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(54) **Title:** COUMARIN DERIVATIVES USEFUL AS TNF α INHIBITORS

(57) **Abstract:** Novel compounds composition capable of inhibiting TNF α and having antiimmunoinflammatory and autoimmune properties useful in a pharmaceutical composition, such as for a drug containing this as an active ingredient; and a therapeutic method with the use of these novel compounds.



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SPECIFICATION**COUMARIN DERIVATIVES USEFUL AS TNF α INHIBITORS**5 **FIELD OF THE INVENTION**

This invention relates to novel coumarin compounds and their pharmaceutically acceptable salts, pharmaceutical compositions containing such compounds and the use of such compounds as TNF α inhibitors.

BACKGROUND

10 Tumor Necrosis Factor alpha or TNF α , is a pro-inflammatory cytokine secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli or external cellular stress. It is a key cytokine in the inflammation cascade causing the production and/or release of other cytokines and agents.

15 Excessive or unregulated TNF α production has been implicated in mediating or exacerbating a number of disease states. Decreasing TNF α levels thus constitutes a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological or malignant diseases. Collectively such disorders may be grouped as "immunoinflammatory maladies." These
20 "immunoinflammatory maladies" include, but are not restricted to rheumatoid arthritis, Paget's disease, osteoporosis, multiple myeloma, uveitis, acute and chronic myelogenous leukemia, pancreatic β cell destruction, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis,
25 anaphylaxis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I and type II diabetes, bone resorption diseases, graft vs. host reaction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, and malgias due to infection.

30 TNF α appears to be involved in bone resorption diseases, including arthritis. In rheumatoid arthritis, TNF α induce synoviocytes and chondrocytes to produce collagenase and neutral proteases, which leads to tissue destruction within the arthritic joints.

It has been reported that TNF α plays a role in head trauma, stroke and ischemia. The TNF α levels increased in the contused hemisphere in rat models of head trauma (Shohami et al., *J. Cereb. Blood Flow Metab.* 14, 615(1994)).

TNF α also plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiration failure caused by a fibrotic reaction.

TNF α blockage has been shown to be beneficial in rheumatoid arthritis and other diseases (Elliot et al., *Int. J. Pharmac.* 17(2), 141 (1995), Pisetsky, *N. Engl. J. Med.* 342(11), 810-1(2000)). Several approaches have been taken to block the effect of TNF α . One approach involves using soluble receptors for TNF α , which have demonstrated efficacy in animal models of TNF α mediated disease states. Enbrel®, a solubilized TNF α receptor, has shown efficacy against moderately to severely active rheumatoid arthritis and has been approved for use in those patients who have an inadequate response to one or more disease-modifying anti-rheumatic drugs. A second approach is to neutralize TNF α using a monoclonal antibody specific to TNF α . For instance, a TNF α -binding chimerical monoclonal antibody, Remicade™, has demonstrated improvement in swollen joint count in a human trial of rheumatoid arthritis and marked in conjunction with methotrexate for the treatment of patients with rheumatoid arthritis who have had an inadequate response to methotrexate alone. Suppression of the effects of TNF α has also been achieved through the utilization of steroids such as dexamethasone and prednisolone in the early experiments (Beutler et al., *Science* 234, 470-474 (1985); WO 92/11383).

High levels of TNF α are associated with Crohn's disease (von Dullemen et al., *Gastroenterology* 109, 129 (1995)) and clinical benefit has been achieved with TNF α antibody treatment. The TNF α -binding chimerical monoclonal antibody, Remicade™, has also been approved for use in treatment of Crohn's disease patients.

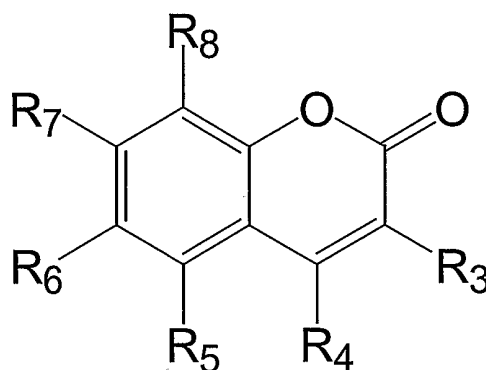
The transcription factor Nuclear Factor kB (NFkB) has been shown to regulate the production of many proinflammatory cytokines including but not limited TNF α and related proteins that are elevated in immunoinflammatory diseases (Grilli et al., *Int. Rev. Cytol.* 143, 1-62(1993)). The TNF α level and

transcription activity of NF κ B are influenced by a reciprocal feedback loop. The compounds described in this invention affect both the TNF α level and transcription activity of NF κ B. NF κ B has been shown to play a role in diseases including osteoarthritis, transplant rejection, ischemia, reperfusion injury, trauma, certain
5 cancers and viral disorders, and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, psoriasis, inflammatory bowel disease, glomerulonephritis, lupus and juvenile diabetes.

SUMMARY OF THE INVENTION

This invention relates to the use of TNF α inhibiting compounds and
10 compositions, which have an anti-immunoinflammatory effect, and thus are useful in treating immunoinflammatory maladies, and as such are useful in treating, among other things, autoimmune diseases.

In relation to these uses, this invention relates to novel compounds of Formula (I) (Compound (I)), and compositions thereof, useful in the prevention and
15 treatment of immunoinflammatory and autoimmune diseases by inhibition of TNF α . The compounds disclosed have the following general structure (Formula (I))



20

(I)

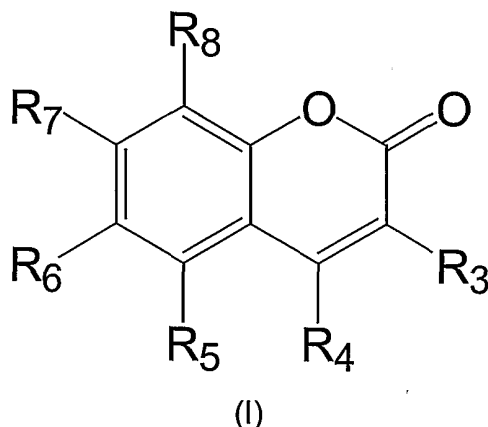
as defined in the following claims, as well as their pharmaceutical compositions and the uses of these compounds both to prepare medicaments generally and for the preferred uses as treatments.

25 DETAILED DESCRIPTION OF THE INVENTION

Without being limited by the theory, it is thought that the compounds of this invention decrease the TNF α blood levels, and thus have utility as

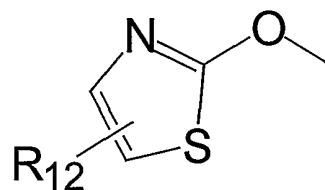
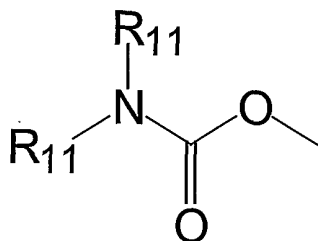
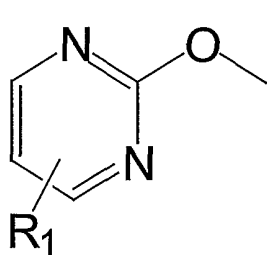
antiinflammatory agents in general and in the prevention and/or treatment of a variety of conditions, including but not limited to immunoinflammatory and autoimmune diseases.

Preferred compounds of this invention are generally represented by the following general structure (I):



wherein R₃ is referred to as an aryl methylene group.

Preferred compounds of this invention include compounds of formula (I) wherein R₇ is selected from:



or

or

As used herein, "Ar" means aryl. "Aryl" means a substituted or unsubstituted radical consisting of an aromatic ring, which may or may not include one or more heteroatoms. Hence the term "heteroaryl" is clearly contemplated in the term "aryl". Preferred are monocyclic heterocycles of 5 or 6 members or bicyclic heterocycles 8 to 10 members. Preferably where the term aryl represents a six membered heterocycle, the heteroatom(s) are from one to three N atoms, and preferably wherein when "aryl" is a heterocycle of five members, it has one or two heteroatoms selected from O, N, or S. When "aryl" is bicyclic, preferably it is an eight to ten membered bicyclic. Preferably if the bicyclic aryl is a heterocycle, the heteroatom(s) are from one to three N atoms, or one to three heteroatoms selected from O, N, or S. Hence, preferred heterocycles have up to three

heteroatoms are present in the aromatic ring. The skilled artisan will recognize that among aryl with heteroatoms included in the aromatic ring, there are both five and six membered rings. Examples of monocyclic "aryl" include; phenyl, thienyl, pyridyl, pyrimidyl, pyridazyl, furyl, oxazolyl, imidazolyl, thiazolyl, oxadiazolyl, triazinyl, triazolyl, thiadiazolyl, and others, which the skilled artisan will recognize. Examples of monocyclic "aryl" include benzofuranyl, benzimidazolyl, pyridazofuranyl, pyridopyranyl, pyridoimidazolyl and the like. Such aryl rings can be connected to the benzopyrane moiety via any carbon or any available valance on the ring. The most preferred aryl rings include phenyl, pyridyl, furyl, or thienyl.

In this definition it is clearly contemplated that substitution on the aryl ring is within the scope of this invention. Where substitution occurs, the radical is called substituted aryl. Preferably one to three, more preferably one or two, and most preferably one substituent occurs on the aryl ring. Preferred substitution patterns in six membered rings are "meta" substituents, that is they are substituted in the 3 position relative to the connection to the benzopyrane. Preferred substitution patterns in five membered rings are substituted in the 2 position relative to the connection to the benzopyrane. Though many substituents will be useful, preferred substituents include carbamates, ureas, sulfonamides, esters, amides, and the like.

As used herein, "alkoxy" means a substituent having the structure R-O-, where R is linear or branched alkanyl or alkenyl. As used herein, "alkanyl" means a saturated hydrocarbon radical substituent, straight, cyclic or branched chain, unsubstituted or substituted. As used herein, "alkenyl" means a hydrocarbon substituent with one double bond, straight or branched chain.

As used herein, "alkyl" means a hydrocarbon substituent, which is linear or branched alkanyl or alkenyl. Preferred alkyls are of 1 to about 5 carbons, More preferred alkyls are C₁ to about C₄ substituents, and most preferred are C₁ to C₄ alkyl.

As used herein, "alkylene" means a hydrocarbon diradical, which is linear or branched alkanyl or alkenyl. Preferred alkyls are of 1 to about 5 carbons, More preferred alkyls are C₁ to about C₄ substituents, and most preferred are C₁ to C₄ alkyl. Examples of such alkylenes, include methylene, ethylene, and the like, such

diradicals may act as spacers between radicals, other atoms, or between the parent ring and another functional group.

"Halo" is a chloro, bromo, fluoro or iodo atom radical. Chloro and fluoro are preferred halides, the term halo also contemplates terms sometimes referred to as "halogen", or "halide".

As used herein, "haloalkyl" means a hydrocarbon substituent, which is linear or branched alkanyl or alkenyl, substituted with chloro, bromo, fluoro or iodo atom(s). Most preferred of these are fluoroalkyls, wherein one or more of the hydrogen atoms have been substituted by fluoro. Preferred haloalkyls are of 1 to about 5 carbons in length, More preferred haloalkyls are C₁ to about C₄ substituents, and most preferred are C₁ to C₃ substituents. The skilled artisan will recognize, then that as used herein, "haloalkylene" means a diradical variant of haloalkyl, such diradicals may act as spacers between radicals, other atoms, or between the parent ring and another functional group.

"Heterocyclyl" includes radical heterocycles which are saturated, unsaturated, and aromatic. These may be substituted or unsubstituted, and are attached to other radicals or the benzopyrane ring via any available valence, preferably any available carbon. Hence this definition contemplated such radicals as heterocyclyl, heterocycloxy, and the like. More preferred heterocycles are of 5 or 6 members. In six membered aromatic monocyclic heterocycles, the heteroatom(s) are from one to three Ns, and wherein when the heterocycle is five membered and aromatic, preferably it has one or two heteroatoms selected from O, N, or S. However, heterocyclyl does not require that the heterocycle is aromatic or unsaturated, it may be saturated or unsaturated or aromatic, such as morpholino, piperidino, pyranonyl, benzimidazolyl, benzofuranyl, oxalolidinyl, oxazolyl, or the like.

"Substituted phenyl" or "substituted aryl" represents any phenyl or other aryl radical, which has one or more substitutions on any of the remaining positions on the ring. The skilled artisan knows suitable substitutions, and methods to prepare substituted phenyls and aryls would be known in the art, and are available through standard sources. See for example, March Advanced Organic Chemistry (Wiley), Carey and Sundberg Advanced Organic Chemistry (vol. 2) and the like.

Certain radicals are not further defined here. The skilled artisan, armed with the knowledge of IUPAC methods of nomenclature is well aware of the meaning of radicals named by this well accepted method. Hence, it is clear that hydroxyethylene refers to HOCH₂CH₂-, methylcarbonyl refers to CH₃CO-. It is also apparent that certain radicals are generally referred to by common names, which are known in the art. Hence, the skilled artisan will recognize that CH₃CO- is also refers to acetyl, HCO- is referred to as formyl, and other examples can be cited here, but are not for the sake of space.

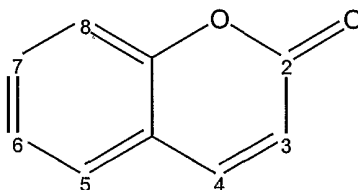
Compounds and compositions herein also specifically contemplate pharmaceutically acceptable salts, whether cationic or anionic. A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein). Preferred salts formable at acidic groups can include cations, such as the alkali metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium) and organic salts. Preferred salts formable at basic sites include anions such as the halides (such as chloride salts). Of course, the skilled artisan is aware that a great number and variation of salts may be used, and examples exist in the literature of both organic or inorganic salts useful in this manner.

It is also clearly contemplated that compounds of the invention can be provided as biohydrolyzable prodrugs, as they are understood in the art. These include for example, biohydrolyzable amides and esters. "Biohydrolyzable amide" is an amide of a compound which does not essentially interfere with the activity of the compound, or that is readily converted in vivo by a human or lower animal subject to yield an active of the invention. A "biohydrolyzable ester" refers to an ester of the compound of the invention that does not interfere with the activity of these compounds or that is readily converted by an animal to yield an active Formula (I) compound. Such biohydrolyzable prodrugs are understood by the skilled artisan and are embodied in regulatory guidelines.

Inasmuch as the compounds of the invention may contain optical centers, "Optical isomer", "stereoisomer", "enantiomer," "diastereomer," as referred to herein have the standard art recognized meanings (Cf., Hawleys Condensed Chemical Dictionary, 11th Ed.) and are included in the compounds
5 claimed, whether as racemates, or their optical isomers, stereoisomers, enantiomers, diastereomers.

The illustration of specific protected forms and other derivatives of the Formula (I) compounds is not intended to be limiting. The application of other useful protecting groups, salt forms, etc. is within the ability of the skilled
10 artisan.

Where nomenclature is simple, for the purposes of nomenclature the numbering follows the IUPAC convention. For illustration purposes, the parent benzopyrane ring structure is IUPAC numbered as follows:



PREPARATION OF THE COMPOUNDS OF THE INVENTION

The starting materials used in preparing the compounds of the invention are known, made by known methods, or are commercially available as a starting
20 material. It will be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature. The skilled artisan given the literature and this disclosure is well equipped to prepare any of the claimed compounds.

It is recognized that the skilled artisan in the art of organic chemistry can
25 readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. These manipulations

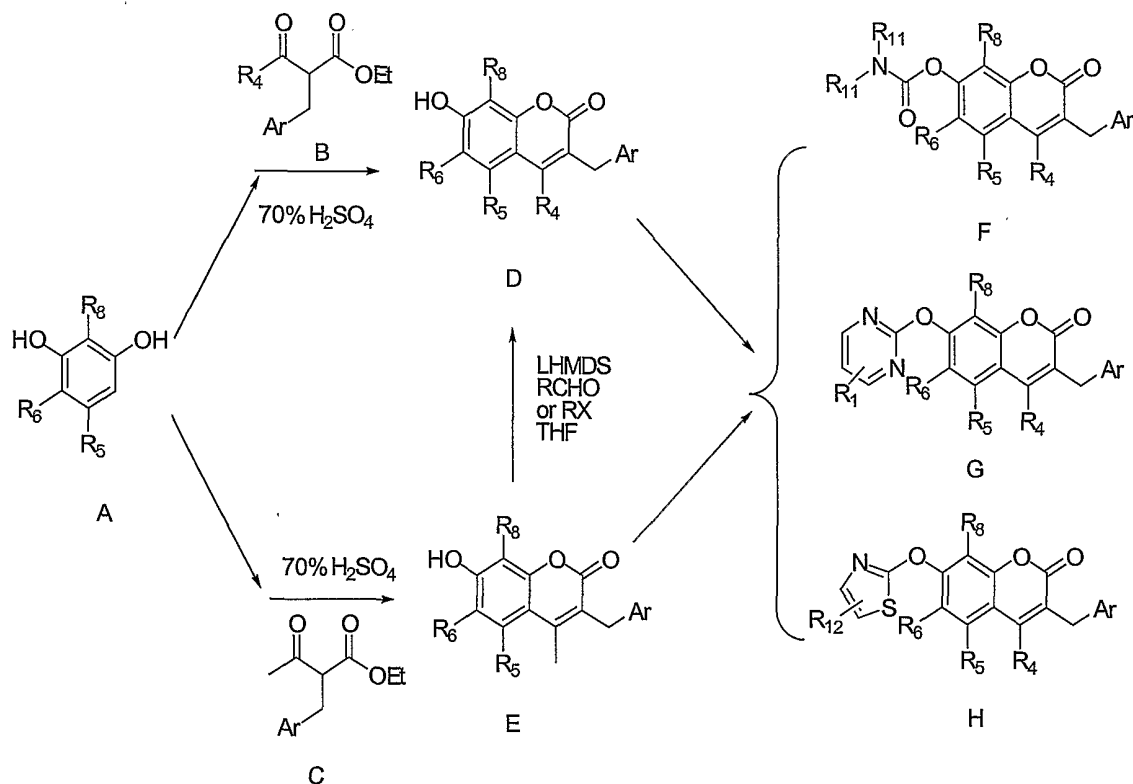
are discussed in standard texts such as March Advanced Organic Chemistry (Wiley), Carey and Sundberg, Advanced Organic Chemistry and the like.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus
5 avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in T. Greene Protecting
10 Groups in Organic Synthesis.

The following example schemes are provided for the guidance of the reader, and represent preferred methods for making the compounds exemplified herein. These methods are not limiting, and it will be apparent that other routes may be employed to prepare these compounds. Such methods specifically
15 include solid phase based chemistries, including combinatorial chemistry. The skilled artisan is thoroughly equipped to prepare these compounds by those methods given the literature and this disclosure.

Note that in these schemes the term "aryl methylene" is used for R_3 by example. The skilled artisan will recognize that R_3 , as defined, includes this
20 preferred moiety, and all R_3 radicals are obtainable by these methods.

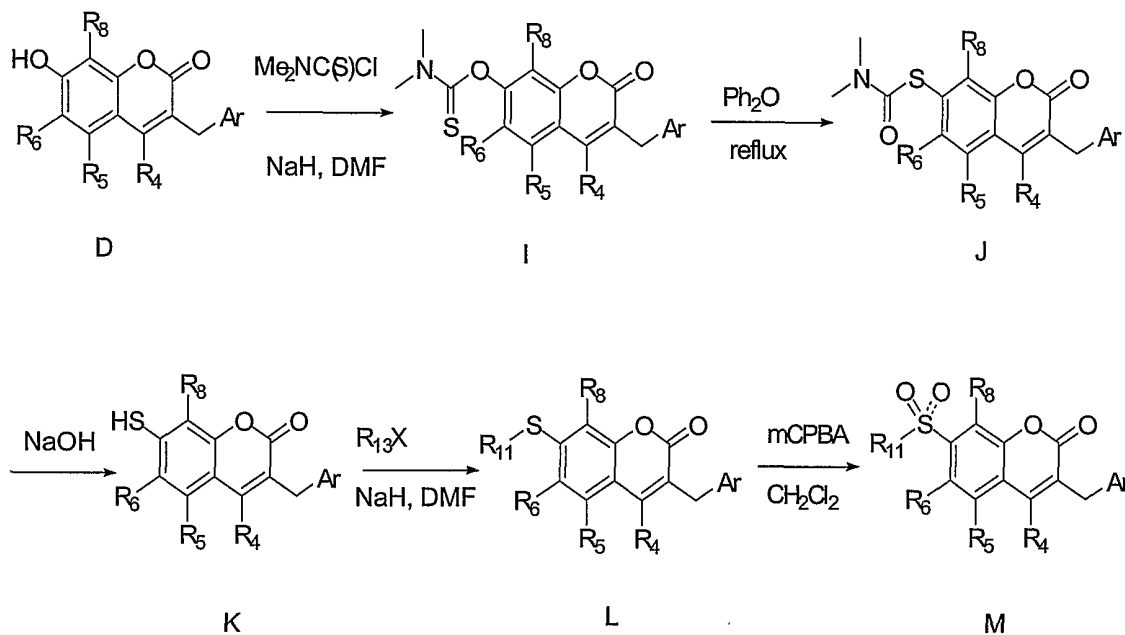
Scheme 1



The C-7 hydroxy coumarin compounds (**D** and **E**) are prepared from resorcinol or substituted resorcinol (**A**) and β-ketoesters (**B** or **C**) according to the published procedures (Usgaonkar et al., *J. Indian Chem. Soc.* 30, 743 (1953)).

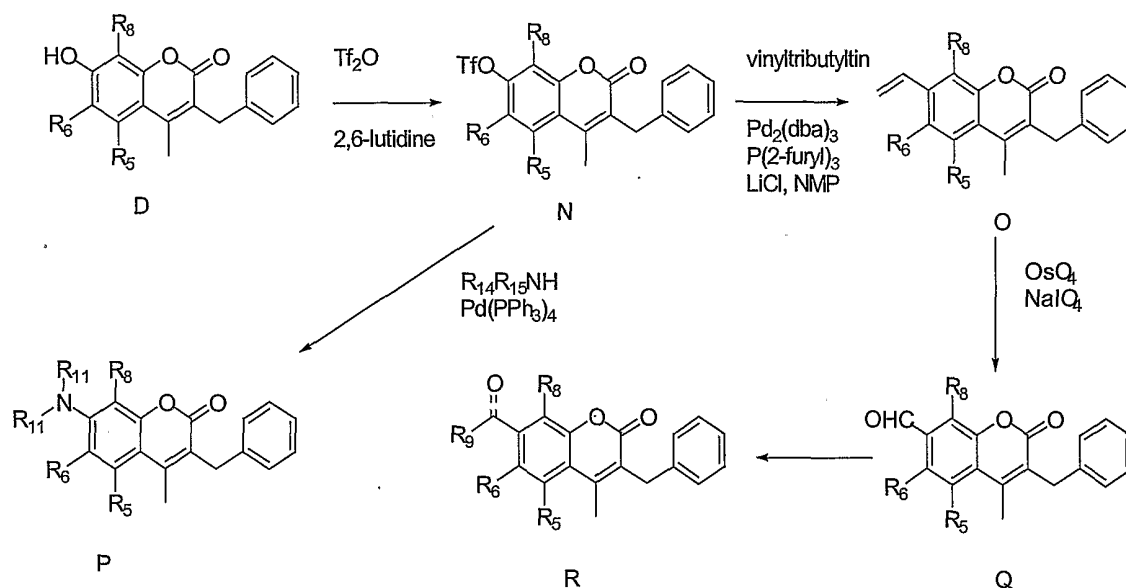
Thus, 2-arylmethyl β-ketoesters (**B**) react with resorcinol or substituted resorcinol in 70% sulfuric acid to furnish 3-arylmethyl-4-substituted coumarins (**D**). Alternatively, they can be prepared through C-4 alkylation of 3-arylmethyl-4-methyl coumarins (**E**), which are in turn prepared from 2-arylmethyl acetoacetates (**C**) with resorcinol derivatives, under the conditions depicted in Scheme 1. Upon treatment with NaH, or other appropriate reagent, and appropriate halides (such as carbamoyl chlorides, 2-halopyrimidines and 2-halothiazoles), these two C-7 hydroxy coumarin intermediates (**D** and **E**) are converted into the desired C-7 carbamates (**F**), oxypyrimidine (**G**) and oxythiazole (**H**) derivatives as shown in Scheme 1.

Scheme 2



The C-7 hydroxyl intermediates **D** or **E** (Scheme 1) are also used to
 5 prepare C-7 thio-containing derivatives according to Scheme 2. Under similar
 conditions, C-7 hydroxyl compounds **D** react with thiocarbamoyl chloride to afford
 the thiocarbamic acid O-esters (**I**). These thiocarbamic acid O-esters are
 rearranged into C-7 thiocarbamic acid S-ester derivatives (**J**) upon refluxing in
 diphenylether. Further elaboration on C-7 thiol intermediates (**K**), which are
 10 obtained through hydrolysis of thiocarbamate (**J**), furnishes the corresponding
 aliphatic or aromatic sulfides (**L**), sulfoxides or sulfones (**M**).

Scheme 3



3-Benzyl-4-methyl C-7 triflates (**N**), prepared from the corresponding C-7 hydroxyl coumarin **C** (Scheme 1) under conventional conditions, are subjected into Still coupling (*Organic Reactions* 50, 1 (1997)) to afford the alkylated derivatives **O** or into directly amination (Wolfe and Buchwald, *J. Org. Chem.* 62, 1264 (1997)) to afford amino derivatives (**P**). The intermediates **O** are then transformed into other derivative (**R**) which contain different groups at C-7 position via aldehyde intermediates (**Q**).

Compositions

The pharmaceutical compositions containing Compound (I) can be administered either orally or parentally, though oral administration thereof is preferred. These pharmaceutical compositions may be in dosage forms appropriate for the administration routes.

Pharmaceutical compositions containing Compound (I) as an active ingredient are formulated by techniques commonly employed in the art. Namely, these compositions are prepared as solids and liquids, such as tablets, capsules, granules, powders, syrups, injections and ointments depending on the purpose, or route of administration. In formulation, solid or liquid carriers or fillers, commonly employed in the art are used.

The amount of Compound (I) in these preparations varies depending on the dosage form. It is generally preferable that these preparations contain from 0.00001 to 20 % by weight of Compound (I). The dose of the compositions of this invention may be varied over a wide range depending on the type of the warm-

blooded animal (for example, mammals, and more preferably humans) to be treated, the severity of the symptoms, a doctor's diagnosis, etc. In general, the daily dose thereof, in terms of an active ingredient, ranges from 0.0001 to 1 g/kg in the case of oral administration or from 0.00001 to 10 mg/kg in the case of
5 parenteral administration. The administration in the dose as specified above may be made once to several times per 1 to 30 days and the administration schedule may be appropriately varied depending on the severity of the symptoms or in accordance with a doctor's judgement.

Preferred compositions of this invention include solids, such as tablets and capsules, and liquids, such as solutions, suspensions and emulsions (preferably in
10 soft gelatin capsules), comprising a safe and effective amount of a subject compound intended for topical administration to the gastrointestinal tract by peroral administration. Such compositions preferably comprise from about 0.01 mg to about 100 mg per dose, more preferably from about 0.1 mg to about 50 mg
15 per dose. Such compositions can be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action.

Another aspect of this invention is compositions which comprise a safe and effective amount of a subject compound, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of the subject compound sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the
20 scope of sound medical judgement. A safe and effective amount of the subject compound will vary with the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician:
25

30 Compositions of this invention preferably comprise from about 0.0001% to about 99% by weight of the subject compound, more preferably from about 0.01% to about 90%; also preferably from about 10% to about 50%, also preferably from

about 5% to about 10%, also preferably from about 1% to about 5%, and also preferably from about 0.1% to about 1%.

In addition to the subject compound, the compositions of this invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

If the subject compound is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with blood-compatible suspending agent, the pH of which has been adjusted to about 7.4.

The preferred mode of administering the subject compounds is perorally. The preferred unit dosage form is therefore tablets, capsules, lozenges, chewable tablets, and the like. Such unit dosage forms comprise a safe and effective amount of the subject compound, which is preferably from about 0.01 mg to about 200 mg, more preferably from about 0.1 mg to about 50 mg, more preferably still from about 0.5 mg to about 25 mg, also preferably from about 1 mg to about 10 mg. The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration are well-known in the art.

Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Such liquid oral compositions preferably comprise from about 0.001% to about 5% of the subject compound, more preferably from about 0.01% to about 0.5%.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual and buccal dosage forms. Such compositions typically comprise soluble filler substances; and binders, as well as optional glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

Preferred compositions of this invention include aqueous solutions comprising a safe and effective amount of a subject compound intended for topical (including ocular or intranasal) administration. Such preferred compositions of this invention include aqueous solutions, suspensions, and dry powders comprising a safe and effective amount of a subject compound which can be administered in a variety of ways, including atomisation and topical inhalation administration. Such compositions preferably comprise from about 0.1% to about 50% of a subject compound, more preferably from about 1% to about 20%. Such compositions are typically contained in a container with attached atomising means. Such compositions also typically include propellants; solvents; stabilisers, preservatives; toxicity adjusters, buffers; and antioxidants. Acids and bases may be used to adjust the pH of these formulations as needed.

EXAMPLES

To further illustrate this invention, the following examples are included. The examples should not, of course, be construed as specifically limiting the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples.

Trademarks used herein are examples only and reflect illustrative materials used at the time of the invention. The skilled artisan will recognize that variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the invention.

^1H nuclear magnetic resonance spectra (NMR) is measured in CDCl_3 or other solvents as indicated by a Varian NMR spectrometer (Unity Plus 400, 400

MHz for ^1H) unless otherwise indicated and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows, s, singlet; d, doublet; t, triplet; m, multiplet.

5 The following abbreviations have the indicated meanings:

Ac = acetyl

Bn = benzyl

CDCl_3 = deuterated chloroform

CD_3OD = deuterated methanol

10 CH_2Cl_2 = dichloromethane

CuCl = copper (I) chloride

CuCN = copper (I) cyanide

DAST = diethylaminosulfur trifluoride

DIBAL = diisobutylaluminum hydride

15 DMAP = 4-(dimethylamino)-pyridine

DMF = N,N-dimethylformamide

DMSO = dimethylsulfoxide

ESIMS = electron spray mass spectrometry

Et_3N = triethylamine

20 EtOAc = ethyl acetate

HCl = hydrochloric acid

HMTA = hexamethylenetetramine

i.p. = intraperitoneal

LDA = lithium diisopropylamide

25 LHDMS = lithium bis(trimethylsilyl)amide

LiCl = lithium chloride

LPS = lipopolysaccharide

MgSO_4 = magnesium sulfate

NaH = sodium hydride

30 NH_4Cl = ammonium chloride

NIS = N-iodosuccinimide

NMP = 1-methyl-2-pyrrolidinone

PBMC = peripheral blood mononuclear cell

$\text{Pd}_2(\text{dba})_3$ = tris(dibenzylideneacetone)dipalladium

PDC = pyridinium dichromate

Ph = phenyl

Ph_2O = diphenyl ether

5 p.o. = *per os*

Py = pyridinyl

PyBOP = benzotriazolyl-tris[pyrrolidino]-phosphonium

hexafluorophosphate

r.t. = room temperature

10 s.c. = subcutaneous

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

Tf_2O = trifluoromethanesulfonic anhydride

15 TMSCN = trimethylsilyl cyanide

ZnI_2 = zinc iodide

The following alkyl group abbreviations are used.

Me = methyl

Et = ethyl

20 n-Pr = normal propyl

i-Pr = isopropyl

n-Bu = normal butyl

i-Bu = isobutyl

t-Bu = tertiary butyl

25 s-Bu = secondary butyl

c-Hex = cyclohexyl

BIOLOGICAL ACTIVITY

In vitro assay

30 Enzyme-linked immunosorbent assays (ELISA) for $\text{TNF}\alpha$ can be performed in a conventional manner (*Blood*, 75, 40-47 (1990)). Human PBMC are isolated from heparinized venous blood obtained from healthy volunteers by Ficoll-Hypaque density centrifugation. The cells are cultured in RPMI1640 medium

supplemented with 5% heat-inactivated fetal calf serum and antibiotics. PBMC (5x10E5 cells/mL) in 0.2 mL aliquot are pretreated with drugs in DMSO for 60 min at 37°C in 96 well round-bottomed tissue culture plates. Thereafter, PBMC in the presence or absence of compound are stimulated with 1 mg/mL LPS from *E. coli* O55:B5 at a final concentration of 100 ng/mL. After overnight culture, the supernatants are harvested and assayed immediately for TNF α levels from each well. The concentration of TNF α in the supernatant is determined by human TNF α ELISA Kit according to the manufacture's directions.

Active compounds are characterized by the concentration of the compound that caused 50% inhibition of TNF α level (IC₅₀). The compounds with IC₅₀ less than or equal to 50 μ M in this assay are considered to be active. The preferred compounds have the IC₅₀ value less than 10 μ M. The most preferred compound have the IC₅₀ value less than 1 μ M.

In vivo assay

Male C3H/HeN mice are administered p.o. or i.p. or s.c. with the compound just or 30 min or 60 min or 120 min before an i.p. challenge of 100 ng LPS. The serum concentration of TNF α for individual mouse is determined 90 min after the LPS challenge by a specific ELISA (*Infection and Immunity*, 64, 769-774 (1996)).

Compounds tested in this assay are considered to be active if the TNF α level is significantly decreased.

On the basis of these studies, and those known to the skilled artisan, it is readily apparent that the pharmacologically active compounds of this invention are useful for preparing pharmaceutical compositions for medical and veterinary use. Compound (I) and pharmaceutical compositions containing the same as an active ingredient have the effects of expected for TNF α reduction.

Table I summarises the *in vitro* biological activity (TNF α inhibition).

Table I *In Vitro* Biological Activity

Compounds	50% Inhibition of TNF α level (IC ₅₀ , μ M)
Example 1	0.36
Example 2	0.09
Example 3	0.58
Example 4	2.1
Example 5	19.3
Example 6	12.9
Example 7	1.17
Example 8	18.7
Example 9	0.85
Example 10	<0.6
Example 11	0.13
Example 12	<0.6
Example 13	0.68
Example 15	9.4
Example 16	6.8
Example 17	50
Example 18	23.6
Example 19	<0.6
Example 21	10.5
Example 23	10.3
Example 24	10.4
Example 25	13.7

In Vitro Biological Activity

Compounds (Number of Examples)	50% Inhibition of TNF α level (IC ₅₀ , μ M)
14-1	0.36
14-2	0.32
14-4	0.44
14-5	3.7
14-6	1.6

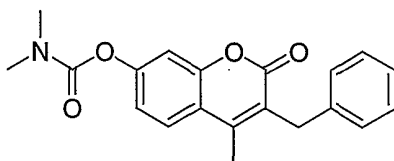
14-7	1.0
14-8	0.14
14-9	4.6
14-10	0.58
14-12	0.06
14-14	0.40
14-15	0.06
14-16	9.6
14-17	0.12
14-18	3.9
14-19	0.85
14-20	0.49
14-21	3.0
14-23	<0.6
14-24	0.46
14-25	0.31
14-26	0.05
14-27	0.06
14-30	6.47
14-31	2.20
14-32	1.3
14-33	8.40
14-35	0.45
14-36	0.13
14-43	6.6
14-44	7.5
14-45	3.2
14-46	5.6
14-52	11.6
14-56	4.5
14-60	1.1
14-61	5.8
14-64	2.1
14-65	2.7
14-66	5.2
14-67	1.7
14-69	2.4

14-71	2.4
14-72	1.9
14-73	1.7
14-74	0.24
14-77	0.9
14-78	1.3
14-79	1.6
14-80	2.4
14-81	0.34
14-82	1.17
14-83	0.78
14-84	1.67
14-104	2.1
14-105	0.09
20-1	9.4
20-2	6.8
20-4	9.5
20-5	8.8
20-10	10.4
20-13	7.5
20-14	9.7
20-19	7.2
20-20	6.6
20-21	2.8
20-22	<0.6
20-26	9.8
20-27	5.1
20-28	1.2
20-29	<0.6
20-30	5.8
20-31	9.8
20-32	11.4
20-34	10.6
20-37	11.8
20-39	5.4
20-40	<0.6
20-41	<0.6

20-42	2.2
20-43	3.1
20-44	0.3
20-45	7.2
20-46	0.96
20-47	0.31
20-48	1.8
20-49	10.9
20-50	4.5
20-54	6.7
20-55	6.4
20-56	7.8
20-57	3.6
20-58	11.9
20-59	5.9
20-60	4.4
20-61	0.65
20-64	11.7
22-1	9.1
22-2	6.6
22-3	10.1
22-4	6.0
22-5	1.8
22-6	0.25
22-7	4.2
22-8	<0.6
22-9	0.27
22-10	2.5
22-11	3.2
26-1	6.30
26-6	10.3
26-11	9.0
26-15	11.8
26-16	8.6
26-22	8.2
26-24	1.7
26-28	10.4

Example 1

Preparation of dimethyl carbamic acid 2-oxo-2H-3-benzyl-4-methyl-1-benzopyran-7-yl ester



5

Step 1

Resorcinol (5.0 g) and ethyl 2-benzylacetoacetate (10.0 g) are mixed in 70% sulfuric acid (50 ml) at room temperature. The reaction mixture is stirred at room temperature overnight and poured into ice water. The solid is filtered and washed with water. The crude product is re-crystallized from EtOAc and hexane to afford 2-oxo-2H-3-benzyl-4-methyl-7-hydroxy-1-benzopyrane (10.6 g).

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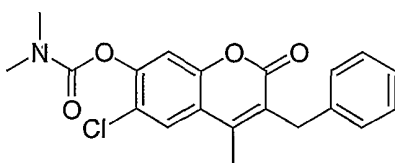
Step 2

To the solution of 2-oxo-2H-3-benzyl-4-methyl-7-hydroxy-1-benzopyrane (150 mg) DMF (4 ml) is added NaH (60%, 27 mg) at room temperature under nitrogen atmosphere. Dimethylcarbamoyl chloride (78 μ l) is added to the reaction mixture after stirring for 15 minutes. The reaction mixture is stirred for 1 hour and poured into saturated NaHCO₃. The aqueous mixture is extracted three times with EtOAc. The combined organic extracts are washed with water three times and brine and dried over MgSO₄. Evaporation of the solvent gives the residue which is purified over preparative TLC (Hexane: EtOAc, 1:1) to afford the title compound (169 mg) as colorless oil. ¹HNMR δ 2.44 (3H, s), 3.03 (3H, s), 3.12 (3H, s), 4.06 (2H, s), 7.07-7.26 (7H, m), 7.59 (1H, d); ESIMS: *m/z* 360 (M+Na).

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Example 2

Preparation of dimethyl carbamic acid 2-oxo-2H-3-benzyl-4-methyl-6-chloro-1-benzopyran-7-yl ester



Step 1

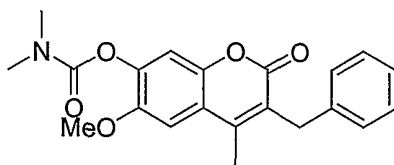
4-Chlororesorcinol (26.25 g, 0.182 mol) and ethyl 2-benzylacetoacetate (40 g, 0.182 mol) are mixed in 70% H₂SO₄ (350 mL) at 0°C. The reaction mixture is stirred at room temperature for 72 hours and poured into ice water. The solid is filtered and washed with water. The crude product is recrystallized from ethanol/chloroform to afford 6-chloro-7-hydroxy coumarin intermediate (37.52 g, 68.7%).

Step 2

To the intermediate obtained above (300 mg, 1.0 mmol) in DMF (12 mL) is added NaH (60%, 50 mg) at room temperature under argon atmosphere. The reaction mixture is stirred for 30 min and dimethylcarbamoyl chloride (0.11 mL) is added. The reaction mixture is stirred at room temperature for 24 hours and poured into ice water. The aqueous mixture is extracted with diethyl ether three times. The combined organic extract is washed with brine and dried over MgSO₄. Evaporation of the solvent furnishes the crude solid which is re-crystallized from ethanol to afford the title compound (279 mg, 75.2%). ¹HNMR δ2.40 (3H, s), 3.03 (3H, s), 3.15 (3H, s), 4.04 (2H, s), 7.19 (1H, m), 7.24 (5H, m), 7.63 (1H, s); ESIMS *m/z* 372 (M+H).

Example 3

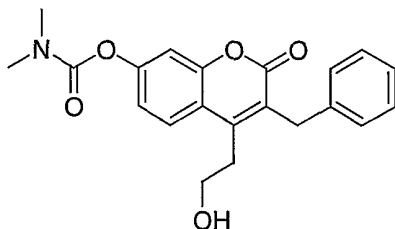
Preparation of dimethyl carbamic acid 2-oxo-2H-3-benzyl-4-methyl-6-methoxy-1-benzopyran-7-yl ester



The title compound is prepared according to the above example. 4-methoxyresorcinol instead of 4-chlororesorcinol is used as starting material. ¹H NMR δ2.40 (3H, s), 3.00 (3H, s), 3.12 (3H, s), 3.85 (3H, s), 4.05 (2H, s), 7.01 (1H, s), 7.10 (1H, s), 7.24(5H, m); ESIMS *m/z* 368 (M+H).

Example 4

Preparation of dimethyl carbamic acid 2-oxo-2H-3-benzyl-4-(2-hydroxyethyl)-1-benzopyran-7-yl ester



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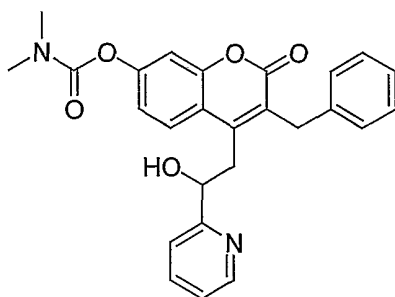
LHDMS (1.5 mL, 1.0 M in THF) is added to the solution of carbamic acid 2-oxo-3-benzyl-4-methyl-2H-1-benzopyran-7-yl ester (169 mg, cf. Example 1) in THF at –78°C under argon atmosphere. The reaction was allowed to stir for 1 hour until the temperature is raised to 0°C. Paraformaldehyde (30 mg, 1 mmol) is added and the reaction is stirred for another 12 hour at room temperature. The reaction mixture is poured into ice water and extracted with EtOAc three times. The combined organic extract is washed with brine and dried over MgSO₄. Evaporation of the solvents gives the crude product that is purified over preparative TLC (CH₂Cl₂: acetone, 95:5) to afford the title compound (76 mg). ¹H NMR δ2.98 (3H, s), 3.06 (2H, t), 3.10 (3H, s), 3.64 (2H, t), 4.02 (2H, s), 7.00 (1H, dd), 7.08 (1H, d), 7.20 (5H, m), 7.60(1H, d); ESIMS *m/z* 368 (M+H).

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Example 5

Preparation of dimethyl carbamic acid 2-oxo-2H-3-benzyl-4-(2-(2-pyridyl)-2-hydroxyethyl)-1-benzopyran-7-yl ester

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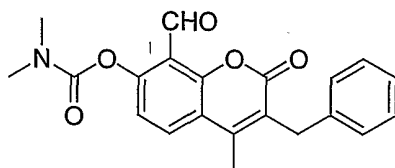
The title compound is prepared according to the above example. 2-Pyridinecarboxaldehyde instead of paraformaldehyde is used. ¹H NMR δ2.98 (3H, s), 3.08 (3H, s), 3.28 (2H, m), 3.90 (2H, dd), 4.50 (1H, brs), 4.90 (1H, m), 6.98

25

(1H, dd), 7.02 (1H, d), 7.10-7.25 (7H, m), 7.62 (1H, ddd), 7.78 (1H, d), 8.50 (1H, dd); ESIMS m/z 445 (M+H).

5 Example 6

Preparation of dimethyl carbamic acid 2-oxo-2H-3-benzyl-4-methyl-8-formyl-1-benzopyran-7-yl ester



10 Step 1

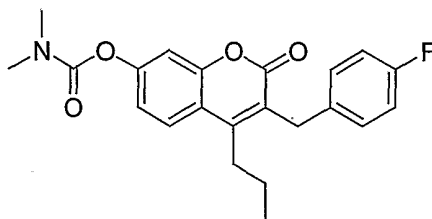
2-Oxo-3-benzyl-4-methyl-7-hydroxyl-2H-1-benzopyrane (512 mg, Example 1) and HMTA (140 mg) are mixed in TFA (5 mL). The reaction mixture is heated at reflux overnight. The solvent is removed under reduced pressure. The residue is purified over silica gel column (Hexanes:EtOAc, 85:15) to afford the desired 8-formyl coumarin (107 mg) and 6-formyl coumarin derivative (35 mg).

Step 2

NaH (27 mg) is added to the solution of 8-formyl coumarin (97.5 mg) in DMF (1 mL) at room temperature under argon atmosphere. Dimethyl carbamoyl chloride (48 μ L) is added to the solution after stirring for 10 minutes. The reaction mixture is stirred at room temperature for 4 hours and poured into ice water. The aqueous solution is extracted with EtOAc three times. The combined organic extract is washed with brine and dried over $MgSO_4$. Preparative TLC purification of the residue after evaporation of the solvent affords the title compound (34 mg). 1H NMR δ 2.42 (3H, s), 3.02 (3H, s), 3.18 (3H, s), 4.05 (2H, s), 7.10 (1H, d), 7.15-7.30 (5H, m), 7.80 (1H, d), 10.68 (1H, s); ESIMS m/z 366 (M+H).

Example 7

Preparation of dimethyl carbamic acid 2-oxo-2H-3-(4-fluorobenzyl)-4-n-propyl-1-benzopyran-7-yl ester



Step 1

NaH (480 mg, 60%) is added to the solution of ethyl butyrylacetate (1.58 mL, 10 mmol) in THF (30 mL) at 0°C under argon atmosphere. The reaction mixture is stirred for 15 minutes and 4-fluorobenzyl bromide (1.37 mL, 11 mmol) is added. The reaction mixture is then heated to 60°C for 2 hours. The reaction mixture is poured into ice cold saturated NH₄Cl and extracted with EtOAc three times. The combined organic extract is washed with brine and dried over MgSO₄. Concentration and column chromatography over silica gel (Hexanes:EtOAc, 75:25) of the residue give 2-(p-fluorophenylmethyl) butyrylacetate (1.21 g) as colorless oil.

Step 2

The ketoester obtained above (879 mg, 3.3 mmol) and resorcinol (330 mg, 3 mmol) are suspended in 5 mL of 70% sulfuric acid at room temperature. The reaction mixture is stirred for 2 hours and poured into ice water and extracted with EtOAc three times. The combined organic extract is washed with brine and dried over MgSO₄. Evaporation of the solvent affords 7-hydroxyl coumarin intermediate as colorless solid (217 mg).

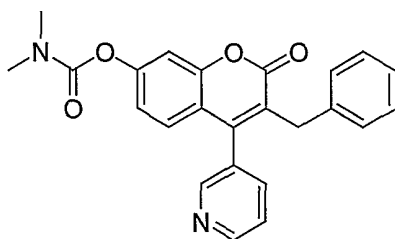
Step 3

To the solution of coumarin intermediate obtained above (125 mg) in DMF (3 mL) is added NaH (19 mg) at room temperature under argon atmosphere. The reaction mixture is stirred for 15 minutes and dimethylcarbonyl chloride (45 mL, 0.48 mmol) is added. The reaction mixture is stirred for another hour and poured into ice water. Extraction with EtOAc three times and the organic extract is combined. The combined organic extract is washed with brine and dried over MgSO₄. Purification of residue affords the title compound (162 mg). ¹H NMR (CD₃OD)

δ 1.00 (3H, t), 1.48 (2H, m), 2.85 (2H, m), 3.00 (3H, s), 3.10 (3H, s), 4.01 (2H, s), 6.98 (2H, m), 7.14 (2H, m), 7.22 (2H, m), 7.78 (1H, d); ESIMS m/z 384 (M+H).

Example 8

- 5 Preparation of dimethyl carbamic acid 2-oxo-2H-3-benzyl-4-(m-pyridyl)-1-benzopyran-7-yl ester



Step 1

NaH (300 mg; 60%) is added to the solution of methyl nicotinoylacetate (896 mg, 5
10 mmol) in THF (15 mL) at 0°C under argon atmosphere. The reaction mixture is stirred for 15 minutes at the temperature and benzyl bromide (0.36 mL) is added. The reaction mixture is heated at reflux overnight. The reaction mixture is poured into iced 1N HCl and extracted with EtOAc three times. The combined organic extract is washed with brine and dried over MgSO₄. Concentration under reduced
15 pressure gives the residue which is purified over column chromatography to afford methyl 2-benzyl-nicotinoylacetate intermediate (389 mg).

Step 2

The methyl 2-benzyl-nicotinoylacetate intermediate obtained above is mixed with
20 resorcinol (159 mg) in 70% sulfuric acid. The reaction mixture is stirred at room temperature for 12 hours. Ice water is added to the reaction mixture which is then extracted with EtOAc three times. The combined organic extract is washed with brine and dried over MgSO₄. The residue (480 mg) obtained upon evaporation of the solvents is used directly in the next step.

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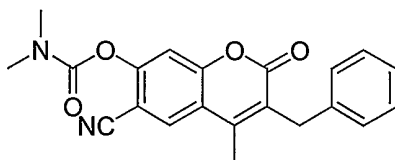
Step 3

The coumarin intermediate obtained in step 2 (170 mg) is dissolved in DMF (5 mL). NaH (60%, 42 mg) is added to the solution at 0°C under argon atmosphere. After stirring for 10 minutes, dimethylcarbamoyl chloride (72 μ L) is added. The

reaction mixture is stirred overnight at room temperature before it is poured into ice water. Extraction with EtOAc three times and the combined organic extract is washed with brine and dried over MgSO₄. Evaporation of the solvents give the residue which is purified over preparative TLC (CH₂Cl₂: MeOH, 95:5) to afford the title compound (40.5 mg). ¹H NMR δ3.00 (3H, s), 3.10 (3H, s), 3.78 (2H, dd), 6.84 (1H, d), 6.92 (2H, m), 7.15 (4H, m), 7.40 (2H, m), 7.45 (1H, m), 8.42 (1H, brs), 8.78 (1H, brs); ESIMS *m/z* 401 (M+H).

Example 9

10 Preparation of dimethyl carbamic acid 2-oxo-2H-3-benzyl-4-methyl-6-cyano-1-benzopyran-7-yl ester



Step 1

15 2-Oxo-2H-3-benzyl-4-methyl-7-hydroxyl-1-benzopyrane (266 mg, 1 mmol, cf. Example 1) is dissolved in TFA (10 mL) at room temperature. NIS (248 mg, 1.1 mmol) is added and the reaction mixture is stirred for 12 hours. The solvent is removed under reduced pressure. The residue is dissolved in EtOAc and washed with water, brine and dried over MgSO₄. The crude product obtained after
20 evaporation of the solvent is re-crystallized from MeOH to afford the 6-iodo derivative (112 mg).

Step 2

NaH (48 mg, 60%) is added to the solution of 6-iodo coumarin obtained above (392 mg) in 5 mL of DMF under nitrogen atmosphere at room temperature. After
25 stirring for 15 minutes, dimethylcarbonyl chloride (0.11 mL, 1.2 mmol) is added and the reaction mixture is stirred for another 4 hours. The reaction mixture is poured into saturated NH₄Cl and extracted with EtOAc three times. The combined organic extract is washed with brine and dried over MgSO₄. Concentration and
30 purification with preparative TLC (Hexane:EtOAc, 4:1) afford 6-iodo carbamic acid ester intermediate (440 mg).

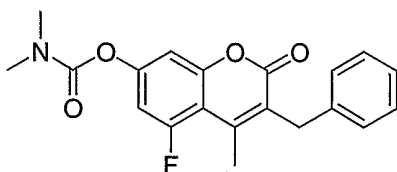
Step 3

The iodo carbamate intermediate obtained above (60 mg, 0.13 mmol) and CuCN (17 mg, 0.19 mmol) are mixed in DMF (5 mL). The mixture is heated at 130°C under nitrogen atmosphere for 5 hours. The reaction mixture is poured into ice water and extracted with EtOAc three times. The combined organic extract is washed with brine and dried over MgSO₄. Concentration under reduced pressure and purification of the crude residue afford the title compound (23 mg). ¹H NMR δ2.42 (3H, s), 3.02 (3H, s), 3.20 (3H, s), 4.02 (2H, s), 7.20 (5H, m), 7.40 (1H, s), 7.82 (1H, s); ESIMS *m/z* 363 (M+H).

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Example 10

Preparation of dimethyl carbamic acid 2-oxo-2H-3-benzyl-4-methyl-5-fluoro-1-benzopyran-7-yl ester



15 Step 1

1-Fluoro-3,5-dihydroxybenzene (1.0 g, 7.8 mmol) and ethyl 2-benzyl acetoacetate (1.72 g, 7.8 mmol) are suspended in 20 mL of 70% sulfuric acid at room temperature. The reaction mixture is stirred for 24 hours and poured into ice water. The solid is filtered and washed with water. The yellowish crude product is recrystallized from hot ethanol to afford the 7-hydroxy coumarin intermediate (929 mg, 42%).

20

Step 2

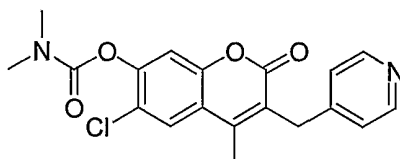
To a suspension of NaH (60%, 45 mg, 1.05 mmol) in anhydrous THF (5 mL) is added the 7-hydroxy coumarin intermediate (200 mg, 0.7 mmol) at room temperature under argon atmosphere. The suspension is stirred for 30 min before adding dimethylcarbamoyl chloride (100 μL, 1.05 mmol). The reaction mixture is stirred overnight before pouring into aqueous ether. The ether is then washed twice with water, brine and dried over MgSO₄. Evaporation of the solvent gives a residue which is purified on a preparative TLC (CHCl₃: MeCN, 95:5) to afford the title compound (135 mg) as a colorless oil. ¹H NMR δ2.53 (3H, s), 3.01 (3H, s),

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3.08 (3H, s), 4.03 (2H, s), 6.84 (1H, m), 6.93 (1H, s), 7.17 (1H, m), 7.23 (4H, m); ESIMS m/z 356 (M+H).

Example 11

- 5 Preparation of dimethyl carbamic acid 2-oxo-2H-3-(p-pyridinylmethyl)-4-methyl-6-chloro-1-benzopyran-7-yl ester



Step 1

- 10 Ethyl acetoacetate (5.20 g), piridine-4-aldehyde (4.28 g), piperidine (0.4 ml) and AcOH (0.24 ml) are mixed in CH_2Cl_2 (150 ml) at room temperature under nitrogen atmosphere. The reaction mixture is stirred overnight and the solvent is removed. The residue is dissolved in EtOH (150 ml). 10% Pd/C (1.0 g) is added and reaction mixture is stirred at room temperature under hydrogen for 7 hours. Concentration
15 under reduced pressure after Celite® filtration afford Ethyl 2-(4-piridylmethyl) acetoacetate (8.0 g) as colorless oil.

Step 2

- The ketoester obtained above (4.59 g) and 4-chlororesorcinol (3.0 g) are
20 suspended in 10 ml of 70% sulfuric acid at room temperature. The reaction mixture is stirred overnight and poured into water and is neutralized with NaOH aq. (Ph=7.0). The aqueous mixture is extracted three times with EtOAc. The combined organic extracts are dried over MgSO_4 . The crude product obtained after evaporation of the solvent is re-crystallized from CH_2Cl_2 to afford the 2-oxo-
25 2H-3-(4-pyridinylmethyl)-4-methyl-6-chloro-7-hydroxy-1-benzopyrane (291 mg).

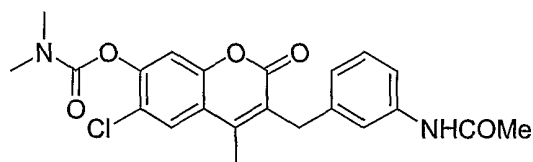
Step 3

- To the solution of 2-oxo-2H-3-(4-pyridinylmethyl)-4-methyl-6-chloro-7-hydroxy-1-benzopyrane (100 mg) DMF (3 ml) is added NaH (60%, 20 mg) at room
30 temperature under nitrogen atmosphere. Dimethylcarbamoil chloride (46 μl) is added to the reaction mixture after stirring for 15 minutes. The reaction mixture is

stirred overnight and poured into saturated NaHCO_3 . The aqueous mixture is extracted three times with EtOAc. The combined organic extracts are washed with water three times and brine and dried over MgSO_4 . Evaporation of the solvent gives the residue which is purified over preparative TLC (CHCl_3 : MeOH, 97:3) to afford the title compound (61 mg) as colorless oil. ^1H NMR δ 2.41 (3H, s), 3.05 (3H, s), 3.18 (3H, s), 4.05(2H, s), 7.16 (2H, d, $J=5.9\text{Hz}$), 7.28(1H, s), 7.67 (1H, s), 8.50 (2H, d, $J = 5.9\text{Hz}$); ESIMS m/z 395 ($\text{M}+\text{Na}$).

Example 12

- 10 Preparation of dimethyl carbamic acid 2-oxo-2H-3-(*m*-acetamidobenzyl)-4-methyl-6-chloro-1-benzopyran-7-yl ester



15 Step 1

NaH (1.94 g, 60%) is added to the solution of ethyl acetoacetate (6.02 g) in THF (100 ml) at 0°C under nitrogen atmosphere. The reaction mixture is stirred for 15 minutes at the temperature and 3-nitrobenzylbromide (10 g) is added. The reaction mixture is stirred at room temperature overnight. The reaction mixture is poured into saturated NH_4Cl aq. and extracted with EtOAc twice. The combined organic extract is washed with brine and dried over MgSO_4 . Concentration under reduced pressure gives the residue which is purified over column chromatography to afford ethyl 2-(3-nitrobenzyl)-acetoacetate (12 g).

25 Step 2

The ketoester intermediate (5.5 g) obtained above is mixed with 4-chlororesorcinol (3.0 g) in 70% sulfuric acid. The reaction mixture is stirred at room temperature for 3 days and poured into water. The solid is filtered and washed with water. The crude product is re-crystallized from acetone and hexane to afford 2-oxo-2H-3-(3-nitrobenzyl)-4-methyl-6-chloro-7-hydroxy-1-benzopyrane (3.20 g).

Step 3

To the solution 2-oxo-2H-3-(3-nitrobenzyl)-4-methyl-6-chloro-7-hydroxy-1-benzopyrane of (200 mg) DMF (5 ml) is added NaH (60%, 28 mg) at room temperature under nitrogen atmosphere. Dimethylcarbamoyl chloride (80 μ l) is added to the reaction mixture after stirring for 15 minutes. The reaction mixture is stirred overnight and poured into saturated NaHCO₃. The aqueous mixture is extracted three times with EtOAc. The combined organic extracts are washed with water three times and brine and dried over MgSO₄. Evaporation of the solvent gives the residue which is re-crystallized from CH₂Cl₂ and hexane to afford dimethyl carbamic acid 2-oxo-2H-3-(3-nitrobenzyl)-4-methyl-6-chloro-1-benzopyrane-7-yl ester (214 mg).

Step 4

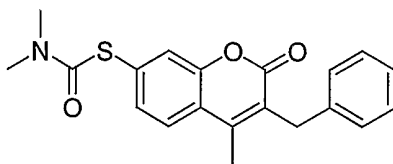
To the solution of 2-oxo-2H-3-(3-nitrobenzyl)-4-methyl-6-chloro-1-benzopyrane-7-yl ester (187 mg) DMF (5 ml) is added SnCl₂·2H₂O (506 mg) at room temperature. The reaction mixture is stirred at room temperature for 4 hours and poured into saturated NaHCO₃ aq. The aqueous mixture is extracted three times with EtOAc. The combined organic extracts are washed with water three times and brine and dried over MgSO₄. Evaporation of the solvent gives the residue which is re-crystallized from CH₂Cl₂ and hexane to afford dimethyl carbamic acid 2-oxo-2H-3-(3-aminobenzyl)-4-methyl-6-chloro-1-benzopyrane-7-yl ester (138 mg).

Step 5

To the solution of 2-oxo-2H-3-(3-aminobenzyl)-4-methyl-6-chloro-1-benzopyrane-7-yl ester (106 mg) CH₂Cl₂ (3 ml) is added AcCl (39 μ l) and Et₃N (114 μ l) at room temperature. The reaction mixture is stirred at room temperature for 1 hour and poured into saturated NaHCO₃ aq. The aqueous mixture is extracted three times with CH₂Cl₂. The combined organic extracts are dried over MgSO₄. Evaporation of the solvent gives the residue which is re-crystallized from CH₂Cl₂ and hexane to afford title compound (87 mg). ¹H NMR δ 2.12 (3H, s), 2.42 (3H, s), 3.05 (3H, s), 3.17 (3H, s), 4.03 (2H, s), 6.99 (1H, d, J=7.6 Hz), 7.20-7.30 (4H, m), 7.43 (1H, d, J=7.6 Hz), 7.64 (1H, s); ESIMS *m/z* 451 (M+Na).

Example 13

Preparation of dimethyl thiocarbamic acid S-2-oxo-2H-3-benzyl-4-methyl-1-benzopyran-7-yl ester



5

Step 1

NaH (90 mg, 60%, 2.25 mmol) is added to the solution of 2-oxo-2H-3-benzyl-4-methyl-7-hydroxyl-1-benzopyrane (500 mg, 1.88 mmol, Example 1) in DMF (5 mL) at 0°C under argon atmosphere. After stirring for 10 minutes, dimethyl thiocarbamoyl chloride (280 mg, 2.25 mmol) is introduced into the reaction. The reaction mixture is stirred at room temperature for 2 hours and poured into ice water. The reaction mixture is extracted with EtOAc three times. Evaporation of the solvent gives the crude residue, which is re-crystallized from MeOH to afford the desired thiocarbamic acid O-ester intermediate (393 mg).

15

Step 2

The thiocarbamic acid O-ester (340 mg) obtained above is dissolved in diphenyl ether and the mixture is heated up to 220°C for 4 hours. The reaction mixture is directly passed through a short silica gel column to afford the title compound (330 mg). ¹H NMR δ2.40 (3H, s), 3.00-3.10 (6H, brs), 4.02 (2H, s), 7.08-7.30 (5H, m), 7.40 (1H, d), 7.48 (1H, s), 7.60 (1H, d); ESIMS *m/z* 354 (M+H).

20

Example 14

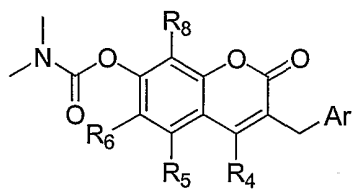
The compounds in table II are prepared according to the indicated examples.

25

Table II

Compounds of formula (I) wherein R₇ is dimethylcarbamoyloxyl group. In addition, for simplicity, R₃ is referred to as "Ar(methylene)" or "ArCH₂" in the structure and the table that follows, and thus only Ar is defined in the table.

30



(II)

Number of Examples	R ₄	R ₅ , R ₆ , R ₈	Ar	Physico-chemical Data (m/z, M+H or M+Na)	Process of Example
14-1	Me	R ₅ =R ₆ =R ₈ =H	Ph	360	1
14-2	Me	R ₅ =R ₆ =R ₈ =H	p-F-Ph	378	1
14-3	Me	R ₅ =Me ₂ NCO ₂ R ₆ =R ₈ =H	Ph	425	10
14-4	Me	R ₅ = F, R ₆ =R ₈ =H	Ph	356	10
14-5	Me	R ₅ = F, R ₆ =R ₈ =H	m-NO ₂ Ph	423	12
14-6	Me	R ₅ = F, R ₆ =R ₈ =H	m-NH ₂ Ph	393	12
14-7	Me	R ₅ = F, R ₆ =R ₈ =H	m- MeCONHPh	435	12
14-8	Me	R ₅ = F, R ₆ =R ₈ =H	m- EtO ₂ CCH ₂ C ONH-Ph	484(M+)	12
14-9	Me	R ₆ = Et, R ₅ =R ₈ =H	Ph	366	2
14-10	Me	R ₆ = OMe, R ₅ =R ₈ =H	Ph	368	2
14-11	Me	R ₅ = OMe, R ₆ =R ₈ =H	Ph	368	10
14-12	Me	R ₆ = I, R ₅ =R ₈ =H	Ph	464	9
14-13	Me	R ₆ = iPr, R ₅ =R ₈ =H	Ph	402	2
14-14	Me	R ₆ = Me, R ₅ =R ₈ =H	Ph	352	2
14-15	Me	R ₆ = Br, R ₅ =R ₈ =H	Ph	417	2
14-16	Me	R ₆ = CHO, R ₅ =R ₈ =H	Ph	366	6
14-17	Me	R ₆ = NO ₂ , R ₅ =R ₈ =H	Ph	383	6
14-18	Me	R ₆ = TMSCC, R ₅ =R ₈ =H	Ph	434	6
14-19	Me	R ₆ = CN, R ₅ =R ₈ =H	Ph	363	9
14-20	Me	R ₆ = Cl, R ₅ =R ₈ =H	o-NH ₂ Ph	409	12
14-21	Me	R ₆ = Cl, R ₅ =R ₈ =H	o-NO ₂ Ph	439	12
14-22	Me	R ₆ = Cl, R ₅ =R ₈ =H	o- MeCONHPh	451	12
14-23	Me	R ₆ = Cl,	m-NO ₂ Ph	439	12

		R ₅ =R ₈ =H			
14-24	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-NH ₂ Ph	409	12
14-25	Me	R ₆ = Cl, R ₅ =R ₈ =H	m- MeCONHPh	429	12
14-26	Me	R ₆ = Cl, R ₅ =R ₈ =H	m- EtOCOCH ₂ C O NH-Ph	500(M+)	12
14-27	Me	R ₆ = Cl, R ₅ =R ₈ =H	(MeSO ₂) ₂ NP h	543(M+)	12
14-28	Me	R ₅ =R ₆ =H, R ₈ =Me	Ph	374	2
14-29	Me	R ₅ =R ₆ =H, R ₈ =CHO	Ph	366	6
14-30	Me	R ₅ =R ₆ =R ₈ =H	o-pyridinyl	361	8
14-31	Me	R ₅ =R ₆ =R ₈ =H	m-pyridinyl	361	8
14-32	Me	R ₅ =R ₆ =R ₈ =H	p-pyridinyl	339	8
14-33	Me	R ₅ =R ₆ =H, R ₈ =Me	m-pyridinyl	375	8
14-34	Me	R ₆ = Cl, R ₅ =R ₈ =H	o-pyridinyl	373	8
14-35	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-pyridinyl	395	8
14-36	Me	R ₆ = Cl, R ₅ =R ₈ =H	p-pyridinyl	395	8
14-37	Me	R ₅ =R ₆ =R ₈ =H	3',4',5'- trimethoxylp henyl	450	2
14-38	Me	R ₅ =R ₆ =R ₈ =H	3',4'- dichlorophen yl		2
14-39	Me	R ₅ =R ₆ =R ₈ =H	2',3',5'- trichlorophe nyl	441	2
14-40	Me	R ₅ =R ₆ =R ₈ =H	2',4',6'- trimethylphe nyl	380	2
14-41	Me	R ₅ =R ₆ =R ₈ =H	Biphenyl	414	2
14-42	Me	R ₅ =H, R ₆ =Et, R ₈ =Me	Phenyl	402	2
14-43	Me	R ₅ =R ₆ =R ₈ =H	p-MeSO ₂ Ph	416	11
14-44	Me	R ₅ =R ₆ =R ₈ =H	o-MeO-Ph	368	11
14-45	Me	R ₅ =R ₆ =R ₈ =H	m-MeO-Ph	368	11
14-46	Me	R ₅ =R ₆ =R ₈ =H	p-MeO-Ph	368	11
14-47	Me	R ₅ =R ₆ =R ₈ =H	p-Me ₂ N-Ph	381	11
14-48	Me	R ₅ =R ₆ =R ₈ =H	p-tBu-Ph	394	11
14-49	Me	R ₅ =R ₆ =R ₈ =H	o-CF ₃ -Ph	406	11
14-50	Me	R ₅ =R ₆ =R ₈ =H	m-CF ₃ -Ph	406	11

14-51	Me	$R_5=R_6=R_8=H$	p-CF ₃ -Ph	406	11
14-52	Me	$R_5=R_6=R_8=H$	p-i-Pr-Ph	380	11
14-53	Me	$R_5=R_6=R_8=H$	P-Et-Ph	366	11
14-54	Me	$R_5=R_6=R_8=H$	p-EtO-Ph	382	11
14-55	Me	$R_5=R_6=R_8=H$	o-NO ₂ -Ph	383	11
14-56	Me	$R_5=R_6=R_8=H$	m-NO ₂ -Ph	383	11
14-57	Me	$R_5=R_6=R_8=H$	p-NO ₂ -Ph	383	11
14-58	Me	$R_5=R_6=R_8=H$	p-MeO ₂ C-Ph	396	11
14-59	Me	$R_5=R_6=R_8=H$	o-MeCONH- Ph	395	12
14-60	Me	$R_5=R_6=R_8=H$	m- MeCONH- Ph	395	12
14-61	Me	$R_5=R_6=R_8=H$	p-MeCONH- Ph	395	12
14-62	Me	$R_5=R_6=R_8=H$	2-Naphthyl	388	11
14-63	Me	$R_5=R_6=R_8=H$	p-HOOC-Ph	382	11
14-64	Me	$R_5=R_6=R_8=H$	o-NH ₂ -Ph	353	12
14-65	Me	$R_5=R_6=R_8=H$	m-NH ₂ -Ph	353	12
14-66	Me	$R_5=R_6=R_8=H$	p-NH ₂ -Ph	353	12
14-67	Me	$R_5=R_6=R_8=H$	m-MeO ₂ C- Ph	396	12
14-68	Me	$R_5=R_6=R_8=H$	m-HOOC-Ph	382	12
14-69	Me	$R_5=R_6=R_8=H$	m- EtNHCONH- Ph	424	12
14-70	Me	$R_5=R_6=R_8=H$	m- MeCONH- Ph	395	12
14-71	Me	$R_5=R_6=R_8=H$	m- EtOCOCH ₂ N HCO NH-Ph	482	12
14-72	Me	$R_5=R_6=R_8=H$	m-Me ₂ N-Ph	403	11
14-73	Et	$R_5=R_6=R_8=H$	Ph	374	1
14-74	Et	$R_6=Cl,$ $R_5=R_8=H$	Ph	408	2
14-75	Et	$R_6=Cl,$ $R_5=R_8=H$	m-NO ₂ Ph	431	7
14-76	Et	$R_6=Cl,$ $R_5=R_8=H$	m-NH ₂ Ph	387	7
14-77	Et	$R_5=R_6=R_8=H$	m-NO ₂ Ph	419	7
14-78	Et	$R_5=R_6=R_8=H$	m-NH ₂ Ph	389	7
14-79	Et	$R_5=R_6=R_8=H$	m- CH ₃ CONHP h	431	7
14-80	Et	$R_5=R_6=R_8=H$	p-pyridinyl	375	7
14-81	Et	$R_6=Cl,$ $R_5=R_8=H$	p-pyridinyl	409	7

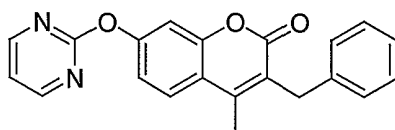
14-82	n-Pr	R ₅ =R ₆ =R ₈ =H	p-F-Ph	384	7
14-83	n-Pr	R ₆ = Cl, R ₅ =R ₈ =H	Ph	400	7
14-84	Ph	R ₅ =R ₆ =R ₈ =H	p-F-Ph	418	7
14-85	o-Pyridinyl	R ₅ =R ₆ =R ₈ =H	Ph	401	8
14-86	PhCH ₂ CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	428	5
14-87	CH ₂ =CHC(M e) ₂ CH(OH)C H ₂	R ₅ =R ₆ =R ₈ =H		450	5
14-88	2-Thiophene- CH(OH)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	450	5
14-89	p- Me ₂ NPhCH(OH)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	487	5
14-90	5-Me-furanyl- CH(OH)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	448	5
14-91	m- NO ₂ PhCH(O H)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	489	5
14-92	MeSCH ₂ CH ₂ C1H(OH)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	442	5
14-93	c- HexylCH(OH) CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	450	5
14-94	CH ₂ CHCH ₂ C H ₂ CH(OH)CH 2	R ₅ =R ₆ =R ₈ =H	Ph	422	5
14-95	p- CNPhCH(OH)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	469	5
14-96	m- MePhCH(OH)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	458	5
14-97	p- MeOPhCH(O H)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	474	5
14-98	2- FuranylCH(O H)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	434	5
14-99	2-Py- CH(OH)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	445	5
14- 100	3-Py- CH(OH)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	445	5
14- 101	2-thiazole- CH(OH)-CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	451	5
14- 102	4-Py- CH(OH)-CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	445	5
14- 103	Ph- CH(OH)CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	444	5

14-104	HOCH ₂ CH ₂	R ₅ =R ₆ =R ₈ =H	Ph	368	4
14-105	Me	R ₆ =Cl, R ₅ =R ₈ =H	Ph	372	2

Example 15

Preparation of 2-oxo-2H-3-benzyl-4-methyl-7-(pyrimidin-2-yloxy)-1-benzopyrane

5

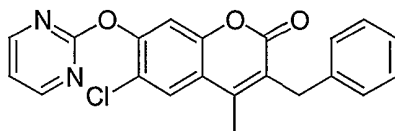


NaH (60%, 9 mg) is added to the solution of 2-oxo-2H-3-benzyl-4-methyl-7-hydroxyl-1-benzopyrane (50 mg) in DMF (2 ml) at room temperature under nitrogen atmosphere. After stirring for 15 minutes, 2-bromopyrimidine (36 mg) is added to the mixture. The reaction mixture is heated at 60°C for 5 days. The reaction mixture is cooled down to room temperature and poured into saturated NaHCO₃ aq. The aqueous mixture is extracted with EtOAc twice. The combined organic extract is washed with water three times and brine and dried over MgSO₄. Evaporation of the solvent gives the residue which is purified over preparative TLC (Hexane: EtOAc, 1:1) to afford the title compound (54 mg) as colorless oil.

¹H NMR δ2.46(3H, s), 4.08 (2H, s), 7.10-7.30 (8H, brs), 7.68 (1H, d, 8.9Hz), 8.59 (2H, d, 4.95 Hz); ESIMS *m/z* 367 (M+Na).

Example 16

20 Preparation of 2-oxo-2H-3-benzyl-4-methyl-6-chloro-7-(pyrimidin-2-yloxy)-1-benzopyrane

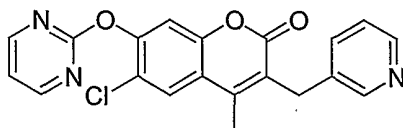


NaH (60%, 48 mg) is added to the solution of 2-oxo-2H-3-benzyl-4-methyl-6-chloro-7-hydroxyl-1-benzopyrane (300 mg) in DMF (10 ml) at room temperature under nitrogen atmosphere. After stirring for 15 minutes, 2-bromopyrimidine (190 mg) is added to the mixture. The reaction mixture is heated at 100°C for 2 days.

The reaction mixture is cooled down to room temperature and poured into saturated NaHCO₃ aq. The aqueous mixture is extracted with EtOAc twice. The combined organic extract is washed with water three times and brine and dried over MgSO₄. Evaporation of the solvent gives the residue which is purified over preparative TLC (CHCl₃: MeOH, 99:1) to afford the title compound (257 mg) as colorless oil. ¹H NMR δ2.45 (3H, s), 4.08 (2H, s), 7.10-7.30 (7H, brs), 7.73 (1H, d), 8.59 (2H, d, J=4.6 Hz); ESIMS *m/z* 401 (M+Na).

Example 17

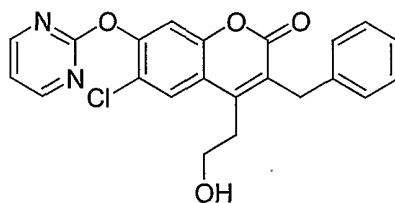
Preparation of 2-oxo-2H-3-(3-pyridylmethyl)-4-methyl-6-chloro-7-(pyrimidin-2-ylloxy)-1-benzopyrane



NaH (60%, 16 mg) is added to the solution of 2-oxo-2H-3-(3-pyridylmethyl)-4-methyl-6-chloro-7-hydroxyl-1-benzopyrane (100 mg) in DMF (3 ml) at room temperature under nitrogen atmosphere. After stirring for 15 minutes, 2-bromopyrimidine (63 mg) is added to the mixture. The reaction mixture is heated at 100°C for 2 days. The reaction mixture is cooled down to room temperature and poured into saturated NaHCO₃ aq. The aqueous mixture is extracted with EtOAc twice. The combined organic extract is washed with water three times and brine and dried over MgSO₄. Evaporation of the solvent gives the residue which is purified over preparative TLC (100% EtOAc) to afford the title compound (28 mg) as colorless oil. ¹H NMR δ2.49 (3H, s), 4.06 (2H, s), 7.13 (1H, t, J=4.6 Hz), 7.19-7.24 (1H, m), 7.30 (1H, s), 7.61 (1H, d, 7.9 Hz), 7.74 (1H, s), 8.46 (1H, m), 8.55 (1H, d, J = 1.6 Hz), 8.58 (2H, d, J=4.6 Hz); ESIMS *m/z* 402 (M+Na).

Example 18

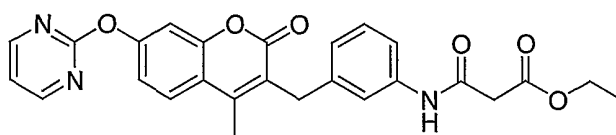
Preparation of 2-oxo-2H-3-benzyl-4-(2-hydroxyethyl)-6-chloro-7-(pyrimidin-2-ylloxy)-1-benzopyrane



LHDMS (1.0M, 0.75 mL) is added to the solution of 2-oxo-2H-3-benzyl-4-methyl-6-chloro-7-(pyrimidin-2-yloxy)-1-benzopyrane (189 mg, Example 16) in THF at –
 5 20°C under argon atmosphere. The reaction mixture is stirred for 1 hour and paraformaldehyde (30 mg) is added. The reaction mixture is stirred at room temperature overnight and poured into saturated NH₄Cl. The mixture is extracted with EtOAc three times. the combined organic extract is washed with 1H HCl, Sat. NaHCO₃ and brine and dried over MgSO₄. Evaporation of the solvent gives the
 10 crude residue which is purified over preparative TLC (CH₂Cl₂:Acetone, 95:5) to afford the title compound (49 mg). ¹H NMR δ3.15 (2H, t), 3.80 (2H, t), 4.10 (2H, s), 7.09 (1H, m), 7.15-7.25(7H, m), 7.79(1H, s), 8.48 (2H, d); ESIMS *m/z* 409 (M+H).

15 Example 19

Preparation of 2-oxo-2H-3-(*m*-ethoxycarbonyl-acetylaminobenzyl)-4-methyl-7-(pyrimidin-2-yloxy)-1-benzopyrane



20

Step 1

Ethyl 2-(3-nitrobenzyl)-acetoacetate(2.65 g) obtained above is mixed with resorcinol (1.1 g) in 70% sulfuric acid. The reaction mixture is stirred at room
 25 temperature for 3 days and poured into water. The aqueous mixture is extracted three times with EtOAc and dried over MgSO₄. Evaporation of the solvent affords 2-oxo-2H-3-(3-nitrobenzyl)-4-methyl-7-hydroxy-1-benzopyrane (2.20 g).

Step 2

To the solution 2-oxo-2H-3-(3-nitrobenzyl)-4-methyl-7-hydroxy-1-benzopyrane of (400 mg) DMF (10 ml) is added NaH (60%, 62 mg) at room temperature under nitrogen atmosphere. 2-bromopyrimidine (306 mg) is added to the reaction mixture after stirring for 15 minutes. The reaction mixture is stirred at 90°C for 2 hours and poured into saturated NaHCO₃. The aqueous mixture is extracted three times with EtOAc. The combined organic extracts are washed with water three times and brine and dried over MgSO₄. Evaporation of the solvent gives the residue which is re-crystallized from Et₂O to afford 2-oxo-2H-3-(3-nitrobenzyl)-4-methyl-7-(pyrimidine-2-yloxy)-1-benzopyrane (404 mg).

10

Step 3

To the solution of 2-oxo-2H-3-(3-nitrobenzyl)-4-methyl-7-(pyrimidine-2-yloxy)-1-benzopyrane (270 mg) in EtOAc (10 ml) and AcOH (2 ml) is added 10% Pd/C (30 mg) at room temperature. The reaction mixture is stirred at room temperature overnight under hydrogen and filtered through Celite®. Evaporation of the solvent gives the residue which is re-crystallized from CH₂Cl₂ and hexane to afford 2-oxo-2H-3-(3-aminobenzyl)-4-methyl-7-(pyrimidine-2-yloxy)-1-benzopyrane (190 mg).

15

Step 4

To the solution of 2-oxo-2H-3-(3-aminobenzyl)-4-methyl-7-(pyrimidine-2-yloxy)-1-benzopyrane (70 mg) CH₂Cl₂ (3 ml) is added ethylmalonylchloride (37 μl) and Et₃N (81 μl) at room temperature. The reaction mixture is stirred at room temperature for overnight and poured into saturated NaHCO₃ aq. The aqueous mixture is extracted three times with CH₂Cl₂. The combined organic extracts are dried over MgSO₄. Evaporation of the solvent gives the residue which is purified over preparative TLC (100% EtOAc) to afford the title compound (76 mg) as colorless oil. ¹H NMR δ 1.31 (3H, t, J=7.25 Hz), 2.48 (3H, s), 3.44 (2H, s), 4.06 (2H, s), 4.25 (1H, q, J=7.25 Hz), 7.00-7.30 (5H, m), 7.43, 1H, d, J=7.6 Hz), 7.40-7.50 (2H, m), 7.68 (1H, d, J=4.6Hz), 8.59 (1H, J=4.6 Hz), 9.10 (1H, brs); ESIMS *m/z* 496 (M+Na).

25

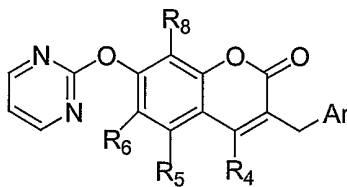
30

Example 20

The compounds in table III are prepared according to the indicated examples.

Table III

Compounds of formula (I) wherein R₇ is pyrimidin-2-yloxy group. In addition, for simplicity, R₃ is referred to as "Ar(methylene)" or "ArCH₂" in the structure and the table that follows, and thus only Ar is defined in the table.



(III)

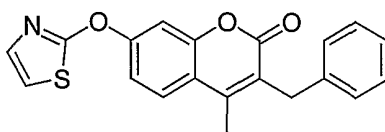
Number of Examples	R ₄	R ₅ , R ₆ , R ₈	Ar	Physico-chemical Data (m/z, M+H or M+Na)	Processes of Example
20-1	Me	R ₅ =R ₆ =R ₈ =H	Ph	367	15
20-2	Me	R ₆ = Cl, R ₅ =R ₈ =H	Ph	401	16
20-3	Me	R ₆ = iPr, R ₅ =R ₈ =H	Ph	409	16
20-4	Me	R ₆ = Br, R ₅ =R ₈ =H	Ph	424	16
20-5	Me	R ₆ = I, R ₅ =R ₈ =H	Ph	471	16
20-6	Me	R ₆ = Me, R ₅ =R ₈ =H	Ph	359	16
20-7	Me	R ₆ = Et, R ₅ =R ₈ =H	Ph	373	16
20-8	Me	R ₆ = OMe, R ₅ =R ₈ =H	Ph	375	16
20-8	Me	R ₅ =R ₆ =R ₈ =H	o-Pyridinyl	346	17
20-9	Me	R ₅ =R ₆ =R ₈ =H	m-Pyridinyl	346	17
20-10	Me	R ₅ =R ₆ =R ₈ =H	p-Pyridinyl	368	17
20-11	Me	R ₆ = Cl, R ₅ =R ₈ =H	o-Pyridinyl	381	17
20-12	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-Pyridinyl	402	17
20-13	Me	R ₆ = Cl, R ₅ =R ₈ =H	p-Pyridinyl	402	17
20-14	Me	R ₅ = F, R ₆ =R ₈ =H	Ph	363	16
20-15	Me	R ₅ =R ₆ =R ₈ =H	m-MeO ₂ C-Ph	403	19
20-16	Me	R ₅ =R ₆ =R ₈ =H	m-HO ₂ C-Ph	399	19
20-17	Me	R ₅ =R ₆ =R ₈ =H	m-Me ₂ N-Ph	410	19
20-18	Me	R ₅ =R ₆ =R ₈ =H	m-NO ₂ -Ph	412	19
20-19	Me	R ₅ =R ₆ =R ₈ =H	m-NH ₂ -Ph	382	19
20-20	Me	R ₅ =R ₆ =R ₈ =H	m-MeCONH-Ph	424	19
20-21	Me	R ₅ =R ₆ =R ₈ =H	m-EtOCOCH ₂ CH ₂ CONH-Ph	510	19
20-22	Me	R ₅ =R ₆ =R ₈ =H	m-EtOCOCH ₂ CONH-Ph	496	19
20-23	Me	R ₅ =R ₆ =R ₈ =H	m-HOOCCH ₂ CH ₂ CONH-Ph	482	19
20-24	Me	R ₅ =R ₆ =R ₈ =H	m-HOOCCH ₂ CONH-Ph	468	19
20-25	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-NO ₂ -Ph	424	19
20-26	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-NH ₂ -Ph	394	19
20-27	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-Me ₂ N-Ph	444	19
20-28	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-EtOCOCH ₂ CH ₂ CONH-Ph	544	19
20-29	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-EtOCOCH ₂ CONH-Ph	530	19
20-30	Me	R ₆ = Cl, R ₅ =R ₈ =H	MeCONHCH ₂ CONH-Ph	515	19

20-31	Me	R ₆ = Cl, R ₅ =R ₈ =H	m- BnOCONHCH ₂ C ONH-Ph	607	19
20-32	Me	R ₆ = Cl, R ₅ =R ₈ =H	m- BnOCONHCH ₂ C H ₂ CONH-Ph	621	19
20-33	Me	R ₆ = Cl, R ₅ =R ₈ =H	m- HOOCCH ₂ CH ₂ C ONH-Ph	516	19
20-34	Me	R ₆ = Cl, R ₅ =R ₈ =H	m- HOOCCH ₂ CONH -Ph	502	19
20-35	Me	R ₅ = Cl, R ₆ =R ₈ =H	m-NO ₂ -Ph	446	19
20-36	Me	R ₅ = Cl, R ₆ =R ₈ =H	m-NH ₂ -Ph	416	19
20-37	Me	R ₅ = Cl, R ₆ =R ₈ =H	m-MeCONH-Ph	458	19
20-38	Me	R ₅ = F, R ₆ =R ₈ =H	m-NO ₂ -Ph	430	19
20-39	Me	R ₅ = F, R ₆ =R ₈ =H	m-MeCONH-Ph	442	19
20-40	Me	R ₅ = F, R ₆ =R ₈ =H	m- EtOCOCH ₂ CON H-Ph	514	19
20-41	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-MeSO ₂ NH-Ph	494	19
20-42	Me	R ₆ = Cl, R ₅ =R ₈ =H	m- MeCOCH ₂ CONH -Ph	477(M+)	10
20-43	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-MeCONH-Ph	436	19
20-44	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-EtSO ₂ NH-Ph	485(M+)	19
20-45	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-(p-tolyl- SO ₂ NH)-Ph	547(M+)	19
20-46	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-nPrSO ₂ NH-Ph	499(M+)	19
20-47	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-iPrSO ₂ NH-Ph	499(M+)	19
20-48	Me	R ₆ = Cl, R ₅ =R ₈ =H	m-nBuSO ₂ NH-Ph	514(M+)	19
20-49	Et	R ₅ =R ₆ =R ₈ =H	Ph	381	15
20-50	Et	R ₆ = Cl, R ₅ =R ₈ =H	Ph	415	16
20-51	Et	R ₅ =R ₆ =R ₈ =H	p-Pyridinyl	382	17
20-52	Et	R ₅ =R ₆ =R ₈ =H	m-NO ₂ -Ph	426	19
20-53	Et	R ₅ =R ₆ =R ₈ =H	m-NH ₂ -Ph	396	19
20-54	Et	R ₅ =R ₆ =R ₈ =H	m-MeCONH-Ph	438	19
20-55	Et	R ₆ = Cl, R ₅ =R ₈ =H	m-NO ₂ -Ph	460	19
20-56	Et	R ₆ = Cl, R ₅ =R ₈ =H	m-NH ₂ -Ph	430	19
20-57	Et	R ₆ = Cl, R ₅ =R ₈ =H	m-MeCONH-Ph	472	19
20-58	Et	R ₅ = F, R ₆ =R ₈ =H	m-NO ₂ -Ph	444	19
20-59	Et	R ₅ = F, R ₆ =R ₈ =H	m-NH ₂ -Ph	414	19
20-60	Et	R ₅ = F, R ₆ =R ₈ =H	m-MeCONH-Ph	456	19
20-61	Et	R ₅ = F, R ₆ =R ₈ =H	m- EtOCOCH ₂ CON H-Ph	528	19
20-62	n-Pr	R ₅ =R ₆ =R ₈ =H	Ph	395	19
20-63	HOO CCH ₂	R ₅ =R ₆ =R ₈ =H	Ph	423	18

20-64	HOC H ₂ CH 2	R ₆ = Cl, R ₅ =R ₈ =H	Ph	409	18
20-65	Ph	R ₅ =R ₆ =R ₈ =H	Ph	429	15
20-66	Ph	R ₅ =R ₆ =R ₈ =H	o-Pyridinyl	408	15
20-67	Ph	R ₅ =R ₆ =R ₈ =H	m-Pyridinyl	408	15
20-68	Ph	R ₅ =R ₆ =R ₈ =H	p-Pyridinyl	430	15
20-69	m- Pyridi nyl	R ₆ = Cl, R ₅ =R ₈ =H	Ph	442	16
20-70	o- Pyridi nyl	R ₆ = Cl, R ₅ =R ₈ =H	Ph	442	16
20-71	p- Pyridi nyl	R ₆ = Cl, R ₅ =R ₈ =H	Ph	442	16
20-72	Me	R ₆ = Cl, R ₅ =R ₈ =H	PhCH ₂ OCH ₂ CO NHPH	542	16

Example 21

Preparation of 2-oxo-3-benzyl-4-methyl-7-(thiazol-2-yloxy)-2H-1-benzopyrane



5

NaH (60%, 18 mg) is added to the solution of 2-oxo-2H-3-benzyl-4-methyl-7-hydroxyl-1-benzopyrane (100 mg) in DMF (3 ml) at room temperature under nitrogen atmosphere. After stirring for 15 minutes, 2-bromothiazole (40 μ l) is added to the mixture. The reaction mixture is heated at 100°C. for 2 days. The reaction mixture is cooled down to room temperature and poured into saturated NaHCO₃ aq. The aqueous mixture is extracted with EtOAc twice. The combined organic extract is washed with water three times and brine and dried over MgSO₄. Evaporation of the solvent gives the residue which is purified over preparative TLC (Hexane:EtOAc, 1:1) to afford the title compound (22 mg) as colorless oil. ¹H NMR δ 2.45 (3H, s), 4.07 (2H, s), 6.91 (1H, d), 7.15-7.32 (8H, m), 7.65 (1, m d); ESIMS *m/z* 372 (M+Na).

15

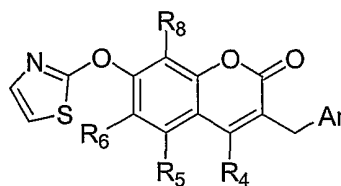
Example 22

The compounds in table IV are prepared in accordance with Example 21.

Table IV

5

Compounds of formula (I) wherein R7 is thiazol-2-yloxy group. In addition, for simplicity, R₃ is referred to as "Ar(methylene)" or "ArCH₂" in the structure and the table that follows, and thus only Ar is defined in the table.



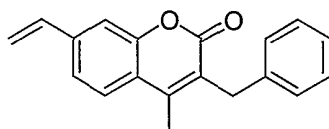
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(IV)

Number of Examples	R ₄	R ₅ , R ₆ , R ₈	Ar	Physico-chemical Data (m/z, M+H or M+Na)
22-1	Me	R ₅ =R ₆ =R ₈ =H	Ph	372
22-2	Me	R ₅ =R ₆ =R ₈ =H	m-NO ₂ Ph	417
22-3	Me	R ₅ = F, R ₆ =R ₈ =H	m-NO ₂ Ph	435
22-4	Me	R ₅ =R ₆ =R ₈ =H	m-NH ₂ -Ph	387
22-5	Me	R ₅ =R ₆ =R ₈ =H	m-MeCONH-Ph	427
22-6	Me	R ₅ =R ₆ =R ₈ =H	m-EtOCOCH ₂ CONH-Ph	501
22-7	Et	R ₅ =R ₆ =R ₈ =H	m-NH ₂ Ph	401
22-8	Et	R ₅ =R ₆ =R ₈ =H	m-MeCONH-Ph	443
22-9	Et	R ₅ =R ₆ =R ₈ =H	EtOCOCH ₂ CONH-Ph	515
22-10	Et	R ₅ =R ₆ =R ₈ =H	Ph	386
22-11	Et	R ₅ =R ₆ =R ₈ =H	m-NO ₂ Ph	431
22-12	Et	R ₅ =R ₆ =R ₈ =H	m-EtO ₂ SNHPh	471
22-13	Et	R ₅ =R ₆ =R ₈ =H	m-PhCH ₂ OCH ₂ OCNHPH	527

15 Example 23

Preparation of 2-oxo-3-benzyl-4-methyl-7-vinyl-2H-1-benzopyrane



Step 1

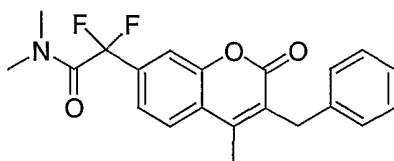
Triflic anhydride (0.38 mL) is dropwise added to the solution of 2-oxo-2H-3-benzyl-4-methyl-7-hydroxyl-1-benzopyrane (284 mg) in 2,6-lutidine (3 mL) at room temperature under argon atmosphere. The reaction mixture is stirred at room temperature for 12 hours and poured into ice water. The aqueous mixture is extracted with EtOAc three times and the combined organic extract is washed with 1N HCl, brine and dried over MgSO₄. Purification of the crude residue with silica gel column (Hexane:EtOAc, 4:1) affords the triflate intermediate in quantitative yield (430 mg).

Step 2

The triflate intermediate obtained above (50 mg, 0.12 mmol) is mixed with LiCl (15 mg), trifurylphosphine (2 mg) and Pd₂(dba)₃ (2 mg) in 2 mL of NMP at room temperature under argon atmosphere. Tributyl vinyltin is added dropwise to the solution and the reaction mixture is stirred overnight. Potassium fluoride is added and the mixture is extracted with EtOAc three time and dried over MgSO₄. Concentration and purification of the residue with preparative TLC (Hexane:EtOAc, 3:1) afford the title compound (26 mg). ¹H NMR δ2.40 (3H, s), 4.02 (2H, s), 5.40 (1H, d), 5.82 (1H, d), 6.70 (1H, dd), 7.15-7.30 (7H, m), 7.58 (1H, m); ESIMS *m/z* 277 (M+H).

Example 24

Preparation of 2-oxo-3-benzyl-4-methyl-7-(N,N-dimethylaminocarboxy-difluoromethyl)-1H-benzopyrane



Step 1

To the suspension of 2-oxo-3-benzyl-4-methyl-7-vinyl-2H-1-benzopyrane (16.0g, Example 23) in dioxane (350 mL) and water (75 mL) is added osmium tetroxide (1.45 mmol) in t-BuOH. The reaction mixture is stirred at room temperature for 30 minutes and sodium periodate (30 g) is added in portions. The solid is filtered out after 30 minutes stirring and the filtrate is partitioned between CH₂Cl₂ and water. Separation and the organic layer is washed further with H₂O and dried over MgSO₄. Evaporation of the organic solvent gives the desired 7-formyl coumarin intermediate (12.0 g).

10 Step 2

To the mixture of the above intermediate (1.5 g) and ZnI₂ (172 mg) in CH₂Cl₂ (40 mL) is added TMSCN (1.44 mL) at room temperature. The reaction mixture is stirred for 16 hours and quenched with 2% HCl (50 mL). The mixture is extracted with CH₂Cl₂ and passed through a pad of Celite®. The organic extract is washed with 1N HCl, brine and dried over MgSO₄. Evaporation of the organic solvent gives the residue which is treated with 2.5 mL of TFA for 30 minutes. Evaporation of the solvent and purification of the crude product with silica gel column (EtOAc: Hexanes; 1:1) afford the desired cyanohydrin intermediate (1.34 g, 82%).

20 Step 3

The cyanohydrin (1.2 g) intermediate obtained above is dissolved in acetic acid (50 mL) and concentrated HCl (50 mL) and stirred for 68 hours at room temperature. The reaction mixture is extracted with EtOAc three times. The organic extract is washed with 1N HCl, brine and dried over MgSO₄. Evaporation of the solvent gives the crude α -hydroxyacid (1.05 g) which is used directly without further purification.

Step 4

To the solution of α -hydroxyacid (400 mg) obtained above in THF (10 mL) is added Me₂N, Et₃N (0.34 mL) followed by PyBOP (1.28 g) at room temperature. The reaction mixture is stirred for 2 hours and solvents are evaporated. The residue is diluted with EtOAc and washed with 1N HCl, saturated NaHCO₃, brine

and dried over MgSO_4 . The residue is purified with preparative TLC (CH_2Cl_2 :
MeOH:AcOH, 10:1:0.5) to afford the α -hydroxyamide (233 mg, 54%).

Step 5

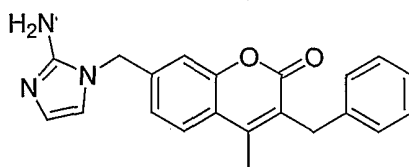
5 PDC (106 mg) is added to the solution of α -hydroxyamide (66 mg) in CH_2Cl_2 (2
mL) at room temperature. The reaction mixture is stirred for 16 hours and filtered
through a pad of Celite®. The filtrate is concentrated and purified over preparative
TLC (CH_2Cl_2 : MeOH, 20:1) to afford the ketoamide derivative (42 mg, 64%).

10 Step 6

DAST is added to the ketoamide intermediate (21 mg) in CH_2Cl_2 at room
temperature. The reaction mixture is stirred for 16 hours. Dichloromethane is
removed and another portion of DAST is added and the reaction mixture is heated
at 60°C for 24 hours. The reaction mixture is diluted with EtOAc and washed with
15 brine and dried over MgSO_4 . Purification of the residue after removal of the
organic solvent affords the title compound (12.0 mg, 63%). ^1H NMR δ 2.42 (3H, s),
3.04 (3H, s), 3.10 (3H, s), 4.08 (2H, s), 7.18 (1H, m), 7.20-7.30 (3H, m), 7.42 (2H,
d), 7.50 (1H, s), 7.70 (1H, d); ESIMS m/z 372 (M+H).

20 Example 25

Preparation of 2-oxo-3-benzyl-4-methyl-7-(2-aminoimidazol-1-yl-methyl)-1H-
benzopyrane



25 Step 1

Sodium borohydride (20.8 mg) is added to the solution of C-7 formyl coumarin
(139 mg, Example 24, step 1) and amino acetaldehyde diethyl acetal (0.29 mL, 2
mmol) in a mixture of MeOH (2 mL) and THF (3 mL) at room temperature. A
spoon of MgSO_4 is added and the reaction mixture is stirred for 24 hours. Solid is
30 filtered out and washed with MeOH. The filtrate is concentrated under reduced
pressure. The residue is re-dissolved in EtOAc and washed with water and brine

and dried over $MgSO_4$. Purification of the residue after evaporation of the solvents affords the amine intermediate (144 mg).

Step 2

5 The above obtained amine intermediate (134 mg, 0.34 mmol) is treated with cyanamide (144 mg, 3.4 mmol) in the mixed solvents of acetic acid (0.2 mL) and water (0.8 mL). The reaction mixture is heated at $80^\circ C$ overnight. The solvents are evaporated under reduced pressure. The residue is partitioned between acetone and ether. The precipitate is filtered out and purified over preparative TLC
 10 $(CH_2Cl_2:MeOH, 85:15)$ to afford the title compound as acetic acid salt (41 mg). 1H NMR (CD_3OD) δ 2.40 (3H, s), 4.02 (2H, s), 5.19 (2H, s), 6.82 (2H, d), 7.10-7.30 (7H, m), 7.79 (1H, d); ESIMS m/z 346 (M+H).

Example 26

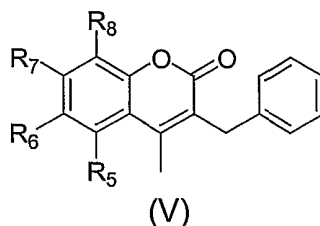
15

The compounds in table V are prepared according to the indicated examples.

Table V

20

Compounds of formula (I) wherein R_3 is benzyl and R_4 is methyl. In addition, for simplicity, R_3 is referred to as phenylmethylene in the structure and (by inference) the table that follows, as the examples defined in the table have phenylmethylene as R_3 .



25

Number of Examples	R_7	R_5, R_6, R_8	Physico-chemical Data ($m/z, M+H$)	Process of Examples
26-1	CHO	$R_5=R_6=R_8=H$	279	24
26-2	$HOCH_2CH_2$	$R_5=R_6=R_8=H$	313	24
26-3	Et	$R_5=R_6=R_8=H$	297	23
26-4	$CH_3(OH)CH$	$R_5=R_6=R_8=H$	313	24
26-5	$Me_2NCOO(CH_2)_2$	$R_5=R_6=R_8=H$	384	24
26-6	Vinyl	$R_5=R_6=R_8=H$	277	23

26-7	Me ₂ NCOOCH ₂	R ₅ =R ₆ =R ₈ =H	352	24
26-8	MeNHCH ₂	R ₅ =R ₆ =R ₈ =H	294	24
26-9	MeOCON(Me)CH ₂	R ₅ =R ₆ =R ₈ =H	352	24
26-10	EtOCON(Me)CH ₂	R ₅ =R ₆ =R ₈ =H	366	24
26-11	CH ₃ CF ₂	R ₅ =R ₆ =R ₈ =H	315	24
26-12	ClCH ₂	R ₅ =R ₆ =R ₈ =H	298	24
26-13	(EtO) ₂ P(O)OCH ₂	R ₅ =R ₆ =R ₈ =H	217	24
26-14	(EtO) ₂ P(O)CH ₂	R ₅ =R ₆ =R ₈ =H	401	24
26-15	1-(2-NH ₂ -imidazolyl)CH ₂	R ₅ =R ₆ =R ₈ =H	346	24
26-16	1-(2-NH ₂ -imidazolyl)CH ₂	R ₆ = Cl, R ₅ =R ₈ =H	381	24
26-17	m-Pyridinyl	R ₅ =R ₆ =R ₈ =H	328	24
26-18	2-(N-Methyl-benzoimidazolyl)	R ₅ =R ₆ =R ₈ =H	381	24
26-19	CH ₃ CO	R ₆ = Cl, R ₅ =R ₈ =H	327	24
26-20	2-(5-Cl-thiophene)-CH(OH)-	R ₅ =R ₆ =R ₈ =H	397	24
26-21	2-Benzofuranyl-CH(OH)	R ₅ =R ₆ =R ₈ =H	397	24
26-22	3-Thiophenyl-CH(OH)-	R ₅ =R ₆ =R ₈ =H	363	24
26-23	CNCH(OH)	R ₅ =R ₆ =R ₈ =H	306	24
26-24	CNCH(F)-	R ₅ =R ₆ =R ₈ =H	308	24
26-25	NH ₂ COCO-	R ₅ =R ₆ =R ₈ =H	322	24
26-26	NH ₂ COCF ₂ -	R ₅ =R ₆ =R ₈ =H	344	24
26-27	Me ₂ NCOCH(F)-	R ₅ =R ₆ =R ₈ =H	354	24
26-28	Me ₂ NCOCF ₂	R ₅ =R ₆ =R ₈ =H	372	24
26-29	(HO) ₂ OPCF ₂ -	R ₅ =R ₆ =R ₈ =H	379(M-H)	24
26-30	2-(N-Methylimidazolyl)-S(O)CH ₂	R ₅ =R ₆ =R ₈ =H	428	25

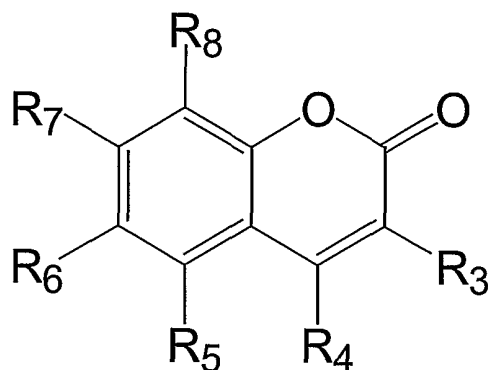
Modification of the preceding embodiments is within the scope of the skilled artisan in formulation, given the guidance of the specification in light of the state of the art.

5 All references described herein are hereby incorporated by reference.

While particular embodiments of this invention have been described, it will be obvious to those skilled in the art that various changes and modifications of this invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are
10 within the scope of this invention.

We claim:

1. The use of a compound of formula in a $\text{TNF}\alpha$ inhibiting amount in a pharmaceutical composition, wherein the compound is of formula:



5

R_1 is hydrogen, hydroxy, C1 to C4 alkyl, phenyl, C1 to C2 haloalkyl, or halo;

R_2 is hydrogen, C1 to C5 alkyl, phenyl or substituted phenyl, wherein

10 R_1 and R_2 together form an alkylene ring or a heteroalkylene ring;

R_3 is aryl methylene, or substituted aryl methylene, wherein the substitution occurs on the aryl ring;

R_4 is hydrogen, C1 to C4 alkyl, C1 to C4 alkyl substituted with phenyl, or heteroaryl, hydroxy, methoxy, or methylthio, C1 to C2 haloalkyl, benzyl, substituted phenyl methylene, phenyl or substituted phenyl, heteroaryl, wherein in any six membered heteroaryl, heteroatoms consist of one or two nitrogen atoms, and wherein in any five membered heteroaryl the heteroatoms consist of one to three of O, N, or S, and wherein substitution on phenyl or heteroaryl is with halo, phenyl, C1 or C2 alkyl;

15

20 R_5 is hydrogen, halo, hydroxy, or C1 to C3 alkoxy, or OCONR_1R_2 ;

R_6 is hydrogen, halo, hydroxy, C1 to C4 alkoxy, C1 to C4 alkyl, cyano, nitro, or formyl;

R_7 is C1 to C4 alkyl, C1 to C4 alkenyl, $\text{CR}_{14}\text{R}_{14}\text{R}_1$, SCONR_1R_2 , OCSNR_1R_2 , (C1 to C4 alkyl) OCONR_1R_2 , $\text{NR}_{12}\text{SO}_2\text{R}_1$, $\text{NR}_1\text{COOR}_{13}$, $\text{NR}_1\text{COR}_1\text{OCOR}_2$, $\text{NR}_1\text{CH}_2\text{CHR}_{11}$, $\text{NCONR}_1\text{R}_2\text{CH}_2\text{CHR}_{11}$, $\text{NR}_1\text{C}=\text{NHNR}_1$, $\text{NCONR}_1\text{OCH}_2\text{CH}_2\text{CHR}_{11}$, NR_1COR_1 , NR_1COR_9 , $\text{NR}_1\text{CH}_2\text{CH}_2\text{OR}_2$, COR_1 , CHR_1R_1 , $\text{CH}_2\text{NR}_1\text{R}_2$, $\text{CH}_2\text{NR}_1\text{COOR}_{13}$, CN, $\text{CH}=\text{NOR}_1$,

25

$\text{CH}_2\text{OPO}(\text{OR}_1)(\text{OR}_2)$, $\text{CH}_2\text{NHCH}_2\text{CHR}_{10}$, COR_9 , CHR_1 , CHR_1CN ,
 $\text{CHR}_1\text{COOR}_1$, $\text{CHR}_9\text{R}_{10}$, $\text{CHR}_1\text{OCONR}_1\text{R}_2$, $\text{CH}_2\text{NHCH}_2\text{CHR}_{11}$, (C1 to C4
 alkyl)carbonyl, R_9 , OR_9 , SR_1 , SOR_1 , SO_2R_1 , CH_2R_1 , $\text{CR}_{12}\text{R}_{12}\text{R}_9$,
 $\text{CH}_2\text{NR}_1\text{COOR}_2$, (C1 to C3alkylene) OR_1 , (C1 to C2alkylene) OR_9 , $\text{CR}_1\text{R}_{12}\text{R}_2$,
 5 $\text{CR}_1\text{R}_{12}\text{R}_9$, $\text{CR}_{12}\text{R}_1\text{PO}(\text{OR}_1)(\text{OR}_2)$, $\text{COCONR}_1\text{R}_2$, $\text{C}\equiv\text{CR}_{10}$, CN , CF_2R_9 ,
 CH_2SOR_1 , CH_2SOR_9 , NR_1R_2 , NR_1R_9 , NR_1COR_2 , CR_1COR_9 , OCONR_1R_2 ,
 $\text{CR}_{12}\text{R}_1\text{CONR}_1\text{R}_2$, $\text{CH}_2\text{NR}_1\text{R}_2$, CONR_1R_2 , CH_2SR_9 , or $\text{NR}_1\text{CONR}_1\text{R}_2$;

R_8 is hydrogen, halo, C1 to C4 alkyl, formyl, or C1 to C4 carbonyl;

R_9 is a monocyclic heterocycle of 5 or 6 members or a bicyclic heterocycle 8 to 10
 10 members, wherein when R_9 is a six membered heterocycle, the
 heteroatom(s) are from one to three N atoms, and wherein when the
 heterocycle is five membered and has one or two heteroatoms selected
 from O, N, or S, wherein when R_9 is an eight to 10 membered bicyclic
 heterocycle, the heteroatom(s) are from one to three N atoms, or one to
 15 three heteroatoms, selected from O, N, or S:

R_{10} is hydrogen, C1 to C4 alkyl, trimethylsilyl, or SO_2R_{11} ;

R_{11} is hydrogen, C1 to C4 alkyl, phenyl, or C1 to C2 haloalkyl;

R_{12} is hydrogen, C1 to C4 alkyl, phenyl, C1 to C2 haloalkyl, or halo;

R_{13} is hydrogen, hydroxy, C1 to C4 alkyl, phenyl, or C1 to C2 haloalkyl;

20 R_{14} is hydrogen, or halo,

and a pharmaceutically acceptable salt thereof.

2. The use of claim 1 wherein the malady treated is an immunoinflammatory
 25 malady.

3. The use of claim 1 wherein the malady treated is an autoimmune disease.

4. The pharmaceutical composition used in Claim 1.

30 5. The use of a composition according to Claim 4 to prepare a medicament.

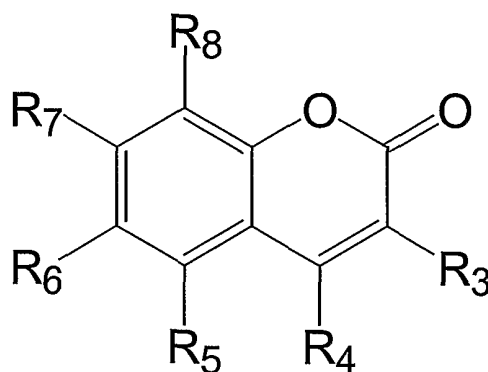
6. The use of a composition according to Claim 4 to prepare a medicament for
 treating autoimmune diseases.

7. The use of a composition according to Claim 4 to prepare a medicament for treating an immunoinflammatory malady.

5 8. A method for the treatment of pulmonary diseases in a patient in need of said treatment, comprising administering to said patient the compound of Claim 1 in an amount efficacious for said treatment.

9. A method for the treatment of immunoinflammatory and autoimmune
10 diseases in a patient in need of said treatment, comprising administering to said patient the compound of Claim 1 in an amount efficacious for said treatment.

10. A compound useful in the use of Claim 1, of formula:



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R₁ is hydrogen, hydroxy, C1 to C4 alkyl, phenyl, C1 to C2 haloalkyl, or halo;

R₂ is hydrogen, C1 to C5 alkyl, phenyl or substituted phenyl, wherein

R₁ and R₂ together form an alkylene ring or a hetero alkylene ring;

20 R₃ is benzyl, substituted phenyl methylene, wherein substitution occurs on the phenyl ring, heteroaryl methylene, or substituted heteroaryl methylene, wherein substitution occurs on the heteroaryl ring;

25 R₄ is hydrogen, C1 to C4 alkyl, C1 to C4 alkyl substituted with phenyl, or heteroaryl, hydroxy, methoxy, or methylthio, C1 to C2 haloalkyl (other than chloroalkyl), benzyl, substituted phenyl methylene, phenyl or substituted phenyl, heteroaryl, wherein in any six membered heteroaryl, heteroatoms consist of one or two nitrogen atoms, and wherein in any five membered heteroaryl the heteroatoms consist of one to three of O, N, or S, and

wherein substitution on phenyl or heteroaryl is with halo, phenyl, or C1 or C2 alkyl;

R₅ is hydrogen, halo, hydroxy, or C1 to C3 alkoxy, or OCONR₁R₂;

R₆ is hydrogen, halo, hydroxy, C1 to C4 alkoxy, C1 to C4 alkyl, cyano, nitro, or
5 formyl;

R₇ is C1 to C4 alkyl, C1 to C4 alkenyl, CR₁₄R₁₄R₁, SCONR₁R₂, OCSNR₁R₂, (C1 to
C4 alkyl)OCONR₁R₂, NR₁₂SO₂R₁, NR₁COOR₁₃, NR₁COR₁OCOR₂,
NR₁CH₂CHR₁₁, NCONR₁R₂CH₂CHR₁₁, CH=NOR₁, NR₁COR₁,
NR₁C=NHNR₁, NCONR₁OCH₂CH₂CHR₁₁, NR₁COR₉, NR₁CH₂CH₂OR₂,
10 COR₁, CHR₁R₁, CH₂NR₁R₂, CH₂NR₁COOR₁₃, CN, CH₂OPO(OR₁)(OR₂),
CH₂NHCH₂CHR₁₀, COR₉, CHR₁, CHR₁CN, CHR₁COOR₁, CHR₉R₁₀,
CHR₁OCONR₁R₂, CH₂NHCH₂CHR₁₁, (C1 to C4 alkylene)carbonyl, R₉, OR₉,
SR₁, SOR₁, SO₂R₁, CH₂R₁, CR₁₂R₁₂R₉, CH₂NR₁COOR₂, (C1 to C3
alkylene)OR₁, (C1 to C2 alkyl)OR₉, CR₁R₁₂R₂, CR₁R₁₂R₉,
15 CR₁₂R₁PO(OR₁)(OR₂), COCONR₁R₂, C≡CR₁₀, CN, CF₂R₉, CH₂SOR₁,
CH₂SOR₉, NR₁R₂, NR₁R₉, NR₁COR₂, CR₁COR₉, OCONR₁R₂,
CR₁₂R₁CONR₁R₂, CH₂NR₁R₂, CONR₁R₂, CH₂SR₉, NR₁CONR₁R₂;

R₈ is hydrogen, halo, C1 to C4 alkyl, or formyl;

R₉ is a monocyclic heterocycle of 5 or 6 members or a bicyclic heterocycle 8 to 10
20 members, wherein when R₉ is a six membered heterocycle, the
heteroatom(s) are from one to three N atoms, and wherein when the
heterocycle is five membered and has one or two heteroatoms selected
from O, N, or S, wherein when R₉ is an eight to 10 membered bicyclic
heterocycle, the heteroatom(s) are from one to three N atoms, or one to
25 three heteroatoms selected from O, N, or S, and when R₃ is other than
benzyl, or C1 to C4 alkyl;

wherein both R₆ and R₇ are other than both hydroxy, or both CH₃NCOO, or both
methoxy, and when R₇ is hydroxy: R₅, R₆, and R₇ are other than hydroxy,
R₃ is other than benzyl and/or R₄ is other than methyl,

30 wherein when R₇ is methoxy R₄ and R₃ are other than methoxy and benzyl
respectively (all this for one compound), and

wherein when R₇ is acyloxy, R₄ and R₃ are other than methoxy and benzyl
respectively (all this for one compound), and

wherein when R₄ is methyl, ethyl or phenyl, R₂ is other than phenyl or substituted phenyl,

R₁₀ is hydrogen, C1 to C4 alkyl, trimethylsilyl, or SO₂R₁₁;

R₁₁ is hydrogen, C1 to C4 alkyl, phenyl, or C1 to C2 haloalkyl;

5 R₁₂ is hydrogen, C1 to C4 alkyl, phenyl, C1 to C2 haloalkyl, or halo;

R₁₃ is hydrogen, hydroxy, C1 to C4 alkyl, phenyl, or C1 to C2 haloalkyl;

R₁₄ is hydrogen, or halo;

and a pharmaceutically acceptable salt thereof.

10 11. The compound of Claim 10 for use as a medicament.

12. A pharmaceutical composition, comprising the compound of Claim 10 as an active ingredient.

15 13. A TNF α inhibiting composition, comprising the compound of Claim 10 as an active ingredient.

14. An antiinflammatory composition, comprising the compound of Claim 10 as an active ingredient.

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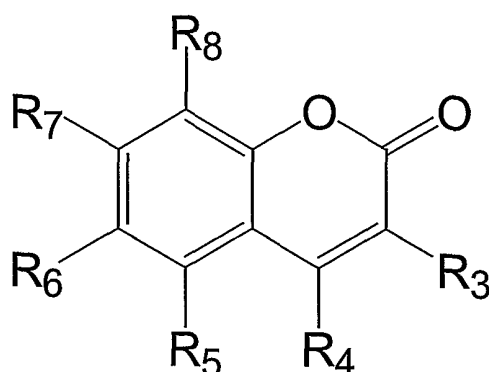
15. Use of the compound of Claim 10 in the manufacture of a pharmaceutical composition.

25 16. A method for the treatment of an immunoinflammatory malady in a patient in need of said treatment, comprising administering to said patient the compound of Claim 10 in an amount efficacious for said treatment.

17. The use of the compound of Claim 10 as a medicament.

30 18. Use of the compound of Claim 10 in the manufacture of a composition for treating an immunoinflammatory malady wherein said malady is selected from a pulmonary disease or an autoimmunoinflammatory disease.

19. A compound useful in the use of Claim 1, of formula:



R₁ is hydrogen, hydroxy, C1 to C4 alkyl, phenyl, C1 to C2 haloalkyl, or halo;

5 R₂ is hydrogen, C1 to C5 alkyl, phenyl or substituted phenyl, wherein

R₁ and R₂ together form an alkylene ring or a hetero alkylene ring;

R₃ is benzyl, or substituted phenyl methylene, wherein the substitution occurs on the phenyl ring;

10 R₄ is C1 to C4 alkyl, C1 to C4 alkyl substituted with phenyl, or heteroaryl, phenyl or substituted phenyl, heteroaryl, wherein in any six membered heteroaryl, heteroatoms consist of one or two nitrogen atoms, and wherein in any five membered heteroaryl the heteroatoms consist of one to three of O, N, or S, and wherein substitution on phenyl or heteroaryl is with halo, phenyl, C1 or C2 alkyl;

15 R₅ is hydrogen or halo;

R₆ is hydrogen, halo, C1 to C4 alkyl, C1 to C4 alkoxy, cyano, nitro, or formyl;

20 R₇ is (C1 to C4 alkylene)carbonyl, R₉, OR₉, OCONR₁R₂, SR₁, SOR₁, SO₂R₁, CH₂R₁, CH₂R₉, CH₂NR₁COOR₂, CH₂NR₁R₂, CH₂OR₁, CH₂OR₉, CH₂OCONR₁R₂, CH₂CONR₁R₂, CH₂CH₂OR₁, CH₂CH₂OCONR₁R₂, C1 to C4 alkyl, C(OH)R₁R₂, C(OH)R₁R₉, CH(OH)COOR₁, CH(OH)CONR₁R₂, CH(OH)PO(OR₁)(OR₂), CO-R₁, COR₉, COCONR₁R₂, COOH, CONR₁R₂, C≡C-R₁₀, CN, COOR₁, CF₂R₁, CF₂CONR₁R₂, CF₂PO(OR₁)(OR₂), CHFR₁, CHFCONR₁R₂, CHFPO(OR₁)(OR₂), CF₂R₉, CH₂OPO(OR₁)(OR₂), CH₂PO(OR₁)(OR₂), CH₂SR₉, CH₂SOR₁, CH₂SOR₉, CH₂SO₂R₉, NR₁CONR₁R₂, NR₁SO₂R₁, NR₁R₂, NR₁R₉, NR₁COR₂, CR₁COR₉;

25 R₈ is hydrogen, halo, C1 to C4 alkyl, or formyl;

R_9 is a monocyclic heterocycle of 5 or 6 members or a bicyclic heterocycle 8 to 10 members, wherein when R_9 is a six membered heterocycle, the heteroatom(s) are from one to three N atoms, and wherein when the heterocycle is five membered and has one or two heteroatoms selected from O, N, or S, wherein when R_9 is an eight to 10 membered bicyclic heterocycle, the heteroatom(s) are from one to three N atoms, or one to three heteroatoms selected from O, N, or S, and when R_3 is other than benzyl, C1 to C4 alkyl;

R_{10} is hydrogen, alkyl, trimethylsilyl, or SO_2R_{11} ;
and a pharmaceutically acceptable salt thereof.

20. The compound according to Claim 10, wherein R_3 is benzyl.

21. The compound according to Claim 10, wherein R_7 is selected from:

