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(71) Applicant *(for all designated States except US)*: **WARNER-LAMBERT COMPANY** [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRATTON, Larry, Don** [US/US]; 9437 Wildwood Lake Drive, Whitmore Lake, MI 48189 (US). **CONNOR, David, Thomas** [GB/US]; 2453 Antietam, Ann Arbor, MI 48105 (US). **MILLER, Steven, Robert** [US/US]; 4450 Hillside Court, Ann Arbor, MI 48105 (US). **TRIVEDI, Bharat, Kalidas** [IN/US]; 36955 Aldgate Court, Farmington Hills, MI 48335 (US). **UNANGST, Paul, Charles** [US/US]; 3659 Middleton Drive, Ann Arbor, MI 48105 (US).

(74) Agents: **FEDERMAN, Evan, J.**; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 et al. (US).

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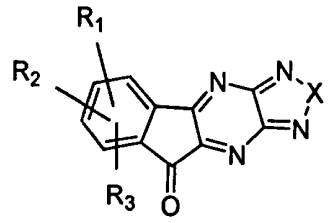
(54) Title: DIAZAFLUORENONE IL-8 RECEPTOR ANTAGONISTS



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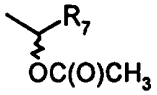

(a)

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(57) Abstract: The present invention relates to diazafluorenone derivatives of Formula (I) or a pharmaceutically acceptable salt thereof wherein: X is O or S; R_1, R_2, and R_3 are independently hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, $(CH_2)_nOC(O)CH_3$, $O(CH_2)_nCO_2R_4$, $O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl, $OC(O)R_5$wherein R_5 is unsubstituted or substitued phenyl, $O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl, Formula (a), or Formula (b) wherein R_7 and R_8 are lower alkyl; and n is an integer from 1 to 3; with the proviso that when X is O, R_1, and R_2, and R_3 are not all hydrogen, which are IL-8 receptor antagonists useful as pharmaceutical agents, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to methods of treating a chemokine-mediated disease state in a mammal, including a human. The diazafluorenones of the present invention are useful in the treatment of chemokine-mediated diseases such as, for example, psoriasis or atopic dermatitis, disease associated with pathological angiogenesis (i.e., cancer), asthma, chronic obstructive pulmory disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, atherosclerosis, cardiac and renal reperfusion injury, glomerulonephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections in a mammal, including a human.

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DIAZAFLUORENONE IL-8 RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

The present invention relates to diazafluorenone derivatives that are pharmaceutical agents useful in the treatment of a mammal, including a human, by virtue of their IL-8 receptor antagonist properties.

IL-8 is a 72 amino acid protein which is a member of the superfamily of leukocyte chemoattractant proteins which have been referred to as intercrines, C-X-C or C-C cytokines or, more recently as chemokines (Oppenheim J.J. et al., "Properties of the novel proinflammatory supergene "intercrine" cytokine family." *Annu. Rev. Immunol.,* 1991;9:617-648). Many members of the chemokine family appear to be involved in the inflammatory process and in the trafficking of leukocytes. The chemokine superfamily is composed of two branches: the α- and the β-chemokines. The α-chemokine branch includes IL-8, neutrophil activating peptide-2 (NAP-2), melanoma growth stimulatory activity (MGSA/gro or GROα), and ENA-78, all of which have attracting and activating effects predominantly on neutrophils. This branch also includes PF4, β-thromboglobulin, and CTAPIII, which do not affect neutrophils.

IL-8 was originally identified by its ability to both attract and activate polymorphonuclear leukocytes (neutrophils) and has now been shown to be rapidly induced in a wide variety of cell and tissue types in response to pro-inflammatory cytokines such as IL-1b or TNFα. Additionally, there is data demonstrating high systemic levels of IL-8 in certain neutrophil-mediated inflammatory diseases, suggesting the IL-8 and closely related factors may be the principal endogenous mediators of neutrophil activation. Many reports have been published regarding disorders in which high levels of IL-8 have been measured, and include rheumatoid arthritis, septic shock, asthma, cystic fibrosis, myocardial infarction, and psoriasis (Baggiolini et al., *FEBS Lett.*, 1992;307:97; Miller et al., *Crit. Rev. Immunol.*, 1992;12:17. Oppenheim et al., *Annu. Rev. Immunol.*, 1991;9:617; Seitz et al., *J. Clin. Invest.*, 1991;87:463; Miller et al., *Am. Rev. Respir. Dis.*, 1992;146:427; Donnely et al., *Lancet*, 1993;341:643). Strong in vivo

evidence indicating a central role of IL-8 in the pathology related to lung ischemia/reperfusion has recently been published (Sekido N., Mukaida N. et al., "Prevention of lung reperfusion injury in rabbits by a monoclonal antibody against interleukin-8," *Nature*, 1993;365(6447):654-7 Issn: 0028-0836). A monoclonal antibody to rabbit IL-8, capable of blocking the in vitro neutrophil chemotactic activity of IL-8, prevented tissue damage in the rabbit lung normally resulting from lung ischemia/reperfusion. More recently, another study has shown beneficial effects of an IL-8 neutralizing antibody in an endotoxin-induced pleurisy model in rabbit (Broaddus V.C., Boylan A.M. et al., "Neutralization of IL-8 inhibits neutrophil influx in a rabbit model of endotoxin-induced pleurisy," *J. Immunol.*, 1994;152(6):2960-2967). There were also reports indicating similar beneficial effects with IL-8 neutralizing antibodies in animal models of dermatitis, joint arthritis, and glomerulonephritis. Additionally, knockout mice have been generated in which the apparent mouse homologue of the IL-8R (closer to IL-8RB) was deleted by homologous recombination (Cacalano G., Lee J. et al., "Neutrophil and b cell expansion in mice that lack the murine IL-8 receptor homolog," *Science*, 1994;265(5172):682-4 Issn: 0036-8075). Although these mice appear healthy, their neutrophils are greatly impaired, as compared to wild-type mice, in their ability to migrate to the peritoneum in response to intraperitoneal thioglycollate injection. All of these results suggest that IL-8 is an important mediator of neutrophil migration and activity in some inflammatory settings. Antagonists to the receptors for IL-8 are useful as anti-inflammatory agents. Also, IL-8 is an important cytokine involved in tumor growth and angiogenesis in a variety of malignancies (Hebert et al., *Cancer Invest.,* 1993;11:743 and Richards et al., *American Journal of Surgery,* 1997;174:507).

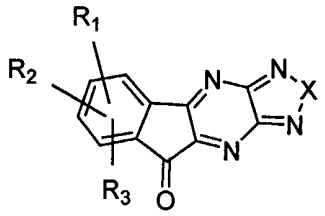
We have identified a series of novel diazafluorenones that are IL-8 receptor antagonists. They can be used in the treatment of psoriasis, or atopic dermatitis, disease associated with pathological angiogenesis (i.e., cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis,

or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections in a mammal, including a human.

SUMMARY OF THE INVENTION

The present invention relates to diazafluorenone derivatives which are IL-8 receptor antagonists useful as pharmaceutical agents, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to methods of treating a chemokine-mediated disease state in a mammal, including a human. More particularly, the diazafluorenones of the present invention are useful in the treatment of chemokine-mediated diseases such as, for example, psoriasis or atopic dermatitis, disease associated with pathological angiogenesis (i.e., cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, atherosclerosis, cardiac and renal reperfusion injury, glomerulonephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections in a mammal, including a human.

The present invention is a compound of Formula I



I

or a pharmaceutically acceptable salt thereof

wherein:

X is O or S;

R_1, R_2, and R_3 are independently

hydrogen,

hydroxy,

lower alkyl,

lower alkoxy,

halogen,

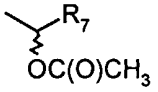
$(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,



, or

wherein R_7 and R_8 are lower alkyl; and

n is an integer from 1 to 3;

with the proviso that when X is O, R_1, R_2, and R_3 are not all hydrogen.

The present invention is also a method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof, or 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one or a pharmaceutically acceptable salt thereof.

The present invention is also a method of treating a chemokine-mediated disease state in a mammal, including a human, wherein the chemokine binds to an IL-8a (CXCR1) or IL-8b (CXCR2) receptor, which comprises administering to said mammal an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof, or 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one or a pharmaceutically acceptable salt thereof.

The present invention is also a compound selected from:

6-Hydroxy-4,5-dimethyl-indan-1-one;

Benzoic acid 6,7-dimethyl-3-oxo-indan-5-yl ester;

(1-Oxo-indan-5-yloxy)-acetic acid methyl ester;

Benzoic acid 3-oxo-indan-5-yl ester;

2,2-Dihydroxy-6-methoxy-4,5-dimethyl-indan-1,3-dione;

Benzoic acid 2,2-dihydroxy-1,3-dioxo-indan-4-yl ester;

Benzoic acid 2,2-dihydroxy-1,3-dioxo-indan-5-yl ester;

2,2-Dihydroxy-5,6-dimethoxy-indan-1,3-dione;

Benzoic acid 6,7-dimethyl-1,2,3,-trioxo-indan-5-yl ester;

(1,2,3-Trioxo-indan-5-yloxy)-acetic acid methyl ester;

4-Bromo-indan-1,2,3-trione;

4,7-Dimethoxy-indan-1,2,3-trione;

5-*tert*-Butyl-indan-1,2,3-trione;

Acetic acid 1-(1,2,3-trioxo-indan-5-yl)-ethyl ester; and

Acetic acid 1-indan-5-yl-ethyl ester.

As inhibitors of chemokine-mediated diseases, the compounds of Formula I or 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one can be used as pharmaceutical agents for treating psoriasis or atopic dermatitis, disease associated with pathological angiogenesis (i.e., cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, atherosclerosis, cardiac and renal reperfusion injury, glomerulonephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections in a mammal, including a human.

Further, the present invention is a pharmaceutical composition comprising a compound of Formula I or 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one in unit dosage form in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is diazafluorenone IL-8 receptor antagonists that are useful as pharmaceutical agents in the treatment of chemokine-mediated diseases.

A preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein X is O.

Another preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein X is S.

Another preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein n is 1.

Another preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein

R_1 is halogen,

lower alkyl,

lower alkoxy,

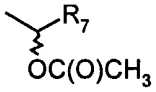
$(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,



, or

wherein R_7 and R_8 are lower alkyl.

Another preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein R_1 is $O(CH_2)_nCO_2R_4$ wherein R_4 is lower alkyl or $O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl.

Another preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein R_2 and R_3 are both hydrogen.

A more preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein

X is O; and

R_1 is halogen,

lower alkyl,

lower alkoxy,

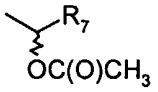
$(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,

 , or  wherein R_7 and R_8 are lower alkyl.

A still more preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein

X is O;

R_1 is halogen,

lower alkyl,

lower alkoxy,

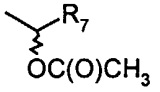
$(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,

 , or  wherein R_7 and R_8 are lower alkyl; and

n is 1.

A still more preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein

X is O;

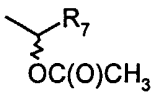
R_1 is $(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,

 , or  wherein R_7 and R_8 are lower alkyl; and

n is 1.

A still more preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof wherein

X is O;

R_1 is $O(CH_2)_nCO_2R_4$ wherein R_4 is lower alkyl or

$O(CH_2)_nR_6$ wherein R_6 is heteroaryl selected from:

2-, 3-, or 4-pyridyl, 2-or 3-thienyl, or 2- or 3-furanyl; and

n is 1.

A still more preferred embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt thereof selected from:

6-Methoxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

Benzoic acid 7,8-dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl ester;

5-Bromo-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid methyl ester;

6-Hydroxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

(7,8-Dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid methyl ester;

(7,8-Dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid tert-butyl ester;

7-Bromo-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

2-Oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

Benzoic acid 9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yl ester;

8-Methyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

5,8-Dimethoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

6,7-Dimethoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-Hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

7-Hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-Methoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yloxy)-acetic acid methyl ester;

(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yloxy)-acetic acid tert-butyl ester;

8-(2-Oxo-propoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Furan-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Thiophen-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-Benzyloxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Pyridin-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Pyridin-3-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Pyridin-3-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one, compound with trifluoro-acetic acid;

8-(Pyridin-4-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

6-tert-Butyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

Acetic acid 1-(9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl)-ethyl ester;

6-(1-Methoxy-ethyl)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one; and

Acetic acid 2-(9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yl)-ethyl ester.

The present invention is also a method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I wherein X is O.

Another preferred embodiment of the present invention is a method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I wherein X is S.

A more preferred embodiment of the present invention is a method of treating a chemokine-mediated disease state in a mammal, including a human,

which comprises administering to said mammal an effective amount of a compound of Formula I wherein:

X is O;

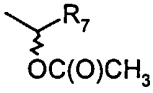
R_1 is $(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,



, or

wherein R_7 and R_8 are lower alkyl; and

n is 1 to 3.

A still more preferred embodiment of the present invention is a method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I wherein:

X is O;

R_1 is $O(CH_2)_nR_6$ wherein R_6 is heteroaryl selected from:

2-, 3-, or 4-pyridyl, 2- or 3-thienyl, or 2- or 3-furanyl; and

n is 1.

A still more preferred embodiment of the present invention is method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I selected from the list of components recited above.

Another preferred embodiment of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable excipient, diluent, or carrier with a compound of Formula I wherein X is O.

Another preferred embodiment of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable excipient, diluent, or carrier with a compound of Formula I wherein X is S.

A more preferred embodiment of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable excipient, diluent, or carrier with a compound of Formula I wherein:

X is O;

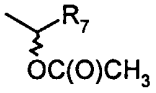
R_1 is $(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,



, or

wherein R_7 and R_8 are lower alkyl; and

n is 1 to 3.

A still more preferred embodiment of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable excipient, diluent, or carrier with a compound of Formula I wherein:

X is O;

R_1 is $O(CH_2)_nR_6$ wherein R_6 is heteroaryl selected from:

2-, 3-, or 4-pyridyl, 2- or 3-thienyl, or 2- or 3-furanyl; and

n is 1.

A still more preferred embodiment of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable excipient, diluent, or carrier with a compound of Formula I selected from the list of compounds recited above.

Some of the compounds of Formula I are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic

acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *J. of Pharma. Sci.*, 1977;66:1).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge supra., 1977).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid that is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 1 to 1000 mg, preferably 10 to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents for the treatment of chemokine-mediated diseases, the compounds utilized in the pharmaceutical method of this invention can be administered at the initial dosage of about 1 to about 100 mg/kg daily. A daily dose range of about 25 mg to about 75 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages that are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

Tablet Formulation

Ingredient	Amount (mg)
(9-Oxo-9*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid, methyl ester	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

The (9-Oxo-9*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid methyl ester, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of chemokine-mediated disease.

As used to define the instant compounds of Formula I, the phrase "lower alkyl" means a straight or branched saturated hydrocarbon group or radical having from 1 to 6 carbon atoms, also known as a C_1-C_6 alkyl. Illustrative examples of a straight or branched alkyl group or radical having from 1 to 3 carbon atoms, also known as a C_1-C_3 alkyl, include methyl, ethyl, 1-propyl, and 2-propyl. Illustrative examples of a straight or branched alkyl group or radical having from 1 to 4 carbon atoms, also known as a C_1-C_4 alkyl, include groups defined for C_1-C_3 alkyl and 1-butyl, 2-butyl, 2-methyl-1-propyl, and 1,1-dimethylethyl. Illustrative examples of a straight or branched alkyl group or radical having from 1 to 6 carbon atoms, also known as a C_1-C_6 alkyl, include groups defined for C_1-C_4 alkyl and 1-pentyl, 2-pentyl, 3-pentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, and 4-methyl-1-pentyl.

The phrase "lower alkoxy" means an alkyl-O- group or radical wherein alkyl is a straight or branched saturated hydrocarbon radical having from 1 to

6 carbon atoms as defined above. Illustrative examples of a straight or branched alkoxy group or radical having from 1 to 3 carbon atoms, also known as a C_1-C_3 alkoxy, include methoxy, ethoxy, 1-propoxy, and 2-propoxy. Illustrative examples of a straight or branched alkoxy group or radical having from 1 to 4 carbon atoms, also known as a C_1-C_4 alkoxy, include groups defined for C_1-C_3 alkoxy and 1-butoxy, 2-butoxy, 2-methyl-1-propoxy, and 1,1-dimethylethoxy. Illustrative examples of a straight or branched alkoxy group or radical having from 1 to 6 carbon atoms, also known as a C_1-C_6 alkoxy, include groups defined for C_1-C_4 alkoxy and 1-pentoxy, 2-pentoxy, 3-pentoxy, 2,2-dimethylpropoxy, 1-hexoxy, 2-hexoxy, 3-hexoxy, and 4-methyl-1-pentoxy.

The term "phenyl" means a cyclic aromatic group or radical having 6 carbon atoms, which group may be optionally substituted with from 1 to 3 substituents selected from: C_1-C_6 alkyl, OH, O-CH_2F, O-CHF_2, O-CF_3, O-(C_1-C_6 alkyl), F, Cl, Br, I, NH_2, N(H)-(C_1-C_6 alkyl), N-(C_1-C_6 alkyl)$_2$, NO_2, CF_3, CN, C≡CH, C≡C-(C_1-C_6 alkyl), CH(OH)-(C_1-C_6 alkyl), CH_2OH, CH_2CO_2H, CO_2H, C(O)-(C_1-C_6 alkyl), C(O)-O-(C_1-C_6 alkyl), CH_2-NH_2, CH_2-N(H)-(C_1-C_6 alkyl), CH_2-N-(C_1-C_6 alkyl)$_2$, C(O)-NH_2, C(O)-N(H)-(C_1-C_6 alkyl), C(O)-N-(C_1-C_6 alkyl)$_2$, O-C(O)-(C_1-C_6 alkyl), O-C(O)-O-(C_1-C_6 alkyl), O-C(O)-N(H)-(C_1-C_6 alkyl), O-C(O)-N-(C_1-C_6 alkyl)$_2$, NH-C(O)-(C_1-C_6 alkyl), N(C_1-C_6 alkyl)-C(O)-(C_1-C_6 alkyl), N(H)-C(O)-O-(C_1-C_6 alkyl), N(C_1-C_6 alkyl)-C(O)-O-(C_1-C_6 alkyl), N(H)-C(O)-NH_2, N(H)-C(O)-N(H)-(C_1-C_6 alkyl), N(C_1-C_6 alkyl)-C(O)-N-(C_1-C_6 alkyl)$_2$, SH, S-(C_1-C_6 alkyl), S(O)-(C_1-C_6 alkyl), S(O)$_2$-(C_1-C_6 alkyl), SO_3H, S(O)$_2$-NH_2, S(O)$_2$-N(H)-(C_1-C_6 alkyl), and S(O)$_2$-N-(C_1-C_6 alkyl)$_2$.

Preferred phenyl substituents are C_1-C_6 alkyl, OH, O-CF_3, O-(C_1-C_6 alkyl), F, Cl, Br, I, NH_2, N(H)-(C_1-C_6 alkyl), N-(C_1-C_6 alkyl)$_2$, NO_2, CF_3, CN, CH_2OH, CH_2CO_2H, CO_2H, C(O)-(C_1-C_6 alkyl), C(O)-O-(C_1-C_6 alkyl), CH_2-NH_2, CH_2-N(H)-(C_1-C_6 alkyl), CH_2-N-(C_1-C_6 alkyl)$_2$, C(O)-NH_2, C(O)-N(H)-(C_1-C_6 alkyl), O-C(O)-(C_1-C_6 alkyl),

O-C(O)-N(H)-(C_1-C_6 alkyl), NH-C(O)-(C_1-C_6 alkyl), N(H)-C(O)-O-(C_1-C_6 alkyl), N(H)-C(O)-NH_2, N(H)-C(O)-N(H)-(C_1-C_6 alkyl), SH, S-(C_1-C_6 alkyl), S(O)-(C_1-C_6 alkyl), $S(O)_2$-(C_1-C_6 alkyl), $S(O)_2$-NH_2, $S(O)_2$-N(H)-(C_1-C_6 alkyl), and $S(O)_2$-N-(C_1-C_6 alkyl)$_2$.

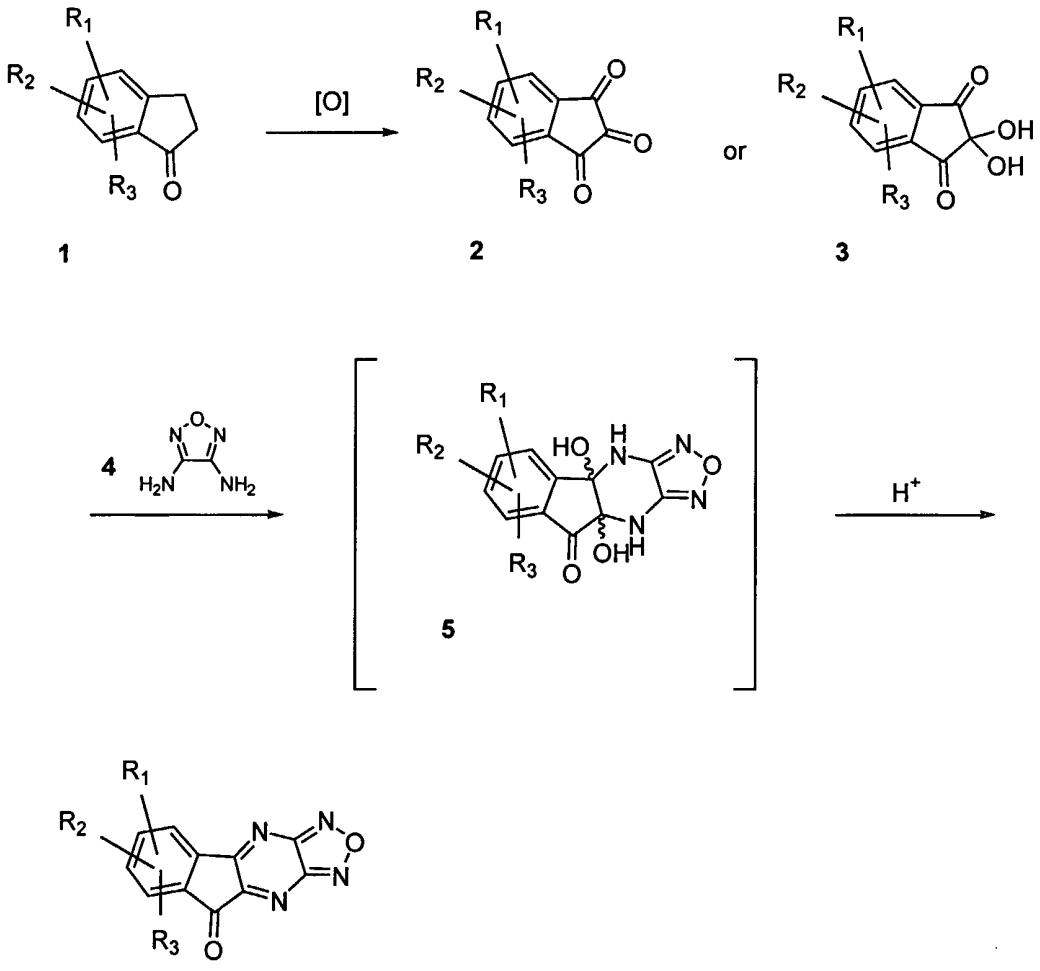
The term "heteroaryl" means a group or radical which is a 5- or 6-membered, monocyclic aromatic ring group containing from 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur, an 8- to 12-membered fused bicyclic ring group wherein at least one ring is aromatic and contains from 1 to 6 heteroatoms selected from nitrogen, oxygen, and sulfur, or a 12- to 14-membered fused tricyclic ring group wherein at least one ring is aromatic and contains from 1 to 6 heteroatoms selected from nitrogen, oxygen, and sulfur. Illustrative examples of monocyclic heteroaryl include 2- or 3-thienyl; 2- or 3-furanyl; 1-, 2-, or 3-pyrrolyl; 1-, 2-, or 4-imidazolyl; 1-, 3-, or 4-pyrazolyl; 2-, 4-, or 5-oxazolyl; 2-, 4-, or 5-thiazolyl; 3-, 4-, or 5-isoxazolyl; 3-, 4-, or 5-isothiazolyl; 1-, 3-, or 5-(1,2,4-triazolyl); 1-, 2-, or 5-(1,3,4-triazolyl); 1-, 4-, or 5-(1,2,3-triazolyl); 1-, 2-, or 5-tetrazolyl; 2-, 3-, or 4-pyridinyl; 3- or 4-pyridazinyl; 2- or 3-pyrazinyl; and 2-, 4-, or 5-pyrimidinyl. Illustrative examples of bicyclic heteroaryl include 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-indolyl; 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl; 2-, 4-, 5-, 6-, or 7-benzofuran; 2-, 4-, 5-, 6-, or 7-benzoxazolyl; 2-, 4-, 5-, 6-, or 7-benzothiazolyl; 4-, 5-, 6-, or 7-benzotriazolyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-benzimidazolyl; 2-, 3-, 4-, 5-, 6-, or 7-benzomorpholine; 2-, 3-, 4-, 5-, 6-, or 7-benzothiomorpholine; and 4-, 5-, 6-, or 7-(2,1,3-benzothiadiazolyl). Illustrative examples of tricyclic heteroaryl include 1-, 2-, 3-, or 4-dibenzofuranyl; 1-, 2-, 3-, or 4-dibenzothienyl; and 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-(1,2,3,4-tetrahydroacridinyl). All with the proviso that when bonded to a heteroatom, the heteroaryl group or radical is connected via a carbon atom.

Preferred heteroaryl groups are 5- or 6-membered monocyclic and 9- or 10-membered bicyclic heteroaryl groups.

The term "halogen" means fluorine, chlorine, bromine, or iodine.

The compounds of Formula I may be prepared by applying synthetic methodology known in the art and synthetic methodology outlined in Schemes 1 to 3.

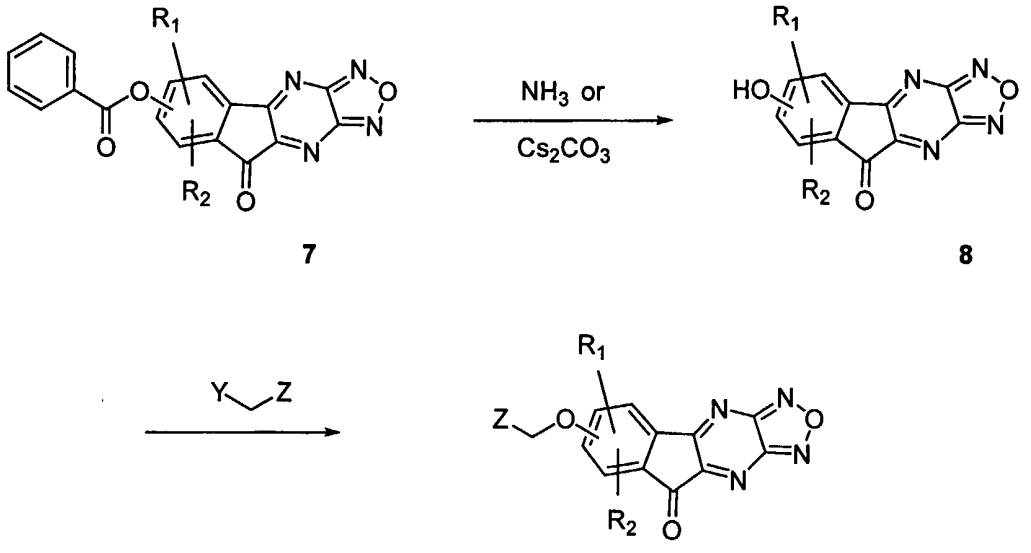
Scheme 1



Substituted indan-1-ones **1** (Scheme 1) are commercially available or may be prepared by well-known methods, such as Cordi A.A., Lacoste J-M., Descombes J-J., Courchay C., Vanhoutte P.M., Laubie M., and Verbeuren T.J., *J. Med. Chem.*, 1995;38:4056; Nilsson J.L.G., Selander H., Sievertsson H., and Skanberg I., *Acta Chem. Scand.*, 1970;24:580; Cornelius L.A.M. and Combs D.W., *Synthetic Communications*, 1994;24:2777; and Adamczyk M., Watt D.S., and Netzel D.A., *J. Org. Chem.*, 1984;49:4226. It is also known that substituted indan-1-ones may be halogenated and the halogenated intermediates oxidized to yield indan-1,2,3-triones **2** or 2,2-dihydroxy-indan-1,3-diones **3**, depending on the reaction conditions employed. See, for example, Heffner R.J. and Joullie M.M., *Synthetic Communications*, 1991;21:2231 and Tatsugi J. and Izawa Y., *Synthetic Communications*, 1998;28:859. Other preparations of

indan-1,2,3-triones beginning with phthalate esters or indan-1,2-diones are also known (Joullie M.M., Thompson T.R., and Nemeroff N.H., *Tetrahedron*, 1991;47:8791). The indan-1,2,3-triones **2** or 2,2-dihydroxy-indan-1,3-diones **3** are reacted with furazan-3,4-diamine **4** (Zelenin A.K. and Trudell M.L., *J. Heterocyclic Chem.*, 1997;34:1057) under acidic conditions by the method of Eremeev A.V., Andrianov V.G., and Piskunova I.P., *Chem. Het. Comp.*, 1978;14:500 to give 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-ones **6**. A similar reaction of **2** or **3** with [1,2,5]thiadiazole-3,4-diamine (Komin A.P. and Carmack M., *J. Heterocyclic Chem.*, 1996;13:13) yields 2-thia-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-ones. The reaction may be run in acetic acid as the solvent or in a mixed solvent consisting of acetic acid and methanol, ethanol, or acetone at -20° to 100° for 2 to 24 hours. In some instances, the diol intermediates **5** may be isolated. Depending on the substituent pattern of the starting substituted indan-1-ones **1,** certain 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-ones **6** may be formed as a mixture of regioisomers. Standard techniques such as chromatography and fractional crystallization may be employed in the separation of these isomer mixtures.

Scheme 2

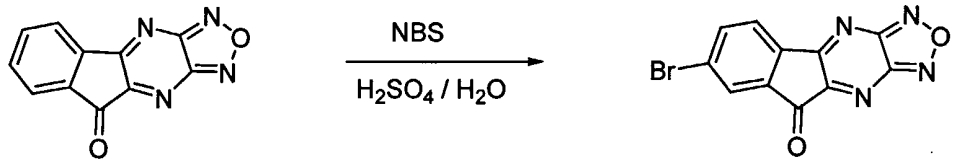


Y = halide, tosylate, or OH

Z = COR_4, CO_2R_4, or R_6

2-Oxa-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-ones containing an esterified phenolic function (**7**, Scheme 2) are prepared by incorporating the ester function into the starting indan-1-one **1**. The esters are treated with ammonia in methanol or ethanol or cesium carbonate in tetrahydrofuran to give the phenolic derivatives **8**. The compounds of type **8** are alkylated with various alkylating agents, such as alkyl halides, alkyl tosylates, or alkyl bromoacetates to form the alkylated products **9**. The alkylation reactions may be conducted with cesium carbonate or potassium carbonate and the appropriate alkylating agents in acetonitrile, acetone or 2-butanone at 25° to 80° for 2 to 24 hours, or with sodium hydride in N,N-dimethylformamide at 25° to 80° for 2 to 24 hours. The compounds of type **8** are also reacted with alcohols by the well-known Mitsunobu reaction (Hughes D.L., *Organic Reactions*, 1992;42:335) as another method of preparing the alkylated products **9**.

Scheme 3

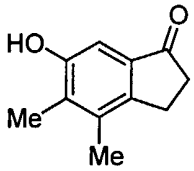


10 **11**

Bromination of the parent 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-one **10** (Scheme 3) under acidic conditions (Dewhurst F. and Shah P.K.J., *J. Chem. Soc.* (C), 1970;1737, and Duan J., Zhang L.H., and Dolbier W.R., Jr., *Synlett*, 1999;1245) yields the mono-brominated derivative **11**.

The following examples are illustrative of the intermediate and final compounds and methods for their preparation. They are not intended to limit the scope of the invention.

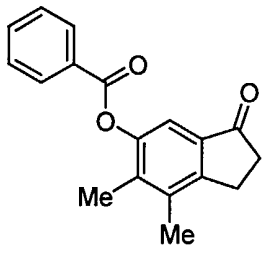
EXAMPLE 1



6-Hydroxy-4,5-dimethyl-indan-1-one

A suspension of aluminum chloride (33.2 g, 249 mmol) in 300 mL of toluene was treated with 6-methoxy-4,5-dimethyl-indan-1-one (22.7 g, 119 mmol; Nilsson J.L.G., Selander H., Sievertsson H., and Skanberg I., *Acta Chem. Scand.*, 1970;24:580). The mixture was stirred at reflux for 1 hour, then added to 2.75 kg of ice and water. The solid was filtered, stirred in 1.5 L of 20% methanol in water, and filtered again to give 19.6 g (93%) of product. A sample recrystallized from aqueous 2-propanol had mp 245°C dec.; ^{1}H NMR (d_6-DMSO): δ 2.10 (s, 3H), 2.15 (s, 3H), 2.49-2.52 (m, 2H), 2.82-2.85 (m, 2H), 6.82 (s, 1H), 9.60 (s, 1H); MS (APCI$^+$), *m/z* 177 (M+1$^+$).

EXAMPLE 2

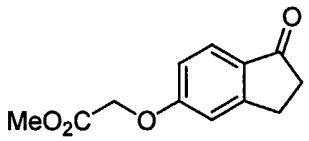


Benzoic acid 6,7-dimethyl-3-oxo-indan-5-yl ester

A suspension of 6-hydroxy-4,5-dimethyl-indan-1-one (21.0 g, 119 mmol) and cesium carbonate (42.9 g, 132 mmol) in 600 mL of acetone was treated dropwise with benzoyl chloride (14.9 mL, 18.0 g, 128 mmol). The mixture was stirred for 24 hours and added to 3.0 kg of ice and water. The solid was filtered, stirred in 1.0 L of 20% methanol in water, and filtered again to give 31.5 g (94%) of product. A sample recrystallized from aqueous acetonitrile had mp 125-127°C; ^{1}H NMR (d_6-DMSO): δ 2.13 (s, 3H), 2.26 (s, 3H), 2.62-2.65 (m, 2H), 2.99-3.02

(m, 2H), 7.29 (s, 1H), 7.57-7.61 (m, 2H), 7.71-7.76 (m, 1H), 8.12-8.14 (m, 2H); MS (APCI$^-$), *m/z* 279 (M-1$^-$).

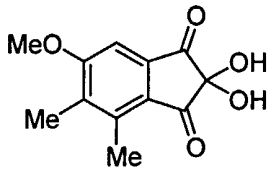
EXAMPLE 3



(1-Oxo-indan-5-yloxy)-acetic acid methyl ester

A suspension of 5-hydroxy-indan-1-one (16.0 g, 108 mmol; Woo L.W.L., Howarth N.M., Purohit A., Hejaz H.A.M., Reed M.J., and Potter B.V.L., *J. Med. Chem.*, 1998;41:1068) cesium carbonate (38.7 g, 119 mmol), and methyl bromoacetate (10.8 mL, 17.5 g, 114 mmol) in 700 mL of acetone was stirred at room temperature for 24 hours. The mixture was filtered, and the filter cake was washed several times with fresh acetone. The combined filtrates were evaporated, and the residue was recrystallized from ethyl acetate/hexane to yield 18.2 g (76%) of product, mp 116-118°C; ^{1}H NMR ($CDCl_3$): δ 2.61 (t, J = 5.9 Hz, 2H), 3.03 (t, J = 5.9 Hz, 2H), 3.76 (s, 3H), 4.66 (s, 2H), 6.82 (s, 1H), 6.86 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H); MS (APCI$^+$), *m/z* 221 (M+1$^+$).

EXAMPLE 4

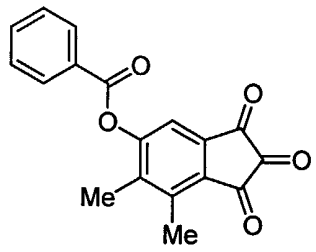


2,2-Dihydroxy-6-methoxy-4,5-dimethyl-indan-1,3-dione

A mixture of 6-methoxy-4,5-dimethyl-indan-1-one (5.0 g, 26.3 mmol) and N-bromosuccinimide (9.5 g, 53.4 mmol) in 65 mL of methyl sulfoxide was heated at 60°C for 3 hours. A vacuum line was attached to the top of the reaction flask condenser, and the mixture was heated at 80°C for 4 hours. The cooled reaction mixture was added to a mixture of 800 mL of brine and 200 mL of

dichloromethane. The precipitated solid was filtered, stirred in a solution of 100 mL of 5% aqueous sodium bicarbonate containing 20 mL of methanol and filtered again to yield 3.1 g (54%) of crude product. A sample recrystallized from water had mp 180°C dec.; ^{1}H NMR (d_6-DMSO): δ 2.19 (s, 3H), 2.61 (s, 3H), 3.96 (s, 3H), 7.25 (s, 1H), 7.30 (s, 2H); MS (APCI$^-$), *m/z* 218 (M-H_2O^-).

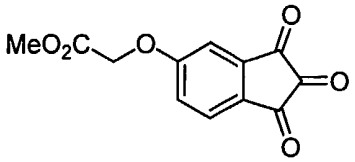
EXAMPLE 5



Benzoic acid 6,7-dimethyl-1,2,3,-trioxo-indan-5-yl ester

A mixture of benzoic acid 6,7-dimethyl-3-oxo-indan-5-yl ester (16.3 g, 58.1 mmol) and N-bromosuccinimide (20.9 g, 117 mmol) in 150 mL of methyl sulfoxide was heated at 40°C for 3 hours. A vacuum line was attached to the top of the reaction flask condenser, and the mixture was heated at 80°C for 4 hours. The cooled reaction mixture was added to 1.5 L of brine and extracted with four 350 mL portions of dichloromethane. The combined extracts were washed with three 500 mL portions of 5% aqueous sodium bicarbonate solution and two 500 mL portions of brine. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by chromatography (eluting with 50% ethyl acetate/hexane) to yield 11.4 g (64%) of product as an oil; ^{1}H NMR (d_6-DMSO): δ 2.24 (s, 3H), 2.69 (s, 3H), 7.46 (s, 1H), 7.57-7.64 (m, 2H), 7.73-7.81 (m, 1H), 8.12-8.19 (m, 2H); MS (APCI$^-$), *m/z* 308 (M$^-$).

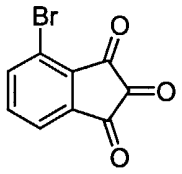
EXAMPLE 6



(1,2,3-Trioxo-indan-5-yloxy)-acetic acid methyl ester

Prepared as an oil in 10% yield from 1-oxo-indan-5-yloxy)-acetic acid methyl ester by the procedure described in Example 5. The crude product was purified by chromatography (eluting with 3% methanol in dichloromethane); ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 4.75 (s, 2H), 7.22 (d, J = 2.2 Hz, 1H), 7.43 (dd, J = 6.1, 2.5 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H); MS (APCI$^-$), *m/z* 248 (M^-).

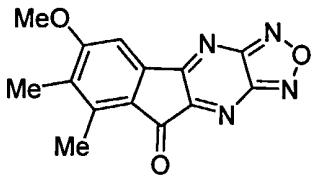
EXAMPLE 7



4-Bromo-indan-1,2,3-trione

Prepared as an oil in 40% yield from 4-bromo-indan-1-one (Cornelius L.A.M. and Combs D.W., *Synthetic Communications*, 1994;24:2777) by the procedure described in Example 5. The crude product was purified by chromatography (eluting with 4% methanol in dichloromethane); ^{1}H NMR ($CDCl_3$): δ 7.65-7.67 (m, 1H), 7.93-8.00 (m, 2H); MS (APCI$^-$), *m/z* 239 (M^-).

EXAMPLE 8

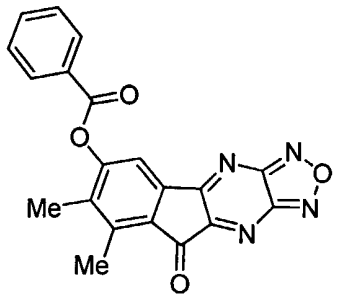


6-Methoxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one

A mixture of 2,2-dihydroxy-4,5-dimethyl-6-methoxy-indan-1,3-dione (2.4 g, 10.0 mmol) and furazan-3,4-diamine (1.1 g, 11.0 mmol; Zelenin A.K. and Trudell M.L, *J. Heterocyclic Chem.*, 1997;34:1057) in 10.0 mL of ethanol and 10.0 mL of glacial acetic acid was stirred at reflux for 4 hours. The precipitated solid was filtered, stirred in 100 mL of 3:1 methanol/water, and filtered again. Recrystallization of the final solid from aqueous acetonitrile gave 1.4 g (50%) of

product, mp 240°C dec.; ^{1}H NMR (d-TFA): δ 2.45 (s, 3H), 2.87 (s, 3H), 4.24 (s, 3H), 11.59 (s, 1H); MS (APCI$^-$), *m/z* 282 (M$^-$).

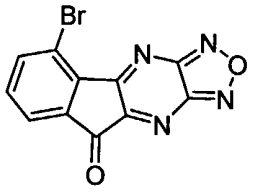
EXAMPLE 9



Benzoic acid 7,8-dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl ester

Prepared in 33% yield from benzoic acid 6,7-dimethyl-1,2,3-trioxo-indan-5-yl ester by the procedure described in Example 8; mp 245°C dec.; ^{1}H NMR (d-TFA): δ 2.56 (s, 3H), 3.00 (s, 3H), 7.71 (t, J = 7.7 Hz, 2H), 7.88 (t, J = 7.5 Hz, 1H), 8.23 (s, 1H), 8.41 (d, J = 7.5 Hz, 2H); MS (APCI$^-$), *m/z* 372 (M$^-$).

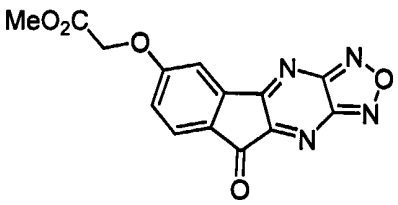
EXAMPLE 10



5-Bromo-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one

Prepared in 11% yield from 4-bromo-indan-1,2,3-trione by the procedure described in Example 8. The crude product was purified by chromatography (eluting with 20% ethyl acetate/hexane). A sample recrystallized from aqueous acetonitrile had mp 290°C dec. ^{1}H NMR ($CDCl_3$): δ 7.74 (t, J = 7.9 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H); MS (APCI$^-$), *m/z* 302 (M-1$^-$).

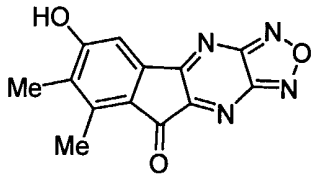
EXAMPLE 11



(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid methyl ester

A mixture of (1,2,3-trioxo-indan-5-yloxy)-acetic acid methyl ester (0.65 g, 3.0 mmol) and furazan-3,4-diamine (0.31 g, 3.1 mmol) in 4.0 mL of ethanol and 4.0 mL of glacial acetic acid was stirred at reflux for 4 hours. The cooled reaction mixture was added to 100 g of ice and water and extracted with four 50 mL portions of ethyl acetate. The combined extracts were washed with three 150 mL portions of 5% aqueous sodium bicarbonate solution and one 150 mL portion of brine. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by chromatography (eluting with 40% ethyl acetate/hexane) to yield 0.26 g (19%) of product. A sample recrystallized from aqueous acetonitrile had mp 203-205°C; ^{1}H NMR (d-TFA): δ 4.09 (s, 3H), 5.16 (s, 2H), 7.61 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 8.27 (d, J = 8.7 Hz, 1H); MS (APCI$^-$), *m/z* 312 (M$^-$).

EXAMPLE 12

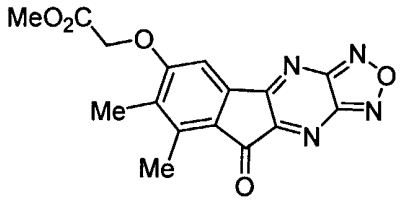


6-Hydroxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one

A suspension of benzoic acid 7,8-dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl ester (5.0 g, 13.4 mmol) in 100 mL of methanol was treated with a solution of 50 mL of 2.0 M ammonia in methanol. The mixture was stirred at room temperature for 18 hours, then added to 500 mL of water. The mixture was filtered, and the filtrate was adjusted to pH 2 by the

addition of 4.0N hydrochloric acid. The precipitated solid was filtered, stirred in 100 mL of 20% methanol in water, and filtered again to yield 3.5 g (97%) of product. A sample recrystallized from aqueous acetonitrile had mp 280°C dec.; ^{1}H NMR (d_6-THF): δ 2.17 (s, 3H), 2.63 (s, 3H), 7.25 (s, 1H); MS (APCI$^-$), *m/z* 267 (M-1$^-$).

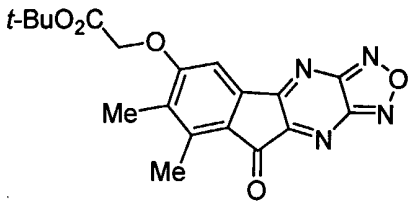
EXAMPLE 13



(7,8-Dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid methyl ester

A mixture of 6-hydroxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one (1.0 g, 3.7 mmol), cesium carbonate (2.4 g, 7.4 mmol), and methyl bromoacetate (1.0 mL, 1.6 g, 10.5 mmol) in 25 mL of acetonitrile was stirred at reflux for 3 hours. The precipitated solid was filtered, stirred in 100 mL of 25% methanol in water, and filtered again. Recrystallization from acetonitrile gave 0.55 g (42%) of product, mp 230°C dec.; ^{1}H NMR (d-TFA): δ 2.51 (s, 3H), 2.89 (s, 3H), 4.08 (s, 3H), 5.20 (s, 2H), 7.76 (s, 1H); MS (APCI$^-$), *m/z* 340 (M$^-$).

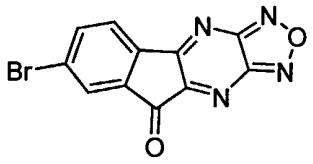
EXAMPLE 14



(7,8-Dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid *tert*-butyl ester

A mixture of 6-hydroxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one (1.0 g, 3.7 mmol) cesium carbonate (2.4 g, 7.4 mmol) and *tert*-butyl bromoacetate (1.5 mL, 2.0 g, 10.2 mmol) in 25 mL of acetonitrile was stirred at reflux for 3 hours. The cooled mixture was filtered, and the filtrate was added to 250 mL of water. The mixture was extracted with four 100 mL portions of ethyl acetate. The combined organic layers were washed with two 250 mL portions of 5% aqueous sodium carbonate solution, followed by one 250 mL portion of brine. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by chromatography (eluting with 30% ethyl acetate/hexane) to yield 0.17 g (12%) of product. A sample recrystallized from aqueous acetonitrile had mp 265°C dec.; ^{1}H NMR (d-TFA): δ 1.68 (s, 9H), 2.53 (s, 3H), 2.90 (s, 3H), 5.24 (s, 2H), 7.79 (s, 1H); MS (APCI$^-$), *m/z* 382 (M$^-$).

EXAMPLE 15

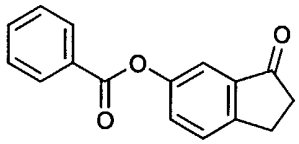


7-Bromo-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one

A suspension of 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one (0.68 g, 3.0 mmol; Eremeev A.V., Andrianov V.G., and Piskunova I.P., *Chem. Het. Comp.*, 1978;14:500) in 20 mL of 80% sulfuric acid was treated with N-bromosuccinimide (0.56 g, 3.1 mmol). The mixture was heated at 55°C for 4 hours, then cooled and added to 300 g of ice and water. The precipitated solid was filtered, stirred in 100 mL of 5% aqueous sodium bicarbonate solution containing 10% methanol and filtered again. The solid was purified by chromatography (eluting with 20% ethyl acetate/hexane) to yield 0.25 g (27%) of product. A sample recrystallized from aqueous acetonitrile had mp 260°C dec.;

^{1}H NMR (d-TFA): δ 8.14-8.18 (m, 1H), 8.19-8.23 (m, 1H), 8.28 (s, 1H); MS (APCI$^-$), *m/z* 302 (M-1$^-$).

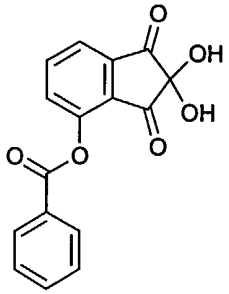
EXAMPLE 16



Benzoic acid 3-oxo-indan-5-yl ester

To a solution of 6-hydroxy-indan-1-one (12.7 g, 85.5 mmol; Woo L.W.L., Howarth N.M., Purohit A., Hejaz H.A.M., Reed M.J., and Potter B.V.L., *J. Med. Chem.*, 1998;41:1068) in 340 mL of acetone was added cesium carbonate (32.2 g, 98.7 mmol), followed by benzoyl chloride (12.6 g, 10.4 mmol). The reaction mixture was stirred at room temperature for 18 hours, filtered, and the filter cake was rinsed with acetone. The solid was triturated in water, filtered, and dried to give 7.3 g of product. The acetone filtrate was evaporated to give a solid, which was triturated in water to afford additional product (12.7 g) for a total yield of 20.0 g (93%), mp 147-148°C; ^{1}H NMR (d$_6$-DMSO): δ 2.69 (t, J = 5.6 Hz, 2H), 3.13 (t, J = 5.6 Hz, 2H), 7.51 (d, J = 2.2 Hz, 1H), 7.53-7.78 (m, 5H), 8.12 (d, J = 7.4 Hz, 2H); MS (APCI$^+$), *m/z* 253 (M+1$^+$).

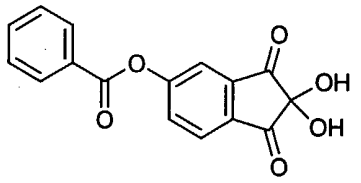
EXAMPLE 17



Benzoic Acid 2,2-Dihydroxy-1,3-dioxo-indan-4-yl ester

To a solution of benzoic acid 1-oxo-indan-4-yl ester (2.00 g, 7.93 mmol) in 40 mL of methyl sulfoxide was added N-bromosuccinimide (2.85 g, 16.02 mmol). The reaction mixture was stirred at 60°C for 3 hours. A vacuum line was attached to the top of the reaction flask condenser, and the mixture was heated at 80°C for 4 hours. The cooled reaction mixture was poured into 200 mL of water. The product was extracted with three portions of 100 mL of dichloromethane. The combined organic extracts were dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography (eluting with 50-70% ethyl acetate/hexane) to yield 1.36 g (61%) of product. A sample recrystallized from water had mp 133-136°C; ^{1}H NMR (d_6-DMSO): δ 7.55 (s, 2H), 7.63 (t, J = 7.7 Hz, 2H), 7.77 (t, J = 7.5 Hz, 1H), 7.89-7.98 (m, 2H), 8.07-8.19 (m, 3H); MS(APCI$^-$), *m/z* 280 (M-H_2O^-).

EXAMPLE 18

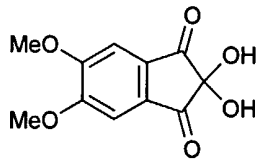


Benzoic acid 2,2-dihydroxy-1,3-dioxo-indan-5-yl ester

To a solution of benzoic acid 3-oxo-indan-5-yl ester (18.9 g, 74.8 mmol) in 350 mL of methyl sulfoxide was added N-bromosuccinimide (28.0 g, 157.2 mmol). The reaction mixture was stirred at 60°C for 3 hours. A vacuum line was attached to the top of the reaction flask condenser, and the mixture was heated at 80°C for 5 hours. The cooled reaction mixture was poured into 400 mL of water. The product was extracted with four portions of 100 mL of dichloromethane. The combined extracts were washed with two 100 mL portions of 5% aqueous sodium bicarbonate solution. A precipitate formed which was filtered and dried to give 3.3 g of product. The organic layer was dried (sodium sulfate), and evaporated to afford a red-brown oil, which was purified by flash chromatography (eluting with 50-70% ethyl acetate/hexane) to afford additional

product (7.9 g), for a total yield of 11.2 g (50%). A sample recrystallized from water had mp 210-211°C; ^{1}H NMR (d_6-DMSO): δ 7.57 (s, 2H), 7.62 (t, J = 7.7 Hz, 2H), 7.77 (t, J = 7.5 Hz, 1H), 7.95-8.02 (m, 2H), 8.09-8.21 (m, 3H); MS(APCI$^-$), *m/z* 280 (M-H_2O^-).

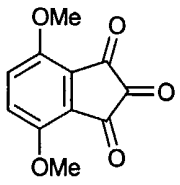
EXAMPLE 19



2,2-Dihydroxy-5,6-dimethoxy-indan-1,3-dione

Prepared in 71% yield from 5,6-dimethoxy-indan-1-one by the procedure described in Example 17. A sample recrystallized from water had mp 260-263°C; ^{1}H NMR (d_6-DMSO): δ 3.94 (s, 6H), 7.32 (s, 2H), 7.36 (s, 2H); MS(APCI$^-$), *m/z* 220 (M-H_2O^-).

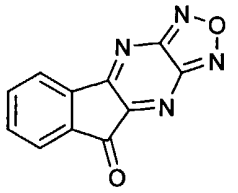
EXAMPLE 20



4,7-Dimethoxy-indan-1,2,3-trione

Prepared as an amorphous solid in 30% yield from 4,7-dimethoxy-indan-1-one by the procedure described in Example 17; ^{1}H NMR (d_6-DMSO): δ 3.87 (s, 6H), 7.57 (s, 2H); MS(APCI$^-$), *m/z* 220 (M$^-$).

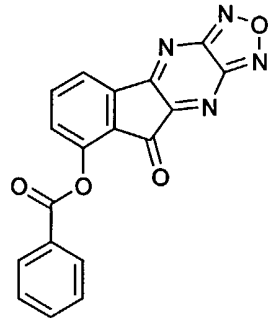
EXAMPLE 21



2-Oxa-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-one

A mixture of 2,2-dihydroxy-indan-1,3-dione (4.4 g, 24.5 mmol) and furazan-3,4-diamine (2.5 g, 24.5 mmol) in 60 mL of ethanol and 60 mL of glacial acetic acid was stirred at room temperature for 1 hour and then heated at reflux for 18 hours. The precipitated solid was filtered and dried to yield 4.5 g (82%) of product; mp 301-302°C; ^{1}H NMR (d_6-DMSO): δ 7.93 (t, J = 7.5 Hz, 1H), 7.99-8.10 (m, 2H), 8.28 (d, J = 7.6 Hz, 1H); MS (APCI$^-$), *m/z* 224 (M$^-$).

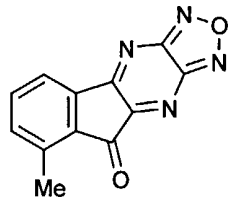
EXAMPLE 22



Benzoic Acid 9-Oxo-9-*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluoren-8-yl ester

A mixture of benzoic acid 2,2-dihydroxy-1,3-dioxo-indan-4-yl ester (1.18 g, 3.96 mmol) and furazan-3,4-diamine (0.40 g, 3.90 mmol) in 12 mL of ethanol and 12 mL of glacial acetic acid was stirred at room temperature for 18 hours and then heated at reflux for 6 hours. The precipitated solid was filtered and washed with water to yield 0.62 g (46%) of product; mp 215-217°C; ^{1}H NMR (d-TFA): δ 7.67 (t, J = 7.8 Hz, 2H), 7.81-7.88 (m, 2H), 8.22 (t, J = 7.9 Hz, 1H), 8.36 (d, J = 7.9 Hz, 2H), 8.44 (d, J = 7.7 Hz, 1H); MS (APCI$^-$), *m/z* 344 (M$^-$).

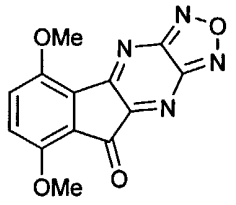
EXAMPLE 23



8-Methyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

A solution of 2,2-dihydroxy-4-methyl-indane-1,3-dione (5.77 g, 30.03 mmol; Kapicak L.A. and Battiste M.A., *Synthesis*, 1971;153) in 100 mL of ethanol was cooled to -10°C and treated with furazan-3,4-diamine (3.01 g, 30.03 mmol). The reaction mixture was stirred at -10°C for 3 days and then at room temperature for 2 hours, at which time 100 mL of glacial acetic acid was added. The reaction mixture was heated at reflux for 18 hours and then filtered to afford 1.70 g (24%) of product; mp 265-267°C; ^{1}H NMR (d-TFA): δ 2.92 (s, 3H), 7.83 (d, J = 7.7 Hz, 1H), 8.00 (t, J = 7.8 Hz, 1H), 8.30 (d, J = 7.6 Hz, 1H); MS (APCI$^-$), *m/z* 238 (M$^-$).

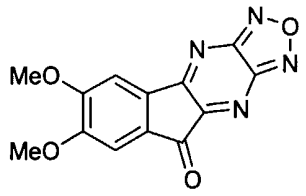
EXAMPLE 24



5,8-Dimethoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

Prepared in 18% yield from 4,7-dimethoxy-indan-1,2,3-trione by the procedure described in Example 22; mp 295-297°C; ^{1}H NMR (d-TFA): δ 4.27 (s, 3H), 4.31 (s, 3H), 7.71 (d, J = 9.5 Hz, 1H), 7.84 (d, J = 9.5 Hz, 1H); MS (APCI$^+$), *m/z* 285 (MH$^+$).

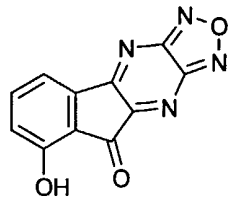
EXAMPLE 25



6,7-Dimethoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

Prepared in 59% yield from 2,2-dihydroxy-5,6-dimethoxy-indan-1,3-dione by the procedure described in Example 22; mp 303-305°C; ^{1}H NMR (d-TFA): δ 4.35 (s, 3H), 4.41 (s, 3H), 7.88 (s, 1H), 8.06 (s, 1H); MS (APCI$^-$), *m/z* 284 (M$^-$).

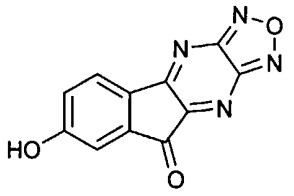
EXAMPLE 26



8-Hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

A mixture of benzoic acid 9-oxo-9-*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluoren-8-yl ester (0.87 g, 2.52 mmol) and cesium carbonate (1.72 g, 5.28 mmol) in 50 mL of tetrahydrofuran was stirred at room temperature for 5 days. The precipitated solid was filtered, washed with fresh tetrahydrofuran, and dissolved in 100 mL of water. The aqueous mixture was acidified with 1N hydrochloric acid to pH 2-3. The precipitated solid was filtered and rinsed with water to yield 0.57 g (94%) of product. A sample recrystallized from methanol had mp 305°C; ^{1}H NMR (d$_8$-THF): δ 7.22 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 7.3 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 9.94 (bs, 1H); MS (APCI$^-$), *m/z* 240 (M$^-$).

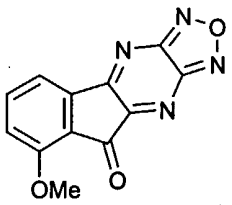
EXAMPLE 27



7-Hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

Benzoic acid 2,2-dihydroxy-1,3-dioxo-indan-5-yl ester was reacted with furazan-3,4-diamine by the procedure described in Example 22 to give in 68% yield a mixture of the regioisomers benzoic acid 9-oxo-9-*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluoren-6-yl ester and benzoic acid 9-oxo-9-*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluoren-7-yl ester. The isomer mixture was purified by flash chromatography (eluting with 20-100% ethyl acetate/hexane), followed by recrystallization from aqueous acetonitrile. The above isomer mixture was reacted with cesium carbonate by the procedure described in Example 26. Recrystallization of the crude product from aqueous acetonitrile gave the pure 7-hydroxy isomer in 6% yield; mp 278-280°C; ^{1}H NMR (d$_8$-THF): δ 7.23 (dd, J = 8.5, 2.3 Hz, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 10.82 (bs, 1H); MS (APCI$^-$), *m/z* 240 (M$^-$).

EXAMPLE 28

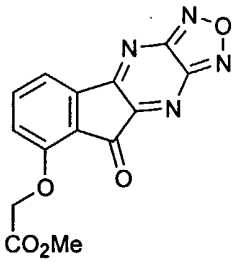


8-Methoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

To a solution of 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one (0.50 g, 2.1 mmol) in 50 mL of N,N-dimethylformamide was added sodium hydride (0.09 g, 2.3 mmol of 60% dispersion in mineral oil), followed by 0.21 mL of iodomethane (2.29 mmol). The reaction mixture was stirred at 60°C for 2 hours, and the solvent was evaporated. The residue was dissolved in ethyl

acetate and washed with three 100 mL portions of water. The organic layer was dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography (eluting with 20% ethyl acetate/dichloromethane) and recrystallized from acetonitrile/hexane to yield 0.12 g (22%) of product; mp 291-293°C; ^{1}H NMR (d-TFA): δ 4.49 (s, 3H), 7.83 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 7.5 Hz, 1H), 8.41 (t, J = 8.4 Hz, 1H); MS (APCI$^-$), *m/z* 254 (M$^-$).

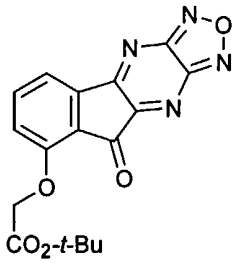
EXAMPLE 29



(9-Oxo-9*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluoren-8-yloxy)-acetic acid methyl ester

A mixture of 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one (0.25 g, 1.04 mmol), cesium carbonate (0.37 g, 1.14 mmol), and methyl bromoacetate (0.10 mL, 0.17 g, 1.09 mmol) in 10 mL of acetone was heated at reflux for 18 hours. The precipitated solid was filtered to give 0.48 g of the cesium salt of the starting phenol. The salt was combined with an additional 0.13 mL (0.21 g, 1.4 mmol) of methyl bromoacetate in 10 mL of N,N-dimethylformamide. The reaction mixture was heated at 60°C for 4 hours, stirred at room temperature for 18 hours, and added to a mixture of ice and water. The precipitated solid was filtered and purified by flash chromatography (eluting with 30% ethyl acetate/hexane) to yield 0.11 g (27%) of product. A sample recrystallized from aqueous acetonitrile had mp 205-206°C; ^{1}H NMR (d-TFA): δ 4.05 (s, 3H), 5.18 (s, 2H), 7.34-7.46 (m, 1H), 8.03-8.16 (m, 2H); MS (APCI$^-$), *m/z* 312 (M$^-$).

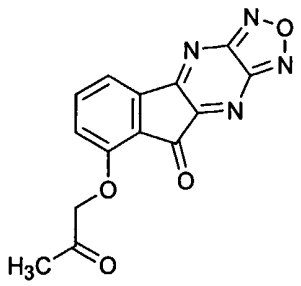
EXAMPLE 30



(9-Oxo-9*H*-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluoren-8-yloxy)-acetic acid *tert*-butyl ester

A mixture of 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one (0.21 g, 0.87 mmol), cesium carbonate (0.31 g, 0.96 mmol), and *tert*-butyl bromoacetate (0.14 mL, 0.18 g, 0.91 mmol) in 10 mL of N,N-dimethylformamide was heated at 60°C for 3 hours, stirred at room temperature for 18 hours, and added to a mixture of ice and water. The precipitated solid was filtered and purified by flash chromatography (eluting with 30-50% ethyl acetate/hexane) to yield 0.21 g (68%) of product. A sample recrystallized from aqueous acetonitrile had mp 184-186°C; ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 9H), 4.80 (s, 2H), 7.09 (dd, J = 8.0, 1.1 Hz, 1H), 7.19 (s, 1H), 7.78-7.87 (m, 1H); MS (APCI$^-$), *m/z* 354 (M^-).

EXAMPLE 31

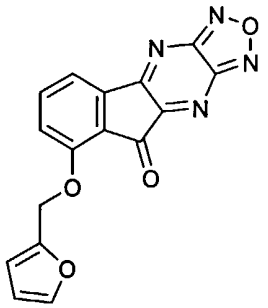


8-(2-Oxo-propoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

A mixture of 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-one (2.00 g, 8.33 mmol), acetol (0.68 g, 9.16 mmol), triphenylphosphine (2.62 g, 10.00 mmol), and diethyl azodicarboxylate (1.74 g, 10.00 mmol) in 60 mL of tetrahydrofuran was stirred at room temperature for 18 hours. The

solvent was evaporated, and the residue was purified by flash chromatography (eluting with 50-70% ethyl acetate/hexane). The chromatographed material was triturated in dichloromethane to give 0.078 g (8%) of product; mp 225°C dec.; ^{1}H NMR (d$_8$-THF): δ 2.31 (s, 3H), 4.92 (s, 2H), 7.31 (dd, J = 9.1, 2.4 Hz, 1H), 7.81-7.91 (m, 2H). MS (APCI$^-$), *m/z* 296 (M$^-$).

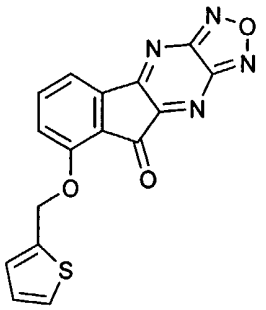
EXAMPLE 32



8-(Furan-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

A mixture of 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-one (2.00 g, 8.33 mmol), furfuryl alcohol (0.79 mL, 0.90 g, 9.16 mmol), triphenylphosphine (2.62 g, 10.00 mmol), triethylamine (1.16 mL, 0.84 g, 8.33 mmol), and diethyl azodicarboxylate (1.74 g, 10.00 mmol) in 60 mL of tetrahydrofuran was stirred at room temperature for 18 hours. The solvent was evaporated, and the residue was purified by flash chromatography (eluting with 30-50% ethyl acetate/hexane). The chromatographed material was triturated in water to give 0.64 g (24%) of product; mp 184-185°C; ^{1}H NMR (d$_8$-THF): δ 5.36 (s, 2H), 6.38-6.42 (m, 1H), 6.59 (d, J = 3.2 Hz, 1H), 7.52-7.55 (m, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H); MS (APCI$^-$), *m/z* 320 (M$^-$).

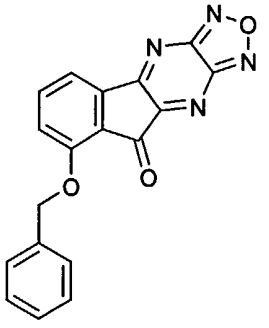
EXAMPLE 33



8-(Thiophen-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one

Prepared in 27% yield from 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one and 2-hydroxymethyl thiophene by the procedure described in Example 32. The chromatographed material was triturated in dichloromethene and recrystallized from aqueous acetonitrile to yield the final product; mp 198-200°C; ^{1}H NMR (d$_8$-THF): δ 5.59 (s, 2H), 6.99 (t, J = 4.3 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 7.42 (dd, J = 5.1, 1.1 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.79-8.00 (m, 2H); MS (APCI$^-$), *m/z* 336 (M$^-$).

EXAMPLE 34

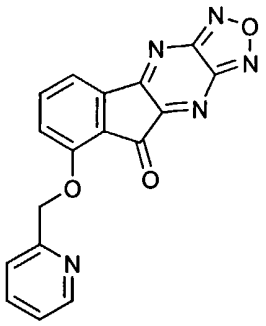


8-Benzyloxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

Prepared in 27% yield from 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-one and benzyl alcohol by the procedure described in Example 32. The precipitated solid was filtered and washed with tetrahydrofuran. The crude product was purified by flash chromatography (eluting with

chloroform). A sample recrystallized from acetonitrile had mp 236-237°C; ^{1}H NMR (d$_8$-THF): δ 5.42 (s, 2H), 7.29 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.3 Hz, 2H), 7.53 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 7.3 Hz, 2H); MS (APCI$^-$), *m/z* 330 (M$^-$).

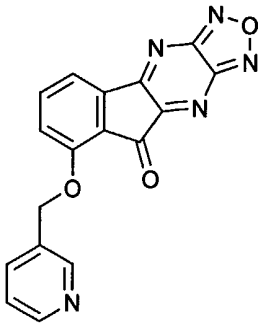
EXAMPLE 35



8-(Pyridin-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

Prepared in 58% yield from 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one and pyridin-2-yl-methanol by the procedure described in Example 32. A sample recrystallized from acetonitrile had mp 230-231°C; ^{1}H NMR (d-TFA): δ 6.10 (s, 2H), 7.75-7.85 (m, 1H), 8.24-8.39 (m, 3H), 8.48 (d, J = 7.9 Hz, 1H), 8.93 (t, J = 7.9 Hz, 1H), 9.27 (d, J = 5.7 Hz, 1H); MS (APCI$^-$), *m/z* 331 (M$^-$).

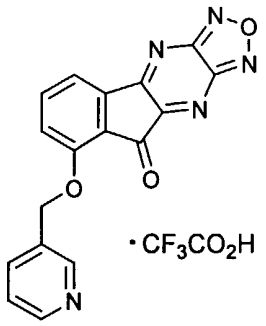
EXAMPLE 36



8-(Pyridin-3-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

Prepared in 35% yield from 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one and pyridin-3yl-methanol by the procedure described in Example 32. A sample recrystallized from acetonitrile had mp 239-240°C; ^{1}H NMR (d-TFA): δ 5.89 (s, 2H), 7.78 (d, J = 7.9 Hz, 1H), 8.20-8.46 (m, 3H), 8.97-9.15 (m, 2H), 9.69 (s, 1H); MS (APCI$^-$), *m/z* 331 (M$^-$).

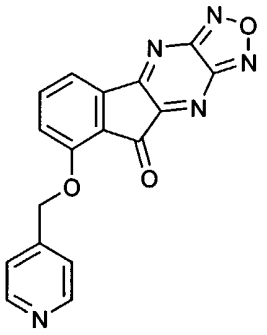
EXAMPLE 37



8-(Pyridine-3-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluorene-9-one Trifluoroacetic Acid Salt

Prepared in 38% yield from 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one and 3-chloromethylpyridine by the procedure described in Example 28. Recrystallization from aqueous acetonitrile followed by purification by preparative HPLC (eluting with acetonitrile/water/trifluoroacetic acid) gave the product as the trifluoroacetic acid salt; mp 233-235°C; ^{1}H NMR (d_6-DMSO): δ 6.03 (s, 2H), 7.93 (d, J = 7.6 Hz, 1H), 8.44 (m, 2H), 8.56 (t, J = 6.1 Hz, 1H), 9.23 (m, 2H), 9.86 (s, 1H); MS (APCI$^-$), *m/z* 331 (M$^-$).

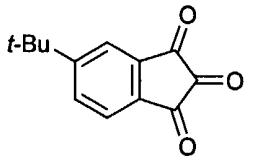
EXAMPLE 38



8-(Pyridine-4-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

A mixture of 8-hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one (2.00 g, 8.33 mmol), 4-pyridyl-carbinol (1.00 g, 9.16 mmol), triphenylphosphine (2.62 g, 10.00 mmol), triethylamine (1.16 mL, 0.84 g, 8.33 mmol), and diethyl azodicarboxylate (1.74 g, 10.00 mmol) in 60 mL of tetrahydrofuran was stirred at room temperature for 18 hours. The precipitated solid was filtered and washed with tetrahydrofuran to yield 1.92 g (70%) of product; mp 200-201°C; ^{1}H NMR (d-TFA): δ 6.07 (s, 2H), 7.89 (d, J = 7.4 Hz, 1H), 8.39-8.47 (m, 2H), 8.89 (d, J = 6.4 Hz, 2H), 9.24 (d, J = 6.5 Hz, 2H); MS (APCI$^-$), *m/z* 331 (M$^-$).

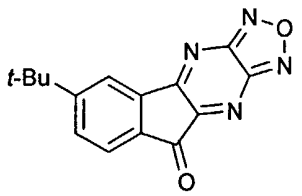
EXAMPLE 39



5-*tert*-Butyl-indan-1,2,3-trione

Prepared as an oil in 52% yield from 6-*tert*-butyl-indan-1-one (Cordi A.A., Lacoste J-M., Descombes J-J., Courchay C., Vanhoutte P.M., Laubie M., and Verbeuren T.J., *J. Med. Chem.*, 1995;38:4056) by the procedure described in Example 17. The crude product was purified by flash chromatography (eluting with 40% ethyl acetate/hexane); MS (APCI$^-$), *m/z* 216 (M$^-$).

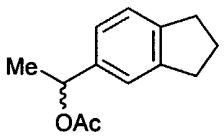
EXAMPLE 40



6-*tert*-Butyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[*b*]fluorene-9-one

A mixture of 5-*tert*-butyl-indan-1,2,3-trione (3.0 g, 13.9 mmol) and furazan-3,4-diamine (1.6 g, 16.0 mmol) in 30 mL of acetone and 10 mL of glacial acetic acid was stirred at reflux for 16 hours. The precipitated solid was filtered and washed with acetone to give 0.56 g (14%) of product; mp 242-244°C; ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 9H), 8.01 (d, J = 6.4 Hz, 1H), 8.09 (s, 1H), 8.21 (d, J = 6.4 Hz, 1H); MS (APCI$^-$), *m/z* 280 (M^-).

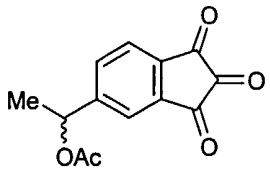
EXAMPLE 41



Acetic acid 1-indan-5-yl-ethyl ester

A mixture of 1-indan-5-yl-ethanol (13.0 g, 80.1 mmol; Loeliger P., Bollag W., and Mayer H., *Eur. J. Med. Chem.-Chim. Ther.*, 1980;15:9) and acetic anhydride (8.0 mL, 8.7 g, 84.8 mmol) in 40 mL of pyridine was stirred at room temperature for 20 hours. The mixture was evaporated, and the residue was purified by flash chromatography (eluting with 20% ethyl acetate/hexane) to yield 11.5 g (70%) of the product as an oil mp; ^{1}H NMR ($CDCl_3$): δ 1.50 (d, J = 6.6 Hz, 3H), 1.99-2.09 (m, 5H), 2.85-2.90 (m, 4H), 5.83 (m, 1H), 7.10-7.26 (m, 3H).

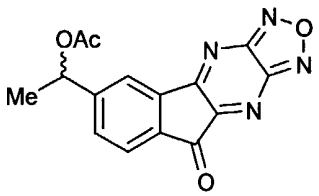
EXAMPLE 42



Acetic acid 1-(1,2,3-trioxo-indan-5-yl)-ethyl ester

A solution of acetic acid 1-indan-5-yl-ethyl ester (11.5 g, 56.3 mmol) in 800 mL of glacial acetic acid was treated dropwise with a solution of chromium (VI) oxide (16.7 g, 167 mmol) in 168 mL of glacial acetic acid and 10 mL of water. The mixture was stirred at room temperature for 3 hours and 240 mL of 2-propanol was added. The mixture was evaporated, and the residue was taken up in diethyl ether. The ether extract was filtered, and the filtrate was washed with 5% aqueous sodium bicarbonate solution, followed by brine. The organic layer was evaporated, and the residue was purified by flash chromatography (eluting with 20% ethyl acetate/hexane) to yield 5.1 g (41%) of an oil consisting of a mixture of acetic acid 1-(1-oxo-indan-5-yl)-ethyl ester and acetic acid 1-(1-oxo-indan-6-yl)-ethyl ester. The above indan one mixture was reacted with N-bromosuccinimide by the procedure described in Example 17 to yield the trione product as an oil in 52% yield. The crude product was purified by flash chromatography (eluting with 40% ethyl acetate/hexane); MS (APCI$^-$), *m/z* 246 (M$^-$).

EXAMPLE 43

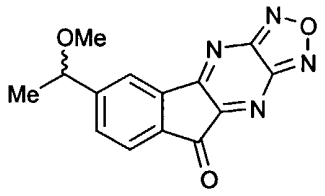


Acetic acid 1-(9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl)-ethyl ester

A mixture of acetic acid 1-(1,2,3-trioxo-indan-5-yl)-ethyl ester (2.5 g, 10.1 mmol) and furazan-3,4-diamine (1.0 g, 10.1 mmol) in 20 mL of ethanol was

stirred at room temperature for 16 hours. Glacial acetic acid (20 mL) was added, and the mixture was stirred at reflux for 5 hours. The precipitated solid was filtered and washed with ethanol to give 0.65 g (20%) of product; mp 198-200°C; ^{1}H NMR ($CDCl_3$): δ 1.60 (d, J = 5.4 Hz, 3H), 2.13 (s, 3H), 5.95 (m, 1H), 7.91 (d, J = 7.3 Hz, 1H), 8.05 (s, 1H), 8.27 (d, J = 7.1 Hz, 1H); MS (APCI$^-$), *m/z* 310 (M^-).

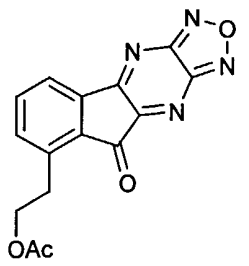
EXAMPLE 44



6-(1-Methoxy-ethyl)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one

A suspension of acetic acid 1-(9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl)-ethyl ester (0.40 g, 1.3 mmol) in 50 mL of methanol and 5.0 mL of 5N hydrochloric acid was stirred at reflux for 3 hours. The mixture was diluted with water, and the insoluble material was filtered. The solid was purified by flash chromatography (eluting with 3% methanol in dichloromethane) to yield 0.23 g (64%) of product; mp 209-211°C; ^{1}H NMR ($CDCl_3$): δ 1.48 (d, J = 6.6 Hz, 3H), 3.32 (s, 3H), 4.48 (m, 1H), 7.93 (d, J = 7.8 Hz, 1H), 8.02 (s, 1H), 8.28 (d, J = 7.8 Hz, 1H); MS (APCI$^-$), *m/z* 282 (M^-).

EXAMPLE 45



Acetic acid 2-(9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yl)-ethyl ester

Acetic acid 2-(1,2,3-trioxo-indan-4-yl)-ethyl ester was prepared as an oil in 31% yield from acetic acid 2-(1-oxo-indan-4-yl)-ethyl ester (Nakada Y., Ohno S., Yoshimoto M., and Yura Y., *Agric. Biol. Chem.,* 1978;42:1365) by the procedure described in Example 17. The crude product was purified by flash chromatography (eluting with 40% ethyl acetate/hexane). The above ester was reacted with furazan-3,4-diamine by the procedure described in Example 43 to give the title compound in 35% yield. A sample recrystallized from ethanol had mp 208-209°C; ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 3H), 3.54 (t, J = 6.5 Hz, 2H), 4.41 (t, J = 6.4 Hz, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.87 (t, J = 7.6 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H).

The compounds of the present invention were evaluated in an IL-8 receptor binding assay.

Interleukin-8 Binding Assay

The binding studies were carried out with reaction mixtures consisting of 80 pM ^{125}I-IL-8, 12 nM cold IL-8 when present (cold IL-8 is not added to every tube, only the tubes that will give non-specific binding data), 0.1% DMSO (v/v), 40 μM to 40 nM of compound, and 40,000 isolated human Neutrophils. Incubations were carried out at room temperature for 3 hours. Assays were terminated by centrifugation through sucrose, and raw data was obtained using a gamma counter.

Chemotaxis Assay

Compounds of Formula I were evaluated for their effect on chemotaxis using methodology known in the art, e.g., Carr M.W., Roth S.J., Luther E., Rose S.S., and Springer T.A., "Monocyte chemoattractant protein 1 acts as a T-lymphocyte chemoattractant," *Proc. Natl. Acad. Sci. USA*, 1994;91:3652; Qin S., Larosa G., Campbell J.J. et al., "Expression of MCP-1 and IL-8 receptors on subset on T-cells, and correlation with transendothelial chemotactic potential," *Eur. J. Immu.*, 1996;26:640. Chemotaxis is movement of cells such as, for example, neutrophils to a site in response to a chemical agent, particularly a

chemokine. Agents such as, for example, IL-8 antagonists block chemokine-mediated activation of cells, which can be shown by their effect on chemotaxis.

Freshly isolated human neutrophils were resuspended in chemotaxis buffer, which is made of one part of RPMI 1640 medium, one part of Medium 199, and 0.5% BSA. The cells were incubated with or without compounds for 5 minutes. Similarly, rhIL-8 was incubated in a separate plate, then transferred into lower chambers of chemotaxis plate. Neutrophils were added onto the top chamber. The plates were incubated at 37°C for 30 minutes. The top chamber was then removed and the plate frozen at -80°C for 30 minutes. After thawing, migrated cells were stained with Cytoquant Cell Proliferation Assay Kit (Molecular Probes No. C-7026) and quantitated by reading the plate on a fluorescent plate reader.

Certain examples were tested in the IL-8 binding assay and demonstrated IC_{50} data from 0.05 to 12 μM, except for one compound which inhibited by 45% and 25% at an inhibitor concentration of 11 μM. IC_{50} is the concentration of inhibitor in micromolar required to inhibit binding by 50%.

IL-8 Rabbit Model

Introduction

Interleukin-8 is a CXC chemokine that activates neutrophils and serves as a strong chemotactic signal both in vitro and in vivo. The recruitment of neutrophils in response to endogenously produced IL-8 is responsible for some of the acute inflammatory response in a variety of diseases (Matsushima K., Baldwin E., Mukaida N. "Interleukin-8 and MCAF: Novel leukocyte recruitment and activating cytokines." In: Kishimoto T. (Ed.) *Interleukins: Molecular Biology and Immunology*, Basel. 1992:236.). Compounds that inhibit IL-8 binding and the subsequent recruitment response would be expected to be useful pharmaceutical agents.

The recruitment response of endogenous neutrophils in rabbit skin in response to intradermal IL-8 injection has been previously demonstrated (Colditz I.G., Zwahlen R.D., Baggiolini M. "Neutrophil accumulation and plasma

leakage induced in vivo by neutrophil-activating peptide-1." *J. Leuk. Biol.*, 1990;48(2):129.

Materials and Methods

Animals

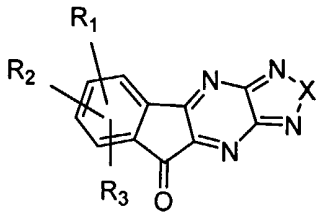
For all experiments, male New Zealand White rabbits are used.

Experimental Protocol

At t = 0, rabbits receive drug 10 mg/kg (IV). At t = 15 minutes, rabbits are anesthetized with isoflurane gas and injected intradermally with either vehicle or 0.01 to 3.3 μg human IL-8. At t = 85 minutes, rabbits are euthanized, and skin biopsies are obtained.

CLAIMS

1. A compound of formula



I

or a pharmaceutically acceptable salt thereof

wherein:

X is O or S;

R_1, R_2, and R_3 are independently hydrogen,

hydroxy,

lower alkyl,

lower alkoxy,

halogen,

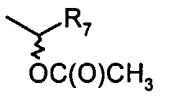
$(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,



, or

wherein R_7 and R_8 are lower alkyl; and

n is an integer from 1 to 3;

with the proviso that when X is O, R_1, R_2, and R_3 are not all hydrogen.

2. A compound according to Claim 1 wherein X is O.

3. A compound according to Claim 1 wherein X is S.

4. A compound according to Claim 1 wherein

X is O; and

R_1 is

halogen,

lower alkyl,

lower alkoxy,

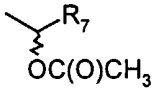
$(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,



, or


wherein R_7 and R_8 are lower alkyl.

5. A compound according to Claim 1 wherein

X is O;

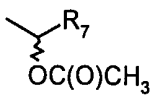
R_1 is $(CH_2)_nOC(O)CH_3$,

$O(CH_2)_nCO_2R_4$,

$O(CH_2)_nC(O)R_4$ wherein R_4 is lower alkyl,

$OC(O)R_5$ wherein R_5 is unsubstituted or substituted phenyl,

$O(CH_2)_nR_6$ wherein R_6 is unsubstituted phenyl, substituted phenyl, or heteroaryl,



, or


wherein R_7 and R_8 are lower alkyl; and

n is 1.

6. A compound according to Claim 1 wherein

X is O;

R_1 is

O(CH2)nCO2R4 wherein R4 is lower alkyl, or

$O(CH_2)_nR_6$ wherein R_6 is heteroaryl selected from:

2-, 3-, or 4-pyridyl, 2- or 3-thienyl, or 2- or 3-furanyl; and

n is 1.

7. A compound according to Claim 1 selected from:

6-Methoxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

Benzoic acid 7,8-dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl ester;

5-Bromo-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid methyl ester;

6-Hydroxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

(7,8-Dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid methyl ester;

(7,8-Dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid tert-butyl ester;

7-Bromo-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

Benzoic acid 9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yl ester;

8-Methyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

5,8-Dimethoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

6,7-Dimethoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-Hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

7-Hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-Methoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yloxy)-acetic acid methyl ester;

(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yloxy)-acetic acid tert-butyl ester;

8-(2-Oxo-propoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Furan-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Thiophen-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-Benzyloxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Pyridin-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Pyridin-3-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Pyridin-3-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one, compound with trifluoro-acetic acid;

8-(Pyridin-4-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

6-tert-Butyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

Acetic acid 1-(9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl)-ethyl ester;

6-(1-Methoxy-ethyl)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one; and

Acetic acid 2-(9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yl)-ethyl ester.

8. A method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I of Claim 1 or 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one.

9. A method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I of Claim 2.

10. A method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I of Claim 3.

11. A method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I of Claim 4.

12. A method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I of Claim 5.

13. A method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I of Claim 6.

14. A method of treating a chemokine-mediated disease state in a mammal, including a human, which comprises administering to said mammal an effective amount of a compound of Formula I of Claim 1 selected from:

6-Methoxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

Benzoic acid 7,8-dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl ester;

5-Bromo-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid methyl ester;

6-Hydroxy-7,8-dimethyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

(7,8-Dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid methyl ester;

(7,8-Dimethyl-9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yloxy)-acetic acid tert-butyl ester;

7-Bromo-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

2-Oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

Benzoic acid 9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yl ester;

8-Methyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

5,8-Dimethoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

6,7-Dimethoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-Hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

7-Hydroxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-Methoxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yloxy)-acetic acid methyl ester;

(9-Oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yloxy)-acetic acid tert-butyl ester;

8-(2-Oxo-propoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Furan-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Thiophen-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-Benzyloxy-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Pyridin-2-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Pyridin-3-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

8-(Pyridin-3-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one, compound with trifluoro-acetic acid;

8-(Pyridin-4-ylmethoxy)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

6-tert-Butyl-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one;

Acetic acid 1-(9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-6-yl)-ethyl ester;

6-(1-Methoxy-ethyl)-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one; and

Acetic acid 2-(9-oxo-9H-2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-8-yl)-ethyl ester.

15. A pharmaceutical composition comprising a compound of Formula I according to Claim 1 or 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren9-one in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

16. A pharmaceutical composition adapted for administration as an agent for treating psoriasis or atopic dermatitis, disease associated with pathological angiogenesis (i.e., cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, atherosclerosis, cardiac and renal reperfusion injury, glomerulonephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections in a mammal, comprising a therapeutically effective amount of a compound of Claim 1 or 2-oxa-1,3,4,10-tetraaza-cyclopenta[b]fluoren-9-one in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

17. A compound selected from:

6-Hydroxy-4,5-dimethyl-indan-1-one;

Benzoic acid 6,7-dimethyl-3-oxo-indan-5-yl ester;

(1-Oxo-indan-5-yloxy)-acetic acid methyl ester;

Benzoic acid 3-oxo-indan-5-yl ester;

2,2-Dihydroxy-6-methoxy-4,5-dimethyl-indan-1,3-dione;

Benzoic acid 2,2-dihydroxy-1,3-dioxo-indan-4-yl ester;

Benzoic acid 2,2-dihydroxy-1,3-dioxo-indan-5-yl ester;

2,2-Dihydroxy-5,6-dimethoxy-indan-1,3-dione;

Benzoic acid 6,7-dimethyl-1,2,3,-trioxo-indan-5-yl ester;

(1,2,3-Trioxo-indan-5-yloxy)-acetic acid methyl ester;

4-Bromo-indan-1,2,3-trione;

4,7-Dimethoxy-indan-1,2,3-trione;

5-*tert*-Butyl-indan-1,2,3-trione;

Acetic acid 1-(1,2,3-trioxo-indan-5-yl)-ethyl ester; and

Acetic acid 1-indan-5-yl-ethyl ester.