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(54) Titre : COMPOSES TRICYCLIQUES ET LEURS UTILISATIONS
(54) Title: TRICYCLIC COMPOUNDS AND USES THEREOF

(57) **Abrégé/Abstract:**

Substituted isoquinolines, isochromanones and isothiochromanones that inhibit the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and/or interleukin-6 (IL-6) and/or the enzyme cyclooxygenase-2 (COX-2) and/or interleukin-10 (IL-10). Compositions containing such compounds and methods of using such compounds for treatment and/or prevention of inflammation, inflammatory diseases, immunologic diseases and other diseases mediated by TNF-alpha, IL-6, COX-2 and/or IL-10 are also disclosed.



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(54) Title: TRICYCLIC COMPOUNDS AND USES THEREOF

(57) Abstract: Substituted isoquinolines, isochromanones and isothiochromanones that inhibit the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and/or interleukin-6 (IL-6) and/or the enzyme cyclooxygenase-2 (COX-2) and/or interleukin-10 (IL-10). Compositions containing such compounds and methods of using such compounds for treatment and/or prevention of inflammation, inflammatory diseases, immunologic diseases and other diseases mediated by TNF-alpha, IL-6, COX-2 and/or IL-10 are also disclosed.

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TRICYCLIC COMPOUNDS AND USES THEREOF

The present application is based on provisional application No.
5 60/238,475, filed October 10, 2000, the contents of which are incorporated
herein.

Field of the Invention

The present invention relates to tricyclic compounds, namely,
10 substituted isoquinolines, isochromanones and isothiochromanones that
inhibit the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha)
and/or interleukin-6 (IL-6) and/or the enzyme cyclooxygenase-2 (COX-2)
and/or the cytokine interleukin-10 (IL-10). This invention also relates to
compositions containing such compounds and methods using such
15 compounds for treatment and/or prevention of inflammation, inflammatory
diseases, immunologic diseases and other diseases mediated by TNF-alpha,
IL-6, IL-10 and/or COX-2.

Background of the Invention

20 The present invention is concerned with the modulation of cellular
signaling pathways involving pro-inflammatory cytokines and cyclooxygenase-
2 (COX-2). Cytokines are molecules secreted by immune cells that are
important in mediating immune responses. Cytokine production may lead to
the secretion of other cytokines, altered cellular function, cell division or
25 differentiation. Inflammation is the body's normal response to injury or
infection. However, in inflammatory diseases such as rheumatoid arthritis,
pathologic inflammatory processes can lead to morbidity and mortality. The
cytokine tumor necrosis factor-alpha (TNF-alpha) plays a central role in the
inflammatory response and has been targeted as a point of intervention in
30 inflammatory disease. TNF-alpha is a polypeptide hormone released by
activated macrophages and other cells. At low concentrations, TNF-alpha
participates in the protective inflammatory response by activating leukocytes
and promoting their migration to extravascular sites of inflammation (Moser et
al., J Clin Invest, 83:444-55, 1989). At higher concentrations, TNF-alpha can

act as a potent pyrogen and induce the production of other pro-inflammatory cytokines (Haworth et al., Eur J Immunol, 21:2575-79, 1991; Brennan et al., Lancet, 2:244-7, 1989). TNF-alpha also stimulates the synthesis of acute-phase proteins. In rheumatoid arthritis, a chronic and progressive
5 inflammatory disease affecting about 1% of the adult U.S. population, TNF-alpha mediates the cytokine cascade that leads to joint damage and destruction (Arend et al, Arthritis Rheum, 38:151-60, 1995). Inhibitors of TNF-alpha, including soluble TNF receptors (etanercept) (Goldenberg, Clin Ther, 21:75-87, 1999) and anti-TNF-alpha antibody (infliximab) (Luong et al, Ann
10 Pharmacother, 34:743-60, 2000), have recently been approved by the U.S. Food and Drug Administration (FDA) as agents for the treatment of rheumatoid arthritis.

Elevated levels of TNF-alpha have also been implicated in many other disorders and disease conditions, including cachexia (Fong et al., Am J
15 Physiol, 256:R659-65, 1989), septic shock syndrome (Tracey et al, Proc Soc Exp Biol Med, 200:233-9, 1992), osteoarthritis (Venn et al., Arthritis Rheum, 36:819-26, 1993), inflammatory bowel disease such as Crohn's disease and ulcerative colitis (Murch et al., Gut, 32:913-7, 1991), Behcet's disease (Akoglu et al., J Rheumatol, 17:1107-8, 1990), Kawasaki disease (Matsubara et al.,
20 Clin Immunol Immunopathol, 56:29-36, 1990), cerebral malaria (Grau et al., N Engl J Med, 320:1586-91, 1989), adult respiratory distress syndrome (Millar et al., Lancet, 2:712-4, 1989), asbestosis and silicosis (Bissonnette et al., Inflammation, 13:329-39, 1989), pulmonary sarcoidosis (Baughman et al., J Lab Clin Med, 115:36-42, 1990), asthma (Shah et al., Clin Exp Allergy,
25 25:1038-44, 1995), AIDS (Dezube et al., J Acquir Immune Defic Syndr, 5:1099-104, 1992), meningitis (Waage et al., Lancet, 1:355-7, 1987), psoriasis (Oh et al., J Am Acad Dermatol, 42:829-30, 2000), graft versus host reaction (Nestel et al., J Exp Med, 175:405-13, 1992), multiple sclerosis (Sharief et al., N Engl J Med, 325:467-72, 1991), systemic lupus erythematosus (Maury et
30 al., Int J Tissue React, 11:189-93, 1989), and diabetes (Hotamisligil et al., Science, 259:87-91, 1993).

It can be seen from the references cited above that inhibitors of TNF-alpha are potentially useful in the treatment of a wide variety of diseases. Compounds that inhibit TNF-alpha have been described in U.S. Pat. Nos.

6,090,763; 6,080,580; 6,075,041; 6,057,369; 6,048,841; 6,046,319;
 6,046,221; 6,040,329; 6,034,100; 6,028,086; 6,022,884; 6,015,558;
 6,004,974; 5,990,119; 5,981,701; 5,977,122; 5,972,936; 5,968,945;
 5,962,478; 5,958,953; 5,958,409; 5,955,480; 5,948,786; 5,935,978;
 5 5,935,977; 5,929,117; 5,925,636; 5,900,430; 5,900,417; 5,891,883; 5,869,677
 and others.

Interleukin-6 (IL-6) is another pro-inflammatory cytokine that exhibits
 pleiotropy and redundancy of action. IL-6 participates in the immune
 response, inflammation and hematopoiesis. It is a potent inducer of the
 10 hepatic acute phase response and is a powerful stimulator of the
 hypothalamic-pituitary-adrenal axis that is under negative control by
 glucocorticoids. IL-6 promotes the secretion of growth hormone but inhibits
 release of thyroid stimulating hormone. Elevated levels of IL-6 are seen in
 several inflammatory diseases, and inhibition of the IL-6 cytokine subfamily
 15 has been suggested as a strategy to improve therapy for rheumatoid arthritis
 (Carroll et al., Inflamm Res, 47:1-7, 1998). In addition, IL-6 has been
 implicated in the progression of atherosclerosis and the pathogenesis of
 coronary heart disease (Yudkin et al., Atherosclerosis, 148:209-14, 1999).
 Overproduction of IL-6 is also seen in steroid withdrawal syndrome, conditions
 20 related to deregulated vasopressin secretion, and osteoporosis associated
 with increased bone resorption, such as in cases of hyperparathyroidism and
 sex-steroid deficiency (Papanicolaou et al., Ann Intern Med, 128:127-37,
 1998).

Since excessive production of IL-6 is implicated in several disease
 25 states, it is highly desirable to develop compounds that inhibit IL-6 secretion.
 Compounds that inhibit IL-6 have been described in U.S. Pat. Nos. 6,004,813;
 5,527,546 and 5,166,137.

Cyclooxygenase is an enzyme that catalyzes a rate-determining step in
 the biosynthesis of prostaglandins, which are important mediators of
 30 inflammation and pain. The enzyme occurs as at least two distinct isomers,
 cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The COX-1
 isomer is constitutively expressed in the gastric mucosa, platelets and other
 cells and is involved in the maintenance of homeostasis in mammals,
 including protecting the integrity of the digestive tract. The COX-2 isomer, on

the other hand, is not constitutively expressed but rather is induced by various agents, such as cytokines, mitogens, hormones and growth factors. In particular, COX-2 is induced during the inflammatory response (DeWitt DL, Biochim Biophys Acta, 1083:121-34, 1991; Seibert et al., Receptor, 4:17-23, 1994). Aspirin and other conventional non-steroid anti-inflammatory drugs (NSAIDs) are non-selective inhibitors of both COX-1 and COX-2. They can be effective in reducing inflammatory pain and swelling, but since they hamper the protective action of COX-1, they produce undesirable side effects of gastrointestinal pathology. Therefore, agents that selectively inhibit COX-2 but not COX-1 are preferable for treatment of inflammatory diseases. Recently, a diarylpyrazole sulfonamide (celecoxib) that specifically blocks COX-2 has been approved by the FDA for use in the treatment of rheumatoid arthritis (Luong et al., Ann Pharmacother, 34:743-60, 2000; Penning et al., J Med Chem, 40:1347-65, 1997). COX-2 is also expressed in many cancers and precancerous lesions, and there is mounting evidence that selective COX-2 inhibitors may be useful for treating and preventing colorectal and other cancers (Taketo MM, J Natl Cancer Inst, 90:1609-20, 1998; Fournier et al., J Cell Biochem Suppl, 34:97-102, 2000). In 1999, celecoxib was approved by the FDA as an adjunct to usual care for patients with familial adenomatous polyposis, a condition which, left untreated, generally leads to colorectal cancer.

Compounds that selectively inhibit COX-2 have been described in U.S. Pat. Nos. 5,344,991; 5,380,738; 5,434,178; 5,466,823; 5,474,995; 5,510,368; 5,521,207; 5,521,213; 5,536,752; 5,550,142; 5,552,422; 5,604,260; 5,639,780; 5,643,933; 5,677,318; 5,691,374; 5,698,584; 5,710,140; 5,733,909; 5,789,413; 5,811,425; 5,817,700; 5,849,943; 5,859,257; 5,861,419; 5,905,089; 5,922,742; 5,925,631; 5,932,598; 5,945,539; 5,968,958; 5,981,576; 5,994,379; 5,994,381; 6,001,843; 6,002,014; 6,004,950; 6,004,960; 6,005,000; 6,020,343; 6,034,256; 6,046,191; 6,046,217; 6,057,319; 6,071,936; 6,071,954; 6,077,850; 6,077,868; 6,077,869 and 6,083,969.

The immunoregulatory cytokine interleukin-10 (IL-10) is a potent down-regulator of specific pro-inflammatory cytokines, but its role in inflammatory diseases and immune disorders is complex. Administration or overexpression

of IL-10 is believed in many cases to counterbalance the action of pro-inflammatory cytokines and therefore to ameliorate inflammatory disease (Verhoef et al, J Rheumatol, 28:1960-6, 2001; McInnes et al, J Immunol, 167:4075-82, 2001; Lamblin et al, J Allergy Clin Immunol, 107:739-41, 2001; 5 Cook et al, Am Surg, 67:237-41, 2001). In other cases, paradoxically, production or overexpression of IL-10 has been correlated with the promotion of inflammatory diseases or immune disorders, including systemic lupus erythematosus (Alarcon-Segovia, Isr Med Assoc J, 3:127-30, 2001; Bussolati et al, Clin Exp Immunol 122:471-6, 2000; Gonzalez-Amaro et al, J 10 Autoimmun, 11:395-402, 1998; Kalechman et al, J Immunol, 159:2658-67, 1997; Mongan et al, Scand J Immunol 46:406-12, 1997; Houssiau et al, Lupus 4:393-5, 1995), multiple sclerosis (Nakashima et al, J Neuroimmunol, 111:64-7, 2000; Navikas et al, Scand J Immunol, 41:171-8, 1995), myasthenia gravis (Ostlie et al, J Immunol, 166:4853-62, 2001; Huang et al, Clin Exp Immunol, 15 118:304-8, 1999) and arthritis (Johansson et al, J Immunol, 167:3505-12, 2001).

Since elevated levels of IL-10 are associated with several disease states, compounds that inhibit IL-10 have potential therapeutic utility. Compositions and methods for inhibition of IL-10 have been described in U.S. 20 Pat. Nos. 6,251,878; 6,239,260; 6,207,154; 6,184,372; 6,184,246 and 5,837,232.

It can be understood from the above discussions that a compound which inhibits both COX-2 and the pro-inflammatory cytokines TNF-alpha and IL-6 would be highly desirable for its potential use in treating diseases 25 mediated by these agents, particularly inflammatory diseases such as rheumatoid arthritis and the like. It will also be apparent that compounds that inhibit IL-10 are desirable for their potential use in treating similar diseases, particularly autoimmune disorders.

Alkaloids such as sinomenine (Liu et al., Int J Immunopharmacol, 30 18:529-43, 1996), bukittingine (Panthong et al., Planta Med, 64:530-5, 1998), tetrandine and berbamine (Wong et al., Agents Actions, 36:112-8, 1992) are well known for their anti-inflammatory activities. Isoquinoline derivatives with demonstrated or potential anti-inflammatory properties have also been described (van Muijlwijk-Koezen et al., J Med Chem, 43:2227-38,

2000; Xu et al., J Nat Prod, 62:1025-7, 1999; Chao et al., J Med Chem, 42:3860-73, 1999; van Muijlwijk-Koezen et al., J Med Chem, 41:3987-93, 1998; van Muijlwijk-Koezen et al., J Med Chem, 41:3994-4000, 1998).

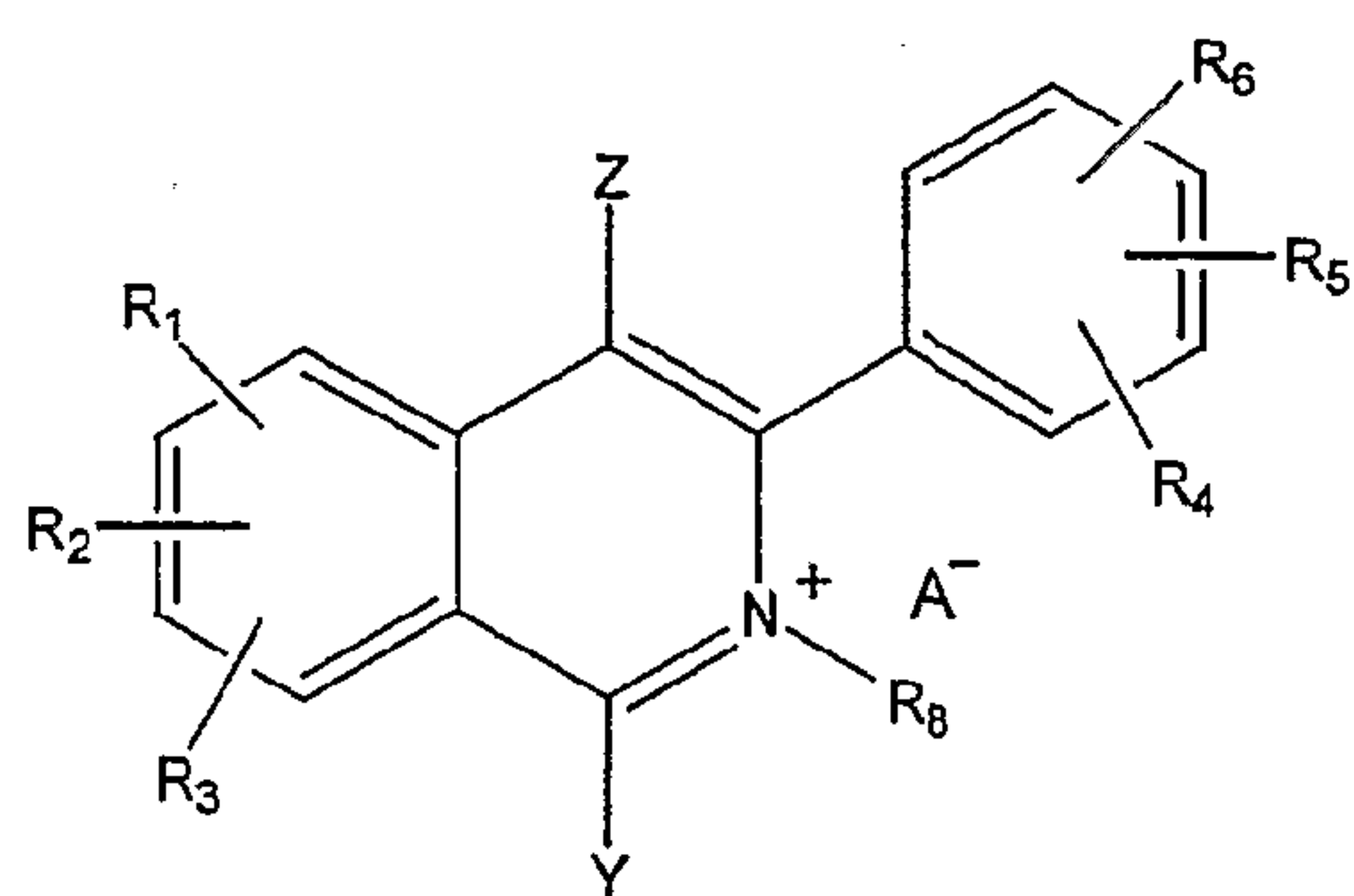
Disease-modifying anti-rheumatic drugs (DMARDs) based on quinoline and

5 related structures are also known (Baba et al., Chem Pharm Bull [Tokyo], 47:993-9, 1999; Baba et al., J Med Chem, 39:5176-82, 1996). Berberine is an isoquinoline alkaloid that occurs naturally in plants belonging to the Berberidaceae and Ranunculaceae families. Extracts from these plants have been used for centuries in Eastern folk medicine as remedies for inflammation and hypertension. The anti-inflammatory effects of berberine and berberine-
10 containing extracts have also been demonstrated in animal models (Ivanovska et al., Int J Immunopharmacol, 18:553-61, 1996; Yasukawa et al., Chem Pharm Bull [Tokyo], 39:1462-5, 1991; Zhang et al., Chung Kuo Yao Li Hsueh Pao, 10:174-6, 1989; Akhter et al., Indian J Med Res, 65:133-41, 1977) and in vitro studies (Ckless et al., J Pharm Pharmacol, 47:1029-31, 1995). The present invention describes novel substituted isoquinolines chemically distinct from, but having some structural features similar to, native berberine.

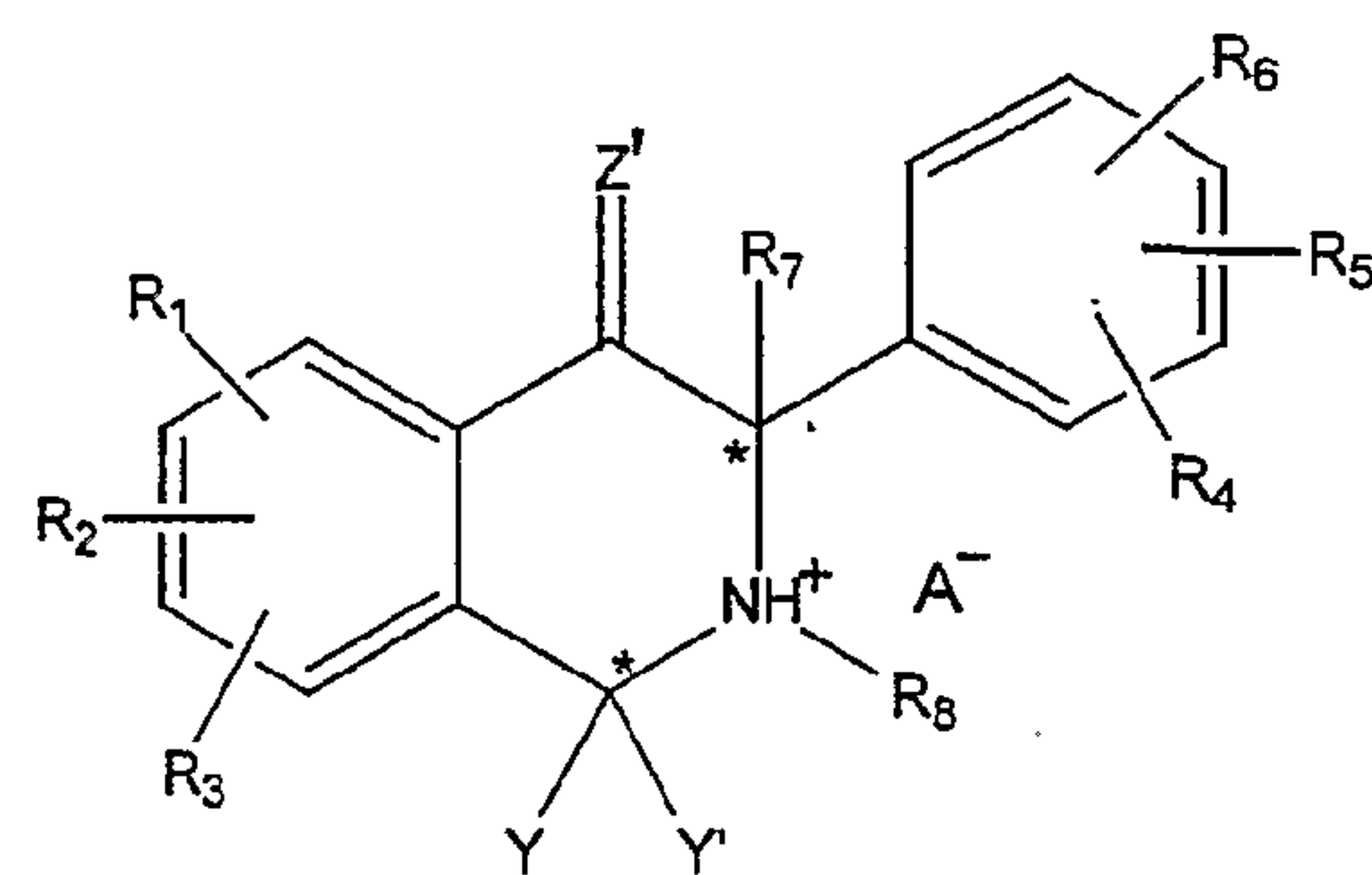
20

Summary of the Invention

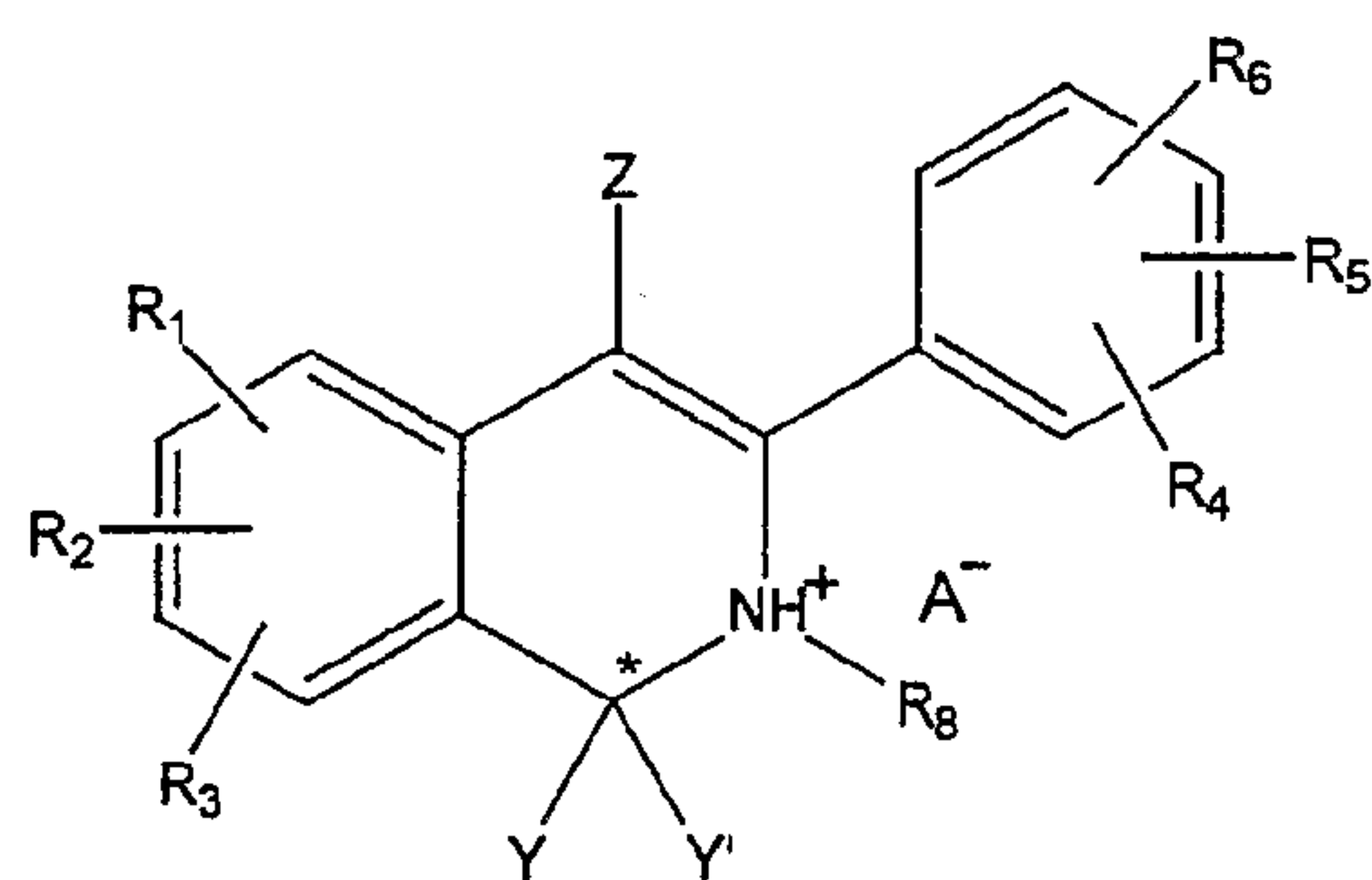
The present invention is directed to compounds that inhibit the production and/or activity of the pro-inflammatory cytokines tumor necrosis factor-alpha, interleukin-6, the enzyme cyclooxygenase-2 and/or interleukin-10, and therefore are useful for the prevention and/or treatment of
25 inflammation, inflammatory diseases, immunologic diseases, autoimmune disorders and other diseases mediated by these agents. In particular, the subject invention discloses substituted isoquinolines of Formulas I-IV, isochromanones of Formulas V-VII, and isothiochromanones of Formulas VIII-X as well as the pharmaceutically acceptable salts and solvates thereof:



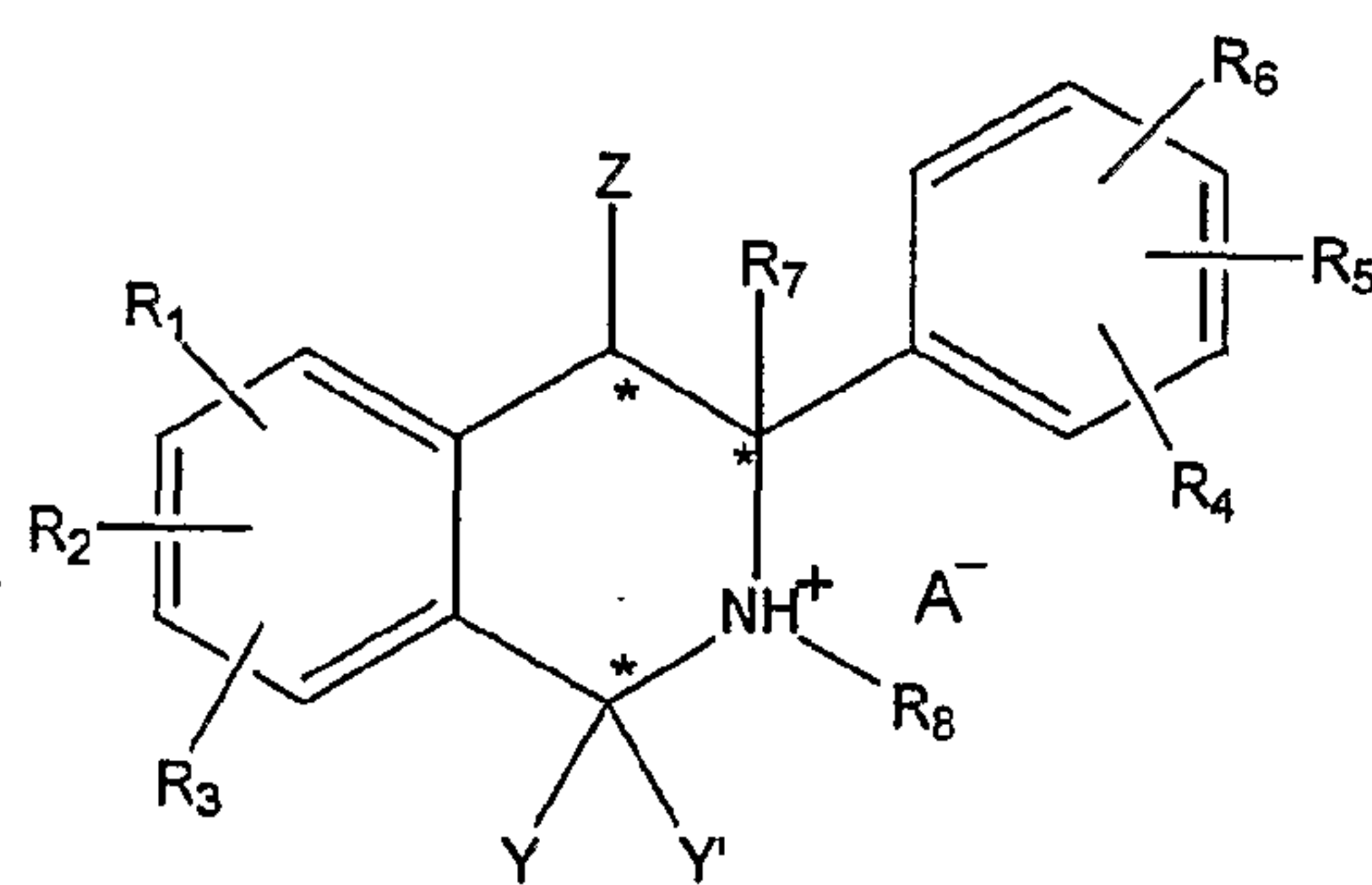
Formula I



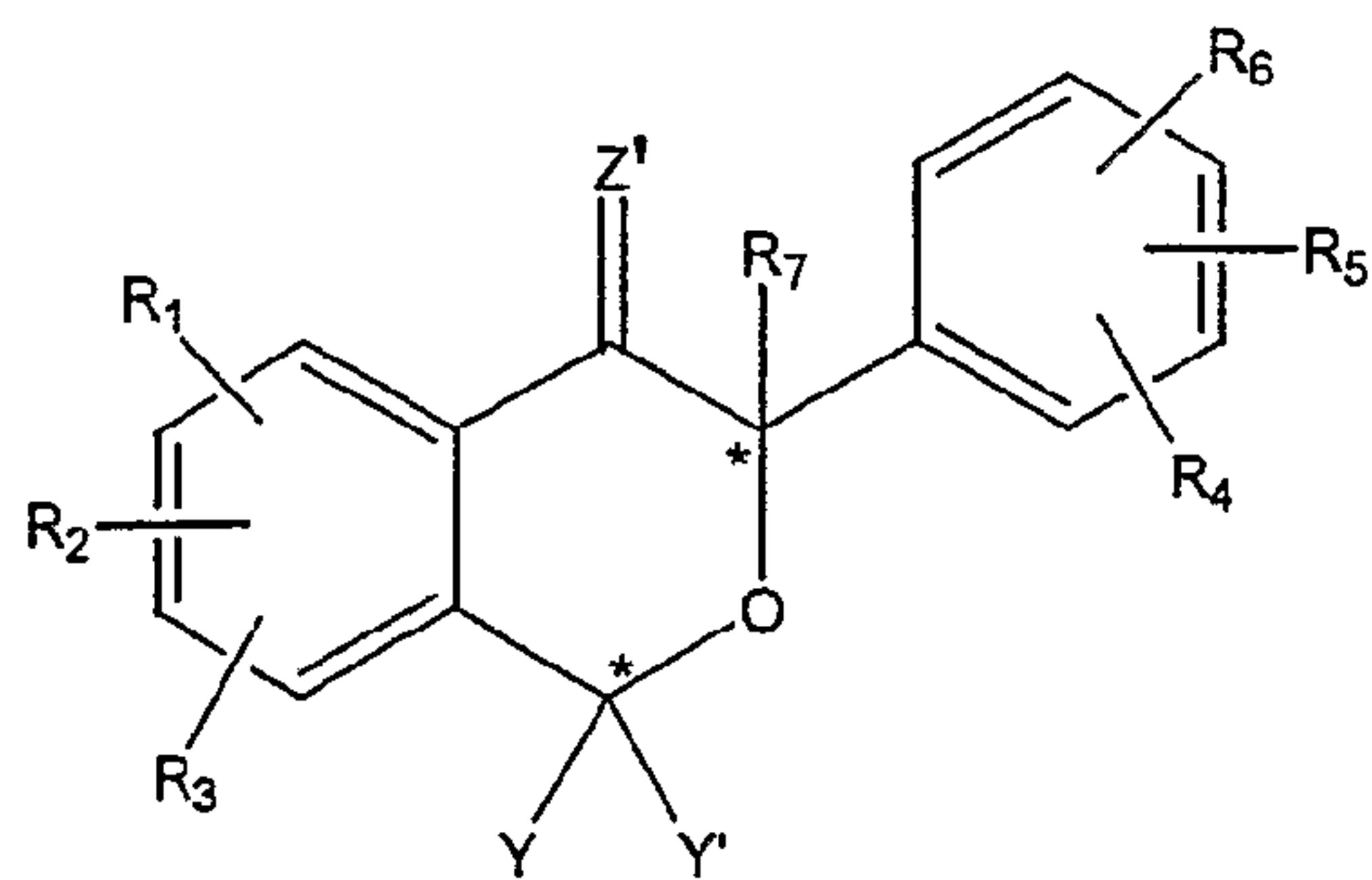
Formula II



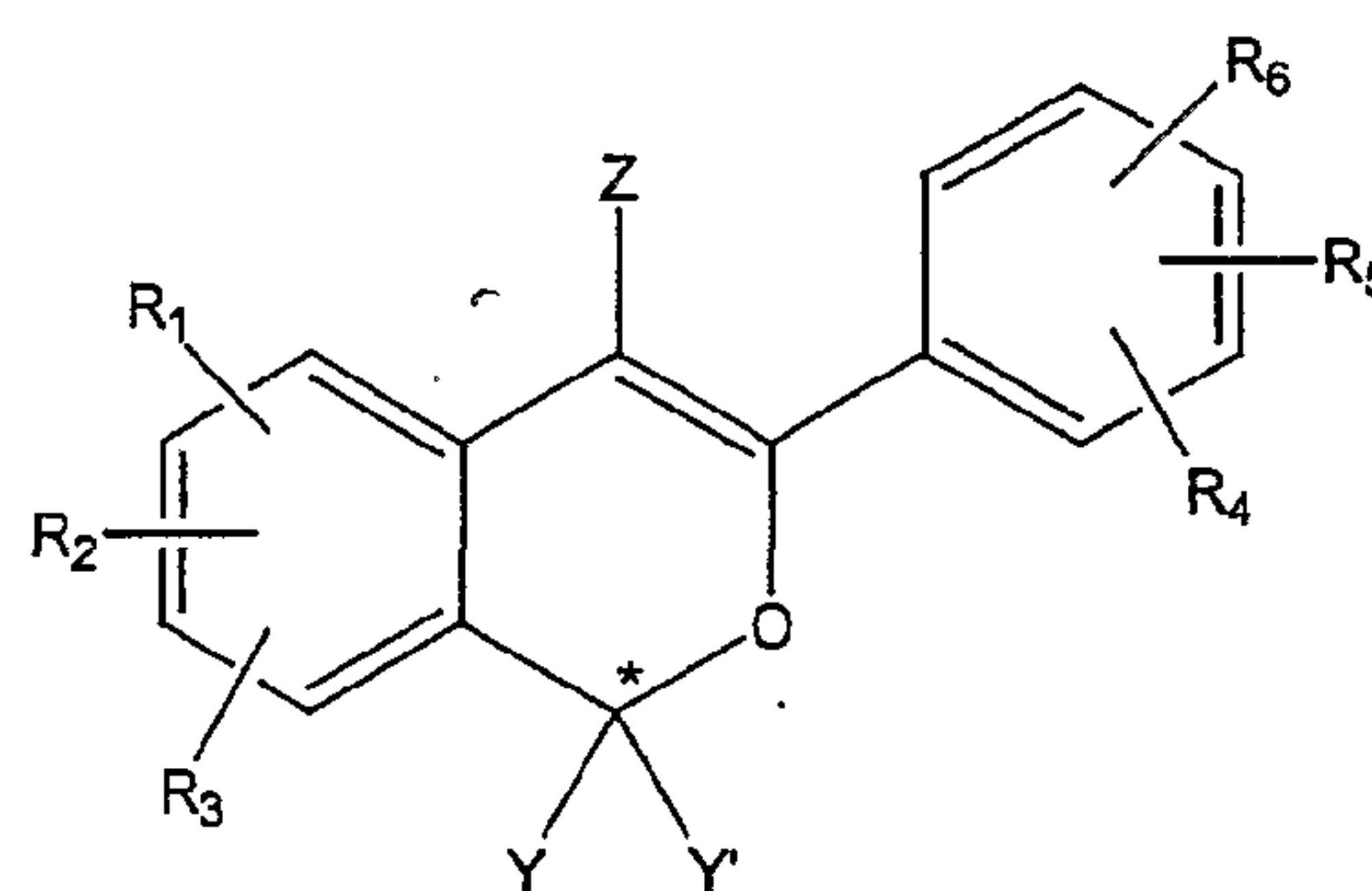
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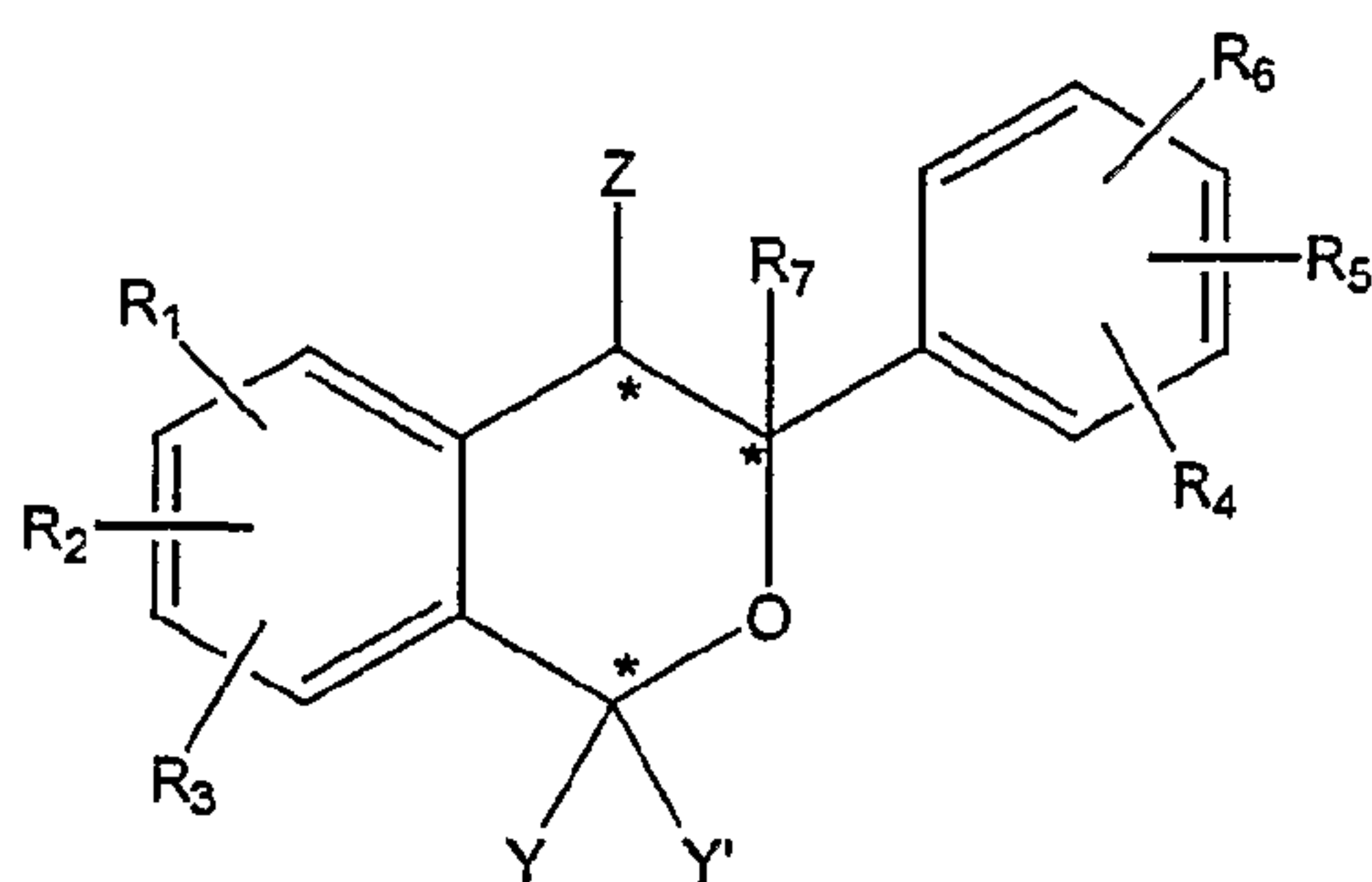
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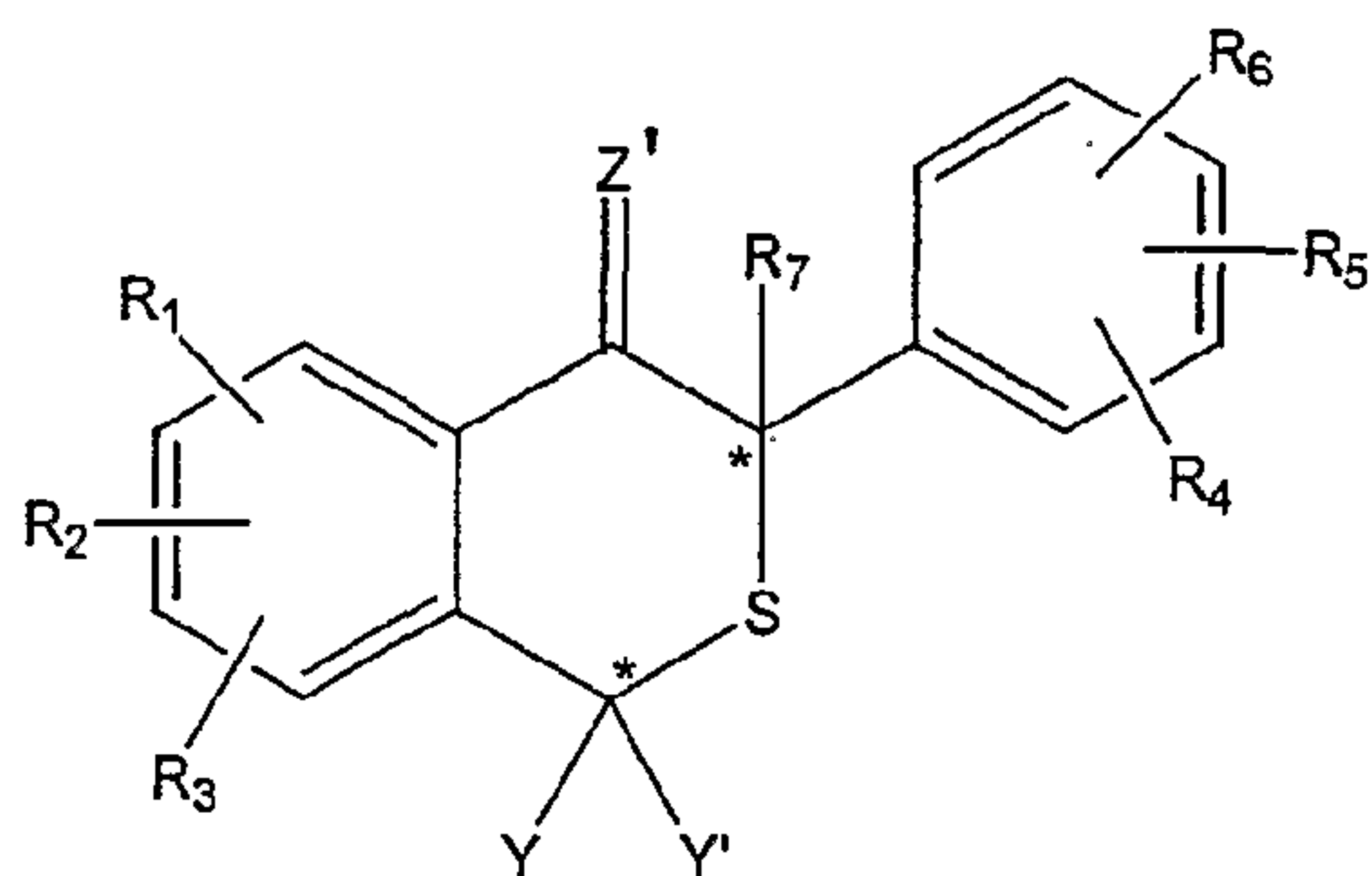
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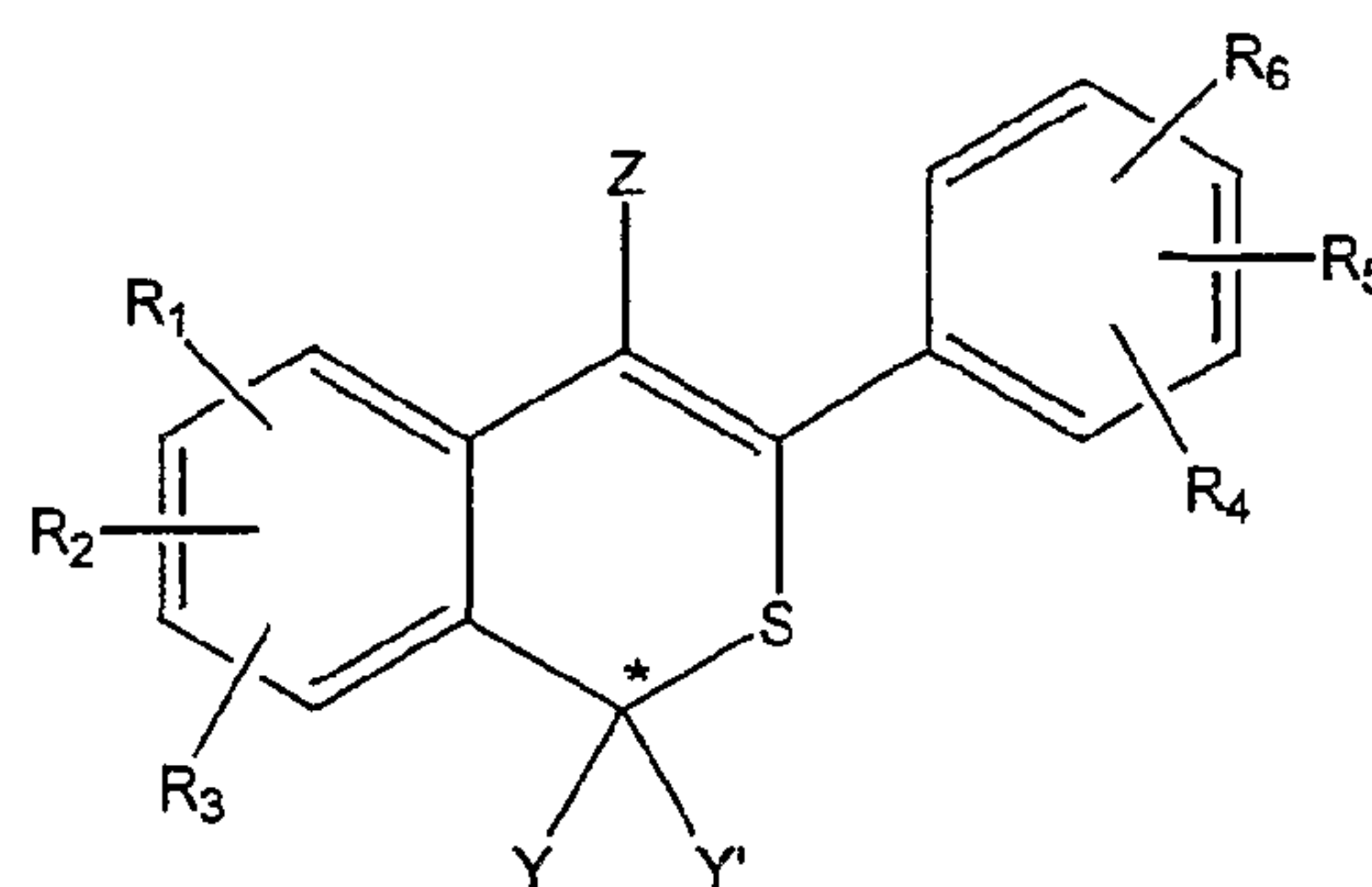
Formula VI



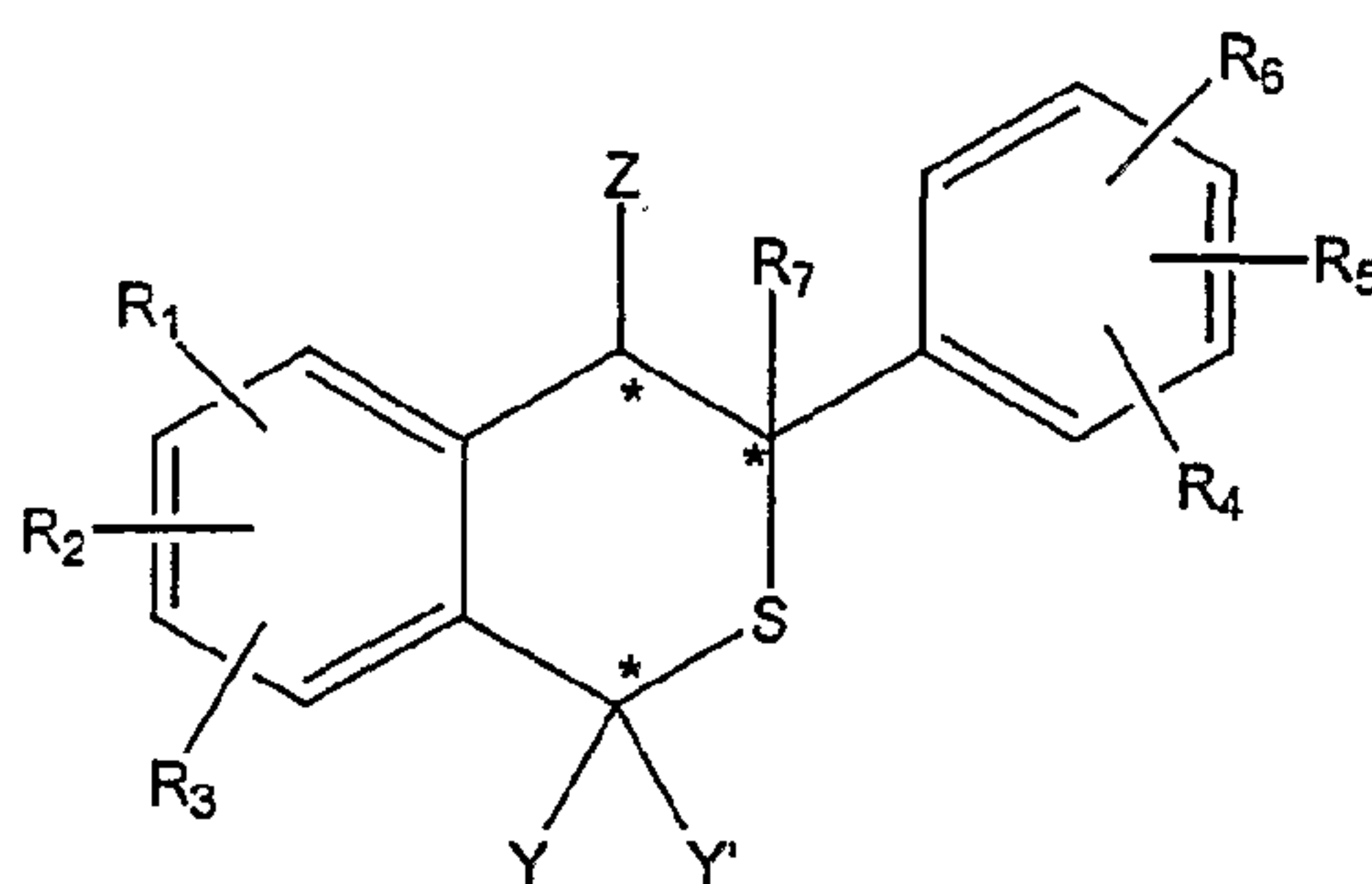
Formula VII



Formula VIII



Formula IX



Formula X

wherein the stereocenters marked with an asterisk (*) may be R- or S- and

5

R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are independently

10

H; optionally substituted C_1 - C_{20} linear or branched alkyl including chloroalkyl or fluoroalkyl; optionally substituted C_2 - C_{20} linear or branched alkenyl; optionally substituted C_6 - C_{20} aryl, linear or branched alkylaryl, linear or branched alkenylaryl; COOR where R is H, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_2 - C_{20} alkenyl or optionally substituted C_6 - C_{10} aryl, sodium, potassium or other pharmaceutically acceptable counter-

ion such as calcium, magnesium, ammonium, tromethamine and the like; CONR'R", where R' and R" are independently H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl or where NR'R" represents a cyclic moiety such as morpholine, piperidine, piperazine and the like; NH₂; optionally substituted C₁-C₂₀ alkylamino, bis(alkylamino), cycloalkylamino or cyclic amino; OH; optionally substituted C₁-C₂₀ alkoxy, including trifluoromethoxy, and the like; optionally substituted C₁-C₂₀ alkanoyl; optionally substituted C₁-C₂₀ acyloxy; halo; optionally substituted C₁-C₂₀ alkylcarboxylamino; cyano; nitro; SO₂NR'''R'''' where R''' and R'''' are independently H, C₁-C₂₀ alkyl or aryl; SO₂R''' where R''' is H, C₁-C₂₀ alkyl or aryl; SO₃R''' where R''' is H, C₁-C₂₀ alkyl or aryl; or C₄-C₈ heterocycles such as tetrazolyl, imidazolyl, pyrrolyl, pyridyl, indolyl and the like; or when individual aromatic rings possess adjacent substituents, these substituents may be joined to form a ring such as a methylenedioxy or ethylenedioxy group, and the like, including lactones and lactams;

R₇ is

H (in which case the compounds may be in tautomeric form) or optionally substituted C₁-C₂₀ linear or branched alkyl including chloroalkyl or fluoroalkyl;

R₈ is

H; OH (or O in the case of Formula I); optionally substituted C₁-C₂₀ linear or branched alkyl including chloroalkyl or fluoroalkyl; optionally substituted C₂-C₂₀ linear or branched alkenyl; optionally substituted C₆-C₂₀ aryl, linear or branched alkylaryl, linear or branched alkenylaryl; COOR where R is H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl, sodium, potassium or

5 other pharmaceutically acceptable counter-ion such as calcium, magnesium, ammonium, tromethamine and the like; CONR'R", where R' and R" are independently H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl or where NR'R" represents a cyclic moiety such as morpholine, piperidine, piperazine and the like; or optionally substituted alkanoyl, alkenoyl, aroyl, alkylaroyl or alkenylaroyl; and "A" represents a pharmaceutically
10 acceptable counter-ion such as chloride, sulfate, phosphate, acetate and the like; or R₈ is absent, in which case the nitrogen does not bear a positive charge and the counter-ion "A" is not present;

Y and Y' are independently

15 H; optionally substituted C₁-C₂₀ linear or branched alkyl including chloroalkyl or fluoroalkyl; optionally substituted C₂-C₂₀ linear or branched alkenyl; optionally substituted C₆-C₂₀ aryl, linear or branched alkylaryl, linear or branched alkenylaryl; COOR where R is H, optionally
20 substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl, sodium, potassium or other pharmaceutically acceptable counter-ion such as calcium, magnesium, ammonium, tromethamine and the like; CONR'R", where R' and R"
25 are independently H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl or where NR'R" represents a cyclic moiety such as morpholine, piperidine, piperazine and the like; NH₂; optionally substituted C₁-C₂₀
30 alkylamino, bis(alkylamino), cycloalkylamino or cyclic amino; OH; optionally substituted C₁-C₂₀ alkoxy, including trifluoromethoxy, and the like; optionally substituted C₁-C₂₀ alkanoyl; optionally substituted C₁-C₂₀ acyloxy; halo; optionally substituted C₁-C₂₀ alkylcarboxylamino; cyano;

nitro; $\text{SO}_2\text{NR}'''\text{R}''''$ where R''' and R'''' are independently H, $\text{C}_1\text{-C}_{20}$ alkyl or aryl; $\text{SO}_2\text{R}'''$ where R''' is H, $\text{C}_1\text{-C}_{20}$ alkyl or aryl; $\text{SO}_3\text{R}'''$ where R''' is H, $\text{C}_1\text{-C}_{20}$ alkyl or aryl; or $\text{C}_4\text{-C}_8$ heterocycles such as tetrazolyl, imidazolyl, pyrrolyl, pyridyl, indolyl and the like; or Y and Y' together may be joined in a ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, including heterocycles such as lactones, lactams and the like;

Z is

OH; optionally substituted $\text{C}_1\text{-C}_{20}$ alkoxy, including trifluoromethoxy, and the like; $\text{NR}'\text{R}''$, where R' and R'' are independently H, optionally substituted $\text{C}_1\text{-C}_{20}$ alkyl, optionally substituted $\text{C}_2\text{-C}_{20}$ alkenyl or optionally substituted $\text{C}_6\text{-C}_{10}$ aryl or where $\text{NR}'\text{R}''$ represents a cyclic moiety such as morpholine, piperidine, piperazine and the like; or SR'''' where R'''' is H, optionally substituted $\text{C}_1\text{-C}_{20}$ alkyl, optionally substituted $\text{C}_2\text{-C}_{20}$ alkenyl or optionally substituted $\text{C}_6\text{-C}_{10}$ aryl;

Z' is

O; S; or NR'''' , where R'''' is H, optionally substituted $\text{C}_1\text{-C}_{20}$ alkyl, optionally substituted $\text{C}_2\text{-C}_{20}$ alkenyl or optionally substituted $\text{C}_6\text{-C}_{10}$ aryl;

with the provisos that in Formula I,

when Y is H, then Z is OH, R_8 is H, and R_1 , R_2 and R_3 are not 6-methoxy; when Y is methyl or substituted benzyl, then R_1 , R_2 and R_3 do not comprise 6,7-dimethoxy or 5,6,7-trimethoxy or 6,7,8-trimethoxy; and when Z is OH, at least one of R_1 , R_2 , R_3 , R_4 , R_5 and R_6 is not H;

in Formula II,

when Y is H and Y' is H, then Z' is O, R_8 is H, and R_1 , R_2 and R_3 are not 6-methoxy; when Y is H and Y' is methyl or substituted benzyl, then R_1 , R_2 and R_3 do not comprise 6,7-dimethoxy or 5,6,7-trimethoxy or 6,7,8-trimethoxy; and

when Z' is O, at least one of R₁, R₂, R₃, R₄, R₅, R₆ and R₇ is not H;

in Formula III, .

when Y is H and Y' is H, then Z is OH, R₈ is H, and R₁, R₂ and R₃ are not 6-methoxy;

when Y is H and Y' is methyl or substituted benzyl, then

R₁, R₂ and R₃ do not comprise 6,7-dimethoxy or 5,6,7-trimethoxy or 6,7,8-trimethoxy; and

when Z is OH or alkoxy, at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H;

in Formula IV,

when Y is H and Y' is H, then Z is OH, R₈ is H, and R₁, R₂ and R₃ are not 6-methoxy;

when Y is H and Y' is methyl or substituted benzyl, then

R₁, R₂ and R₃ do not comprise 6,7-dimethoxy or 5,6,7-trimethoxy or 6,7,8-trimethoxy; and

when Z is OH, at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H;

in Formula V,

when Z' is O and Y and/or Y' is phenyl, then at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H'

when Z' is O and Y and/or Y' is alkoxy, then R₄, R₅ and R₆ are not aminoethyl; and

when Z' is O and Y is H and Y' is H, then R₁ is not H;

in Formula VI,

when Z is OH and Y and/or Y' is phenyl, then at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H;

in Formula VII,

when Z is methyl or phenyl, then at least one of R₁, R₂, R₃, R₄, R₅, R₆ and R₇ is not H;

when Z is OH and Y and/or Y' is phenyl, then at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H;

when Z is OH and Y and/or Y' is alkoxy, then R₄, R₅ and R₆ are not aminoethyl; and

when Z is OH and Y is H and Y' is H, then R₇ is not H;
in Formula VIII,

when Y and/or Y' is substituted alkyl, arylamide or COOR,
and R₁ and R₂ comprise 6,7-dimethyl or 5,6-
5 dihydroxy, then at least one of R₄, R₅ and R₆ is not H;
and

when Z' is O, then at least one of R₁, R₂, R₃, R₄, R₅, R₆
and R₇ is not H, and R₁, R₂ and R₃ do not comprise 7-
methoxy;

10 in Formula IX,

when Y and/or Y' is substituted alkyl, arylamide or COOR,
and R₁ and R₂ comprise 6,7-dimethyl or 5,6-
dihydroxy, then at least one of R₄, R₅ and R₆ is not H;
and

15 when Z is OH or alkoxy, then at least one of R₁, R₂, R₃,
R₄, R₅ and R₆ is not H, and R₁, R₂ and R₃ do not comprise
7-methoxy;

in Formula X,

20 when Y is substituted alkyl, arylamide or COOR, and R₁
and R₂ comprise 6,7-dimethyl or 5,6-dihydroxy, then
at least one of R₄, R₅ and R₆ is not H;

when Z is H, then at least one of Y, Y', R₄, R₅ and R₆ is
not H; and

25 when Z is OH, at least one of R₁, R₂, R₃, R₄, R₅, R₆ and
R₇ is not H and provided further that Z may be H in the
case of compounds of Formula IX or Formula X.

30 Another aspect of the present invention relates to pharmaceutical
compositions containing the compounds of Formulas I to X, which
compositions are suitable for administration to animals, more preferably
mammals, and most preferably humans.

In another aspect of the present invention, methods are disclosed for using the compounds of Formulas I to X for the treatment and/or prevention of inflammation, inflammatory diseases, immunologic diseases and other diseases mediated by TNF-alpha, IL-6, COX-2 and/or interleukin-10 (IL-10).

5

Brief Description of the Drawings

FIG. 1 shows the ability of compounds B and E, representing compounds according to Formulas I and II, respectively, to inhibit TNF-alpha activity in an in vitro assay for TNF-alpha induced cell killing;

10 FIG. 2 shows the dose response of the ability of compound B to inhibit TNF-alpha activity in an in vitro assay for TNF-alpha induced cell killing;

FIG. 3 shows the ability of compound B to inhibit LPS-stimulated TNF-alpha production in an in vitro model of inflammation;

15 FIG. 4 shows the ability of compound B to inhibit LPS-stimulated IL-6 production in an in vitro model of inflammation; and

FIG. 5 shows the ability of compound B to selectively inhibit LPS-stimulated COX-2 activity in an in vitro model of inflammation.

FIG. 6 shows the effect of compound B in suppressing collagen-induced arthritis in mice.

20 FIG. 7 shows the effect of compound B in inhibiting LPS-induced IL-10 production.

Detailed Description of the Invention

25 The present invention is based on the discovery that the compounds described herein appear to inhibit the production and/or activity of the pro-inflammatory cytokines TNF-alpha, interleukin-10 and IL-6 and to inhibit the activity of the enzyme COX-2.

Definitions

30 As utilized herein, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing preferably 1-20 carbon atoms, more preferably 1-10 carbon atoms, and most preferably 1-6 carbon atoms. Exemplary alkyl

radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

"Alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds, preferably 1-2
 5 double bonds and more preferably one double bond, and containing preferably 2-20 carbon atoms, more preferably 2-10 carbon atoms, and still more preferably 2-6 carbon atoms. Exemplary alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like.

"Alkoxy", alone or in combination, means a radical of the type "R--O--"
 10 wherein "R" is an alkyl radical as previously defined and "O" is an oxygen atom. Exemplary alkoxy radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

"Alkoxycarbonyl", alone or in combination, means a radical of the type "R--O--C(O)--" wherein "R--O--" is an alkoxy radical as previously defined and
 15 "C(O)--" is a carbonyl radical. Exemplary alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl.

"Alkanoyl", alone or in combination, means a radical of the type "R--C(O)--" wherein "R" is an alkyl radical as previously defined and "--C(O)--" is a carbonyl radical. Exemplary alkanoyl radicals include acetyl, trifluoroacetyl,
 20 hydroxyacetyl, propionyl, butyryl, valeryl, 4-methylvaleryl and the like.

"Halo" or "halogen", alone or in combination, means chloro, bromo, fluoro or iodo radicals.

"Aryl", alone or in combination, means an aromatic carbocyclic radical containing about 6 to about 10 carbon atoms, which is optionally substituted
 25 with one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, azido, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, alkanoylamino, amido, amidino, alkoxycarbonylamino, N-alkylamidino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, N-alkylamido, N,N-dialkylamido, aralkoxycarbonylamino, alkylthio, alkylsulfinyl,
 30 alkylsulfonyl, oxo and the like. Exemplary aryl radicals include phenyl, o-tolyl, 4-methoxyphenyl, 2-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 2-amino-3-(aminomethyl)phenyl, 6-methyl-2-aminophenyl, 2-amino-3-methylphenyl, 4,6-dimethyl-2-aminophenyl, 4-hydroxyphenyl, 3-

methyl-4-hydroxyphenyl, 4-(2-methoxyphenyl)phenyl, 2-amino-1-naphthyl, 2-naphthyl, 1-methyl-3-amino-2-naphthyl, 2,3-diamino-1-naphthyl, 4,8-dimethoxy-2-naphthyl and the like.

The reference to "optionally substituted" in the definition of the
 5 compounds of Formulas I to X is intended to include any substituent which does not negatively affect the activity of the compounds. Typical substitution includes, for example, halogen such as chlorine, nitro, amino, hydroxy, sulfonamide, cyano or the like.

10 Preferred Embodiments

While the invention broadly contemplates compounds of Formulas I to X as set forth earlier, a preferred group of compounds is represented by the Formula I compounds wherein two to four, preferably three, of R₁-R₆ are lower alkoxy, e.g. methoxy or ethoxy, and the remainder of R₁-R₆ are hydrogen; R₈
 15 is H, lower alkyl or lower alkoxy carbonyl; Y is H, lower alkyl or lower alkoxy; Z is OH, lower alkoxy or NH₂, it being understood that by the references to "lower alkyl" and "lower alkoxy", carbon contents of from 1 to 8 carbons are contemplated. Particularly preferred compounds according to Formula I are those wherein R₁, R₂ and R₄ are methoxy; R₃, R₅, R₆ and R₈ are hydrogen, Y
 20 is hydrogen and Z is OH.

A correspondingly preferred subgroup of compounds are those according to Formula II wherein at least two, preferably three, of R₁ to R₆ are lower alkoxy, notably methoxy or ethoxy; R₇ is H; R₈ is H, lower alkyl or lower alkoxy carbonyl; Y and Y' are H, lower alkyl or lower alkoxy and Z' is O (oxo).
 25 Particularly preferred are those compounds of the Formula II structure where R₁, R₂ and R₄ are methoxy, R₃, R₅ and R₆ are hydrogen, R₇ is H; R₈ is H or ethoxycarbonyl; Y and Y' are hydrogen and Z' is O.

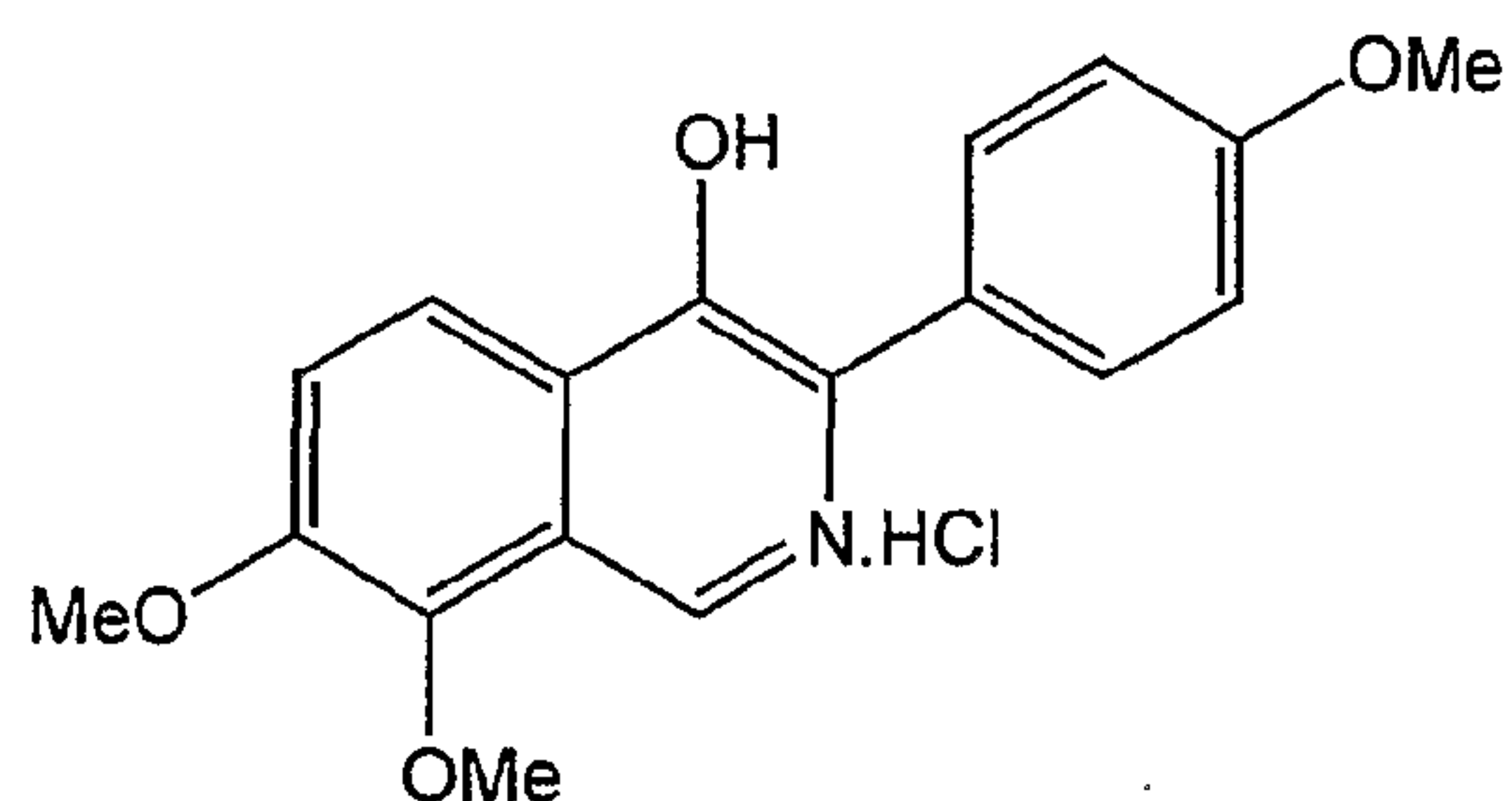
Generally speaking, the compounds of Formulas I to X wherein Y is hydrogen, Z is OH or Z' is O, R₁, R₂ and R₆ are methoxy are particularly
 30 preferred.

The following compounds are representative of the preferred subgroups for compounds within Formulas I through X according to the invention:

Formula I

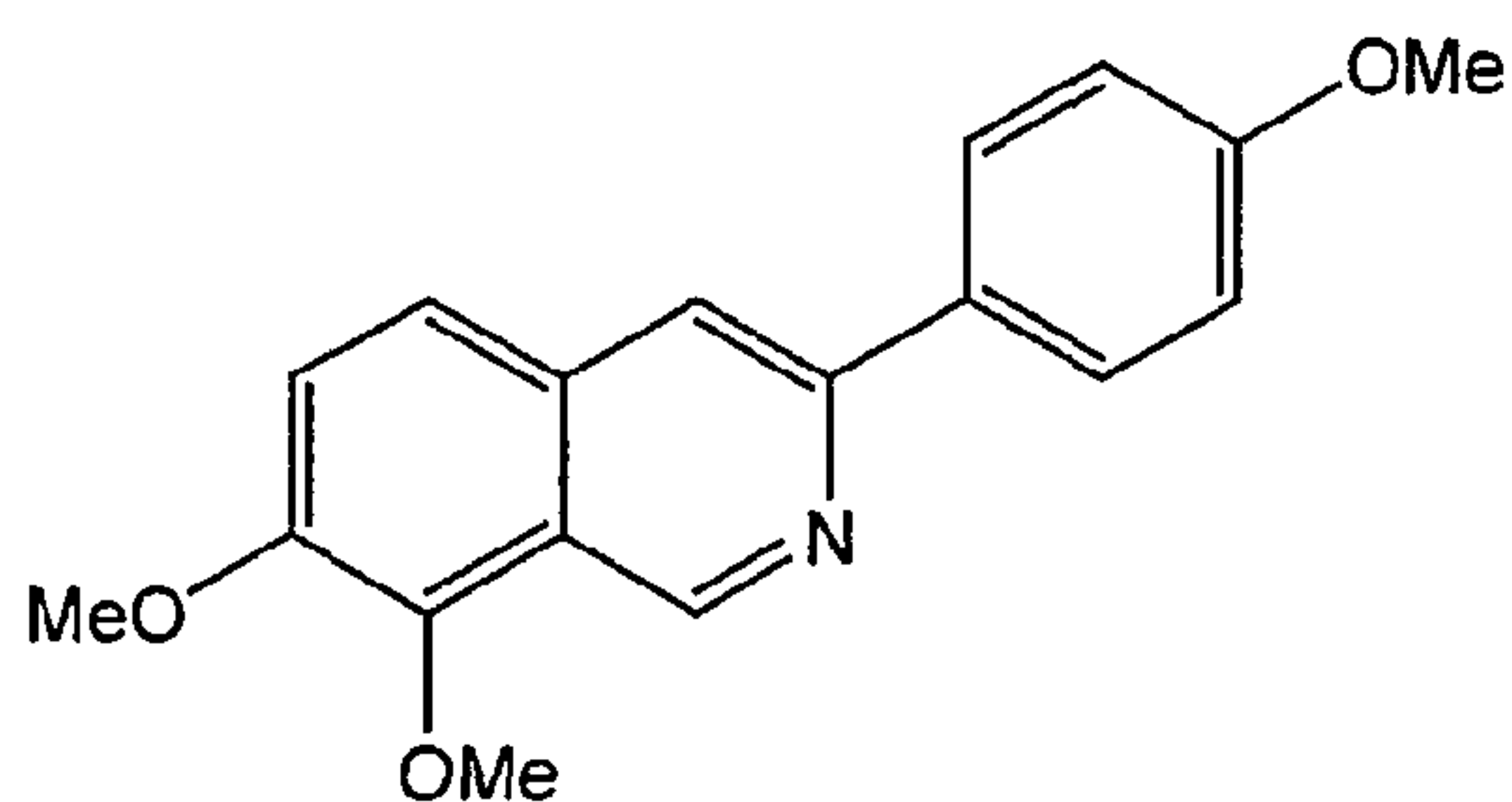
7,8-Dimethoxy-3-(4-methoxy-phenyl)-isoquinolin-4-ol hydrochloride

(Compound B)



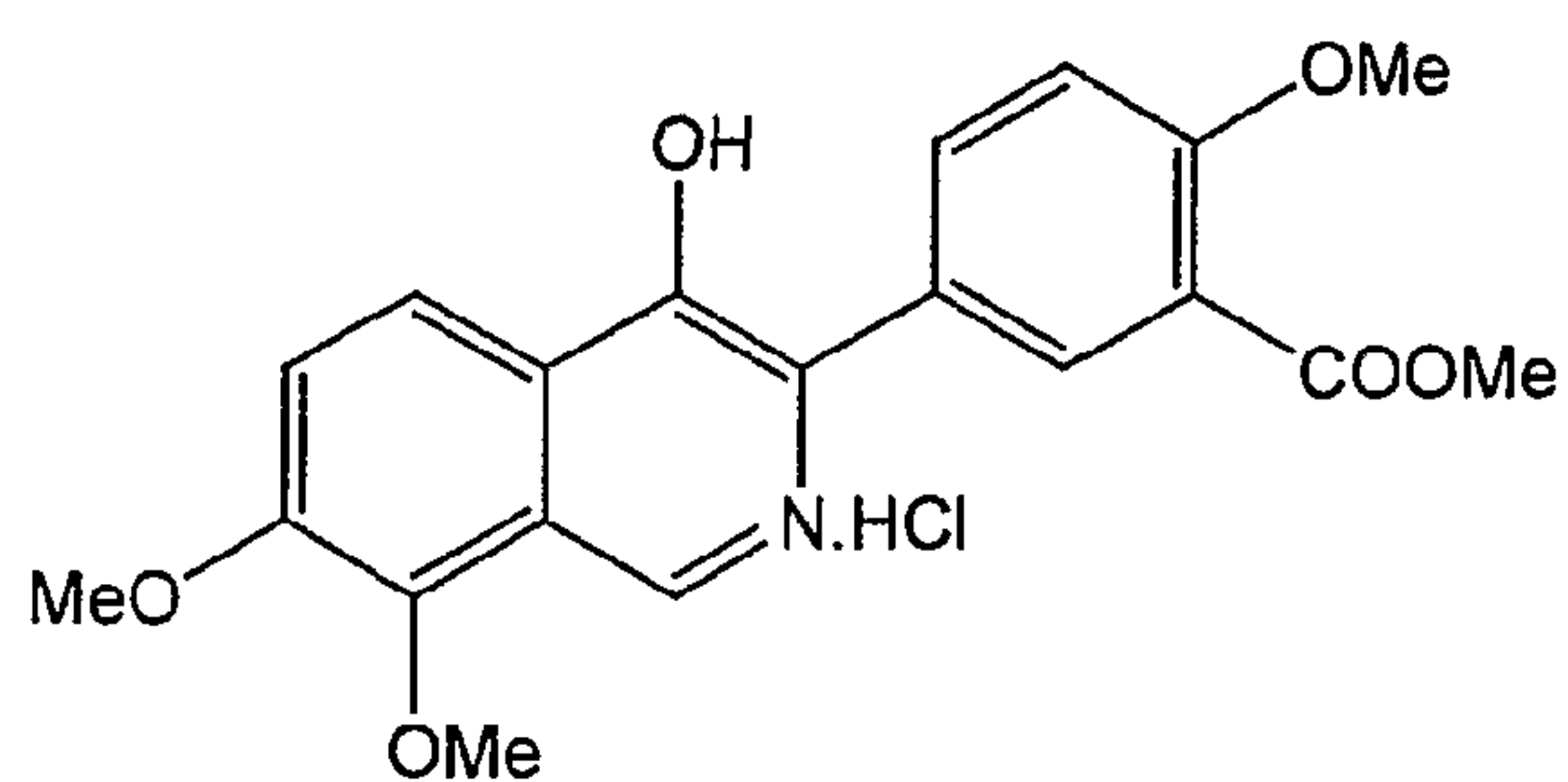
5 7,8-Dimethoxy-3-(4-methoxy-phenyl)-isoquinoline

(Compound C)



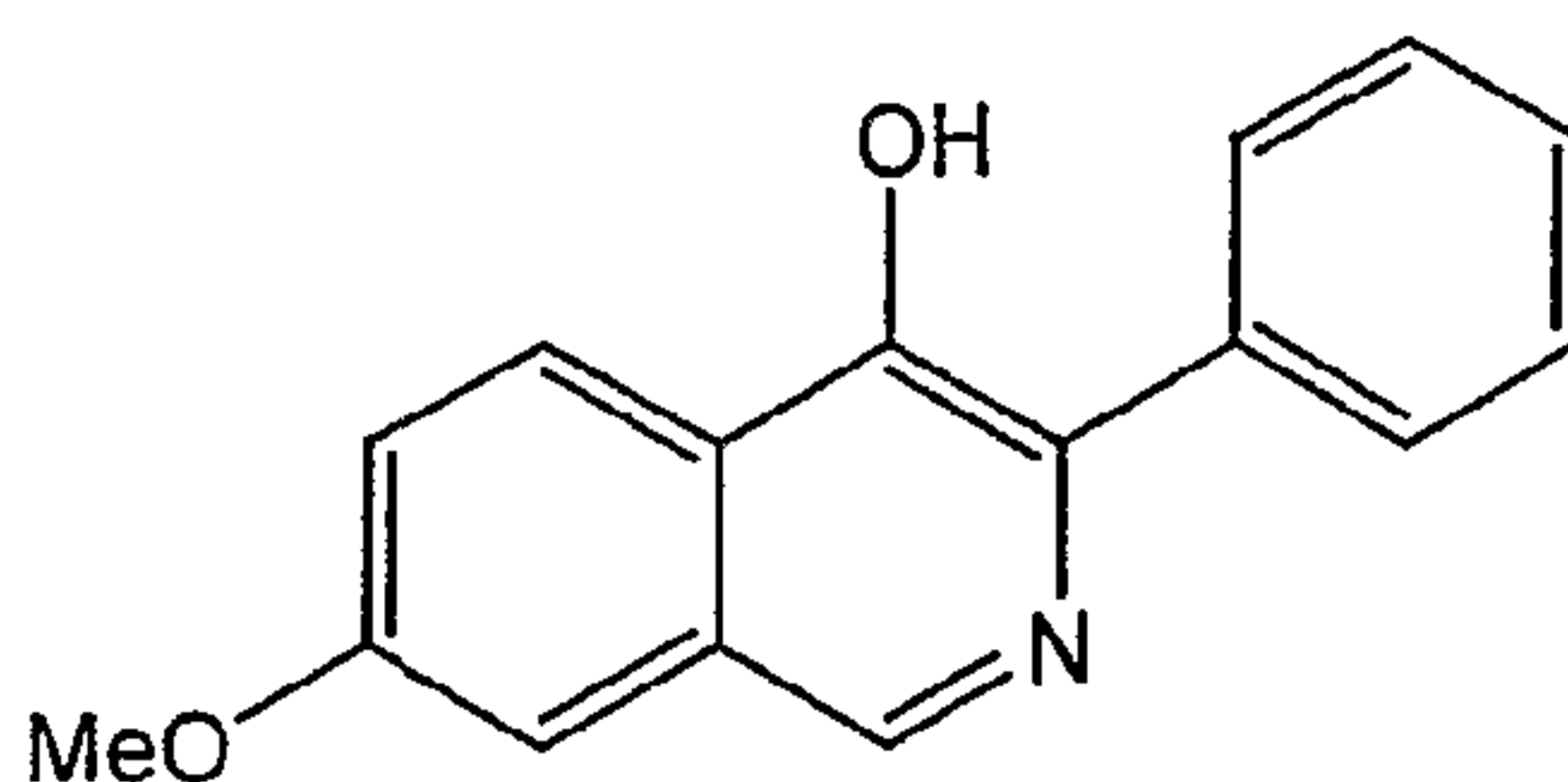
10 5-(4-Hydroxy-7,8-dimethoxy-isoquinoline-3-yl)-2-methoxy-benzoic acid methyl ester hydrochloride

(Compound G)



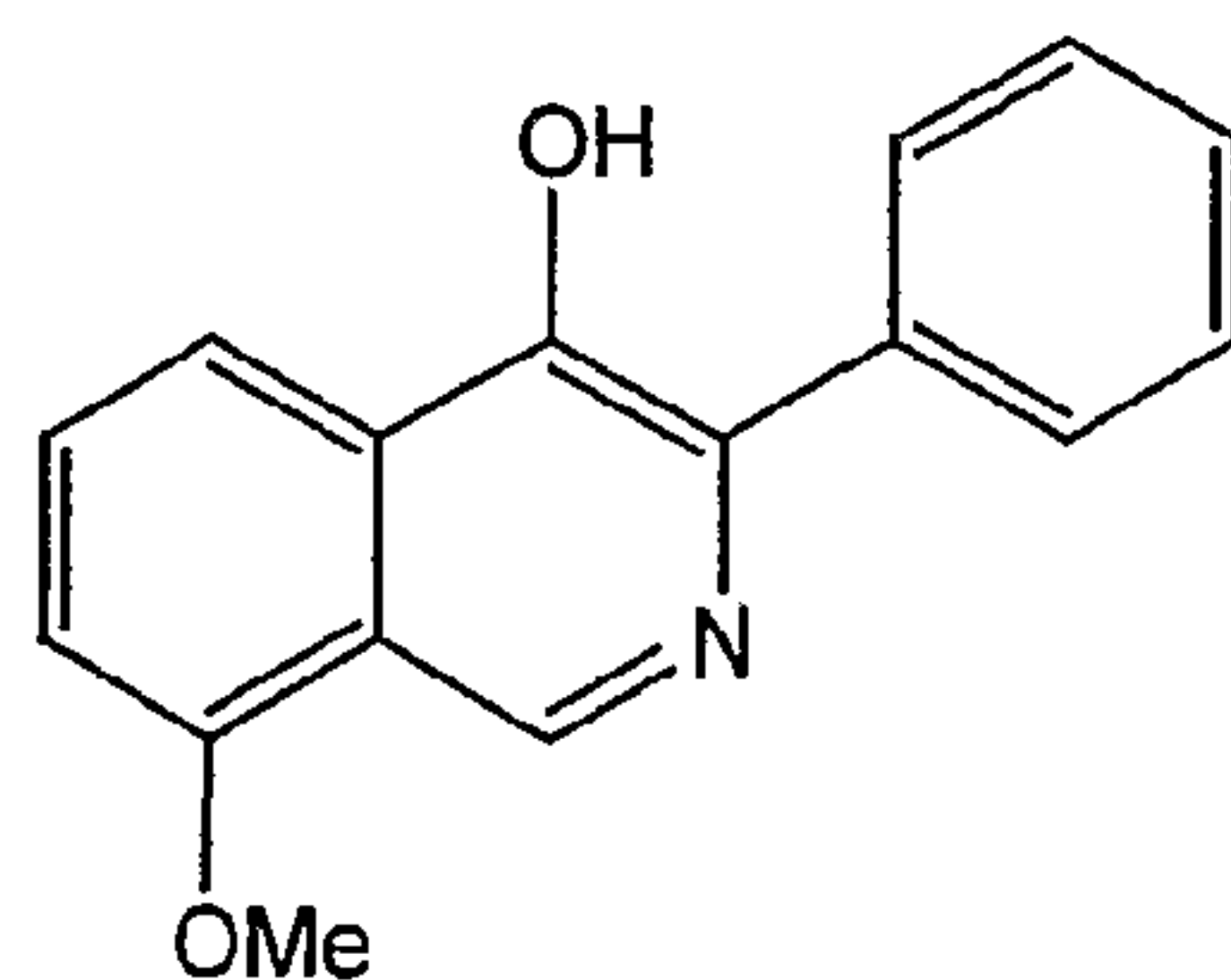
15 7-Methoxy-3-phenyl-isoquinolin-4-ol

(Compound H)



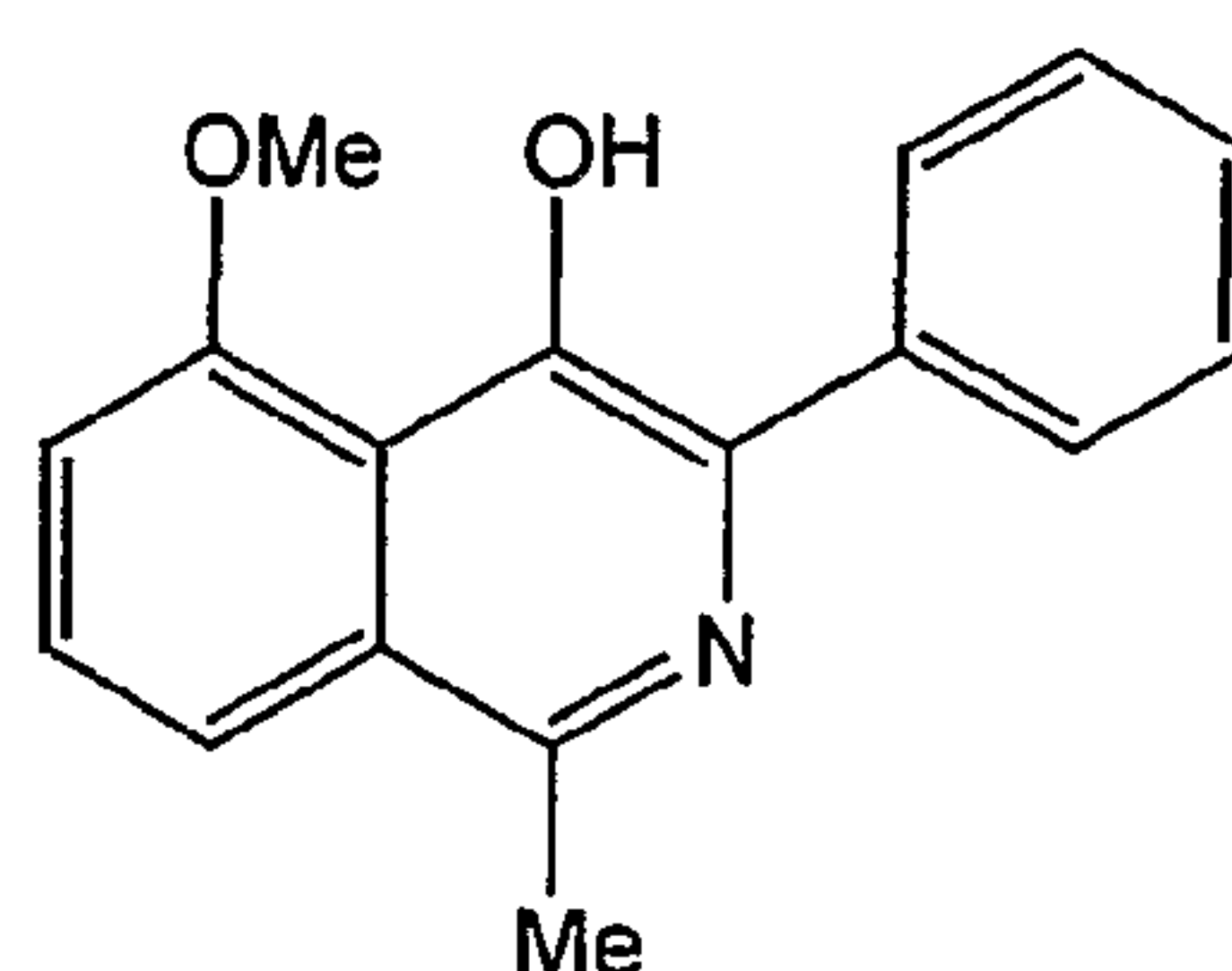
8-Methoxy-3-phenyl-isoquinolin-4-ol

(Compound J)



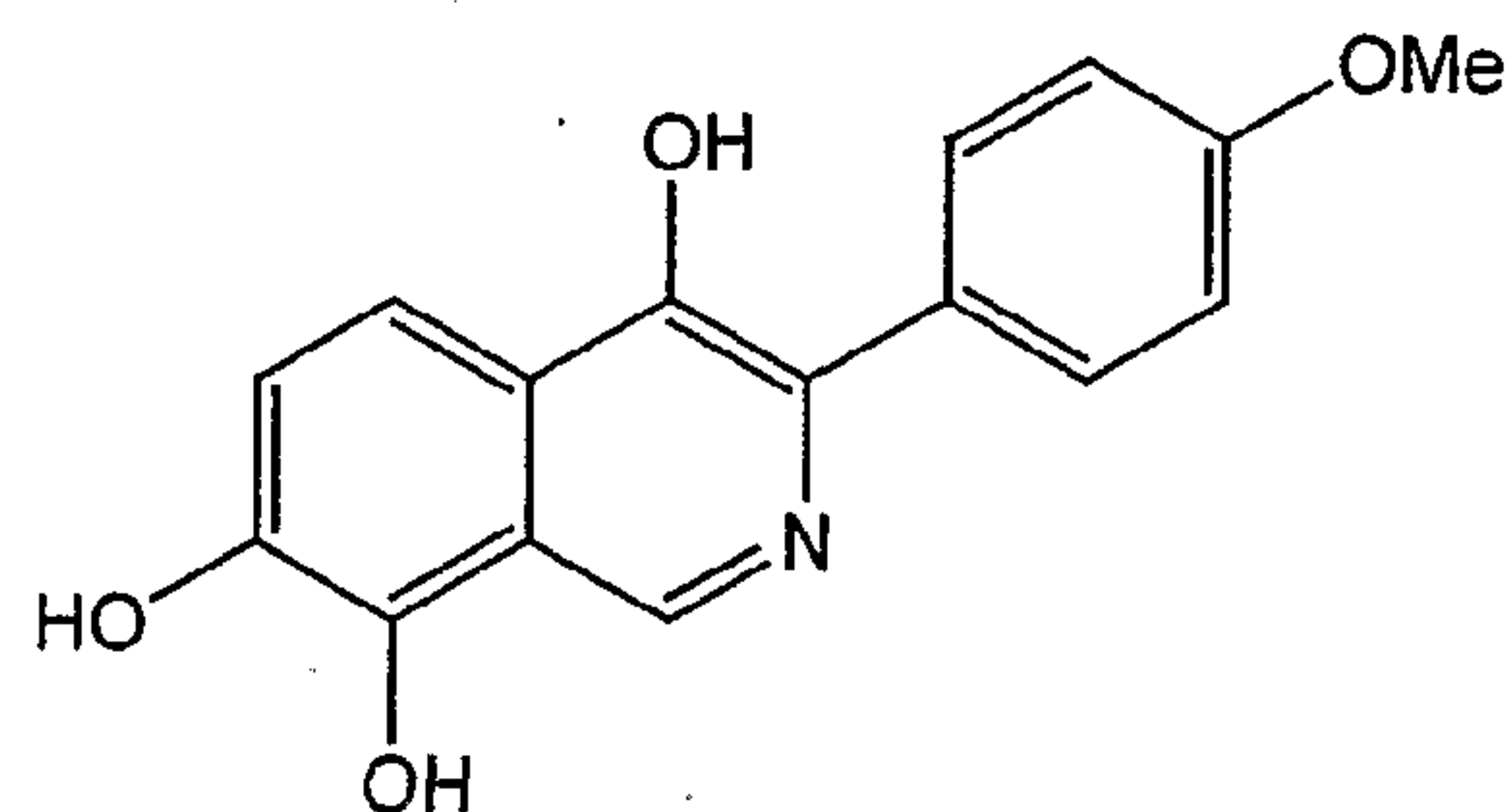
5 5-Methoxy-1-methyl-3-phenyl-isoquinolin-4-ol

(Compound K)



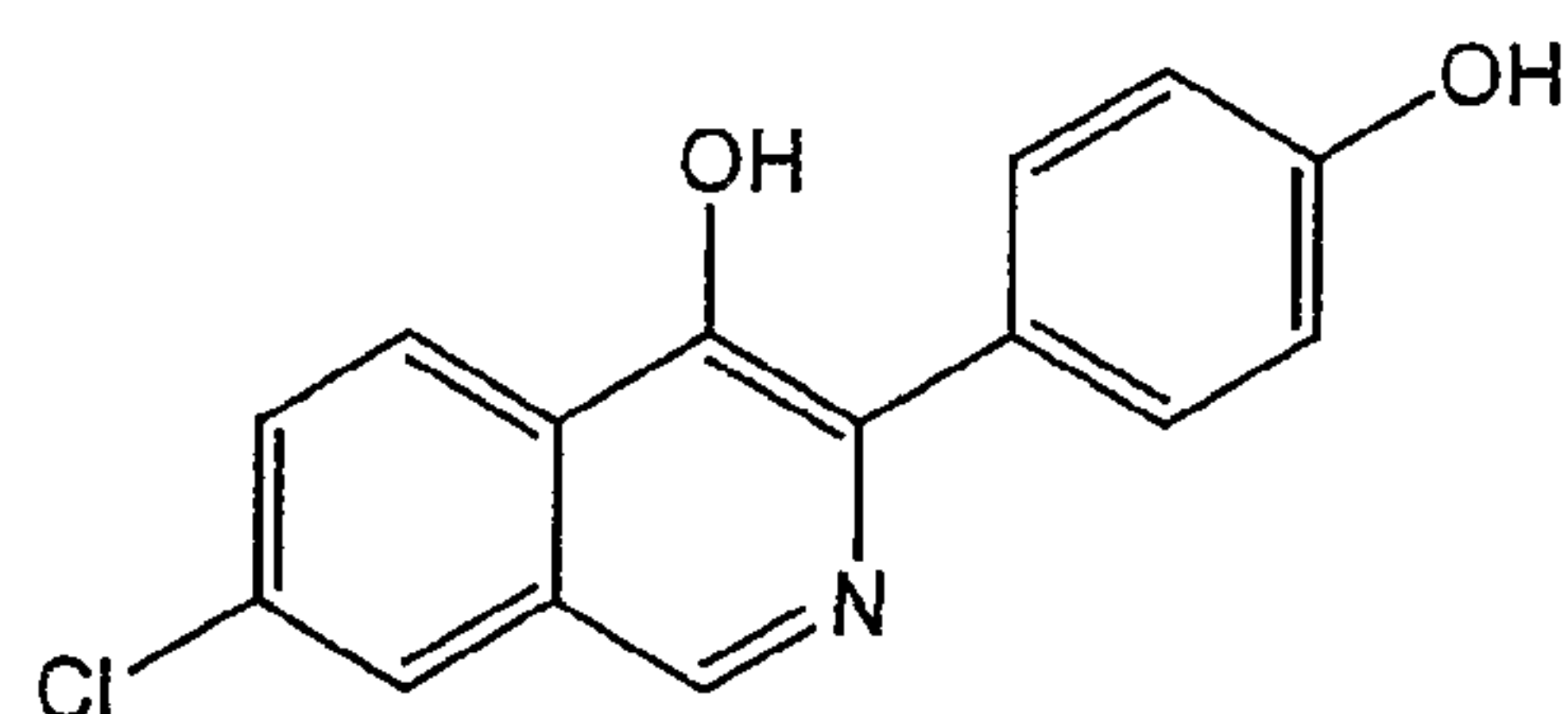
10 3-(4-Methoxy-phenyl)-isoquinoline-4,7,8-triol

(Compound L)



7-Chloro-3-(4-hydroxy-phenyl)-isoquinolin-4-ol

(Compound M)

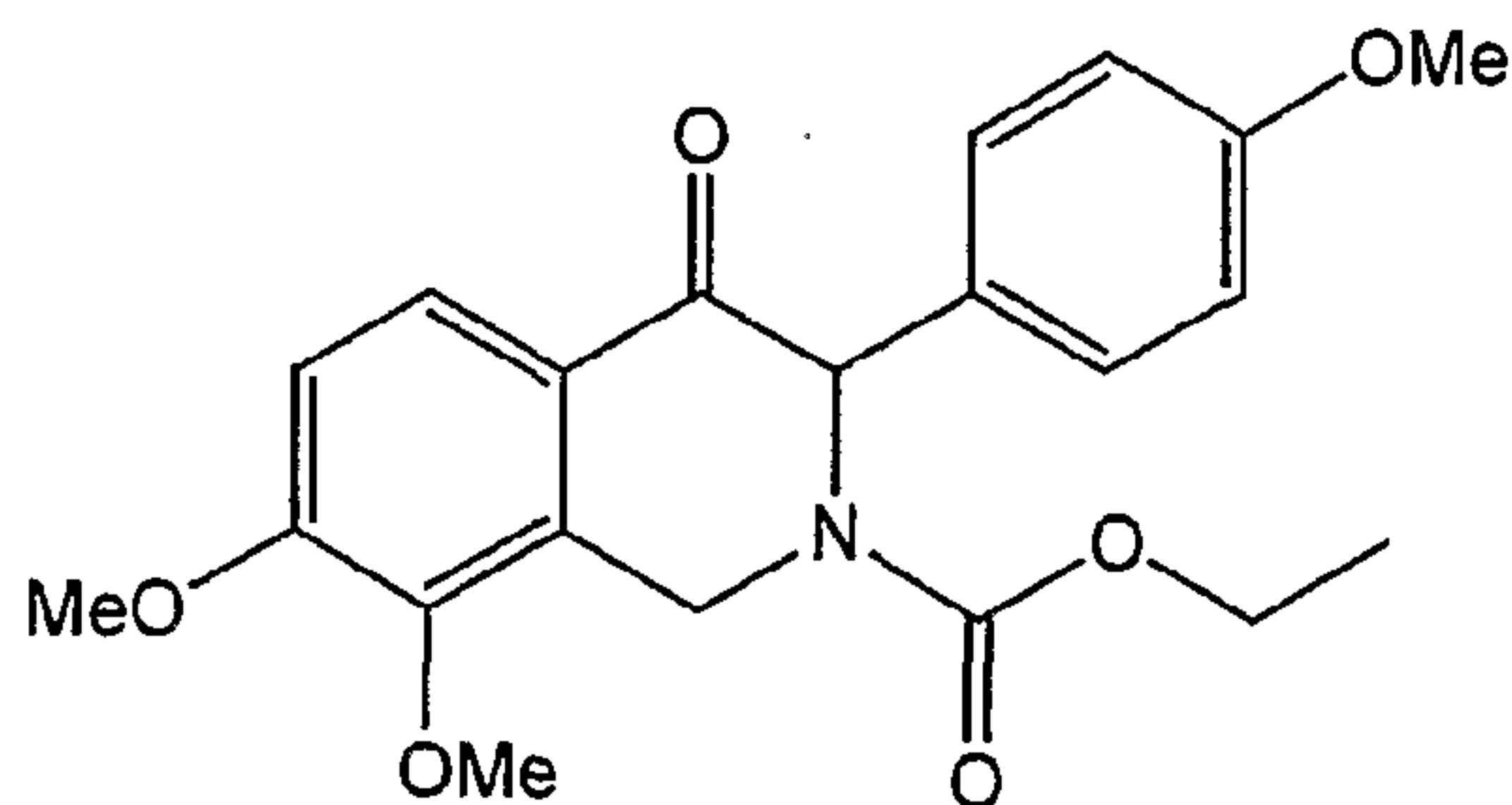


15

FORMULA II

7,8-Dimethoxy-3-(4-methoxy-phenyl)-4-oxo-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid ethyl ester

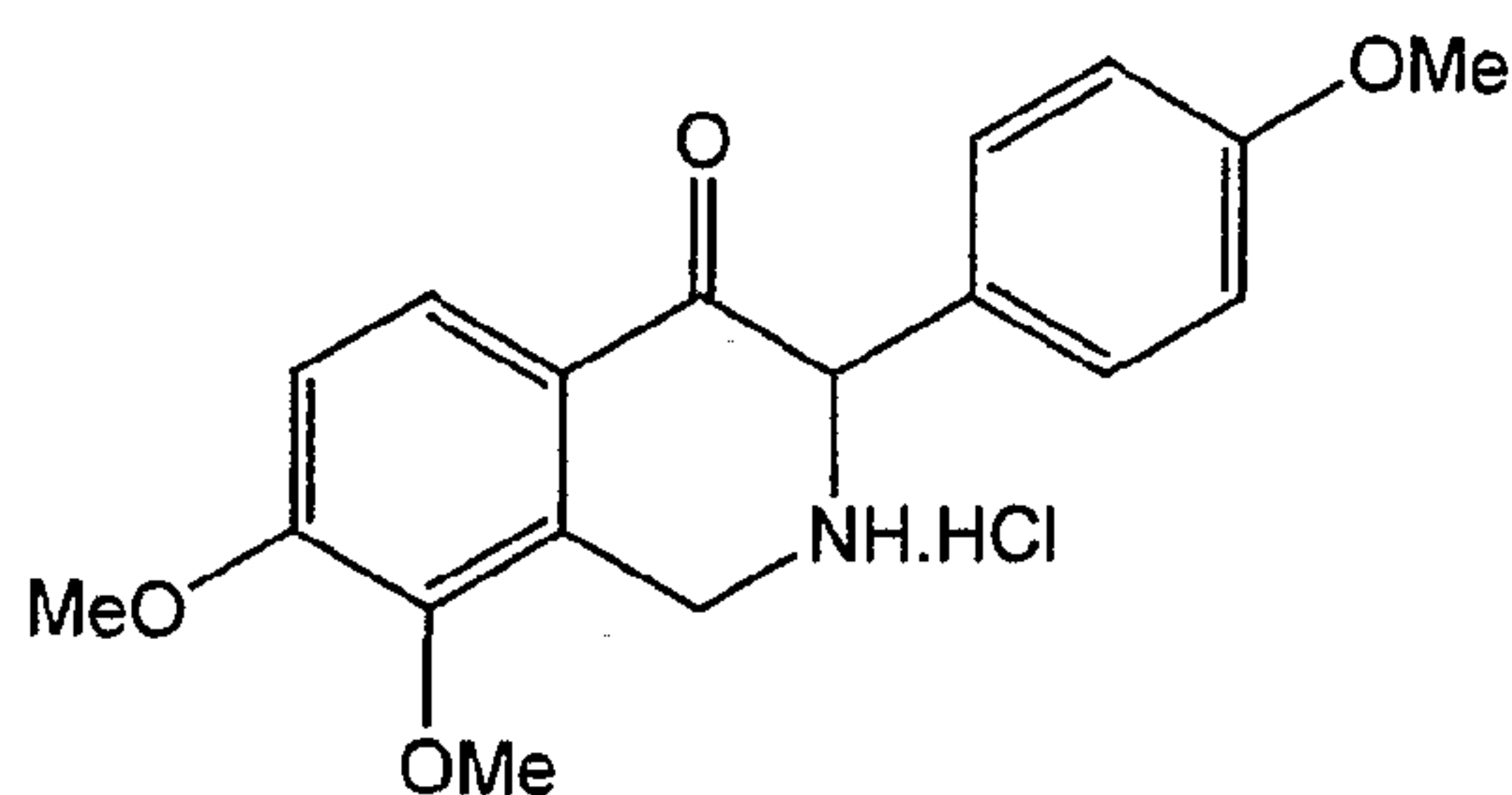
(Compound D)



5

7,8-Dimethoxy-3-(4-methoxy-phenyl)-2,3-dihydro-1*H*-isoquinoline-4-one hydrochloride

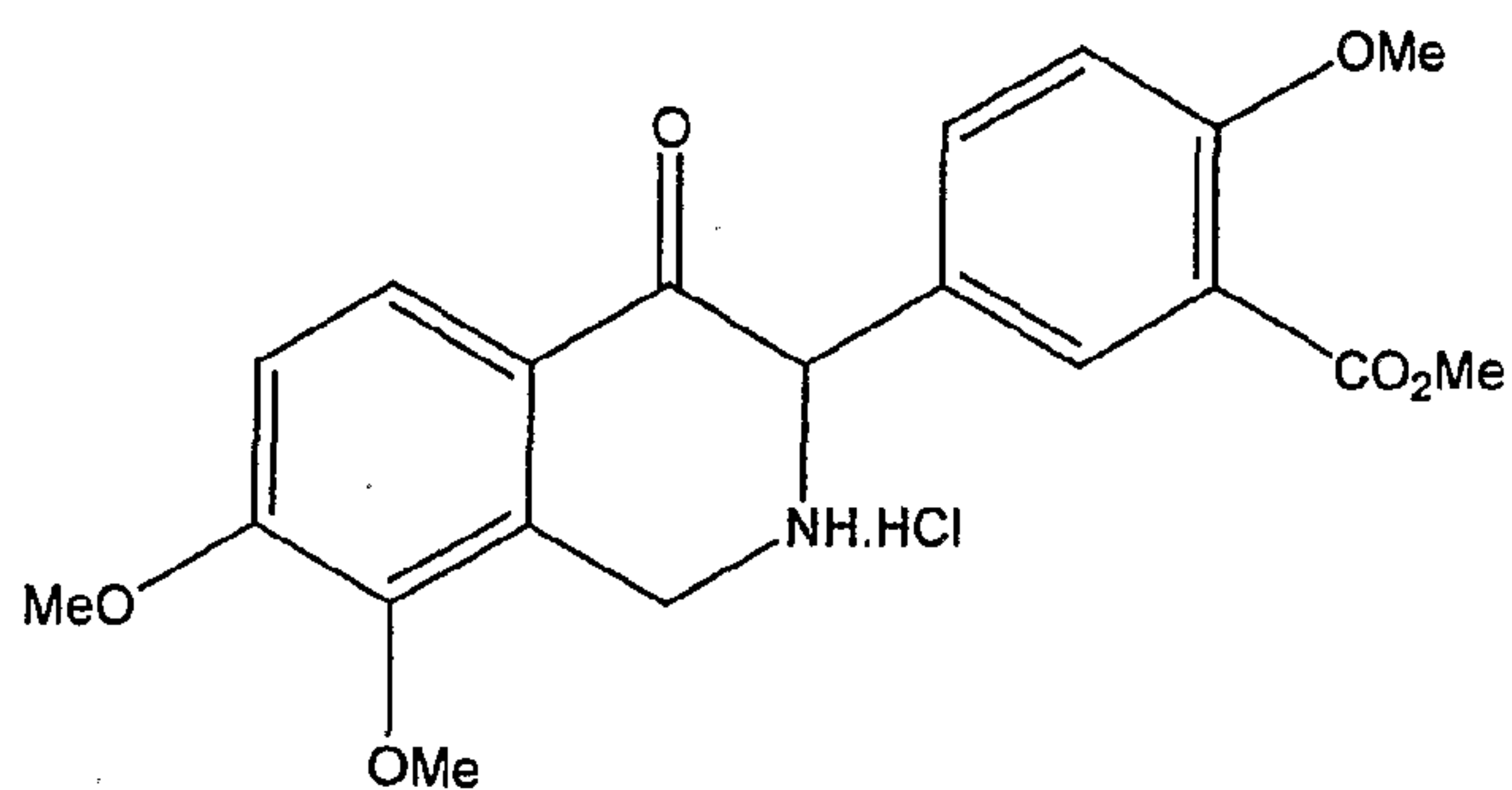
(Compound E)



10

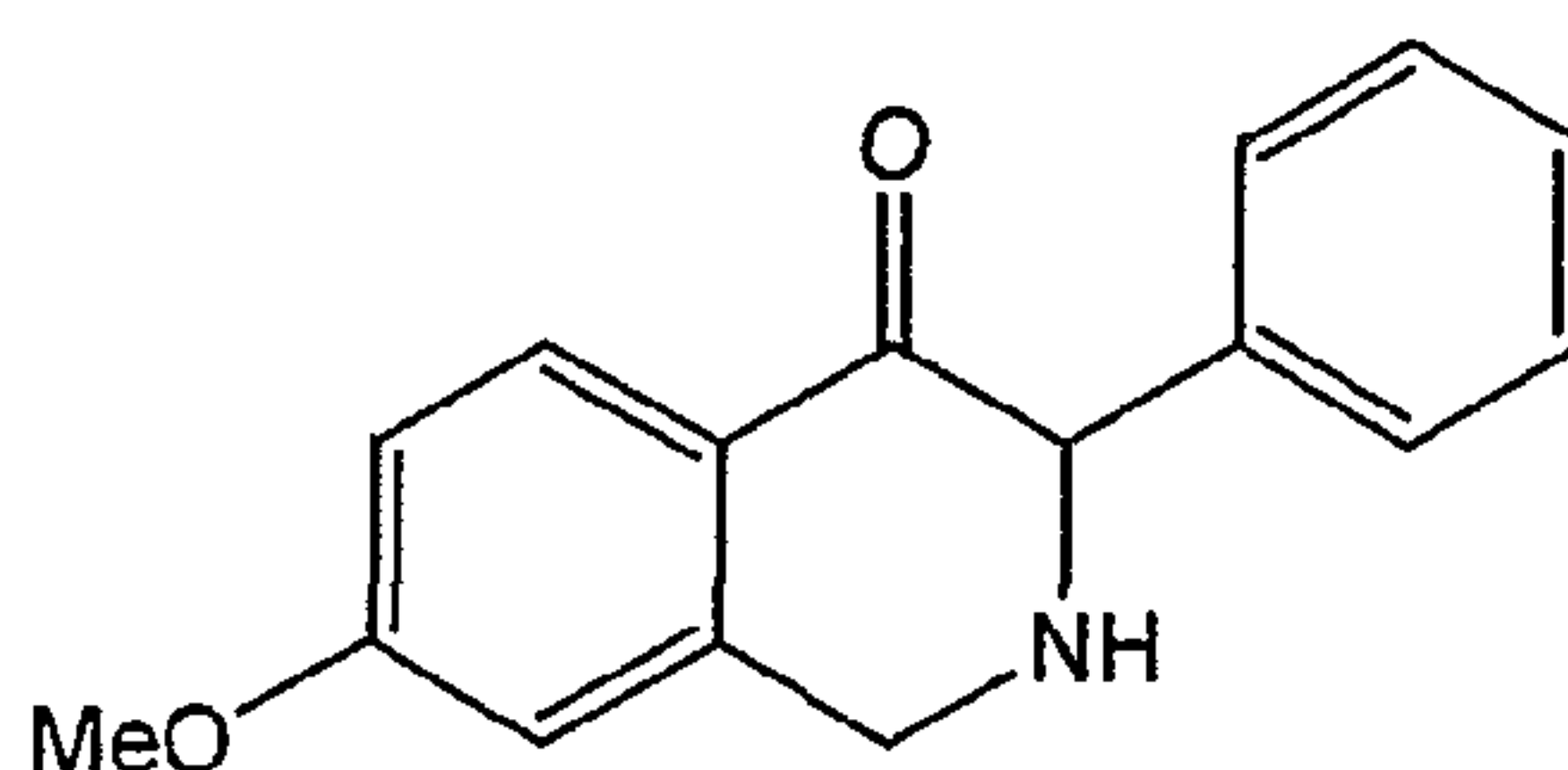
5-(7,8-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-isoquinolin-3-yl)-2-methoxybenzoic acid methyl ester hydrochloride

(Compound F)



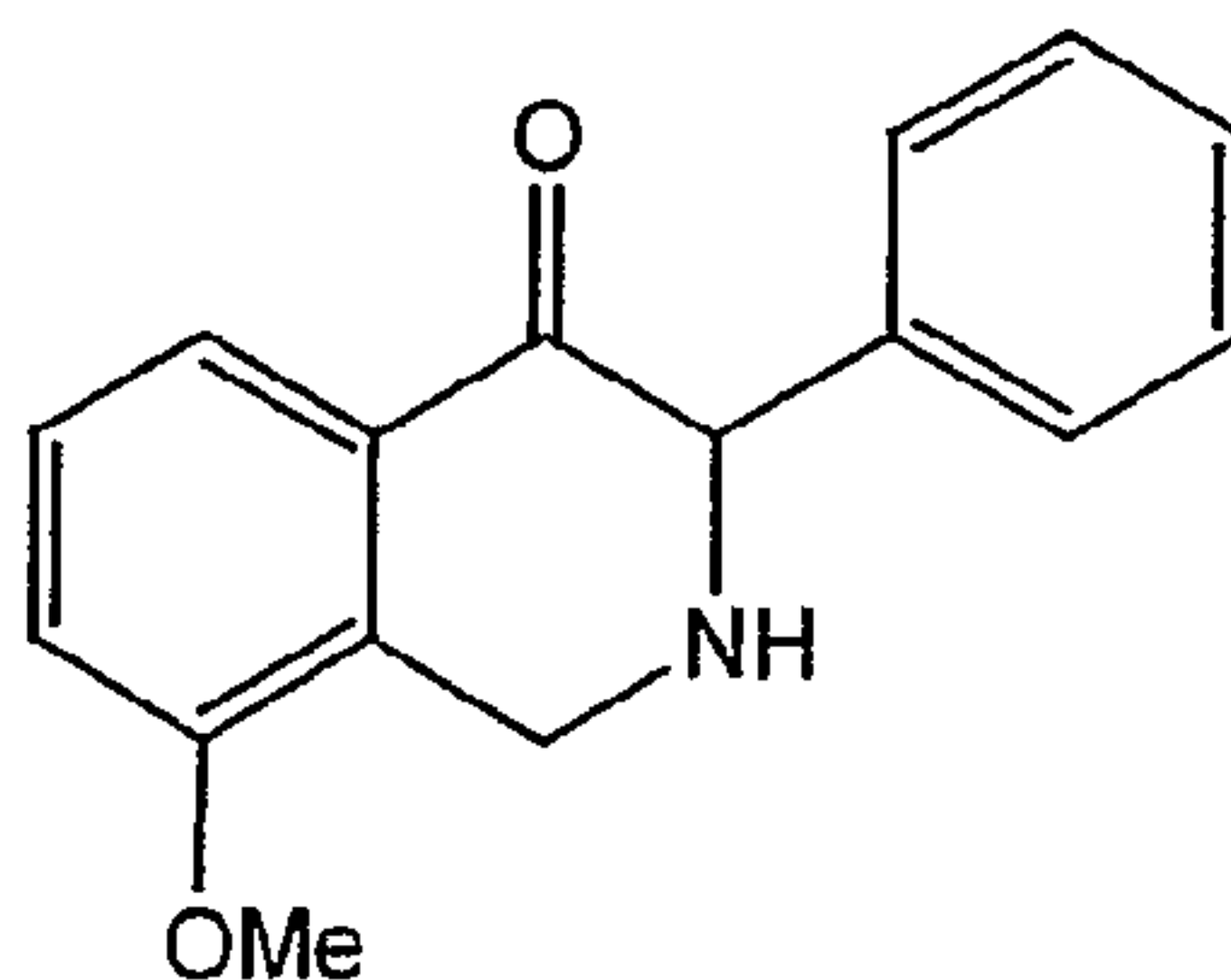
15 7-Methoxy-3-phenyl-2,3-dihydro-1*H*-isoquinolin-4-one

(Compound N)

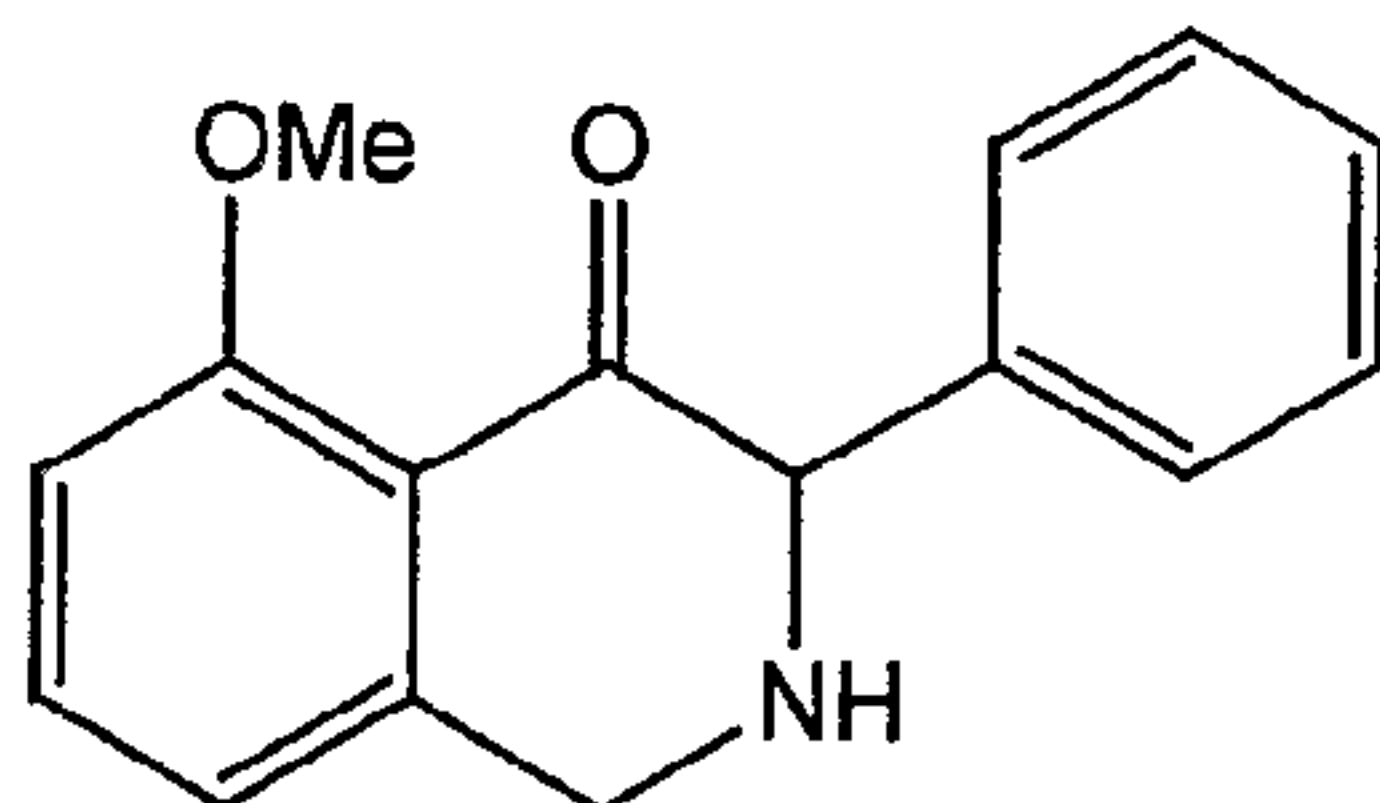


8-Methoxy-3-phenyl-2,3-dihydro-1*H*-isoquinolin-4-one

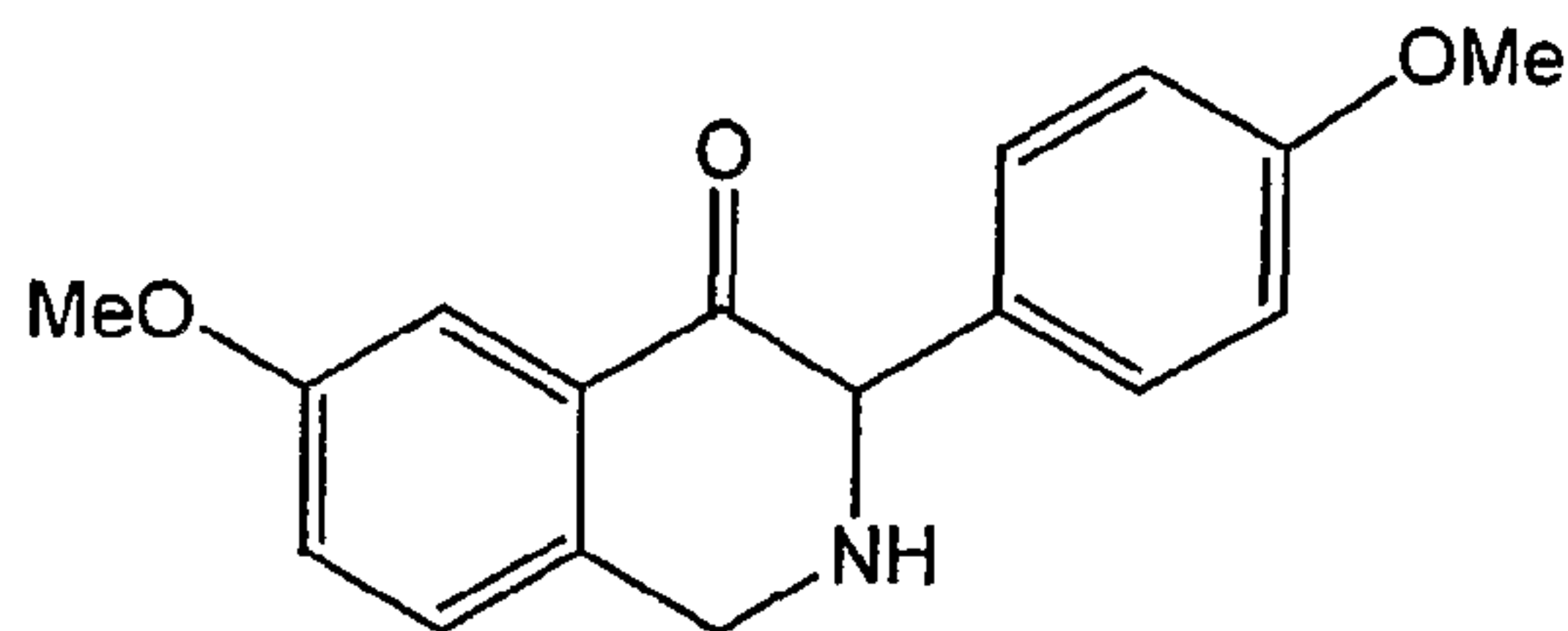
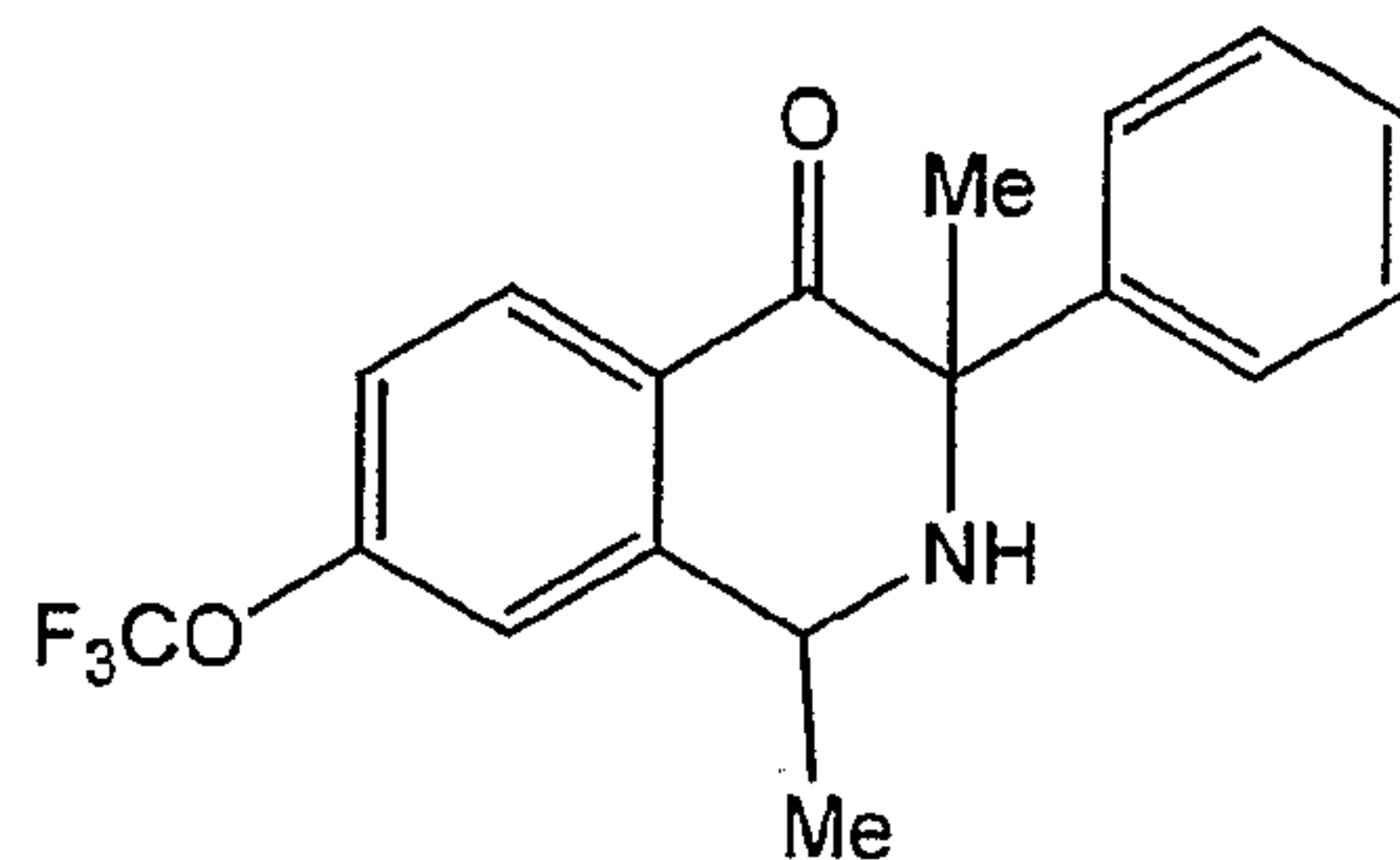
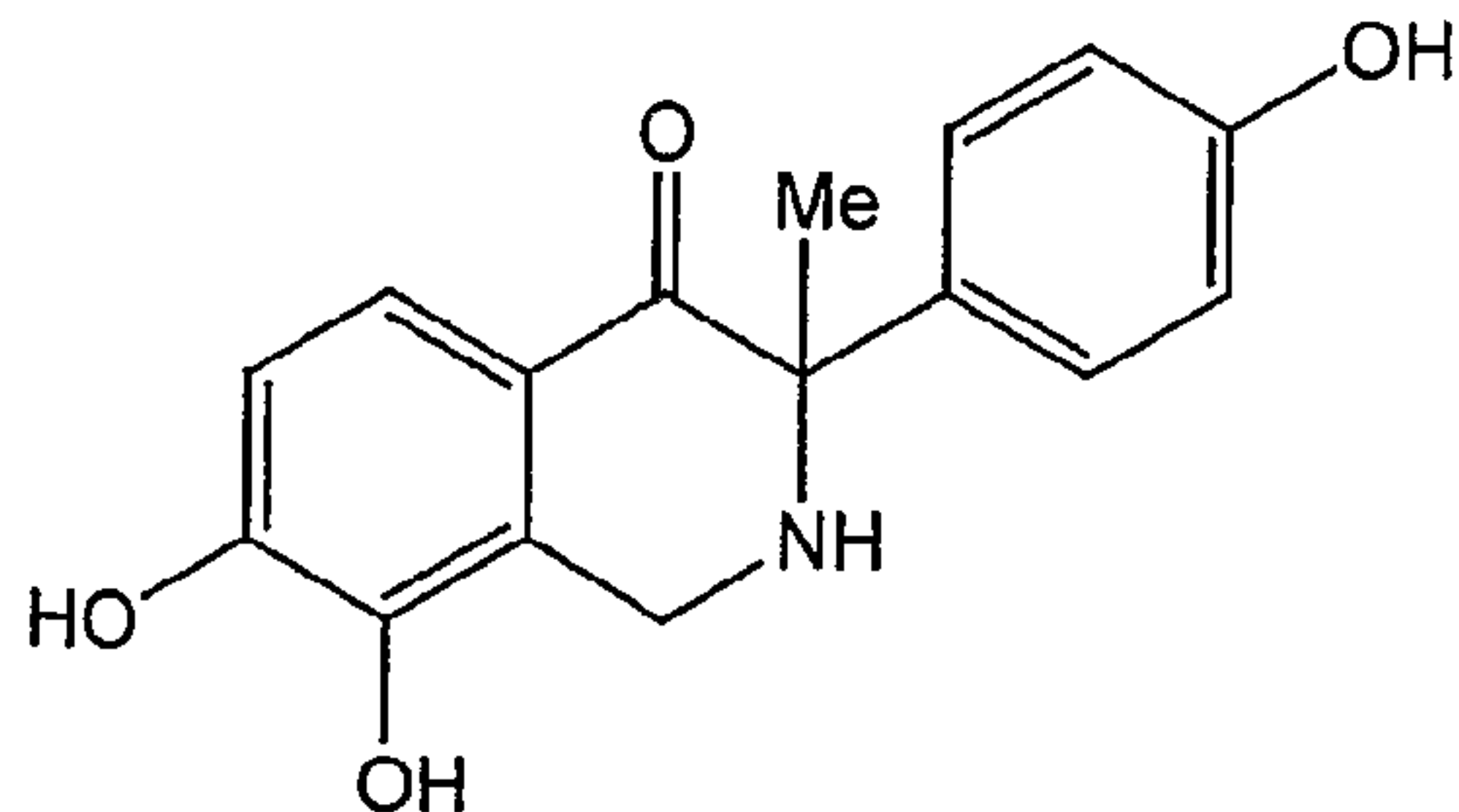
(Compound P)

5-Methoxy-3-phenyl-2,3-dihydro-1*H*-isoquinolin-4-one

(Compound Q)

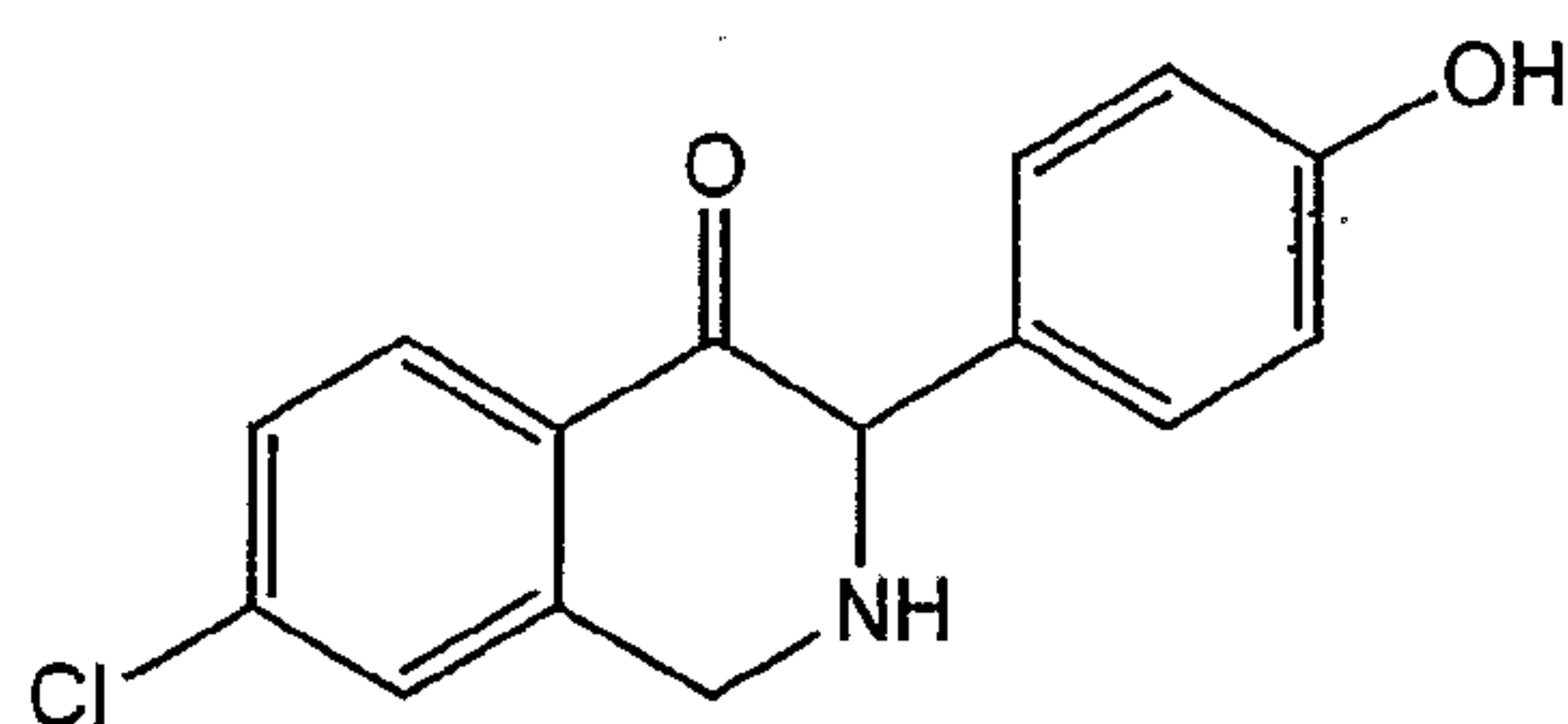
6-Methoxy-3-(4-methoxy-phenyl)-2,3-dihydro-1*H*-isoquinolin-4-one

(Compound R)

10 1,3-Dimethyl-3-phenyl-7-trifluoromethoxy-2,3-dihydro-1*H*-isoquinolin-4-one
(Compound S)7,8-Dihydroxy-3-(4-hydroxy-phenyl)-3-methyl-2,3-dihydro-1*H*-isoquinolin-4-one
one (Compound T)

7-Chloro-3-(4-hydroxy-phenyl)-2,3-dihydro-1*H*-isoquinolin-4-one

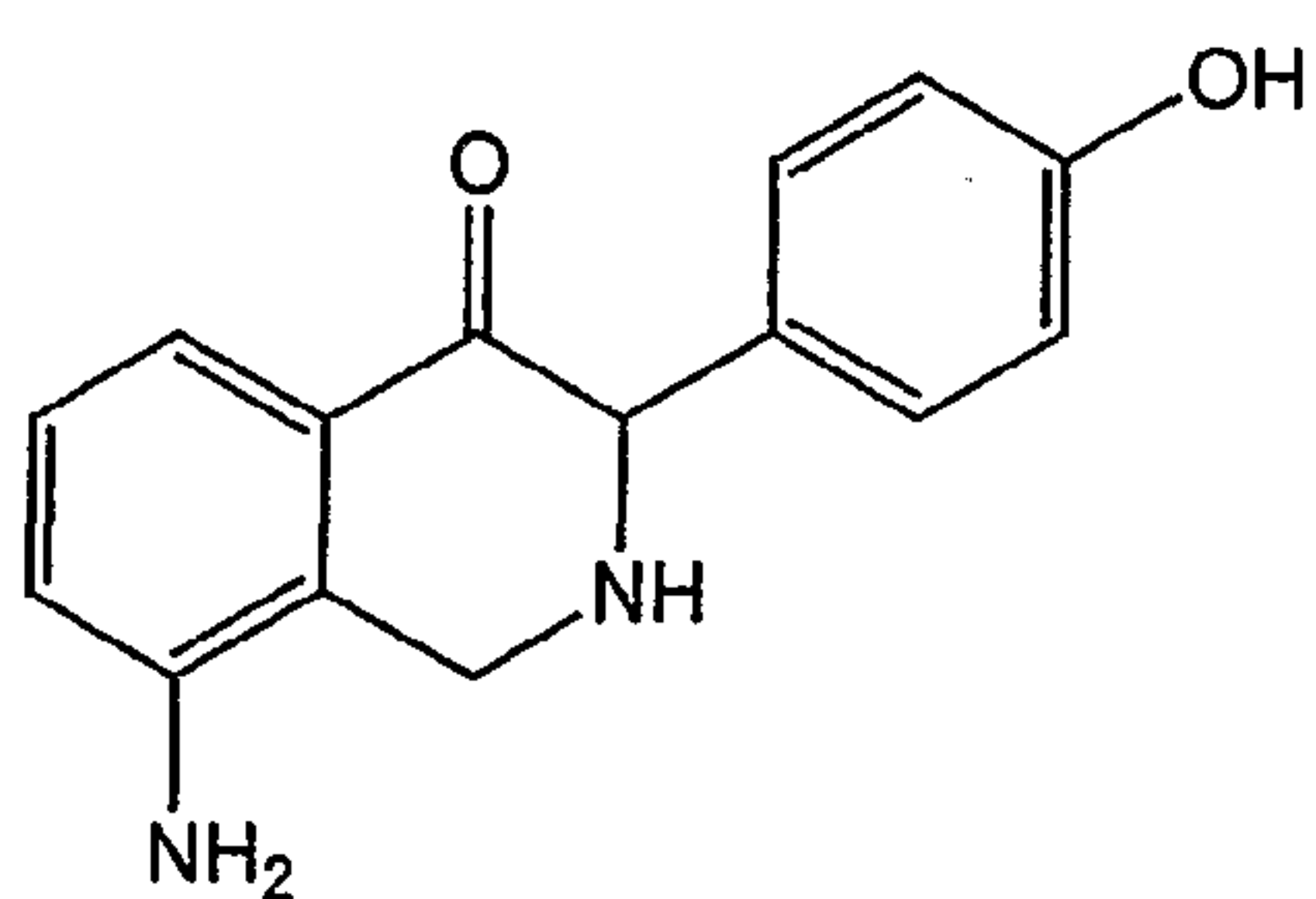
(Compound V)



5

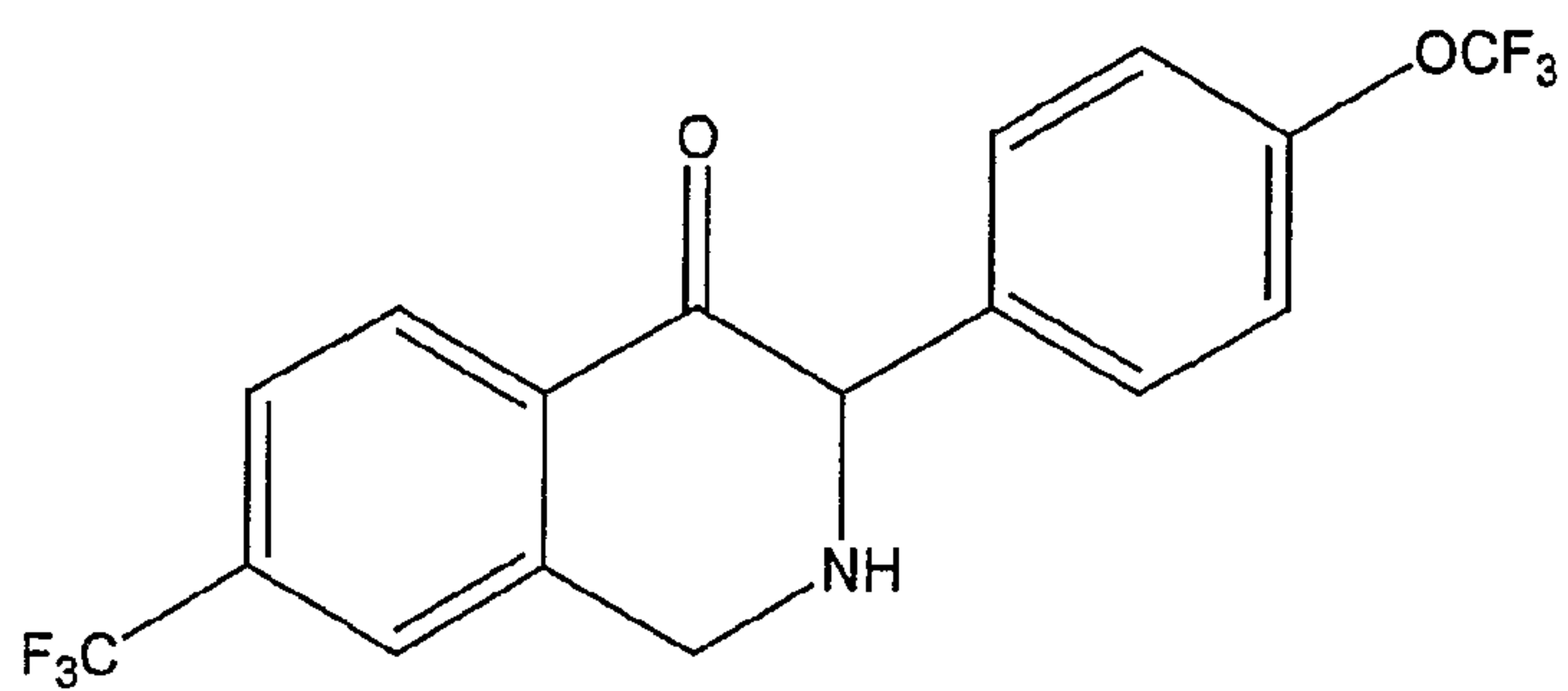
8-Amino-3-(4-hydroxy-phenyl)-2,3-dihydro-1*H*-isoquinolin-4-one

(Compound W)



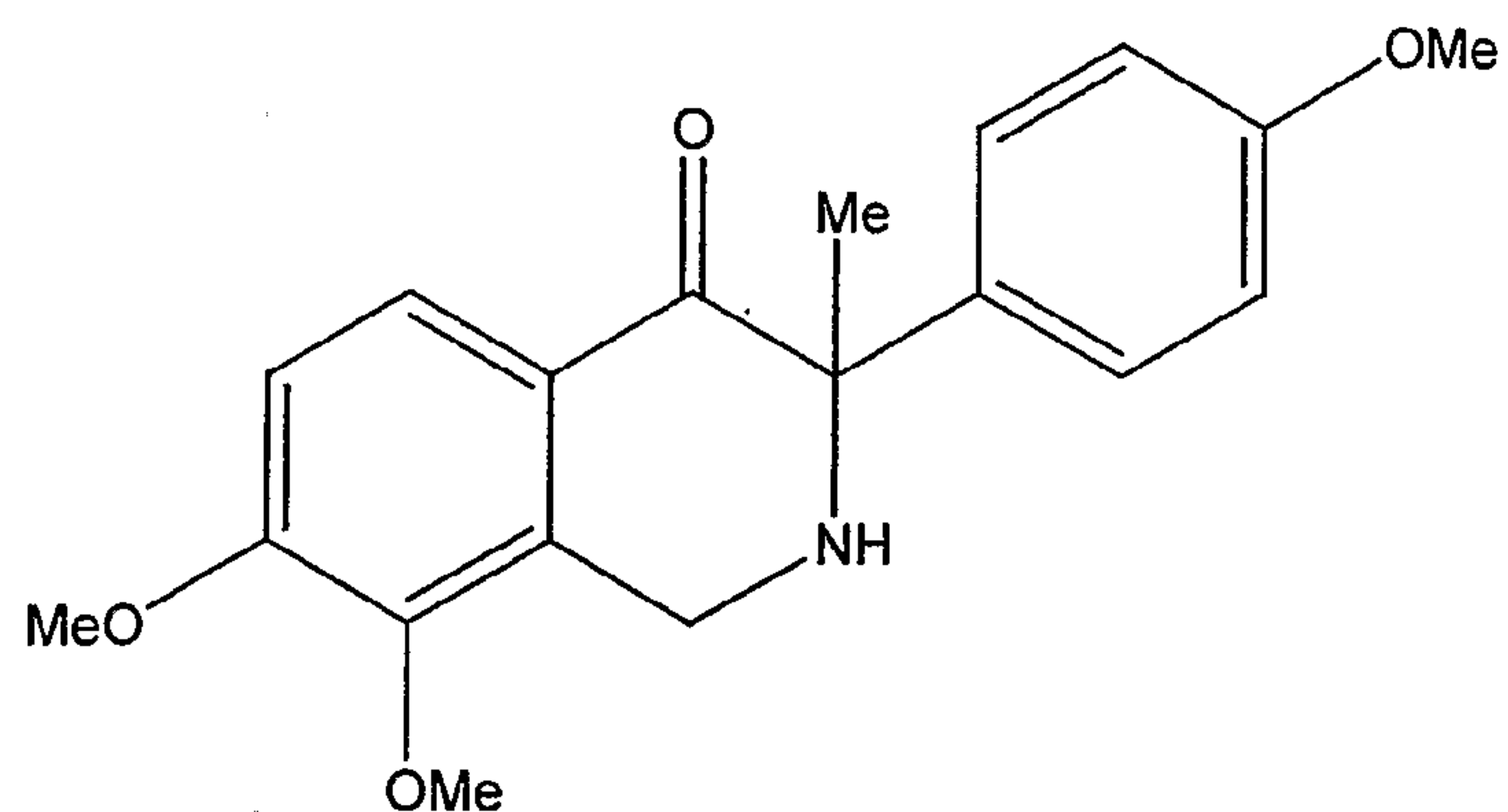
10 3-(4-Trifluoromethoxy-phenyl)-7-trifluoromethyl-2,3-dihydro-1*H*-isoquinolin-4-one

(Compound NA)



7,8-Dimethoxy-3-(4-methoxy-phenyl)-3-methyl-2,3-dihydro-1*H*-isoquinolin-4-one

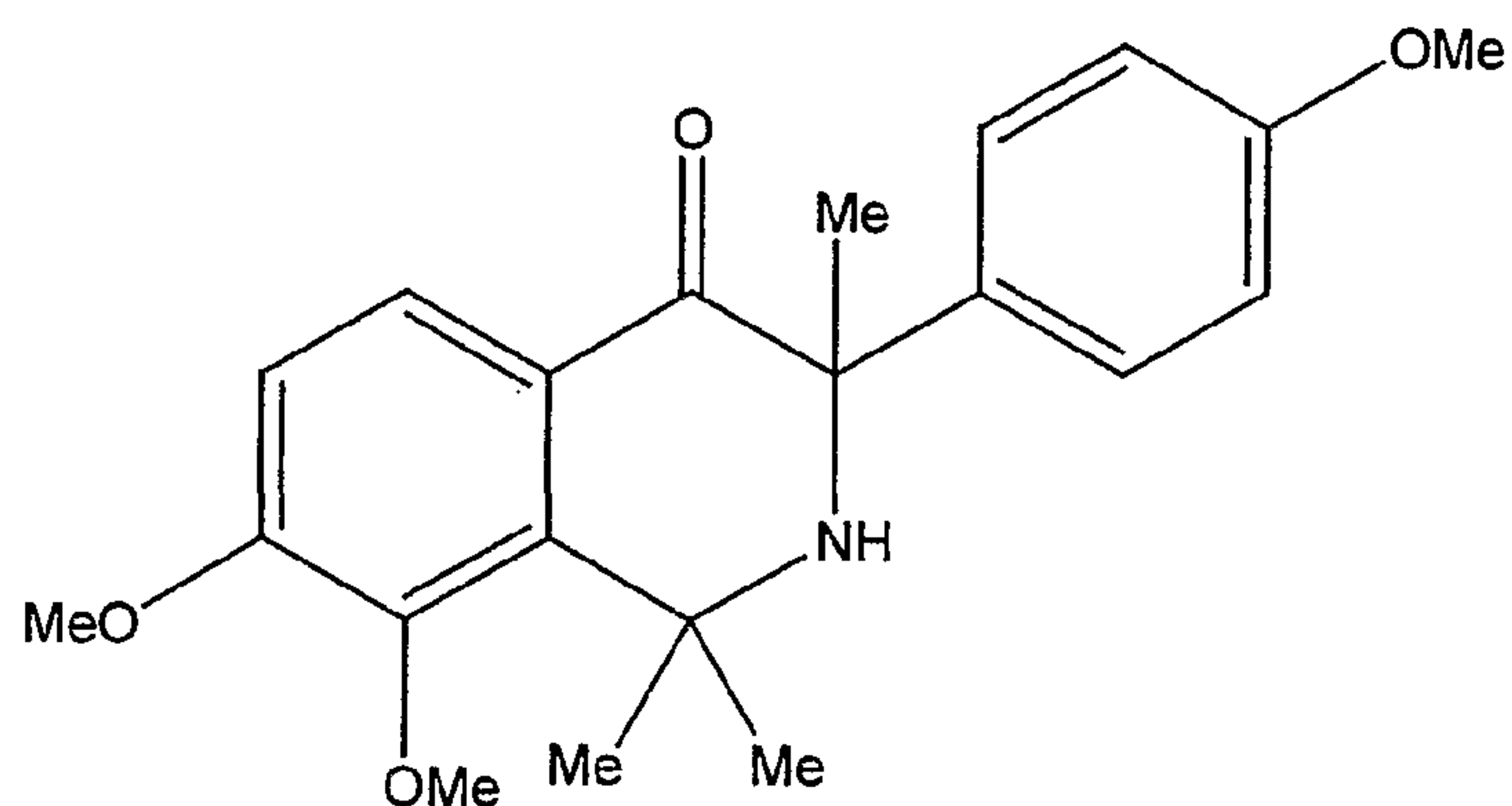
(Compound NB)



5

7,8-Dimethoxy-3-(4-methoxy-phenyl)-1,1,3-trimethyl-2,3-dihydro-1*H*-isoquinolin-4-one

(Compound NC)

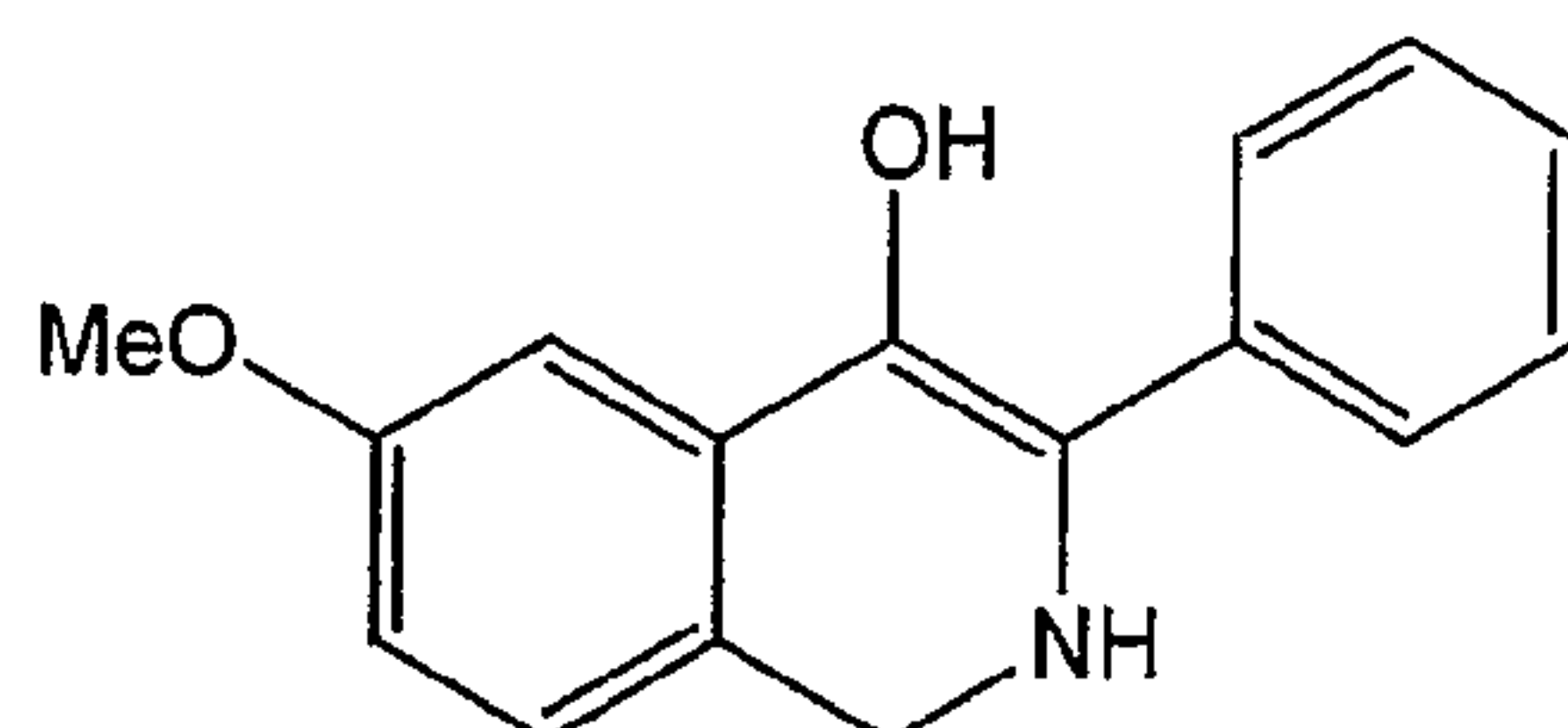


10

Formula III

6-Methoxy-3-phenyl-1,2-dihydro-isoquinolin-4-ol

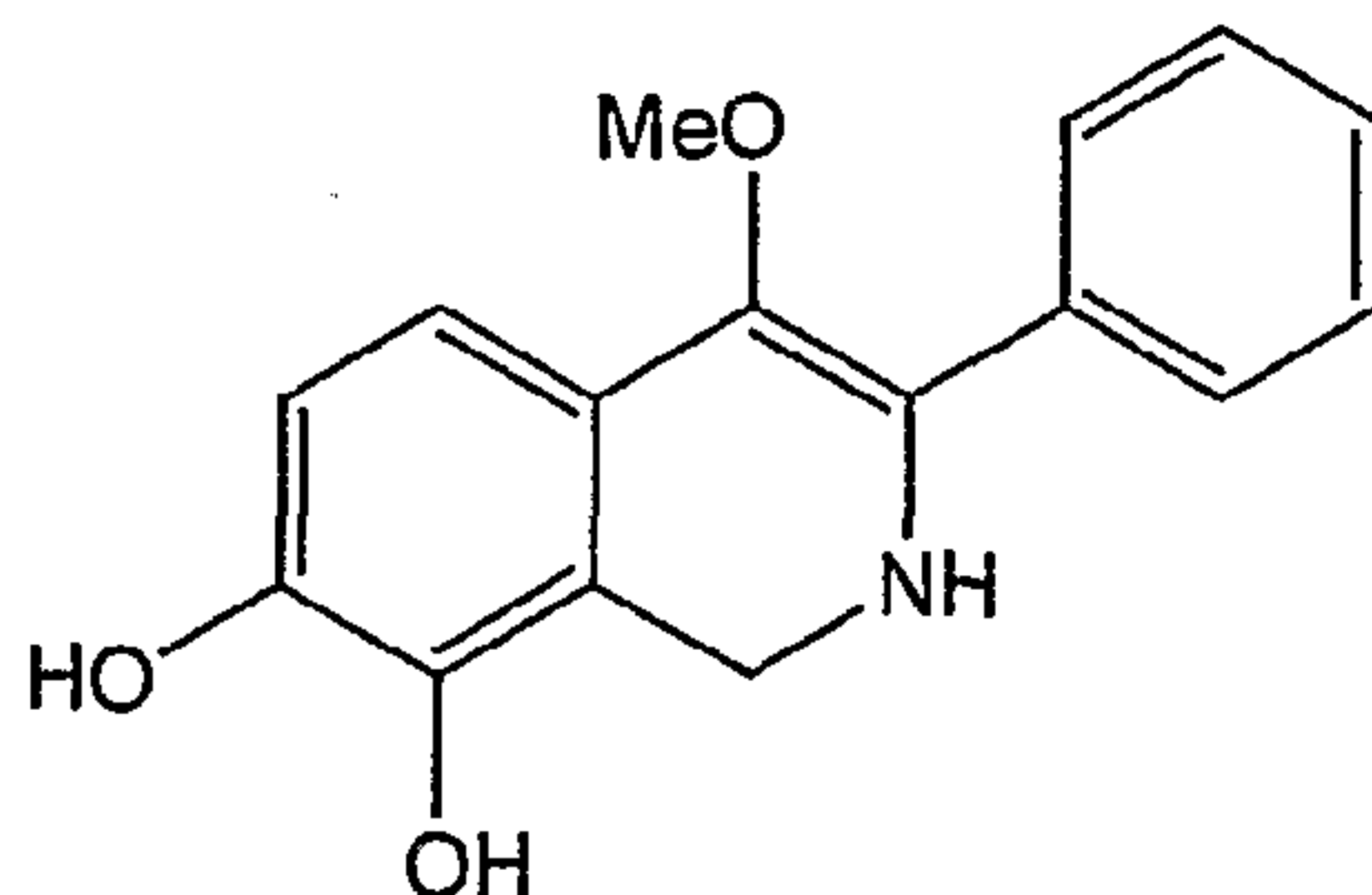
(Compound X)



15

4-Methoxy-3-phenyl-1,2-dihydro-isoquinoline-7,8-diol

(Compound Y)

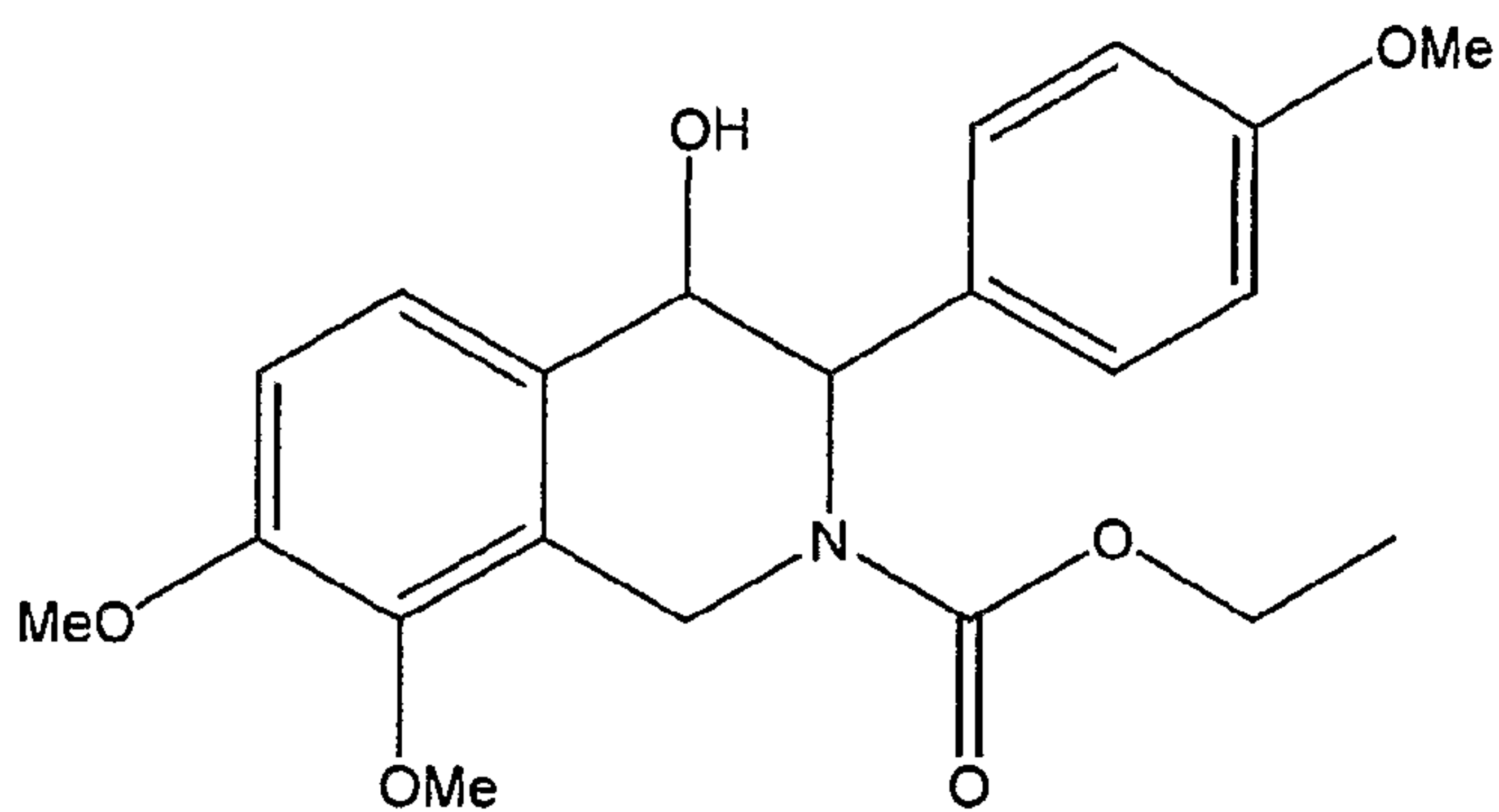


5

Formula IV

4-Hydroxy-7,8-dimethoxy-3-(4-methoxy-phenyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid ethyl ester

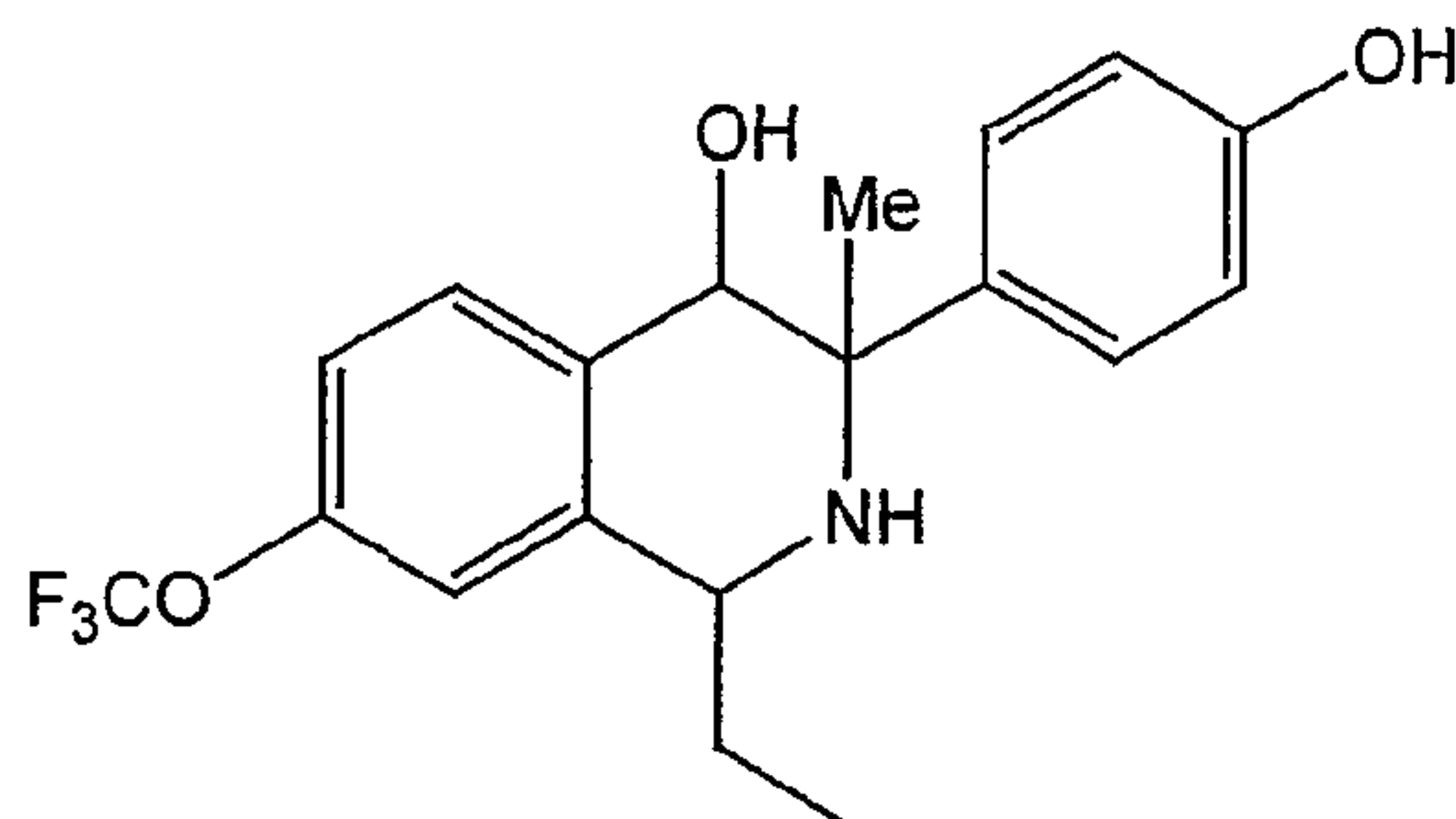
(Compound A)



10

1-Ethyl-3-(4-hydroxy-phenyl)-3-methyl-7-trifluoromethoxy-1,2,3,4-tetrahydro-isoquinolin-4-ol

(Compound Z)

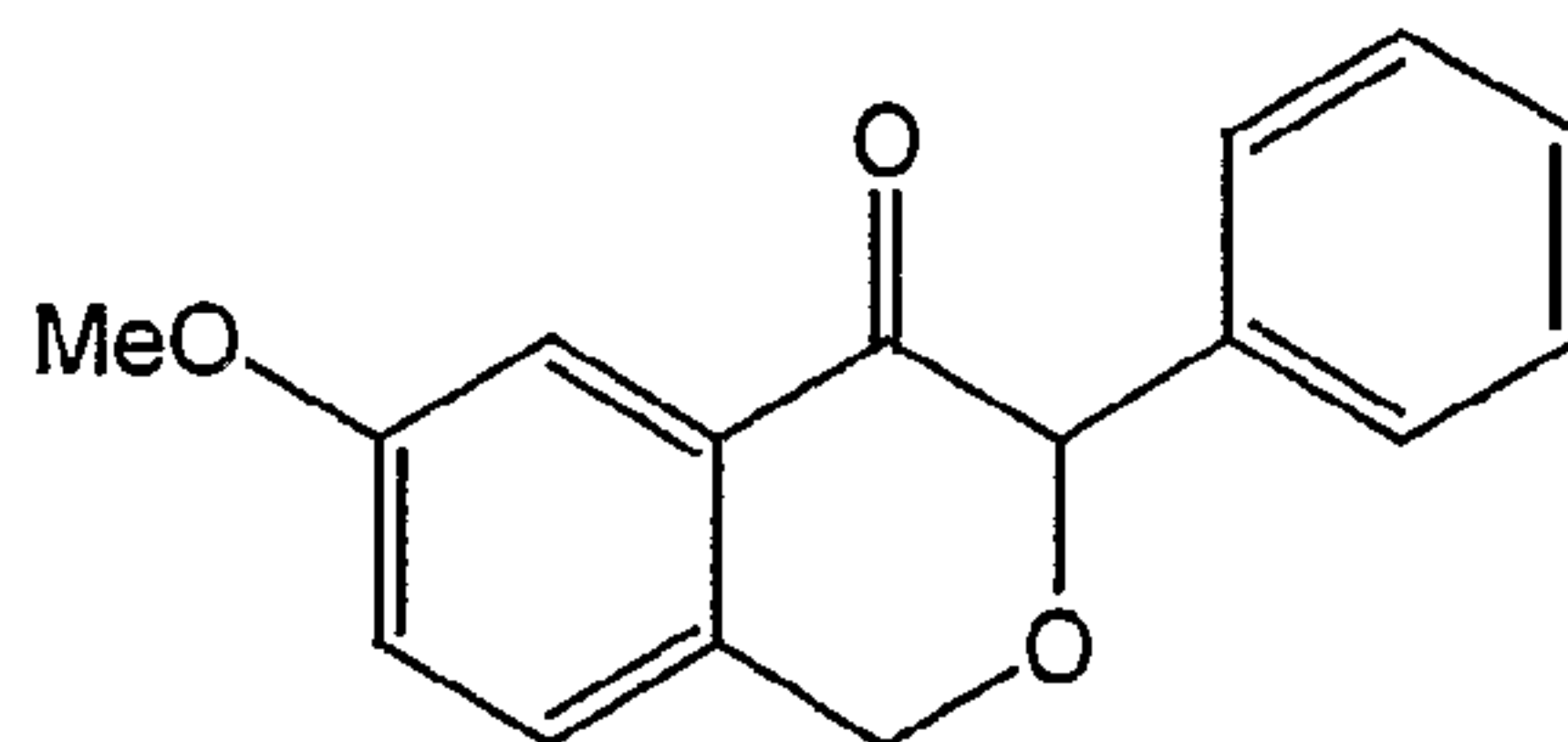


15

Formula V

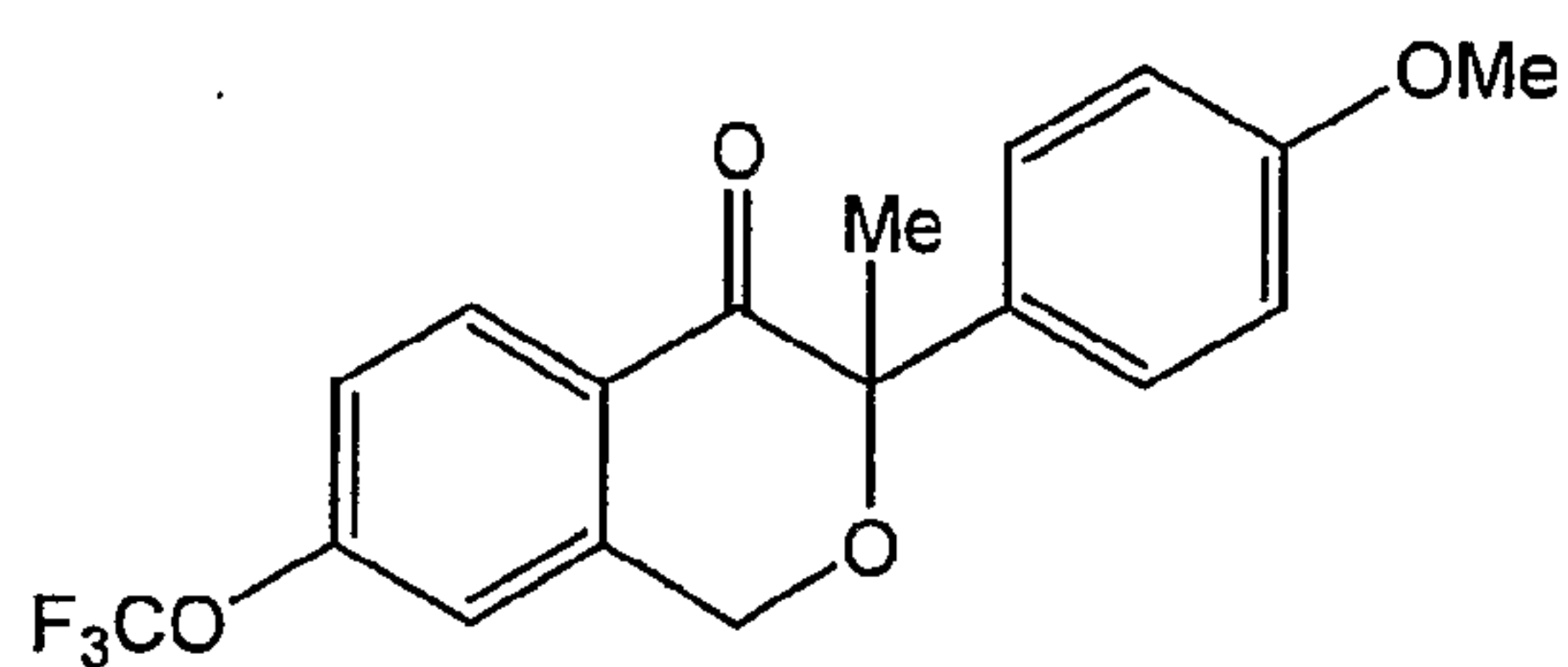
6-Methoxy-3-phenyl-isochroman-4-one

(Compound OA)



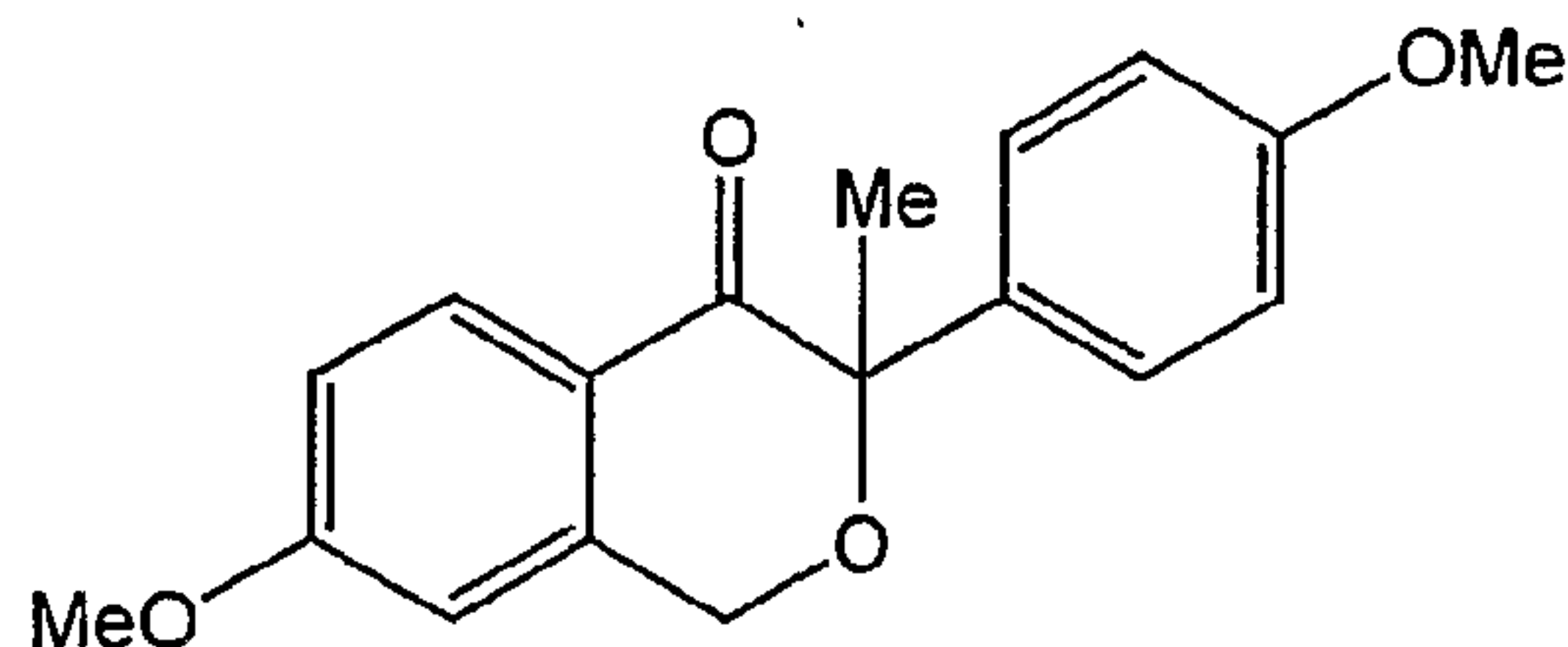
5 3-(4-Methoxy-phenyl)-3-methyl-7-trifluoromethoxy-isochroman-4-one

(Compound OB)



7-Methoxy-3-(4-methoxy-phenyl)-3-methyl-isochroman-4-one

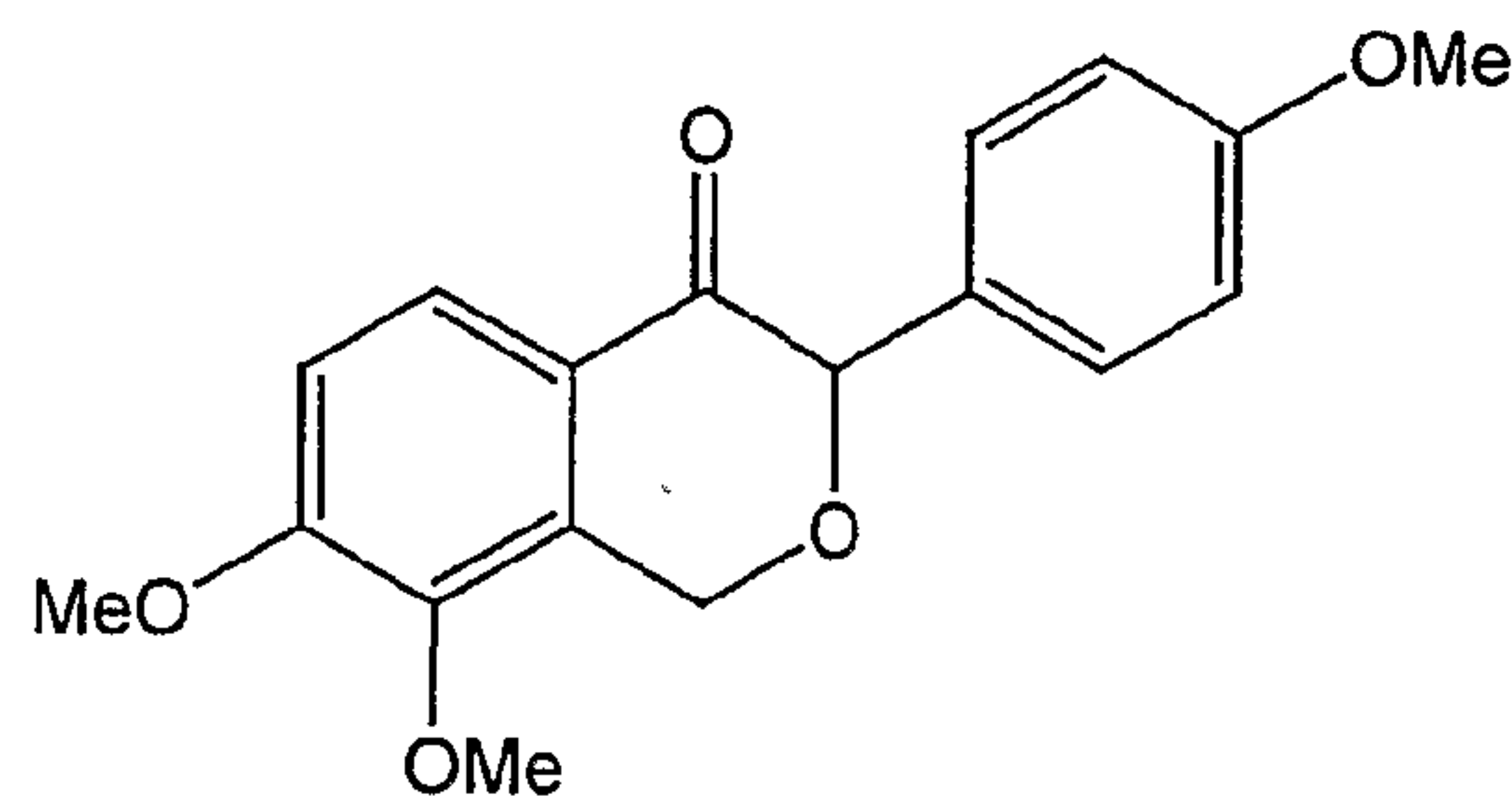
(Compound OC)



10

7,8-Dimethoxy-3-(4-methoxy-phenyl)-isochroman-4-one

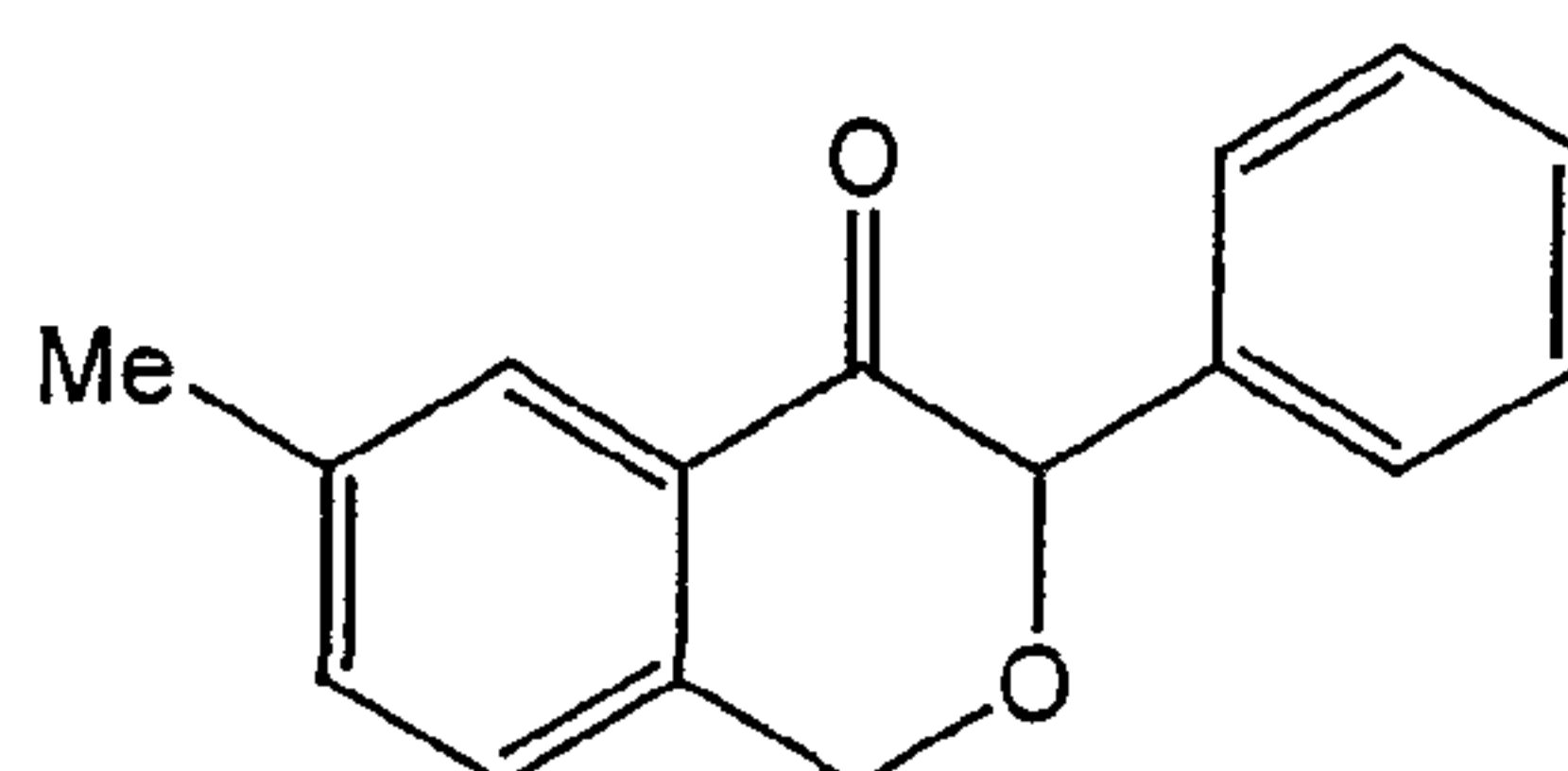
(Compound OD)



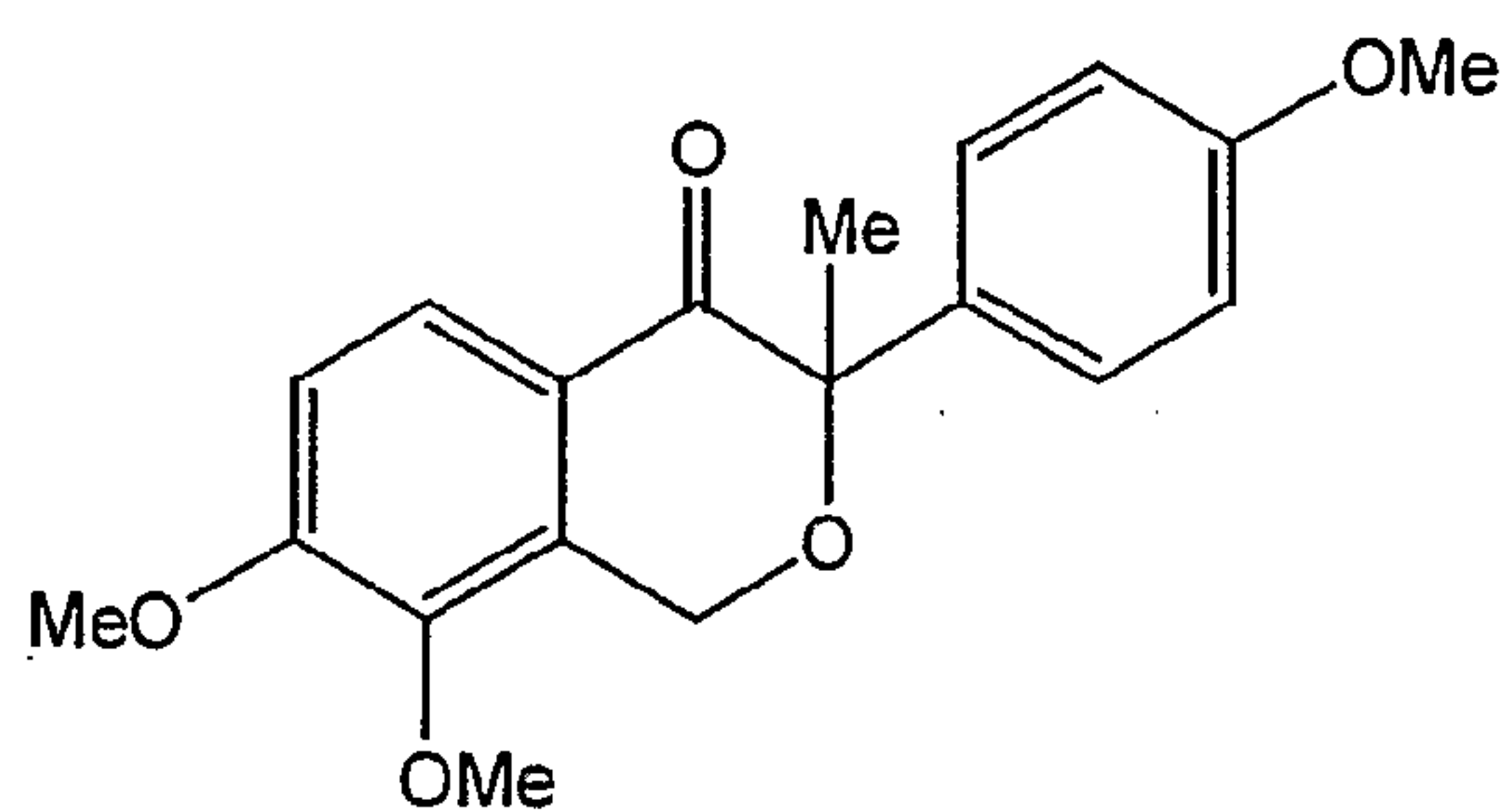
15

6-Methyl-3-phenyl-isochroman-4-one

(Compound OE)



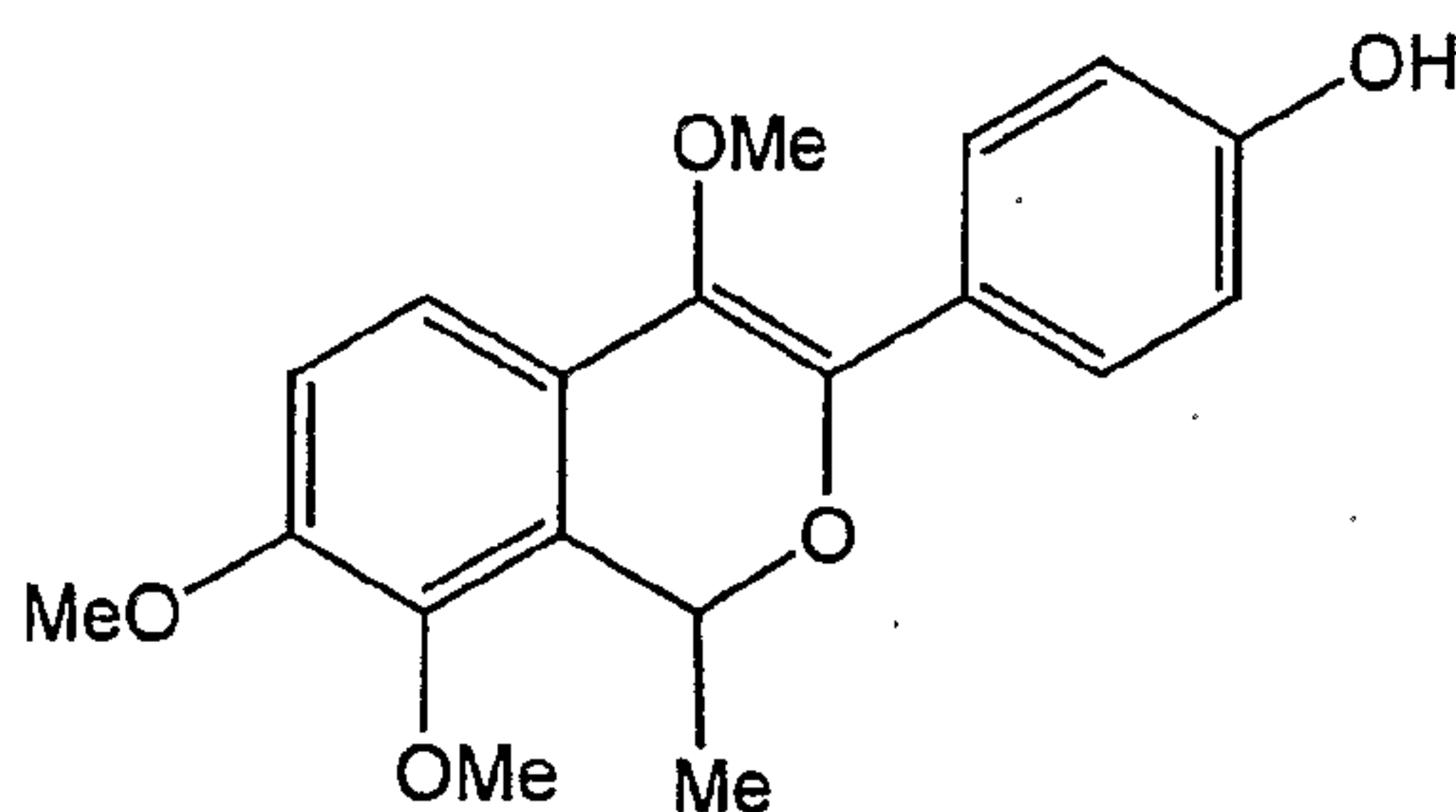
7,8-Dimethoxy-3-(4-methoxy-phenyl)-3-methyl-isochroman-4-one
(Compound OF)



5

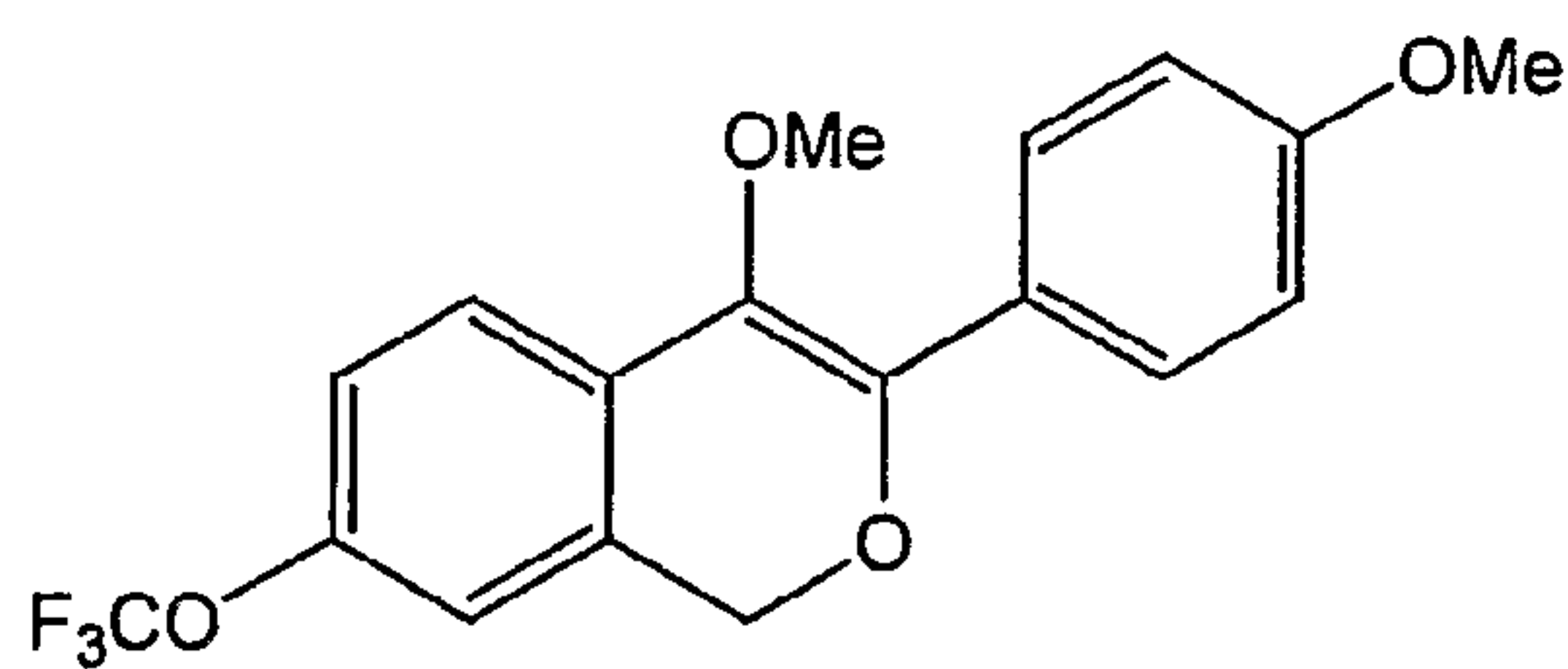
Formula VI

4-(4,7,8-Trimethoxy-1-methyl-1*H*-isochromen-3-yl)-phenol
(Compound OG)

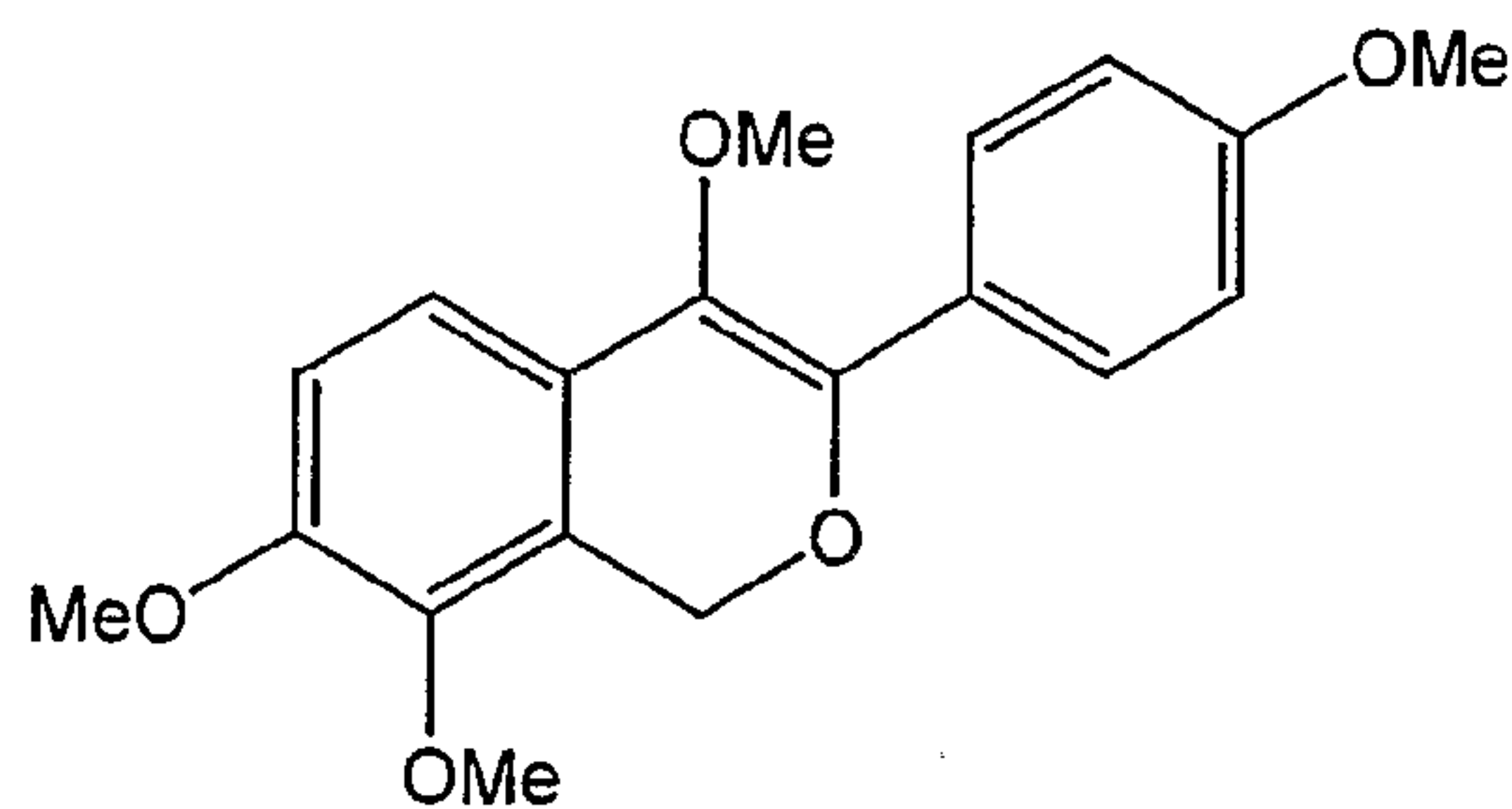


10

4-Methoxy-3-(4-methoxy-phenyl)-7-trifluoromethoxy-1*H*-isochromene
(Compound OH)



4,7,8-Trimethoxy-3-(4-methoxy-phenyl)-1*H*-isochromene
(Compound OJ)

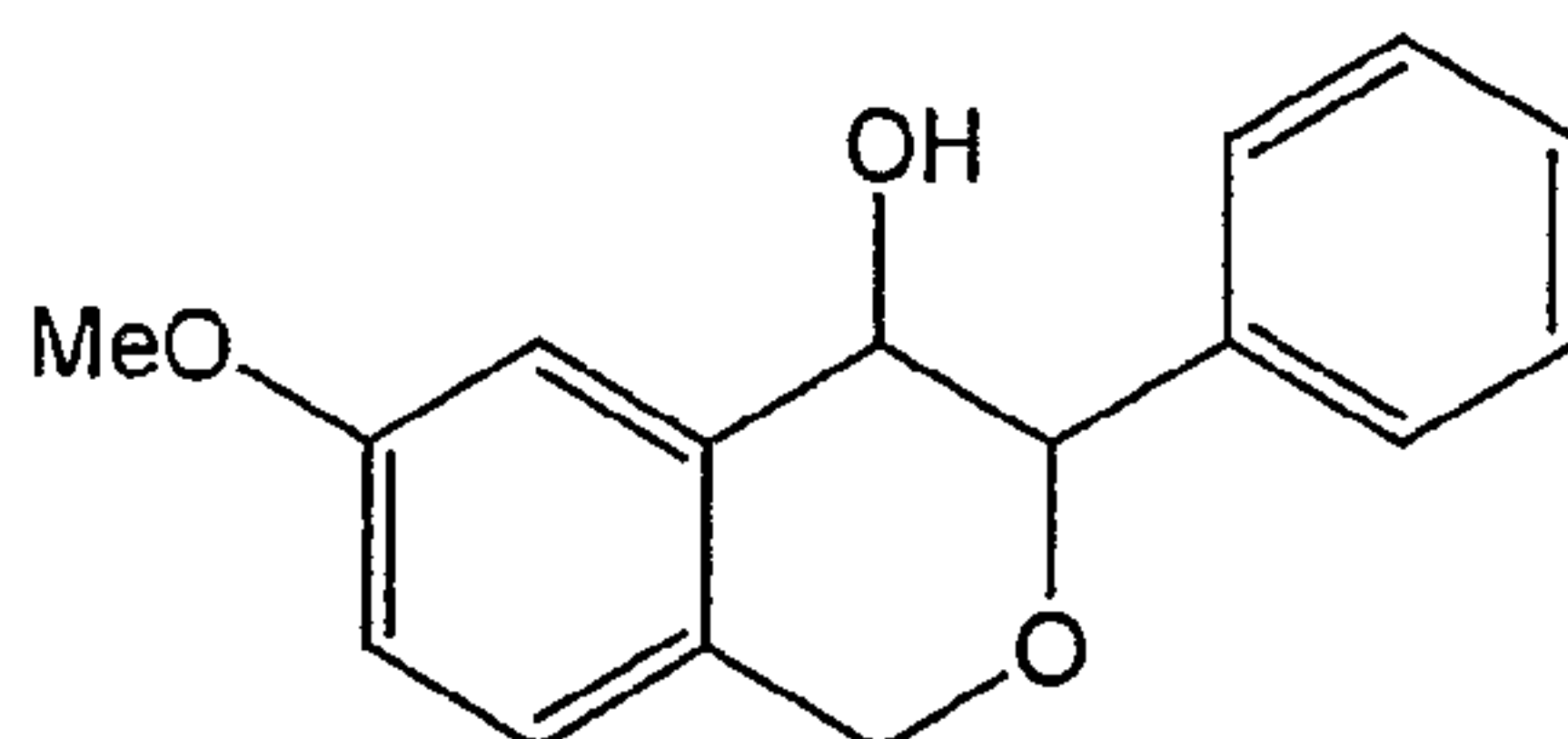


15

Formula VII

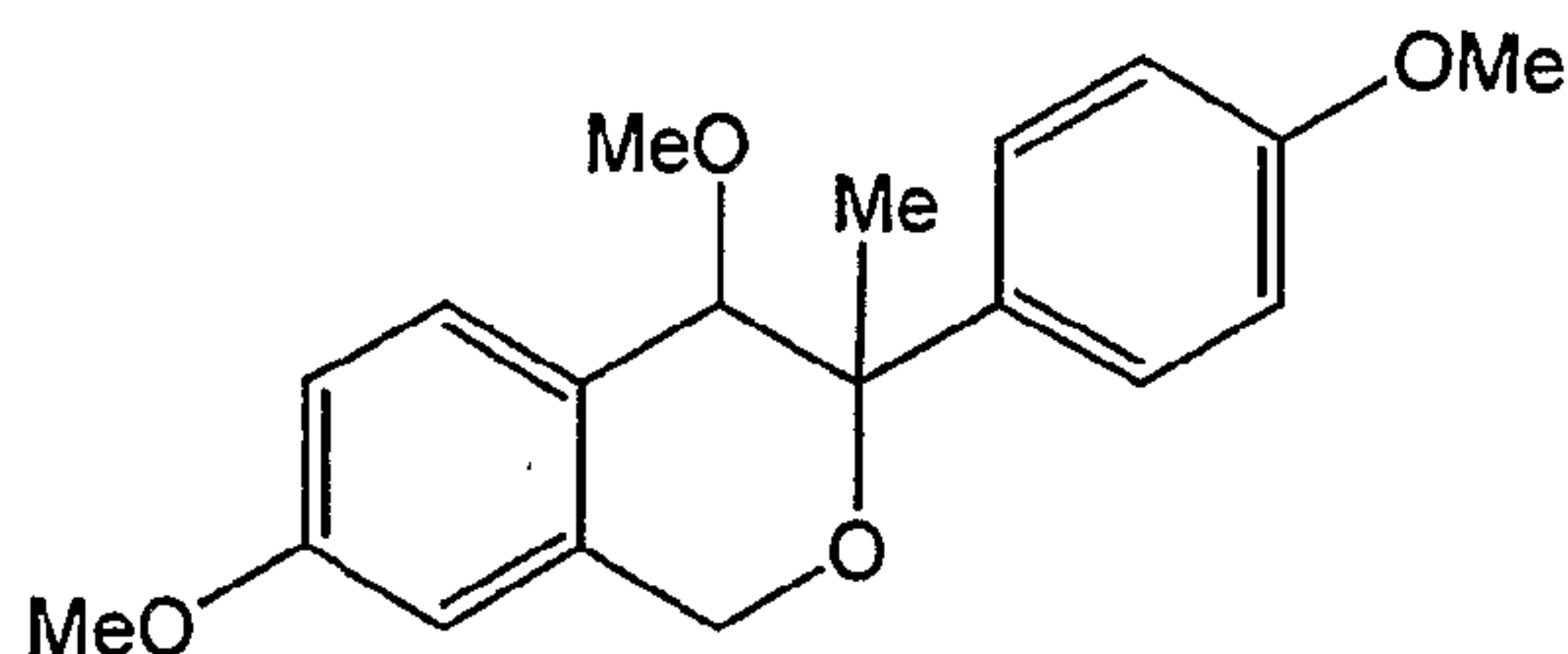
6-Methoxy-3-phenyl-isochroman-4-ol

(Compound OK)



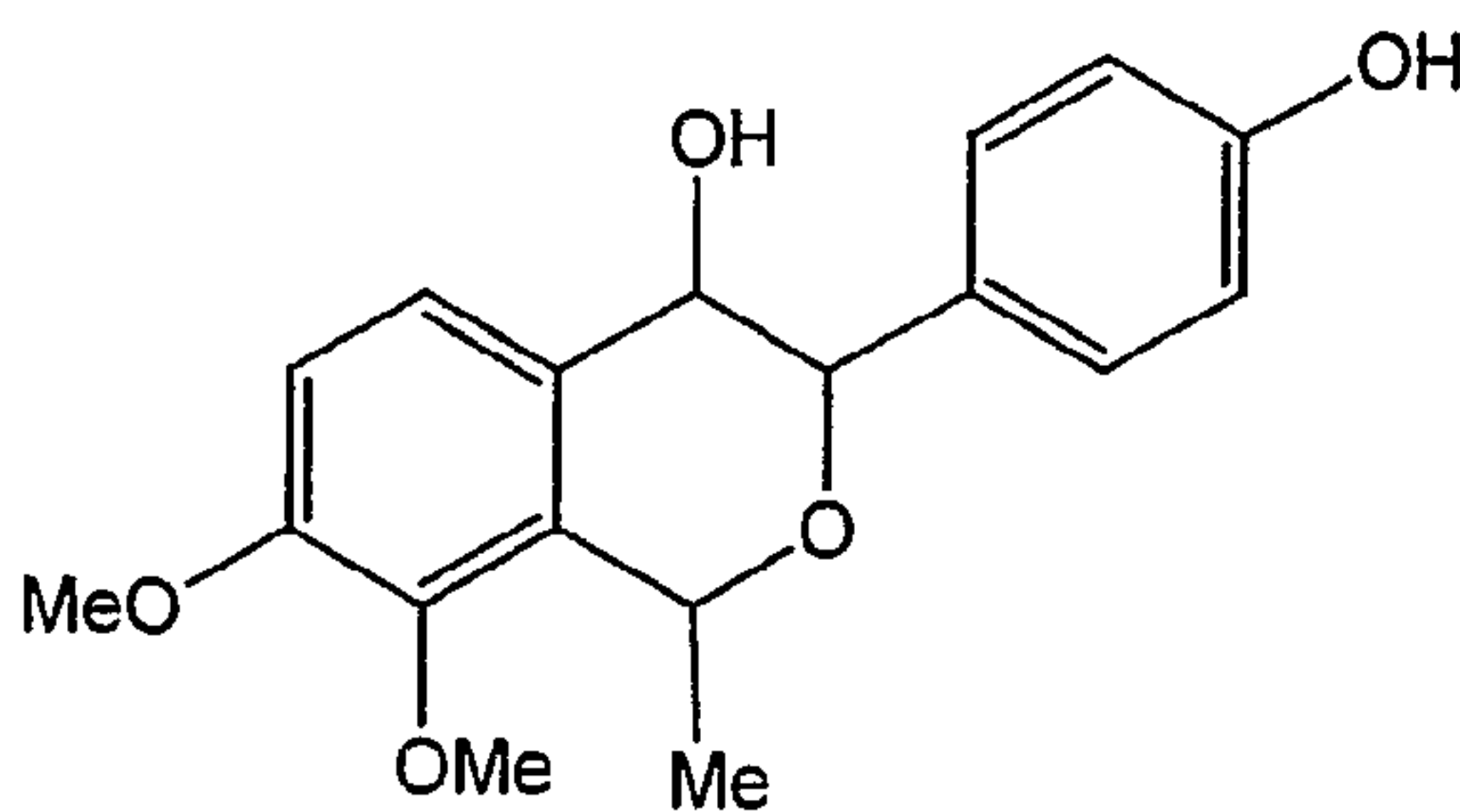
5 4,7-Dimethoxy-3-(4-methoxy-phenyl)-3-methyl-isochroman

(Compound OL)



3-(4-Hydroxy-phenyl)-7,8-dimethoxy-1-methyl-isochroman-4-ol

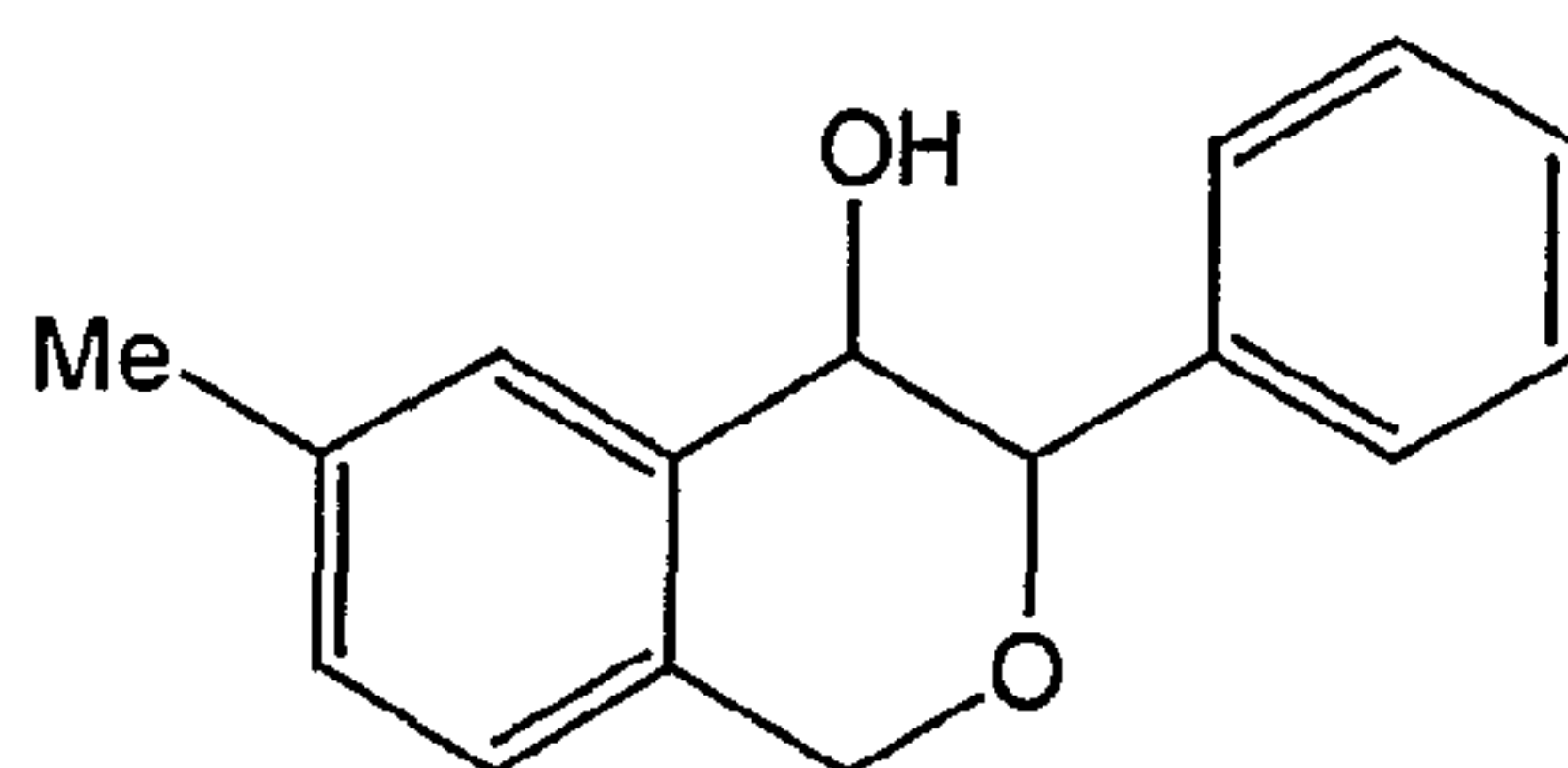
(Compound OM)



10

6-Methyl-3-phenyl-isochroman-4-ol

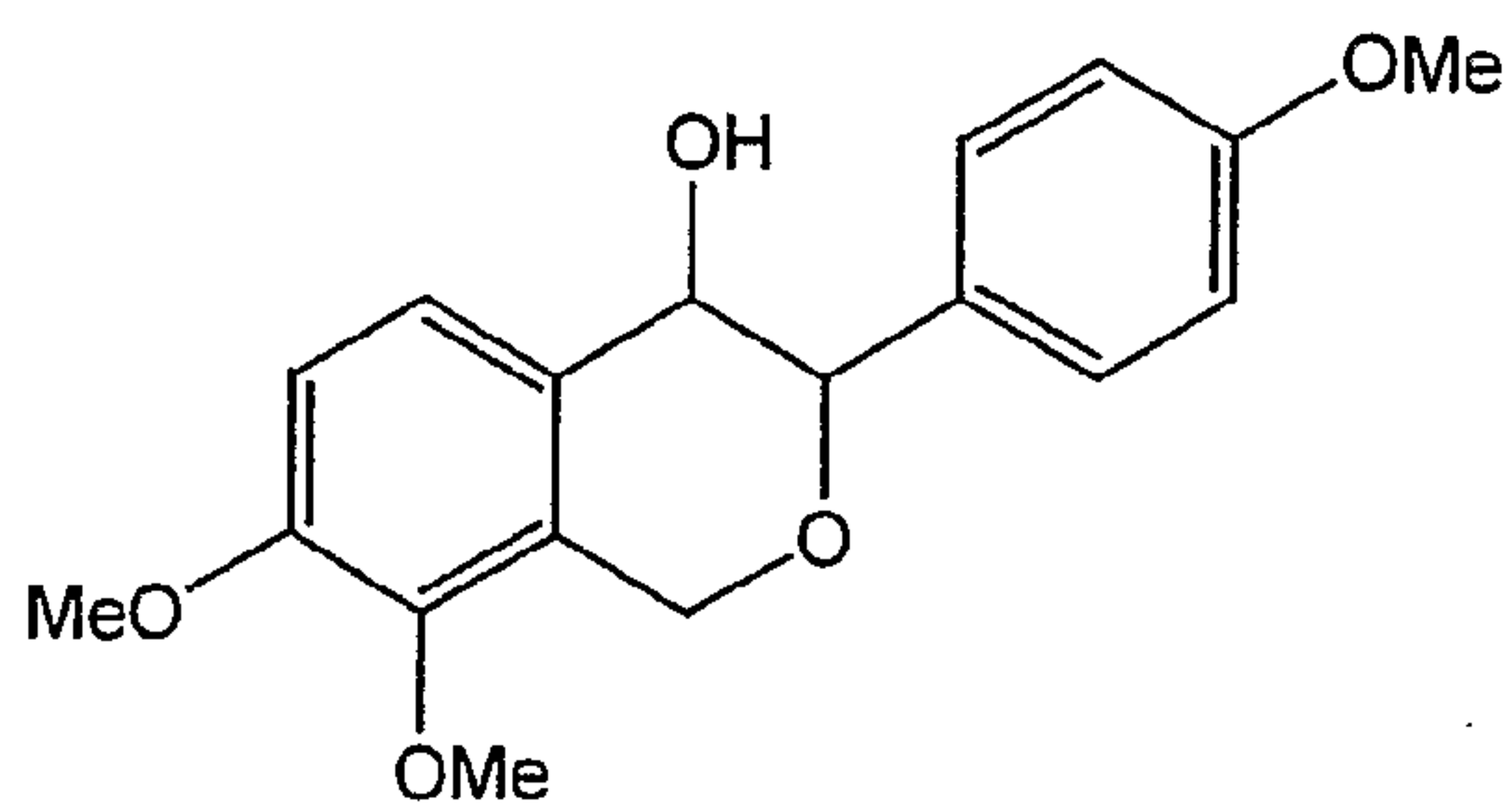
(Compound ON)



15

7,8-Dimethoxy-3-(4-methoxy-phenyl)-isochroman-4-ol

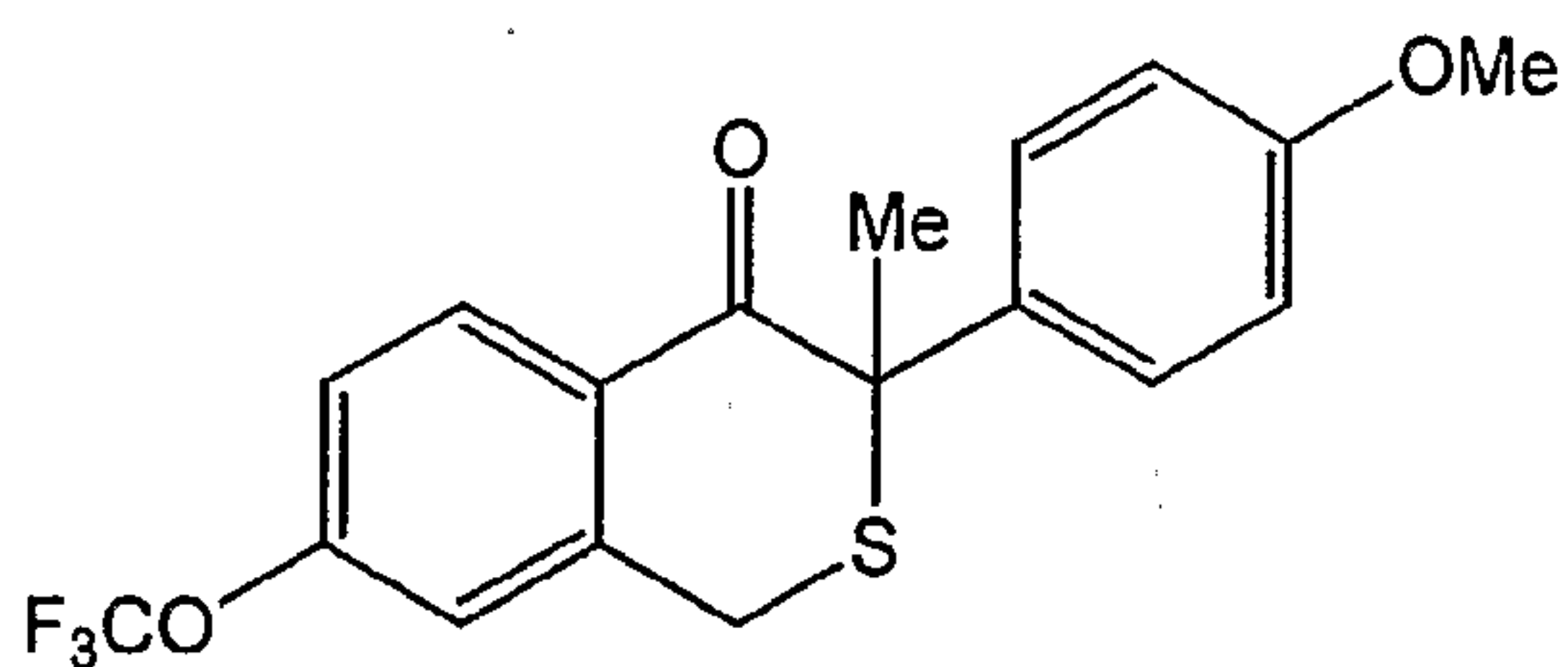
(Compound OP)



Formula VIII

3-(4-Methoxy-phenyl)-3-methyl-7-trifluoromethoxy-isothiochroman-4-one

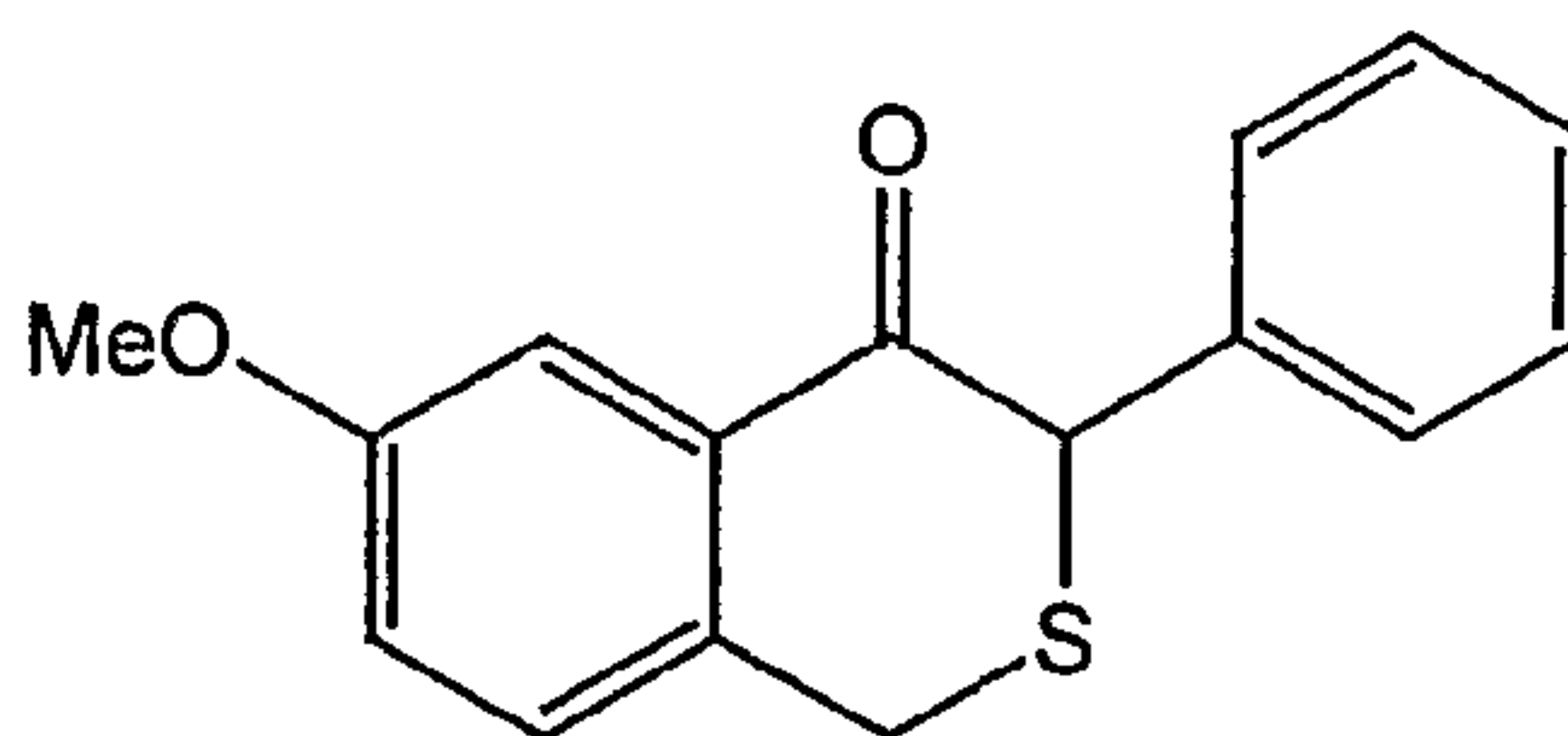
(Compound SA)



5

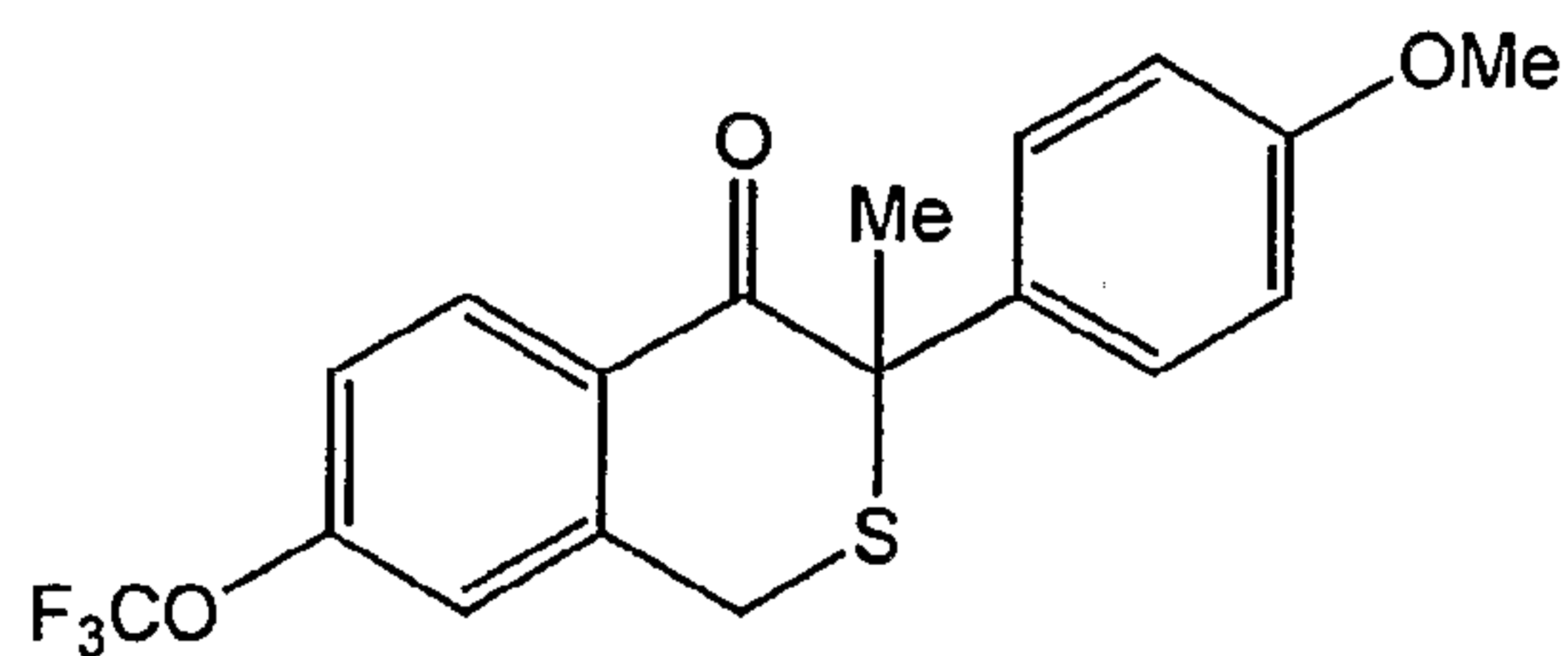
6-Methoxy-3-phenyl-isothiochroman-4-one

(Compound SB)



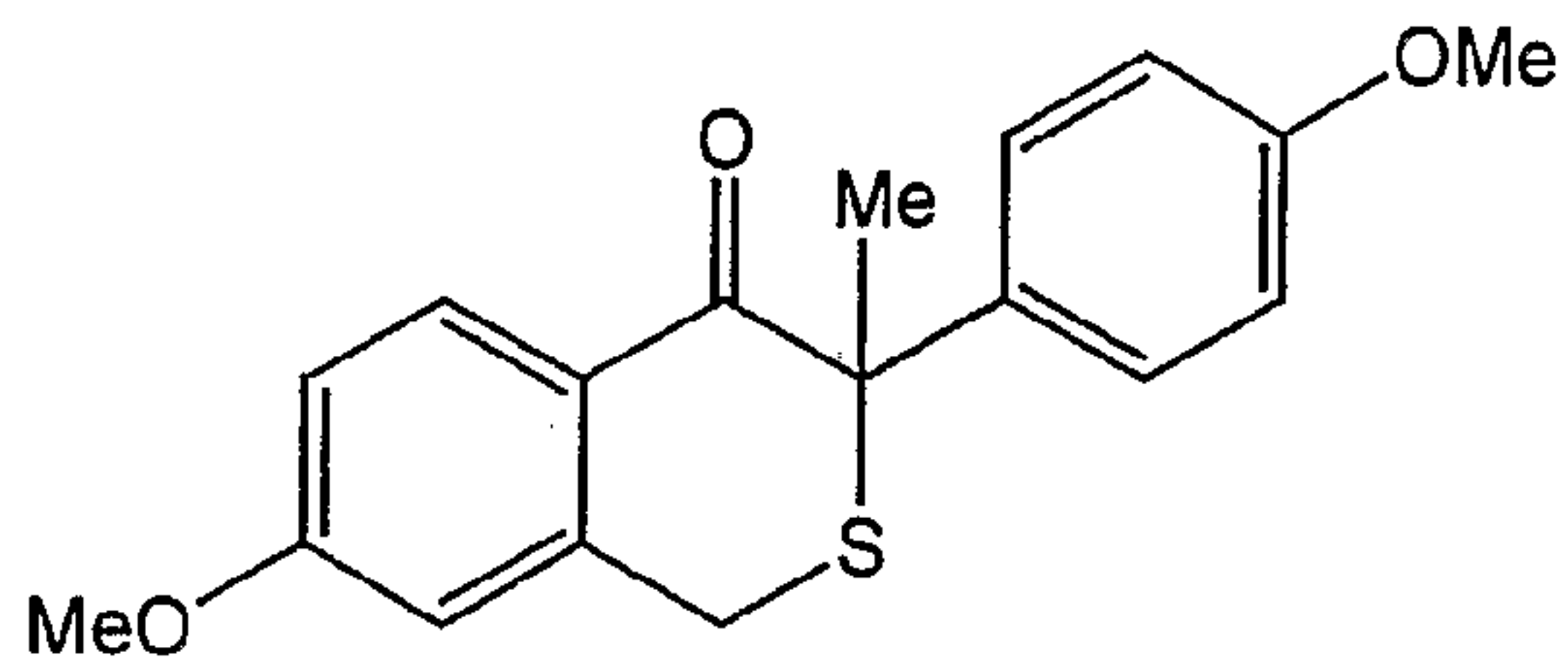
10 3-(4-Methoxy-phenyl)-3-methyl-7-trifluoromethoxy-isothiochroman-4-one

(Compound SC)



7-Methoxy-3-(4-methoxy-phenyl)-3-methyl-isothiochroman-4-one

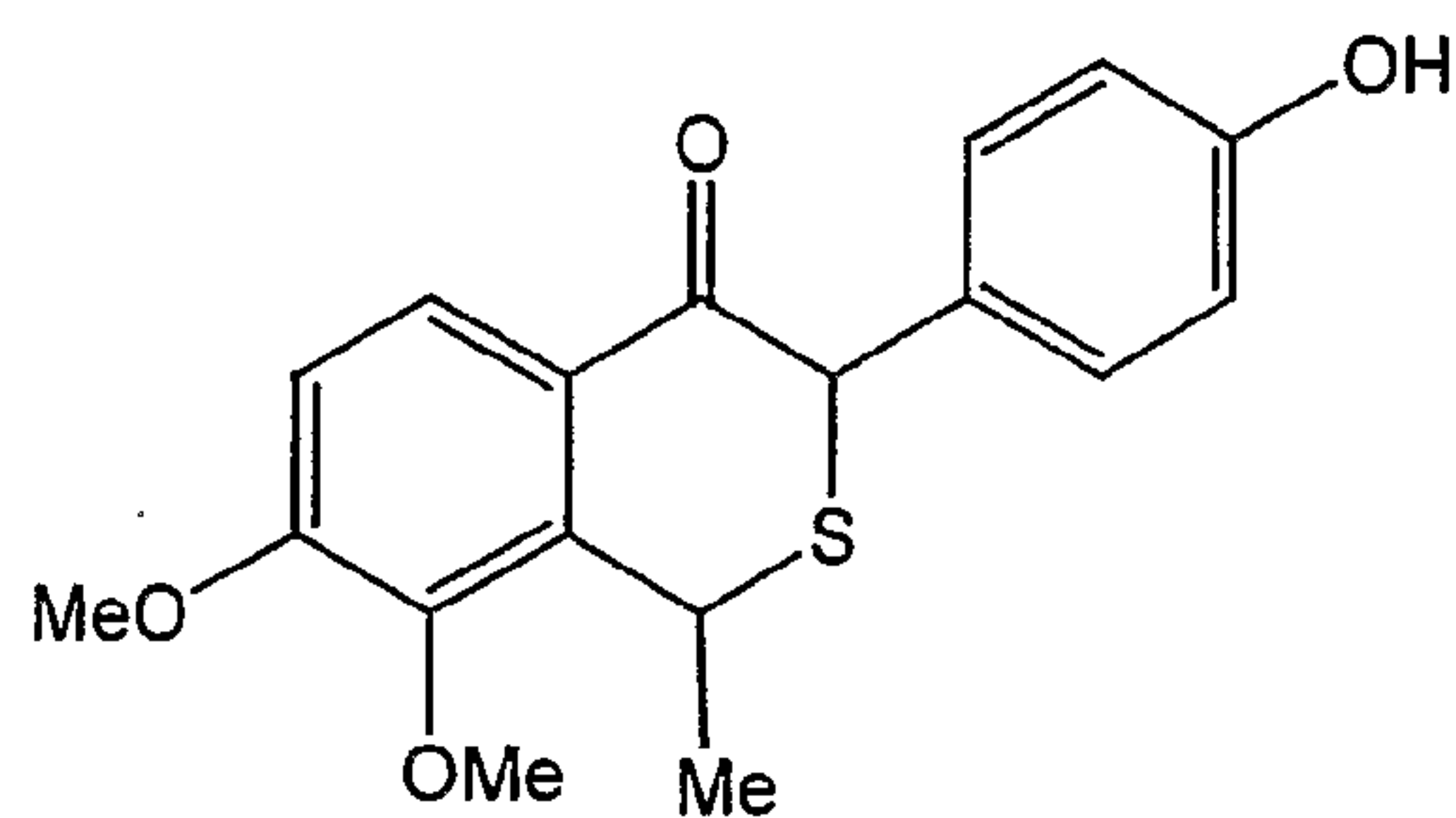
(Compound SD)



15

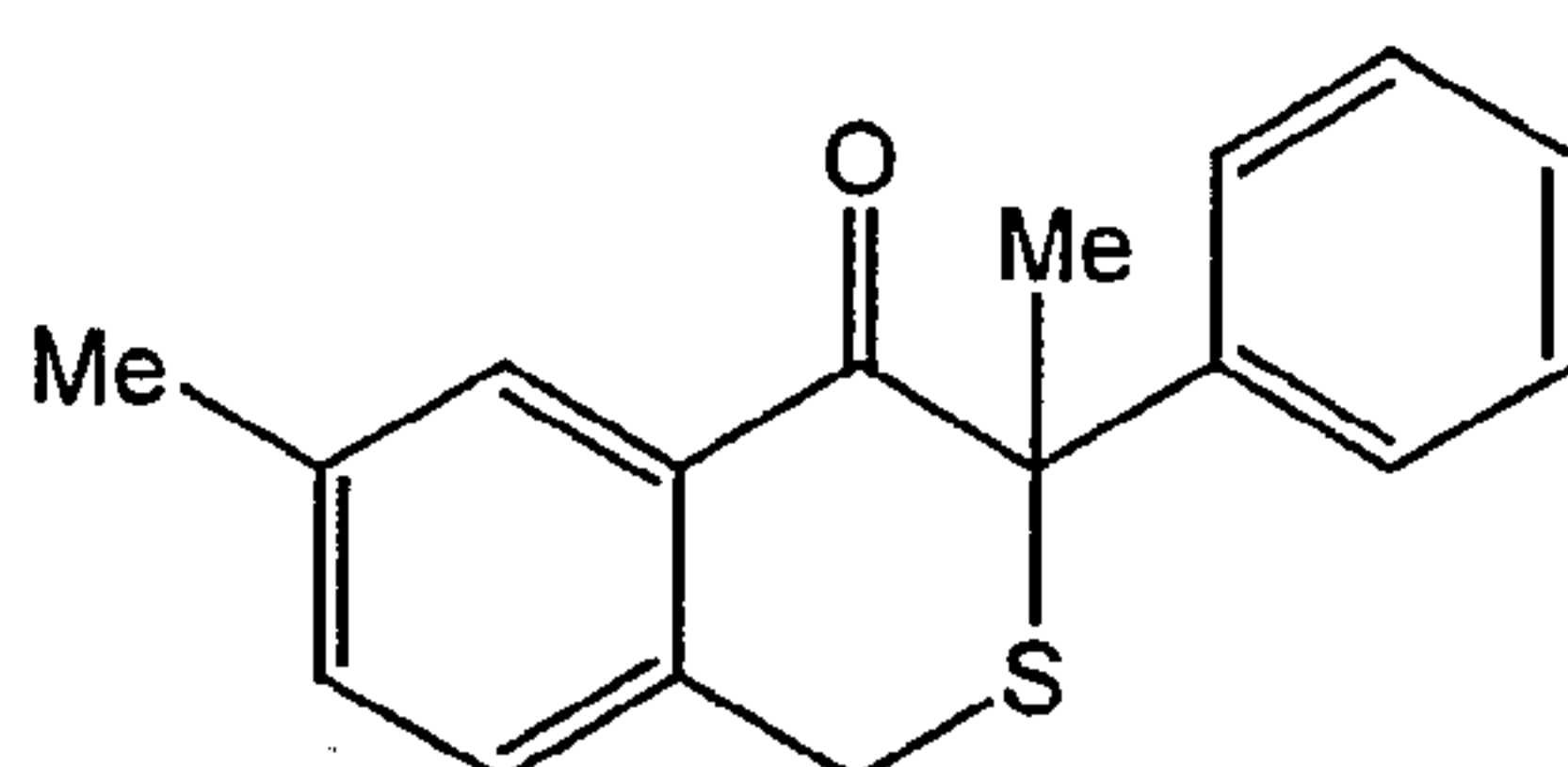
3-(4-Hydroxy-phenyl)-7,8-dimethoxy-1-methyl-isothiochroman-4-one

(Compound SE)



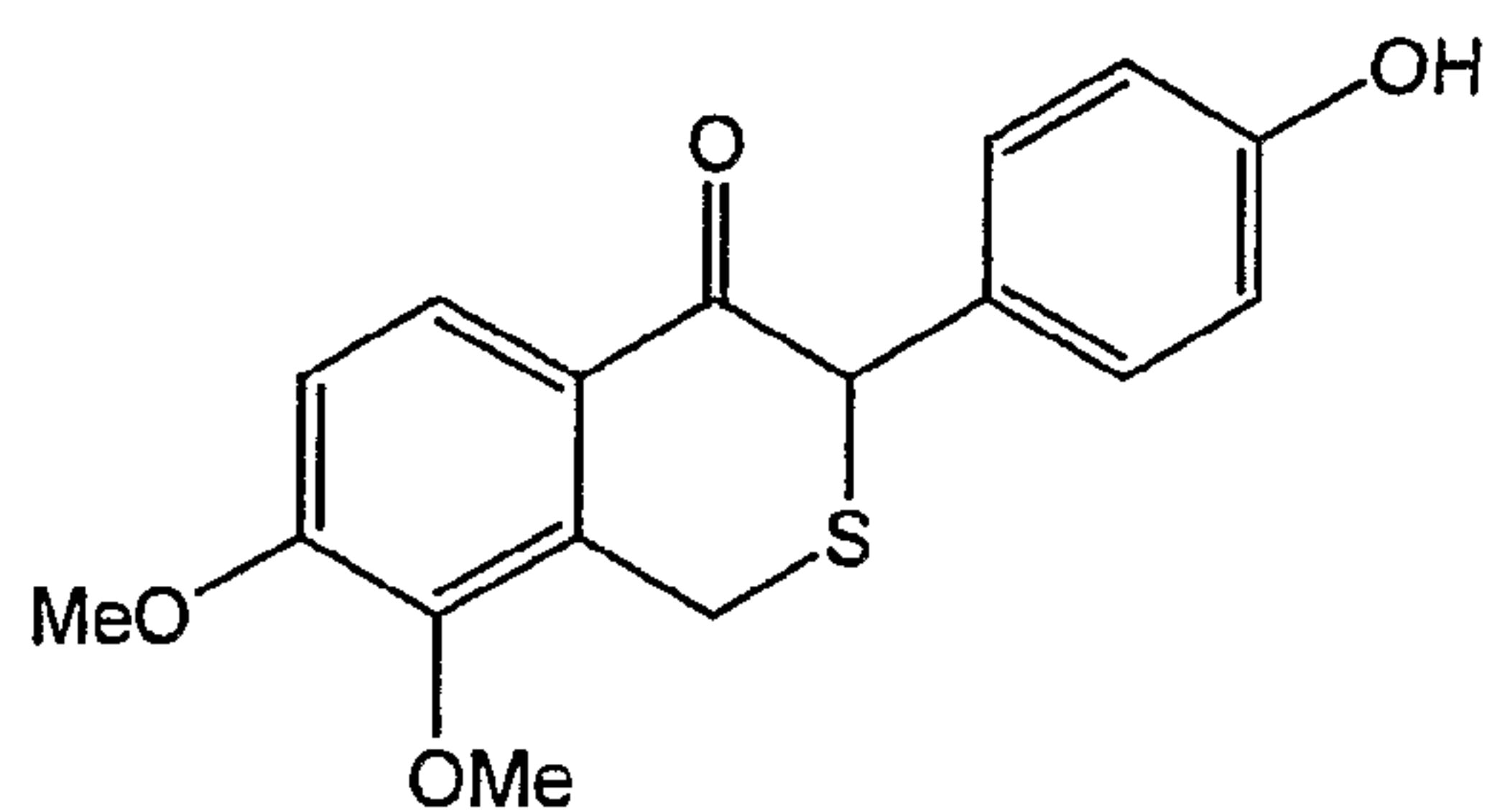
3,6-Dimethyl-3-phenyl-isothiochroman-4-one

(Compound SF)



3-(4-Hydroxy-phenyl)-7,8-dimethoxy-isothiochroman-4-one

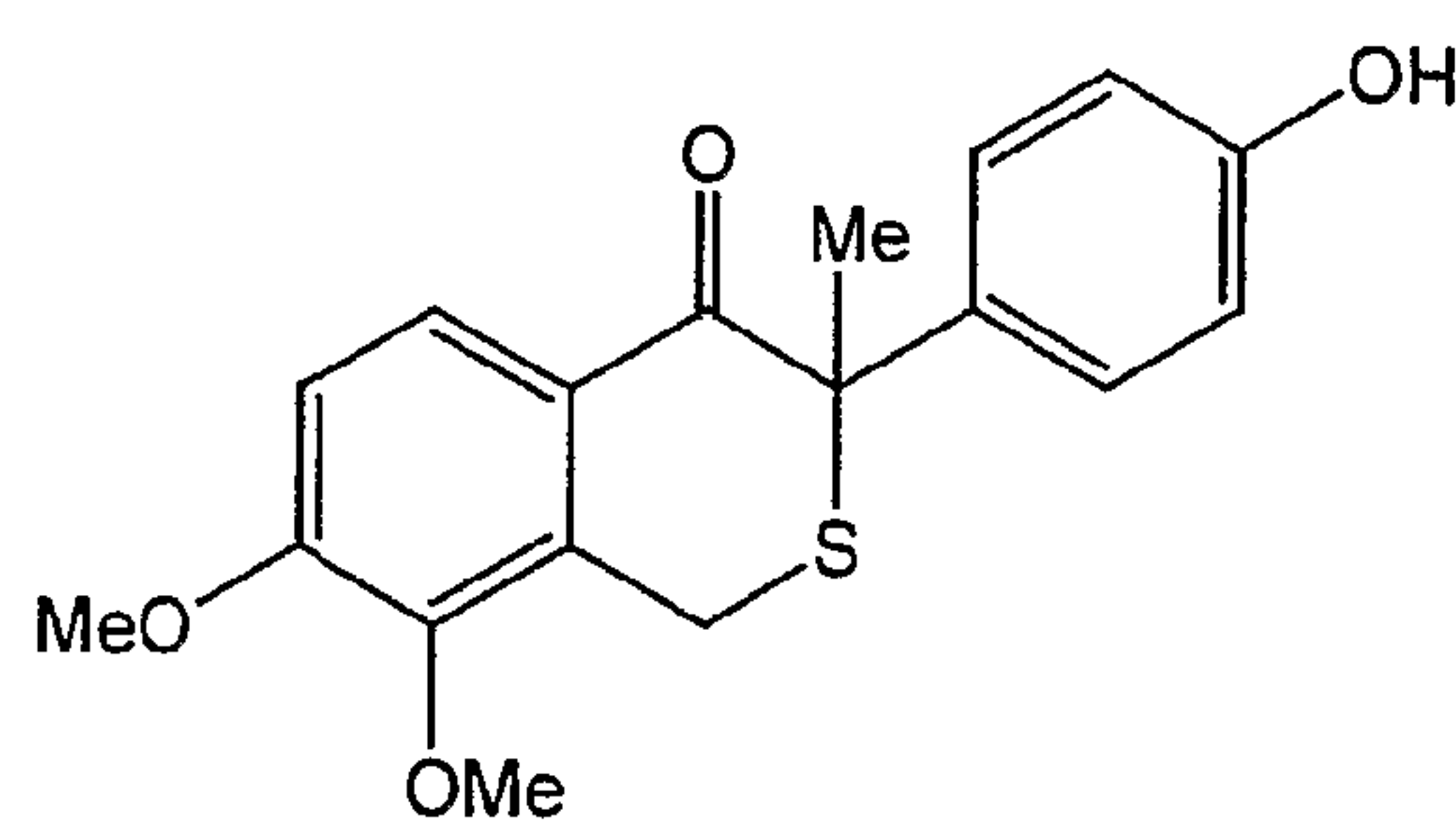
(Compound SG)



10

3-(4-Hydroxy-phenyl)-7,8-dimethoxy-3-methyl-isothiochroman-4-one

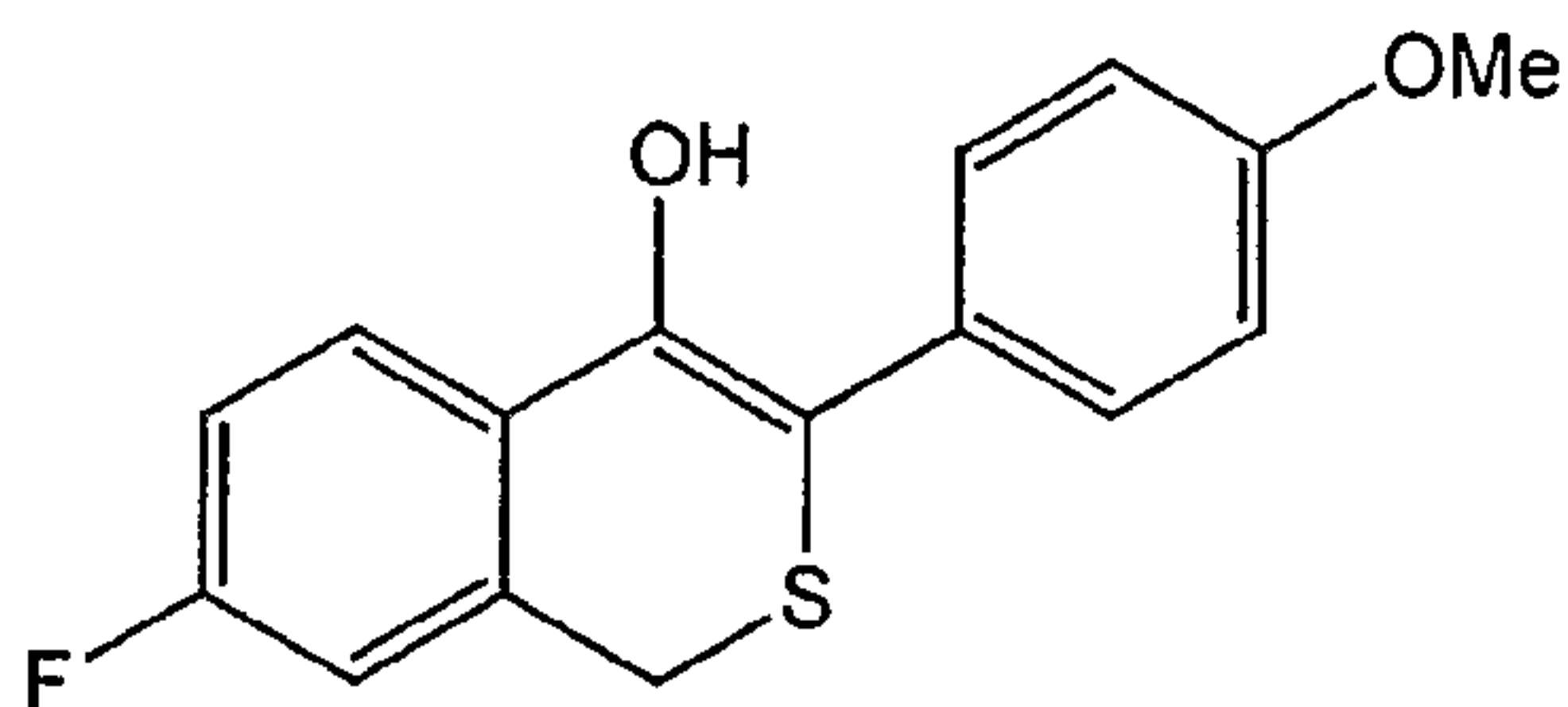
(Compound SH)



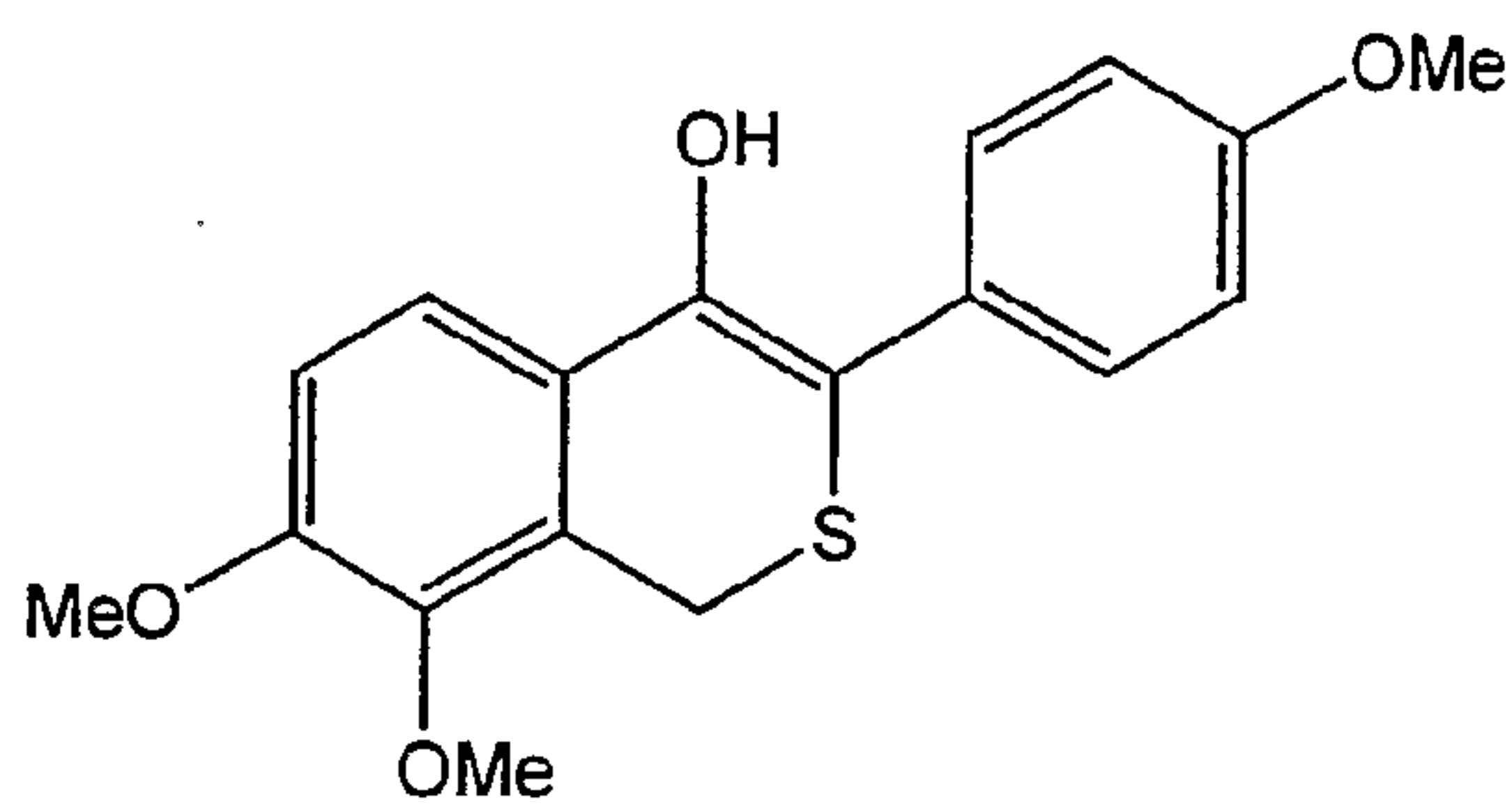
15

Formula IX7-Fluoro-3-(4-methoxy-phenyl)-1*H*-isothiochromen-4-ol

(Compound SJ)

5 7,8-Dimethoxy-3-(4-methoxy-phenyl)-1*H*-isothiochromen-4-ol

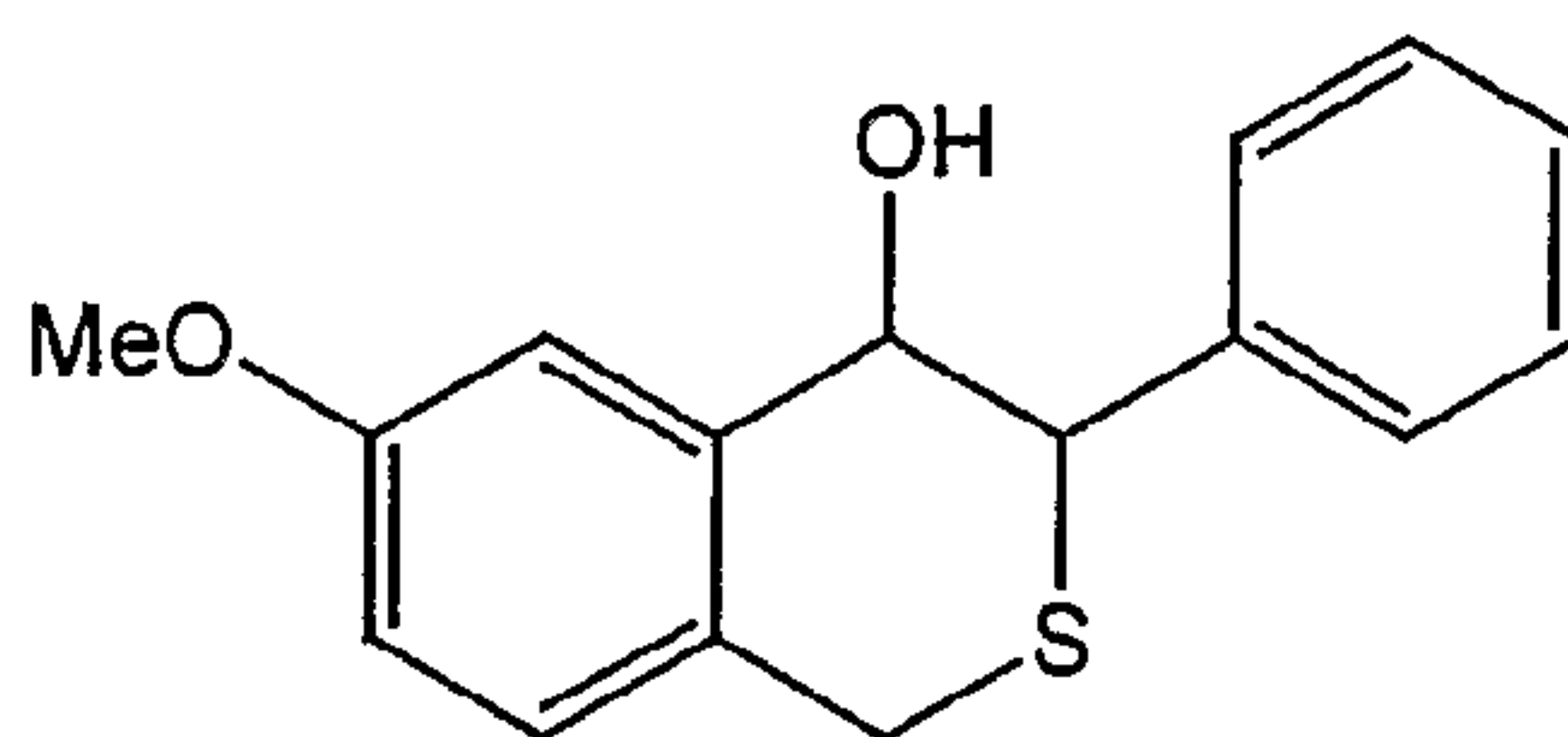
(Compound SK)

Formula X

6-Methoxy-3-phenyl-isothiochroman-4-ol

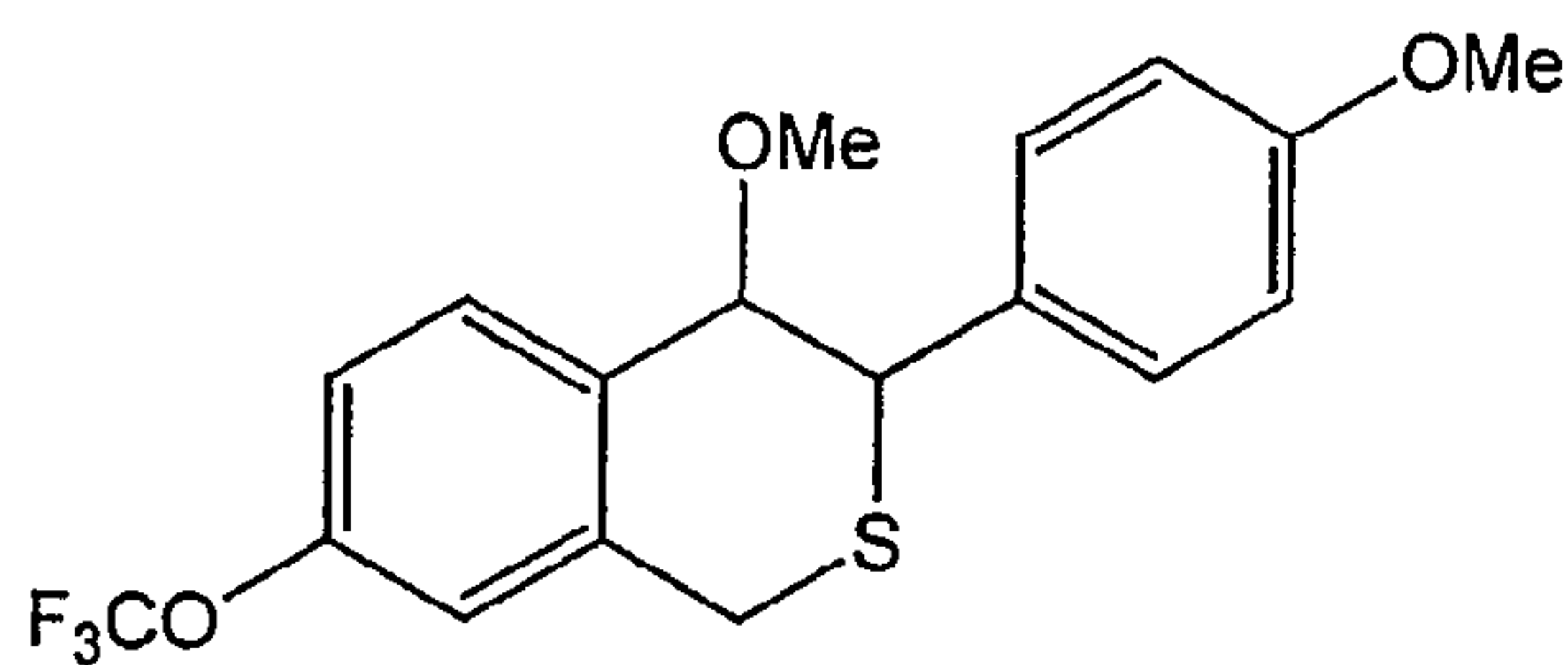
10

(Compound SL)



4-Methoxy-3-(4-methoxy-phenyl)-7-trifluoromethoxy-isothiochroman

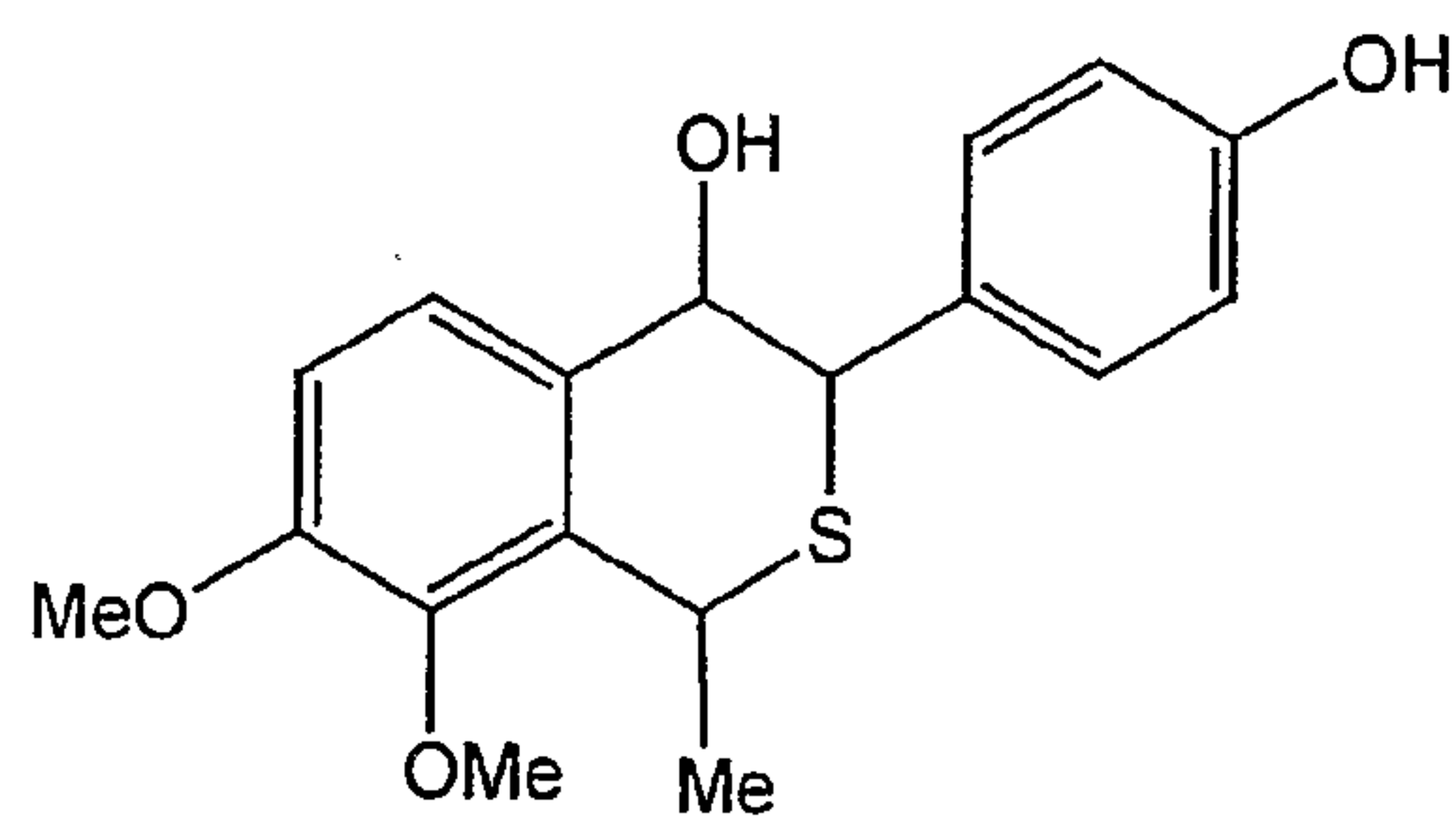
(Compound SM)



15

3-(4-Hydroxy-phenyl)-7,8-dimethoxy-1-methyl-isothiochroman-4-ol

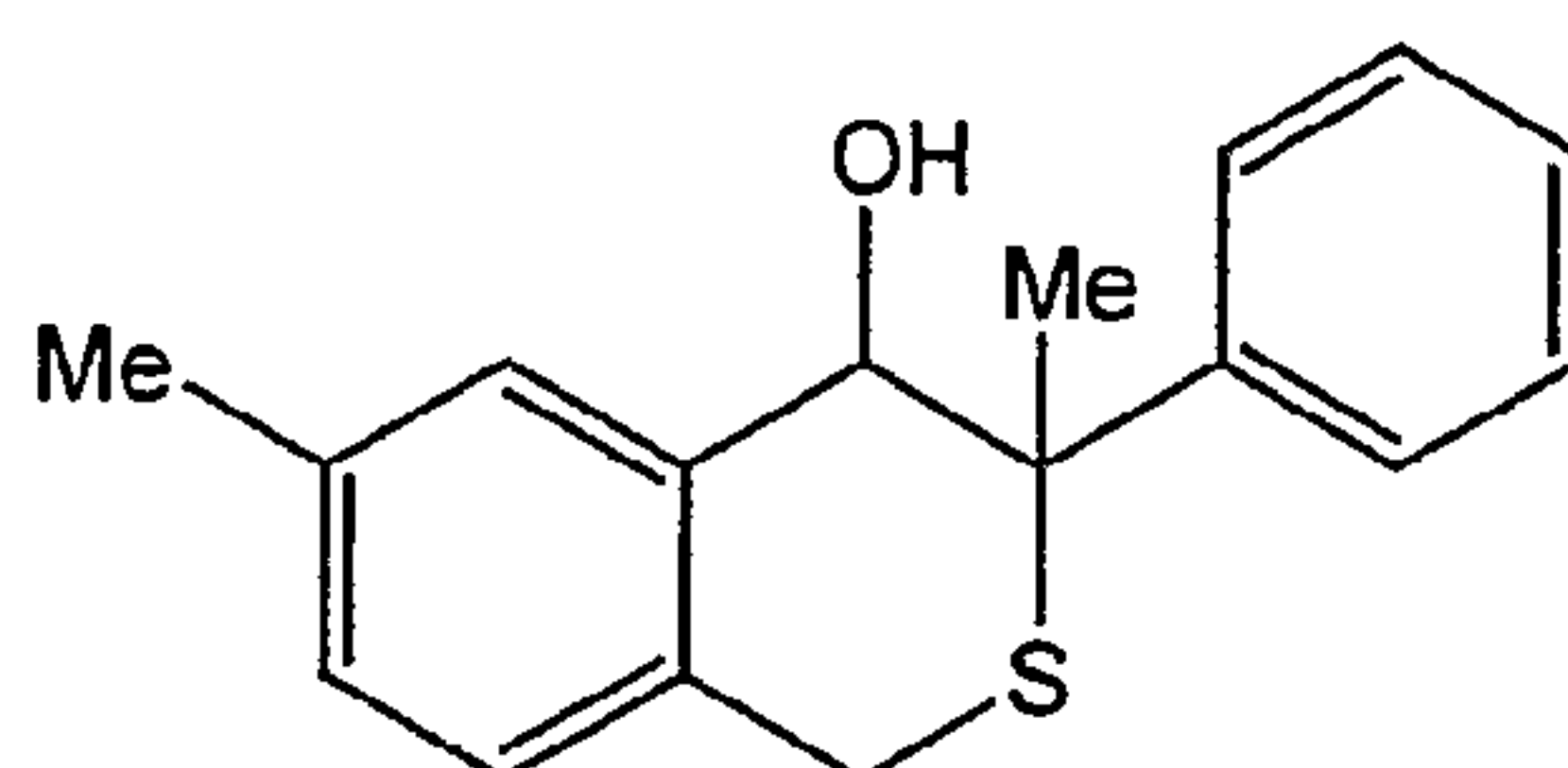
(Compound SN)



3,6-Dimethyl-3-phenyl-isothiochroman-4-ol

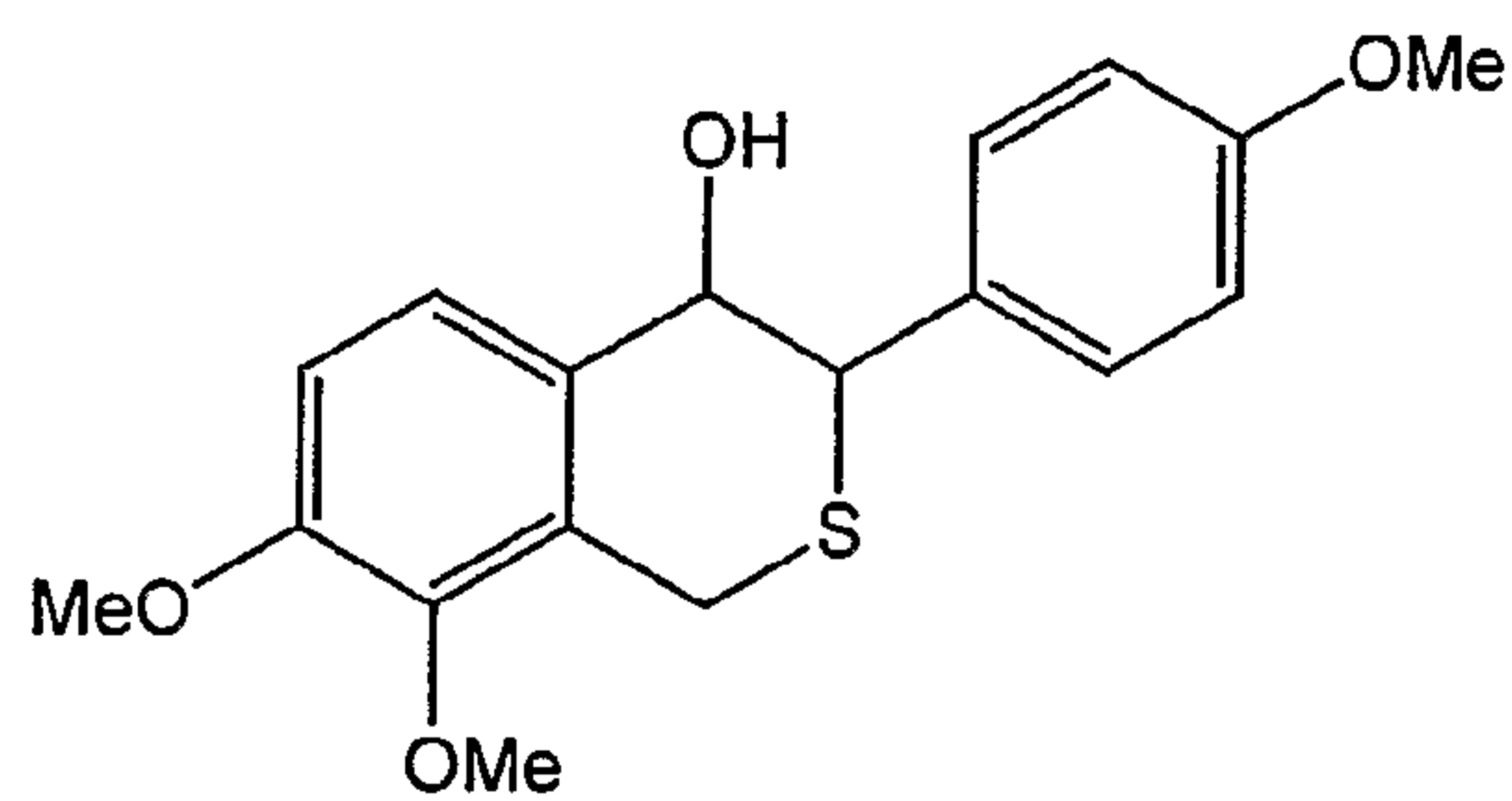
5

(Compound SP)



7,8-Dimethoxy-3-(4-methoxy-phenyl)-isothiochroman-4-ol

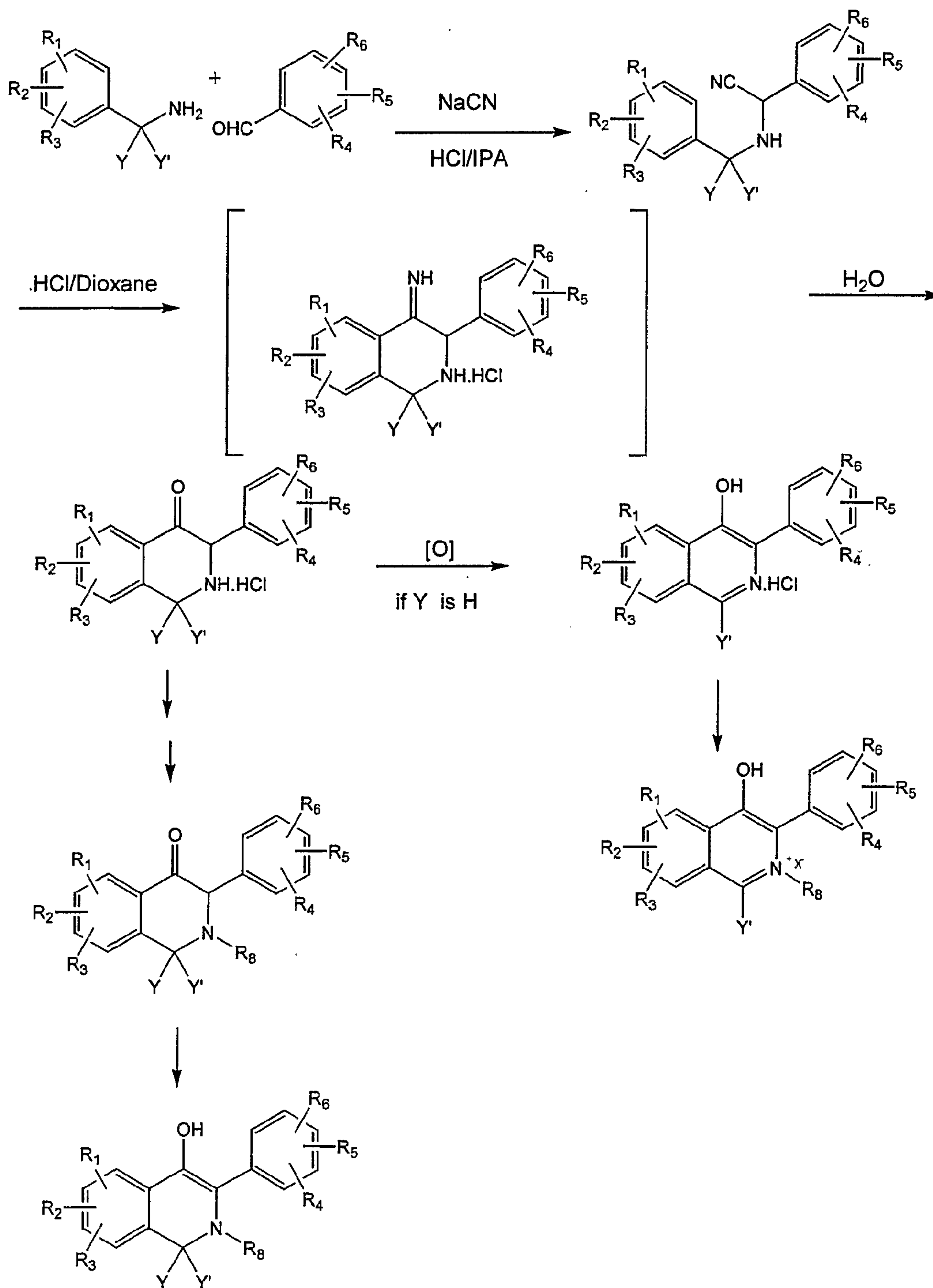
(Compound SQ)



10

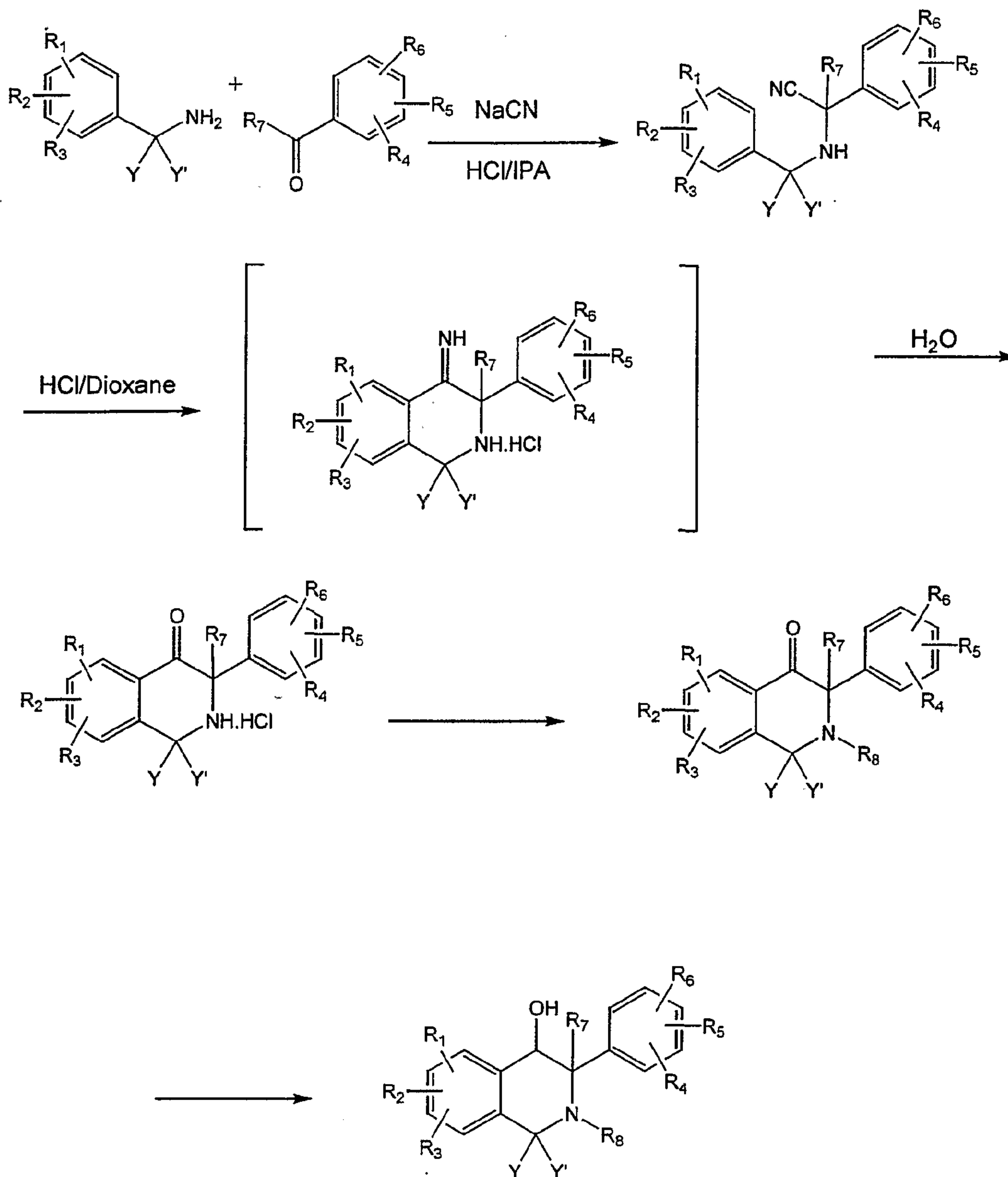
The compounds of the invention may be obtained by synthetic methods known in the art. Preferred reaction schemes for preparing the compounds of the invention are illustrated below:

5 Scheme I
Synthesis of Compounds of Formulas I and III



Scheme II
Synthesis of Compounds of Formulas II and IV

5



It will be appreciated that the invention is not limited to the foregoing reaction schemes as variations in the procedures will be evident to those in the art.

10

Some of the compounds of the invention contain one or more chiral centers and each center may exist in different configurations. Thus, the compounds of Formulas I to X can form stereoisomers. The invention encompasses both the individual isomers and mixtures, including racemates,

thereof. In addition, both the preparation of individual isomers by stereospecific synthesis techniques and the preparation of mixtures of isomers, which may then be resolved by conventional methods or used as is, are contemplated by the invention.

5 Many of the compounds of the present invention are capable of forming pharmaceutically acceptable salts, such as acid and base addition salts, as well as solvates, such as hydrates and alcoholates. All such pharmaceutically acceptable salts and solvates are contemplated by the present invention and incorporated herein. Representative pharmaceutically acceptable acid
10 addition salts of the free base compounds of Formulas I and II include chloride, bromide, iodide, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, acetate, trifluoroacetate, propionate, isobutyrate, oxalate, malonate, succinate, fumarate, maleate, benzoate,
15 chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated by the present invention are salts of amino acids such as arginate and the like and gluconate, galacturonate and the like. The acid addition salts may be formed
20 by conventional methods using inorganic acids, such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or organic acids, such as aromatic acids, aliphatic sulfonic acids, aromatic sulfonic acids, aliphatic monocarboxylic acids, aliphatic dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, and the like.

25 Pharmaceutically acceptable base addition salts may be formed by conventional methods using metals, such as sodium, potassium, magnesium, calcium, and the like, or using amines, such as diethanolamine, dicyclohexylamine, ethylenediamine, dibenzylethylenediamine, chloroprocaine, choline, and the like.

30 Compounds within the scope of the present invention are inhibitors of the production and/or activity of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), interleukin-10 (IL-10), as well as selective inhibitors of the activity of the enzyme cyclooxygenase-2 (COX-2). The compounds disclosed herein exhibit useful

pharmacological activity and accordingly may be incorporated into pharmaceutical compositions and used in the treatment and/or prevention of inflammation, inflammatory diseases, immunologic disorders, infectious diseases, malignant diseases and other conditions mediated by TNF-alpha, IL-6, interleukin-10 (IL-10) and/or COX-2. By way of example, without limitation, compounds within the scope of the present invention may be used in the treatment of the following conditions: rheumatoid arthritis, cachexia, septic shock syndrome, osteoarthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Behcet's disease, Kawasaki disease, cerebral malaria, adult respiratory distress syndrome, asbestosis, silicosis, pulmonary sarcoidosis, asthma, AIDS, meningitis, psoriasis, contact dermatitis, allergy, graft versus host reaction, multiple sclerosis, systemic lupus erythematosus, diabetes, myasthenia gravis, leprosy, hypertoxic alveolar injury, reperfusion injury, atherosclerosis, coronary heart disease, steroid withdrawal syndrome, vasopressin secretion disorders, osteoporosis, hyperparathyroidism, sex-steroid deficiency, familial adenomatous polyposis and colorectal cancer.

The compounds of the invention may be administered to animals, preferably mammals, and most preferably humans, using any convenient administration technique, including intravenously, intradermally, intramuscularly, subcutaneously, orally, rectally, transdermally, topically, by inhalation, and the like. The dosage delivered may be determined by a physician or qualified medical professional and will depend on the route of administration, the desired therapeutic effect, the duration of treatment, and the condition of the patient, but will generally range from 1 to 500 mg/70 kg human body weight/day.

The compounds of the invention may be used in formulations using acceptable pharmaceutical vehicles for enteral, or parenteral administration, such as, for example, water, alcohol, gelatin, gum arabic, lactose, amylase, magnesium stearate, talc, vegetable oils, polyalkylene glycol, and the like. The compounds can be formulated in solid form, for example, as tablets, capsules, dragees and suppositories, or in liquid form, for example, as solutions, suspensions and emulsions.

The following examples are presented by way of illustration, and are not intended to limit the invention in any way.

EXAMPLE 1

Synthesis of Representative Compounds

Compounds B and E, representative of the compounds of Formula I and II, respectively, were synthesized using the method illustrated below as Scheme III.

2,3-Dimethoxybenzylamine (6.06 mL, 41.0 mmol) was dissolved in anhydrous isopropanol (50 mL) at room temperature and concentrated HCl (3.3 mL, 1.0 equiv) was added all at once with good stirring.

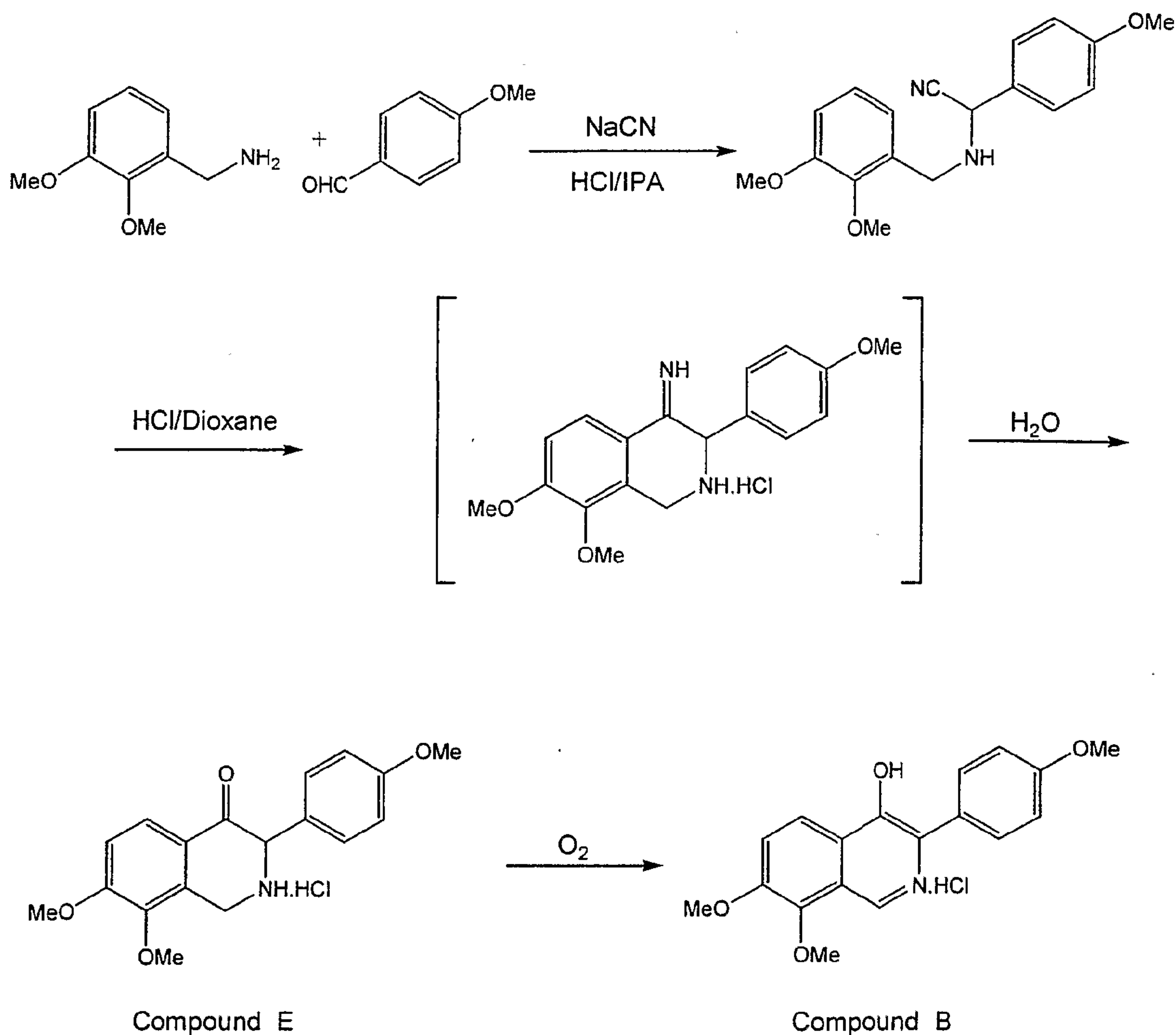
4-Methoxybenzaldehyde (5.0 mL, 1.0 equiv) was then added, followed by sodium cyanide (2.4 g, 1.2 equiv). The flask was stoppered and stirred at room temperature overnight. The solvent was roto-evaporated (*caution*: HCN vapors) and the residue triturated with 300 mL EtOAc, dried (Na_2SO_4) and filtered (*caution*: solid contains excess NaCN). The filtrate was evaporated.

The residue was dissolved in 65 mL CH_2Cl_2 , and HCl (65 mL, 4 N in dioxane) was added. The flask was stoppered and stirred at room temperature for 2 days. CH_2Cl_2 was roto-evaporated. To the remainder was added 65 mL H_2O with stirring for 2 h. The precipitate was collected on a Buchner funnel and rinsed with isopropanol, then EtOAc and air-dried. The product was a pale yellow solid, 7.5 g of 52% pure compound E.

To a two-liter Erlenmeyer flask, open to the atmosphere, Compound E (25 g) was added, followed by absolute ethanol (500 mL) and deionized water (500 mL), and the mixture was stirred for 48 hr at room temperature. The solvent was slowly evaporated under reduced pressure to near dryness. The residue was dissolved by boiling in a minimal amount of absolute ethanol (300 to 400 mL), and the solution was then incubated for 48 hr at 0°C to allow recrystallization. The crystals of the resulting Compound B were filtered, rinsed with hexane until the filtrate became colorless (~500 mL) and then dried overnight in an oven at 50°C. The dried, purified Compound B (15.7 g, yellow solid, HPLC purity ~99%) was obtained in 62.8% yield for the final step (see Scheme III).

Analysis: ^1H -NMR, 400 MHz ($\text{DMSO}-d_6$): δ 9.02 (s, 1H), 8.43 (d, J = 9.2 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 6.8 Hz, 2H), 7.15 (d, J = 7.2 Hz, 2H), 4.06 (s, 6H), 3.86 (s, 3H).

SCHEME III



5

EXAMPLE 2Inhibition of TNF-alpha Induced Cell Killing

Compounds B and E were tested for their ability to inhibit TNF-alpha induced killing of cultured mouse fibrosarcoma cells. WEHI-13VAR cells were grown in buffered RPMI-1640 medium containing 3% FBS and assayed for TNF-alpha induced cell death as described by Khabar et al. (Immunol Lett 46:107-10, 1995). Cells were co-incubated for 20 hr with 100 pg/ml (Figure 1A) or 1 pg/ml (Figure 1B) of TNF-alpha and 100 µg/ml of berberine, compound B or compound E. Controls included cells receiving TNF-alpha but no drug, as well as cells receiving no TNF-alpha and treated with or without NP-40 lysis buffer. Cell viability was assayed using the dye MTT (3-(4,5-

dimethylthiozol-2-yl)-2,5-diphenyl tetrazolium bromide) as described. As shown in Figure 1, co-incubation with compound E or B inhibited TNF-alpha induced cell killing (i.e., increased cell viability) relative to untreated or berberine-treated cells.

5

EXAMPLE 3

Dose Response of Inhibition of TNF-alpha Induced Cell Killing

The dose response was measured for the ability of compound B to inhibit TNF-alpha induced killing of cultured mouse fibrosarcoma cells. In this experiment, the inhibitory action of compound B was compared to that of a chimeric recombinant protein dimer containing soluble TNF receptor fused to the Fc portion of immunoglobulin heavy chain (Mohler KM et al., J Immunol 151:1548-61, 1993), a known antagonist of TNF-alpha mediated cell killing. WEHI-13VAR cells were grown in buffered RPMI-1640 medium containing 3% FBS and assayed for TNF-alpha induced cell death as described by Khabar et al. (Immunol Lett 46:107-10, 1995). Cells were co-incubated for 20 hr with 100 pg/ml, 50 pg/ml or no TNF-alpha and varying concentrations of soluble TNF receptor/Fc chimera (Figure 2A) or compound B (Figure 2B). Cell viability was assayed using the dye MTT (3-(4,5-dimethylthiozol-2-yl)-2,5-diphenyl tetrazolium bromide) as described. As shown in Figure 2B, for both concentrations of TNF-alpha tested, the inhibition of TNF-alpha induced cell killing (i.e., increased cell viability) was proportional to the dose of compound B up to a concentration of 10 μ M, at which concentration the maximal inhibitory effect was attained.

25

EXAMPLE 4

Inhibition of LPS-induced TNF-alpha Production

The ability of compound B to inhibit TNF-alpha production was examined in a standard in vitro model of inflammation – the murine macrophage-like cell line RAW264.7 stimulated with lipopolysaccharides (LPS). RAW264.7 cells were grown in RPMI-1640 medium containing 3% FBS and pre-incubated for 1 hr at 37°C with varying concentrations (1, 3, 10, 30 or 100 μ M) of compound B. LPS (0.1 μ g/ml) was then added, and the cells were further incubated for 6 hr at 37°C in a 5% carbon dioxide atmosphere.

30

Cell supernatants were then collected, aliquoted, and assayed for TNF-alpha by ELISA with anti-TNF-alpha antibody. As shown in Figure 3, treatment with compound B inhibited LPS-induced TNF-alpha production by nearly 50%.

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EXAMPLE 5

Inhibition of LPS-induced IL-6 Production

The ability of compound B to inhibit IL-6 production was also examined in LPS-stimulated RAW cells. RAW264.7 cells were grown in RPMI-1640 medium containing 3% FBS and pre-incubated for 1 hr at 37°C with varying concentrations (1, 3, 10, 30 or 100 µM) of compound B. LPS (0.1 µg/ml) was then added, and the cells were further incubated for 6 hr at 37°C in a 5% carbon dioxide atmosphere. Cell supernatants were then collected, aliquoted, and assayed for IL-6 by ELISA with anti-IL-6 antibody. As shown in Figure 3, treatment with compound B inhibited LPS-induced IL-6 production by up to 60%.

15

EXAMPLE 6

Selective Inhibition of LPS-induced COX-2 Activity

The ability of compound B to selectively inhibit COX-2 activity was also examined in LPS-stimulated RAW cells. In this experiment, the inhibitory effect of compound B was compared to that of dexamethasone, a potent inhibitor of COX-2 expression. RAW264.7 cells were grown in RPMI-1640 medium containing 3% FBS and pre-incubated for 1 hr at 37°C with compound B (1, 3, 10, 30 or 100 µM), dexamethasone (Dex, 1 µM), or without drug. After 1 hr LPS (0.1 µg/ml) was added, and the cells were further incubated for 6 hr at 37°C. Control cells received neither drug nor LPS. Cells were collected, lysed and assayed for cyclooxygenase activities essentially according to the method of Brideau et al. (Inflamm Res 45:68-74, 1996). COX-2 activity was measured using the Biotrak Prostaglandin E2 (PGE2) EIA Kit, and COX-1 activity was determined using the Biotrak Thromboxane B2 (TXB2) EIA Kit, both from Amersham Pharmacia Biotech (Piscataway, NJ). As with treatment with dexamethasone, pre-incubation with the higher concentrations of compound B completely and selectively abrogated the

20

25

30

inducible COX-2 activity (Figure 5A) while having no effect on the constitutively expressed COX-1 activity (Figure 5B).

EXAMPLE 7

5 Suppression of Collagen-induced Arthritis in Mice

The ability of compound B to reduce inflammation in an animal model of arthritis was also studied. Arthritis was induced by intradermal administration of collagen (100 µg/mice) in complete adjuvant in male DBA/1Lac mice 7 weeks old. The booster immunization (100 µg/mice) in
10 incomplete adjuvant was given subcutaneously on day 21. Two days later, when arthritic scores were around 1, animals were divided into two groups. One group received 50 mg/kg dose of compound B orally for 17 days daily. The second group received 10% PEG in water and was used as a vehicle-treated group. Body weight (Figure 6, panel A), clinical score (Figure 6, panel
15 B), the number of joints affected (Figure 6, panel C) and paw thickness (Figure 6, panel D) were monitored 24 hours after drug administration during the treatment period. As shown in Figure 6, mice treated with compound B showed significantly lower clinical scores, fewer joints affected, and reduced paw thickness when compared to the vehicle-treated group. No change in
20 body weight was observed between the vehicle and the treatment groups.

EXAMPLE 8

Inhibition of LPS-Induced IL-10 Production in Human PBC

Human peripheral blood mononuclear cells (PBMC) were purified from
25 human blood using Ficoll-Paque PLUS separation medium (Amersham Pharmacia Biotech) according to the manufacturer's recommended protocol. After centrifugation, the central PBMC layer was collected, washed twice with phosphate buffered saline (PBS) and then plated in a 96-well plate at a density of 2×10^5 cells/well in RPMI-1640 medium containing 10% FBS. The
30 cells were preincubated with dexamethasone (1 µM) or Compound B (1, 10, 30 or 100 µM) for 1 hr and then challenged with LPS (1 µg/ml) for 20 hr. Cells receiving no drug treatment, incubated with or without LPS, served as controls. The cell supernatants were collected, and the amount of IL-10 in

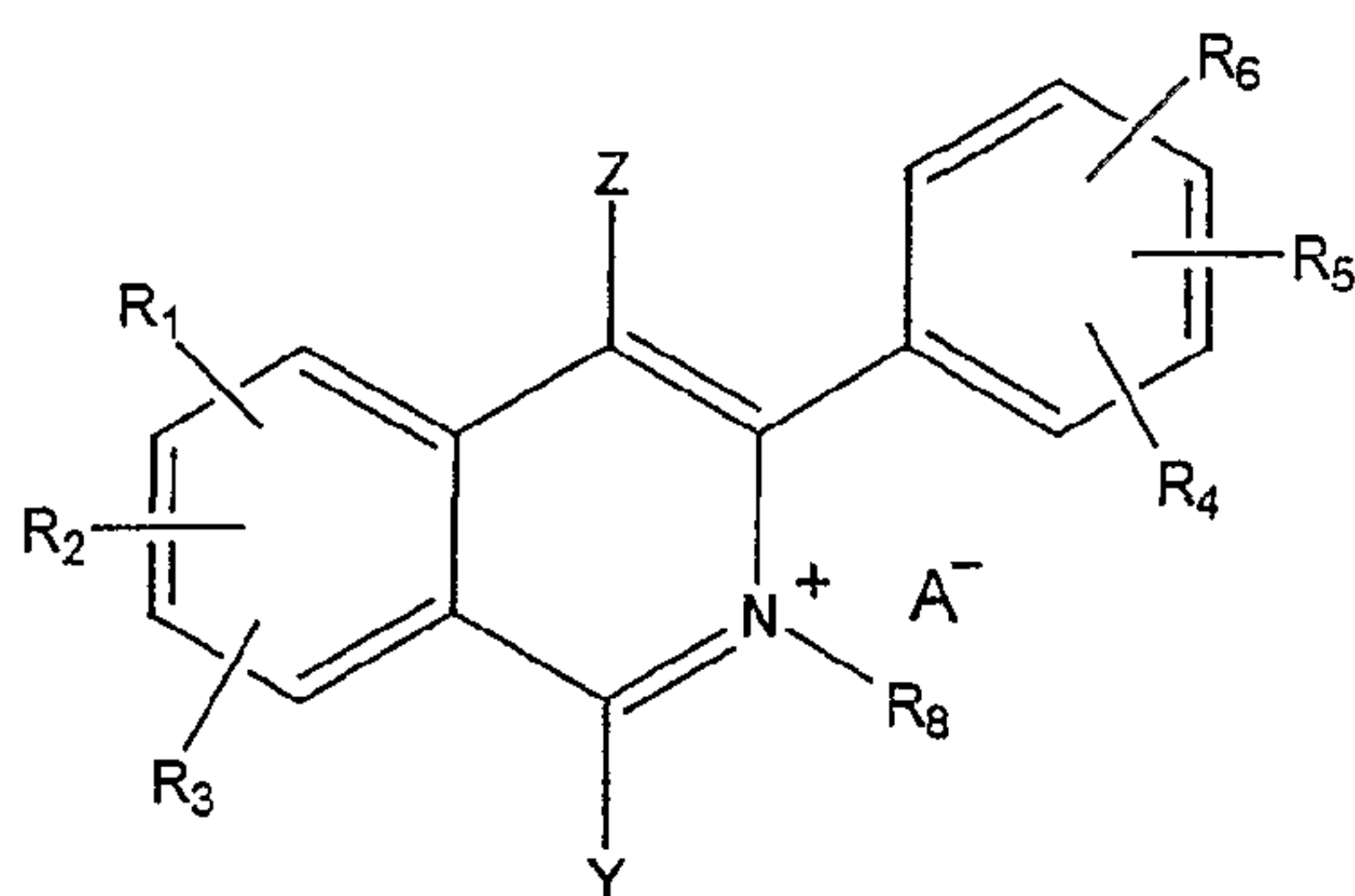
each was measured by standard ELISA. As shown in Figure 7, preincubation of cells with Compound B resulted in a dose-dependent inhibition of LPS-induced IL-10 production. To confirm that the observed decrease in IL-10 was not due to cytotoxicity, the PBMC were plated in a separate plate, incubated
5 for 20 hr with the same range of doses of Compound B, and the cell viability was assessed by a standard MTS dye exclusion assay (4-hr incubation with MTS). There was no significant loss in cell viability over the range of doses tested (data not shown).

It will be appreciated from the foregoing that various modifications of
10 the invention are contemplated beyond the specific exemplification given herein. Accordingly, the invention is defined by the following claims where:

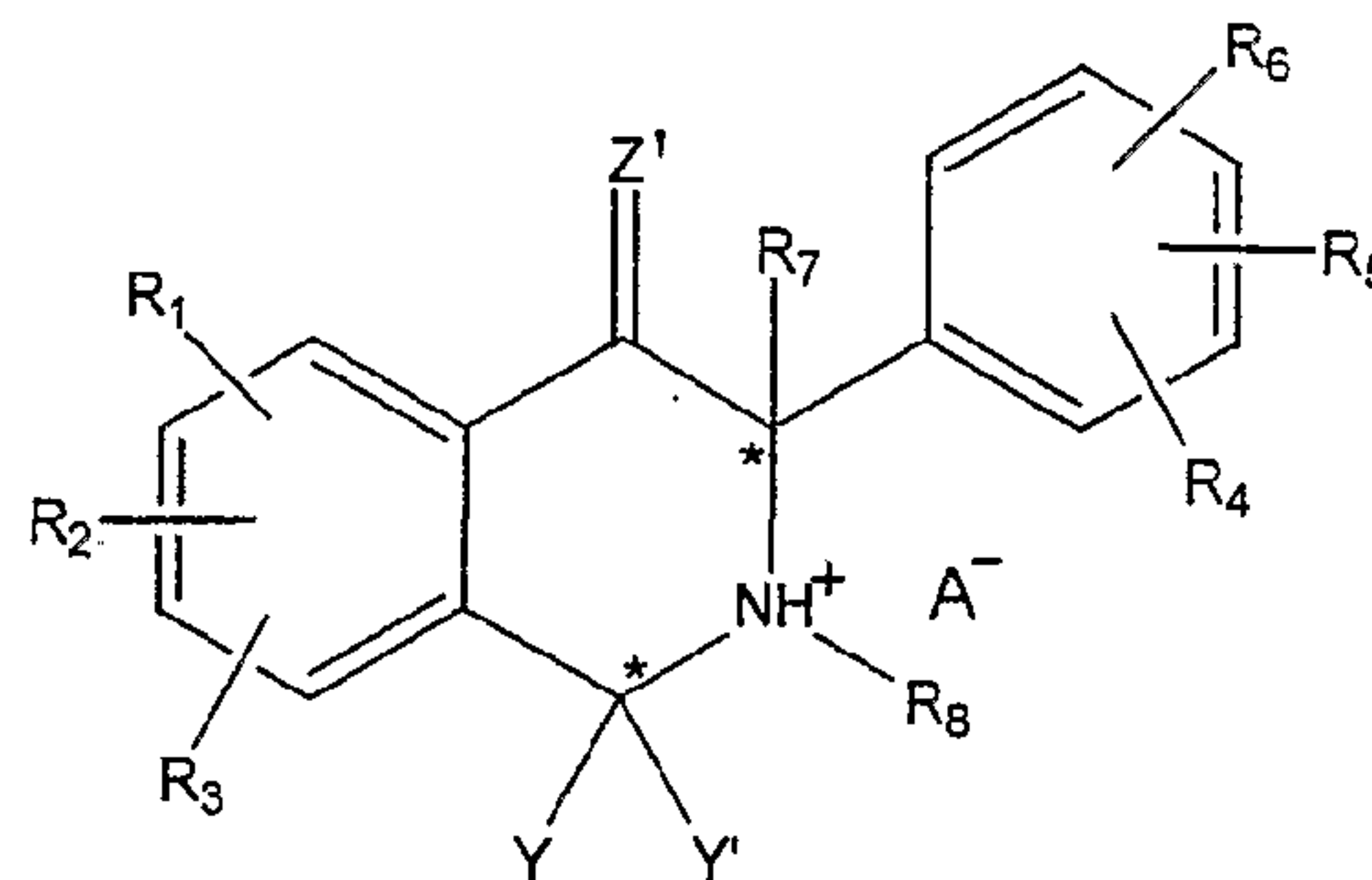
We claim:

1. A compound having a structure selected from Formulas I to X:

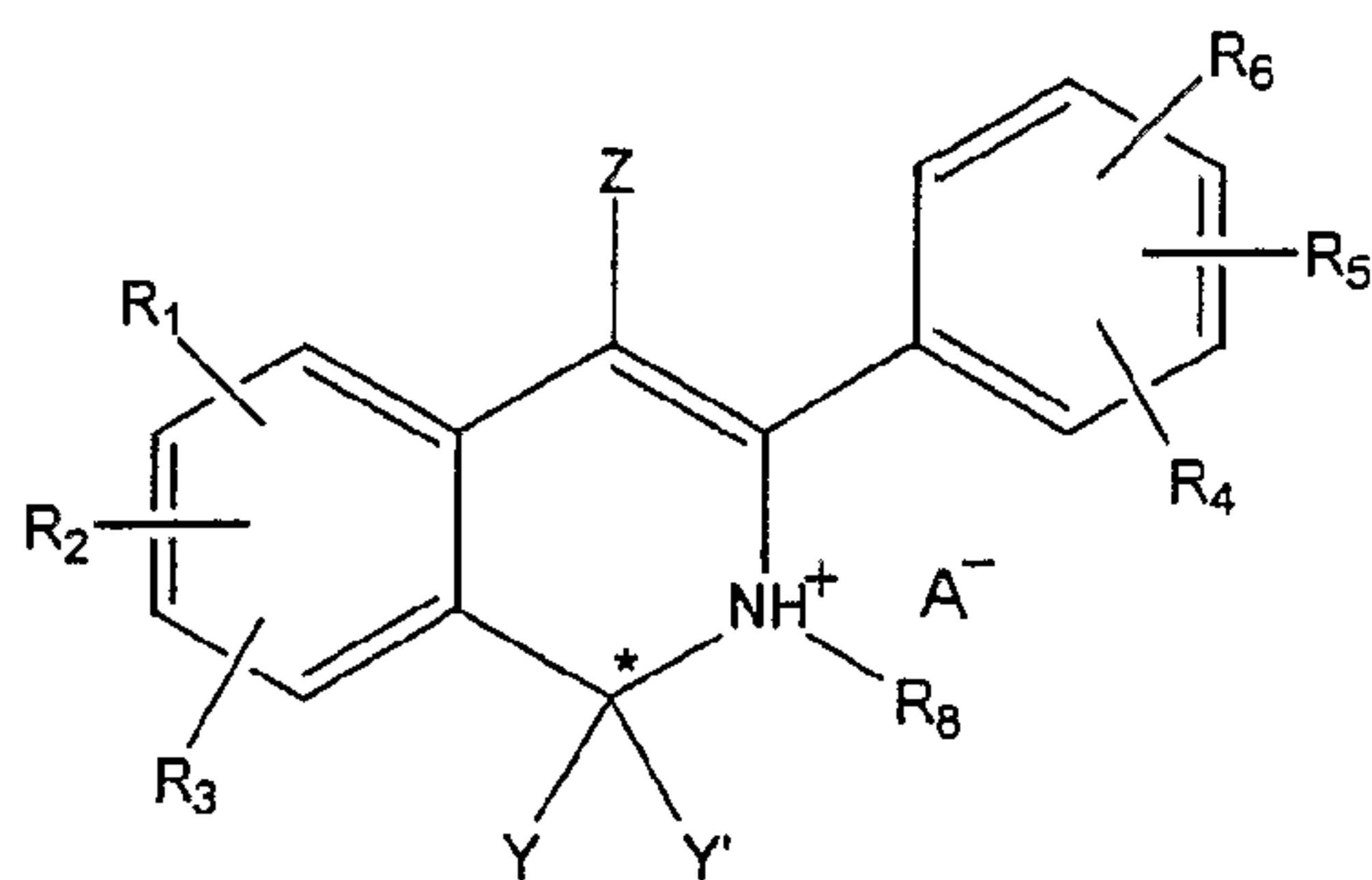
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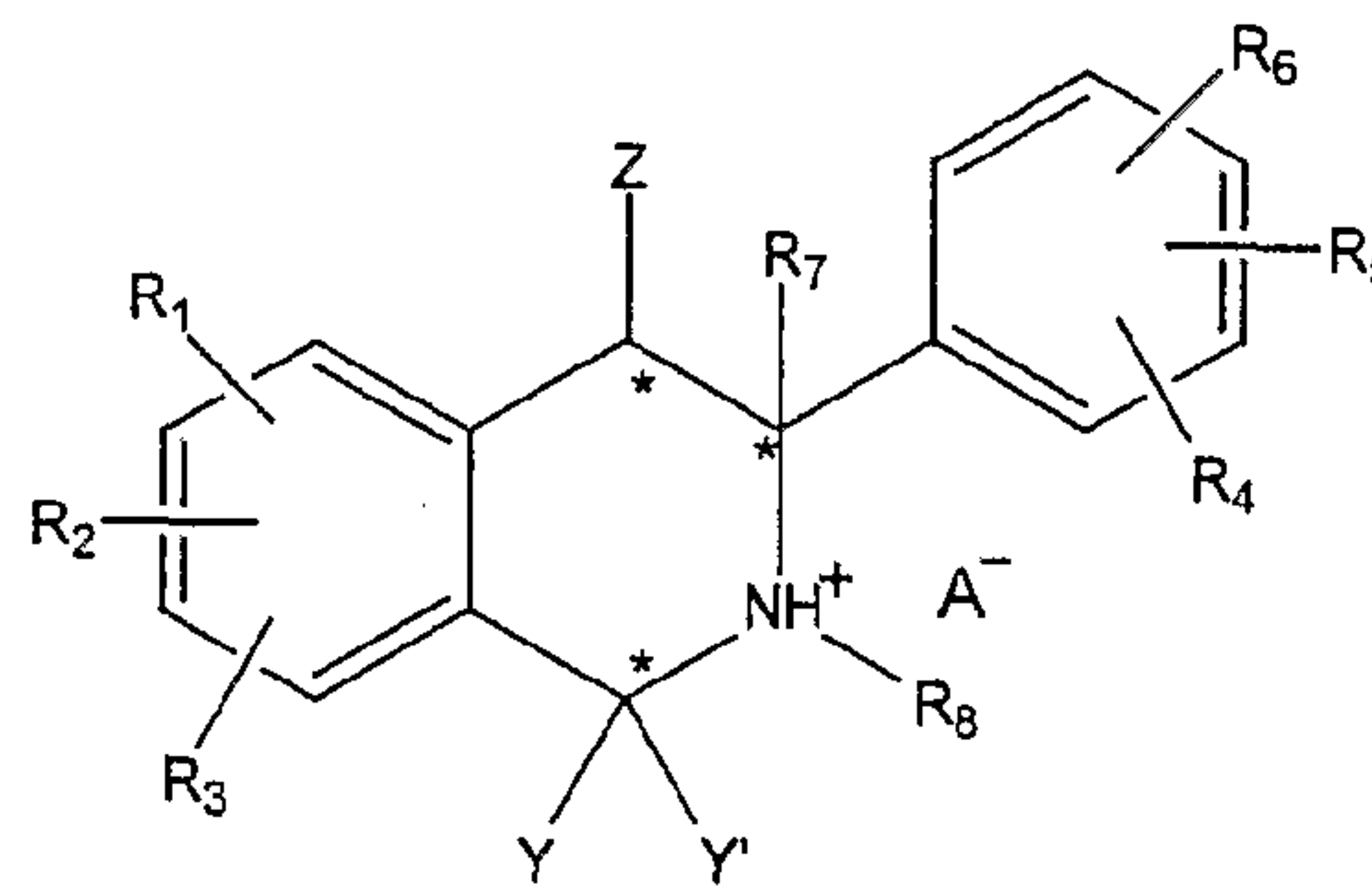
Formula I



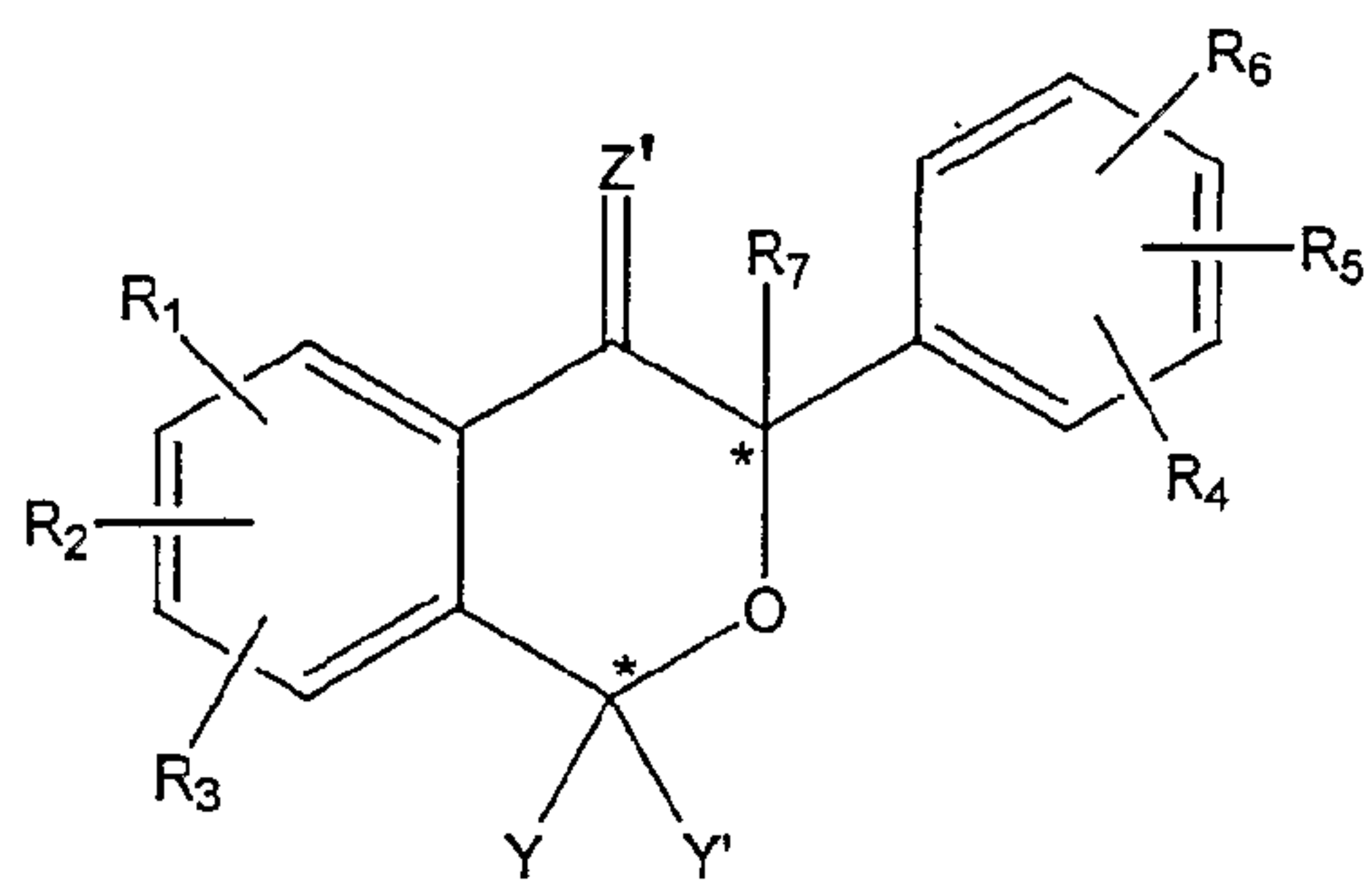
Formula II



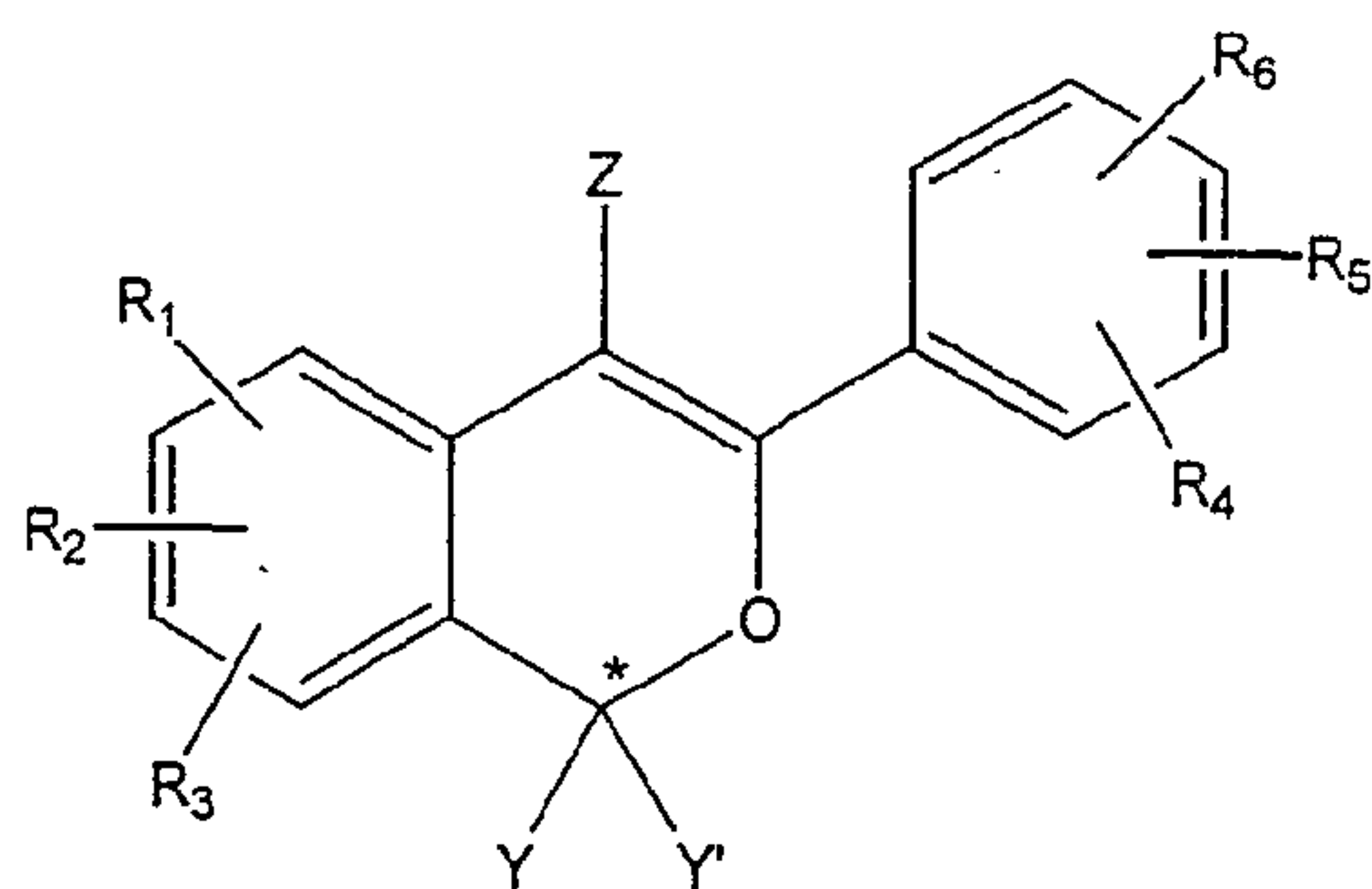
Formula III



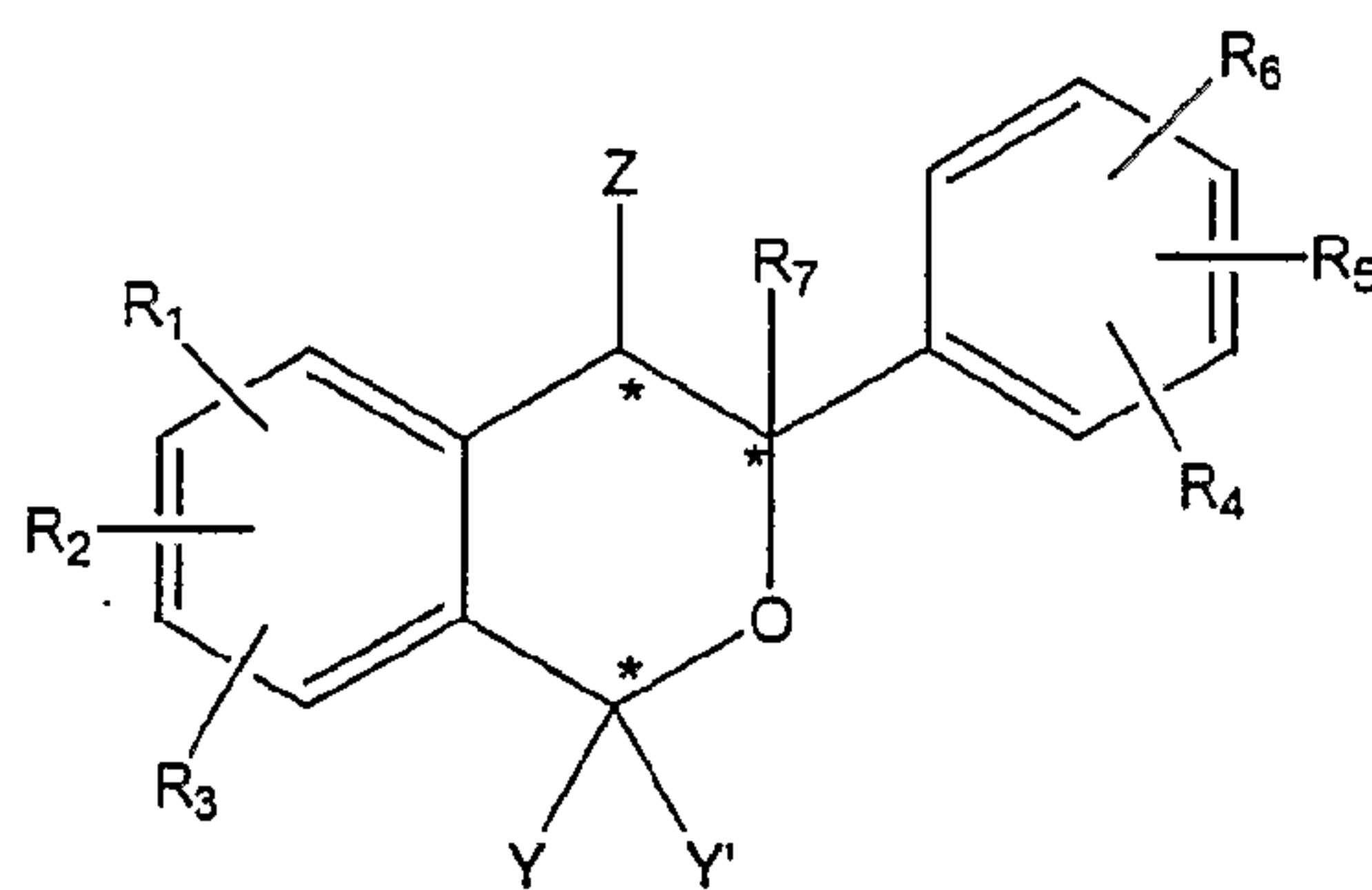
Formula IV



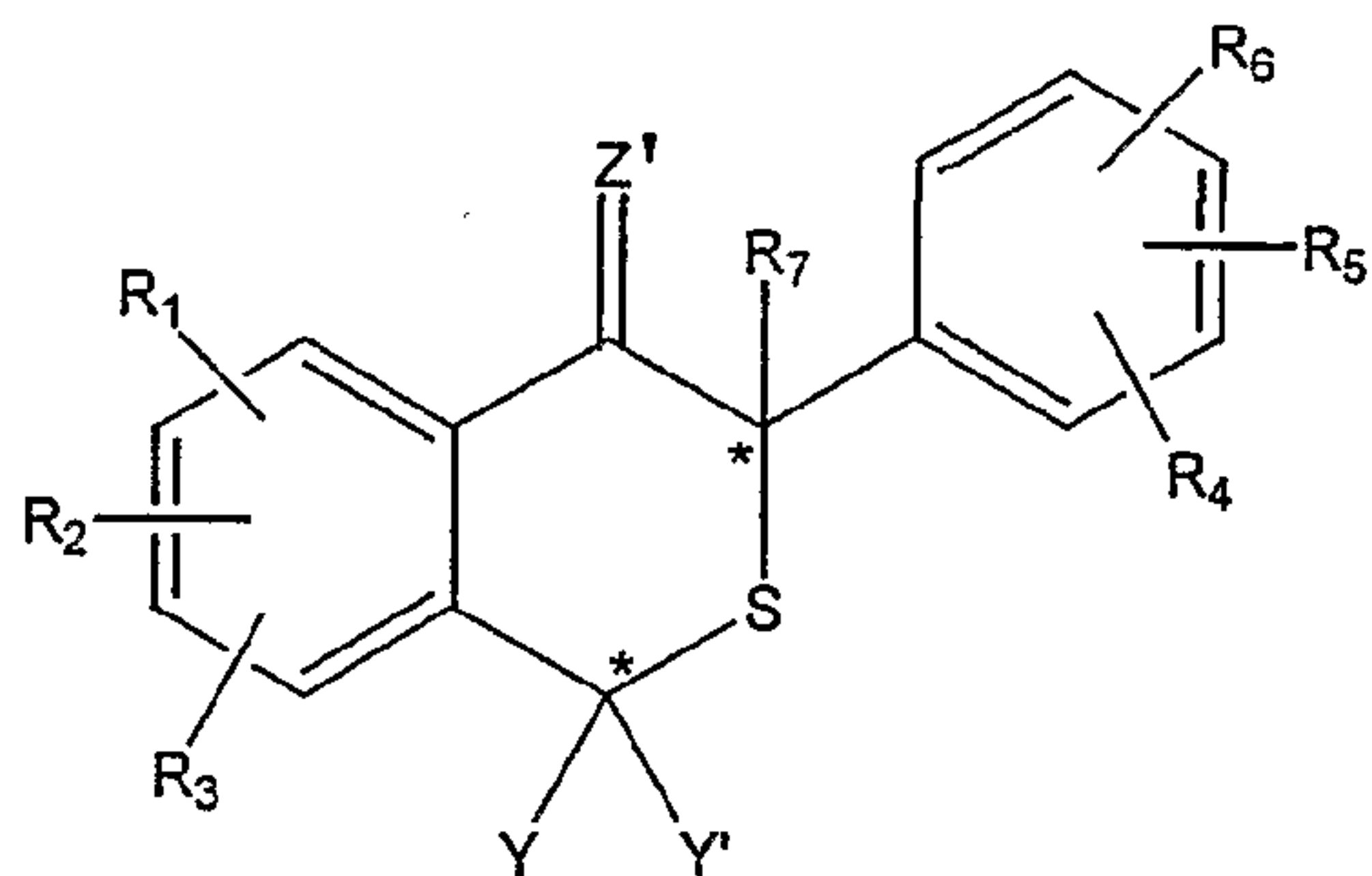
Formula V



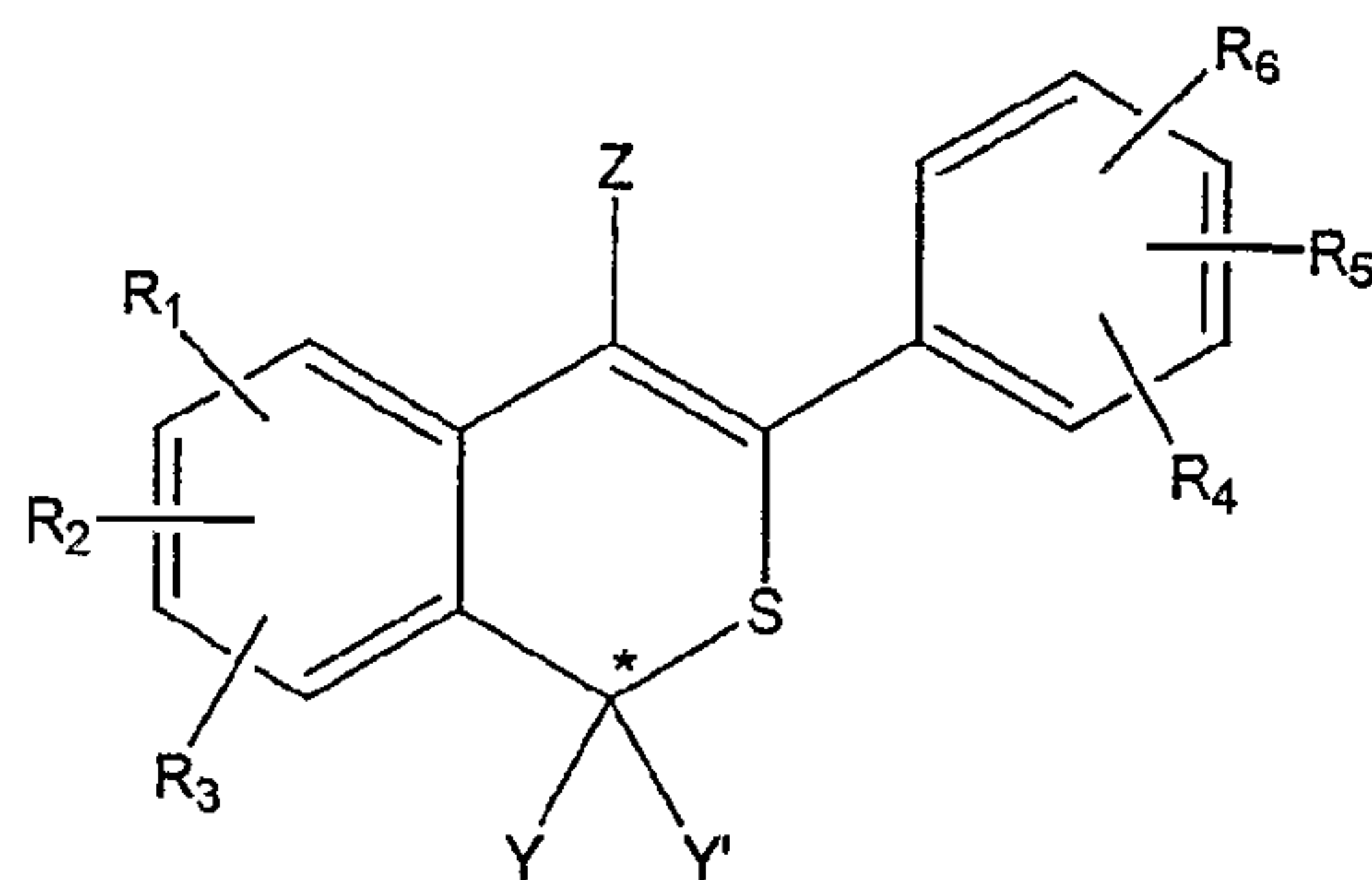
Formula VI



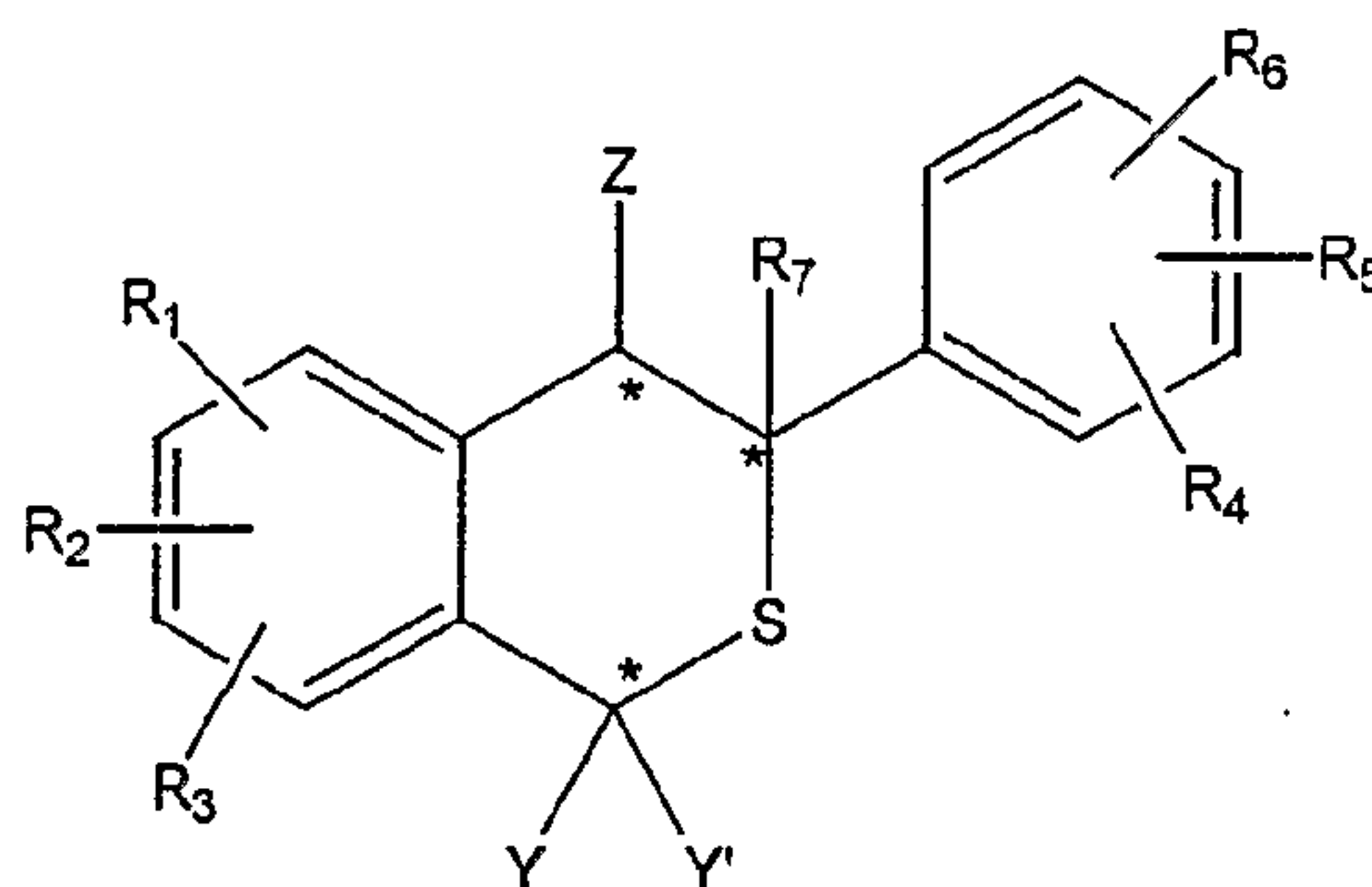
Formula VII



Formula VIII



Formula IX



Formula X

wherein the stereocenters marked with an asterisk (*) may be R- or S- and

R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are independently

5

H; optionally substituted C_1 - C_{20} linear or branched alkyl including chloroalkyl or fluoroalkyl; optionally substituted C_2 - C_{20} linear or branched alkenyl; optionally substituted C_6 - C_{20} aryl, linear or branched alkylaryl, linear or branched alkenylaryl; COOR where R is H, optionally substituted C_1 - C_{20} alkyl, optionally substituted C_2 - C_{20} alkenyl or optionally substituted C_6 - C_{10} aryl, sodium, potassium or other pharmaceutically acceptable counter-ion such as calcium, magnesium, ammonium,

10

tromethamine and the like; CONR'R", where R' and R"
 are independently H, optionally substituted C₁-C₂₀ alkyl,
 optionally substituted C₂-C₂₀ alkenyl or optionally
 substituted C₆-C₁₀ aryl or where NR'R" represents a
 5 cyclic moiety such as morpholine, piperidine, piperazine
 and the like; NH₂; optionally substituted C₁-C₂₀
 alkylamino, bis(alkylamino), cycloalkylamino or cyclic
 amino; OH; optionally substituted C₁-C₂₀ alkoxy, including
 trifluoromethoxy, and the like; optionally substituted C₁-
 10 C₂₀ alkanoyl; optionally substituted C₁-C₂₀ acyloxy; halo;
 optionally substituted C₁-C₂₀ alkylcarboxylamino; cyano;
 nitro; SO₂NR'''R'''' where R''' and R'''' are independently H,
 C₁-C₂₀ alkyl or aryl; SO₂R''' where R''' is H, C₁-C₂₀ alkyl or
 aryl; SO₃R''' where R''' is H, C₁-C₂₀ alkyl or aryl; or C₄-C₈
 15 heterocycles such as tetrazolyl, imidazolyl, pyrrolyl,
 pyridyl, indolyl and the like; or when individual aromatic
 rings possess adjacent substituents, these substituents
 may be joined to form a ring such as a methylenedioxy or
 ethylenedioxy group, and the like, including lactones and
 20 lactams;

R₇ is

H (in which case the compounds may be in tautomeric
 form) or optionally substituted C₁-C₂₀ linear or branched
 alkyl including chloroalkyl or fluoroalkyl;

25 R₈ is

H; OH (or O in the case of Formula I compounds);
 optionally substituted C₁-C₂₀ linear or branched alkyl
 including chloroalkyl or fluoroalkyl; optionally substituted
 C₂-C₂₀ linear or branched alkenyl; optionally substituted
 30 C₆-C₂₀ aryl, linear or branched alkylaryl, linear or
 branched alkenylaryl; COOR where R is H, optionally
 substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀
 alkenyl or optionally substituted C₆-C₁₀ aryl, sodium,
 potassium or other pharmaceutically acceptable counter-

ion such as calcium, magnesium, ammonium, tromethamine and the like; CONR'R", where R' and R" are independently H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl or where NR'R" represents a cyclic moiety such as morpholine, piperidine, piperazine and the like; or optionally substituted alkanoyl, alkenoyl, aroyl, alkylaroyl or alkenylaroyl; and "A" represents a pharmaceutically acceptable counter-ion such as chloride, sulfate, phosphate, acetate and the like; or R₈ is absent, in which case the nitrogen does not bear a positive charge and the counter-ion "A" is not present;

Y and Y' are independently

H; optionally substituted C₁-C₂₀ linear or branched alkyl including chloroalkyl or fluoroalkyl; optionally substituted C₂-C₂₀ linear or branched alkenyl; optionally substituted C₆-C₂₀ aryl, linear or branched alkylaryl, linear or branched alkenylaryl; COOR where R is H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl, sodium, potassium or other pharmaceutically acceptable counter-ion such as calcium, magnesium, ammonium, tromethamine and the like; CONR'R", where R' and R" are independently H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl or where NR'R" represents a cyclic moiety such as morpholine, piperidine, piperazine and the like; NH₂; optionally substituted C₁-C₂₀ alkylamino, bis(alkylamino), cycloalkylamino or cyclic amino; OH; optionally substituted C₁-C₂₀ alkoxy, including trifluoromethoxy, and the like; optionally substituted C₁-C₂₀ alkanoyl; optionally substituted C₁-C₂₀ acyloxy; halo; optionally substituted C₁-C₂₀ alkylcarboxylamino; cyano; nitro; SO₂NR'''R''' where R''' and R''' are independently H,

C₁-C₂₀ alkyl or aryl; SO₂R''' where R''' is H, C₁-C₂₀ alkyl or aryl; SO₃R''' where R''' is H, C₁-C₂₀ alkyl or aryl; or C₄-C₈ heterocycles such as tetrazolyl, imidazolyl, pyrrolyl, pyridyl, indolyl and the like; or Y and Y' together may be joined in a ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, including heterocycles such as lactones, lactams and the like;

Z is

OH; optionally substituted C₁-C₂₀ alkoxy, including trifluoromethoxy, and the like; NR'R'', where R' and R'' are independently H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl or where NR'R'' represents a cyclic moiety such as morpholine, piperidine, piperazine and the like; or SR'''' where R'''' is H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl;

Z' is

O; S; or NR''''', where R''''' is H, optionally substituted C₁-C₂₀ alkyl, optionally substituted C₂-C₂₀ alkenyl or optionally substituted C₆-C₁₀ aryl;

with the provisos that in Formula I,

when Y is H, then Z is OH, R₈ is H, and R₁, R₂ and R₃ are not 6-methoxy; when Y is methyl or substituted benzyl, then R₁, R₂ and R₃ do not comprise 6,7-dimethoxy or 5,6,7-trimethoxy or 6,7,8-trimethoxy; and when Z is OH, at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H;

in Formula II,

when Y is H and Y' is H, then Z' is O, R₈ is H, and R₁, R₂ and R₃ are not 6-methoxy;

when Y is H and Y' is methyl or substituted benzyl, then R₁, R₂ and R₃ do not comprise 6,7-dimethoxy or 5,6,7-trimethoxy or 6,7,8-trimethoxy; and

when Z' is O, at least one of R₁, R₂, R₃, R₄, R₅, R₆ and R₇ is not H;

in Formula III,

when Y is H and Y' is H, then Z is OH, R₈ is H, and R₁, R₂ and R₃ are not 6-methoxy;

when Y is H and Y' is methyl or substituted benzyl, then

R₁, R₂ and R₃ do not comprise 6,7-dimethoxy or 5,6,7-trimethoxy or 6,7,8-trimethoxy; and

when Z is OH or alkoxy, at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H;

in Formula IV,

when Y is H and Y' is H, then Z is OH, R₈ is H, and R₁, R₂ and R₃ are not 6-methoxy;

when Y is H and Y' is methyl or substituted benzyl, then

R₁, R₂ and R₃ do not comprise 6,7-dimethoxy or 5,6,7-trimethoxy or 6,7,8-trimethoxy; and

when Z is OH, at least one of R₁, R₂, R₃, R₄, R₅, R₆ and R₇ is not H;

in Formula V,

when Z' is O and Y and/or Y' is phenyl, then at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H'

when Z' is O and Y and/or Y' is alkoxy, then R₄, R₅ and R₆ are not aminoethyl; and

when Z' is O and Y is H and Y' is H, then R₇ is not H;

in Formula VI,

when Z is OH and Y and/or Y' is phenyl, then at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H;

in Formula VII,

when Z is methyl or phenyl, then at least one of R₁, R₂, R₃, R₄, R₅, R₆ and R₇ is not H;

when Z is OH and Y and/or Y' is phenyl, then at least one of R₁, R₂, R₃, R₄, R₅ and R₆ is not H;

when Z is OH and Y and/or Y' is alkoxy, then R₄, R₅ and R₆ are not aminoethyl; and

when Z is OH and Y is H and Y' is H, then R₇ is not H;
in Formula VIII,

when Y and/or Y' is substituted alkyl, arylamide or COOR,
and R₁ and R₂ comprise 6,7-dimethyl or 5,6-
5 dihydroxy, then at least one of R₄, R₅ and R₆ is not H;
and

when Z' is O, then at least one of R₁, R₂, R₃, R₄, R₅, R₆
and R₇ is not H, and R₁, R₂ and R₃ do not comprise 7-
methoxy;

10 in Formula IX,

when Y and/or Y' is substituted alkyl, arylamide or COOR,
and R₁ and R₂ comprise 6,7-dimethyl or 5,6-
dihydroxy, then at least one of R₄, R₅ and R₆ is not H;
and

15 when Z is OH or alkoxy, then at least one of R₁, R₂, R₃,
R₄, R₅ and R₆ is not H, and R₁, R₂ and R₃ do not comprise
7-methoxy;

in Formula X,

20 when Y is substituted alkyl, arylamide or COOR, and R₁
and R₂ comprise 6,7-dimethyl or 5,6-dihydroxy, then
at least one of R₄, R₅ and R₆ is not H;

when Z is H, then at least one of Y, Y', R₄, R₅ and R₆ is
not H; and

25 when Z is OH, at least one of R₁, R₂, R₃, R₄, R₅, R₆ and
R₇ is not H and provided further that Z may be H in the
case of compounds of Formula IX or Formula X.

2. A compound according to claim 1 which is of Formula I.

30 3. A compound according to claim 1 which is of Formula II.

4. A compound according to claim 1 which is of Formula III.

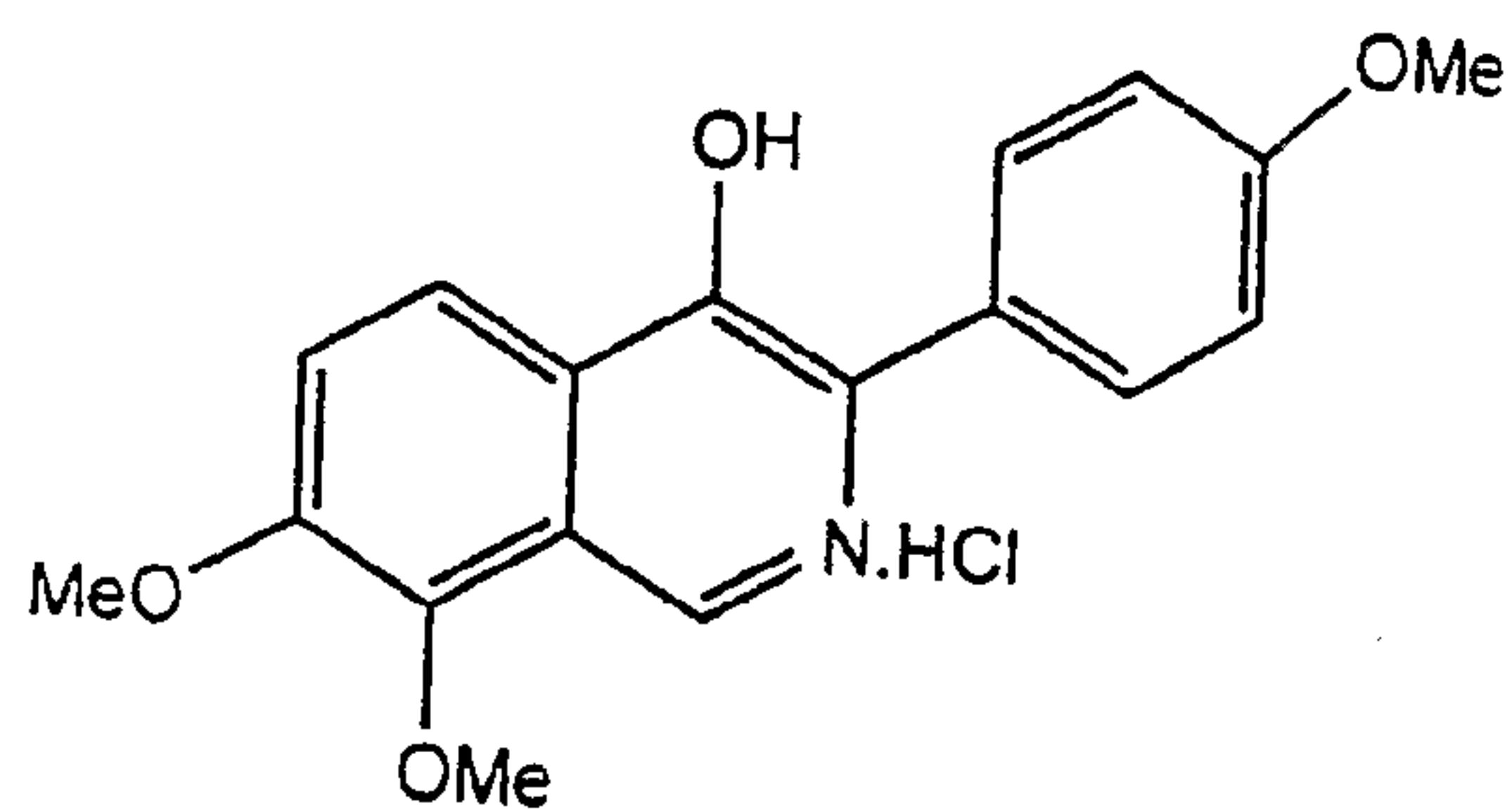
5. A compound according to claim 1 which is of Formula IV.

6. A compound according to claim 1 which is of Formula V.
7. A compound according to claim 1 which is of Formula VI.
- 5 8. A compound according to claim 1 which is of Formula VII.
9. A compound according to claim 1 which is of Formula VIII.
- 10 10. A compound according to claim 1 which is of Formula IX.
11. A compound according to claim 1 which is of Formula X.
12. A compound according to claim 1 of Formula I wherein two to four of R_1 - R_6 are lower alkoxy, and the remainder of R_1 - R_6 are hydrogen; R_8 is H, lower alkyl or lower alkoxy carbonyl; Y is H, lower alkyl or lower alkoxy; Z is OH, lower alkoxy or NH_2 .
13. A compound according to claim 12 wherein R_1 , R_2 and R_4 are methoxy; R_3 , R_5 , R_6 and R_8 are hydrogen; Y is hydrogen and Z is OH.
- 20 14. A compound according to claim 1 of Formula II wherein at least two of R_1 to R_6 are lower alkoxy; R_7 is H; R_8 is H, lower alkyl or lower alkoxy carbonyl; Y and Y' are H, lower alkyl or lower alkoxy and Z' is O.
- 25 15. A compound according to claim 14 wherein R_1 , R_2 and R_4 are methoxy; R_3 , R_5 and R_6 are hydrogen; R_7 is H; R_8 is H or ethoxycarbonyl, Y and Y' are hydrogen and Z' is O.
- 30 16. A compound according to claim 1 selected from the group consisting of:
7,8-Dimethoxy-3-(4-methoxy-phenyl)-isoquinolin-4-ol hydrochloride
7,8-Dimethoxy-3-(4-methoxy-phenyl)-isoquinoline
5-(4-Hydroxy-7,8-dimethoxy-isoquinoline-3-yl)-2-methoxy-benzoic acid methyl ester hydrochloride

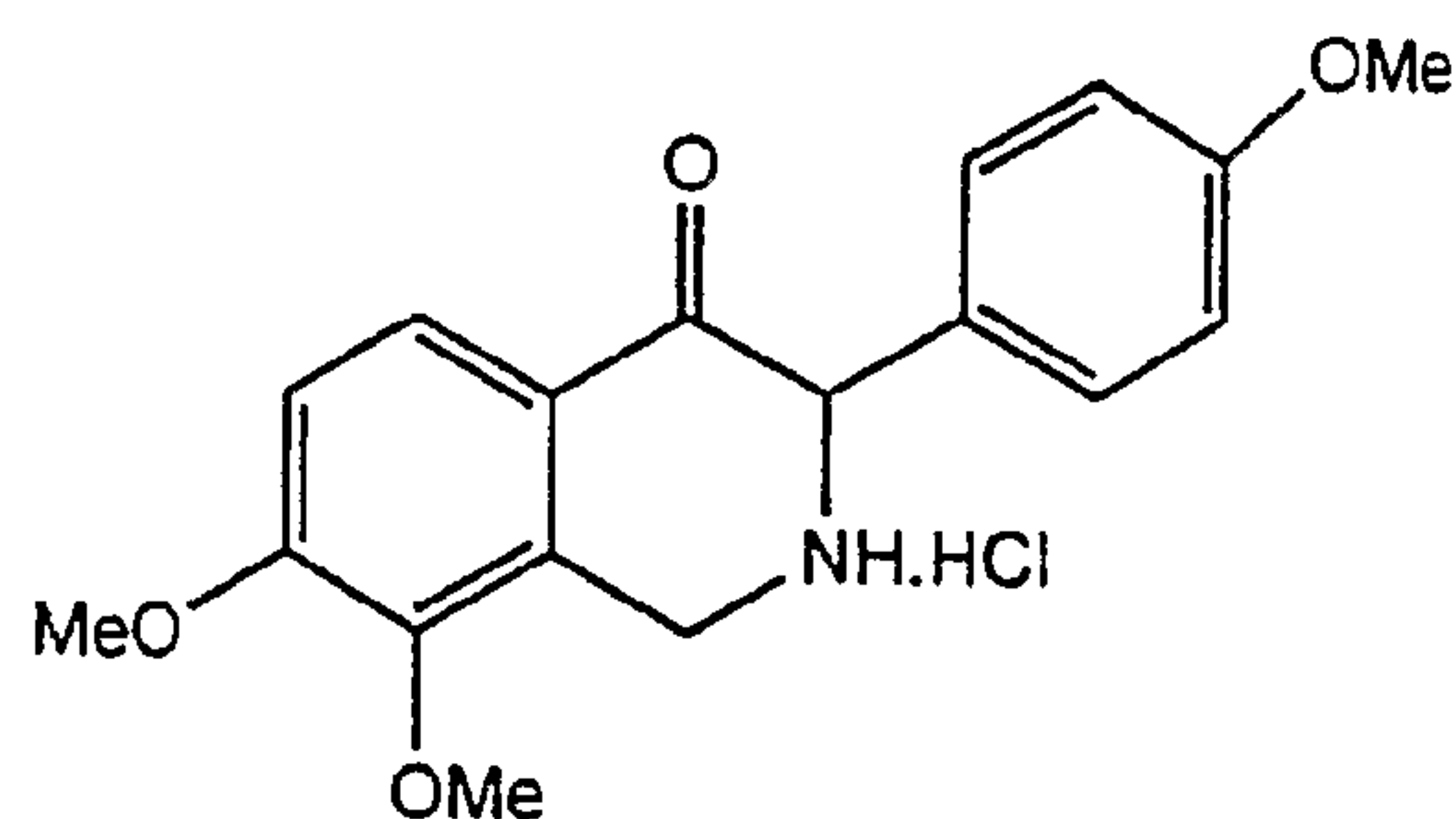
- 7-Methoxy-3-phenyl-isoquinolin-4-ol
 8-Methoxy-3-phenyl-isoquinolin-4-ol
 5-Methoxy-1-methyl-3-phenyl-isoquinolin-4-ol
 3-(4-Methoxy-phenyl)-isoquinoline-4,7,8-triol
 5 7-Chloro-3-(4-hydroxy-phenyl)-isoquinolin-4-ol
 7,8-Dimethoxy-3-(4-methoxy-phenyl)-4-oxo-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid ethyl ester
 10 7,8-Dimethoxy-3-(4-methoxy-phenyl)-2,3-dihydro-1*H*-isoquinoline-4-one hydrochloride
 5-(7,8-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-isoquinolin-3-yl)-2-methoxybenzoic acid methyl ester hydrochloride
 15 7-Methoxy-3-phenyl-2,3-dihydro-1*H*-isoquinolin-4-one
 8-Methoxy-3-phenyl-2,3-dihydro-1*H*-isoquinolin-4-one
 20 5-Methoxy-3-phenyl-2,3-dihydro-1*H*-isoquinolin-4-one
 6-Methoxy-3-(4-methoxy-phenyl)-2,3-dihydro-1*H*-isoquinolin-4-one
 1,3-Dimethyl-3-phenyl-7-trifluoromethoxy-2,3-dihydro-1*H*-isoquinolin-4-one
 25 7,8-Dihydroxy-3-(4-hydroxy-phenyl)-3-methyl-2,3-dihydro-1*H*-isoquinolin-4-one
 7-Chloro-3-(4-hydroxy-phenyl)-2,3-dihydro-1*H*-isoquinolin-4-one
 30 8-Amino-3-(4-hydroxy-phenyl)-2,3-dihydro-1*H*-isoquinolin-4-one
 6-Methoxy-3-phenyl-1,2-dihydro-isoquinolin-4-ol
 35 4-Methoxy-3-phenyl-1,2-dihydro-isoquinoline-7,8-diol
 4-Hydroxy-7,8-dimethoxy-3-(4-methoxy-phenyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid ethyl ester
 1-Ethyl-3-(4-hydroxy-phenyl)-3-methyl-7-trifluoromethoxy-1,2,3,4-tetrahydro-isoquinolin-4-ol
 40 6-Methoxy-3-phenyl-isochroman-4-one
 3-(4-Methoxy-phenyl)-3-methyl-7-trifluoromethoxy-isochroman-4-one
 7-Methoxy-3-(4-methoxy-phenyl)-3-methyl-isochroman-4-one
 45 7,8-Dimethoxy-3-(4-methoxy-phenyl)-isochroman-4-one

- 6-Methyl-3-phenyl-isochroman-4-one
- 7,8-Dimethoxy-3-(4-methoxy-phenyl)-3-methyl-isochroman-4-one
- 4-(4,7,8-Trimethoxy-1-methyl-1*H*-isochromen-3-yl)-phenol
- 5 4-Methoxy-3-(4-methoxy-phenyl)-7-trifluoromethoxy-1*H*-isochromene
- 4,7,8-Trimethoxy-3-(4-methoxy-phenyl)-1*H*-isochromene
- 10 6-Methoxy-3-phenyl-isochroman-4-ol
- 4,7-Dimethoxy-3-(4-methoxy-phenyl)-3-methyl-isochroman
- 3-(4-Hydroxy-phenyl)-7,8-dimethoxy-1-methyl-isochroman-4-ol
- 6-Methyl-3-phenyl-isochroman-4-ol
- 15 7,8-Dimethoxy-3-(4-methoxy-phenyl)-isochroman-4-ol
- 3-(4-Methoxy-phenyl)-3-methyl-7-trifluoromethoxy-isothiochroman-4-one
- 6-Methoxy-3-phenyl-isothiochroman-4-one
- 3-(4-Methoxy-phenyl)-3-methyl-7-trifluoromethoxy-isothiochroman-4-one
- 7-Methoxy-3-(4-methoxy-phenyl)-3-methyl-isothiochroman-4-one
- 20 3-(4-Hydroxy-phenyl)-7,8-dimethoxy-1-methyl-isothiochroman-4-one
- 3,6-Dimethyl-3-phenyl-isothiochroman-4-one
- 3-(4-Hydroxy-phenyl)-7,8-dimethoxy-isothiochroman-4-one
- 3-(4-Hydroxy-phenyl)-7,8-dimethoxy-3-methyl-isothiochroman-4-one
- 7-Fluoro-3-(4-methoxy-phenyl)-1*H*-isothiochromen-4-ol
- 25 7,8-Dimethoxy-3-(4-methoxy-phenyl)-1*H*-isothiochromen-4-ol
- 6-Methoxy-3-phenyl-isothiochroman-4-ol
- 4-Methoxy-3-(4-methoxy-phenyl)-7-trifluoromethoxy-isothiochroman
- 3-(4-Hydroxy-phenyl)-7,8-dimethoxy-1-methyl-isothiochroman-4-ol
- 30 3,6-Dimethyl-3-phenyl-isothiochroman-4-ol
- 7,8-Dimethoxy-3-(4-methoxy-phenyl)-isothiochroman-4-ol
- 3-(4-Trifluoromethoxy-phenyl)-7-trifluoromethyl-2,3-dihydro-1*H*-isoquinolin-4-one
- 35 7,8-Dimethoxy-3-(4-methoxy-phenyl)-3-methyl-2,3-dihydro-1*H*-isoquinolin-4-one
- 7,8-Dimethoxy-3-(4-methoxy-phenyl)-1,1,3-trimethyl-2,3-dihydro-1*H*-isoquinolin-4-one.
- 40

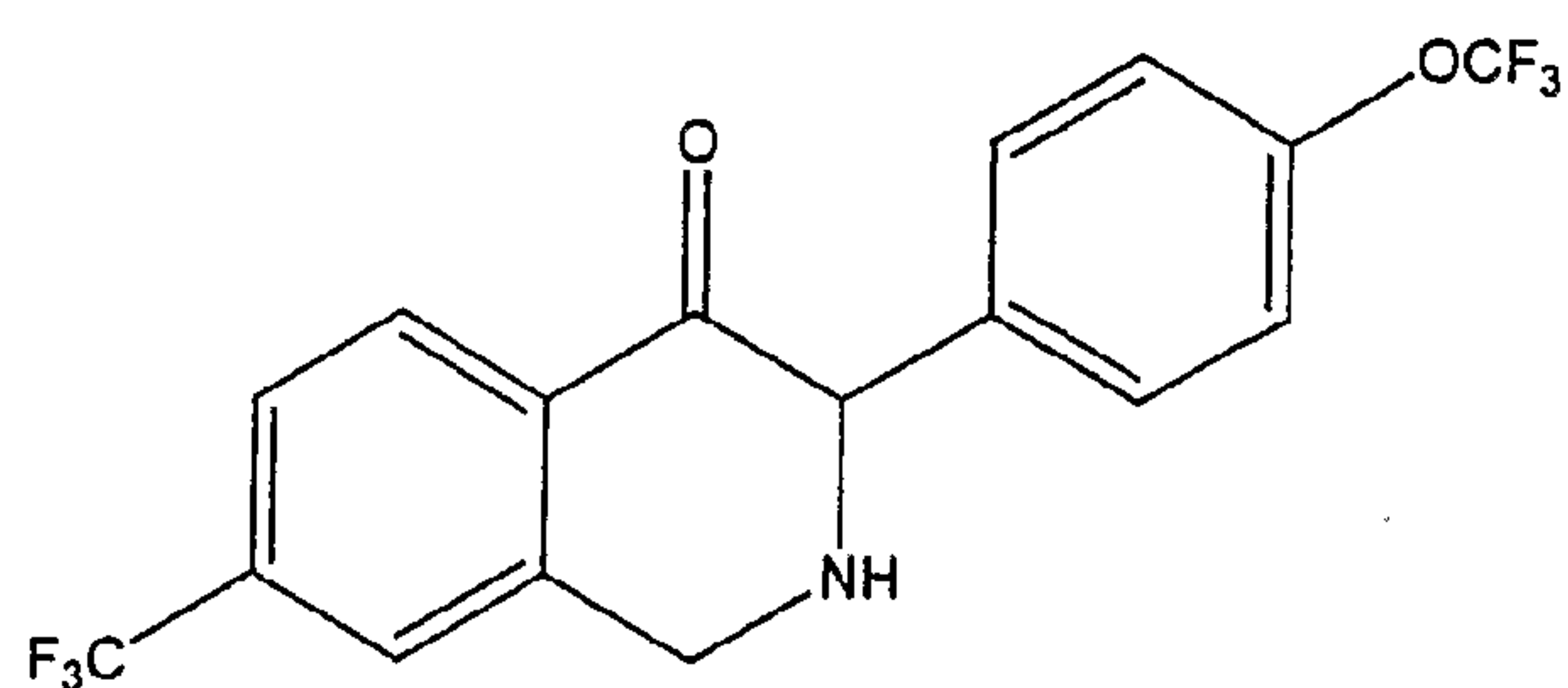
17. A compound according to claim 1 which in hydrochloride salt form is represented by the formula:



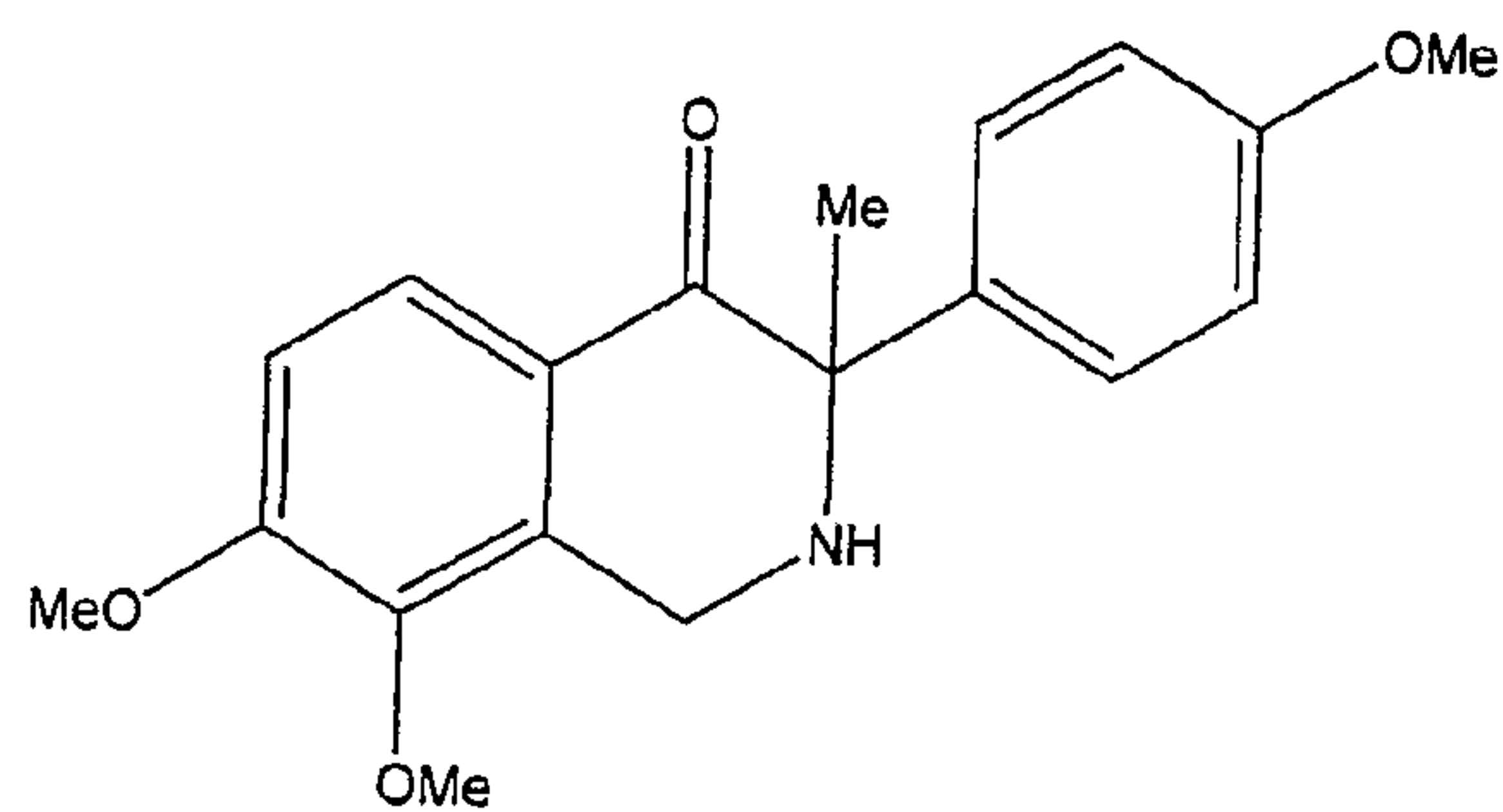
18. A compound according to claim 1 which in hydrochloride salt form is represented by the formula:



19. A compound according to claim 1 as represented by the formula:

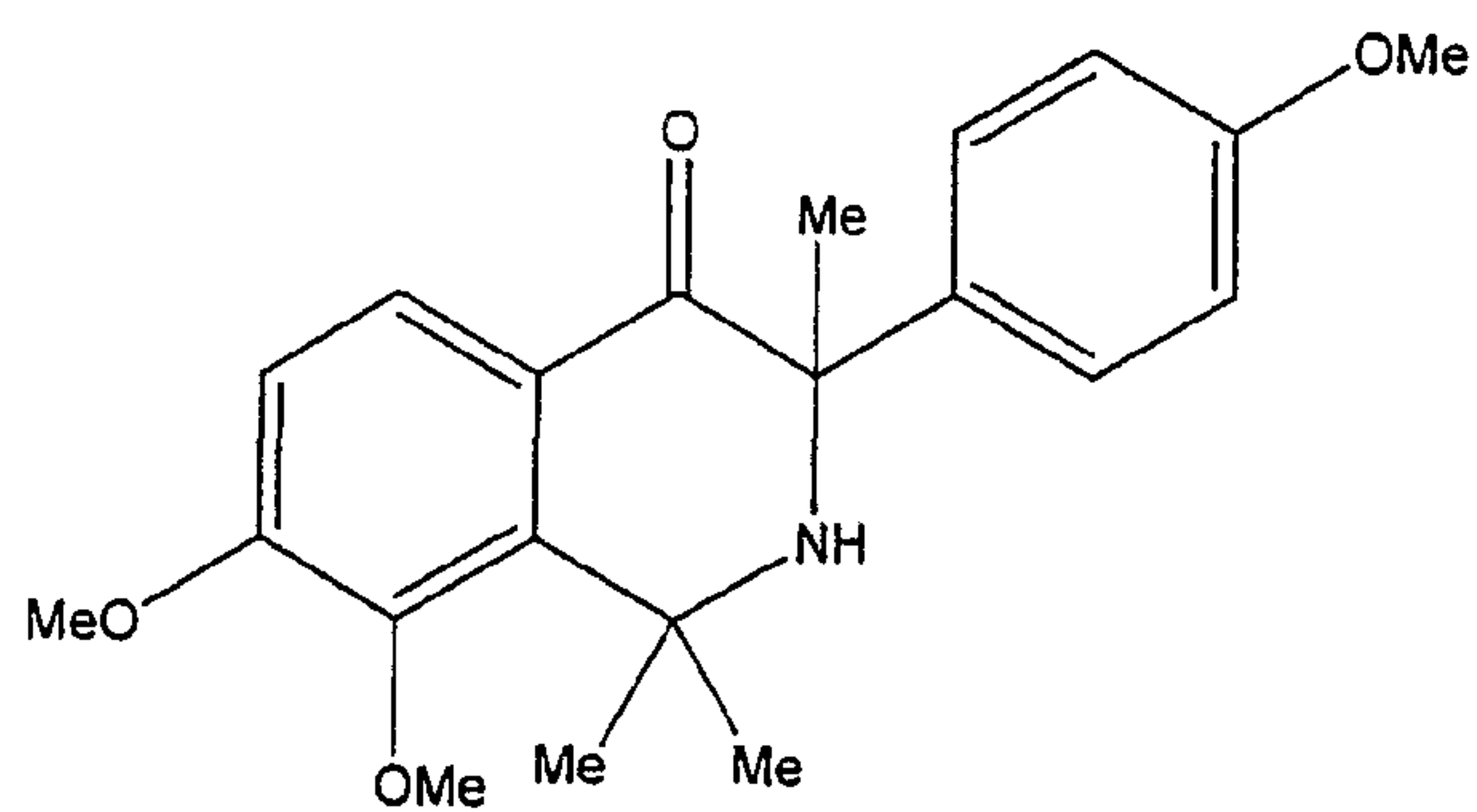


20. A compound according to claim 1 as represented by the formula:



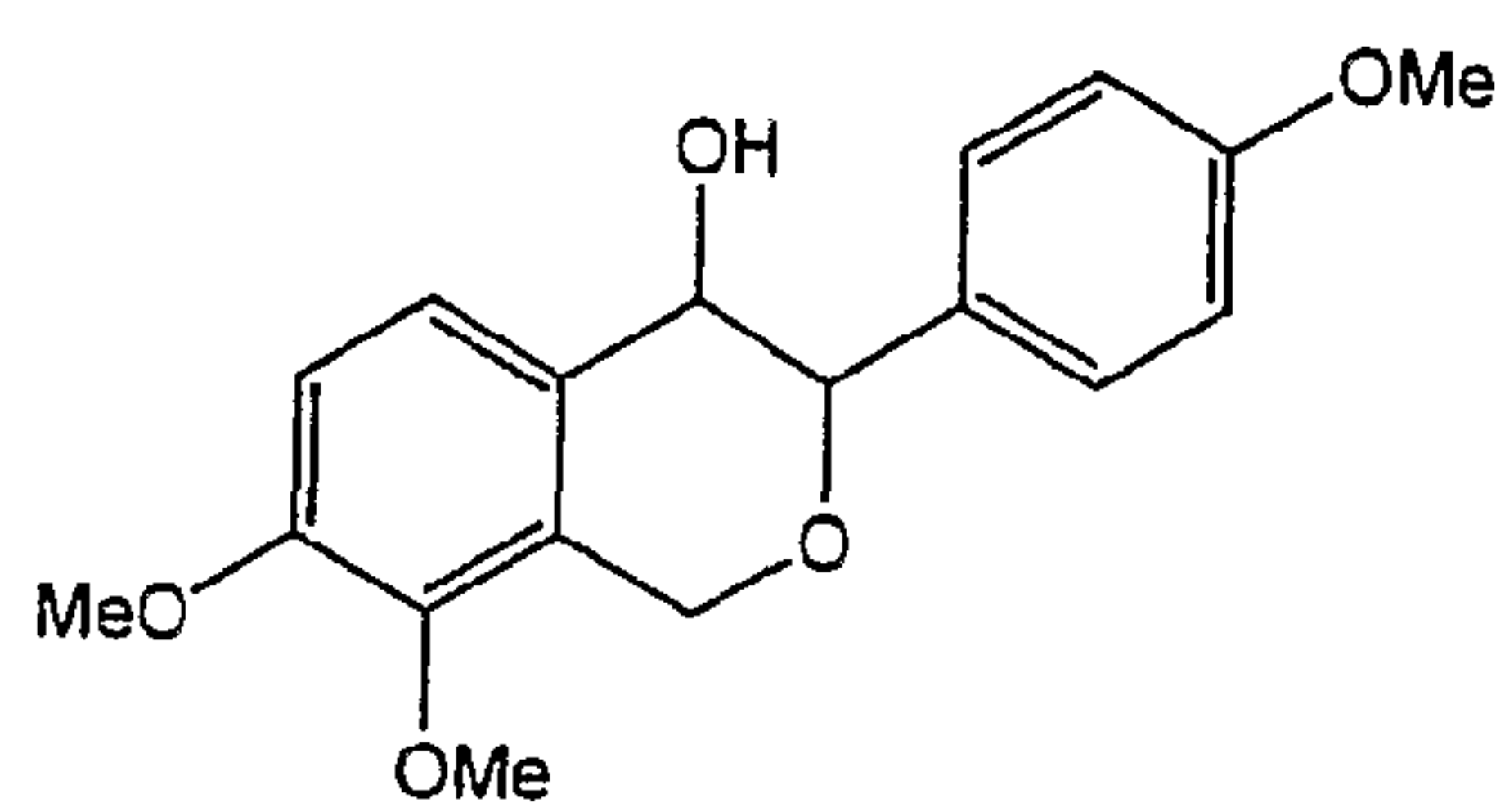
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21. A compound according to claim 1 as represented by the formula:



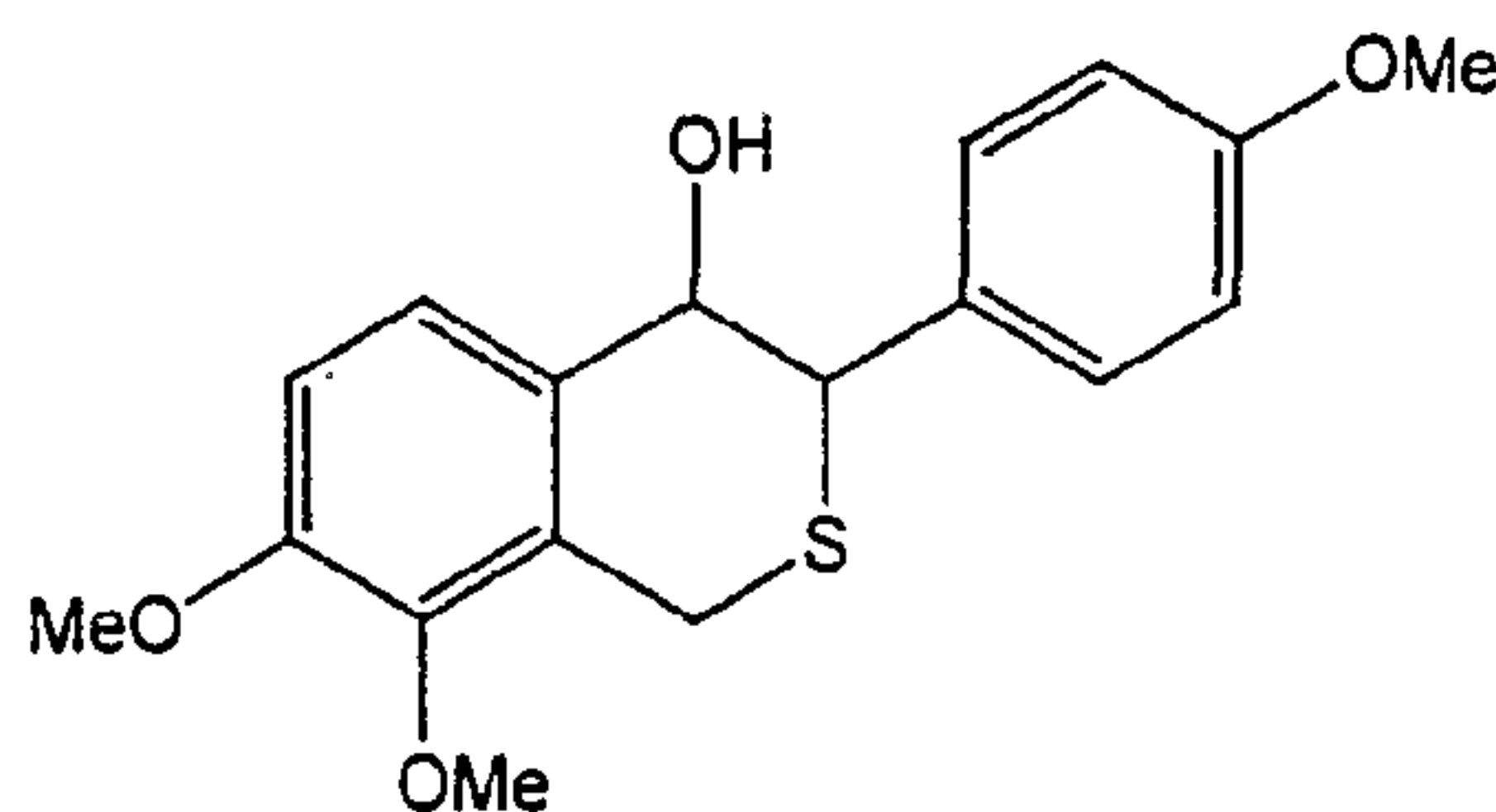
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22. A compound according to claim 1 as represented by the formula:



23. A compound according to claim 1 as represented by the formula:

5



24. A method of inhibiting the activity of at least one of TNF-alpha, IL-6, IL-10 and COX-2 which comprises administering to a mammal in need of such inhibition, an effective amount of a compound according to claim 1.

25. A method of treating inflammation, inflammatory diseases and other diseases mediated by at least one of TNF-alpha, IL-6, IL-10 and COX-2 which comprises administering to a mammal in need of such treatment, an effective amount of a compound according to claim 1.

26. A pharmaceutical composition in unit dosage form comprising a compound according to claim 1 together with a pharmaceutically acceptable carrier thereof.

27. A method of inhibiting the activity of at least one of TNF-alpha, IL-6, IL-10 and COX-2 which comprises administering to a mammal in need of such inhibition, an effective amount of a compound according to claim 16.

28. A method of treating inflammation, inflammatory diseases and other diseases mediated by at least one of TNF-alpha, IL-6, IL-10 and COX-2 which comprises administering to a mammal in need of such treatment, an effective amount of a compound according to claim 16.

29. A pharmaceutical composition in unit dosage form comprising a compound according to claim 16 together with a pharmaceutically acceptable carrier thereof.

Figure 1. Inhibition of TNF-alpha Induced Cell Killing

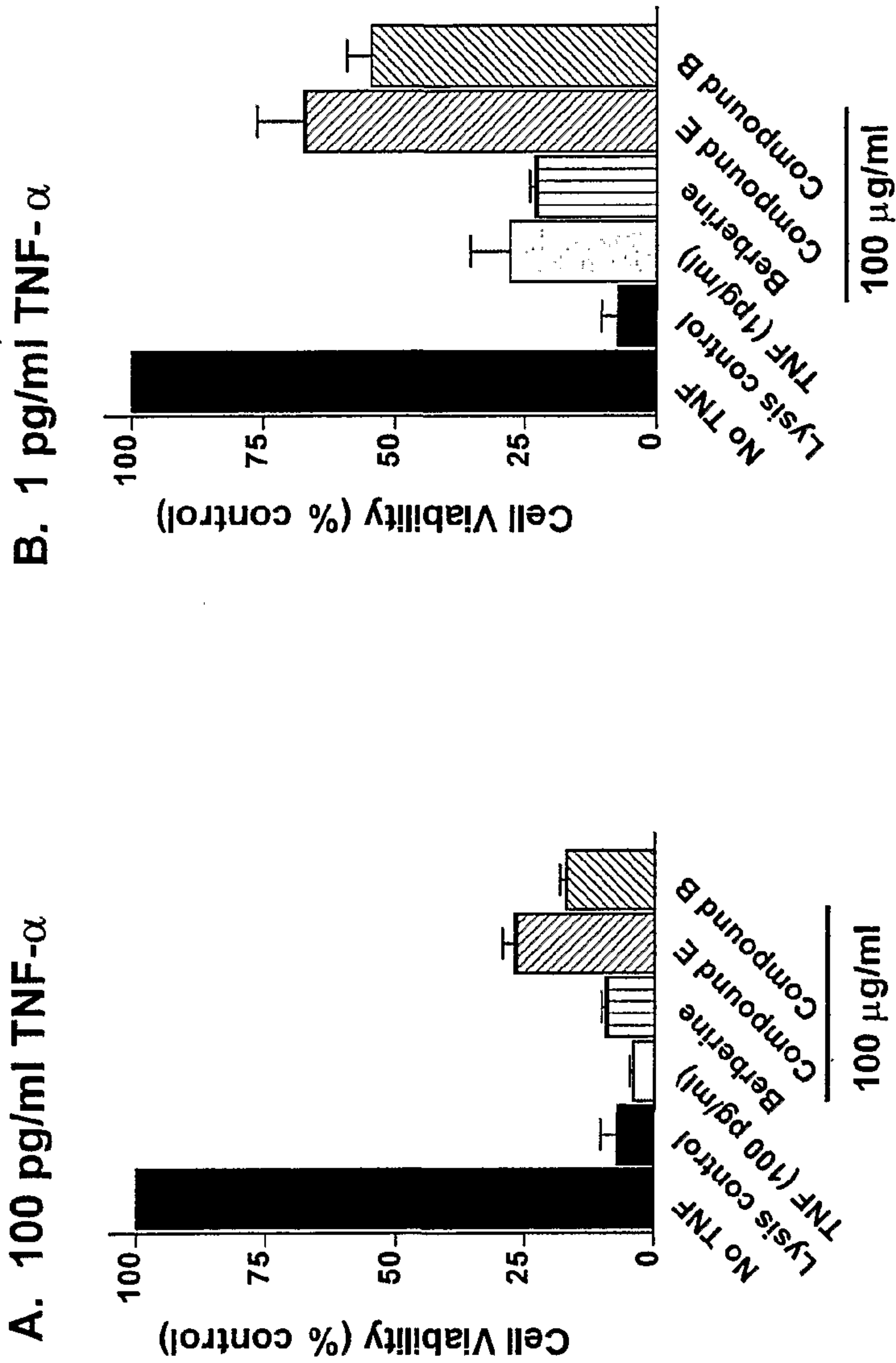


Figure 2. Dose Response of Inhibition of TNF-alpha Induced Cell Killing

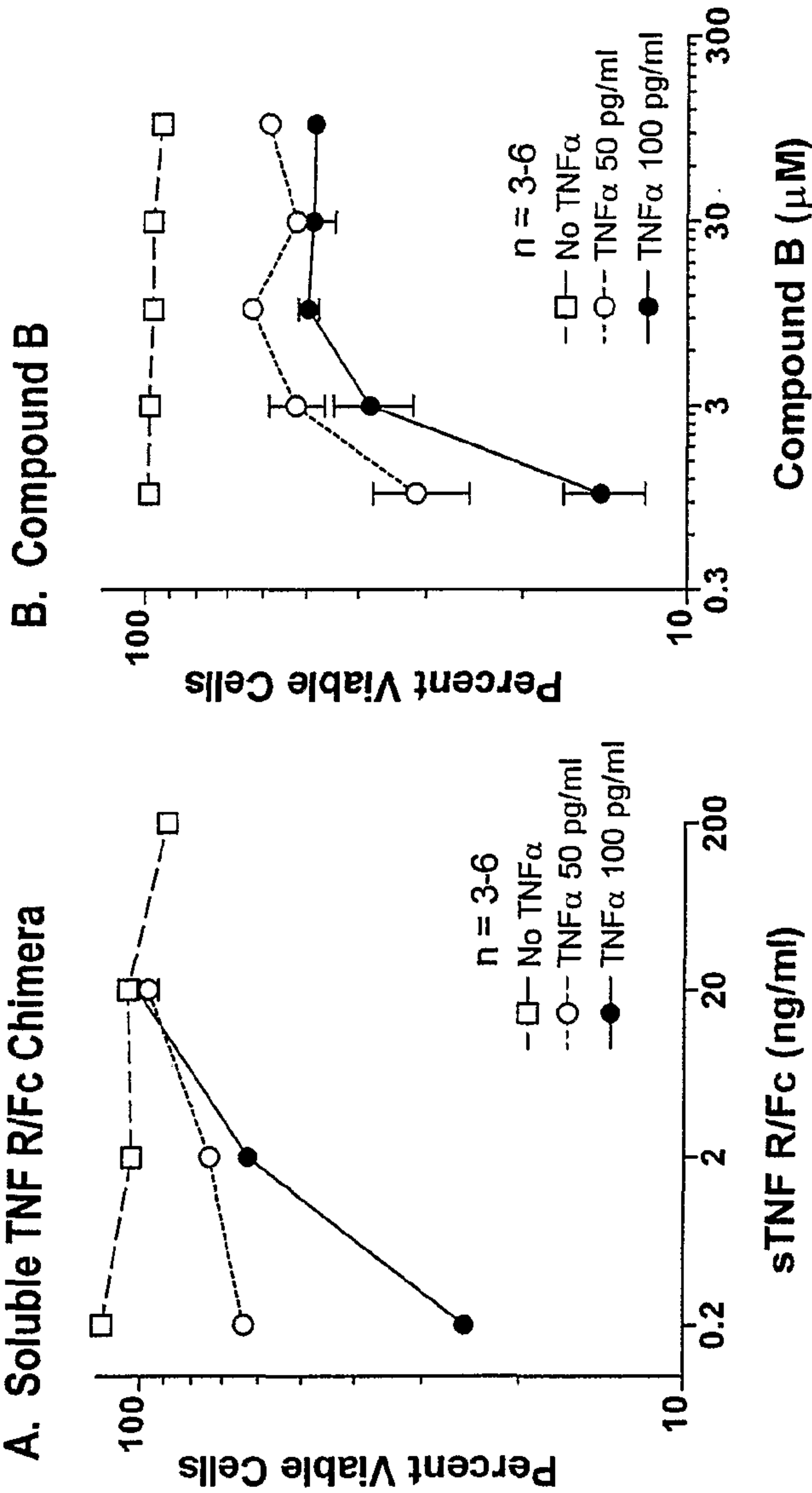


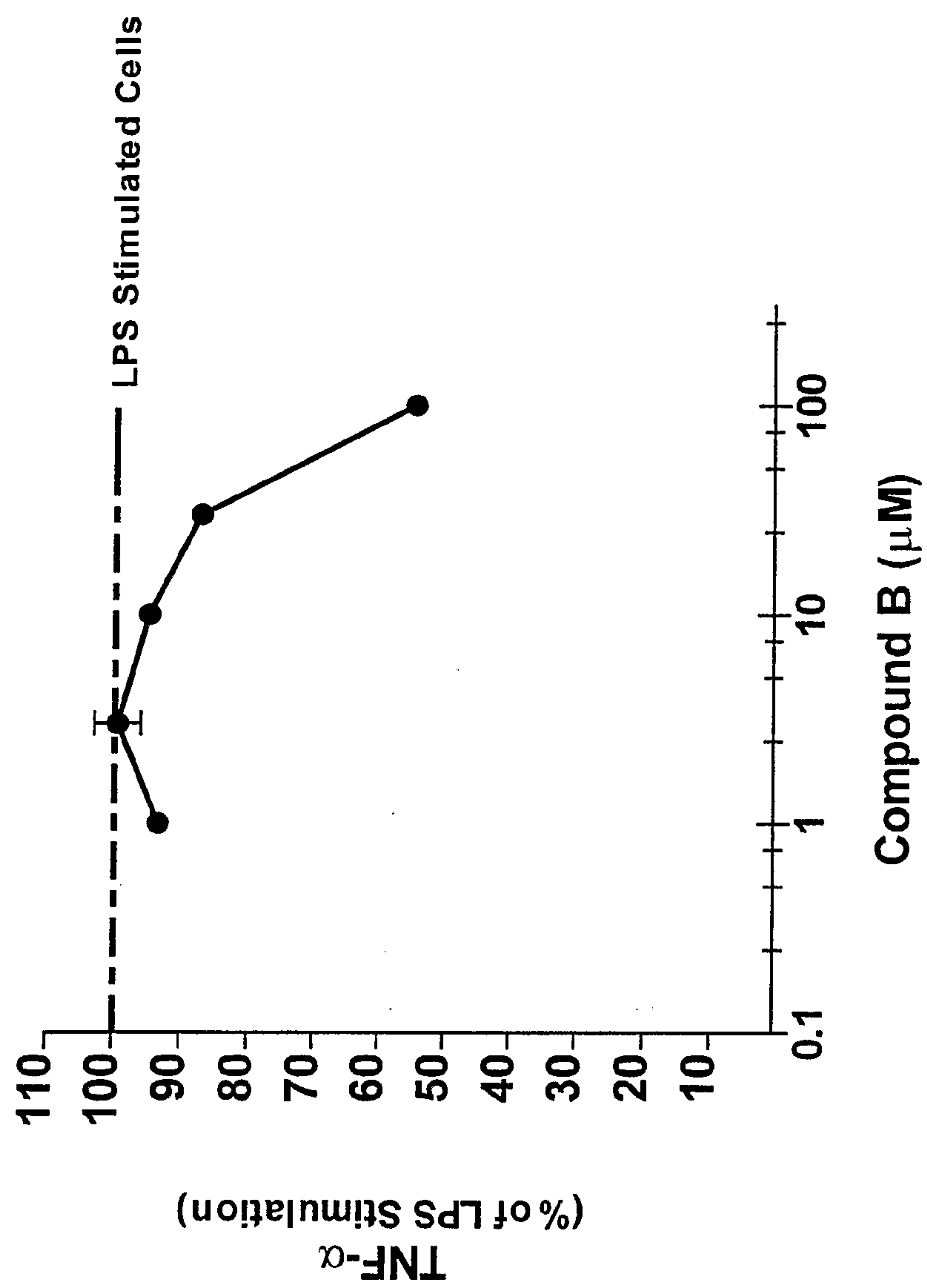
Figure 3. Inhibition of LPS-induced TNF-alpha Production

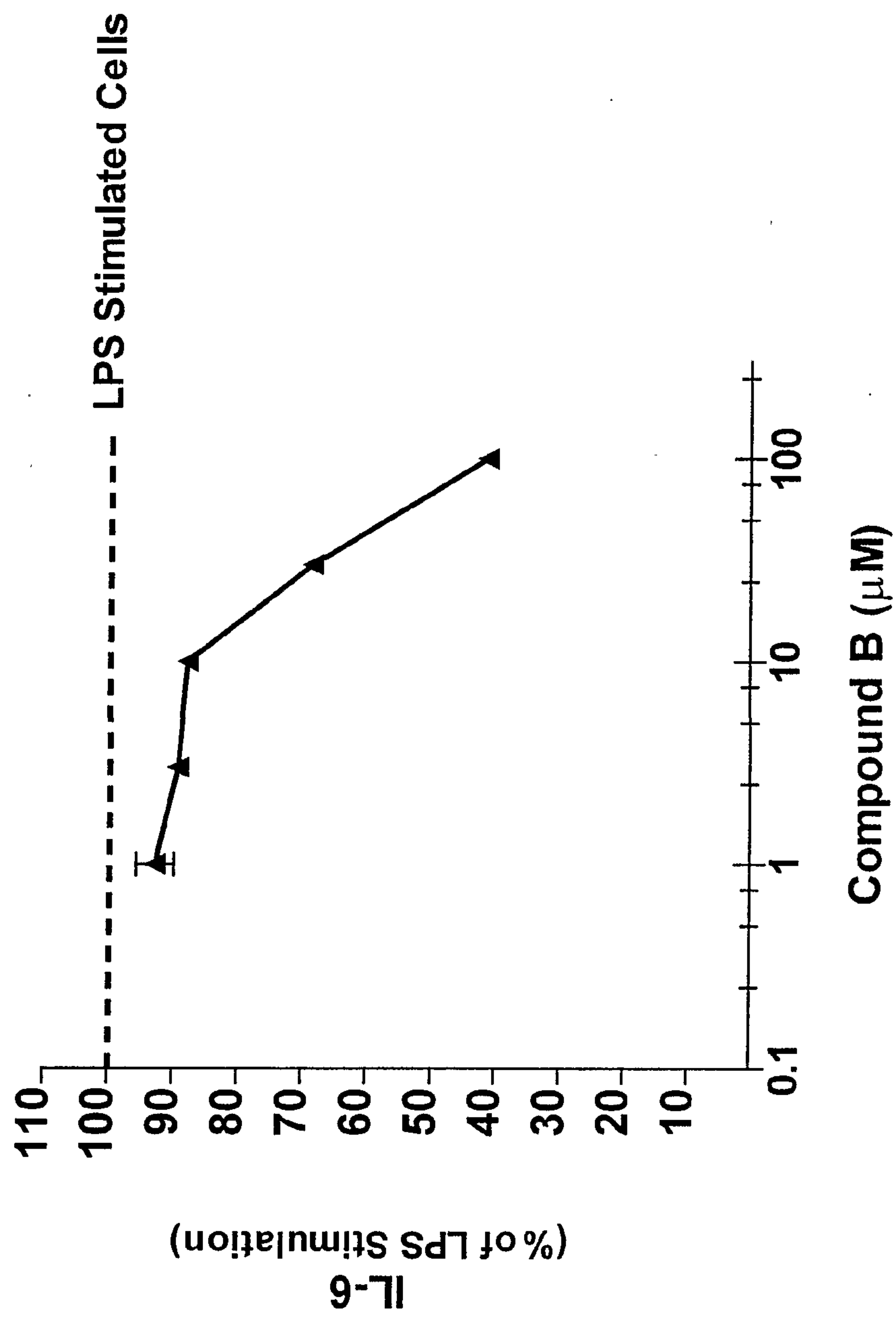
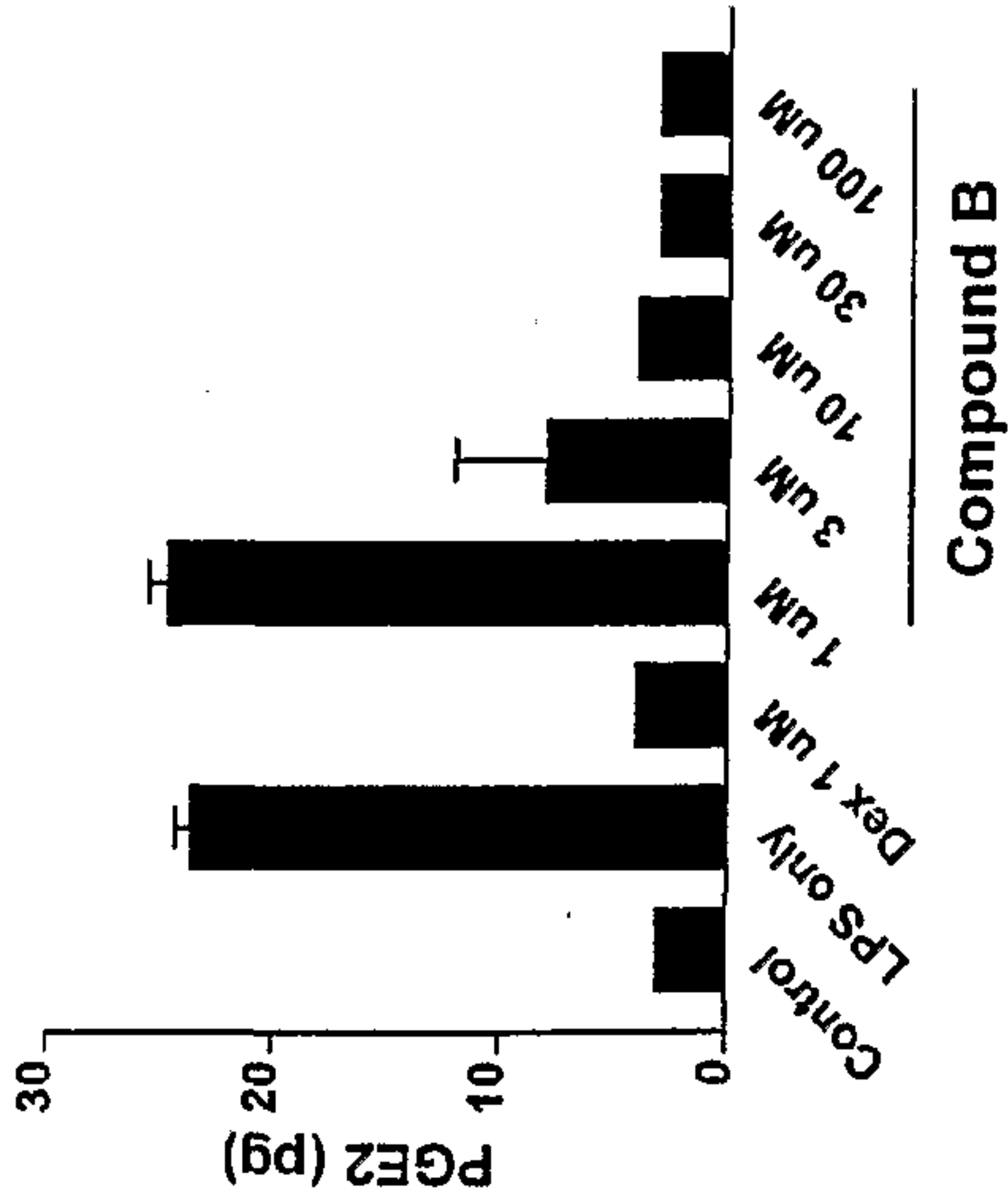
Figure 4. Inhibition of LPS-induced IL-6 Production

Figure 5. Selective Inhibition of LPS-induced COX-2 Activity

A. COX-2 Activity



B. COX-1 Activity

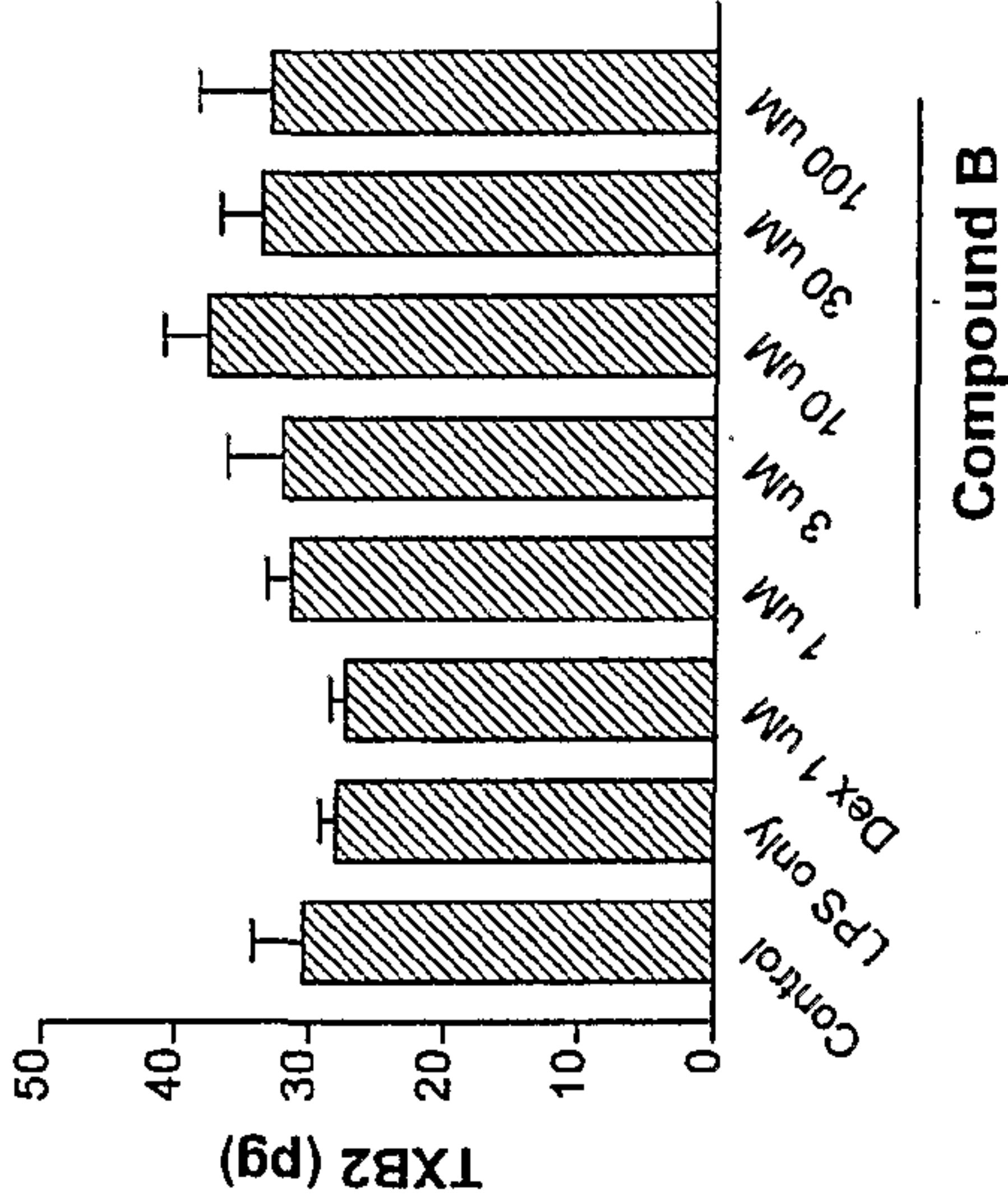


Figure 6. Suppression of Collagen-Induced Arthritis in Mice

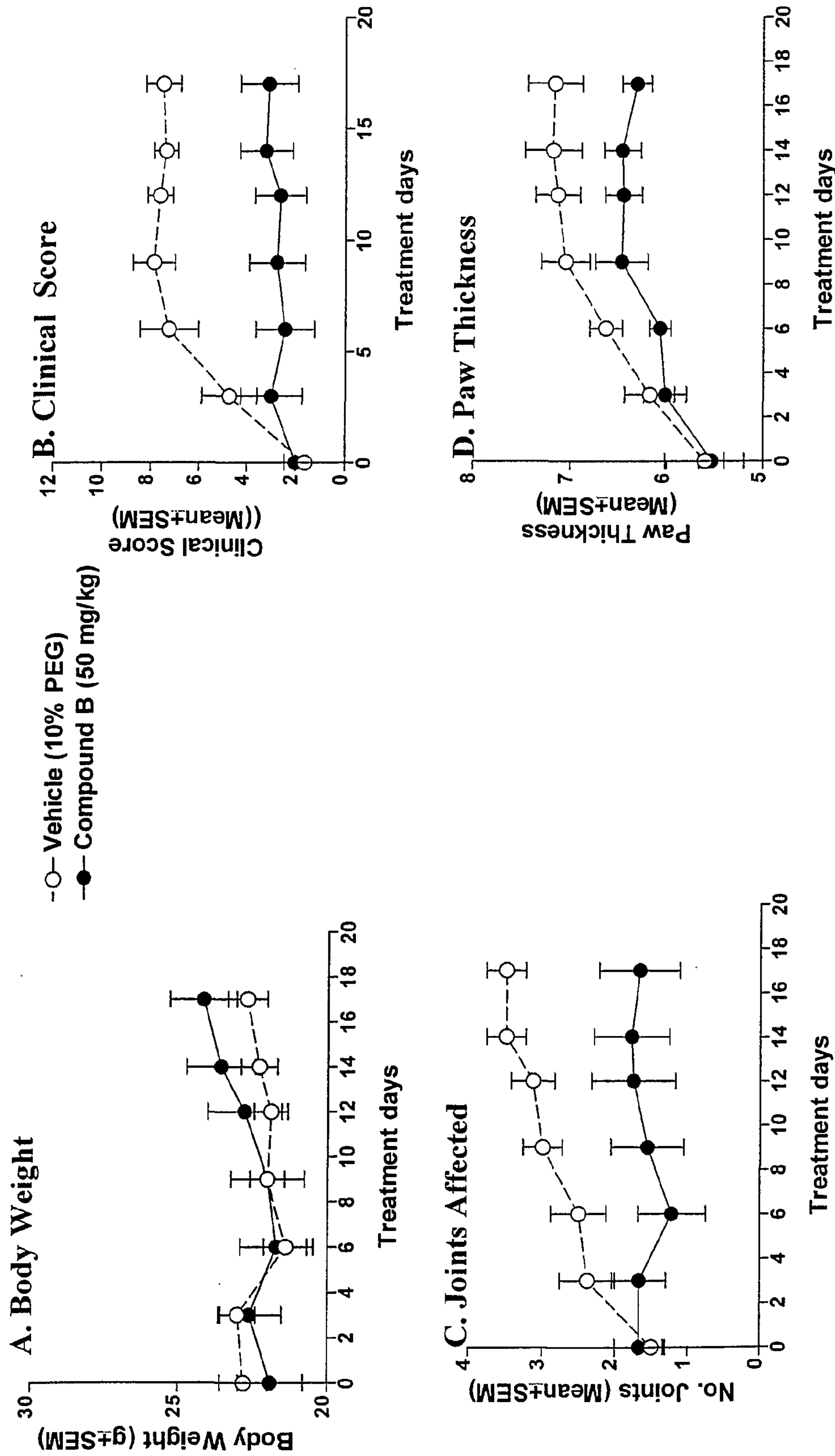


Figure 7. Inhibition of LPS-Induced IL-10 Production in PBMC

