Patent US 6,492,529 describes pyrazole derivatives which are used for the treatment of inflammatory diseases. These compounds present in the 5 position a urea group, linked in some cases to a morpholine ethoxy group.

International patent application WO 04/016592 refers to pyrazole compounds for inhibiting protein prenylation which comprises in the 5 position, among others, an alkoxy group directly bonded to a cyclic amide.

However, none of these documents suggests the effect of these compounds on the sigma receptor.

WO 2006/021462 and WO 2007/098964 describe pyrazole derivatives as selective inhibitors of the sigma receptor. These compounds present in the 3 position an alkoxy group.

There is still a need to find compounds that have pharmacological activity towards the sigma receptor, being both effective and selective, and having good "drugability" properties, i.e. good pharmaceutical properties related to administration, distribution, metabolism and excretion.

BRIEF DESCRIPTION OF THE INVENTION

The inventors of the present disclosure~~invention~~ have surprisingly found a family of structurally distinct pyrazole derivatives which are particularly selective inhibitors of the sigma receptor. The compounds present a pyrazole group which are characterized by the substitution at position 3 by an alkyl chain containing an amine at its end and optionally an intermediate oxa moiety.

~~Therefore, one aspect of the present invention relates to~~There is provided a compound of general formula (I):

together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl group;

X represents an oxygen atom or a CH-R^{12} group wherein R^{12} is selected from H, CH_3, SH, OH, NH_2, CF_3, Cl, F, Br, I, and CN;

m is selected from 1, 2, 3 and 4;

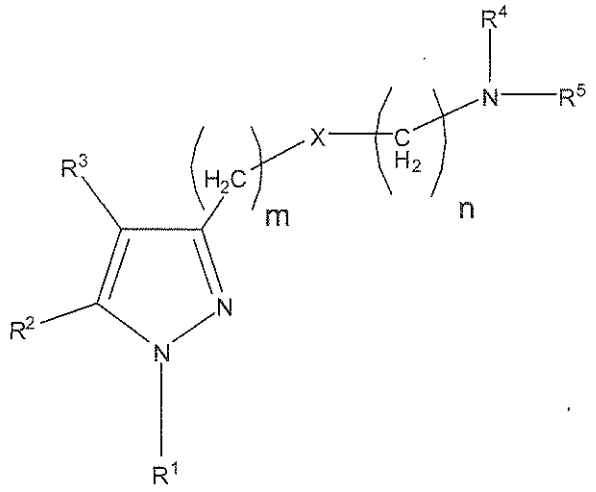
n is selected from 1, 2, 3 and 4;

t is selected from 1, 2 and 3;

$\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$ and $\mathbf{R^{11}}$, identical or different, represent a hydrogen atom; substituted or unsubstituted C_{1-6} alkyl; substituted or unsubstituted C_{2-6} alkenyl; substituted or unsubstituted C_{1-6} alkoxy; substituted or unsubstituted cycloalkyl; substituted or unsubstituted aryl; substituted or unsubstituted, aromatic or non-aromatic heterocyclyl; substituted or unsubstituted cycloalkylalkyl; substituted or unsubstituted arylalkyl; substituted or unsubstituted, aromatic or non-aromatic heterocyclylalkyl;

or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

In a first aspect, there is provided a compound of general formula (I):



(I)

wherein

R^1 represents substituted or unsubstituted, aromatic or non-aromatic heterocyclyl; substituted or unsubstituted aryl; or substituted or unsubstituted cycloalkyl;

R^2 represents a hydrogen atom; F; Cl; Br; I; CF_3; OH; SH; CN; substituted or unsubstituted methyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkoxy; substituted or unsubstituted cycloalkyl; substituted or unsubstituted, non-aromatic heterocyclyl; substituted or unsubstituted cycloalkylalkyl; substituted or unsubstituted arylalkyl; substituted or unsubstituted, aromatic or non-aromatic heterocyclylalkyl; a (C=O)-R^7 group; a (C=O)-O-R^8 group; a $S(O)_t$-R^9 group; or a (C=O)-$NR^{10}R^{11}$ group;

R^3 represents a hydrogen atom; F; Cl; Br; I; CF_3; OH; SH; NH_2; CN; substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkoxy; substituted or unsubstituted cycloalkyl; substituted or unsubstituted aryl; substituted or unsubstituted, aromatic or non-aromatic heterocyclyl; substituted or unsubstituted cycloalkylalkyl; substituted or unsubstituted arylalkyl; substituted or unsubstituted, aromatic or non-aromatic heterocyclylalkyl; a (C=O)-R^7 group; a (C=O)-O-R^8 group; a $S(O)_t$-R^9 group; or a (C=O)-$NR^{10}R^{11}$ group;

R^4 and R^5, identical or different, represent a hydrogen atom; substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkoxy; substituted or unsubstituted cycloalkyl; substituted or unsubstituted aryl; substituted or unsubstituted, aromatic or non-aromatic heterocyclyl; substituted or unsubstituted cycloalkylalkyl; substituted or unsubstituted arylalkyl; substituted or unsubstituted, aromatic or non-aromatic heterocyclylalkyl; a (C=O)-R^7 group; a (C=O)-O-R^8 group; a $S(O)_t$-R^9 group; or a (C=O)-$NR^{10}R^{11}$ group;

or

together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted, aromatic or non-aromatic heterocyclyl group;

X represents an oxygen atom or a CH-R^{12} group wherein R^{12} is selected from H, CH_3, SH, OH, NH_2, CF_3, Cl, F, Br, I, and CN;

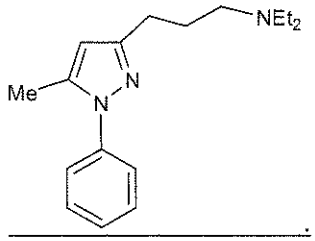
m is selected from 1, 2, 3 and 4;

n is selected from 1, 2, 3 and 4;

t is selected from 1, 2 and 3;

R^7, R^8, R^9, R^{10} and R^{11}, identical or different, represent a hydrogen atom; substituted or unsubstituted C_{1-6} alkyl; substituted or unsubstituted C_{2-6} alkenyl; substituted or unsubstituted C_{1-6} alkoxy; substituted or unsubstituted cycloalkyl; substituted or unsubstituted aryl; substituted or unsubstituted, aromatic or non-aromatic heterocyclyl; substituted or unsubstituted cycloalkylalkyl; substituted or unsubstituted arylalkyl; substituted or unsubstituted, aromatic or non-aromatic heterocyclylalkyl;

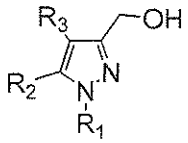
or a pharmaceutically acceptable salt, enantiomer, diastereoisomer or solvate thereof; with the proviso that the compound of general formula (I) is not



~~Another aspect of this invention refers to~~There is also provided the process for the preparation of a compound of formula (I) as defined above, or a salt, isomer or solvate thereof.

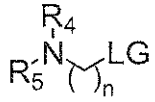
In a second aspect, there is provided a process for the preparation of a compound of formula (I) as defined above, or a salt, enantiomer, diastereoisomer or solvate thereof, which is selected from one of the following:

a) a process which comprises the reaction of a compound of formula (II)



(II)

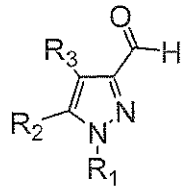
in which R_1, R_2 and R_3 are as defined above, with a compound of formula (III)



(III)

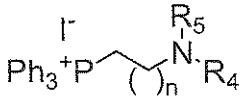
in which R_4, R_5 and n are as defined above and LG represents a leaving group;

b) a process which comprises the oxidation of a compound of formula (II) to afford a compound of formula (VII)



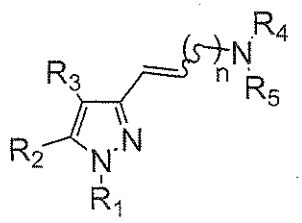
(VII)

in which R_1, R_2 and R_3 are as defined above, followed by the reaction of the compound of formula (VII) with a phosphonium salt of formula (VIII)



(VIII)

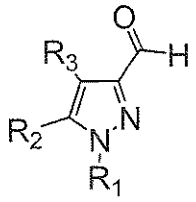
in which R_4, R_5 and n are as defined above, to afford a compound of formula (IX)



(IX)

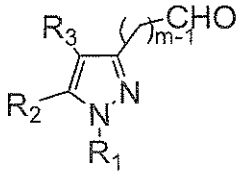
in which R_1, R_2, R_3, R_4, R_5 and n are as defined above, and reduction of the compound of formula (IX);

c) a process which comprises the oxidation of a compound of formula (II) to afford a compound of formula (VII)



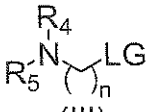
(VII)

in which R_1, R_2 and R_3 are as defined above, followed by the reaction of the compound of formula (VII) with a suitable phosphonium salt and subsequent acid hydrolysis to afford a compound of formula (XI)



(XI)

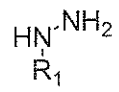
in which R_1, R_2, R_3 and m are as defined above, reduction of the compound of formula (XI) and subsequent reaction with a compound of formula (III)



(III)

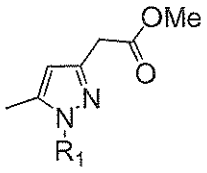
in which R_4, R_5 and n are as defined above and LG represents a leaving group;

d) a process which comprises reaction of 3-acetyl-6-methyl-pyran-2,4-dione with magnesium and subsequent reaction with a compound of formula (V):



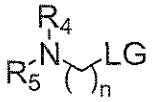
(V)

in which in which R_1 is as defined above, to afford a compound of formula (XV)



(XV)

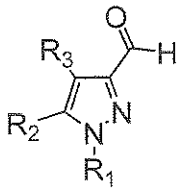
in which in which R_1 is as defined in above, and reduction of the compound of formula (XV) and subsequent reaction with a compound of formula (III)



(III)

in which R_4, R_5 and n are as defined in above and LG represents a leaving group;

e) a process which comprises the oxidation of a compound of formula (II) to afford a compound of formula (VII)



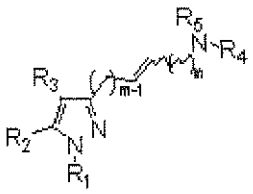
(VII)

in which R_1, R_2 and R_3 are as defined above, followed by the reaction of the compound of formula (VII) with a phosphonium salt of formula (XVII)



(XVII)

in which R_4, R_5, m and n are as defined above, to afford a compound of formula (XVII)



(XVIII)

in which R_1, R_2, R_3, R_4, R_5, m and n are as defined above, and reduction of the compound of formula (XVIII).

~~Another aspect of this invention refers to~~There is also provided a medicament or pharmaceutical composition comprising at least one compound of formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof and a pharmaceutically acceptable excipient.

In a third aspect, there is provided a medicament comprising at least one compound of formula (I) as defined above, or a pharmaceutically acceptable salt, enantiomer, diastereoisomer or solvate thereof and a pharmaceutically acceptable excipient.

In a fourth aspect, there is provided the compound of formula (I) as defined above for use as a medicament.

~~Another aspect~~An embodiment of this ~~invention~~disclosure refers to a compound of formula (I) as defined above for use as a medicament, particularly for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition.

~~Another aspect of this invention refers to~~In a fifth aspect, there is provided the use of a compound of formula (I) as defined above in the manufacture of a medicament for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition.

~~Another aspect~~An embodiment of the present ~~invention~~disclosure refers to a method for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition, the method comprising administering to the subject in need of such a treatment or prophylaxis a therapeutically effective amount of a compound of formula (I) as defined above.

In a sixth aspect, there is provided the compound of general formula (I) as defined above for use as a pharmacological tool.

In one embodiment, said sigma receptor-mediated disease or condition is selected from the group consisting of diarrhoea; lipoprotein disorders; migraine; obesity; elevated triglyceride levels; chylomicronemia; dysbetalipoproteinemia; hyperlipoproteinemia; hyperlipidemia; mixed hyperlipidemia; hypercholesterolemia; lipoprotein disorders; hypertriglyceridemia; sporadic hypertriglyceridemia; inherited hypertriglyceridemia; dysbetalipoproteinemia; arthritis; hypertension; arrhythmia; ulcer; learning, memory and attention deficits; cognition disorders; neurodegenerative diseases; demyelinating diseases; addiction to drugs and chemical substances including cocaine, amphetamine, ethanol and nicotine; tardive dyskinesia; ischemic stroke; epilepsy; stroke; stress; cancer; psychotic conditions, in particular depression, anxiety or schizophrenia; inflammation; and autoimmune diseases.

In another embodiment, said sigma receptor-mediated disease or condition is selected from the group consisting of pain, preferably neuropathic pain, inflammatory pain or other pain conditions involving allodynia and/or hyperalgesia.

In another embodiment, the compound of formula (I) is used as a pharmacological tool.

These aspects and preferred embodiments thereof are additionally also defined in the claims.

DETAILED DESCRIPTION OF THE INVENTION

In the context of the present invention, the following terms have the meaning detailed below.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting of 1 to 12 carbon atoms, containing no unsaturation, and which is attached to the rest of the molecule by a single bond, e. g., methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-