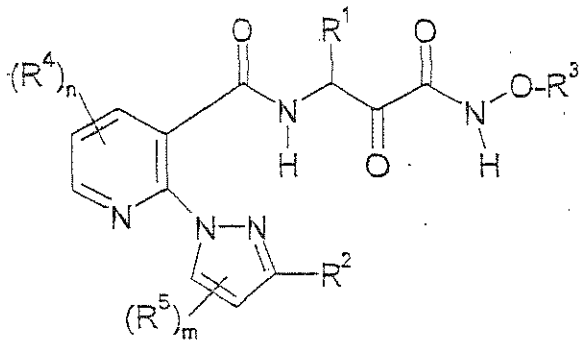
CARBOXAMIDE COMPOUNDS AND THEIR USE AS CALPAIN INHIBITORS

~~Description~~

The present invention relates to novel carboxamide compounds and their use for the manufacture of a medicament. The carboxamide compounds are inhibitors of calpain (calcium dependant cysteine proteases). The invention therefore also relates to the use of these carboxamide compounds for treating a disorder associated with an elevated calpain activity.

SUMMARY

In a first aspect, there is provided a carboxamide compound of the formula I



(I)

in which

R^1 is C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkynyl, where the last 3 radicals mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a},

C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkyl, where a CH_2 group in the cycloalkyl moiety of the last two radicals mentioned may be replaced by O, NH, or S, or two adjacent C atoms may form a double bond, where the cycloalkyl moiety may further have 1, 2, 3 or 4 radicals R^{1b},

aryl, hetaryl, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, hetaryl-C_1-C_4-alkyl or hetaryl-C_2-C_6-alkenyl, where aryl and hetaryl in the last 6 radicals mentioned may be unsubstituted or carry 1, 2, 3 or 4 identical or different radicals R^{1c}; where

R^{1a} is selected independently of one another from OH, SH, COOH, CN, OCH_2COOH, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_3-C_7-cycloalkyloxy, C_1-C_6-alkylthio, C_1-C_6-haloalkylthio, $COOR^{a1}$, $CONR^{a2}R^{a3}$, $SO_2NR^{a2}R^{a3}$,
$-NR^{a2}-SO_2-R^{a4}$, $NR^{a2}-CO-R^{a5}$, SO_2-R^{a4} and $NR^{a6}R^{a7}$,

R^{1b} is selected independently of one another from OH, SH, COOH, CN, OCH_2COOH, halogen, phenyl which optionally has 1, 2 or 3

substituents R^{1d},

C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, where the alkyl moieties in the last 3 substituents mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a},

$COOR^{b1}$, $CONR^{b2}R^{b3}$, $SO_2NR^{b2}R^{b3}$, NR^{b2}-SO_2-R^{b4}, NR^{b2}-CO-R^{b5}, SO_2-R^{b4} and $NR^{b6}R^{b7}$,

in addition two R^{1b} radicals may together form a C_1-C_4-alkylene group, or 2 R^{1b} radicals bonded to adjacent C atoms of cycloalkyl may form together with the carbon atoms to which they are bonded also a benzene ring,

R^{1c} is selected independently of one another from OH, SH, halogen, NO_2, NH_2, CN, COOH, OCH_2COOH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_1-C_6-alkylthio, where the alkyl moieties in the last 4 substituents mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a},

C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkyl, C_3-C_7-cycloalkyloxy, where the cycloalkyl moiety of the last three radicals mentioned may have 1, 2, 3 or 4 R^{1b} radicals,

aryl, hetaryl, O-aryl, O-CH_2-aryl, where the last three radicals mentioned are unsubstituted in the aryl moiety or may carry 1, 2, 3 or 4 R^{1d} radicals,

$COOR^{c1}$, $CONR^{c2}R^{c3}$, $SO_2NR^{c2}R^{c3}$, NR^{c2}-SO_2-R^{c4}, NR^{c2}-CO-R^{c5}, SO_2-R^{c4},

-$(CH_2)_p$-$NR^{c6}R^{c7}$ with p = 0, 1, 2, 3, 4, 5 or 6 and

O-$(CH_2)_q$-$NR^{c6}R^{c7}$ with q = 2, 3, 4, 5 or 6; where

R^{a1}, R^{b1} and R^{c1} are independently of one another H, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkyl which has 1, 2 or 3 substituents R^{1a}, or C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkyl, C_3-C_7-heterocycloalkyl-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, aryl, aryl-C_1-C_4-alkyl, hetaryl or hetaryl-C_1-C_4-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d},

R^{a2}, R^{b2} and R^{c2} are independently of one another H, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkyl which has 1, 2 or 3 substituents R^{1a}, or C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkyl, C_3-C_7-heterocycloalkyl-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, aryl, aryl-C_1-C_4-alkyl, hetaryl or hetaryl-C_1-C_4-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, and

R^{a3}, R^{b3} and R^{c3} are independently of one another H, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkyl which has 1, 2 or 3 substituents R^{1a}, or C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkyl, C_3-C_7-heterocycloalkyl-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, aryl, aryl-C_1-C_4-alkyl, hetaryl or hetaryl-C_1-C_4-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, or the two radicals R^{a2} and R^{a3}, or R^{b2} and R^{b3} or R^{c2} and R^{c3} form together with the N atom a 3 to 7-membered, optionally substituted nitrogen heterocycle which may optionally have 1, 2 or 3 further different or identical heteroatoms from the group of O, N, S as ring members,

R^{a4}, R^{b4} and R^{c4} are independently of one another C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkyl which has 1, 2 or 3 substituents R^{1a}, or C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkyl, C_3-C_7-heterocycloalkyl-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, aryl, aryl-C_1-C_4-alkyl, hetaryl or hetaryl-C_1-C_4-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, and

R^{a5}, R^{b5} and R^{c5} have independently of one another one of the meanings mentioned for R^{a1}, R^{b1} and R^{c1};

R^{a6}, R^{b6} and R^{c6} are independently of one another H, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkyl, C_1-C_6-alkyl which has 1, 2 or 3 substituents R^{1a}, or C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_7-

cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkyl, C_3-C_7-heterocycloalkyl-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, CO-C_1-C_6-alkyl, CO-O-C_1-C_6-alkyl, SO_2-C_1-C_6-alkyl, aryl, hetaryl, O-aryl, OCH_2-aryl, aryl-C_1-C_4-alkyl, hetaryl-C_1-C_4-alkyl, CO-aryl, CO-hetaryl, CO-(aryl-C_1-C_4-alkyl), CO-(hetaryl-C_1-C_4-alkyl), CO-O-aryl, CO-O-hetaryl, CO-O-(aryl-C_1-C_4-alkyl), CO-O-(hetaryl-C_1-C_4-alkyl), SO_2-aryl, SO_2-hetaryl, SO_2-(aryl-C_1-C_4-alkyl) or SO_2-(hetaryl-C_1-C_4-alkyl), where aryl and hetaryl in the last 18 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, and

R^{a7}, R^{b7} and R^{c7} are independently of one another H, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkyl which has 1, 2 or 3 substituents R^{1a}, or C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkyl, C_3-C_7-heterocycloalkyl-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, aryl, aryl-C_1-C_4-alkyl, hetaryl or hetaryl-C_1-C_4-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, or the two radicals R^{a6} and R^{a7}, or R^{b6} and R^{b7} or R^{c6} and R^{c7} form together with the N atom a 3 to 7-membered, optionally substituted nitrogen heterocycle which may optionally have 1, 2 or 3 further different or identical heteroatoms from the group of O, N and S as ring members,

or two radicals R^{1b} or two radicals R^{1c} bonded to adjacent C atoms form together with the C atoms to which they are bonded a 4, 5, 6 or 7-membered, optionally substituted carbocycle or an optionally substituted heterocycle which has 1, 2 or 3 different or identical heteroatoms from the group of O, N and S as ring members;

R^{1d} is selected from halogen, OH, SH, NO_2, COOH, $C(O)NH_2$, CHO, CN, NH_2, OCH_2COOH, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_1-C_6-alkylthio, C_1-C_6-haloalkylthio, CO-C_1-C_6-alkyl, CO-O-C_1-C_6-alkyl, NH-C_1-C_6-alkyl, NHCHO, NH-$C(O)C_1$-C_6-alkyl, and SO_2-C_1-C_6-alkyl;

R^2 is C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkyl, where a CH_2 group in the cycloalkyl moiety of the last two radicals mentioned may be replaced by O, NH, or S, or two adjacent C atoms may form a double bond, where the cycloalkyl moiety may additionally have 1, 2, 3 or 4 R^{2b} radicals;

aryl, O-aryl, O-CH_2-aryl, hetaryl, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, hetaryl-C_1-C_4-alkyl or hetaryl-C_2-C_6-alkenyl, where aryl and hetaryl in the last 8 radicals mentioned may be unsubstituted or carry 1, 2, 3 or 4 identical or different R^{2c} radicals; where

R^{2b} has one of the meanings indicated for R^{1b}, and
R^{2c} has one of the meanings indicated for R^{1c};

R^3 is C_1-C_4-haloalkyl or C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-C_1-C_2-alkyl, C_3-C_6-heterocycloalkyl-C_1-C_2-alkyl, C_1-C_4-alkoxy-C_1-C_2-alkyl, where alkyl, alkenyl, alkoxy, alkynyl, cycloalkyl, heterocycloalkyl in the last 7 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{xa},
aryl, aryl-C_1-C_4-alkyl, hetaryl or hetaryl-C_1-C_4-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{xd},

where R^{xa} has one of the meanings indicated for R^{1a}, and R^{xd} has one of the meanings indicated for R^{1d};

R^4 and R^5 are selected independently of one another from halogen, NH_2, CN, CF_3, CHF_2, CH_2F, O-CF_3, O-CHF_2, O-CH_2F, COOH, OCH_2COOH, C_1-C_2-alkyl, C_1-C_2-alkoxy, C_1-C_2-alkoxy-C_1-C_2-alkyl, C_1-C_2-alkylthio, CH_2NRR', where

R and R' are selected independently of one another from hydrogen and C_1-C_4-alkyl;

m is 0, 1 or 2;

n is 0, 1 or 2; and

the tautomers thereof, the hydrates thereof, the prodrugs thereof and the pharmaceutically suitable salts thereof.

In a second aspect, there is provided a carboxamide compound which is selected from the group consisting of

2-[3-(4-Fluorophenyl)-1H-pyrazol-1-yl]-N-[4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl]pyridine-3-carboxamide,

(2R)-2-[3-(4-Fluorophenyl)-1H-pyrazol-1-yl]-N-[4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl]pyridine-3-carboxamide,

(2S)-2-[3-(4-Fluorophenyl)-1H-pyrazol-1-yl]-N-[4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl]pyridine-3-carboxamide,

N-(4-(Methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-(4-(Methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-(4-(Methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

2-(4-Fluoro-3-phenyl-1H-pyrazol-1-yl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide,

(2R)-2-(4-Fluoro-3-phenyl-1H-pyrazol-1-yl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide,

(2S) 2-(4-Fluoro-3-phenyl-1H-pyrazol-1-yl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide,

N-[4-(Methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl]-2-(4-methyl-3-phenyl-1H-pyrazol-1-yl)pyridine-3-carboxamide,

(2R)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl]-2-(4-methyl-3-phenyl-1H-pyrazol-1-yl)pyridine-3-carboxamide,

(2S)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl]-2-(4-methyl-3-phenyl-1H-pyrazol-1-yl)pyridine-3-carboxamide,

N-(1-(4-Fluorophenyl)-4-(methoxyamino)-3,4-dioxo-butan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-(1-(4-Fluorophenyl)-4-(methoxyamino)-3,4-dioxo-butan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-(1-(4-Fluorophenyl)-4-(methoxyamino)-3,4-dioxo-butan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-(1-(3-Fluorophenyl)-4-(methoxyamino)-3,4-dioxobutan-2-yl)-2-(3-phenyl-1H-

pyrazol-1-yl)nicotinamide,
(2R)-N-(1-(3-Fluorophenyl)-4-(methoxyamino)-3,4-dioxobutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
(2S)-N-(1-(3-Fluorophenyl)-4-(methoxyamino)-3,4-dioxobutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
N-(4-(Ethoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
(2R)-N-(4-(Ethoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
(2S)-N-(4-(Ethoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
N-(4-(Allyloxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
(2R)-N-(4-(Allyloxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
(2S)-N-(4-(Allyloxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
N-(4-(Methoxyamino)-1-(4-methoxyphenyl)-3,4-dioxo-butan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
(2R)-N-(4-(Methoxyamino)-1-(4-methoxyphenyl)-3,4-dioxo-butan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
(2S)-N-(4-(Methoxyamino)-1-(4-methoxyphenyl)-3,4-dioxo-butan-2-yl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
2-(4-Chloro-3-phenyl-1H-pyrazol-1-yl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide,
(2R)-2-(4-Chloro-3-phenyl-1H-pyrazol-1-yl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide,
(2S)-2-(4-Chloro-3-phenyl-1H-pyrazol-1-yl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide,
N-[4-(Isopropoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,
(2R)-N-[4-(Isopropoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-[4-(Isopropoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-[3,4-Dioxo-1-phenyl-4-(propoxyamino)-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-[3,4-Dioxo-1-phenyl-4-(propoxyamino)-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-[3,4-Dioxo-1-phenyl-4-(propoxyamino)-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-{3-[4-(4-morpholinyl)phenyl]-1H-pyrazol-1-yl}nicotinamide,

(2R)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-{3-[4-(4-morpholinyl)phenyl]-1H-pyrazol-1-yl}nicotinamide,

(2S)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-{3-[4-(4-morpholinyl)phenyl]-1H-pyrazol-1-yl}nicotinamide,

N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-{3-[4-(4-morpholinylmethyl)phenyl]-1H-pyrazol-1-yl}nicotinamide,

(2R)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-{3-[4-(4-morpholinylmethyl)phenyl]-1H-pyrazol-1-yl}nicotinamide,

(2S)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-{3-[4-(4-morpholinylmethyl)phenyl]-1H-pyrazol-1-yl}nicotinamide,

2-(3-{4-[(Diethylamino)methyl]phenyl}-1H-pyrazol-1-yl)-N-[4-(methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]nicotinamide,

(2R)-2-(3-{4-[(Diethylamino)methyl]phenyl}-1H-pyrazol-1-yl)-N-[4-(methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]nicotinamide,

(2S)-2-(3-{4-[(Diethylamino)methyl]phenyl}-1H-pyrazol-1-yl)-N-[4-(methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]nicotinamide,

N-(4-{[(2-Methyl-2-propanyl)oxy]amino}-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-(4-{[(2-Methyl-2-propanyl)oxy]amino}-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-(4-{[(2-Methyl-2-propanyl)oxy]amino}-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-{4-[(Cyclopentyloxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-

pyrazol-1-yl)nicotinamide,

(2R)-N-{4-[(Cyclopentyloxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-{4-[(Cyclopentyloxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-[4-(Ethoxyamino)-1-(4-fluorophenyl)-3,4-dioxo-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-[4-(Ethoxyamino)-1-(4-fluorophenyl)-3,4-dioxo-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-[4-(Ethoxyamino)-1-(4-fluorophenyl)-3,4-dioxo-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-[4-(Ethoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-(4-fluoro-3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-[4-(Ethoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-(4-fluoro-3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-[4-(Ethoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-(4-fluoro-3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-{4-[(Cyclobutyloxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-{4-[(Cyclobutyloxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-{4-[(Cyclobutyloxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-{4-[(2,2-Dimethylpropoxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-{4-[(2,2-Dimethylpropoxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-{4-[(2,2-Dimethylpropoxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-(4-{[2-(4-Morpholinyl)ethoxy]amino}-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-(4-{[2-(4-Morpholinyl)ethoxy]amino}-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-(4-{[2-(4-Morpholinyl)ethoxy]amino}-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-{4-[(Cyclopropylmethoxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2R)-N-{4-[(Cyclopropylmethoxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

(2S)-N-{4-[(Cyclopropylmethoxy)amino]-3,4-dioxo-1-phenyl-2-butanyl}-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamide,

N-[4-(Ethoxyamino)-1-(4-methoxyphenyl)-3,4-dioxo-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamid

(2R)-N-[4-(Ethoxyamino)-1-(4-methoxyphenyl)-3,4-dioxo-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamid

(2S)-N-[4-(Ethoxyamino)-1-(4-methoxyphenyl)-3,4-dioxo-2-butanyl]-2-(3-phenyl-1H-pyrazol-1-yl)nicotinamid

2-[3-(2-Fluorophenyl)-1H-pyrazol-1-yl]-N-[4-(methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]nicotinamide,

(2R)-2-[3-(2-Fluorophenyl)-1H-pyrazol-1-yl]-N-[4-(methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]nicotinamide,

(2S)-2-[3-(2-Fluorophenyl)-1H-pyrazol-1-yl]-N-[4-(methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]nicotinamide,

N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-{3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}nicotinamide,

(2R)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-{3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}nicotinamide,

(2S)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-{3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}nicotinamide,

N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-[3-(2-pyridinyl)-1H-pyrazol-1-yl]nicotinamide,

(2R)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-[3-(2-pyridinyl)-1H-pyrazol-1-yl]nicotinamide,

(2S)-N-[4-(Methoxyamino)-3,4-dioxo-1-phenyl-2-butanyl]-2-[3-(2-pyridinyl)-1H-pyrazol-1-yl]nicotinamide,

1-benzyl-N-(4-(ethoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-

carboxamide,
(2R)-1-benzyl-N-(4-(ethoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
(2S)-1-benzyl-N-(4-(ethoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
1-benzyl-N-(4-(isopropoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
(2R)-1-benzyl-N-(4-(isopropoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
(2S)-1-benzyl-N-(4-(isopropoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
1-benzyl-N-(4-(cyclopropylmethoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
(2R)-1-benzyl-N-(4-(cyclopropylmethoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
(2S)-1-benzyl-N-(4-(cyclopropylmethoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
1-(2-fluorobenzyl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
(2R)-1-(2-fluorobenzyl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
(2-S)-1-(2-fluorobenzyl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
1-(2-chlorobenzyl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
(2R)-1-(2-chlorobenzyl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
(2S)-1-(2-chlorobenzyl)-N-(4-(methoxyamino)-3,4-dioxo-1-phenylbutan-2-yl)-5-oxopyrrolidine-2-carboxamide,
the tautomers thereof, the hydrates thereof, the prodrugs thereof and the pharmaceutically suitable salts thereof.

In a third aspect, there is provided the carboxamide compound as defined herein for use in therapy.

In a fourth aspect, there is provided a pharmaceutical composition comprising at least one carboxamide compound as defined herein and a carrier.

In a fifth aspect, there is provided the carboxamide compound as defined herein for the treatment of a disorder, an impairment or a condition which is selected from the group consisting of neurodegenerative disorders or impairments, epilepsy, pain, damage to the heart following cardiac ischemias, skeletal muscle damage, muscular dystrophies, damage resulting from proliferation of smooth muscle cells, coronary vasospasms, cerebral vasospasms, macular degeneration, cataracts of the eyes, restenosis of the blood vessels following angioplasty, damages to the kidney, chronic kidney diseases, disorder or an impairment associated with an elevated interleukin-I, TNF or Aß level, impairment associated with a protozoan infection such as malaria or toxoplasmosis,
for the treatment of HIV patents or
for chemotherapy of tumors and metastasis thereof.

In a sixth aspect, there is provided the use of an effective amount of at least one compound as defined herein in the manufacture of a medicament for the treatment of a disease, of a condition or of an impairment as defined herein.

DETAILED DESCRIPTION

Calpains are intracellular, proteolytic enzymes from the cysteine protease group and are found in many cells. The enzyme calpain is activated by elevated calcium concentration, with a distinction being made between calpain I or μ-calpain, which is activated by μ-molar concentrations of calcium ions, and calpain II or m-calpain, which is activated by m-molar concentrations of calcium ions. Currently, further calpain isoenzymes are also postulated (M.E. Saez et al.; Drug Discovery Today **2006**, *11 (19/20)*, pp. 917-923; K. Suzuki et al., Biol. Chem. Hoppe-Seyler, **1995**, *376 (9)*, pp.523-9).

Calpains play an important role in various physiological processes. These processes include the cleavage of different regulatory proteins such as protein kinase C, cytoskeletal proteins such as MAP 2 and spectrin, and muscle proteins, protein degradation in rheumatoid arthritis, proteins in the activation of platelets, neuropeptide metabolism, proteins in mitosis, and others which are listed in: M.J.Barrett et al., Life Sci. **1991**, *48*, pp.1659-69; K. Wang et al., Trends in Pharmacol.Sci. **1994**, *15*, pp. 412-419.

Elevated calpain levels have been measured in various pathophysiological processes, for example: ischemias of the heart (e.g. myocardial infarction), the kidney, the lung, the liver or the central nervous system (e.g. stroke), inflammations, muscular dystrophies, cataracts of the eyes, diabetes, HIV disorders, injuries to the central nervous system (e.g. brain trauma), Alzheimer's, Huntington's, Parkinson's diseases, multiple sclerosis etc. (see K.K. Wang, above) and infectious diseases such as malaria (IM Medana et al.,