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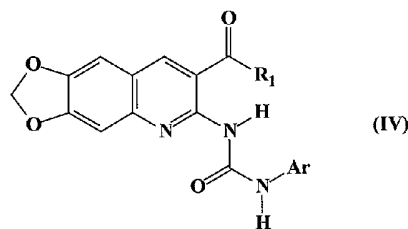
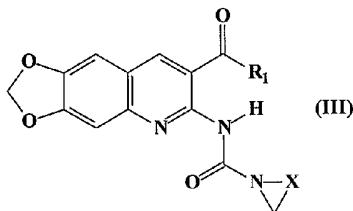
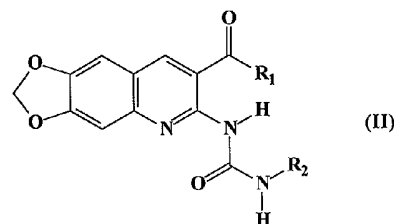
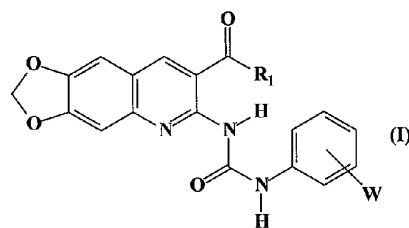
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(54) Title: UREIDIC COMPOUNDS, PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME AND THEIR USE ON THE TREATMENT OF INFLAMMATORY DISEASES



(57) Abstract: The present invention describes functionalized derivatives of ethyl 6-N- alkyl and/or 6-N-aryl ureas [1 ,3]dioxolo[5,4-g]quinolin-7-carboxylate (3a-z, 4a-z) and similar types (5a-z), of general formula (I, II, III and IV), useful in the treatment and/or prevention of inflammatory diseases, such as acute or chronic inflammatory conditions, different types of arthritis, asthma, Crohn's Disease and diabetes mellitus Type I, among others. These derivatives have the ability of modulate the inflammatory process, acting in mitogen activated protein kinase p-38 (MAPK-p38). Moreover, the derivatives of the present invention present expressive anti-inflammatory properties evaluated in in vivo models. The present invention also discloses processes for the production of such derivatives and pharmaceutical compositions containing the same.

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Description

UREIDIC COMPOUNDS, PHARMACEUTICAL COMPOSITIONS CONTAINING
THE SAME AND THEIR USE ON THE TREATMENT OF INFLAMMATORY
DISEASES

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Field of the invention

The present invention is related to ethyl functionalized derivatives of 6-N-alkyl and/or 6-N-aryl urea [1,3]dioxolo[5,4-g]quinolin-7-carboxylate (**3a-Z**, **4a-Z**);
10 and congeners (**5a-Z**). Even particularly, the present invention is related to
derivates of ethyl 6-phenylurea-[1,3]-dioxolo-[5,4-g]-quinolin-7-carboxylate
(**LASSBio-948**), ethyl 6-(4-bromophenylurea)-6-phenylurea-[1,3]-dioxolo-[5,4-
g]-quinolin-7-carboxylate (**LASSBio-947**), ethyl 6-(4-chlorophenylurea)-[1,3]-
dioxolo-[5,4-g]-quinolin-7-carboxylate (**LASSBio-949**) and ethyl 6-
15 cyclohexylurea-[1,3]-dioxolo-[5,4-g]-quinolin-7-carboxylate (**LASSBio-998**) and
their isosters and regioisomers, the process for their preparation, the
pharmaceutical compositions containing them and their use as therapeutic
agent for the treatment of inflammatory diseases, like different forms of arthritis,
osteoarthritis, asthma, Crohn's disease and COPD (*chronic obstructive*
20 *pulmonary disease*).

Background of the invention

Several members of kinases proteins family were already identified until
the present moment. These enzymes catalyze the phosphorylation of different
25 substrates, playing primordial roles on practically all the stages of the cell life.
Considering that about 1/3 of the known proteins in mammals contain covalent
bonded phosphate, any modification in the function of these proteins can
generate inadequate cell responses, contributing for pathologies development
such as diabetes, cancer, rheumatic arthritis, among others [Cohen, P., J. *Biol.*
30 *Chem.*, **1999**, 3, 459].

Among kinases, there are those activated by mitogen (*mitogen-activated protein kinase*, **MAPK**), belonging to the family of Serine-Threonine kinases that include the kinase regulated by extracellular signals (*extra-cellular signal regulated kinase-2*, **ERKs**), the amino-terminal kinase of junction c (*c-jun amino terminal kinase*, **JNKs**) and the protein p38 activated by mitogen (*mitogen-activated protein kinase p38*, **MAPK p38**). These kinases have 60-70% of homology among each other and are characterized by the presence of the sequence Thr-Xaa-Tyr in the active site, so it could be doubly phosphorylated in the threonine and tyrosine aminoacid residues for MAPK kinases (MKK) in response to extracellular stimulus [Muzio, M. *et. Al.*, *Science*, **1997**, 278, 1612].

MAPK-p38 activation occurs in response to osmotic shock, heat, ultraviolet light, pathogenic agents such as lipopolysaccharides of gram-negative bacteria (LPS) and different interleukins (IL) like IL-1, IL-2, IL-7, IL-17, IL-18, the cytokines such as the transforming growth factor β (TGF- β) and the tumor necrosis factor α (TNF- α). Once activated, MAPK-p38 acts promoting the activation of other kinases, nuclear transcription factors responsible for the expression of pro-inflammatory cytokines, adhesion molecules and cytoplasmatic proteins [Clark, A.R, *et Al.*, *FEBS Letters*, **2003**, 546].

Nowadays, it is known four members of the MAPK-p38family, designated by the letters α , β , γ and δ . These isoforms differ regarding the tissue distribution, activation of other kinases and phosphorylation of substrates [Lee, J. C. *et Al.*, *Nature*, **1994**, 372, 739].

The homology degree of p38 α in view of p38 β , p38 γ e p38 δ is 75, 62, and 64%, respectively. Although the expression of the p38 α and related kinases may vary, this enzyme is predominantly expressed in cells involved with the inflammatory and immunomodulatory response of the organism [Lee, J. C. *et Al.*, *Nature*, **1994**, 372, 739], justifying its central role in the development of pathologies of inflammatory origin.

MAPK-p38 α is involved in cellular events in response to cellular adhesion induced by LPS and may lead to activation of nuclear transcription factors with

subsequent synthesis of TNF- α and IL-1 β [Reingeaud, J. *et. Al.*, *Mol. Cell. Biol.* **1995**, 16, 1247]. The biological action of these cytokines can be attributed to the activation of nuclear transcription factor κ B (NF κ B), contributing for the inflammatory response orchestration [Baeuerle, P. A. and Baltimore, D, *Cell*,
5 **1996**, 87, 13].

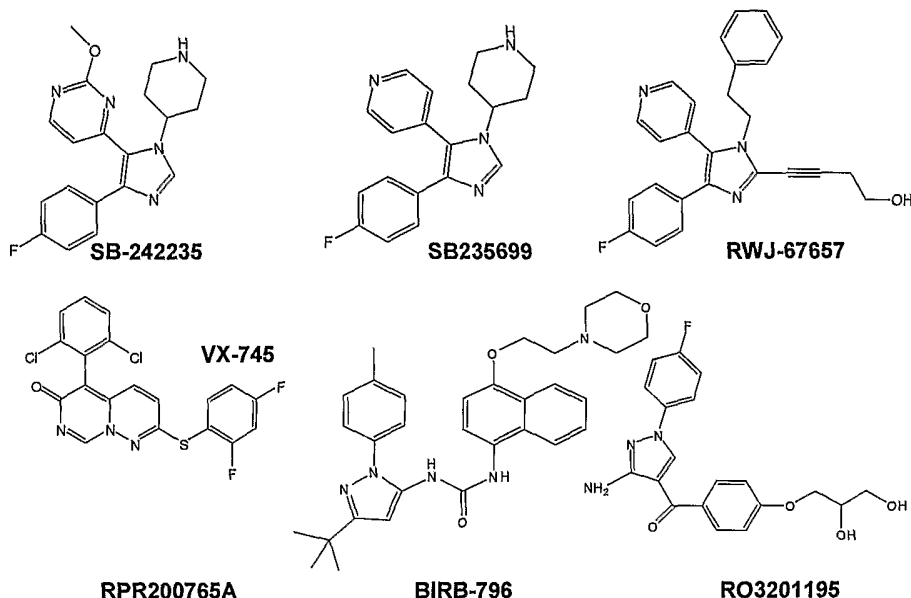
Due to the central role performed in the different stages of the inflammatory process, MAPK-p38 activity has been linked to several diseases, being important to stress the rheumatoid arthritis [Kumar, S. *et. Al.*, *Nature Drug Discovery* **2003**, 2, 717]. In rheumatoid arthritis inflammatory process
10 development the presence of a great number of mononuclear cells in synovia is intimately related to the magnitude of the disease. The macrophages in rheumatoid synovia have a high concentration of activated MAPK-p38 with consequent production of TNF- α and IL-1 β , essential cytokines in the pathogeny development.

15 The evidence that MAPK-p38 played a key role in inflammatory processes made the enzyme inhibition an attractive therapeutic strategy for the treatment of different inflammatory pathological conditions.

The first synthetic prototype able to inhibit selectively MAPK-p38 was the piridinyl imidazolic derivative SFK-86002 [Lee, J. C. *et. Al.*, *Int. J.*
20 *Immunopharmacol.* **1988**, 10, 835; Lee, J. C. *et Al. Ann. NY Acad. Sci.* **1993**, 696, 149], that afterwards was substituted by the derivative 2,4,5-triaryl imidazolic SB-203580 [Gallagher, T. F. *et Al. Bioorg. Med. Chem. Lett.* **1995**, 5, 1171], both used as a pharmacological tool in the research of new molecular targets involving cytokines regulation.

25 Several patents describe MAP kinase inhibitors, and some describe p38 MAP Kinase inhibitors of. Several document can be cited, such as WO 95/09851, WO 97/16442, WO 98/06715, WO 98/07425, WO 98/56377, WO 99/01136, WO 00/01688, WO 00/07991, WO 00/06563, WO 00/12074, WO 01/29041, WO 01/62731, WO 01/05744, WO 04/089929, WO 04/016267.

Nowadays several inhibitors of MAPK-p38 are in clinical trial stages [Jessie M. *et. Al.*, *TRENDS in Pharm. Sciences*, **2002**, 23, 40] and some examples are illustrated below.



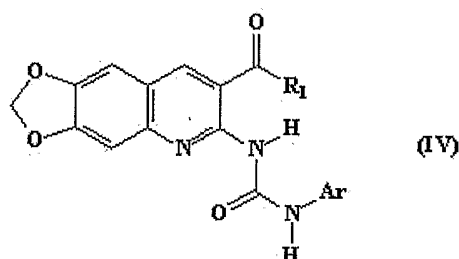
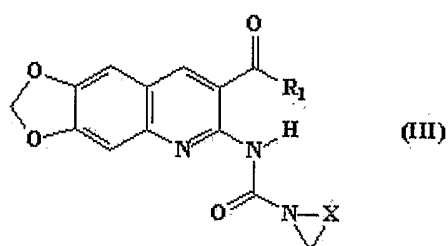
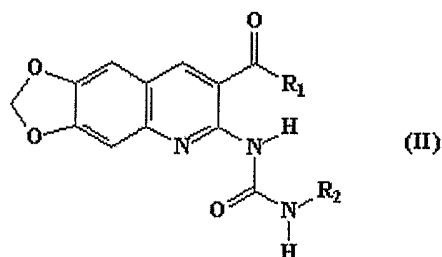
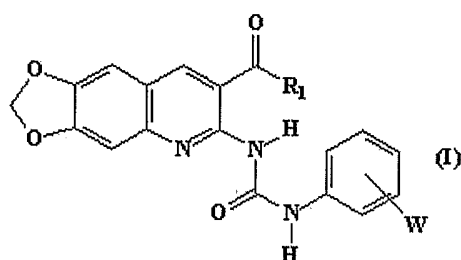
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Summary of the invention

It is an object of the present invention to provide alternatives for the treatment and prevention of inflammatory diseases, especially, different types of arthritis, osteoarthritis and asthma, among others. In another aspect of the invention, the main limitations and complications associated with the drug therapy, usually in the treatment of inflammatory diseases, would be circumvented or minimized by the use of ureidic derivatives that act as MAPK-p38 inhibitors of and/or NF κ B's activation inhibitors.

It is an additional object of the present invention a derivative of the general formula (I) and/or (II) and/or (III) and/or (IV) below:

15



wherein

R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

W is (2 and/or 3 and/or 4 and/or 5 and/or 6)-F or (2 and/or 3 and/or 4
 5 and/or 5 and/or 6)-Cl or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Br or (2 and/or 3
 and/or 4 and/or 5 and/or 6)- CH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)-
 CH_2CH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CF_3 or (2 and/or 3 and/or 4
 and/or 5 and/or 6)- OCH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- OCF_3 or (2
 and/or 3 and/or 4 and/or 5 and/or 6)- (2 and/or 3 and/or 4 and/or 5 and/or 6)-
 10 NO_2 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- NH_2 ; (2 and/or 3 and/or 4 and/or
 5 and/or 6)- $NHCH_3$ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHCOCH_3$ or (2
 and/or 3 and/or 4 and/or 5 and/or 6)- $NHSO_2CH_3$;

R_2 is CH_3 or CH_2CH_3 or $(CH_2)_2CH_3$ or $(CH_2)_3CH_3$ or $(CH_2)_4CH_3$ or
 (CH₂)₅CH₃ or $CH(CH_3)_2$ or $C(CH_3)_3$ or cyclopropyl, or cyclopentyl or cyclohexyl
 15 or cycloheptyl;

Ar is 2-Py or 3-Py or 4-Py or 2-thiophene or 2-furane or 2-pyrrole or 1-
 naphthyl or 2-naphthyl or quinoline, or quinoxaline or oxazole or thiazole or
 thiadiazole, oxadiazole or pyrimidine or triazole or imidazole;

It is an additional object of the present invention the process of preparation of ureidic derivatives. More specifically, such process comprises synthetics steps such as: regioselective electrophilic aromatic substitution; aldolic condensation with ethyl cyanoacetate; reduction followed by cyclization
5 through intramolecular addition nucleophilic; condensation (intermediary amine with functionalized isocyanates); interconversion of functional groups.

It is an additional object of the present invention the preparation of pharmaceutical compositions comprising the ureidic derivatives and their use in the treatment of inflammatory diseases and conditions. More specifically, such
10 pharmaceutical compositions are able of inhibit to p38 MAP-Kinase and/or to inhibit NF κ B activation.

Description of Figures

Figure 1: Genesis of new derivatives (**3a-Z**; **4a-Z**; **5a-Z**), drawn from the
15 prototypes (GK00687, **1**) and (**2**)

Figure 2: Values of pIC₅₀ proposed for some of the ureidic derivatives planned as MAPK-p38 inhibitors, comparative to the values of prototypes GK 00687 and SB 203580 pIC₅₀, from model of CoMFA.

Figure 3: Effect of LASSBio-947 (**3d**) and of SB202190 on MAPK-p38
20 activation of peritoneal murine macrophage stimulated with LPS, showing the autoradiography (A) with the respective columns representing the relative optical densities of each band (B). Preparations: RPMI = *naïve* macrophages; LPS = macrophages stimulated with LPS 10 g/ml; LASSBio-947 = macrophages stimulated with LPS in the presence of different concentrations of
25 LASSBio-947 (**3d**) (1, 10, 100 and 1000 μ M); SB = macrophages stimulated with LPS in the presence of different concentrations of SB202190 (1 and 10 μ M). IC₅₀ (LASSBio-947 (**3d**))= 8,7 μ M.

Figure 4: Effect of LASSBio-948 (**3a**) in MAPK-p38 activation of peritoneal murine macrophages stimulated with LPS, showing the
30 autoradiography (A) with the respective columns representing the relative optical densities of each band (B). Preparations: RPMI = *naïve* macrophages;

RPMI+DMSO = *naive* macrophages in the presence of DMSO 0,5%; LPS = macrophages stimulated with LPS 10 $\mu\text{g/ml}$; LPS+DMSO = macrophages stimulated with LPS 10 $\mu\text{g/ml}$ in the presence of DMSO 0,5%; LASSBio-948 = macrophages stimulated with LPS in the presence of different concentrations of LASSBio-948 (**3a**) (1, 10, 100 and 1000 μM). IC_{50} (LASSBio-948 (**3a**)) = 13,6 μM .

Figure 5: Effect of LASSBio-949 (**3c**) on MAPK-p38 activation of peritoneal murine macrophages stimulated with LPS, showing the autoradiography (A) with the respective columns that represent the relative optical densities of each band (B). Preparations: RPMI = *naive* macrophages; RPMI+DMSO = *naive* macrophages in the presence of DMSO 0,5%; LPS = macrophages stimulated with LPS 10 $\mu\text{g/ml}$; LASSBio-949 = macrophages stimulated with LPS in the presence of different concentrations of LASSBio-949 (**3c**) (1, 10, 100 and 1000 μM); SB = macrophages stimulated with LPS in the presence of different concentrations of SB202190 (1, 10 and 100 μM). IC_{50} (LASSBio-949 (**3c**)) = 30 μM .

Figure 6: Effect of LASSBio-998 (**4m**) on MAPK-p38 activation of peritoneal murine macrophages stimulated with LPS, showing the autoradiography (A) with the respective columns that represent the relative optical densities of each band (B). Preparations: RPMI = *naive* macrophages; LPS = macrophages stimulated with LPS 10 $\mu\text{g/ml}$; LASSBio-998 = macrophages stimulated with LPS in the presence of different concentrations of LASSBio-998 (**4m**) (1, 10, 100 and 1000 μM); SB = macrophages stimulated with LPS in the presence of different concentrations of SB202190 (10 μM). IC_{50} (LASSBio-998 (**4m**)) = 5,5 μM .

Figure 7: Decrease of weight gain on left popliteus lymphonode in mice that received zymosan and were treated with LASSBio-947 (**3d**), LASSBio-948 (**3a**) and LASSBio-949 (**3c**). Groups of 8 animals received s.c. injection of sterile saline or injection of 150 μg of zymosan (prepared in saline) on the left paw. Seventy two hours after the injection, the animals were treated i.p. with 10

mg/kg of L-947, L-948 and L-949 for 4 days. After that period, the left popliteus lymphonode was dissected and weighed. The values are presented as the average + WITHOUT, in which **p<0,01 and ***p<0,001.

Figure 8: Lymphocytes number reduction in the left popliteus lymphonode in mice that received zymosan and were treated with **LASSBio-947 (3d)**, **LASSBio-948 (3a)** and **LASSBio-949 (3c)**. Groups of 8 animals received injection s.c. of sterile saline or of 150 µg of zymosan (prepared in saline) on the left paw. Seventy two hours after the injection, the animals were treated with i.p 10 mg/kg of the substances L-947, L-948 and L-949 for 4 days. After that period, the lymphonodes cells were isolated and counted in Neubauer chamber.

Figure 9: Inhibition of NFκB translocation of mice C57Bl6 lymphonodes lymphocytes treated with the compounds **LASSBio-947 (3d)**, **LASSBio-948 (3a)** and **LASSBio-949 (3c)**. Auto-radigraph image obtained from the nuclear extract of the lymphocytes after eletroforetic run in polyacrilamide gel. Ctr+= positive control, cells HeLa treated with 10 µg of LPS; SF= negative control, not radioactive probe; Salt= animals injected with saline; Animals injected with 150 µg of zymosan and treated i.p. with 0,5% of DMSO for 4 days (Veic); with 10 mg/kg of rofecoxib (Vioxx) or with 10 mg/kg of the compound LASSBio-947, LASSBio-948 or LASSBio-949.

Detailed Description of the Invention

After a brief reference to the present invention objects, they will be described now in more details, using, whenever necessary, the preferential embodiments of the invention.

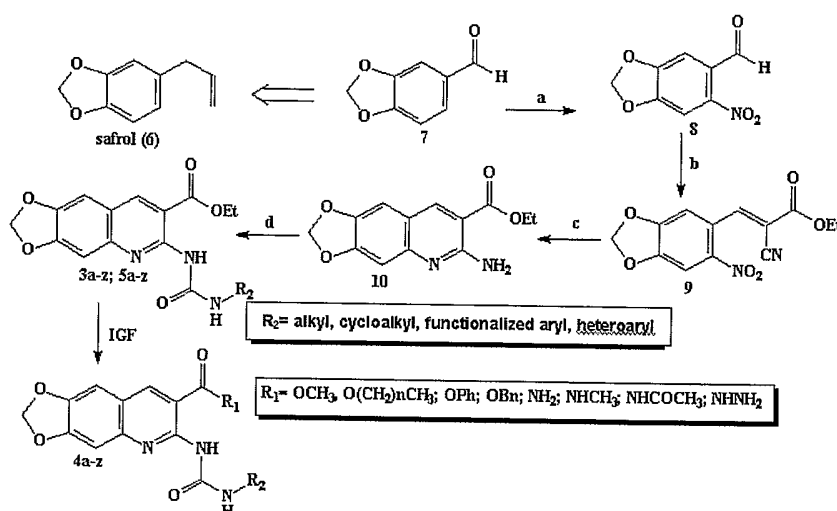
One innovative characteristic of the present invention is the synthesis of ethyl functionalized derivatives of 6-N-alkyl and/or 6-N-aryl urea [1,3]dioxolo[5,4-g]quinolin-7-carboxylate (**3a-Z**, **4a-Z**); and congeners (**5a-Z**). More specifically, one of the ethyl 6-phenylurea-[1,3]-dioxolo-[5,4-g]-quinolin-7-carboxylate derivatives (herein referred as **LASSBio-948**), ethyl 6-(4-bromophenylurea)-[1,3]dioxolo[5,4-g]quinolin-7-carboxylate (herein referred as

LASSBio-947), ethyl 6-(4-chlorophenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (herein referred as **LASSBio-949**), ethyl 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (herein referred as **LASSBio-998**), their isomers and regioisomers (**3a-Z**, **4a-Z**, **5a-Z**), planned from structural
 5 modifications in ureidic prototypes (**1**) and (**2**) and rationally designed as MAPK-p38 inhibitors using QSAR/CoMFA techniques (*Quantitative Structure-Activity Relationship/Comparative Molecular Field Analysis*) (Figures 1 and 2).

The new compounds were obtained in good to excellent chemical yields, employing the synthetic methodology herein described, according to scheme
 10 below, that is characterized by presenting few steps, starting from commercially available compounds, qualifying this synthetic methodology for industrial application.

The compounds of the present invention were planned through convergent synthesis, using classical chemical reactions such as:

- 15 ▪ Regioselective Aromatic Electrophilic Substitution
- Aldolic condensation with ethyl cyanoacetate
- Reduction followed by cyclization through intramolecular nucleophilic addition
- Condensation (amino intermediary with functionalized isocyanates)
- 20 ▪ Interconversion of Functional Groups



Condition: a) HNO_3 , r.t., 15 min. 95%; b) $\text{NCCH}_2\text{OOCH}_2\text{CH}_3$, EtOH, $\text{KF/Al}_2\text{The}_3$, 35°C , 2h30min., 94%; c) Zn, TiCl_4 , THF, reflux, 3h30min., 84%; d) 4-W-phenyl-isocyanate (or cyclohexylisocyanate), Toluene, reflux, 72h.

More specifically, the compounds (**3a-Z**; **4a-Z**; **5a-Z**) of the present invention can be prepared from a process that comprises the steps of:

- Regiosselective aromatic eletrophilic substitution of the benzo[d][1,3]dioxole-5-carbaldehyde or piperonal system (**7**).
- Treatment of nitrated intermediate **8** with ethyl cyanoacetate, in the presence of potassium fluoride doped alumina ($\text{KF/Al}_2\text{The}_3$) as base, ethanol as solvent, at a temperature of 35°C , exploring a reaction of aldolic diastereoselective condensation.
- Reduction of nitro-acrilate of configuration (*E*) **9**, through titanium tetrachloride (TiCl_4) in the presence of zinc (Zn) and tetrahydrofurane as solvent, at reflux temperature, for posterior cyclization of the amino-formed intermediate through intramolecular nucleophilic addition to the nitrile group.
- Condensation of aminated derivative **10** with arylisocyanates and/or cycloalkylisocyanates and/or alkylisocyanates and/or heteroarylisocyanates, in the presence of anhydrous toluene at reflux temperature.
- Functional groups interconversion from intermediate (**10**) or derivatives (**3a-Z**; **4a-Z**; **5a-Z**), exploring transesterification, hydrolysis, aminolysis and hidrazinolysis reactions.

As examples, in this description it is described the synthesis of the following compounds:

- ethyl 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3a**);
- ethyl 6-(4-fluoro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3b**);
- ethyl 6-(4-chloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3c**);
- ethyl 6-(4-bromo-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3d**);
- ethyl 6-(4-methyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3e**);
- ethyl 6-(4-trifluoromethyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3f**);
- ethyl 6-(4-methoxy-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3g**);

- ethyl 6-(4-trifluoromethyleter-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3h**);
ethyl 6-(4-nitro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3i**);
ethyl 6-(4-amino-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3j**);
ethyl 6-(4-methylaminophenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3l**);
5 ethyl 6-(4-acetamide-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3m**);
ethyl 6-(4-methanesulfonamide-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3n**);
ethyl 6-(2,6-difluoro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3o**);
ethyl 6-(2-chloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3p**);
10 ethyl 6-(3-chloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3q**);
ethyl 6-(2,3-dichloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3r**);
ethyl 6-(2,6-dichloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3s**);
ethyl 6-(4-ethyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3t**);
ethyl 6-(2,6-ethyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3u**);
15 ethyl 6-(2,6-methyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3v**);
ethyl 6-(2-methoxy-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3x**);
ethyl 6-(2-nitro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3z**);
ethyl 6-methylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4a**);
ethyl 6-ethylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4b**);
20 ethyl 6-propylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4c**);
ethyl 6-isopropylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4d**);
ethyl 6-terbutylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4e**);
ethyl 6-butylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4f**);
ethyl 6-pentylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4g**);
25 ethyl 6-hexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4h**);
ethyl 6-benzylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4i**);
ethyl 6-cyclopropylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4j**);
ethyl 6-cyclopentylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4l**);
ethyl 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4m**);
30 ethyl 6-cycloheptylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4n**);
methyl 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4o**);

- fenyla 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4p**);
benzyl 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4q**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-acid carboxamide (**4r**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-methylcarboxamide (**4s**);
5 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carbonylhydrazine (**4t**);
methyl 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4u**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxamide (**4v**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-acid carboxylic(**4x**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carbonylhydrazine (**4z**);
10 ethyl 6-(2-pyridinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5a**);
ethyl 6-(3-pyridinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5b**);
ethyl 6-(4-pyridinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5c**);
ethyl 6-(2-thienylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5d**);
ethyl 6-(2-furylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5e**);
15 ethyl 6-(2-imidazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5f**);
ethyl 6-(2-pirrollylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5g**);
ethyl 6-(2-pirazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5h**);
ethyl 6-(1,3,4-thiadiazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5i**);
ethyl 6-(1,3,4-oxadiazolylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5j**);
20 ethyl 6-(1-naphtylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5l**);
ethyl 6-(2-naphtylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5m**);
ethyl 6-(2-quinolinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5n**);
ethyl 6-(4-pyrimidinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5o**);
ethyl 6-(4-quinazolinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5p**);
25 ethyl 6-(1,3-oxazolinyurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5q**);
ethyl 6-(1,3-thiazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5r**);
ethyl 6-(1*H*-5-imidazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5s**);
ethyl 6-(4*H*-1,2,4-triazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5t**);
methyl 6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate
30 (**5u**);

6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxamide(**5v**);

6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-acid carboxylic(**5x**);

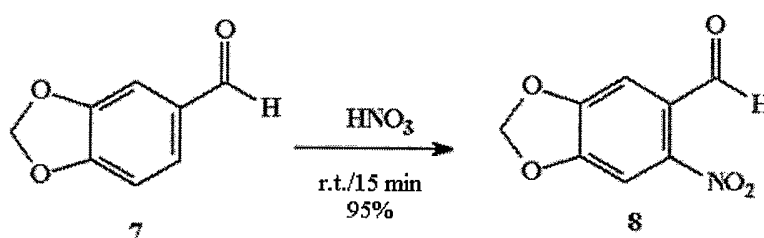
- 5 6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carbonylhydrazine(**5z**).

A detailed description of the synthetic methods of this invention for some of the claimed compounds is shown below. The following examples only illustrate, but do not limit present invention.

10

Example 1

6-nitrobenzo [d] [1,3]dioxolo-5-carbaldehyde [adapted from Barreiro, E. J. *et Al.*, *J. Chem. Res.*, (S), **1982**, 102]

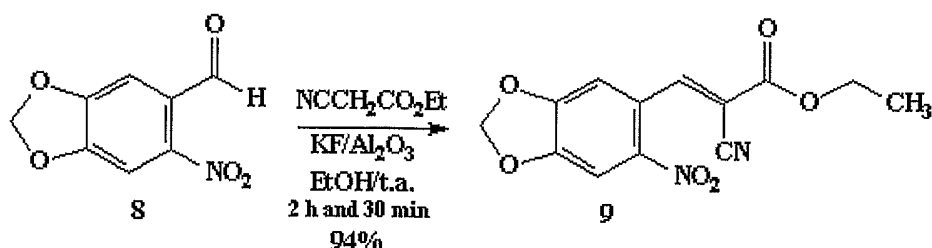


15

It was mixed in a round-bottom flask piperonal (7) (6,66 mmol; 1g) and 3,3 mL of concentrated HNO₃, remaining the result suspension in r.t. under vigorous magnetic agitation. It is observed immediate change of color (colorless to yellow). TLC reveals the end of reaction in 15 minutes. The isolation is performed through ice-bath cooling of reactional medium, observing immediate precipitation. The yellow solid precipitated is filtrate in bückner funnel and washed with NaHCO₃ solution saturated, followed by washing with distilled water until the pH=7.

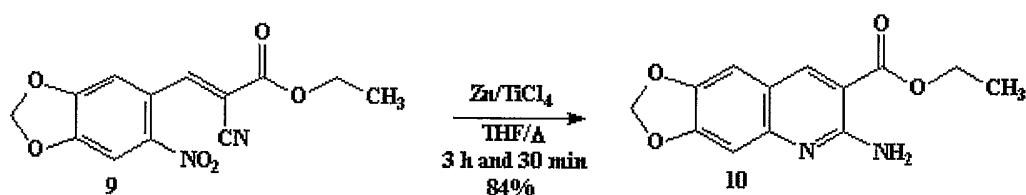
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25 **Ethyl 2-cyano-3-(6-nitrobenzene[d][1,3]dioxol-5-yl)-(E)-2-propenoate** [adapted from Zhou, L. *et Al.*, *J. Chem. Research* (S), **1998**, 398],



In a round-bottom flask containing nitro-piperonal (8) (1,9512g; 10 mmol) it was added $\text{KF}/\text{Al}_2\text{O}_3$ (200 mg), ethyl cyanoacetate (1,131g; 10 mmol) and 10 ml of dry ethanol. The result suspension was kept under vigorous magnetic agitation and heated to the temperature of 35°C. TLC reveals the end of reaction in 2 hours and 30 minutes. The solution presents yellow coloration from beginning to end. The isolation is made by reduction of solvent volume in rotaevaporator, followed by the dilution of the medium with dichloromethane, followed by filtration in buckner funnel of the white solid ($\text{KF}/\text{Al}_2\text{O}_3$). The filtrate is added to a separation funnel, washed with distilled water and the organic phase is dried with anhydrous Na_2SO_4 and concentrated in an amorphous yellow solid (9) in an yield of 94%.

Ethyl 6-amino-[1,3]dioxolo-[5,4-G]-quinolin-7-carboxylate [adapted from Zhou, *et Al.*, *Synthesis*, 1998, 851]

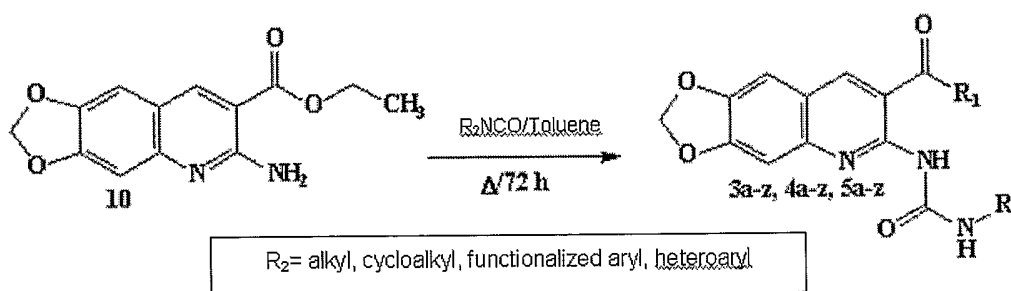


In a two neck flask equipped with a condenser and N_2 atmosphere, containing zinc (1,04g; 16 mmol), previously treated with HCl 10% and dried in laboratory oven for 24h, it is added with the help of a syringe 8 mL of THF, initiating the magnetic agitation. Soon afterwards, also with a syringe it is

dripped carefully 0,88 mL of TiCl (8 mmol). It is observed the immediate change of reactional medium color to a dark green coloration, the medium remains with agitation in reflux temperature for 2 hours. The heating is turned off, and after cooling of the reactional medium the cyano-derivative **9** (0,580g, 2mmol)
 5 solubilized in 5 mL of THF is dripped into the solution. It is observed a change in the coloration, in the reactional medium to a black-reddish color. The reactional mixture is submitted to the magnetic agitation in r.t. for 1 hour and 30min.

The isolation is done pouring the flask content to a beaker containing 40 mL of aqueous solution of K₂CO₃ 10%. Then it is added about 100 mL of
 10 dichloromethane letting the resultant suspension under vigorous magnetic agitation until there is extraction to the organic phase. The suspension is vacuum filtered, washing exhaustively with dichloromethane. The filtrate is transferred to a separation funnel and is washed with water. The organic phase is dried with anhydrous Na₂SO₄ and concentrated to an amorphous solid of
 15 brown coloration in yield of 84%. Afterwards it is accomplished the purification through recrystallization in hydroalcoholic mixture.

General procedure for the synthesis of ethyl 6-N-alkyl and/or 6-N-aryl ureas [1,3]dioxolo[5,4-g]quinolin-7-carboxylate functionalized derivatives (3a-Z, 4a-Z, 5a-Z) [adapted from Dumas, J. *et Al.*, *Bioorg. Med. Chem. Lett.* **2000**, 10, 2054]
 20



In a round-bottom flask connected to a reflux condenser, containing the *ortho*-aminoquinolinic derivative **10** (0,5g; 1,823 mmol), it is added duly functionalized isocyanate (3,65 mmol) and anhydrous toluene as solvent (100
 25 mL). The reactional mixture is magnetically stirred at reflux temperature for 72 hours.

The isolation begins through the dilution of the medium with dichloromethane, followed by the solvent volume reduction in rotaevaporator. Then, it is added 100 mL of AcOEt, and the flask content is transferred to a separatory funnel, washing with a saturated solution of NaCl, followed by distilled water. The organic phase is dried with anhydrous Na₂SO₄, concentrated in rotaevaporator to produce the desired ureas in yield of 78% after purification through recrystallization in hydroalcoholic mixture.

Ethyl 6-phenylurea-[1,3]dioxolo[5,4-g]quinolin-7-carboxylate (3a)

This derivative was obtained in 96% yield, through the nucleofilic addition of the 2-amino-quinolin derivative (10) to phenylisocyanate, as a clear brown amorphous solid with mp.: 202-203°C.

NMR ¹H (200 MHz; DMSO-*d*₆) δ: 1, 39 (3H, t, RCOOCH₂CH₃, J= 6, 95 Hz); 4, 41 (2H, q, RCOOCH₂CH₃, J= 6, 95 Hz); 6, 27 (2H, s, OCH₂O); 7, 09 (1H, t, C4'-H, J=7, 28 Hz); 7, 37 (2H, t, C3'-H e C5'-H, J= 7,33 Hz); 7, 52 (1H, s, C8-H); 7, 54 (1H, s, C5-H); 7, 75 (2H, d, C2'-H e C6'-H, J=7,33 Hz); 8, 88 (1H, s, C4-H); 10,26 (1H, s, CO-NH-Ph); 12, 19 (1H, s, Pyr-NH-OC) ppm.

NMR ¹³C (50 MHz, DMSO-*d*₆) δ: 13, 9 (RCOOCH₂CH₃); 61, 8 (RCOOCH₂CH₃); 102, 5 (OCH₂O); 103, 1 (C8); 104, 0 (C3); 107, 5 (C4'); 119, 2 (C5); 119, 4 (C2' e C6'); 123, 1 (C4a); 128, 9 (C3' e C5'); 138, 4 (C1'); 141, 3 (C4); 145,0 (NCON); 146, 8 (C8a); 149, 1 (C7); 151, 1 (C6); 157, 5 (C2); 162, 0 (RCOOR') ppm.

IR (KBr pellet): 3273 (ν_{as} N-H); 3214 (ν_s N-H); 1683 (ν C=O ester); 1616 (ν C=O urea); 1527 (ν C-O-C ester); 1480 (ν C=C); 1240 (ν_{as} C-O-C); 1032 (ν_s C-O-C) cm⁻¹.

Ethyl 6-(4-chloro-phenylurea)-[1,3]dioxolo[5,4-g]quinolin-7-carboxylate (3c);

This derivative was obtained in 85% yield, through the nucleofilic addition of the 2-amino-quinolin derivative (10) to 4-chloro-phenylisocyanate, as a clear brown amorphous solid with mp.: 199-201°C.

NMR ^1H (200 MHz, DMSO- d_6) δ : 1, 39 (3H, t, $\text{RCOOCH}_2\text{CH}_3$, $J=6,95$ Hz); 4, 40 (2H, q, $\text{RCOOCH}_2\text{CH}_3$, $J=6,95$ Hz); 6, 26 (2H, s, OCH_2O); 7, 39 (2H, d, C3'-H e C5'-H , $J=8,79$ Hz); 7, 46 (1H, s, C8-H); 7, 80 (2H, d, C2'-H e C6'-H , $J=8,79$ Hz); 8, 86 (1H, s, C5-H); 8, 87 (1H, s, C4-H); 10,28 (1H, s, CO-NH-PhCl); 12, 25 (1H, s, Pyr-NH-OC) ppm.

NMR ^{13}C (50 MHz, DMSO- d_6) δ : 15, 1 ($\text{RCOOCH}_2\text{CH}_3$); 60, 4 ($\text{RCOOCH}_2\text{CH}_3$); 105, 5 (OCH_2O); 109, 7 (C8); 119, 9 (C3); 120, 0 (C2' e C6'); 122, 2 (C5); 125, 1 (C4'); 125, 3 (C4a); 128, 8 (C3' e C5'); 138, 4 (C1'); 138, 6 (C4); 145,0 (NCON); 147, 8 (C8a); 149, 8 (C7); 151, 1 (C6); 154, 6 (C2); 167, 0 (RCOOR') ppm.

IR (KBr pellet): 3292 (ν_{as} N-H); 3268 (ν_{s} N-H); 1683 (ν C=O ester); 1618 (ν C=O urea); 1526 (ν C-O-C ester); 1492 (ν C=C); 1243 (ν_{as} C-O-C); 1030 (ν_{s} C-O-C) cm^{-1} .

Ethyl 6-(4-bromo-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin -7-carboxylate (3d);

This derivative was obtained in 95% yield, through the nucleophilic addition of the 2-amino-quinolin derivative (10) to the 4-bromo-phenylisocyanate, as a clear brown amorphous solid with mp.: 213-215°C.

NMR ^1H (200 MHz, Pyd_5) δ : 1, 04 (3H, t, $\text{RCOOCH}_2\text{CH}_3$, $J=7,12$ Hz); 4, 10 (2H, q, $\text{RCOOCH}_2\text{CH}_3$, $J=7,14$ Hz); 5, 99 (2H, s, OCH_2O); 7, 39 (2H, d, C3'-H e C5'-H , $J=8,79$ Hz); 7, 78 (2H, d, C2'-H e C6'-H , $J=8,78$ Hz); 8, 49 (1H, s, C8-H); 9, 27 (2H, s, C4-H e C5-H); 10,58 (1H, s, CO-NH-PhBr); 12, 44 (1H, s, Pyr-NH-OC) ppm.

NMR ^{13}C (50 MHz, Pyd_5) δ : 14, 5 ($\text{RCOOCH}_2\text{CH}_3$); 60, 8 ($\text{RCOOCH}_2\text{CH}_3$); 104, 6 (OCH_2O); 108, 5 (C8); 133, 9 (C3); 115, 1 (C5); 119, 9 (C4'); 120, 8 (C2' e C6'); 122, 0 (C4a); 132, 1 (C3' e C5'); 138, 3 (C1'); 139, 4 (C4); 145, 7 (NCON); 147, 4 (C8a); 151, 7 (C7); 152, 8 (C6); 154, 3 (C2); 167, 3 (RCOOR') ppm.

IR (KBr pellet): 3299 (ν_{as} N-H); 3218 (ν_{s} N-H); 1682 (ν C=O ester); 1616 (ν C=O urea); 1525 (ν C-O-C ester); 1488 (ν C=C); 1243 (ν_{as} C-O-C); 1030 (ν_{s} C-O-C) cm^{-1} .

Ethyl 6-(4-nitro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin -7-carboxylate (3i);

5 This derivative was obtained in 75% yield, through the nucleophilic addition of the 2-amino-quinolin derivative (10) to the 4-nitro-phenylisocyanate, as an amorphous yellow solid with mp.: 227-230°C.

NMR ^1H (200 MHz, Pyd_5) δ : RMN ^1H (200 MHz; $\text{DMSO}-d_6$) δ : 1, 39 (3H, t, $\text{RCOOCH}_2\text{CH}_3$, $J=7,08$); 4, 45 (2H, q, $\text{RCOOCH}_2\text{CH}_3$, $J=7,09$); 6, 54 (2H, s, OCH_2O); 8, 11 (2H, d, $\text{C}_3\text{'-H}$ e $\text{C}_5\text{'-H}$, $J=9,28$ Hz); 8, 84 (2H, d, $\text{C}_2\text{'-H}$ e $\text{C}_6\text{'-H}$, $J=9,28$); 8, 92 (1H, s, $\text{C}_8\text{-H}$); 9, 47 (1H, s, $\text{C}_5\text{-H}$); 9, 48 (1H, s, $\text{C}_4\text{-H}$), 10,67 (1H, s, CO-NH-PhNO_2); 13, 19 (1H, s, Pyr-NH-OC) ppm.

NMR ^{13}C (50 MHz, $\text{DMSO}-d_6$) δ : 15, 3 ($\text{RCOOCH}_2\text{CH}_3$); 60, 7 ($\text{RCOOCH}_2\text{CH}_3$); 105, 8 (OCH_2O); 109, 7 (C8); 117, 9 (C3); 118, 4 (C2' e C6'); 15 127, 2 (C5); 128, 5 (C4a); 130, 1 (C4'); 136, 5 (C3' e C5'); 143, 4 (C1'); 145, 0 (C4); 145,7 (NCON); 148, 8 (C8a); 150, 2 (C7); 154, 4 (C6); 158, 4 (C2); 170, 1 (RCOOR') ppm.

IR (KBr pellet): 3270 (ν_{as} N-H); 3253 (ν_{s} N-H); 1747 (ν C=O ester); 1684 (ν C=O urea); 1598 (ν C-O-C ester); 1499 (ν C=C); 1247 (ν_{as} C-O-C); 1033 (ν_{s} C-O-C) cm^{-1} .

Ethyl 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin -7-carboxylate (4m);

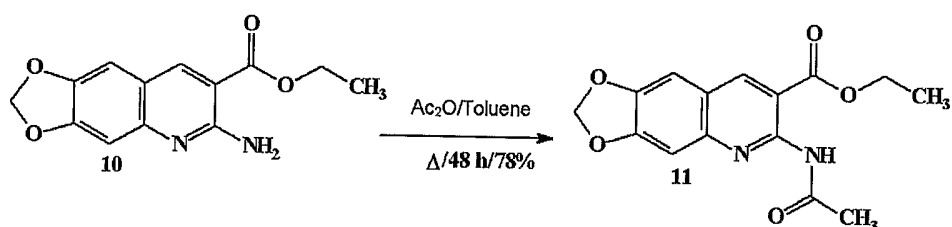
25 This derivative was obtained in 80% yield, through the nucleophilic addition of the derivative 2-amino-quinolin (10) to cyclohexylisocyanate, as an amorphous brown solid with mp.: 179-182°C.

NMR ^1H (200 MHz, $\text{DMSO}-d_6$) δ : 1, 42 (3H, t, $\text{RCOOCH}_2\text{CH}_3$, $J=6,96$ Hz); 1, 61-2, 17 (10 H, m, $\text{C}_2\text{'-H}_2/\text{C}_6\text{'-H}_2$, $\text{C}_3\text{'-H}_2/\text{C}_5\text{'-H}_2$, $\text{C}_4\text{'-H}_2$); 3, 80-4, 01 (1H, m, C1'); 4, 38 (2H, q, $\text{RCOOCH}_2\text{CH}_3$, $J=6,96$ Hz); 6, 13 (1H, s, OCH_2O); 7, 02 (2H, s, C5 e C8); 8, 62 (1H, s, C4); 10,01 (1H, d, $\text{CO-NH-C}_6\text{H}_{11}$, $J=7,69$ Hz); 10, 12 (1H, s, Pyr-NH-OC) ppm.

NMR ^{13}C (50 MHz, DMSO- d_6) δ : 14, 1 ($\text{RCOOCH}_2\text{CH}_3$); 24, 2 e 24, 6 (C3' e C5'); 25, 3 (C4'); 32, 5 e 33, 4 (C2' e C6'); 47, 9 (C1'); 54, 9 ($\text{RCOOCH}_2\text{CH}_3$); 102, 6 (OCH_2O); 102, 7 (C8); 105, 0 (C5); 107, 8 (C3); 119, 0 (C4a); 141, 4 (C4); 145, 0 (C8a); 146, 7 (NCON); 150, 0 (C7); 153, 0 (C6); 154, 2 (C1); 166, 1 (RCOOR') ppm.

IR (pastille KBr): 3285 (ν_{as} N-H); 3213 (ν_{s} N-H); 1681 (ν C=O ester); 1617 (ν C=O urea); 1528 (ν C-O-C de ester); 1480 (ν C=C); 1240 (ν_{as} C-O-C); 1032 (ν_{s} C-O-C) cm^{-1} .

Ethyl 6-acetylamino [1,3]dioxolo [5,4-G] quinolin -7-carboxylate (11)



10

In a round-bottom flask, containing the *orto*-aminoquinoline derivative **10** (6,04mg; 2,21mmol), it was added anhydrous toluene (30mL) and acetic anhydride (0,5mL), maintaining the resultant mixture in vigorous magnetic stir at reflux temperature for 48 hours. The isolation was achieved by cooling the reaction medium in ice-bath, followed by buckner funnel filtration of the formed solid, that was then washed with hot AcOEt, to produce a powder-like brown solid in 78% yield.

15

NMR ^1H (200 MHz; DMSO- d_6) δ : 1, 21 (3H, t, $\text{RCOOCH}_2\text{CH}_3$, $J = 6, 95$); 2, 11 (3H, s, NCOCH_3); 4, 2 (2H, q, $\text{RCOOCH}_2\text{CH}_3$, $J = 6, 95$); 6, 27 (2H, s, OCH_2O); 7, 2 (1H, s, $\text{C}_8\text{-H}$); 7, 43 (1H, s, $\text{C}_5\text{-H}$); 8, 47 (1H, s, $\text{C}_4\text{-H}$); 10, 66 (1H, s, Pyr-NH-OC) ppm.

20

IR (KBr pellet): 3284(ν_{as} N-H); 3217 (ν_{s} N-H); 1666(ν C=O ester); 1605 (ν C=O acetyl); 1526 (ν C-O-C ester); 1439 (ν C=C); 1200 (ν_{as} C-O-C); 1040 (ν_{s} C-O-C) cm^{-1} .

25

The new ureidic compounds **LASSBio-947 (3d)**, **LASSBio-948 (3a)**, **LASSBio-949 (3c)** and **LASSBio-998 (4m)** were spectroscopically

characterized and initially evaluated in *in vitro* models using Western blot technique

Western blot is one immunochemical technique usually employed to proteins detection in complex mixtures. The method is based on proteins electrophoretic separation in polyacrilamide gel in the presence of the anionic detergent sodium dodecyl sulfate (SDS), which are transferred for a immobilizing membrane and incubated with specific antibodies for the desired protein-antigen (primary antibody), and thereafter with the antibody conjugated with an indicator (secondary antibody). The optical density of the signal produced can be quantified with an image analysis system [Thursdays L. E. M. *et Al.*, *Biochem Pharmacol.* **2000**, 60, 741; Thursdays, L. E. M. *et Al.*, *Biochem Pharmacol.* **2002**, 64, 1431].

The *Western blot* detection of the MAPK-p38 enzyme in its active, phosphorilated form, is widely used employing specific polyclonal antibodies for the phosphopeptidic sequence that contains the aminoacids threonine and tyrosine in positions 180 and 182, respectively. This technique has been employed for identification and characterization of suitable inhibitors for MAPK-p38 activation, such as pyridinylimidazoles [Chun, K. S. *et Al.*, *Carcinogenesis*, 2004, 25, 713].

In the assays herein described, macrophages obtained from peritoneal washes of lineage C57Bl6 male mice weighing about 25g were used. The macrophages put in culture medium RPMI and distributed in 24 wells plates were stimulated with 10 µg/ml LPS in the absence or presence of the molecules LASSBio-947 (**3d**), LASSBio-948 (**3a**), LASSBio-949 (**3c**) and LASSBio-998 (**4m**). At the same time, controls in the presence of 0.5% of DMSO were done, the same concentration used to dissolve the original molecules. After 1 hour, the cells were lysed and the proteins separated in 10% SDS-PAGE electrophoresis. The macrophages were stimulated with LPS in the presence of synthetic molecules **3a**, **3c**, **3d**, **4m** in concentrations of 1, 10, 100 and 1000 µM or prototype pyridinylimidazole **SB202190** in concentrations 1, 10 and/or 100 µM, used as standard inhibitor. After the electrophoretic run, the transfer to

nitrocellulose matrix took place for 1 hour and was then incubated for another 1h with Tris-PBS buffer with 0.1% of Tween 20 containing 5% of skim milk powdered, in order to impregnate all nitrocellulose pores with milk casein. Afterwards, the same nitrocellulose was incubated for 1h with polyclonal
5 primary antibody anti-MAPK-p38 phosphorylated (BioSource International, USA), followed by incubation with secondary antibody conjugated to peroxidase enzyme (Promega Corporation, USA). Immunoreactivity was detected by ECL system (*enhanced chemiluminescence*, Amersham Bioscience, UK). The quantification of the present reactive regions in autoradiographs was made by
10 image capture through a densitometer GS-700 (Bio-Rad Laboratories, USA) and analyzed by *software* Quantity One (Bio-Rad Laboratories, USA). The obtained values were represented as arbitrary units of relative optical density.

The results shown in Figures 3, 4, 5 and 6 reveal the enzyme activation MAPK-p38 in LPS stimulated macrophages, indicating that the used
15 concentration DMSO as vehicle to prepare the substances did not interfere with this activation. The Figures 3, 5 and 6 confirm that the process was inhibited by **SB202190**, validating the model. It can be seen that the derivatives LASSBio-947 (**3d**), LASSBio-948 (**3a**), LASSBio-949 (**3c**) and LASSBio-998 (**4m**) inhibited in a concentration-dependent manner the enzyme MAPK-p38
20 activation induced by LPS. The IC₅₀ values obtained, determined by densitometry, for derivatives LASSBio-947 (**3d**), LASSBio-948 (**3a**), LASSBio-949 (**3c**) and LASSBio-998 (**4m**) were 8.7 μ M, 13.6 μ M, 30 μ M e 5.5 μ M, respectively (Figures 3, 4, 5 and 6).

From these results, confirming the action of the functionalized derivatives
25 ethyl 6-N-cycloalkyl and 6-N-aryl ureas-[1,3]-dioxolo[4,5-g]quinolin-7-carboxylate as MAPK-p38 enzyme inhibitors, designed by Sperandio da Silva and col. [Sperandio da Silva, G. M. *et. al.*, *Bioorg. Med. Chem.* **2004**, 12, 3159], through QSAR studies, using CoMFA model, one decided to investigate the anti-inflammatory *in vivo* activity in the zymosan induced arthritis inflammation
30 model in C57Bl6 mice.

The inflammation was induced by zymosan intraplantar injection and evaluated by the correspondent popliteus lymphonode weight increase, compared with non-treated animals [Ibrahim, T. et al International Immunopharmacology 2002, 2, 875].

5 The popliteus lymphonode weight used as inflammation evaluation parameter is based on similarities found between the synovial membrane and the lymphonode, such as:

- organization of lymphoid infiltrated and high levels of TNF- α associated to lymphocytes produced IFN- γ .
- 10 • Interaction between macrophages and lymphocytes in paracortical area rich in CD4+ lymphocytes, with occasional formation of germinatives centers and areas characterized by the predominance of CD8+ lymphocytes.

Groups of from 6 to 8 C57Bl6 mice received a subcutaneous injection of 150 μ g zymosan (solution prepared in sterile saline) in the left paw. The control group received sterile saline. 72 hours after the injection, the animals were treated daily with intraperitoneal injections containing derivatives LASSBio-947 (3d), LASSBio-948 (3a), LASSBio-949 (3c) in doses of 10 mg/kg, during four (4) days. After this period, the animals have been sacrificed, the lymphonodes extracted and weighed.

20 Figure 7 show that the zymosan intraplantar injection increases about 10 times the left paw drainage lymphonode weight. The treatment with compound L-949 (3c) reduced this increase in 60% ($p < 0,001$), with compound L-948 (3a) reduced in 45% and with compound **L-947 (3d)** in 10%, indicating the anti-inflammatory action of these compounds.

25 The compound ethyl 6-(4-chloro-phenylurea)-[1,3]dioxolo[5,4-g]quinolin-7-carboxylate (3c; **LASSBio-949**), new MAPK-p38 inhibitor prototype, displayed anti-inflammatory profile similar to rofecoxibe (10 mg/kg), used as reference (data not shown).

30 The after treatment weight reduction with original compounds was followed by a lymphonode lymphocytes number reduction, as shown in Figure 8, suggesting an immunomodulator effect for these substances.

Considering that the MAPK-p38 pathway can be involved in NF κ B activation and pro-inflammatory cytokines synthesis, one decided to investigate the effect of the treatment with the ureidic compounds, designed as MAPK-p38 inhibitors, on the NF κ B translocation from the cytoplasm to the nucleus of lymphocytes. In non-stimulated cells, the NF κ B is inactive in the cytoplasm forming a complex with protein I κ B. The activation of MAPK kinases induces the phosphorylation of others kinases such as I κ B-kinase, freeing NF κ B to translocate to the nucleus and to bind in DNA sequences promoting the transcription of pro-inflammatory cytokines. [Sem, R et al., Cell 1986, 46, 705; Min-Jean, Y. et. al., Nature, 1998, 396, 77].

Figure 9 shows that the treatment with compounds **LASSBio-947 (3d)**, **LASSBio-948 (3a)** and **LASSBio-949 (3c)** inhibited the NF κ B translocation to the lymphocytes nucleus, measured through the electrophoretic mobility shift assay. These results support the hypothesis that the zymosan inflammatory response reduction for these derivatives in the arthritis model is MAPK-p38 inhibition-dependent. The anti-inflammatory profile of the ureidic derivatives were different from rofecoxib, a well-known COX-2 inhibitor, used as reference.

These results show the ability of the new functionalized derivatives ethyl 6-N-alkyl and/or 6-N-aryl ureas-[1,3]dioxolo[5,4-g]quinolin-7-carboxylate to inhibit the MAPK-p38 enzyme and the NF κ B activation pathways, with consequent reduction of inflammatory response, evaluated in chronic inflammation *in vivo* model, suggesting the therapeutical use of these substances in the treatment of inflammatory conditions such as different types of arthritis, asthma, Crohn's disease and *diabetes mellitus* of type I, among others.

Protocols used for bioassays

p38 α -MAPK Western-blotting Assay

Peritoneal macrophages: C57Bl6 mice weighing approximately 25g were chosed. The cells were collected through washing of peritoneal cavity with

5 mL RPMI 1640/sodium bicarbonate media (Sigma Chemical Co., the USA) without serum. After that, the cells were washed 3 times with this same media and counted in Neubauer chamber. To separate the macrophages, 10^6 cells had been resuspended in 300 μ L of RPMI/BIC media and placed to adhere in 24-wells plates at 37°C in a moist atmosphere of 5% CO₂. After 1 hour, the plates were washed with media in order to remove the loose cells. The adhered cells had then been used for the assay.

MAPK-p38 inhibition Assay: The adhered macrophages had been stimulated with 1 μ g/mL LPS for 1 h, in presence of compounds LASSBio-947, LASSBio-948, LASSBio-949 and LASSBio-998 in increasing logarithmic concentrations (Figures 3, 4, 5 and 6). The control was treated with 0.5% DMSO.

Cell harvesting for Immunodetection (Western blotting): After treatment with LASSBio 948, 100 μ L of sample buffer (Tris 1mM pH 6.8, 20% glycerol, 10% sodium dodecylsulphate - SDS, 20% β -mercaptoethanol) to each well of the 24-well plate with rotatory movements of the pipette tip. The cells were collected, kept at 100°C for 5 minutes and centrifuged for 10 min at 6000 g (Costar Mini Centrifuge). The supernatant was stored at -20°C until the moment for western blotting.

SDS-PAGE and Western Blotting: SDS-PAGE was carried according Laemmli (1970). The samples were separated in gel with 10% of polyacrylamide and transferred to nitrocellulose papers. The nitrocellulose was incubated for 1 h in TBS (Tris-buffered saline) + Tween 20 (TTBS) containing 5% of skim milk powdered. Then, the same nitrocellulose was incubated for 1 h with monoclonal antibody anti-MAP kinase p38-MAPK phosphorylated ((Biosource), followed by the incubation with rabbit anti-IgG antibody conjugated with peroxidase. The immunoreactivity was detected by ECL system (enhanced chemiluminescence's, Amersham) [Quintas et al., 2000]. The densitometric analysis quantification to compare different groups is performed by computer readings of the autoradiograph.

NF κ B detection in nuclear extract

Nuclear Extract: Lymphonode lymphocytes were incubated with 100 μ L of HEPES buffer 10 mM; KCl 10 mM; MgCl₂ 2 mM; EDTA 0.1 mM - pH 8.0; PMSF 0.01 mM, DTT 1.0 mM, aprotinin 10 mg/mL and NaF 100mM (Buffer A) at 4°C for 10 minutes. After the incubation period 6 μ L of nonidet P 40 were added and centrifuged at 16000g for 20 s. After the centrifugation, the precipitated was resuspended in 100 μ L Buffer A and re-centrifuged at 16000g at 4° C for 20 s. This protocol was repeated 2 times. After the last Buffer A wash, the precipitated containing the nuclei was incubated for 10 min at 4° C in nuclear lysis buffer containing HEPES 50 mM; KCl 50 mM; NaCl 300 mM; EDTA 0.1 mM - pH 8,0; glycerol 10%, PMSF 0.01 mM, DTT 1.0 mM, aprotinin 10 mg/mL and NaF 100mM (Buffer C). After the incubation period, it was centrifugated at 16000g for 10 min at 4° C. The supernatant containing the nuclear extract was collected and stored at -70° C.

Nucleotide labeling: the oligonucleotides were radioactively labeled with ³²Pi isotope through the use of T4 polynucleotide kinase enzyme. The technique transfer the Pi radical of ATP position γ for the oligonucleotide terminal 5' hydroxyl region. For the labeling, 5 pM of oligonucleotide, 4 μ L of [γ -³²P] -ATP (10 μ Ci - Amersham, USA), 4 μ L of incubation buffer Tris-HCl 70 mM, MgCl₂ 10 mM, DTT 5 mM pH 7.6 25°C, containing 1.0 μ L of T4 polynucleotide kinase enzyme (20 Richardson units) and 7.5 μ L of deionized water were used.

Electrophoretic mobility shift assay: electrophoreses was made in 6% nondenaturing polyacrylamide gel. HeLa cells were used as positive control. The extracts had been incubated with ³²Pi labeled oligonucleotides (Gibco BRL Tech, USA) for 30 min at 37° C. In each well 4 μ g of protein and approximately 100,000 cpm of labeled probe were addeds. After 2h at 150 V, the gel was dehydrated and analyzed for autoradiography in the Storm Molecular Scan Dynamics (USA).

Induction of zymosan induced inflammation

Male C57Bl6 mice, weighing approximately 25 g, acquired at the Biotério of Rio de Janeiro Federal University were used. All animals handling are

according to the international norms used by the Brazilian College of Animal Experimentation. Each mouse received a 150 µg subcutaneous injection of zymosan prepared in sterile saline in the left paw. The group control received saline.

5 **Treatment of inflammatory process with test-compounds L-947, L-948 and L-949.**

Seventy two hours after the injection of zymosan, the animals were treated with the test-compounds intraperitoneally (i.p.) in doses of 10 mg/kg dissolved in 0.5% of DMSO, during four days. After this, the animals were
10 sacrificed by cervical displacement and the popliteus lymphonodes were extracted and weighed. The cells were counted in Neubauer chamber and used for the nuclear extract preparation.

The compounds of the invention can be administered in a multitude of dosage forms, for example, orally, in the form of tablets, capsules, sugar or
15 tablets covered with films, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, i.e. intramuscular, or by infusion or intravenous and/or intrathecal and/or intraspinal injection.

The present invention also includes pharmaceutical compositions comprising compounds of formula (3a-z; 4a-z; 5a-z), or their acceptable salts, in
20 associations with one pharmaceutically acceptable vehicle (which can be a carrier or diluent).

The pharmaceutical compositions containing the compounds of the invention are prepared following conventional methods and are administered in appropriate pharmaceutical forms.

25 For example, the solid oral forms can contain, along with the active compound, diluents, such as lactose, dextrose, sucrose, cellulose, corn starch or potato starch; lubricants, such as silica, talc, stearic acid, calcium or magnesium stearate, and/or polyethylene glycols; linking agents, for example
30 starches, Arabic gum, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, for example starch, alginic acid, sodium starch alginates or glycolate; effervescent mixtures; colorants; wetting

agents such as lecithin, polysorbates, lauryl sulphates; generally, not toxic and pharmacologically inactive substances common in pharmaceutical formulations. The pharmaceutical preparations can be manufactured using well-known steps, for example, mixture, granulation, tableting, coating or film covering processes.

5 The liquid dispersions for oral administration can be, for example, syrup, emulsions and suspensions. The syrups can contain as carrier, for example, sucrose or sucrose with glycerin and/or manita and/or sorbitol. The suspensions and the emulsions can contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl
10 alcohol.

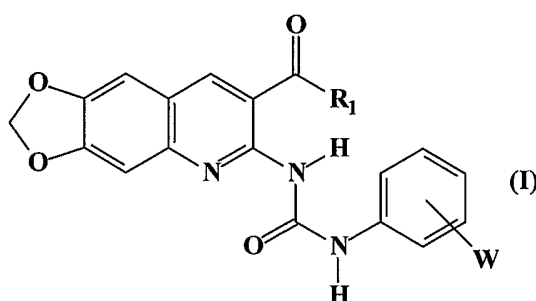
 The suspensions or solutions for intramuscular injections can contain, along with the active substance, a pharmaceutically acceptable carrier, that is sterile water, olive oil, ethyl oleate, glycols, such as propylene glycol of, and, if desired, adequate amount of lidocaine hydrochloride. The solutions for
15 intravenous injections or infusions can contain as carrier, for example, sterile water or preferential they can be in form of sterile water, isotonic or aqueous solutions or they may contain as carrier propylene glycol.

 The suppository can contain along with the active substance a pharmaceutically acceptable carrier, for example, cocoa butter, polyethylene
20 glycol, sorbitan polyoxyethylene, fatty acid ester surfactant or lecithin.

Claims

UREIDIC COMPOUNDS, PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME AND THEIR USE ON THE TREATMENT OF INFLAMMATORY DISEASES

1- Compound N-aryl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized characterized in that it has general formula (I):



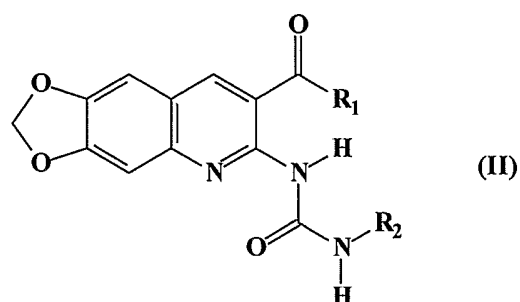
wherein:

R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

W is (2 and/or 3 and/or 4 and/or 5 and/or 6)-F or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Cl or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Br or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CH_2CH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CF_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- OCH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- OCF_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- (2 and/or 3 and/or 4 and/or 5 and/or 6)- NO_2 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- NH_2 ; (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHCH_3$ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHCOCH_3$ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHSO_2CH_3$;

or their salts, pharmaceutically acceptable isosters, solvates and/or hydrates.

2- Compound N-alkyl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized characterized in that it has general formula (II):



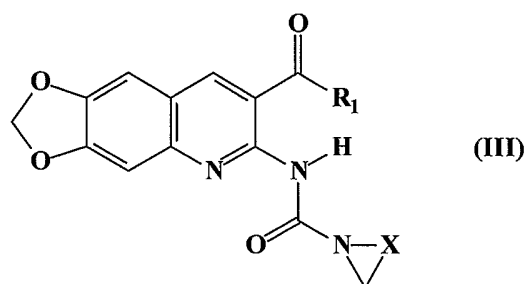
wherein:

R₁ is OCH₃ or OCH₂CH₃ or OPh or OBn or NH₂ or NHCH₃ or NHHNH₂;

R₂ is CH₃ or CH₂CH₃ or (CH₂)₂CH₃ or (CH₂)₃CH₃ or (CH₂)₄CH₃ or
 5 (CH₂)₅CH₃ or CH(CH₃)₂ or C(CH₃)₃ or cyclopropyl, or cyclopentyl or cyclohexyl
 or cycloheptyl;

or their salts, pharmaceutically acceptable isomers, solvates and/or
 hydrates.

3- Compound N-cycloalkyl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized
 10 characterized in that it has general formula (III):



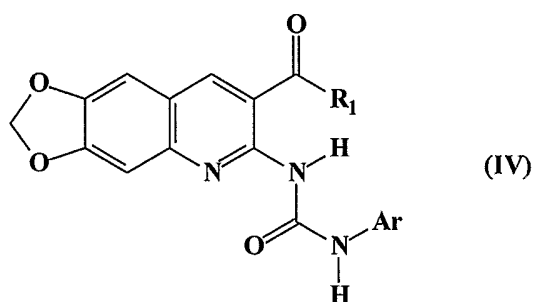
wherein

R₁ is OCH₃ or OCH₂CH₃ or OPh or OBn or NH₂ or NHCH₃ or NHHNH₂;

X is CH₂ or (CH₂)₃ or (CH₂)₄ or (CH₂)₅;

15 or their salts, pharmaceutically acceptable isomers, solvates and/or
 hydrates.

4- Compound N-heteroaryl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized
 characterized in that it has general formula (IV):



wherein

R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

5 Ar is 2-Py or 3-Py or 4-Py or 2-thiophene or 2-furane or 2-pirrole or 1-naphtyl or 2-naphtyl or quinoline, or quinoxaline or oxazole or thiazole or thiadiazole, oxadiazole or pyrimidine or triazole or imidazole;

or their salts, pharmaceutically acceptable isosters, solvates and/or hydrates.

10 **5-** Compound, according to claims 1 and/or 2 and/or 3 and/or 4, characterized in that it is chosen from a group that comprises:

- ethyl 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3a**);
 ethyl 6-(4-fluoro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3b**);
 ethyl 6-(4-chloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3c**);
 15 ethyl 6-(4-bromo-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3d**);
 ethyl 6-(4-methyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3e**);
 ethyl 6-(4-trifluoromethyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3f**);
 ethyl 6-(4-methoxy-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3g**);
 20 ethyl 6-(4-trifluoromethyleter-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3h**);
 ethyl 6-(4-nitro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3i**);
 ethyl 6-(4-amino-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3j**);
 ethyl 6-(4-methylaminophenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3l**);
 ethyl 6-(4-acetamide-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3m**);
 25 ethyl 6-(4-methanesulfonamide-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3n**);

- ethyl 6-(2,6-difluoro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3o**);
ethyl 6-(2-chloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3p**);
ethyl 6-(3-chloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3q**);
ethyl 6-(2,3-dichloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3r**);
5 ethyl 6-(2,6-dichloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3s**);
ethyl 6-(4-ethyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3t**);
ethyl 6-(2,6-ethyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3u**);
ethyl 6-(2,6-methyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3v**);
ethyl 6-(2-methoxy-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3x**);
10 ethyl 6-(2-nitro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3z**);
ethyl 6-methylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4a**);
ethyl 6-ethylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4b**);
ethyl 6-propylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4c**);
ethyl 6-isopropylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4d**);
15 ethyl 6-terbutylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4e**);
ethyl 6-butylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4f**);
ethyl 6-pentylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4g**);
ethyl 6-hexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4h**);
ethyl 6-benzylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4i**);
20 ethyl 6-cyclopropylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4j**);
ethyl 6-cyclopentylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4l**);
ethyl 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4m**);
ethyl 6-cycloheptylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4n**);
methyl 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4o**);
25 fenyla 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4p**);
benzyl 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4q**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-acid carboxamide (**4r**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-methylcarboxamide (**4s**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carbonylhydrazine (**4t**);
30 methyl 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4u**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxamide (**4v**);

- 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-acid carboxylic(**4x**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carbonylhydrazine (**4z**);
ethyl 6-(2-pyridinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5a**);
ethyl 6-(3-pyridinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5b**);
5 ethyl 6-(4-pyridinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5c**);
ethyl 6-(2-thienylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5d**);
ethyl 6-(2-furylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5e**);
ethyl 6-(2-imidazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5f**);
ethyl 6-(2-pirrollylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5g**);
10 ethyl 6-(2-pirazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5h**);
ethyl 6-(1,3,4-thiadiazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5i**);
ethyl 6-(1,3,4-oxadiazolylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5j**);
ethyl 6-(1-naphtylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5l**);
ethyl 6-(2-naphtylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5m**);
15 ethyl 6-(2-quinolinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5n**);
ethyl 6-(4-pyrimidinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5o**);
ethyl 6-(4-quinazolinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5p**);
ethyl 6-(1,3-oxazolinyurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5q**);
ethyl 6-(1,3-thiazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5r**);
20 ethyl 6-(1*H*-5-imidazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5s**);
ethyl 6-(4*H*-1,2,4-triazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5t**);
methyl 6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate
(**5u**);
6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-
25 carboxamide(**5v**);
6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-acid
carboxylic(**5x**);
6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-
carbonylhydrazine(**5z**);
30 and mixtures thereof.

6- Compound, according to claims 1 and/or 2 and/or 3 and/or 4, characterized in that it has anti-inflammatory properties.

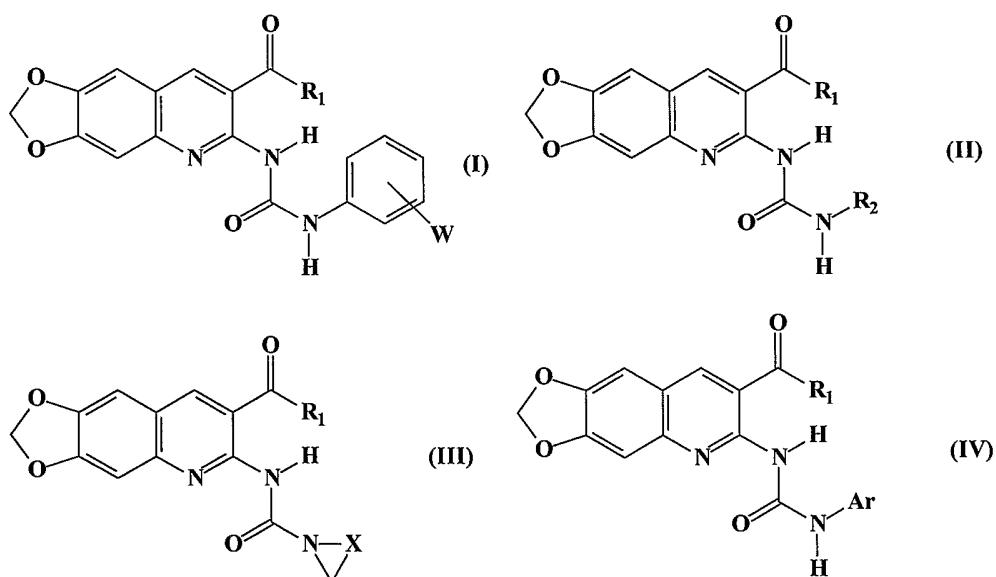
7- Compound, according to claim 6, characterized in that it has the capacity to inhibit MAPK-p38 enzyme.

5 8- Compound, according to claim 6, characterized in that it has the capacity to inhibit NF κ B activation.

9- Compound, according to claim 6, characterized in that it is used as anti-inflammatory.

10 10- Compound, according to claim 9, characterized in that it is used in the treatment and/or control of acute and/or chronic inflammatory conditions.

11- Process of production of compounds of general formula (I) and/or (II) and/or (III) and/or (IV) below:



15

wherein:

R₁ is OCH₃ or OCH₂CH₃ or OPh or OBn or NH₂ or NHCH₃ or NHHNH₂;

W is (2 and/or 3 and/or 4 and/or 5 and/or 6)-F or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Cl or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Br or (2 and/or 3 and/or 4 and/or 5 and/or 6)-CH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-CH₂CH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-CF₃ or (2 and/or 3 and/or 4

20

and/or 5 and/or 6)-OCH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-OCF₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- (2 and/or 3 and/or 4 and/or 5 and/or 6)-NO₂ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-NH₂; (2 and/or 3 and/or 4 and/or 5 and/or 6)-NHCH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-NHCOCH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-NHSO₂CH₃;

R₂ is CH₃ or CH₂CH₃ or (CH₂)₂CH₃ or (CH₂)₃CH₃ or (CH₂)₄CH₃ or (CH₂)₅CH₃ or CH(CH₃)₂ or C(CH₃)₃ or cyclopropyl, or cyclopentyl or cyclohexyl or cycloheptyl;

Ar is 2-Py or 3-Py or 4-Py or 2-thiophene or 2-furane or 2-pirrole or 1-naphtyl or 2-naphtyl or quinoline, or quinoxaline or oxazole or thiazole or thiadiazole, oxadiazole or pyrimidine or triazole or imidazole;

characterized in that it comprises the steps of:

a) Regioselective aromatic electrophilic substitution of the benzo[d][1,3]dioxole-5-carbaldehyde or piperonal system;

b) Treatment of the nitro intermediate with ethyl cyanoacetate, in presence of potassium fluoride doped alumina (KF/Al₂O₃) as base, ethanol as solvent, at a temperature of 35°C, exploring a diastereoselective aldolic condensation reaction;

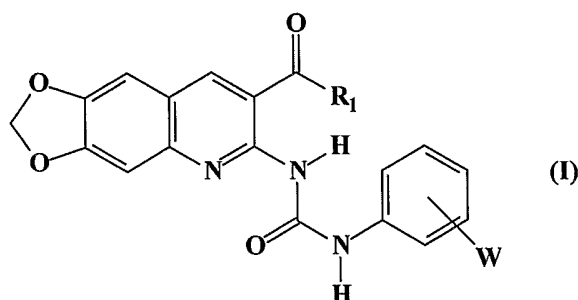
c) Nitro-acrylate of configuration (E) reduction, using titanium tetrachloride (TiCl₄) in presence of zinc (Zn) and tetrahydrofuran as solvent, at reflux temperature, for posterior cyclization of the amino-formed intermediate through intramolecular nucleophilic addition at the nitrile moiety;

d) Condensation of the aminated derivative with arylisocyanates and/or cicloalkylisocyanates and/or alkylisocyanates and/or heteroarylisocyanates, in presence of anhydrous toluene at reflux temperature;

e) Functional groups interconversions of intermediates, such as transsterification, hydrolysis, aminolysis and hidrazinolysis reactions.

12- Pharmaceutical composition characterized in that it comprises:

A) Compound N-aryl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized of general formula (I):



wherein:

R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

5 W is (2 and/or 3 and/or 4 and/or 5 and/or 6)-F or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Cl or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Br or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CH_2CH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CF_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- OCH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- OCF_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- $(2 \text{ and/or } 3 \text{ and/or } 4 \text{ and/or } 5 \text{ and/or } 6)-NO_2$ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- NH_2 ; (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHCH_3$ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHCOCH_3$ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHSO_2CH_3$;

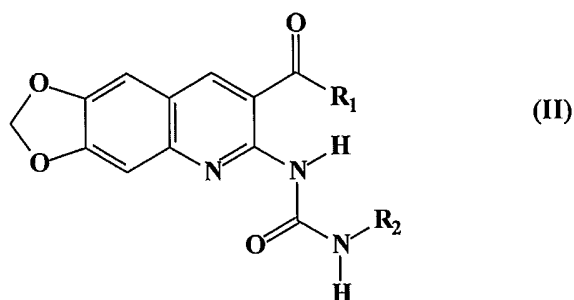
15 or their salts, pharmaceutically acceptable isomers, solvates and/or hydrates.

B) a pharmaceutically acceptable vehicle.

13- Pharmaceutical composition characterized in that it comprises:

A) Compound N-alkyl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized of general formula (II):

20



wherein:

R₁ is OCH₃ or OCH₂CH₃ or OPh or OBn or NH₂ or NHCH₃ or NHHNH₂;

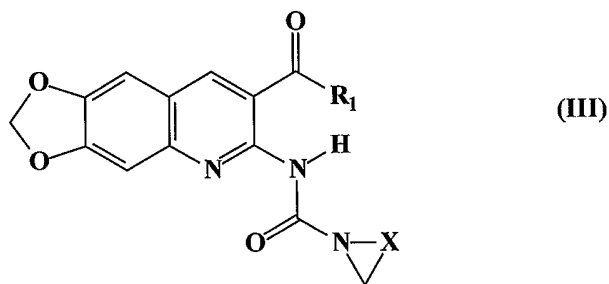
5 R₂ is CH₃ or CH₂CH₃ or (CH₂)₂CH₃ or (CH₂)₃CH₃ or (CH₂)₄CH₃ or (CH₂)₅CH₃ or CH(CH₃)₂ or C(CH₃)₃ or cyclopropyl, or cyclopentyl or cyclohexyl or cycloheptyl;

or their salts, pharmaceutically acceptable isomers, solvates and/or hydrates.

10 B) a pharmaceutically acceptable vehicle.

14- Pharmaceutical composition characterized in that it comprises:

A) Compound N-cycloalkyl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized of general formula (III):



15 wherein

R₁ is OCH₃ or OCH₂CH₃ or OPh or OBn or NH₂ or NHCH₃ or NHHNH₂;

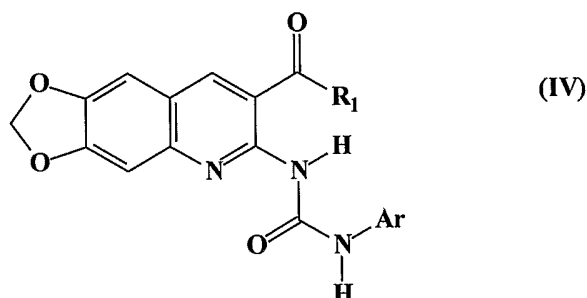
X is CH₂ or (CH₂)₃ or (CH₂)₄ or (CH₂)₅;

or their salts, pharmaceutically acceptable isomers, solvates and/or hydrates.

20 B) a pharmaceutically acceptable vehicle.

15- Pharmaceutical composition, characterized in that it comprises:

A) Compound N-heteroaryl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized of general formula (IV):



wherein

R₁ is OCH₃ or OCH₂CH₃ or OPh or OBn or NH₂ or NHCH₃ or NHNH₂;

Ar is 2-Py or 3-Py or 4-Py or 2-thiophene or 2-furane or 2-pyrrole or 1-naphthyl or 2-naphthyl or quinoline, or quinoxaline or oxazole or thiazole or thiadiazole, oxadiazole or pyrimidine or triazole or imidazole;

or their salts, pharmaceutically acceptable isomers, solvates and/or hydrates.

16- Pharmaceutical composition, according to claims 12 and/or 13 and/or 14 and/or 15, characterized in that it has anti-inflammatory properties.

17- Pharmaceutical composition, according to claim 16, characterized in that it has the capacity to inhibit MAPK-p38 enzyme.

18- Pharmaceutical composition, according to claim 16, characterized in that it has the capacity to inhibit NFκB activation.

19- Pharmaceutical composition, according to claim 16, characterized in that it is used as anti-inflammatory.

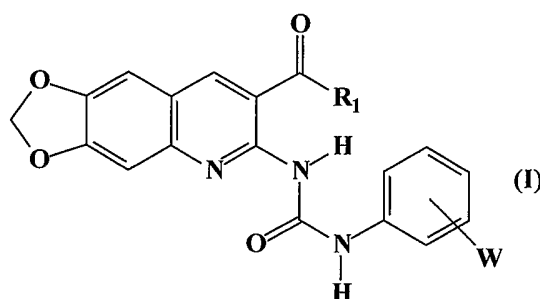
20- Pharmaceutical composition, according to claim 19, characterized in that it is used in the treatment and/or control of acute and/or chronic inflammatory conditions.

AMENDED CLAIMS

Received by the International Bureau on 23 october 2006 (23.10.06)

UREIDIC COMPOUNDS, PHARMACEUTICAL COMPOSITIONS CONTAINING
THE SAME AND THEIR USE ON THE TREATMENT OF INFLAMMATORY
DISEASES

1- Compound N-aryl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized characterized in that it has general formula (I):



wherein:

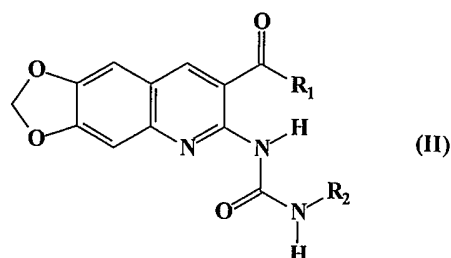
R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

W is (2 and/or 3 and/or 4 and/or 5 and/or 6)-F or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Cl or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Br or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CH_2CH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- CF_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- OCH_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- OCF_3 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- (2 and/or 3 and/or 4 and/or 5 and/or 6)- NO_2 or (2 and/or 3 and/or 4 and/or 5 and/or 6)- NH_2 ; (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHCH_3$ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHCOCH_3$ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- $NHSO_2CH_3$;

or their salts, pharmaceutically acceptable isosters, solvates and/or hydrates.

2- Compound N-alkyl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized characterized in that it has general formula (II):

AMENDED SHEET (ARTICLE 19)



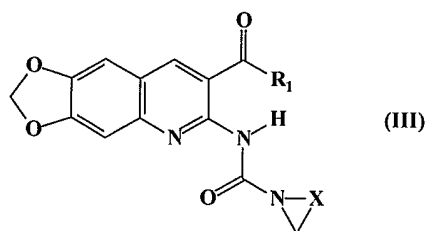
wherein:

R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

R_2 is CH_3 or CH_2CH_3 or $(CH_2)_2CH_3$ or $(CH_2)_3CH_3$ or $(CH_2)_4CH_3$ or
 5 $(CH_2)_5CH_3$ or $CH(CH_3)_2$ or $C(CH_3)_3$ or cyclopropyl, or cyclopentyl or cyclohexyl
 or cycloheptyl;

or their salts, pharmaceutically acceptable isosters, solvates and/or
 hydrates.

3- Compound N-cycloalkyl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized
 10 characterized in that it has general formula (III):



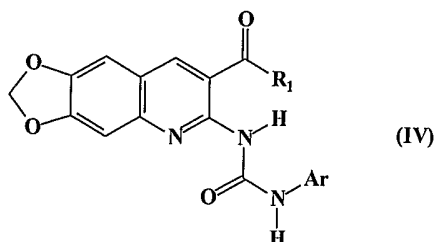
wherein

R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

X is CH_2 or $(CH_2)_3$ or $(CH_2)_4$ or $(CH_2)_5$;

15 or their salts, pharmaceutically acceptable isosters, solvates and/or
 hydrates.

4- Compound N-heteroaryl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized
 characterized in that it has general formula (IV):



wherein

R₁ is OCH₃ or OCH₂CH₃ or OPh or OBn or NH₂ or NHCH₃ or NHNH₂;

Ar is 2-Py or 3-Py or 4-Py or 2-thiophene or 2-furane or 2-pirrole or 1-naphtyl or 2-naphtyl or quinoline, or quinoxaline or oxazole or thiazole or thiadiazole, oxadiazole or pyrimidine or triazole or imidazole;

or their salts, pharmaceutically acceptable isosters, solvates and/or hydrates.

5- Compound, according to claims 1 and/or 2 and/or 3 and/or 4, characterized in that it is chosen from a group that comprises:

ethyl 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3a**);

ethyl 6-(4-fluoro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3b**);

ethyl 6-(4-chloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3c**);

ethyl 6-(4-bromo-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3d**);

ethyl 6-(4-methyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3e**);

ethyl 6-(4-trifluoromethyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3f**);

ethyl 6-(4-methoxy-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3g**);

ethyl 6-(4-trifluoromethyleter-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3h**);

ethyl 6-(4-nitro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3i**);

ethyl 6-(4-amino-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3j**);

ethyl 6-(4-methylaminophenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3l**);

ethyl 6-(4-acetamide-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3m**);

ethyl 6-(4-methanesulfonamide-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3n**);

ethyl 6-(2,6-difluoro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3o**);

ethyl 6-(2-chloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3p**);

- ethyl 6-(3-chloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3q**);
ethyl 6-(2,3-dichloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3r**);
ethyl 6-(2,6-dichloro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3s**);
ethyl 6-(4-ethyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3t**);
5 ethyl 6-(2,6-ethyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3u**);
ethyl 6-(2,6-methyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3v**);
ethyl 6-(2-methoxy-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3x**);
ethyl 6-(2-nitro-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**3z**);
ethyl 6-methylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4a**);
10 ethyl 6-ethylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4b**);
ethyl 6-propylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4c**);
ethyl 6-isopropylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4d**);
ethyl 6-terbutylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4e**);
ethyl 6-butylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4f**);
15 ethyl 6-pentylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4g**);
ethyl 6-hexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4h**);
ethyl 6-benzylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4i**);
ethyl 6-cyclopropylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4j**);
ethyl 6-cyclopentylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4l**);
20 ethyl 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4m**);
ethyl 6-cycloheptylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4n**);
methyl 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4o**);
fenyla 6-cyclohexylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4p**);
benzyl 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4q**);
25 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-acid carboxamide (**4r**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-methylcarboxamide (**4s**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carbonylhydrazine (**4t**);
methyl 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**4u**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxamide (**4v**);
30 6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-acid carboxylic(**4x**);
6-phenylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carbonylhydrazine (**4z**);

- ethyl 6-(2-pyridinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5a**);
ethyl 6-(3-pyridinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5b**);
ethyl 6-(4-pyridinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5c**);
ethyl 6-(2-thienylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5d**);
5 ethyl 6-(2-furylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5e**);
ethyl 6-(2-imidazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5f**);
ethyl 6-(2-pyrrolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5g**);
ethyl 6-(2-pirazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5h**);
ethyl 6-(1,3,4-thiadiazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5i**);
10 ethyl 6-(1,3,4-oxadiazolylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5j**);
ethyl 6-(1-naphtylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5l**);
ethyl 6-(2-naphtylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5m**);
ethyl 6-(2-quinolinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5n**);
ethyl 6-(4-pyrimidinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5o**);
15 ethyl 6-(4-quinazolinylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5p**);
ethyl 6-(1,3-oxazolinyurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5q**);
ethyl 6-(1,3-thiazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5r**);
ethyl 6-(1*H*-5-imidazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5s**);
ethyl 6-(4*H*-1,2,4-triazolylurea-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate (**5t**);
20 methyl 6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-carboxylate
(**5u**);
6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-
carboxamide(**5v**);
6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-acid
25 carboxylic(**5x**);
6-(4-methanesulfonyl-phenylurea)-[1,3]dioxolo[5,4-*g*]quinolin-7-
carbonylhydrazine(**5z**);
and mixtures thereof.

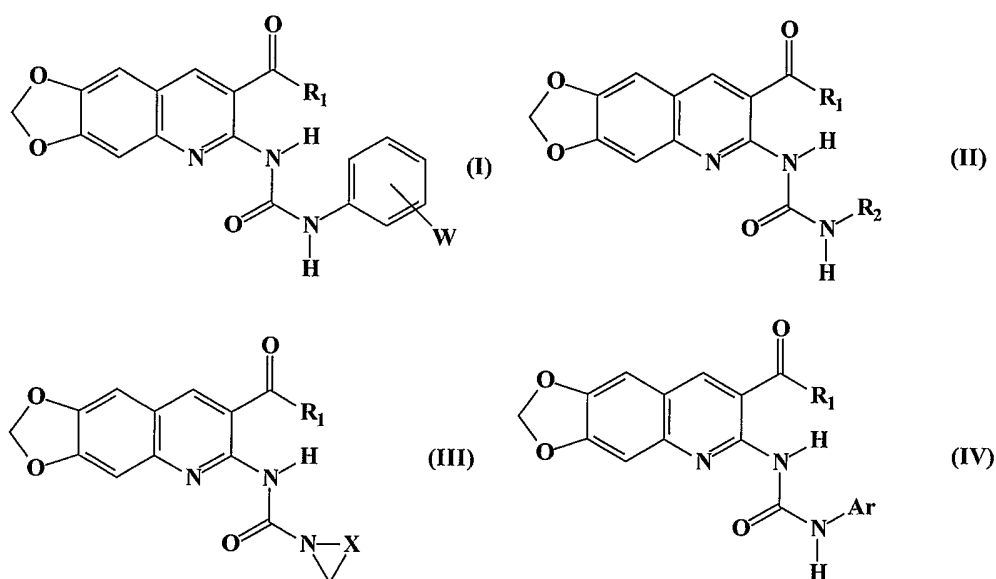
- 6- Compound, according to claims 1 and/or 2 and/or 3 and/or 4,
30 characterized in that it has anti-inflammatory properties.

7- Compound, according to claim 6, characterized in that it has the capacity to inhibit MAPK-p38 enzyme.

8- Compound, according to claim 6, characterized in that it has the capacity to inhibit NF κ B activation.

5 9- Compound, according to claim 6, characterized in that it is used as anti-inflammatory.

10- Process of production of compounds of general formula (I) and/or (II) and/or (III) and/or (IV) below:



wherein:

R₁ is OCH₃ or OCH₂CH₃ or OPh or OBn or NH₂ or NHCH₃ or NHNH₂;

15 W is (2 and/or 3 and/or 4 and/or 5 and/or 6)-F or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Cl or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Br or (2 and/or 3 and/or 4 and/or 5 and/or 6)-CH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-CH₂CH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-CF₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-OCH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-OCF₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)- (2 and/or 3 and/or 4 and/or 5 and/or 6)-NO₂ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-NH₂; (2 and/or 3 and/or 4 and/or

20

5 and/or 6)-NHCH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-NHCOCH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-NHSO₂CH₃;

R₂ is CH₃ or CH₂CH₃ or (CH₂)₂CH₃ or (CH₂)₃CH₃ or (CH₂)₄CH₃ or (CH₂)₅CH₃ or CH(CH₃)₂ or C(CH₃)₃ or cyclopropyl, or cyclopentyl or cyclohexyl or cycloheptyl;

Ar is 2-Py or 3-Py or 4-Py or 2-thiophene or 2-furane or 2-pirrole or 1-naphtyl or 2-naphtyl or quinoline, or quinoxaline or oxazole or thiazole or thiadiazole, oxadiazole or pyrimidine or triazole or imidazole;

characterized in that it comprises the steps of:

10 a) Regioselective aromatic electrophilic substitution of the benzo[d][1,3]dioxole-5-carbaldehyde or piperonal system;

b) Treatment of the nitro intermediate with ethyl cyanoacetate, in presence of potassium fluoride doped alumina (KF/Al₂O₃) as base, ethanol as solvent, at a temperature of 35°C, exploring a diastereoselective aldolic condensation reaction;

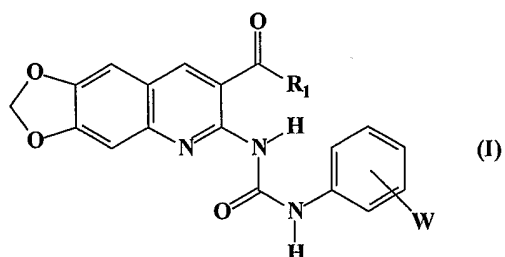
c) Nitro-acrylate of configuration (E) reduction, using titanium tetrachloride (TiCl₄) in presence of zinc (Zn) and tetrahydrofuran as solvent, at reflux temperature, for posterior cyclization of the amino-formed intermediate through intramolecular nucleophilic addition at the nitrile moiety;

20 d) Condensation of the aminated derivative with arylisocyanates and/or cicloalkylisocyanates and/or alkylisocyanates and/or heteroarylisocyanates, in presence of anhydrous toluene at reflux temperature;

e) Functional groups interconversions of intermediates, such as transsterification, hydrolysis, aminolysis and hidrazinolysis reactions.

25 **11-** Pharmaceutical composition characterized in that it comprises:

A) Compound N-aryl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized of general formula (I):



wherein:

R₁ is OCH₃ or OCH₂CH₃ or OPh or OBn or NH₂ or NHCH₃ or NHNH₂;

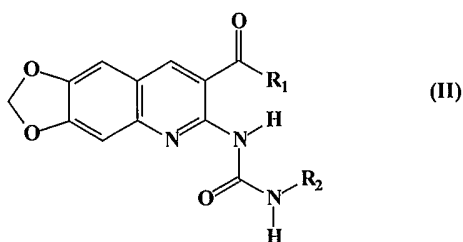
W is (2 and/or 3 and/or 4 and/or 5 and/or 6)-F or (2 and/or 3 and/or 4
 5 and/or 5 and/or 6)-Cl or (2 and/or 3 and/or 4 and/or 5 and/or 6)-Br or (2 and/or 3
 and/or 4 and/or 5 and/or 6)-CH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-
 CH₂CH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-CF₃ or (2 and/or 3 and/or 4
 and/or 5 and/or 6)-OCH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-OCF₃ or (2
 and/or 3 and/or 4 and/or 5 and/or 6)- (2 and/or 3 and/or 4 and/or 5 and/or 6)-
 10 NO₂ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-NH₂; (2 and/or 3 and/or 4 and/or
 5 and/or 6)-NHCH₃ or (2 and/or 3 and/or 4 and/or 5 and/or 6)-NHCOCH₃ or (2
 and/or 3 and/or 4 and/or 5 and/or 6)-NHSO₂CH₃;

or their salts, pharmaceutically acceptable isosters, solvates and/or
 hydrates.

15 B) a pharmaceutically acceptable vehicle.

12- Pharmaceutical composition characterized in that it comprises:

A) Compound N-alkyl-urea-[1,3]dioxolo[5,4-g]quinolin-7-functionalized of
 general formula (II):



20

wherein:

R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

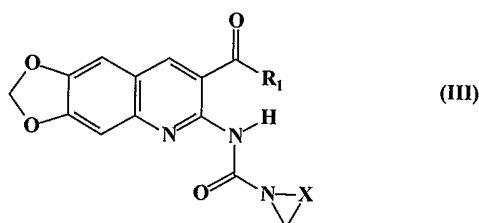
R_2 is CH_3 or CH_2CH_3 or $(CH_2)_2CH_3$ or $(CH_2)_3CH_3$ or $(CH_2)_4CH_3$ or $(CH_2)_5CH_3$ or $CH(CH_3)_2$ or $C(CH_3)_3$ or cyclopropyl, or cyclopentyl or cyclohexyl or cycloheptyl;

5 or their salts, pharmaceutically acceptable isosters, solvates and/or hydrates.

B) a pharmaceutically acceptable vehicle.

13- Pharmaceutical composition characterized in that it comprises:

A) Compound N-cycloalkyl-urea-[1,3]dioxolo[5,4-g]quinolin-7-
10 functionalized of general formula (III):



wherein

R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

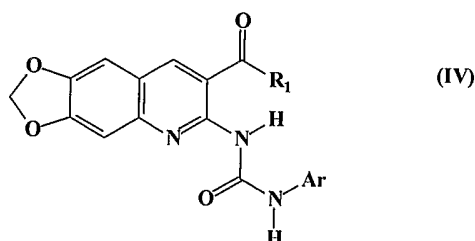
X is CH_2 or $(CH_2)_3$ or $(CH_2)_4$ or $(CH_2)_5$;

15 or their salts, pharmaceutically acceptable isosters, solvates and/or hydrates.

B) a pharmaceutically acceptable vehicle.

14- Pharmaceutical composition, characterized in that it comprises:

A) Compound N-heteroaryl-urea-[1,3]dioxolo[5,4-g]quinolin-7-
20 functionalized of general formula (IV):



wherein

R_1 is OCH_3 or OCH_2CH_3 or OPh or OBn or NH_2 or $NHCH_3$ or $NHNH_2$;

Ar is 2-Py or 3-Py or 4-Py or 2-thiophene or 2-furane or 2-pirrole or 1-naphtyl or 2-naphtyl or quinoline, or quinoxaline or oxazole or thiazole or thiadiazole, oxadiazole or pyrimidine or triazole or imidazole;

5 or their salts, pharmaceutically acceptable isosters, solvates and/or hydrates.

15- Pharmaceutical composition, according to claims 12 and/or 13 and/or 14 and/or 15, characterized in that it has anti-inflammatory properties.

10 **16-** Pharmaceutical composition, according to claim 16, characterized in that it has the capacity to inhibit MAPK-p38 enzyme.

17- Pharmaceutical composition, according to claim 16, characterized in that it has the capacity to inhibit $NF\kappa B$ activation.

18- Pharmaceutical composition, according to claim 16, characterized in that it is used as anti-inflammatory.

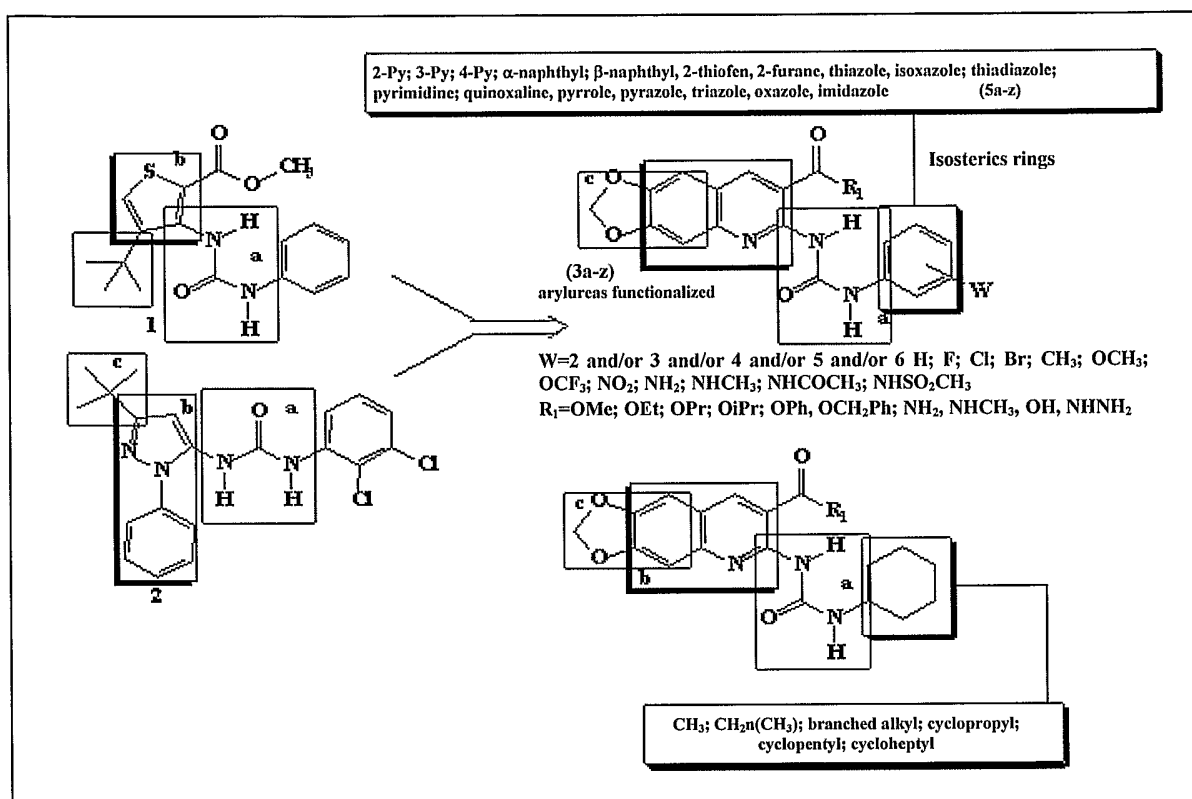


Figure 1

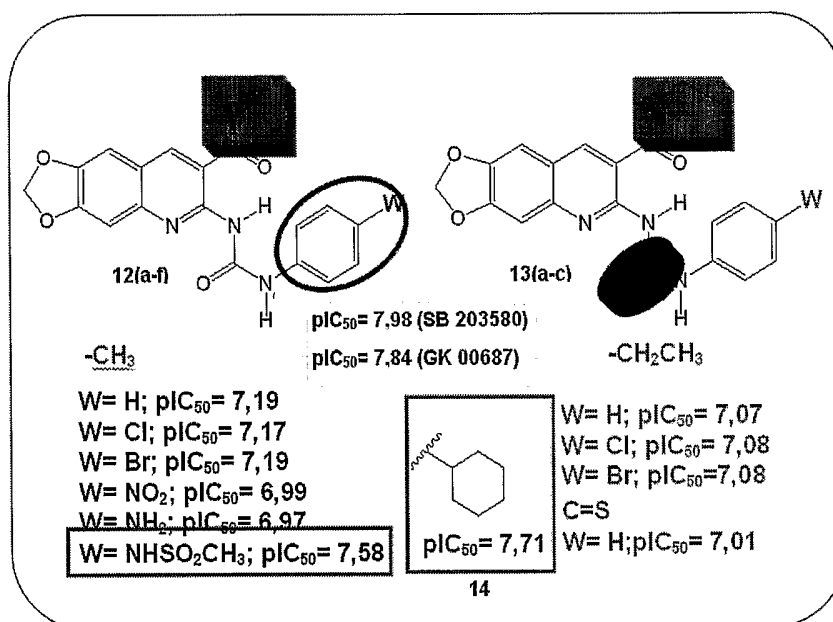


Figure 2

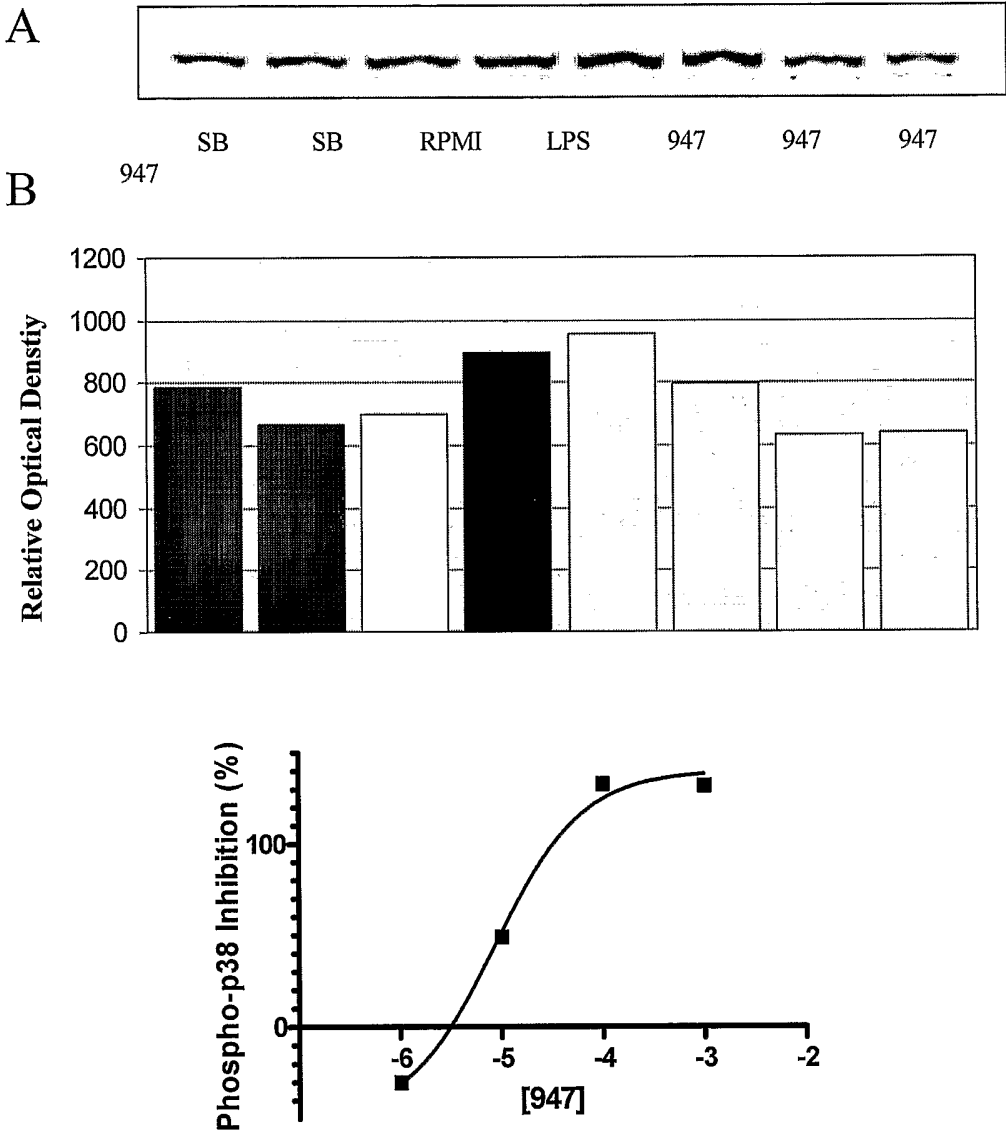


Figure 3

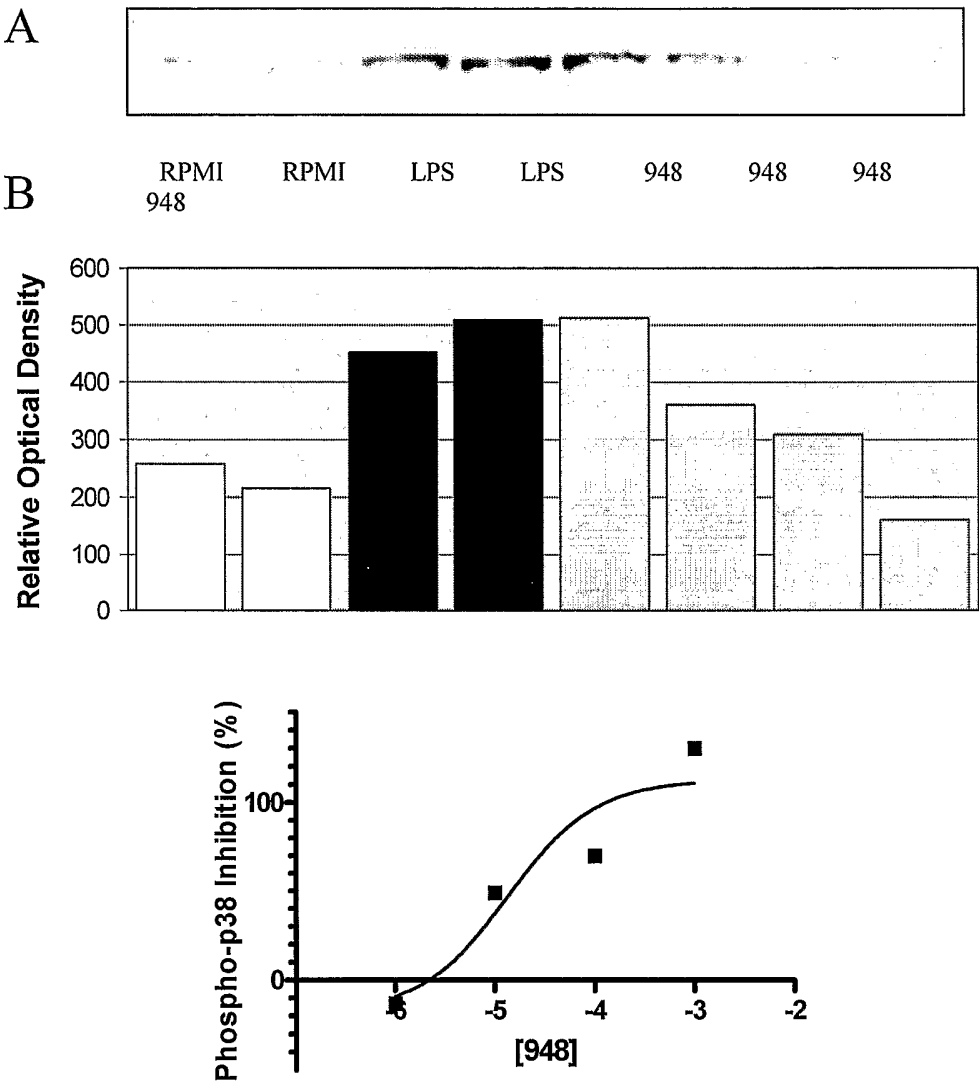


Figure 4

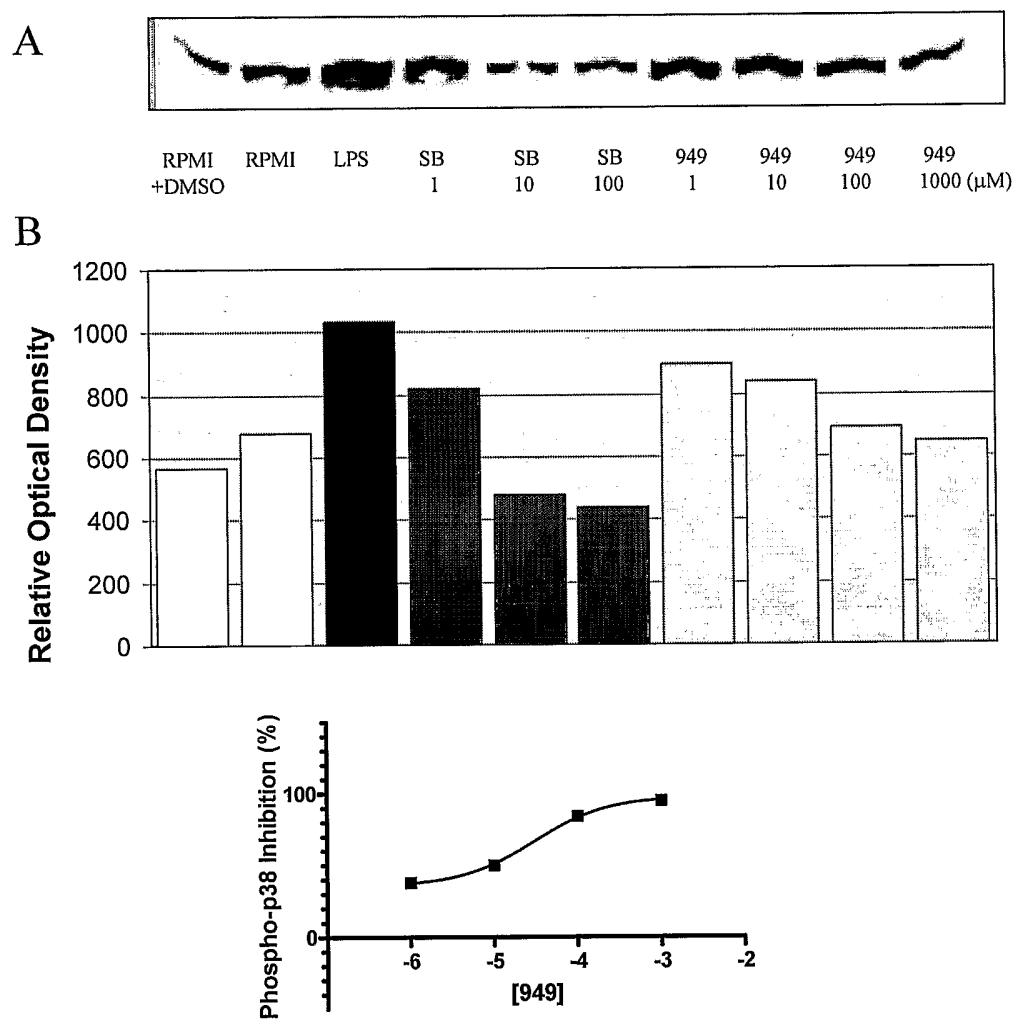


Figure 5

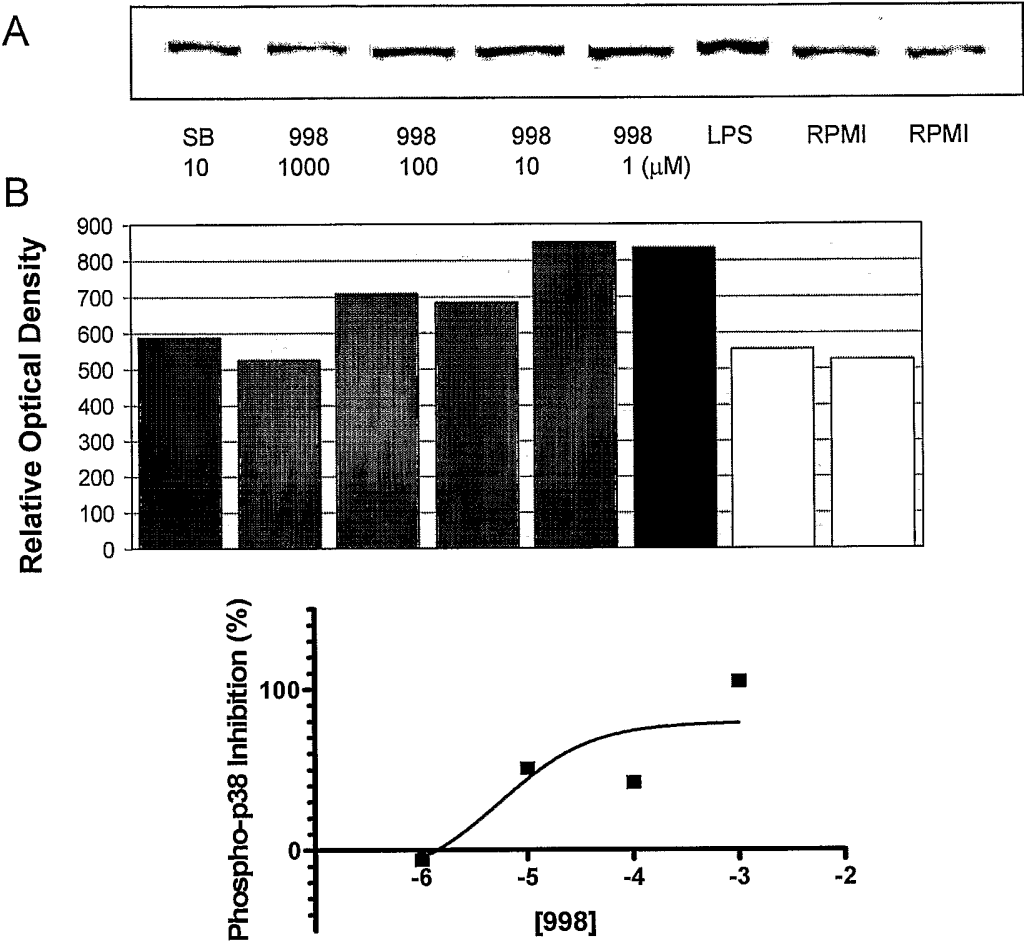


Figure 6

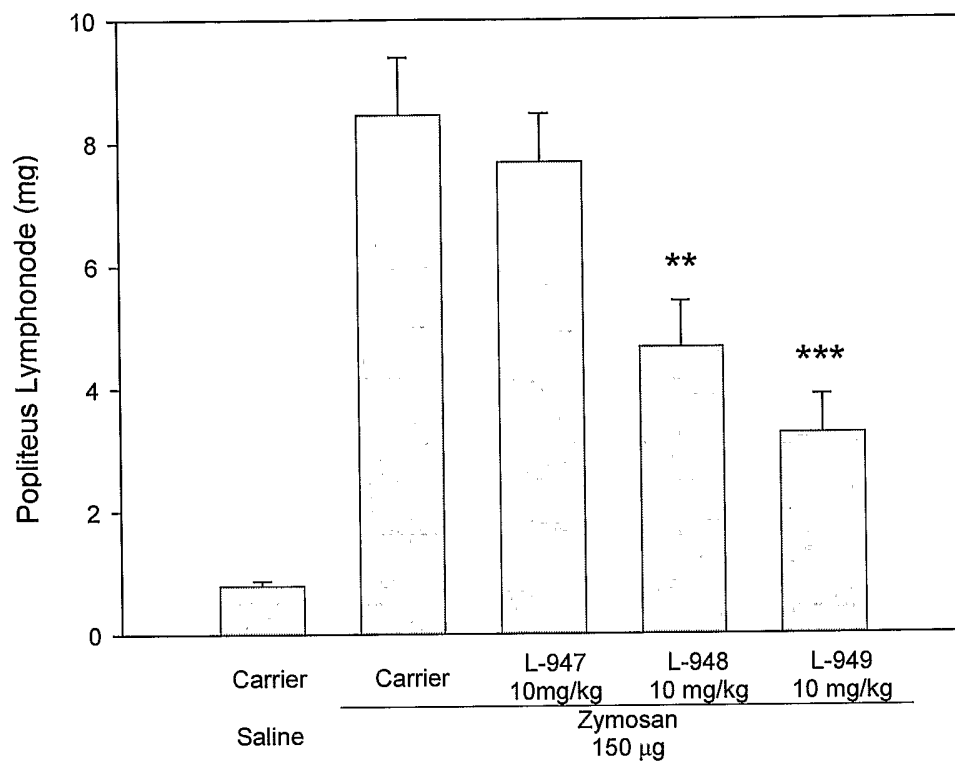


Figure 7

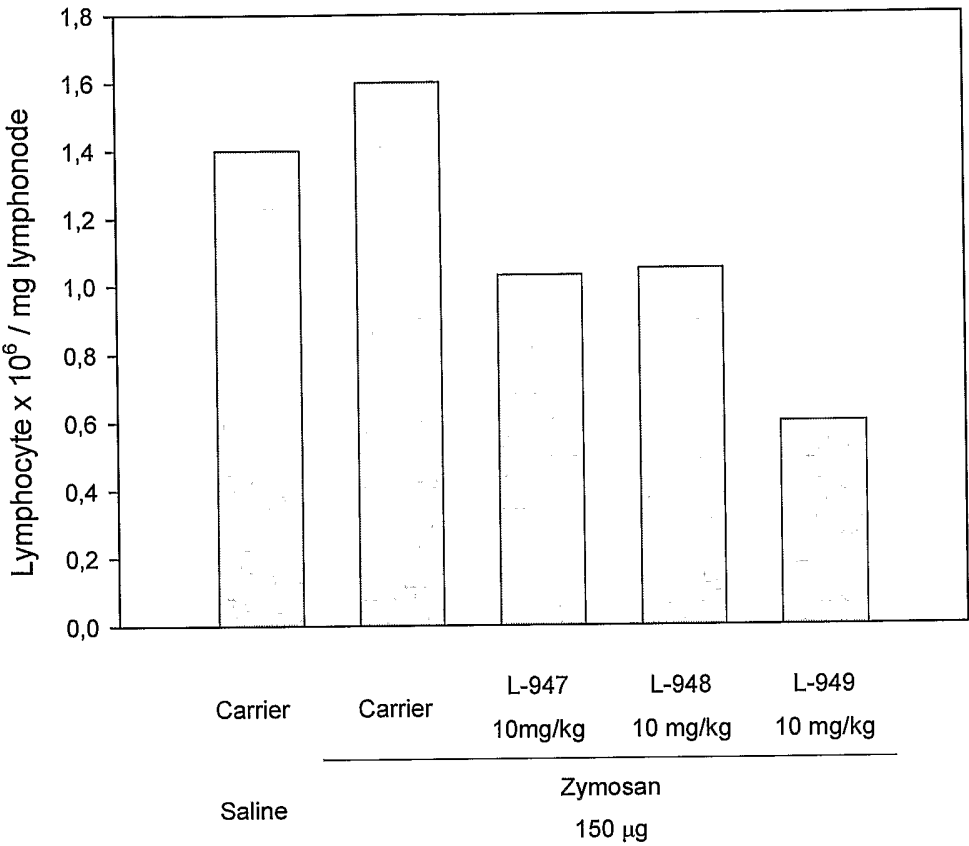


Figure 8

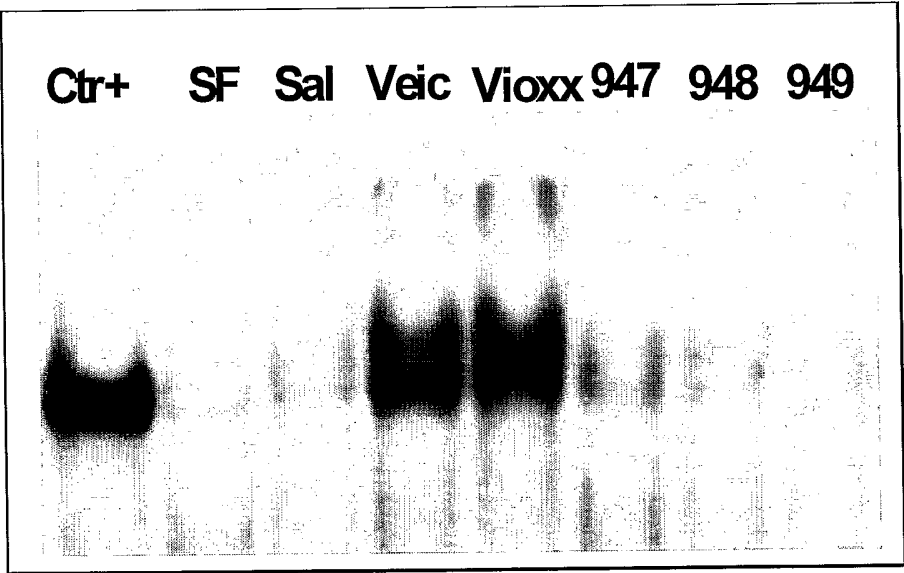


Figure 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR 2006/000107

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁸: **C07D 491/14** (2006.01); **C07C 275/38** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁸: C07D, C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, Epodoc, Paj, Internet, Registry, Pubmed, Marpat

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 1999/058502 A1 (VERTEX PHARMA) 18 November 1999 (18.11.1999) *claims*	1-20

A	WO2004016267 A1 (BOEHRINGER INGELHEIM PHARMA) 26 February 2004 (26.02.2004) *claims*	1-20

A	WO2004078748 A2 (BAYER PHARMACEUTICAL CORPORAION) 16 September 2004 (16.09.2004) *claims*	1-20

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
22 August 2006 (22.08.2006)Date of mailing of the international search report
25 September 2006 (25.09.2006)Name and mailing address of the ISA/ AT
Austrian Patent Office
Dresdner Straße 87, A-1200 ViennaAuthorized officer
GÖRNER W.

Facsimile No. +43 / 1 / 534 24 / 535

Telephone No. +43 / 1 / 534 24 / 558

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/BR 2006/000107

Patent document cited in search report			Publication date	Patent family member(s)		Publication date	
WO	A	1999058502		none			
WO	A1	2004016267	2004-02-26	JP	T	2006500365T	2006-01-05
				US	A1	2005159417	2005-07-21
				US	A1	2004033222	2004-02-19
				EP	A1	1545514	2005-06-29
				CA	A1	2496445	2004-02-26
WO	A	2004078748		MX	A	PA05009104	2006-05-31
				MX	A	PA05009067	2005-11-17
				BR	A	PI0407897	2006-03-01
				EP	A2	1608639	2005-12-28
				EP	A1	1599467	2005-11-30
				CA	A1	2517361	2004-09-16