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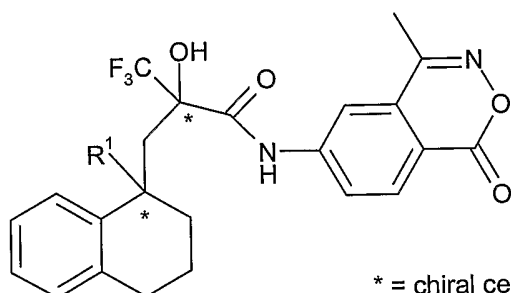
Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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[Continued on next page]

(54) Title: SUBSTITUTED OXAZINES AS GLUCOCORTICOID RECEPTOR MODULATORS



* = chiral centre

(57) Abstract: The present invention is directed to compounds of formula (I), wherein R¹ represents a C₃₋₆cycloalkyl group; or a physiologically functional derivative thereof, pharmaceutical compositions comprising the compounds, the use of the compounds for the manufacture of medicaments particularly for the treatment of inflammatory and/or allergic conditions, processes for the preparation of the compounds, and chemical intermediates in the processes for the manufacture of the compounds.



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PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference SCH/PB60927	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2005/006762	International filing date (day/month/year) 22/06/2005	(Earliest) Priority Date (day/month/year) 28/06/2004
Applicant GLAXO GROUP LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

SUBSTITUTED OXAZINES AS GLUCOCORTICOID RECEPTOR MODULATORS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

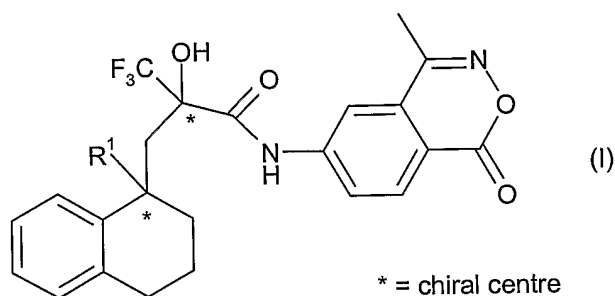
☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

ABSTRACTNovel Compounds

5 The present invention is directed to compounds of formula (I):



wherein R¹ represents a C₃₋₆cycloalkyl group; or a physiologically functional derivative thereof, pharmaceutical compositions comprising the compounds, the use of the
 10 compounds for the manufacture of medicaments particularly for the treatment of inflammatory and/or allergic conditions, processes for the preparation of the compounds, and chemical intermediates in the processes for the manufacture of the compounds.

Novel Compounds

The present invention relates to compounds which are non-steroidal glucocorticoid receptor modulators, pharmaceutical compositions comprising the compounds, the use of
5 the compounds for the manufacture of medicaments particularly for the treatment of inflammatory and/or allergic conditions, processes for the preparation of the compounds, and chemical intermediates in the processes for the manufacture of the compounds.

Nuclear receptors are a class of structurally related proteins involved in the regulation of
10 gene expression. The steroid hormone receptors are a subset of this family whose natural ligands typically comprise endogenous steroids such as estradiol (estrogen receptor), progesterone (progesterone receptor) and cortisol (glucocorticoid receptor). Man-made ligands to these receptors play an important role in human health, in particular the use of glucocorticoid agonists to treat a wide range of inflammatory conditions.

15 Glucocorticoids exert their actions at the glucocorticoid receptor (GR) through at least two intracellular mechanisms, transactivation and transrepression (see: Schacke, H, Docke, W-D. & Asadullah, K (2002) *Pharmacol and Therapeutics* **96**: 23-43; Ray, A., Siegel, M.D., Prefontaine, K.E. & Ray, P. (1995) *Chest* **107**: 139S; and Konig, H., Ponta, H.,
20 Rahmsdorf, H.J. & Herrlich, P. (1992) *EMBO J* **11**: 2241-2246). Transactivation involves direct binding of the glucocorticoid receptor to distinct deoxyribonucleic acid (DNA) response elements (GREs) within gene promoters, usually but not always increasing the transcription of the downstream gene product. Recently, it has been shown that the GR can also regulate gene expression through an additional pathway (transrepression) in
25 which the GR does not bind directly to DNA. This mechanism involves interaction of the GR with other transcription factors, in particular NFkB and AP1, leading to inhibition of their pro-transcriptional activity (Schacke, H, Docke, W-D. & Asadullah, K (2002) *Pharmacol and Therapeutics* **96**: 23-43; Ray, A., Siegel, M.D., Prefontaine, K.E. & Ray, P. (1995) *Chest* **107**: 139S). Many of the genes involved in the inflammatory response are
30 transcriptionally activated through the NFkB and AP1 pathways and therefore inhibition of this pathway by glucocorticoids may explain their anti-inflammatory effect (see: Barnes, P.J. & Adcock, I. (1993) *Trend Pharmacol Sci* **14**: 436-441; Cato, A.C. & Wade, E. (1996) *Bioessays* **18**: 371-378).

Despite the effectiveness of glucocorticoids in treating a wide range of conditions, a number of side-effects are associated with pathological increases in endogenous cortisol or the use of exogenous, and particularly systemically administered, glucocorticoids. These include reduction in bone mineral density (Wong, C.A., Walsh, L.J., Smith, C.J. et al. (2000) *Lancet* **355**: 1399-1403), slowing of growth (Allen, D.B. (2000) *Allergy* **55**: suppl 62, 15-18), skin bruising (Pauwels, R.A., Lofdahl, C.G., Latinen, L.A. et al. (1999) *N Engl J Med* **340**: 1948-1953), development of cataracts (Cumming, R.G., Mitchell, P. & Leeder, S.R. (1997) *N Engl J Med* **337**: 8-14) and dysregulation of lipid and glucose metabolism (Faul, J.L., Tormey, W., Tormey, V. & Burke, C. (1998) *BMJ* **317**: 1491; Andrews, R.C. & Walker, B. R. (1999) *Clin Sci* **96**: 513-523). The side-effects are serious enough often to limit the dose of glucocorticoid that can be used to treat the underlying pathology leading to reduced efficacy of treatment.

It has been suggested that excessive activation of the transactivation-GRE pathway may mediate some of these side-effects (see Schacke, H, Docke, W-D. & Asadullah, K (2002) *Pharmacol and Therapeutics* **96**: 23-43). Development of glucocorticoids that selectively modulate the transrepression pathway compared with the transactivation pathway may therefore have a superior anti-inflammatory to side-effect therapeutic index, allowing more effective and safer treatment of the patient. This new class of glucocorticoids could be used to treat more effectively and more safely the whole spectrum of disease currently treated by current glucocorticoids.

Current known glucocorticoids have proved useful in the treatment of inflammation, tissue rejection, auto-immunity, various malignancies, such as leukemias and lymphomas, Cushing's syndrome, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Th1/Th2 cytokine balance, chronic kidney disease, stroke and spinal cord injury, hypercalcemia, hyperglycemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia and Little's syndrome.

Glucocorticoids are especially useful in disease states involving systemic inflammation such as inflammatory bowel disease, systemic lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, osteoarthritis, seasonal rhinitis, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary

disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis and cirrhosis. Glucocorticoids have also been used as immunostimulants and repressors and as wound healing and tissue repair agents.

5

Glucocorticoids have also found use in the treatment of diseases such as inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type 1

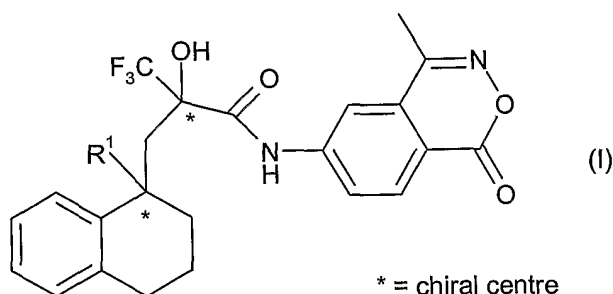
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reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitis, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma.

15

WO00/32584, WO02/10143, WO03/082827, WO/03082280 and DE10261874 disclose certain non-steroidal glucocorticoid receptor modulators.

The present invention provides compounds of formula (I):



20

wherein R¹ represents a C₃₋₆cycloalkyl group

and physiologically functional derivatives thereof (hereinafter "the compounds of the invention").

25

By the term C₃₋₆cycloalkyl, as used herein, is meant a cycloalkyl group having 3 to 6 carbon atoms. Examples of C₃₋₆cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In one embodiment of the invention R¹ represents a cyclopropyl group. In a second embodiment of the invention R¹ represents a cyclobutyl group. In another embodiment of the invention R¹ represents a cyclopentyl group. In a further embodiment of the invention R¹ represents a cyclohexyl group.

5

The compounds of formula (I) each contain two chiral centres and there are four possible stereoisomers of each compound of formula (I). Further, at least one of the possible stereoisomers of each compound of formula (I) modulates the glucocorticoid receptor.

10 The terms D1 and D2 are used herein to refer to the diastereomers of a compound of formula (I), based on the order of their elution using the chromatography methodology described herein (LCMS System A). D1 refers to the first diastereomer to elute, and D2 refers to the second diastereomer to elute.

15 The terms D1E1, D1E2, D2E1 and D2E2 are used herein to refer to the isomers of a compound of formula (I), D1E1 refers to the first enantiomer to elute, and D1E2 refers to the second enantiomer to elute, during chiral separation of diastereomer D1 according to the methodology described herein. D2E1 refers to the first enantiomer to elute, and D2E2 refers to the second enantiomer to elute, during chiral separation of diastereomer D2
20 according to the methodology described herein.

It will be appreciated by those skilled in the art that although the absolute retention time on chromatography can be variable, the order of elution remains the same when a similar column and conditions are employed. However, the use of a different chromatography
25 column and conditions may alter the order of elution.

A mixture of isomers, such as a racemic mixture, may be preferred, for example, a mixture of all four isomers, or a racemic mixture of two isomers may be preferred, for example diastereomer D2. Thus, in one embodiment of the invention the diastereomer D2
30 is preferred.

Alternatively, a single isomer may be preferred, for example the isomer D2E2. Therefore, in one embodiment of the invention the isomer D2E2 is preferred.

For example, when the group R¹ represents cyclopentyl, preferably the compound is isomer D2E2. Isomer D2E2 of the compound of formula (I) wherein the group R¹ represents cyclopentyl is characterised by having a circular dichroism as described below:
Circular Dichroism (Jasco Spectrophotometer Model J-720) acetonitrile, room
5 temperature, concentration 0.000173M, ν = 350-200 nm, cell length = 0.2 cm, 211.4 nm (de = -13.99; E = 15811), 243.2 nm (de = 13.85; E = 29182), 280.8 nm (de = 5.64; E = 13071).

Additionally or alternatively, isomer D2E2 of the compound of formula (I) wherein the
10 group R¹ represents cyclopentyl is characterised by having a retention time of about 18.3 min when eluted on an analytical chiral HPLC on a 25 x 0.46 cm Chiralpak AD column using a mobile phase of 5% ethanol in heptane at 1 mL/min. Isomer D2E2 is the later running enantiomer of the racemic mixture of isomers D2E1 and D2E2.

15 Compounds of the invention which are of particular interest include:

2-[(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-*N*-(4-methyl-1-oxo-1*H*-2,3-benzoxazin-6-yl)propanamide isomer D2E2;

2-[(1-cyclopropyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-*N*-(4-methyl-1-oxo-1*H*-2,3-benzoxazin-6-yl)propanamide isomer D2E2;

20 2-[(1-cyclobutyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-*N*-(4-methyl-1-oxo-1*H*-2,3-benzoxazin-6-yl)propanamide isomer D2E2;

2-[(1-cyclohexyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-*N*-(4-methyl-1-oxo-1*H*-2,3-benzoxazin-6-yl)propanamide isomer D2E2; and
physiologically functional derivatives thereof.

25 The compounds of the invention may provide agonism of the glucocorticoid receptor.

It has been found that at least one of the possible stereoisomers of each of the compounds of formula (I) binds to the glucocorticoid receptor. Further, it appears that at
30 least one of the possible stereoisomers of each of the compounds of formula (I) has glucocorticoid receptor agonist activity. Additionally, it appears that at least one of the possible stereoisomers of each of the compounds of formula (I) possesses advantageous selectivity in respect of maintaining transrepression activity whilst reducing the transactivation activity. These observations are believed to be indicative that the

compounds of the invention may provide anti-inflammatory properties with fewer or less severe related side effects.

5 It will be appreciated by those skilled in the art that at least one isomer (e.g. an enantiomer in a diastereomer) has the described activity. The other isomers may have similar activity, less activity, no activity or may have some antagonist activity in a functional assay. For example, in the case of the compound of formula (I) wherein the group R¹ represents cyclopentyl, both the racemic mixture of isomers D2E1 and D2E2 (ie. the diastereomer D2), and the single isomer D2E2 alone have been shown to
10 demonstrate glucocorticoid receptor agonist activity.

The invention includes physiologically functional derivatives of the compounds of formula (I). By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of
15 formula (I), for example, by being convertible in the body thereto and includes any pharmaceutically acceptable esters, carbonates and carbamates, solvates of compounds of formula (I) and solvates of any pharmaceutically acceptable esters, carbonates and carbamates or salts of compounds of formula (I), which, upon administration to the recipient, are capable of providing (directly or indirectly) compounds of formula (I) or
20 active metabolite or residue thereof. Thus one embodiment of the invention embraces compounds of formula (I) and salts and solvates thereof. Another embodiment of the invention embraces compounds of formula (I) and salts thereof. A further embodiment of the invention embraces compounds of formula (I).

25 Solvates of the compounds of formula (I) and physiologically functional derivatives thereof which are suitable for use in medicine are those wherein the associated solvent is pharmaceutically acceptable. However, solvates having non-pharmaceutically acceptable counter-ions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I)
30 and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

Examples of solvates include hydrates.

The compounds of the invention are expected to have potentially beneficial anti-inflammatory or anti-allergic effects, particularly upon topical administration, demonstrated by, for example, their ability to bind to the glucocorticoid receptor and to illicit a response via that receptor. Hence, the compounds of the invention may be useful in the treatment of inflammatory and/or allergic disorders.

Examples of disease states in which the compounds of the invention are expected to have utility include skin diseases such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis and hypersensitivity reactions; inflammatory conditions of the nose, throat or lungs such as asthma (including allergen-induced asthmatic reactions), rhinitis (including hayfever), nasal polyps, chronic obstructive pulmonary disease (COPD), interstitial lung disease, and fibrosis; inflammatory bowel conditions such as ulcerative colitis and Crohn's disease; and auto-immune diseases such as rheumatoid arthritis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of the invention are expected to be of use in human or veterinary medicine, in particular as anti-inflammatory and anti-allergic agents.

There is thus provided as a further aspect of the invention a compound of the invention for use in human or veterinary medicine, particularly in the treatment of patients with inflammatory and/or allergic conditions, such as rheumatoid arthritis, asthma, COPD, allergy or rhinitis.

In a further aspect there is provided a compound of the invention for use in the treatment of patients with skin disease such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis and hypersensitivity reactions.

According to another aspect of the invention, there is provided the use of a compound of the invention for the manufacture of a medicament for the treatment of patients with inflammatory and/or allergic conditions, such as rheumatoid arthritis, asthma, COPD, allergy or rhinitis.

According to yet to another aspect of the invention, there is provided the use of a compound of the invention for the manufacture of a medicament for the treatment of patients with skin disease such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis and hypersensitivity reactions.

5

In a further or alternative aspect, there is provided a method for the treatment of a human or animal subject with an inflammatory and/or allergic condition, which method comprises administering to said human or animal subject an effective amount of a compound of the invention.

10

In yet a further or alternative aspect, there is provided a method for the treatment of a human or animal subject with for skin disease such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis and hypersensitivity reactions, which method comprises administering to said human or animal subject an effective amount of a compound of the invention.

15

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising a compound of the invention together, if desirable, in admixture with one or more physiologically acceptable diluents or carriers.

20

Further, there is provided a process for the preparation of such pharmaceutical compositions which comprises mixing the ingredients.

25 The compounds of the invention may, for example, be formulated for oral, buccal, sublingual, parenteral, local rectal administration or other local administration.

Local administration as used herein, includes administration by insufflation and inhalation. Examples of various types of preparation for local administration include ointments, lotions, creams, gels, foams, preparations for delivery by transdermal patches, powders, 30 sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops), solutions/suspensions for nebulisation, suppositories, pessaries, retention enemas and chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) or liposome or microencapsulation preparations.

35

Ointments, creams and gels, may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agent and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a solvent such as polyethylene glycol.

5 Thickening agents and gelling agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, woolfat, beeswax, carboxypolymethylene and cellulose derivatives, and/or glyceryl monostearate and/or non-ionic emulsifying agents.

10 Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-
15 aqueous base also comprising one or more dispersing agents, solubilising agents, suspending agents or preservatives.

Spray compositions may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the
20 use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain a compound of formula (I) and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, especially 1,1,1,2-tetrafluoroethane,
25 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. The aerosol composition may optionally contain additional formulation excipients well known in the art such as surfactants e.g. oleic acid or lecithin and cosolvents e.g. ethanol.

Advantageously, the formulations of the invention may be buffered by the addition of
30 suitable buffering agents.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatine, may be formulated containing a powder mix for inhalation of a compound of the invention and a suitable powder base such as lactose or starch. Each capsule or cartridge may
35 generally contain between from 20µg to 10mg of the compound of formula (I).

Alternatively, the compound of the invention may be presented without excipients such as lactose.

The proportion of the active compound of formula (I) in the local compositions according to the invention depends on the precise type of formulation to be prepared but will generally be within the range of from 0.001 to 10% by weight. Generally, however for most types of preparations advantageously the proportion used will be within the range of from 0.005 to 1% and preferably from 0.01 to 0.5%. However, in powders for inhalation or insufflation the proportion used will be within the range of from 0.1 to 5%.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains from 20 μ g to 10mg preferably from 20 μ g to 2000 μ g, more preferably about 20 μ g-500 μ g of a compound of formula (I). Administration may be once daily or several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose with an aerosol will be within the range from 100 μ g to 10mg preferably, from 200 μ g to 2000 μ g. The overall daily dose and the metered dose delivered by capsules and cartridges in an inhaler or insufflator will generally be double that delivered with aerosol formulations.

In the case of suspension aerosol formulations, the particle size of the particular (e.g., micronised) drug should be such as to permit inhalation of substantially all the drug into the lungs upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than 20 microns, and, in particular, in the range of from 1 to 10 microns, such as from 1 to 5 microns, more preferably from 2 to 3 microns.

The formulations of the invention may be prepared by dispersal or dissolution of the medicament and a compound of the invention in the selected propellant in an appropriate container, for example, with the aid of sonication or a high-shear mixer. The process is desirably carried out under controlled humidity conditions.

The chemical and physical stability and the pharmaceutical acceptability of the aerosol formulations according to the invention may be determined by techniques well known to those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay, for example, after prolonged storage of the product.

Physical stability data may be gained from other conventional analytical techniques such

as, for example, by leak testing, by valve delivery assay (average shot weights per actuation), by dose reproducibility assay (active ingredient per actuation) and spray distribution analysis.

- 5 The stability of the suspension aerosol formulations according to the invention may be measured by conventional techniques, for example, by measuring flocculation size distribution using a back light scattering instrument or by measuring particle size distribution by cascade impaction or by the "twin impinger" analytical process. As used herein reference to the "twin impinger" assay means "Determination of the deposition of
10 the emitted dose in pressurised inhalations using apparatus A" as defined in British Pharmacopoeia 1988, pages A204-207, Appendix XVII C. Such techniques enable the "respirable fraction" of the aerosol formulations to be calculated. One method used to calculate the "respirable fraction" is by reference to "fine particle fraction" which is the amount of active ingredient collected in the lower impingement chamber per actuation
15 expressed as a percentage of the total amount of active ingredient delivered per actuation using the twin impinger method described above.

MDI canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or
20 preferably a metal can, for example, aluminium or an alloy thereof which may optionally be anodised, lacquer-coated and/or plastic-coated (for example incorporated herein by reference WO96/32099 wherein part or all of the internal surfaces are coated with one or more fluorocarbon polymers optionally in combination with one or more non-fluorocarbon polymers), which container is closed with a metering valve. The cap may be secured onto
25 the can via ultrasonic welding, screw fitting or crimping. MDIs taught herein may be prepared by methods of the art (e.g., see Byron, above and WO/96/32099). Preferably the canister is fitted with a cap assembly, wherein a drug-metering valve is situated in the cap, and said cap is crimped in place.

- 30 The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as, for example, low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Suitable valves are commercially available from manufacturers
35 well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30,

DF60), Bepak plc, UK (e.g. BK300, BK357) and 3M-Neotechnic Ltd, UK (e.g. Spraymiser™).

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large-scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminium can to form an empty canister. The particulate medicament is added to a charge vessel and liquefied propellant is pressure filled through the charge vessel into a manufacturing vessel, together with liquefied propellant containing the surfactant. The drug suspension is mixed before recirculation to a filling machine and an aliquot of the drug suspension is then filled through the metering valve into the canister.

In an alternative process, an aliquot of the liquefied formulation is added to an open canister under conditions which are sufficiently cold to ensure formulation does not vaporise, and then a metering valve crimped onto the canister.

Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.

In one aspect the present invention provides a pharmaceutical aerosol formulation comprising a compound of formula (I) or a physiologically functional derivative thereof, and a fluorocarbon or hydrogen containing chlorofluorocarbon as propellant, optionally in combination with a surfactant and/or cosolvent.

Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may advantageously be used. Continuous or prolonged delivery may be achieved by an adhesive reservoir system.

For internal administration the compounds according to the invention may, for example, be formulated in conventional manner for oral, parenteral or rectal administration. Formulations for oral administration include syrups, elixirs, powders, granules, tablets and capsules which typically contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, wetting agents, suspending agents, emulsifying agents,

preservatives, buffer salts, flavouring, colouring and/or sweetening agents as appropriate. Dosage unit forms are, however, preferred as described below.

The compounds according to the invention may in general be given by internal
5 administration in cases where systemic adreno-cortical therapy is indicated.

Slow release or enteric coated formulations may be advantageous, particularly for the treatment of inflammatory bowel disorders.

10 In some embodiments, the compound of formula (I) will be formulated for oral administration. In other embodiments the compounds of formula (I) will be formulated for inhaled administration.

The compound and pharmaceutical formulations according to the invention may be used
15 in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an $M_1/M_2/M_3$ receptor antagonist), β_2 -adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or
20 physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example another corticosteroid or an NSAID), an anticholinergic agent, a β_2 -adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. One embodiment of the invention encompasses combinations comprising
25 a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a β_2 -adrenoreceptor agonist, and/or an anticholinergic, and/or a PDE-4 inhibitor. Suitable combinations are those comprising one or two other therapeutic agents.

30 It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the
35 therapeutic ingredients may be used in optically pure form.

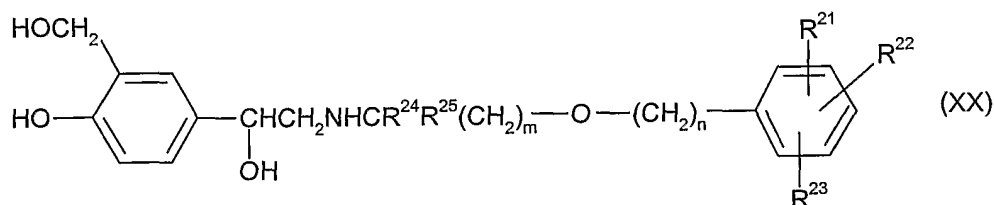
Suitable combinations include a combination comprising of a compound of the invention together with a β_2 -adrenoreceptor agonist.

- 5 Examples of β_2 -adrenoreceptor agonists include salmeterol (e.g. as racemate or a single enantiomer such as the *R*-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline and salts thereof, for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. In one embodiment the β_2 -adrenoreceptor agonists are long-acting β_2 -adrenoreceptor agonists for example;
- 10 those having a therapeutic effect over a 24 hour period such as salmeterol or formoterol.

Suitable long acting β_2 -adrenoreceptor agonists may include those described in WO 02/066422, WO 02/070490, WO 02/076933, WO 03/024439, WO 03/072539, WO 03/091204, WO 04/016578, WO 2004/022547, WO 2004/037807, WO 2004/037773, WO

15 2004/037768, WO 2004/039762, WO 2004/039766, WO01/42193 and WO03/042160.

Examples of long-acting β_2 -adrenoreceptor agonists may include compounds of formula (XX):



20

or a salt or solvate thereof, wherein:

m is an integer of from 2 to 8;

n is an integer of from 3 to 11,

with the proviso that m + n is 5 to 19,

- 25 R^{21} is $-XSO_2NR^{26}R^{27}$ wherein X is $-(CH_2)_p-$ or C_{2-6} alkenylene;

R^{26} and R^{27} are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, $C(O)NR^{28}R^{29}$, phenyl, and phenyl (C_{1-4} alkyl)-,

or R^{26} and R^{27} , together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R^{26} and R^{27} are each optionally substituted by

- 30 one or two groups selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy-substituted C_{1-6} alkoxy, $-CO_2R^{28}$, $-SO_2NR^{28}R^{29}$, $-CONR^{28}R^{29}$,

-NR²⁸C(O)R²⁹, or a 5-, 6- or 7-membered heterocyclic ring;

R²⁸ and R²⁹ are independently selected from hydrogen, C₁₋₆alkyl,

C₃₋₆cycloalkyl, phenyl, and phenyl (C₁₋₄alkyl)-; and

p is an integer of from 0 to 6, preferably from 0 to 4;

- 5 R²² and R²³ are independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo, phenyl, and C₁₋₆haloalkyl; and

R²⁴ and R²⁵ are independently selected from hydrogen and C₁₋₄alkyl with the proviso that the total number of carbon atoms in R²⁴ and R²⁵ is not more than 4.

- 10 Other examples of long-acting β_2 -adrenoreceptor agonists include:

3-(4-[[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy]butyl)benzenesulfonamide;

3-(3-[[7-(((2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl)-amino)heptyl]oxy]propyl)benzenesulfonamide;

- 15 4-((1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

4-((1R)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

N-[2-hydroxyl-5-[(1R)-1-hydroxy-2-[[2-4-[(2R)-2-hydroxy-2-

- 20 phenylethyl]amino]phenyl]ethyl]amino]ethyl]phenyl]foramide, and

N-2{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1H)-quinolinon-5-yl)ethylamine.

Suitable anti-inflammatory agents include corticosteroids. Suitable corticosteroids which

- 25 may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity.

Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-

- 30 carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-

17 β -carbothioic acid S-fluoromethyl ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy- androsta-1,4-diene-17 β -carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone

- 35 acetonide, rofleponide, ciclesonide (16 α ,17-[[[(R)-cyclohexylmethylene]bis(oxy)]-11 β ,21-

dihydroxy-pregna-1,4-diene-3,20-dione), butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester and 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, more preferably 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

Non-steroidal compounds having glucocorticoid agonism that may possess selectivity for transrepression over transactivation and that may be useful in combination therapy include those covered in the following patents: WO03/082827, WO01/10143, WO98/54159, WO04/005229, WO04/009016, WO04/009017, WO04/018429, WO03/104195, WO03/082787, WO03/082280, WO03/059899, WO03/101932, WO02/02565, WO01/16128, WO00/66590, WO03/086294, WO04/026248, WO03/061651, WO03/08277.

Suitable anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAID's).

Suitable NSAID's include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis (e.g. montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists, such as a CCR3 antagonist) or inhibitors of cytokine synthesis, or 5-lipoxygenase inhibitors. Suitable other β_2 -adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof. An iNOS (inducible nitric oxide synthase inhibitor) is preferably for oral administration. Suitable iNOS inhibitors include those disclosed in WO93/13055, WO98/30537, WO02/50021, WO95/34534 and WO99/62875. Suitable CCR3 inhibitors include those disclosed in WO02/26722.

Of particular interest is use of the compounds of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor, especially in the case of a formulation adapted for inhalation. The PDE4-specific inhibitor useful in this aspect of the invention may be any

compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family, such as PDE3 and PDE5, as well as PDE4.

5 Compounds of interest include *cis*-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]. Also, *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as
10 cilomilast) and its salts, esters, pro-drugs or physical forms, which is described in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference.

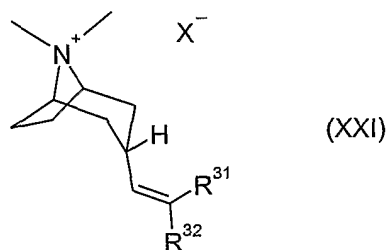
Other compounds of interest include AWD-12-281 from Elbion (Hofgen, N. et al. 15th
15 EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al.
20 al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a
25 mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther, 1998, 284(1): 162), and T2585.

30 Further compounds of interest are disclosed in the published international patent application WO04/024728 (Glaxo Group Ltd), PCT/EP2003/014867 (Glaxo Group Ltd) and PCT/EP2004/005494 (Glaxo Group Ltd).

Suitable anticholinergic agents are those compounds that act as antagonists at the
35 muscarinic receptors, in particular those compounds which are antagonists of the M₁ or

M₃ receptors, dual antagonists of the M₁/M₃ or M₂/M₃ receptors or pan-antagonists of the M₁/M₂/M₃ receptors. Exemplary compounds for administration via inhalation include ipratropium (e.g. as the bromide, CAS 22254-24-6, sold under the name Atrovent), oxitropium (e.g. as the bromide, CAS 30286-75-0) and tiotropium (e.g. as the bromide, CAS 136310-93-5, sold under the name Spiriva). Also of interest are revatropate (e.g. as the hydrobromide, CAS 262586-79-8) and LAS-34273 which is disclosed in WO01/04118. Exemplary compounds for oral administration include pirenzepine (CAS 28797-61-7), darifenacin (CAS 133099-04-4, or CAS 133099-07-7 for the hydrobromide sold under the name Enablex), oxybutynin (CAS 5633-20-5, sold under the name Ditropan), terodiline (CAS 15793-40-5), tolterodine (CAS 124937-51-5, or CAS 124937-52-6 for the tartrate, sold under the name Detrol), otilonium (e.g. as the bromide, CAS 26095-59-0, sold under the name Spasmomen), trospium chloride (CAS 10405-02-4) and solifenacin (CAS 242478-37-1, or CAS 242478-38-2 for the succinate also known as YM-905 and sold under the name Vesicare).

Other suitable anticholinergic agents include compounds of formula (XXI), which are disclosed in US patent application 60/487981:



in which the preferred orientation of the alkyl chain attached to the tropane ring is endo; R³¹ and R³² are, independently, selected from the group consisting of straight or branched chain lower alkyl groups having preferably from 1 to 6 carbon atoms, cycloalkyl groups having from 5 to 6 carbon atoms, cycloalkyl-alkyl having 6 to 10 carbon atoms, 2-thienyl, 2-pyridyl, phenyl, phenyl substituted with an alkyl group having not in excess of 4 carbon atoms and phenyl substituted with an alkoxy group having not in excess of 4 carbon atoms;

X⁻ represents an anion associated with the positive charge of the N atom. X⁻ may be but is not limited to chloride, bromide, iodide, sulfate, benzene sulfonate, and toluene sulfonate,

including, for example:

(3-*endo*)-3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;

(3-*endo*)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane 4-

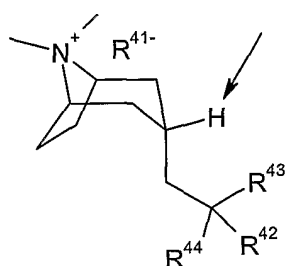
5 methylbenzenesulfonate;

(3-*endo*)-8,8-dimethyl-3-[2-phenyl-2-(2-thienyl)ethenyl]-8-azoniabicyclo[3.2.1]octane
bromide; and/or

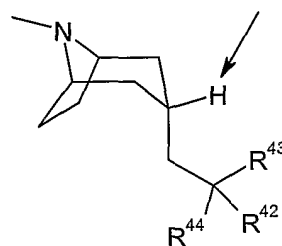
(3-*endo*)-8,8-dimethyl-3-[2-phenyl-2-(2-pyridinyl)ethenyl]-8-azoniabicyclo[3.2.1]octane
bromide.

10

Further suitable anticholinergic agents include compounds of formula (XXII) or (XXIII),
which are disclosed in US patent application 60/511009:



(XXII)



(XXIII)

15

wherein:

the H atom indicated is in the exo position;

R⁴¹ represents an anion associated with the positive charge of the N atom. R⁴¹ may be
but is not limited to chloride, bromide, iodide, sulfate, benzene sulfonate and toluene
sulfonate;

20

R⁴² and R⁴³ are independently selected from the group consisting of straight or branched
chain lower alkyl groups (having preferably from 1 to 6 carbon atoms), cycloalkyl groups
(having from 5 to 6 carbon atoms), cycloalkyl-alkyl (having 6 to 10 carbon atoms),
heterocycloalkyl (having 5 to 6 carbon atoms) and N or O as the heteroatom,
heterocycloalkyl-alkyl (having 6 to 10 carbon atoms) and N or O as the heteroatom, aryl,
optionally substituted aryl, heteroaryl, and optionally substituted heteroaryl;

25

R⁴⁴ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-
C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl,
aryl, heteroaryl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl, -OR⁴⁵, -CH₂OR⁴⁵, -CH₂OH, -CN,
-CF₃, -CH₂O(CO)R⁴⁶, -CO₂R⁴⁷, -CH₂NH₂, -CH₂N(R⁴⁷)SO₂R⁴⁵, -SO₂N(R⁴⁷)(R⁴⁸), -

30

CON(R⁴⁷)(R⁴⁸), -CH₂N(R⁴⁸)CO(R⁴⁶), -CH₂N(R⁴⁸)SO₂(R⁴⁶), -CH₂N(R⁴⁸)CO₂(R⁴⁵),
CH₂N(R⁴⁸)CONH(R⁴⁷);

R⁴⁵ is selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl,
(C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl;

- 5 R⁴⁶ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-
C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl,
aryl, heteroaryl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl;

- R⁴⁷ and R⁴⁸ are, independently, selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-
C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-
10 C₇)heterocycloalkyl, (C₁-C₆)alkyl-aryl, and (C₁-C₆)alkyl-heteroaryl, including, for example:

(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-
bicyclo[3.2.1]octane iodide;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile;

(Endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane;

- 15 3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid;

(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane

bromide;

- 20 3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol;

N-Benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;

(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
iodide;

1-Benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;

- 25 1-Ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;

N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide;

N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile;

(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane

- 30 iodide;

N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-
benzenesulfonamide;

[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;

N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-

- 35 methanesulfonamide; and/or

(Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

For example, compounds useful in the present invention include:

(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-

5 bicyclo[3.2.1]octane iodide;

(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;

10 (Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; and/or

(Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

15

Suitable antihistamines (also referred to as H1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H1-receptors, and are safe for human use. First generation antagonists, include derivatives of ethanolamines, ethylenediamines, and alkylamines, e.g diphenylhydramine, pyrilamine, clemastine, chloropheniramine. Second generation antagonists, which are non-sedating, include loratidine, desloratidine, terfenadine, astemizole, acrivastine, azelastine, levocetirizine fexofenadine and cetirizine.

20

Examples of suitable anti-histamines include loratidine, desloratidine, fexofenadine and cetirizine.

25

The invention provides in one aspect, a pharmaceutical composition comprising a compound of formula (I), or a physiologically functional derivative thereof, in admixture with one or more physiologically acceptable diluents or carriers which further comprises another therapeutically active agent.

30

A further aspect of the invention provides a pharmaceutical composition comprising a compound of formula (I), or a physiologically functional derivative thereof, in admixture with one or more physiologically acceptable diluents or carriers which further comprises a β_2 -adrenoreceptor agonist.

35

In another aspect of the invention a combination is provided comprising a compound of formula (I), or a physiologically functional derivative thereof, together with a PDE4 inhibitor.

5

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a PDE4 inhibitor.

10 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a β_2 -adrenoreceptor agonist.

The invention thus provides, in a further aspect, a combination comprising a compound of
15 formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a compound of
20 formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of
formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional
derivative thereof together with a PDE4 inhibitor and a β_2 -adrenoreceptor agonist.

25

The invention thus provides, in a further aspect, a combination comprising a compound of
formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional
derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

30 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. In one embodiment the individual compounds will be administered simultaneously in a combined pharmaceutical formulation. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

There are four possible isomers of compounds of formula (I). These are called isomers D1E1, D1E2, D2E1 and D2E2 herein.

Isomer D2E1 of the compound of formula (I) wherein R¹ represents cyclopentyl is characterised in having a retention time in analytical chiral HPLC on a 25 x 0.46 cm Chiralpak AD column using a mobile phase of 5% ethanol in heptane eluting at 1 mL/min of about 14.2min. Isomer D2E2 of the compound of formula (I) wherein R¹ represents cyclopentyl has a retention time of about 18.3min under the same conditions, and under the same conditions, isomers D1E1 and D1E2 elute at about 11.9min and 14.9min respectively.

It will be appreciated by those skilled in the art that although the absolute retention time on chiral chromatography can be variable, the order of elution of the enantiomers remains the same when the same chiral column and conditions are employed.

Preferred isomers of the compounds of formula (I) may be prepared by chromatographic separation of the isomer from a mixture of enantiomeric isomers (e.g. a racemic mixture, such as a diastereomer D2).

There are also provided methods for the preparative separation of isomer D2E2 of a compound of formula (I) from a mixture of isomers D2E1 and D2E2 (e.g. a racemic mixture, such as diastereomer D2) by chromatography.

According to another aspect of the invention there is provided a mixture of isomer D2E2 of a compound of formula (I) with one or more other isomers e.g. a racemic mixture of isomers D2E1 and D2E2 (diastereomer D2).

A mixture (e.g. racemic mixture) of enantiomeric isomers D2E1 and D2E2 may be prepared by chromatographic separation from a mixture of isomers D1E1, D1E2, D2E1 and D2E2.

- 5 The racemic mixture of isomers D2E1 and D2E2 of the compound of formula (I) wherein R^1 represents cyclopentyl (diastereomer D2) has an LCMS: t_{ret} of about 4.02min, while the racemic mixture of isomers D1E1 and D1E2 of the compound of formula (I) wherein R^1 represents cyclopentyl (diastereomer D1) has an LCMS: t_{ret} of about 3.87min under the conditions described for LCMS System A.

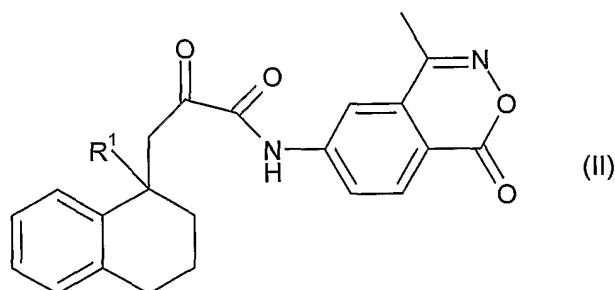
10

The invention also provides a mixture (e.g. a racemic mixture) of isomers D1E1, D1E2, D2E1 and D2E2.

15

There are also provided methods for the separation of a mixture of isomers D2E1 and D2E2 (diastereomer D2) from a mixture of isomers D1E1, D1E2, D2E1 and D2E2 (e.g. a mixture of D1 and D2) by chromatography.

A process according to the invention for the preparation of compounds of formula (I) comprises treatment of a compound of formula (II):



20

wherein R^1 represents a C_{3-6} cycloalkyl group

with a trifluoromethylating agent of formula (III)

25



wherein R^{10} represents an activating group, for example, trimethylsilyl (TMS).

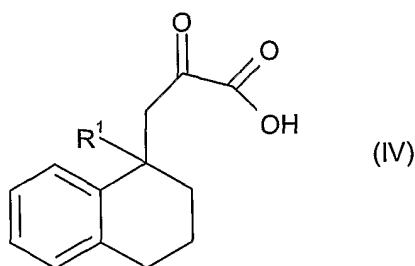
The reaction will generally be performed in the presence of an inert solvent, such as dimethylformamide (DMF) and a base, such as caesium fluoride (CsF) at a non- extreme temperature, for example, 0-120°C, and more suitably at room temperature.

- 5 Alternative conditions with PhSCF₃, Et₃GeNa in HMPA (Yokoyama, Y. and Mochida, K. *Syn. Lett.* **1997**, 907-8) may also be suitable. Further alternative reagents include CF₃H, CF₃I, PhSOCF₃ and PhSO₂CF₃. Alternative methods featuring trifluoromethylating reagents are described in: Prakash, G.K.S., Hu, J. and Olah, G.A. *Org. Lett.* **2003**, 5, 3253-6; Caron, S., Do, N.M., Arpin, P. and Larivee, A. *Synthesis*, **2003**, 1693-98;
- 10 Langlois, B.R. *et al Synthesis* **2003**, 185-194; and further methods cited in these papers. Further conditions which may be suitable are described in Langlois, B.R. *et al Angew. Chem. Int. Ed.* **2003**, 42, 3133-3136.

- Alternatively, the reaction of compound of formula (II) and a compound of formula (III) wherein R¹⁰ represents TMS may be effected in a solvent such as DMF in the presence of
- 15 excess (5 equivalents) lithium fluoride (LiF) or caesium carbonate (Cs₂CO₃) at a non-extreme temperature, for example, between room temperature and 100°C, preferably at room temperature, wherein the compound of formula (III) is present in a large excess (10 equivalents). Where R¹⁰ represents a trialkylsilyl group the final step may include
- 20 deprotection using a suitable reagent, for example, when R¹⁰ is TMS it may be removed by treatment with TBAF (tetrabutylammonium fluoride) in tetrahydrofuran.

Compounds of formula (II) may be prepared from compounds of formula (IV):

25

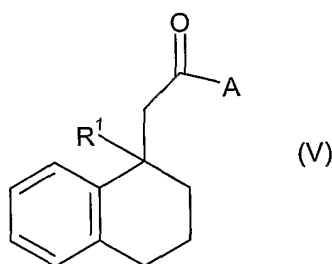


wherein R¹ represents a C₃₋₆cycloalkyl group,

by treatment with an activating agent and 6-amino-4-methyl-1H-2,3-benzoxazin-1-one. A suitable method for preparing 6-amino-4-methyl-1H-2,3-benzoxazin-1-one is described in WO 98/54159. An example of a suitable activating agent is thionyl chloride.

- 5 The reaction is generally effected in the presence of a suitable solvent, for example, dimethylacetamide or dimethylformamide, in the presence of thionyl chloride at a non-extreme temperature. For example, the reaction may be carried out in dimethylacetamide in the presence of thionyl chloride at a temperature of -15 to 25°C, such as -5°C
- 10 The compounds of formula (IV) have proved difficult to synthesise. We have now provided a process which enables the compound to be made.

In this process, compounds of formula (IV) may be prepared by reaction of compounds of formula (V):



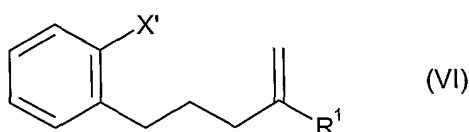
- 15 wherein R¹ represents a C₃₋₆cycloalkyl group and A is a group selected from -CO-2-furanyl, -CO-C(=CH₂)OC₁₋₆alkyl, -ethynyl or -C(=CH₂)CO₂C₁₋₆alkyl

by reaction with a suitable oxidising agent.

- 20 When A is -CO-2-furanyl, -CO-C(=CH₂)OC₁₋₆alkyl or -C(=CH₂)CO₂C₁₋₆alkyl, suitable oxidising agents include ozone, potassium permanganate or sodium periodate with a catalytic ruthenium salt. When A is an ethynyl group, suitable oxidising conditions include bromination followed by treatment with permanganate (see Y.-L.Wu *et al.*, *Tetrahedron Lett.*, **2002**, 43, 2427-2430). Other suitable oxidising conditions include osmium tetroxide/*tert*-butylhydroperoxide, osmium tetroxide/sodium periodate and MoOPH (oxodiperoxymolybdenum-pyridine-hexamethylphosphoric triamide) (as set out in, for example in *Oxidations in Organic Chemistry*, ACS Monograph 186, M. Hudlický, 1990).
- 25

Ozonolysis may be carried out in any suitable solvent, for example methanol or dichloromethane or mixtures of those solvents in a ratio between 100:0 and 0:100. The ozonolysis may take place over a temperature range -78 °C to 0 °C. When A is -CO-2-furanyl the ozonolysis is optimally carried out in methanol at -78 °C. A variety of work-up conditions may be used to decompose ozonide intermediates; those work-up conditions include treatment with Me₂S, Ph₃P or H₂O₂. In this case, dimethylsulphide is preferred.

Compounds of formula (V) may be prepared by reaction of compounds of formula (VI)



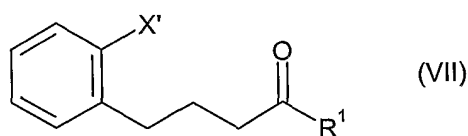
wherein R¹ represents a C₃₋₆cycloalkyl group and X' is selected from Br, I and OTf

by reaction with trialkylSnC(=CH₂)CO₂C₁₋₆alkyl or with carbon monoxide and a stannane such as trialkylfuran-2-ylstannane, trialkylethynylstannane, or a (1-alkoxyvinyl)trialkylstannane or carbon monoxide and a boronic acid such as furan-2-ylboronic acid in the presence of a source of Pd(0). The source of Pd(0) may for example be Pd(OAc)₂, PdCl₂(MeCN)₂, Pd(PPh₃) or Pd₂(dba)₃. Preferably, the reaction is carried out in the presence of a phosphine ligand, for example Ph₃P, (2-furyl)₃P or (o-tolyl)₃P. Preferably, the reaction is carried out at a temperature in the range of 25 °C to 140 °C.

The reaction solvent is preferably an aprotic solvent and it may, for example, be selected from toluene, xylene, benzene or DMF. Most preferably, the reaction is carried out on a starting material with X'=I, and the reaction is with (2-furyl)tributylstannane and carbon monoxide in the presence of palladium acetate and triphenylphosphine in toluene at 110 °C. General conditions for reactions of this type are described in further detail in: J. K. Stille *et al.*, *J. Org. Chem.*, **1990**, 55, 3114-3118 and R. Grigg *et al.*, *Tetrahedron*, **2001**, 57, 1347-1359.

OTf represents OSO₂CF₃, known as triflate.

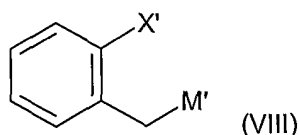
Compounds of formula (VI) may be prepared from compounds of formula (VII):



wherein R¹ represents a C₃₋₆cycloalkyl group and X' is as defined above for compounds of formula (VI)

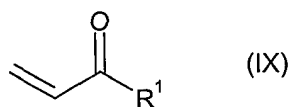
- 5 by reaction with a suitable olefinating reagent. Suitable olefinating reagents include Wittig reagents, for example methyltriphenylphosphonium salts. Peterson, Tebbe, Petasis and Lombardo reagents are also suitable. Reactions of this type are described in further detail in: R. C. Hartley *et al.*, *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2763-2793 and *Tetrahedron Lett.*, **1985**, 26, 5579-5580 A Wittig reaction on compound (VII) may suitably be carried
- 10 out in a polar solvent, for example a solvent selected from diethylether, tetrahydrofuran, ethylene glycol, dimethylether, diglyme or dioxane, in the presence of a strong base, for example *n*-BuLi, *sec*-BuLi, *t*-BuLi, LDA, LiHMDS, NaHMDS, KHMDS, NaH or KO^tBu, at a temperature in the range of -78 °C to +70 °C. Preferably, a Wittig reaction is carried out using methyltriphenylphosphonium bromide in Et₂O as the solvent with *n*-BuLi or KO^tBu as
- 15 the base at a temperature of 0 °C warming to room temperature..

Compounds of formula (VII) may be prepared by reaction of compounds of formula (VIII):



- 20 wherein X' is as defined above for compounds of formula (VI) and M' is MgQ or ZnQ, where Q is Cl, Br or I

with compounds of formula (IX):



- 25 wherein R¹ represents a C₃₋₆cycloalkyl group

The compound of formula (IX) can be prepared *in situ* by reaction of R¹zinc halide with acryloyl chloride in the presence of a palladium(0) source and can then be further reacted with compounds of formula (VIII) as defined above to afford compound of formula (VII).

- 5 Preferably the reaction is carried out in a polar solvent, for example a solvent selected from tetrahydrofuran and diethylether at a temperature in the range of from -78 °C to +25 °C. If M' is a magnesium halide, the reaction is preferably carried out in the presence of a copper(I) salt. In one embodiment, the reaction is carried out with a magnesium bromide reagent in diethylether at -78 °C in the presence of a CuBr.Me₂S complex. The reaction is particularly suitable for use with compounds of formula (VIII) in which X' is bromine atom.

- 10 If M' is a zinc halide, the reaction is carried out in the presence of a complex of LiCl and CuCN. In one embodiment, the reaction is carried out using a compound of formula (VIII) in which M' is ZnQ where Q represents Br in the presence of a 2:1 LiCl:CuCN complex as well as one equivalent of TMSCl in THF at -78 °C. The reaction is particularly suitable for use with compounds of formula (VIII) in which X' is a bromine or an iodine atom.

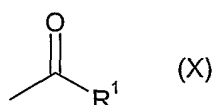
- 15 Compounds of formula (VIII) where X' represents bromine or iodine are commercially available.

20

There are numerous approaches to the synthesis of the vinyl ketone (IX).

- 25 In one approach, the zinc reagent R¹ZnQ is coupled with acryloyl chloride in the presence of a palladium(0) source such as Pd(OAc)₂, PdCl₂(MeCN)₂, Pd(PPh₃)₄ or Pd₂(dba)₃ with a phosphine ligand such as Ph₃P, (2-furyl)₃P or (o-tolyl)₃P over a temperature range of from -25 °C to +75 °C in an ether solvent such as THF, dioxane or ether. Optimal conditions are in THF at 0 °C. By this method, the vinyl ketone (IX) may be isolated or used *in situ* as described above.

- 30 Another approach to access the vinyl ketone (IX) involves a Mannich reaction with the appropriate ketone of formula (X):



wherein R¹ represents a C₃₋₆cycloalkyl group

using a formaldehyde source such as trioxymethylene, paraformaldehyde or formaldehyde itself along with a secondary amine salt such as dimethylamine hydrochloride or methylanilinium trifluoroacetate. Suitable solvents include THF and dioxane with temperatures in the range 0°C to 100°C. Optimally methylanilinium trifluoroacetate and paraformaldehyde are used in THF with a temperature range 25°C to 70°C. The vinyl ketone (IX) generated by this method is isolated before reaction with (VIII) as outlined above.

10 Certain compounds of formula (II), (IV), (V), (VI) and (VII) are new and form an aspect of the invention.

In addition processes for preparing formulations including one or more compounds of formula (I) form an aspect of this invention.

15 Processes for the preparation of the compounds of the invention and processes for the preparation of the novel intermediates also form an aspect of the invention.

20 Compositions comprising a compound of the invention also constitute an aspect of the invention.

Solvates of compounds of formula (I), or physiologically functional derivatives thereof or salts thereof, which are not physiologically acceptable may be useful intermediates in the preparation of other compounds of formula (I) or physiologically functional derivatives or salts thereof.

30 Compounds of the invention may be expected to demonstrate good anti-inflammatory properties. They also may be expected to have an attractive side-effect profile, demonstrated, for example, by increased selectivity for glucocorticoid receptor mediated transrepression over transactivation and are expected to be compatible with a convenient regime of treatment in human patients.

The invention will now be illustrated by way of the following non-limiting examples.

EXAMPLES**SYNTHETIC EXPERIMENTAL****5 Abbreviations**

THF	Tetrahydrofuran
DCM	Dichloromethane
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
EtOH	Ethanol
HCl	Hydrochloric acid
TLC	Thin layer chromatography
TMSCF ₃	Trimethyl(trifluoromethyl)silane
NH ₄ Cl	Ammonium chloride
HPLC	High performance liquid chromatography
MeCN	Acetonitrile
CDCl ₃	Deuteriochloroform
SPE	Solid phase extraction
EtOAc	Ethyl acetate
NH ₄ Cl	Ammonium chloride
RT	Room Temperature

General Experimental Conditions

10

LC/MS System A

Column: 3.3cm x 4.6mm ID, 3µm ABZ+PLUS; Flow Rate: 3ml/min; Injection Volume: 5µl;
Temp. RT; UV Detection Range: 215 to 330nm

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.
B: 95% Acetonitrile + 0.05% Formic Acid

15

Gradient: Time	A%	B%
0.00	100	0
0.70	100	0

4.20	0	100
5.30	0	100
5.50	100	0

Mass Spectra

The mass spectra were recorded on Waters Micromass ZQ spectrometer using electrospray positive and negative ionisation modes (ES+ve and ES-ve).

5

Chiral Separations

Chiral separations were carried out on Chiralpak AD columns made by Daicel Industries Ltd.

10 Circular Dichroism

Circular dichroism was carried out on a Jasco Spectrophotometer Model J-720 at room temperature in MeCN as a solvent in the range 350 – 200 nm

NMR

- 15 ^1H NMR spectra were obtained in CDCl_3 on a Bruker DPX 400 spectrometer working at 400.13 MHz and 9.4 Tesla using as internal standard the signal from the residual protonated solvent at 7.25 ppm.

Mass Directed Autoprep

- 20 Purification was carried out using a Waters Micromass ZQ platform (ES^+ and ES^- ionisation) and a Supelcosil ABZ+plus column of internal diameter 10 cm x 21.2 mm with particle size 5 μm .

Solvents **A:** Water + 0.1% formic acid
 B: MeCN:water 95:5 + 0.05% formic acid

25

Gradient: Time	A%	B%
0.00	70	30
10.00	20	80

Experimental

Method A

Method A is the process for the conversion of 2-iodophenylalkyl ketone such as Intermediate 1 into a keto-amide such as Intermediate 5 via a four stage process. The four stages are firstly a methylenation, then a "one pot" palladium based cyclisation, carbonylation and furylation, followed by ozonolysis with a basic work-up and finally amide formation.

10 Intermediate 1

1-cyclopentyl-4-(2-iodophenyl)-1-butanone

Tetrahydrofuran (12.5 mL) was added to anhydrous lithium chloride (1.06 g, 25 mmol) and copper(I) cyanide (1.12 g, 12.5 mmoles) whilst stirring under an atmosphere of nitrogen at 25 °C. After stirring for 10 minutes this solution was cooled to -78 °C and 2-iodobenzylzinc bromide (25 mL, 0.5 M in THF, 12.5 mmoles) was added. The solution was then warmed to -15 °C for 20 minutes before re-cooling to -78 °C. In a second flask, cyclopentylzinc bromide (25 mL, 0.5 M in THF, 12.5 mmoles) was added to tetrakis(triphenylphosphine) palladium(0) (145 mg, 0.125 mmoles, 1 mol%) under nitrogen at 0 °C. After 5 minutes acryloyl chloride (1.1 mL, 13.5 mmoles) was added and the mixture was left to stir at 0° C for approximately 1 hour. To the first flask containing the copper/zinc complex, chlorotrimethylsilane (3.2 mL, 25.2 mmoles) was added (solution still at -78 °C) followed by the vinyl ketone in THF solution which was prepared in the second flask. Stirring was continued at -78 ° C for about 3 hours and then the reaction was warmed to room temperature and stirring continued for a further 1 hour. The reaction mixture was partitioned between water (100 mL) and diethyl ether (100 mL) and the aqueous layer was extracted with two further portions of ether (2 x 100 mL). The combined ether extracts were washed with brine (2 x 100 mL) and were dried over magnesium sulfate. The solvent was removed to give a crude product which after purification (silica column, 19:1 cyclohexane:ethyl acetate) gave the title compound as a colourless oil (3.84 g, 90%).

¹H-NMR: δ_H (CDCl₃, 400 MHz) 7.82 (d, 1H), 7.32-7.18 (m, 2H), 6.94-6.85 (m, 1H), 2.88 (qn, 1H), 2.73 (t, 2H), 2.53 (t, 2H) and 2.0-1.45 (t, 10 H)

Intermediate 2

35 1-(4-cyclopentyl-4-penten-1-yl)-2-iodobenzene

Methyltriphenylphosphonium bromide (5.72 g, 16.0 mmoles) was suspended in anhydrous diethyl ether (80 mL) and was cooled to 0 °C. *n*-Butyllithium (8.8 mL, 1.6 M solution in hexanes, 14 mmoles) was added dropwise over 10 minutes maintaining the temperature below 5 °C to give a bright yellow suspension. This suspension was left to stir for 2 hours at 0 °C. 1-cyclopentyl-4-(2-iodophenyl)-1-butanone (Intermediate 1) (3.42 g, 10.0 mmoles) in anhydrous ether (7 mL) was slowly added to the ylide solution, maintaining the solution below 5 °C. After stirring the reaction at 0 °C for 30 minutes the ice-bath was removed and the reaction warmed to room temperature. After a further 3 hours saturated NH₄Cl solution (10 mL) was added and the reaction was partitioned between ether and water. The organic phase was dried over magnesium sulfate and the solvent removed under vacuum to give a crude product. This product was suspended in cyclohexane and the solid was filtered off. The solid was washed with cyclohexane and the filtrate and wash were loaded onto a silica column and eluted with cyclohexane to give the title compound as a colourless liquid (1.98 g, 58%).

¹H-NMR: δ_H (CDCl₃, 400 MHz) 7.82 (d, 1H), 7.32-7.19 (m, 2H, ArH), 6.93-6.84 (m, 1H), 4.80 (br. s, 1H), 4.74 (br. s, 1H), 2.73 (t, 2H), 2.48-2.38 (m, 1H), 2.15 (t, 2H) and 1.86-1.33 (m, 10H)

Intermediate 3

2-(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)-1-(2-furanyl)ethanone

Palladium acetate (135 mg, 0.6 mmole) and triphenylphosphine (315 mg, 1.2 mmoles) were dissolved in toluene (60 mL) and 1-(4-cyclopentyl-4-penten-1-yl)-2-iodobenzene (Intermediate 2) (1.02 g, 3.0 mmoles) was added followed by (2-furyl)tributylstannane (1.04 mL, 3.3 mmoles). The apparatus was evacuated and filled with carbon monoxide (3 times). The reaction mixture was then heated to 110 °C for 18 hours. The reaction was cooled to room temperature and was poured into water (100 mL). The aqueous layer was extracted with diethyl ether (50 mL) and the combined organic extracts were dried over magnesium sulfate. The solvent was evaporated to give a crude product. Purification was achieved on silica gel eluting with (1) cyclohexane; (2) cyclohexane-DCM 9:1 and then (3) cyclohexane-DCM 1:1 to give the title compound as an oil (406 mg, 44%).

LCMS: t_{ret} 3.96 min; 309 (MH)⁺; 326 (MNH₄)⁺

Intermediate 4

3-(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)-2-oxopropanoic acid

2-(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)-1-(2-furanyl)ethanone

(Intermediate 3) (200 mg, 0.65 mmole) was dissolved in methanol (30 mL) and the reaction was cooled to -70 °C (internal temperature). Ozone was bubbled through the solution until TLC indicated there was no starting material remaining. The ozone generator was switched off and oxygen was bubbled through the solution for 10 minutes, followed by nitrogen for 10 minutes. Dimethyl sulfide (2 mL, 27.2 mmoles) was added and the reaction was allowed to warm to room temperature. Stirring was continued at room temperature for 40 minutes. The solvent was then removed to give a crude product. Potassium hydroxide pellets (200 mg) were dissolved in methanol (30 mL) and added to the crude product. This solution was stirred for 1.5 hours and the methanol was removed by rotary evaporation. The residue was dissolved in 2 M potassium hydroxide solution (30 mL) and was washed with 1:1 cyclohexane-diethyl ether (2 x 30 mL). The aqueous phase was then acidified to pH 1 (2 M HCl) and was extracted with DCM (3 x 20 mL). The DCM extracts were dried on magnesium sulfate and the solvent removed to give a crude product that was not purified further. The crude product consisted mainly of the required ketoacid (113 mg).

¹H-NMR: δ_H (CDCl₃, 400 MHz) 8.1-7.0 (m, 4H), 3.50 (d, 1H), 3.05 (d, 1H), 2.95-2.40 (m, 2H, ArCH₂) and 2.20-0.80 (m, 13H)

Intermediate 5

3-(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide

Thionyl chloride (47 μ L, 0.65 mmole) was added to a solution of 3-(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)-2-oxopropanoic acid (Intermediate 4) (103 mg, 0.360 mmole) in DMA (9 mL) cooled to -10 °C to give a yellow solution. After 1 hour, 6-amino-4-methyl-1H-2,3-benzoxazin-1-one (127 mg, 0.72 mmole) was added in dimethylacetamide (3 mL) and the solution became dark brown. The ice-methanol bath was removed and stirring was continued for 4 hours. The reaction was then partitioned between 2 M HCl (60 mL) and DCM (60 mL). The aqueous layer was then extracted with a further portion of DCM (30 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed under vacuum to give a crude product. Purification was achieved on silica gel eluting with (1) cyclohexane-ethyl acetate 9:1 then (2) cyclohexane-ethyl acetate 4:1 to give the title compound as a white solid (30 mg, 19%).

LCMS: t_{ret} 3.97 min; 445 (MH)⁺; 462 (MNH₄)⁺; 443 (MH)⁻

Intermediate 61-cyclopropyl-2-propen-1-one

A mixture of *N*-methylanilinium trifluoroacetate (16.57 g; 7.5 mmoles), cyclopropyl methyl ketone (4.95 mL, 50 mmoles) and paraformaldehyde (6.75 g, 225 mmoles) were heated under reflux under nitrogen in dry THF (50 mL) for 7 hours then allowed to cool to room temp overnight. Additional paraformaldehyde (3.37 g), *N*-methylanilinium trifluoroacetate (8.3 g) and THF (25 mL) were added and the mixture was heated under reflux for a further 5.5 hours, allowed to cool then treated with pentane. A red oil separated. Supernatant pentane/THF was decanted and the red oil was triturated twice more with pentane. The combined extracts were carefully evaporated (using a cold water bath) to give the title compound containing residual pentane and THF (5.78 g). The yield based on NMR was 1.73 g (36%). The product was used without further purification.

¹H-NMR: δ_{H} (CDCl₃, 400 MHz) 6.51 (m, 1H), 6.30 (m, 1H), 5.88 (d, 1H), 2.25 (m, 1H), 1.15 (m, 4H)

Intermediate 71-cyclopropyl-4-(2-iodophenyl)-1-butanone

Dried lithium chloride (2.12 g, 50 mmoles) and copper (I) cyanide (2.24 g, 25 mmoles) were combined and dry THF (12.5 mL) added. The mixture was stirred for 10 minutes at room temperature under nitrogen then cooled to -78 °C. To this was added a solution of 2-iodobenzylzinc bromide (0.5M in THF, 50 mL, 25 mmoles). When addition was complete the mixture was warmed to 0 °C for 20 minutes then cooled back to -78 °C. Chlorotrimethylsilane (6.4 mL, 50.4 mmoles) was then added followed by Intermediate 6 (ca 2.4 g, 25 mmoles). After 1 hour the mixture was poured onto water and extracted with diethyl ether. The combined extracts were dried and evaporated to give an oil (8.84 g) with two layers. Purification (70 g silica SPE cartridge eluting with petrol:DCM 10:1) gave the title compound (2.75 g)

LCMS: t_{ret} 3.42 min; 315 (MH)⁺

Intermediate 8

3-(1-cyclopropyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide

Prepared from 1-cyclopropyl-4-(2-iodophenyl)-1-butanone (Intermediate 7) according to Method A.

5 LCMS: t_{ret} 3.77 min; 417 (MH)⁺; 415 (MH)⁻

Intermediate 9

1-cyclobutyl-4-(2-iodophenyl)-1-butanone

A suspension of Rieke zinc in dry THF (38 mL, ca 29.05 mmoles) was stirred at room temperature under nitrogen. Cyclobutyl bromide (3.15 g, 23.33 mmoles) was added and the mixture was heated under reflux for 3 hours, diluted with dry THF (10 mL) then allowed to cool overnight. The supernatant was removed via a syringe to give a solution of cyclobutyl zinc bromide. This solution was added to tetrakis(triphenylphosphine)palladium(0) (0.27 g, 0.23 mmoles) and cooled to 0°C under nitrogen. After 5 minutes acryloyl chloride (2.28g, 25.2 mmoles) was added and an exothermic reaction occurred. Stirring at 0°C was continued for 1 hour to give a solution of vinyl cyclobutyl ketone. Dried lithium chloride (1.98g, 46.66 mmoles) and copper(I) cyanide (2.09 g, 23.33 mmoles) were combined and dry THF (24 mL) added. The mixture was stirred for 15 minutes then cooled to -72°C. A solution of 2-iodobenzylzinc bromide (0.5M in THF, 47 mL, 23.5 mmoles) was added and then the mixture was warmed to 0°C for 20 minutes then cooled again to -72°C. Chlorotrimethylsilane (5.22g, 48 mmoles) was added followed by the vinyl cyclobutyl ketone solution prepared above. The mixture was then stirred at -72°C for 3 hours and allowed to come to room temperature overnight. Water was added and the mixture was evaporated under vacuum. Further water was added and the aqueous mixture was extracted three times with dichloromethane. The combined extracts were dried over magnesium sulfate and evaporated under vacuum to a pale brown oil (8.25 g). Purification (silica column, chloroform:40-60 petrol 1:2) gave the title compound as a colourless oil (5.98g).

LCMS: t_{ret} 3.75 min; 329 (MH)⁺

Intermediate 10

3-(1-cyclobutyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide

Prepared from 1-cyclobutyl-4-(2-iodophenyl)-1-butanone (Intermediate 9) according to Method A.

5 LCMS: t_{ret} 3.78 min; 431 (MH)⁺; 429 (MH)⁻

Intermediate 11

1-cyclohexyl-4-(2-iodophenyl)-1-butanone

10 A solution of cyclohexyl zinc bromide (0.5M in THF, 50 mL, 25 mmoles) was added to tetrakis(triphenylphosphine)palladium(0) (288 mg, 0.25 mmoles) in a flask cooled to 0°C under nitrogen. After 5 minutes acryloyl chloride (2.45g, 27 mmoles) was added and an exothermic reaction occurred. The mixture was stirred at 0°C for 1 hour to give a solution of vinyl cyclohexyl ketone. Dried lithium chloride (2.12g, 50 mmoles) and copper(I) cyanide (2.24 g, 25 mmoles) were mixed under nitrogen and dry THF (25 mL) added.

15 The mixture was stirred for 10 minutes and then cooled to -78°C and a solution of 2-iodobenzylzinc bromide (0.5M in THF, 50 mL, 25 mmoles) was added. When addition was complete the mixture was warmed to 0°C for 20 minutes then cooled back to -78°C. Chlorotrimethylsilane (5.47 g, 50.4 mmoles) was then added followed by the vinyl cyclohexyl ketone solution prepared above. The reaction mixture was then maintained at

20 -78°C for 3 hours, warmed to room temperature and stirred for a further 1 hour. The crude reaction mixture was then poured into water (200 mL) and extracted with ether. The combined extracts were washed with brine, dried over magnesium sulfate and evaporated under vacuum to give a crude product (9.6 g). Purification (70g silica SPE, DCM) gave the title compound (7.9g, 88%).

25 LCMS: t_{ret} 4.06 min; 357 (MH)⁺

Intermediate 12

3-(1-cyclohexyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide

30 Made from 1-cyclohexyl-4-(2-iodophenyl)-1-butanone (Intermediate 11) according to Method A.

LCMS: t_{ret} 4.0 min; 459 (MH)⁺; 457 (MH)⁻

¹H-NMR: δ_{H} (CDCl₃, 400 MHz) 8.88 s, (1H), 8.31 (d, 1H), 8.13 (d, 1H), 7.69 (dd, 1H), 7.19 (m, 1H), 7.02 (m, 3H), 3.43 (q, 2H), 2.83-2.64 (m, 2H), 2.56 (s, 3H), 2.0 –1.58 (m, 11H),

35 1.31-0.92 (m, 4H +excess)

Example 1

Racemic mixtures of isomers D2E1 and D2E2 and Racemic mixtures of isomers D1E1 and D1E2 of 2-[(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)propanamide

3-(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide (Intermediate 5) (32 mg, 72 μ mol) was dissolved in anhydrous DMF (1 mL) and dried cesium fluoride (25 mg, 165 μ mol) was added in one portion. CF₃SiMe₃ (55 μ L, 0.372 mmol) was then added. After approximately 16 hours stirring at 25 °C under nitrogen, the reaction mixture was partitioned between 1 M HCl (50 mL) and DCM (30 mL). The aqueous layer was extracted with a further portion of DCM (30 mL). The DCM extracts were dried on sodium sulfate and the solvent was removed to give a crude product.

The reaction product Example 1 was purified by chromatography on silica, eluting with (1) cyclohexane-ethyl acetate 15% and then (2) cyclohexane-ethyl acetate 20% to give recovered starting material, diastereomer D2 (Example 1a) and diastereomer D1 (in order of elution).

Diastereomer D2 and diastereomer D1 (i.e. isomers D2E1/D2E2 and D1E1/D1E2 respectively) were separated satisfactorily but diastereomer D2 was contaminated with starting material that necessitated repeated purification. The final distribution of products was: starting material (3 mg, 9%); diastereomer D1, (4.7 mg, 13%) and diastereomer D2 (Example 1a) (6.2 mg, 17%).

Example 1a was further preparatively separated into its enantiomers (isomers D2E1 and D2E2) using a 2 x 25cm Chiralpak AD column eluting with 5% EtOH in heptane with a flow rate of 15 mL/min. Enantiomer 1 (i.e. isomer D2E1) eluted around 19 min (0.3 mg) and Example 1b (Enantiomer D2E2) eluted around 25 min (0.4 mg).

Racemic diastereomer D1

i.e. Racemic mixture of isomers D1E1 and D1E2 of 2-[(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)propanamide

LCMS: t_{ret} 3.87 min; 515 (MH)⁺; 532 (MNH₄)⁺; 513 (MH)⁻

¹H-NMR: δ_{H} (CDCl₃, 400 MHz) 8.27 (d, 1H), 8.13 (br. s, 1H), 8.02 (d, 1H), 7.35 (dd, 1H), 7.30 (d, 1H), 6.94 (d, 1H), 6.84 (t, 1H), 6.79 (t, 1H), 3.23 (br. s, 1H), 2.98 (d, 1H), 2.78-2.68 (m, 2H), 2.58 (s, 3H), 2.48-2.34 (m, 1H), 2.34 (d, 1H) and 1.99-1.01 (12H)

¹⁹F-NMR: δ_{F} (CDCl₃, 376 MHz) -79.9

5

Example 1a

Racemic diastereomer D2 i.e. Racemic mixture of isomers D2E1 and D2E2 of 2-[(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)propanamide

10 LCMS: t_{ret} 4.02 min; 515 (MH)⁺; 532 (MNH₄)⁺; 513 (MH)⁻

¹H-NMR: δ_{H} (CDCl₃, 400 MHz) 8.98 (br. s, 1H), 8.36 (d, 1H), 8.31 (d, 1H), 7.69 (dd, 1H), 7.44 (br. d, 1H), 7.30-7.15 (m, 3H), 2.98 (br. d, 1H), 2.82 (s, 1H), 2.80-2.71 (m, 3H), 2.60 (s, 3H), 2.22-2.10 (m, 1H) and 1.92-1.15 (m, 12H)

¹⁹F-NMR: δ_{F} (CDCl₃, 376 MHz) -80.9

15

Diastereomer 2 enantiomer 1

i.e. Isomer D2E1 of 2-[(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)propanamide

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 5% EtOH in heptane eluting at 1 mL/min) retention time 14.2 min.

20 LCMS: t_{ret} 4.03 min; 515 (MH)⁺; 532 (MNH₄)⁺; 513 (MH)⁻

Circular Dichroism (MeCN, RT, 0.000187M, ν = 350 – 200 nm, cell length = 0.2 cm

211.6 nm (de = 14.32; E = 16039)

243.0 nm (de = -13.57; E = 29638)

25 281.0 nm (de = -5.70; E = 13150)

Example 1b

(Diastereomer 2 enantiomer 2) i.e. Isomer D2E2 of

2-[(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)propanamide

30

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 5% EtOH in heptane eluting at 1 mL/min) retention time 18.3 min.

LCMS: t_{ret} 4.02 min; 515 (MH)⁺; 532 (MNH₄)⁺; 513 (MH)⁻

Circular Dichroism (MeCN, RT, 0.000173M, ν = 350 – 200 nm, cell length = 0.2 cm

35 211.4 nm (de = -13.99; E = 15811)

243.2 nm (de = 13.85; E = 29182)

280.8 nm (de = 5.64; E = 13071)

5 The compounds of Examples 1a and 1b are binders and agonists of the glucocorticoid receptor.

Example 2

2-[(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)propanamide

10 Cesium fluoride (99 mg, 652 μ moles) was dried in a round-bottomed flask for 2 hours under vacuum. The flask was filled with nitrogen and cooled to room temperature. 3-(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide (Intermediate 5) (58 mg, 120 μ moles) in DMF (2 mL) was then added followed by TMSF₃ (207 μ L, 1.4 mmoles) and the mixture was stirred at room
15 temperature overnight. The reaction mixture was concentrated under vacuum, diluted with DCM (20 mL) and washed with 2M HCl (10 mL). The aqueous phase was extracted with DCM (20 mL) and the organic extract was dried over magnesium sulfate then evaporated under vacuum to give the crude product. Purification (20g silica SPE, gradient of cyclohexane:EtOAc 9:1 to 8:2) gave (in order of elution) diastereomer 2 and
20 diastereomer 1. The recovery was Example 1-D1 (diastereomer 1, 18.8 mg) and Example 1-D2 (diastereomer 2, 19.1 mg). A mixed fraction containing diastereomer 2 plus 3-(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide (Intermediate 5) was also obtained.

25 Example 2-D1 (racemic diastereomer 1)

LCMS: t_{ret} 3.87 min; 532 (M+18)⁺; 513 (MH)⁻

¹H-NMR: δ_{H} (CDCl₃, 400 MHz) 8.25 (d, 1H), 8.18 (s, 1H), 8.01 (d, 1H), 7.35 (dd, 1H), 7.30 (d, 1H), 6.91 (d, 1H), 6.82 (t, 1H), 6.77 (t, 1H), 3.42 (s, 1H), 2.98 (d, 1H), 2.72 (m, 2H), 2.58 (s, 3H), 2.45-2.30 (m, 2H), 2.0-1.75 (m, 4H), 1.70-1.35 (m, 6H), 1.21 (m, 1H), 1.09
30 (m, 1H)

Example 2-D2 (racemic diastereomer 2)

LCMS: t_{ret} 4.02 min; 532 (M+18)⁺; 513 (MH)⁻

$^1\text{H-NMR}:\delta_{\text{H}}$ (CDCl_3 , 400 MHz) 9.0 (s, 1H), 8.31 (m, 2H), 7.69 (dd, 1H), 7.41 (d, 1H), 7.26 (m, 1H), 7.18 (m, 2H), 2.98 (d, 1H), 2.76 (m, 4H), 2.60 (s, 3H), 2.19 (m, 1H), 1.82 (m, 2H), 1.72-1.42 (m, 8H), 1.35 (m, 1H), 1.25 (m, 1H)

- 5 Example 2-D1 was separated into its enantiomers using a 2 x 25 cm Chiralpak AD column eluting with 5% EtOH in heptane with a flow rate of 15 mL/min.

Example 2-D1E1 (enantiomer 1 of diastereomer 1)

- 10 Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 5% EtOH in heptane eluting at 1 mL/min) retention time 11.9 min.

Example 2-D1E2 (enantiomer 2 of diastereomer 1)

- 15 Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 5% EtOH in heptane eluting at 1 mL/min) retention time 14.9 min.

- Example 2-D2 was separated into its enantiomers using a 2 x 25 cm Chiralpak AD column eluting with 5% EtOH in heptane with a flow rate of 15 mL/min. Example 2-D2E1 (enantiomer 1) eluted around 19.7 min (0.3 mg) and Example 2-D2E2 (enantiomer 2) eluted around 22.2 min (0.4 mg).

- 20 **Example 2-D2E1 (enantiomer 1 of diastereomer 2)**

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 5% EtOH in heptane eluting at 1 mL/min) retention time 14.2 min.

LCMS: t_{ret} 4.03 min; 515 (MH^+); 532 (MNH_4^+); 513 (MH^-)

- 25 Circular Dichroism (0.000187M, cell length = 0.2 cm)

211.6 nm (de = 14.32; E = 16039)

243.0 nm (de = -13.57; E = 29638)

281.0 nm (de = -5.70; E = 13150)

- 30 **Example 2-D2E2 (enantiomer 2 of diastereomer 2)**

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 5% EtOH in heptane eluting at 1 mL/min) retention time 18.3 min.

LCMS: t_{ret} 4.02 min; 515 (MH^+); 532 (MNH_4^+); 513 (MH^-)

Circular Dichroism (0.000173M, cell length = 0.2 cm)

- 35 211.4 nm (de = -13.99; E = 15811)

243.2 nm (de = 13.85; E = 29182)

280.8 nm (de = 5.64; E = 13071)

5 Example 3

2-[(1-cyclopropyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)propanamide

Cesium fluoride (36.5 mg, 2.4 mmoles) was dried at 120°C for 1 hour then suspended in dry DMF (0.5 mL) and 3-(1-cyclopropyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide (Intermediate 8) (50 mg, 0.12 mmole) was added. The mixture was cooled in an ice bath and TMSCF₃ (88.8 µL, 0.6 mmole) was added. The mixture was kept cool overnight then additional cesium fluoride (2 equivalents) and TMSCF₃ (5 equivalents) were added and the mixture was kept cool overnight again. Additional cesium fluoride (2 equivalents) and TMSCF₃ (5 equivalents) were added every hour for the next 2 hours after which time acetic acid was added and the mixture was concentrated. The residue was triturated with water and the solid obtained was then triturated with DCM and filtered. Purification was by mass directed autoprep followed by preparative TLC using DCM:EtOAc 10:1 as solvent to give (in order of elution) diastereomer 2 and diastereomer 1. The recovery was Example 2-D1 (diastereomer 1, 12.2 mg) and Example 2-D2 (diastereomer 2, 10.8 mg).

Example 3-D1 (racemic diastereomer 1)

LCMS: t_{ret} 3.58 min; 487 (MH)⁺; 485 (MH)⁻

¹H-NMR: δ_H (CDCl₃, 400 MHz) 8.95 (s, 1H), 8.34 (d, 1H), 8.21 (s, 1H), 7.65 (dd, 1H), 7.28 (m, 1H), 7.04 (m, 3H), 3.05 (d, 1H), 2.72 (m, 2H), 2.60 (s, 3H), 2.37 (d, 1H), 1.85 (m, 2H), 1.74 (m, 1H), 1.45 (m, 1H), 1.35 (m, 1H), 0.87 (m, 1H), 0.65 (m, 1H), 0.52 (m, 1H), 0.29 (m, 2H)

Example 3-D2 (racemic diastereomer 2)

LCMS: t_{ret} 3.67 min; 487 (MH)⁺; 485 (MH)⁻

¹H-NMR: δ_H (CDCl₃, 400 MHz) 8.98 (s, 1H), 8.35 (m, 2H), 7.69 (dd, 1H), 7.25 (m, 4H), 2.97-2.75 (m, 5H), 2.6 (s, 3H), 2.20 (m, 1H), 1.87 (m, 1H), 1.78 (m, 2H), 0.9 (m, 1H), 0.38 (m, 2H), 0.12 (m, 1H), -0.33 (m, 1H)

Example 3-D2 was separated into its enantiomers using a 2 x 25 cm Chiralpak AD column eluting with 10% EtOH in heptane with a flow rate of 15 mL/min. Example 2-D2E1 (enantiomer 1) eluted around 11 min (3.1 mg) and Example 3-D2E2 (enantiomer 2) eluted around 13.4 min (3.0 mg).

5

Example 3-D2E1 (enantiomer 1 of diastereomer 2)

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 10% EtOH in heptane eluting at 1 mL/min) retention time 8.22 min

LCMS: t_{ret} 3.77 min; 487 (MH)⁺

10 Circular Dichroism (0.000138M, cell length = 0.5 cm)

211.0 nm (de = 5.22; E = 17191)

246.6 nm (de = -11.25; E = 29727)

277.8 nm (de = -5.23; E = 13135)

15 **Example 3-D2E2 (enantiomer 2 of diastereomer 2)**

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 10% EtOH in heptane eluting at 1 mL/min) retention time 10.08 min

LCMS: t_{ret} 3.78 min; 487 (MH)⁺

Circular Dichroism (0.000131M, cell length = 0.5 cm)

20 211.0 nm (de = -3.84; E = 13369)

243.4 nm (de = 8.66; E = 23345)

280.6 nm (de = 4.05; E = 10391)

Example 4

25 2-[(1-cyclobutyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)propanamide

Cesium fluoride (28.2 mg, 186 μ moles) was dried in a round bottomed flask at 120°C for 2 hours. The flask was filled with nitrogen then cooled to room temperature. 3-(1-cyclobutyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-

30 2-oxopropanamide (Intermediate 10) (40 mg, 92.9 μ moles) in DMF (1 mL) was added followed by TMSCF₃ (66 mg, 465 μ moles) and the mixture was stirred at room temperature for 4 hours after which time LCMS showed 3-(1-cyclobutyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide (Intermediate 10) and the product in the ratio 2:3. The reaction mixture was concentrated

35 under vacuum, diluted with DCM (10 mL) then washed with 2M HCl (5 mL) and the

aqueous layer was extracted with DCM. The combined organic layers were dried over magnesium sulfate and evaporated under vacuum to give a crude oil (43 mg). Purification (20g silica SPE, solvent gradient cyclohexane:EtOAc 9:1 to 8:2) gave (in order of elution) diastereomer 2 and diastereomer 1. The recovery was Example 3-D1 (diastereomer 1, 10.6 mg) and Example 3-D2 (diastereomer 2, 9.3 mg).

Example 4-D1 (racemic diastereomer 1)

LCMS: t_{ret} 3.69 min; 518 ($M+18$)⁺; 499 (MH)⁻

¹H-NMR: δ_H ($CDCl_3$, 400 MHz) 8.31 (s, 1H), 8.26 (d, 1H), 8.03 (s, 1H), 7.42 (dd, 1H), 7.18 (m, 1H), 6.95 (m, 1H), 6.86 (m, 2H), 3.48 (s, 1H), 3.03 (d, 1H), 2.88-2.68 (m, 3H), 2.60 (s, 3H), 2.22 (d, 1H), 2.19-1.54 (m, 10H)

Example 4-D2 (racemic diastereomer 2)

LCMS: t_{ret} 3.80 min; 518 ($M+18$)⁺; 499 (MH)⁻

¹H-NMR: δ_H ($CDCl_3$, 400 MHz) 9.1 (s, 1H), 8.32 (m, 2H), 7.71 (dd, 1H), 7.35-7.15 (m, 4H), 2.88 (d, 1H), 2.76 (m, 4H), 2.6 (m, 4H), 1.97-1.52 (m, 10H)

Example 4-D2 was separated into its enantiomers using a 2 x 25 cm Chiralpak AD column eluting with 5% EtOH in heptane with a flow rate of 15 mL/min. Example 3-D2E1 (enantiomer 1) eluted around 18 min (1.7 mg) and Example 3-D2E2 (enantiomer 2) eluted around 22.8 min (1.7 mg). Example 3-D2E2 was further purified by preparative TLC eluting with cyclohexane:EtOAc 3:1 to give a final yield of 1.3 mg.

Example 4-D2E1 (enantiomer 1 of diastereomer 2)

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 5% EtOH in heptane eluting at 1 mL/min) retention time 14.01 min

LCMS: t_{ret} 3.91 min; 501 (MH)⁺

Circular Dichroism (8.39E-005M, cell length = 0.5 cm)

211.4 nm (de = 6.23; E = 11683)

242.6 nm (de = -7.89; E = 17805)

279.2 nm (de = -3.43; E = 8376)

Example 4-D2E2 (enantiomer 2 of diastereomer 2)

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 5% EtOH in heptane eluting at 1 mL/min) retention time 18.52 min

LCMS: t_{ret} 3.91 min; 501 (MH)⁺

Example 5

2-[(1-cyclohexyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)propanamide

Cesium fluoride (26.5 mg, 174 μmoles) was dried in a round bottomed flask at 120°C for 2 hours. The flask was filled with nitrogen and cooled to room temperature. 3-(1-cyclohexyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide (Intermediate 12) (40 mg, 87.2 μmoles) in DMF (1mL) was added followed by TMSF₃ (62 mg, 436 μmoles) and the mixture was stirred at room temperature for 4 hours after which time LCMS showed 3-(1-cyclohexyl-1,2,3,4-tetrahydro-1-naphthalenyl)-N-(4-methyl-1-oxo-1H-2,3-benzoxazin-6-yl)-2-oxopropanamide (Intermediate 12) and the product in the ratio 4:1. Stirring at room temperature was continued overnight then dried cesium fluoride (2 equivalents) and TMSF₃ (5 equivalents) were added and stirring was continued overnight. The reaction mixture was concentrated under vacuum and diluted with DCM then washed with 2M HCl (5 mL). The aqueous layer was extracted with DCM (5 mL) and the combined organic layers were dried over magnesium sulfate then evaporated under vacuum to give a crude product (65 mg). Purification (20g silica SPE, solvent gradient cyclohexane:EtOAc 9:1 to 8:2) gave (in order of elution) diastereomer 2 and diastereomer 1. The recovery was Example 4-D1 (diastereomer 1, 5.8 mg) and Example 4-D2 (diastereomer 2, 5.0 mg).

Example 5-D1 (racemic diastereomer 1)

LCMS: t_{ret} 4.02 min; 529 (MH)⁺; 527 (MH)⁻

¹H-NMR: δ_{H} (CDCl₃, 400 MHz) 8.28 (d, 1H), 8.14 (s, 1H), 8.09 (s, 1H), 7.38 (dd, 1H), 7.22 (m, 1H), 6.98 (m, 1H), 6.75 (m, 2H), 3.25 (s, 1H), 2.90 (d, 1H), 2.72 (m, 2H), 2.59 (s, 3H), 2.40 (d, 1H), 2.10 (m, 1H), 2.0-1.64 (m, 4H, excess), 1.35-0.8 (m, 10H)

Example 5-D2 (racemic diastereomer 2)

LCMS: t_{ret} 4.10 min; 529 (MH)⁺; 527 (MH)⁻

¹H-NMR: δ_{H} (CDCl₃, 400 MHz) 8.97 (s, 1H), 8.32 (d, 1H), 8.27 (s, 1H), 7.68 (dd, 1H), 7.38 (d, 1H), 7.28 (m, 1H), 7.22 (m, 2H), 3.09 (d, 1H), 2.85 (s, 1H), 2.72 (m, 2H), 2.61 (m, 4H), 2.01-1.42 (m, 5H, excess), 1.32-0.95 (m, 10H)

Example 5-D2 (10.5 mg) was separated into its enantiomers using a 2 x 25 cm Chiralpak AD column eluting with 10% EtOH in heptane with a flow rate of 15 mL/min. Example 4-D2E1 (enantiomer 1) eluted around 8.4 min (2.3 mg) and Example 4-D2E2 (enantiomer 2) eluted around 10.5 min (2.3 mg).

5

Example 5-D2E1 (enantiomer 1 of diastereomer 2)

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 10% EtOH in heptane eluting at 1 mL/min) retention time 6.21 min

LCMS: t_{ret} 4.14 min; 529 (MH)⁺

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Example 5-D2E2 (enantiomer 2 of diastereomer 2)

Analytical chiral HPLC (25 x 0.46 cm Chiralpak AD column, 10% EtOH in heptane eluting at 1 mL/min) retention time 7.74 min

LCMS: t_{ret} 4.14 min; 529 (MH)⁺

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BIOLOGICAL EXPERIMENTAL

Glucocorticoid receptor binding assay

The ability of compounds to bind to the glucocorticoid receptor was determined by assessing their ability to compete with fluorescent-labelled glucocorticoid using a kit supplied by Pan Vera (Madison, WI, USA). Compounds were solvated and diluted in DMSO, and transferred directly into assay plates. Fluorescent glucocorticoid and partially purified glucocorticoid receptor were added to the plates and incubated at 4°C for 16 hours in the dark. Binding of the compound was assessed by analysing the displacement of fluorescent ligand by measuring the decrease in fluorescence polarisation signal from the mixture.

The pIC₅₀ values for compounds of Examples 1-D1, 1a-D2, 1b-D2E2, 2-D1, 2-D2, 2-D1E2, 2-D2E2, 3-D1, 3-D2, 3-D2E2, 4-D1, 4-D2, 4-D2E2, 5-D1, 5-D2 and 5-D2E2 are > 7 for the glucocorticoid receptor binding assay.

Glucocorticoid mediated Transrepression of NFkB activity.

Human A549 lung epithelial cells were engineered to contain a secreted placental alkaline phosphatase gene under the control of the distal region of the NFkB dependent ELAM promoter as previously described in Ray, K.P., Farrow, S., Daly, M., Talabot, F. and Searle, N. "Induction of the E-selectin promoter by interleukin 1 and tumour necrosis factor alpha, and inhibition by glucocorticoids" *Biochemical Journal*. 1997 **328** 707-15.

Compounds were solvated and diluted in DMSO, and transferred directly into assay plates such that the final concentration of DMSO was 0.7%. Following the addition of cells (40K per well), plates were incubated for 1hr prior to the addition of 3ng/ml human recombinant TNFα. Following continued incubation for 16 hours, alkaline phosphatase activity was determined by measuring the change in optical density at 405nm with time following the addition of 0.7 volumes of assay buffer (1mg/ml p-nitrophenylphosphate dissolved in 1M diethanolamine, 0.28M NaCl, 0.5mM MgCl₂).

The pIC₅₀ values for the diastereomers Examples 3-D2, 4-D2 and 5-D2 and for the single enantiomers Examples 3-D2E2, 4-D2E2 and 5-D2E2 are > 7.5 Examples 1a-D2 and 3-D2

and for the single enantiomer Examples 1b-D2E2, 2-D2E2 and 5-D2E2 are >8 for the NFkB assay.

Glucocorticoid mediated Transactivation of MMTV driven gene expression

- 5 Human A549 lung epithelial cells or human MG63 osteosarcoma were engineered to contain a renilla luciferase gene under the control of the distal region of the LTR from the mouse mammary tumour virus as previously described (Austin, R.H., Maschera, B., Walker, A., Fairbairn, L., Meldrum, E., Farrow, S. and Uings, I.J. Mometasone furoate is a less specific glucocorticoid than fluticasone propionate. *European Respiratory Journal* 10 2002 **20** 1386-1392).

- Compounds were solvated and diluted in DMSO, and transferred directly into assay plates such that the final concentration of DMSO was 0.7%. Following the addition of cells (40K per well), plates were incubated for 6hr. Luciferase activity was determined using the 15 Firelight kit (Packard, Pangbourne, UK).

- The diastereomers Examples 1a-D2, 2-D2, 3-D2, 4-D2 and 5-D2 and the single enantiomers Examples 1b-D2E2, 2-D2E2, 3-D2E2, 4-D2E2 and 5-D2E2 all have reduced efficacy in the MMTV transactivation assay compared with the efficacies in the NFkB 20 assay.

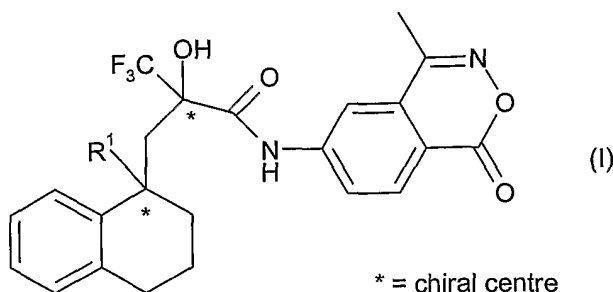
Diastereomer Examples 1a-D2 and 2-D2 and enantiomer Examples 1b-D2E2 and 2-D2E2 have reduced efficacy in both A549 and MG63 cell lines.

- 25 Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.
- 30 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims.

The patents and patent applications described in this application are herein incorporated by reference.

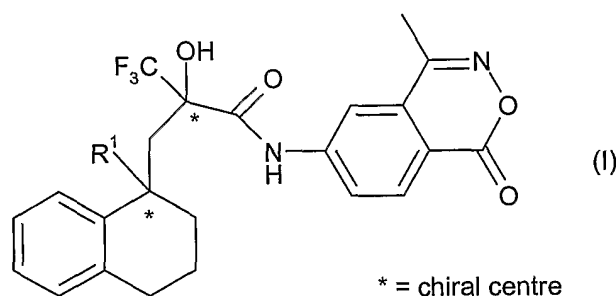
CLAIMS

1. A compound of formula (I):



wherein R¹ represents a C₃₋₆cycloalkyl group; or a physiologically functional derivative thereof.

2. A compound of formula (I):



wherein R¹ represents a C₃₋₆cycloalkyl group.

3. A compound as claimed in either claim 1 or 2 wherein R¹ represents a cyclopropyl group.

4. A compound as claimed in either claim 1 or 2 wherein R¹ represents a cyclobutyl group.

5. A compound as claimed in either claim 1 or 2 wherein R¹ represents a cyclopentyl group.

6. A compound as claimed in either claim 1 or 2 wherein R¹ represents a cyclohexyl group.

7. A compound as claimed in any one of claims 1 to 6 which is the diastereomer D2 of the compound of formula (I).

5 8. A compound as claimed in any one of claims 1 to 6 which is the isomer D2E2 of the compound of formula (I).

9. A compound which is:

10 2-[(1-cyclopentyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-*N*-(4-methyl-1-oxo-1*H*-2,3-benzoxazin-6-yl)propanamide isomer D2E2;
2-[(1-cyclopropyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-*N*-(4-methyl-1-oxo-1*H*-2,3-benzoxazin-6-yl)propanamide isomer D2E2;
2-[(1-cyclobutyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-*N*-(4-methyl-1-oxo-1*H*-2,3-benzoxazin-6-yl)propanamide isomer D2E2; or
15 2-[(1-cyclohexyl-1,2,3,4-tetrahydro-1-naphthalenyl)methyl]-3,3,3-trifluoro-2-hydroxy-*N*-(4-methyl-1-oxo-1*H*-2,3-benzoxazin-6-yl)propanamide isomer D2E2; or
a physiologically functional derivative thereof.

10 10. A compound as claimed in any one of claims 1 to 9, or a physiologically functional derivative thereof, for use in human or veterinary medicine.

11. A compound as claimed in any one of claims 1 to 9, or a physiologically functional derivative thereof, for use in the treatment of inflammatory and/or allergic conditions, such as rheumatoid arthritis, asthma, COPD, allergy or rhinitis.

25

12. A compound as claimed in any one of claims 1 to 9, or a physiologically functional derivative thereof, for use in the treatment of patients with skin disease such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis and hypersensitivity reactions.

30 13. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 9, or a physiologically functional derivative thereof, in admixture with one or more physiologically acceptable diluents or carriers.

14. A pharmaceutical aerosol formulation comprising a compound of formula (I) as
35 claimed in any one of claims 1 to 9, or a physiologically functional derivative thereof, and

a fluorocarbon or hydrogen containing chlorofluorocarbon as propellant, optionally in combination with a surfactant and/or cosolvent.

15. A pharmaceutical composition according to claim 13 which further comprises
5 another therapeutically active agent.

16. A pharmaceutical composition according to claim 15 in which said therapeutically active agent is a β_2 -adrenoreceptor agonist.

10 17. A combination comprising a compound of formula (I) as claimed in any of claims 1 to 9, or a physiologically functional derivative thereof, together with a PDE4 inhibitor.

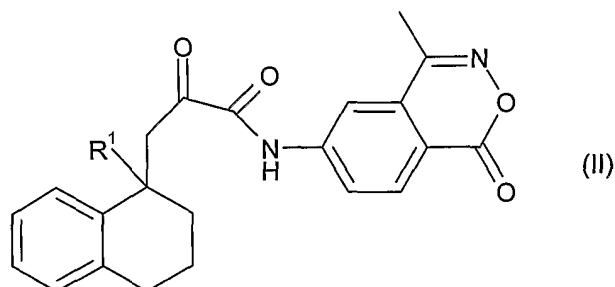
18. Use of a compound as claimed in any one of claims 1 to 9, or a physiologically functional derivative thereof, for the manufacture of a medicament for the treatment of
15 patients with inflammatory and/or allergic conditions, such as rheumatoid arthritis, asthma, allergy or rhinitis.

19. Use of a compound as claimed in any one of claims 1 to 9, or a physiologically functional derivative thereof, for the manufacture of a medicament for the treatment of
20 patients with skin disease such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis and hypersensitivity reactions

20. A method for the treatment of a human or animal subject with an inflammatory and/or allergic condition, which method comprises administering to said human or animal
25 subject an effective amount of a compound as claimed in any one of claims 1 to 9, or a physiologically functional derivative thereof.

21. A method for the treatment of a human or animal subject with skin disease such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis or hypersensitivity
30 reactions, which method comprises administering to said human or animal subject an effective amount of a compound as claimed in any one of claims 1 to 9, or a physiologically functional derivative thereof.

22. A process for the preparation of a compound of formula (I) as claimed in any one of claims 1 to 9, or a physiologically acceptable derivative thereof, comprising treatment of a compound of formula (II):



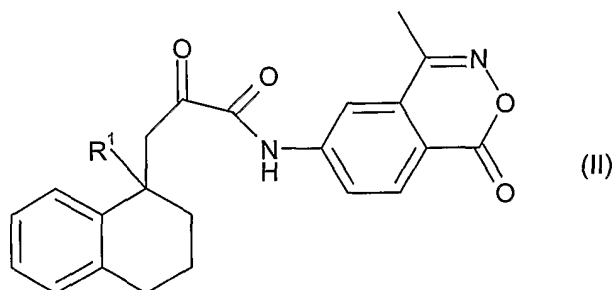
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wherein R¹ represents a C₃₋₆cycloalkyl group, with a trifluoromethylating agent of formula (III):



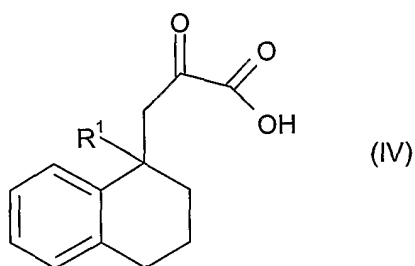
10 wherein R¹⁰ represents an activating group.

23. A compound of formula (II):



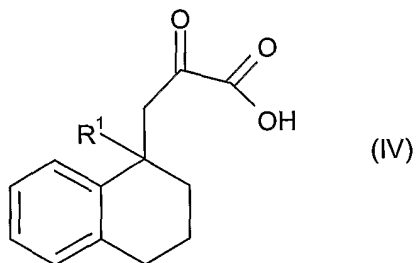
15 wherein R¹ represents a C₃₋₆cycloalkyl group.

24. A process for the preparation of a compound of formula (II) as claimed in claim 23 comprising treatment of a compound of formula (IV):



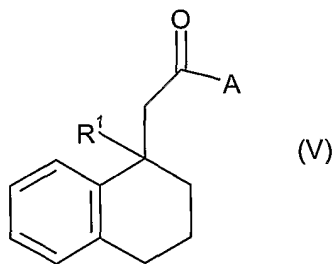
wherein R¹ represents a C₃₋₆cycloalkyl group, with an activating agent and 6-amino-4-methyl-1H-2,3-benzoxazin-1-one.

- 5 25. A compound of formula (IV):



wherein R¹ represents a C₃₋₆cycloalkyl group.

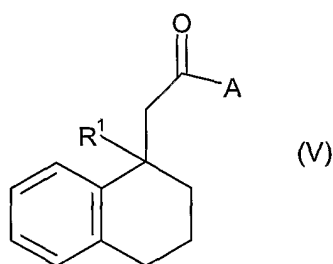
- 10 26. A process for the preparation of a compound of formula (IV) as claimed in claim 25 comprising reaction of a compound of formula (V)



- 15 wherein R¹ represents a C₃₋₆cycloalkyl group and A is a group selected from -CO-2-furanyl, -CO-C(=CH₂)OC₁₋₆alkyl, -ethynyl or -C(=CH₂)CO₂C₁₋₆alkyl, with a suitable oxidising agent.

27. A compound of formula (V)

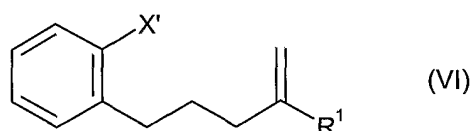
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wherein R^1 represents a C_{3-6} cycloalkyl group and A is a group selected from -CO-2-furanyl, -CO-C(=CH₂)OC₁₋₆alkyl, -ethynyl or -C(=CH₂)CO₂C₁₋₆alkyl.

5

28. A process for the preparation of a compound of formula (V) as claimed in claim 27 comprising reaction of a compound of formula (VI)

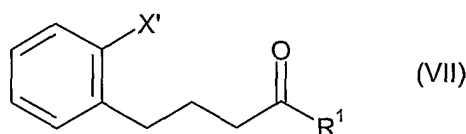


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wherein R^1 represents a C_{3-6} cycloalkyl group and X' is selected from Br, I and OTf, by reaction with trialkylSnC(=CH₂)CO₂C₁₋₆alkyl or with carbon monoxide and a stannane such as tributylfuran-2-ylstannane, trimethylfuran-2-ylstannane, trialkylethynylstannane, or a (1-alkoxyvinyl)trialkylstannane or carbon monoxide and a boronic acid such as furan-2-ylboronic acid in the presence of a source of Pd(0).

15

29. A process for the preparation of a compound of formula (VI) as claimed in claim 28 by reaction of a compound of formula (VII)

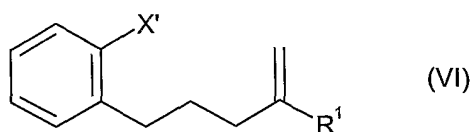


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wherein R^1 represents a C_{3-6} cycloalkyl group and X' is as defined above for compounds of formula (VI) in claim 28, with a suitable olefinating reagent.

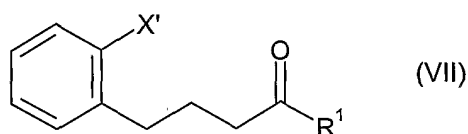
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30. A compound of formula (VI)



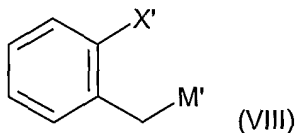
wherein R¹ represents a C₃₋₆cycloalkyl group and X' is selected from Br, I and OTf.

5 31. A compound of formula (VII)



10 wherein R¹ represents a C₃₋₆cycloalkyl group and X' is as defined above for compounds of formula (VI) in claim 30.

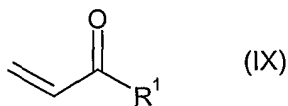
32. A process for the preparation of a compound of formula (VII) as claimed in claim 31, comprising reaction of a compound of formula (VIII):



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wherein

X' is as defined in claim 30 for compounds of formula (VI) and M' is MgQ or ZnQ, where Q is Cl, Br or I with a compound of formula (IX):



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wherein R¹ represents a C₃₋₆cycloalkyl group.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/006762

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D265/36 C07C49/807 C07C25/24 C07D307/46 C07C59/205
A61K31/536

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)

IPC 7 C07C C07D 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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	DE 102 61 874 A1 (SCHERING AG) 8 July 2004 (2004-07-08) cited in the application abstract examples claims	1-32
A	----- DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002339812 Database accession no. brn2386449, ID 7570699 abstract & J.CHEM.SOC.PERKIN TRANS 1, 1975, pages 129-138, ----- -/--	31,32



Further documents are listed in the continuation of box C.



Patent family members are listed in 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

9 August 2005

Date of mailing of the international search report

19/08/2005

Name and mailing address of the ISA

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Authorized officer

Stix-Malaun, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2005/006762

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/10143 A (SCHERING AKTIENGESELLSCHAFT) 7 February 2002 (2002-02-07) cited in the application abstract examples claims -----	1-32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/006762

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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 20,21 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/EP2005/006762

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 10261874	A1	08-07-2004	AU 2003293843 A1	22-07-2004
			WO 2004058733 A1	15-07-2004
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			SK 812003 A3	01-07-2003
			US 2004254249 A1	16-12-2004
			US 2002077356 A1	20-06-2002
			US 2005143415 A1	30-06-2005
			ZA 200301639 A	22-06-2004