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(71) Applicant *(for all designated States except US)*: **7TM PHARMA A/S** [DK/DK]; Fremtidsvej 3, DK-2790 Hoersholm (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ULVEN, Trond** [NO/DK]; Department of Chemistry, University of Southern Denmark, Campusvej 55, DK-5230 Odense (DK). **FRIMURER, Thomas** [DK/DK]; 7TM Pharma A/S, Fremtidsvej 3, DK-2790 Hoersholm (DK). **RIST, øystein** [NO/DK]; 7TM Pharma A/S, Fremtidsvej 3, DK-2790 Hoersholm (DK). **KOSTENIS, Evi** [DE/DK]; 7TM Pharma A/S, Fremtidsvej 3, DK-2790 Hoersholm (DK). **HÖGBERG, Thomas** [SE/DK]; 7TM Pharma A/S, Fremtidsvej 3, DK-2790 Hoersholm (DK). **RECEVEUR, Jean-Marie** [FR/DK]; 7TM Pharma A/S, Fremtidsvej 3, DK-2790 Hoersholm (DK). **GRIMSTRUP, Marie** [NO/DK]; 7TM Pharma A/S, Fremtidsvej 3, DK-2790 Hoersholm (DK).

(74) Agent: **WALLS, Alan, James**; P.O. Box 223, Tadworth, Surrey KT20 5YF (GB).

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(54) **Title:** THIAZOLYL- AND PYRIMIDINYL-ACETIC ACIDS AND THEIR USE AS CRTH2 RECEPTOR LIGANDS

(57) **Abstract:** [2-[Bis-(4-fluoro-phenyl)methyl]-4-(2-methylpyridin-4-yl)thiazol-5-yl]acetic acid, {4-(2aminopyridin-4-yl)-2-[bis-(4-fluorophenyl)methyl]thiazol-5-yl}acetic acid, [2-[bis-(4-fluorophenyl)-methyl]-4-(3-fluoro-phenyl)-pyrimidin-5-yl]acetic acid, and salts, hydrates and solvates thereof are ligands of the CRTH2 receptor, and of value for the treatment of, inter alia, asthma, rhinitis, allergic airway syndrome, or allergic rhinobronchitis.

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THIAZOLYL- AND PYRIMIDINYL-ACETIC ACIDS AND THEIR USE AS CRTH2 RECEPTOR LIGANDS

This invention relates to the use of a class of compounds which are ligands of the CRTH2 receptor (Chemoattractant Receptor-homologous molecule expressed on T Helper cells type 2), in the treatment of diseases responsive to modulation of CRTH2 receptor activity, principally diseases having a significant inflammatory component. The invention also relates to novel members of that class of ligands and pharmaceutical compositions containing them.

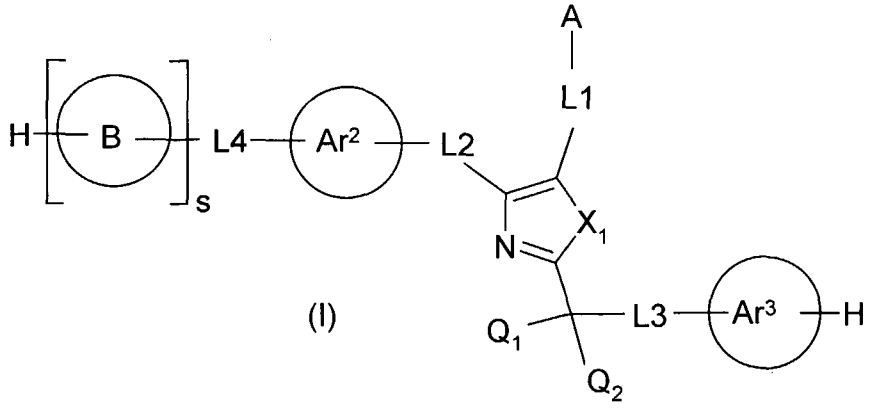
Many classes of antiinflammatory agents are known, including the non-steroidal antiinflammatory compounds known as NSAIDs and the inhibitors of cyclooxygenase (COX-1 and COX-2). Benzoylphenylacetic acid and some benzophenone derivatives with carboxymethoxy substituents in one of the rings have been identified as antiinfammatory agents (see, for example, Khanum et. al. Bioorganic Chemistry Vol 32, No. 4, 2004, pages 211-222 and the references cited therein). Some o-phenyl carbamoyl-phenoxyacetic acids and o-benzamido-phenoxymethyl tetrazoles have been reported as potential antiinflammatory agent, see for example Drain et. al. J. Pharm. Pharmac., 1971, 23, 857-864, and ibid 1970, 22, 684-693. WO 99/15520 discloses a few benzophenone derivatives with carboxymethoxy or tetrazolylmethoxy substituents in one of the rings, synthesised as members of a group of compounds said to have activity as inhibitors of peroxisome proliferator-activated receptor (PPAR), and utility in a variety of disease states including diabetes, cardiac disease, andcirculatory disease.

The natural ligand of the G-protein coupled receptor CRTH2 is prostaglandin D2. As its name implies, CRTH2 is expressed on T helper cells type 2 (Th2 cells) but it is also known to be expressed on eosinophils and basophil cells. Cell activation as a result of binding of PGD2 to the CRTH2 receptor results in a complex biological response, including release of inflammatory mediators. Elevated levels of PGD2 are therefore associated with many diseases which have a strong inflammatory component, such as asthma, rhinitis and allergies. Blocking binding of PGD2 to the CRTH2 receptor is therefore a useful therapeutic strategy for treatment of such diseases.

Some small molecule ligands of CRTH2, apparently acting as antagonists of PGD2, are known, for example as proposed in the following patent publications: WO 03/097042, WO 03/097598, WO 03/066046, WO 03/066047, WO 03/101961, WO 03/101981, GB 2388540, WO 04/089885 and WO 05/018529.

CONFIRMATION COPY

Our copending international application PCT/EP2005/005882 is concerned with the use of a compound of formula (IA) or a salt, hydrate or solvate thereof in the manufacture of a composition for the treatment of disease responsive to modulation of CRTH2 receptor activity



wherein

X_1 is -S-, -O-, -N=N-. $-NR_7$-, $-CR_7=CR_8$-, $-CR_7=N$-, wherein R_7 and R_8 are independently hydrogen or C_1-C_3 alkyl;

A is a carboxyl group –COOH, or a carboxyl bioisostere;

rings **Ar^2** and **Ar^3** each independently represent a phenyl or 5- or 6-membered monocyclic heteroaryl ring, or a bicyclic ring system consisting of a 5- or 6-membered carbocyclic or heterocyclic ring which is benz-fused or fused to a 5- or 6-membered monocyclic heteroaryl ring, said ring or ring system being optionally substituted;

ring **B** is as defined for Ar^2 and Ar^3, or an optionally substituted N-pyrrolidinyl, N-piperidinyl or N-azepinyl ring;

s is 0 or 1;

L1 represents a divalent radical of formula $-(Alk^1)_m$- and **L2** and **L4** each independently represents a divalent radical of formula $-(Alk^1)_m$-$(Z)_n$-$(Alk^2)_p$-
wherein

m, **n** and **p** are independently 0 or 1,

Alk^1 and **Alk**^{2} are independently optionally substituted straight or branched chain C_1-C_3 alkylene or C_2-C_3 alkenylene radicals which may contain a compatible –O-, -S- or –NR- link wherein R is hydrogen or C_1-C_3 alkyl, and

Z is –O-; -S-; -C(=O)-; -SO_2-; -SO-; -NR-, -$NRSO_2$-, -C(=O)NR-, -NRCONH-, NRC(=NR)NH-, or =N-NR- wherein R is hydrogen or C_1-C_3 alkyl; or a divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical;

L3 represents a divalent radical of formula –$(Alk^3)_m$-$(Z)_n$-$(Alk^2)_p$- wherein m, n, p, Alk^2 and Z are as defined in relation to L2 and L4, and Alk3 is an optionally substituted straight or branched chain C_1-C_2 alkylene or C_1-C_2 alkenylene radical which may contain a compatible –O-, -S- or –NR- link wherein R is hydrogen or C_1-C_3 alkyl;

Q_1 represents hydrogen or (C_1-C_6)alkyl;

Q_2 represents
(i) (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, hydroxy(C_1-C_6)alkyl, nitrile (-CN), phenyl, phenoxy, monocyclic heteroaryl or heteroaryloxy with 5 or 6 ring atoms, -$CONR^AR^B$, -NR^BCOR^A, -$NR^BSO_2R^A$ or -$NR^ACONR^AR^B$ wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group, or R^A and R^B are linked to the same N atom to form a cyclic amino ring, and when Q is phenyl, phenoxy or monocyclic heteroaryl or heteroaryloxy with 5 or 6 ring atoms the phenyl or heteroaryl ring is optionally substituted by any of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkylthio, halo, fully or partially fluorinated (C_1-C_3)alkyl, (C_1-C_3)alkoxy or (C_1-C_3)alkylthio, trifluoromethylthio, nitro, nitrile (-CN), -$COOR^A$, -COR^A, -$OCOR^A$, -SO_2R^A, -$CONR^AR^B$, -$SO_2NR^AR^B$, -NR^AR^B, -NR^BCOR^A, -NR^BCOOR^A, -$NR^BSO_2R^A$ or
-$NR^ACONR^AR^B$ wherein R^A and R^B are independently hydrogen or a (C_1-C_6)alkyl group, or R^A and R^B are linked to the same N atom to form a cyclic amino ring, or

(ii) hydrogen, but only when, in L3, Z represents an optionally substituted divalent 5- or 6-membered monocyclic carbocyclic or heterocyclic radical;

or **Q_1 and Q_2** taken together with the carbon atom to which they are attached form a C_3-C_6 cycloalkyl ring or a monocyclic non-aromatic heterocyclic ring with 4-6 ring atoms;

and wherein the total length of L2 and L3 does not exceed that of an unbranched saturated chain of 10 carbon atoms.

This invention relates to certain compounds falling withinthe general ambit of, but not specifically disclosed in PCT/EP2005/005882, and which have the CRTH2 receptor activity and utilities described in that application.

According to the present invention, there is provided a compound selected from the group consisting of [2-[bis-(4-fluoro-phenyl)methyl]-4-(2-methylpyridin-4-yl)thiazol-5-yl]acetic acid, {4-(2-aminopyridin-4-yl)-2-[bis-(4-fluorophenyl)methyl]thiazol-5-yl}acetic acid, [2-[bis-(4-fluoro-phenyl)-methyl]-4-(3-fluoro-phenyl)-pyrimidin-5-yl]acetic acid, and salts, hydrates and solvates thereof. Pharmaceutical compositions comprising a compound selected from the foregoing group together with a pharmaceutically acceptable carrier, also form part of the invention.

In a further aspect, the invention provides the use of a compound selected from the foregoing group in medicine, particularly in the manufacture of a medicament for treatment diseases responsive to modulation of CRTH2 receptor activity,

In another aspect, the invention provides a method of treatment of a subject suffering from a disease responsive to modulation of CRTH2 receptor activity, which comprised administering to the subject an amount of a compound selected from the foregoing group effective to ameliorate the disease.

In particular, compounds with which the invention is concerned are useful in the treatment of disease associated with elevated levels of prostaglandin D2 (PGD2) or one or more active metabolites thereof.

Examples of such diseases include asthma, rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer's lung, fibroid lung, cystic fibrosis, chronic cough, conjunctivitis, atopic dermatitis, Alzheimer's disease, amyotrophic lateral sclerosis, AIDS dementia complex, Huntington's disease, frontotemporal dementia, Lewy body dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating polyradiculoneurophathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration and encephalomyelitis, CNS trauma, migraine, stroke, rheumatoid arthritis,

ankylosing spondylitis, Behçet's Disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn´s disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, myofascial pain, osteoarthritis (OA), osteonecrosis, psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's Syndrome, soft tissue disease, Still's Disease, tendinitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia fascitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations, and graft versus host disease.

However, the compounds with which the invention is concerned are primarily of value for the treatment of asthma, rhinitis, allergic airway syndrome, and allergic rhinobronchitis.

As used herein, the term "treatment" includes prophylactic treatment.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as ammonium hydroxide; alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, p-toluenesulphonic, benzoic, benzenesunfonic, glutamic, lactic, and mandelic acids and the like.

Compositions

As mentioned above, the compounds with which the invention is concerned are capable of modulating CRTH2 activity, and are useful in the treatment of diseases which benefit from such modulation. Examples of such diseases are referred to above, and include asthma, allergy and rhinitis.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing treatment. Optimum dose levels and frequency of dosing will be determined by clinical trial, as is required in the pharmaceutical art.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal

agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The drug may also be formulated for inhalation, for example as a nasal spray, or dry powder or aerosol inhalers.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

The compounds with which the invention is concerned may be administered alone, or as part of a combination therapy with other drugs used for treatment of diseases with a major inflammatory component. In the case of asthma, rhinitis, and allergic airway syndrome such drugs include corticosteroids, long-acting inhaled beta agonists, cromolyn, nedocromil, theophylline, leukotriene receptor antagonists, antihistamines, and anticholinergics (e.g. ipratropium), and are often administered as nasal sprays, dry powder or aerosol inhalers.

In the case of arthritis and related inflammatory diseases other known drugs include glucocorticoids, NSAIDs (Non Steroidal Anti-Inflammatory Drugs – conventional prostaglandin synthesis inhibitors, COX-2 inhibitors, salicylates), and DMARDs (disease-modifying anti-rheumatic drugs such as methotrexate, sulfasalazine, gold, cyclosporine).

Synthesis of compounds of the invention:

General comments:

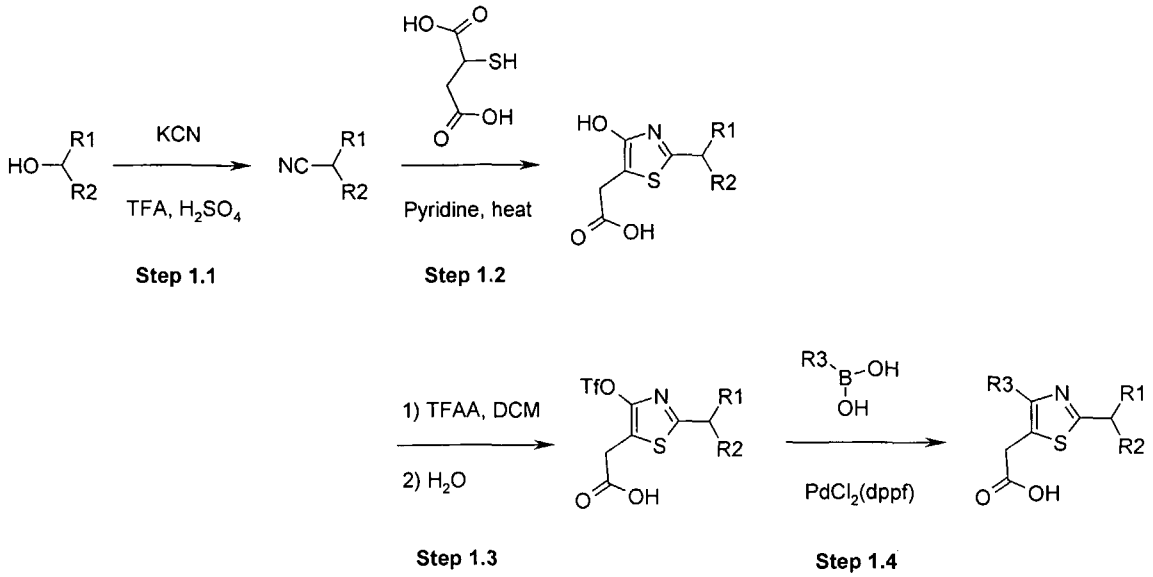
Microwave chemistry was performed in a Personal Chemistry Emrys Optimizer. NMR spectra were obtained on a Bruker Avance AMX 300 MHz instrument. LC/MS was performed on an Agilent 1100-series instrument. LC/MS methods are as follows:

Analytical an20p5: Column: Gemini 5μ C18 2.0x50 mm; Flow: 1.2 mL/min; Gradient: 0-3.5 min: 10-95% MeCN in water, 3.5-4.5 min: 95% MeCN; Modifier: 5 mM ammonium formate; MS-ionisation mode: API-ES (pos.)

Analytical an20n5: Column: Gemini 5μ C18 2.0x50 mm; Flow: 1.2 mL/min; Gradient: 0-3.5 min: 10-95% MeCN in water, 3.5-4.5 min: 95% MeCN; Modifier: 5 mM ammonium formate; MS-ionisation mode: API-ES (neg.)

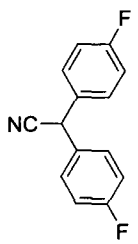
Analytical tfa20p5: Column: Gemini 5µ C18 2.0x50 mm; Flow: 1.2 mL/min; Gradient: 0-3.5 min: 10-95% MeCN in water, 3.5-4.5 min: 95% MeCN; Modifier: 0.1% TFA; MS-ionisation mode: API-ES (pos.)

General Synthetic Route 1



Intermediate-1 (prepared by Step 1.1)

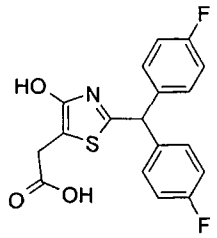
Synthesis of nitrile



Bis-(4-fluorophenyl)acetonitrile. 4,4'-Fluorodiphenylhydrol (5.0 g, 22.70mmol) was suspended in TFA (25 mL) and potassium cyanide (3.2 g, 49.94 mmol) was added. The reaction mixture was cooled to 0 °C on ice bath and conc. H_2SO_4 (10 mL) was added dropwise under cooling. The reaction mixture was stirred at room temperature for 2 h. Then poured into ice/water (100 mL) and extracted with EtOAc (3 x 60 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification on a SiO_2 column (100% DCM) gave the crude product as an oil (3.0 g, 58%). LC/MS (an20n5): Rt = 2.9 min, *m/z* 228 $[M-H]^-$. ^1H NMR ($CDCl_3$): δ 5.02 (s, 1H), 6.95 (t, 4H), 7.19 (t, 4H)

Intermediate-2 (prepared by Step 1.2)

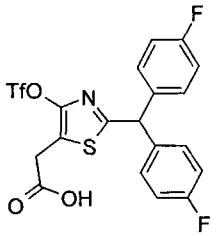
Synthesis of thiazole ring



(2-(Bis-(4-fluorophenyl)methyl)-4-hydroxythiazol-5-yl)acetic acid. Intermediate-1 (3.0 g, 13.1 mmol) was dissolved in pyridine (13 mL). Mercaptosuccinic acid (2.4 g, 15.7 mmol) was added. The reaction mixture was heated at 100 °C for 24 h. The mixture was concentrated and stripped with Et_2O (2 x 20 mL). EtOH (50 mL) was added and the mixture was left over night to precipitate. The precipitate was filtered off and washed with Et_2O and then dried to give the product as a solid (1.5 g, 32%). LC/MS (an20p5): Rt = 2.1 min, *m/z* 362 $[M+H]^+$. ^1H NMR (DMSO-d_6): δ 2.79 (m, 1H), 3.00 (dd, 1H), 4.31 (dd, 1H), 7.17 (m, 8H), 10.54 (s, 1H).

Intermediate-3 (prepared by Step 1.3)

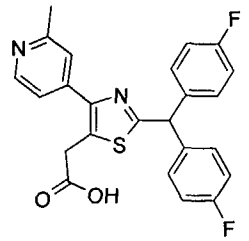
Synthesis of triflate



(2-(Bis-(4-fluorophenyl)methyl)-4-trifluoromethanesulfonyloxythiazol-5-yl)acetic acid. Intermediate-2 (1.5 g, 4.2 mmol) was dissolved in dry DCM (70 mL) in a flame dried flask. Trifluoromethanesulfonic anhydride (2.2 mL, 12.5 mmol) was added very slow at 0 °C under N_2. The reaction mixture was stirred at room temperature for 4 h, then poured into icewater (100 mL) and left for quenching over night. The mixture was extracted with DCM and the combined organic phase was dried (MgSO4) and concentrated to give the product as an oil (1.1 g, 54%). LC/MS (an20p5): Rt = 2.4 min, *m/z* 494 $[M+H]^+$.

<u>Example 1</u> – Compound A1 (prepared by Step 1.4)

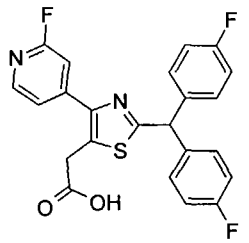
[2-[Bis-(4-fluoro-phenyl)methyl]-4-(2-methylpyridin-4-yl)thiazol-5-yl]acetic acid.



Suzuki coupling: Intermediate-3 (0.38 g, 0.77 mmol), 2-picoline-4-boronic acid (0.21 g, 1.5 mmol) and sat. Na_2CO_3 solution (1.2 mL) was suspended in dry dioxane (3 mL). The reaction mixture was flushed with N_2 for 15 min. $PdCl_2$(dppf) (10 mg, 0.038 mmol) was added under under N_2. The reaction mixture was stirred at 80 °C over night. 1 N HCl was added and then the mixture was extracted with DCM. The organic phase was passed through a phase separation filter and concentrated. The residue was purified on a PEAX SPE column (equilibrated with 100% MeOH and then eluted with 10% AcOH in MeOH) and then on a SiO_2 column (0-5% MeOH in DCM) to give the product as a solid (89.7 mg, 27%). LC/MS (tfa20p5): Rt = 2.1 min, *m/z* 437 $[M+H]^+$. ^1H NMR (DMSO-d_6): δ 2.52 (m, 3H), 4.00 (s, 2H), 6.06 (s, 1H), 7.20 (t, 4H), 7.40 (m, 6H), 8.51 (d, 1H).

Intermediate-4 (prepared by Step 1.4)

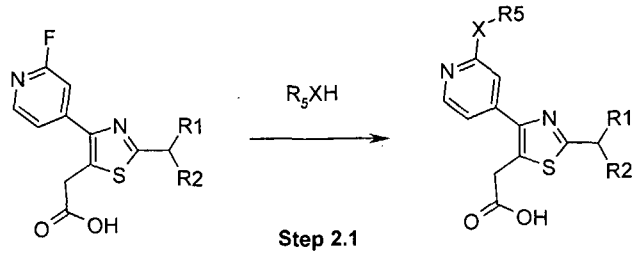
Suzuki coupling



[2-[Bis-(4-fluorophenyl)methyl]-4-(2-fluoropyridin-4-yl)thiazol-5-yl]acetic acid.

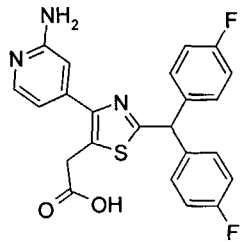
Intermediate-3 (1.0 g, 2.0 mmol), 2-fluoropyridine-4-boronic acid (0.57 g, 4.1 mmol) and sat. Na_2CO_3 solution (2.0 mL) was suspended in dry dioxane (9 mL). The reaction mixture was flushed with N_2 for 15 min. $PdCl_2$(dppf) (82 mg, 0.10 mmol) was added under under N_2. The reaction mixture was stirred at 90 °C for 2 h. 1 N HCl was added and then the mixture was extracted with DCM. The organic phase was passed through a phase-separation filter and concentrated. The residue was purified on a PEAX SPE column (equilibrated with 100% MeOH and then eluted with 10% AcOH in MeOH) to give the product (500 mg, 56%). LC/MS (an20p5): Rt = 2.9 min, *m/z* 441 $[M+H]^+$.

General Synthetic Route 2



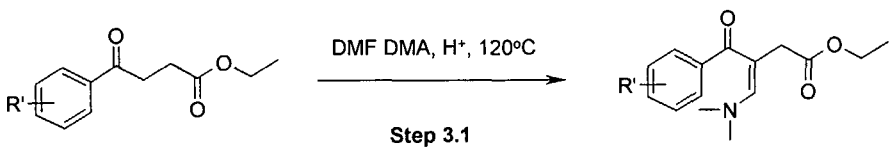
Example 2 – Compound A2 (prepared by Step 2.1)

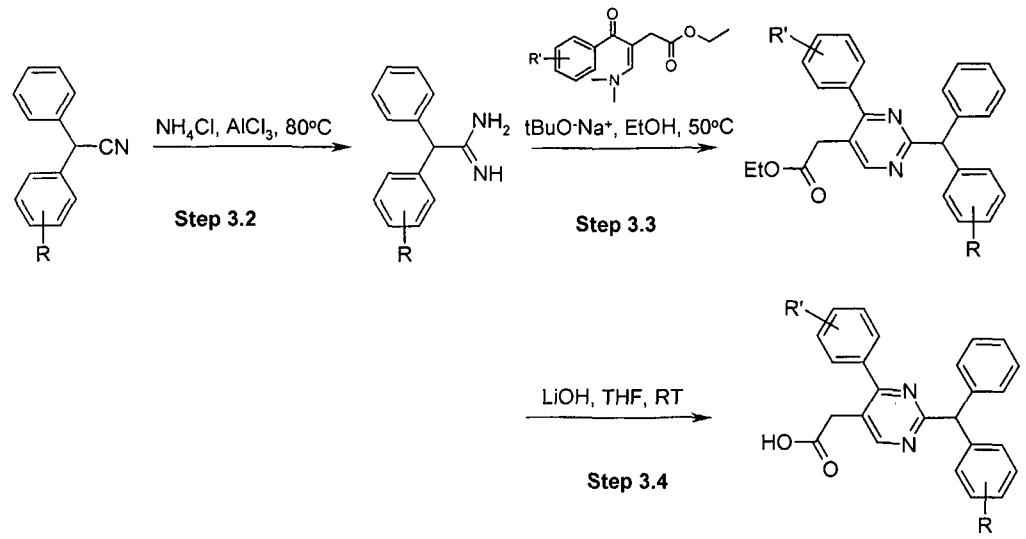
{4-(2-Aminopyridin-4-yl)-2-[bis-(4-fluorophenyl)methyl]thiazol-5-yl}acetic acid.



Nucleophilic aromatic substitution of fluorine: Intermediate-4 (0.5 g, 1.1 mmol) was dissolved in 28% ammonium hydroxide (15 mL). The reaction mixture was heated to 90 °C for a week. 1 N HCl, H_2O and DCM were added. The product seemed to be a solid between the two layers and was collected by filtration. The solid was dried and purified on a PEAX SPE column (equilibrated with 100% MeOH and then eluted with 10% AcOH in MeOH) and then on a SiO_2 column (0:0:100 – 2:20:100 NH_3/MeOH/DCM) to give the product as a solid (79.6 mg, 16%). LC/MS (tfa20p5): Rt = 2.1 min, *m/z* 438 $[M+H]^+$. ^1H NMR (DMSO-d_6): δ 3.92 (s, 2H), 6.02 (bs, 3H), 6.65(m, 1H), 6.68 (s, 1H), 7,19 (t, 4H), 7.38 (m, 4H), 7.94 (d, 1H).

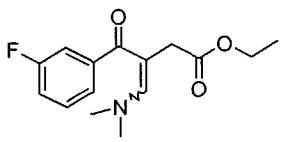
General Synthetic Route 3





Intermediate-5 (prepared by Step 3.1)

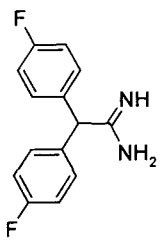
Synthesis of enamine



(Z, E)-4-Dimethylamino-3-(3-fluorobenzoyl)-but-3-enoic acid ethyl ester. To a solution of commercially available 4-(3-fluorophenyl)-4-oxobutyric acid ethyl ester (200 mg, 0.89 mmol) in *N,N*-dimethylformamide dimethyl acetal (1mL) was added catalytic amount of glacial acetic acid (1 drop). The reaction mixture was heated 3x30 min at 120 °C in a microwave reactor. Solvent was removed *in vacuo* to give the crude product, which was used directly in the next step. LC/MS (an20p5): Rt 1.8 min, *m/z* 280 $[M+H]^+$.

Intermediate-6 (prepared by Step 3.2)

Synthesis of amidine

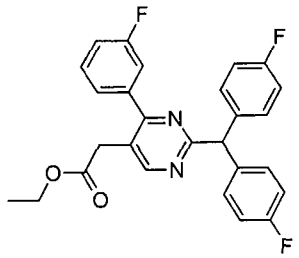


2,2-Bis-(4-fluorophenyl)acetamidine. To a flame dried flask was added ammonium chloride (230 mg, 4.32 mmol) and toluene (2 mL). To the cooled mixture (0 °C) was slowly added, under an argon atmosphere, a 2M solution of trimethylaluminium in toluene (2 ml, 4 mmol). After completion, the mixture was allowed to stir for 2 hours at room temperature upon which a solution of intermediate-1 (550 mg, 2.40 mmol) in toluene (20 mL) was added. The reaction

mixture was heated to 80 °C for 3 days. After cooling to 0 °C, water (10 mL) was slowly added, followed by the addition of EtOAc. The mixture was filtered through celite and the organic and aqueous phases were separated. The aqueous phase was concentrated *in vacuo* and the residue was taken up in DCM/MeOH (9/1). Solid ammonium chloride was filtered off and the filtrate was concentrated *in vacuo* to give the title compound (567 mg, 96%). ^{1}H NMR (DMSO-d_6): δ 5.48 (s, 1H), 7.17 (m, 8H), 9.05 (s br, 3H).

Intermediate-7 (prepared by Step 3.3)

Synthesis of pyrimidine ring

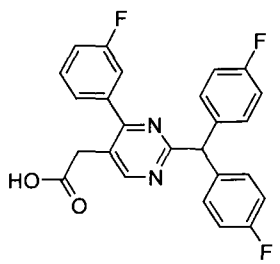


[2-[Bis-(4-fluoro-phenyl)-methyl]-4-(3-fluoro-phenyl)-pyrimidin-5-yl]-acetic acid ethyl ester

To a solution of intermediate-5 (200 mg, 0.72 mmol) and intermediate-6 (180 mg, 0.72 mmol) in absolute ethanol (2 mL) was added a solution of sodium *tert*-butoxide (69 mg, 0.72 mmol) in absolute ethanol (2mL). The reaction mixture was heated to 50 °C for 2 days. After cooling, solvent was removed in vacuo. The residue was partitioned between EtOAc and brine. The phases were separated and the organic phase was dried over MgSO4 and concentrated in vacuo. The residue was purified on a SiO_2 column (EtOAc/Heptane: 1/4) to give the title compound (67 mg, 20%): LC/MS (tfa20p5): Rt 2.8 min, *m/z* 463.1 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 3H), 3.59 (s, 2H), 4.10 (q, 2H), 5.70 (s, 1H), 6.85-7.45 (m, 12H), 8.68 (s, 1H).

<u>Example 3</u> - Compound A3 (prepared by Step 3.4)

[2-[Bis-(4-fluoro-phenyl)-methyl]-4-(3-fluoro-phenyl)-pyrimidin-5-yl]acetic acid.



Hydrolysis of ester: To a solution of intermediate-7 (64 mg, 0.14 mmol) in THF (0.6mL) was added a solution of lithium hydroxide·H_2O (12 mg, 0.28 mmol) in water (0.6 mL). The reaction

mixture was stirred for 1 hour at room temperature. 1N aq. HCl (up to pH ~1) and DCM were added. The phases were separated on a phase separation filter and the organic phase was concentrated in vacuo to give title compound (59 mg, 97%): LC/MS (tfa20p5.m): Rt 3.0 min, *m/z* 435.1 $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 3.65 (s, 2H), 5.70 (s, 1H), 6.92 (m, 4H), 7.08-7.39 (m, 8H), 8.68 (s, 1H).

Biological data:

Compounds were tested in the receptor binding assay and the functional antagonist assay described below, and their IC_{50} values were assessed. The compounds are grouped in three classes:

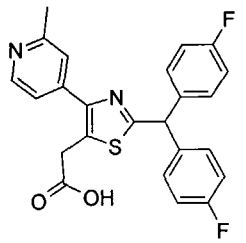
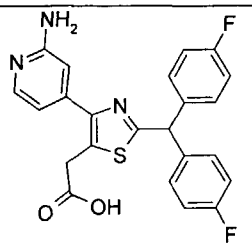
A: IC_{50} value lower than 0.5 μM

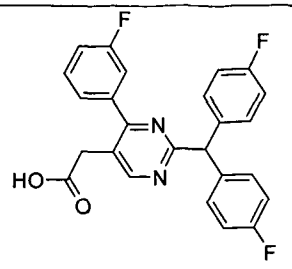
B: IC_{50} value between 0.5 μM and 5 μM

C: IC_{50} value higher than 5 μM

Table 1 gives the biological test results for the compounds synthesised above

Table 1

Compound		Binding IC_{50}	Antag. IC_{50}
A1		A	A
A2		A	A

A3		A	A

Biological Assays

Materials and Methods

Generation/origin of the cDNA Constructs. The coding sequence of the human CRTH2 receptor (genbank accession no NM_004778) was amplified by PCR from a human hippocampus cDNA library and inserted into the pcDNA3.1(+) expression vector (invitrogen) via 5' Hind*III* and 3' EcoR*I*. To generate a CRTH2-Renilla luciferase (CRTH2-Rluc) fusion protein, the CRTH2 coding sequence without a STOP codon and Rluc were amplified, fused in frame by PCR and subcloned into the pcDNA3.1(+)Zeo expression vector (invitrogen). Human β-arrestin2 (β-arr2) N-terminally tagged with GFP^2 (βarr2-GFP^2) and Renilla luciferase were purchased from BioSignal Packard Inc, (Montreal, Canada). The sequence identity of the construct was verified by restriction endonuclease digests and sequencing in both directions on an ABI Prism (Applied Biosystems, Foster City, CA).

Cell Culture and Transfection. COS-7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) 1885 supplemented with 10% fetal bovine serum, 100 units/ml penicillin, 1000 µg/ml streptomycin, and kept at 37°C in a 10% CO_2 atmosphere. HEK293 cells were maintained in Minimum Essential medium (MEM) supplemented with 10% (v/v) heat inactivated fetal calf serum (HIFCS), 2mM Glutamax™-I, 1% non essential amino acids (NEAA), 1% sodium pyruvate and 10 µg/ml gentamicin. For binding experiments, COS7 cells were transiently transfected with the CRTH2 receptor using a calcium phosphate-DNA coprecipitation method with the addition of chloroquine (as described by Holst et al., 2001+). To perform the functional **B**ioluminescence **R**esonance **E**nergy **T**ransfer (BRET) assays, a HEK293 cell clone stably expressing βarr2-GFP^2 and CRTH2-Rluc was generated (CRTH2-HEK293 cells).

Binding assay. 24h after transfection COS-7 cells were seeded into 96well plates at a density of 30.000 cells/well. Competition binding experiments on whole cells were then performed about 18-24 h later using 0.1 nM [^{3}H]PGD2 (NEN, 172 Ci/mmol) in a binding buffer consisting of HBSS (GIBCO) and 10 mM HEPES. Competing ligands were diluted in DMSO which was

kept constant at 1% (v/v) of the final incubation volume. Total and nonspecific binding were determined in the absence and presence of 10 μM PGD2. Binding reactions were routinely conducted for 3 h at 4°C and terminated by 2 washes (100 μl each) with ice cold binding buffer. Radioactivity was determined by liquid scintillation counting in a TOPCOUNTER (Packard) following over night incubation in Microscint 20. Stable HEK293 cells were seeded at a density of 30.000 cells/well 18-24 h prior to the binding assay which was performed essentially as described for COS7 cells above. Determinations were made in duplicates.

BRET assay. Functional BRET assays were performed on HEK293 cells stably expressing human CRTH2-Rluc and GFP^2-β-arr2. Prior to their use in the BRET assay cells were detached and re-suspended in D-PBS with 1000 mg/L L-Glucose at a density of $2x10^6$ cells/mL. DeepBlueC™ was diluted to 50 μM in D-PBS with 1000 mg/L L-Glucose (light sensitive). 100 μL of cell suspension was transferred to wells in a 96-well microplate (white OptiPlate) and placed in the Mithras LB 940 instrument (BERTHOLD TECHNOLOGIES, Bad Wildbad, Germany). 12 μL/well agonist was then injected by injector 1 and 10 μL/well DeepBlueC™ was injected simultaneously by injector 2. Five seconds after the injections the light output from the well was measured sequentially at 400 nm and 515 nm, and the BRET signal (mBRET ratio) was calculated by the ratio of the fluorescence emitted by GFP^2-β-arr2 (515 nm) over the light emitted by the receptor-Rluc (400 nm). Antagonists were added before placing the microplates into the Mithras LB 940 and allowed to incubate for 15 minutes prior to the addition of agonist and DeepBlueC™. Compounds were dissolved in DMSO and the final DMSO concentration was kept constant at 1% in the assay.

Claims:

1. A compound selected from [2-[bis-(4-fluoro-phenyl)methyl]-4-(2-methylpyridin-4-yl)thiazol-5-yl]acetic acid, {4-(2-aminopyridin-4-yl)-2-[bis-(4-fluorophenyl)methyl]thiazol-5-yl}acetic acid, [2-[bis-(4-fluoro-phenyl)-methyl]-4-(3-fluoro-phenyl)-pyrimidin-5-yl]acetic acid, and salts, hydrates and solvates thereof.

2. A pharmaceutical composition comprising a compound as claimed in claim 1, together with a pharmaceutically acceptable carrier.

3. A compound as claimed in claim 1 for use in medicine.

4. The use of a compound as claimed in claim 1 in the manufacture of a medicament for treatment diseases responsive to modulation of CRTH2 receptor activity,

5. A method of treatment of a subject suffering from a disease responsive to modulation of CRTH2 receptor activity, which comprises administering to the subject an amount of a compound as claimed in claim 1 effective to ameliorate the disease.

6. The use as claimed in claim 4 or a method as claimed in claim 5 wherein the disease is asthma, rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer´s lung, fibroid lung, cystic fibrosis, chronic cough, conjunctivitis, atopic dermatitis, Alzheimer's disease, amyotrophic lateral sclerosis, AIDS dementia complex, Huntington's disease, frontotemporal dementia, Lewy body dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating polyradiculoneurophathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration and encephalomyelitis, CNS trauma, migraine, stroke, rheumatoid arthritis, ankylosing spondylitis, Behçet's Disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn´s disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, myofascial pain, osteoarthritis (OA), osteonecrosis, psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's Syndrome, soft tissue disease, Still's Disease, tendinitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia

fascitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations, or graft versus host disease.

7. The use as claimed in claim 4 or a method as claimed in claim 5 wherein the disease is asthma, rhinitis, allergic airway syndrome, or allergic rhinobronchitis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/012870

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/04 C07D239/26 A61K31/4439 A61K31/505 A61P11/06

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)
C07D A61K A61P

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 practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/096777 A (BAYER HEALTHCARE AG) 11 November 2004 (2004-11-11) the whole document	1,4
A	NAGATOMI H ET AL: "Studies on the anti-inflammatory activity and ulcerogenic adverse effects of thiazole derivatives, especially 2-amino-thiazoleacetic acid derivatives" ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH, vol. 34(I), no. 5, 1984, pages 599-603, XP001074027 the whole document	1,4

☐ 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 document 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
28 July 2006	04/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/012870

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/012870

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004096777 A	11-11-2004	AT 316077 T	15-02-2006
		AU 2004233966 A1	11-11-2004
		BR PI0409733 A	09-05-2006
		CA 2523439 A1	11-11-2004
		DK 1471057 T3	15-05-2006
		EP 1471057 A1	27-10-2004