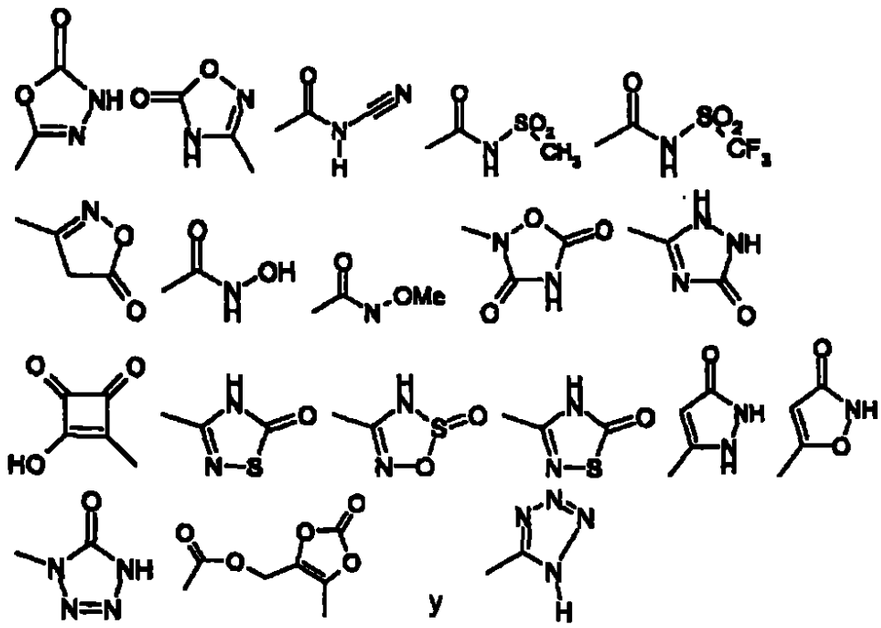
25) -alquileno (C_0-C_4)-O-CH_2-perfluoroalquileno (C_1-C_3)-CH_2-O-alquilo (C_0-C_4),

26) -SO_w-N(R^{11})-R^{13}, donde w es 1 ó 2,

27) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{13}, o

28) -alquileno (C_0-C_4)-N(R^{11})-R^{13}, o

29) *un resto de la siguiente lista*



y

donde Me es metilo, o

si dos restos -OR19 están unidos a átomos adyacentes, pueden formar junto con los átomos a los que están unidos un anillo de 5 ó 6 miembros que está sin sustituir o sustituido una, dos, tres o cuatro veces con R^{13},

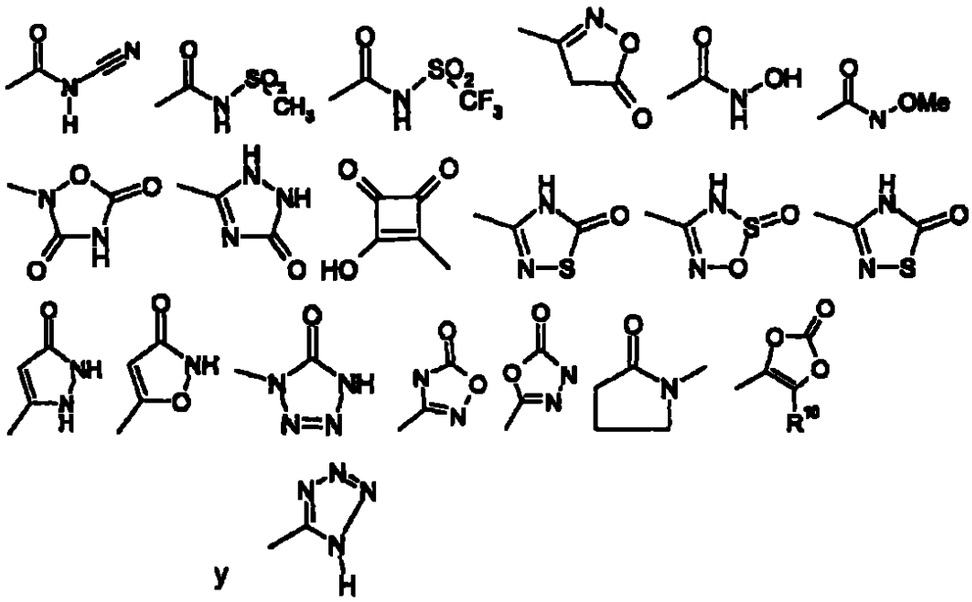
R^{11} y R^{12} son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,
2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
3) -alquil (C_0-C_8)-cicloalquilo (C_3-C_8),
4) -SO_t-R^{10}, donde t es 1 ó 2,
5) -alquil (C_0-C_8)-arilo (C_6-C_{14}), donde el alquilo y el arilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13,
6) -perfluoroalquilo (C_1-C_3),
7) -O-R^{17}, o
8) -alquil (C_0-C_8)-heterociclilo (C_4-C_{14}), donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo heterocíclico monocíclico de 4 a 8 miembros que además del átomo de

nitrógeno puede contener uno o dos heteroátomos en el anillo iguales o diferentes seleccionados entre oxígeno, azufre y nitrógeno; donde dicho anillo heterocíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es halógeno, $-NO_2$, -CN, =O, -OH, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, - cicloalquilo (C_3-C_8), -alquileno (C_0-C_3)-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_u-R^{10}$, donde u es 1 ó 2, $-S-R^{10}$, $-SO_r-R^{10}$, donde r es 1 ó 2, $-S(O)_v-N(R^{10})-R^{20}$, donde v es 1 ó 2, $-C(O)-R^{10}$, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, feniloxi-, $-O-CF_3$, -alquil (C_0-C_4)-C(O)-O-C(R15,R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -perfluoroalquilo (C_1-C_3), -O-R15, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, o un resto de la siguiente lista



y

donde Me es metilo, o

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), o junto con el átomo de carbono al que están unidos pueden formar un anillo carbocíclico de 3 a 6 miembros que está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_8), -alquil (C_1-C_8)-OH, -alquil (C_1-C_8)-O-alquilo (C_1-C_8), -cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-O-alquil (C_1-C_8)-cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquil (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

2. Un compuesto de fórmula de acuerdo con la reivindicación 1, donde

R^0 es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico del grupo de fenilo, naftilo, bifenililo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo, donde el heterociclilo se selecciona entre el grupo de acridinilo, azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo,

1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo,

donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y

que además está sustituido con un heterociclilo seleccionado entre el grupo de acridinilo, azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo,

tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

R8 es 1) halógeno,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con halógeno o -O-alquilo (C_1-C_8),

9) alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

10) -O-alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

11) $-SO_2CH_3$ o

12) $-SO_2-CF_3$,

con la condición de que R8 sea al menos un halógeno, $-C(O)-NH_2$ o un resto -O-alquilo (C_1-C_8), si R^0 es un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo es como se ha definido anteriormente,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R^0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo azetidina, azetina, azocano, azocano-2-ona, ciclobutilo, ciclooctano, ciclooctano, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, [1,4]diazocano, [1,2]diazocan-3-ona, [1,3]diazocan-2-ona, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,2-oxa-tiepano, 1,2-oxatiolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, [1,4]oxazocano, [1,3]oxazocan-2-ona, oxetano, oxocano, oxocan-2-ona, piperazina, piperidina, fenilo, pirano, pirazina, pirazol, pirazolina, pirazolidina,

piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, 5,6,7,8-tetrahidro-1H-azocin-2-ona, tetrahidrofurano, tetrahidropirano, tetrahidropiridina, tetrazina, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tietano, tiocano, tiocano-1,1-dióxido, tiocano-1-óxido, tiocan-2-ona, tiomorfolina, tifeno, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol y está sin sustituir o sustituido 1, 2, 3, 4, 5 ó 6 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -alquileno (C_0-C_2)-C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{10}-, -NR^{10}-C( )-, -SO_2-, metileno, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-S-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -C$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$-, -alquileno (C_2-C_3)-O-alquileno (C_0-C_3), -alquileno (C_2-C_3)-S(O)-, -alquileno (C_2-C_3)-$S(O)_2$-, -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-, -alquileno (C_2-C_3)-$S(O)_2$-NH-(R^{10})-, -alquileno (C_2-C_3)-N(R^{10})- o -alquileno (C_0-C_3)-C(O)-O-$(CH_2)_m$-,

donde R^{10} es como se define más adelante, y donde n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6, donde los restos alquileno que se forman con -$(CH_2)_m$- o -$(CH_2)_n$- están sin sustituir o mono-, di- o trisustituidos independientemente entre sí con halógeno, -NH_2 o -OH; o

-cicloalquileno (C_3-C_6), donde el cicloalquileno está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, -NH_2 o -OH;

R^1 es un átomo de hidrógeno, -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13; -alquileno (C_1-C_3)-C(O)-NH-R^0, -alquileno (C_1-C_3)-C(O)-O-R15, un arilo del grupo de fenilo, naftilo, bifenililo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8, donde R8 es como se ha definido anteriormente;

un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, que es como se ha definido anteriormente;

-perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4), -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3), -alquileno (C_1-C_3)-$S(O)_2$-N($R^{4'}$)-$R^{5'}$, -alquileno (C_1-C_3)-O-alquilo (C_1-C_4), -alquileno (C_0-C_3)-cicloalquilo (C_3-C_6) o alquileno (C_0-C_3)-het, donde het es un resto seleccionado entre el grupo de azepina, azetidina, aziridina, azirina, 1,4-diazapano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diaziridina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,4-oxazepano, 1,2-oxa-tiepano, 1,2-

oxatiolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

$R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros seleccionado entre el grupo de azepina, azetidina, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, bromo, yodo, -OH, =O, alquilo (C_1-C_8), -alcoxi (C_1-C_4), -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-perfluoroalquilo (C_1-C_3), -alquil (C_0-C_8)-SO_2-N(R^{18})-R^{21}, -C(O)-NH-alquilo (C_1-C_8), -C(O)-N-[alquilo (C_1-C_8)]$_2$, -NR^{18}-C(O)-NH-alquilo (C_1-C_8), -C(O)-NH_2, -S-R^{18} o -NR^{18}-C(O)-NH-[alquilo (C_1-C_8)]$_2$,

donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o -alquilo (C_1-C_8),

V es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico del grupo de fenilo, naftilo, bifenililo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R14,

2) un heterociclilo del grupo de acridinilo, 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol-(1H-pirrolopiridina), azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 1,4-diazepano, 4,5-

dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopirazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

G es un enlace directo, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$ o $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6,

M es 1) un átomo de hidrógeno,

2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

3) -C(O)-N(R11)-R12,

4) $-(CH_2)_m-NR^{10}$,

5) -arilo (C_6-C_{14}), donde el arilo es como se ha definido anteriormente y donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

6) -heterociclilo (C_4-C_{18}), donde el heterociclilo es como se ha definido anteriormente y está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

7) -cicloalquilo (C_3-C_8), donde dicho cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está no sustituido o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) $-CHF_2$,

7) $-NO_2$,

8) -CN,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{12}$,

14) -alquileno (C_0-C_4)-$N(R^{11})-R^{12}$,

15) $-NR^{10}-SO_2-R^{10}$,

16) $-S-R^{10}$,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_8),

20) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

21) -alquileno (C_0-C_4)-arilo (C_6-C_{14}), donde el arilo está mono-, di- o trisustituido independientemente entre sí con R13,

22) -alquileno (C_0-C_4)-heterociclilo (C_4-C_{15}), donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

23) -alquileno (C_0-C_4)-cicloalquilo (C_3-C_8), donde el cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

24) alquileno (C_0-C_4)-het, donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

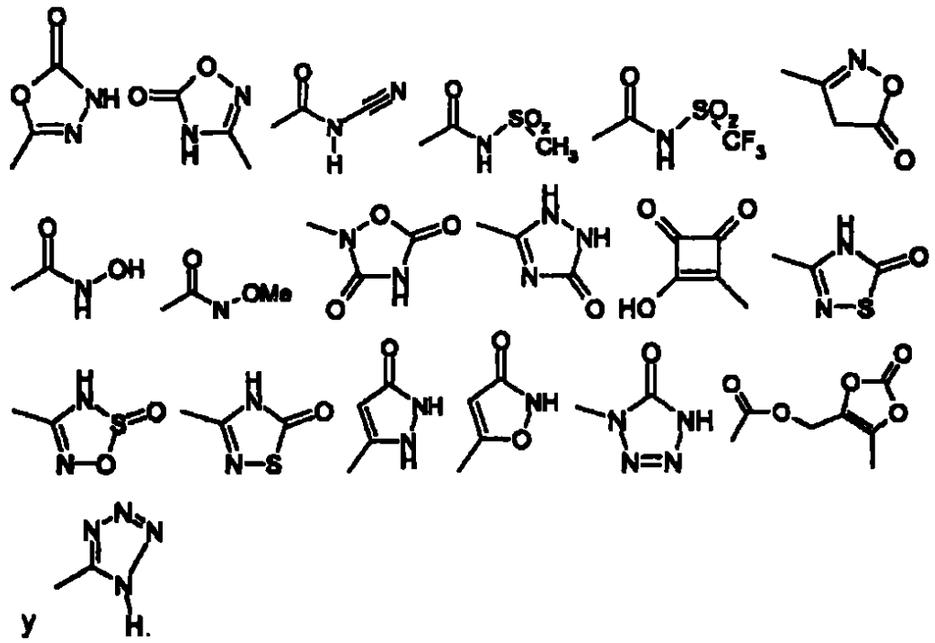
25) -alquileno (C_0-C_4)-O-CH_2-perfluoroalquileno (C_1-C_3)-CH_2-O-alquilo (C_0-C_4),

26) -SO_w-N(R^{11})-R^{13}, donde w es 1 ó 2,

27) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{13}, o

28) -alquileno (C_0-C_4)-N(R^{11})-R^{13}, o

29) *un resto de la siguiente lista*



y

donde Me es metilo o,

si dos restos -OR19 están unidos a átomos adyacentes pueden formar junto con los

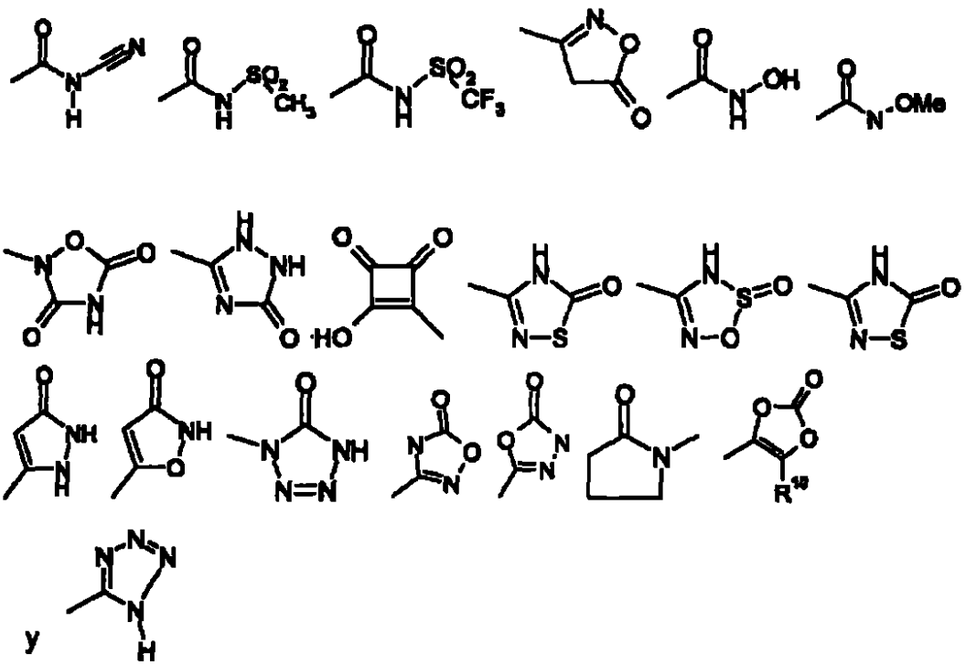
átomos a los que están unidos un anillo 1,3-dioxol o un anillo 2,3-dihidro-[1,4]dioxina, que está sustituido una, dos, tres o cuatro veces con R13,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,
2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
3) -alquil (C_0-C_8)-cicloalquilo (C_3-C_8),
4) -SO_t-R^{10}, donde t es 1 ó 2,
5) -alquil (C_0-C_8)-arilo (C_6-C_{14}), donde el alquilo y el arilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13,
6) -perfluoroalquilo (C_1-C_3),
7) -O-R^{17}, o
8) -alquil (C_0-C_8)-heterociclilo (C_4-C_{14}), donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo heterocíclico del grupo de azepina, azetidina, dioxazol, dioxazina, 1,4-diazepano, 1,2-diazepina, 1,4-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho anillo heterocíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es halógeno, -NO_2, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})R^{20}, -cicloalquilo (C_3-C_8), -alquileno (C_0-C_3)-O-R^{10}, -Si-(CH_3)$_3$, -N(R^{10})-$S(O)_u$-R^{10}, donde u es 1 ó 2, -S-R^{10}, -SO_r-R^{10}, donde r es 1 ó 2, -$S(O)_v$-N(R^{10})-R^{20}, donde v es 1 ó 2, -C(O)-R^{10}, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, fenil-oxi-, -O-CF_3, -alquil (C_0-C_4)-C(O)-O-C(R15,R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15,R16)-O-C(O)-R17, -perfluoroalquilo (C_1-C_3), -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, o un resto de la siguiente lista



y

donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_6), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_6), ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH, -alquil (C_1-C_6)-O-alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-O-alquil (C_1-C_6)-cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-cicloalquilo (C_3-C_6), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

3. Un compuesto de fórmula I de acuerdo con las reivindicaciones 1 a 2, donde

R^0 es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico del grupo de fenilo, naftilo, bifenilo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo,

fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo del grupo de azabencimidazolilo, bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzotiazolilo, benzotiofenilo, benzoxazolilo, cromanilo, cinolinilo, 2-furilo, 3-furilo; imidazolilo, indolilo, indazolilo, isocromanilo, isoindolilo, isoquinolinilo, isotiazolilo, isoxazolilo, oxazolilo, ftalazinilo, pteridinilo, purinilo, pirazinilo, pirazolilo, piridazinilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, 2-piridilo, 3-piridilo, 4-piridilo, pirimidinilo, pirrolilo; 2-pirrolilo, 3-pirrolilo, quinolinilo, quinazolinilo, quinoxalinilo, tetrazolilo, tiadiazolilo, tiazolilo, 2-tienilo o 3-tienilo, que además está sustituido con un heterociclilo seleccionado entre el grupo acridinilo, azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo(bencimidazolilo), isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridinilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo,

tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo,

donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

R8 es 1. flúor, cloro o bromo,

2. $-NO_2$,

3. -CN,

4. $-C(O)-NH_2$,

5. -OH,

6. $-NH_2$,

7. $-OCF_3$

8. un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo es como se ha definido anteriormente y está mono-, di- o trisustituido independientemente entre sí con halógeno o -O-alquilo (C_1-C_6),

9. -alquilo (C_1-C_6), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi, o

10. -O-alquilo (C_1-C_6), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

11. $-SO_2CH_3$ o

12. $-SO_2CF_3$,

con la condición de que R8 sea al menos un halógeno, $-C(O)-NH_2$ o un resto -O-alquilo (C_1-C_6), si R0 es un arilo o un heterociclilo, que son como se han definido anteriormente,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_6), si R^0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido piridilo, pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo, pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -alquileno (C_0-C_2)-$C(O)-NR^{10}$, $-NR^{10}-C(O)-NR^{10}$-, $-NR^{10}$-

C(O)-, -SO_2-, metileno o -alquileno (C_0-C_3)-C(O)-O-alquileno (C_0-C_2),

R^1 es un átomo de hidrógeno, -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13; -alquileno (C_1-C_3)-C(O)-NH-R^0, -alquileno (C_1-C_3)-C(O)-O-R15, -perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4), -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3), -alquileno (C_1-C_3)-$S(O)_2$-N($R^{4'}$)-$R^{5'}$, -alquileno (C_1-C_3)-O-alquilo (C_1-C_4), -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8), o -alquileno (C_0-C_3)-het, donde het es un resto seleccionado entre el grupo de azepina, azetidina, aziridina, azirina, 1,4-diazapano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diazirina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,2-oxatiepano, 1,2-oxatiolano, 1,4-oxazepano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

$R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V forma un grupo cíclico de 4 a 8 miembros seleccionado entre el grupo de azepina, azetidina, 1,4-diazepano, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,4-oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, bromo, yodo, -OH, =O, alquilo (C_1-C_8), -alcoxi (C_1-C_4), -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-perfluoroalquilo (C_1-C_3), -alquil (C_0-C_8)-SO_2-N(R^{18})-R^{21}, -C(O)-NH-alquilo (C_1-C_8), -C(O)-N-[alquilo (C_1-C_8)]$_2$, -NR^{18}-C(O)-NH-alquilo (C_1-C_8), -C(O)-NH_2-, -S-R^{18} o

$-NR^{18}-C(O)-NH-[alquilo\ (C_1-C_8)]_2$,

donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o -alquilo (C_1-C_8).

V es 1) un resto het del grupo de 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol(1H-pirrolopiridina), azepina, azetidina, aziridina, azirina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diazirina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,2-oxa-tiepano, 1,2-oxatiolano, 1,4-oxazepano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, que es como se ha definido anteriormente y donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

2) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

G es un enlace directo, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$ o $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6,

M es 1) un átomo de hidrógeno,

2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

3) $-C(O)-N(R11)-R12$,

4) $-(CH_2)_m-NR^{10}$,

5) fenilo o naftilo, donde el fenilo o el naftilo están sin sustituir o mono-, di- o trisustituidos, independientemente entre sí, con R14,

6) heterociclilo, donde el heterociclilo es un resto del grupo que puede derivarse de azepano, azepina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina,

1,4-diazepina, imidazol, isotiazol, isoxazol, isoxazolidina, 2-isoxazolina, cetomorfolina, cetopiperazina, morfolina, oxazol, [1,4]-oxazepano, piperazina, piperazinona, piperidina, piperidinona, pirazina, piridazina, piridazinona, piridina, piridona, pirimidina, pirrolidina, pirrolidinona, tetrahidropirano, 1,4,5,6-tetrahidro-piridazinilo, tetrazina, tetrazol, tiadiazol, tiazol, tiomorfolina, 1λ6-tiomorfolinilo, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

7) -cicloalquilo (C_3-C_8), donde dicho cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) $-CHF_2$,

7) -CN,

8) -alquileno (C_0-C_4)-heterociclilo (C_4-C_{15}), donde el heterociclilo es como se ha definido anteriormente y está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-$C(O)-R^{11}$,

12) -alquileno (C_0-C_4)-$C(O)-O-R^{11}$,

13) -alquileno (C_0-C_4)-$C(O)-N(R^{11})-R^{12}$,

14) -alquileno (C_0-C_4)-N(R^{11})-R^{12},

15) -NR^{10}-SO_2-R^{10},

16) -alquileno (C_0-C_4)-het, donde het es como se ha definido anteriormente y está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_8),

20) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

21) -alquileno (C_0-C_4)-arilo (C_6-C_{14}), donde el arilo es como se ha definido anteriormente y está mono-, di- o trisustituido independientemente entre sí con R13,

22) -alquileno (C_0-C_4)-cicloalquilo (C_3-C_8), donde el cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

23) -alquileno (C_0-C_3)-O-CH_2-CF_2-CH_2-O-alquilo (C_0-C_3),

24) -alquileno (C_0-C_3)-O-CH_2-CF_2-CF_2-CH_2-O-alquilo (C_0-C_3),

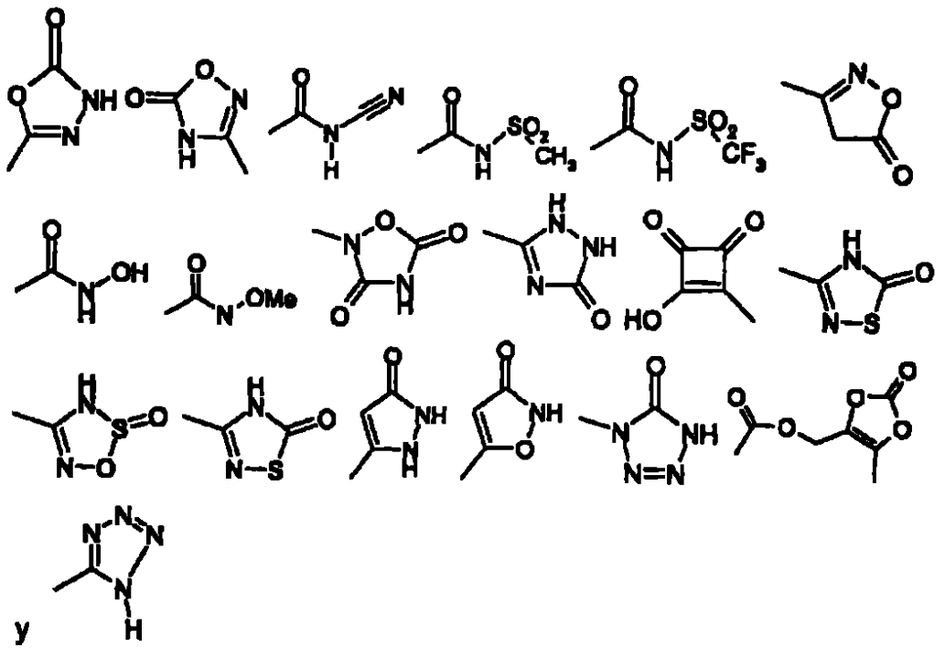
25) -alquileno (C_0-C_3)-O-CH_2-perfluoroalquileno (C_1-C_3)-CH_2-OH,

26) -SO_w-N(R^{11})-R^{13}, donde w es 1 ó 2,

27) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{13},

28) -alquileno (C_0-C_4)-N(R^{11})-R^{13}, o

29) un resto de la siguiente lista



y

donde Me es metilo,

si dos restos -OR19 están unidos a átomos adyacentes pueden formar junto con los átomos a los que están unidos un anillo 1,3-dioxol o un anillo 2,3-dihidro-[1,4]dioxina que está sustituido una, dos, tres o cuatro veces con R13,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

3) -alquil (C_0-C_8)-arilo (C_6-C_{14}), donde el arilo es como se ha definido anteriormente y donde el alquilo y el arilo están, independientemente entre sí, sin sustituir o mono-, di- o trisustituidos con R13,

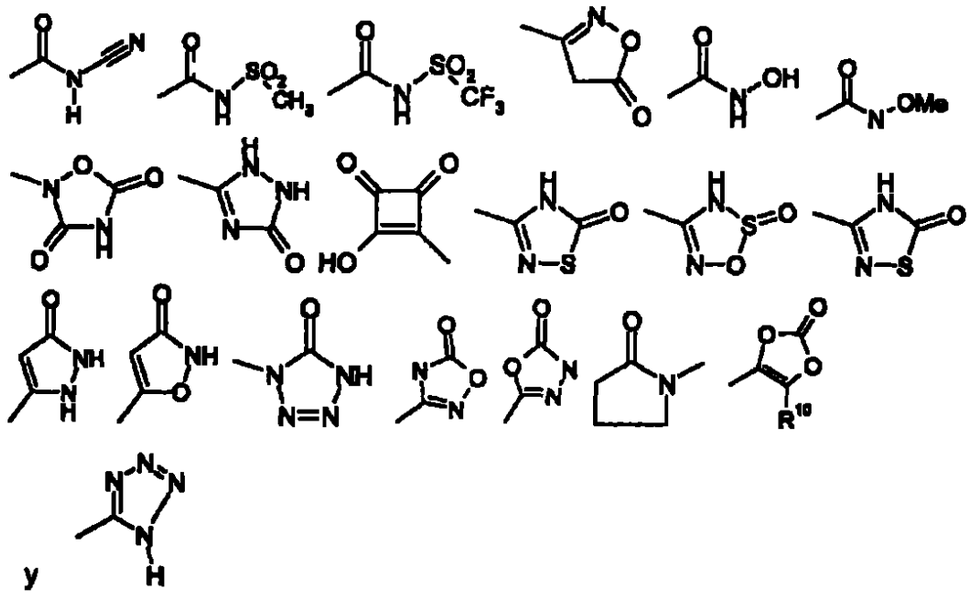
4) -O-R^{17}, o

5) -alquilo (C_0-C_8)-heterociclilo (C_4-C_{15}), donde el alquilo y el heterociclilo son como se han definido anteriormente y están, independientemente entre sí, sin sustituir o mono-, di- o trisustituidos con R13, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo seleccionado entre el grupo de azepina, azetidina, 1,4-diazepano, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]-

oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, que está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, cloro, bromo, yodo, $-NO_2$, -CN, =O, -OH, $-CF_3$, $C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, -alquileno $(C_0-C_3)-O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, feniloxi-, $-O-CF_3$, -perfluoroalquilo (C_1-C_3), -alquil $(C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17$, -alcoxi (C_1-C_4)-fenilo, -alquil $(C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-O-R17$, $-O-R15$, $-NH-C(O)-NH-R^{10}$, $-NH-C(O)-O-R^{10}$, o un resto de la siguiente lista



donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R10, y

R17 es -alquilo (C_1-C_8), -alquil (C_1-C_8)-OH, -alquil (C_1-C_8)-O-alquilo (C_1-C_8), -cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-O-alquil (C_1-C_8)-cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o

sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

4. Un compuesto de fórmula I de acuerdo con las reivindicaciones 1 a 3, donde

R0 es 1) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo del grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y además está sustituido con un resto seleccionado entre el grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho resto está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8

R8 es 1. F, Cl Br o I,

2. -C(O)-NH_2,

3. -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, -OH o un resto metoxi, o

4. -O-alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno o un resto metoxi,

con la condición de que R8 sea al menos un halógeno, -C(O)-NH_2 o un resto -O-

alquilo (C_1-C_8), si R0 es un arilo o un heterocicilo, que son como se han definido anteriormente,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido, pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo, pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -C(O)-; -SO_2-, metileno, -alquileno (C_0-C_2)-C(O)-NR^{10}- o -alquileno (C_0-C_3)-C(O)-O-alquileno (C_0-C_2),

R^1 es un átomo de halógeno, -alquilo (C_1-C_2), -alquileno (C_1-C_3)-C(O)-NH-R0, -perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-C(O)-O-R^{15}, -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3) o -alquileno (C_1-C_3)-$S(O)_2$-$N(R^{4'})$-$R^{5'}$, donde $R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 7 miembros del grupo de azetidina, azetidinona, piperidina, piperazina, piridina, pirimidina, pirrolidina, pirrolidinona, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol, 1,2,4-triazol, tetrazina, tetrazol, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, azepina, cetopiperidina, 1,4-oxazepano, oxazol, isoxazol, isoxazolidina, 2-isoxazolina, morfolina, tiazol, isotiazol, tiadiazol o tiomorfolina, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, -OH, =O, -alquilo (C_1-C_8), -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -C(O)-NH-alquilo (C_1-C_8), -C(O)-N-[alquilo (C_1-C_8)]$_2$, -C(O)-NH_2 o -$N(R^{18})$-R^{21}, donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o -alquilo (C_1-C_4),

V es 1. un resto cíclico del grupo que contiene compuestos que se derivan de 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol(1H-pirrolopiridina), aziridina, azirina, azetidina, azetidinona, 1,4-diazepano, pirrol, pirrolidina, piridonilo, imidazol, pirazol, 1,2,3-triazol, 1,2,4-triazol, tetrazol, piridina, pirimidina, pirazina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, tetrazina, tetrazol, azepina, diazirina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, piridazina, piperidina, piperazina, pirrolidinona, cetopiperazina, furano, pirano, dioxol, 1,4-oxazepano, oxazol, isoxazol, 2-isoxazolina, isoxazolidina, morfolina, oxirano, oxaziridina, 1,3-dioxoleno, 1,3-dioxolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxaziridina,

tiofeno, tiopirano, tietano, tiazol, isotiazol, isotiazolina, isotiazolidina, 1,2-oxatiolano, tiodiazol, tiopirano, 1,2-tiazina, 1,3-tiazol, 1,3-tiazina, 1,4-tiazina, tiadiazina o tiomorfolina, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

2. fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

G es un enlace directo, $-(CH_2)_m-$ o $-(CH_2)_m-NR^{10}-$,

m son los números enteros cero, 1, 2, 3 ó 4,

M es 1. un átomo de hidrógeno,

2. heterociclilo, donde el heterociclilo es un resto del grupo que puede derivarse de azepano, azepina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, isotiazol, isoxazol, isoxazolidina, 2-isoxazolina, cetomorfolina, cetopiperazina, morfolina, oxazol, [1,4]-oxazepano, piperazina, piperazinona, piperidina, piperidinona, pirazina, piridazina, piridazinona, piridina, piridona, pirimidina, pirrolidina, pirrolidinona, tetrahidropirano, 1,4,5,6-tetrahidro-piridazinilo, tetrazina, tetrazol, tiadiazol, tiazol, tiomorfolina, 1λ6-tiomorfolinilo, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

3. -alquilo (C_1-C_6), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

4. -cicloalquilo (C_3-C_6), o

5. $-C(O)-N(R^{11})-R^{12}$,

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) CHF_2,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{12}$,

14) -alquileno (C_0-C_4)-$N(R^{11})-R^{12}$,

15) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

18) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

19) -alquileno (C_0-C_3)-O-$CH_2-CF_2-CH_2$-O-alquilo (C_0-C_3),

20) -alquileno (C_0-C_3)-O-$CH_2-CF_2-CF_2-CH_2$-O-alquilo (C_0-C_3),

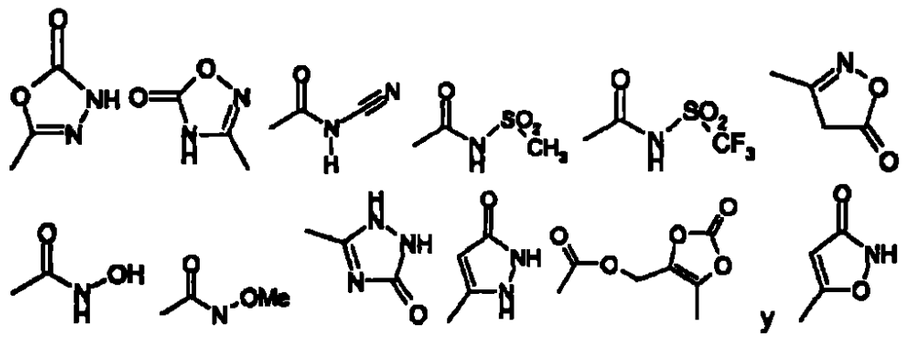
21) -alquileno (C_0-C_3)-O-CH_2-perfluoroalquilo $(C_1-C_3)-CH_2-OH$,

22) $-SO_w-N(R^{11})-R^{13}$, donde w es 1 ó 2,

23) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{13}$,

24) -alquileno (C_0-C_4)-$N(R^{11})-R^{13}$, o

25) un resto de la siguiente lista



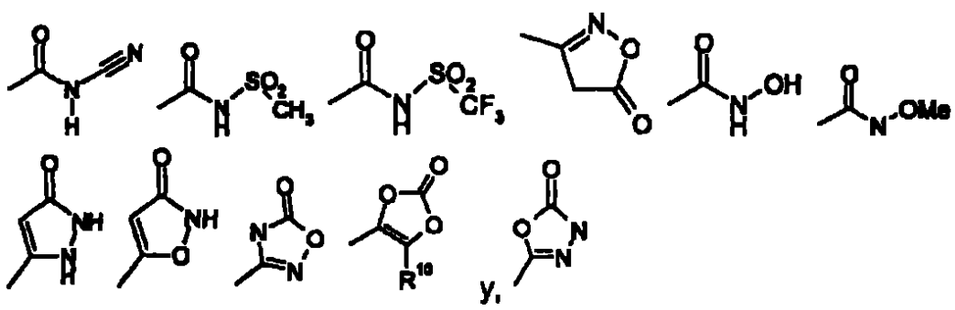
y

donde Me es metilo,

si dos restos -OR19 están unidos a átomos adyacentes pueden formar junto con los átomos a los que están unidos un anillo 1,3-dioxol o un anillo 2,3-dihidro-[1,4]dioxina, que está sustituido una, dos, tres o cuatro veces con R13,

R^{11} y R^{12} junto con el átomo de nitrógeno al que están unidos pueden formar un anillo seleccionado entre el grupo de azepina, azetidina, 1,4-diazepano, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]-oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho anillo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, cloro, $-NO_2$, -CN, =O, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, -alquileno (C_0-C_3)-$O-R^{10}$, $-Si-(CH_3)_3$, $-N(R^{10})-S(O)_2-R^{10}$, $-S-R^{10}$, $-SO_2-R^{10}$, $-S(O)_2-N(R^{10})-R^{20}$, $-C(O)-R^{10}$, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, feniloxi, $-O-CF_3$, -perfluoroalquilo (C_1-C_3), $-NH-C(O)-NH-R^{10}$, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -O-R15, $-NH-C(O)-O-R^{10}$, o un resto de la siguiente lista



y,

donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8) o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10} y

R17 es -alquilo (C_1-C_8), -alquil (C_1-C_8)-OH, -alquil (C_1-C_8)-O-alquilo (C_1-C_8), -cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-O-alquil (C_1-C_8)-cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquil (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

5. Un compuesto de fórmula I de acuerdo con las reivindicaciones 1 a 4, donde

R0 es 1. fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

2. un heterociclilo seleccionado entre el grupo de indolilo, isoindolilo, benzofuranilo, benzotiofenilo, 1,3-benzodioxolilo, indazolilo, bencimidazolilo, benzoxazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, cromanilo, isocromanilo, cinolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, piridilo, purinilo y pteridinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

3. un heterociclilo del grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y además está sustituido con un resto seleccionado entre el grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho resto está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8

R8 es 1. F, Cl Br o I,

2. $-C(O)-NH_2$,

3. -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, -OH o un resto metoxi, o

4. -O-alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno o un resto metoxi,

con la condición de que R8 sea al menos un halógeno, $-C(O)-NH_2$ o un resto -O-alquilo (C_1-C_8), si R0 es un arilo o un heterociclilo, que son como se han definido anteriormente,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-

óxido, pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo, pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -C(O)-; -SO_2-, -C(O)-O-metileno, metileno o -alquileno (C_0-C_2)-C(O)-NR^{10},

R^1 es un átomo de hidrógeno o -alquilo (C_1-C_2),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 7 miembros del grupo de piperidina, piperazina, piridina, pirimidina, pirrolidina, pirrolidinona, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol, 1,2,4-triazol, tetrazina, tetrazol, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, azepina, cetopiperazina, oxazol, isoxazol, isoxazolidina, 2-isoxazolina, morfolina, tiazol, isotiazol, tiadiazol o tiomorfolina, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, -alquilo (C_1-C_4) o -NH_2,

V es 1. un resto cíclico del grupo que contiene compuestos que se derivan de 8-aza-biciclo[3.2.1]oct-3-ilo, azaindolil(1H-pirrolopiridilo), azetidina, azepina, aziridina, azirina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diazirina, 1,3-dioxolano, dioxazol, furano, imidazol, isoquinolina, isotiazol, isotiazolidina, isotiazolina, isoxazol, 2-isoxazolina, isoxazolidina, cetopiperazina, morfolina, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, 1,2-oxatiolano, piperidina, pirano, pirazina, pirazol, piridazina, piperazina, piridina, piridona, pirimidina, pirrol, pirrolidina, pirrolidinona, quinazolina, quinolina, tetrazina, tetrazol, tiadiazina, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tietano, tiomorfolina, tiofeno, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

2. fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

G es un enlace directo, -(CH_2)$_m$- o -(CH_2)$_m$-NR^{10}-,

m son los números enteros cero, 1, 2, 3 ó 4,

M es 1. un átomo de hidrógeno,

2. heterociclilo, donde el heterociclilo es un resto del grupo que puede derivarse de 1,4-diazepano, cetomorfolina, tiofeno, piridazona, piperidina, piperazina, piridina, pirimidina, pirrolidina, pirrolidinona, piridonilo, imidazol,

piridazina, pirazina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol, 1,2,4-triazol, tetrazina, tetrazol, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, azepina, cetopiperazina, oxazol, isoxazol, isoxazolidina, 2-isoxazolina, morfolina, tiazol, isotiazol, tetrahidropirano, 1,4,5,6-tetrahidro-pirazinilo, tiadiazol, 1λ6-tiomorfolinilo o tiomorfolina, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

3. -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

4. -cicloalquilo (C_3-C_8),

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) CHF_2,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{12}$,

14) -alquileno (C_0-C_4)-$N(R^{11})-R^{12}$,

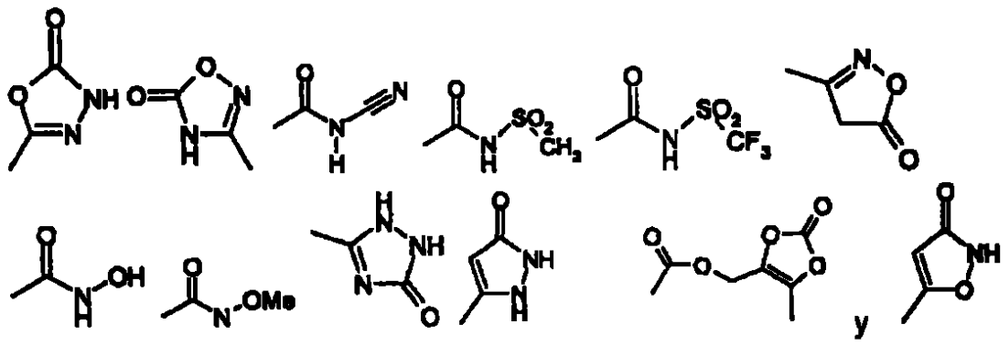
15) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

18) -C(O)-O-C(R15, R16)-O-C(O)-O-R17, o

19) un resto de la siguiente lista



y

donde Me es metilo,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

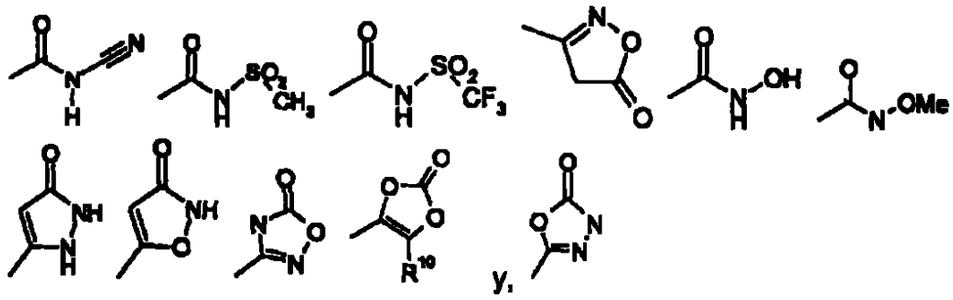
3) -alquil (C_0-C_6)-cicloalquilo (C_3-C_6),

4) -O-R^{17}, o

5) -alquil (C_0-C_6)-heterociclilo (C_4-C_{15}), donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13 y donde el heterociclilo se selecciona entre el grupo de azetidina, ciclopropilo, ciclobutilo, 4,5-dihidro-oxazol, imidazolidina, morfolina, (1,4)-oxazepano, oxazolidina, piperidina, piperazina, pirrolidina, tetrahidrotiofeno, tiazolidina o tiomorfolina, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico que se selecciona entre el grupo de azetidina, ciclopropilo, ciclobutilo, 4,5-dihidrooxazol, imidazolidina, morfolina, (1,4)-oxazepano, oxazolidina, piperidina, piperazina, pirrolidina, tetrahidrotiofeno, tiazolidina o tiomorfolina, donde dicho anillo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -cicloalquilo (C_3-C_6), -alquileno (C_0-C_3)-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -perfluoroalquilo (C_1-C_3) o un resto de la siguiente lista



y,

donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R^{15} y R^{16} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_8), -alquil (C_1-C_8)-OH, -alquil (C_1-C_8)-O-alquil (C_1-C_8)-cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-O-alquilo (C_1-C_8) o -alquil (C_0-C_8)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

6. Un compuesto de fórmula I de acuerdo con las reivindicaciones 1 a 5, donde

R0 es 1. fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R8,

2. piridilo o 1H-indazolilo, donde el piridilo y el 1H-indazolilo están sin sustituir o mono- o disustituidos independientemente entre sí con R8, o

3. un heterociclilo del grupo de tienilo, tiadiazolilo, isoxazolilo y tiazolilo, donde dicho heterociclilo está sustituido con un resto seleccionado entre el grupo de tienilo, 2-tienilo y 3-tienilo, donde dicho resto está sin sustituir o mono- o disustituido independientemente entre sí con R8,

R8 es F, Cl, Br, -O-CH_3 o -C(O)-NH_2,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_8), si R^0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido, pirrolilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo o pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -C(O)-; -SO_2-, -C(O)-O-metileno, -CH_2-C(O)-NH- o metileno,

R^1 es un átomo de hidrógeno,

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros del grupo de azetidina, pirrolidina, piperidina y piperazina,

R14 es flúor, cloro, metilo, etilo, =O, -SO_2-CH_3 o -NH_2,

V es 1. un resto del grupo que contiene los compuestos que se derivan de 8-aza-biciclo[3.2.1]oct-3-ilo, azaindolil(1H-pirrolopiridilo), azetidina, 1,4-diazepano, isoxazol, isoquinolina, piperazina, piperidina, pirazina, piridazina, pirimidina, pirrolidina, quinazolina, quinolina o tetrahidropirano, donde dicho resto cíclico está sin sustituir o mono- o disustituido independientemente entre sí con R14, o

2. fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R14,

G es un enlace directo, -$(CH_2)_m$-, -C(O)- o -$(CH_2)_m$-NR^{10}-,

m son los números enteros cero, 1 ó 2,

M es un átomo de hidrógeno, alquilo (C_2-C_4), azepanilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, imidazolilo, cetomorfolinilo, morfolinilo, [1,4]oxazepanilo, piperazinilo, piperidinilo, piperidonilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidilo, pirrolidinilo, 1λ6-tiomorfolinilo, 1,4,5,6-tetrahidro-piridazinilo o tetrahidropiranilo, donde los restos están sin sustituir o mono- o disustituidos independientemente entre sí con R14

R3 es 1) un átomo de hidrógeno,

2) flúor, cloro,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_2)-O-R19, donde R19 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) $-CHF_2$,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{12}$,

14) -alquileno (C_0-C_4)-$N(R^{11})-R^{12}$,

15) -alquileno (C_0-C_4)-C(O)-O-alquileno (C_2-C_4)-C(O)-alquilo (C_1-C_4),

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6) o

18) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

3) -alquil (C_0-C_6)-cicloalquilo (C_3-C_6),

4) $-O-R^{17}$, o

5) -alquil (C_0-C_6)-heterociclilo, donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos independientemente entre sí con R13 y donde el heterociclilo se selecciona entre el grupo de azetidina, imidazolidina, morfolina, (1,4)-oxazepano o pirrolidina o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo que se selecciona entre el grupo de azetidina, imidazolidina, morfolina, (1,4)-oxazepano, piperazina, piperidina, pirrolidina o tiomorfolina, donde dicho anillo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, -CN, =O, $-CF_3$, $-C(O)-O-R^{10}$, $-C(O)-N(R^{10})-R^{20}$, $-N(R^{10})-R^{20}$, -alquilo (C_1-C_3), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_3)-$O-R^{10}$, $-Si-(CH_3)_3$, $-S-R^{10}$, $-SO_2-R^{10}$, $-SO_2-NH$ o -perfluoroalquilo (C_1-C_3),

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o -

perfluoroalquilo (C_1-C_3),

R^{15} y R^{16} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH, -alquil (C_1-C_6)-O-alquil (C_1-C_6)-cicloalquilo (C_3-C_8), -alquil (C_1-C_6)-O-alquilo (C_1-C_6) o -alquil (C_0-C_6)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

7. Un compuesto de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 6, donde

R0 es 1. fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R8,

2. piridilo o 1H-indazolilo, donde el piridilo y el 1H-indazolilo están sin sustituir o mono- o disustituidos independientemente entre sí con R8, o

3. un heterociclilo del grupo tiadiazolilo, isoxazolilo y tiazolilo, donde dicho heterociclilo está sustituido con un resto seleccionado entre el grupo de tienilo, 2-tienilo y 3-tienilo, donde dicho resto está sin sustituir o mono- o disustituido independientemente entre sí con R8,

R8 es Cl o -O-CH_3,

con la condición de que R8 no sea un resto -O-alquilo (C_1-C_6), si R^0 y V son fenilo,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, tienilo o pirimidinilo, y está sustituido o sin sustituir 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es -CH_2-C(O)-NH- o metileno,

R^1 es un átomo de hidrógeno,

R^2 es un enlace directo,

R14 es flúor o =O,

V es piperidinilo o fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R14,

G es un enlace directo o -C(O)-

M es un átomo de hidrógeno, -alquilo (C_2-C_4), isopropilo, ciclopropilo, morfolinilo, piperazinilo, piperidinilo, pirazinilo, piridilo, pirimidilo, pirrolidinilo o 1λ6-

tiomorfolinilo, donde los restos están sin sustituir o mono- o disustituidos independientemente entre sí con R14,

R3 es 1) un átomo de hidrógeno,

2) flúor, cloro,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -alquileno (C_0-C_2)-O-R19, donde R19 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) $-CF_3$,

5) $-SO_2-R^{11}$,

6) -alquileno (C_0-C_4)-C(O)-O-R^{11},

7) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{12},

8) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_6) o

9) -C(O)-O-C(R15, R16)-O-C(O)-R17,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

3) -alquil (C_0-C_6)-cicloalquilo (C_3-C_6) o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo que se selecciona entre el grupo de azetidina, morfolina, (1,4)-oxazepano o piperidina, donde dicho anillo está sin sustituir o mono-, di- o trisustituido con R13,

R13 es flúor, =O, -OH, $-CF_3$, -C(O)-O-R^{10}, -alquilo (C_1-C_3), -cicloalquilo (C_3-C_6) o -alquileno (C_0-C_3)-O-R^{10},

R^{10} es un átomo de hidrógeno o -alquilo (C_1-C_4),

R^{15} y R^{16} son, independientemente entre sí, un átomo de hidrógeno o -alquilo (C_1-C_4), y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH o -alquil (C_0-C_4)-cicloalquilo (C_3-C_6).

8. Un compuesto de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7, donde el compuesto es

(1-Isopropil-piperidin-4-il)-amida del ácido 1[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(4-cloro-fenilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

(1-Pirimidin-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

éster metílico del ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]piridina-2-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-

4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofeno-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofeno-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,4-dicarboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,4-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,5-dicarboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

[4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil)-H-benzoimidazol-4-carboxílico,

[4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-(3-metoxi-bencil)-1H-benzoimidazol-2-carboxílico,

[4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

(8-Metil-8-aza-biciclo[3.2.1]oct-3-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-oxazolidin-3-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-oxazolidin-3-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(4-Oxo-piperidin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(1,1-Dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(1,1-Dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-il]-

1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-piperazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-piperazin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico,

Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-3H-benzoimidazol-2,5-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-metil-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-3H-benzoimidazol-2,5-dicarboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

2-Hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

2-Hidroxi-etil éster del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 1-(3-metoxi-bencil)-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,

Ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

2-Metoxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-hidroximetil-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoximetil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(morfolina-4-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2,6-dimetil-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(4,4-difluoro-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico,

2-Hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

Ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-4-carboxílico,

Ácido 2-(1-Isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-4-

carboxílico,

Ácido 1-[2-(4-cloro-fenil)(-etil]-2-1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 4-(3-hidroxi-azetidina-1-carbonil)-1-(3-metoxi-bencil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 1-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

Ácido 1-(5-cloro-1H-indazol-3-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(4-hidroxi-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 7-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico,

Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 6-[(2-hidroxi-etil)-amida] del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-tieno[3,4-d]imidazol-2,6-dicarboxílico,

Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico,

Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-([1,4]oxazepano-4-carbonil)-3H-tieno[3,4-d]imidazol-2-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico,

Ácido 1-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-

ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-ilcarbamoil)-metil]-4-(2-etoxi-etoxi)(-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-hidroxi-etoxi)-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-trifluoroetoxi)-1H-benzoimidazol-4-carboxílico, o

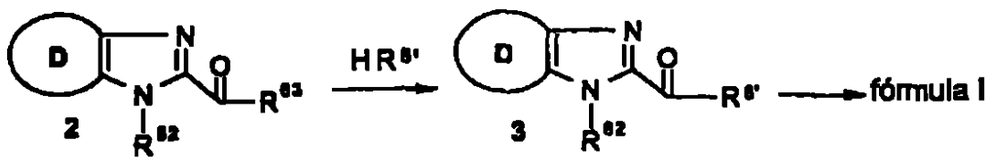
(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-2-carboxílico.

9. Una preparación farmacéutica, que comprende al menos un compuesto de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 8 en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación y/o sus sales fisiológicamente tolerables y un vehículo farmacéuticamente aceptable.

10. El uso de un compuesto de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 8 en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación y/o sus sales fisiológicamente tolerables para la producción de productos farmacéuticos para la inhibición del factor Xa y/o el factor VIIa o para influir sobre la coagulación sanguínea o la fibrinolisis.

11. El uso de acuerdo con la reivindicación 10 para una formación anormal de trombos, infarto de miocardio agudo, trastornos cardiovasculares, angina inestable, tromboembolia, cierre de vasos agudo asociado con una terapia trombolítica o angioplastia coronaria transluminal percutánea (PTCA), ataques isquémicos transitorios, apoplejía, claudicación intermitente, injerto de bypass de las arterias coronarias o periféricas, estrechamiento del lumen de vasos, reestenosis después de una angioplastia coronaria o venosa, mantenimiento de la patencia de acceso vascular en pacientes con hemodiálisis a largo plazo, formación patológica de trombos que tiene lugar en las venas de las extremidades inferiores después de una cirugía abdominal, de rodilla o de cadera, riesgo de tromboembolia pulmonar, coagulopatía intravascular sistémica diseminada que se produce en sistemas vasculares durante el choque séptico, ciertas infecciones víricas o cáncer, o para reducir una respuesta inflamatoria, fibrinolisis, o tratamiento de la enfermedad cardiaca coronaria, infarto de miocardio, angina de pecho, reestenosis vascular, por ejemplo reestenosis posterior a una angioplastia tal como PTCA, síndrome de distrés respiratorio en adultos, insuficiencia de múltiples órganos, trastorno de coagulación intravascular diseminada, y trombosis de venas profundas y de venas proximales, que pueden producirse después de una cirugía.

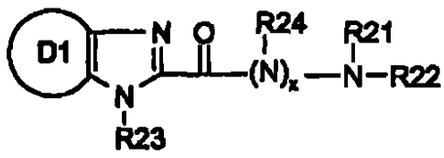
12. Un proceso para la preparación de un compuesto de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 8, que comprende condensar un compuesto de la fórmula 2 con un compuesto de la fórmula $HR^{6'}$ para dar un compuesto de la fórmula 3 y opcionalmente convertir el compuesto de la fórmula 3 en un compuesto de la fórmula I,



donde el resto $R^{6'}$ tiene la donación de $-N(R^1)-R^2-V-G-M$ como se indica en las reivindicaciones 1 a 8, pero donde en $R^{6'}$ los grupos funcionales también pueden estar presentes en forma de grupos que posteriormente se transforman en los grupos funcionales finales presentes en $-N(R^1)-R^2-V-G-M$, y donde el resto R^{62} denota el grupo $-Q-R^0$ o puede denotar un grupo que posteriormente se transforma en el grupo $-Q-R^0$, y donde el grupo $-C(O)-R^{63}$ puede ser un grupo de ácido carboxílico o derivados

del mismo, como se define en las reivindicaciones 1 a 8, donde dichos grupos funcionales también pueden estar presentes en forma protegida o en forma de grupos precursores.

13. Un proceso para la preparación de un compuesto de fórmula IV,



(IV)

en la que

x es el número entero cero o 1,

R21 y R24 son idénticos o diferentes y son, independientemente entre sí

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13,

c) -alquileno (C_1-C_3)-C(O)-NH-R^0,

d) -alquileno (C_1-C_3)-C(O)-O-R^{10},

e) -alquil (C_0-C_4)-arilo, donde el arilo es un arilo de 6 a 14 miembros monocíclico o bicíclico y está mono-, di- o trisustituido independientemente entre sí con R8,

f) -alquil (C_0-C_4)-heteroarilo, donde el heteroarilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está mono-, di- o trisustituido independientemente entre sí con R8,

g) -alquil (C_1-C_4)-heterociclilo, donde el heterociclilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y que está adicionalmente sustituido con un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

h) -perfluoroalquileno (C_1-C_3),

i) -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4),

j) -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3),

k) -alquileno (C_1-C_3)-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

l) -alquileno (C_1-C_3)-O-alquilo (C_1-C_4),

m) -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8) o

n) -alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

donde R^0, $R^{4'}$, $R^{5'}$, R8, R^{10}, R^{13} y R^{14} son como se han definido en la reivindicación 1 para el compuesto de fórmula I,

R22 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13,

c) -alquileno (C_1-C_3)-C(O)-NH-R^0,

d) -alquileno (C_1-C_3)-C(O)-O-R^{10},

e) -alquil (C_0-C_4)-arilo, donde el arilo es un arilo de 6 a 14 miembros monocíclico o bicíclico y está mono-, di- o trisustituido independientemente entre sí con R8,

f) -alquil (C_0-C_4)-heteroarilo, donde el heteroarilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está mono-, di- o trisustituido independientemente entre sí con R8,

g) -alquil (C_1-C_4)-heterociclilo, donde el heterociclilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y que está adicionalmente sustituido con un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

h) -perfluoroalquileno (C_1-C_3),

i) -alquileno (C_0-C_3)-S(O)-alquilo (C_1-C_4),

j) -alquileno (C_0-C_3)-$S(O)_2$-alquilo (C_1-C_3),

k) -alquileno (C_0-C_3)-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

l) -alquileno (C_1-C_3)-O-alquilo (C_1-C_4),

m) -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8),

n) -alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

o) R^2-V-G-M,

donde R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, $R14^4$, V, G y M son como se han definido en la reivindicación 1 para el compuesto de fórmula I, o la subestructura R21-N-R^2-V en la fórmula IV puede formar un grupo cíclico de 4 a 8 miembros que contiene 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, donde el resto R14 es como se ha definido en la reivindicación 1 para el compuesto de fórmula I,

R23 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13,

c) -alquileno (C_1-C_3)-C(O)-NH-R^0,

d) -alquileno (C_1-C_3)-C(O)-O-R^{10},

e) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

f) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno,

g) -perfluoroalquileno (C_1-C_3),

h) -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4),

j) -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3),

k) -alquileno (C_1-C_3)-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

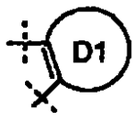
l) -alquileno (C_1-C_3)-O-alquilo (C_1-C_4),

m) -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8),

n) -alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

o) -Q-R^0,

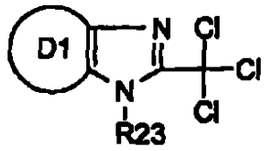
donde R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, R14, Q, V, G y M son como se han definido en la reivindicación 1 para el compuesto de fórmula I, y la



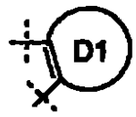
subestructura en la fórmula IV es

un grupo cíclico saturado, parcialmente insaturado o aromático de 4 a 8 miembros que contiene cero, 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está sin sustituir o sustituido 1, 2, 3, 4, 5 ó 6 veces con R3, donde R3 es como se ha definido en la reivindicación 1 para el compuesto de fórmula I,

que comprende hacer reaccionar un compuesto de la fórmula V



(V)



en la que R23 es como se ha definido en la fórmula IV y la subestructura en la fórmula V es como se ha definido en la fórmula IV,

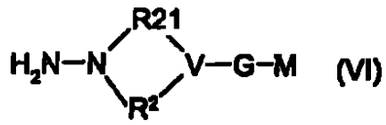
con una amina primaria o con una amina secundaria en presencia de agua, al menos una base y al menos un disolvente orgánico miscible con agua.

14. Un proceso para la preparación de un compuesto de fórmula IV de acuerdo con la reivindicación 13, donde la amina primaria es

a) NH_2-R21, donde R21 es como se ha definido en la fórmula IV,

b) NH_2-R^2-V-G-M, donde R^2, V, G y M son como se han definido en la fórmula IV,

c) -NH_2-N(R21)-R22, donde R21 y R22 son como se han definido en la fórmula IV o

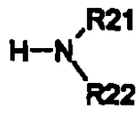


(VI)

d) un compuesto de fórmula VI

en la que R^2, R21, V, G y M son como se han definido en la fórmula IV.

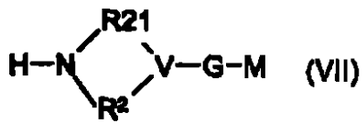
15. Un proceso para la preparación de un compuesto de fórmula IV de acuerdo con la reivindicación 13, donde la amina secundaria es



a)

donde R21 y R22 son como se han definido en la fórmula IV,

b) un compuesto de la fórmula VII

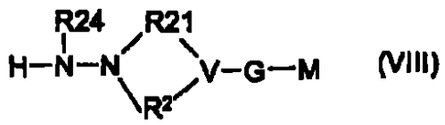


(VII)

en la que R21, R^2, V, G y M son como se han definido en la fórmula IV,

o

c) un compuesto de fórmula VIII



(VIII)

en la que R^2, R21, R24, V, G y M son como se han definido en la fórmula IV.

16. Un proceso para la preparación de un compuesto de fórmula IV de acuerdo con las reivindicaciones 13 ó 15, donde el disolvente miscible con agua es tetrahidrofurano, acetonitrilo, 1,2-dimetoxietano, dimetilsulfóxido, dioxano, N,N-dimetilformamida, N-metilpirrolidona, acetona o sulfolano y la base es un carbonato de metal alcalino, bicarbonato sódico, bicarbonato potásico, una amina terciaria, trietilamina o diisopropiletilamina.

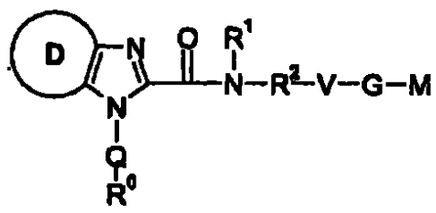
17. Un proceso para la preparación de un compuesto de fórmula IV de acuerdo con las reivindicaciones 13 ó 15, donde la cantidad de disolvente orgánico miscible con agua usada es de 5 g a 300 g por 1 g del compuesto de fórmula V, preferiblemente de 10 g a 200 g.

18. Un proceso para la preparación de un compuesto de fórmula IV de acuerdo con las reivindicaciones 13 ó 15, donde la temperatura de reacción es de 5°C a 120°C, preferiblemente de 10°C a 35°C, en particular 25°C.

Resumen

DERIVADOS DE BENCIMIDAZOL COMO INHIBIDORES DEL FACTOR Xa

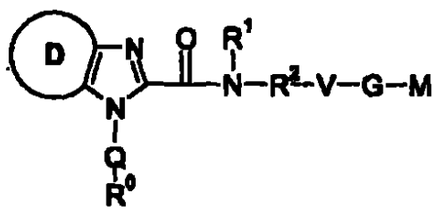
La presente invención se refiere a compuestos de la fórmula (I),

(I) 

en la que R^0, R^1, R^2, Q, V, G y M tienen los significados indicados en las reivindicaciones. Los compuestos de la fórmula (I) son compuestos farmacológicamente activos valiosos. Muestran un fuerte efecto antitrombótico y son adecuados, por ejemplo, para la terapia y profilaxis de trastornos cardiovasculares tales como enfermedades tromboembólicas o reestenosis. Son inhibidores reversibles de las enzimas de la coagulación sanguínea factor Xa (FXa) y/o factor VIIa (FVIIa) y, en general, pueden aplicarse en situaciones en las que está presente una actividad indeseada del factor Xa y/o del factor VIIa o en situaciones para cuya curación o prevención se desea la inhibición del factor Xa y/o del factor VIIa. Además, la invención se refiere a procesos para la preparación de compuestos de la fórmula (I), a su uso, en particular como ingredientes activos en productos farmacéuticos, y a preparaciones farmacéuticas que los contienen.

REIVINDICACIONES

1. Un compuesto de la fórmula I,

(I) 

, en la que

R^0 es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo,

donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y que está adicionalmente sustituido con un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno,

donde el heterociclilo está sin sustituir, mono-, di- o trisustituido independientemente entre sí con R8,

R8 es
1) halógeno,
2) $-NO_2$,
3) -CN,
4) $-C(O)-NH_2$,
5) -OH,
6) $-NH_2$,
7) $-O-CF_3$

8) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con halógeno o -O-alquilo (C_1-C_8),

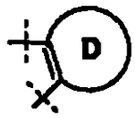
9) alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

10) $-SO_2CH_3$ o

11) $-SO_2-CF_3$,

con la condición de que R8 sea al menos un halógeno o un resto $-C(O)-NH_2$, si R^0 es un arilo de 6 a 14 miembros monocíclico o bicíclico,

la subestructura



en la fórmula I es un grupo cíclico saturado, parcialmente insaturado o aromático de 4 a 8 miembros que contiene cero, 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está sin sustituir o sustituido 1, 2, 3, 4, 5 ó 6 veces con R3 o sustituido 1 ó 2 veces con =0,

Q es -alquileno (C_0-C_2)-$C(O)-NR^{10}$-, $-NR^{10}-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$-, metileno, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$-, $-(CH_2)_m-S-(CH_2)_n$-, $-(CH_2)_m-C(O)-(CH_2)_n$-, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-CH(OH)-(CH_2)_n$-, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$-, -alquileno ($C_2$-$C_3$)-O-alquileno ($C_0$-$C_3$), -alquileno ($C_2$-$C_3$)-S(O)-, -alquileno ($C_2$-$C_3$)-$S(O)_2$-, $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n$-, -alquileno ($C_2$-$C_3$)-$S(O)_2-NH-(R^{10})$-, -alquileno ($C_2$-$C_3$)-$N(R^{10})$- o -alquileno ($C_0$-$C_3$)-$C(O)-O-(CH_2)_m$-,

donde R^{10} es como se define a continuación, y donde n y m son independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6 donde los restos alquileno que se forman por $-(CH_2)_m$- o $-(CH_2)_n$- están sin sustituir o mono-, di- o trisustituidos independientemente entre sí con halógeno, $-NH_2$ o -OH; o -cicloalquileno (C_3-C_6), donde el cicloalquileno está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, $-NH_2$ o -OH;

R^1 es un átomo de hidrógeno, -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13; -alquileno (C_1-C_3)-$C(O)-NH-R^0$, -alquileno (C_1-C_3)-$C(O)-O-R^{10}$, un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8, donde R8 es como se ha definido anteriormente; un heterociclilo de 4 a 15 miembros monocíclico o bicí-

clico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno; -perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4), -alquileno (C_1-C_3)-S(O)$_2$-alquilo (C_1-C_3), -alquileno (C_1-C_3)-S(O)$_2$-N($R^{4'}$)-$R^{5'}$, -alquileno (C_1-C_3)-O-alquilo (C_1-C_4), -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8) o alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

$R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros que contiene 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es halógeno, -OH, =O, -alquilo (C_1-C_8), -alcoxi (C_1-C_4), -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-perfluoroalquilo (C_1-C_3), -alquil (C_0-C_8)-SO_2-N(R^{18})-R^{21}, -C(O)-NH-alquilo (C_1-C_8), -C(O)-N[alquilo (C_1-C_8)]$_2$, -NR^{18}-C(O)-NH-alquilo (C_1-C_8), -C(O)-NH_2, -S-R^{18} o -NR^{18}-C(O)-NH-[alquilo (C_1-C_8)]$_2$,

donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o alquilo (C_1-C_8),

V es 1) un arilo de 6 a 14 miembros, donde el arilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14, o

2) un heterociclilo del grupo compuesto por acridinilo, 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol-(1H-pirrolopiridina), azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 1,4-diazepano, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, oc-

tahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,

G es un enlace directo, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ o $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6,

M es
1) un átomo de hidrógeno,
2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,
3) -C(O)-N(R11)-R12,
4) $-(CH_2)_m-NR^{10}$,
5) un arilo de 6 a 14 miembros, donde el arilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,
6) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, donde el heterociclilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14,

7) -cicloalquilo (C_3-C_8), donde dicho cicloalquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14, o

8) un resto cíclico de 3 a 7 miembros que contiene 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R14, donde R14 es como se ha definido anteriormente,

R3 es 1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

d) $-CF_3$, o

e) $-CHF_2$,

7) $-NO_2$,

8) -CN,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{12},

14) -alquileno (C_0-C_4)-N(R^{11})-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) $-S-R^{10}$,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

20) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

21) -alquileno (C_0-C_4)-arilo (C_6-C_{14}), donde el arilo está mono-, di- o trisustituido, independientemente entre sí, con R13,

22) -alquileno (C_0-C_4)-heterociclilo (C_4-C_{15}), donde el heterociclilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

23) -alquileno (C_0-C_4)-cicloalquilo (C_3-C_8), donde el cicloalquilo está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

24) alquileno (C_0-C_4)het, donde het está sin sustituir o mono-, di- o trisustituido, independientemente entre sí, con R13,

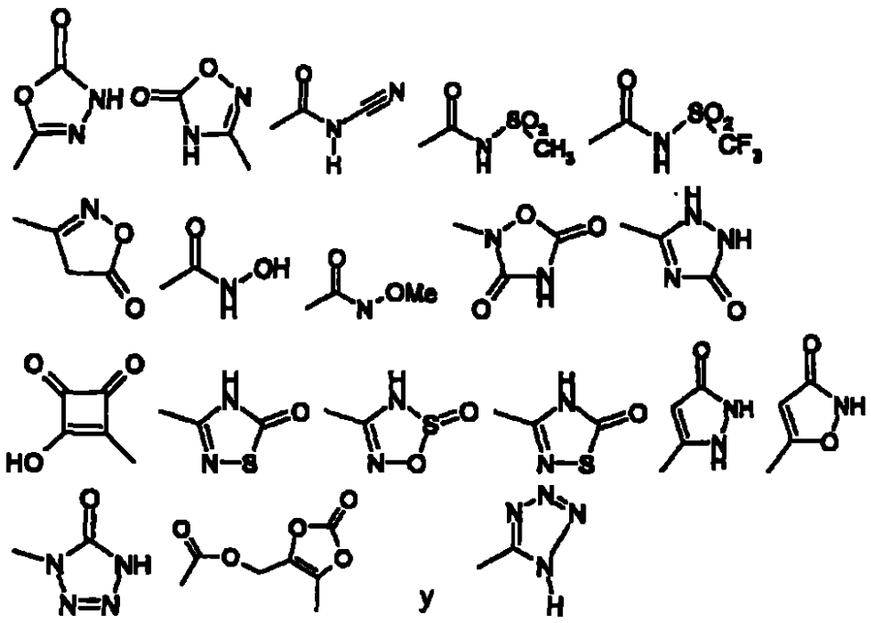
25) -alquileno (C_0-C_4)-O-CH_2-perfluoroalquileno (C_1-C_3)-CH_2-O-alquilo (C_0-C_4),

26) -SO_w-N(R^{11})-R^{13}, donde w es 1 ó 2,

27) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{13}, o

28) -alquileno (C_0-C_4)-N(R^{11})-R^{13}, o

29) un resto de la siguiente lista



y

donde Me es metilo, o

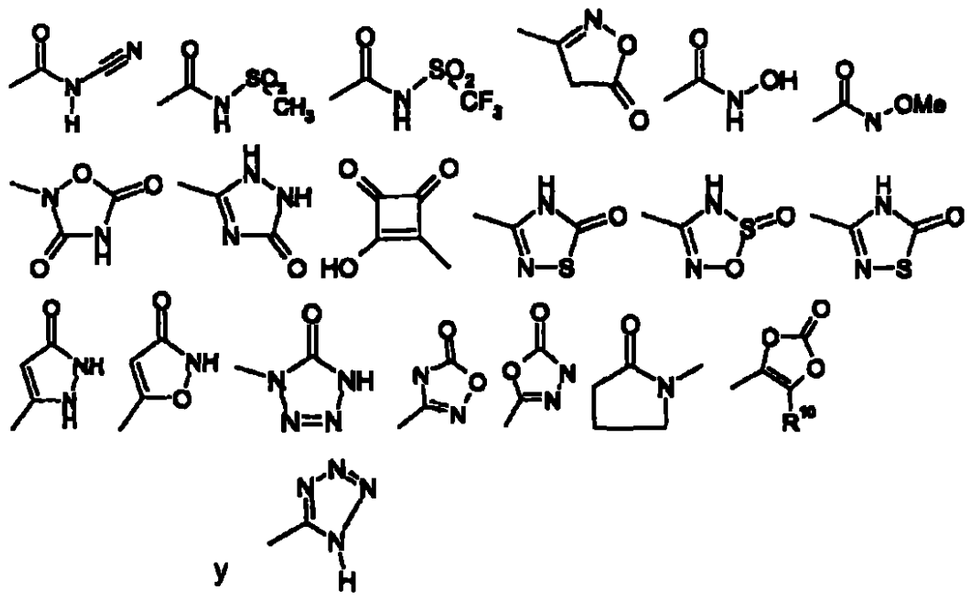
si dos restos -OR19 están unidos a átomos adyacentes, pueden formar junto con los átomos a los que están unidos un anillo de 5 ó 6 miembros que está sin sustituir o sustituido una, dos, tres o cuatro veces con R^{13},

R^{11} y R^{12} son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,
2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
3) -alquil (C_0-C_8)-cicloalquilo (C_3-C_8),
4) -SO_r-R^{10}, donde t es 1 ó 2,
5) -alquil (C_0-C_8)-arilo (C_6-C_{14}), donde el alquilo y el arilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13,
6) -perfluoroalquilo (C_1-C_3),
7) -O-R^{17}, o
8) -alquil (C_0-C_8)-heterociclilo (C_4-C_{14}), donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo heterocíclico monocíclico de 4 a 8 miembros que además del átomo de nitrógeno puede contener uno o dos heteroátomos en el anillo iguales o diferentes seleccionados entre oxígeno, azufre y nitrógeno; donde dicho anillo heterocíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es halógeno, -NO_2, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -cicloalquilo (C_3-C_8), -alquileno (C_0-C_3)-O-R^{10}, -Si-$(CH_3)_3$, -N(R^{10})-$S(O)_u$-R^{10}, donde u es 1 ó 2, -S-R^{10}, -SO_r-R^{10}, donde r es 1 ó 2, -$S(O)_v$-N(R^{10})-R^{20}, donde v es 1 ó 2, -C(O)-R^{10}, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, feniloxi-, -O-CF_3, -alquil (C_0-C_4)-C(O)-O-C(R15,R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -perfluoroalquilo (C_1-C_3), -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, o un resto de la siguiente lista



y

donde Me es metilo, o

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), o junto con el átomo de carbono al que están unidos pueden formar un anillo carbocíclico de 3 a 6 miembros que está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_8), -alquil (C_1-C_8)-OH, -alquil (C_1-C_8)-O-alquilo (C_1-C_8), -cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-O-alquil (C_1-C_8)-cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquil (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

2. Un compuesto de fórmula de acuerdo con la reivindicación 1, donde

R^0 es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico del grupo de fenilo, naftilo, bifenililo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimi-

lo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con

R8 es R8,) halógeno,

2) $-NO_2$,

3) -CN,

4) $-C(O)-NH_2$,

5) -OH,

6) $-NH_2$,

7) $-O-CF_3$

8) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con halógeno o -O-alquilo (C_1-C_6),

9) alquilo (C_1-C_6), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi,

10) $-SO_2CH_3$ o

11) $-SO_2-CF_3$,

con la condición de que R8 sea al menos un halógeno o un resto $-C(O)-NH_2$, si R^0 es un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo es como se ha definido anteriormente,

la subestructura D es un resto seleccionado entre el grupo azetidina, azetina, azocano, azocano-2-ona, ciclobutilo, ciclooctano, ciclooctano, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, [1,4]diazocano, [1,2]diazocan-3-ona, [1,3]diazocan-2-ona, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,2-oxa-tiepano, 1,2-oxatiolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, [1,4]oxazocano, [1,3]oxazocan-2-ona, oxetano, oxocano, oxocan-2-ona, piperazina, piperidina, fenilo, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, 5,6,7,8-tetrahidro-1H-azocin-2-ona, tetrahidrofurano, tetrahidropirano, tetrahidropiridina, tetrazina, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tietano, tiocano, tiocano-1,1-dióxido, tiocano-1-óxido, tiocan-2-ona, tiomorfolina, tifeno, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol y está sin sustituir o sustituido 1, 2, 3, 4, 5 ó 6 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es -alquileno (C_0-C_2)-$C(O)-NR^{10}$-, $-NR^{10}-C(O)-NR^{10}$-, $-NR^{10}-C(O)$-, $-SO_2$-, metileno, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n$-, $-(CH_2)_m-S-(CH_2)_n$-, $-(CH_2)_m-C(O)-(CH_2)_n$-, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n$-, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-CH(OH)-(CH_2)_n$-, $-C(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$-, -alquileno ($C_2$-$C_3$)-O-alquileno ($C_0$-$C_3$), -alquileno ($C_2$-$C_3$)-S(O)-, -alquileno ($C_2$-$C_3$)-$S(O)_2$-, $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n$-, -alquileno ($C_2$-$C_3$)-$S(O)_2-NH-(R^{10})$-, -alquileno ($C_2$-$C_3$)-$N(R^{10})$- o -alquileno ($C_0$-$C_3$)-$C(O)-O-(CH_2)_m$-,

donde R^{10} es como se define más adelante, y donde n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6, donde los restos alquileno que se forman con $-(CH_2)_m-$ o $-(CH_2)_n-$ están sin sustituir o mono-, di- o trisustituidos independientemente entre sí con halógeno, $-NH_2$ o -OH; o

-cicloalquileno (C_3-C_8), donde el cicloalquileno está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, $-NH_2$ o -OH;

R^1 es un átomo de hidrógeno, -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13; -alquileno (C_1-C_3)-C(O)-NH-R^0, -alquileno (C_1-C_3)-C(O)-O-R15, un arilo del grupo de fenilo, naftilo, bifenililo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8, donde R8 es como se ha definido anteriormente;

un heterociclilo de 4 a 15 miembros monocíclico o bicíclico, que es como se ha definido anteriormente;

-perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4), -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3), -alquileno (C_1-C_3)-$S(O)_2$-N($R^{4'}$)-$R^{5'}$, -alquileno (C_1-C_3)-O-alquilo (C_1-C_4), -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8) o alquileno (C_0-C_3)-het, donde het es un resto seleccionado entre el grupo de azepina, azetidina, aziridina, azirina, 1,4-diazapano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diaziridina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,4-oxazepano, 1,2-oxa-tiepano, 1,2-oxatiolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

$R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros seleccionado entre el grupo de azepina, azetidina, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, oxazol,

piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, bromo, yodo, -OH, =O, alquilo (C_1-C_8), -alcoxi (C_1-C_4), -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-perfluoroalquilo (C_1-C_3), -alquil (C_0-C_8)-SO_2-$N(R^{18})$-R^{21}, -C(O)-NH-alquilo (C_1-C_8), -C(O)-N-[alquilo (C_1-C_8)]$_2$, -NR^{18}-C(O)-NH-alquilo (C_1-C_8), -C(O)-NH_2-, -S-R^{18} o -NR^{18}-C(O)-NH-[alquilo (C_1-C_8)]$_2$,

donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o -alquilo (C_1-C_8),

V es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico del grupo de fenilo, naftilo, bifenililo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R14,

2) un heterociclilo del grupo de acridinilo, 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol-(1H-pirrolopiridina), azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 1,4-diazepano, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopirazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofu-

ranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidropiridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, 1λ6-tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

G es un enlace directo, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n$ o $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6,

M es
1) un átomo de hidrógeno,
2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,
3) $-C(O)-N(R11)-R12$,
4) $-(CH_2)_m-NR^{10}$,
5) -arilo (C_6-C_{14}), donde el arilo es como se ha definido anteriormente y donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,
6) -heterociclilo (C_4-C_{18}), donde el heterociclilo es como se ha definido anteriormente y está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o
7) -cicloalquilo (C_3-C_8), donde dicho cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R3 es
1) un átomo de hidrógeno,
2) halógeno,
3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está no sustituido o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) $-CHF_2$,

7) $-NO_2$,

8) -CN,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{12},

14) -alquileno (C_0-C_4)-N(R^{11})-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) $-S-R^{10}$,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

20) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

21) -alquileno (C_0-C_4)-arilo (C_6-C_{14}), donde el arilo está mono-, di- o trisustituido independientemente entre sí con R13,

22) -alquileno (C_0-C_4)-heterociclilo (C_4-C_{15}), donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

23) -alquileno (C_0-C_4)-cicloalquilo (C_3-C_8), donde el cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

24) alquileno (C_0-C_4)-het, donde het está sin sustituir o mono-, di- o tri-sustituido independientemente entre sí con R13,

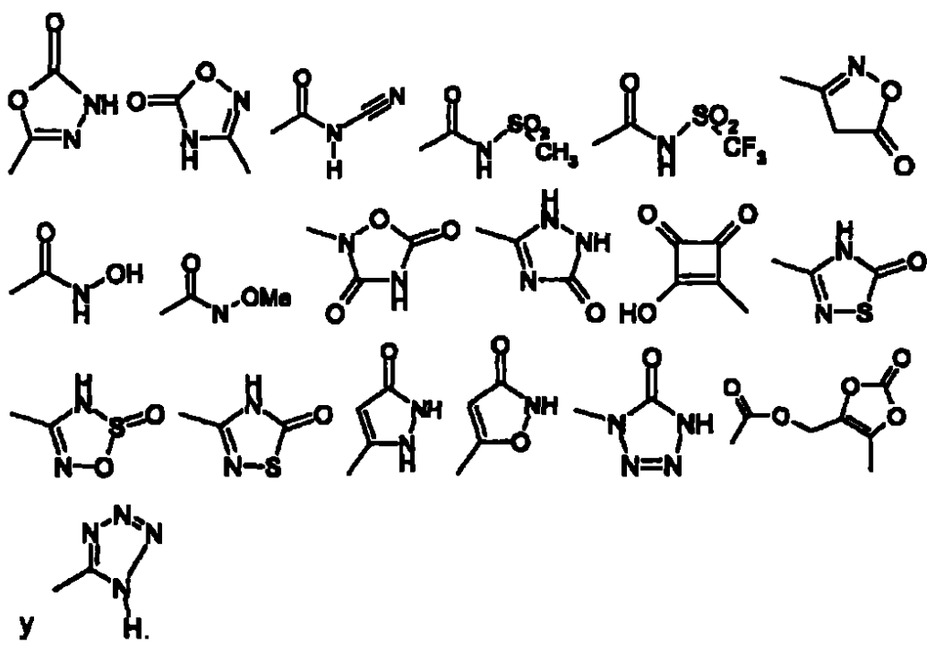
25) -alquileno (C_0-C_4)-O-CH_2-perfluoroalquileno (C_1-C_3)-CH_2-O-alquilo (C_0-C_4),

26) -SO_w-N(R^{11})-R^{13}, donde w es 1 ó 2,

27) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{13}, o

28) -alquileno (C_0-C_4)-N(R^{11})-R^{13}, o

29) un resto de la siguiente lista



y

donde Me es metilo o,

si dos restos -OR19 están unidos a átomos adyacentes pueden formar junto con los átomos a los que están unidos un anillo 1,3-dioxol o un anillo 2,3-dihidro-[1,4]dioxina, que está sustituido una, dos, tres o cuatro veces con R13,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o tri-sustituido independientemente entre sí con R13,

3) -alquil (C_0-C_8)-cicloalquilo (C_3-C_8),

4) -SO_t-R^{10}, donde t es 1 ó 2,

5) -alquil (C_0-C_8)-arilo (C_6-C_{14}), donde el alquilo y el arilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13,

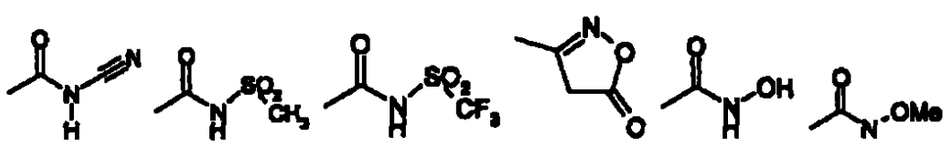
6) -perfluoroalquilo (C_1-C_3),

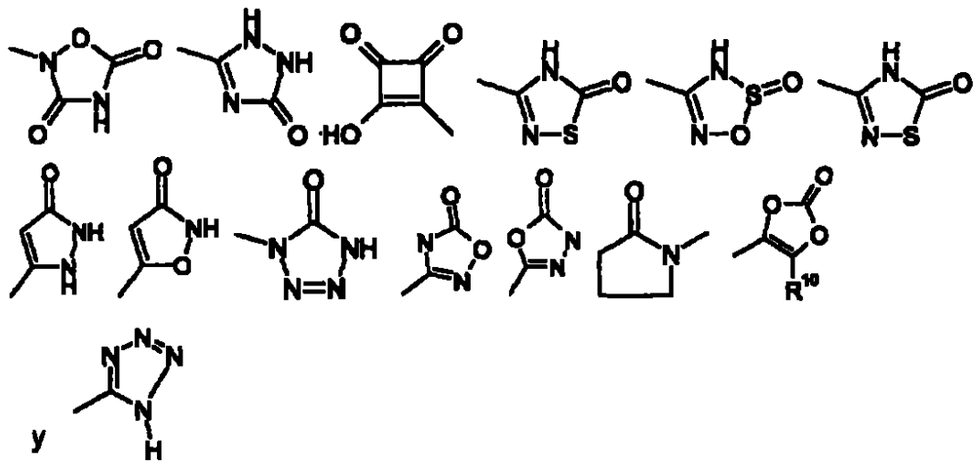
7) -O-R^{17}, o

8) -alquil (C_0-C_8)-heterociclilo (C_4-C_{14}), donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo heterocíclico del grupo de azepina, azetidina, dioxazol, dioxazina, 1,4-diazepano, 1,2-diazepina, 1,4-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho anillo heterocíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es halógeno, -NO_2, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})R^{20}, -cicloalquilo (C_3-C_8), -alquileno (C_0-C_3)-O-R^{10}, -Si-(CH_3)$_3$, -N(R^{10})-S(O)$_u$-R^{10}, donde u es 1 ó 2, -S-R^{10}, -SO_r-R^{10}, donde r es 1 ó 2, -S(O)$_v$-N(R^{10})-R^{20}, donde v es 1 ó 2, -C(O)-R^{10}, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, feniloxi-, -O-CF_3, -alquil (C_0-C_4)-C(O)-O-C(R15,R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15,R16)-O-C(O)-R17, -perfluoroalquilo (C_1-C_3), -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, o un resto de la siguiente lista





y

donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_8), ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_8), -alquil (C_1-C_8)-OH, -alquil (C_1-C_8)-O-alquilo (C_1-C_8), -cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-O-alquil (C_1-C_8)-cicloalquilo (C_3-C_8), -alquil (C_1-C_8)-cicloalquilo (C_3-C_8), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

3. Un compuesto de fórmula I de acuerdo con las reivindicaciones 1 a 2, donde

R^0 es 1) un arilo de 6 a 14 miembros monocíclico o bicíclico del grupo de fenilo, naftilo, bifenilo, antrilo o fluorenilo, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalinilo o 1,4,5,6-tetrahidro-piridazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, o

3) un heterociclilo del grupo de azabencimidazolilo, bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzotiazolilo, benzotiofenilo, benzoxazolilo, cromanilo, cinolinilo, 2-furilo, 3-furilo; imidazolilo, indolilo, indazolilo, isocromanilo, isoindolilo, isoquinolinilo, isotiazolilo, isoxazolilo, oxazolilo, ftalazinilo, pteridinilo, purinilo, pirazinilo, pirazolilo, piridazinilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, 2-piridilo, 3-piridilo, 4-piridilo, pirimidinilo, pirrolilo; 2-pirrolilo, 3-pirrolilo, quinolinilo, quinazolinilo, quinoxalinilo, tetrazolilo, tiadiazolilo, tiazolilo, 2-tienilo o 3-tienilo, que además está sustituido con un heterociclilo seleccionado entre el grupo acridinilo, azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzoisoxazolilo, benzoisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo(bencimidazolilo), isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridinilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 1,4,5,6-tetrahidro-piridazinilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tietanilo, tiomorfolinilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo,

donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

R8 es
1. flúor, cloro o bromo,
2. $-NO_2$,
3. -CN,
4. $-C(O)-NH_2$,
5. -OH,
6. $-NH_2$,
7. $-OCF_3$
8. un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo es como se ha definido anteriormente y está mono-, di- o trisustituido independientemente entre sí con halógeno o -O-alquilo (C_1-C_6),
9. -alquilo (C_1-C_6), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, NH_2, -OH o un resto metoxi, o
10. $-SO_2CH_3$ o
11. $-SO_2CF_3$,

con la condición de que R8 sea al menos un halógeno o un resto $-C(O)-NH_2$, si R0 es un arilo o un heterociclilo, que son como se han definido anteriormente,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido piridilo, pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo, pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es -alquileno (C_0-C_2)-$C(O)-NR^{10}$, $-NR^{10}-C(O)-NR^{10}-$, $-NR^{10}-C(O)-$, $-SO_2-$, metileno o -alquileno (C_0-C_3)-C(O)-O-alquileno (C_0-C_2),

R^1 es un átomo de hidrógeno, -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13; -alquileno (C_1-C_3)-$C(O)-NH-R^0$, -alquileno (C_1-C_3)-C(O)-O-R15, -perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4), -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3), -alquileno (C_1-C_3)-$S(O)_2-N(R^{4'})-R^{6'}$, -alquileno (C_1-C_3)-O-alquilo (C_1-C_4), -alquileno (C_0-C_3)-cicloalquilo (C_3-C_6), o -alquileno (C_0-C_3)-het, donde het es un resto seleccionado entre el grupo de azepina, azetidina, aziridina, azirina, 1,4-diazapano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diazirina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,2-oxatiepano, 1,2-oxatiolano,

1,4-oxazepano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

$R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V forma un grupo cíclico de 4 a 8 miembros seleccionado entre el grupo de azepina, azetidina, 1,4-diazepano, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,4-oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, bromo, yodo, -OH, =O, alquilo (C_1-C_8), -alcoxi (C_1-C_4), -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-alquilo (C_1-C_4), -alquil (C_0-C_8)-SO_2-perfluoroalquilo (C_1-C_3), -alquil (C_0-C_8)-SO_2-N(R^{18})-R^{21}, -C(O)-NH-alquilo (C_1-C_8), -C(O)-N-[alquilo (C_1-C_8)]$_2$, -NR^{18}-C(O)-NH-alquilo (C_1-C_8), -C(O)-NH_2, -S-R^{18} o -NR^{18}-C(O)-NH-[alquilo (C_1-C_8)]$_2$,

donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o -alquilo (C_1-C_8).

V es 1) un resto het del grupo de 8-aza-biciclo[3.2.1]oct-3-ilo, azaindol(1H-pirrolopiridina), azepina, azetidina, aziridina, azirina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diaziridina, diazirina, dioxazol, dioxazina, dioxol, 1,3-dioxoleno, 1,3-dioxolano, furano, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, 1,2-oxa-tiepano, 1,2-oxatiolano, 1,4-oxazepano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, oxaziridina, oxirano, piperazina, piperidina, pirano, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridi-

na, tetrazina, tetrazol, tiadiazina, tiadiazol, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tiazol, tiazolidina, tiazolina, tienilo, tietano, tiomorfolina, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, que es como se ha definido anteriormente y donde het está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

2) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

G es un enlace directo, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ o $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n y m son, independientemente entre sí, iguales o diferentes y son los números enteros cero, 1, 2, 3, 4, 5 ó 6,

M es
1) un átomo de hidrógeno,
2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,
3) -C(O)-N(R11)-R12,
4) $-(CH_2)_m-NR^{10}$,
5) fenilo o naftilo, donde el fenilo o el naftilo están sin sustituir o mono-, di- o trisustituidos, independientemente entre sí, con R14,
6) heterociclilo, donde el heterociclilo es un resto del grupo que puede derivarse de azepano, azepina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, isotiazol, isoxazol, isoxazolidina, 2-isoxazolina, cetomorfolina, cetopiperazina, morfolina, oxazol, [1,4]-oxazepano, piperazina, piperazinona, piperidina, piperidinona, pirazina, piridazina, piridazinona, piridina, piridona, pirimidina, pirrolidina, pirrolidinona, tetrahidropirano, 1,4,5,6-tetrahidro-piridazinilo, tetrazina, tetrazol, tiadiazol, tiazol, tiomorfolina, 1λ6-tiomorfolinilo, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o
7) -cicloalquilo (C_3-C_8), donde dicho cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R3 es
1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) $-CHF_2$,

7) -CN,

8) -alquileno (C_0-C_4)-heterociclilo (C_4-C_{15}), donde el heterociclilo es como se ha definido anteriormente y está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{12},

14) -alquileno (C_0-C_4)-N(R^{11})-R^{12},

15) $-NR^{10}-SO_2-R^{10}$,

16) -alquileno (C_0-C_4)-het, donde het es como se ha definido anteriormente y está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

18) -C(O)-O-C(R15, R16)-O-C(O)-R17,

19) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

20) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

21) -alquileno (C_0-C_4)-arilo (C_6-C_{14}), donde el arilo es como se ha definido anteriormente y está mono-, di- o trisustituido independientemente entre sí con R13,

22) -alquileno (C_0-C_4)-cicloalquilo (C_3-C_8), donde el cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

23) -alquileno (C_0-C_3)-O-CH_2-CF_2-CH_2-O-alquilo (C_0-C_3),

24) -alquileno (C_0-C_3)-O-CH_2-CF_2-CF_2-CH_2-O-alquilo (C_0-C_3),

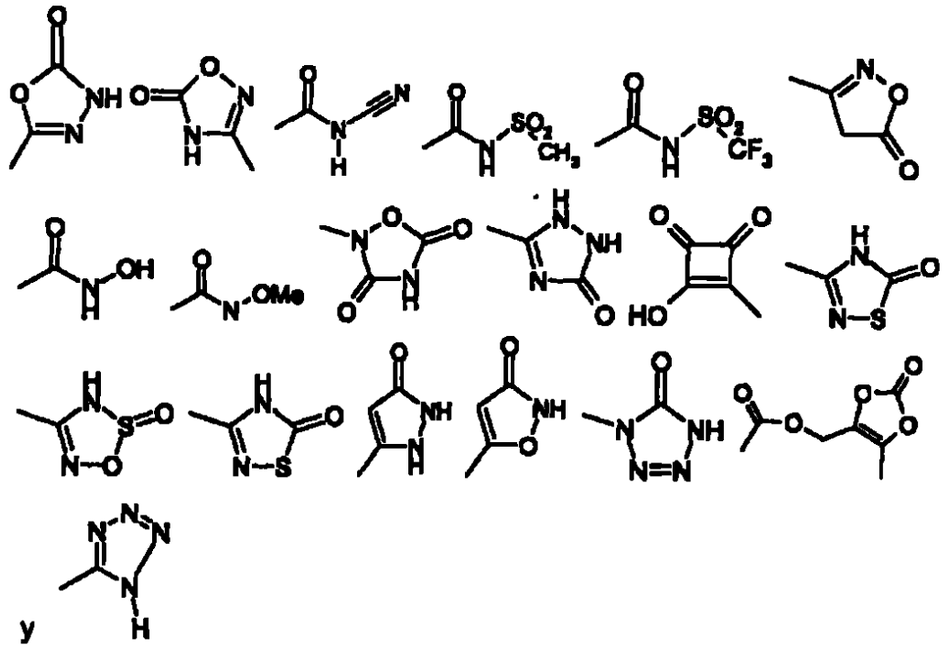
25) -alquileno (C_0-C_3)-O-CH_2-perfluoroalquileno (C_1-C_3)-CH_2-OH,

26) -SO_w-N(R^{11})-R^{13}, donde w es 1 ó 2,

27) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{13},

28) -alquileno (C_0-C_4)-N(R^{11})-R^{13}, o

29) un resto de la siguiente lista



y

donde Me es metilo,

si dos restos -OR19 están unidos a átomos adyacentes pueden formar junto con los átomos a los que están unidos un anillo 1,3-dioxol o un anillo 2,3-dihidro-[1,4]dioxina que está sustituido una, dos, tres o cuatro veces con R13,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

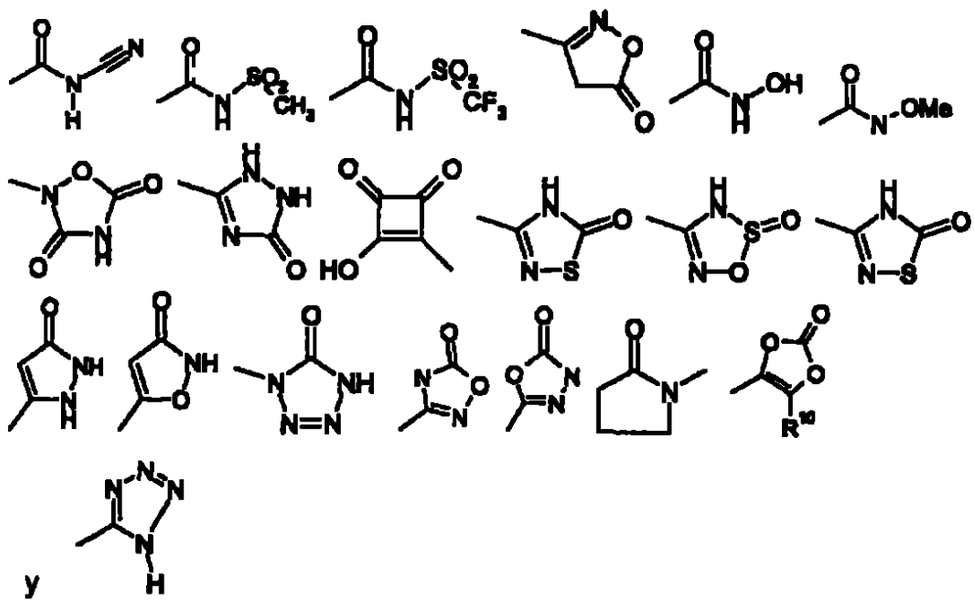
3) -alquil (C_0-C_8)-arilo (C_6-C_{14}), donde el arilo es como se ha definido anteriormente y donde el alquilo y el arilo están, independientemente entre sí, sin sustituir o mono-, di- o trisustituidos con R13,

4) -O-R^{17}, o

5) -alquilo (C_0-C_8)-heterociclilo (C_4-C_{15}), donde el alquilo y el heterociclilo son como se han definido anteriormente y están, independientemente entre sí, sin sustituir o mono-, di- o trisustituidos con R13, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo seleccionado entre el grupo de azepina, azetidina, 1,4-diazepano, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]-oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, que está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, cloro, bromo, yodo, -NO_2, -CN, =O, -OH, -CF_3, C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -alquileno (C_0-C_3)-O-R^{10}, -Si-(CH_3)$_3$, -N(R^{10})-S(O)$_2$-R^{10}, -S-R^{10}, -SO_2-R^{10}, -S(O)$_2$-N(R^{10})-R^{20}, -C(O)-R^{10}, -alquilo (C_1-C_8), -alcoxi (C_1-C_8), fenilo, feniloxi-, -O-CF_3, -perfluoroalquilo (C_1-C_3), -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-O-R17, -O-R15, -NH-C(O)-NH-R^{10}, -NH-C(O)-O-R^{10}, o un resto de la siguiente lista



y

donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_6), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_6), o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R10, y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH, -alquil (C_1-C_6)-O-alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-O-alquil (C_1-C_6)-cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-cicloalquilo (C_3-C_6), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

4. Un compuesto de fórmula I de acuerdo con las reivindicaciones 1 a 3, donde

R0 es 1) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

2) un heterociclilo del grupo de bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiofenilo, cinolinilo, cromanilo, indazolilo, indolilo, isocromanilo, isoindolilo, isoquinolinilo, fenilpiridilo, ftalazinilo, pteridinilo, purinilo, piridilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, pirimidinilo, quinazolinilo, quinolilo, quinoxalil-

nilo o 1,4,5,6-tetrahidro-piridazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

o

3) un heterociclilo del grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y además está sustituido con un resto seleccionado entre el grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho resto está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8

R8 es

1. F, Cl Br o I,
2. $-C(O)-NH_2$ o
3. -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, -OH o un resto metoxi, o

con la condición de que R8 sea al menos un halógeno o $-C(O)-NH_2$ o un resto –O-alquilo (C_1-C_8), si R0 es un arilo o un heterociclilo, que son como se han definido anteriormente,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido, pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo, pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es $-C(O)-$; $-SO_2-$, metileno, -alquileno (C_0-C_2)-$C(O)-NR^{10}$- o -alquileno (C_0-C_3)-C(O)-O-alquileno (C_0-C_2),

R^1 es un átomo de halógeno, -alquilo (C_1-C_2), -alquileno (C_1-C_3)-C(O)-NH-R0, -perfluoroalquileno (C_1-C_3), -alquileno (C_1-C_3)-$C(O)-O-R^{15}$, -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3) o -alquileno (C_1-C_3)-$S(O)_2-N(R^{4'})-R^{5'}$, donde $R^{4'}$ y $R^{5'}$ son, independientemente entre sí, iguales o diferentes y son un átomo de hidrógeno o -alquilo (C_1-C_4),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 7 miembros del grupo de azetidina, azetidinona, piperidina, piperazina, piridina, pirimidina, pirrolidina, pirrolidinona, 1,2,3-

triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol, 1,2,4-triazol, tetrazina, tetrazol, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, azepina, cetopiperidina, 1,4-oxazepano, oxazol, isoxazol, isoxazolidina, 2-isoxazolina, morfolina, tiazol, isotiazol, tiadiazol o tiomorfolina, donde dicho grupo cíclico está sin sustituir o mono-, di- o tri-sustituido independientemente entre sí con R14,

R14 es flúor, cloro, -OH, =O, -alquilo (C_1-C_8), -C(O)-OH, -CN, -NH_2, -C(O)-O-alquilo (C_1-C_4), -C(O)-NH-alquilo (C_1-C_8), -C(O)-N-[alquilo (C_1-C_8)]$_2$, -C(O)-NH_2 o -N(R^{18})-R^{21}, donde R^{18} y R^{21} son, independientemente entre sí, un átomo de hidrógeno, -perfluoroalquilo (C_1-C_3) o -alquilo (C_1-C_4),

V es 1. un resto cíclico del grupo que contiene compuestos que se derivan de 8-azabiciclo[3.2.1]oct-3-ilo, azaindol(1H-pirrolopiridina), aziridina, azirina, azetidina, azetidinona, 1,4-diazepano, pirrol, pirrolidina, piridonilo, imidazol, pirazol, 1,2,3-triazol, 1,2,4-triazol, tetrazol, piridina, pirimidina, pirazina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, tetrazina, tetrazol, azepina, diazirina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, piridazina, piperidina, piperazina, pirrolidinona, cetopiperazina, furano, pirano, dioxol, 1,4-oxazepano, oxazol, isoxazol, 2-isoxazolina, isoxazolidina, morfolina, oxirano, oxaziridina, 1,3-dioxoleno, 1,3-dioxolano, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxaziridina, tiofeno, tiopirano, tietano, tiazol, isotiazol, isotiazolina, isotiazolidina, 1,2-oxatiolano, tiodiazol, tiopirano, 1,2-tiazina, 1,3-tiazol, 1,3-tiazina, 1,4-tiazina, tiadiazina o tiomorfolina, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

2. fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

G es un enlace directo, -$(CH_2)_m$- o -$(CH_2)_m$-NR^{10}-,

m son los números enteros cero, 1, 2, 3 ó 4,

M es 1. un átomo de hidrógeno,

2. heterociclilo, donde el heterociclilo es un resto del grupo que puede derivarse de azepano, azepina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, isotiazol, isoxazol, isoxazolidina, 2-isoxazolina, cetomorfolina, cetopiperazina, morfolina, oxazol, [1,4]-oxazepano, piperazina, piperazinona, piperidina, piperidinona, pirazina, piridazina, piridazinona, piridina, piridona, pirimidina, pirrolidina, pirrolidinona, tetrahidropirano, 1,4,5,6-tetrahidropiridazinilo, tetrazina, tetrazol, tiadiazol, tiazol, tiomorfolina, 1λ6-tiomorfolinilo, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol,

donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

3.-alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

4. -cicloalquilo (C_3-C_8), o

5. -C(O)-N(R^{11})-R^{12},

R3 es

1) un átomo de hidrógeno,

2) halógeno,

3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

4) -perfluoroalquilo (C_1-C_3),

5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

6) -alquileno (C_0-C_4)-O-R19, donde R19 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) -CF_3, o

e) CHF_2,

7) -CN,

8) -NR^{10}-SO_2-R^{10},

9) -SO_s-R^{11}, donde s es 1 ó 2,

10) -SO_t-N(R^{11})-R^{12}, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{12},

14) -alquileno (C_0-C_4)-N(R^{11})-R^{12},

15) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

18) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

19) -alquileno (C_0-C_3)-O-CH_2-CF_2-CH_2-O-alquilo (C_0-C_3),

20) -alquileno (C_0-C_3)-O-CH_2-CF_2-CF_2-CH_2-O-alquilo (C_0-C_3),

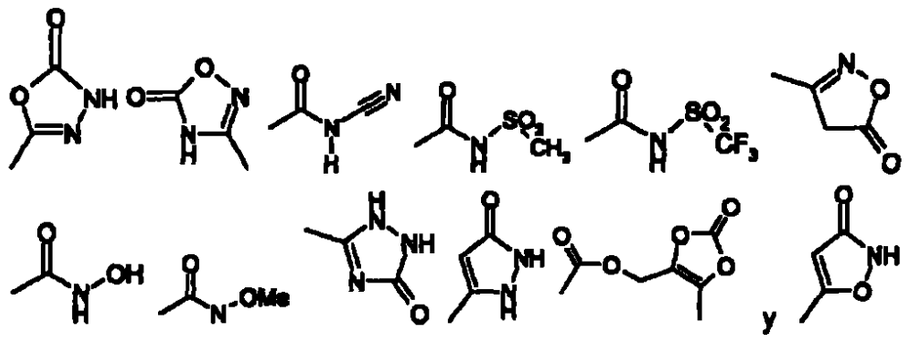
21) -alquileno (C_0-C_3)-O-CH_2-perfluoroalquilo (C_1-C_3)-CH_2-OH,

22) -SO_w-N(R^{11})-R^{13}, donde w es 1 ó 2,

23) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{13},

24) -alquileno (C_0-C_4)-N(R^{11})-R^{13}, o

25) un resto de la siguiente lista



y

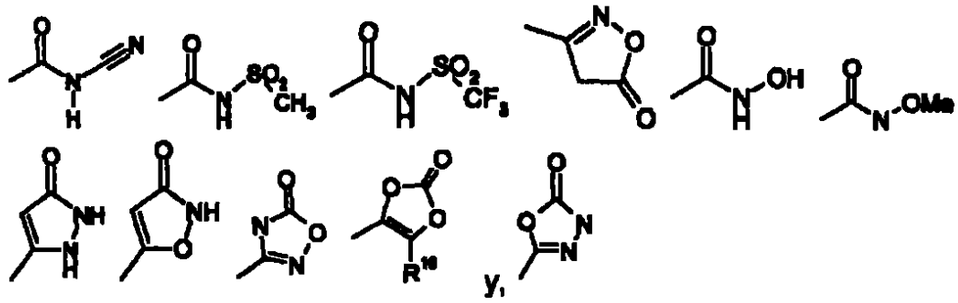
donde Me es metilo,

si dos restos -OR19 están unidos a átomos adyacentes pueden formar junto con los átomos a los que están unidos un anillo 1,3-dioxol o un anillo 2,3-dihidro-[1,4]dioxina, que está sustituido una, dos, tres o cuatro veces con R13,

R^{11} y R^{12} junto con el átomo de nitrógeno al que están unidos pueden formar un anillo seleccionado entre el grupo de azepina, azetidina, 1,4-diazepano, dioxazol, dioxazina, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, imidazol, imidazolina, imidazolidina, isotiazol, isotiazolidina, isotiazolina, isoxazol, isoxazolina, isoxazolidina, 2-isoxazolina, cetopiperazina, morfolina, [1,4]-oxazepano, oxazol, piperazina, piperidina, pirazina, pirazol, pirazolina, pirazolidina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolidinona, pirrolina, tetrahidropiridina, tetrazina, tetrazol, tiazol, tiadiazol, tiazolidina, tiazolina, tiomorfolina, tiofeno, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho anillo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, cloro, -NO_2, -CN, =O, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -alquileno (C_0-C_3)-O-R^{10}, -Si-(CH_3)$_3$, -N(R^{10})-S(O)$_2$-R^{10}, -S-R^{10}, -SO_2-R^{10}, -S(O)$_2$-N(R^{10})-R^{20}, -C(O)-R^{10}, -alquilo (C_1-C_8), -alcoxi (C_1-C_6), fenilo, feniloxi, -O-CF_3, -perfluoroalquilo (C_1-C_3), -NH-C(O)-NH-R^{10}, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-

O-C(O)-R17, -alcoxi (C_1-C_4)-fenilo, -alquil (C_0-C_4)-C(O)-O-C(R15, R16)-O-C(O)-R17, -O-R15, -NH-C(O)-O-R^{10}, o un resto de la siguiente lista



y,

donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_6), -alquil (C_0-C_4)-OH, -alquil (C_0-C_4)-O-alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R15 y R16 son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_6) o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10} y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH, -alquil (C_1-C_6)-O-alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-O-alquil (C_1-C_6)-cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-cicloalquilo (C_3-C_6), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquil (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

5. Un compuesto de fórmula I de acuerdo con las reivindicaciones 1 a 4, donde R0 es 1. fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

2. un heterociclilo seleccionado entre el grupo de indolilo, isoindolilo, benzofuranilo, benzotiofenilo, 1,3-benzodioxolilo, indazolilo, bencimidazolilo, benzoxazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, cromanilo, isocromanilo, cinolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, piridoimidazolilo, piridopiridinilo, piridopirimidinilo, piridilo, purinilo y pteridinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

3. un heterociclilo del grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetra-

zolilo, piridazinilo y pirazinilo, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y además está sustituido con un resto seleccionado entre el grupo de piridilo, 2-piridilo, 3-piridilo, 4-piridilo, pirrolilo, 2-pirrolilo, 3-pirrolilo, furilo, 2-furilo, 3-furilo; tienilo, 2-tienilo, 3-tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, triazolilo, tetrazolilo, piridazinilo y pirazinilo, donde dicho resto está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8

R8 es 1. F, Cl Br o I,

2. -C(O)-NH_2 o

3. -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con halógeno, -OH o un resto metoxi,

con la condición de que R8 sea al menos un halógeno o -C(O)-NH_2, si R0 es un arilo o un heterociclilo, que son como se han definido anteriormente,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido, pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo, pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es un enlace directo, -C(O)-; -SO_2-, -C(O)-O-metileno, metileno o -alquileno (C_0-C_2)-C(O)-NR^{10},

R^1 es un átomo de hidrógeno o -alquilo (C_1-C_2),

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 7 miembros del grupo de piperidina, piperazina, piridina, pirimidina, pirrolidina, pirrolidinona, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol, 1,2,4-triazol, tetrazina, tetrazol, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, azepina, cetopiperazina, oxazol, isoxazol, isoxazolidina, 2-isoxazolina, morfolina, tiazol, isotiazol, tiadiazol o tiomorfolina, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

R14 es flúor, cloro, -alquilo (C_1-C_4) o -NH_2,

V es 1. un resto cíclico del grupo que contiene compuestos que se derivan de 8-azabiciclo[3.2.1]oct-3-ilo, azaindolil(1H-pirrolopiridilo), azetidina, azepina, aziridina, azirina, 1,4-diazepano, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, diazirina, 1,3-dioxolano, dioxazol, furano, imidazol, isoquinolina, isotiazol, isotiazolidina, isotiazolina, isoxazol, 2-isoxazolina, isoxazolidina, cetopiperazina, morfolina, 1,2-oxazina, 1,3-oxazina, 1,4-oxazina, oxazol, 1,2-oxatiolano, piperidina, pirano,

pirazina, pirazol, piridazina, piperazina, piridina, piridona, pirimidina, pirrol, pirrolidina, pirrolidinona, quinazolina, quinolina, tetrazina, tetrazol, tiadiazina, 1,2-tiazina, 1,3-tiazina, 1,4-tiazina, 1,3-tiazol, tietano, tiomorfolina, tiofeno, tiopirano, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol o 1,2,4-triazol, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

2. fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

G es un enlace directo, $-(CH_2)_m-$ o $-(CH_2)_m-NR^{10}-$,

m son los números enteros cero, 1, 2, 3 ó 4,

M es
1. un átomo de hidrógeno,
2. heterociclilo, donde el heterociclilo es un resto del grupo que puede derivarse de 1,4-diazepano, cetomorfolina, tiofeno, piridazona, piperidina, piperazina, piridina, pirimidina, pirrolidina, pirrolidinona, piridonilo, imidazol, piridazina, pirazina, 1,2,3-triazina, 1,2,4-triazina, 1,3,5-triazina, 1,2,3-triazol, 1,2,4-triazol, tetrazina, tetrazol, 1,2-diazepina, 1,3-diazepina, 1,4-diazepina, azepina, cetopiperazina, oxazol, isoxazol, isoxazolidina, 2-isoxazolina, morfolina, tiazol, isotiazol, tetrahidropirano, 1,4,5,6-tetrahidro-pirazinilo, tiadiazol, 1λ6-tiomorfolinilo o tiomorfolina, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,
3. -alquilo (C_1-C_8), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o
4. -cicloalquilo (C_3-C_8),

R3 es
1) un átomo de hidrógeno,
2) halógeno,
3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
4) -perfluoroalquilo (C_1-C_3),
5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
6) -alquileno (C_0-C_4)-O-R19, donde R19 es
   a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

d) $-CF_3$, o

e) CHF_2,

7) -CN,

8) $-NR^{10}-SO_2-R^{10}$,

9) $-SO_s-R^{11}$, donde s es 1 ó 2,

10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,

11) -alquileno (C_0-C_4)-C(O)-R^{11},

12) -alquileno (C_0-C_4)-C(O)-O-R^{11},

13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{12}$,

14) -alquileno (C_0-C_4)-$N(R^{11})-R^{12}$,

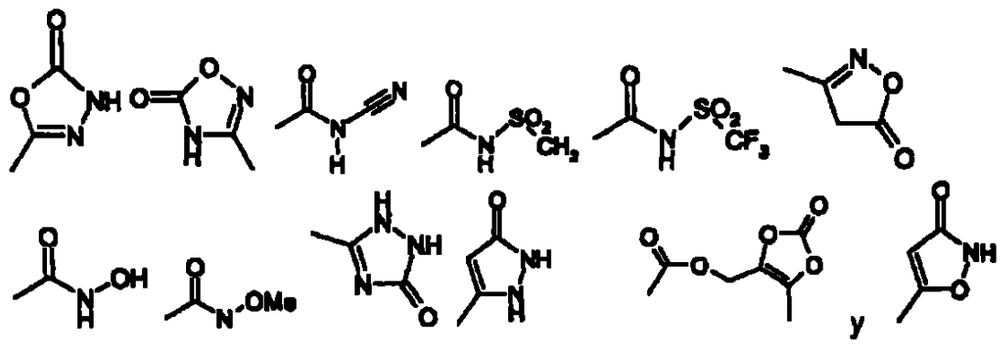
15) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_4),

16) -C(O)-O-C(R15, R16)-O-C(O)-R17,

17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6),

18) -C(O)-O-C(R15, R16)-O-C(O)-O-R17, o

19) un resto de la siguiente lista



y

donde Me es metilo,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o tri-sustituido independientemente entre sí con R13,

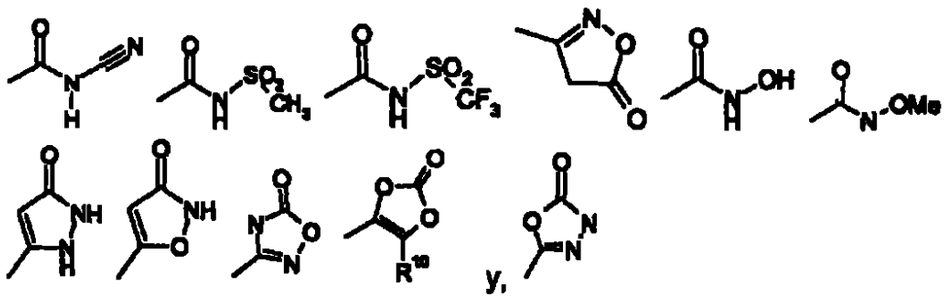
3) -alquil (C_0-C_6)-cicloalquilo (C_3-C_6),

4) -O-R^{17}, o

5) -alquil (C_0-C_6)-heterociclilo (C_4-C_{15}), donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos con R13 y donde el heterociclilo se selecciona entre el grupo de azetidina, ciclopropilo, ciclobutilo, 4,5-dihidro-oxazol, imidazolidina, morfolina, (1,4)-oxazepano, oxazolidina, piperidina, piperazina, pirrolidina, tetrahidrotiofeno, tiazolidina o tiomorfolina, o

R11 y R12 junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico que se selecciona entre el grupo de azetidina, ciclopropilo, ciclobutilo, 4,5-dihidrooxazol, imidazolidina, morfolina, (1,4)-oxazepano, oxazolidina, piperidina, piperazina, pirrolidina, tetrahidrotiofeno, tiazolidina o tiomorfolina, donde dicho anillo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, -CN, =O, -OH, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -cicloalquilo (C_3-C_6), -alquileno (C_0-C_3)-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -perfluoroalquilo (C_1-C_3) o un resto de la siguiente lista



y,

donde Me es metilo,

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R^{15} y R^{16} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH, -alquil (C_1-C_6)-O-alquil (C_1-C_6)-cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-O-alquilo (C_1-C_6) o -alquil (C_0-C_6)-cicloalquilo (C_3-C_6), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

6. Un compuesto de fórmula I de acuerdo con las reivindicaciones 1 a 5, donde

R0 es 1. fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R8,

2. piridilo o 1H-indazolilo, donde el piridilo y el 1H-indazolilo están sin sustituir o mono- o disustituidos independientemente entre sí con R8, o

3. un heterociclilo del grupo de tienilo, tiadiazolilo, isoxazolilo y tiazolilo, donde dicho heterociclilo está sustituido con un resto seleccionado entre el grupo de tienilo, 2-tienilo y 3-tienilo, donde dicho resto está sin sustituir o mono- o disustituido independientemente entre sí con R8,

R8 es F, Cl, Br o -C(O)-NH_2,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, piridil-N-óxido, pirrolilo, tienilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, tiadiazolilo, pirimidinilo, piridazinilo o pirazinilo y está sin sustituir o sustituido 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es -C(O)-; -SO_2-, -C(O)-O-metileno, -CH_2-C(O)-NH- o metileno,

R^1 es un átomo de hidrógeno,

R^2 es un enlace directo,

R^1-N-R^2-V puede formar un grupo cíclico de 4 a 8 miembros del grupo de azetidina, pirrolidina, piperidina y piperazina,

R14 es flúor, cloro, metilo, etilo, =O, -SO_2-CH_3 o -NH_2,

V es 1. un resto del grupo que contiene los compuestos que se derivan de 8-aza-bicíclo[3.2.1]oct-3-ilo, azaindolil(1H-pirrolopiridilo), azetidina, 1,4-diazepano, isoxazol, isoquinolina, piperazina, piperidina, pirazina, piridazina, pirimidina, pirrolidina, quinazolina, quinolina o tetrahidropirano, donde dicho resto cíclico está sin sustituir o mono- o disustituido independientemente entre sí con R14, o

2. fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R14,

G es un enlace directo, -$(CH_2)_m$-, -C(O)- o -$(CH_2)_m$-NR^{10}-,

m son los números enteros cero, 1 ó 2,

M es un átomo de hidrógeno, alquilo (C_2-C_4), azepanilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, imidazolilo, cetomorfolinilo, morfolinilo, [1,4]oxazepanilo, piperazinilo, piperidinilo, piperidonilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pi-

rimidilo, pirrolidinilo, 1λ6-tiomorfolinilo, 1,4,5,6-tetrahidro-piridazinilo o tetrahidropiranilo, donde los restos están sin sustituir o mono- o disustituidos independientemente entre sí con R14

R3 es
1) un átomo de hidrógeno,
2) flúor, cloro,
3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
4) -perfluoroalquilo (C_1-C_3),
5) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
6) -alquileno (C_0-C_2)-O-R19, donde R19 es
   a) un átomo de hidrógeno,
   b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
   c) fenilo, donde el fenilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
   d) $-CF_3$, o
   e) $-CHF_2$,
7) -CN,
8) $-NR^{10}-SO_2-R^{10}$,
9) $-SO_s-R^{11}$, donde s es 1 ó 2,
10) $-SO_t-N(R^{11})-R^{12}$, donde t es 1 ó 2,
11) -alquileno (C_0-C_4)-C(O)-R^{11},
12) -alquileno (C_0-C_4)-C(O)-O-R^{11},
13) -alquileno (C_0-C_4)-C(O)-$N(R^{11})-R^{12}$,
14) -alquileno (C_0-C_4)-$N(R^{11})-R^{12}$,
15) -alquileno (C_0-C_4)-C(O)-O-alquileno (C_2-C_4)-C(O)-alquilo (C_1-C_4),
16) -C(O)-O-C(R15, R16)-O-C(O)-R17,
17) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-O-alquilo (C_1-C_6) o
18) -C(O)-O-C(R15, R16)-O-C(O)-O-R17,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son
1) un átomo de hidrógeno,

2) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

3) -alquil (C_0-C_6)-cicloalquilo (C_3-C_6),

4) -O-R^{17}, o

5) -alquil (C_0-C_6)-heterociclilo, donde el alquilo y el heterociclilo, independientemente entre sí, están sin sustituir o mono-, di- o trisustituidos independientemente entre sí con R13 y donde el heterociclilo se selecciona entre el grupo de azetidina, imidazolidina, morfolina, (1,4)-oxazepano o pirrolidina o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo que se selecciona entre el grupo de azetidina, imidazolidina, morfolina, (1,4)-oxazepano, piperazina, piperidina, pirrolidina o tiomorfolina, donde dicho anillo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,

R13 es flúor, -CN, =O, -CF_3, -C(O)-O-R^{10}, -C(O)-N(R^{10})-R^{20}, -N(R^{10})-R^{20}, -alquilo (C_1-C_3), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_3)-O-R^{10}, -Si-(CH_3)$_3$, -S-R^{10}, -SO_2-R^{10}, -SO_2-NH o -perfluoroalquilo (C_1-C_3),

R^{10} y R^{20} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o -perfluoroalquilo (C_1-C_3),

R^{15} y R^{16} son, independientemente entre sí, hidrógeno, -alquilo (C_1-C_4) o juntos forman un anillo del grupo de ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, donde cada anillo está sin sustituir o sustituido de una a tres veces con R^{10}, y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH, -alquil (C_1-C_6)-O-alquil (C_1-C_6)-cicloalquilo (C_3-C_6), -alquil (C_1-C_6)-O-alquilo (C_1-C_6) o -alquil (C_0-C_6)-cicloalquilo (C_3-C_6), donde dicho anillo cicloalquilo está sin sustituir o sustituido una, dos o tres veces con -OH, -O-alquilo (C_1-C_4) o R^{10},

en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación, y sus sales fisiológicamente tolerables.

7. Un compuesto de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 6, donde

R0 es 1. fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R8,

2. piridilo o 1H-indazolilo, donde el piridilo y el 1H-indazolilo están sin sustituir o mono- o disustituidos independientemente entre sí con R8, o

3. un heterociclilo del grupo tiadiazolilo, isoxazolilo y tiazolilo, donde dicho heterociclilo está sustituido con un resto seleccionado entre el grupo de tienilo, 2-tienilo y 3-tienilo, donde dicho resto está sin sustituir o mono- o disustituido independientemente entre sí con R8,

R8 es Cl,

la subestructura D es un resto seleccionado entre el grupo de fenilo, piridilo, tienilo o pirimidinilo, y está sustituido o sin sustituir 1, 2, 3 ó 4 veces con R3 o está sustituido 1 ó 2 veces con =O,

Q es $-CH_2-C(O)-NH-$ o metileno,

R^1 es un átomo de hidrógeno,

R^2 es un enlace directo,

R14 es flúor o =O,

V es piperidinilo o fenilo, donde el fenilo está sin sustituir o mono- o disustituido independientemente entre sí con R14,

G es un enlace directo o -C(O)-

M es un átomo de hidrógeno, -alquilo (C_2-C_4), isopropilo, ciclopropilo, morfolinilo, piperazinilo, piperidinilo, pirazinilo, piridilo, pirimidilo, pirrolidinilo o 1λ6-tiomorfolinilo, donde los restos están sin sustituir o mono- o disustituidos independientemente entre sí con R14,

R3 es

1) un átomo de hidrógeno,
2) flúor, cloro,
3) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13,
4) -alquileno (C_0-C_2)-O-R19, donde R19 es
   a) un átomo de hidrógeno,
   b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o
   c) $-CF_3$,
5) $-SO_2-R^{11}$,
6) -alquileno (C_0-C_4)-C(O)-O-R^{11},
7) -alquileno (C_0-C_4)-C(O)-N(R^{11})-R^{12},
8) -alquileno (C_0-C_2)-C(O)-O-alquileno (C_2-C_4)-O-C(O)-alquilo (C_1-C_6) o
9) -C(O)-O-C(R15, R16)-O-C(O)-R17,

R11 y R12 son, independientemente entre sí, iguales o diferentes y son

1) un átomo de hidrógeno,

2) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R13, o

3) -alquil (C_0-C_3)-cicloalquilo (C_3-C_8) o

R11 y R12 junto con el átomo de nitrógeno al que están unidos pueden formar un anillo que se selecciona entre el grupo de azetidina, morfolina, (1,4)-oxazepano o piperidina, donde dicho anillo está sin sustituir o mono-, di- o trisustituido con R13,

R13 es flúor, =O, -OH, $-CF_3$, -C(O)-O-R^{10}, -alquilo (C_1-C_3), -cicloalquilo (C_3-C_6) o -alquileno (C_0-C_3)-O-R^{10},

R^{10} es un átomo de hidrógeno o -alquilo (C_1-C_4),

R^{15} y R^{16} son, independientemente entre sí, un átomo de hidrógeno o -alquilo (C_1-C_4), y

R17 es -alquilo (C_1-C_6), -alquil (C_1-C_6)-OH o -alquil (C_0-C_4)-cicloalquilo (C_3-C_6).

8. Un compuesto de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7, donde el compuesto es

(1-Isopropil-piperidin-4-il)-amida del ácido 1[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(4-cloro-fenilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

(1-Pirimidin-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

éster metílico del ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[2-(5-cloro-tiofen-2-il)-tiazol-5-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

(1-isopropil-piperidin-4-il)-amida del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-imidazo[4,5-b]piridina-2-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofeno-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofeno-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,4-dicarboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,4-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2,5-dicarboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 4-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,4-dicarboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

[4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil)-H-benzoimidazol-4-carboxílico,

[4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-(3-metoxi-bencil)-1H-benzoimidazol-2-carboxílico,

[4-(4-Oxo-4H-piridin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

(8-Metil-8-aza-biciclo[3.2.1]oct-3-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-oxazolidin-3-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-oxazolidin-3-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(2,4-Dioxo-3,4-dihidro-2H-pirimidin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(4-Oxo-piperidin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(1,1-Dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(1,1-Dioxo-1λ6-tiomorfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-il]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-2H-pirazin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-piperazin-1-il)-fenil]-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1H-benzoimidazol-2-carboxílico,

[4-(2-Oxo-piperazin-1-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2-carboxílico,

[4-(3-Oxo-morfolin-4-il)-fenil]-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico,

Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-3H-benzoimidazol-2,5-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-metil-amida] del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-1H-benzoimidazol-2,5-dicarboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de [5-[(2-hidroxi-etil)-metil-amida] del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-3H-benzoimidazol-2,5-dicarboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

1-Ciclohexiloxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

1-Etoxicarboniloxi-etil éster del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

2-Hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

2-Hidroxi-etil éster del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 1-(3-metoxi-bencil)-2-[4-(3-oxo-morfolin-4-il)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-(2-hidroxi-etanosulfonil)-1H-benzoimidazol-2-carboxílico,

Ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

2-Metoxi-etil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-hidroximetil-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoximetil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(morfolina-4-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2,6-dimetil-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(4,4-difluoro-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-5-([1,4]oxazepano-4-carbonil)-1H-benzoimidazol-2-carboxílico,

2-Hidroxi-etil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Carboximetil éster del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

Ácido 2-(1-Isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-4-carboxílico,

Ácido 2-(1-Isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-3H-benzoimidazol-4-carboxílico,

Ácido 1-[2-(4-cloro-fenil)(-etil]-2-1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 4-(3-hidroxi-azetidina-1-carbonil)-1-(3-metoxi-bencil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-hidroxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[2-(4-cloro-fenil)-etil]-4-(3-metoxi-azetidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 2-(1-Isopropil-piperidin-4-ilcarbamoil)-1-(3-metoxi-bencil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 2-(1-isopropil-piperidin-4-ilcarbamoil)-3-(3-metoxi-bencil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[2-(4-cloro-fenil)-etil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 1-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-(5-cloro-benzo[b]tiofen-2-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

Ácido 1-(5-cloro-1H-indazol-3-ilmetil)-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(4-hidroxi-piperidina-1-carbonil)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 7-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-1,3-dimetil-2,6-dioxo-2,3,6,7-tetrahidro-1H-purina-8-carboxílico,

Éster metílico del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-4-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ciclopropilmetil éster del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico,

2-[(1-Isopropil-piperidin-4-il)-amida] de 6-[(2-hidroxi-etil)-amida] del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-3H-tieno[3,4-d]imidazol-2,6-dicarboxílico,

Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-6-carboxílico,

Ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-3H-tieno[3,4-d]imidazol-4-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 3-[(5-cloro-piridin-2-ilcarbamoil)-metil]-6-([1,4]oxazepano-4-carbonil)-3H-tieno[3,4-d]imidazol-2-carboxílico,

Éster metílico del ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-6-(2,2,2-trifluoro-etoxi)-3H-tieno[3,4-d]imidazol-4-carboxílico,

Ácido 1-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[3-(5-cloro-tiofen-2-il)-isoxazol-5-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-[1,3,4]tiadiazol-2-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-3H-benzoimidazol-5-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-metoxi-etoxi)-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-ilcarbamoil)-metil]-4-(2-etoxi-etoxi)(-1H-benzoimidazol-2-carboxílico,

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-4-(2-hidroxi-etoxi)-1H-benzoimidazol-2-carboxílico,

Éster metílico del ácido 1-[(5-cloro-piridin-2-ilcarbamoil)-metil]-2-[2-fluoro-4-(pirrolidina-1-carbonil)-fenilcarbamoil]-1H-benzoimidazol-4-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-1H-benzoimidazol-5-carboxílico,

Ácido 3-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-ciclopropil-piperidin-4-ilcarbamoil)-7-metil-3H-benzoimidazol-5-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-5-fluoro-2-(1-isopropil-piperidin-4-ilcarbamoil)-1H-benzoimidazol-4-carboxílico,

Ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-2-(1-isopropil-piperidin-4-ilcarbamoil)-5-(2,2,2-trifluoroetoxi)-1H-benzoimidazol-4-carboxílico, o

(1-Isopropil-piperidin-4-il)-amida del ácido 1-[5-(5-cloro-tiofen-2-il)-isoxazol-3-ilmetil]-4-(3-hidroxi-azetidina-1-carbonil)-5-(2,2,2-trifluoro-etoxi)-1H-benzoimidazol-2-carboxílico.

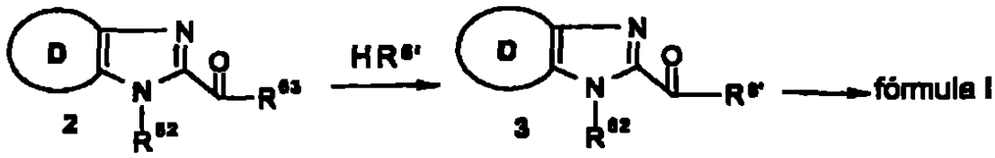
9. Una preparación farmacéutica, que comprende al menos un compuesto de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 8 en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación y/o sus sales fisiológicamente tolerables y un vehículo farmacéuticamente aceptable.

10. El uso de un compuesto de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 8 en todas sus formas estereoisoméricas y mezclas de las mismas en cualquier relación y/o sus sales fisiológicamente tolerables para la producción de productos farmacéuticos para la inhibición del factor Xa y/o el factor VIIa o para influir sobre la coagulación sanguínea o la fibrinolisis.

11. El uso de acuerdo con la reivindicación 10 para una formación anormal de trombos, infarto de miocardio agudo, trastornos cardiovasculares, angina inestable, tromboembolia, cierre de vasos agudo asociado con una terapia trombolítica o angioplastia coronaria transluminal percutánea (PTCA), ataques isquémicos transitorios, apoplejía, claudicación intermitente, injerto de bypass de las arterias coronarias o periféricas, estrechamiento del lumen de vasos, reestenosis después de una angioplastia coronaria o venosa, mantenimiento de la patencia de acceso vascular en pacientes con hemodiálisis a largo plazo, formación patológica de trombos que tiene lugar en las venas de las extremidades inferiores después de una cirugía abdominal, de rodilla o de cadera, riesgo de tromboembolia pulmonar, coagulopatía intravascular sistémica diseminada que se produce en sistemas vasculares durante el choque séptico, ciertas

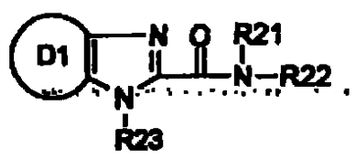
infecciones víricas o cáncer, o para reducir una respuesta inflamatoria, fibrinolisis, o tratamiento de la enfermedad cardiaca coronaria, infarto de miocardio, angina de pecho, reestenosis vascular, por ejemplo reestenosis posterior a una angioplastia tal como PTCA, síndrome de distrés respiratorio en adultos, insuficiencia de múltiples órganos, trastorno de coagulación intravascular diseminada, y trombosis de venas profundas y de venas proximales, que pueden producirse después de una cirugía.

12. Un proceso para la preparación de un compuesto de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 8, que comprende condensar un compuesto de la fórmula 2 con un compuesto de la fórmula $HR^{6'}$ para dar un compuesto de la fórmula 3 y opcionalmente convertir el compuesto de la fórmula 3 en un compuesto de la fórmula I,



donde el resto $R^{6'}$ tiene la donación de $-N(R^1)-R^2-V-G-M$ como se indica en las reivindicaciones 1 a 8, pero donde en $R^{6'}$ los grupos funcionales también pueden estar presentes en forma de grupos que posteriormente se transforman en los grupos funcionales finales presentes en $-N(R^1)-R^2-V-G-M$, y donde el resto R^{62} denota el grupo $-Q-R^0$ o puede denotar un grupo que posteriormente se transforma en el grupo $-Q-R^0$, y donde el grupo $-C(O)-R^{63}$ puede ser un grupo de ácido carboxílico o derivados del mismo, como se define en las reivindicaciones 1 a 8, donde dichos grupos funcionales también pueden estar presentes en forma protegida o en forma de grupos precursores.

13. Un proceso para la preparación de un compuesto de fórmula IV,



(IV)

en la que

R21 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13,

c) -alquileno (C_1-C_3)-C(O)-NH-R^0,

d) -alquileno (C_1-C_3)-C(O)-O-R^{10},

e) -alquil (C_0-C_4)-arilo, donde el arilo es un arilo de 6 a 14 miembros monocíclico o bicíclico y está mono-, di- o trisustituido independientemente entre sí con R8,

f) -alquil (C_0-C_4)-heteroarilo, donde el heteroarilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está mono-, di- o trisustituido independientemente entre sí con R8,

g) -alquil (C_1-C_4)-heterociclilo, donde el heterociclilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y que está adicionalmente sustituido con un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

h) -perfluoroalquileno (C_1-C_3),

i) -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4),

j) -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3),

k) -alquileno (C_1-C_3)-$S(O)_2$-N($R^{4'}$)-R^5,

l) -alquileno (C_1-C_3)-O-alquilo (C_1-C_4),

m) -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8) o

n) -alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14,

donde R^0, $R^{4'}$, R^5, R8, R^{10}, R^{13} y R^{14} son como se han definido en la reivindicación 1 para el compuesto de fórmula I,

R22 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13,

c) -alquileno (C_1-C_3)-C(O)-NH-R^0,

d) -alquileno (C_1-C_3)-C(O)-O-R^{10},

e) -alquil (C_0-C_4)-arilo, donde el arilo es un arilo de 6 a 14 miembros monocíclico o bicíclico y está mono-, di- o trisustituido independientemente entre sí con R8,

f) -alquil (C_0-C_4)-heteroarilo, donde el heteroarilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está mono-, di- o trisustituido independientemente entre sí con R8,

g) -alquil (C_1-C_4)-heterociclilo, donde el heterociclilo es un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8, y que está adicionalmente sustituido con un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde el heterociclilo está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R8,

h) -perfluoroalquileno (C_1-C_3),

i) -alquileno (C_0-C_3)-S(O)-alquilo (C_1-C_4),

j) -alquileno (C_0-C_3)-$S(O)_2$-alquilo (C_1-C_3),

k) -alquileno (C_0-C_3)-$S(O)_2$-$N(R^{4'})$-$R^{5'}$,

l) -alquileno (C_1-C_3)-O-alquilo (C_1-C_4),

m) -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8),

n) -alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

o) R^2-V-G-M,

donde R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, $R14^4$, V, G y M son como se han definido en la reivindicación 1 para el compuesto de fórmula I, o la subestructura R21-N-R^2-V en la fórmula IV puede formar un grupo cíclico de 4 a 8 miembros que contiene 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho grupo cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, donde el resto R14 es como se ha definido en la reivindicación 1 para el compuesto de fórmula I,

R23 es

a) un átomo de hidrógeno,

b) -alquilo (C_1-C_4), donde el alquilo está sin sustituir o sustituido de una a tres veces con R13,

c) -alquileno (C_1-C_3)-C(O)-NH-R^0,

d) -alquileno (C_1-C_3)-C(O)-O-R^{10},

e) un arilo de 6 a 14 miembros monocíclico o bicíclico, donde el arilo está mono-, di- o trisustituido independientemente entre sí con R8,

f) un heterociclilo de 4 a 15 miembros monocíclico o bicíclico que contiene uno, dos, tres o cuatro heteroátomos seleccionados entre nitrógeno, azufre u oxígeno,

g) -perfluoroalquileno (C_1-C_3),

h) -alquileno (C_1-C_3)-S(O)-alquilo (C_1-C_4),

j) -alquileno (C_1-C_3)-$S(O)_2$-alquilo (C_1-C_3),

k) -alquileno (C_1-C_3)-$S(O)_2$-N($R^{4'}$)-$R^{5'}$,

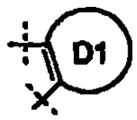
l) -alquileno (C_1-C_3)-O-alquilo (C_1-C_4),

m) -alquileno (C_0-C_3)-cicloalquilo (C_3-C_8),

n) -alquileno (C_0-C_3)-het, donde het es un resto cíclico de 3 a 7 miembros que contiene hasta 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno, donde dicho resto cíclico está sin sustituir o mono-, di- o trisustituido independientemente entre sí con R14, o

o) -Q-R^0,

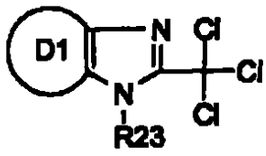
donde R^0, R^2, $R^{4'}$, $R^{5'}$, R8, R^{10}, R13, R14, Q, V, G y M son como se han definido en la reivindicación 1 para el compuesto de fórmula I, y la subestructura



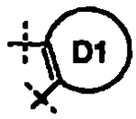
en la fórmula IV es

un grupo cíclico saturado, parcialmente insaturado o aromático de 4 a 8 miembros que contiene cero, 1, 2, 3 ó 4 heteroátomos seleccionados entre nitrógeno, azufre u oxígeno y está sin sustituir o sustituido 1, 2, 3, 4, 5 ó 6 veces con R3, donde R3 es como se ha definido en la reivindicación 1 para el compuesto de fórmula I,

que comprende hacer reaccionar un compuesto de la fórmula V



(V)



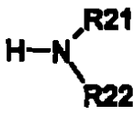
en la que R23 es como se ha definido en la fórmula IV y la subestructura en la fórmula V es como se ha definido en la fórmula IV,

con una amina primaria, en donde la amina primaria se selecciona del grupo

a) NH_2-R21, donde R21 es como se ha definido en la fórmula IV, o

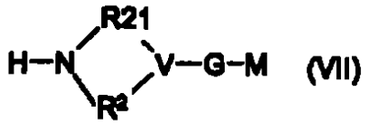
b) NH_2-R^2-V-G-M, donde R^2, V, G y M son como se han definido en la fórmula IV,

o una amina secundaria, en donde la amina secundaria se selecciona del grupo



a)

donde R21 y R22 son como se han definido en la fórmula IV o



(VII)

b) un compuesto de fórmula VII

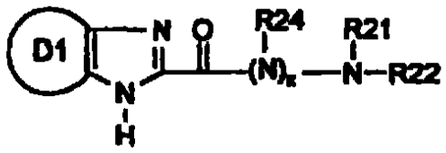
en la que R21, R^2, V, G y M son como se han definido en la fórmula IV,
con la condición de que R21 no sea 8-aza-biciclo[3.2.1]octano o
con la condición de que R21-N-R2-V no forme un resto piperazina o [1,4]diazepano,
en presencia de agua, al menos una base y al menos un disolvente orgánico miscible con agua, en donde el disolvente orgánico miscible con agua se selecciona del grupo tetrahidrofurano, acetonitrilo, 1,2-dimetoxietano, dimetilsulfóxido, dioxano, N,N-dimetilformamida, N-metilpirrolidona, acetona o sulfolano.

14. Un proceso para la preparación de un compuesto de fórmula IV de acuerdo con la reivindicación 13, donde la base es un carbonato de metal alcalino, bicarbonato sódico, bicarbonato potásico, una amina terciaria, trietilamina o diisopropiletilamina.

15. Un proceso para la preparación de un compuesto de fórmula IV de acuerdo con la reivindicación 13, donde la cantidad de disolvente orgánico miscible con agua usada es de 5 g a 300 g por 1 g del compuesto de fórmula V, preferiblemente de 10 g a 200 g.

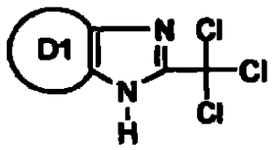
16. Un proceso para la preparación de un compuesto de fórmula IV de acuerdo con la reivindicación 13, donde la temperatura de reacción es de 5°C a 120°C, preferiblemente de 10°C a 35°C, en particular 25°C.

17. Un proceso para la preparación de un compuesto de fórmula IX,

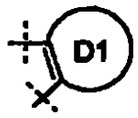


(IX)

en la que
x es el número entero 1,
R24 es idéntico a R21, que es como se define en la fórmula IV en la reivindicación 13, y .
R22 es como se define en la fórmula IV,
que comprende hacer reaccionar un compuesto de fórmula X



(X)



en donde la subestructura en la fórmula X es como se define en la fórmula IV, con una amina primaria, en donde la amina primaria se selecciona del grupo

a) NH_2-N(R21)-R22, donde R21 y R22 son como se han definido en la fórmula IV, o

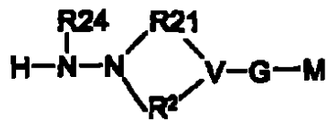


(VI)

b) un compuesto de la fórmula

en donde R^2, R21, V, G y M son como se han definido en la fórmula IV, o

o una amina secundaria, en donde la amina secundaria es un compuesto de fórmula VIII



(VIII)

donde R^2, R21, R24, V, G y M son como se han definido en la fórmula IV

en presencia de agua, al menos una base y al menos un disolvente orgánico miscible con agua, en donde el disolvente orgánico miscible con agua se selecciona del grupo tetrahidrofurano, acetonitrilo, 1,2-dimetoxietano, dimetilsulfóxido, dioxano, N,N-dimetilformamida, N-metilpirrolidona, acetona o sulfolano.

18. Un proceso para la preparación de un compuesto de fórmula IX de acuerdo con la reivindicación 17, donde la base es un carbonato de metal alcalino, bicarbonato sódico, bicarbonato potásico, una amina terciaria, trietilamina o diisopropiletilamina.

19. Un proceso para la preparación de un compuesto de fórmula IX de acuerdo con la reivindicación 17, donde la cantidad de disolvente orgánico miscible con agua

usada es de 5 g a 300 g por 1 g del compuesto de fórmula V, preferiblemente de 10 g a 200 g.

20. Un proceso para la preparación de un compuesto de fórmula IX de acuerdo con la reivindicación 17, donde la temperatura de reacción es de 5°C a 120°C, preferiblemente de 10°C a 35°C, en particular 25°C.

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PCT

REQUEST

The undersigned requests that the present International application be processed according to the Patent Cooperation Treaty.

PCT/EP 2004 / 004750
International Application No.

05.05.2004
International Filing Date

05 MAY 2004

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 2003/0034

Box No. I TITLE OF INVENTION
Benzimidazole-derivatives as factor Xa inhibitors

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

Aventis Pharma Deutschland GmbH
Brüningstraße 50
65929 Frankfurt
Germany

Telephone No. (069) 305-6047
Facsimile No. (069) 357175
Teleprinter No.
Applicant's registration No. with the Office

State *(that is, country)* of nationality: DE
State *(that is, country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated states ☒ all designated states except the United States of America ☐ the United States of America only ☐ the states indicated in the Supplement Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

NAZARÉ, Marc
Felix-Lahnstein-Str. 4b
65510 Idstein
Germany

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: DE
State *(that is, country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated states ☐ all designated states except the United States of America ☒ the United States of America only ☐ the states indicated in the Supplement Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Aventis Pharma Deutschland GmbH
Patent- und Lizenzabteilung
Industriepark Höchst, Geb. K 801
65926 Frankfurt
Germany

Telephone No. (069) 305-6047
Facsimile No. (069) 357175
Teleprinter No.
Agent's registration No. with the Office

☒ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

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PCT/EP2004/004750

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*
WAGNER, Michael
Alte Bergstr. 42a
64665 Alsbach
Germany

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*
Applicant's registration No. with the Office

State (*that is, country*) of nationality: DE
State (*that is, country*) of residence: DE

This person is applicant for the purposes of: ☐ All designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*
WEHNER, Volkmar
Lindenstraße 1
97657 Sandberg
Germany

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*
Applicant's registration No. with the Office

State (*that is, country*) of nationality: DE
State (*that is, country*) of residence: DE

This person is applicant for the purposes of: ☐ All designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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MATTER, Hans
Feldbergring 37
63505 Langenselbold
Germany

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*
Applicant's registration No. with the Office

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This person is applicant for the purposes of: ☐ All designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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URMANN, Matthias
Im Sylvaner 4b
65760 Eschborn
Germany

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*
Applicant's registration No. with the Office

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☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

RITTER, Kurt
Gutzkowstr. 2
60594 Frankfurt am Main
Germany

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State (*that is, country*) of nationality: DE

State (*that is, country*) of residence: DE

This person is applicant for the purposes of: ☐ All designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State (*that is, country*) of nationality:

State (*that is, country*) of residence:

This person is applicant for the purposes of: ☐ All designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:

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- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

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State (*that is, country*) of residence:

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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State (*that is, country*) of nationality:

State (*that is, country*) of residence:

This person is applicant for the purposes of: ☐ All designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany is not designated for any kind of national protection

☐ KR Republic of Korea is not designated for any kind of national protection

☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.).

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing Date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		National application: country	Regional application:* regional office	International application: receiving office
Item(1) 19. May 2003 19.05.2003	03011305.4	EP		
Item(2)				
Item(3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental box

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)).....*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / .....

Request to use results of earlier search; reference to that search *(If an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)*:	Number:	Country (or regional Office):
16/01/2004	EP 03 01 1305	EP

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

			Number of declarations
☐	Box No. VIII (i)	Declaration as to identify of the inventor :	
☐	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and to be granted a patent :	
☐	Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :	
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America) :	
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :	

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) In paper form, the following number of sheets:

request (including declaration sheets):	: 5
description (excluding sequence listings and/or tables related thereto)	: 165
claims	: 81
abstract	: 1
drawings	:
Sub-total number of sheets:	: 232
sequence listings	:
tables related thereto	:
of description description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)*	
Total number of sheets:	:

(b) ☐ Only in computer readable form (Section 801 (a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related hereto

(c) ☐ also in computer readable form (Section 801 (a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related hereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listings: .....
- ☐ tables related hereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒	fee calculation sheet	: 1
2. ☐	separate signed power of attorney	:
3. ☐	original general power of attorney	:
4. ☐	copy of general power of attorney reference number, if any:	:
5. ☐	statement explaining lack of signature	:
6. ☒	priority document(s) identified in Box No. VI as item(s):	: 1
7. ☐	translation of international application into (language):	:
8. ☐	separate indications concerning deposited microorganism or other biological material	:
9. ☐	Sequence listing in computer readable form (indicate type and number of carriers)	:
	(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	
	(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequences listing part mentioned in left column	:
10. ☐	tables in computer readable form related to sequence listings (indicate type and number of carriers)	
	(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application)	:
	(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quarter)	:
	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:
11. ☐	other *(specify)*:	

Figure of the drawings which should accompany the abstract:

Language of filing of the International application: english

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)

AVENTIS PHARMA DEUTSCHLAND GMBH

Dr. Jacobi i.V. Dr. Then

For receiving Office use only

1. Date of actual receipt of the purported international application: 05 MAY 2004 (05.05.04)
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

57174 430

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DEAV2003/0034	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/004750	International filing date *(day/month/year)* 05.05.2004	Priority date *(day/month/year)* 19.05.2003

International Patent Classification (IPC) or national classification and IPC

C07D413/14, C07D401/14, C07D417/14, C07D471/04, A61K31/4184, A61P7/02, C07D401/12, C07D451/06, C07D413/12, C07D409/14, C07D473/08, C07D495/04

Applicant

AVENTIS PHARMA DEUTSCHLAND GMBH

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 61 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.12.2004	08.08.2005

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Kollmannsberger, M Telephone No. +49 89 2399-7384

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/EP2004/004750

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-165 as originally filed

   Claims, Numbers

   1-20 received on 27.11.2004 with letter of 24.11.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 13-20
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/004750

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

INTERNATIONAL PRELIMINARY REPORT N PATENTABILITY

International application No.
PCT/EP2004/004750

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	13-18
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	13-18
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item I
Basis of the report

Claims 13-20 as amended are considered to go beyond the disclosure as originally filed (Rule 70.2(c) PCT) and are not basis of the present preliminary examination.

New independent claim 13 has been amended by a disclaimer based on document D11. However, the IPEA is of the opinion that disclaimers without a basis in the originally filed application documents are only allowable in order to restore novelty in view of accidental disclosures. D11 has been cited as a P-document but, since the priority of the relevant claims is not valid, is also relevant for inventive step under Art. 33(3) PCT (see item 2.). D11 is thus not an accidental disclusure since it deals with the synthesis of the same compounds and the amendment is not allowable.

New independent claim 17 has been restricted to the synthesis of compounds of structure (IV) having R23=H and x=1 (i. e. hydrazides unsubstituted on the benzimidazole nitrogen atom). However, there does not appear to be any basis in the application documents that discloses this newly introduced combination (neither preferred generic ranges nor example compounds appear to be covered by amended claim 17). It is thus considered that claim 17 is a result of singling out a previously undisclosed combination of features and introduces subject-matter going beyond the original disclosure.

This preliminary report is thus based on claims 13-18 as originally filed.

Re Item II
Priority

The priority document does not provide a basis for generic claims relating to invention 2, since only specific examples (examples 5, 11, 29 and 36) deal with the use of 2-trichlorobenzimidazoles as synthesis intermediates and neither generic formulae nor generic reaction conditions are disclosed. The IPEA is of the opinion that for a valid priority claim the claimed subject-matter has to be directly and unambigiously derivable from the priority document. This is not the case here. The claims directed to invention 2 do not enjoy the

claimed priority. The document D11 (cited as P in the search report) is thus state of the Art relevant for Art. 33(2) and 33(3) PCT according to Rule 64.1(b) i) PCT.

Re Item IV

Lack of unity of invention

The application claims on the one hand compounds of structure (I) and on the other hand preparation processes for the intermediates (IV). The intermediates (IV) and processes for their preparation are known (see description page 74). Rule 13 PCT requires for an application to be unitary that the different groups of inventions share special technical features which link them together to form a single general inventive concept. Since the intermediates (IV) are known, no such features are present. The first part of the application deals with the problem of finding novel compounds having a certain activity. The second part of the application deals with the problem of finding novel preparation processes for known intermediates. The application deals thus with two entirely different problems for which two different solutions are proposed, not linked to form a single general inventive concept.

The two inventions are thus:

1. Claims 1-12 (compounds of structure (I) and corresponding uses)

2. Claims 13-18 as originally filed (a process for the preparation of compounds (IV)

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citati ns and explanations supporting such statement

V-1. Prior art

The following documents have been cited:

D1: US-B-6 562 8281 (HAYASHI MIKIO ET AL) 13 May 2003 (2003-05-13)

D2: MATTER, HANS ET AL: "Design and Quantitative Structure-Activity Relationship of 3-Amidinobenzyl-1H-indole-2-carboxamides as Potent, Nonchiral, and Selective Inhibitors of Blood Coagulation Factor Xa" JOURNAL OF MEDICINAL CHEMISTRY (2002), 45(13), 2749-2769 CODEN: JMCMAR; ISSN: 0022-2623, 2002, XP0002256632

D3: PATENT ABSTRACTS OF JAPAN vol. 1997, no. 03, 31 March 1997 (1997-03-31) & JP 8 295667 A (TAKEDA CHEM IND LTD), 12 November 1996 (1996-11-12)

D4: EP-A-0 254 322 (NISSHIN FLOUR MILLING CO) 27 January 1988 (1988-01-27)

D5: PATENT ABSTRACTS OF JAPAN vol. 1998, no. 12, 31 October 1998 (1998-10-31) & JP 10 182459 A (OTSUKA PHARMACEUT CO LTD), 7 July 1998 (1998-07-07)

D6: PATENT ABSTRACTS OF JAPAN vol. 1997, no. 09, 30 September 1997 (1997-09-30) & JP 9 124609 A (NISSAN CHEM IND LTD), 13 May 1997 (1997-05-13)

D7: DE 38 28 537 A (BASF AG) 1 March 1990 (1990-03-01)

D8: PATENT ABSTRACTS OF JAPAN vol. 1996, no. 12, 26 December 1996 (1996-12-26) & JP 8 208640 A (NISSHIN FLOUR MILLING CO LTD), 13 August 1996 (1996-08-13)

D9: DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2003, XP002256742

D10: DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICES, COLUMBUS, OHIO, US; 2003, XP002256743

D11: WO 2004/022060 A (JANSSEN PHARMACEUTICA NV ; CARRUTHERS NICHOLAS I (US); SHAH CHANDRAVAD) 18 March 2004 (2004-03-18)

D12: US-A-4 269 846 (HUANG FU C ET AL) 26 May 1981 (1981-05-26)

D13: DE 43 04 650 A (THOMAE GMBH DR K) 18 August 1994 (1994-08-18)

D14: GARUTI, L. ET AL: "Synthesis and antiviral assays of some 2-substituted benzimidazole-N-carbamates" FARMACO , 55(1), 35-39 CODEN: FRMCE8; ISSN: 0014-827X, 2000, XP002297116

V-2. Novelty (Art. 33(2) PCT):

invention 1:

The claims differ from the compounds disclosed in D3 due to the fact that the cyclic substituent B of D3 is attached directly to the bicyclic core whereas the present claims no longer encompass this possibility (cf. definition of Q in claim 1).

D4 discloses a generic formula (see structure (I) of D4) largely overlapping with structure (I) of present claims. Relevant example compounds have been excluded by the proviso for R8 (i. e. the requirement that R0 must be substituted by halo or amide in case of R0 being carbocyclic, see e. g. compounds 25/26 of D4). The overlapping range is nevertheless considered as a novel selection from D4 since the only possible substituents at the substituent corresponding to R0 specified in D4 are alkoxy substituents which are no longer claimed. The other substituents R8 are not disclosed in D4.

D1 discloses compounds which are not covered by the present claims due to the amidine substituent at the benzimidazole core. D2 discloses indoles.

The compounds disclosed in D5-D10 (see passages cited in the search report) are excluded from the present claims by means of the provisos for R8, by the definition of methylene for Q or by the definition of R2 as bond.

Invention 2:

D11-D14 all disclose preparation processes for compounds according to formula (IV) of claim 13 in which 2-trichloromethylbenzimidazoles are reacted with amines in the presence of water, at least one base and at least one water-miscible solvent (see passages indicated in the search report). Also the features of dependent claims 14-18 are disclosed. These claims are thus not novel.

V-3. Inventive step (Art. 33(3) PCT)

Invention 1:

D1 is seen as the closest state of the art since D1 also deals with benzimidazole derivatives as factor xa-inhibitors. The difference of the present claims with respect to D1 lies in the removal/replacement of the amidine substituent in position 5 of the compounds disclosed in D1 by R3. Since there is no direct hint to remove the amidine substituent of the compounds in D1 (the compounds of D2 are indoles and also have amidine substituents, although at a different position), these compounds cannot be obviously derived from the prior art. The problem of finding further factor xa inhibitors has thus been solved in a non-obvious way.

Invention 2:

Since the claimed process is known from D11-14 claims 13-18 also do not fulfil Art. 33(3) PCT.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-2004/022060	18 March 2004	4 September 2003	6 September 2002

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD
(Capítulo II del tratado de Cooperación en materia de Patentes)

(Artículo 36 y Regla 70 del PCT)

Referencia del expediente del solicitante o del agente DEAV2003/0034	PARA ACCIÓN	Véase formulario PCT/IPEA/416
Solicitud Internacional nº PCT/EP2004/004750	Fecha de presentación internacional *(día/mes/año)* 05.05.2004	Fecha de prioridad *(día/mes/año)* 19.05.2003
Clasificación internacional de patentes (CIP) o a la vez clasificación nacional y CIP C07D413/14, C07D401/14, C07D417/14, C07D471/04, A61K31/4184, A61P7/02, C07D401/12, C07D451/06, C07D413/12, C07D409/14, C07D473/08, C07D495/04		
Solicitante AVENTIS PHARMA DEUTSCHLAND GMBH		

1. El presente Informe preliminar internacional es el Informe de examen, establecido por la Administración encargada del examen preliminar internacional según el Artículo 35 y se transmite al solicitante conforme al Artículo 36.

2. Este INFORME comprende un total de 9 hojas, incluida la presente hoja de portada.

3. Este Informe también contiene ANEXOS, que comprenden:

   a. ☒ *(remitido al solicitante y a la Oficina Internacional)* un total de 61 hojas, descritas a continuación:

      ☒ hojas de la descripción, las reivindicaciones y/o los dibujos que han sido modificadas y que sirven de base al presente informe, y/o de hojas que contienen rectificaciones autorizadas por esta Administración (véase la Regla 70.16 y la Instrucción Administrativa 607 del PCT).

      ☒ hojas que reemplazan a otras hojas anteriores, pero que esta Administración considera que contienen modificaciones que se extienden más allá de la divulgación de la invención tal como fue originalmente presentada, según se indica en el punto 4 del Recuadro I y en el Recuadro Suplementario.

   b. ☐ (remitido únicamente a la Oficina Internacional) un total de (indicar tipo y número de soporte(s) electrónico(s)), que contiene una lista de secuencias y/o tabla(s) relativas(s), solo en formato legible por ordenador, como se indica en el Recuadro Suplementario relativo a Listas de Secuencias (véase Instrucción Administrativa 802).

4. El presente Informe contiene indicaciones relativas a los puntos siguientes:

☒	Recuadro I	Base de la opinión
☒	Recuadro II	Prioridad
☐	Recuadro III	No formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial
☒	Recuadro IV	Falta de unidad de invención
☒	Recuadro V	Declaración motivada según el Artículo 35(2) sobre la novedad, la actividad inventiva y la aplicación industrial; citas y explicaciones en apoyo de esta declaración
☒	Recuadro VI	Ciertos documentos citados
☐	Recuadro VII	Defectos en la solicitud internacional
☐	Recuadro VIII	Observaciones relativas a la solicitud internacional

Fecha de presentación de la petición de examen preliminar internacional 09.12.2004	Fecha de terminación del presente informe 08.08.2005
Nombre y dirección postal de la administración encargada del examen preliminar internacional Oficina Europea de Patentes D-80298 Munich Tél. +49 89 2399 -0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Funcionario autorizado Kollmannsberger, M Teléfono Nº +49 89 2399-7384

INF RME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD

Solicitud Internacional nº PCT/EP2004/004750

Recuadro I. Base de este Informe

1. Por lo que respecta al **idioma**, este informe se ha establecido sobre la base de la solicitud internacional en el idioma en el cual se depositó, salvo indicación en contra señalada sobre este punto.

   ☐ Este informe está basado en una traducción del idioma original al siguiente idioma, que es el de una traducción proporcionada a los fines de:
   - ☐ búsqueda internacional (según Reglas 12.3 y 23.1.b))
   - ☐ publicación de la solicitud internacional (según Regla 12.4)
   - ☐ examen preliminar internacional (según Reglas 55.2 y/o 55.3)

2. Por lo que respecta a los **elementos*** de la solicitud internacional, esta opinión se ha establecido sobre la base de *(las hojas de reemplazo que hayan sido enviadas a la Oficina receptora en respuesta a un requerimiento según el artículo 14 se las denomina en este informe como "inicialmente presentadas" y no se anexan al informe):*

   Descripción, páginas:
   1-165 como se depositaron inicialmente
   Reivindicaciones, Nº.:
   1-20 recibidas el 27.11.2004 con carta de 24.11.2004

   ☐ una lista de secuencias y/o tabla(s) relativa(s) - ver recuadro suplementario relativo a listas de secuencias

3. ☐ Las modificaciones ha ocasionado la anulación de:

   - ☐ la descripción, páginas
   - ☐ las reivindicaciones, nos. 1-12
   - ☐ los dibujos, hojas/fig.
   - ☐ la lista de secuencias *(precisar)*
   - ☐ tabla(s) relativa(s)a la lista de secuencias *(precisar)*

4. ☒ El presente informe ha sido establecido como si no se hubiesen presentado (algunas de) las modificaciones anexadas a este informe y listadas abajo, ya que se ha considerado que iban más allá de la divulgación de la invención tal como fue presentada, como se indica en el Recuadro Suplementario (Regla 70.2.c)).

   - ☐ la descripción, páginas
   - ☒ las reivindicaciones, Nºs 13-20
   - ☐ los dibujos, hojas/fig.
   - ☐ la lista de secuencias *(precisar)*
   - ☐ tabla(s) relativa(s)a la lista de secuencias *(precisar)*

* *Si se utiliza el punto 4, algunas o todas estas páginas pueden llevar el sello de "sustituida"*

INF RME PRELIMINAR INTERNACIONAL
S BRE PATENTABILIDAD

Solicitud internacional nº
PCT/EP2004/004750

Recuadro II. Prioridad

1. ☐ El presente informe se ha formulado como si no se hubiese reivindicado ninguna prioridad, debido a que no se han entregado en el plazo prescrito los documentos siguientes:
   - ☐ copia de la solicitud anterior cuya prioridad se ha reivindicado (Regla 66.7a))
   - ☐ traducción de solicitud anterior cuya prioridad se ha reivindicado (Regla 66.7b))

2. ☒ El presente informe se ha formulado como si no se hubiese reivindicado ninguna prioridad, debido a que no se ha considerado válida la reivindicación de prioridad (Regla 64.1). En consecuencia, a los efectos del presente informe, se considera como pertinente la fecha de presentación internacional indicada más arriba.

3. Observaciones adicionales, si procede:
   Véase hoja separada

Recuadro IV. Falta de unidad de invención

1. ☒ En respuesta al requerimiento para limitar o pagar tasas adicionales, el solicitante ha:
   - ☐ limitado las reivindicaciones
   - ☒ pagado tasas adicionales
   - ☐ pagado tasas adicionales bajo protesta
   - ☐ no ha limitado ni pagado tasas adicionales

2. ☐ Esta Administración considera que no se cumple la exigencia de unidad de la invención, por los motivos indicados, y conforme a la Regla 68.1, decide no requerir al solicitante a limitar o pagar tasas adicionales

3. ☐ Esta Administración considera que el requerimiento de unidad de invención de acuerdo con las Reglas 13.1, 13.2 y 13.3 :
   - ☐ se cumple
   - ☒ no se cumple por las razones siguientes:
     Véase hoja separada

4. ☐ En consecuencia, el presente informe se ha establecido con relación a las partes siguientes de la solicitud internacional:
   - ☒ todas las partes
   - ☐ las partes relativas a las reivindicaciones nos. ..

INF RME PRELIMINAR INTERNACIONAL
S BRE PATENTABILIDAD

Solicitud internacional nº
PCT/EP2004/004750

Recuadro V. Declaración motivada según el artículo 35(2) sobre la novedad, la actividad inventiva y la aplicación industrial; citas y explicaciones en apoyo de esta declaración

1. Declaración

Novedad	Sí:	Reivindicaciones	1-12
	No:	Reivindicaciones	13-18
Actividad inventiva	Sí:	Reivindicaciones	1-12
	No:	Reivindicaciones	13-18
Aplicabilidad industrial	Sí:	Reivindicaciones	1-18
	No:	Reivindicaciones	

2. Citas y explicaciones (Regla 70.7)

véase hoja separada

Recuadro VI. Ciertos documentos citados

1. Ciertos documentos publicados (Regla 70.10)
y / o

2. Divulgaciones no escritas (Regla 70.9)

véase hoja separada

Re Párrafo I

Base del Informe

Las reivindicaciones 13-20, según han quedado modificadas, se consideran que van más allá de la descripción originalmente presentada (Regla 70.2(c) PCT), y no son la base del presente examen preliminar.

La nueva reivindicación 13 independiente ha sido modificada mediante un "disclaimer" basado en el documento D11. Sin embargo, el IPEA es de la opinión que los "disclaimers" sin una base en los documentos de solicitud originalmente presentados, son únicamente permisibles con el fin de restaurar la novedad a la vista de descripciones accidentales. D11 ha sido citado como un documento P pero, dado que la prioridad de las reivindicaciones relevantes no es válida, también es relevante para la actividad inventiva bajo el Art. 33(3) PCT (véase el párrafo 2). Así, D11 no es una descripción accidental, ya que trata de la síntesis de los mismos compuestos, y la modificación no es permisible.

La nueva reivindicación 17 independiente ha sido limitada a la síntesis de compuestos de estructura (IV) con R23=H y x=1 (es decir, hidrazidas no sustituidas en el átomo de nitrógeno del bencimidazol). Sin embargo, no parece existir ninguna base en los documentos de la solicitud que describa esta combinación introducida recientemente (ni los intervalos genéricos preferidos ni los compuestos de los ejemplos parecen quedar cubiertos por la reivindicación 17 modificada). Así, se considera que la reivindicación 17 es el resultado de particularizar una combinación de características previamente no descritas e introduce materia que va más allá de la descripción original.

Así, el informe preliminar se basa en las reivindicaciones 13-18 según fueron originalmente presentadas.

Re Párrafo II

Prioridad

El documento de prioridad no proporciona una base para las reivindicaciones genéricas relacionadas con la invención 2, ya que sólo los ejemplos específicos (ejemplos 5, 11, 29 y 36) tratan del uso del 2-triclorobencimidazoles en calidad de compuestos intermedios de la síntesis y no se describen ni fórmulas genéricas ni condiciones de reacción genéricas. El IEPA es de la opinión de que para una reivindicación válida de la prioridad la materia reivindicada ha de poderse deducir directa y de forma no ambigua del documento de prioridad. Aquí no es éste el caso. Las reivindicaciones dirigidas a la invención 2 no gozan de la prioridad reivindicada. El documento D11 (citado como P en el informe de búsqueda) es, por lo tanto, Estado de la Técnica relevante para Art. 33(2) y 33(3) PCT de acuerdo con la Regla 64.1(b) i) PCT.

Re Párrafo IV

Falta de unidad de la invención

La solicitud reivindica, por una parte, compuestos de estructura (I) y, por otra parte, procedimientos de preparación de los compuestos intermedios (IV). Son conocidos los productos intermedios (IV) y procedimientos para su preparación (véase la página 74 de la memoria descriptiva). La Regla 13 PCT requiere, para que una solicitud sea unitaria, que los diferentes grupos de invenciones compartan características técnicas especiales que los unan entre sí para formar un único concepto inventivo general. Dado que los productos intermedios (IV) son conocidos, no están presentes características de este tipo. La primera parte de la solicitud trata del problema de encontrar nuevos compuestos con una cierta actividad. La segunda parte de la invención trata del problema de encontrar nuevos procedimientos de preparación para productos intermedios conocidos. Así, la solicitud trata de dos problemas totalmente diferentes para los que se proponen dos

soluciones diferentes, no enlazadas para formar un único concepto inventivo general.

Así, las dos invenciones son:

1. Reivindicaciones 1-12 (compuestos de estructura (I) y correspondientes usos)
2. Reivindicaciones 13-18 según se presentaron originalmente (un procedimiento para la preparación de compuestos (IV))

Re Párrafo V

Declaración razonada con respecto a la novedad, actividad inventiva o aplicabilidad industrial; citas y explicaciones que sustentan dicha declaración.

V-1. Técnica anterior

Se han citado los siguientes documentos (D):

D1: US-B-6 562 8281 (HAYASHI MIKIO ET AL)13 Mayo 2003 (2003-05-13)

D2: MATTER, HANS ET AL: "Design and Quantitative Structure-Activity Relationship of 3-Amidinobenzyl-1H-indole-2-carboxamides as Potent, Nonchiral, and Selective Inhibitors of Blood Coagulation Factor Xa" JOURNAL OF MEDICINAL CHEMISTRY (2002), 45(13), 2749-2769 CODEN: JMCMAR; ISSN: 0022-2623, 2002, XP0002256832

D3: PATENT ABSTRACTS OF JAPAN vol. 1997, no. 03, 31 Marzo 1997 (1997-03-31) & JP 8 295667 A (TAKEDA CHEM IND LTD), 12 Noviembre 1996 (1996-11-12)

D4: EP-A-0 254 322 (NISSHIN FLOUR MILLING CO) 27 Enero 1988 (1988-01-27)

D5: PATENT ABSTRACTS OF JAPAN vol. 1998, no. 12, 31 Octubre 1998 (1998-10-31) & JP 10 182459 A (OTSUKA PHARMACEUT CO LTD), 7 Julio 1998 (1998-07-07)

D6: PATENT ABSTRACTS OF JAPAN vol. 1997, no. 09, 30 Septiembre 1997 (1997-09-30) & JP 9 124609 A (NISSAN CHEM IND LTD), 13 Mayo 1997 (1997-05-13)

D7: DE 38 28 537 A (BASF AG) 1 Marzo 1990 (1990-03-01)

D8: PATENT ABSTRACTS OF JAPAN vol. 1996, no. 12, 26 Diciembre 1996 (1996-12-26) & JP 8 208640 A (NISSHIN FLOUR MILLING CO LTD), 13 Agosto 1996 (1996-08-13)

D9: DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2003, XP002256742

D10: DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICES, COLUMBUS, OHIO, US; 2003, XP002256743

D11: WO 2004/022060 A (JANSSEN PHARMACEUTICA NV ; CARRUTHERS NICHOLAS I (US); SHAH CHANDRAVAD) 18 Marzo 2004 (2004-03-18)

D12: US-A-4 269 846 (HUANG FU C ET AL) 26 Mayo 1981 (1981-05-26)

D13: DE 43 04 650 A (THOMAE GMBH DR K) 18 Agosto 1994 (1994-08-18)

D14: GARUTI, L. ET AL: "Synthesis and antiviral assays of some 2-substituted benzimidazole-N-carbamates" FARMACO , 55(1), 35-39 CODEN: FRMCE8; ISSN: 0014-827X, 2000, XP002297116

V-2. Novedad (Art. 33(2) PCT:

Invención 1:

Las reivindicaciones difieren de los compuestos descritos en D3 debido al hecho de que el sustituyente B cíclico de D3 está fijado directamente al núcleo

bicíclico, mientras que las presentes reivindicaciones no abarcan ya esta posibilidad (véase la definición de Q en la reivindicación 1).

D4 describe una fórmula genérica (véase la estructura (I) de D4) que se solapa ampliamente con la estructura (I) de las actuales reivindicaciones. Compuestos a título de ejemplo relevantes han sido excluidos por la condición para R8 (es decir, el requisito de que R0 debe ser sustituido con halo o amida en el caso de que R0 sea carbocíclico, véanse, por ejemplo, los compuestos 25/26 de D4). No obstante, el intervalo solapante se considera como una nueva selección de D4, ya que los únicos sustituyentes posibles en el sustituyente correspondiente a R0 especificado en D4 son sustituyentes alcoxi que ya no se reivindican. Los otros sustituyentes R8 no se describen en D4.

D1 describe compuestos que no quedan cubiertos por las presentes reivindicaciones, debido al sustituyente amidina en el núcleo de bencimidazol. D2 describe indoles.

Los compuestos descritos en D5-D10 (véanse los pasajes citados en el informe de búsqueda) quedan excluidos de las presentes reivindicaciones por medio de las condiciones de R8, por la definición de metileno para Q o por la definición de R2 como enlace.

Invención 2:

D11-D14 describen todos procedimientos de preparación para compuestos de acuerdo con la fórmula (IV) de la reivindicación 13, en los que 2-triclorometilbencimidazoles se hacen reaccionar con aminas en presencia de agua, al menos una base y al menos un disolvente miscible con agua (véanse los pasajes indicados en el informe de búsqueda). También se describen las características de las reivindicaciones dependientes 14-18. Así, estas reivindicaciones no son nuevas.

V-3. Actividad inventiva (Art. 33(3) PCT)

Invención 1:

D1 se considera el estado más próximo de la técnica, ya que D1 también trata de derivados de bencimidazol en calidad de inhibidores del factor Xa. La diferencia de las presentes reivindicaciones con respecto a D1 se encuentra en la separación/reemplazamiento del sustituyente amidina en la posición 5 de los compuestos descritos en D1 por R3. Ya que no existe ningún indicio directo para separar el sustituyente amidina de los compuestos en D1 (los compuestos de D2 son indoles y tienen también sustituyentes amidina, aunque en una posición diferente), estos compuestos no se pueden derivar obviamente de la técnica anterior. El problema de encontrar inhibidores de factor Xa adicionales ha sido, por lo tanto, resuelto de una manera no obvia.

Invención 2:

Dado que el procedimiento reivindicado es conocido a partir de D11-14, las reivindicaciones 13-18 tampoco cumplen con el Art. 33(3) PCT.

Re Párrafo VI

Determinados documentos citados

Determinados documentos publicados

Solicitud No. Patente No.	Fecha de publicación *(Día/mes/año)*	Fecha de presentación *(Día/mes/año)*	Fecha de prioridad (reivindicación válida) *(Día/mes/año)*
WO-A-2004/022060	18 Marzo 2004	4 Septiembre 2003	6 Septiembre 2002

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

AVENTIS PHARMA DEUTSCHLAND GMBH
Patent- und Lizenzabteilung
Industriepark Höchst, Geb. K 801
65926 Frankfurt
Germany

Date of mailing (day/month/year) 07 July 2004 (07.07.2004)	
Applicant's or agent's file reference 2003/0034	IMPORTANT NOTIFICATION
International application No. PCT/EP2004/004750	International filing date (day/month/year) 05 May 2004 (05.05.2004)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 19 May 2003 (19.05.2003)
Applicant AVENTIS PHARMA DEUTSCHLAND GMBH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

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Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
19 May 2003 (19.05.2003)	03011305.4	EP	27 May 2004 (27.05.2004)

The International Bureau of WIPO
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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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PATENTE DE INVENCIÓN PCT MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	(X)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(X)
- Descripción de la invención.	( )	(X)
- Dibujos de ser estos pertinentes.	( )	(X)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA (X) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
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- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que Incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
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Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

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