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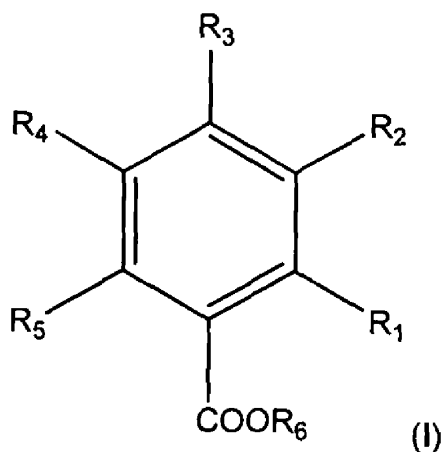
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[Continued on next page]

(54) Title: BENZOIC ACID DERIVATIVES AS IL-15R α RECEPTOR INHIBITORS



(57) Abstract: The present invention relates to the
benzoic acid derivatives of the formula (I), as de-
scribed in the claims, their tautomers, isomers, phar-
maceutically acceptable salts and solvates, for the use
in the treatment of diseases related to interleukin 15
overproduction.

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Benzoic acid derivatives as IL-15R α receptor inhibitors

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Field of the invention

The present invention relates to the benzoic acid derivatives for the use in the treatment of the diseases related to the overproduction of interleukin 15. The benzoic acid derivatives of the formula (I), as described hereinafter, inhibit interleukin 15 specific IL-15R α receptor and thus can be used in the prevention and therapy of such diseases as rheumatoid arthritis.

Background of the invention

Interleukin 15 (IL-15) is the cytokine exerting pleiotropic activity towards immune system cells as well as other cell types. IL-15 exhibits broad spectrum bioactivity, therefore it is placed at the top of the pro-inflammatory cytokines cascade. The impairment of the mechanisms regulating the expression of the IL-15 results in the overproduction of this cytokine and contributes directly to the development of such pathologies as inflammatory processes, autoimmune diseases, infections and neoplastic changes. IL-15 is considered a crucial cytokine in the etiology of rheumatoid arthritis (McInnes I.B. et al., Nat. Med. 2, 175-82 (1996); McInnes I.B. et al., Nat. Med. 3, 189-95 (1007); McInnes I.B. et al., Immunol Today 19, 75-9 (1998), psoriasis (Villadsen L.S. et al., J. Clin. Invest. 112, 1571-80 (2003), inflammatory bowel disease (Kirman I, Nielsen O.H., Am. J. Gastroenterol 91, 1789-1794 (1996); Sakai T. et al., Gastroenterology 114, 1237-1243 (1998)), sarcoidosis (Agostini C.T.L. et al., J. Immunol. 157, 910-8 (1996)) and T-cell leukemias (Dobbeling U. et al., Blood 92, 252-8 (1998)). Much attention is given to IL-15, on account of this cytokine's participation in transplant rejection (Baan C.C. et al., Transplant Proc. 31, 2726-8 (1999); Lewis E.C. et al., Cytokine 34, 106-13 (2006); Shi R. et al., Transpl. Immunol. 12, 103-8 (2004); Ferrari-Lacraz S. et al., Transplantation 82, 1510-7 (2006); Zheng X.X. et al., Transplantation 81, 109-16 (2006)).

Significant involvement of IL-15 in the development of the pathogeneses of the aforementioned afflictions suggests that targeting this cytokine pathway can reduce or eliminate the occurrence of IL-15 related disorders. This strategy has been proved lately by a number of biological assays. Reduction of the IL-15-mediated biological effects using the soluble receptor IL-15R α (Liew F.Y., McInnes I.B., Ann. Rheum. Dis. 61 Supl. 2, ii100-2 (2002); Ruchatz H. et al., J Immunol. 160, 5664-60 (1998); Smith X.G. et al., J. Immunol. 165, 3444-50 (2000); Wei X et al., J. Immunol. 167, 277-82 (2001)), antibodies inhibiting receptor IL-2/IL-15R β (Morris J.C., Proc. Natl. Acad. Sci. USA 103, 401-6 (2001); Tinubu S.A. et al., J. Immunol. 153, 4330-8 (1994), antibodies inhibiting IL-15 (Villadsen L.S. et al. J. Clin. Invest. 112, 1571-80 (2003) or modified IL-15 molecule of competitive antagonist activity (Ferrari-Lacraz S. et al., J. Immunol. 173, 5818-26 (2004); Kim Y.S. et al., J. Immunol. 160, 5742-8 (1998)) always resulted in the

alleviation of disease symptoms. Experimental therapies demonstrated decreased collagen-induced rheumatoid arthritis incidence in mice (Ruchatz H. et al., J Immunol. 160, 5664-60 (1998); Ferrari-Lacraz S. et al., J. Immunol. 173, 5818-26 (2004); Kim Y.S. et al., J. Immunol. 160, 5742-8 (1998)) and primates (Liew F.Y., McInnes I.B., Ann. Rheum. Dis. 61 Supl. 2, ii100-2 (2002)), attenuation of psoriasis symptoms in the mice model of the disease (Villadsen L.S. et al., J. Clin. Invest. 112, 1571-80 (2003)), reduction of carrageenan-induced inflammation in mice (Wei X et al., J. Immunol. 167, 277-82 (2001)) and, also in mice, prolonged survival of heart allotransplants (Smith X.S. et al., J. Immunol. 165, 3444-50 (2000); Tinubu S.A. et al., J. Immunol. 153, 4330-8 (1994) and islets of Langerhans (Ferrari-Lacraz S. et al., J. Immunol. 173, 5818-26 (2004)). Currently adopted strategies, based on inhibiting the IL-15, seem to be effective, but none of them has been approved for clinical use so far. The most advanced and promising, from the medical application point of view, are the trials aimed at the inhibition of the IL-15 activity by anti-IL-15 human antibodies (HuMax-IL15, AMG-714) (Baslund B. et al., Arthritis Rheum 52, 2686-92 (2005)). However, the matter of serious concern is the effect of 'reverse signaling' (Budagian V. et al., J. Biol. Chem. (2004)). It is assumed that the antibody HuMax-IL15 and IL-15 complex can itself induce a cell response, thus limiting the therapeutic effectiveness of this antibody directed toward IL-15 neutralization (Budagian V. et al. Cytokine Growth Factor Rev. 17, 259-80 (2006).

In addition, our unpublished results demonstrate significant angiogenic activity of IL-15. The participation of IL-15 in angiogenesis *in vivo* has already been reported (Angiolillo A.L. et al., Biochem. Biophys. Res. Commun. 233, 231-7 (1997); Kuniyasu H. et al., Pathobiology 69, 86-95 (2001)), but our recent outcomes have shown the IL-15-induced proliferation and migration of endothelial cells. The identification of another angiogenic factor was not surprising, because its presence had already been detected in rheumatoid arthritis, where the impaired mechanism of angiogenesis is considered to be the main pathogenesis of this illness.

Rheumatoid arthritis (RA) is the most common systemic disease of connective tissue which affects on average about 1% of the world's population. Recent estimates showed higher prevalence in women than in men (3:1). The highest prevalence of RA has been reported in the 30-60 age range. According to the estimates, about 30% of people afflicted with RA suffer from severe symptoms and within several years end up with a disability. The average life span of people suffering from RA is about 10 years shorter, according to the statistical data. It is thought that the onset of RA results from the complex combination of many factors, such as genetic predisposition, impaired innate and acquired immune response and environmental components. Pharmacological treatment of RA, currently available on the medical market, does not remove the cause of the disease. Non-steroidal anti-inflammatory drugs (NSAIDs) are medications which as well as having pain-relieving (analgesic) effects have the effect of reducing the inflammation when used over a period of time. They suppresses the symptoms of the disease, but do not stop the progress of the illness.

Among the disease-modifying antirheumatic drugs (DMARDs), the first line treatment in RA is methotrexate. The other synthetic DMARDs are leflunomide, sulfasalazine,

hydroxychloroquine, D-penicillamine, gold salts, azathioprine, cyclosporine and cyclophosphamide. However, even in patients responding to the treatment, the disease progresses and diminished medical efficacy is observed after long term treatment.

The other class of DMARDs are biological. Among the drugs available on the pharmaceutical market, the inhibitors of the tumor necrosis factor (TNF) could be mentioned:

- infliximab (chimeric anti-TNF monoclonal antibody);
- etanercept (fusion protein, consisting of the extracellular receptor domain p75 for TNF and the Fc fragment of the human antibody IgG1);
- adalimumab (human anti-TNF monoclonal antibody),

as well as the inhibitors of other proteins:

- anakinra, IL-1 receptor antagonist;
- abatacept, fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4. By binding co-stimulating molecules B7-1 and B7-2 located on the antigen-presenting cells it inhibits the co-stimulatory signal transduction by CD28 on T cells;
- rituximab, chimeric monoclonal antibody against the protein CD20 primary found on the surface of mature B cells acting by eliminating B cells.

Tocilizumab, humanized monoclonal antibody against the interleukin-6 receptor, has been approved for the European pharmaceutical market as the first IL-6 inhibitor.

Positive results of phase II clinical trials carried out by Amgen company with AMG-714 (previously HuMax-IL15) - human monoclonal antibody that targets IL-15, were disclosed in 2004 (McInnes, I., et al.). However, to date there is no available information about the phase III clinical trials.

The introduction of biologic medical products into rheumatoid arthritis therapy is considered big progress in the RA treatment, but these biologics (usually used in combination with methotrexate of cytostatic and immunosuppressive properties) are only effective in limiting the disease symptoms and delaying joint degradation in about 30% of treated patients.

Due to the limited therapeutic effects and high production costs of currently available biopharmaceuticals, the demand for an efficacious anti-RA drug of new generation still remains valid. Ongoing research is aimed at discovering new molecular mechanisms for targeted therapies.

Peptides of modified sequences mimicking IL-15 (revealed, among others, in WO 2006/029578 and WO 2010/037351) have been proposed as potential pharmaceuticals in the rheumatoid arthritis treatment. These peptides are supposed to bind to the receptor IL-15R α subunit, which should result in the inhibition of the T cells proliferation, TNF- α induction and expression of IL-8 and IL-6. To date the efficacy of these new compounds has not been proved in clinical studies.

A need to design a new drug based on a small synthetic molecule inspired the authors of the present invention to alter the concept of the treatment of the IL-15 overexpression related diseases. This approach relates to the inhibition of the IL-15 biological activity by a compound selectively binding to IL-15R α receptor. According to the current state of knowledge and our own unpublished results, the strategy, while implemented, should reduce the pro-inflammatory cascade as well as angiogenesis caused by the pro-inflammatory cytokine IL-15. The effect of additive synergism is likely to be a so far unrecognized mechanism of biologicals inhibiting IL-15 biological activity.

Phenylpyrazole anilide derivatives, disclosed by Ushio H. et al. in Letters in Drug Design Discovery, 5, 292-296 (2008), are the only small chemical molecules of potential application in rheumatoid arthritis which interfere with the interaction of the receptor IL-15R α and its ligand (IL-15). The compound Y-320 belonging to the aforementioned group of compounds with proven high bioavailability and *in vitro* activity inhibits the IL-15-induced T cells activity.

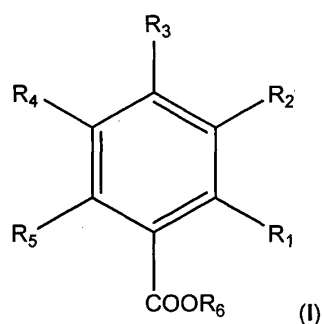
The aim of the present invention was the discovery of a small molecule which will selectively and effectively inhibit the biological activity of IL-15 cytokine due to its specific binding and blocking the activity of IL-15 specific IL-15R α receptor.

Summary of the invention

The identification of a chemical compound which will fit in the IL-15R α receptor was facilitated due to the evaluation of the receptor domain structure which is of key importance while binding to IL-15 (Wei X. et al., J. Immunol. 167, 277-82 (2001)). The search for small chemical molecules to fit in the IL-15 specific receptor domain was carried out on the basis of the model of the [IL-15R α – IL-15] complex structure, elaborated on the basis of the crystal structure of the complex fragment (2Z3Q code of Protein Data Bank). The assignment of receptor binding sites pharmacophores, while considering specific interactions with IL-15, was enabled due to the determination of the 3D structure of the [IL-15R α – IL-15] complex. It was followed by the search of small molecules data base ZINC, embracing about 20 million chemical compounds, to find the molecules which can meet the structural requirements for pharmacophores. The screening included more than 10 thousand compounds fulfilling the established criteria. The calculations were also carried out to theoretically predict the binding affinity and strength of the selected compounds and the receptor active site. Molecular docking of the chosen molecules was performed using GLIDE software. While docking, the IL-15 binding site of the receptor remained rigid, but the molecule was able to undergo conformational changes due to the modifications of rotating chemical bonds. Additional docking carried out for the pre-selected 500 molecules allowed the induction fitting in of the two interacting partners (protein receptor and small molecule).

Using the above described screening methods, a group of benzoic acid derivatives was selected. *In vitro* studies proved their efficiency in inhibiting the interleukin 15 specific receptor IL-15R α .

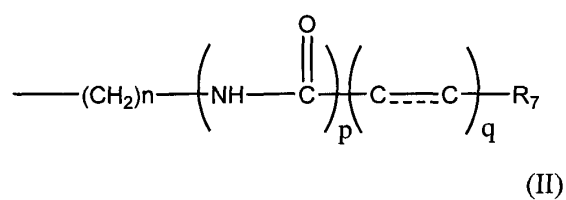
The present invention provides the benzoic acid derivatives of the formula (I),



5 wherein,

R₁ and R₅ are the same or different and independently represent H, OH or alkyl C1-C3;

10 R₂, R₃ and R₄ are the same or different and independently represent H, OH or the group of the formula (II)



wherein

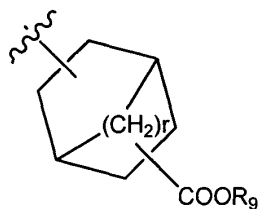
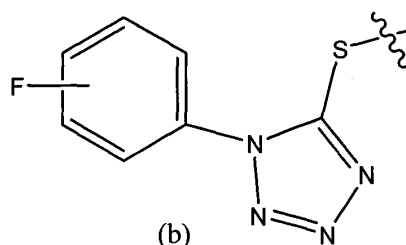
n is the whole number 0, 1 or 2,

15 p is the whole number 0 or 1,

q is the whole number 0 or 1,

----- represents single or double bond,

R₇ represents ---COOR_8 or the group of the formula (a) or (b):



20

wherein

R₈ and R₉ represent H or alkyl C1-C3; and

r is the whole number from 0 to 3;

R₆ represents H or alkyl C1-C3,

- 5 and their tautomers, isomers, pharmaceutically acceptable salts and solvates,
for the use in the treatment of the diseases related to interleukin 15 overproduction.

The *in vitro* biological activity studies of the abovementioned compounds demonstrated the efficacious inhibition of the IL-15-induced cell proliferation and TNF- α and IL-17 expression
10 by the benzoic acid derivatives of the formula (I).

Thus, the benzoic acid derivatives of the formula (I) could be used to inhibit IL-15 overproduction due to binding to the IL-15 specific IL-15R α receptor.

In particular, the benzoic acid derivatives of the formula (I) can be used in the prevention or treatment of diseases from the group including rheumatoid arthritis, psoriasis,
15 inflammatory bowel disease, sarcoidosis, T-cell leukemias or transplant rejection.

Preferably, the benzoic acid derivatives of the formula (I) can be used in the treatment of rheumatoid arthritis.

According to the present invention, the benzoic acid derivatives of the formula (I) can be administered to an individual in the need of such a treatment, in particular to a human, in
20 therapeutically effective doses.

Although the administration of the benzoic acid derivatives of the formula (I) *per se* is considered, in general they will be used as active ingredients of the pharmaceutical preparation, of appropriate form suited to the particular route of administration.

Another embodiment of the present invention relates to the use of the benzoic acid
25 derivatives of the formula (I), their tautomers, isomers, pharmaceutically acceptable salts or solvates for manufacturing pharmaceutical preparations for use in the prevention or treatment of the diseases, such as rheumatoid arthritis, psoriasis, inflammatory bowel disease, sarcoidosis, T-cell leukemias or transplant rejection.

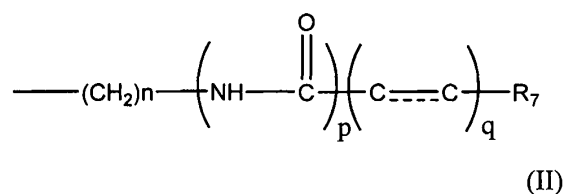
Another embodiment of the present invention relates to the pharmaceutical preparation
30 containing a therapeutically effective dose of the benzoic acid derivative of the formula (I) or its tautomer, isomer, pharmaceutically acceptable salt or solvate as the active ingredient together with the pharmaceutically acceptable carriers and/or excipients.

Description of the invention

35

In one embodiment, the compounds for use according to the present invention are the benzoic acid derivatives of the formula (I), wherein:

R₂ and R₄ are the same and represent the groups of the formula (II)



wherein

$n=0$,

$p=1$,

5 $q=1$,

----- represents single or double bond,

R_7 represents $-\text{COOR}_8$ group, where R_8 is H or alkyl C1-C3;

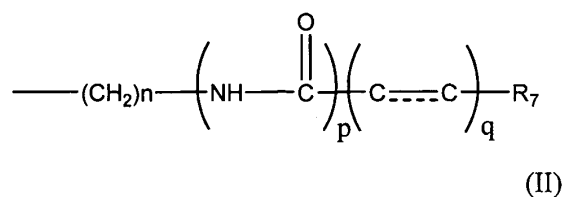
R_8 represents H or alkyl C1-C3,

and the other substituents represent H.

10

In another embodiment, the compounds for use according to the present invention are the benzoic acid derivatives of the formula (I), wherein:

R_3 represents the group of the formula (II)



15

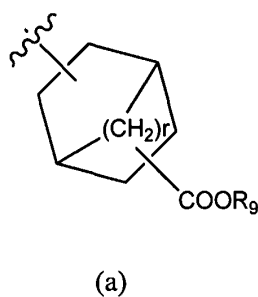
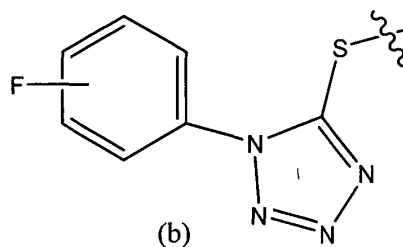
wherein

$n=1$;

$p=1$,

20 $q=0$,

R_8 represents the group of the formula (a) or (b):



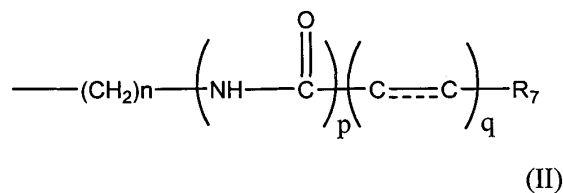
25

wherein

R_8 and R_9 independently represent H or alkyl C1-C3; and
 $r = 0$ or 1 ;
 and other substituents are H.

- 5 In the other preferred embodiment, the compounds for use according to the present invention are the benzoic acid derivatives of the formula (I), wherein:

R_3 represents the group of the formula (II)



10 wherein

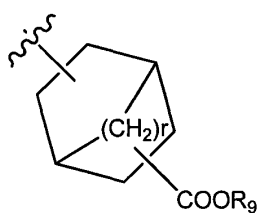
$n = 1$;

$p = 1$,

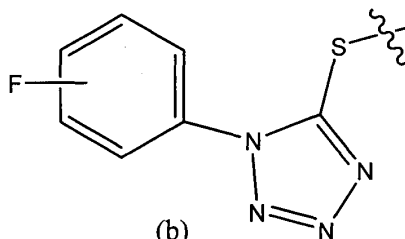
$q = 0$,

R_8 represents the group of the formula (a) or (b):

15



(a)



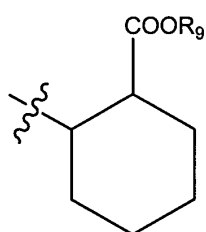
(b)

wherein

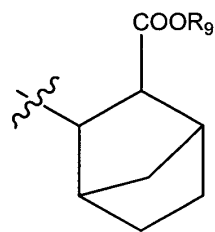
- 20 R_8 and R_9 independently represent H or alkyl C1-C3; and
 $r = 0$ or 1 ;
 and other substituents represent H.

- 25 In the more preferably embodiment, the compounds for use according to the present invention are the benzoic acid derivatives of the formula (I), wherein:

R_8 represents the group of the formula (a') or (a''):



(a')



(a'')

and R₉ represents H or alkyl C1-C3.

In the other embodiment, the compounds for use according to the present invention are the benzoic acid derivatives of the formula (I), wherein:

R₃ and R₅ represent OH,

and other substituents represent H or alkyl C1-C3.

The chemical structures of the benzoic acid derivatives according to the present invention, exhibiting high biological activity, are set forth in Table 1 below.

10

Table 1. The benzoic acid derivatives of the formula (I)

<div style="text-align: right;">(I)</div>												
Compound	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈	n	p	-----	q
R9	H	H	(II)	H	H	H	(c) (r=1)		1			
R10	H	H	OH	Me	H	Me						
R12	H	(II)	H	(II)	H	H	COOR ₈	H	0	1	==	1
R13	H	H	(II)	H	H	H	(b)	H	1	1	---	1
R14	H	H	(II)	H	H	H	(a)	H	1	1	---	0
R22	H	(II)	H	(II)	H	H	COOR ₈	H	0	1	---	0
R23	H	H	(II)	H	H	Me	COOR ₈	Me	1	1	---	1

Most preferred benzoic acid derivatives of the formula (I) are selected from the group comprising:

4-([1-(4-Fluorophenyl)-1*H*-tetrazol-5-yl]-thio)methyl)benzoic acid,
Methyl 2,4-dihydroxy-3-methyl benzoate,
3,5-bis[(3-Carboxy-1-oxo-2-(*E,E*)-propen-2-enyl-1-yl)amino]benzoic acid,
4-([2-Carboxybicyclo[2.2.1]heptan)carbonyl]amino)methyl)benzoic acid,
4-([2-Carboxycyclohexyl)carbonyl]amino)methyl)benzoic acid,
3,5-bis[(4-Carboxyethyl-2-oxo)amino]benzoic acid,
Methyl 4-([3-methoxycarboxyethyl)carbonyl]amino)methyl benzoate.

The benzoic acid derivatives of the formula (I) are commercially available or they can be obtained synthetically, according to the methods described for the similar compounds.

The benzoic acid derivatives of the formula (I) can exist as tautomers or isomers or the mixture of optical isomers at any ratio, for example as racemic mixtures. All the tautomers, their isomers and mixtures thereof are the subject matter of the present invention. Single optical isomers can be obtained according to the methods known to those who are skilled in the art, like for example chiral HPLC, enzymatic or chiral auxiliary separation, or they can be obtained synthetically under stereocontrolled conditions.

The benzoic acid derivatives of the formula (I) can be obtained and/or used as pharmaceutically acceptable salts with acids. The term 'pharmaceutically acceptable salts' refers to the salts formed with pharmaceutically acceptable inorganic and organic acids. The representative acids are hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, adipic, ascorbic, salicylic, succinic, tartaric, acetic, citric, formic, benzoic, malic, *p*-toluenesulfonic, methanesulfonic, naphthalene-2-sulfonic, benzenesulfonic acids and others. Most preferred salts of the benzoic acid derivatives of the formula (I) are hydrochlorides.

As it was said before, the benzoic acid derivatives of the formula (I) can be used alone or in combination with other active ingredients at effective therapeutic doses, in the treatment diseases which have been diagnosed to be related to IL-15 overproduction.

The term 'treatment' refers to the suppression of a state, a disorder or a disease, which means inhibition, reduction or delay of the disease development, recurrence of the illness or at least one of its symptoms, or recovery meaning the regression of a state, a disorder or a disease or at least one of its symptoms.

The term 'therapeutically effective dose' refers to the amount of the compound sufficient to produce a therapeutic response when administered to an individual in order to cure a state, a disorder or a disease. The 'therapeutically effective dose' will vary depending on the nature of the selected compound and the route of administration, kind of disease and its status, age, body weight, physical condition, susceptibility to treatment, and it can be recommended by a medical doctor on the basis of their own experience and the results of clinical trials.

The therapeutic dose of the benzoic acid derivatives of the formula (I) can be administered as a single dose or divided doses given in certain intervals of time, for example as two, three, four or more daily doses.

5 In order to produce a particular pharmaceutical form, a pharmaceutical preparation - apart from the active ingredient - may also contain known and pharmaceutically acceptable carriers and/or excipients which are inert and do not interact with the active ingredient.

According to the invention, the pharmaceutical composition may be formulated in any pharmaceutical form suitable for the systemic administration, for example oral administration, such as tablets and capsules, starch capsules, coated tablets or enteral tablets; as powders or
10 granules; as a solution, a suspension or an emulsion. Tablets and capsules for oral administration may contain excipients routinely used in pharmaceutical practice, such as binders, diluents, disintegrants or lubricants. The tablets may be coated by any method known in the art. Liquid pharmaceutical compositions for oral administration may be manufactured as, for example, aqueous or oily suspensions, solutions, emulsions, syrups and elixirs or they may
15 be produced as dry substances for the preparation of solutions or suspensions *ex tempore* with water or other suitable diluent. Liquid pharmaceutical preparations may contain excipients routinely used in pharmaceutical practice, such as dispersing and emulsifying agents, non-aqueous carriers (they may comprise edible oils) or preservatives. The selection and amount of the excipients depends on the pharmaceutical dosage form and the route of drug
20 administration. The pharmaceutical composition may be formulated into any suitable pharmaceutical form, by any method known in the art, using any pharmaceutically acceptable carriers, diluents, fillers and other excipients.

The pharmaceutical preparation for oral administration may be formulated in particular as capsules. In such case the active substance is combined with the carrier and the resulting
25 composition is used to fill in gelatin shells. The gelatin capsules can be manufactured as having soft or hard gelatin shells, depending on the composition of gel mass used in the production process. Soft capsules' gel mass consists of plasticizers, such as glycerol, sorbitol; preservatives, such as benzoic acid, its salts and alkyl hydroxybenzoates; colorants and flavors. The capsules' filling may be used as oily solution, suspension or emulsion. The suitable diluents
30 embrace, for example castor oil, coconut oil, olive oil, palm oil, corn oil, arachis oil, synthetic and natural triglycerides of fatty acids, unsaturated medium-chain fatty acids, modified long-chain fatty acids, glycol esters, polyethylene glycols and others. Suitable excipients comprise tensides, for example lecitin, mono- and diglycerides, fatty acids esters with polyoxoethylene sorbitane.

35 The pharmaceutical preparation suitable for parenteral administration, for example for intramuscular, subcutaneous or intravenous administration, may be used as a ready suspension, lyophilizate, suspension *ex tempore* or concentrate for intravenous infusions. These preparations may be formulated as unit dosage forms in ampoules, initially filled syringes, low capacity infusions, or in multi-dosage containers consisting of preservatives and
40 carriers, diluents, stabilizers and/or dispersing agents. The carriers suitable for the intravenous

administration of the pharmaceutical preparation comprise, for example, sterile aqueous solutions, such as the solution of physiological salt, the solutions of carbohydrates, for example, glucose, mannitol, dextrose, lactose and aqueous buffer solutions, for example, phosphate buffers. The pharmaceutical composition may also contain other excipients, routinely used to maintain isoosmoticity, antioxidants, preservatives and other. Alternatively, the active ingredient may be in used as the powder obtained due to the isolation of a solid compound under septic conditions, or by lyophilisation from the solvent, for the preparation of suspensions *ex tempore* in a suitable diluent, for example sterile water deprived of pyrogenic substances.

The biological activity of the benzoic acid derivatives of the formula (I) has been demonstrated during *in vitro* studies. After proving the efficacy of these compounds during *in vivo* studies in animal models of the diseases, the benzoic acid derivatives can become drug candidates to be used in the prevention and treatment of IL-15 overproduction related diseases and inflammation processes, such as rheumatoid arthritis, psoriasis, inflammatory bowel disease, sarcoidosis, T-cell leukemias or transplant rejection.

Biological studies

In vitro studies

All experiments were carried out on peripheral blood mononuclear cells (PBMC) from healthy donors. The cells were isolated under the standard protocol regarding density gradient centrifugation. According to the general protocol, 6 ml of blood was layered on 3 ml of Lymphoprep (Axis-shield, Norway), then centrifuged at 800 x g for 15 min. The layer of PBMC was collected, the cells were washed twice with phosphate buffered saline (PBS) (BIOMED-LUBLIN, Poland) and suspended in medium RPMI1640 (Gibco, Great Britain), containing 10 mM HEPES (Sigma, USA), 10% fetal calf serum (BIOMED-LUBLIN, Poland) and antibiotic (streptomycin sulfate, sodium penicillate G, amphotericin B, PAA, Austria).

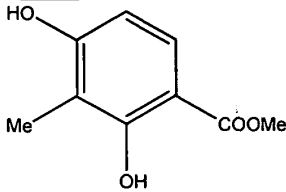
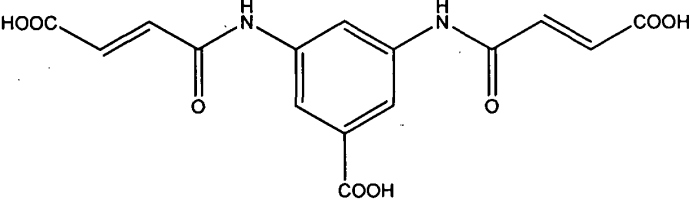
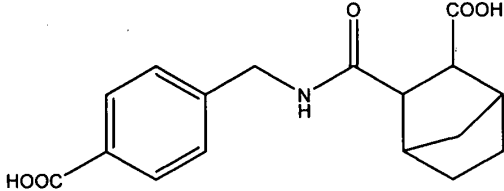
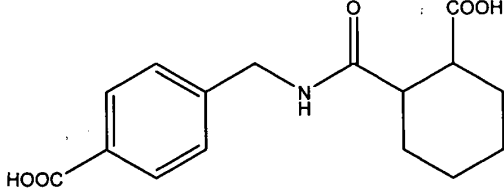
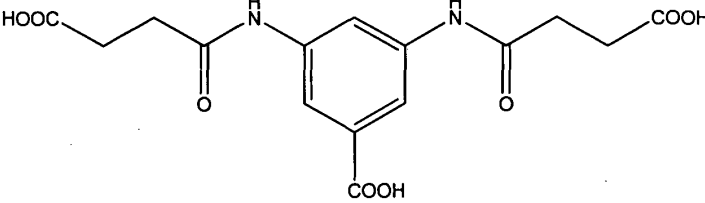
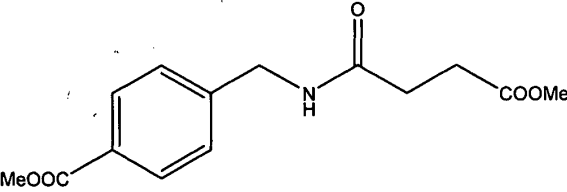
The efficacy assessment of the compounds initially selected at the screening stage was performed, as well as the evaluation of the fit in the IL-15R α receptor active site and the IL-15R α - IL-15 complex was used as the model. The tested compounds were commercially available or synthesized according to the known synthetic procedures.

In all the *in vitro* experiments PBMC stimulated with IL-15 were used as the control.

The benzoic acid derivatives of the general formula (I) showing the highest biological activity are collected in Table 1.

Table 1. Chemical structures and names of the compounds.

Compound	Chemical structure
R9	<chem>O=C(O)c1ccc(cc1)SC2=CN=CN=C2c3ccc(F)cc3</chem>

R10	
R12	
R13	
R14	
R22	
R23	

Chemical structures of the compounds characterized by different stereoisometry, substituents and functional groups present were determined by means of spectroscopic methods: ^1H and ^{13}C NMR (proton and carbon nuclear magnetic resonance), IR (infra-red spectroscopy), GC/MS (gas chromatography-mass spectrometry), HR MS (high resolution mass spectrometry) as well as microanalysis. The compounds were purified by crystallization or silica-

gel chromatography to obtain the final products of purity not lower than 95%. The compounds' purity was determined by HPLC (high performance liquid chromatography) analyses. The final products were stored in vials at 0 – 5°C. *In vitro* experiments were carried out using freshly prepared stock solutions in water, ethanol or DMSO, depending on the polarity and physico-chemical properties of the tested compounds.

Example 1

Effect of the tested compounds on the interleukin 15-induced PBMC proliferation.

The PBMC proliferation was evaluated using commercially available BrdU Cell Proliferation Assay (Calbiochem, Merck, Germany). The PBMC were seeded in a 96-well plate (25×10^3 cells in 200 μ l of the culture medium/well). Next day the cells were treated with the tested compounds at final concentrations: 20 μ M, 50 μ M, 100 μ M and 200 μ M. After 30 min. incubation with the compounds, the cells were stimulated with IL-15 at the final concentration 5 ng/ml, incubated for 4 days, then for last 24 h bromodeoxyuridine (BrdU) was added to the culture medium at the concentration recommended by the manufacturer. After the completion of the incubation the cells were centrifuged (10 min., 160xg) and fixed. Further experimental steps were performed according to the manufacturer's protocol.

The results of the influence of the selected compounds used at 200 μ M concentration on the IL-15-induced PBMC proliferation are presented in Table 2. The results are expressed as the percentage change of proliferating cells with regard to the control cells stimulated with IL-15.

Table 2. Influence of the tested compounds (200 μ M) on the IL-15-induced PBMC proliferation

Compound	Proliferation [%] $\pm$ SD
Control	100
R9	71,22 $\pm$ 12,44
R10	34,55 $\pm$ 5,98
R12	60,01 $\pm$ 11,67
R13	66,55 $\pm$ 3,30
R14	80,63 $\pm$ 3,80
R22	79,52 $\pm$ 1,54
R23	69,65 $\pm$ 8,52

The results collected in Table 2 demonstrate that a statistically significant inhibition of the PBMC proliferation occurs upon treatment with all the tested compounds. The strongest anti-proliferating activity is observed for the R10 derivative.

To evaluate the tested compound's concentration-dependent inhibitory effect on the proliferation, the experiment was repeated using the R10 derivative at different concentrations: 20 μ M, 50 μ M, 100 μ M and 200 μ M. The influence of the compound's R10 concentration on the

IL-15-induced PBMC proliferation is depicted in the diagram in Fig. 1. The results are presented as OD values (absorbance) measured at 450 nm against the reference of 540 nm.

Example 2

5 Effect of the tested compounds on the IL-15-induced TNF- α synthesis in PBMC

The evaluation of the TNF- α synthesis in IL-15-stimulated PBMC was performed using the ELISA method and commercially available tests (R&D, USA). The experiment was carried out strictly according to the manufacturer's recommendations.

10 The PBMC were seeded in a 24-well plate (2×10^6 cells in 1ml of the culture medium/well), treated with the tested compounds and after 30 min stimulated with IL-15 (5 ng/ml). After 48 h incubation, the culture medium was collected from each well to determine the TNF- α concentration, the cells were harvested and lysed, and the concentration of total protein was measured in cell lysates. The obtained values of the TNF- α concentration were calculated
15 for 1 mg of protein. The results are expressed as the percentage change of the concentration of TNF- α synthesized in PBMC with regard to the control cells stimulated with IL-15.

The influence of the selected compounds R9, R10, R12, R13, R14, R22 and R23 at 200 μ M concentration on the IL-15-induced TNF- α synthesis in PBMC is depicted in Fig. 2.

20 All tested compounds significantly reduce the IL-15-induced TNF- α synthesis in PBMC in comparison with the IL-15-stimulated control cells.

Example 3

Effect of the tested compounds on the IL-15-induced IL-17 synthesis in PBMC

25 The evaluation of the IL-17 synthesis in IL-15-stimulated PBMC was performed using the ELISA method and commercially available tests (R&D, USA). The experiment was carried out strictly according to the manufacturer's recommendations.

The PBMC were seeded in a 24-well plate (2×10^6 cells in 1ml of the culture medium/well), treated with inhibitors, after 30 min. stimulated with IL-15 (5 ng/ml). After 48 h
30 incubation, the culture medium was collected from each well to determine the IL-17 concentration, the cells were harvested and lysed, and the concentration of total protein was measured in cell lysates. The obtained values of the IL-17 concentration were calculated for 1 mg of protein. The results are expressed as the percentage change of concentration of the IL-17 synthesized in PBMC with regard to the control cells stimulated with IL-15.

35 The influence of the selected compounds R9, R10, R12, R13, R14, R22 and R23 (200 μ M) on the IL-15-induced IL-17 synthesis in PBMC is depicted in Fig. 3.

All tested compounds significantly reduce the IL-15-induced IL-17 synthesis in PBMC in comparison with the IL-15-stimulated control cells.

40

Discussion

1. Screening for the selected compounds efficacy of inhibition of the IL-15-induced cell proliferation and cytotoxicity evaluation.

Increased cell proliferation is one of the characteristic responses to the IL-15-stimulation. Selective blocking of the IL-15 specific receptor IL-15R α results in the inhibition of this cytokine biological activity. As a consequence, the IL-15-induced increased cell proliferation does not occur. The influence of the selected compounds on the proliferation of peripheral blood mononuclear cells (PBMC) isolated from blood of healthy donors was evaluated in the assay using a fluorescent CFSE dye (Molecular Dynamics, Great Britain) and in the bromodeoxyuridine incorporation test (BrdU) (BrdU Cell Proliferation Assay, Calbiochem, USA). The PBMC population consists of several cell types, these are lymphocytes and monocytes, which are characterized by the expression of the IL-15 specific IL-15R α receptor that explains their extensive proliferation in response to the interleukin 15-stimulation. The inhibition of the cell proliferation in the presence of the tested compounds can also be a visible sign of the cells' death caused by the cytotoxic or apoptotic activity of the analyzed derivatives. The influence of the selected benzoic acid derivatives on the cells viability was tested by two methods:

- a. Measurement of the lactate dehydrogenase (LDH) concentration in the culture medium and cultured cells (CytoTox 96 Non-Radioactive Cytotoxicity Assay, Promega, USA). LDH is a cytosolic enzyme which under physiological conditions is not released from cells. However, when a cell membrane damage or cell death occurs, LDH enzyme is released into the matrix. Increased LDH activity in the culture medium correlates with the increased number of dead cells resulting from the cytotoxic effect of the tested compounds. LDH activity measured in cell lysates is used for the assessment of a number of living cells;
- b. Cytofluorometric assay with annexin V and propidium iodide for the apoptosis and necrosis assessment. Annexin V shows high affinity towards phosphatidylserine (PS), which is transferred to the outer leaflet of the plasma membrane in apoptosis. The appearance of PS on the cell surface is an indicator of an initial or intermediate stage of cell apoptosis. An intact plasma membrane is not permeable for propidium iodide, but when the outer membrane loses its integrity, which occurs in necrosis, propidium iodide enters the cytosol and stains the necrotic cells.

Only the compounds which inhibit the IL-15-induced PBMC proliferation and do not exert apoptotic effect were chosen for the next research step. Each compound was tested twice on PBMC cells isolated from the blood of different donors.

2. Efficacy assessment of the selected benzoic acid derivatives of the formula (I), inhibiting the IL-15-induced TNF- α and IL-17 production.

Peripheral blood mononuclear cells (PBMC) respond to the IL-15 stimulation not only by increased proliferation, but also by synthesizing many pro-inflammatory cytokines, among

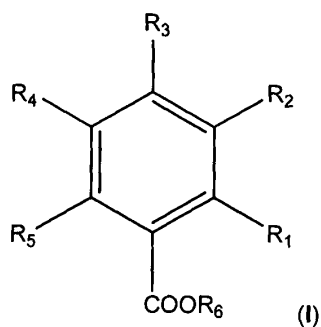
others for example TNF- α and IL-17. The inhibition of IL-15 biological activity should result in the reduced proliferation and decreased synthesis of TNF- α and IL-17.

The selected benzoic acid derivatives at different concentrations were used to assess their influence on the IL-15-related cytokine synthesis. The biological activity of the compounds
5 was evaluated measuring the TNF- α and IL-17 concentrations in the culture medium collected after the completion of the incubation using the immunoenzymatic ELISA tests.

The results obtained in these test prove the inhibition of the cytokine synthesis and they serve as evidence of the tested compounds' biological activity.

Claims

1. The benzoic acid derivatives of the formula (I),



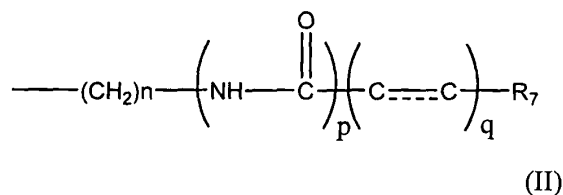
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wherein

R₁ and R₅ are the same or different and independently represent H, OH or alkyl C1-C3;

10

R₂, R₃ and R₄ are the same or different and independently represent H, OH or the group of the formula (II)



(II)

15

wherein

n is the whole number from 0, 1 or 2,

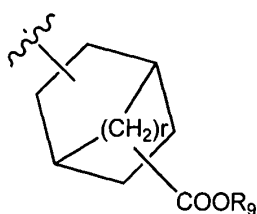
p is the whole number 0 or 1,

q is the whole number 0 or 1,

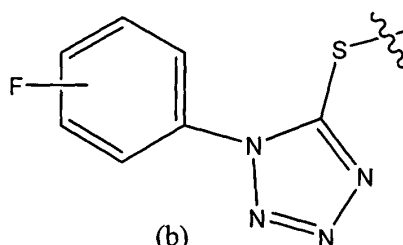
----- represents single or double bond,

20

R₇ represents ---COOR_8 or the group of the formula (a) or (b):



(a)



(b)

wherein

R₈ and R₉ represent H or alkyl C1-C3; and

r is the whole number from 0 to 3;

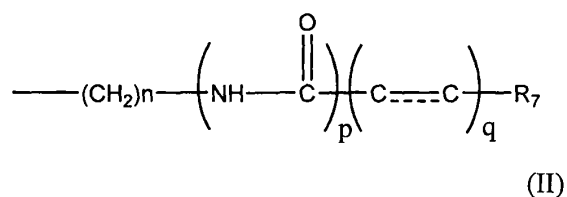
5 R₆ represents H or alkyl C1-C3,

and their tautomers, isomers, pharmaceutically acceptable salts and solvates,

for use in prevention and treatment of diseases related to interleukin 15 overproduction.

10 2. The compounds for use according to claim 1, wherein in the formula (I):

R₂ and R₄ are the same and represent groups of the formula (II)



wherein

n= 0,

15 p=1,

q=1,

----- represents single or double bond,

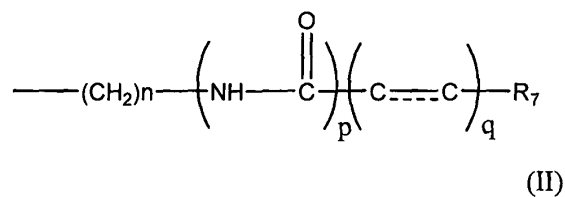
R₇ represents -COOR₈, wherein R₈ is H or alkyl C1-C3;

R₆ represents H or alkyl C1-C3,

20 and other substituents are H.

3. The compounds for use according to claim 1, wherein in the formula (I):

R₃ represents the group of the formula (III)



25

wherein

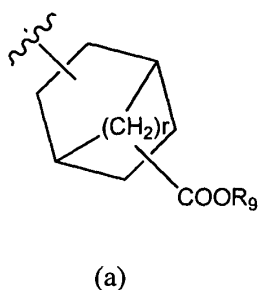
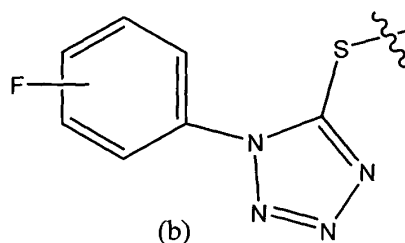
n= 1;

p= 1,

q= 0,

30

R₈ represents the group of the formula (a) or (b):



wherein

R_8 and R_9 independently represent H or alkyl C1-C3; and

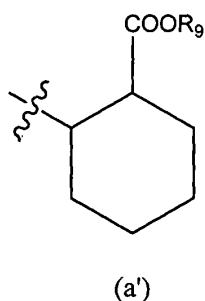
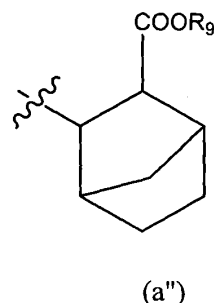
5 $r = 0$ or 1 ;

and other substituents are H.

4. The compound for use according to claim 3, wherein in the formula (I)

R_8 represents the group of the formula (a') or (a''):

10



and R_9 represents H or alkyl C1-C3.

15 5. The compound for use according to claim 1, wherein in the formula (I):

R_3 and R_5 represent OH,

and other substituents represent H or alkyl C1-C3.

20 6. The compound for use according to claim 1, wherein the benzoic acid derivative of the formula (I) is selected from the group comprising:

4-({[1-(4-Fluorophenyl)-1H-tetrazol-5-yl]-thio}methyl)benzoic acid,

Methyl 2,4-dihydroxy-3-methyl benzoate,

3,5-bis[(3-Carboxy-1-oxo-2-(E,E)-prop-2-en-1-yl)amino]benzoic acid,

25 4-({[(2-Carboxybicyclo[2.2.1]heptan)carbonyl]amino}methyl)benzoic acid,

4-({[(2-Carboxycyclohexyl)carbonyl]amino}methyl)benzoic acid,

3,5-bis[(4-Carboxyethyl-2-oxo)amino]benzoic acid,

Methyl 4-[[[3-methoxycarboxyethyl)carbonyl]amino]methyl benzoate.

7. The compound for use according to claim 1, wherein the benzoic acid derivative of the formula (I) inhibits IL-15 overproduction due to the inhibition of the IL-15 specific IL-15R α receptor.

8. The compound for use according to claim 1, wherein the benzoic acid derivative of the formula (I) inhibits IL-15 overproduction due to the selective inhibition of the IL-15 specific IL-15R α receptor.

10

9. The compound for use according to claim 1, wherein the benzoic acid derivative of the formula (I) is to be used in the prevention or the therapeutic treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease, sarcoidosis, T-cell leukemias or transplant rejection.

15 10. The compound for use according to claim 1, wherein the benzoic acid derivative of the formula (I) is to be used in to the treatment of rheumatoid arthritis.

11. The compound for use according to claim 1, wherein the benzoic acid derivative of the formula (I), its isomer, tautomer, salt or solvate according to claim 1 is to be administered in a therapeutically effective dose to an individual in need of such a treatment.

20

12. The compound for use according to claim 11, wherein the therapeutically effective dose of the benzoic acid derivative of the formula (I), its isomer, tautomer, salt or solvate is to be administered as the active ingredient of the pharmaceutical preparation or a single dosage form.

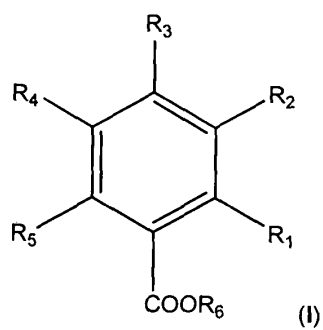
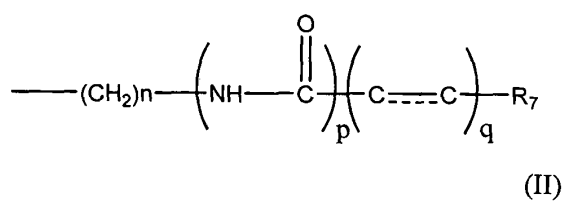
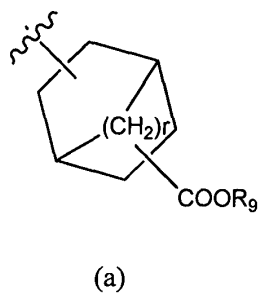
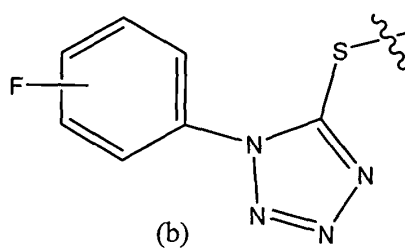
25

13. Use of the benzoic acid derivatives of the formula (I), their tautomers, isomers, salts or solvates according to claim 1 for manufacturing of the pharmaceutical preparation to prevent or treat the diseases listed in claim 8.

14. The pharmaceutical preparation containing a therapeutically effective dose of the benzoic acid derivative of the formula (I) or its tautomer, isomer, pharmaceutically acceptable salt or solvate according to claim 1 as the active ingredient together with the pharmaceutically acceptable carriers and/or excipients.

30

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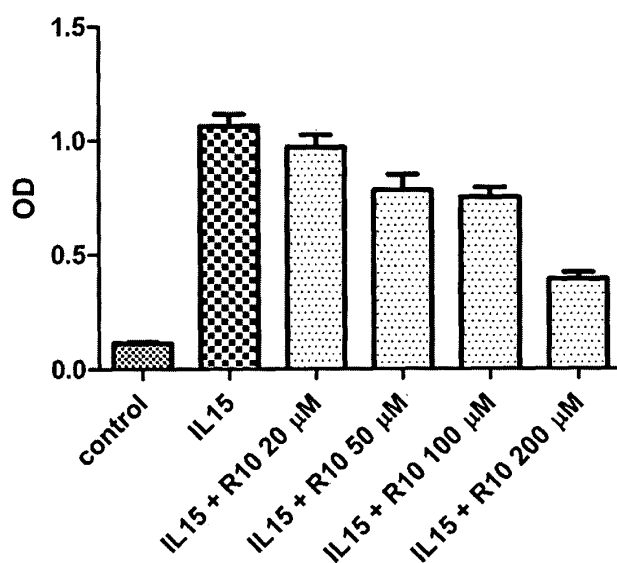


Fig. 1. Effect of the compound R10 (20 μ M, 50 μ M, 100 μ M and 200 μ M) on the IL-15-stimulated PBMC proliferation.

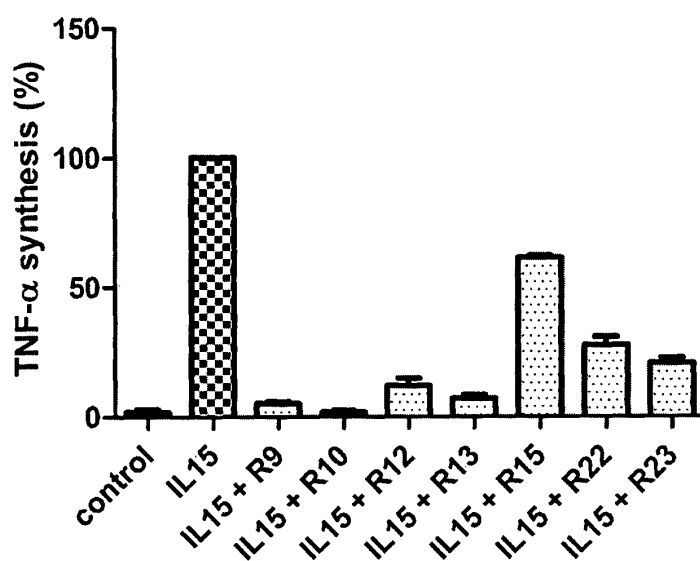


Fig. 2. Effect of the compounds R9, R10, R12, R13, R14, R22 and R23 (200 μ M) on the IL-15-induced TNF- α synthesis in PBMC.

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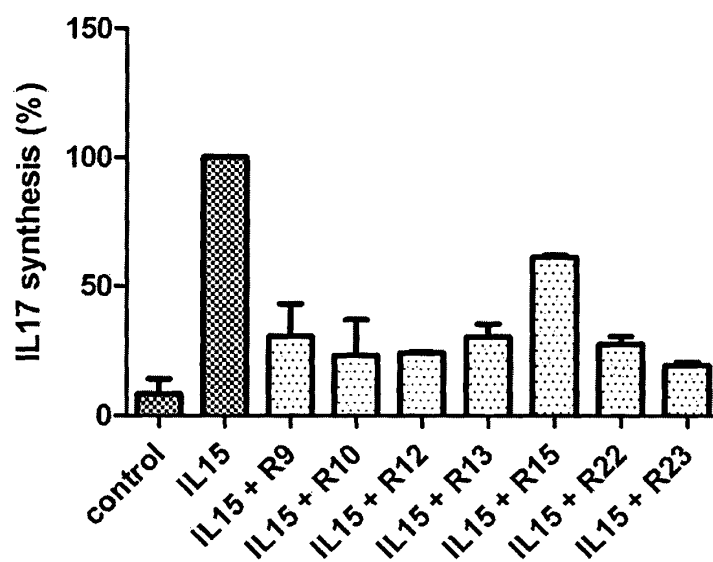


Fig. 3. Effect of the compounds R9, R10, R12, R13, R14, R22 and R23 (200 μ M) on the IL-15-induced IL-17 synthesis in PBMC.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/000894

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/194 A61K31/235 A61K31/41 A61P19/02 A61P29/00 ADD.		
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) A61K		
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) EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZAHRAH ZAWAHIR ET AL: "Pharmacophore Guided Discovery of Small-Molecule Human Apurinic/Apyrimidinic Endonuclease 1 Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 52, no. 1, 8 January 2009 (2009-01-08), pages 20-32, XP008144539, ISSN: 0022-2623, DOI: 10.1021/JM800739M [retrieved on 2008-12-10] page 26, right-hand column -/--	1,3,4, 6-8, 11-14
☒ 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		Date of mailing of the international search report
3 September 2014		29/09/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Steendijk, Martin

Form PCT/ISA/210 (second sheet) (April 2005)

page 1 of 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/000894

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>-& ZAHRAH Z. ET AL: "Supplementary Information Tables S1-S4: Pharmacophore Guided Discovery of Small-Molecule Human Apurinic/Apyrimidinic Endonuclease 1 Inhibitors", Journal of Medicinal Chemistry 8 January 2009 (2009-01-08), XP055137843, Retrieved from the Internet: URL:http://pubs.acs.org/doi/suppl/10.1021/jm800739m/suppl_file/jm800739m_si_002.pdf [retrieved on 2014-09-02] table s1; compound s9 -----</p> <p>DATABASE PubChem BioAssay [Online] 12 April 2011 (2011-04-12), XP002729247, retrieved from NCBI Database accession no. AID 504652 reference from AC1LH8XN -& DATABASE PubChem Compound [Online] "Compound Summary", XP002729248, retrieved from NCBI Database accession no. CID 834173 -----</p>	1,3,4, 6-8, 11-14
Y	<p>WO 2010/034003 A2 (CALCIMEDICA INC [US]; WHITTEN JEFFREY P [US]; PEI YAZHONG [US]; STAUDE) 25 March 2010 (2010-03-25) pages 72-73; claims 56,58 -----</p>	1,3,6-14
X	<p>WO 2011/006158 A2 (UNIV MARYLAND [US]; SANFORD BURNHAM MED RES INST [US]; UNIV TEXAS [US]) 13 January 2011 (2011-01-13) page 99; compound 238 -----</p>	1,7,8, 11-14
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