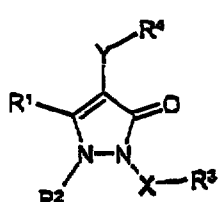


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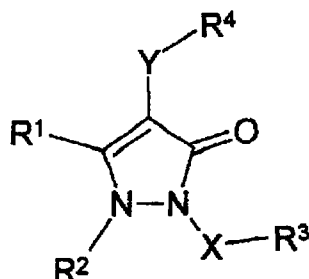
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(21) International application number: PCT/EP00/01695 (22) International filing date: 29 February 2000 (29.02.00) (30) Data relating to the priority: 199 09 237.0 3 March 1999 (03.03.99) DE (71) Applicant (for all designated States except US): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, D-64293 Darmstadt (DE). (72) Inventors; and (75) Inventors/Applicants (US only): DORSCH, Dieter [DE/DE]; Königsberger Strasse 17A, D-64372 Ober- Ramstadt (DE). JURASZYK, Horst [DE/DE]; Kleiner Ring 14, D-64342 Seeheim (DE). MEDERSKI, Werner [DE/DE]; Am Ohlenberg 29, D-64390 Erzhausen (DE). TSAKLAKIDIS, Christos [GR/DE]; Rosenbrunnenstrasse 25, D-69469 Weinheim (DE). WÜRZIGER, Hanns [DE/DE]; Greinstrasse 7b, D-64291 Darmstadt (DE). BERNOTAT-DANIELOWSKI, Sabine [DE/DE]; Liebigstrasse 5, D- 61231 Bad Nauheim (DE). MELZER, Guido [DE/DE]; Mörikestrasse 6, D-65719 Hofheim (DE). (74) Joint Representative: MERCK PATENT GMBH; D-64271 Darmstadt (DE).		(81) Designated states: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With the International Search Report. Before expiry of the period provided for amending the claims, will be republished if such amendments are received.
As printed (54) Title: PYRAZOLE-3-ON-DERIVATIVE AS FACTOR Xa INHIBITORS (54) Bezeichnung: PYRAZOL-3-ON-DERIVATE ALS FAKTOR Xa INHIBITOREN  (I) (57) Abstract The invention relates to novel compounds of formula (I) wherein R¹, R², R³, R⁴, X and Y have the meaning given in Claim 1. Said compounds are inhibitors of the coagulation factor Xa and can be used for the prophylaxis and/or therapy of thrombo-embolic diseases. (57) Zusammenfassung Neue Verbindungen der Formel (I), worin R¹, R², R³, R⁴, X und Y die in Patentanspruch 1 angegebene Bedeutung haben, sind Inhibitoren des Koagulationsfaktors Xa und können zur Prophylaxe und/oder Therapie von thromboembolischen Erkrankungen eingesetzt werden.		

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Pyrazol-3-one derivatives

Pyrazol-3-one derivatives

The invention relates to compounds of the formula I

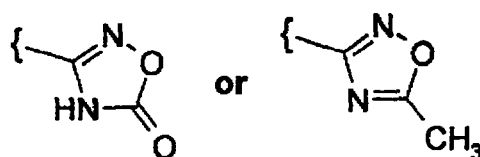


in which

R^1, R^2 in each case independently of one another are H, A, cycloalkyl- $[C(R^7R^{7'})]_n$ - or $Ar-[C(R^7R^{7'})]_n$ -,

R^3, R^4 in each case independently of one another are H, Ar, Het, R^5 , where at least one of the two radicals is R^5 ,

R^5 is phenyl, naphthyl or biphenyl [sic], which is substituted by $-C(=NH)-NH_2$ which can also be monosubstituted by $-COA$, $Ar-[C(R^7R^{7'})]_n-CO-$, $COOA$, OH or by a conventional amino protective group, $-NH-C(=NH)-NH_2$, $-CO-N=C(NH_2)_2$,



and which can optionally additionally be mono- or disubstituted by A, Ar' , Het, OR^6 , $NR^6R^{6'}$, NO_2 , CN, Hal, NR^6COA , NR^6COAr' , NR^6SO_2A , NR^6SO_2Ar' , $COOR^6$, $CO-NR^6R^{6'}$, COR^7 , $CO-Ar'$, $SO_2NR^6R^{6'}$, $S(O)_nAr'$ or $S(O)_nA$,

$R^6, R^{6'}$ in each case independently of one another are H, A, $CR^7R^{7'}-Ar'$ or $CR^7R^{7'}-Het$,

$R^7, R^{7'}$ in each case independently of one another are H or A,

- X, Y in each case independently of one another are $(CR^7R^{7'})_n$,
- A is alkyl having 1-20 C atoms, in which one or two CH_2 groups can be replaced by O or S atoms and/or by $-CH=CH-$ groups and/or 1-7 H atoms can be replaced by F,
- Ar is phenyl, naphthyl or biphenyl [sic], which is unsubstituted or mono-, di- or trisubstituted by A, Ar', Het, OR^6 , $NR^6R^{6'}$, NO_2 , CN, Hal, NR^6COA , NR^6COAr' , NR^6SO_2A , NR^6SO_2Ar' , $COOR^6$, $CO-NR^6R^{6'}$, CON^6Ar' , COR^7 , $COAr'$, $SO_2NR^6R^{6'}$, $S(O)_nAr'$ or $S(O)_nA$,
- Ar' is phenyl or naphthyl, which is unsubstituted or mono-, di- or trisubstituted by A, OR^7 , $NR^7R^{7'}$, NO_2 , CN, Hal, NR^7COA , NR^7SO_2A , $COOR^7$, $CO-NR^7R^{7'}$, COR^7 , $SO_2NR^7R^{7'}$ or $S(O)_nA$,
- Het is a mono- or binuclear saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which can be unsubstituted or mono-, di- or trisubstituted by A, OR^7 , $NR^7R^{7'}$, NO_2 , CN, Hal, NR^7COA , NR^7SO_2A , $COOR^7$, $CO-NR^7R^{7'}$, COR^7 , $SO_2NR^7R^{7'}$, $S(O)_nA$ and/or carbonyl oxygen,
- Hal is F, Cl, Br or I,
- n is 0, 1 or 2,
- and their pharmaceutically tolerable salts and solvates.

The invention also relates to the optically active forms, the racemates, the diastereomers and also the hydrates and solvates, e.g. alcoholates, of these compounds.

The invention was based on the object of finding novel compounds having valuable properties, in particular those which can be used for the production of medicaments.

It has been found that the compounds of the formula I and their salts have very valuable pharmacological properties together with good tolerability. In particular, they exhibit factor Xa-inhibiting properties and can therefore be employed for

the control and prevention of thromboembolic disorders such as thrombosis, myocardial infarct, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty and intermittent
5 claudication.

The compounds of the formula I according to the invention can furthermore be inhibitors of the clotting factors factor VIIa, factor IXa and thrombin of the blood-clotting cascade.

10 Aromatic amidine derivatives having antithrombotic action are disclosed, for example, in EP 0 540 051 B1. Cyclic guanidines for the treatment of thromboembolic disorders are described, for example, in WO 97/08165. Aromatic heterocycles having factor Xa-
15 inhibitory activity are disclosed, for example, in WO 96/10022. Substituted N-[(aminoiminomethyl)phenyl-alkyl]azaheterocyclylamides as factor Xa inhibitors are described in WO 96/40679.

The antithrombotic and anticoagulant effect of
20 the compounds according to the invention is attributed to the inhibitory action against the activated clotting protease, known under the name factor Xa, or to the inhibition of other activated serin proteases such as factor VIIa, factor IXa or thrombin.

25 Factor Xa is one of the proteases which is involved in the complex process of blood clotting. Factor Xa catalyses the conversion of prothrombin into thrombin. Thrombin cleaves fibrinogen into fibrin monomers, which, after crosslinking, contribute
30 elementarily to thrombus formation. Activation of thrombin can lead to the occurrence of thromboembolic disorders. Inhibition of thrombin, however, can inhibit the fibrin formation involved in thrombus formation. The inhibition of thrombin can be measured, for
35 example, according to the method of G.F. Cousins et al., in *Circulation* **1996**, 94, 1705-1712.

Inhibition of factor Xa can thus prevent thrombin being formed.

The compounds of the formula I according to the invention, and their salts, intervene in the blood-clotting process by inhibition of factor Xa and thus inhibit the formation of thrombi.

5 The inhibition of factor Xa by the compounds according to the invention and the measurement of the anticoagulating and antithrombotic activity can be determined by customary in vitro or in vivo methods. A suitable process is described, for example, by
10 J. Hauptmann et al., in *Thrombosis and Haemostasis* **1990**, 63, 220-223.

The inhibition of factor Xa can be measured, for example, by the method of T. Hara et al., in *Thromb. Haemostas.* **1994**, 71, 314-319.

15 After binding to tissue factor, the clotting factor VIIa initiates the extrinsic part of the clotting cascade and contributes to the activation of factor X to factor Xa. Inhibition of factor VIIa thus prevents the formation of factor Xa and thereby
20 subsequent thrombin formation.

The inhibition of factor VIIa by the compounds according to the invention and the measurement of the anticoagulant and antithrombotic activity can be determined by customary in vitro or in vivo methods. A
25 customary process for measuring the inhibition of factor VIIa is described, for example, by H.F. Ronning et al., in *Thrombosis Research* **1996**, 84, 73-81.

The clotting factor IXa is generated in the intrinsic clotting cascade and is likewise involved in
30 the activation of factor X to factor Xa. Inhibition of factor IXa can therefore prevent factor Xa being formed in other ways.

The inhibition of factor IXa by the compounds according to the invention and the measurement of the
35 anticoagulant and antithrombotic activity can be determined by customary in vitro or in vivo methods. A suitable process is described, for example, by J. Chang et al., in *Journal of Biological Chemistry* **1998**, 273, 12089-12094.

The compounds of the formula I can be employed as pharmaceutical active compounds in human and veterinary medicine, in particular for the control and prevention of thromboembolic disorders such as
5 thrombosis, myocardial infarct, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty and intermittent claudication.

The invention relates to the compounds of the formula I and their salts, and to a process for the
10 preparation of compounds of the formula I according to Claim 1 and their salts, characterized in that

a) they are liberated from one of their functional derivatives by treating with a solvolysing or
15 hydrogenolysing agent by

i) liberating an amidino group from its oxadiazole derivative or oxazolidinone derivative by hydrogenolysis or solvolysis,
20

ii) replacing a conventional amino protective group by hydrogen by treating with a solvolysing or hydrogenolysing agent or liberating an amino group protected by a
25 conventional protective group,

or

b) in a compound of the formula I, converting one or
30 more radicals R^1 , R^2 , R^3 and/or R^4 into one or more radicals R^1 , R^2 , R^3 and/or R^4 ,

by, for example,

35 i) hydrolysing an ester group to a carboxyl group,

ii) reducing a nitro group,

iii) acylating an amino group,

iv) converting a cyano group into an amidino group

5

and/or

c) converting a base or acid of the formula I into one of its salts.

10

For all radicals which occur a number of times, it is recognized that their meanings are independent of one another.

15 Above and below, the radicals or parameters R^1 , R^2 , R^3 , R^4 , X and Y have the meanings indicated in the formula I, if not expressly stated otherwise.

A is alkyl, is unbranched (linear) or branched, and has 1 to 20, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms. A is preferably methyl, furthermore
20 ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, in addition also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1-
25 or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example, trifluoromethyl. A is very particularly preferably alkyl having 1-6 C atoms, preferably methyl, ethyl, propyl, isopropyl,
30 butyl, isobutyl, sec-butyl, tert-butyl, pentyl or hexyl.

Cycloalkyl is preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

Hal is preferably F, Cl or Br, but also I.

35 Ar is phenyl, naphthyl or biphenyl [sic], which is unsubstituted or mono-, di- or trisubstituted by A, Ar' , Het, OR^6 , NR^6R^6' , NO_2 , CN, Hal, NR^6COA , NR^6COAr' , NR^6SO_2A , NR^6SO_2Ar' , $COOR^6$, $CO-NR^6R^6'$, CON^6Ar' , COR^7 , $COAR^7$,

$\text{SO}_2\text{NR}^6\text{R}^{6'}$, $\text{S(O)}_n\text{Ar}'$ or $\text{S(O)}_n\text{A}$. Preferred substituents for biphenyl [sic] are fluorine, SO_2NH_2 or SO_2NHA .

Ar' is phenyl or naphthyl, which is unsubstituted or mono-, di- or trisubstituted by A, Het, OR^6 , $\text{NR}^6\text{R}^{6'}$, NO_2 , CN, Hal, NR^6COA , $\text{NR}^6\text{SO}_2\text{A}$, $\text{NR}^6\text{SO}_2\text{Ar}'$, COOR^6 , $\text{CO-NR}^6\text{R}^{6'}$, COR^7 , $\text{SO}_2\text{NR}^6\text{R}^{6'}$ or $\text{S(O)}_n\text{A}$.

Ar is preferably unsubstituted phenyl, naphthyl or biphenyl [sic], furthermore preferably phenyl, naphthyl or biphenyl [sic], which is mono-, di- or trisubstituted, for example, by methyl, ethyl, propyl, isopropyl, butyl, fluorine, chlorine, bromine, hydroxyl, methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, cyano, nitro, trifluoromethyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, pyrrolidin-1-yl, piperidin-1-yl, sulfonamido, methylsulfonamido, ethylsulfonamido, propylsulfonamido, butylsulfonamido, tert-butylsulfonamido, tert-butylaminosulfonyl, dimethylsulfonamido, phenylsulfonamido, methoxycarbonyl, carboxyl, dimethylaminocarbonyl, phenylaminocarbonyl, acetyl, propionyl, benzoyl, methylsulfonyl or phenylsulfonyl.

Ar' is preferably unsubstituted phenyl or naphthyl, furthermore preferably phenyl or naphthyl, which is mono-, di- or trisubstituted, for example, by methyl, ethyl, propyl, isopropyl, butyl, fluorine, chlorine, bromine, hydroxyl, methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, cyano, nitro, trifluoromethyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, pyrrolidin-1-yl, piperidin-1-yl, sulfonamido, methylsulfonamido, ethylsulfonamido, propylsulfonamido, butylsulfonamido, dimethylsulfonamido, phenylsulfonamido, methoxycarbonyl, carboxyl, dimethylaminocarbonyl, phenylaminocarbonyl, acetyl, propionyl, benzoyl, methylsulfonyl or phenylsulfonyl.

Ar is particularly preferably, for example, phenyl, naphthyl, biphenyl [sic], o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl,

o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-,
m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl,
o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-
acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or
5 p-ethoxyphenyl, o-, m- or p-(N,N-dimethylamino)phenyl,
o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m-
or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-
diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m-
or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or
10 p-(methylsulfonamido)phenyl, 3-fluoro-2'-sulfamoyl-
biphenyl-4-yl, 3-fluoro-2'-N-tert-butylsulfamoyl-
biphenyl-4-yl, 2'-sulfamoyl-biphenyl-4-yl, 2'-N-tert-
butylsulfamoylbiphenyl-4-yl, o-, m- or p-(pyrrolidin-1-
yl)phenyl, o-, m- or p-(piperidin-1-yl)phenyl,
15 furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or
3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or
3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or
3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or
3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-
20 chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-
5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-
dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl,
2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6- 2,4,6- or
3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-
25 hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-
4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-
bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-
methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-
acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-
30 methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-
dimethyl-4-chlorophenyl.

Ar' is preferably, for example, phenyl,
naphthyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl,
o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl,
35 o-, m- or p-tert-butylphenyl, o-, m- or p-
hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-
aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m-
or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-
acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or

p-ethoxyphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, 3-fluoro-2'-sulfamoyl-biphenyl-4-yl, 3-fluoro-2'-N-tert-butylsulfamoyl-biphenyl-4-yl, 2'-sulfamoyl-biphenyl-4-yl, 2'-N-tert-butylsulfamoylbiphenyl-4-yl, o-, m- or p-(pyrrolidin-1-yl)phenyl, o-, m- or p-(piperidin-1-yl)phenyl.

Het is preferably, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxaliny, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo[1,4]oxazinyl, furthermore preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiaazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

The heterocyclic radicals can also be partially or completely hydrogenated.

Het can thus also be, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl,

tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-,
 5 -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-,
 10 -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-,
 15 -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benz [1,4]oxazinyl, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)-
 20 phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-(2-oxo-methylenedioxy)phenyl or alternatively 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, in addition preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

25 Het is unsubstituted or mono-, di- or trisubstituted by A, OR⁷, NR⁷R^{7'}, NO₂, CN, Hal, NR⁷COA, NR⁷SO₂A, COOR⁷, CO-NR⁷R^{7'}, COR⁷, SO₂NR⁷R^{7'}, S(O)_nA and/or carbonyl oxygen.

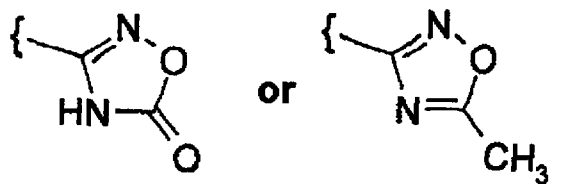
30 Het is very particularly preferably, for example, furyl, thienyl, thiazolyl, imidazolyl, [2,1,3]-benzothiadiazolyl, oxazolyl, pyridyl, indolyl, piperidinyl or pyrrolidinyl.

35 R¹ is preferably, for example, H, A, cycloalkyl-CH₂- or Ar-CH₂-, particularly preferably H, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpenyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-

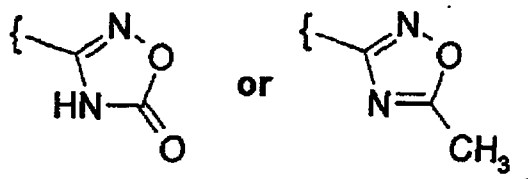
methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example, trifluoromethyl. H, methyl, ethyl, propyl, isopropyl, butyl, pentyl or hexyl is very particularly preferred.

5 R^2 is preferably, for example, H, A, cycloalkyl- CH_2 - or $Ar-CH_2$ -, very particularly preferably H, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3-
10 or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example, trifluoromethyl. H is very particularly preferred.

15 R^3 is preferably, for example, H, Ar, Het, phenyl, naphthyl or biphenyl [sic], which is substituted by $-C(=NH)-NH_2$ which can also be monosubstituted by $-COA$, $Ar-CH_2-CO$ -, $COOA$, OH or by a conventional amino protective group,
20 $-NH-C(=NH)-NH_2$, $-CO-N=C(NH_2)_2$,



R^3 is very particularly preferably, for example,
25 H, phenyl, phenyl, naphthyl or biphenyl [sic], which is monosubstituted by NH_2SO_2 -,
or phenyl, naphthyl or biphenyl [sic], which is substituted by $-C(=NH)-NH_2$

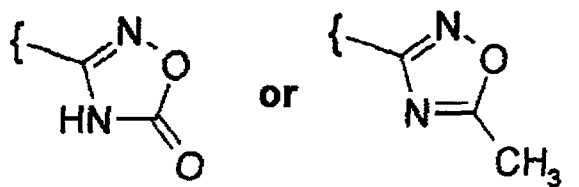


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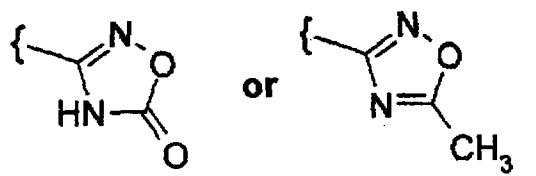
R^4 is preferably, for example, H, Ar, Het,

or phenyl, naphthyl or biphenyl [sic], which is substituted by $-C(=NH)-NH_2$ which can also be monosubstituted by $-COA$, $Ar-CH_2-CO-$, $COOA$, OH or by a conventional amino protective group,

5 $-NH-C(=NH)-NH_2$, $-CO-N=C(NH_2)_2$,



R^4 is very particularly preferably, for example,
 10 H, phenyl, phenyl, naphthyl or biphenyl [sic], which is monosubstituted by NH_2SO_2- ,
 or phenyl, naphthyl or biphenyl [sic], which is substituted by $-C(=NH)-NH_2$



15

R^6 , $R^{6'}$ are in each case independently of one another preferably, for example, H, methyl, ethyl, propyl, butyl or benzyl, very particularly preferably
 20 H, methyl, ethyl, propyl or butyl.

R^7 , $R^{7'}$ are in each case independently of one another preferably, for example, H, methyl, ethyl or propyl, very particularly preferably H.

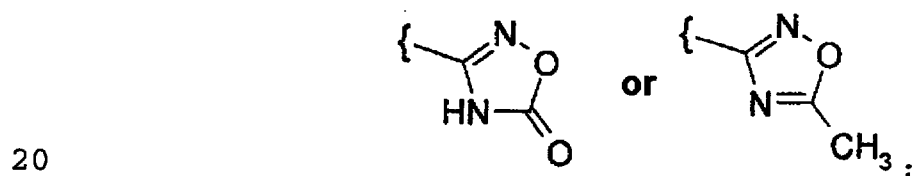
X, Y are in each case independently of one another preferably, for example, $(CH_2)_n$, where n is very particularly preferably 0 or 1.

The compounds of the formula I can have one or more chiral centres and therefore occur in various stereoisomeric forms. The formula I includes all these
 30 forms.

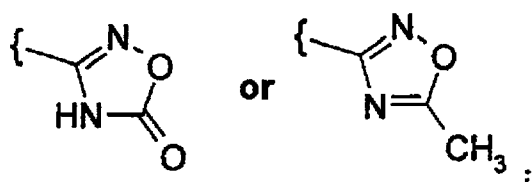
Accordingly, the invention relates in particular to those compounds of the formula I in which at least one of the radicals mentioned has one of the

preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following subformulae Ia to Ie, which correspond to the formula I and in which the radicals not designated in greater detail have the meaning indicated in the formula I, but in which

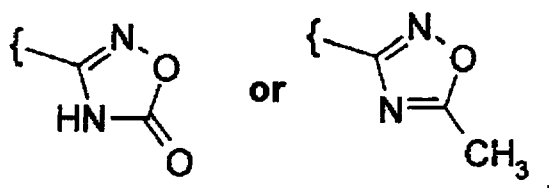
in Ia R^1, R^2 in each case independently of one another is [sic] H or A;
 10 in Ib R^3, R^4 in each case independently of one another is [sic] H, Ar or R^5 , where at least one of the two radicals is R^5 ,
 R^5 is phenyl, naphthyl or biphenyl [sic], which is substituted by $-C(=NH)-NH_2$ which can also be monosubstituted by $-COA$, $Ar-(CH_2)_n-CO-$, $COOA$, OH or by a conventional amino protective group,
 15 $-NH-C(=NH)-NH_2$, $-CO-N=C(NH_2)_2$,



in Ic R^1 is A,
 R^2 is H,
 R^3, R^4 in each case independently of one another is [sic] H, Ar or R^5 , where at least one of the two radicals is R^5 ,
 25 R^5 is phenyl, naphthyl or biphenyl [sic], which is substituted by $-C(=NH)-NH_2$ which can also be monosubstituted by $-COA$, $Ar-(CH_2)_n-CO-$, $COOA$, OH or by a conventional amino protective group,
 30 $-NH-C(=NH)-NH_2$, $-CO-N=C(NH_2)_2$,

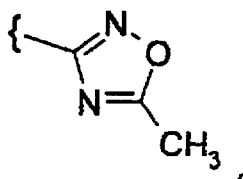


in Id R^1 is A,
 R^2 is H,
 5 R^3, R^4 in each case independently of one another is [sic] H, Ar or R^5 , where at least one of the two radicals is R^5 ,
 R^5 is phenyl, naphthyl or biphenyl [sic], which is substituted by $-C(=NH)-NH_2$ which
 10 can also be monosubstituted by $-COA$, $Ar-(CH_2)_n-CO-$, $COOA$, OH or by a conventional amino protective group, $-NH-C(=NH)-NH_2$, $-CO-N=C(NH_2)_2$,



15

A is alkyl having 1-6 C atoms,
 X, Y in each case independently of one another is [sic] $(CH_2)_n$;
 20 in Ie R^1 is A,
 R^2 is H,
 R^3, R^4 in each case independently of one another is [sic] H, Ar or R^5 , where at least one of the two radicals is R^5 ,
 25 R^5 is phenyl, naphthyl or biphenyl [sic] which is substituted by $-C(=NH)-NH_2$ or



Ar is biphenyl [sic] which is
monosubstituted by $\text{SO}_2\text{NR}^6\text{R}^{6'}$,
 $\text{R}^6, \text{R}^{6'}$ in each case independently of one
another is [sic] H or A,
5 A is alkyl having 1-6 C atoms,
X, Y in each case independently of one
another is [sic] $(\text{CH}_2)_n$.

The compounds of the formula I and also the
10 starting substances for their preparation are otherwise
prepared by methods known per se, such as are described
in the literature (e.g. in the standard works such as
Houben-Weyl, Methoden der organischen Chemie [Methods
of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart),
15 namely under reaction conditions which are known and
suitable for the reactions mentioned. In this case, use
can also be made of variants which are known per se,
but not mentioned here in greater detail.

The starting substances can, if desired, also
20 be formed in situ, such that they are not isolated from
the reaction mixture, but immediately reacted further
to give the compounds of the formula I.

Compounds of the formula I can preferably be
obtained by liberating compounds of the formula I from
25 one of their functional derivatives by treating with a
solvolysing or hydrogenolysing agent.

Preferred starting substances for solvolysis or
hydrogenolysis are those which otherwise correspond to
the formula I, but instead of one or more free amino
30 and/or hydroxyl groups contain corresponding protected
amino and/or hydroxyl groups, preferably those which
instead of an H atom which is linked to an N atom carry
an amino protective group, in particular those which
instead of an HN group carry an $\text{R}'\text{-N}$ group, in which R'
35 is an amino protective group, and/or those which
instead of the H atom of a hydroxyl group carry a
hydroxyl protective group, e.g. those which correspond
to the formula I, but instead of a group $-\text{COOH}$ carry a

group -COOR", in which R" is a hydroxyl protective group.

Preferred starting substances are also the oxadiazole derivatives, which can be converted into the
5 corresponding amidino compounds.

The liberation of the amidino group from its oxadiazole derivative can be cleaved [sic], for example, by treating with hydrogen in the presence of a catalyst (e.g. water-moist Raney nickel). Suitable
10 solvents are those indicated below, in particular alcohols such as methanol or ethanol, organic acids such as acetic acid or propionic acid or mixtures thereof. As a rule, the hydrogenolysis is carried out at temperatures between approximately 0 and 100° and
15 pressures between approximately 1 and 200 bar, preferably at 20-30° (room temperature) and 1-10 bar.

The oxadiazole group is introduced, for example, by reaction of the cyano compounds with hydroxylamine and reaction with phosgene, dialkyl
20 carbonate, chloroformic acid ester, N,N'-carbonyldiimidazole or acetic anhydride.

A number of - identical or different - protected amino and/or hydroxyl groups can also be present in the molecule of the starting substance. If
25 the protective groups present are different from one another, in many cases they can be removed selectively.

The expression "amino protective group" is generally known and relates to groups which are suitable for protecting (for blocking) an amino group
30 from chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at other positions in the molecule. Typical groups of this type are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl
35 groups. Since the amino protective groups are removed after the desired reaction (or reaction sequence), their nature and size is otherwise uncritical; however, those having 1-20, in particular 1-8, C atoms are preferred. The expression "acyl group" is to be

interpreted in the widest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulphonic acids and also, in particular, alkoxycarbonyl, aryloxy carbonyl and especially aralkoxycarbonyl groups. Examples of acyl groups of this type are alkanoyl such as acetyl, propionyl, butyryl; aralkanoyl such as phenylacetyl; aroyl such as benzoyl or toluyyl; aryloxyalkanoyl such as POA; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC (tert-butyloxycarbonyl), 2-iodoethoxycarbonyl; aralkyloxycarbonyl such as CBZ ("carbobenzoxo"), 4-methoxybenzyloxycarbonyl, FMOC; arylsulfonyl such as Mtr. Preferred amino protective groups are BOC and Mtr, and in addition CBZ, Fmoc, benzyl [sic] and acetyl.

The liberation of the compounds of the formula I from their functional derivatives is possible - depending on the protective group used - e.g. using strong acids, expediently using TFA or perchloric acid, but also using other strong inorganic acids such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids such as trichloroacetic acid or sulfonic acids such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but not always necessary. Suitable inert solvents are preferably organic, for example carboxylic acids such as acetic acid, ethers such as tetrahydrofuran or dioxane, amides such as DMF, halogenated hydrocarbons such as dichloromethane, in addition also alcohols such as methanol, ethanol or isopropanol, and also water. Mixtures of the abovementioned solvents are additionally suitable. TFA is preferably used in excess without addition of a further solvent, perchloric acid in the form of a mixture of acetic acid and 70% strength perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are expediently between approximately 0 and

approximately 50°, it is preferably carried out between 15 and 30° (room temperature).

5 The groups BOC, OBut and Mtr can, for example, preferably be cleaved using TFA in dichloromethane or using approximately 3 to 5N HCl in dioxane at 15-30°, the FMOC group using an approximately 5 to 50% strength solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

10 Hydrogenolytically removable protective groups (e.g. CBZ, benzyl or the release of the amidino group from its oxadiazole derivative), can be removed, for example, by treating with hydrogen in the presence of a catalyst (e.g. of a noble metal catalyst such as palladium, expediently on a support such as carbon).
15 Suitable solvents here are those indicated above, in particular, for example, alcohols such as methanol or ethanol or amides such as DMF. As a rule, the hydrogenolysis is carried out at temperatures between approximately 0 and 100° and pressures between
20 approximately 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group is readily possible, for example, on 5 to 10% Pd/C in methanol or using ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°.

25 Suitable inert solvents are, for example, hydrocarbons such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, trifluoromethylbenzene, chloroform or
30 dichloromethane; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers such as ethylene glycol monomethyl or monoethyl ether (methyl
35 glycol or ethyl glycol), ethylene glycol dimethyl ether (diglyme); ketones such as acetone or butanone; amides such as acetamide, dimethylacetamide, N-methylpyrrolidone (NMP) or dimethylformamide (DMF); nitriles such as acetonitrile; sulfoxides such as

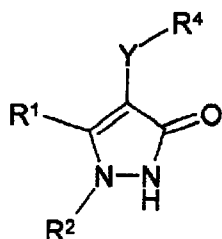
dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids such as formic acid or acetic acid; nitro compounds such as nitromethane or nitrobenzene; esters such as ethyl acetate or mixtures of the solvents mentioned.

The biphenyl-SO₂NH₂ [sic] group is preferably employed in the form of its tert-butyl derivative. The tert-butyl group is removed, for example, using TFA with or without addition of an inert solvent, preferably with addition of a small amount of anisole (1-10% by volume).

A cyano group is converted into an amidino group by reaction with, for example, hydroxylamine and subsequent reduction of the N-hydroxyamidino using hydrogen in the presence of a catalyst such as, for example, Pd/C.

For the preparation of an amidine of the formula I (e.g. Ar = phenyl monosubstituted by C(=NH)-NH₂), ammonia can also be added to a nitrile. The addition is preferably carried out in several stages in that, in a manner known per se, a) the nitrile is converted, using H₂S, into a thioamide, which is converted using an alkylating agent, e.g. CH₃I, into the corresponding S-alkylimidothio ester, which for its part reacts with NH₃ to give the amidine, b) the nitrile is converted using an alcohol, e.g. ethanol, in the presence of HCl into the corresponding imido ester and this is treated with ammonia, or c) the nitrile is reacted with lithium bis(trimethylsilyl)amide and the product is then hydrolysed.

The radical -X-R³ is introduced into the pyrazolone system, where X = CH₂, for example, by reaction of compounds of the formula II



II

in which R^1 , R^2 and R^4 in each case are those radicals according to Claim 1 which are not alkylatable and Y has the meaning indicated in Claim 1, with a compound of the formula III

5



III.

10 In the compounds of the formula III, R^3 is a radical which is not alkylatable according to Claim 1, such as, for example, a phenyl radical substituted by 5-methyl[1,2,4]oxadiazol-3-yl and in which L is Cl, Br, I or a free or reactive functionally modified OH group. L is preferably Cl, Br, I or a reactive modified OH group such as, for example, an activated ester, an
15 imidazolidine or alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulfonyloxy).

20 The pyrazolone ring system is synthesized according to known methods by reaction of a suitable β -keto ester with hydrazine or a hydrazine derivative.

It is additionally possible to convert a compound of the formula I into another compound of the formula I by converting one or more radicals R^1 , R^2 , R^3 and/or R^4 into one or more radicals R^1 , R^2 , R^3 and/or R^4 ,
25 for example, by acylating an amino group or reducing nitro groups (for example by hydrogenation on Raney nickel or Pd-carbon in an inert solvent such as methanol or ethanol) to give amino groups.

30 Esters can be hydrolysed, for example, using acetic acid or using NaOH or KOH in water, water-THF or water-dioxane at temperatures between 0 and 100°.

In addition, free amino groups can be acylated in a customary manner using an acid chloride or
35 anhydride or alkylated using an unsubstituted or substituted alkyl halide, expediently in an inert solvent such as dichloromethane or THF and/or in the presence of a base such as triethylamine or pyridine at temperatures between -60 and +30°.

A base of the formula I can be converted into the associated acid addition salt using an acid, for example by reaction of equivalent amounts of the base and of the acid in an inert solvent such as ethanol and subsequent evaporation. Acids which are particularly suitable for this reaction are those which yield physiologically acceptable salts. Thus, it is possible to use inorganic acids, e.g. sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, in addition organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and -disulfonic acids, laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formula I.

On the other hand, compounds of the formula I can be converted using bases (e.g. sodium or potassium hydroxide or carbonate) into the corresponding metal salts, in particular alkali metal or alkaline earth metal salts, or into the corresponding ammonium salts. Physiologically acceptable organic bases, such as, for example, ethanolamine, can also be used.

On account of their molecular structure, compounds of the formula I according to the invention can be chiral and can correspondingly occur in various enantiomeric forms. They can therefore be present in racemic or in optically active form.

Since the pharmaceutical activity of the racemates or of the stereoisomers of the compounds according to the invention can differ, it may be desirable to use the enantiomers. In these cases, the
5 final product or else even the intermediates can be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed as such in the synthesis.

In the case of racemic amines, diastereomers
10 are formed from the mixture by reaction with an optically active resolving agent. Suitable resolving agents are, for example, optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic
15 acid, lactic acid, suitably N-protected amino acids (e.g. N-benzoylproline or N-benzenesulfonylproline) or the various optically active camphorsulfonic acids. Chromatographic resolution of enantiomers with the aid of an optically active resolving agent (e.g.
20 dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatized methacrylate polymers immobilized on silica gel) is also advantageous. Suitable eluents for this are aqueous or alcoholic solvent mixtures such as, for
25 example, hexane/isopropanol/acetonitrile, e.g. in the ratio 82:15:3.

The invention additionally relates to the use of the compounds of the formula I and/or their physiologically acceptable salts for the production of
30 pharmaceutical preparations, in particular by a non-chemical route. In this connection, they can be brought into a suitable dosage form together with at least one solid, liquid and/or semi-liquid vehicle or excipient and, if appropriate, in combination with one or more
35 further active compounds.

The invention additionally relates to pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts.

These preparations can be used as medicaments in human or veterinary medicine. Suitable vehicles are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or
5 topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc, petroleum
10 jelly. Tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, in particular, are used for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, in
15 addition suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the lyophilizates obtained used, for example, for the production of
20 injection preparations. The preparations indicated can be sterilized and/or can contain excipients such as lubricants, preservatives, stabilizing agents and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colourants,
25 flavourings and/or several [sic] further active compounds, e.g. one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be used in the control and prevention of thromboembolic disorders such
30 as thrombosis, myocardial infarct, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty and intermittent claudication.

As a rule, the substances according to the invention are preferably administered here in doses of
35 between approximately 1 and 500 mg, in particular between 5 and 100 mg, per dose unit. The daily dose is preferably between approximately 0.02 and 10 mg/kg of body weight. The specific dose for each patient depends, however, on all sorts of factors, for example

on the efficacy of the specific compound employed, on the age, body weight, general state of health and sex, on the diet, on the time and route of administration, and on the excretion rate, pharmaceutical combination
5 and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

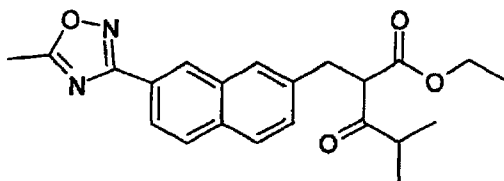
Above and below, all temperatures are indicated in °C. In the following examples "customary working up" means: if necessary, water is added, the mixture is
10 adjusted, if necessary, depending on the constitution of the final product, to a pH of between 2 and 10 and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate and evaporated, and the residue is purified by
15 chromatography on silica gel and/or by crystallization. Rf [sic] values on silica gel; eluent: ethyl acetate/methanol 9:1.

Mass spectrometry (MS):

EI (electron impact ionization) M⁺
20 FAB (fast atom bombardment) (M+H)⁺

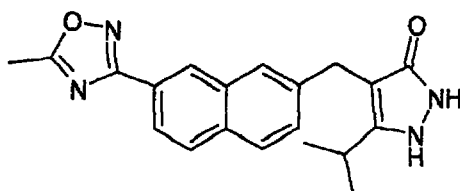
Example 1

4.3 g of caesium carbonate are added to 4.0 g of 3-(7-bromomethylnaphthalen-2-yl)-5-methyl[1,2,4]oxa-
25 diazole and 2.1 g of ethyl isobutyrylacetate in 50 ml of acetonitrile. The suspension is stirred at room temperature for 20 hours. The mixture is filtered, the solvent is removed and the residue is chromatographed on a silica gel column. Ethyl 4-methyl-2-[7-(5-
30 methyl[1,2,4]oxadiazol-3-yl)naphthalen-2-ylmethyl]-3-oxopentanoate ("AA") is obtained as a colourless oil, FAB 381



"AA".

A solution of 1.30 g of "AA" and 0.62 ml of hydrazinium hydroxide in 10 ml of acetic acid is heated to boiling for 24 hours. After customary working up, 5-isopropyl-4-[7-(5-methyl[1,2,4]oxadiazol-3-yl)naphthalen-2-ylmethyl]-1,2-dihydropyrazol-3-one ("AB"), FAB 349 is obtained



"AB".

10 A solution of 60 mg of "AB" in 5 ml of methanol is treated with 60 mg of Raney nickel and 30 mg of acetic acid and hydrogenated at room temperature for 18 hours. The catalyst is filtered off, the solvent is removed and the compound

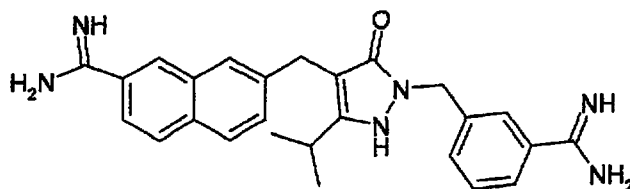
15 7-[5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-4-ylmethyl]-2-amidinonaphthalene, diacetate, FAB 309 is obtained.

Example 2

20 A solution of 100 mg of "AB" and 68 mg of 3-(3-bromomethylphenyl)-5-methyl[1,2,4]oxadiazole in 10 ml of acetonitrile is treated with 94 mg of caesium carbonate and stirred at room temperature for 20 hours. After customary working up and chromatography on silica
25 gel, 5-isopropyl-2-[3-(5-methyl[1,2,4]oxadiazol-3-yl)-benzyl]-4-[7-(5-methyl[1,2,4]oxadiazol-3-yl)naphthalen-2-ylmethyl]-1,2-dihydropyrazol-3-one, FAB 521, is obtained.

Analogously to Example 1, the following
30 compound is obtained therefrom by hydrogenation

3-[4-(7-amidinonaphth-2-ylmethyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]benzamidine, diacetate, FAB 441



The following compound is obtained analogously

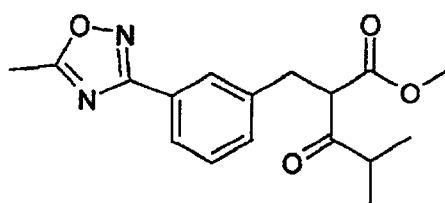
- 5 4-[4-(7-amidinonaphth-2-ylmethyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]benzamidine.

The following compound is obtained analogously by reaction of "AB" with 3-(7-bromomethylnaphthalen-2-yl)-5-methyl[1,2,4]oxadiazole and subsequent
10 hydrogenation

7-[4-(7-amidinonaphth-2-ylmethyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-amidinonaphthalene, diacetate, FAB 491.

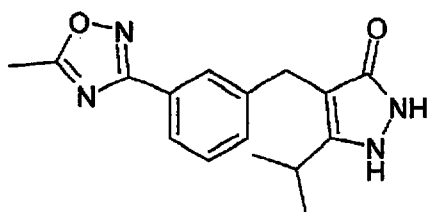
15 Example 3

Analogously to Example 1, by reaction of 3-(5-methyl[1,2,4]oxadiazol-3-yl)benzyl bromide with methyl isobutyrylacetate the compound ethyl 4-methyl-2-[3-(5-methyl[1,2,4]oxadiazol-3-yl)benzyl]-3-oxopentanoate
20 ("AC") is obtained as a colourless oil, FAB 317



"AC".

By reaction with hydrazinium hydroxide, 5-isopropyl-4-[3-(5-methyl[1,2,4]oxadiazol-3-yl)benzyl]-1,2-dihydropyrazol-3-one, FAB 299 ("AD"), is obtained
25 therefrom



"AD".

By hydrogenation, the compound 3-[5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-4-ylmethyl]benzamidinium is obtained therefrom.

Analogously, the following compounds are obtained by reaction of "AD" with 3-(3-bromomethylphenyl)-5-methyl[1,2,4]oxadiazole, 3-(7-bromomethylnaphthalen-2-yl)-5-methyl[1,2,4]oxadiazole, 2-(tert-butylaminosulfonyl)-4'-bromomethylbiphenyl and, after subsequent hydrogenation, the following compounds

3-[4-(3-amidinobenzyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]benzamidinium triacetate, FAB 391;

7-[4-(3-amidinobenzyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-amidinonaphthalene, 4'-[4-(3-amidinobenzyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-(tert-butylaminosulfonyl)biphenyl,

and the following compound is obtained therefrom by removal of the tert-butyl group

4'-[4-(3-amidinobenzyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-aminosulfonylbiphenyl.

Analogously, the following compound is obtained

7-[4-(4-amidinobenzyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-amidinonaphthalene.

Example 4

Analogously to Example 1, the following compound is obtained by reaction of 5-isopropyl-1,2-dihydropyrazol-3-one with 3-(7-bromomethylnaphthalen-2-

yl)-5-methyl[1,2,4]oxadiazole and subsequent hydrogenation

5-isopropyl-2-[7-amidinonaphthalen-2-ylmethyl]-1,2-dihydropyrazol-3-one ("AB"), diacetate, FAB 309.

5

Example 5

Analogously to Example 1, starting from 3-(7-bromomethylnaphthalen-2-yl)-5-methyl[1,2,4]oxadiazole and ethyl 3-oxobutyrate, reaction with hydrazine and subsequent reaction with 3-(7-bromomethylnaphthalen-2-yl)-5-methyl[1,2,4]oxadiazole and hydrogenation the following compound is obtained

7-[4-(7-amidinonaphth-2-ylmethyl)-5-methyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-amidinonaphthalene.

If ethyl 3-oxobutyrate is replaced by ethyl 3-oxoheptanoate, the following compound is thus obtained analogously

7-[4-(7-amidinonaphth-2-ylmethyl)-5-butyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-amidinonaphthalene.

Example 6

Analogously to Example 1, starting from 2-(tert-butylaminosulfonyl)-4'-bromomethylbiphenyl and ethyl isobutyrylacetate, reaction with hydrazine and subsequent reaction with 3-(3-bromomethylphenyl)-5-methyl[1,2,4]oxadiazole, hydrogenation and removal of the tert-butyl group, the following compound is obtained

3-[4-(2-aminosulfonylbiphenyl-4'-ylmethyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]benzamidine, trifluoroacetate, FAB 504.

35

The following compound is obtained analogously

7-[4-(2-aminosulfonylbiphenyl-4'-ylmethyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-amidinonaphthalene, trifluoroacetate, FAB 554.

5 Example 7

Analogously to Examples 1 and 2, the compounds below are obtained

10 7-(4-benzyl-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl)-2-amidinonaphthalene,

7-[2-benzyl-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-4-ylmethyl]-2-amidinonaphthalene.

15 Example 8

Analogously to Example 1, on replacement of hydrazine by phenylhydrazine the following compound is obtained

20 7-[5-isopropyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylmethyl]-2-amidinonaphthalene.

The following examples relate to pharmaceutical preparations:

Example A: Injection vials

5 A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2N hydrochloric acid, sterile-filtered, filled into injection vials, lyophilized under sterile
10 conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

15 A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

20 **Example C: Solution**

 A solution of 1 g of an active compound of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water is prepared. The
25 solution is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

30 500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

35 A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to give tablets in a customary manner such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

Analogously to Example E, tablets are pressed and are then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G: Capsules

2 kg of active compound of the formula I are filled into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

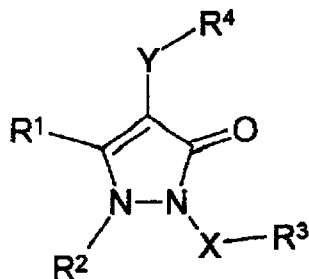
Example H: Ampoules

A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, filled into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.



Patent Claims

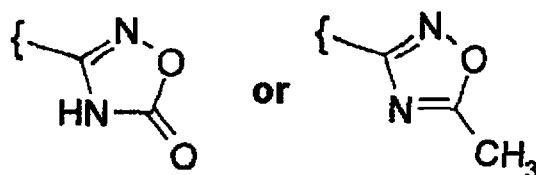
1. Compounds of the formula I



5

in which

- R^1, R^2 in each case independently of one another are H, A, cycloalkyl- $[C(R^7R^{7'})]_n$ - or Ar- $[C(R^7R^{7'})]_n$ -,
 10 R^3, R^4 in each case independently of one another are H, Ar, Het, R^5 , where at least one of the two radicals is R^5 ,
 R^5 is phenyl, naphthyl or biphenyl [sic], which is substituted by $-C(=NH)-NH_2$ which can also be monosubstituted by $-COA$, Ar- $[C(R^7R^{7'})]_n-CO$ -,
 15 $COOA$, OH or by a conventional amino protective group, $-NH-C(=NH)-NH_2$, $-CO-N=C(NH_2)_2$,



20

- and which can optionally additionally be mono- or disubstituted by A, Ar', Het, OR^6 , $NR^6R^{6'}$, NO_2 , CN, Hal, NR^6COA , NR^6COAr' , NR^6SO_2A , NR^6SO_2Ar' , $COOR^6$, $CO-NR^6R^{6'}$, COR^7 , $CO-Ar'$,
 25 $SO_2NR^6R^{6'}$, $S(O)_nAr'$ or $S(O)_nA$,
 $R^6, R^{6'}$ in each case independently of one another are H, A, $CR^7R^{7'}-Ar'$ or $CR^7R^{7'}-Het$,
 $R^7, R^{7'}$ in each case independently of one another are H or A,
 30 X, Y in each case independently of one another are $(CR^7R^{7'})_n$,



- A is alkyl having 1-20 C atoms, in which one or two CH₂ groups can be replaced by O or S atoms and/or by -CH=CH- groups and/or 1-7 H atoms can be replaced by F,
- 5 Ar is phenyl, naphthyl or biphenyl [sic], which is unsubstituted or mono-, di- or trisubstituted by A, Ar', Het, OR⁶, NR⁶R^{6'}, NO₂, CN, Hal, NR⁶COA, NR⁶COAr', NR⁶SO₂A, NR⁶SO₂Ar', COOR⁶, CO-NR⁶R^{6'}, CON⁶Ar', COR⁷, COAr', SO₂NR⁶R^{6'},
10 S(O)_nAr' or S(O)_nA,
- Ar' is phenyl or naphthyl, which is unsubstituted or mono-, di- or trisubstituted by A, OR⁷, NR⁷R^{7'}, NO₂, CN, Hal, NR⁷COA, NR⁷SO₂A, COOR⁷, CO-NR⁷R^{7'}, COR⁷, SO₂NR⁷R^{7'} or S(O)_nA,
- 15 Het is a mono- or binuclear saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which can be unsubstituted or mono-, di- or trisubstituted by A, OR⁷, NR⁷R^{7'}, NO₂, CN, Hal, NR⁷COA, NR⁷SO₂A, COOR⁷, CO-NR⁷R^{7'},
20 COR⁷, SO₂NR⁷R^{7'}, S(O)_nA and/or carbonyl oxygen,
- Hal is F, Cl, Br or I,
n is 0, 1 or 2,
and their pharmaceutically tolerable salts and solvates.
- 25 2. Compounds according to Claim 1
- a) 7-[5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-amidinonaphthalene;
- b) 7-[4-(7-amidinonaphth-2-ylmethyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]-2-amidinonaphthalene;
- 30 c) 3-[4-(3-amidinobenzyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]benzamidine;
- d) 3-[4-(7-amidinonaphth-2-ylmethyl)-5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-2-ylmethyl]benzamidine;
- 35 e) 7-[5-isopropyl-3-oxo-2,3-dihydro-1H-pyrazol-4-ylmethyl]-2-amidinonaphthalene



and their pharmaceutically tolerable salts and solvates.

3. Process for the preparation of compounds of the formula I according to Claim 1 and their salts,
5 characterized in that

a) they are liberated from one of their functional derivatives by treating with a solvolysing or hydrogenolysing agent by

10

i) liberating an amidino group from its oxadiazole derivative or oxazolidinone derivative by hydrogenolysis or solvolysis,

15

ii) replacing a conventional amino protective group by hydrogen by treating with a solvolysing or hydrogenolysing agent or liberating an amino group protected by a conventional protective group,

20

or

b) in a compound of the formula I, converting one or more radicals R^1 , R^2 , R^3 and/or R^4 into one or more
25 radicals R^1 , R^2 , R^3 and/or R^4 ,

by, for example,

i) hydrolysing an ester group to a carboxyl
30 group,

ii) reducing a nitro group,

iii) acylating an amino group,

35

iv) converting a cyano group into an amidino group

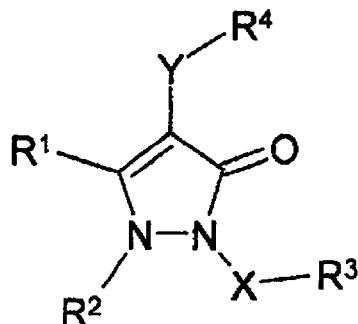
and/or



- c) converting a base or acid of the formula I into one of its salts.
4. Process for the production of pharmaceutical preparations, characterized in that a compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts is brought into a suitable dosage form together with at least one solid, liquid or semi-liquid vehicle or excipient.
5. Pharmaceutical preparation, characterized in that it contains at least one compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts.
6. Compounds of the formula I according to Claim 1 and their physiologically acceptable salts or solvates as pharmaceutical active compounds.
7. Compounds of the formula I according to Claim 1 and their physiologically acceptable salts for the control of thromboses, myocardial infarct, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty and intermittent claudication.
8. Medicaments of the formula I according to Claim 1 and their physiologically acceptable salts as inhibitors of coagulation factor Xa.
9. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts for the production of a medicament.
10. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts in the control of thromboses, myocardial infarct, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty and intermittent claudication.

Abstract

Novel compounds of the formula I



in which

R¹, R², R³, R⁴, X and Y have the meaning indicated in Patent Claim 1,

are inhibitors of coagulation factor Xa and can be employed for the prophylaxis and/or therapy of thromboembolic disorders.