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(54) Title: 2-OXO-2/-CHROMENE COMPOUNDS

(57) Abstract: Compounds of structural formula (1) modulate CRTH2 activity and are of utility in, for example, respiratory diseases formula (1): in which: A represents a direct bond, an optionally substituted alkylene or alkenylene group, or a group of formula Z-(optionally substituted)alkylene; B represents a direct bond, an optionally substituted alkylene or alkenylene group, or a group of formula Z-(optionally substituted)alkylene or (optionally substituted)alkylene-Z. Z represents an oxygen atom, an NH or N-alkyl group, or a group of formula S(O)ₙ, in which n = 0 to 2; X represents a carboxylic acid, tetrazole, 3-hydroxyisoxazole, hydroxamic acid, phosphinate, phosphonate, phosphonamide, sulfonic acid or a group of formula C=O(NH)SO₂W or SO_NH(C=O)W; W represents an optionally substituted aryl or heteroaryl group or an optionally substituted alkyl or cycloalkyl group. Y represents an optionally substituted phenyl or 5- or 6-membered heteroaryl group, R₁, R₂, and R₃ independently represent hydrogen, acyl, alkoxycarbonyl, alkylamino, alkyloxysulfanyl, alkylthio, -NH₂, aminocarboxyl, hydroxyalkyl, alkoxyalkyl, aroylalkyl, cyano, dialkylamino, halo, haloalkoxy, haloalkyl, alkyl, alkenyl, -OH, optionally substituted aryl, optionally substituted heteroaryl, heterocycloalkyl, aminocarboxyl, alaminosulfanyl, acylaminio, sulfonamido, heteroaryloxyalkyl, cyclic amino, aryloxy, heteroaryloxy, arylalkyloxy or heteroarylalkyloxy.
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
2-Oxo-2/-/-chromene Compounds

Field of the Invention

This invention relates to 2-Oxo-2H-chromene compounds, and their use in therapy.

5 Background of the Invention


15 The CRTH2 receptor has been shown to be expressed on cell types associated with allergic inflammation, such as basophils, eosinophils, and Th2-type immune helper cells (Hirai et al; J. Exp. Med., 2001, 193, 255-261). The CRTH2 receptor has been shown to mediate PGD₂-mediated cell migration in these cell types (Hirai et al; J. Exp. Med., 2001, 193, 255-261), and also to play a major role in neutrophil and eosinophil cell recruitment in a model of contact dermatitis (Takeshita et al; Int. Immunol., 2004, 16, 947-959). Ramatroban {(3R)-3-[(4-fluorophenyl)sulphonylamino]-1,2,3,4-tetrahydro-9H-carbazole-9-propanoic
acid), a dual CRTH2 and thromboxane A\textsubscript{2} receptor antagonist, has been shown to attenuate these responses (Sugimoto et al; J. Pharmacol. Exp. Ther., 2003, 305, 347-352; Takeshita et al; op. cit). The potential of PGD\textsubscript{2} both to enhance allergic inflammation and induce an inflammatory response has been demonstrated in mice and rats. Transgenic mice over expressing PGD\textsubscript{2} synthase exhibit an enhanced pulmonary eosinophilia and increased levels of Th2 cytokines in response to allergen challenge (Fujitani et al; J. Immunol., 2002, 168, 443-449). In addition, exogenously administered CRTH2 agonists enhance the allergic response in sensitised mice (Spik et al; J. Immunol., 2005, 174, 3703-3708). In rats exogenously applied CRTH2 agonists cause a pulmonary eosinophilia but a DP agonist (BW 245C) or a TP agonist (I-BOP) showed no effect (Shirashi et al; J. Pharmacol. Exp Ther., 2005, 312, 954-960). These observations suggest that CRTH2 antagonists may have valuable properties for the treatment of diseases mediated by PGD\textsubscript{2}.


Summary of the invention

One aspect of the invention provides the use of a compound of structural formula [1] or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of conditions responsive to modulation of CRTH2 activity:
in which:

A represents a direct bond, an optionally substituted alkylene or alkenylene group, or a group of formula Z-(optionally substituted)alkylene;

B represents a direct bond, an optionally substituted alkylene or alkenylene group, or a group of formula Z-(optionally substituted)alkylene or (optionally substituted)alkylene-Z;

Z represents an oxygen atom, an NH or N-alkyl group, or a group of formula S(O)_n, in which n = 0 to 2;

X represents a carboxylic acid, tetrazole, 3-hydroxyisoxazole, hydroxamic acid, phosphinate, phosphonate, phosphonamide, sulfonic acid or a group of formula C(=O)NHSO_2W or SO_2NH(=O)W;

W represents an optionally substituted aryl or heteroaryl group or an optionally substituted alkyl or cycloalkyl group;

Y represents an optionally substituted phenyl or 5- or 6-membered heteroaryl group;

R^a, R^b, and R^° independently represent hydrogen, acyl (e.g. -COCH_3), alkoxy (e.g. -OCH_3), alkoxy carbonyl (e.g. -COOCH_3), alkylamino (e.g. -NHCH_3), alkylsulfinyl (e.g. -SOCH_3), alkylsulfonyl (e.g. -SO_2CH_3), alkylthio (e.g. -SCH_3), -NH_2, aminoalkyl (e.g. -CH_2NH_2), hydroxyalkyl (e.g. -CH_2OH), alkoxyalkyl (e.g. -CH_2OCH_3), arylalkyl (e.g. -CH_2Ph or -CH_2-CH_2-Ph), cyano, dialkylamino (e.g. -N(CH_3)_2), halo, haloalkoxy (e.g. -OCF_3 or -OCHF_2), haloalkyl (e.g. -CF_3), alkyl (e.g. -CH_3 or -CH_2CH_3), alkenyl (e.g. -CH=CH_2), -OH, aryl (optionally substituted with alkoxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with alkoxy, haloalkoxy, halogen, alkyl or haloalkyl), heterocycloalkyl, aminoacetyl (e.g. -CONH_2, -CONHCH_3), aminosulfonyl (e.g. -SO_2NH_2, -SO_2NHCH_3), acylamino (e.g. -NHCOCH_3), sulfonylamino (e.g. -NHSO_2CH_3),
heteroarylalkyl, cyclic amine (e.g. morpholine), aryloxy, heteroaryloxy, aryalkyloxy (e.g. benzyloxy) and heteroaryalkyloxy;

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four compatible substituents, each of which independently may be, for example, alkyl, cycloalkyl, (d-C₆)alkoxy, hydroxy, hydroxyalkyl, mercapto, mercaptoalkyl, alkylthio, phenyl, monocyclic heteroaryl having 5 or 6 ring atoms, halo (including fluoro, bromo and chloro), haloalkyl such as trifluoromethyl, haloalkoxy such as trifluoromethoxy, nitro, nitrile (-CN), oxo, -COOH, -COOR, -COR, -SO₂RA, -CONH₂, -SO₂NH₂, -CONHR₂, -SO₂NHRA, -CONRAR₂, -SO₂NRAR₂, -NH₂, -NHRA, -NRAR₂, -CONHR, -CONH₂, -OCNR₂, -OCNR₂A, -OCONHR₂, -NHCOAR₂, -NHCOOR₂, -NR₂COOR₂, -NHSO₂OR₂, -NR₂SO₂OH, -NR₂SO₂OR₂, -NHCONH₂, -NR₂CONH₂, -NHCONH₂, -NR₂CONHR₂, -NHCONNR₂, or -NR₂CONNR₂ wherein RA and R₂ are independently an alkyl, cycloalkyl, phenyl or monocyclic heteroaryl having 5 or 6 ring atoms, or RA and R₂ when attached to the same nitrogen atom form a cyclic amino ring, such as piperidinyl, morpholinyl or piperazinyl. An "optional substituent" may be one of the foregoing substituent groups.

Alkylene or alkenylene groups may be optionally substituted. Suitable optional substituent groups include alkoxy, alkylamino, alkylsulfanyl, alkylsulfonyl, alkylthio, -NH₂, aminoalkyl, aryalkyl, cyano, dialkylamino, halo, haloalkoxy, haloalkyl, alkyl, and -OH.

Many compounds [1] as defined above are novel per se, and the invention includes all such novel compounds. Specifically, the invention includes compounds [1] as defined above, and pharmaceutically acceptable salts thereof, independent of use, excluding: 2-(7-methyl-2-oxo-4-phenyl-2H-chromen-5-yloxy)propionic acid; (7-methyl-2-oxo-4-phenyl-2H-chromen-5-yloxy)acetic acid; 2-(3-benzyl-4,7-dimethyl-2-oxo-2/-/-chromen-5-yloxy)propionic acid; 3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetic acid; (4,7-dimethyl-2-oxo-3-phenyl-2H-chromen-5-yloxy) acetic acid.

Also part of the invention is a pharmaceutical composition comprising a compound of formula [1] or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier or excipient.
Also part of the invention is a compound of formula [1] or a pharmaceutically acceptable salt thereof for use in therapy.

Also part of the invention is a method for treating a disease in a patient in which a CRTH2 antagonist can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the patient a therapeutically effective amount of compound of formula [1] or a pharmaceutically acceptable salt thereof.

Conditions responsive to modulation of CRTH2 activity include asthma, chronic obstructive pulmonary disease, allergic airway syndrome, bronchitis, cystic fibrosis, emphysema and rhinitis, as well as psoriasis, atopic and non-atopic dermatitis Crohn's disease, ulcerative colitis, and irritable bowel disease.

**Terminology**

For purposes of the present invention, the following definitions as used throughout the description of the invention shall be understood to have the following meanings:

"Compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula [1] as hereinbefore described, their pharmaceutically acceptable salts and their hydrates and solvates, where the context so permits.

"Patient" includes both human and other mammals.

For purposes of the present invention, the following chemical terms as used above, and throughout the description of the invention, and unless otherwise indicated, shall be understood to have the following meanings:

"Acyl" means a -CO-alkyl group in which the alkyl group is as described herein. Exemplary acyl groups include -COCH\(_3\) and -COCH(CH\(_3\)\(_2\)).

"Acylamino" means a -NR-acyl group in which R and acyl are as described herein. Exemplary acylamino groups include -NHCOCH\(_3\) and -N(CH\(_3\)\(_2\))COCH\(_3\).

"Alkoxy" and "alkyloxy" means an -O-alkyl group in which alkyl is as defined below. Exemplary alkoxy groups include methoxy (OCH\(_3\)) and ethoxy (OC\(_2\)H\(_5\)).
"Alkoxycarbonyl" means a -COO-alkyl group in which alkyl is as defined below. Exemplary alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl.

"Alkyl" as a group or part of a group refers to a straight or branched chain saturated hydrocarbon group having from 1 to 12, preferably 1 to 6, carbon atoms, in the chain. Exemplary alkyl groups include methyl, ethyl, 1-propyl and 2-propyl.

"Alkenyl" as a group or part of a group refers to a straight or branched chain hydrocarbon group having from 1 to 12, preferably 1 to 6, carbon atoms and one carbon-carbon double bond in the chain. Exemplary alkenyl groups include ethenyl, 1-propenyl, and 2-propenyl.

"Alkylamino" means a -NH-alkyl group in which alkyl is as defined above. Exemplary alkylamino groups include methylamino and ethylamino.

"Alkylene means an -alkyl- group in which alkyl is as defined previously. Exemplary alkylene groups include -CH=CH-, -CH=CHCH=CH2-.

"Alkenylene" means an -alkenyl- group in which alkenyl is as defined previously. Exemplary alkenylene groups include -CH=CH-, -CH=CHCH=CH2- and -CH2CH=CH-.

"Alkylsulfinyl" means a -SO-alkyl group in which alkyl is as defined above. Exemplary alkylsulfinyl groups include methylsulfinyl and ethylsulfinyl.

"Alkylsulfonyl" means a -SO2-alkyl group in which alkyl is as defined above. Exemplary alkylsulfonyl groups include methylsulfonyl and ethylsulfonyl.

"Alkylthio" means a -S-alkyl group in which alkyl is as defined above. Exemplary alkylthio groups include methylthio and ethylthio.

"Aminoacyl" means a -CO-NR2 group in which R is as herein described. Exemplary aminoacyl groups include -CONH2 and -CONHCH3.

"Aminoalkyl" means an alkyl-NH2 group in which alkyl is as previously described. Exemplary aminoalkyl groups include -CH2NH2.

"Aminosulfonyl" means a -SO2-NR2 group in which R is as herein described. Exemplary aminosulfonyl groups include -SO2NH2 and -SO2NHCH3.

"Aryl" as a group or part of a group denotes an optionally substituted monocyclic or multicyclic aromatic carbocyclic moiety of from 6 to 14 carbon atoms, preferably from 6 to 10 carbon atoms, such as phenyl or naphthyl, and in
one embodiment preferably phenyl. The aryl group may be substituted by one or more substituent groups.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a C₁₄ alkyl moiety. Exemplary arylalkyl groups include benzyl, phenethyl and naphthlenemethyl.

"Arylalkyloxy" means an aryl-alkyloxy- group in which the aryl and alkyloxy moieties are as previously described. Preferred arylalkyloxy groups contain a C₁₄ alkyl moiety. Exemplary arylalkyl groups include benzyl.

"Aryl-fused-cycloalkyl" means a monocyclic aryl ring, such as phenyl, fused to a cycloalkyl group, in which the aryl and cycloalkyl are as described herein. Exemplary aryl-fused-cycloalkyl groups include tetrahydronaphthyl and indanyl. The aryl and cycloalkyl rings may each be substituted by one or more substituent groups. The aryl-fused-cycloalkyl group may be attached to the remainder of the compound of formula [1] by any available carbon atom.

"Aryl-fused-heterocycloalkyl" means a monocyclic aryl ring, such as phenyl, fused to a heterocycloalkyl group, in which the aryl and heterocycloalkyl are as described herein. Exemplary aryl-fused-heterocycloalkyl groups include tetrahydroquinolinyl, indolinyl, benzodioxinyl, benxodioxolyl, dihydrobenzofuranyl and isoindolonyl. The aryl and heterocycloalkyl rings may each be substituted by one or more substituent groups. The aryl-fused-heterocycloalkyl group may be attached to the remainder of the compound of formula [1] by any available carbon or nitrogen atom.

"Aryloxy" means an -O-aryl group in which aryl is described above.

Exemplary arylxy groups include phenoxy.

"Cyclic amine" means an optionally substituted 3 to 8 membered monocyclic cycloalkyl ring system where one of the ring carbon atoms is replaced by nitrogen, and which may optionally contain an additional heteroatom selected from O, S or NR (where R is as described herein). Exemplary cyclic amines include pyrrolidine, piperidine, morpholine, piperazine and N-methylpiperazine. The cyclic amine group may be substituted by one or more substituent groups.
"Cycloalkyl" means an optionally substituted saturated monocyclic or bicyclic ring system of from 3 to 12 carbon atoms, preferably from 3 to 8 carbon atoms, and more preferably from 3 to 6 carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl group may be substituted by one or more substituent groups.

"Cycloalkylalkyl" means a cycloalkyl-alkyl-group in which the cycloalkyl and alkyl moieties are as previously described. Exemplary monocyclic cycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl.

"Dialkylamino" means a -N(alkyl)₂ group in which alkyl is as defined above. Exemplary dialkylamino groups include dimethylamino and diethylamino.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo.

"Haloalkoxy" means an -O-alkyl group in which the alkyl is substituted by one or more halogen atoms. Exemplary haloalkyl groups include trifluoromethoxy and difluoromethoxy.

"Haloalkyl" means an alkyl group which is substituted by one or more halo atoms. Exemplary haloalkyl groups include trifluoromethyl.

"Heteroaryl" as a group or part of a group denotes an optionally substituted aromatic monocyclic or multicyclic organic moiety of from 5 to 14 ring atoms, preferably from 5 to 10 ring atoms, in which one or more of the ring atoms is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. Examples of such groups include benzimidazolyl, benzoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, furyl, imidazolyl, indolyl, indolizynl, isoxazolyl, isoquinolinyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, tetrazolyl, 1,3,4-thiadiazolyl, thiazolyl, thieryl and triazolyl groups. The heteroaryl group may be substituted by one or more substituent groups. The heteroaryl group may be attached to the remainder of the compound of formula [1] by any available carbon or nitrogen atom.

"Heteroarylalkyl" means a heteroaryl-alkyl-group in which the heteroaryl and alkyl moieties are as previously described. Preferred heteroarylalkyl groups contain a lower alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl.
"Heteroarylalkyloxy" means a heteroaryl-alkyloxy- group in which the heteroaryl and alkyloxy moieties are as previously described. Preferred heteroarylalkyloxy groups contain a lower alkyl moiety. Exemplary heteroarylalkyloxy groups include pyridylmethyloxy.

"Heteroaryloxy" means a heteroaryloxy- group in which the heteroaryl is as previously described. Exemplary heteroaryloxy groups include pyridyloxy.

"Heteroaryl-fused-cycloalkyl" means a monocyclic heteroaryl group, such as pyridyl or furanyl, fused to a cycloalkyl group, in which heteroaryl and cycloalkyl are as previously described. Exemplary heteroaryl-fused-cycloalkyl groups include tetrahydroquinolinyl and tetrahydrobenzofuranyl. The heteroaryl and cycloalkyl rings may each be substituted by one or more substituent groups. The heteroaryl-fused-cycloalkyl group may be attached to the remainder of the compound of formula [1] by any available carbon or nitrogen atom.

"Heteroaryl-fused-heterocycloalkyl" means a monocyclic heteroaryl group, such as pyridyl or furanyl, fused to a heterocycloalkyl group, in which heteroaryl and heterocycloalkyl are as previously described. Exemplary heteroaryl-fused-heterocycloalkyl groups include dihydrodioxinopyridinyl, dihydropyrrolopyridinyl, dihydrofuranopyridinyl and dioxolopyridinyl. The heteroaryl and heterocycloalkyl rings may each be substituted by one or more substituent groups. The heteroaryl-fused-heterocycloalkyl group may be attached to the remainder of the compound of formula [1] by any available carbon or nitrogen atom.

"Heterocycloalkyl" means: (i) an optionally substituted cycloalkyl group of from 4 to 8 ring members which contains one or more heteroatoms selected from O, S or NR; (ii) a cycloalkyl group of from 4 to 8 ring members which contains CONR and CONR-CO (examples of such groups include succinimidyl and 2-oxopyrrolidiny). The heterocycloalkyl group may be substituted by one or more substituent groups. The heterocycloalkyl group may be attached to the remainder of the compound of formula [1] by any available carbon or nitrogen atom.

"Heterocycloalkylalkyl" means a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as previously described.
"Hydroxamate" means a group -C(O)NHOR where R is as described herein. Exemplary groups are -C(O)NHOH and -C(O)NHOCH₃.

"Lower alkyl" as a group means unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having 1 to 4 carbon atoms in the chain, i.e. methyl, ethyl, propyl (n-propyl or /so-propyl) or butyl (n-butyl, /so-butyl or te/f-butyl).

"Phosphinate" means a -P(O)R(OR) group in which R is as described herein. Exemplary groups are -P(O)(OH)CH₃ and -P(O)(OH)H.

"Phosphonate" means a -P(O)(OH)OR group in which R is as described herein. Exemplary groups are -P(O)(OH)₂ and -P(O)(OH)OC₂H₅.

"Phosphonamide" means a -P(O)(OR)NR₂ group in which R is as described herein. An exemplary group is -P(O)(OH)NH₂.

"Sulfonate" means a -S(O)₂OR group where R is as described herein. Exemplary groups are -S(O)₂OH (sulfonic acid) and -S(O)₂OCH₃.

"Sulfonylamino" means a -NR-sulfonyl group in which R and sulfonyl are as described herein. Exemplary sulfonylamino groups include -NHSO₂CH₃.

For the avoidance of doubt the numbering system used for the 2-oxo-2H-chromene ring system is shown below:

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, N-ethyl piperidine, dibenzylamine and the like. Specific salts with bases include the benzathine, calcium, diolamine, meglumine, olamine, potassium, procaine, sodium, tromethamine and zinc salts. Those compounds of the invention which are basic can form salts, including pharmaceutically
acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, p-toluenesulphonic, benzoic, benzenesulphonic, glutamic, lactic, and mandelic acids and the like. Where a compound contains a quaternary ammonium group acceptable counter-ions may be, for example, chlorides, bromides, sulfates, methanesulfonates, benzenesulfonates, toluenesulfonates (tosylates), napadisylates (naphthalene-1,5-disulfonates or naphthalene-1-(sulfonic acid)-5-sulfonates), edisylates (ethane-1,2-disulfonates or ethane-1-(sulfonic acid)-2-sulfonates), isethionates (2-hydroxyethylsulfonates), phosphates, acetates, citrates, lactates, tartrates, mesylates, maleates, malates, fumarates, succinates, xinafoates, p-acetamidobenzoates and the like; wherein the number of quaternary ammonium species balances the pharmaceutically acceptable salt such that the compound has no net charge.


It will be understood that, as used in herein, references to the compounds of formula [1] are meant to also include the pharmaceutically acceptable salts.

The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

It will be understood that, as used in herein, references to the compounds of formula [1] are meant to also include the hydrate and solvate forms.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of formula [1]. For example an ester prodrug of a compound of formula [1] containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of formula [1] containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates,
methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyl-
tartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluene-
sulfonates, cyclohexylsulfamates and quinates. As another example an ester
prodrug of a compound of formula [1] containing a carboxyalkyl group may be
convertible by hydrolysis in vivo to the parent molecule. Examples of ester
prodrugs are those described by F. J. Leinweber, Drug Metab. Res., 1987, 18,
379.

It will be understood that, as used in herein, references to the compounds
of formula [1] are meant to also include the prodrug forms.

"Saturated" pertains to compounds and/or groups which do not have any
carbon-carbon double bonds or carbon-carbon triple bonds.

The cyclic groups referred to above, namely, aryl, heteroaryl, cycloalkyl,
aryl-fused-cycloalkyl, heteroaryl-fused-cycloalkyl, heterocycloalkyl, aryl-fused-
heterocycloalkyl, heteroaryl-fused-heterocycloalkyl and cyclic amine may be
substituted by one or more substituent groups. Suitable optional substituent
groups include acyl (e.g. -COCH₃), alkoxy (e.g. -OCH₃), alkoxy carbonyl (e.g.
-OCOCH₃), alkylamino (e.g. -NHCH₃), alkylsulfinyl (e.g. -SOCH₃), alkylsulfanyl
(e.g. -SO₂CH₃), alkylthio (e.g. -SCH₃, -NH₂), aminoalkyl (e.g. -CH₂NH₂), arylalkyl
(e.g. -CH₂Ph or -CH₂-CH₂-Ph), cyano, dialkylamino (e.g. -N(CH₃)₂), halo,
haloalkoxy (e.g. -OCF₃ or -OCHF₂), haloalkyl (e.g. -CF₃), alkyl (e.g. -CH₃ or
-CH₂CH₃), -OH, -CHO, -NO₂, aryl (optionally substituted with alkoxy, haloalkoxy,
halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with alkoxy,
haloalkoxy, halogen, alkyl or haloalkyl), heterocycloalkyl, aminoacyl (e.g.
-CONH₂, -CONHCH₃), aminosulfonyl (e.g. -SO₂NH₂, -SO₂NHCH₃), acylamino
(e.g. -NHSO₂CH₃), sulfonamido (e.g. -NH₄SO₂CH₃), heteroarylmethyl, cyclic amine
(e.g. morpholine), arylxy, heteroaryloxy, arylalkyloxy (e.g. benzyloxy) and
heteroarylmethylxy.

Alkylene or alkenylene groups may be optionally substituted. Suitable
optional substituent groups include alkoxy, alkylamino, alkylsulfinyl, alkylsulfonyl,
alkythio, -NH₂, aminoalkyl, arylalkyl, cyano, dialkylamino, halo, haloalkoxy,
haloalkyl, alkyl, and -OH.

Compounds of the invention may exist in one or more geometrical,
optical, enantiomeric, diastereomeric and tautomeric forms, including but not
limited to cis- and transforms, E- and Z-forms, R-, S- and meso-forms, keto-, and enol-forms. Unless otherwise stated a reference to a particular compound includes all such isomeric forms, including racemic and other mixtures thereof. Where appropriate such isomers can be separated from their mixtures by the application or adaptation of known methods (e.g. chromatographic techniques and recrystallisation techniques). Where appropriate such isomers may be prepared by the application or adaptation of known methods (e.g. asymmetric synthesis).

Structural features of compounds [1]

With reference to formula [1] above, particular structural features are described below.

The radical -B-Y may be bonded, for example, to the carbon in the 3-position of the 2-oxo-2/-/-chromene ring system.

Y may be, for example, optionally substituted phenyl, pyridyl, pyrimidinyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, or pyrrolyl. Presently preferred is the case where Y is optionally substituted phenyl. Optional substituents in Y may be selected from, for example, fluoro, methylsulfonyl, ethylsulfonyl, carbamate, methylcarbamate, methylaminosulfonyl, ethylaminosulfonyl, methylsulfonylamino, ethylsulfonylamino, morpholin-1-ylsulfonyl, piperidin-1-ylsulfonyl, piperizin-1-ylsulfonyl, 4-methylpiperizin-1-ylsulfonyl, and tetrahydropyrrolylsulfonyl. Optional substituents in Y may also be selected from, for example, chloro, methyl, methoxy, fluoro, cyano, bromo, tert-butyl, and phenyl.

Specific examples of Y include 4-methylphenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3-, or 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl, 4-phenylphenyl, 4-cyanophenyl, or 4-tert-butylphenyl.

B may be, for example, a bond, -CH₂-, or -CH₂CH₂-.

Rc may be, for example, hydrogen, methyl or ethyl.

A may be, for example, -CH₂-, -CH₂CH₂-, -OCH₂-, -OCH₂CH₂CH₂- where the oxygen is attached to the ring carrying Ra and Rb.

X may be, for example, -CO₂H or a group -C(=O)NHSO₂W where W is as defined for formula [1] above, for example -CONHSO₂CH₃, or -CONHSO₂Ph.
Ra may be in the 8-position, for example, and Rb may be in the 7-position, for example, of the 2-oxo-2H-chromene ring system.

Ra may be selected from, for example, hydrogen, chloro and fluoro.

Rb may be selected from, for example, hydrogen, methyl, trifluormethyl, chloro and fluoro.

Specific compounds of the invention include those of the Examples herein, and pharmaceutically acceptable salts thereof.

Utilities of the Invention

Whilst the compounds of the present invention can be shown to antagonise the effects of the CRTH2 receptor according to the tests described in the Biological Methods section of this document, the mechanism of action by which the compounds act is not a limiting embodiment of the present invention. For example, compounds of the present invention may also have beneficial effects at other prostanoid receptors, such as the DP receptor or the thromboxane A2 receptor.

The therapeutic application of these compounds is pertinent to any disease that is known to be at least partially mediated by the activation of the CRTH2 receptor. Examples of such diseases include, but are not limited to: asthma, chronic obstructive pulmonary disease, bronchitis, cystic fibrosis, emphysema, rhinitis, psoriasis, dermatitis (atopic and non-atopic), Crohn’s disease, ulcerative colitis, and irritable bowel disease.

The present invention is also concerned with treatment of these conditions, and the use of compounds of the present invention for manufacture of a medicament useful in treating these conditions.

Combinations

Other compounds may be combined with compounds of this invention of formula [I] for the prevention and treatment of prostaglandin-mediated diseases. Thus the present invention is also concerned with pharmaceutical compositions for preventing and treating PGD2-mediated diseases comprising a therapeutically effective amount of a compound of the invention of formula [1] and one or more other therapeutic agents. Suitable therapeutic agents for a combination therapy with compounds of formula [1] include, but are not limited to: (1) corticosteroids, such as fluticasone, ciclesonide or budesonide; (2) β2-
adrenoreceptor agonists, such as salmeterol, indacaterol or formoterol; (3) leukotriene modulators, for example leukotriene antagonists such as montelukast, zafirlukast or pranlukast or leukotriene biosynthesis inhibitors such as Zileuton or BAY-1005; (4) anticholinergic agents, for example muscarinic-3 (M3) receptor antagonists such as tiotropium bromide; (5) phosphodiesterase-IV (PDE-IV) inhibitors, such as roflumilast or cilomilast; (6) antihistamines, for example selective histamine-1 (H1) receptor antagonists, such as fexofenadine, citirizine, loratidine or astemizole; (7) antitussive agents, such as codeine or dextramorphan; (8) non-selective COX-1 / COX-2 inhibitors, such as ibuprofen or ketoprofen; (9) COX-2 inhibitors, such as celecoxib and rofecoxib; (10) VLA-4 antagonists, such as those described in WO97/03094 and WO97/02289; (11) TACE inhibitors and TNF-α inhibitors, for example anti-TNF monoclonal antibodies, such as Remicade and CDP-870 and TNF receptor immunoglobulin molecules, such as Enbrel; (12) inhibitors of matrix metalloprotease, for example MMP12; (13) human neutrophil elastase inhibitors, such as those described in WO2005/026124, WO2003/053930 and WO06/082412; (14) A2a agonists such as those described in EP1 052264 and EP1241 176 (15) A2b antagonists such as those described in WO2002/42298; (16) modulators of chemokine receptor function, for example antagonists of CCR3 and CCR8; (17) compounds which modulate the action of other prostanoid receptors, for example a DP receptor antagonist or a thromboxane A₂ antagonist; and (18) agents that modulate Th2 function, such as PPAR agonists

The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

Pharmaceutical Formulations

The present invention is also concerned with pharmaceutical formulations comprising one of the compounds as an active ingredient.

The magnitude of prophylactic or therapeutic dose of a compound may be determined by any suitable method known to one skilled in the art. It will be understood, however, that the specific amount for any particular patient will depend upon a variety of factors, including the activity of the specific compound that is used, the age, body weight, diet, general health and sex of the patient,
time of administration, the route of administration, the rate of excretion, the use of any other drugs, and the severity of the disease undergoing treatment.

In general, the daily dose range will lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for the intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound of formula [1] per kg of body weight per day.

In the cases where an oral composition is employed, a suitable dosage range is, for example, from about 0.01 mg to about 300 mg of a compound of formula [1] per day, preferably from about 0.1 mg to about 30 mg per day. For oral administration, the compositions are preferably provided in the form of tablets containing from 0.01 to 1,000 mg, preferably 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 40.0, 50.0 or 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

The compounds of the invention may be administered by inhalation at a dose range from 0.0005 mg to 10 mg (preferably 0.005 mg to about 0.5 mg) per kg of body weight per day.

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of the invention and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention
encompass any composition made by admixing a compound of the invention, additional active ingredient(s), and pharmaceutically acceptable excipients.

The pharmaceutical compositions of the present invention comprise a compound of the invention as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

Compounds of the invention may be used in combination with other drugs that are used in the treatment, prevention, suppression or amelioration of the diseases or conditions for which present compounds are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the invention.

When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the invention.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dosage of a compound of the present invention. In therapeutic use, the active compound may be administered by any convenient, suitable or effective route. The compositions include those compositions suitable for routes of administration known to those skilled in the art, and include oral, intravenous, rectal, parenteral, topical, ocular, nasal, buccal and pulmonary. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For delivery by inhalation, the active compound is preferably in the form of microparticles. They may be prepared by a variety of techniques, including spray-drying, freeze-drying and micronisation. Aerosol generation can be carried
out using, for example, pressure-driven jet atomizers or ultrasonic atomizers, preferably using propellant-driven metered aerosols or propellant-free administration of micronized active compounds from, for example, inhalation capsules or other "dry powder" delivery systems.

By way of example, a composition of the invention may be prepared as a suspension for delivery from a nebuliser or as an aerosol in a liquid propellant, for example for use in a pressurised metered dose inhaler (PMDI). Propellants suitable for use in a PMDI are known to the skilled person, and include CFC-12, HFA-134a, HFA-227, HCFC-22 (CCl₂F₂) and HFA-152 (CH₂F₂) and isobutane.

Microparticles for delivery by administration may be formulated with excipients that aid delivery and release, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For example, in a dry powder formulation, microparticles may be formulated with large carrier particles that aid flow from the DPI into the lung. Suitable carrier particles are known, and include lactose particles; they may have a mass median aerodynamic diameter of greater than 90 µm.

In the case of an aerosol-based formulation, a preferred composition is:

<table>
<thead>
<tr>
<th>Compound of the invention</th>
<th>24 mg / canister</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lecithin, NF Liq. Cone.</td>
<td>1.2 mg / canister</td>
</tr>
<tr>
<td>Trichlorofluoromethane, NF</td>
<td>4.025 g / canister</td>
</tr>
<tr>
<td>Dichlorodifluoromethane, NF</td>
<td>12.15 g / canister</td>
</tr>
</tbody>
</table>

For the purposes of inhalation, a large number of systems are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is appropriate for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhalers for example as described EP-A-0505321).

In practical use, the compounds of formula [1] can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to
conventional pharmaceutical compounding techniques. The carrier may take a
c wide variety of forms depending on the form of preparation desired for
administration, e.g. oral or parenteral (including intravenous). In preparing the
compositions for oral dosage form, any of the usual pharmaceutical media may
be employed, such as, for example, water, glycols, oils, alcohols, flavouring
agents, preservatives, colouring agents and the like in the case of oral liquid
preparations, such as, for example, suspensions, elixirs and solutions; or carriers
such as starches, sugars, microcrystalline cellulose, diluents, granulating agents,
lubricants, binders, disintegrating agents and the like in the case of oral solid
preparations such as, for example, powders, capsules and tablets, with the solid
oral preparations being preferred over the liquid preparations. Because of their
ease of administration, tablets and capsules represent the most advantageous
oral dosage unit form in which case solid pharmaceutical carriers are obviously
employed. If desired, tablets may be coated by standard aqueous or
nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of
formula [1] may also be administered by controlled release means and / or
delivery devices such as those described in U.S. patents 3845770, 3916899,
3536809, 3598123, 3630200 and 4008719.

Pharmaceutical compositions of the present invention suitable for oral
administration may be presented as discrete units such as capsules, cachets or
tables each containing a predetermined amount of the active ingredient, as a
powder or granules or as a solution or a suspension in an aqueous liquid, a non-
aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such
compositions may be prepared by any of the methods of pharmacy but all
methods include the step of bringing into association the active ingredient with
the carrier which constitutes one or more necessary ingredients. In general, the
compositions are prepared by uniformly and intimately admixing the active
ingredient with liquid carriers or finely divided solid carriers or both, and then, if
necessary, shaping the product into the desired presentation. For example, a
tablet may be prepared by compression or moulding, optionally with one or more
accessory ingredients. Compressed tablets may be prepared by compressing in
a suitable machine, the active ingredient in a free-flowing form such as powder
or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of formula [1]:

Injectable Suspension (I.M.):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of formula [1]</td>
<td>10 mg / ml</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>5.0 mg / ml</td>
</tr>
<tr>
<td>Tween 80</td>
<td>0.5 mg / ml</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>9.0 mg / ml</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>1.0 mg / ml</td>
</tr>
<tr>
<td>Plus water for injection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to a total volume of 1 mL</td>
</tr>
</tbody>
</table>

500 mg Tablet:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of formula [1]</td>
<td>25 mg / tablet</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>415 mg/mL</td>
</tr>
<tr>
<td>Povidone</td>
<td>14.0 mg/mL</td>
</tr>
<tr>
<td>Pregelatinized Starch</td>
<td>43.5 mg/mL</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2.5 mg/mL</td>
</tr>
</tbody>
</table>

600 mg Capsule:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of formula [1]</td>
<td>25 mg / tablet</td>
</tr>
<tr>
<td>Lactose Powder</td>
<td>573.5 mg / tablet</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.5 mg / tablet</td>
</tr>
</tbody>
</table>

Methods of Synthesis

The present invention is also concerned with processes for preparing the compounds of this invention.

The compounds of formula [1] of the present invention can be prepared according to the procedures of the following schemes and examples, using appropriate materials, and are further exemplified by the following specific examples. Moreover, by utilizing the procedures described with the disclosure contained herein, one of ordinary skill in the art can readily prepare additional
compounds of the present invention claimed herein. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

The compounds of the invention of formula [1] may be isolated in the form of their pharmaceutically acceptable salts, such as those described previously herein above. The free acid form corresponding to isolated salts can be generated by acidification with a suitable acid such as acetic acid and hydrochloric acid and extraction of the liberated free acid into an organic solvent followed by evaporation. The free acid form isolated in this manner can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent followed by addition of the appropriate base and subsequent evaporation, precipitation, or crystallisation.

It may be necessary to protect reactive functional groups (e.g. hydroxy, amino, thio or carboxy) in intermediates used in the preparation of compounds of formula [1] to avoid their unwanted participation in a reaction leading to the formation of compounds of formula [1]. Conventional protecting groups, for example those described by T. W. Greene and P. G. M. Wuts in "Protective groups in organic chemistry" John Wiley and Sons, 1999, may be used.

Compounds of the invention of general formula [1a], in which group A is represented by a group of formula O-(optionally substituted)alkylene, may conveniently be prepared by the reaction between a compound of formula [2] and a suitable alkylating agent of formula [3], where group LG represents a suitable leaving group (for example, chloro, bromo, or methanesulfonyloxy). Typically, the alkylation reaction is carried out in the presence of a base (for example, potassium carbonate) in an inert solvent (for example, acetone or N,N-dimethylformamide). It will be understood by those who are practiced in the art that it may be convenient to carry out the transformation of intermediate [2] to final compound [1a] using a form of alkylating agent [3] in which the group is suitably protected. For example, if group X represents a carboxylic acid it may be convenient to carry out the reaction using an alkylating agent in which the acid
group is protected as an ester (for example, an ethyl or tert-butyl ester). It is to be understood that if the reaction is carried out on a protected form of alkylating agent [3] an appropriate deprotection step will be required to obtain the desired compound [1a] of the invention.

Intermediate compounds of formula [2a] may conveniently be prepared by the reaction between a benzene-1,3-diol of formula [4] and a β-ketoester of formula [5], in which PG represents an appropriate ester function (such as methyl and ethyl) in the presence of a suitable dehydrating agent, such as phosphorus oxychloride, phosphorus pentoxide, or sulfuric acid.

Similarly, intermediate compounds of formula [2b] may conveniently be prepared by the reaction between a benzene-1,3-diol of formula [4] and a β-
ketoester of formula [6], in which PG represents an appropriate ester function (such as methyl and ethyl) in the presence of a suitable dehydrating agent, such as phosphorus oxychloride or phosphorus pentoxide.

Compounds of the invention of general formula [1b], in which group A represents an optionally substituted alkenylene group in which the double bond is directly attached to the 5-position of the chromenone nucleus (for example -CH=CH-), may conveniently be prepared by the reaction between an intermediate compound of formula [7], in which group T represents a chloro, bromo, or iodo atom, or a trifluoromethanesulfonyloxy group, and an alkenylene compound of general formula [8]. The reaction may conveniently be carried out in the presence of a suitable catalyst (for example a palladium compound) in the presence of a base such as triethylamine. It will be understood by those who are practiced in the art that it may be convenient to carry out the transformation of intermediate [7] to final compound [1b] using a form of intermediate [8] in which the group is suitably protected. For example, if group X represents a carboxylic acid it may be convenient to carry out the reaction using an alkylation agent in which the acid group is protected as an ester (for example, an ethyl or tert-butyl ester). It is to be understood that if the reaction is carried out on a protected form of intermediate [8] an appropriate deprotection step will be required to obtain the desired compound [1b] of the invention.
Similarly, compounds of the invention of general formula [1c] may be prepared by the reaction between an intermediate compound of formula [7], in which group T represents a chloro, bromo, or iodo atom, or a trifluoromethanesulfonyloxy group, and (i-tert-butoxyvinyloxy)-fert-butyldimethylsilane. The reaction may conveniently be carried out in the presence of a suitable catalyst (for example a palladium compound) and a base (such as sodium acetate).

Intermediates of formula [7], in which T is trifluoromethanesulfonyloxy, may be prepared from the reaction of intermediates of formula [2] with triflic anhydride in the presence of a base such as 2,6-lutidine.

It will be understood by those practiced in the art that compounds of the invention may be prepared by transformations of other compounds of the
invention. For example, compounds of the invention of formula [1d], in which group A represents an optionally substituted alkenylene group, may conveniently be prepared by the reduction of compounds of the invention of formula [1b], in which group A represents an optionally substituted alkenylene group. The transformation of compounds of formula [1b] to those of formula [1d] may conveniently be achieved by reduction with hydrogen in the presence of a suitable catalyst, such as palladium supported on carbon.

Examples

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

$^1$H NMR spectra were recorded at ambient temperature using a Varian Unity Inova (400MHz) spectrometer with a triple resonance 5 mm probe spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations have been used: br s = broad singlet, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiple!

Mass Spectrometry (LCMS) experiments to determine retention times and associated mass ions were performed using the following methods:

Method A: experiments were performed on a Micromass Platform LCT spectrometer with positive ion electrospray and single wavelength UV 254 nm detection using a Higgins Clipeus C18 5 µm 100 x 3.0 mm column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent
B) for the first minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 14 minutes. The final solvent system was held constant for a further 2 minutes.

Method B: experiments were performed on a Micromass Platform LC spectrometer with positive and negative ion electrospray and ELS / Diode array detection using a Phenomenex Luna C18(2) 30 x 4.6 mm column and a 2 mL / minute flow rate. The solvent system was 95% solvent A and 5% solvent B for the first 0.50 minutes followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 0.50 minutes

Microwave experiments were carried out using a Personal Chemistry Smith Synthesizer™, which uses a single-mode resonator and dynamic field tuning, both of which give reproducibility and control. Temperatures from 40-250 °C can be achieved, and pressures of up to 20 bar can be reached. Two types of vial are available for this processor, 0.5-2.0 mL and 2.0-5.0 mL.

Reverse-phase preparative HPLC purifications were carried out using Genesis 7 micron C-18 bonded silica stationary phase in columns 10 cm in length and 2 cm internal diameter. The mobile phase used was mixtures of acetonitrile and water (both buffered with 0.1% v/v trifluoroacetic acid) with a flow rate of 10 mL per minute and typical gradients of 40 to 90% organic modifier ramped up over 30 to 40 minutes. Fractions containing the required product (identified by LC-MS analysis) were pooled, the organic fraction removed by evaporation, and the remaining aqueous fraction lyophilised, to give the final product.
Example 1: (3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetic acid

Preparation (1a) 3-benzyl-5-hydroxy-4,7-dimethylchromen-2-one

5-Methylbenzene-1,3-diol (25 g) was dissolved in anhydrous toluene (190 mL), and this solution was treated successively with ethyl (2-benzyl)acetoacetate (56 mL) and phosphorus oxychloride (19 mL). The mixture was heated to reflux under a nitrogen atmosphere for three hours, allowed to cool to room temperature, then treated with water (~400 mL). After stirring for 20 minutes the resulting precipitate was collected by filtration. The filtrate layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried and evaporated and the residue combined with the original precipitate. The combined solids were purified by flash chromatography on silica gel, eluting with a gradient mixture of ethyl acetate in pentane (1:4 to 3:2 by volume) to give 3-benzyl-5-hydroxy-4,7-dimethylchromen-2-one as a cream solid, 28 g. $^1$H NMR analysis indicated that this material was contaminated with about 11 mole percent of the regioisomer 3-benzyl-7-hydroxy-4,5-dimethylchromen-2-one.

$^1$H NMR (DMSO-d6): $\delta$ 2.25 (s, 3H), 2.55 (s, 3H), 3.9 (s, 2H), 6.60 (m, 2H), 7.25-7.30 (m, 5H), 10.5 (br s, 1H).

Preparation (1b) ethyl (3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetate

3-Benzyl-5-hydroxy-4,7-dimethylchromen-2-one (3.0 g) was suspended in acetone (35 mL) and treated with ethyl bromoacetate (1.3 mL) and potassium carbonate (1.8 g). The mixture was stirred at 60°C overnight, allowed to cool to
room temperature, then evaporated to dryness. The residue was partitioned between ethyl acetate and water, the layers separated, and the organic layer was washed with water, dried over magnesium sulfate, and evaporated. The residue was triturated with a mixture of ether and pentane and the resulting solid collected by filtration to give ethyl(3-benzyl-4,7-dimethyl-2-oxo-2/-/-chromen-5-yloxy)acetate as a cream solid, 3.0 g. 1H NMR analysis indicated that this material was contaminated with about 9 mole percent of the regioisomer ethyl (3-benzyl-4,5-dimethyl-2-oxo-2H-chromen-7-yloxy)acetate.

1H NMR (DMSO-d6): δ 1.20 (t, J = 7.1 Hz, 3H), 2.35 (s, 3H), 2.65 (s, 3H), 4.0 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.90 (s, 2H), 6.80-6.85 (m, 2H), 7.15-7.30 (m, 5H).

Preparation (1c) (3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetic acid

5 M sodium hydroxide solution (20 ml) was added to a stirred suspension of ethyl (3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetate (3.0 g) in ethanol (20 ml) and the mixture allowed to stir at room temperature for two hours. The reaction mixture was evaporated to low bulk and acidified by the addition of 5 M hydrochloric acid (~ 3 mL). The resulting precipitate was collected by filtration, washed with water and ether, and dried. Crystallisation from methanol gave (3-benzyl-4,7-dimethyl-2-oxo-2/-/-chromen-5-yloxy)acetic acid as a white solid, 1.7 g.

1H NMR (DMSO-d6): δ 2.45 (s, 3H), 2.65 (s, 3H), 3.95 (s, 2H), 4.80 (s, 2H), 6.75 (m, 1H), (6.85 (m, 1H), 7.15-7.30 (m, 5H).

MS: ESI (+ve) (Method A): 339 (M+H)+, Retention time 10.7 min.
Example 2: 4-(3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)butyric acid

Preparation (2a) ethyl 4-(3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)butyrate

A mixture of 3-benzyl-5-hydroxy-4,7-dimethylchromen-2-one (compound of Preparation (1a), 0.50 g), ethyl 4-bromobutyrate (0.28 ml_) and potassium carbonate (0.30 g) in acetone (10 ml_) was stirred at 60°C overnight. The mixture was allowed to cool to room temperature, and then evaporated to dryness. The residue was partitioned between ethyl acetate and water, the layers separated, and the organic layer was washed with water, dried over magnesium sulfate, and evaporated. The residue was triturated with a mixture of ether and pentane and the resulting solid collected by filtration to give ethyl 4-(3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)butyrate as a cream solid, 0.45 g.

1H NMR (DMSO-d6): δ 1.15 (t, J = 7.1 Hz, 3H), 2.05 (m, 2H), 2.35 (s, 3H), 2.45 (m 2H), 2.55 (s, 3H), 3.95 (s, 2H), 4.00-4.10 (m, 4H), 6.80 (m, 2H), 7.15-7.30 (m, 5H).

Preparation (2b) 4-(3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)butyric acid

A mixture of ethyl 4-(3-benzyl-4,7-dimethyl-2-oxo-2/-/-chromen-5-yloxy)butyrate (0.44 g) and 5 M aqueous sodium hydroxide solution (3.5 ml_) in ethanol (4 ml_) was stirred at room temperature for two hours, then at 80°C for 30 minutes, to
give a clear solution. After cooling to room temperature the solution was evaporated to low bulk and the residue acidified by the addition of 5 M aqueous hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and dried to give 4-(3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)butyric acid as a cream solid, 0.28 g.

$^1$H NMR (DMSO-d6): δ 2.00 (m, 2H), 2.35 (s, 3H), 2.40 (m, 2H), 2.55 (s, 3H), 3.95 (s, 2H), 4.05 (m, 2H), 6.80 (m, 2H), 7.15-7.30 (m, 5H).

MS: ESI (+ve) (Method A): 367 (M+H)$^+$, Retention time 11.4 min.

Example 3: [3-(4-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)]acetic acid

Preparation (3a) ethyl 2-(4-methoxybenzyl)acetoacetate

A suspension of potassium tert-butoxide (0.88 g) in anhydrous tetrahydrofuran was flushed with nitrogen and cooled in an ice-bath. This suspension was treated successively with tert-butanol (0.067 mL) and ethyl acetoacetate (1.0 g). After stirring for a further 30 minutes 4-methoxybenzyl chloride (1.0 mL) was added and the mixture stirred at 70°C for 18 hours. After cooling to room temperature the reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution and extracted with ether. The combined extracts were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated. Purification of the residue by flash chromatography on silica gel, eluting with a mixture of ethyl acetate and
cyclohexane (1:3 by volume), gave ethyl 2-(4-methoxybenzyl)acetoacetate as a colourless oil, 1.3 g.

\(^1\)H NMR (CDCl\(_3\)): 1.20 (m, 3H), 2.20 (s, 2H), 3.10 (m, 2H), 3.70 (m, 1H), 3.75 (s, 3H), 4.15 (m, 2H), 6.80 (m, 2H), 7.05 (m, 3H).

Preparation (3b) 5-hydroxy-3-(4-methoxybenzyl)-4,7-dimethylchromen-2-one

A mixture of ethyl 2-(4-methoxybenzyl)acetoacetate (0.55 g) and 5-methylbenzene-1,3-diol (0.15 g) in phosphorus oxychloride (1.5 mL) was stirred at room temperature under nitrogen for 18 hours. The reaction mixture was evaporated to dryness and the residue partitioned between ethyl acetate and water. The layers were separated and the aqueous layer further extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and evaporated to dryness. The residue was triturated with a mixture of ether and cyclohexane (1:1 by volume) to give 5-hydroxy-3-(4-methoxybenzyl)-4,7-dimethylchromen-2-one as an orange solid, 0.039 g. Evaporation of the mother liquors and a second trituration with cyclohexane gave a second crop of material, 0.044 g.

\(^1\)H NMR (DMSO-d6): δ 2.25 (s, 3H), 2.55 (s, 3H), 3.70 (s, 3H), 3.85 (s, 2H), 6.60 (s, 1H), 6.65 (s, 1H), 6.80 (m, 2H), 7.10 (m, 2H), 10.5 (br S, 1H).

Preparation (3c) ethyl [3-(4-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)]acetate

A solution of 5-hydroxy-3-(4-methoxybenzyl)-4,7-dimethylchromen-2-one (0.073 g) in \(\text{L.L}\)-dimethylformamide (2.4 mL) was treated with potassium carbonate (0.068 g) and ethyl bromoacetate (0.052 mL) and the resulting mixture stirred at 90°C overnight. The reaction mixture was evaporated to dryness and the residue partitioned between ethyl acetate and water. The layers were separated and the organic layer further extracted with ethyl acetate. The combined extracts were washed with aqueous citric acid solution (10% w/v), then saturated aqueous
sodium hydrogen carbonate solution, dried over sodium sulfate and evaporated to dryness. Purification of the residual brown solid by flash chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane (1:3 by volume) gave ethyl [3-(4-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate as a yellow solid, 0.051 g.

\[ ^1H \text{NMR (DMSO-d6):} \delta 1.20 \text{ (t, } J = 7.0 \text{ Hz, 3H)}, 2.35 \text{ (s, 3H)}, 2.60 \text{ (s, 3H)}, 3.70 \text{ (s, 3H)}, 3.90 \text{ (s, 2H)}, 4.20 \text{ (q, } J = 7.0 \text{ Hz, 2H)}, 4.90 \text{ (s, 2H)}, 6.75-6.85 \text{ (m, 4H)}, 7.10 \text{ (m, 2H)}. \]

Preparation (3d) [3-(4-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

Lithium hydroxide monohydrate (0.010 g) was added to a stirred suspension of ethyl [3-(4-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate (0.047 g) in a mixture of methanol (0.96 ml) and water (0.24 ml). The resulting mixture was stirred at room temperature overnight, to give a yellow suspension. The insolubles were collected by filtration, washed with ether, and then dissolved in water. Acidification of this solution with dilute hydrochloric acid produced a milky suspension, which was extracted with ethyl acetate. The combined organic extracts were washed with saturated sodium aqueous chloride solution, dried over sodium sulfate, and evaporated. Trituration of the resulting solid with ether followed by filtration gave [3-(4-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid as a white solid, 0.0047 g.

\[ ^1H \text{NMR (CD}_3\text{OD):} 2.40 \text{ (s, 3H)}, 2.70 \text{ (s, 3H)}, 3.75 \text{ (s, 3H)}, 3.95 \text{ (s, 2H)}, 4.75 \text{ (s, 2H)}, 6.65 \text{ (m, 1H)}, 6.80-6.85 \text{ (m, 3H)}, 7.10 \text{ (m, 2H)}. \]

MS: ESI (+ve) (Method A): 369 (M+H)$^+$, Retention time 10.7 min.
Example 4: 3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yl)acetic acid

Preparation (4a): tert-butyl 3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yl)acetate

A mixture of 3-benzyl-4,7-dimethyl-5-(trifluoromethanesulfonyloxy)chromen-2-one (compound of Preparation (12a), 0.20 g), (i-tert-butoxyvinyloxy)-tert-butyl(dimethyl)silane (0.56 g), sodium acetate (0.050 g), tris(dibenzylideneacetone)dipalladium (0) (0.022 g), and 1,1'-bis(diphenylphosphino)ferrocene (0.013 g) in N,N-dimethylformamide (3 ml) was heated by microwave irradiation at 120°C for ten minutes. The reaction mixture was diluted with ethyl acetate, and this solution was washed with water, dried over magnesium sulfate, and evaporated to give a black semi-solid. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate in pentane (1:9 by volume) gave tert-butyl 3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yl)acetate as a yellow solid, 0.13 g.

1H NMR (DMSO-d6): δ 1.35 (s, 9H), 2.40 (s, 3H), 2.50 (s, 3H), 4.00 (s, 2H), 4.1 (S, 2H), 7.05 (m, 1H), 7.15-7.30 (m, 6H).

Preparation (4b) 3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yl)acetic acid

tert-Butyl-3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yl)acetate (0.13 g) was dissolved in a 4 M solution of hydrogen chloride in dioxane (1.5 mL) and the resulting solution was allowed to stand at room temperature overnight. The solution was evaporated to dryness and the residue triturated with ether. The resulting solid was collected by filtration, washed with pentane, and dried to give...
S-benzylmy-dimethyl^-oxo^H-chromen-δ-yOacetic acid as a pale yellow solid, 0.085 g.

^1H NMR (DMSO-d6): δ 2.35 (s, 3H), 2.45 (s, 3H), 4.00 (s, 2H), 4.10 (s, 2H), 7.10 (m, 1H), 7.15-7.30 (m, 6H), 12.60 (br s, 1H).

MS: ESI (+ve) (Method A): 323 (M+H)^+, Retention time 10.2 min.

**Example 5:** [3-(2-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy])acetic acid

Preparation (5a) ethyl 2-(2-methoxybenzyl)acetoacetate

A suspension of potassium tert-butoxide (0.88 g) in anhydrous tetrahydrofuran (20 mL) was cooled in an ice-bath under an atmosphere of nitrogen. This suspension was treated with 2-methoxybenzyl chloride (1.1 mL) and tert-butanol (0.067 mL) and the resulting mixture stirred at 70°C under nitrogen for five hours. After cooling to room temperature the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution and extracted with ether. The combined ether extracts were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated to afford a golden oil. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane (1:6 by volume) gave ethyl 2-(2-methoxybenzyl)acetoacetate as a colourless oil, 0.91 g.

MS: ESI (-ve) (Method B): 249 (M-H)^-, Retention time 3.4 min.

Preparation (5b) 5-hydroxy-3-(2-methoxybenzyl)-4,7-dimethylchromen-2-one
A mixture of ethyl 2-(2-methoxybenzyl)acetoacetate (0.81 g) and 5-methylbenzene-1,3-diol (0.31 g) was treated with phosphorus oxychloride (3.1 mL) under an atmosphere of nitrogen. This mixture was stirred at room temperature for 22 hours and then evaporated to dryness. The residue was partitioned between ethyl acetate and water, the layers separated, and the aqueous layer re-extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated to give an orange semi-solid. Trituration with a mixture of ether and cyclohexane (1:1 by volume) gave a solid, which was collected by filtration and dried to give 5-hydroxy-3-(2-methoxybenzyl)-4,7-dimethylchromen-2-one as an orange solid, 0.21 g.

\[ ^1H \text{ NMR (DMSO-d}_6\text{): } \delta 2.30 (s, 3H), 2.40 (s, 3H), 3.80 (s, 2H), 3.85 (s, 3H), 6.60 (m, 1H), 6.65 (m, 1H), 6.75-6.85 (m, 2H), 7.00 (m, 1H), 7.15-7.20 (m, 1H), 10.50 (br s, 1H). \]

Preparation (5c) ethyl [3-(2-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate

A solution of 5-hydroxy-3-(2-methoxybenzyl)-4,7-dimethylchromen-2-one (0.20 g) in N,N-dimethylformamide (3.2 mL) was treated with potassium carbonate (0.19 g) and ethyl bromoacetate (0.14 mL), and the resulting mixture was stirred at 90°C for five hours. The mixture was evaporated to low bulk and the residue triturated with water. The solid product was collected by filtration, washed with water and ether, and dried to give ethyl [3-(2-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate as a white solid, 0.19 g.

\[ ^1H \text{ NMR (DMSO-d}_6\text{): } \delta 1.20 (t, J = 7.0 \text{ Hz}, 3H), 2.35 (s, 3H), 2.50 (s, 3H), 3.80 (s, 3H), 3.85 (s, 2H), 4.20 (q, J = 7.0 \text{ Hz}, 2H), 4.90 (s, 2H), 6.80-6.85 (m, 4H), 7.00 (m, 1H), 7.15-7.20 (m, 1H). \]
Preparation (5d) \([3\text{-}(2\text{-methoxybenzyl})\text{-}4,7\text{-dimethyl-}2\text{-oxo-}2\text{H-chromen-5-yloxy})\text{]acetic acid}\)

A suspension of ethyl \([3\text{-}(2\text{-methoxybenzyl})\text{-}4,7\text{-dimethyl-}2\text{-oxo-}2\text{H-chromen-5-yloxy})\text{]aceta... (0.18 g) in methanol (3.6 mL) and water (0.9 mL) was treated with lithium hydroxide hydrate (0.039 g) and the mixture stirred at room temperature for two hours. The pH of the solution was adjusted to \(~1\) by the addition of dilute hydrochloric acid, and the resulting precipitate was collected by filtration, washed with water and ether, and dried to give \([3\text{-}(2\text{-methoxybenzyl})\text{-}4,7\text{-dimethyl-}2\text{-oxo-}2\text{H-chromen-5-yloxy})\text{]acetic acid}\) as a yellow solid, 0.12 g.

\(^1\)H NMR (DMSO-d6): \(\delta\) 2.30 (s, 3H), 2.50 (s, 3H), 3.75 (s, 3H), 3.80 (s, 2H), 4.75 (s, 2H), 6.70-6.80 (m, 4H), 6.95 (m, 1H), 7.10-7.15 (m, 1H), 13.00 (br s, 1H).

MS: ESI (+ve) (Method A): 369 (M+H)+, Retention time 10.9 min.

Example 6: \([4,7\text{-dimethyl-}3\text{-}(2\text{-methylbenzyl})\text{-}2\text{-oxo-}2\text{H-chromen-5-yloxy})\text{]acetic acid}\)

Preparation (6a) ethyl 2-(2-methylbenzyl)acetoacetate

Ethyl 2-(2-methylbenzyl)acetoacetate was prepared by the reaction between ethyl acetoacetate (1.0 g) and 2-methylbenzyl bromide (1.0 mL) using the method described in Preparation (5a) as a pale yellow oil, 1.4g.

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.20 (t, \(J = 7.0\) Hz, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 3.10-3.20 (m, 2H), 3.75 (t, \(J = 7.5\) Hz, 1H), 4.10-4.20 (m, 2H), 7.05-7.15 (m, 4H).
Preparation (6b) 5-hydroxy-3-(2-methylbenzyl)-4,7-dimethyl-2-oxo-2/-/\-chromen-2-one

A mixture of ethyl 2-(2-methylbenzyl)acetoacetate (1.3 g) and 5-methylbenzene-1,3-diol (0.52 g) in phosphorus oxychloride (5.2 mL) was stirred at room temperature under an atmosphere of nitrogen for 23 hours. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate and water. A small amount of insoluble material was collected by filtration, to give 5-hydroxy-3-(2-methylbenzyl)-4,7-dimethyl-2-oxo-2H-chromen-2-one as an orange solid, 0.088 g. The two layers of the extraction mixture were separated, and the organic layer was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated. The residue was triturated with a mixture of ether and cyclohexane (1:1 by volume) and the resulting solid was collected by filtration, washed with ether, and dried to give a second crop of 5-hydroxy-3-(2-methylbenzyl)-4,7-dimethyl-2-oxo-2H-chromen-2-one as an orange solid, 0.059 g.

^1H NMR (DMSO-d6): δ 2.30 (s, 3H), 2.35 (s, 3H), 2.50 (s, 3H), 3.85 (s, 2H), 6.60-6.65 (m, 2H), 6.75 (m, 1H), 7.00-7.20 (m, 3H), 10.5 (br s, 1H).

Preparation (6c) ethyl [4,7-dimethyl-3-(2-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetate

Ethyl [4,7-dimethyl-3-(2-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetate was prepared by the reaction of 5-hydroxy-3-(2-methylbenzyl)-4,7-dimethyl-2-oxo-2/-/\-chromen-2-one (0.13 g) and ethyl bromoacetate following the method described in Preparation (5c) as a white solid, 0.14 g.

^1H NMR (DMSO-d6): δ 1.20 (t, J = 7.1 Hz, 3H), 2.35 (m, 6H), 2.50 (s, 3H), 3.85 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 4.90 (s, 2H), 6.75 (m, 1H), 6.80 (m, 1H), 6.85 (m, 1H), 7.00-7.10 (m, 2H), 7.20 (m, 1H).
Preparation (6d) [4,7-dimethyl-3-(2-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetic acid

Ethyl [4,7-dimethyl-3-(2-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetate (0.13 g) was hydrolysed with lithium hydroxide following the method described in Preparation (5d) to give [4,7-dimethyl-3-(2-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetic acid as a white solid, 0.070 g.

$^1\text{H NMR (DMSO-d}_6\text{)}$: $\delta$ 2.30 (m, 6H), 2.50 (s, 3H), 3.80 (s, 2H), 4.75 (s, 2H), 6.70-6.75 (m, 2H), 6.80 (m, 1H), 6.95-7.05 (m, 2H), 7.15 (m, 1H), 13.10 (br s, 1H).

MS: ESI (+ve) (Method A): 353 (M+H)$^+$, Retention time 11.2 min.

Example 7: [4,7-dimethyl-3-(4-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetic acid

Preparation (7a) ethyl 2-(4-methylbenzyl)acetoacetate

Ethyl 2-(4-methylbenzyl)acetoacetate was prepared from the reaction between ethyl acetoacetate (1.0 g) and 4-methylbenzyl chloride (1.0 mL) using the method described in Preparation (5a) as a colourless oil, 0.97 g.

$^1\text{H NMR (CDCl}_3\text{)}$: $\delta$ 1.20 (t, J = 7.2 Hz, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 3.10 (d, J = 7.7 Hz, 2H), 3.75 (t, J = 7.7 Hz, 1H), 4.10-4.20 (m, 2H), 7.05 (m, 4).
Preparation (7b) 5-hydroxy-3-(4-methylbenzyl)-4,7-dimethyl-2-oxo-2/-/-chromen-2-one

5-Hydroxy-3-(4-methylbenzyl)-4,7-dimethyl-2-oxo-2/-/-chromen-2-one was prepared from the reaction between ethyl 2-(4-methylbenzyl)acetoacetate (0.90 g) and 5-methylbenzene-1,3-diol (0.37 g) following the method described in Preparation (6b). Two crops of materiel were obtained as orange solids, 0.062 g and 0.037 g.

1\textsuperscript{H} NMR (DMSO-d6): $\delta$ 2.20 (s, 3H), 2.25 (s, 3H), 2.55 (s, 3H), 3.85 (s, 2H), 6.55 (m, 1H), 6.60 (m, 1H), 7.05 (m, 4H), 10.45 (br s, 1H).

Preparation (7c) ethyl [4,7-dimethyl-3-(4-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetate

Ethyl [4,7-dimethyl-3-(4-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetate was prepared from the reaction between 5-hydroxy-3-(4-methylbenzyl)-4,7-dimethyl-2-oxo-2H-chromen-2-one (0.084 g) and ethyl bromoacetate (0.063 ml) following the method described in Preparation (5c) as a white solid, 0.062 g.

1\textsuperscript{H} NMR (DMSO-d6): $\delta$ 1.20 (J = 7.2 Hz, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.60 (s, 3H), 3.90 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 4.90 (s, 2H), 6.80 (m, 1H), 6.85 (m, 1H), 7.05 (m, 4H).

Preparation (7d) [4,7-dimethyl-3-(4-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetic acid

[4,7-Dimethyl-3-(4-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetic acid was prepared by the hydrolysis of ethyl [4,7-dimethyl-3-(4-methylbenzyl)-2-oxo-2H-chromen-5-yloxy]acetate (0.055 g) following the method described in Preparation (5d) as a white solid, 0.024 g.
\(^1\)H NMR (DMSO-d6): \(\delta 2.25 (s, 3H), 2.35 (s, 3H), 2.60 (s, 3H), 3.90 (s, 2H), 4.80 (s, 2H), 6.75 (m, 1H), 6.80 (m, 1H), 7.05 (m, 4H), 13.10 (br s, 1H).

MS: ESI (+ve) (Method A): 353 (M+H)^+, Retention time 11.4 min.

Example 8: 3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxyjacetic acid

Preparation (8a) ethyl 2-(4-chlorobenzyl)acetoacetate

Fert-Butanol (0.10 mL) and ethyl acetoacetate (1.3 g) were added with stirring and ice-cooling under a nitrogen atmosphere to a suspension of potassium tert-butoxide (1.1 g) in anhydrous tetrahydrofuran (25 mL). After stirring in the ice bath for 30 minutes 4-chlorobenzyl chloride was added (1.6 g) and the mixture stirred at 70°C overnight. After cooling to room temperature the mixture was treated with water (~ 5 mL) and evaporated to low bulk. The residue was partitioned between ethyl acetate and water, the layers separated, and the organic layer dried over sodium sulfate and evaporated.

Purification of the residue by flash chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane (1:5.6 by volume) gave ethyl 2-(4-chlorobenzyl)acetoacetate as a clear oil, 1.5 g.

\(^1\)H NMR (CDCl\(_3\)): \(\delta 1.20 (t, J = 7.2 \text{ Hz}, 3H), 2.20 (s, 3H), 3.05-3.15 (m, 2H), 3.75 (t, J = 7.4 \text{ Hz}, 1H), 4.10-4.20 (m, 2H), 7.10 (m, 2H), 7.25 (m, 2H).

Preparation (8b) 3-(4-chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one
A mixture of 5-methylbenzene-1,3-diol (1.5 g), ethyl 2-(4-chlorobenzyl)acetoacetate (1.5 g), and phosphorus oxychloride (5.5 ml) was stirred at room temperature overnight. The mixture was evaporated to dryness and the orange residue partitioned between ethyl acetate and water. The layers were separated, and the organic layer dried over sodium sulfate and evaporated to give an orange oil. Trituration of this oil with ether produced a solid, which was collected by filtration and dried to give 3-(4-chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one as a white solid, 0.27 g.

$^1$H NMR (DMSO-d6): δ 2.25 (s, 3H), 2.55 (s, 3H), 3.90 (s, 2H), 6.60 (m, 1H), 6.65 (m, 1H), 7.20 (m, 2H), 7.30 (m, 2H), 10.50 (br s, 1H).

Preparation (8c) ethyl [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate

A mixture of 3-(4-chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one (0.27 g), ethyl bromoacetate (0.16 g), and potassium carbonate (0.24 g) in acetone (5 ml) was stirred at 70°C for two hours. After cooling to room temperature the mixture was treated with water (~ 2 ml) and evaporated to low bulk. The residue was treated with water and the resulting precipitate collected by filtration and washed with water, then with cyclohexane to give ethyl [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2/-/-chromen-5-yloxy]acetate as a white solid, 0.19 g.

$^1$H NMR (DMSO-d6): δ 1.20 (t, J = 7.0 Hz, 3H), 2.35 (s, 3H), 2.60 (s, 3H), 3.95 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H), 4.90 (s, 2H), 6.80 (m, 1H), 6.85 (m, 1H), 7.25 (m, 2H), 7.35 (m, 2H).

Preparation (8d) [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

A suspension of ethyl [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate (0.19 g) in methanol (3 ml) was treated with 4 M aqueous sodium hydroxide solution (1 ml) and the mixture stirred at room temperature for two
hours. The mixture was acidified by the addition of 1 M hydrochloric acid and the product collected by filtration. Purification by flash chromatography on silica gel, eluting with a mixture of dichloromethane / methanol / acetic acid / water (240:20:3:2 by volume) gave [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid as a white solid, 0.035 g.

\[ \text{1H NMR (DMSO-d6): } \delta \text{ 2.35 (s, 3H), 2.60 (s, 3H), 3.95 (s, 2H), 4.80 (s, 2H), 6.75 (m, 1H), 6.85 (m, 1H), 7.20-7.35 (m, 4H), 13.10 (br s, 1H). MS: ESI (+ve) (Method A): 373 (M+H)+, Retention time 11.7 min.} \]

Example 9: [3-(2-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

Preparation (9a) ethyl 2-(2-chlorobenzyl)acetoacetate

The reaction between ethyl acetoacetate (1.3 g) and 2-chlorobenzyl chloride (1.6 g) using the method described in Preparation (8a) gave ethyl 2-(2-chlorobenzyl)acetoacetate as a colourless oil, 1.4 g.

\[ \text{1H NMR (CDCl}_3\text{): } \delta \text{ 1.20 (t, J = 7.2 Hz, 3H), 2.20 (s, 3H), 3.20-3.30 (m, 2H), 3.95 (m, 1H), 4.10-4.20 (m, 2H), 7.15-7.20 (m, 2H), 7.25 (m, 1H), 7.35 (m, 1H).} \]

Preparation (9b) 3-(2-chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one

The reaction between 5-methylbenzene-1,3-diol (0.55 g), phosphorus oxychloride (5 ml), and ethyl 2-(2-chlorobenzyl)acetoacetate (1.4 g) using the
method described in Preparation (8b) gave 3-(2-chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one as a white solid, 0.30 g.

$^1$H NMR (DMSO-d$_6$): $\delta$ 2.30 (s, 3H), 2.50 (s, 3H), 3.95 (s, 2H), 6.60 (m, 1H), 6.65 (m, 1H), 6.95 (m, 1H), 7.20-7.25 (m, 2H), 7.50 (m, 1H), 10.5 (br s, 1H).

Preparation (9c) ethyl [3-(2-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate

A suspension of 3-(2-chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one (0.30 g) in acetone (5 ml) was treated with solid potassium carbonate (0.26 g) and ethyl bromoacetate (0.18 g) and the resulting mixture stirred at 70°C for one hour. After cooling to room temperature, water (~ 2 ml) was added and the mixture evaporated to low bulk. The residue was diluted with water, and the resulting precipitate was collected by filtration, washed with water, and then with cyclohexane, and dried to give ethyl [3-(2-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate as a white solid, 0.34 g.

$^1$H NMR (DMSO-d$_6$): $\delta$ 1.20 (t, $J$ = 7.1 Hz, 3H), 2.35 (s, 3H), 2.55 (s, 3H), 4.00 (s, 2H), 4.20 (q, $J$ = 7.1 Hz, 2H), 4.90 (s, 2H), 6.80 (m, 1H), 6.90 (m, 1H), 6.95-7.00 (m, 1H), 7.20-7.30 (m, 2H), 7.45-7.50 (m, 1H).

Preparation (9d) [3-(2-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

A suspension of ethyl [3-(2-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate (0.34 g) in methanol (3 ml) was treated with 4 M aqueous sodium hydroxide solution (2 ml) and the resulting mixture stirred at room temperature for two hours. The pH of the solution was adjusted to ~ 1 by the addition of dilute hydrochloric acid and the resulting solid was collected by filtration and washed with water. Purification of the product by flash chromatography on silica gel, eluting with a mixture of dichloromethane / methanol / acetic acid / water
(300:20:3:2 by volume) gave [3-(2-chlorobenzyl)-4,7-dimethyl-2-oxo-2/-/-
chromen-5-yloxy]acetic acid as a white solid, 0.13 g.

$^1$H NMR (DMSO-d$_6$): $\delta$ 2.35 (s, 3H), 2.55 (s, 3H), 4.00 (s, 2H), 4.80 (s, 2H), 6.80
(m, 1H), 6.85 (m, 1H), 6.95-7.00 (m, 1H), 7.20-7.25 (m, 2H), 7.70 (m, 1H), 13.10
(br s, 1H).

MS: ESI (+ve) (Method A): 373 (M+H)$^+$, Retention time 11.5 min.

Example 10: [3-(3-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-
yloxy]acetic acid

Preparation (10a) ethyl 2-(3-methoxybenzyl)acetoacetate

Ethyl 2-(3-methoxybenzyl)acetoacetate was prepared from the reaction between
ethyl acetoacetate (1.0 g) and 3-methoxybenzyl chloride (1.1 ml) following the
method described in Preparation (5a) as a colourless oil, 0.55 g.

$^1$H NMR (CDCl$_3$): $\delta$ 1.20 (t, J = 7.2 Hz, 3H), 2.20 (s, 3H), 3.10 (m, 2H), 3.75 (m,
4H), 4.10-4.20 (m, 2H), 6.70-6.75 (m, 3H), 7.15 (m, 1H).

Preparation (10b) 5-hydroxy-3-(3-methoxybenzyl)-4,7-dimethylchromen-2-one

5-Hydroxy-3-(3-methoxybenzyl)-4,7-dimethylchromen-2-one was prepared from
the reaction between ethyl 2-(3-methoxybenzyl)acetoacetate (0.35 g) and 5-
methylbenzene-1,3-diol (0.13 g) following the method described in Preparation
(5b) as an orange solid, 0.16 g.
1\textsuperscript{H} NMR (DMSO-d\textsubscript{6}): $\delta$ 2.25 (s, 3H), 2.55 (s, 3H), 3.70 (s, 3H), 3.90 (s, 2H), 6.60-6.75 (m, 5H), 7.15 (m, 1H), 10.5 (s, 1H).

Preparation (10c) ethyl [3-(3-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate

Ethyl [3-(3-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate was prepared by the reaction between 5-hydroxy-3-(3-methoxybenzyl)-4,7-dimethyl-chromen-2-one (0.16 g) and ethyl bromoacetate (0.14 ml) following the method described in Preparation (5c). The crude product was purified by flash chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane (1:3 by volume), to give ethyl [3-(3-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate as a white solid, 0.035 g.

$\text{^1} \text{H NMR (DMSO-d6): } \delta$ 1.20 (t, $J = 7.2$ Hz, 3H), 2.35 (s, 3H), 2.60 (s, 3H), 3.70 (s, 3H), 3.95 (s, 2H), 4.20 (q, $J = 7.2$ Hz, 2H), 4.90 (s, 2H), 6.756.85 (m, 5H), 6.15-6.70 (m, 1H).

Preparation (1Od) [3-(3-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

[3-(3-Methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid was prepared by the hydrolysis of ethyl [3-(3-methoxybenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate (0.032 g) following the method described in Preparation (5d) as a white solid, 0.09 g.

$\text{^1} \text{H NMR (DMSO-d6): } \delta$ 2.35 (s, 3H), 2.60 (s, 3H), 3.70 (s, 3H), 3.95 (s, 2H), 4.80 (s, 2H), 6.75-6.85 (m, 5H), 7.15-7.20 (m, 1H), 13.2 (br s, 1H).

MS: ESI (+ve) (Method A): 369 (M+H)$^+$, Retention time 10.7 min.
Example 11: [3-(3-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

Preparation (11a) ethyl 2-(3-chlorobenzyl)acetoacetate

The reaction between ethyl acetoacetate (1.3 g) and 3-chlorobenzyl bromide (2.1 g) using the method described in Preparation (8a) gave ethyl 2-(3-chlorobenzyl)acetoacetate as a colourless oil, 1.5 g.

\[ \text{\textsuperscript{1}H NMR (CDCl}_3\text{): } \delta 1.20 \text{ (t, J = 7.2 Hz, 3H), } 2.20 \text{ (s, 3H), } 3.10 \text{ (m, 2H), } 3.75 \text{ (t, J = 7.5 Hz, 1H), } 4.20 \text{ (m, 2H), } 7.05-7.10 \text{ (m, 1H), } 7.15-7.20 \text{ (m, 3H).} \]

Preparation (11b) 3-(3-chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one

The reaction between 5-methylbenzene-1,3-diol (0.6 g), phosphorus oxychloride (5.5 ml), and ethyl 2-(3-chlorobenzyl)acetoacetate (1.5 g) using the method described in Preparation (8b) gave 3-(3-chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one as a white solid, 0.12 g.

\[ \text{\textsuperscript{1}H NMR (DMSO-d}_6\text{): } \delta 2.25 \text{ (s, 3H), } 2.60 \text{ (s, 3H), } 3.95 \text{ (s, 2H), } 6.60 \text{ (m, 1H), } 6.65 \text{ (m, 1H), } 7.15 \text{ (m, 1H), } 7.25-7.35 \text{ (m, 3H), } 10.55 \text{ (br s, 1H).} \]

Preparation (11c) ethyl [3-(3-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate

A mixture of 3-(3-chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one (0.12 g), ethyl bromoacetate (0.070 g) and potassium carbonate (0.01 g) in acetone (5
ml_) was stirred at 70°C for two hours. After cooling to room temperature, water (~ 2 ml_) was added and the mixture evaporated to low bulk. The residue was diluted with water, and the resulting precipitate was collected by filtration, washed with water, and then with cyclohexane, and dried to give ethyl [3-(3-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate as a white solid, 0.11 g.

1H NMR (DMSO-d6): δ 1.20 (t, J = 7.0 Hz, 3H), 2.35 (s, 3H), 2.65 (s, 3H), 4.00 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H), 4.90 (s, 2H), 6.80 (m, 1H), 6.85 (m, 1H), 7.15 (m, 1H), 7.25-7.30 (m, 3H).

Preparation (11d) [3-(3-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]-acetic acid

A suspension of ethyl [3-(3-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate (0.1 g) in methanol (3 ml) was treated with 4 M aqueous sodium hydroxide solution (1 ml) and allowed to stir at room temperature for six hours. The pH of the solution was adjusted to ~ 1 by the addition of dilute hydrochloric acid and the methanol was removed by evaporation. The resulting solid was collected by filtration, washed with water, and dried. LC-MS analysis indicated the presence of a small amount of ring opened by-product, 3-(2-carboxymethoxy-6-hydroxy-4-methylphenyl)-2-(3-chlorobenzyl)but-2-enoic acid, so the solid was dissolved in dioxane (5 ml) and treated with 4 M hydrogen chloride in dioxane (2 ml). After standing for 45 minutes LC-MS analysis indicated the presence of only one compound. The solution was evaporated to dryness and the residue was triturated with water. The resulting solid was collected by filtration, washed with water, and dried to give [3-(3-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid as a white solid, 0.070 g.

1H NMR (DMSO-d6): δ 2.35 (s, 3H), 2.65 (s, 3H), 4.00 (s, 2H), 4.80 (s, 2H), 6.75 (m, 1H), 6.85 (m, 1H), 7.15 (m, 1H), 7.25-7.30 (m, 3H), 13.2 (br s, 1H).

MS: ESI (+ve) (Method A): 373 (M+H)+, Retention time 10.7 min.
Example 12: 3-(3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)propionic acid

Preparation (12a) 3-benzyl-4,7-dimethyl-5-(trifluoromethanesulfonyloxy)chromen-2-one

3-Benzyl-5-hydroxy-4,7-dimethylchromen-2-one (compound of Preparation (1a), 4.1 g) was suspended in anhydrous dichloromethane (100 ml) and this solution was placed under an atmosphere of nitrogen and cooled in a cardice / acetone bath. This solution was treated successively with 2,6-lutidine (4.1 mL) and triflic anhydride (3.0 mL) whilst keeping the internal temperature at or below -60°C. The resulting mixture was stirred at -60°C for 45 minutes, and then allowed to warm to room temperature over about 30 minutes. The reaction mixture was diluted with water and then treated with saturated aqueous sodium hydrogen carbonate solution. The layers were separated and the organic layer was washed with 1 M aqueous citric acid solution, then with water, dried over magnesium sulfate, and evaporated. The resulting brown oil was combined with the crude product from a previous reaction carried out on the same scale, and this material was purified by flash chromatography on silica gel, eluting with a gradient mixture of ethyl acetate in pentane to give 3-benzyl-4,7-dimethyl-5-(trifluoromethanesulfonyloxy)chromen-2-one as a pale yellow solid, 5.8 g.

\[ ^1H \text{ NMR (DMSO-d6): } \delta 2.45 \text{ (s, 3H), 2.55 (s, 3H), 4.05 (s, 2H), 7.15-7.30 (m, 6H), 7.45 (m, 1H).} \]

Preparation (12b) 3-(3-benzyl-4,7-dimethyl)-2-oxo-2H-chromen-5-yl)acrylic acid
3-Benzyl-4,7-dimethyl-5-(trifluoromethanesulfonyloxy)chromen-2-one (0.50 g) was dissolved in \(m/m\)-dimethylformamide (10 ml) and this solution was treated successively with acrylic acid (0.42 ml), triethylamine (0.21 ml), palladium (2) acetate (0.015 g), and 1,10-phenanthroline (0.013 g). The resulting mixture was heated in the microwave reactor at 180°C for 15 minutes. After cooling to room temperature the mixture was diluted with ethyl acetate and this solution was washed with dilute hydrochloric acid, dried over magnesium sulfate, and evaporated. The reaction was repeated on the same scale, and the combined products were purified by flash chromatography on silica gel, eluting with a gradient mixture of ethyl acetate in pentane (10 - 100% ethyl acetate by volume), followed by a gradient mixture of methanol in ethyl acetate (5 - 10% by volume), to give a yellow solid, 0.55 g. This solid was recrystallised from methanol to give 3-(3-benzyl-4,7-dimethyl)-2-oxo-2H-chromen-5-yl)acrylic acid as a cream solid, 0.20 g.

\[ ^1H \text{ NMR (DMSO-d6): } \delta 2.40 (s, 3H), 2.50 (s, 3H), 4.0 (s, 2H), 6.15 (d, J = 15.6 \text{ Hz}, 1H), 7.15-7.30 (m, 7H), 8.15 (d, J = 15.6 \text{ Hz}, 1H), 12.5 (or S, 1H). \]

Preparation (12c) 3-(3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)propionic acid

A mixture of 3-(3-benzyl-4,7-dimethyl)-2-oxo-2H-chromen-5-yl)acrylic acid (0.10 g) and 10% w/w palladium on charcoal (0.005 g) in ethanol (7.5 ml) was stirred under an atmosphere of hydrogen at room temperature overnight. The spent catalyst was removed by filtration, fresh catalyst (0.005 g) was added, and reaction continued for a further 24 hours. The spent catalyst was removed by filtration and the filtrate was evaporated to give a white solid. This product was dissolved in tetrahydrofuran and the solution treated with sufficient pentane to produce a precipitate, which was collected by filtration and dried to give 3-(3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)propionic acid as a white solid, 0.065 g.
Example 13: [3-(4-fluorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

Preparation (13a) ethyl 2-(4-fluorobenzyl)acetoacetate

The reaction between ethyl acetoacetate (1.3 g) and 4-fluorobenzyl bromide (1.9 g) using the method described in Preparation (8a) gave ethyl 2-(4-fluorobenzyl)acetoacetate as a colourless oil, 1.5 g.

Preparation (13b) 3-(4-fluorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one

The reaction between 5-methylbenzene-1,3-diol (0.60 g), phosphorus oxychloride (5.5 mL), and ethyl 2-(4-fluorobenzyl)acetoacetate (1.5 g) using the method described in Preparation (8b) gave 3-(4-fluorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one as a white solid, 1.0 g.
Preparation (13c) Ethyl [3-(4-fluorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate

Ethyl [3-(4-fluorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate was prepared by the reaction between 3-(4-fluorobenzyl)-5-hydroxy-4,7-dimethyl-chromen-2-one (0.98 g) and ethyl bromoacetate (0.73 ml) following the method described in Preparation (5c) as a white solid, 1.1 g.

1H NMR (DMSO-d6): δ 1.20 (t, J = 7.2 Hz, 3H), 2.35 (s, 3H), 2.60 (s, 3H), 3.95 (S, 2H), 4.20 (q, J = 7.0 Hz, 2H), 4.90 (s, 2H), 6.80 (m, 1H), 6.85 (m, 1H), 7.05-7.10 (m, 2H), 7.20-7.25 (m, 2H).

Example 14: (4,7-dimethyl-2-oxo-3-phenethyl-2H-chromen-5-yloxy)acetic acid

Preparation (13d) [3-(4-fluorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

[3-(4-Fluorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid was prepared from the hydrolysis of ethyl [3-(4-fluorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate (1.1 g) following the method described in Preparation (5d) as a white solid, 0.76 g.

1H NMR (DMSO-d6): δ 2.35 (s, 3H), 2.65 (S, 3H), 3.95 (s, 2H), 4.80 (s, 2H), 6.75 (m, 1H), 6.85 (m, 1H), 7.05-7.10 (m, 2H), 7.20-7.25 (m, 2H), 13.1 (br s, 1H) MS: ESI (+ve) (Method A): 357 (M+H) Retention time 11.0 min.
Preparation (14a) ethyl 2-(phenethyl)acetoacetate

The reaction between ethyl acetoacetate (1.3 g) and phenethyl bromide (1.9 g) using the method described in Preparation (8a) gave ethyl 2-(phenethyl)acetoacetate as a colourless oil, 1.0 g.

\(^1\)H NMR (CDCl\(_3\)) \(\delta \): 1.25 (t, J = 7.2 Hz, 3H), 2.15-2.20 (m, 5H), 2.55-2.70 (m, 2H), 3.40 (t, J = 7.2 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 7.15-7.30 (m, 5H).

Preparation (14b) 5-hydroxy-4,7-dimethyl-3-phenethylchromen-2-one

The reaction between 5-methylbenzene-1,3-diol (0.50 g), phosphorus oxychloride (5.5 ml), and ethyl 2-(phenethyl)acetoacetate (1.0 g) using the method described in Preparation (8b) gave 5-hydroxy-4,7-dimethyl-3-phenethylchromen-2-one as a white solid, 0.55 g.

\(^1\)H NMR (DMSO-d6): \(\delta \): 2.25 (s, 3H), 2.45 (s, 3H), 2.70 (m, 2H), 2.80 (m, 2H), 6.55 (m, 1H), 6.60 (m, 1H), 7.20-7.30 (m, 5H), 10.40 (s, 1H).

Preparation (14c) ethyl (4,7-dimethyl-2-oxo-3-phenethyl-2H-chromen-5-yloxy)acetate

Ethyl (4,7-dimethyl-2-oxo-3-phenethyl-2/-/-chromen-5-yloxy)acetate was prepared from the reaction between 5-hydroxy-4,7-dimethyl-3-phenethylchromen-2-one (0.54 g) and ethyl bromoacetate (0.41 ml) following the method described in Preparation (5c) as a white solid, 0.67 g.

\(^1\)H NMR (DMSO-d6): \(\delta \): 1.20 (t, J = 7.2 Hz, 3H), 2.35 (s, 3H), 2.50 (s, 3H), 2.70-2.75 (m, 2H), 2.80-2.85 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 4.90 (s, 2H), 6.75 (m, 1H), 6.80 (m, 1H), 7.15-7.30 (m, 5H).

Preparation (14d) (4,7-dimethyl-2-oxo-3-phenethyl-2/-/-chromen-5-yloxy)acetic acid
4,7-Dimethyl-2-oxo-3-phenethyl-2H-chromen-5-yloxy)acetic acid was prepared by the hydrolysis of ethyl 4,7-dimethyl-2-oxo-3-phenethyl-2H-chromen-5-yloxy)acetate following the method described in Preparation (5d) as a white solid, 0.48 g.

\[ ^1\text{H NMR (DMSO-d6): } \delta 2.35 \text{ (s, } 3\text{H}), 2.50 \text{ (s, } 3\text{H}), 2.70 \text{ (m, } 2\text{H}), 2.85 \text{ (m, } 2\text{H)}, 4.80 \text{ (s, } 2\text{H}), 6.75 \text{ (m, } 1\text{H}), 6.80 \text{ (m, } 1\text{H}), 7.15-7.30 \text{ (m, } 5\text{H}), 13.10 \text{ (br s, } 1\text{H}). \]

MS: ESI (+ve) (Method A): 353 (M+H)^+, Retention time 11.5 min.

**Example 15: (4,7-dimethyl-2-oxo-3-phenyl-2H-chromen-5-yloxy)acetic acid**

Preparation (15a) ethyl 2-phenylacetoacetate

Ethyl phenylacetate (2.0 g) was added dropwise under nitrogen at -78°C to a stirred solution of lithium bis(trimethylsilazide) in anhydrous tetrahydrofuran (30 ml). This mixture was stirred at -78°C for one hour, and was then treated with acetyl chloride (1.0 ml). The resulting mixture was stirred at -78°C for a further one and one-half hours, and was then poured onto a saturated aqueous ammonium chloride solution. The mixture was extracted with ether and the combined extracts were washed with an aqueous citric acid solution (10% w/v), followed by saturated sodium hydrogen carbonate solution, then dried over sodium sulfate and evaporated. Purification of the residue by flash chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane (1:8 by volume) gave ethyl 2-phenylacetoacetate as a colourless oil, 0.31 g.
Preparation (15b) 5-hydroxy-4,7-dimethyl-3-phenylchromen-2-one

5-Hydroxy-4,7-dimethyl-3-phenylchromen-2-one was prepared from the reaction between ethyl 2-phenylacetoacetate (0.03 g) and 5-methylbenzene-1,3-diol (0.14 g) following the method described in Preparation (5b). The crude product was purified by flash chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane (1:2 by volume), to give 5-hydroxy-4,7-dimethyl-3-phenylchromen-2-one as a pale brown semi-solid, 0.081 g.

Preparation (15c) ethyl (4,7-dimethyl-2-oxo-3-phenyl-2H-chromen-5-yloxy)acetate

Ethyl (4,7-dimethyl-2-oxo-3-phenyl-2H-chromen-5-yloxy)acetate was prepared from the reaction between 5-hydroxy-4,7-dimethyl-3-phenylchromen-2-one (0.075 g) and ethyl bromoacetate (0.063 ml) following the method described in Preparation (5c). The crude product was purified by flash chromatography on silica gel eluting with a mixture of ethyl acetate and cyclohexane (1:3 by volume) to give ethyl (4,7-dimethyl-2-oxo-3-phenyl-2H-chromen-5-yloxy)acetate as a white solid, 0.019 g.

Preparation (15d) (4,7-dimethyl-2-oxo-3-phenyl-2H-chromen-5-yloxy)acetic acid

(4,7-Dimethyl-2-oxo-3-phenyl-2H-chromen-5-yloxy)acetic acid was prepared by hydrolysis of ethyl (4,7-dimethyl-2-oxo-3-phenyl-2H-chromen-5-yloxy)acetate (0.019 g) following the method described in Preparation (5d) as a white solid, 0.0074 g.
$^1$H NMR (DMSO-d$_6$): $\delta$ 2.35 (s, 3H), 2.40 (s, 3H), 4.85 (s, 2H), 6.80 (m, 1H), 6.85 (m, 1H), 7.25-7.30 (m, 2H), 7.35-7.45 (m, 3H), 13.10 (br s, 1H).

MS: ESI (+ve) (Method A): 325 (M+H)$^+$, Retention time 10.1 min.

Example 16: [3-(4-cyanobenzyl)-4,7-dimethyl-2-oxo-2Afchromen-5-yloxy]acetic acid

Preparation (16a) ethyl 2-(4-cyanobenzyl)acetoacetate.

A suspension of potassium tert-butoxide (1.1 g) and tert-butanol (0.10 mL) in anhydrous tetrahydrofuran (25 mL) was flushed with nitrogen and cooled in an ice-bath. Ethyl acetoacetate (1.3 g) was added and the resulting clear solution stirred in the ice-bath for 30 minutes. 4-Cyanobenzyl bromide (2.0 g) was added and the resulting mixture stirred at 70°C overnight. After cooling to room temperature water (~20 mL) was added and the mixture evaporated to low bulk. The residue was partitioned between ethyl acetate and water, the layers separated, and the organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and evaporated. Crystallisation of the residue from a mixture of ethyl acetate and cyclohexane gave 0.85 g of a white solid identified as ethyl 2,2-bis(4-cyanobenzyl)acetoacetate. The mother liquors from the crystallisation were evaporated to dryness and the residue purified by flash chromatography on silica gel, eluting with a gradient mixture of ethyl acetate in cyclohexane (15-30% by volume) to give ethyl 2-(4-cyanobenzyl)acetoacetate as a colourless oil, 0.75 g.
1H NMR (CDCl₃): δ 1.20 (t, J = 7.0 Hz, 3H), 2.20 (s, 3H), 3.15-3.25 (m, 2H), 3.75 (t, J = 7.4 Hz, 1H), 4.10-4.20 (m, 2H), 7.30-7.35 (m, 2H), 7.55-7.60 (m, 2H).

Preparation (16b) 4-(5-hydroxy-4,7-dimethyl-2-oxo-2H-chromen-3-ylmethyl)-benzonitrile

Ethyl 2-(4-cyanobenzyl)acetoacetate (0.75 g) and 5-methylbenzene-1,3-diol (0.40 g) were dissolved in phosphorus oxychloride (3.5 mL) under an atmosphere of nitrogen and the mixture stirred at room temperature overnight. The reaction mixture was evaporated to dryness and the residue partitioned between ethyl acetate and water. The layers were separated and the organic layer was washed with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated. Trituration of the residue with water gave a solid, which was collected by filtration, washed with ether and cyclohexane, and dried to give 4-(5-hydroxy-4,7-dimethyl-2-oxo-2H-chromen-3-ylmethyl)-benzonitrile as a dark red solid, 0.28 g.

1H NMR (DMSO-d₆): δ 2.25 (s, 3H), 2.55 (s, 3H), 4.00 (s, 2H), 6.60 (m, 1H), 6.65 (m, 1H), 7.40 (m, 2H), 7.75 (m, 2H), 10.55 (s, 1H).

Preparation (16c) ethyl [3-(4-cyanobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate

A mixture of 4-(5-hydroxy-4,7-dimethyl-2-oxo-2H-chromen-3-ylmethyl)-benzonitrile (0.28 g), ethyl bromoacetate (0.17 g) and potassium carbonate (0.28 g) in acetone (5 mL) was stirred at reflux for two hours. After cooling to room temperature water (~ 5 mL) was added and the mixture evaporated to low bulk. The residue was triturated with water and the resulting solid was collected by filtration, washed with water and then with ether, to give ethyl [3-(4-cyanobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate as a beige solid, 0.12 g.
H NMR (DMSO-d6): δ 1.20 (t, J = 7.2 Hz, 3H), 2.35 (s, 3H), 2.60 (s, 3H), 4.05 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.90 (s, 2H), 6.80 (m, 1H), 6.85 (m, 1H), 7.40 (m, 2H), 7.75 (m, 2H).

Preparation (16d) [3-(4-cyanobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

Ethyl [3-(4-cyanobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate (0.12 g) was suspended in methanol (2.5 ml) and treated with a solution of lithium hydroxide hydrate (0.026 g) in water (0.61 ml). After stirring at room temperature for 90 minutes a clear solution was produced, followed by a heavy precipitate. The pH of the mixture was adjusted to ~ 1 by the addition of dilute hydrochloric acid and the solid was collected by filtration, washed with water and ether, and dried to give [3-(4-cyanobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid as an off-white solid, 0.070 mg.

H NMR (DMSO-d6): δ 2.35 (s, 3H), 2.60 (s, 3H), 4.05 (s, 2H), 4.80 (s, 2H), 6.75 (m, 1H), 6.85 (m, 1H), 7.40 (m, 2H), 7.75 (m, 2H), 13.00 (br s, 1H).

MS: ESI (+ve) (Method A): 364 (M+H)$^+$, Retention time 10.3 min.

Example 17: [3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

Preparation (17a) ethyl 2-(4-bromobenzyl)acetoacetate
The reaction between ethyl acetoacetate (15 ml) and 4-bromobenzyl bromide (30 g) using the method described in Preparation (8a) gave ethyl 2-(4-bromobenzyl)acetoacetate as a colourless oil, 20.6 g.

$^1$H NMR (CDCl$_3$): $\delta$ 1.20 (t, $J = 7.1$ Hz, 3H), 2.20 (s, 3H), 3.10-3.15 (m, 2H), 3.70 (t, $J = 7.8$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 7.05 (m, 2H), 7.40 (m, 2H).

Preparation (17b) 3-(4-bromobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one

The reaction between 5-methylbenzene-1,3-diol (6.6 g) and ethyl 2-(4-bromobenzyl)acetoacetate (21 g) following the method described in Preparation (8b) gave 3-(4-bromobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one as a white solid, 10 g.

$^1$H NMR (DMSO-d$_6$): $\delta$ 2.25 (s, 3H), 2.55 (s, 3H), 3.90 (s, 2H), 6.60 (m, 2H), 7.15 (m, 2H), 7.45 (m, 2H), 10.55 (br s, 1H).

Preparation (17c) ethyl [3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate

The reaction between 3-(4-bromobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one (9.8 g) and ethyl bromoacetate (3.3 ml) following the method described in Preparation (8c) gave ethyl [3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetate as a white solid, 10.5 g.

$^1$H NMR (DMSO-d$_6$): $\delta$ 1.20 (t, $J = 7.1$ Hz, 3H), 2.35 (s, 3H), 2.60 (s, 3H), 3.95 (s, 2H), 4.20 (q, $J = 7.1$ Hz, 2H), 4.90 (s, 2H), 6.75 (m, 1H), 6.80 (m, 1H), 7.15 (m, 2H), 7.45 (m 2H).

Preparation (17d) [3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]-acetic acid
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5 M aqueous sodium hydroxide solution (200 ml) was added to a stirred suspension of ethyl [3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetate (10.5 g) in ethanol (200 ml), and the mixture stirred at room temperature for one hour, by which time complete dissolution had occurred. The clear solution was evaporated to low bulk and the residue was taken to pH ~ 1 by the addition of concentrated hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and dried to give [3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid as a white solid, 9.7 g.

1H NMR (DMSO-d6): δ 2.35 (s, 3H), 2.60 (s, 3H), 3.95 (s, 2H), 4.80 (s, 2H), 6.75 (m, 1H), 6.80 (m, 1H), 7.15 (m, 2H), 7.45 (m, 2H).

MS: ESI (+ve) (Method A): 419 (M+H)+, Retention time 12.3 min.

Example 18: [3-(4-fert-butylbenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

Preparation (18a) ethyl 2-(4-fert-butylbenzyl)acetoacetate

The reaction between ethyl acetoacetate (2.8 mL) and 4-terf-butylbenzyl bromide (4.0 mL) following the method described in Preparation (8a) gave ethyl 2-(4-tert-butylbenzyl)acetoacetate as a colourless oil, 3.9 g.

1H NMR (CDCl3): δ 1.20 (t, J = 7.0 Hz, 3H), 1.30 (s, 9H), 2.20 (s, 3H), 3.10 (m, 2H), 3.75 (t, J = 7.8 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 7.10 (m, 2H), 7.30 (m, 2H).
Preparation (18b) 3-(4-tert-butylbenzyl)-5-hydroxy-4,7-dimethylchromen-2-one

The reaction between 5-methylbenzene-1,3-diol (1.4 g) and ethyl 2-(4-tert-butylbenzyl)acetoacetate (3.9 g) following the method described in Preparation (8b), followed by purification of the crude material by flash chromatography on silica gel, eluting with a gradient mixture of ethyl acetate in pentane (1:9 to 1:1 by volume), gave 3-(4-tert-butylbenzyl)-5-hydroxy-4,7-dimethylchromen-2-one as a white solid, 2.6 g.

1H NMR (DMSO-d6): δ 1.25 (s, 9H), 2.30 (s, 3H), 2.65 (s, 3H), 4.00 (s, 2H), 6.45 (m, 1H), 7.20 (m, 2H), 7.25 (m, 2H).

Preparation (18c) ethyl [3-(4-tert-butylbenzyl)-4,7-dimethyl]-2-oxo-2H-chromen-5-yloxy]acetate

The reaction between 3-(4-tert-butylbenzyl)-5-hydroxy-4,7-dimethylchromen-2-one (2.6 g) and ethyl bromoacetate (0.94 ml) following the method described in Preparation (8c) gave ethyl [3-(4-tert-butylbenzyl)-4,7-dimethyl]-2-oxo-2H-chromen-5-yloxy]acetate as a colourless oil, 3.0 g.

1H NMR (CDCl3): δ 1.25-1.30 (m, 12H), 2.35 (s, 3H), 2.70 (s, 3H), 4.00 (s, 2H), 4.25 (q, J = 7.0 Hz, 2H), 4.65 (s, 2H), 6.40 (m, 1H), 6.80 (m, 1H), 7.20 (m, 2H), 7.25 (m 2H).

Preparation (18d) [3-(4-tert-butylbenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid

5 M aqueous sodium hydroxide solution (100 ml) was added to a stirred suspension of ethyl [3-(4-tert-butylbenzyl)-4,7-dimethyl]-2-oxo-2H-chromen-5-yloxy]acetate (3.0 g) in ethanol (100 ml), and the resulting mixture stirred at room temperature for three hours. The organic solvent was removed by evaporation and the residue taken to pH = 1 by the addition of concentrated hydrochloric acid to produce an oily precipitate. After stirring for one hour the
product was collected by filtration, washed with water, and dried to give a tan solid. Crystallisation from methanol gave [3-(4-tert-butylbenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid as a white solid, 0.70 g.

$^1$H NMR (DMSO-d$_6$): $\delta$ 1.25 (s, 9H), 2.35 (s, 3H), 2.65 (s, 3H), 3.90 (s, 2H), 4.80 (s, 2H), 6.75 (m, 1H), 6.80 (m, 1H), 7.10 (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 13.00 (br s, 1H).

MS: ESI (+ve) (Method A): 395 (M+H)$^+$, Retention time 12.9 min.

Example 19: $N$-[2-[3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetyl]benzenesulfonamide

A mixture of [3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid (compound of Preparation (17d), 0.50 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.29 g), benzenesulfonamide (0.24 g), and 4-(N,N-dimethylamino)pyridine (0.18 g) in dichloromethane (25 mL) was stirred at room temperature overnight. The reaction mixture was treated with dilute hydrochloric acid (~ 100 mL) and the resulting precipitate collected by filtration, washed with dilute hydrochloric acid, then water, and then dried. Purification by preparative reverse-phase HPLC using a gradient over 30 minutes of acetonitrile in water (60% to 95% of organic modifier) gave $N$-[2-[3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetyl]benzenesulfonamide as a white solid, 0.064 g.
$^1$H NMR (DMSO-d$_6$): $\delta$ 2.25 (s, 3H), 2.50 (s, 3H), 3.90 (s, 2H), 4.80 (s, 2H), 6.45 (m, 1H), 6.80 (m, 1H), 7.15 (m, 2H), 7.45 (m, 2H), 7.60-7.65 (m, 2H), 7.70-7.75 (m, 1H), 7.95 (m, 2H), 12.55 (br s, 1H).

MS: ESI (+ve) (Method A): 558 (M+H)$^+$, Retention time 13.3 min.

Example 20: (3-biphenyl-4-ylmethyl-4,7-dimethyl-2-oxo-2-Afchromen-5-yloxy)acetic acid

Preparation (20a) (3-biphenyl-4-ylmethyl-4,7-dimethyl-2-oxo-2/-/-chromen-5-yloxy)acetic acid

A mixture of [3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2/-/-chromen-5-yloxy]acetic acid (compound of Preparation (17d), 0.30 g), phenylboronic acid (0.13 g), and tetra/c/s(triphenylphosphine)palladium (0) (0.042 g) in dioxane (3.0 ml) was treated with 2 M aqueous caesium carbonate solution (3.0 ml) and the mixture heated in the Microwave reactor for five minutes at 100oC. After cooling to room temperature the reaction mixture was taken to pH ~ 1 by the addition of dilute hydrochloric acid and then extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated. Purification of the residue by flash chromatography on silica gel, eluting with a mixture of acetic acid and ethyl acetate in dichloromethane (1:30:69 by volume), followed by preparative reverse-phase HPLC using a gradient over 40 minutes of acetonitrile in water (40% to 90% of organic
modifier) gave (3-biphenyl-4-ylmethyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetic acid as a white solid, 0.10 g.

\(^1\)H NMR (DMSO-d6): \(\delta\) 2.35 (s, 3H), 2.65 (s, 3H), 4.00 (s, 2H), 4.80 (s, 2H), 6.75 (m, 1H), 6.85 (m, 1H), 7.25-7.35 (m, 3H), 7.45 (m, 2H), 7.55-7.65 (m, 4H).

MS: ESI (+ve) (Method A): 415 (M+H\(^+\)), Retention time 12.3 min.

Example 21: \(\text{N}^{\text{N}}\)-[2-[3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetyl]methanesulfonamide

Preparation (21a) \(\text{N}^{\text{N}}\)-[2-[3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetyl]methanesulfonamide

The reaction between [3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetic acid (compound of Preparation (17d), 0.30 g) and methanesulfonamide (0.085 g) following the method described in Preparation (19a) gave \(\text{N}^{\text{N}}\)-[2-[3-(4-bromobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy]acetyl]methanesulfonamide as a white solid, 0.030 g.

\(^1\)H NMR (DMSO-d6): \(\delta\) 2.35 (s, 3H), 2.60 (s, 3H), 3.25 (s, 3H), 3.95 (s, 2H), 4.80 (s, 2H), 6.65 (s, 1H), 6.85 (s, 1H), 7.20 (m, 2H), 7.45 (m, 2H).

MS: ESI (+ve) (Method A): 496 (M+H\(^+\)), Retention time 11.5 min.
Example 22: (4-benzyl-3,7-dimethyl-2-oxo-2/+-chromen-5-yloxy)acetic acid

Preparation (22a) ethyl 2-methyl-3-oxo-4-phenylbutyrate

Activated zinc powder (67 g) was suspended in anhydrous tetrahydrofuran (200 ml) under an atmosphere of nitrogen. A few drops of benzyl cyanide and one crystal of iodine were added, and the mixture sonicated until the reaction was initiated. The mixture was then brought to reflux with stirring, and benzyl cyanide (2.0 ml) was added in one portion, followed by the dropwise addition over one hour of ethyl 2-bromopropionate (4.9 ml). The mixture was then stirred at reflux for a further two hours, allowed to cool to room temperature, and quenched by pouring onto saturated aqueous potassium carbonate solution (100 ml). After stirring for 30 minutes the layers were separated and the organic layer was stirred with 1 M hydrochloric acid (200 mL) for 30 minutes. The mixture was then evaporated to low bulk and partitioned between ethyl acetate and aqueous sodium hydrogen carbonate solution. The layers were separated and the organic layer was dried over sodium sulfate and evaporated. Purification of the residue by flash chromatography on silica gel, eluting with a mixture of ethyl acetate and pentane (1:19 by volume) gave ethyl 2-methyl-3-oxo-4-phenylbutyrate as a colourless oil, 1.9 g.

Preparation (22b) 4-benzyl-5-hydroxy-3,7-dimethylchromen-2-one

A mixture of 5-methylbenzene-1,3-diol (0.82 g), ethyl 2-methyl-3-oxo-4-phenylbutyrate (1.9 g) and phosphorus oxychloride (0.61 mL) in toluene (25 mL) was stirred at room temperature under a nitrogen atmosphere for 48 hours. The reaction mixture was diluted with ethyl acetate, washed with water and saturated
aqueous sodium chloride solution, dried over sodium sulfate and evaporated to give a yellow oil. Purification by flash chromatography on silica gel, eluting with a gradient mixture of ethyl acetate in pentane (1:9 to 1:5 by volume) gave 4-benzyl-5-hydroxy-3,7-dimethylchromen-2-one as a tan semi-solid, 0.10 g.

MS: ESI (+ve) (Method B): 281 (M+H)^+. Retention time 3.3 min.

Preparation (22c) ethyl (4-benzyl-3,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetate

A mixture of 4-benzyl-5-hydroxy-3,7-dimethylchromen-2-one (0.10 g), ethyl bromoacetate (0.044 mL), and potassium carbonate (0.059 g) in acetone (20 mL) was stirred at 60°C overnight. After cooling to room temperature the reaction mixture was evaporated to dryness and the residue partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with water and saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated to give ethyl (4-benzyl-3,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetate as a pale yellow solid, 0.020 g.

MS: ESI (+ve) (Method B): 367 (M+H)^+, Retention time 4.0 min.

Preparation (22d) (4-benzyl-3,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetic acid

A suspension of ethyl (4-benzyl-3,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetate (0.020 g) in ethanol (20 mL) was treated with 5 M aqueous sodium hydroxide solution (5 mL) and the resulting mixture stirred at room temperature for one hour. The ethanol was removed by evaporation and the remaining aqueous layer was taken to pH ~ 1 by the addition of concentrated hydrochloric acid. The volume of this mixture was reduced to ~ 5 mL and the aqueous layer was removed by decantation. Purification of the residue by preparative reverse-phase HPLC using a gradient over 50 minutes of acetonitrile in water (40% to 75% of organic modifier) gave (4-benzyl-3,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetic acid as a white solid, 0.005 g.
1H NMR (CD3OD): δ 2.05 (s, 3H), 2.40 (s, 3H), 4.40 (s, 3H), 4.65 (s, 2H), 6.60 (s, 1H), 6.85 (s, 1H), 7.10-7.25 (m, 5H).

MS: ESI (+ve) (Method A): 339 (M+H)+, Retention time 10.3 min.

Example 23: [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yl]acetic acid

Preparation (23a) trifluoromethanesulfonic acid 3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yl ester

3-(4-Chlorobenzyl)-5-hydroxy-4,7-dimethylchromen-2-one (compound of Preparation (8b), 1.0 g) was suspended in anhydrous dichloromethane (10 mL) and this solution was placed under an atmosphere of nitrogen and cooled to 0°C. This solution was treated dropwise with a solution of pyridine (0.38 mL), dichloromethane (12 mL) and triflic anhydride (0.59 mL) whilst keeping the temperature at 0°C. The resulting mixture was stirred at 0°C for 1 hour, and then diluted with water and dichloromethane. The layers were separated and the organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and evaporated. The resulting orange oil was purified by flash chromatography on silica gel, eluting with a mixture of ethyl acetate in cyclohexane (15% by volume) to give trifluoromethanesulfonic acid 3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yl ester as a pale yellow solid, 1.1 g.
1H NMR (DMSO-d6): δ 2.45 (s, 3H), 2.60 (s, 3H), 4.05 (s, 2H), 7.05-7.40 (m, 6H).
MS: ESI (+ve) (Method B): 447 (M+H)^+, Retention time 4.7 min.

Preparation (23b) [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yl]acetic acid methyl ester

A mixture of trifluoromethanesulfonic acid 3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yl ester (1.1 g), tert-butyl (i-methoxyvinyloxy)dimethylsilane (1.7 mL), sodium acetate (0.25 g), tris(dibenzylideneacetone)dipalladium (0) (0.12 g), and 1,1'-bis(diphenylphosphino)ferrocene (0.07 g) in Λ,Λ/-dimethylformamide (15 mL) was heated by microwave irradiation at 120°C for twelve minutes. The reaction mixture was diluted with water, and this mixture was extracted with ethyl acetate. The combined organic layers were washed with 1 M aqueous hydrochloric acid solution, saturated aqueous sodium hydrogen carbonate solution, followed by saturated aqueous sodium chloride solution, then dried over sodium sulfate and evaporated to give a brown solid. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate in cyclohexane (10% by volume) gave [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yl]acetic acid methyl ester as a cream solid, 0.13 g.

1H NMR (DMSO-d6): δ 1.35 (s, 9H), 2.40 (s, 3H), 2.50 (s, 3H), 4.00 (s, 2H), 4.1 (s, 2H), 7.05 (m, 1H), 7.15-7.30 (m, 6H).
MS: ESI (+ve) (Method B): 371 (M+H)^- Retention time 4.1 min.

Preparation (23c) [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yl]acetic acid

A solution of [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yl]acetic acid methyl ester (1.3 g) in tetrahydrofuran (20 mL) was treated with 1 M aqueous sodium hydroxide solution (7 mL) and the resulting mixture stirred at room temperature for three hours. The tetrahydrofuran was removed by evaporation and the remaining aqueous layer was taken to pH ~ 2 by the addition of
concentrated hydrochloric acid and the resulting precipitate was collected by filtration, washed with water and dried to give [3-(4-chlorobenzyl)-4,7-dimethyl-2-oxo-2H-chromen-5-yl] acetic acid as a white solid, 0.26 g.

5 $^1$H NMR (DMSO-d6): $\delta$ 2.35 (s, 3H), 2.45 (s, 3H), 4.00 (s, 2H), 4.10 (s, 2H), 7.10 (m, 1H), 7.15 (m, 1H), 7.25 (m, 2H), 7.35 (m, 2H).

MS: ESI (+ve) (Method A): 357 (M+H)$^+$, Retention time 10.8 min.

**Biological Methods**

Compounds of the invention of formula [1] were tested using the following biological test methods to determine their ability to displace PGD$_2$ from the CRTH2 receptor and for their ability to antagonise the functional effects of PGD$_2$ at the CRTH2 receptor in a whole cell system.

**Radioligand Binding Assay**

The receptor binding assay is performed in a final volume of 200 µL binding buffer [10 mM BES (pH 7.4), 1 mM EDTA, 10 mM manganese chloride, 0.01% BSA] and 1 nM [3H]-PGD$_2$ (Amersham Biosciences UK Ltd). Ligands are added in assay buffer containing a constant amount of DMSO (1% by volume). Total binding is determined using 1% by volume of DMSO in assay buffer and non-specific binding is determined using 10 µM of unlabeled PGD$_2$ (Sigma). Human embryonic kidney (HEK) cell membranes (3.5 µg) expressing the CRTH2 receptor are incubated with 1.5 mg wheatgerm agglutinin SPA beads and 1 nM [3H]-PGD$_2$ (Amersham Biosciences UK Ltd) and the mixture incubated for 3 hours at room temperature. Bound [3H]-PGD$_2$ is detected using a Microbeta TRILUX liquid scintillation counter (Perkin Elmer). Compound IC$_{50}$ value is determined using a 6-point dose response curve in duplicate with a semi-log compound dilution series. IC$_{50}$Ocalculations are performed using Excel and XLfit (Microsoft), and this value is used to determine a Ki value for the test compound using the Cheng-Prusoff equation.

**Functional Assay: GTP$\gamma$S**

The GTP$\gamma$S Assay is performed in a final volume of 200 mL assay buffer (20mM HEPES pH 7.4, 10mM MgCl$_2$, 100mM NaCl, 10µg/mL saponin). DMSO concentrations are kept constant at 1% by volume. Human embryonic kidney
(HEK) cell membranes (3.5 µg) expressing the CRTH2 receptor are incubated with the compounds for 15 min at 30°C prior to addition of PGD₂ (30nM final concentration) and GTP (10µM final concentration). The assay solutions are then incubated for 30 minutes at 30°C, followed by addition of [³⁵S]-GTPγS (0.1nM final concentration). The assay plate is then shaken and incubated for 5 minutes at 30°C. Finally, SPA beads (Amersham Biosciences, UK) are added to a final concentration of 1.5mg/well and the plate shaken and incubated for 30 minute at 30°C. The sealed plate is centrifuged at 1000g for 10mins at 30°C and the bound [³⁵S]-GTPγS is detected on Microbeta scintillation counter (Perkin Elmer). Compound IC₅₀ value is determined using a 6-point dose response curve in duplicate with a semi-log compound dilution series. IC₅₀ calculations are performed using Excel and XLfit (Microsoft), and this value is used to determine a Ki value for the test compound using the Cheng-Prusoff equation.

**Biological Results:**

The compounds of the Examples above were tested in the CRTH2 radioligand binding described above; the compounds all have Ki values of less than 10µM in the binding assay. For example, compounds of Examples 4 and 23 have Ki values of 32 and 53 nM, respectively. The compounds also have Ki values of less than 10µM in the GTPγS functional assay. For example, compounds of Examples 4 and 23 have Ki values of 89 and 190 nM, respectively.
Claims

1. A compound, for use in therapy, of structural formula [1]

![Structural Formula](image)

5 in which:

- A represents a direct bond, an optionally substituted alkylene or alkenylene group, or a group of formula Z-(optionally substituted)alkylene;
- B represents a direct bond, an optionally substituted alkylene or alkenylene group, or a group of formula Z-(optionally substituted)alkylene or (optionally substituted)alkylene-Z;
- Z represents an oxygen atom, an NH or N-alkyl group, or a group of formula S(O)$_n$, in which $n = 0$ to 2;
- X represents a carboxylic acid, tetrazole, 3-hydroxyisoxazole, hydroxamic acid, phosphinate, phosphonate, phosphonamide, sulfonic acid or a group of formula C(=O)NHSO$_2$Wor SO$_2$NHC(=O)W;
- W represents an optionally substituted aryl or heteroaryl group or an optionally substituted alkyl or cycloalkyl group;
- Y represents an optionally substituted phenyl or 5- or 6-membered heteroaryl group; and
- $R^a$, $R^b$, and $R^c$ independently represent hydrogen, acyl, alkoxy, alkoxy carbonyl, alkylamino, alkylsulfanyl, alkylsulfonyl, alkythio, -NH$_2$, aminoalkyl, hydroxyalkyl, alkoxyalkyl, arylalkyl, cyano, dialkylamino, halo, haloalkoxy, haloalkyl, alkyl, alkenyl, -OH, optionally substituted aryl, optionally substituted heteroaryl, heterocycloalkyl, aminoacyl, aminosulfonyl, acylamino, sulfonlamino, heteroarylalkyl, cyclic amino, aryloxy, heteroaryloxy, arylalkyloxy or heteroarylalkyloxy;
- or a pharmaceutically acceptable salt thereof.
2. A compound as claimed in claim 1, wherein Y is optionally substituted pyridyl, pyrimidinyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, or pyrrolyl.

3. A compound as claimed in claim 1, wherein Y is optionally substituted phenyl.

4. A compound as claimed in claim 2 or claim 3, wherein optional substituents in Y are selected from fluoro, methylsulfonyl, ethylsulfonyl, carbamate, methylcarbamate, methylaninosulfonyle, ethylaninosulfonyle, methylsulfonylamino, ethylsulfonylamino, morpholin-1-ylsulfonyle, piperizin-1-ylsulfonyle, 4-methylpiperizin-1-ylsulfonyle, and tetrahydropyrrol-ylsulfonyle.

5. A compound as claimed in claim 2 or claim 3, wherein optional substituents in Y are selected from chloro, methyl, methoxy, fluoro, cyano, bromo, tert-butyl, and phenyl.

6. A compound as claimed in claim 3, wherein Y is 4-methylphenyle, 2-, 3- or 4-methoxyphenyle, 2-, 3-, or 4-chlorophenyle, 4-fluorophenyle, 4-bromophenyle, 4-phenylphenyle, 4-cyanophenyle, or 4-tert-butylphenyle.

7. A compound as claimed in any of the preceding claims, wherein the radical -B-Y is bonded to the carbon in the 3-position of the 2-oxo-2/-/-chromene ring system.

8. A compound as claimed in any of the preceding claims, wherein B is a bond, -CH₂⁻, or -CH₂CH₂⁻.

9. A compound as claimed in any of the preceding claims, wherein R_e is hydrogen, methyl or ethyl.

10. A compound as claimed in any of the preceding claims, wherein A is -CH₂⁻, -CH₂CH₂⁻, -OCH₂⁻, or -OCH₂CH₂CH₂⁻ wherein the oxygen is attached to the ring carrying R_a and R_b.

11. A compound as claimed in any of the preceding claims, wherein X is -CO₂H, -CONHSO₂CH₃, or -CONHSO₂Ph.  

12. A compound as claimed in any of the preceding claims, wherein R_a is in the 8-position and R_b is in the 7-position of the 2-oxo-2H-chromene ring system.

13. A compound as claimed in claim 12, wherein R_a is selected from hydrogen, chloro and fluoro.
14. A compound as claimed in claim 12 or claim 13, wherein \( R^b \) is selected from hydrogen, methyl, trifluoromethyl, chloro and fluoro.

15. A compound, as claimed in claim 1, which is the subject of any of the Examples herein, or a pharmaceutically acceptable salt thereof.

16. A compound as defined in claim 1, independent of use, excluding:

- 2-(7-methyl-2-oxo-4-phenyl-2H-chromen-5-yloxy)propionic acid;
- (7-methyl-2-oxo-4-phenyl-2H-chromen-5-yloxy)acetic acid;
- 2-(3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)propionic acid;
- 3-benzyl-4,7-dimethyl-2-oxo-2H-chromen-5-yloxy)acetic acid;
- (4,7-dimethyl-2-oxo-3-phenyl-2/-/-chromen-5-yloxy)acetic acid;
- and 2-(4,7-dimethyl-2-oxo-3-phenyl-2H-chromen-5-yloxy)propionic acid.

17. A compound as claimed in claim 16, as additionally defined in any of claims 2 to 15.

18. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims, together with a pharmaceutically acceptable carrier.

19. Use of a compound as claimed in any of claims 1 to 17, for the manufacture of a medicament for use in the treatment of a condition responsive to modulation of CRTH2 activity.

20. A method of treatment of a condition responsive to modulation of CRTH2 receptor activity, comprising administering to a patient suffering such condition an effective amount of a compound as defined in any of claims 1 to 17.

21. The use as claimed in claim 19 or a method as claimed in claim 20, wherein the condition is selected from asthma, chronic obstructive pulmonary disease, allergic airway syndrome, bronchitis, cystic fibrosis, emphysema and rhinitis.

22. The use as claimed in claim 19 or a method as claimed in claim 20, wherein the condition is selected from psoriasis, atopic and non-atopic dermatitis, Crohn's disease, ulcerative colitis, and irritable bowel disease.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

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

INV. C07D311/16 A61K31/352 A61P11/00 A61P17/06 A61P17/00

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, WPI Data, BEILSTEIN Data, CHEMABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<td>X</td>
<td>WO 99/00132 A (ORION CORP [FI]; PYSTYNEN JARMO [FI]; HAIKALA HEIMO [FI]; KAHEINEN PET) 7 January 1999 (1999-01-07) examples</td>
<td>1-22</td>
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D. Further documents are listed in the continuation of Box C

* 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

"I" later document published after the international filing date or priority date and not in conflict with the application but cited & understood 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: 11 October 2007

Date of mailing of the international search report: 22/10/2007

Name and mailing address of the ISA/

European Patent Office P B 5818 Patentlaan 2 NL-2280 HV RIJSWIJK

Tel (+31-70) 340-2040, Tx 31 651 epo ml,

Fax (+31-70) 340-3316

Authorized officer

Fazzi, Raffael l
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 20-22 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)

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**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 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
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