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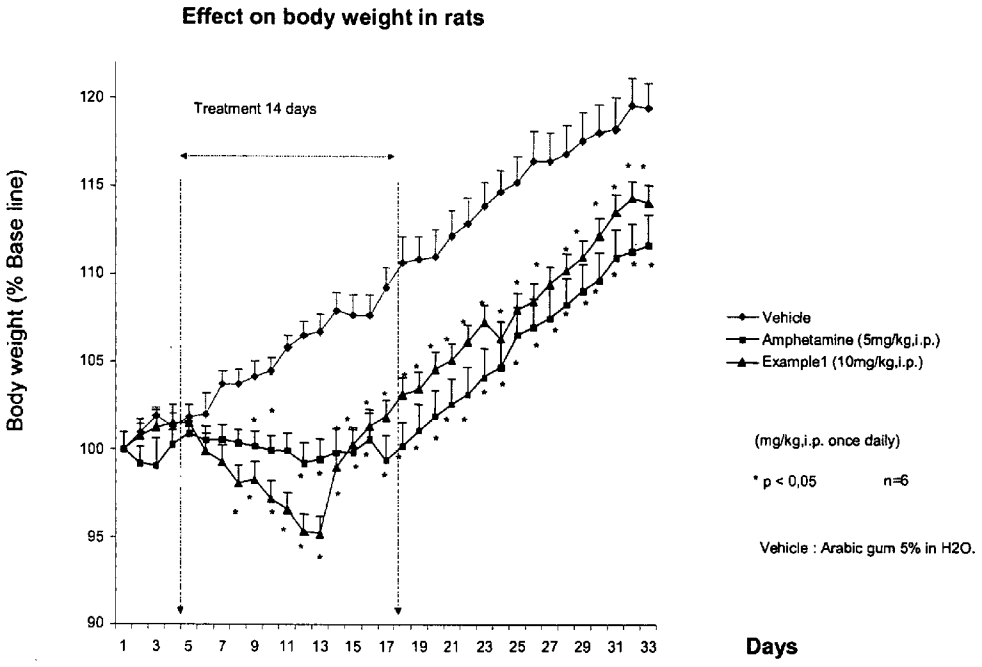
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(54) Title: PHARMACEUTICAL FORMULATIONS OF SUBSTITUTED PYRAZOLINE COMPOUNDS



(57) Abstract: The present invention relates to the use of substituted pyrazoline compounds characterized in that the pharmaceutical formulation is in the form selected from: • An oral osmotically driven system for the release of the compound • A parenteral implant • A Multipore tablet • A Transdermal application system • A parenteral depotsystem • An oral formulation using a sweet tastemasker with a natural flavour or • A chewable formulation, preferably a chewing gum.

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Pharmaceutical formulations of substituted pyrazoline compounds

The present invention relates to pharmaceutical formulations comprising substituted pyrazoline compounds.

Cannabinoids are compounds, which are derived from the cannabis sativa plant which is commonly known as marijuana. The most active chemical compound of the naturally occurring cannabinoids is tetrahydrocannabinol (THC), particularly Δ^9-THC.

These naturally occuring cannabinoids as well as their synthetic analogues promote their physiological effects via binding to specific G-coupled receptors, the so-called cannabinoid-receptors.

At present, two distinct types of receptors that bind both the naturally occurring and synthetic cannabinoids have been identified and cloned. These receptors, which are designated CB_1 and CB_2 are involved in a variety of physiological or pathophysiological processes in humans and animals, e.g. processes related to the central nervous system, immune system, cardiovascular system, endocrinous system, respiratory system, the gastrointestinal tract or to reproduction, as described for example, in Hollister, Pharm. Rev. 38, 1986, 1-20; Reny and Singha, Prog. Drug. Res., 36, 71-114, 1991; Consroe and Sandyk, in Marijuana/Cannabinoids, Neurobiology and Neurophysiology, 459, Murphy L. and Barthe A. Eds., CRC Press, 1992.

Therefore, compounds, which have a high binding affinity for these cannabinoid receptors and which are suitable for modulating these receptors are useful in the prevention and/or treatment of cannabinoid-receptor related disorders.

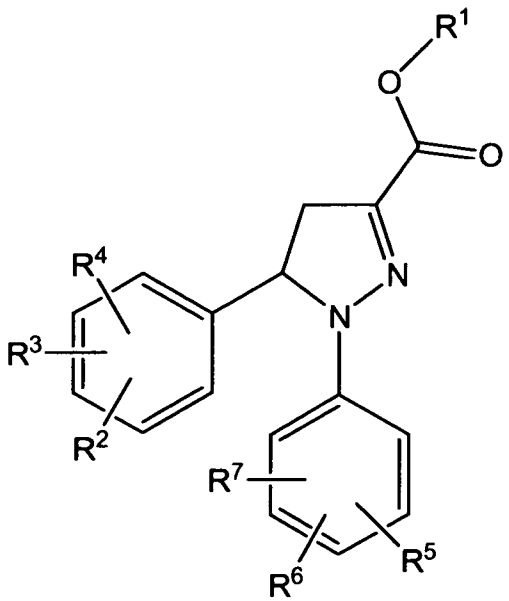
In particular, the CB_1-Receptor is involved in many different food-intake related disorders such as bulimia or obesity, including obesity associated with type II diabetes (non-insulin-dependent diabetes) and thus, compounds suitable for regulating this receptor may be used in the prophylaxis and/or treatment of these disorders.

Thus, it was an object of the present invention to provide suitable pharmaceutical formaulations for novel compounds for use as active substances in medicaments. In particular, these active substances should be suitable for the modulation of Cannabinoid receptors, more particularly for the modulation of Cannabinoid 1 (CB_1) receptors.

Said object was achieved by providing the substituted pyrazoline compounds of general formula X given below, their stereoisomers, corresponding salts and corresponding solvates thereof.

It has been found that these compounds have a high affinity for cannabinoid receptors, particularly for the CB_1-receptor, and that they act as modulators e.g. antagonists, inverse agonists or agonists on these receptors. They are therefore suitable for the prophylaxis and/or treatment of various disorders related to the central nervous system, the immune system, the cardiovascular system, the endocrinous system, the respiratory system, the gastrointestinal tract or food disorders or reproduction in humans and/or animals, preferably humans including infants, children and grown-ups.

In one of its aspects the present invention relates to a pharmaceutical formulation comprising at least one substituted pyrazoline compounds of general formula I,



I

wherein

R^1 represents hydrogen or a linear or branched, substituted or unsubstituted, saturated or unsaturated, C_{1-4}-alkyl group,

R^2, R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^8, SH, SR^8, SOR^8, SO_2R^8, NH_2, NHR^8, NR^8R^9, -(C=O)-NH_2, -(C=O)-NHR^8 or -(C=O)-NR^8R^9 whereby R^8 and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

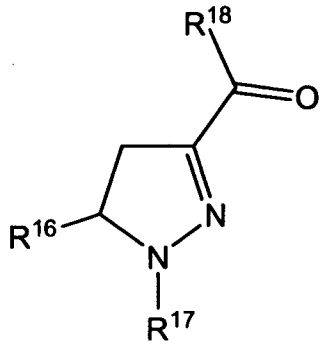
R^5 and R^6 independently of each other represent a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^{10}, SH, SR^{10}, SOR^{10}, NH_2, NHR^{10}, $NR^{10}R^{11}$, -(C=O)-NH_2, -(C=O)-NHR^{10} and -(C=O)-$NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

R^7 represents hydrogen, a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^{10}, SH, SR^{10}, SOR^{10}, NH_2, NHR^{10}, $NR^{10}R^{11}$, -(C=O)-NH_2, -(C=O)-NHR^{10} and -(C=O)-$NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof,

or

at least one substituted pyrazoline compounds of general formula X,



X

wherein

R^{16} represents an optionally at least mono-substituted phenyl group,

R^{17} represents an optionally at least mono-substituted phenyl group,

R^{18} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an –$NR^{19}R^{20}$-moiety,

R^{19} and R^{20}, identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or

bonded via a linear or branched alkylene group, an $-SO_2-R^{21}$-moiety, or an $-NR^{22}R^{23}$-moiety, with the proviso that R^{19} and R^{20} do not identically represent hydrogen,

R^{21} represents a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic group, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with a mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

R^{22} and R^{23}, identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

with the proviso:

that R^{19} and R^{20} do not both represent a hydrogen atom, and

that if one of the residues R^{19} and R^{20} represents a hydrogen atom or an alkyl group, which is optionally at least mono-substituted with an alkoxy group, an alkoxyalkoxy group, a halogen atom or a phenyl group, the other one of these residues R^4 and R^5 does not represent a pyrid-2-yl group, which is optionally mono-substituted in the 5-position, a pyrid-5-yl group, which is optionally mono-substituted in the 2-position, a pyrimid-5-yl group, which is optionally mono-substituted in the 2-position, a pyridaz-3-yl group, which is optionally mono-substituted in the 6-position, a pyrazin-5-yl group, which is optionally mono-substituted in the 2-position, a thien-2-yl group, which is

optionally mono-substituted in the 5 position, a thien-2-yl group, which is optionally at least mono-substituted in the 4-position, a benzyl group, which is optionally mono-substituted in the 4-position of the ring, a phenethyl group, which is optionally mono-substituted in the 4-position of the ring, an optionally mono-, di- or tri-substituted phenyl group, a di-substituted phenyl group, wherein the two substituents together form an $-OCH_2O-$, $-OCH_2CH_2O-$ or $-CH_2CH_2O-$ chain, which is optionally substituted with one or more halogen atoms or one or two methyl groups, an –NH-phenyl-moiety, wherein the phenyl group may be mono-substituted in the 4-position, and

that if one of the residues R^{19} and R^{20} represents an alkynyl group, the other one of these residues R^{19} and R^{20} does not represent a phenyl group, which is optionally substituted in the 4-position, and

that if one of the residues R^{19} and R^{20} represents a hydrogen atom or a linear or branched, saturated or unsaturated, unsubstituted or substituted aliphatic radical, the other one of these residues R^{19} and R^{20} does not represent an unsubstituted or substituted thiazole group or an unsubstituted or substituted [1,3,4]thiadiazole group,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof,

or comprising at least one of each of the compound according to general formula I and according to general formula X,

characterized in that the pharmaceutical formulation is in the form selected from:

- An oral osmotically driven system for the release of the compound
- A parenteral Implant
- A Multipore Tablet
- A Gel-Matrix-Tablet
- A Transdermal application system
- A parenteral depotsystem

- An oral formulation using a sweet tastemaskers with a natural flavor or
- A chewable formulation, preferably a chewing gum.

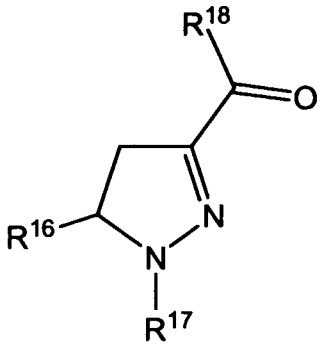
It has been found that the substituted pyrazoline compounds of general formula X, stereoisomers thereof, N-oxides thereof, corresponding salts and corresponding solvates have a high affinity to cannabinoid receptors, particularly cannabinoid 1 (CB_1)-receptors, i.e. they are selective ligands for the (CB_1)-receptor and act as modulators, e.g. antagonists, inverse agonists or agonists, on these receptors. Thus, this applies also to the inventive formulations comprising these compounds. In particular, these pyrazoline compounds show little or no development of tolerance during treatment, particularly with respect to food intake, i.e. if the treatment is interrupted for a given period of time and then continued afterwards, the inventively used pyrazoline compounds will again show the desired effect. After ending the treatment with the pyrazoline compounds, the positive influence on the body weight is found to continue.

Compounds according to formulas I or II (namely example 0) are inhibitors of high blood levels of triglicerides. Again, this clearly applies also to the inventive formulations comprising these compounds.

Furthermore, all these pyrazoline compounds seem to show relatively weak Herg channel affinity, thus a low risk of prolongation of the QT-interval is to be expected for these compounds.

In summary, the inventively used pyrazoline compounds are distinguished by a broad spectrum of beneficial effects, while at the same time showing relatively little undesired effects, i.e. effects which do not positively contribute to or even interfere with the well being of the patient. So generally speaking this effect can be seen with the pharmaceutical formulations according to the invention as well.

A very highly preferred aspect of the present invention relates to pharmaceutical formulations comprising at least one substituted pyrazoline compound of general formula X,



X

wherein

R^{16} represents an optionally at least mono-substituted phenyl group,

R^{17} represents an optionally at least mono-substituted phenyl group,

R^{18} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an –$NR^{19}R^{20}$-moiety,

R^{19} and R^{20}, identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group, an –SO_2-R^{21}-moiety, or an –$NR^{22}R^{23}$-moiety, with the proviso that R^{19} and R^{20} do not identically represent hydrogen,

R^{21} represents a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic group, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with a mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

R^{22} and R^{23}, identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof;

characterized in that the pharmaceutical formulation is in the form selected from:

- An oral osmotically driven system for the release of the compound
- A parenteral Implant
- A Multipore Tablet
- A Gel-Matrix-Tablet
- A Transdermal application system
- A parenteral depotsystem
- An oral formulation using a sweet tastemaskers with a natural flavor or
- A chewable formulation, preferably a chewing gum.

Compounds according to formula X have a high affinity for cannabinoid receptors, particularly for the CB_1-receptor, and show a marked and prolonged effect on body weight.

Particularly preferably the following provisos (disclaimers) apply (either singly or combined in any combination) for the pyrazoline compounds of general formula X given above:

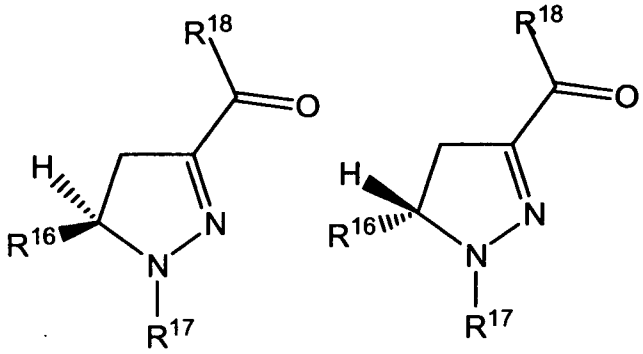
- With the proviso that R^{19} and R^{20} do not both represent a hydrogen atom.

- With the proviso that if one of the residues R^{19} and R^{20} represents a hydrogen atom or an alkyl group, which is optionally at least mono-substituted with an alkoxy group, an alkoxyalkoxy group, a halogen atom or a phenyl group, the other one of these residues R^4 and R^5 does not represent a pyrid-2-yl group, which is optionally mono-substituted in the 5-position, a pyrid-5-yl group, which is optionally mono-substituted in the 2-position, a pyrimid-5-yl group, which is optionally mono-substituted in the 2-position, a pyridaz-3-yl group, which is optionally mono-substituted in the 6-position, a pyrazin-5-yl group, which is optionally mono-substituted in the 2-position, a thien-2-yl group, which is optionally mono-substituted in the 5 position, a thien-2-yl group, which is optionally at least mono-substituted in the 4-position, a benzyl group, which is optionally mono-substituted in the 4-position of the ring, a phenethyl group, which is optionally mono-substituted in the 4-position of the ring, an optionally mono-, di- or tri-substituted phenyl group, a di-substituted phenyl group, wherein the two substituents together form an $-OCH_2O-$, $-OCH_2CH_2O-$ or $-CH_2CH_2O-$ chain, which is optionally substituted with one or more halogen atoms or one or two methyl groups, an –NH-phenyl-moiety, wherein the phenyl group may be mono-substituted in the 4-position.

- With the proviso that if one of the residues R^{19} and R^{20} represents an alkynyl group, the other one of these residues R^{19} and R^{20} does not represent a phenyl group, which is optionally substituted in the 4-position, and

- With the proviso that if one of the residues R^{19} and R^{20} represents a hydrogen atom or a linear or branched, saturated or unsaturated, unsubstituted or substituted aliphatic radical, the other one of these residues R^{19} and R^{20} does not represent an unsubstituted or substituted thiazole group or an unsubstituted or substituted [1,3,4]thiadiazole group.

In a preferred embodiment of the invention the substituted pyrazoline compound of general formula X, has a general formula according to general formula Xa or Xb



Xa Xb

In a preferred embodiment of the invention in the compound according to general formulas X, Xa or Xb R^{16} represents a phenyl group, which is optionally substituted by one or more substituents independently selected from the group consisting of a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R', SH, SR', SOR', SO_2R', NH_2, NHR', NR'R", -(C=O)-NH_2, -(C=O)-NHR' and -(C=O)-NR'R" whereby R' and R" for each substituent independently represent linear or branched C_{1-6} alkyl, preferably R^{16} represents a phenyl group, which is optionally substituted by one or more substituents selected from the group consisting of methyl, ethyl, F, Cl, Br and CF_3, more preferably R^{16} represents a phenyl group, which is mono-substituted with a chlorine atom in the 4-position.

In a preferred embodiment of the invention in the compound according to general formulas X, Xa or Xb R^{17} represents a phenyl group, which is optionally substituted by one or more substituents independently selected from the group consisting of a

linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R', SH, SR', SOR', SO_2R', NH_2, NHR', NR'R'', -(C=O)-NH_2, -(C=O)-NHR' and -(C=O)-NR'R'', whereby R' and optionally R'' for each substituent independently represent linear or branched C_{1-6} alkyl, preferably R^{17} represents a phenyl group, which is optionally substituted by one or more substituents independently selected from the group consisting of methyl, ethyl, F, Cl, Br and CF_3, more preferably R^{17} represents a phenyl group, which is di-substituted with two chlorine atoms in its 2- and 4-position.

In a preferred embodiment of the invention in the compound according to general formulas X, Xa or Xb R^{18} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an –$NR^{19}R^{20}$-moiety, preferably R^{18} represents a saturated, optionally at least mono-substituted, optionally one or more nitrogen-atoms as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an –$NR^{19}R^{20}$-moiety, more preferably R^{18} represents a pyrrolidinyl group, a piperidinyl group or a piperazinyl group, whereby each of these groups may be substituted with one or more C_{1-6}-alkyl groups, or an –$NR^{18}R^{19}$-moiety.

In a preferred embodiment of the invention in the compound according to general formulas X, Xa or Xb R^{19} and R^{20}, identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6}-aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8}-cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a methylene (-CH_2-) or ethylene (-CH_2-CH_2)-group, an –SO_2-R^{21}-moiety,

or an $-NR^{22}R^{23}$-moiety, preferably one of these residues R^{19} and R^{20} represents a hydrogen atom and the other one of these residues R^{19} and R^{20} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8}-cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, an $-SO_2-R^{21}$-moiety, or an $-NR^{22}R^{23}$-moiety, or R^{19} and R^{20}, identical or different, each represent a C_{1-6} alkyl group, more preferably one of these residues R^{19} and R^{20} represents a hydrogen atom and the other one of these residues R^{19} and R^{20} represents an optionally at least mono-substituted pyrrolidinyl group, an optionally at least mono-substituted piperidinyl group, an optionally at least mono-substituted piperazinyl group, an optionally at least mono-substituted triazolyl group, an $-SO_2-R^{21}$-moiety, or an $-NR^{22}R^{23}$-moiety, or R^{19} and R^{20}, identical or different, represent a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group or a tert.-butyl group.

In a preferred embodiment of the invention in the compound according to general formulas X, Xa or Xb R^{21} represents a linear or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6} aliphatic group, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with a mono- or polycyclic ring system and/or bonded via a methylene ($-CH_2-$) or ethylene ($-CH_2-CH_2$)-group, preferably R^{21} represents a C_{1-6}-alkyl group, a saturated, optionally at least mono-substituted cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or a phenyl group, which is optionally substituted with one or more C_{1-6} alkyl groups.

In a preferred embodiment of the invention in the compound according to general formulas X, Xa or Xb R^{22} and R^{23}, identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6} aliphatic radical, a saturated or unsaturated, optionally at least mono-

substituted, optionally at least one heteroatom as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6 membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a methylene (-CH_2-) or ethylene (-CH_2-CH_2)-group, preferably R^{22} and R^{23}, identical or different, represent a hydrogen atom or a C_{1-6} alkyl radical.

In a preferred embodiment of the invention the compound according to general formulas X, Xa or Xb is represented by a structure wherein

R^{16} represents a phenyl ring, which is mono-substituted with a halogen atom, preferably a chlorine atom, in its 4-position,

R^{17} represents a phenyl ring, which is di-substituted with two halogen atoms, preferably chlorine atoms, in its 2- and 4-position,

R^{18} represents a pyrrolidinyl group, a piperidinyl group, a piperazinyl group, a homo-piperazinyl group, a morpholinyl group, or an –$NR^{19}R^{20}$-moiety,

R^{19} represents a hydrogen atom or a linear or branched C_{1-6}-alkyl group,

R^{20} represents a linear or branched C_{1-6} alkyl group, an -SO_2-R^{21}-moiety, a pyrrolidinyl group, a piperidinyl group, a piperazinyl group, a homo-piperazinyl group, a morpholinyl group, a triazolyl group, whereby each of the heterocyclic rings may be substituted with one or more, identical or different, C_{1-6}-alkyl groups, and

R^{21} represents a phenyl group, which is optionally substituted with one or more C_{1-6} alkyl groups, which may be identical or different,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing

ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

In a preferred embodiment of the invention at least one compound according to formulas X, Xa or Xb is selected from the group consisting of:

N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,

(rac)-N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,

(R)-N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,

(S)-N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-[1,2,4]-triazole-4-yl-amide,

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-(4-methyl-piperazin-1-yl)-amide,

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid diethylamide,

[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-yl]-piperidine-1-yl-methanone,

N-[5-(4-Chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazole-3-carbonyl]-4-methylphenylsulfonamide,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

Preferred linear or branched, saturated or unsaturated aliphatic groups, which may be substituted by one or more substituents, may preferably be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, vinyl, ethinyl, propenyl, propinyl, butenyl and butinyl.

In the context of this invention, alkyl and cycloalkyl radicals are understood as meaning saturated and unsaturated (but not aromatic), branched, unbranched and cyclic hydrocarbons, which can be unsubstituted or mono- or polysubstituted. In these radicals, C_{1-2}-alkyl represents C1- or C2-alkyl, C_{1-3}-alkyl represents C1-, C2- or C3-alkyl, C_{1-4}-alkyl represents C1-, C2-, C3- or C4-alkyl, C_{1-5}-alkyl represents C1-, C2-, C3-, C4-, or C5-alkyl, C_{1-6}-alkyl represents C1-, C2-, C3-, C4-, C5- or C6-alkyl, C_{1-7}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6- or C7-alkyl, C_{1-8}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7- or C8-alkyl, C_{1-10}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9- or C10-alkyl and C_{1-18}-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9-, C10-, C11-, C12-, C13-, C14-, C15-, C16-, C17- or C18-alkyl. Furthermore, C_{3-4}-cycloalkyl represents C3- or C4-cycloalkyl, C_{3-5}-cycloalkyl represents C3-, C4- or C5-cycloalkyl, C_{3-6}-cycloalkyl represents C3-, C4-, C5- or C6-cycloalkyl, C_{3-7}-cycloalkyl represents C3-, C4-, C5-, C6- or C7-cycloalkyl, C_{3-8}-cycloalkyl represents C3-, C4-, C5-, C6-, C7- or C8-cycloalkyl, C_{4-5}-cycloalkyl represents C4- or C5-cycloalkyl, C_{4-6}-cycloalkyl represents C4-, C5- or C6-cycloalkyl, C_{4-7}-cycloalkyl represents C4-, C5-, C6- or C7-cycloalkyl, C_{5-6}-cycloalkyl represents C5- or C6-cycloalkyl and C_{5-7}-cycloalkyl represents C5-, C6- or C7-cycloalkyl. In respect of cycloalkyl, the term also includes saturated cycloalkyls in which one or 2 carbon atoms are replaced by a heteroatom, S, N or O. However, mono- or polyunsaturated, preferably monounsaturated, cycloalkyls without a heteroatom in the ring also in particular fall under the term cycloalkyl as long as the cycloalkyl is not an aromatic system. The alkyl and cycloalkyl radicals are preferably methyl, ethyl, vinyl (ethenyl), propyl, allyl (2-propenyl), 1-propinyl, methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, cyclopropyl, 2-

methylcyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl, cyclooctyl, and also adamantyl, (if substituted also CHF_2, CF_3 or CH_2OH) as well as pyrazolinone, oxopyrazolinone, [1,4]-dioxane or dioxolane.

Here, in connection with alkyl and cycloalkyl - unless expressly defined otherwise - the term substituted in the context of this invention is understood as meaning replacement of at least one hydrogen radical by F, Cl, Br, I, NH_2, SH or OH, "polysubstituted" radicals being understood as meaning that the replacement takes effect both on different and on the same atoms several times with the same or different substituents, for example three times on the same C atom, as in the case of CF_3, or at different places, as in the case of -CH(OH)-CH=CH-$CHCl_2$. Particularly preferred substituents here are F, Cl and OH. In respect of cycloalkyl, the hydrogen radical can also be replaced by OC_{1-3}-alkyl or C_{1-3}-alkyl (in each case mono- or polysubstituted or unsubstituted), in particular methyl, ethyl, n-propyl, i-propyl, CF_3, methoxy or ethoxy.

The term $(CH_2)_{3-6}$ is to be understood as meaning -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-CH_2- and -CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-, $(CH_2)_{1-4}$ is to be understood as meaning -CH_2-, -CH_2-CH_2-, -CH_2-CH_2-CH_2- and -CH_2-CH_2-CH_2-CH_2-, $(CH_2)_{4-5}$ is to be understood as meaning -CH_2-CH_2-CH_2-CH_2- and -CH_2-CH_2-CH_2-CH_2-CH_2-, etc.

An aryl radical is understood as meaning ring systems with at least one aromatic ring but without heteroatoms even in only one of the rings. Examples are phenyl, naphthyl, fluoranthenyl, fluorenyl, tetralinyl or indanyl, in particular 9H-fluorenyl or anthracenyl radicals, which can be unsubstituted or monosubstituted or polysubstituted.

A heteroaryl radical is understood as meaning heterocyclic ring systems which have at least one unsaturated ring and can contain one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur and can also be mono- or polysubstituted. Examples which may be mentioned from the group of heteroaryls are furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole,

benzothiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline.

Here, in connection with aryl and heteroaryl, substituted is understood as meaning substitution of the aryl or heteroaryl by R, OR, a halogen, preferably F and/or Cl, a CF_3, a CN, an NO_2, an NRR, a C_{1-6}-alkyl (saturated), a C_{1-6}-alkoxy, a C_{3-8}-cycloalkoxy, a C_{3-8}-cycloalkyl or a C_{2-6}-alkylene.

The term "salt" is to be understood as meaning any form of the active compound used according to the invention in which it assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. By this are also to be understood complexes of the active compound with other molecules and ions, in particular complexes which are complexed via ionic interactions. It especially includes physiologically acceptable salts, which is to be used equivalently to pharmacologically acceptable salts.

The term "physiologically acceptable salt" means in the context of this invention any salt that is physiologically tolerated (most of the time meaning not being toxic- especially not caused by the counter-ion) if used appropriately for a treatment especially if used on or applied to humans and/or mammals.

These physiologically acceptable salts can be formed with cations or bases and in the context of this invention is understood as meaning salts of at least one of the compounds used according to the invention - usually a (deprotonated) acid - as an anion with at least one, preferably inorganic, cation which is physiologically tolerated - especially if used on humans and/or mammals. The salts of the alkali metals and alkaline earth metals are particularly preferred, and also those with NH4, but in particular (mono)- or (di)sodium, (mono)- or (di)potassium, magnesium or calcium salts.

These physiologically acceptable salts can also be formed with anions or acids in the context of this invention is understood as meaning salts of at least one of the compounds used according to the invention - usually protonated, for example on the nitrogen - as the cation with at least one anion which are physiologically tolerated -

especially if used on humans and/or mammals. By this is understood in particular, in the context of this invention, the salt formed with a physiologically tolerated acid, that is to say salts of the particular active compound with inorganic or organic acids which are physiologically tolerated - especially if used on humans and/or mammals.

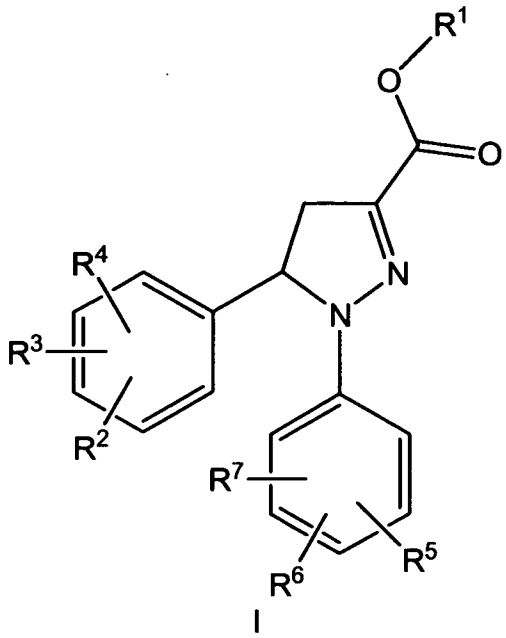
Examples of physiologically tolerated salts of particular acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid or citric acid.

The term "solvate" according to this invention is to be understood as meaning any form of the active compound according to the invention in which this compound has attached to it via non-covalent binding another molecule (most likely a polar solvent) especially including hydrates and alcoholates, e.g. methanolate.

Unless otherwise stated, the compounds of the invention are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon or ^{15}N-enriched nitrogen are within the scope of this invention.

The invention also covers the use of any prodrug of the compounds described for the invention. Examples of well known methods of producing a prodrug of a given acting compound are known to those skilled in the art and can be found e.g. in Krogsgaard-Larsen et al., Textbook of Drugdesign and Discovery, Taylor & Francis (April 2002).

Another preferred aspect of the present invention is a pharmaceutical formulation comprising at least one substituted pyrazoline compounds of general formula I



I

wherein

R^1 represents hydrogen or a linear or branched C_{1-4}-alkyl group,

R^2, R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^8, SH, SR^8, SOR^8, NH_2, NHR^8, NR^8R^9, -(C=O)-NH_2, -(C=O)-NHR^8 or -(C=O)-NR^8R^9 whereby R^8 and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 and R^6 independently of each other represent a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^{10}, SH, SR^{10}, SOR^{10}, NH_2, NHR^{10}, $NR^{10}R^{11}$, -(C=O)-NH_2, -(C=O)-NHR^{10} and -(C=O)-$NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

R^7 represents hydrogen, a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^{10}, SH, SR^{10}, SOR^{10}, NH_2, NHR^{10}, $NR^{10}R^{11}$, -(C=O)-NH_2, -(C=O)-

NHR^{10} and $-(C=O)-NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof;

characterized in that the pharmaceutical formulation is in the form selected from:

- An oral osmotically driven system for the release of the compound
- A parenteral Implant
- A Multipore Tablet
- A Gel-Matrix-Tablet
- A Transdermal application system
- A parenteral depotsystem
- An oral formulation using a sweet tastemaskers with a natural flavor or
- A chewable formulation, preferably a chewing gum.

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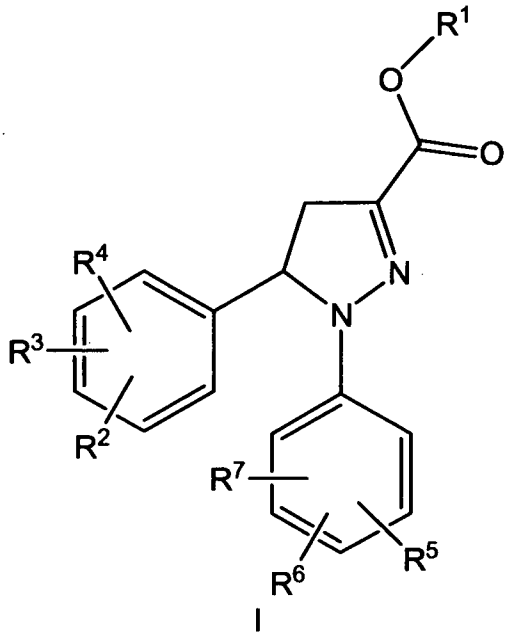
It is very preferred if to these compounds according to formula I the following proviso (disclaimer) applies:

with the proviso that

if R^1 and R^7 are H and R^5 and R^6 both represent Cl in the 3- and 4-position of the phenyl ring neither of R^2, R^3 and R^4 may represent F in the 4-position of the phenyl ring if the other two of R^2, R^3 and R^4 both represent H.

These compounds had a surprising effect on the blood levels of diet relevant substances, e.g. Triglycerides.

Another preferred aspect of the present invention is a pharmaceutical formulation comprising at least one substituted pyrazoline compounds of general formula I



I

wherein

R^1 represents hydrogen or a linear or branched C_{1-4}-alkyl group,

R^2, R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^8, SH, SR^8, SOR^8, SO_2R^8, NH_2, NHR^8, NR^8R^9, -(C=O)-NH_2, -(C=O)-NHR^8 or -(C=O)-NR^8R^9 whereby R^8 and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 and R^6 independently of each other represent a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^{10}, SH, SR^{10}, SOR^{10}, NH_2, NHR^{10}, $NR^{10}R^{11}$, -(C=O)-NH_2, -(C=O)-NHR^{10} and -(C=O)-$NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

R^7 represents hydrogen, a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2,

-(C=O)-R^{10}, SH, SR^{10}, SOR^{10}, NH_2, NHR^{10}, $NR^{10}R^{11}$, -(C=O)-NH_2, -(C=O)-NHR^{10} and -(C=O)-$NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

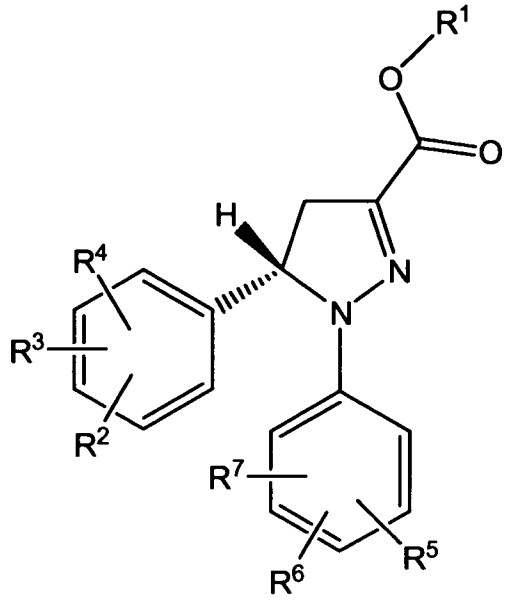
It is very preferred if to these compounds according to formula I the following proviso (disclaimer) applies:

neither of R^2, R^3 or R^4 may represent SO_2R^8 in para-position with R^8 being methyl.

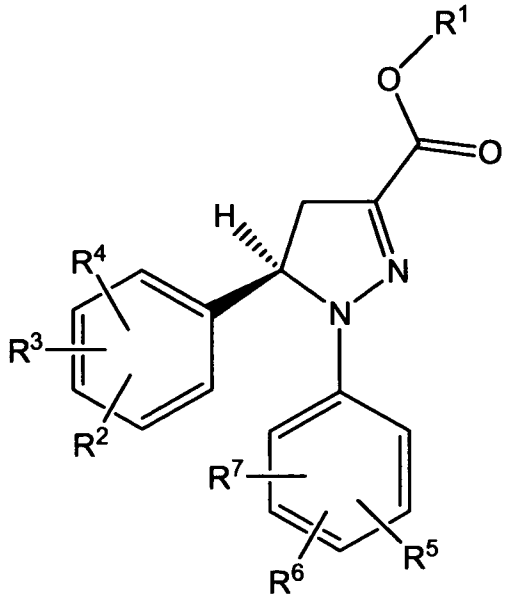
Compounds according to formula I had a surprising effect on the blood levels of diet relevant substances, e.g. Triglycerides.

Triglycerides are the chemical form in which most fat exists in food as well as in the body. Triglycerides are present in blood plasma and, in association with cholesterol, form the plasma lipids. Triglycerides in blood plasma are derived from fats consumed directly or are synthesized from e.g. carbohydrates. Superfluous food intake is converted to triglycerides and transported to fat cells to be stored. Elevated triglycerides may also be a consequence of disease states, such as untreated diabetes mellitus. Excess of triglycerides in plasma (hypertriglyceridemia) is linked to the occurrence of coronary artery disease and possibly other disorders.

In a preferred embodiment of the invention the compound according to general formula I is selected from compounds according to general formula Ia or Ib or any mixture thereof



Ia



Ib

In a preferred embodiment of the invention for a compound according to formula I at least one of R^2, R^3 or R^4 represents hydrogen, while at least one of R^2, R^3 or R^4 is different from hydrogen.

In a preferred embodiment of the invention for a compound according to formula I R^7 represents hydrogen.

In a preferred embodiment of the invention for a compound according to formula I R^2, R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6}-alkyl group, a halogen atom, or CF_3, preferably R^2, R^3 and R^4 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3.

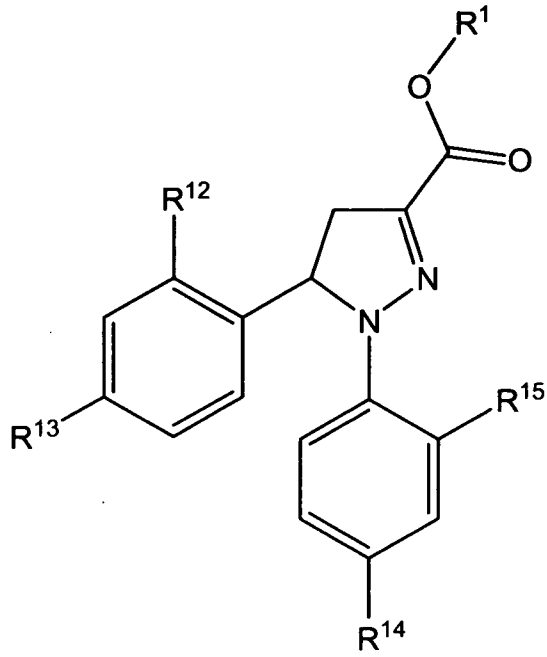
In a preferred embodiment of the invention for a compound according to formula I R^5 and R^6 independently of each other represent a linear or branched C_{1-6}-alkyl group, a halogen atom, or CF_3, preferably R^5 and R^6 independently of each other represent methyl, ethyl, F, Cl, Br and CF_3.

In a preferred embodiment of the invention for a compound according to formula I R^2 represents a chlorine atom in the 4-position of the phenyl ring, while R^3 and R^4 represent hydrogen.

In a preferred embodiment of the invention for a compound according to formula I R^5 and R^6 each represent a chlorine atoms in the 2- and 4-position of the phenyl ring, while R^7 represents hydrogen.

In a preferred embodiment of the invention for a compound according to formula I R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.

In a highly preferred further aspect of the invention the compound of general formula I is represented by a compound of general formula II



II

wherein

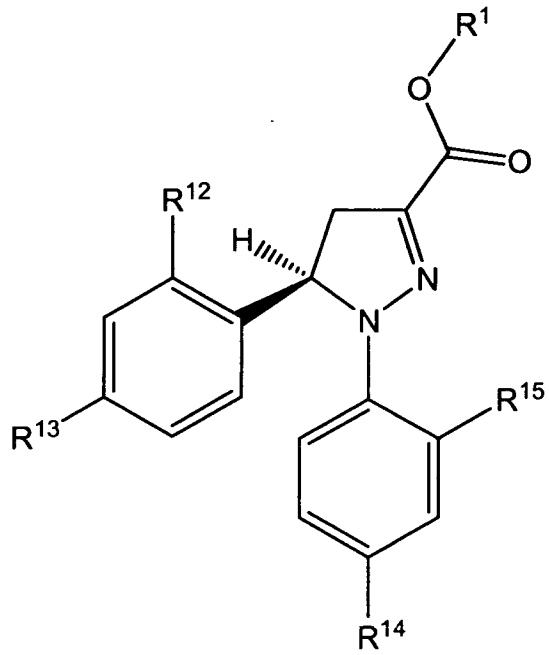
R^1 represents hydrogen or a linear or branched, substituted or unsubstituted, saturated or unsaturated, C_{1-4}-alkyl group,

R^{12} or R^{13} independently of each other represent a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, SH, NH_2, hydrogen, methyl, ethyl, F, Cl, Br and CF_3,

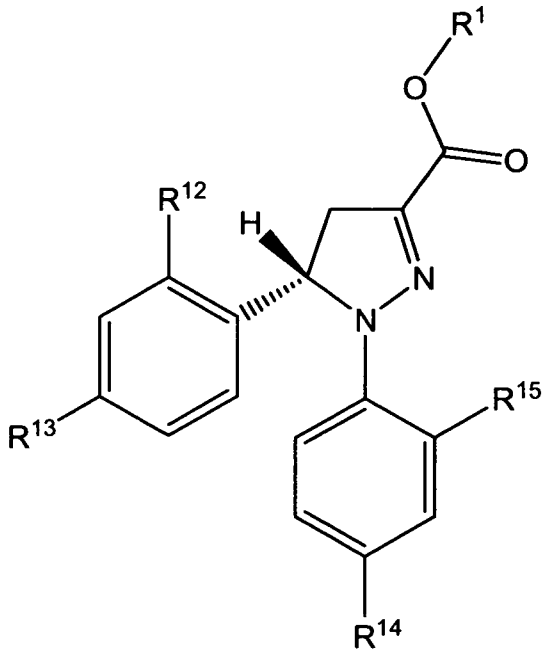
R^{14} or R^{15} independently of each other represent a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, SH, NH_2, methyl, ethyl, F, Cl, Br and CF_3,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

In a preferred embodiment of the invention the compound according to general formula II is selected from compounds according to general formula IIa or IIb or any mixture thereof



IIa



IIb

In a preferred embodiment of the invention for a compound according to formula II R^{12} and R^{13} independently of each other represent hydrogen, a linear or branched C_{1-6}-alkyl group, a halogen atom, or CF_3, preferably R^{12} and R^{13} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3.

In a preferred embodiment of the invention for a compound according to formula II R^{14}, and R^{15} independently of each other represent a linear or branched C_{1-6}-alkyl group, a halogen atom, or CF_3, preferably R^{14} and R^{15} independently of each other represent methyl, ethyl, F, Cl, Br and CF_3.

In a preferred embodiment of the invention for a compound according to formula II R^{13} represents Cl and R^{12} represents hydrogen.

In a preferred embodiment of the invention for a compound according to formula II R^{14} and R^{15} each represent Cl.

In a preferred embodiment of the invention for a compound according to formula II R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.

In another preferred embodiment the compound according to formula I or II is selected from the group consisting of:

- 5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,
- (rac)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,
- (R)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,
- (S)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

or any mixture thereof

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

A further preferred aspect of the invention is pharmaceutical formulation comprising a combination of at least one compound according to either of general formulas I, Ia, Ib, II, IIa or IIb and at least one substituted pyrazoline compound according to general formula X , Xa or Xb.

In a preferred embodiment ofabovementioned combination according to the invention at least the following compounds are used in the formulation:

- 5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,
- (rac)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,
- (R)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,
- (S)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

or any mixture thereof

and

- N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide;
- (rac)-N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide;
- (R)-N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide;

- (S)-N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide;

or any mixture thereof

each optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

By pharmaceutical formulation is especially meant any form suitable for the application to humans and/or animals, preferably humans including infants, children and adults and can be produced by standard procedures known to those skilled in the art. The composition of the medicament may vary depending on the route of administration.

The pharmaceutical formulations of the present invention may for example be administered parentally in combination with conventional injectable liquid carriers, such as water or suitable alcohols. Conventional pharmaceutical excipients for injection, such as stabilizing agents, solubilizing agents, and buffers, may be included in such injectable compositions. These medicaments may for example be injected intramuscularly, intraperitoneally, or intravenously.

Solid oral compositions (which are preferred as are liquid ones) may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art. The tablets may for example be prepared by wet or dry granulation and optionally coated according to the methods well known in normal pharmaceutical practice., in particular with an enteric coating.

The mentioned formulations will be prepared using standard methods such as those described or referred to in the Spanish and US Pharmacopeias and similar reference texts.

Pharmaceutical formulation according to the present invention may also be formulated into orally administrable compositions containing one or more physiologically compatible carriers or excipients, in solid or liquid form. These compositions may contain conventional ingredients such as binding agents, fillers, lubricants, and acceptable wetting agents. The formulations may take any convenient form, such as tablets, pellets, capsules, lozenges, aqueous or oily solutions, suspensions, emulsions, or dry powdered forms suitable for reconstitution with water or other suitable liquid medium before use, for immediate or retarded release.

The liquid oral forms for administration may also contain certain additives such as sweeteners, flavoring, preservatives, and emulsifying agents. Non-aqueous liquid compositions for oral administration may also be formulated, containing edible oils. Such liquid compositions may be conveniently encapsulated in e.g., gelatin capsules in a unit dosage amount.

The pharmaceutical formulations of the present invention may also be administered topically or via a suppository.

The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, sex, weight or degree of illness and so forth. The daily dosage for humans in the pharmaceutical formulations according to the invention may preferably be in the range from1 to 2000, preferably 1 to 1500, more preferably 1 to 1000 milligrams of active substance to be administered during one or several intakes per day.

More specifically the pharmaceutical formulations comprise:

(a) An oral osmotically driven system for the release of the compound. Especially this refers to the OROS-SYSTEM of Alza, a system in form of a tablet with a release orifice, an osmotic nucleus comprising the compound, a semipermeable membrane and a polymeric part designed to deliver pressure. Thus, a preferred embodiment of the invention relates to a pharmaceutical formulation according to the invention, wherein the pharmaceutical formulation is an oral osmotically driven system for the release of the compound.

(b) A parenteral Implant. Especially this is any form of non bioresorbable Implant, slowly releasing the compound over a long time. An example is the DUROS SYSTEM of ALZA, described e.g. in WO 00/54745, which consists of an inert tube, a semipermeable membrane, an "osmotic engine", a lever, an release orifice, as well as a depot for storing the compound to be released (most of the time in a highly concentrated dose). Examples can be seen in US 4,612,008, US 4,765,989, US 4,783,337, US5,264,446, US4,519,801, US4,612,008, US4,783,337 and US 5,082,668. Another example is based on non bioresorbable polymers based on ethylen-vinylacetate copolymers used e.g. for contraceptives as described by De Nijs et al. (US4,957,119, US5,088,505). Thus, a preferred embodiment of the invention relates to a pharmaceutical formulation according to the invention, wherein the pharmaceutical formulation is a parenteral Implant.

(c) A Multipore Tablet. Examples are the products of Gacell, Andrx, Elan (examples include Modas, Sodas). Usable examples can be found in EP 122077 A2, EP360562 B1, EP 320 097A1 und US 499276. Thus, a preferred embodiment of the invention relates to a pharmaceutical formulation according to the invention, wherein the pharmaceutical formulation is a multipore tablet.

(d) A Gel-Matrix-Tablet. Examples are the formulations developed by Penwest Pharmaceuticals (e.g. TimeRX). Usable examples can be found in US 5,330, 761, US 5,399, 362, US 5,472, 711 und US 5,455, 046. Thus, a preferred embodiment of the invention relates to a pharmaceutical formulation according to the invention, wherein the pharmaceutical formulation is a Gel-Matrix-Tablet.

(e) Transdermal application system. This are systems, which being placed – optionally using penetration enhancers, as well as plasticizers –on the skin releases the active principle through the skin into the body. Examples include especially patches and are shown in DE 10033853, US 5,411, 740, EP 767659, AT185694E, DE 69326848T2. Additional examples include patches according to EP 0 430 019 B1, WO 98/36728 or W096/19975. Thus, a

preferred embodiment of the invention relates to a pharmaceutical formulation according to the invention, wherein the pharmaceutical formulation is a transdermal application system.

(f) A parenteral depotsystem. These are especially depotsystems on the basis of slowly degrading or biodegradable polymers. Examples include polylactid-polymers or polyglycolid-polymers or especially polylactid-/polyglycolid-copolymers (PLGA). Known examples include products by Alkermes or Medisorb or Enantone and Trenantone by Takeda.
This includes in addition the injectable gels especially such that will solidify in situ and slowly release the compound soluted in the gel. Examples include the Atrigel-Technology and other systems of Atrix (US5,278, 201, US5, 739, 176, US6, 143, 314), mixing PLGA polymera and active compounds with a pharmaceutically acceptable solvent, which will solidify upon entering the body in form of an implant, the SABER-Technology of DURECT, using a 3 to 4 component system with succrose acteat/isobutyrat (SAIB), a pharmaceutically acceptable solvent like e.g. ethanol and one or more additives as well as the active compound. Included as well is the ALZAMER-Technology of ALZA, in which stabilized particles are injected in a polymeric solution of PLGA. A further example can be found in EP729357. Thus, a preferred embodiment of the invention relates to a pharmaceutical formulation according to the invention, wherein the pharmaceutical formulation is a parenteral depotsystem.

All the pharmaceutical formulations according to the invention will be prepared in parallel to the well known examples in the market described above.

g) Another aspect are pharmaceutical formulations for oral administration using sweet tastemaskers with a natural flavor. Examples include sweeteners with vanilla taste, strawberry taste, raspberry taste, orange taste, blueberry taste, banana taste, chocolate taste, lemon taste etc. These are especially useful as the compounds have - in the majority - a bitter taste. Thus, a preferred embodiment of the invention relates to a pharmaceutical formulation

according to the invention, wherein the pharmaceutical formulation is an oral formulation using a sweet tastemaskers with a natural flavor.

h) Another aspect are pharmaceutical formulations for oral administration in the form of chewing gums. Thus, a preferred embodiment of the invention relates to a pharmaceutical formulation according to the invention, wherein the pharmaceutical formulation is a chewable formulation, preferably a chewing gum.

Another aspect of the invention is a medicament comprising a pharmaceutical formulation according to the invention comprising compounds according to general formula X, Xa or Xb, or compounds according to general formula I, Ia, Ib, II, IIa or IIb or their combination.

Another aspect of the invention is the use of pharmaceutical formulations comprising compounds according to general formula X, Xa or Xb, or compounds according to general formula I, Ia, Ib, II, IIa or IIb or their combination for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetus mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetis.

Another aspect of the invention is the use of pharmaceutical formulations comprising compounds according to general formula X, Xa or Xb, or compounds according to general formula I, Ia, Ib, II, IIa or IIb or their combination for the manufacture of a medicament for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

Another aspect of the invention is the use of pharmaceutical formulations comprising compounds according to general formula X, Xa or Xb, or or their combination with

compounds according to general formula I, Ia, Ib, II, IIa or IIb for the manufacture of a medicament for the modulation of cannabinoid-receptors, preferably cannabinoid 1 (CB_1) receptors, for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

Another aspect of the invention is the use of pharmaceutical formulations comprising compounds according to general formula X, Xa or Xb, or compounds according to general formula I, Ia, Ib, II, IIa or IIb or their combination for the manufacture of a medicament for the prophylaxis and/or treatment of one or more disorders selected from the group consisting of schizophrenia, anxiety, depression, epilepsy, neurodegenerative disorders, cerebellar disorders, spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheric neuropathy, glaucoma, migraine, Morbus Parkinson, Morbus Huntington, Morbus Alzheimer, Raynaud's disease, tremblement disorders, compulsive disorders, senile dementia, thymic disorders, tardive dyskinesia, bipolar disorders; bone disorders including osteoporosis or Paget's disease of bone; cancer, preferably for the prophylaxis and/or treatment of one or more types of cancer selected from the group consisting of brain cancer, bone cancer, lip cancer, mouth cancer, esophageal cancer, stomach cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin camcer, colon cancer, bowl cancer and prostate cancer, more preferably for the prophylaxis and/or treatment of one or more types of cancer selected from the group consisting of colcon cancer, bowel cancer and prostate cancer; medicament-induced movement disorders, dystonia, endotoxemic shock, hemorragic shock, hypotension, insomnia, immunologic disorders, sclerotic plaques, vomiting, diarrhea, asthma, memory disorders, pruritus, pain, or for potentiation of the analgesic effect of narcotic and non-narcotic analgesics, or for influencing intestinal transit.

Another aspect of the invention is the use of pharmaceutical formulations comprising compounds according to general formula X, Xa or Xb, or compounds according to general formula I, Ia, Ib, II, IIa or IIb or their combination for the manufacture of a medicament for the prophylaxis and/or treatment of alcohol abuse and/or addiction,

nicotine abuse and/or addiction, medicament abuse and/or addiction and/or drug abuse and/or addiction, preferably drug abuse and/or addiction or nicotine abuse and/or addiction.

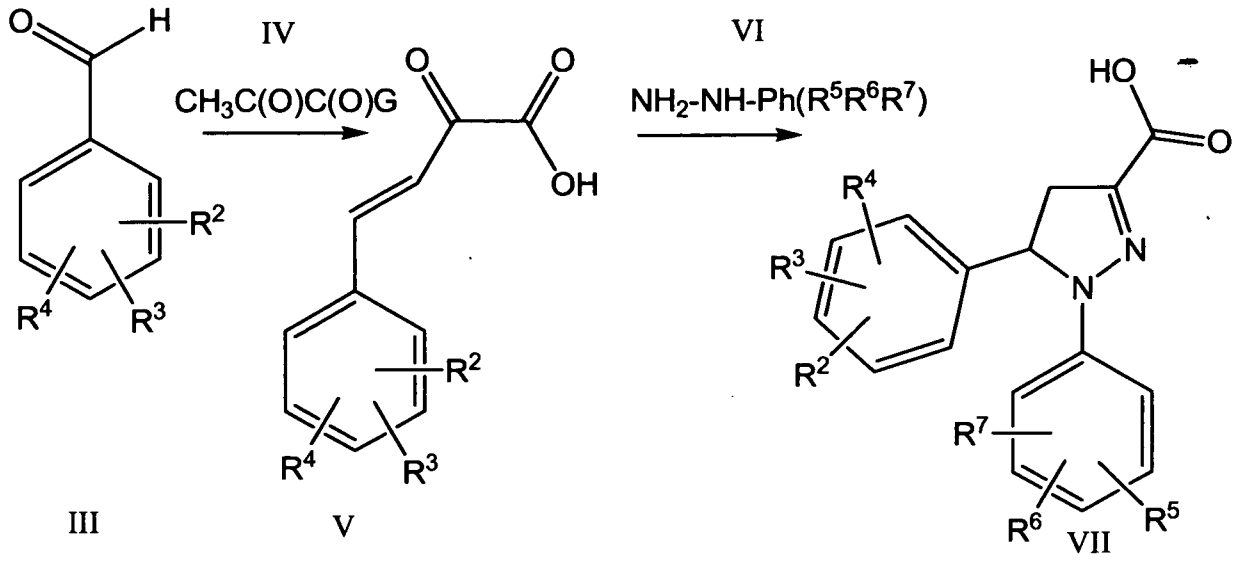
Medicaments and/or drugs, which are frequently the subject of misuse include opioids, barbiturates, cannabis, cocaine, amphetamines, phencyclidine, hallucinogens and benzodiazepines.

Another aspect of the invention is the use of pharmaceutical formulations comprising compounds according to general formula X, Xa or Xb, or compounds according to general formula I, Ia, Ib, II, IIa or IIb or their combination for the manufacture of a medicament for the prophylaxis and/or treatment of psychosis.

Another aspect of the invention is the use of pharmaceutical formulations comprising compounds according to general formula X, Xa or Xb, or compounds according to general formula I, Ia, Ib, II, IIa or IIb or their combination for the manufacture of a medicament for the prophylaxis and/or treatment of food intake disorders, preferably bulimia, anorexia, cachexia, obesity, type II diabetus mellitus (non-insuline dependent diabetes mellitus), preferably obesity.

The process to acquire compounds according to general formula I is illustrated in scheme I given below:

Scheme I:



The reaction of the benzaldehyde compound of general formula III with a pyruvate compound of general formula IV is preferably carried out in the presence of at least one base, more preferably in the presence of an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide or an alkali metal methoxide such as sodium methoxide, as described, for example, in Synthetic communications, 26(11), 2229-33, (1996). The respective description is hereby incorporated by reference and forms part of the disclosure. Preferably said reaction is carried out in a protic reaction medium such as a C_{1-4} alkyl alcohol or mixtures of these.

Reaction temperature as well as the duration of the reaction may vary over a broad range. Preferred reaction temperatures range from –10 °C to the boiling point of the reaction medium. Suitable reaction times may vary for example from several minutes to several hours.

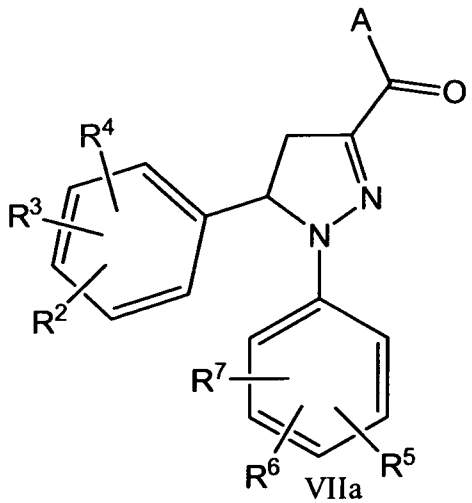
The reaction of the benzaldehyde compound of general formula III with a pyruvate compound of general formula IV is preferably carried out under acid catalysed conditions, more preferably by refluxing the mixture in dichloromethane in the presence of copper(II)trifluoromethanesulfonate as described, for example, in Synlett, (1), 147-149, 2001. The respective

description is hereby incorporated by reference and forms part of the disclosure.

The reaction of the compound of general formula (V) with an optionally substituted phenyl hydrazin of general formula (VI) is preferably carried out in a suitable reaction medium such as C_{1-4}-alcohols or ethers such as dioxane or tetrahydrofurane or mixtures of at least two of these afore mentioned compounds. Also preferably, said reaction may be carried out in the presence of an acid, whereby the acid may be organic such as acetic acid and/or inorganic such as hydrochloric acid. Furthermore, the reaction may also be carried out in the presence of a base such as piperidine, piperazine, sodium hydroxide, potassium hydroxide, sodium methoxide or sodium ethoxide, or a mixture of at least two of these bases may also be used.

Reaction temperature as well as the duration of the reaction may vary over a broad range. Suitable reaction temperatures range from room temperature, i.e. approximately 25 °C to the boiling point of the reaction medium. Suitable reaction times may vary for example from several minutes to several hours.

The carboxylic group of the compound of general formula (VII) may be activated for further reactions by the introduction of a suitable leaving group according to conventional methods well known to those skilled in the art, leading to a compound according to general formula (VIIa).



VIIa

Preferably the compounds of general formula (VII) are transferred into an acid chloride, an acid anhydride, a mixed anhydride, a C_{1-4} alkyl ester, an activated ester such as p-nitrophenylester. Other well known methods for the activation of acids include the activation with N,N-dicyclohexylcarbodiimide or benzotriazol-N-oxotris(dimethylamino) phosphonium hexafluorophosphate (BOP)).

If said activated compound of general formula (VIIa) is an acid chloride, it is preferably prepared by reaction of the corresponding acid of general formula (VII) with thionyl chloride or oxalyl chloride, whereby said chlorinating agent is also used as the solvent. Also preferably an additional solvent may be used. Suitable solvents include hydrocarbons such as benzene, toluene or xylene, halogenated hydrocarbons such as dichloromethane, chloroform or carbon tetrachloride, ethers such as diethyl ether, dioxane, tetrahydrofurane or dimethoxyethane. Mixtures of two or more solvents from one class or two or more solvents from different classes may also be used. Preferred reaction temperature range from 0° C to the boiling point of the solvent and reaction times from several minutes to several hours.

If said activated compound of general formula (VIIa) is a mixed anhydride, said anhydride may preferably be prepared, for example, by reaction of the corresponding acid of general formula (VIIa) with ethyl chloroformiate in the presence of a base such as triethylamine or pyridine, in a suitable solvent.

Following that the activated compound can be reacted with an alkyl-alcohol to arrive at compounds according to general formulas I or II with R^1 being a a linear or branched, substituted or unsubstituted, saturated or unsaturated, C_{1-4}-alkyl group.

In addition, as A represented in general formula VIIa represents a leaving group, via the reaction with an activating agent, said compound being optionally isolated and/or optionally purified, and at least one compound of general formula (VIIa) is reacted with a compound of general formula $R^{18}H$, wherein R^{18} represents an $-NR^{19}R^{20}$-moiety, wherein R^{19} and R^{20} have the meaning given above for compounds of general formula X, to yield a substituted pyrazoline compound of general formula X, wherein R^{18} represents an $-NR^{19}R^{20}$-moiety,

During the processes described above the protection of sensitive groups or of reagents may be necessary and/or desirable. The introduction of conventional protective groups as well as their removal may be performed by methods well-known to those skilled in the art.

If the substituted pyrazoline compounds of general formula I or II themselves are obtained in form of a mixture of stereoisomers, particularly enantiomers or diastereomers, said mixtures may be separated by standard procedures known to those skilled in the art, e.g. chromatographic methods or fractionalized crystallization with chiral reagents. It is also possible to obtain pure stereoisomers via stereoselective synthesis, especially using chiral bases like brucine, quinine, (-)-Cinchonidine, (+)-Cinchonine or R-(+)-1-Phenylethylamine.

In a process for the preparation of salts of substituted pyrazoline compounds of general formula I or II and stereoisomers thereof, at least one compound of general formula I or II having at least one basic group is reacted with at least one inorganic and/or organic acid, preferably in the presence of a suitable reaction medium. Suitable reaction media include, for example, any of the ones given above. Suitable inorganic acids include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, nitric acid, suitable organic acids are e.g. citric acid, maleic acid, fumaric acid, tartaric acid, or derivatives thereof, p-toluenesulfonic acid, methanesulfonic acid or camphersulfonic acid.

In a process for the preparation of salts of substituted pyrazoline compounds of general formula I or II or stereoisomers thereof, at least one compound of general formula I or II having at least one acidic group is reacted with one or more suitable bases, preferably in the presence of a suitable reaction medium. Suitable bases are e.g. hydroxides, carbonates or alkoxides, which include suitable cations, derived e.g. from alkaline metals, alkaline earth metals or organic cations, e.g. $[NH_nR_{4-n}]^+$, wherein n is 0, 1, 2, 3 or 4 and R represents a branched or unbranched C_{1-4}-alkyl-radical. Suitable reaction media are, for example, any of the ones given above.

Solvates, preferably hydrates, of the substituted pyrazoline compounds of general formula I or II, of corresponding stereoisomers, of corresponding N-oxides or of corresponding salts thereof may also be obtained by standard procedures known to those skilled in the art.

Substituted pyrazoline compounds of general formula I or II, which comprise nitrogen-atom containing saturated, unsaturated or aromatic rings may also be obtained in the form of their N-oxides by methods well known to those skilled in the art.

The purification and isolation of the substituted pyrazoline compounds of general formula I or II, of a corresponding stereoisomer, or salt, or solvate or any intermediate thereof may, if required, be carried out by conventional methods known to those skilled in the art, e.g. chromatographic methods or recrystallization.

The present invention is illustrated below with the aid of examples. These illustrations are given solely by way of example and are not intended to limit the present invention.

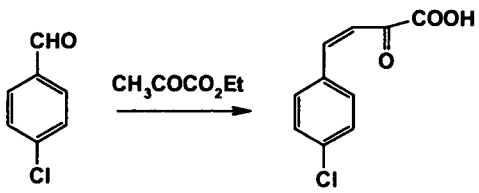
Examples:

Example 0 represent a compound according to formula I or II.

Example 0:

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid

a) 4-(4-chlorophenyl)-2-oxo-3-butenoic acid



In a three neck flask p-chlorobenzaldehyde (13,3 g, 95 mmoles) and ethyl pyruvate (10 g, 86 mmoles) were dissolved in 150 ml of absolute ethanol.The solution was ice-cooled to 0°C and an aqueous solution of NaOH (3.8 g in 45 mL water) was added dropwise keeping the temperature below or equal to 10°C, whereby a yellow-orange colored precipitate was formed. The reaction mixture was stirred for 1 hour at 0°C and an additional 1.5 hours at room temperature (approximately 25 °C). Afterwards the reaction mixture was cooled down to approximately 5°C and the insoluble sodium salt of 4-(4-chlorophenyl)-2-oxo-3-butenoic acid was isolated by filtration.

The filtrate was left in the refrigerator overnight, whereby more precipitate is formed, which was filtered off, combined with the first fraction of the salt and washed with diethyl ether. The sodium salt of 4-(4-chlorophenyl)-2-oxo-3-butenoic acid was then treated with a solution of 2N HCl, stirred for some minutes and solid 4-(4-chlorophenyl)-2-oxo-3-butenoic acid was separated via filtration and dried to give 12.7 g of the desired product (70% of theoretical yield).

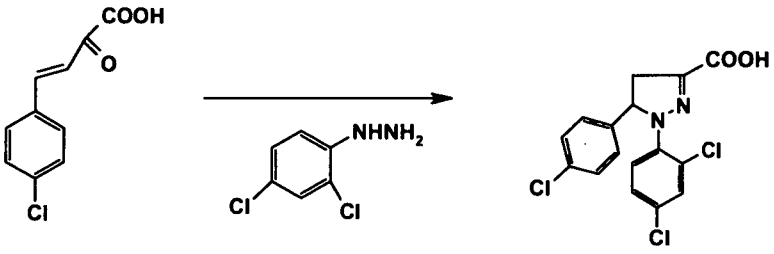
IR (KBr, cm^{-1}) : 3500-2500, 1719,3, 1686,5, 1603,4, 1587,8, 1081,9.

^1H NMR($CDCl_3$, δ) : 7,4 (d, J=8,4Hz, 2H), 7,5 (d, J=16,1Hz, 1H), 7,6 (d, J=8,4Hz, 2H), 8,1(d, J=16,1Hz, 1H).

a2) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid

In an alternative route instead of using ethylpyruvate the salt CH_3-C(O)-C(O)-O^- Na^+ (sodiumpyruvate) was used, dissolved ethanolic water.

b) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid



4-(4-chlorophenyl)-2-oxo-3-butenoic acid obtained according to step a) (12.6 g, 60 mmoles), 2,4-dichlorophenylhydrazine hydrochloride (12.8 g, 60 mmoles) and glacial acetic acid (200 mL) were mixed under a nitrogen atmosphere and heated to reflux for 4 hours, cooled down to room temperature (approximately 25 °C) and given into ice-water, whereby a sticky mass was obtained, which was extracted with methylene chloride. The combined methylene chloride fractions were washed with water, dried with sodium sulfate, filtered and evaporated to dryness to give a pale yellow solid (12.7 g, 57% of theoretical yield).

IR (KBr, cm^{-1}) : 3200-2200, 1668,4, 1458, 1251,4, 1104,8.

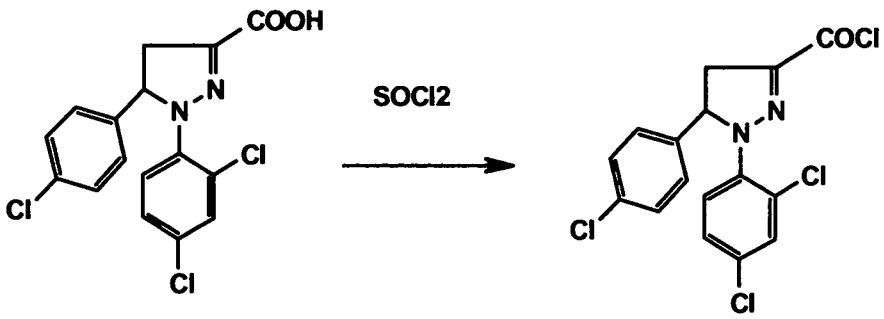
^1H NMR ($CDCl_3$, δ) : 3,3 (dd, 1H), 3,7 (dd, 1H), 5,9 (dd, 1H), 7,09-7,25 (m, 7H).

The Examples 1 to 6 represent compounds according to formula X.

Example 1:

N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxamide

(a) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid chloride

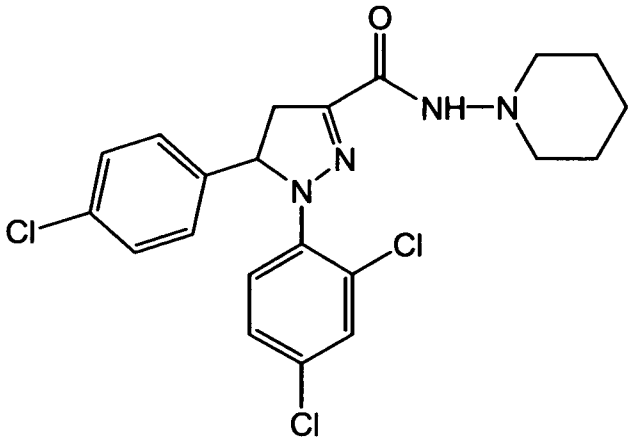


Under nitrogen atmosphere 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid (2.5 g, 6.8 mmols) obtained according to Example 0 was dissolved in 4 mL of in thionyl chloride and heated to reflux for 2.5 hours. The excess thionyl chloride is removed from the reaction mixture under reduced pressure and the resulting crude residue (2.6 g) is used without any further purification.

IR (KBr, cm^{-1}) : 1732,3, 1700, 1533,3, 1478,1, 1212,9, 826,6.

Starting from this compound compounds according to general formulas I and II wherein R^1 is a linear or branched C_{1-4}-alkyl group can be prepared reacting this compound with the appropriate alkyl alcohol.

(b) N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide



Under nitrogen atmosphere N-aminopiperidine (0.6 mL, 5.6 mmoles) and triethylamine (4 mL) were dissolved in methylene chloride (25 mL). The resulting mixture was ice-cooled down to 0°C and a solution of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid chloride obtained in step (b) in methylene chloride (15 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature (approximately 25 °C) overnight. Afterwards the reaction mixture was washed with water, followed by a saturated aqueous solution of sodium bicarbonate, then again with water, dried over sodium sulfate, filtered and evaporated to dryness in a rotavapor. The resulting crude solid was crystallized from ethanol. The crystallized solid was removed via filtration and the mother liquors were concentrated to yield a second fraction of crystallized product. The two fractions were combined to give a total amount of 1.7 g (57% of theoretical yield) of N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide having a melting point of 183-186°C.

IR (KBr, cm^{-1}) : 3222,9, 2934,9, 1647,4, 1474,7, 1268,3, 815,6.

^1H NMR ($CDCl_3$, δ) : 1,4 (m, 2H), 1,7 (m, 4H), 2,8 (m, 4H), 3,3 (dd, J=6,1 y 18,3Hz, 1H), 3,7 (dd, J=12,5 and 18,3 Hz, 1H), 5,7 (dd, J=6,1 and 12,5 Hz, 1H), 7,0-7,2 (m, 6H), 7,4 (s, 1H).

The compounds according to the following examples 2-6 have been prepared analogously to the process described in Example 1 in combination with Example 0.

Example 2:

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-[1,2,4]triazol-4-yl amide

Melting point: 134-138 °C.

IR (KBr, cm^{-1}): 3448, 1686, 1477, 1243, 1091, 821.

^1H NMR($CDCl_3$, δ): 3,1 (dd, J=6,2 and 17,9Hz, 1H), 3,7 (dd, J=12,3 and 17,9Hz, 1H), 5,9 (dd, J=6,2 and 12,3 Hz, 1H), 7,2-7,5 (m, 7H), 8,7 (s, 2H), 12,0 (bs, 1H).

Example 3:

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-(4-methyl-piperazin-1-yl)-amide hydrochloride

Melting point: 150-155°C.

IR (KBr, cm^{-1}) : 3433, 1685, 1477, 1296, 1246, 1088, 1014, 825.

^1H NMR ($CDCl_3$, δ): 2,7 (d, J=4,2Hz, 3H), 3,0-3,4 (m, 9H), 3,6 (dd, J=11,9 and 17,9 Hz, 1H), 5,8 (dd, J=5,5 and 11,9 Hz, 1H), 7,1 (d, J=8,4Hz, 2H), 7,25 (2d, J= 8,4 and 8,7 Hz, 3H), 7,4 (d, J=2,2Hz, 1H), 7,5 (d, J=8,7Hz, 1H), 9,8 (s, 1H), 11,2 (bs).

Example 4:

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid diethylamide

This compound was obtained in form of an oil.

IR (film, cm^{-1}) : 2974, 1621, 1471, 1274, 1092, 820.

^1H NMR ($CDCl_3$, δ): 1,2 (m, 6H), 3,3-3,9 (m, 6H), 5,6 (dd, J=5,8 and 11,7 Hz, 1H), 7-7,25 (m, 7H).

Example 5:

[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazol-3-yl]-piperidin-1-yl-methanone

Melting point: 105-110ºC.
IR (KBr, cm^{-1}) : 2934, 1622, 1470, 1446, 1266, 1010, 817.
^1H NMR ($CDCl_3$, δ): 1,7 (m, 6H), 3,4 (dd, J=5,7 and 17,9Hz, 1H), 3,7 (m, 3H), 3,9 (m, 2H), 5,6 (dd, J=6,1 y 11,9 Hz, 1H), 7-7,25 (m, 7H).

Example 6:

N-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carbonyl]-4-methyl-phenylsulfonamide

This compound was obtained in form of an amorph solid.
IR (KBr, cm^{-1}) : 1697, 1481, 1436, 1340, 1169, 1074, 853.
^1H NMR ($CDCl_3$, δ): 2,4 (s, 3H), 3,2 (dd, J=6,6 and 18,3Hz, 1H), 3,6 (dd, J=12,8 and 18,3Hz, 1H), 5,8 (dd, J=6,6 and 12,8Hz, 1H), 7 (d, J=8,2Hz, 2H), 7,2 (s, 1H), 7,3-7,4 (m, 6H), 8 (d, J=8,1Hz, 2H), 9 (s, 1H).

Example 7:

N-oxide of N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide

Under nitrogen gas as an inert atmosphere N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide (0,15 g, 332 mmoles) was dissolved in 7 ml of dichloromethane. The resulting solution was ice-cooled to 0 °C and m-chloroperbenzoic acid (0,204 g, 0,83 mmoles) added in several portions. After stirring for 15 minutes a control via thin layer chromatography showed that no starting material was remaining. A saturated solution of sodium bicarbonate was then slowly added, the organic phase separated, washed with water, dried over sodium sulfate

and filtered. The filtered solution was evaporated to dryness and the crude product was purified via column chromatography yielding 78 mg (50 % of theoretical yield) of the N-oxide of N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide in form of a white solid having a melting point of 115-120 °C.

IR (KBr, cm^{-1}): 3202, 1678, 1654, 1474, 1309, 1107.

^{1}H-NMR ($CDCl_3$, δ): 1.6 (m, 2H), 1.8-2.0 (m, 4H), 2.55 (m, 2H), 3.3 (dd, J = 6.3 Hz and 18.2 Hz, 1H), 3.7 (m, 3H), 5.8 (dd, J = 6.3 Hz and 12.5 Hz, 1H), 7.0-7.3 (m, 7H), 8.5 (s, 1H.)

Pharmacological Methods

I. In-vitro determination of affinity to CB1/CB2-Receptors

The in-vitro determination of the affinity of the inventive substituted pyrazoline compounds to CB_1/CB_2-Rezeptors is carried out as described in the publication of Ruth A. Ross, Heather C. Brockie et al., "Agonist-inverse agonist characterization at CB_1 and CB_2 cannabinoid receptors of L-759633, L759656 and AM630", British Journal of Pharmacology, 126, 665-672, (1999), whereby the transfected human CB_1 and CB_2 receptors of Receptor Biology, Inc. are used. The radioligand used for both receptors is [^{3}H]-CP55940. The respective parts of the description is hereby incorporated by reference and forms part of the present disclosure.

The affinity of the inventive substituted pyrazoline compounds according to formula X to CB_1/CB_2 receptors was determined as described above. Some of the values obtained are given in the following table I:

Table I:

Compound according to Example	CB_1-Receptor Radiologand:[^{3}H]-CP55940		CB_2-Receptor Radiologand:[^{3}H]-CP55940	
	% Inhibition 10^{-6} M	K_i(nM)	% Inhibition 10^{-6} M	K_i(nM)
1	93 %	< 25	33 %	> 1000
5	79 %	111	54 %	≈ 1000

As can be seen from the values given in table 1 the inventive pyrazoline compounds according to formula X are particularly suitable for regulating the CB_1-Receptor.

II. In-vivo bioassay system for determination of cannabinoid activity

Mouse tetrad model

Substances with affinity for cannabinoid receptors are known to produce a wide range of pharmacological effects. It is also known that intravenous administration of a substance with affinity for cannabinoid receptors in mice produces analgesia , hypothermia, sedation and catalepsy. Individually, none of these effects can be considered as proof that a tested substance has affinity for cannabinoid-receptors, since all of these effects are common for various classes of centrally active agents. However, substances, which show all of these effects, i.e. substances that are active in this so-called tetrad model are considered to have affinity for the cannabinoid receptors. It has further been shown that cannabinoid receptor antagonists are higly effective in blocking the effects of a cannabinoid agonist in the mouse tetrad model. The tetrad model is described, for example, in the publication of A. C. Howlett et al, International Union of Pharmacology XXVII. Classification of Cannabinoid Receptors, Pharmacol Rev 54, 161-202 , 2002 and David R. Compton et al., „In-vivo Characterization of a Specific Cannabinoid Receptor Antagonist (SR141716A) :Inhibition of Tetrahydrocannbinol- induced Responses and Apparent Agonist Activity", J. Pharmacol. Exp. Ther. 277 , 2, 586-594, 1996. The corresponding parts of the description are hereby incorporated by reference.

Material and Methods

Male NMRI mice with a weight of 20-30 g (Harlan, Barcelona, Spain) are used in all of the following experiments.

Before testing in the behavioral procedures given below, mice are acclimatized to the experimental setting. Pre-Treatment control values are determined for analgesia hot plate latency (in seconds), rectal temperature, sedation and catalepsy.

In order to determine the agonistic activty of the substance to be tested, the mice are injected intravenously with the substance to be tested or the vehicle alone. 15 minutes after injection, latency in hot plate analgesia is measured.

Rectal temperature, sedation and catalepsy are measured 20 minutes after injection.

In order to determine the antagonistic activity the identical procedure is used as for the determination of the agonistic effects, but with the difference that the substance to be evaluated for its antagonistic activity is injectected 5 minutes before the intravenous injection of 1.25 mg/kg Win-55,212 a known cannabinoid-receptor agonist.

Hot plate analgesia

The hot plate analgesia is determined according to the method described in Woolfe D. et al. „The evaluation of analgesic action of pethidine hydrochloride (Demerol)", J. Pharmacol. Exp. Ther. 80, 300-307,1944. The respective description is hereby incorporated by reference and forms part of the present disclosure.

The mice are placed on a hot plate (Harvard Analgesimeter) at 55 ± 0.5 °C until they show a painful sensation by licking their paws or jumping and the time for these sensations to occur is recorded. This reading is considered the basal value (B). The maximum time limit the mice are allowed to remain on the hot plate in absence of any painful response is 40 seconds in order to prevent skin damage. This period is called the cut-off time (PC).

Fifteen minuts after the administration of the substance to be tested, the mice are again placed on the hot plate and the afore described procedure is repeated. This period is called the post-treatment reading (PT).

The degree of analgesia is calculated from the formula :

% MPE of Analgesia = (PT- B) / (PC-B) x 100

MPE = Maximum possible effect.

Determination of sedation and ataxia

Sedation and ataxia is determined according to the method described in Desmet L. K. C. et al. „Anticonvulsive properties of Cinarizine and Flunarizine in Rats and Mice", Arzneim. -Forsch. (Frug Res) 25, 9, 1975. The respective description is hereby incorporated by reference and forms part of the present disclosure.

The chosen scoring system is

0: no ataxia;

1: doubful;

2: obvious calmness and quiet;

3 pronounced ataxia;

prior to as well as after treatment.

The percentage of sedation is determined according to the formula:

% of sedation = arithmetic mean / 3 X 100

Hypothermia:

Hypothermia is determined according to the method described in David R. Compton et al. „In-vivo Characterization of a Specific Cannabinoid Receptor Antagonist (SR141716A) Inhibition of Tetrahydrocannbinol- induced Responses and Apparent Agonist Activity", J. Pharmacol Exp Ther. 277 , 2, 586-594, 1996. The respective

description is hereby incorporated by reference and forms part of the present disclosure.

The base-line rectal temperatures are determined with a thermometer (Yello Springs Instruments Co., Panlabs) and a thermistor probe inserted to 25mm before the administration of the substance to be tested. Rectal temperature is again measured 20 minutes after the administration of the substances to be tested. The temperature difference is calculated for each animal, whereby differences of ≥-2 °C are considered to represent activity.

Catalepsy:

Catalepsy is determined according to the method described in Alpermann H. G. et al. „Pharmacological effets of Hoe 249: A new potential antidepressant", Drugs Dev. Res. 25, 267-282. 1992. The respective description is hereby incorporated by reference and forms part of the present disclosure.

The cataleptic effect of the substance to be tested is evaluated according to the duration of catalepsy, whereby the animals are placed head downwards with their kinlegs upon the top of the wooden block.

The chosen scoring system is:

Catalepsy for:

more than 60 seconds = 6; 50 -60 seconds = 5, 40–50 seconds = 4, 30–40 seconds = 3, 20–30 seconds = 2, 5–10 seconds = 1, and less than 5 seconds =0.

The percentage of catalepsy is determined according ot the following formula:

% Catalepsy = arithmetic mean / 6 X 100

The determinination of cannabinoid activity in-vivo was determined as described above. Some of the values obtained are given in the following table II:

Table II:

i.v. intravenous

Compound according to example:	dosis administered: 5 mg/kg i.v. Agonistic effect				dosis administered 5 mg/kg i.v. prior to Win 55212-2 in a dose of 1,25mg/kg i.v. Antagonistic Effect			
	A	B	C	D	A	B	C	D
1	0	0	0	0	74	100	100	100
5	0	50	0	0	50	40	20	20

A: Hot-Plate test

B: Hypothermia

C: Catalepsy

D: Sedation

As can be seen from the values given in table II the inventive pyrazoline compounds according to formula X show an antagonistic effect.

III. In vivo testing for antiobesic activity

The in-vivo testing for antiobesic activity of the inventive pyrazoline compounds according to formula X is carried out as described in the publication of G. Colombo et al., „Appetite Suppression and Weight Loss after the Cannabinoid Antagonist SR 141716"; Life Sciences, 63 (8), 113-117, (1998). The respective part of the description is hereby incorporated by reference and forms part of the present disclosure.

The in-vivo testing for antiobesic activity was carried out as described above, whereby three different groups of 10 rats each were treated as follows:

Group I:

Group was treated with vehicle, namely arabic gum (5 wt.-%) in water.

Group II:

The second group of rats was treated with the inventive compound N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide according to Example 1. Said compound was administered intraperitoneally to the rats over a period of 14 days in a daily dosis of (10 mg/kg body weight).

Group III:

The third group of rats was treated with Amphetamine, an active ingredient known to reduce appetite. Said compound was administered intraperitoneally to the rats over a period of 14 days in a daily dosis of (5 mg/kg body weight).

Example 1 (a compound according to formula X) showed a marked and prolonged effect on body weight. The result can be seen in Figure 1.

IV. In-vivo testing for regulation of triglycerides in blood plasma

Compounds according to formulas I or II (namely example 0) are inhibitors of high blood levels of triglicerides. This effect has been probed in obese mice fed with high fat diet. In the following paragraphs it is described the method and the results obtained in this study.

The study was done using six weeks old male mice B6 Lep ob/ob, obtained from Charles River (France). Mice were divided in 3 groups : I (control), II (vehicle), III (example 0).

Group I:

The animals of the group I received the standard diet (D-12450B, Research Diets, NJ, USA).

Group II:

The animals of the groups II and III were fed with a High Fat Diet (D-12492, Research Diets, NJ, USA), in both cases for 7 weeks (References 1 and 2).

Group III:

The animals of the groups III were fed with a High Fat Diet (D-12492, Research Diets, NJ, USA), in both cases for 7 weeks (References 1 and 2).

At the end of the feeding period of 7 weeks, it was started the treatment period (14 days): Group II mice received the vehicle (10 ml/kg/day, po, of the aqueous solution of acacia gum, 5% W/V). Group III was administered with 30 mg/kg/day, po, of the inventive compound 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid according to Example 0. Group I didn't received any treatment. The three groups of mice had the same diet than in the previous period.

At the end of the 14 days period of treatment, the blood levels of triglicerides of the animals were determined.

The analysis of the whole blood samples was done using test strips "Lipid panel" and the photometric Analyzer Cardio-Check Test System, from PA Instruments Polymer Technology Systems Indianapolis, IN-46268, USA (Distributed in Spain by Novalab Iberica S.A.L, Madrid, Spain).

The results obtained were the following :

Group	Diet	Treatment	Triglicerides, whole blood levels (mg/dl)	Relative levels
I	Standard	-none-	61	100%
II	High Fat	Vehicle 10 ml/kg/day po	122.4 (*)	200.6%
III	High Fat	Example 0 30 mg/kg/day po	67.5 (N.S.)	110.6%

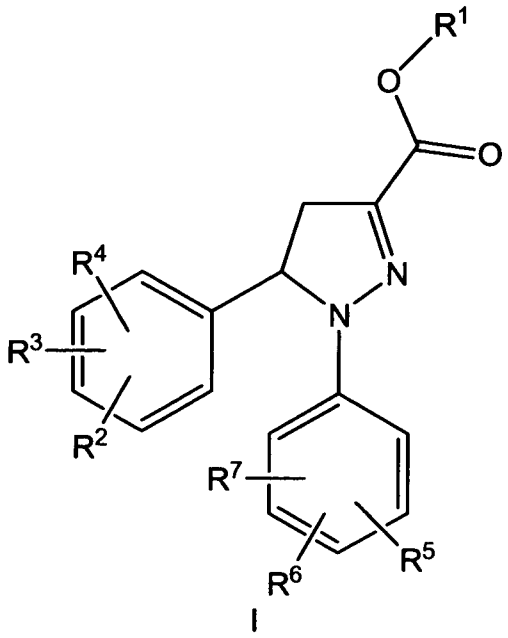
(*) : $p<0.05$, Anova followed Bonferroni t-test, compared with Group I.

NS : Not significant diference, compared with Group I.

The results showed that Group II mice receiving high fat diet had significantly higher triglicerides blood levels than the control Group I. But the administration of the compound according to Example 0 (Group III) improved the triglicerides blood levels, which were not different of the levels of the group I, which received standard diet.

Claims:

1. Pharmaceutical formulation comprising at least one substituted pyrazoline compounds of general formula I,



I

wherein

R^1 represents hydrogen or a linear or branched, substituted or unsubstituted, saturated or unsaturated, C_{1-4}-alkyl group,

R^2, R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^8, SH, SR^8, SOR^8, SO_2R^8, NH_2, NHR^8, NR^8R^9, -(C=O)-NH_2, -(C=O)-NHR^8 or -(C=O)-NR^8R^9 whereby R^8 and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 and R^6 independently of each other represent a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^{10}, SH, SR^{10}, SOR^{10}, NH_2, NHR^{10}, $NR^{10}R^{11}$, -(C=O)-NH_2, -(C=O)-NHR^{10} and -(C=O)-$NR^{10}R^{11}$, whereby R^{10} and

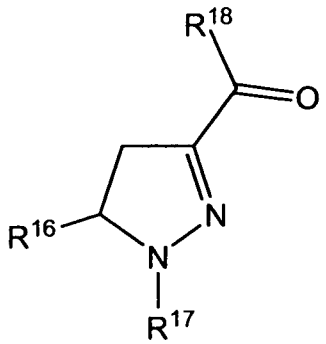
optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

R^7 represents hydrogen, a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, -(C=O)-R^{10}, SH, SR^{10}, SOR^{10}, NH_2, NHR^{10}, $NR^{10}R^{11}$, -(C=O)-NH_2, -(C=O)-NHR^{10} and -(C=O)-$NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof,

or

at least one substituted pyrazoline compounds of general formula X,



X

wherein

R^{16} represents an optionally at least mono-substituted phenyl group,

R^{17} represents an optionally at least mono-substituted phenyl group,

R^{18} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an –$NR^{19}R^{20}$-moiety,

R^{19} and R^{20}, identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group, an –SO_2-R^{21}-moiety, or an –$NR^{22}R^{23}$-moiety, with the proviso that R^{19} and R^{20} do not identically represent hydrogen,

R^{21} represents a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic group, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with a mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

R^{22} and R^{23}, identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least

mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

with the proviso:

that R^{19} and R^{20} do not both represent a hydrogen atom, and

that if one of the residues R^{19} and R^{20} represents a hydrogen atom or an alkyl group, which is optionally at least mono-substituted with an alkoxy group, an alkoxyalkoxy group, a halogen atom or a phenyl group, the other one of these residues R^4 and R^5 does not represent a pyrid-2-yl group, which is optionally mono-substituted in the 5-position, a pyrid-5-yl group, which is optionally mono-substituted in the 2-position, a pyrimid-5-yl group, which is optionally mono-substituted in the 2-position, a pyridaz-3-yl group, which is optionally mono-substituted in the 6-position, a pyrazin-5-yl group, which is optionally mono-substituted in the 2-position, a thien-2-yl group, which is optionally mono-substituted in the 5 position, a thien-2-yl group, which is optionally at least mono-substituted in the 4-position, a benzyl group, which is optionally mono-substituted in the 4-position of the ring, a phenethyl group, which is optionally mono-substituted in the 4-position of the ring, an optionally mono-, di- or tri-substituted phenyl group, a di-substituted phenyl group, wherein the two substituents together form an $-OCH_2O-$, $-OCH_2CH_2O-$ or $-CH_2CH_2O-$ chain, which is optionally substituted with one or more halogen atoms or one or two methyl groups, an –NH-phenyl-moiety, wherein the phenyl group may be mono-substituted in the 4-position, and

that if one of the residues R^{19} and R^{20} represents an alkynyl group, the other one of these residues R^{19} and R^{20} does not represent a phenyl group, which is optionally substituted in the 4-position, and

that if one of the residues R^{19} and R^{20} represents a hydrogen atom or a linear or branched, saturated or unsaturated, unsubstituted or substituted aliphatic radical, the other one of these residues R^{19} and R^{20} does not represent an unsubstituted or substituted thiazole group or an unsubstituted or substituted [1,3,4]thiadiazole group,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof,

or comprising at least one of each of the compound according to general formula I and according to general formula X,

characterized in that the pharmaceutical formulation is in the form selected from:

- An oral osmotically driven system for the release of the compound
- A parenteral Implant
- A Multipore Tablet
- A Gel-Matrix-Tablet
- A Transdermal application system
- A parenteral depotsystem
- An oral formulation using a sweet tastemaskers with a natural flavor or
- A chewable formulation, preferably a chewing gum.

2. A pharmaceutical formulation according to claim 1, wherein the substituted pyrazoline compound is a compound of general formula X.

3. A pharmaceutical formulation according to claim 2, wherein the substituted pyrazoline compound according to general formula X is represented by a structure wherein

R^{16} represents a phenyl ring, which is mono-substituted with a halogen atom, preferably a chlorine atom, in its 4-position,

R^{17} represents a phenyl ring, which is di-substituted with two halogen atoms, preferably chlorine atoms, in its 2- and 4-position,

R^{18} represents a pyrrolidinyl group, a piperidinyl group, a piperazinyl group, a homo-piperazinyl group, a morpholinyl group, or an $-NR^{19}R^{20}$-moiety,

R^{19} represents a hydrogen atom or a linear or branched C_{1-6}-alkyl group,

R^{20} represents a linear or branched C_{1-6} alkyl group, an $-SO_2-R^{21}$-moiety, a pyrrolidinyl group, a piperidinyl group, a piperazinyl group, a homo-piperazinyl group, a morpholinyl group, a triazolyl group, whereby each of the heterocyclic rings may be substituted with one or more, identical or different, C_{1-6}-alkyl groups, and

R^{21} represents a phenyl group, which is optionally substituted with one or more C_{1-6} alkyl groups, which may be identical or different,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

4. A pharmaceutical formulation according to any of claim 1, 2 or 3, wherein said substituted pyrazoline compound of general formula X is selected from the group consisting of:

- N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,
- (rac)-N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,
- (R)-N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,
- (S)-N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,

- 5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-[1,2,4]-triazole-4-yl-amide,

- 5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-(4-methyl-piperazin-1-yl)-amide,

- 5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid diethylamide,

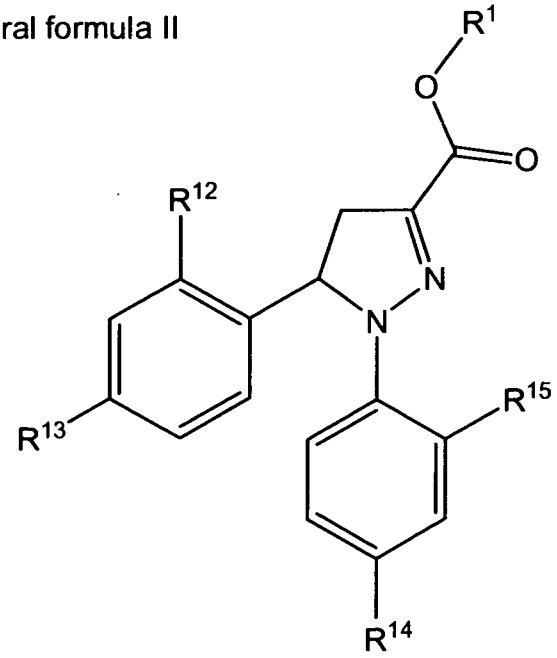
- [5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-yl]-piperidine-1-yl-methanone,

- N-[5-(4-Chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazole-3-carbonyl]-4-methylphenylsulfonamide,

optionally in form of a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

5. A pharmaceutical formulation according to claim 1, wherein the substituted pyrazoline compound is a compound of general formula I.

6. A pharmaceutical formulation according to claim 5, wherein the substituted pyrazoline compound according to general formula I is represented by a compound of general formula II



wherein

R^1 represents hydrogen or a linear or branched, substituted or unsubstituted, saturated or unsaturated, C_{1-4}-alkyl group,

R^{12} or R^{13} independently of each other represent a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, SH, NH_2, hydrogen, methyl, ethyl, F, Cl, Br and CF_3,

R^{14} or R^{15} independently of each other represent a linear or branched C_{1-6}-alkyl group, a linear or branched C_{1-6}-alkoxy group, a halogen atom, CH_2F, CHF_2, CF_3, CN, OH, NO_2, SH, NH_2, methyl, ethyl, F, Cl, Br and CF_3,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

7. A pharmaceutical formulation according to claim 5 or 6, wherein said substituted pyrazoline compound of general formula I or II is selected from the group consisting of:

- 5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

- (rac)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

- (R)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

- (S)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

or any mixture thereof

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

8. A pharmaceutical formulation according to claim 1, characterized in that the pharmaceutical formulation is an oral osmotically driven system for the release of the compound.

9. A pharmaceutical formulation according to claim 1, characterized in that the pharmaceutical formulation is a parenteral Implant.

10. A pharmaceutical formulation according to claim 1, characterized in that the pharmaceutical formulation is a multipore tablet.

11. A pharmaceutical formulation according to claim 1, characterized in that the pharmaceutical formulation is a Gel-Matrix-Tablet.

12. A pharmaceutical formulation according to claim 1, characterized in that the pharmaceutical formulation is an oral osmotically driven system for the release of the compound.

13. A pharmaceutical formulation according to claim 1, characterized in that the pharmaceutical formulation is a transdermal application system.

14. A pharmaceutical formulation according to claim 1, characterized in that the pharmaceutical formulation is a parenteral depotsystem.

15. A pharmaceutical formulation according to claim 1, characterized in that the pharmaceutical formulation is an oral formulation using a sweet tastemaskers with a natural flavor.

16. A pharmaceutical formulation according to claim 1, characterized in that the pharmaceutical formulation is a chewable formulation, preferably a chewing gum.

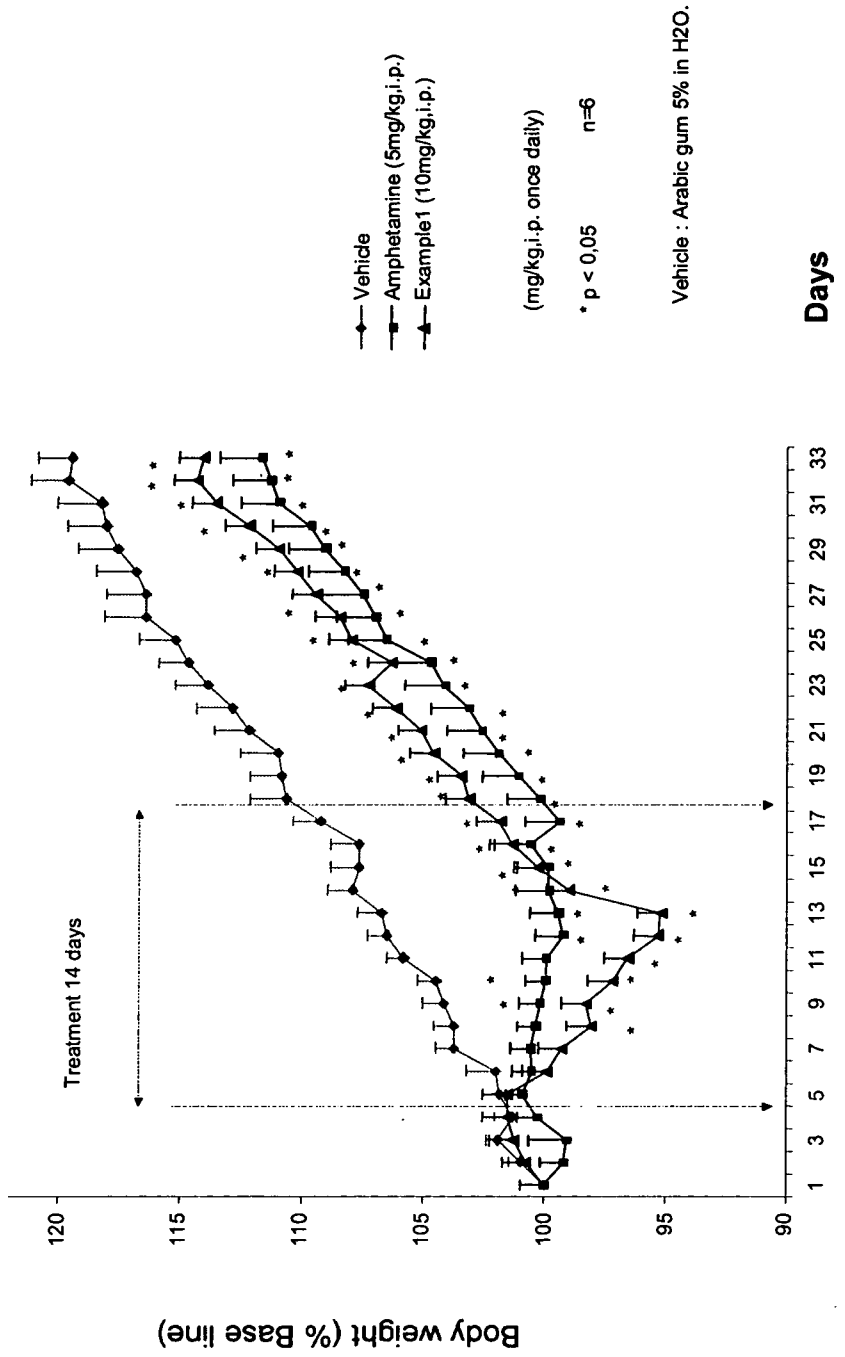

Effect on body weight in rats
Treatment 14 days
Body weight (% Base line)
120
115
110
105
100
95
90
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33
Days
Vehicle
Amphetamine (5mg/kg,i.p.)
Example1 (10mg/kg,i.p.)
(mg/kg,i.p. once daily)
* p < 0,05 n=6
Vehicle : Arabic gum 5% in H2O.

Figure 1)