CHALCONE DERIVATIVES AND THEIR USE TO TREAT DISEASES

This patent application claims priority to U.S. Provisional Patent Application Serial No. 60/342,034 filed December 19, 2001 and U.S. Provisional Patent Application Serial No. 60/386,482 filed June 5, 2002.

The present invention is in the field of novel chalcone derivatives, pharmaceutical compositions and methods for treating a variety of diseases and disorders, including inflammation and cardiovascular disease.

BACKGROUND OF THE INVENTION

Adhesion of leukocytes to the endothelium represents a fundamental, early event in a wide variety of inflammatory conditions, autoimmune disorders and bacterial and viral infections. Leukocyte recruitment to endothelium is mediated in part by the inducible expression of adhesion molecules on the surface of endothelial cells that interact with counterreceptors on immune cells. Endothelial cells determine which types of leukocytes are recruited by selectively expressing specific adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin. VCAM-1 binds to the integrin VLA-4 expressed on lymphocytes, monocytes, macrophages, eosinophils, and basophils but not neutrophils. This interaction facilitates the firm adhesion of these leukocytes to the endothelium. VCAM-1 is an inducible gene that is not expressed, or expressed at very low levels, in normal tissues. VCAM-1 is upregulated in a number of inflammatory diseases, including arthritis (including rheumatoid arthritis), asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation late and chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosis, inflammatory bowel diseases, autoimmune diabetes, diabetic retinopathy, rhinitis, ischemia-reperfusion injury, post-angioplasty restenosis, chronic obstructive pulmonary disease (COPD), glomerulonephritis, Graves disease, gastrointestinal allergies, conjunctivitis, atherosclerosis, coronary artery disease, angina and small artery disease.

Coronary heart disease (CHD), primarily as a result of atherosclerosis, remains the leading cause of death in industrialized countries. Atherosclerosis is a disease characterized by vascular inflammation, deposition of lipids in the arterial vessel wall and smooth muscle cell proliferation resulting in a narrowing of the vessel passages. In advanced stages of the disease atherosclerotic lesions can become unstable resulting in plaque rupture, thrombosis, myocardial infarction and ischemic heart disease. It is now well accepted that the initiating events in atherosclerosis are local injury to the arterial endothelium that results in the induction of VCAM-1 and recruitment of mononuclear leukocytes that express the integrin counterreceptor, VLA-4, (O'Brien, et al., *J. Clin. Invest.*, 92: 945-951, 1993). Subsequent conversion of leukocytes to foamy macrophages results in the synthesis of a wide variety of inflammatory cytokines, growth factors, and chemoattractants that help propagate formation of the mature atheromatous plaque by further inducing endothelial activation, leukocyte recruitment, smooth muscle cell proliferation, and extracellular matrix deposition. Pharmacological inhibition of VCAM-1 expression has been shown to inhibit atherosclerosis in several animal models (Sundell et al., *Circulation,* 100: 42, 1999). A monoclonal antibody against VCAM-1 has also been shown to inhibit neointimal formation in a mouse model of arterial wall injury (Oguchi, S., et al., *Arterioscler. Thromb. Vasc. Biol.*, 20: 1729-1736, 2000).

Asthma, which is increasing in prevalence and morbidity world-wide, is a chronic inflammatory disease characterized by lung eosinophilia and bronchial hyperreactivity. The interaction between VCAM-1 on lung endothelial cells and VLA-4, which is the integrin counterreceptor expressed on eosinophils, is thought to be important for selective eosinophil recruitment. Eosinophils have been considered an important effector cell in the pathogenesis of asthma and other allergic diseases. Activated eosinophils release proteins such as major basic protein (MBP) that have been demonstrated to induce bronchial hyperreactivity, one of the defining criteria of asthma (Bousquot, et al., *N. Engl. J. Med.*, 323: 1033-1039, 1990). It has been demonstrated that VCAM-1 is markedly upregulated on human bronchial vascular endothelium of subjects with asthma who have air flow limitation, when compared with subjects without asthma (Pilewski, et al., *Am. J. Respir. Cell Mol. Biol.*, 12, 1-3,1995; Ohkawara, Y., et al., *Am. J. Respir. Cell Mol. Biol.*, 12, 4-12, 1995; Gosset, P., et al., *Int. Arch. Allergy Immunol.* 106: 69-77, 1995; Hacken, N. H., et al., *Clin. Exp. Allergy*, 28 (12): 1518-1525, 1998). An elevation in serum soluble VCAM-1 levels has also been demonstrated in

patients undergoing a bronchial asthma attack compared with levels under stable conditions (Montefort, S., Koizumi, A., *Clin. Exp. Immunol.,* 101: 468-73, 1995). Several animal studies further demonstrate a spatial and temporal association between VCAM-1 and asthma. In a mouse model of allergic asthma, VCAM-1 expression was shown to be induced by allergen challenge, and administration of an anti-VCAM-1 antibody was effective in inhibiting eosinophil infiltration that occurred in this model (Metzger, W. J., et al., *J. Allergy Clin. Immunol.*, 93: 183, 1994). Further evidence for the importance of VCAM-1 in allergic asthma comes from work in IL-12 knockout mice. IL-12 knockout mice had fewer eosinophils and VCAM-1 expression than wildtype mice; however, administration of recombinant IL-12 at the time of ova sensitization and challenge restored lung VCAM-1 expression and eosinophilia (Wang, S., et al., *J. Immunol.,* 166:2741-2749, 2001). There are several examples where blocking the integrin receptors for VCAM-1 have had positive effects on animal models of asthma (Rabb et al., *Am. J. Respir. Care Med.* 149: 1186-1191, 1994; Abraham, W, et al., *Am. J. Respir. Crit. Care Med.* 156: 696-703. 1997) further demonstrating the importance of VCAM-1/VLA-4 interactions in allergic inflammation. Eosinophils are also important effector cells in allergic rhinitis. VCAM-1 has been demonstrated to be upregulated 24 hrs after nasal allergen provocation in patients with seasonal allergic rhinitis but not in normal subjects (Braunstahl, G. J., et al., *J. Allergy Clin. Immunol.*, 107: 469-476, 2001).

Rheumatoid arthritis (RA) is a clinical syndrome of unknown cause characterized by symmetric, polyarticular inflammation of synovial-lined joints. The role of adhesion molecules in the pathogenesis of RA has also been well documented, and VCAM-1 expression on synovial fibroblasts is a clinical hallmark of RA (Li, P., et al., *J. Immunol.* 164: 5990-7, 2000). VLA-4/VCAM-1 interactions may be the predominant mechanism for recruitment of leukocytes to the synovium (Dinther-Janssen, et al., *J. Immunol.* 147: 4207-4210, 1991; Issekeutz and Issekeutz, *Clin. Immunol. Immunopathol.* 61:436-447, 1991; Morales-Ducret et al., *J. Immunol.* 149:1424-1431, 1992; Postigo et al., *J. Clin. Invest.* 89:1445-1452, 1992; Matsuyama, T., et al, *Hum. Cell*, 9: 187-192,1996). In support of this, increased VCAM-1 expression has been found in RA synovial tissue compared with osteoarthritis and control tissue (Wilkinson et al., *Lab. Invest.* 69:82-88, 1993; Furuzawa-Carballeda, J., et al., *Scand. J. Immunol.* 50: 215-222; 1999). Soluble VCAM-1 is higher in RA patients than in control subjects (Kolopp-Sarda, M. N., et al., *Clin. Exp. Rheumatol.* 19: 165-70, 2001). Soluble

VCAM-1 has been shown to be chemotactic for T cells (Kitani, A., et al., *J. Immun.* 161: 4931-8, 1998), and in addition to being a possible diagnostic marker for RA, may contribute to its pathogenesis by inducing migration and recruitment of T cells. VCAM-1 expressed on fibroblast-like synoviocytes has also been implicated in enhanced survival of activated synovial fluid B cells (Marinova, Mutafcheia, L., *Arthritis Rheum.* 43: 638-644, 2000) that may further contribute to RA pathogenesis.

Chronic inflammation and accompanying vascular complications and organ damage characterize systemic lupus erythematosis (SLE). Recent studies suggest that VCAM-1 plays a role in SLE. Expression of VCAM-1 is increased on dermal vessel endothelial cells in patients with active systematic lupus erythematosus (Jones, S. M., *British J. Dermatol.* 135: 678-686, 1996) and correlates with increased disease severity (Belmont et al., *Arthritis Rheum.* 37:376-383, 1994). SLE muscle samples with perivascular infiltrate have greater endothelial cell expression of VCAM-1 compared with SLE patients without a perivascular infiltrate or with control samples (Pallis et al., *Ann. Rheum. Dis.* 52:667-671, 1993). Increased expression of VCAM-1 has also been demonstrated in kidneys of lupus-prone MRL/lpr mice compared to nonautoimmune strains and its expression increased with disease severity (McHale, J. F., et al., *J. Immunol.* 163: 3993-4000, 1999). VCAM-1 expression on mesangial cells *in vitro* can be stimulated by IL-1, TNF-α, and INFγ exposure as well as by anti-endothelial cell IgG fraction and anti-DNA autoantibodies from SLE patients (Wuthrich, *Kidney Int.* 42: 903-914, 1992; Papa, N. D., et al., *Lupus*, 8: 423-429, 1999; Lai, K. N., et al., *Clin Immunol Immunopathol*, 81: 229-238, 1996). Furthermore, soluble VCAM-1 is higher in SLE patients than in normal subjects (Mrowka, C., et al., *Clin. Nephrol.* 43: 288-296, 1995; Baraczka, K., et al., *Acta. Neurol. Scand.* 99: 95-99, 1999; Kaplanski, G., et al., *Arthritis Rheumol.* 43: 55-64, 2000; Ikeda, Y., *Lupus*, 7: 347-354, 1998) and correlates with disease activity (Scudla, V., *Vnitr. Lek.*, 43: 307-311, 1997).

Increased VCAM-1 expression has also been demonstrated in solid organ transplant rejection. Acute transplant rejection occurs when the transplant recipient recognizes the grafted organ as "non-self "and mounts an immune response characterized by massive infiltration of immune cells, edema, and hemorrage that result in the death of the transplanted organ. Acute rejection occurs in a matter of hours or days and has been correlated with increased levels of

VCAM-1 in tissues and in plasma (Tanio et al., *Circulation,* 89:1760-1768, 1994; Cosimi et al., *J. Immunol.* 144: 4604-4612, 1990; Pelletier, R., et al., *Transplantation,* 55: 315, 1992). A monoclonal antibody to VCAM-1 has been shown to inhibit cardiac allograft rejection in mice (Pelletier, R., *J. Immunol.*, 149: 2473-2481, 1992; Pelletier, R., et al., *Transplantation Proceedings*, 25: 839-841, 1993; Orosz, C. G., et al., *J. Heart and Lung Transplantation*, 16: 889-904, 1997) and when given for 20 days can cause complete inhibition of rejection and long-term graft acceptance (Orosz C. G., et al., *Transplantation*, 56: 453-460, 1993). Chronic graft rejection also known as allograft vasculopathy is distinct from acute transplant rejection and is a leading cause of late graft loss after renal and heart transplantation. Histologically it is characterized by concentric neointimal growth within vessels that is largely due to smooth muscle migration and proliferation. It is thought to be the result of endothelial damage brought about by several factors including: ischemia-reperfusion injury, immune complexes, hypertension, hyperlipidemia and viruses. All of these factors have been associated with induction of VCAM-1 in endothelial cells. There is also a strong correlation of soluble and tissue VCAM-1 levels with chronic rejection (Boratynska, *M.,. Pol. Arch. Med. Wewn*, 100: 410-410, 1998; Zembala, M., et al., *Ann. Transplant.* 2: 16-9, 1998; Solez K., et al., *Kidney International.*, 51: 1476-1480, 1997; Koskinen P. K., et al., *Circulation*, 95: 191-6, 1997).

Multiple sclerosis is a common demyelinating disorder of the central nervous system, causing patches of sclerosis (plaques) in the brain and spinal cord. It occurs in young adults and has protean clinical manifestations. It is well documented that VCAM-1 is expressed on brain microvascular endothelial cells in active lesions of multiple sclerosis (Lee S. J., et al., *J. Neuroimmunol.,* 98: 77-88, 1998). Experimental therapy of experimental autoimmune encephalomyelitis, which is an animal model for multiple sclerosis, using antibodies against several adhesion molecules, including VCAM-1, clearly shows that adhesion molecules are critical for the pathogenesis of the disease (Benveniste et al., *J. Neuroimmunol.* 98:77-88, 1999). A time and dose dependent expression of VCAM-1 and release of soluble VCAM-1 were detected in cultures of human cerebral endothelial cells induced by TNFα, but not in peripheral blood mononuclear cells (Kallmann et al., *Brain,* 123:687-697, 2000). Clinical data also show that adhesion molecules in blood and cerebrospinal fluid are up-regulated throughout the clinical spectrum of multiple sclerosis (Baraczka, K., et al., *Acta. Neurol. Scand.* 99: 95-99, 1999; Reickmann, P., et al., *Mult. Scler.*, 4: 178-182, 1998; Frigerio, S., et al., *J.*

Neuroimmunol., 87: 88-93, 1998) supporting the notion that therapies which interfere with cell adhesion molecules such as VCAM-1 may be beneficial in modifying this disease (Elovaara et al., *Arch. Neurol.* 57:546-551, 2000).

Diabetes mellitus is a metabolic disease in which carbohydrate utilization is reduced and that of lipid and protein is enhanced. Evidence has accumulated that increased levels of adhesion molecules may play a functional pathophysiological role in diabetes (Wagner and Jilma, *Hormone and Metabolic Research,* 29: 627-630, 1997; Kado, S., *Diabetes Res. Clin. Pract.*, 46: 143-8, 1999). It is caused by an absolute or relative deficiency of insulin and is characterized by chronic hyperglycemia, glycosuria, water and electrolyte loss, ketoacidosis, and coma. Elevated circulating adhesion molecules including VCAM-1 have been detected in patients with diabetes and in experimental models of diabetes in animals (Lorini et al., *Hormone Research,* 48: 153, 1997; Otsuki et al., *Diabetologia,* 40: A440, 1997; Hart et al., *FASEB J.* 11:A340, 1997; Albertini et al., *Diabetologia,* 39: A240, 1996; Wagner et al., *Diabetologia,* 39: A205, 1996; Enghofer et al., *Diabetologia,* 39: A97, 1996; Koga M., *Diabet. Med.*, 15: 661-667, 1998). In addition, complications of diabetes often include peripheral vasculopathies such as diabetic retinopathy and diabetic nephropathy. It is believed that adhesion of leukocytes to the peripheral vasculature plays a central role in the vasculopathies often associated with diabetes.

Crohn's disease, also known as regional enteritis, is a subacute chronic inflammatory condition of unknown cause, involving the internal ileum and less frequently other parts of the gastrointestinal tract. It is characterized by patchy deep ulcers that may cause fistulas, and narrowing and thickening of the bowel by fibrosis and lymphocytic infiltration. Ulcerative colitis is a chronic disease of unknown cause characterized by ulceration of the colon and rectum, with rectal bleeding, mucosal crypt abscesses, inflammatory pseudopolyps, abdominal pain, and diarrhea. It has been reported that serum VCAM-1 reflects the grade of intestinal inflammation in patients with Crohn's disease or ulcerative colitis (Jones, et al., *Gut*, 36: 724-30, 1995; Goggins et al., *Gastroenterology,* 108: A825, 1995; Goeke and Manns, *Gastroenterology,* 106: A689, 1994; Goeke et al., *J. Gasterokenterol.* 32:480-486, 1997; Loftus et al., *Gastroenterology,* 108: A684, 1995; Tahami et al., *Gastroenterology,* 118: A344, 2000).

Antibodies to VCAM-1 have been shown to ameliorate experimentally-induced colitis in mice (Soriano, A., *Lab. Invest.* 80: 1541-1551, 2000).

Psoriasis is a chronic skin disease characterized by erythematous scaling plaques as a result of keratinocyte hyperplasia, influx of immune cells and endothelial activation (Nickoloff, B. J., et al., *J. Invest. Dermatol.*, 127: 871-884, 1991). VCAM-1 is upregulated in psoriatic skin as compared to normal skin (Groves, R. W., *J. Am. Acad. Dermatol.*, 29: 67-72, 1993; Uyemura, K., et al., *J. Invest. Dermatol.* 101: 701-705, 1993) and levels of circulating VCAM-1 correlate with disease activity (Schopf, R. E., *Br. J. Dermatol.*, 128: 34-7, 1993).

U.S. Patent Nos. 5,750,351; 5,807,884; 5,811,449; 5,846,959; 5,773,231, and 5,773,209 to Medford, et al., as well as the corresponding WO 95/30415 to Emory University indicate that polyunsaturated fatty acids ("PUFAs") and their hydroperoxides ("ox-PUFAs"), which are important components of oxidatively modified low density lipoprotein (LDL), induce the expression of VCAM-1, but not intracellular adhesion molecule-1 (ICAM-1) or E-selectin in human aortic endothelial cells, through a mechanism that is not mediated by cytokines or other noncytokine signals. This is a fundamental discovery of an important and previously unknown biological pathway in VCAM-1 mediated immune responses. As non-limiting examples, linoleic acid, linolenic acid, arachidonic acid, linoleyl hydroperoxide (13-HPODE) and arachidonic hydroperoxide (15-HPETE) induce cell-surface gene expression of VCAM-1 but not ICAM-1 or E-selectin. Saturated fatty acids (such as stearic acid) and monounsaturated fatty acids (such as oleic acid) do not induce the expression of VCAM-1, ICAM-1 or E-selectin.

WO 98/51662, filed by AtheroGenics, Inc. and listing as inventors Russell M. Medford, Patricia K. Somers, Lee K. Hoong, and Charles Q. Meng, claims priority to provisional application U.S.S.N. 60/047,020, filed on May 14, 1997. This application discloses the use of a broad group of compounds as cardiovascular protectants that exhibit at least one, and sometimes a composite profile, of reducing cholesterol, lowering LDL, and inhibiting the expression of VCAM-1.

U.S. Patent No. 5,155,250 to Parker, et al. discloses that 2,6-dialkyl-4-silylphenols are antiatherosclerotic agents. The same compounds are disclosed as serum cholesterol lowering agents in PCT Publication No. WO 95/15760, published on June 15, 1995. U.S. Patent No.

5,608,095 to Parker, et al. discloses that alkylated-4-silyl-phenols inhibit the peroxidation of LDL, lower plasma cholesterol, and inhibit the expression of VCAM-1, and thus are useful in the treatment of atherosclerosis.

WO 98/51289, which claims priority to provisional application U.S.S.N. 60/047,020, filed on May 14, 1997 by Emory University listing Patty Somers as sole inventor, discloses the use of a group of compounds as cardiovascular protectants and antiinflammatory agents which exhibit at least one, and sometimes a composite profile, of reducing cholesterol, lowering LDL, and inhibiting the expression of VCAM-1 and thus can be used as antiinflammatory and cardivascular treating agents.

U.S. Patent Nos. 5,380,747; 5,792,787; 5,783,596; 5,750,351; 5,821,260; 5,807,884; 5,811,449; 5,846,959; 5,877,203; and 5,773,209 to Medford, et al., teach the use of dithiocarbamates of the general formula A-SC(S)-B for the treatment of cardiovascular and other inflammatory diseases. Examples include sodium pyrrolidine-N-carbodithioate, tri-sodium N,N-di(carboxymethyl)-N-carbodithioate, and sodium N,N-diethyl-N-carbodithioate. The patents teach that the compounds inhibit the expression of VCAM-1.

WO 98/23581 discloses the use of benzamidoaldehydes and their use as cysteine protease inhibitors.

WO 97/12613 of Cornicelli et al. discloses compounds for the inhibition of 15-lipogenase to treat and prevent inflammation or atherosclerosis. Compounds disclosed include benzopyranoindole, benzimidazole, catacholes, benzoxadiazines, benzo[a]phenothiazine, or related compounds thereof.

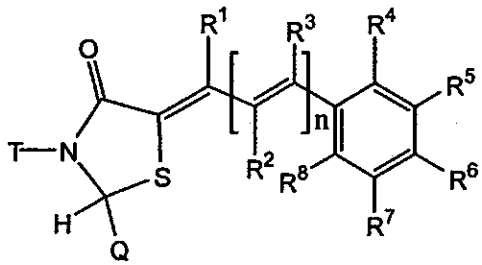
Japanese Patent No. 06092950 to Masahiko et al. discloses preparation of epoxy compounds wherein electron deficient olefins such as acylstyrene derivatives, styrene derivatives, and cyclohexenone derivatives are efficiently oxidized by a hydrogen peroxide derivative in the presence of a primary or secondary amine in an organic solvent to give said epoxides which are useful intermediates for pharmaceutical and flavoring materials.

U.S. Patent No. 5,217,999 to Levitzki et al. discloses substituted styrene compound as a method of inhibiting cell proliferation.

Chalcone (1, 3-bis-aromatic-prop-2-en-1-ones) compounds are natural products related to flavonoids. WO 99/00114 (PCT/DK98/00283) discloses the use of certain chalcones, 1,3-bis-aromatic-propan-1-ones (dihydrochalcones), and 1,3-bisaromatic-prop-2-yn-1-ones for the preparation of pharmaceutical compositions for the treatment of prophylaxis of a number of serious diseases including i) conditions relating to harmful effects of inflammatory cytokines, ii) conditions involving infection by Helicobacter species, iii) conditions involving infections by viruses, iv) neoplastic disorders, and v) conditions caused by microorganisms or parasites.

WO 00/47554 filed by Cor Therapeutics describes a broad class of substituted unsaturated compounds for use as antithrombotic agents.

WO 96/20936 (PCT/KR95/00183) discloses thiazolidin-4-one derivatives of the formula:



which act as PAF antagonists or 5-lipoxygenase inhibitors. The compounds are used in the prevention and treatment of inflammatory and allergic disorders mediated by platelet-activating factor and /or leukotrienes.

U.S. Patent No. 4,085,135 discloses 2'-(carboxymethoxy)-chalcones with antigastric and antiduodenal ulcer activities.

U.S. Patent No. 5,744,614 to Merkle et al. discloses a process for preparing 3,5-diarylpyrazoles and various derivatives thereof by reacting hydrazine hydrate with 1,3-diarylpropenone in the presence of sulfuric acid and an iodine compound.

U.S. Patent No. 5,951,541 to Wehlage et al. discloses the use of salts of aromatic hydroxy compounds, such as (hydroxyaryl)alkenone salts, as brighteners in aqueous acidic electroplating baths. In addition the invention discloses that such compounds have a lower

vapor pressure than the known brighteners, as a single substance and in the electroplating baths,in order to avoid losses of substance. They also have high water solubility properties.

Japanese Patent No. 07330814 to Shigeki et al. discloses benzylacetophenone compounds as photoinitiator compounds.

Japanese Patent No. 04217621 to Tomomi discloses siloxane chalcone derivatives in sunscreens.

U.S. Patent No. 4,085,135 to Kyogoku et al. discloses a process for preparation of 2'-(carboxymethoxy)-chalcones having antigastric and anti duodenal activities with low toxicity and high absorptive ratio in the body. This patent suggests that the high absorptive ratio in the body is due to the 2'-carboxymethoxy group attached to the chalcone derivative.

U.S. Patent No. 4,855,438 discloses the process for preparation of optically active 2-hydroxyethylazole derivatives which have fungicidal and plant growth-regulating action by reacting an α-β-unsaturated ketone which could include a chalcone or a chalcone derivative with an enantiomerically pure oxathiolane in the presence of a strongly basic organometallic compound and at temperatures ranging from -80 to 120 °C.

European Patent No 307762 assigned to Hofmann-La Roche discloses substituted phenyl chalcones.

E. Bakhite et al. in J. Chem. Tech. Biotech. 1992, 55, 157-161, have disclosed a process for the preparation of some phenyloxazole derivatives of chalcone by condensing 5-(*p*-acetylphenyl)-2-phenyloxazole with aromatic aldehydes.

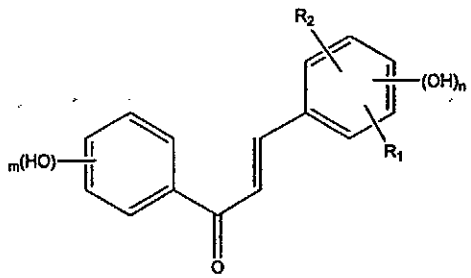
Herencia, et al., in Synthesis and Anti-inflammatory Activity of Chalcone Derivatives, *Bioorganic & Medicinal Chemistry Letters* 8 (1998) 1169-1174, discloses certain chalcone derivatives with anti-inflammatory activity.

Hsieh, et al., Synthesis and Antiinflammatory Effect of Chalcones, *J. Pharm. Pharmacol.* 2000, 52; 163-171 describes that certain chalcones have potent antiinflammatory activity.

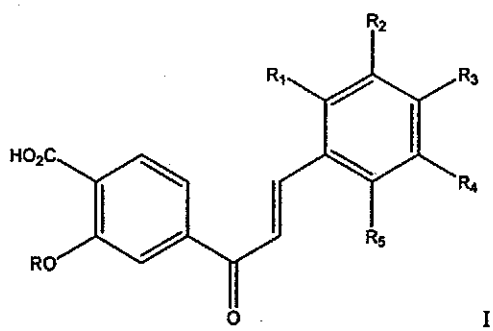
Zwaagstra, et al., Synthesis and Structure-Activity Relationships of Carboxylated Chalcones: A Novel Series of $CysLT_1$ (LT_4) Receptor Antagonists; J. Med. Chem., 1997, 40,

1075-1089 discloses that in a series of 2-, 3-, and 4-(2-quinolinylmethoxy)- and 3- and 4-[2-(2-quinolinyl)ethenyl]-substituted, 2', 3', 4', or 5' carboxylated chalcones, certain compounds are $CysLT_1$ receptor antagonists.

JP 63010720 to Nippon Kayaku Co., LTD discloses that chalcone derivatives of the following formula (wherein R^1 and R^2 are hydrogen or alkyl, and m and n are 0-3) are 5-lipoxygenase inhibitors and can be used in treating allergies.



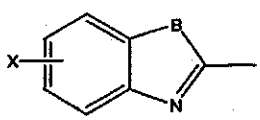
JP 06116206 to Morinaga Milk Industry Co. Ltd, Japan, discloses chalcones of the following structure as 5-lipoxygenase inhibitors, wherein R is acyl and R^1-R^5 are hydrogen, lower alkyl, lower alkoxy or halo, and specifically that in which R is acyl and R^1-R^5 are hydrogen.



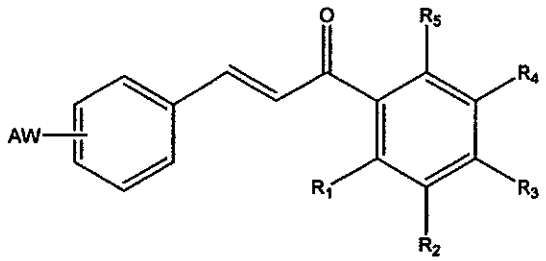
I R= Ac

II R-R_5=H

U.S. Patent No. 6,046,212 to Kowa Co. Ltd. discloses heterocyclic ring-containing chalcones of the following formula as antiallergic agents, wherein A represents a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, or a group :



in which X represents a hydrogen or halogen atom or a hydroxyl, lower alkyl or lower alkoxyl group and B represents -CH=CH-,-N(R_6)-, R_6 is a lower alkyl group or a lower alkoxyalkyl group, -O- or -S-; W represents -CH=CH- or -CH_2O-, and R_{1-5} is the same or different and each independently represent a hydrogen or halogen atom, a hydroxyl, a lower alkyl, lower alkoxyl, carboxyl, cyano, alkyloxycarbonyl or tetrazolyl group, a group -$CONHR_7$ in which R_7 represents a hydrogen atom or a lower alkyl group, or a group -$O(CH_2)_n$ R_8 in which R_8 represents a carboxyl, alkyloxycarbonyl or tetrazolyl group and n is from 1 to 4, with the proviso that at least one of the groups R_{1-5} represents a carboxyl, cyano, alkyloxycarbonyl or tetrazolyl group, the group --$CONHR_7$ or the group --$O(CH_2)nR_8$; or a salt or solvate thereof.



Reported bioactivies of chalcones have been reviewed by Dimmock, et al., in Bioactivities of Chalcones, *Current Medicinal Chemistry* 1999, 6, 1125-1149; Liu et al., Antimalarial Alkoxylated and Hydroxylated Chalones: Structure-Activity Relationship Analysis, *J.Med. Chem.* 2001, 44, 4443-4452; Herencia et al, Novel Anit-inflammatory Chalcone Derivatives Inhibit the Induction of Nitric Oxide Synthase and Cyclooxygenase-2 in Mouse Peritoneal Macrophages, *FEBS Letters*, 1999, 453, 129-134; and Hsieh et al., Synthesis and Anti-inflammatory Effect of Chalcones and Related Compounds, *Pharmaceutical Research*, 1998, Vol.15, No. 1, 39-46.

Given that VCAM-1 is a mediator of chronic inflammatory disorders, it is a goal of the present work to identify new compounds, compositions and methods that can inhibit the expression of VCAM-1. A more general goal is to identify selective compounds and methods for suppressing the expression of redox sensitive genes or activating redox sensitive genes that are suppressed. An even more general goal is to identify selective compounds, pharmaceutical compositions and methods of using the compounds for the treatment of inflammatory diseases.

Accordingly, disclosed herein are new compounds for the treatment of disorders mediated by VCAM-1.

Disclosed also are new pharmaceutical compositions for the treatment of diseases and disorders mediated by the expression of VCAM-1.

Disclosed further are compounds, compositions, and methods of treating disorders and diseases mediated by VCAM-1, including cardiovascular and inflammatory diseases.

Disclosed further are compounds, compositions, and method of treating cardiovascular and inflammatory diseases.

Disclosed further are compounds, compositions and methods to treat arthritis.

Disclosed further are compounds, compositions and methods to treat rheumatoid arthritis. The compounds, compositions and methods can also be suitable as disease modifying anti-rheumatoid arthritis drugs (DMARDs).

Disclosed yet further are compounds, compositions and methods to treat asthma.

Disclosed further are compounds, methods and compositions to inhibit the progression of atherosclerosis.

Disclosed still further are compounds, compositions, and methods to treat or prevent transplant rejection.

Disclosed further are compounds, methods and compositions for the treatment of lupus.

Disclosed further are compounds, methods and compositions for the treatment of inflammatory bowel disease.

Disclosed further are compounds, methods and compositions for the treatment of autoimmune diabetes.

Disclosed further are compounds, methods and compositions for the treatment of multiple sclerosis.

Disclosed further are compounds, methods and compositions for the treatment of diabetic retinopathy.

Disclosed further are compounds, methods and compositions for the treatment of diabetic nephropathy.

Disclosed further are compounds, methods and compositions for the treatment of diabetic vasculopathy.

Disclosed further are compounds, methods and compositions for the treatment of rhinitis.

Disclosed further are compounds, methods and compositions for the treatment of ischemia-reperfusion injury.

Disclosed further are compounds, methods and compositions for the treatment of post-angioplasty restenosis.

Disclosed further are compounds, methods and compositions for the treatment of chronic obstructive pulmonary disease (COPD).

Disclosed further are compounds, methods and compositions for the treatment of glomerulonephritis.

Disclosed further are compounds, methods and compositions for the treatment of Graves disease.

Disclosed further are compounds, methods and compositions for the treatment of gastrointestinal allergies.

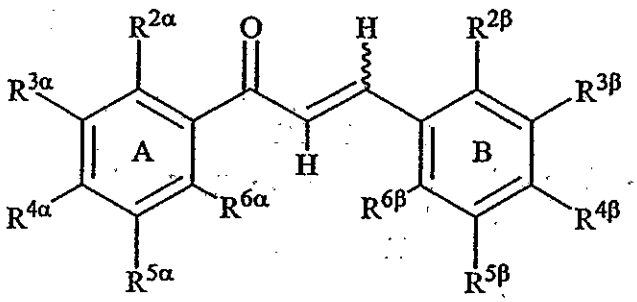
Disclosed further are compounds, methods and compositions for the treatment of conjunctivitis.

Disclosed further are compounds, methods and compositions for the treatment of dermatitis.

Disclosed further are compounds, methods and compositions for the treatment of psoriasis.

SUMMARY OF THE INVENTION

According to a first aspect of the present invention, there is provided a compound of Formula I



(I)

or its pharmaceutically acceptable salt or ester, wherein:

the wavy line indicates that the compound can be in the form of the E- or Z- isomer;

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl, hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$,

$-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $-SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein lower alkyl refers to a C1 to C4 alkyl group;

wherein one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$, or one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl;

wherein when one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

wherein when one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; or

at least one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$ or one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$ must be selected from the group consisting of cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$,

$-SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

According to a second aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I or its pharmaceutically acceptable salt or ester, together with one or more pharmaceutically acceptable carrier.

According to a third aspect of the present invention, there is provided a use of a compound of Formula I or its pharmaceutically acceptable salt or ester, in the manufacture of a medicament for the treatment or prophylaxis of an inflammatory disorder.

According to a fourth aspect of the present invention, there is provided a use for a compound of Formula I or its pharmaceutically acceptable salt or ester, in the manufacture of a medicament for inhibiting the expression of VCAM-1.

It has been discovered that particular chalcone derivatives inhibit the expression of VCAM-1, and thus can be used to treat a patient with a disorder mediated by VCAM-1. Examples of inflammatory disorders that are mediated by VCAM-1 include, but are not limited to arthritis, asthma, dermatitis, cystic fibrosis, post transplantation late and chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosis, inflammatory bowel diseases, autoimmune diabetes, diabetic retinopathy, diabetic nephropathy, diabetic vasculopathy, rhinitis, ischemia-reperfusion injury, post-angioplasty restenosis, chronic obstructive pulmonary disease (COPD), glomerulonephritis, Graves disease, gastrointestinal allergies, conjunctivitis, atherosclerosis, coronary artery disease, angina and small artery disease.

The compounds disclosed herein can also be used in the treatment of inflammatory skin diseases that are mediated by VCAM-1, as well as human endothelial disorders that are mediated by VCAM-1, which include, but are not limited to psoriasis, dermatitis, including eczematous dermatitis, Kaposi's sarcoma, multiple sclerosis, as well as proliferative disorders of smooth muscle cells.

In yet another embodiment, the compounds disclosed herein can be selected to treat anti-inflammatory conditions that are mediated by mononuclear leucocytes.

In one embodiment, the compounds of the present invention are selected for the prevention or treatment of tissue or organ transplant rejection. Treatment and prevention of organ or tissue transplant rejection can include, but is not limited to treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, spleen, small bowel, or corneal transplants. The compounds can also be used in the prevention or treatment of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation.

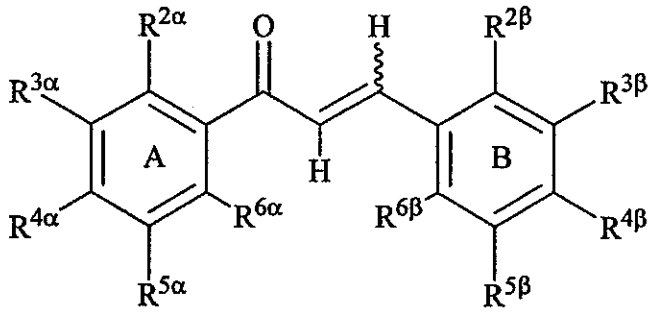
In an alternative embodiment, the compounds described herein are useful in both the primary and adjunctive medical treatment of cardiovascular disease. The compounds can be used

in primary treatment of, for example, coronary disease states including atherosclerosis, post-angioplasty restenosis, coronary artery diseases and angina. The compounds can be administered to treat small vessel disease that is not treatable by surgery or angioplasty, or other vessel disease in which surgery is not an option. The compounds can also be used to stabilize patients prior to revascularization therapy.

DETAILED DESCRIPTION OF THE INVENTION

It has been discovered that compounds of the invention inhibit the expression of VCAM-1, and thus can be used to treat a patient with a disorder mediated by VCAM-1. These compounds can be administered to a host as monotherapy, or if desired, in combination with another compound of the invention or another biologically active agent, as described in more detail below.

In a 1st embodiment, the invention is represented by Formula I



(I)

or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$,

thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$, or one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl; and/or

wherein when one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$; and/or

wherein when one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$; and/or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; and/or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; and/or

at least one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$ or one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$,

-NHC(O)SR^2, -NHSO$_2$NHR^2, -NHSO$_2$R^2, -NHSO$_2$NR^{7}R^8, -N(C(O)NHR^2)$_2$, -NR^{2}SO$_2$R^2, -NHC(O)NHR^2, -NHC(O)NR^{7}R^8, and –NHC(O)N(R^2)$_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^{7}R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^{7}R^8, and –C(O)N(R^2)$_2$.

In a 2nd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

R$^{2\alpha}$, R$^{3\alpha}$, R$^{4\alpha}$, R$^{5\alpha}$, R$^{6\alpha}$, R$^{2\beta}$, R$^{3\beta}$, R$^{4\beta}$, R$^{5\beta}$ and R$^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-S(O)$_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, -C(O)R^2, R^{2}C(O)alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, -(O(CH$_2$)$_2$)$_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -OC(R^1)$_2$C(O)OH, -OC(R^1)$_2$C(O)OR^2, -OC(R^1)$_2$C(O)NH$_2$, -OC(R^1)$_2$C(O)NHR^2, -OC(R^1)$_2$C(O)N(R^2)$_2$, -OC(R^1)$_2$C(O)NR^{7}R^8, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, -NHR^2, N(R^2)$_2$, -NR^{7}R^8, -NHC(R^1)$_2$C(O)OH, -NHC(R^1)$_2$C(O)OR^2, -NHC(O)R^2, -N(R^2)C(O)R^2, -NHC(O)OR^2, -NHC(O)SR^2, -NHSO$_2$NHR^2, -NHSO$_2$R^2, -NHSO$_2$NR^{7}R^8, -N(C(O)NHR^2)$_2$, -NR^{2}SO$_2$R^2, -NHC(O)NHR^2, -NHC(O)NR^{7}R^8, –NHC(O)N(R^2)$_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, -SC(R^1)$_2$C(O)OH, -SC(R^1)$_2$C(O)OR^2, -SCH$_2$C(O)OH, -SCF$_2$C(O)OH, -

SO_2NH_2, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$, or one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl; and/or

wherein when one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$; and/or

wherein when one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$; and/or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; and/or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; and/or

at least one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, or one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 3rd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid,

sulfenic acid, cyano, tetrazol-5-yl, carboxy, -C(O)OR^2, -C(O)NH$_2$, -C(O)NHR^2, -C(O)N(R^2)$_2$, -C(O)NR^{7}R^8, -C(O)NHC(O)R^2, -C(O)NHC(O)NHR^2, -C(O)NHC(O)N(R^2)$_2$, -C(O)NHC(O)NR^{7}R^8, -C(O)NHSO$_2$R^2, -C(O)NHSO$_2$NHR^2, -C(O)NHSO$_2$N(R^2), -C(O)NHSO$_2$NR^{7}R^8, -C(CH$_3$)$_2$C(O)OH, -(CH$_2$)$_y$C(O)OH, wherein y is 1, 2, 3, 4, 5, or 6, -PO$_2$H$_2$, -PO$_3$H$_2$, -P(R^2)O$_2$H, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^{7}R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^{7}R^8, and –C(O)N(R^2)$_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^{7}R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^{7}R^8, and –C(O)N(R^2)$_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^{7}R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^{7}R^8, and –C(O)N(R^2)$_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of R$^{2\beta}$, R$^{3\beta}$, R$^{4\beta}$, R$^{5\beta}$ or R$^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of R$^{2\alpha}$, R$^{3\alpha}$, R$^{4\alpha}$, R$^{5\alpha}$ or R$^{6\alpha}$ can be –OCH$_3$; and/or

R$^{2\alpha}$ and R$^{3\alpha}$ taken together or R$^{3\alpha}$ and R$^{4\alpha}$ taken together or R$^{4\alpha}$ and R$^{5\alpha}$ taken together, or R$^{2\beta}$ and R$^{3\beta}$ taken together or R$^{3\beta}$ and R$^{4\beta}$ taken together or R$^{4\beta}$ and R$^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected

from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; and/or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; and/or

at least one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, or $R^{6\alpha}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 4th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle,

cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$; and/or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; and/or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy,

carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be –$OC(R^1)_2C(O)OH$; and/or

at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, -C(O)OR^2, -C(O)NH_2, -C(O)NHR^2, -C(O)$N(R^2)_2$, -C(O)NR^7R^8, -C(O)$NHC(O)NHR^2$, -C(O)$NHC(O)N(R^2)_2$, -C(O)$NHC(O)NR^7R^8$, -C(O)$NHSO_2NHR^2$, -C(O)$NHSO_2N(R^2)$, -C(O)$NHSO_2NR^7R^8$, -C(O)$NHC(O)R^2$, -C(O)$NHSO_2R^2$, -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -$SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, -$OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$, amino, -NHR^2, $N(R^2)_2$, NR^7R^8, -$NHC(R^1)_2C(O)OH$, -$NHC(R^1)_2C(O)OR^2$, -$NHC(O)R^2$, -$N(R^2)C(O)R^2$, -$NHC(O)OR^2$, -$NHC(O)SR^2$, -$NHSO_2NHR^2$, -$NHSO_2R^2$, -$NHSO_2NR^7R^8$,- $N(C(O)NHR^2)_2$, -$NR^2SO_2R^2$, -$NHC(O)NHR^2$, -$NHC(O)NR^7R^8$, and –$NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$.

In a 5th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, -C(O)R^2, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, -$OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, -NHR^2, $N(R^2)_2$, -NR^7R^8, -$NHC(R^1)_2C(O)OH$, -$NHC(R^1)_2C(O)OR^2$, -$NHC(O)R^2$, -$N(R^2)C(O)R^2$, -$NHC(O)OR^2$, -$NHC(O)SR^2$, -$NHSO_2NHR^2$, -$NHSO_2R^2$, -$NHSO_2NR^7R^8$, -$N(C(O)NHR^2)_2$, -$NR^2SO_2R^2$, -$NHC(O)NHR^2$, -$NHC(O)NR^7R^8$, –$NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -$SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(O)NHC(O)R^2$, -$C(O)NHC(O)NHR^2$, -$C(O)NHC(O)N(R^2)_2$, -$C(O)NHC(O)NR^7R^8$, -$C(O)NHSO_2R^2$, -$C(O)NHSO_2NHR^2$, -$C(O)NHSO_2N(R^2)$, -$C(O)NHSO_2NR^7R^8$, -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, -PO_2H_2, -PO_3H_2, -$P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 6th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, -

PO_2H_2, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 7th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, and $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the

group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be –OCH_3;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In an 8th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, and $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl,

hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $–OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(CH_3)_2C(O)OH$, $(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 9th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, heterocyclicamino lower alkyl, hydroxyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, dialkylamino, $N(R^2)_2$, -NR^7R^8, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(CH_3)_2C(O)OH$, and -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 8-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be –OCH_3;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 10th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1\text{-}3}$-O-lower alkyl, polyoxyalkylene, heteroaryl lower alkoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, carboxy, -$C(O)OR^2$, -$C(O)N(R^2)_2$, and -$C(O)NR^7R^8$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, hydroxy, hydroxyalkyl, heterocyclic, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, and lower alkyl, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, -NR^7R^8, alkoxy, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 5- to 7-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from carboxy or $-C(O)OR^2$;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In an 11th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic,

lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, and carboxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

In a 12th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl,

heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

In a 13th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

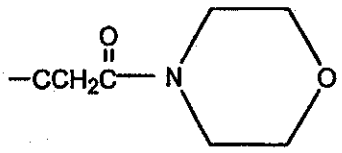
wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heteroaryl;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

In a 14th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, fluorine, chlorine, methoxy, ethoxy, propoxy, 3-(1-morpholino) propoxy, 2-(1-morpholino) ethoxy, $CH_3O(CH_2)_2O(CH_2)_2$-,



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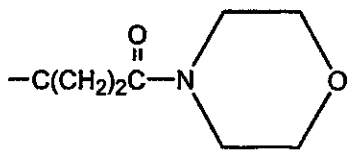


;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be selected from the group consisting of thiophen-s-yl, thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, indol-2-yl, indol-3-yl, pyrrol-2-yl, pyrrol-3-yl, 1-methyl-indol-2-yl, 1-methyl-indol-3-yl, N-Boc-indol-2-yl, N-Boc-indol-3-yl, N-Boc-pyrrol-2'yl, and N-Boc-pyrrol-3-yl;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

In a 15th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, methoxy, 3-(1-morpholino) propoxy, 2-(1-morpholino) ethoxy, and$CH_3O(CH_2)_2O(CH_2)_2$;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be selected from the group consisting of thiophen-s-yl, benzo[b]thiophen-2-yl, indol-2-yl, 1-methyl-indol-2-yl, N-Boc-indol-2-yl, N-Boc-pyrrol-2'yl, and N-Boc-pyrrol-3-yl;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

In a 16th embodiment, the invention is selected from a compound A compound selected from the group consisting of

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid;

4-[3*E*-(4-Pyrimidin-5-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(4-Thiazol-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

2-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(3,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

2-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid, sodium salt;

4-[3*E*-(4-Thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3-{4-(thien-2-yl)-phenyl}-3-oxo-*E*-propenyl]-benzoic acid, sodium salt;

4-[3-{4-(thien-2-yl)-phenyl}-3-oxo-*E*-propenyl]-benzoic acid;

4-[3-(2-Methoxy-4-thiophen-2-yl-phenyl)-3-oxo-*E*-propenyl]-benzoic acid;

4-[3*E*-(4-Pyrrolidin-1-yl-3-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-{4-Fluoro-3-(thiophen-2-yl)-phenyl}-acryloyl]-benzoic acid;

4-(3*E*-{4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic Acid;

4-[3*E*-(2-Fluoro-4-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-pyrimidin-5-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2-Cyclopropylmethoxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[5-(3,5-Dimethyl-isoxazol-4-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(4-Methoxy-2-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

2-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

2-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-indole-1-carboxylic acid *tert*-butyl ester;

4-[3*E*-(2,6-Dimethoxy-4-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[5-(2,4-Dimethoxy-pyrimidin-5-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-6-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[2,4-Dimethoxy-5-(5-methyl-thiophen-2-yl)-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(4-Methoxy-3-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(3-Thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

3-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(3-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2-Methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-pyrazin-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[4-(1-Carboxy-1-methyl-ethoxy)-2-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

2-[3*E*-(4-Methoxy-3-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-(3*E*-{2-Methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic acid;

4-{3*E*-[4-(3-Hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

5-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-thiophene-2-carboxylic acid methyl ester;

5-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-thiophene-2-carboxylic acid;

4-[3*E*-(4-Ethoxy-2-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(4-Hydroxy-2-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-thiazol-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid, sodium salt;

2-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-pyrrole-1-carboxylic acid *tert*-butyl ester;

4-[3*E*-(2-Hydroxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[2-(1-Carboxy-1-methyl-ethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride;

2 4-{3*E*-[5-(1H-Indol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[2-(3,5-Dimethyl-isoxazol-4-ylmethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(2-Pyrrolidin-1-yl-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[2-(3-Hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[2-(3-Morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride;

4-{3*E*-[4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride;

4-[3*E*-(2-Dimethylcarbamoylmethoxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(4-Methoxy-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[2,4-Dimethoxy-5-(2-methyl-thiazol-4-yl)-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[5-(1*H*-Benzoimidazol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(2-Carbamoylmethoxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-2-oxo-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

4-(3*E*-{4-Methoxy-2-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic acid, hydrochloride;

4-{3*E*-[2,4-Dimethoxy-5-(1*H*-pyrazol-4-yl)-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[2,4-Dimethoxy-5-(2*H*-tetrazol-5-yl)-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[5-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

2-{4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-phenyl}-2-methyl-propionic acid;

4-{3*E*-[5-(2-Cyclopropyl-1*H*-imidazol-4-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid, hydrochloride;

4-{3*E*-[5-(4-Isobutyl-4H-[1,2,4]triazol-3-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[2,4-Dimethoxy-5-(1-methyl-1*H*-indol-2-yl)-phenyl]-acryloyl}-benzoic acid; and

4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid ethyl ester, or its pharmaceutically acceptable salt or ester.

In a 17th embodiment, the invention is a compound selected from the group consisting of

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-(3*E*-{4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic Acid; and

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride,or its pharmaceutically acceptable salt or ester.

In an 18th embodiment, the invention is 4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid or its pharmaceutically acceptable salt or ester.

In a 19th embodiment, the invention is 4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid, or its pharmaceutically acceptable salt or ester.

In a 20th embodiment, the invention is 4-(3*E*-{4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic Acid; and,or its pharmaceutically acceptable salt or ester.

In a 21st embodiment, the invention is 4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride,or its pharmaceutically acceptable salt or ester.

In a 22nd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

In a 23rd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked tetrahydrofurn-2-yl or dihydrofuran-2-yl;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

In a 24th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 25th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$,

$R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino-NHR^2, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, and $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, and $-C(O)NHSO_2R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 26th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy,

heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, and $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of -C(O)NH_2, -C(O)NHR^2, -C(O)$N(R^2)_2$, -C(O)NR^7R^8, -C(O)NHC(O)NHR^2, -C(O)NHC(O)$N(R^2)_2$, -C(O)NHC(O)NR^7R^8, -C(O)$NHSO_2NHR^2$, -C(O)$NHSO_2N(R^2)$, -C(O)$NHSO_2NR^7R^8$, -C(O)NHC(O)R^2, and -C(O)$NHSO_2R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$.

In a 27th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, dialkylamino, $N(R^2)_2$, -NR^7R^8, -$N(R^2)C(O)R^2$, -C(O)NH_2, -C(O)NHR^2, -C(O)$N(R^2)_2$, -C(O)NR^7R^8, and -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl,

wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 8-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(O)NHC(O)R^2$, and -$C(O)NHSO_2R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 28th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, heteroaryl lower alkoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$N(R^2)C(O)R^2$, -$C(O)NH_2$, and -$C(O)NHR^2$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, and lower alkyl which may be optionally substituted by one or more selected from the group consisting of halo, lower alkyl, -NR^7R^8, alkoxy, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, heteroaryl, and heterocyclic, wherein all may be substituted by one or more selected

from the group consisting of halo, lower alkyl, -NR^7R^8, alkoxy, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 5- to 7-membered monocyclic ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)NHC(O)R^2$, and -$C(O)NHSO_2R^2$;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, heterocyclic, amino, aminoalkyl, and -NR^7R^8.

In a 29th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, -$N(R^2)C(O)R^2$, -$C(O)NH_2$, and -$C(O)NHR^2$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is hydrogen;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)NHC(O)R^2$, and $-C(O)NHSO_2R^2$;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of heterocyclic, amino, aminoalkyl, and $-NR^7R^8$.

In a 30th embodiment, the invention is represented by the following compounds:

4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-N-(2-morpholin-4-yl-ethyl)-benzamide;

4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-N-(2,2,2-trifluoro-ethyl)-benzamide;

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzamide;

4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide;

4-{3*E*-[4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzamide;

N-Acetyl-4-[3*E*-(5-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide; and

4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-*N*-isobutyryl-benzamide.

In a 31st embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy,

arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group

consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be –OCH_3;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of thiol, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, $SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 32nd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, -$C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl,

alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, $OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, -NHR^2, $N(R^2)_2$, -NR^7R^8, -$NHC(R^1)_2C(O)OH$, -$NHC(R^1)_2C(O)OR^2$, -$NHC(O)R^2$, -$N(R^2)C(O)R^2$, -$NHC(O)OR^2$, -$NHC(O)SR^2$, -$NHSO_2NHR^2$, -$NHSO_2R^2$, -$NHSO_2NR^7R^8$, -$N(C(O)NHR^2)_2$, -$NR^2SO_2R^2$, -$NHC(O)NHR^2$, -$NHC(O)NR^7R^8$, -$NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -$SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(O)NHC(O)R^2$, -$C(O)NHC(O)NHR^2$, -$C(O)NHC(O)N(R^2)_2$, -$C(O)NHC(O)NR^7R^8$, -$C(O)NHSO_2R^2$, -$C(O)NHSO_2NHR^2$, -$C(O)NHSO_2N(R^2)$, -$C(O)NHSO_2NR^7R^8$, -$C(CH_3)_2C(O)OH$, and -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and

heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or R^4 must be selected from the group consisting of thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 33rd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl, hydroxyl, hydroxyalkyl, polyol alkyl,

alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -

$OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$ $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, and $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, arylarylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, SO_2NH_2, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 34th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, dialkylamino, $N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-SCH_2C(O)OH$ $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, and $-C(O)NHSO_2R^2$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 8-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 35th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, alkenyl, alkynyl, carbocycle, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl,

hydroxyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, heteroaryl lower alkoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-N(R^2)C(O)R^2$, $-SCH_2C(O)OH$ - SO_2NH_2, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, - $SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, and $-C(O)NHSO_2R^2$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen and lower alkyl, which may be optionally substituted by one or more selected from the group consisting of halo, lower alkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl and lower alkyl, which may be substituted by one or more selected from the group consisting of halo, lower alkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 5- to 7-membered monocyclic ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, and $-SO_2NHC(O)R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 36th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, alkenyl, alkynyl, carbocycle, heteroaryl, heterocyclic, hydroxyl, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, $-N(R^2)C(O)R^2$, $-SO_2NH_2$, $-SO_2NHR_2$, $SO_2NHC(O)R^2$, $-SR_2$, $SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, and $-C(O)NHSO_2R^2$, all of which can be optionally substituted by one or more selected from the group consisting of alkenyl, acyl, hydroxy, hydroxyalkyl, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is hydrogen;

R^2 is lower;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-SC(R^1)_2C(O)OR^2$, $-SO_2NH_2$, $-SO_2NR^7R^8$, and $-SO_2NHC(O)R^2$.

In a 37th embodiment, the invention is represented by the following compound:

4-[3*E*-(4-Thiophen-2-yl-phenyl)-acryloyl]-benzenesulfonamide;

4-[3*E*-(5-Benzo[b]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzenesulfonamide;

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide;

2-{5-Methoxy-2-[3-oxo-3-(4-sulfamoyl-phenyl)-*E*-propenyl]-4-thiophen-2-yl-phenoxy}-2-methyl-propionic acid;

2-{2,4-Dimethoxy-5-[3-oxo-3-(4-sulfamoyl-phenyl)-*E*-propenyl]-phenyl}-indole-1-carboxylic acid *tert*-butyl ester;

4-{3*E*-[5-(1*H*-Indol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzenesulfonamide;

4-{3*E*-[4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide;

4-{3*E*-[2-(3-Hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide;

4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-*N*-isobutyryl-benzenesulfonamide;

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide, hydrochloride;

4-{3*E*-[4-Methoxy-2-(1*H*-tetrazol-5-ylmethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide;

4-[3*E*-(2,4-Dimethoxy-5-pyridin-3-yl-phenyl)-acryloyl]-benzenesulfonamide;

4-{3*E*-[4-(3-Hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide;

4-{3*E*-[5-(4-Isobutyl-4H-[1,2,4]triazol-3-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzenesulfonamide;

4-{3*E*-[5-(2-Cyclopropyl-1H-imidazol-4-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzenesulfonamide;

4-{3*E*-[5-(3*H*-Imidazo[4,5-b]pyridin-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzenesulfonamide;

4-{3*E*-[2-(1*H*-Benzoimidazol-2-ylmethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide;

4-{3*E*-[4-Methoxy-2-(pyridin-2-ylmethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide;

4-{3*E*-[2-(Benzotriazol-1-ylmethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide; and

4-{3*E*-[2,4-Dimethoxy-5-(1-methyl-1*H*-indol-2-yl)-phenyl]-acryloyl}-benzenesulfonamide.

In a 38th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl,

alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$,

amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, NHR^2, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$,

thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 39th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, , all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl optionally substituted by alkoxycarbonyl.

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of amino, $-N(C(O)NHR^2)_2$, $NR^2SO_2R^2$ and $-NR^2SO_2R^2$;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 40th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl,

alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio,

heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -$SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(O)NHC(O)R^2$, -$C(O)NHC(O)NHR^2$, -$C(O)NHC(O)N(R^2)_2$, -$C(O)NHC(O)NR^7R^8$, -$C(O)NHSO_2R^2$, -$C(O)NHSO_2NHR^2$, -$C(O)NHSO_2N(R^2)$, -$C(O)NHSO_2NR^7R^8$, -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, -PO_2H_2, -PO_3H_2, -$P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be –OCH_3;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 41st embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is hydrogen or lower alkyl optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from -$OC(R^1)_2C(O)OH$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 42nd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, -$C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, -$OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, -NHR^2, $N(R^2)_2$, -NR^7R^8, -$NHC(R^1)_2C(O)OH$, -$NHC(R^1)_2C(O)OR^2$, -$NHC(O)R^2$, -$N(R^2)C(O)R^2$, -$NHC(O)OR^2$, -$NHC(O)SR^2$, -$NHSO_2NHR^2$, -$NHSO_2R^2$, -$NHSO_2NR^7R^8$, -$N(C(O)NHR^2)_2$, -$NR^2SO_2R^2$, -$NHC(O)NHR^2$, -$NHC(O)NR^7R^8$, –$NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl,

haloalkylsulfonyl, -SC(R^1)$_2$C(O)OH, -SC(R^1)$_2$C(O)OR^2, -SCH$_2$C(O)OH, -SCF$_2$C(O)OH, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, -C(O)OR^2, -C(O)NH_2, -C(O)NHR^2, -C(O)N(R^2)$_2$, -C(O)NR^7R^8, -C(O)NHC(O)R^2, -C(O)NHC(O)NHR^2, -C(O)NHC(O)N(R^2)$_2$, -C(O)NHC(O)NR^7R^8, -C(O)NHSO_2R^2, -C(O)NHSO_2NHR^2, -C(O)NHSO_2N(R^2), -C(O)NHSO_2NR^7R^8, -C(CH_3)$_2$C(O)OH, -(CH_2)$_y$C(O)OH, wherein y is 1, 2, 3, 4, 5, or 6, -PO_2H_2, -PO_3H_2, -P(R^2)O_2H, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)N(R^2)$_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)N(R^2)$_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)N(R^2)$_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be –OCH_3; and/or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; and/or

At least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 43rd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $(O(CH_2)_2)_{1\text{-}3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy,

all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently alkyl or lower alkyl;

R^7 and R^8 are independently selected from the group consisting of alkyl, linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$; and/or

$R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic ring optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, or hydroxyalkyl groups.

In a 44th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, -$C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, -$OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$,

amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$; and/or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; and/or

at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$,

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 45th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy,

all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently alkyl or lower alkyl;

R^7 and R^8 are independently selected from the group consisting of alkyl, linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$; and/or

$R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of alkyl, lower alkyl, cycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonyl; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2COOH$.

In a 46th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$,

$R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl,

heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$, or one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl; and/or

wherein when one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$; and/or

wherein when one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$; and/or

$R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together, or $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, -NR^7R^8, and halo; and/or

$R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together or $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy,

carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$; provided that $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ cannot be –$OC(R^1)_2C(O)OH$; and/or

at least one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, or one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, -C(O)OR^2, -C(O)NH_2, -C(O)NHR^2, -C(O)$N(R^2)_2$, -C(O)NR^7R^8, -C(O)NHC(O)NHR^2, -C(O)NHC(O)$N(R^2)_2$, -C(O)NHC(O)NR^7R^8, -C(O)$NHSO_2NHR^2$, -C(O)$NHSO_2N(R^2)$, -C(O)$NHSO_2NR^7R^8$, -C(O)NHC(O)R^2, -C(O)$NHSO_2R^2$, -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -$SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, $SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, -$OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$, amino, -NHR^2, $N(R^2)_2$, NR^7R^8, -$NHC(R^1)_2C(O)OH$, -$NHC(R^1)_2C(O)OR^2$, -NHC(O)R^2, -$N(R^2)C(O)R^2$, -NHC(O)OR^2, -NHC(O)SR^2, -$NHSO_2NHR^2$, -$NHSO_2R^2$, -$NHSO_2NR^7R^8$, -$N(C(O)NHR^2)_2$, -$NR^2SO_2R^2$, -NHC(O)NHR^2, -NHC(O)NR^7R^8, and –NHC(O)$N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$.

In a 47th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, -C(O)R^2, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, -$OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, -NHR^2, $N(R^2)_2$, -NR^7R^8, -$NHC(R^1)_2C(O)OH$, -$NHC(R^1)_2C(O)OR^2$, -$NHC(O)R^2$, -$N(R^2)C(O)R^2$, -$NHC(O)OR^2$, -$NHC(O)SR^2$, -$NHSO_2NHR^2$, -$NHSO_2R^2$, -$NHSO_2NR^7R^8$, -$N(C(O)NHR^2)_2$, -$NR^2SO_2R^2$, -$NHC(O)NHR^2$, -$NHC(O)NR^7R^8$, -$NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -$SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(O)NHC(O)R^2$, -$C(O)NHC(O)NHR^2$, -$C(O)NHC(O)N(R^2)_2$, -$C(O)NHC(O)NR^7R^8$, -$C(O)NHSO_2R^2$, -$C(O)NHSO_2NHR^2$, -$C(O)NHSO_2N(R^2)$, -$C(O)NHSO_2NR^7R^8$, -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, -PO_2H_2, -PO_3H_2, -$P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together, or $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; or

$R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together or $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ cannot be $-OC(R^1)_2C(O)OH$; and

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, or $R^{6\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4,

5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 48th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, -

$NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together, or $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; or

$R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together or $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ cannot be $-OC(R^1)_2C(O)OH$; and

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl,

hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 49th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, -$C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, -$OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, -NHR^2, $N(R^2)_2$, -NR^7R^8, -$NHC(R^1)_2C(O)OH$, -$NHC(R^1)_2C(O)OR^2$, -$NHC(O)R^2$, -$N(R^2)C(O)R^2$, -$NHC(O)OR^2$, -$NHC(O)SR^2$, -$NHSO_2NHR^2$, -$NHSO_2R^2$, -$NHSO_2NR^7R^8$, -$N(C(O)NHR^2)_2$, -$NR^2SO_2R^2$, -$NHC(O)NHR^2$, -$NHC(O)NR^7R^8$, –$NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -$SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(O)NHC(O)R^2$, -$C(O)NHC(O)NHR^2$, -$C(O)NHC(O)N(R^2)_2$, -

$C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, -

SO_2NH_2, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 50th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, -

$NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(CH_3)_2C(O)OH$, $(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 51st embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$,

-$NR^2SO_2R^2$, -NHC(O)NHR^2, -NHC(O)NR^7R^8, –NHC(O)$N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -$SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, carboxy, -C(O)OR^2, -$C(O)NH_2$, -C(O)NHR^2, -C(O)$N(R^2)_2$, -C(O)NR^7R^8, -C(O)NHC(O)R^2, -C(O)NHC(O)NHR^2, -C(O)NHC(O)$N(R^2)_2$, -C(O)NHC(O)NR^7R^8, -$C(O)NHSO_2R^2$, -$C(O)NHSO_2NHR^2$, -$C(O)NHSO_2N(R^2)$, -$C(O)NHSO_2NR^7R^8$, -$C(CH_3)_2C(O)OH$, and -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -C(O)NR^7R^8, and –C(O)$N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $–OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(CH_3)_2C(O)OH$, $(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In an 52nd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, and $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(CH_3)_2C(O)OH$, $(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 53rd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, heterocyclicamino lower alkyl, hydroxyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl,

polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, dialkylamino, $N(R^2)_2$, -NR^7R^8, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(CH_3)_2C(O)OH$, and -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 8-membered monocyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be –OCH_3;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(CH_3)_2C(O)OH$, $(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 54th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, heteroaryl lower alkoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, carboxy, -$C(O)OR^2$, -$C(O)N(R^2)_2$, and -$C(O)NR^7R^8$, all of which can be optionally substituted by one or more

selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, hydroxy, hydroxyalkyl, heterocyclic, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, and lower alkyl, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, -NR^7R^8, alkoxy, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 5- to 7-membered monocyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $–OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from carboxy or –$C(O)OR^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 55th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic,

lower alkoxy, -$(O(CH_2)_2)_{1\text{-}3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, and carboxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $–OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be carboxy.

In a 56th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, and $R^{6\beta}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be carboxy.

In a 57th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, and $R^{6\beta}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

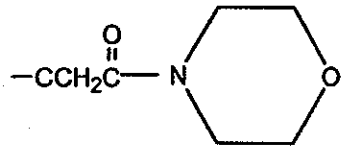
wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heteroaryl;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be carboxy.

In a 58th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, and $R^{6\beta}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, fluorine, chlorine, methoxy, ethoxy, propoxy, 3-(1-morpholino) propoxy, 2-(1-morpholino) ethoxy, $CH_3O(CH_2)_2O(CH_2)_2$-,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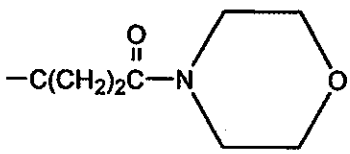

;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be selected from the group consisting of thiophen-s-yl, thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, indol-2-yl, indol-3-yl, pyrrol-2-yl, pyrrol-3-yl, 1-methyl-indol-2-yl, 1-methyl-indol-3-yl, N-Boc-indol-2-yl, N-Boc-indol-3-yl, N-Boc-pyrrol-2'yl, and N-Boc-pyrrol-3-yl;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be carboxy.

In a 59th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, and $R^{6\beta}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, methoxy, 3-(1-morpholino) propoxy, 2-(1-morpholino) ethoxy, and$CH_3O(CH_2)_2O(CH_2)_2$;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be selected from the group consisting of thiophen-s-yl, benzo[b]thiophen-2-yl, indol-2-yl, 1-methyl-indol-2-yl, N-Boc-indol-2-yl, N-Boc-pyrrol-2'yl, and N-Boc-pyrrol-3-yl;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be carboxy.

In a 60th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, and $R^{6\beta}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be carboxy.

In a 23rd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, and $R^{6\beta}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked tetrahydrofurn-2-yl or dihydrofuran-2-yl;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be carboxy.

Embodiment 6c. Amide Branch

In a 61st embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, -

SO_2NH_2, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, -

$C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 62nd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino-NHR^2, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, -

SO_2NH_2, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, and $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, -

$C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, and $-C(O)NHSO_2R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 63rd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, and $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, and $-C(O)NHSO_2R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 64th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, cycloalkyl, cycloalkylalkyl,

haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, dialkylamino, $N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, and $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 8-membered monocyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, and $-C(O)NHSO_2R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 65th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, heteroaryl lower alkoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-N(R^2)C(O)R^2$, $-C(O)NH_2$, and $-C(O)NHR^2$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, and lower alkyl which may be optionally substituted by one or more selected from the group consisting of halo, lower alkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, heteroaryl, and heterocyclic, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, $-NR^7R^8$, alkoxy, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 5- to 7-membered monocyclic ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)NHC(O)R^2$, and $-C(O)NHSO_2R^2$;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, heterocyclic, amino, aminoalkyl, and -NR^7R^8.

In a 66th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, -$N(R^2)C(O)R^2$, -$C(O)NH_2$, and -$C(O)NHR^2$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is hydrogen;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be –OCH_3;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)NHC(O)R^2$, and -$C(O)NHSO_2R^2$;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of heterocyclic, amino, aminoalkyl, and -NR^7R^8.

In a 67th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl,

heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 68th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl,

alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, and $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -

NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 69th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl, hydroxyl, hydroxyalkyl, polyol alkyl,

alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$ $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, tetrazol-5-yl, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, and $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, arylarylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 70th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, dialkylamino, $N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-SCH_2C(O)OH$ $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, -

$SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, and $-C(O)NHSO_2R^2$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 8-membered monocyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 71st embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, alkenyl, alkynyl, carbocycle, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl,

hydroxyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, heteroaryl lower alkoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$N(R^2)C(O)R^2$, -$SCH_2C(O)OH$ - SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, - $SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, and -$C(O)NHSO_2R^2$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen and lower alkyl, which may be optionally substituted by one or more selected from the group consisting of halo, lower alkyl, -NR^7R^8, alkoxy, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl and lower alkyl, which may be substituted by one or more selected from the group consisting of halo, lower alkyl, - NR^7R^8, alkoxy, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 5- to 7-membered monocyclic ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be –OCH_3;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, and -$SO_2NHC(O)R^2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 72nd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, alkenyl, alkynyl, carbocycle, heteroaryl, heterocyclic, hydroxyl, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, $-N(R^2)C(O)R^2$, $-SO_2NH_2$, $-SO_2NHR_2$, $SO_2NHC(O)R^2$, $-SR_2$, $SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, and $-C(O)NHSO_2R^2$, all of which can be optionally substituted by one or more selected from the group consisting of alkenyl, acyl, hydroxy, hydroxyalkyl, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is hydrogen;

R^2 is lower;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of $-SC(R^1)_2C(O)OR^2$, $-SO_2NH_2$, $-SO_2NR^7R^8$, and $-SO_2NHC(O)R^2$.

In a 73rd embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl,

alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, $OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$,

amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, NHR^2, $N(R^2)_2$, -NR^7R^8, -$NHC(R^1)_2C(O)OH$, -$NHC(R^1)_2C(O)OR^2$, -$NHC(O)R^2$, $N(R^2)C(O)R^2$, -$NHC(O)OR^2$, -$NHC(O)SR^2$, -$NHSO_2NHR^2$, -$NHSO_2R^2$, -$NHSO_2NR^7R^8$, -$N(C(O)NHR^2)_2$, -$NR^2SO_2R^2$, -$NHC(O)NHR^2$, -$NHC(O)NR^7R^8$, -$NHC(O)N(R^2)_2$,

thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, $SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(O)NHC(O)R^2$, -$C(O)NHC(O)NHR^2$, -$C(O)NHC(O)N(R^2)_2$, -$C(O)NHC(O)NR^7R^8$, -$C(O)NHSO_2R^2$, -$C(O)NHSO_2NHR^2$, -$C(O)NHSO_2N(R^2)$, -$C(O)NHSO_2NR^7R^8$, -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, -PO_2H_2, -PO_3H_2, -$P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 74th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, , all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl optionally substituted by alkoxycarbonyl.

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of amino, $-N(C(O)NHR^2)_2$, $NR^2SO_2R^2$ and $-NR^2SO_2R^2$;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 75th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl,

alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino,

cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 76th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is hydrogen or lower alkyl optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic,

amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from -$OC(R^1)_2C(O)OH$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$.

In a 77th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, -$C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, -$OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$,

amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$; and/or

$R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together, or $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; and/or

at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 78th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy,

all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently alkyl or lower alkyl;

R^7 and R^8 are independently selected from the group consisting of alkyl, linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$; and/or

$R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together, or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a heterocyclic ring optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, or hydroxyalkyl groups.

In a 79th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl,

hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, -$OC(R^1)_2C(O)OH$, -$OC(R^1)_2C(O)OR^2$, -$OC(R^1)_2C(O)NH_2$, -$OC(R^1)_2C(O)NHR^2$, -$OC(R^1)_2C(O)N(R^2)_2$, -$OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, -NHR^2, $N(R^2)_2$, -NR^7R^8, -$NHC(R^1)_2C(O)OH$, -$NHC(R^1)_2C(O)OR^2$, -$NHC(O)R^2$, -$N(R^2)C(O)R^2$, -$NHC(O)OR^2$, -$NHC(O)SR^2$, -$NHSO_2NHR^2$, -$NHSO_2R^2$, -$NHSO_2NR^7R^8$, -$N(C(O)NHR^2)_2$, -$NR^2SO_2R^2$, -$NHC(O)NHR^2$, -$NHC(O)NR^7R^8$, –$NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, -$SC(R^1)_2C(O)OH$, -$SC(R^1)_2C(O)OR^2$, -$SCH_2C(O)OH$, -$SCF_2C(O)OH$, -SO_2NH_2, -SO_2NHR_2, -$SO_2N(R^2)_2$, $SO_2NR^7R^8$, -$SO_2NHC(O)R^2$, -SR_2, -$SO_2NHC(O)NHR^2$, -$SO_2NHC(O)N(R^2)_2$, -$SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, tetrazol-5-yl, carboxy, -$C(O)OR^2$, -$C(O)NH_2$, -$C(O)NHR^2$, -$C(O)N(R^2)_2$, -$C(O)NR^7R^8$, -$C(O)NHC(O)R^2$, -$C(O)NHC(O)NHR^2$, -$C(O)NHC(O)N(R^2)_2$, -$C(O)NHC(O)NR^7R^8$, -$C(O)NHSO_2R^2$, -$C(O)NHSO_2NHR^2$, -$C(O)NHSO_2N(R^2)$, -$C(O)NHSO_2NR^7R^8$, -$C(CH_3)_2C(O)OH$, -$(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, -PO_2H_2, -PO_3H_2, -$P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, -NR^7R^8, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$; and/or

$R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together or $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ cannot be $-OC(R^1)_2C(O)OH$; and/or

at least one of $R^{2\beta}$, $R^{3\beta}$, or $R^{4\beta}$ must be selected from the group consisting of cyano, tetrazol-5-yl, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, NR^7R^8, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, -

$NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$,

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

In a 80th embodiment, the invention is represented by Formula I or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy,

all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently alkyl or lower alkyl;

R^7 and R^8 are independently selected from the group consisting of alkyl, linked together forming a 6-membered monocyclic ring;

wherein one of $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$; and/or

$R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together form a 5-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of alkyl, lower alkyl, cycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonyl; provided that $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ and $R^{6\alpha}$ cannot be $-OC(R^1)_2COOH$.

As an 81st embodiment, the invention is a pharmaceutical composition coprising any of the above 80 embodiments or any of the specific Examples below together with one or more pharmaceutically acceptable carriers.

An 82nd embodiment includes embodiments 1-80 above or any of the Examples as a means to treat or prophylactically treat an inflammatory disorder including arthritis, rheumatoid arthritis, asthma, diabetic retinopathy, diabetic nephropathy, diabetic vasculopathy, multiple sclerosis, allergic rhinitis, chronic obstructive pulmonary disease, systemic lupus erthematosus, atherosclerosis, and restinosis.

A further embodiment includes the intermediates used to make the final compounds of the invention. Said intermediates are useful as starting materials for making the compounds of the invention as well as having pharmaceutical activity alone.

Another embodiment of the invention includes the process for making both the intermediates as well as the final compounds.

Definitions

A wavy line used as a bond" ∿∿∿ ", denotes a bond which can be either the E- or Z-geometric isomer.

When not used as a bond, the wavy line indicates the point of attachment of the particular substituent.

The terms **"alkyl"** or **"alk"**, alone or in combination, unless otherwise specified, refers to a saturated straight or branched primary, secondary, or tertiary hydrocarbon from 1 to 10 carbon atoms, including, but not limited to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, and sec-butyl,. The term **"lower alkyl"** alone or in combination refers to an alkyl having from 1 to 4 carbon atoms. The alkyl group may be optionally substituted with any moiety that does not otherwise interfere with the reaction or that provides an improvement in the process, including but not limited to but limited to halo, haloalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene *et al.*, Protective Groups in Organic Synthesis, John Wiley & Sons, Second Edition, 1991, hereby incorporated by reference. Specifically included are CF_3 and CH_2CF_3.

The term **"alkenyl"**, alone or in combination, means a non-cyclic alkyl of 2 to 10 carbon atoms having one or more unsaturated carbon-carbon bonds. The alkenyl group may be optionally substituted with any moiety that does not otherwise interfere with the reaction or that provides an improvement in the process, including but not limited to but limited to halo, haloalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene *et al.*, Protective Groups in Organic Synthesis, John Wiley & Sons, Second Edition, 1991, hereby incorporated by reference. Specifically included are CF_3 and CH_2CF_3.

The term **"alkynyl"**, alone or in combination, means a non-cyclic alkyl of 2 to 10 carbon atoms having one or more triple carbon-carbon bonds, including but not limited to ethynyl and propynyl. The alkynyl group may be optionally substituted with any moiety that does not otherwise interfere with the reaction or that provides an improvement in the process, including but not limited to but limited to halo, haloalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene *et al.*, Protective Groups in Organic Synthesis, John Wiley & Sons, Second Edition, 1991, hereby incorporated by reference. Specifically included are CF_3 and CH_2CF_3.

The terms **"carboxy"**, **"COOH"** and **"C(O)OH"** are used interchangeably.

The terms **"alkoxycarbonyl"** and **"carboalkoxy"** are used interchangeably. Used alone or in combination, the terms mean refer to the radical –C(O)OR, wherein R is alkyl as defined herein.

The term **"thio"**, alone or in combination, means the radical -S-.

The term **"thiol"**, alone or in combination, means the radical –SH.

The term **"hydroxy"**, alone or in combination means the radical –OH.

The term **"sulfonyl"**, alone or in combination means the radical $-S(O)_2-$.

The term **"oxo"** refers to an oxygen attached by a double bond (=O).

The term **"carbocycle"**, alone or in combination, means any stable 3- to 7-membered monocyclic or bicyclic or 7- to 14-membered bicyclic or tricyclic or an up to 26-membered polycyclic carbon ring, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocyles include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, biphenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

The term **"cycloalkyl"**, alone or in combination, means a saturated or partially unsaturated cyclic alkyl, having from 1 to 10 carbon atoms, including but not limited to mono- or bi-cyclic ring systems such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexenyl, and cyclohexyl.

The term **"aryl"**, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The "aryl" group can be optionally substituted with one or more of the moieties selected from the group consisting of alkyl, alkenyl, alkynyl, heteroaryl, heterocyclic, carbocycle, alkoxy, oxo, aryloxy, arylalkoxy, cycloalkyl, tetrazolyl, heteroaryloxy; heteroarylalkoxy, carbohydrate, amino acid, amino acid esters, amino acid amides, alditol, halogen, haloalkylthi, haloalkoxy, haloalkyl, hydroxyl, carboxyl, acyl, acyloxy, amino, aminoalkyl, aminoacyl, amido, alkylamino, dialkylamino, arylamino, nitro, cyano, thiol, imide, sulfonic acid, sulfate, sulfonate, sulfonyl, alkylsulfonyl, aminosulfonyl, alkylsulfonylamino, haloalkylsulfonyl, sulfanyl, sulfinyl, sulfamoyl, carboxylic ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, thioester, thioether, oxime, hydrazine, carbamate, phosphonic acid, phosphate, phosphonate, phosphinate, sulfonamido, carboxamido, hydroxamic acid, sulfonylimide or any other desired functional group that does not inhibit the pharmacological activity of this compound, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in *Greene, et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1999. In

addition, adjacent groups on an "aryl" ring may combine to form a 5- to 7-membered saturated or partially unsaturated carbocyclic, aryl, heteroaryl or heterocyclic ring, which in turn may be substituted as above.

The term **"heterocyclic"**, alone or in combination, refers to a nonaromatic cyclic group that may be partially (containing at least one double bond) or fully saturated and wherein the ring contains at least one heteroatom selected from oxygen, sulfur, nitrogen, or phosphorus. The terms **"heteroaryl"** or **"heteroaromatic"**, alone or in combination, refer to an aromatic ring containing at least one heteroatom selected from sulfur, oxygen, nitrogen or phosphorus. The heteroaryl or heterocyclic ring may optionally be substituted by one or more substituent listed as optional substituents for aryl. In addition, adjacent groups on the heteroaryl or heterocyclic ring may combine to form a 5- to 7-membered carbocyclic, aryl, heteroaryl or heterocyclic ring, which in turn may be substituted as above. Nonlimiting examples of heterocylics and heteroaromatics are pyrrolidinyl, tetrahydrofuryl, tetrahydrofuranyl, pyranyl, purinyl, tetrahydropyranyl, piperazinyl, piperidinyl, morpholino, thiomorpholino, tetrahydropyranyl, imidazolyl, pyrolinyl, pyrazolinyl, indolinyl, dioxolanyl, or 1,4-dioxanyl. aziridinyl, furyl, furanyl, pyridyl, pyridinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, indazolyl, triazinayl, 1,3,5-triazinyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, benzofuranyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, oxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, isooxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyrrolyl, quinazolinyl, quinoxalinyl, benzoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, xanthinyl, hypoxanthinyl, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,3-oxadiazole, thiazine, pyridazine, triazolopyridinyl or pteridinyl wherein said heteroaryl or heterocyclic group can be optionally substituted with one or more substituent selected from the same substituents as set out above for aryl groups. Functional oxygen and nitrogen groups on the heteroaryl group can be protected as necessary or desired. Suitable protecting groups can include trimethylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl, trityl or substituted trityl, alkyl groups, acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

The term **"thienyl"**, alone or in combination, refers to a five member cyclic group wherein the ring contains one sulfur atom and two double bonds.

The term **"benzothienyl"**, alone or in combination, refers to a five member cyclic group wherein the ring contains one sulfur atom and two double bonds fused to a phenyl ring.

The term **"aryloxy"**, alone or in combination, refers to an aryl group bound to the molecule through an oxygen atom.

The term **"heteroaryloxy"**, alone or in combination, refers to a heteroaryl group bound to the molecule through an oxygen atom.

The term **"aralkoxy"**, alone or in combination, refers to an aryl group attached to an alkyl group which is attached to the molecule through an oxygen atom.

The term **"heterocyclearalkoxy"** refers to a heterocyclic group attached to an aryl group attached to an alkyl-O- group. The heterocyclic, aryl and alkyl groups can be optionally substituted as described above.

The terms **"halo"** and **"halogen"**, alone or in combination, refer to chloro, bromo, iodo and fluoro.

The terms **"alkoxy"** or **"alkylthio"**, alone or in combination, refers to an alkyl group as defined above bonded through an oxygen linkage (–O-) or a sulfur linkage (-S-), respectively. The terms **"lower alkoxy"** or **"lower alkylthio"**, alone or in combination, refers to a lower alkyl group as defined above bonded through an oxygen linkage (–O-) or a sulfur linkage (-S-), respectively.

The term **"acyl"**, alone or in combination, refers to a group of the formula C(O)R', wherein R' is an alkyl, aryl, alkaryl or aralkyl group, or substituted alkyl, aryl, aralkyl or alkaryl, wherein these groups are as defined above.

The term **"acetyl"**, alone or in combination, refers to the radical $-C(O)CH_3$.

The term **"amino"**, alone or in combination, denotes the radical $-NH_2$ or –NH-.

The term **"nitro"**, alone or in combination, denotes the radical $-NO_2$.

The term **"substituted"**, means that one or more hydrogen on the designated atom or substituent is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and the that the substitution results in a stable compound. When a subsitutent is "oxo" (keto) (i.e., =O), then 2 hydrogens on the atom are replaced.

The term **"alditol"**, as referred to herein, and unless otherwise specified, refers to a carbohydrate in which the aldehyde or ketone group has been reduced to an alcohol moiety. The alditols of the present invention can also be optionally substituted or deoxygenated at one or more positions. Exemplary substituents include hydrogen, halo, haloalkyl, carboxyl, acyl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, amino acid, amino acid esters and amides, phosphonyl, phosphinyl, phosphoryl, thioester, thioether, oxime, hydrazine, carbamate, phosphonic acid, and phosphonate,. Particular exemplary substituents include amine and halo, particularly fluorine. The substituent or alditol can be either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1999, hereby incorporated by reference. The alditol may have 3, 4, 5, 6 or 7 carbons. Examples of useful alditols are those derived from reduction of monosaccharides, including specifically those derived from the reduction of pyranose and furanose sugars.

The term **"carbohydrate"**, as referred to herein, and unless otherwise specified, refers to a compound of carbon, hydrogen and oxygen that contains an aldehyde or ketone group in combination with at least two hydroxyl groups.. The carbohydrates of the present invention can also be optionally substituted or deoxygenated at one or more positions. Carbohydrates thus include substituted and unsubstituted monosaccharides, disaccharides, oligosaccharides, and polysaccharides. The saccharide can be an aldose or ketose, and may comprise 3, 4, 5, 6, or 7 carbons. In one embodiment the carbohydrates are monosaccharides. In another embodiment the carbohydrates are pyranose and furanose sugars.

As used herein, the term **"patient"** refers to warm-blooded animals or mammals, and in particular humans, who are in need of the therapy described herein. The term "host", as used

herein, refers to a unicellular or multicellular organism, including cell lines and animals, and preferably a human.

Synthesis of the Active Compounds

The compounds of the present invention can be readily prepared by those skilled in the art of organic synthesis using commonly known methods, many of which are described by J, March, in *Advanced Organic Chemistry*, 4th Edition (Wiley Interscience, New York, 1992) and D. N. Dnar in *The Chemistry of Chalcones and Related Compounds* (Wiley-Interscience, New York, 1981), incorporated herein by reference.

Compounds of the present invention are prepared either by reacting a heteroaryl- or heterocyclic-substituted aryl or heteroaryl ketone with a suitably substituted aryl aldehyde or by reacting a suitably substituted aryl ketone with a heteroaryl- or heterocyclic-substituted aryl or heteroaryl aldehyde. This reaction, which is a condensation reaction, is suitably carried out under base- or acid-catalyzed conditions. The reaction may be suitably carried out in water or protic organic solvents such as lower alcohols (e.g. methanol, ethanol, *tert*-butanol), lower carboxylic acid (e.g. formic acid, glacial acetic acid, propionic acid), or in aprotic organic solvents such as ethers (e.g. tetrahydrofuran, dioxane, diethyl ether), liquid amides (e.g. dimethylformamide, hexamethylphosphordiamide), dimethylsulfoxide, or hydrocarbons (e.g. toluene, benzene), or mixtures of such solvents. When carrying out the reaction under basic conditions, the base may be selected from sodium, lithium, potassium, barium, calcium, magnesium, aluminum, ammonium, or quarternary ammonium hydroxides, lower alkoxides (e.g. methoxides, ethoxides, *tert*-butoxides), carbonates, borates, oxides, hydrides, or amides of lower secondary amines (e.g. diisopropyl amides, methylphenyl amides). Primary aromatic amines such as aniline, free secondary amines such as dimethyl amine, diethyl amine, piperidine, or pyrrolidine, tertiary amines such as pyridine, as well as basic ion exchange resins may also be used. Alternatively, a phase-transfer catalyst such as cetyl trimethyl ammonium chloride can also be used to facilitate the reaction, particularly when water is the solvent.

Alternatively, the aldol condensation reaction can also be carried out in an aprotic solvent such as tetrahydrofuran (THF) with an organic base. The preferred solvent is THF and

the preferred base is lithium diisopropylamide (LDA). In this manner an aldol reaction may take place first and the subsequent dehydration reaction may take place during an aqueous workup.

Acid catalysts may be selected from hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, sulfonic acids (such as paratoluenesulfonic or methansulfonic acid), lower carboxylic acid (such as formic, acetic, or propionic acid), lower halogenated carboxylic acid (such as trifluoroacetic acid), Lewis acids (such as BF_3, $POCl_3$, PCl_5, $FeCl_3$), or acid ion exchange resins.

The reaction may be carried out at temperatures in the range of –80 °C to +150 °C, preferrably in the range of 0 °C to +100 °C, and more preferably at room temperature. The time of reaction may be from 30 minutes to approximately 24 hours.

Compounds of the invention may be isolated as either mixtures of cis (*Z*) and trans (*E*) geometric isomers or either pure trans (*E*) isomers. If desired, either the mixtures or the pure trans isomers may be isomerized to the corresponding predominantly cis (*Z*) iomers using methods well known in the literature.

In the above reactions, it may be preferred or necessary to protect various sensitive or reactive groups present in the starting materials so as to prevent said groups from interfering with the reactions. Such protection may be carried out in a well-known manner as taught by Theodora W. Green and Peter G. M. Wuts, in *Protective Groups in Organic Chemistry Third Edition* (Wiley, 1999) or using methods from references cited therein or of the like. The protecting group may be removed after the reaction in a manner known *per se*.

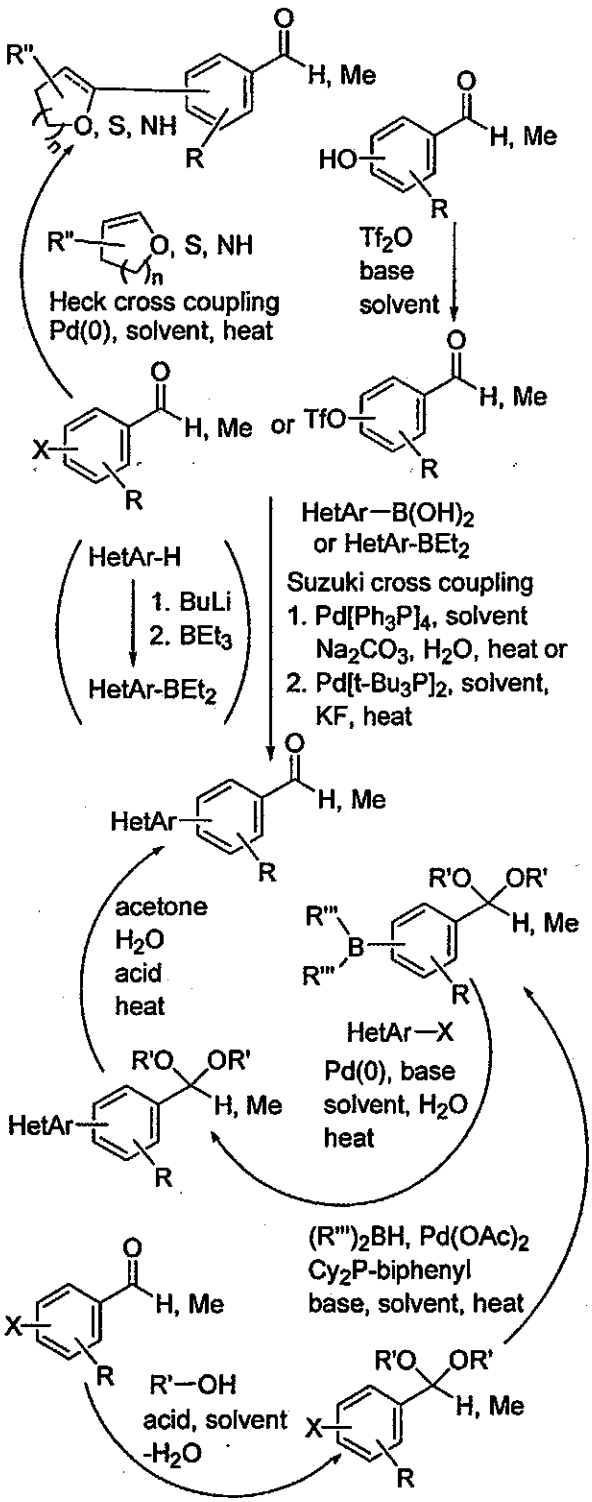
The following schemes will prove useful to those skilled in the art in manufacturing the compounds of the invention:

Legend for all schemes:

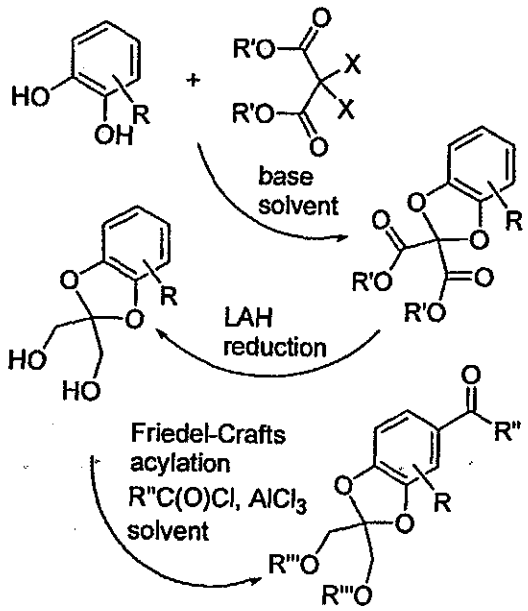
1. R, R', R'', R''', and R'''' can be any substitution including H;
2. R, R', R'', R''', and R'''' can be suitabaly functionalized;
3. R, R', R'', R''', and R'''' can represent multiple substitutions;
4. Two adjacent R, R', R'', R''', or R'''' can form a ring;
5. Dashed double bond can be at any location of a ring;

6. Y, Y', Y'', and Y''' independently represent N(H), O, or S,
7. X and X' independently represent Cl, Br, or I;
8. Each R, R', R'', R''', R'''', Y, Y', Y'', Y''', X or X' is independent in each scheme;
9. HetAr represents suitably substituted heterocyclic aryl;
10. Cy represents cyclohexyl.

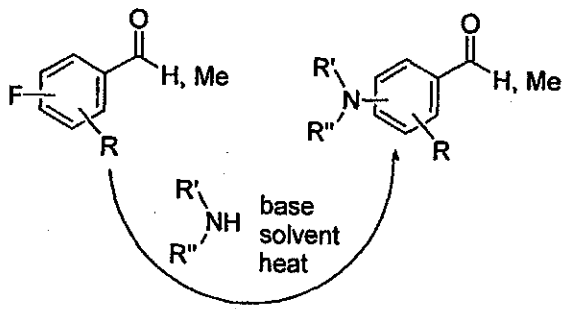
Scheme 1


R"
O, S, NH
H, Me
R
HO
Tf2O
base
solvent
Heck cross coupling
Pd(0), solvent, heat
X
or TfO
HetAr—B(OH)2
or HetAr-BEt2
Suzuki cross coupling
1. Pd[Ph3P]4, solvent
Na2CO3, H2O, heat or
2. Pd[t-Bu3P]2, solvent,
KF, heat
HetAr-H
1. BuLi
2. BEt3
HetAr-BEt2
HetAr
acetone
H2O
acid
heat
R'O
OR'
R'''
B
HetAr—X
Pd(0), base
solvent, H2O
heat
(R''')2BH, Pd(OAc)2
Cy2P-biphenyl
base, solvent, heat
R'—OH
acid, solvent
-H2O

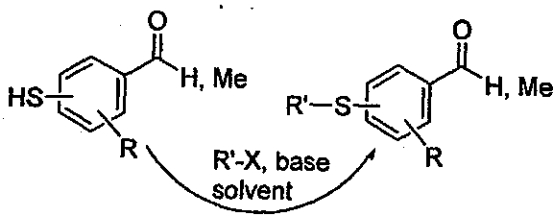
Scheme 2



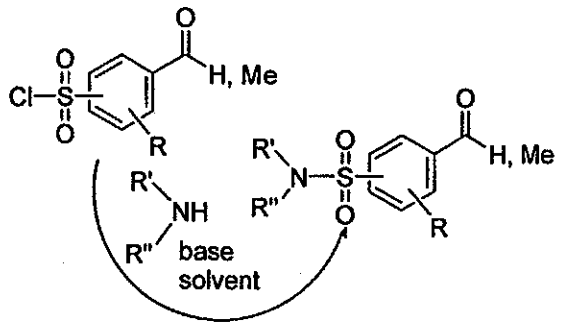
Scheme 3



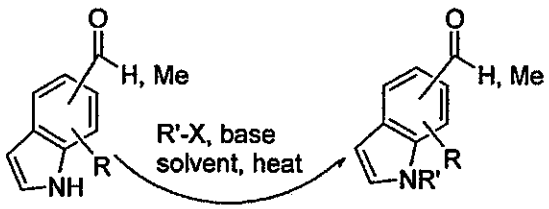
Scheme 4



Scheme 5

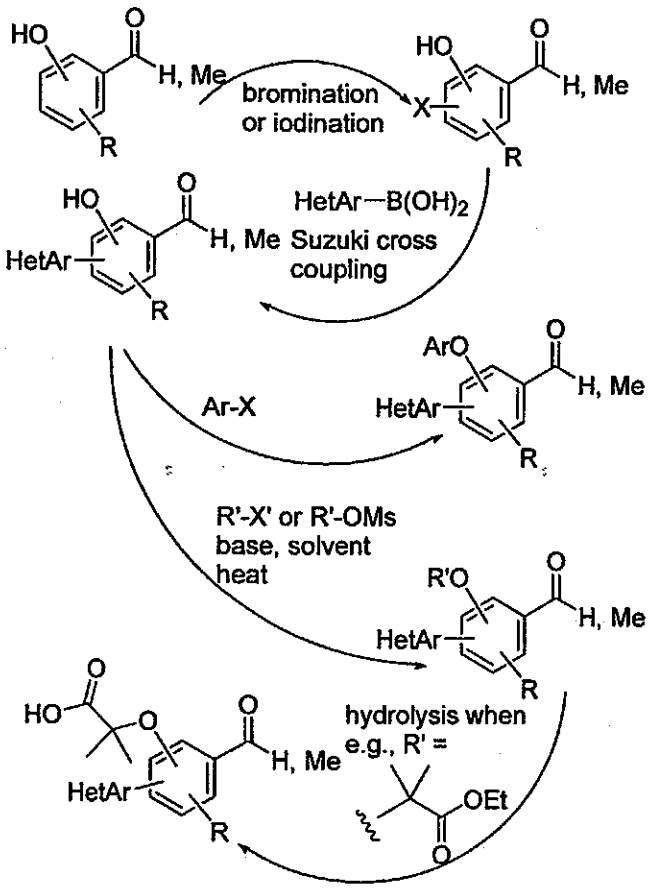


Scheme 6

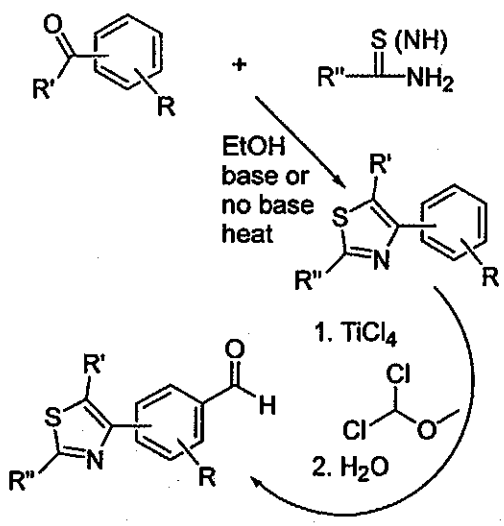


5

Scheme 7

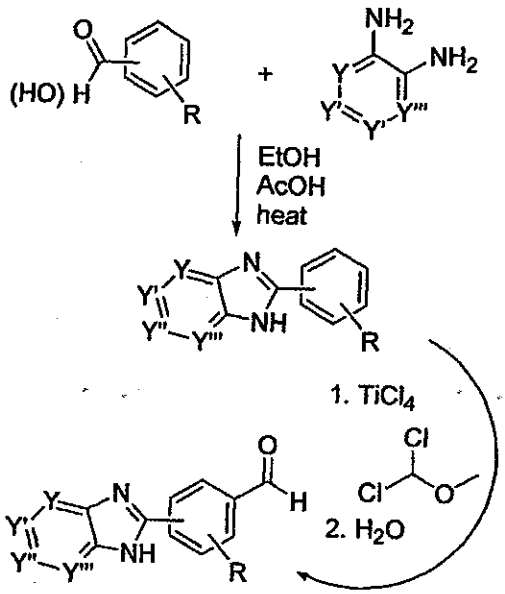

HO
O
H, Me
R
bromination
or iodination
X
HetAr—B(OH)2
Suzuki cross
coupling
HetAr
Ar-X
ArO
R'-X' or R'-OMs
base, solvent
heat
R'O
hydrolysis when
e.g., R' =
OEt

Scheme 8

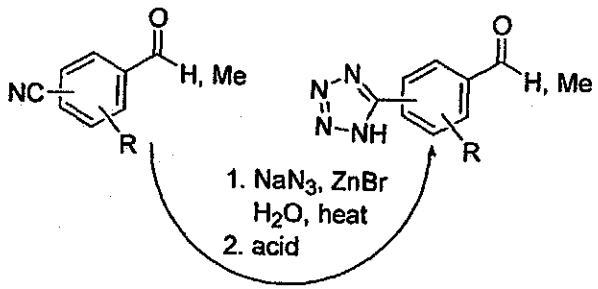

R'
R
S (NH)
R"
NH2
EtOH
base or
no base
heat
S
N
1. TiCl4
Cl
2. H2O

5

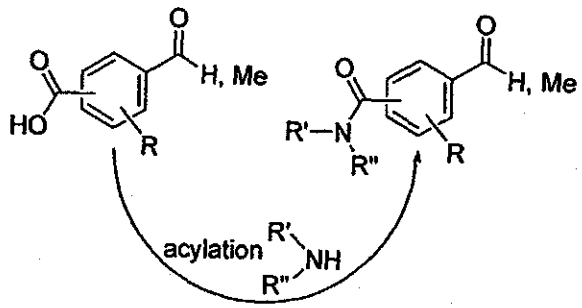
Scheme 9



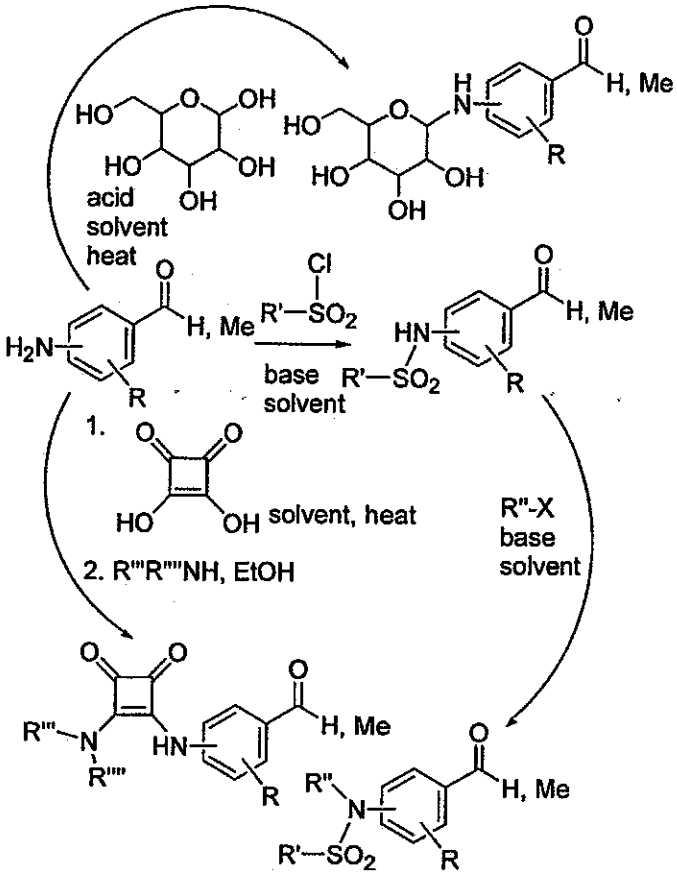
Scheme 10



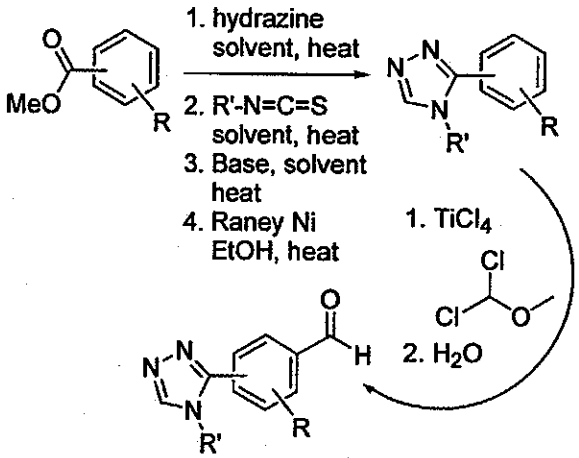
Scheme 11



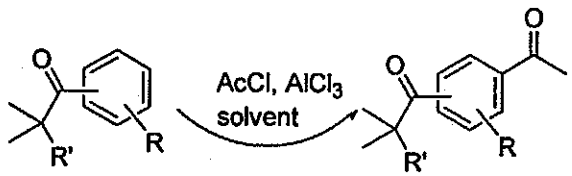
Scheme 12



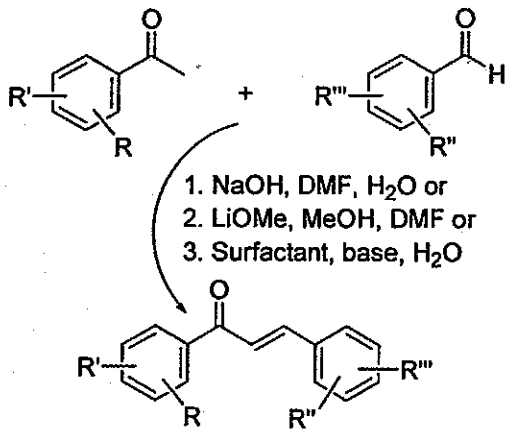
Scheme 13



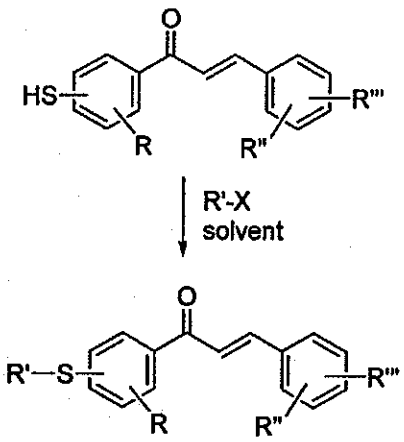
Scheme 14



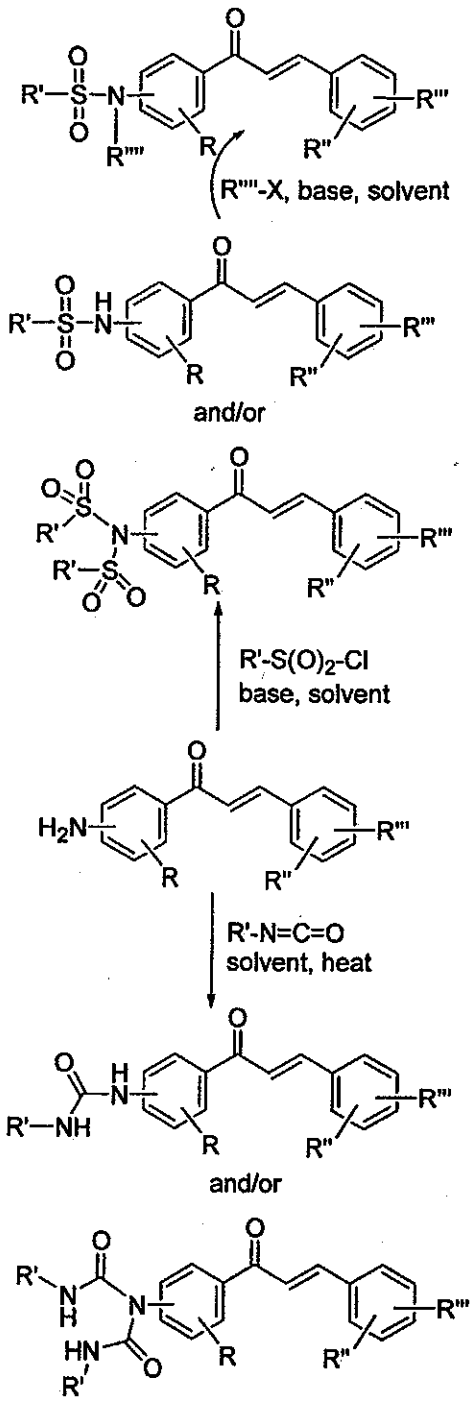
Scheme 15



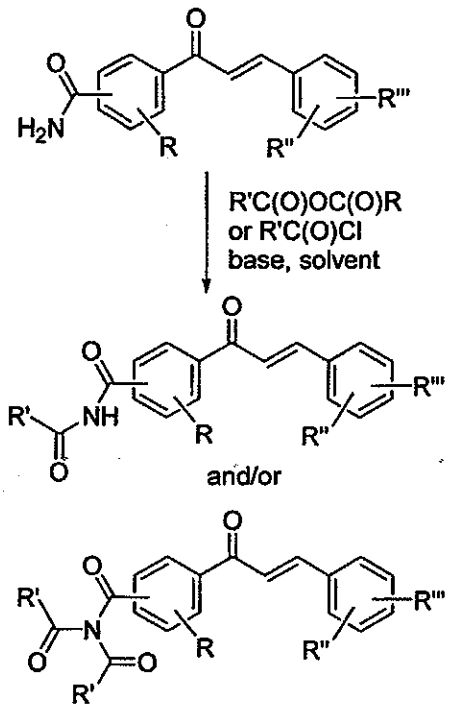
Scheme 16



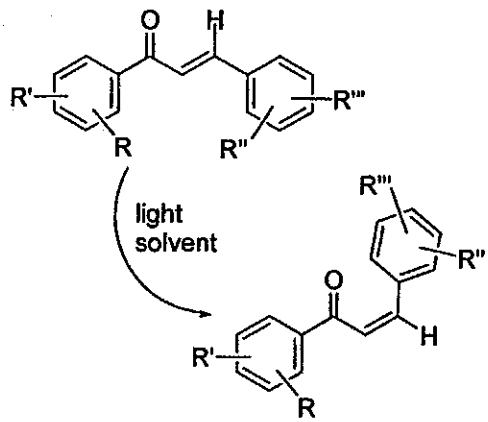
Scheme 17


R''''-X, base, solvent
and/or
R'-S(O)2-Cl
base, solvent
R'-N=C=O
solvent, heat
and/or

Scheme 18



Scheme 19

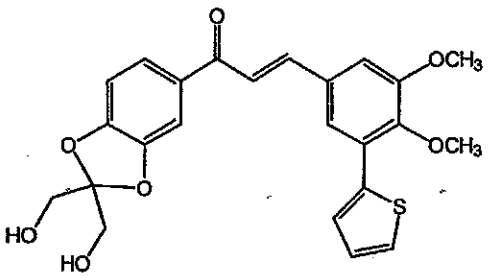


Examples

The following examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. All intermediates and final products have

been completely characterized by conventional proton NMR, mass spectral analyses and standard analytical methods known to those skilled in the art.

EXAMPLE 1



1-(2,2-Bis-hydroxymethyl-benzo[1,3]dioxol-5-yl)-3*E*-(3,4-dimethoxy-5-thiophen-2-yl-phenyl)-propenone

Ex-1A: Catechol (2.2 g, 20 mmol) was dissolved in acetone. Diethyl dibromomalonate (7.0 g, 22 mmol) and potassium carbonate (2.76 g) were added, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and water was added to the residue. The residue was extracted with dichloromethane, and the organic phase was washed with brine, dried over magnesium sulfate and evaporated. Chromatography (hexanes/ethyl acetate, 4:1) gave 3.9 g of benzo[1,3]dioxole-2,2-dicarboxylic acid diethyl ester. ^{1}H-NMR ($CDCl_3$) δ 6.90-6.97 (m, 4H), 4.37(q, J = 7 Hz, 4H), 1.32(t, J = 7 Hz, 6H).

Ex-1B: [Bis(ethoxycarbonyl)methyldenedioxy]benzene obtained from **Ex-1A** (3.9 g, 14.7 mmol) was dissolved in THF (100 mL) and cooled with ice-water. Lithium aluminum hydride (1 M solution in THF, 44 mL) was added dropwise, and the mixture was stirred overnight. The reaction was carefully quenched with saturated sodium sulfate until there was no further bubbling. The mixture was stirred overnight, then filtered, and the filtrate was dried over magnesium sulfate. Chromatography (dichloromethane/methanol, 10:1) gave 0.5 g of the desired (2-hydroxymethyl-benzo[1,3]dioxol-2-yl)-methanol. ^{1}H-NMR ($CDCl_3$) δ 6.82 (s, 4H), 3.94 (d, J = 7 Hz, 4H), 1.98 (t, J = 7 Hz, 2H).

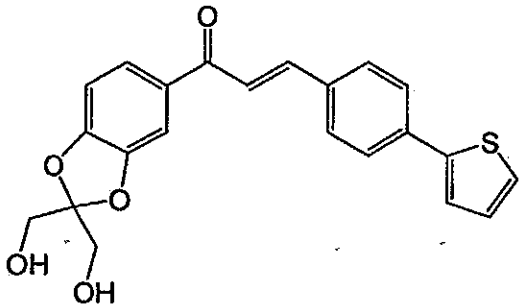
Ex-1C: Aluminum chloride (1.3 g) was added to nitromethane followed by the addition of acetyl chloride (1.86 g). Then (2-hydroxymethyl-benzo[1,3]dioxol-2-yl)-methanol obtained from **Ex-1B** (0.5 g) in nitromethane was added dropwise. The mixture was stirred overnight. Water was added to the reaction mixture, and it was extracted with dichloromethane. The organic phase was washed with brine, dried over magnesium sulfate and evaporated. Chromatography gave 0.28 g of 5-acetyl-benzo[1,3]dioxole-2,2-dicarboxylic acid diethyl ester. ^{1}H-NMR ($CDCl_3$) δ 7.56 (d, J = 7 Hz, 1H), 7.43 (s, 1H), 6.85 (d, J = 7 Hz, 1H), 4.42 (s, 4H), 2.53 (s, 3H), 2.05 (s, 6H).

Ex-1D: A solution of 5-bromo-3,4-dimethoxybenzaldehyde (10.23 g, 41.7 mmol) in 359 mL of ethylene glycol dimethyl ether was purged with nitrogen gas for 30 min. The solution was treated with tetrakis(triphenylphosphine)palladium(0) (5.0 g, 4.3 mmol), thiophene-2-boronic acid (8.01 g, 62.6 mmol), and a solution of 2 N sodium carbonate 72 mL, 3.45 mmol). The reaction was refluxed for 16 h. The reaction mixture was concentrated, diluted with an aqueous solution of saturated sodium bicarbonate (75 mL), and extracted with dichloromethane (2 x 100 mL). The organic layer was dried over sodium sulfate and concentrated to a brown solid. The crude material was purified by silica gel chromatography (1:1 ethyl acetate/hexanes) to give 9.42 g (90%) of the desired 3,4-dimethoxy-5-(thien-2-yl)benzaldehyde product. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1 H), 7.79 (d, 1 H), 7.57 (dd, 1 H), 7.41 (d, 1 H), 7.36 (d, 1 H), 7.13 (dd, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H).

5-Acetyl-benzo[1,3]dioxole-2,2-dicarboxylic acid diethyl ester obtained from **Ex-1C** (0.28 g, 1.11 mmol) and 3,4-dimethoxy-5-(thien-2-yl)benzaldehyde obtained from **Ex-1D** (0.275 g, 1.11 mmol) were dissolved in ethanol, and 50% sodium hydroxide solution (0.4 mL) was added. The mixture was stirred at room temperature overnight. Most of the solvent was removed under reduced pressure, and water was added to the remainder. The resulting product was extracted with dichloromethane. The organic phase was dried over magnesium sulfate and evaporated. Chromatography gave 0.19 g (38%) of the title compound as a yellow solid, m.p. 74-80 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 1 H), 7.63 (dd, 1 H), 7.49-7.55 (m, 3 H), 7.38 (d, 1 H), 7.37 (d, 1 H), 7.12 (dd, 1 H), 7.07 (d, 1 H), 6.88 (d, 1 H), 3.99 (s, 4 H), 3.98 (s, 3

H), 3.88 (s, 3 H). Anal. Calculated for $C_{24}H_{22}O_7S$: C, 63.42; H, 4.88; S, 7.06; found: C, 63.46; H, 5.11; S, 6.55.

EXAMPLE 2

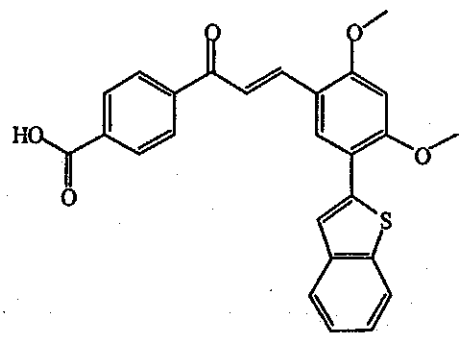


1-(2,2-Bis-hydroxymethyl-benzo[1,3]dioxol-5-yl)-3*E*-(4-thiophen-2-yl-phenyl)-propenone

Ex-2A: 4-(Thien-2-yl)benzaldehyde was obtained in a similar manner as described in **Ex-1D** from 4-bromobenzaldehyde. ^{1}H-NMR ($CDCl_3$) δ 10.00 (s, 1H), 7.88 (d, J = 9 Hz, 2H), 7.77 (d, J = 9 Hz, 2H), 7.46 (d, J = 4 Hz, 1H), 7.39-7.41 (m, 1H), 7.12-7.15 (m, 1H).

The title compound was obtained when 5-acetyl-benzo[1,3]dioxole-2,2-dicarboxylic acid diethyl ester from **Ex-1C** was condensed with 4-(Thien-2-yl)benzaldehyde from **Ex-2A** in a similar manner as described in **Ex-1**. Yellow solid, mp 166-168°C, 23.6% yield. ^{1}H-NMR ($CDCl_3$) δ 7.77 (d, J = 15Hz, 1H), 7.60-7.65 (m, 5H), 7.51 (d, J = 2 Hz, 1H), 7.45 (d, J = 15 Hz, 1H), 7.37-7.38 (m, 1H), 7.32(d, J = 5 Hz, 1H), 7.09 (dd, J= 4, 5 Hz, 1H), 6.88 (d, J = 8 Hz, 1H), 3.96 (d, J = 7 Hz, 4H). MS *m/z* = 394 ([M]$^+$, 50%), 363 (100%). HRMS (EI) Calcd. for $C_{22}H_{18}O_5S$: 394.0875. Found: 394.0869.

EXAMPLE 3



4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid

Ex-3A: A sample of 5-bromo-2,4-dimethoxybenzaldehyde (4.9 g, 20.0 mmol) was dissolved in ethylene glycol dimethyl ether (50 mL). Tetrakis(triphenylphosphine)palladium(0) (2.32 g, 2 mmol) was added, and the mixture was stirred at room temperature under nitrogen for 5 min. Benzo[*b*]thiophene-2-boronic acid (4.27 g, 24 mmol) and sodium carbonate solution (2 M, 20 mL) were added. The mixture was stirred at reflux under nitrogen for 24 hours. Upon cooling to room temperature, the mixture was poured into water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated. Silica gel chromatography (hexane/ethyl acetate 2:1 then 1:1) gave 4.75 g (83%) of the desired 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde. ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.20 (s, 1H), 7.83-7.78 (m, 2H), 7.68 (s, 1H), 7.36-7.27 (m, 2H), 6.54 (s, 1H), 4.06 (s, 3H), 4.00 (s, 3H).

An alternative procedure: 5-bromo-2,4-dimethoxybenzaldehyde (20 g), benzo[*b*]thiophene-2-boronic acid (16 g) and THF (200 mL) were sequentially charged into a clean reaction vessel fitted with a reflux condenser, mechanical stirrer and nitrogen inlet adapter. Nitrogen was bubbled into the resulting solution for 20 min followed by the sequential addition of KF (10 g), and $Pd(^tBu_3P)_2$ (0.417 g). The solution was immediately heated to 60 °C and aged for 1.5 h. (Note: The HPLC assay at this point routinely indicated complete consumption of 5-bromo-2,4-dimethoxybenzaldehyde, < 0.5 area% of benzo[*b*]thiophene-2-boronic acid along with 0.5 area% of an unknown (0.55 RRT). These impurities are removed during crystallization.) Upon completion, as determined by HPLC, the reaction was diluted with H_2O (200 mL) and transferred to a separatory funnel containing EtOAc (200 mL) and H_2O (200 mL). The layers were cut and the aqueous layer was extracted with EtOAc (100 mL). The combined organic cuts were filtered through a pre-washed pad of solka floc (5 g). The pad of solka floc and spent catalyst were washed with fresh EtOAc (200 mL) and this wash combined with the batch. The resultant filtrate was batch concentrated and solvent switched to 33 wt% 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde in THF in preparation for crystallization. (Note: The internal temperature during batch concentration should be kept above 45 °C to prevent premature crystallization.) The resulting THF solution of 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde was then charged with heptane (20 mL) and slowly cooled to ambient

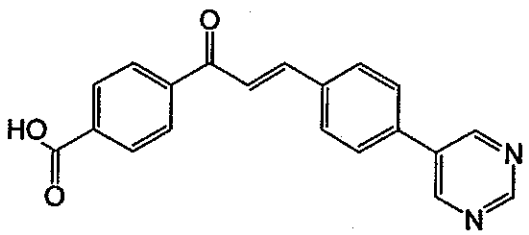
temperature. Crystallization was then completed with the slow addition of heptane (175 mL) and cooling to 4 °C. After aging for 1 h, the batch was filtered and then dried on the filter funnel under a stream of N_2. The semi-wet cake was then transferred to clean trays and dried to a constant weight in the vacuum oven (40 °C, 20 inHg) affording 23.74 g (97% yield) of desired 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde as a light orange crystalline solid, m.p. 134-136 °C. HPLC assay of this solid indicated > 99.9 LCAP. ^{1}H-NMR identical as above.

To a solution of 4-acetylbenzoic acid (1.50 g, 9.1 mmol) and 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde from **Ex-3A** (3.27 g, 11.0 mmol) in *N,N*-dimethylformamide (76 mL) was added a solution of sodium hydroxide (5 M, 7.3 mL, 36.5 mmol). The reaction mixture was allowed to stir at room temperature for 2 h and was then diluted with water to a volume of 150 mL. The solution was washed with dichloromethane and acidified with concentrated sulfuric acid to pH = 3. The resulting solution was then extracted with dichloromethane. The dichloromethane extract was washed with brine, dried over sodium sulfate and concentrated. The resulting oily product solidified in ethanol. The solid was further stirred in ethanol for one day and collected by filtration. The solid was washed with ethanol, then dried *in vacuo* to afford the title compound as a yellow solid (2.2 g, 54%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.21 (d, 2H), 8.07 (m, 3H), 7.93 (m, 3H), 7.82 (d, 1H), 7.32 (m, 2H), 6.86 (s, 1H), 4.08 (s, 3H), 4.00 (s, 3H). Anal. Calculated for $C_{26}H_{20}O_5S \cdot 1/6H_2O$: C, 69.78; H, 4.58; S, 7.17; found: C, 69.95; H, 4.69; S, 7.15. HPLC purity: 97.9% (area percentage).

An alternative procedure: 5-(Benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde from **Ex-3A** (42.3 g), 4-acetylbenzoic acid (22.1 g), MeOH (250 mL) and DMF (600 mL) were sequentially charged into a clean reaction vessel fitted with a mechanical stirrer and nitrogen inlet adapter. After complete dissolution, LiOMe (10.5 g) was added in one portion and the resulting solution was aged at 40 °C for 2 h. Upon completion, as determined by HPLC, the reaction mixture was transferred to a separatory funnel containing cold H_2O (800 mL, precooled to 10 deg C). An additional 400 mL cold H_2O was used to rinse the reaction vessel and this rinse was also added to the seperatory funnel. The combined aqueous was washed with iPrOAc (500 mL) and then acidified to a pH of 3 with 6 N HCl (ca. 60 mL). The resulting heterogeneous solution was aged

for 30 min and then the precipitate was filtered, washed with 70% EtOH (100 mL) and dried on the filter funnel under a stream of N_2 affording desired acid **5** as a crude yellow solid. The crude dry product and THF (260 mL) were charged into a clean reaction vessel fitted with a mechanical stirrer and nitrogen inlet adapter. Heptane (30 mL) was slowly added to the resulting solution over 30 min and then aged resulting in crystallization. Additional heptane (270 mL) was added over 1 h, aged for an additional 1 h and then filtered. The reaction vessel was then rinsed with 70% EtOH (100 mL) and this rinse was added to the filter cake. The wet cake was then transferred to a clean reaction vessel containing 70% EtOH (750 mL) and the resulting heterogeneous mixture was stirred overnight. The product was then filtered, rinsed with fresh 70% EtOH (100 mL) and then dried on the filter funnel under a stream of N_2. The semi-wet cake was then transferred to clean trays and dried to a constant weight in the vacuum oven (40 °C, 20 inHg) affording 52.05 g (87% yield) of desired 4-[3-(5-benzo[b]thiophen-2-yl-2,4-dimethoxy-phenyl)-*E*-acryloyl]-benzoic acid **5** as a yellow crystalline solid, m.p. 231-232 °C (dec.). HPLC assay of this solid indicated > 99.9 LCAP. ^{1}H-NMR identical as above.

EXAMPLE 4



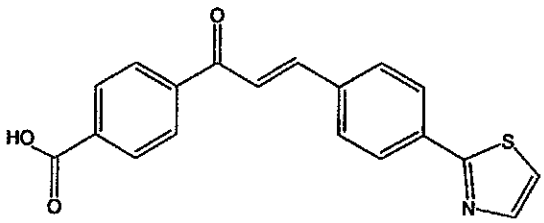
4-[3*E*-(4-Pyrimidin-5-yl-phenyl)-acryloyl]-benzoic acid

Ex-4A: 4-Pyrimidin-5-yl-benzaldehyde was obtained pyrimidine-5-boronic acid and 4-bromobenzaldehyde in a similar manner as described in **Ex-3A**, 88.6% yield. ^{1}H-NMR ($CDCl_3$) δ 10.11 (s, 1H), 9.28 (s, 1H), 9.01(s, 2H), 8.05 (d, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 2H).

The title compound was obtained in a similar manner as described in **Ex-3** from 4-pyrimidin-5-yl-benzaldehyde (**Ex-4A**) and 4-acetylbenzoic acid. Yellow solid, mp >260°C, 45% yield. ^{1}H-NMR (DMSO-d_6) δ 9.21 (s, 2H), 9.19 (s, 1H), 8.24 (d, J = 9 Hz, 2H), 8.01-8.09 (m, 5H), 7.9

(d, J = 6 Hz, 2H), 7.81(d, J = 15Hz, H), MS *m/z* = 330 ([M]$^+$, 100%). HRMS (EI) Calcd. for $C_{20}H_{14}N_2O_3$: 330.1004. Found: 330.1000.

EXAMPLE 5

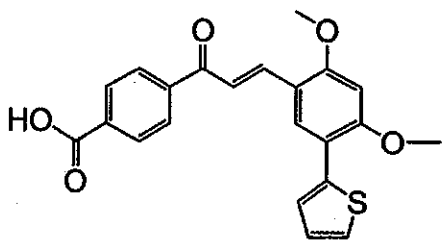


4-[3*E*-(4-Thiazol-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-5A: 4-Thiazol-2-yl-benzaldehyde was prepared from 4-bromobenzaldehyde and thiazole-2-boronic acid in a similar manner as described in **Ex-3A**, 82% yield. ^{1}H-NMR ($CDCl_3$) δ 10.07 (s, 1H), 8.15 (d, J = 8 Hz, 2H), 7.95-7.98 (m, 3H), 7.45 (d, J = 3 Hz, 1H). HMRS (EI) calcd. for $C_{10}H_7NOS$: 189.0248; found: 189.0242.

The title compound was obtained in a similar manner as described in **Ex-3** from 4-thiazol-2-yl-benzaldehyde (**Ex-5A**) and 4-acetylbenzoic acid. Yellow solid, mp 232-235°C, 20% yield. ^{1}H-NMR ($CDCl_3$) δ 8.24 (d, J = 9 Hz, 2H), 8.11 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H), 7.93 (d, J = 3 Hz, 1H), 7.86 (d, J = 15 Hz, 1H), 7.74(d, J = 9Hz, 2H), 7.57 (d, J = 15 Hz, 1H), 7.41 (d, J = 3 Hz, 1H), MS *m/z* = 335 ([M]$^+$, 100%). HRMS (EI) Calcd. for $C_{19}H_{13}NO_3S$: 335.0616. Found: 335.0618.

EXAMPLE 6

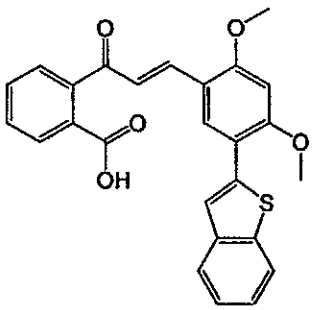


4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-6A: 5-bromo-2,4-dimethoxybenzaldehyde (20.3 g), thiophene-2-boronic acid (11.6 g) and THF (200 mL) were sequentially charged into a clean reaction vessel fitted with a reflux condenser, mechanical stirrer and nitrogen inlet adapter. Nitrogen was bubbled into the resulting solution for 20 min followed by the sequential addition of KF (10.1 g), and $Pd(^tBu_3P)_2$ (0.424 g). The solution was immediately heated to 60 °C and aged for 1.5 h. The reaction was diluted with H_2O (200 mL) and transferred to a separatory funnel containing EtOAc (200 mL) and H_2O (200 mL). The layers were cut and the aqueous layer was extracted with EtOAc (100 mL). The combined organic cuts were filtered through a pre-washed pad of solka floc (5 g). The pad of solka floc and spent catalyst were washed with fresh EtOAc (200 mL) and this wash combined with the batch. The resultant filtrate was concentrated to dryness. The crude product was dissolved in THF (38 mL) and crystallized upon heptane (152 mL) addition. The product was filtered and then dried to a constant weight in the vacuum oven (38 °C, 20 inHg) affording 19.32 g (94% yield) of desired 2,4-dimethoxy-5-thiophen-2-yl-benzaldehyde as a light off-white solid, m.p. 125-126°C. ^{1}H-NMR (300 MHz, $CDCl_3$): 10.34 (s, 1 H), 8.12 (s, 1 H), 7.44 (dd, 1 H, J = 3.5 and 1.5 Hz), 7.31 (dd, 1 H, J = 5.2 and 1.5 Hz), 7.07 (dd, 1 H, J = 5.2 and 3.5 Hz), 6.51 (s, 1 H), 4.02 (s, 3 H), 3.99 (s, 3 H).

2,4-Dimethoxy-5-thiophen-2-yl-benzaldehyde from **Ex-6A** (7.81 g), 4-acetylbenzoic acid (4.9 g), MeOH (60 mL) and DMF (150 mL) were sequentially charged into a clean reaction vessel fitted with a stir bar and nitrogen inlet adapter. After complete dissolution LiOMe (4.60 g) was added and the resulting solution was aged for 5 h. The reaction was diluted with H_2O (200 mL) and transferred to a separatory funnel containing iPrOAc (100 mL). The layers were cut and the aqueous layer was acidified to a pH of 1 with 3 N HCl. The resulting precipitate was filtered and then dried on the filter funnel under a stream of N_2. The crude product was then dissolved in THF (60 mL) and crystallized with the addition of heptane (60 mL). The product was filtered and then dried to a constant weight in the vacuum oven affording 8.9 g (75% yield) of the title compound as a yellow solid, m.p. 213-216°C. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.20 (d, 2 H, J = 8.5 Hz), 8.09 (d, 1 H, J = 16.1 Hz), 8.06 (d, 2 H, J = 8.5 Hz), 7.85 (s, 1 H), 7.52 (d, 1 H, J = 16.1 Hz), 7.40 (m, 1 H), 7.30 (dd, 1 H, J = 5.2 and 1.7 Hz), 7.08 (dd, 1 H, J = 5.2 and 3.6 Hz), 6.53 (s, 1 H), 3.98 (s, 3 H), 3.97 (s, 3 H); EIMS m/z = 394 (M^+). Anal. calc. for $C_{22}H_{18}O_5S$: C, 66.99; H, 4.60; S, 8.13; found: C, 66.71; H, 4.59; S, 8.10.

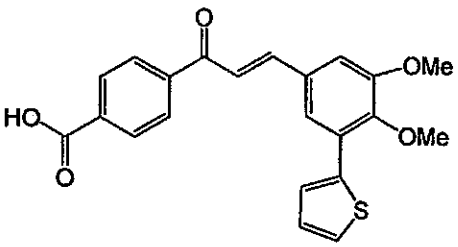
EXAMPLE 7



2-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid

The title compound was obtained starting from 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde from **Ex-3A** and 2-acetylbenzoinc acid in a similar manner as described in **Ex-3**. Yellow solid, mp 220-223 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ 8.01 (s, 1H), 7.88 (d, J = 7.3 Hz, 1H), 7.80-7.75 (m, 2H), 7.45-7.24 (m, 7H), 7.11 (d, J = 16.2 Hz, 1H), 6.79 (s, 1H), 4.00 (s, 3H), 3.88 (s, 3H). MS *m/z* = 445 (M^+, 100%).

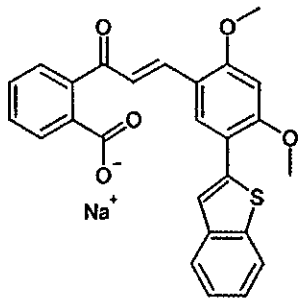
EXAMPLE 8



4-[3*E*-(3,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

The title compound was obtained in a similar manner as described in **Ex-3** from 3,4-dimethoxy-5-(thien-2-yl)benzaldehyde (**Ex-1D**) and 4-acetylbenzoic acid. Yellow solid, mp 231°C. ^{1}H-NMR (DMSO-d_6) δ 8.23 (d, 2H), 8.08 (d, 2H), 7.96 (d, 1H), 7.90 (m, 1H), 7.77 (m, 2H), 7.59 (d, 1H), 7.54 (m, 1H), 7.13 (dd, J= 4, 4 Hz, 1H). MS *m/z* = 395 ($[M+H]^+$, 100%).

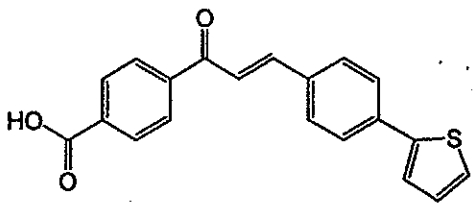
EXAMPLE 9



2-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid, sodium salt

To a solution of 2-acetyl-benzoic acid (0.75g, 4.6 mmol) and 5-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-benzaldehyde (**Ex-3A**, 1.64g, 5.5 mmol) in *N,N*-dimethylformamide (38 mL) was added sodium hydroxide (5M, 3.7 mL, 18.5 mmol). The reaction mixture was allowed to stir for 2 hours at ambient temperature and was diluted with water (50 mL) and sodium carbonate (2M, 20 mL). The aqueous solution was extracted with dichloromethane. A yellow precipitate formed in dichloromethane and was collected by filtration, washed with dichloromethane, dried *in vacuo* to give the title compound as a yellow solid (1.53g, 67 %), mp 214-217 °C (dec). ^{1}H-NMR (DMSO-d_6) δ 7.93-7.87 (m, 3H), 7.77(d, J = 8.0 Hz, 2H), 7.33-7.26 (m, 4H), 7.09-7.06 (m, 2H), 7.01 (d, J = 17.0 Hz, 1H), 6.78 (s, 1H), 3.99 (s, 3H), 3.88 (s, 3H). MS *m/z* = 467([M + Na]$^+$, 75%), 445 ([M + H]$^+$, 100%). Anal. ($C_{26}H_{19}O_5SNa$•1.3H_2O) Calc. C 63.55, H 4.35, S 6.52, found C 63.74, H, 4.44, S 6.55.

EXAMPLE 10

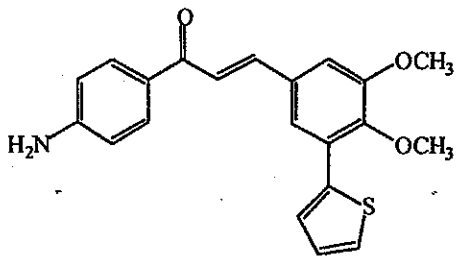


4-[3*E*-(4-Thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

The title compound was obtained by condensing 4-(thien-2-yl)benzaldehyde from **Ex-2A** and 4-acetylbezoic acid in a similar manner as described in **Ex-3**. Yellow solid, 56% yield, mp >260 °C. ^{1}H-NMR (DMSO-d_6) δ 8.01-8.08 (m, 4H), 7.72 (d, J = 8 Hz, 2H), 7.68 (s, 2H), 7.61 (d, J = 8 Hz, 2H), 7.41 (d, J = 4 Hz, 1H), 7.35 (d, J = 4 Hz, 1H), 7.04 (dd, J = 4, 8 Hz, 1H). MS

m/z = 334([M + Na]$^+$, 100%). Anal. ($C_{22}H_{14}O_3S$) Calc. C 71.84, H 4.22, S 9.59, found C 71.44, H 4.32, S 9.43.

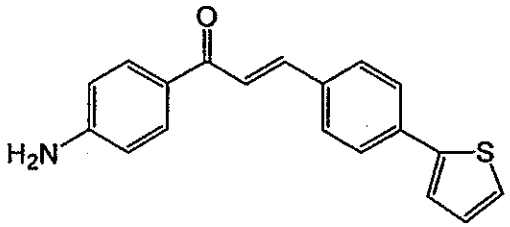
EXAMPLE 11



1-(4-Amino-phenyl)-3*E*-(3,4-dimethoxy-5-thiophen-2-yl-phenyl)-propenone

A suspension of 3,4-dimethoxy-5-(thien-2-yl)benzaldehyde (1.8 g, 7.4 mmol) from **Ex-1D** in an aqueous solution of 5 N potassium hydroxide (37 mL) was treated with cetyltrimethyl ammonium chloride (39 mL, 29.6 mmol) and 4-aminoacetophenone (1.0 g, 7.4 mmol). The reaction was stirred for 16 h at room temperature. The reaction mixture was titrated with 6 M H_2SO_4 to a pH of 7. The mixture was extracted with dichloromethane (2 x 75 mL). The organic layer was washed with aqueous $NaHCO_3$ (2 x 25 mL), brine, dried over sodium sulfate, and concentrated to a yellow foam. The crude material was purified by silica gel chromatography (1:1 ethyl acetate and hexanes) to give 720.0 mg (27%) of the title compound as a yellow solid, mp. 67–71 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (d, 2 H), 7.75 (d, 1 H), 7.54 (s, 1H), 7.53 (s, 1 H), 7.46 (d, 1 H), 7.39 (d, 1H), 7.13 (d, 1H), 7.11 (m, 1H), 6.72 (d, 2H), 4.16 (s, 2H), 3.97 (s, 3H), 3.87 (s, 3H). Anal. calculated for $C_{21}H_{19}NO_3S$•1/5 H_2O: C, 68.60, H, 5.28, S, 8.72; found C: 68.51, H: 5.40, S: 8.69. MS (Pos. Ion ES): calcd for $C_{21}H_{20}NO_3S$: *m/z* = 366 [M+H]$^+$, found: *m/z* = 366 [M+H]$^+$.

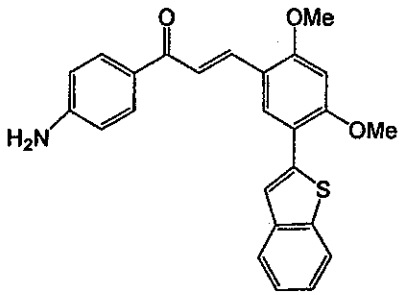
EXAMPLE 12



1-(4-Amino-phenyl)-3*E*-(4-thiophen-2-yl-phenyl)-propenone

The title compound was prepared from 4-(thien-2-yl)benzaldehyde (**Ex-2A**) and 4-aminoacetophenone in a similar manner as described in **Ex-11**. Yellow solid, 45% yield, mp 185-187°C. ^{1}H-NMR ($CDCl_3$) δ 7.95 (d, 2 H), 7.79 (d, 1H), 7.65 (m, 4H), 7.55 (d, 1H), 7.39 (d, 1H), 7.33 (dd,J=5, 5 Hz, 1H), 7.11 (dd, J= 5, 5 Hz, 1H), 6.71 (d, 2H), 4.16 (s, 2H). MS *m/z* = 305 ($[M]^+$, 100%). Anal. calculated for $C_{19}H_{15}NOS$: C, 74.72, H, 4.95, S, 10.50; found C: 74.60, H: 5.05, S: 10.42.

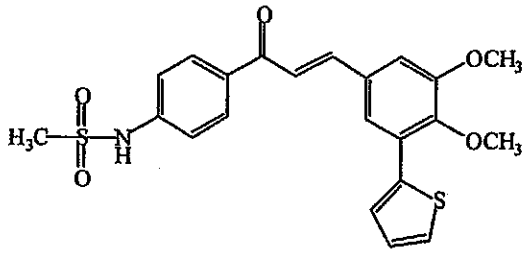
EXAMPLE 13



1-(4-Amino-phenyl)-3*E*-(5-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-propenone

The title compound was prepared from 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde (**Ex-3A**) and 4-aminoacetophenone in a similar manner as described in **Ex-11**. Yellow solid, 24% yield, mp 98-104°C. ^{1}H-NMR ($CDCl_3$) δ 8.10 (d, 1 H), 7.95 (m, 3H), 7.82 (m, 2H), 7.67 (s, 1H), 7.60 (d, 1H), 7.32 (dd, J = 8.8 Hz, 2H), 6.71 (d, 2H), 6.57 (s, 1H), 4.11(br s, 2H), 4.02 (s, 3H), 3.99 (s, 3H). MS *m/z* = 415 ($[M]^+$, 39%), 384 (100%). Anal. calculated for $C_{25}H_{21}NO_3S \cdot 1/3\ H_2O$: C, 71.24, H, 5.18, S, 7.61; found C: 71.63, H: 5.18, S: 7.55.

EXAMPLE 14

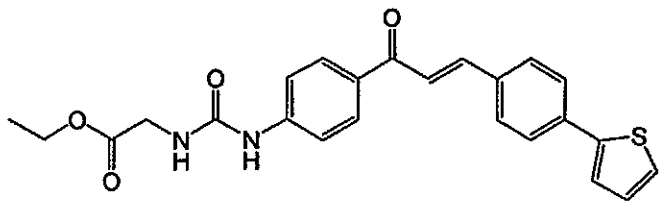


***N*-{4-[3*E*-(3,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-phenyl}-methanesulfonamide**

Ex-14A: A solution of 1-(4-amino-phenyl)-3*E*-(3,4-dimethoxy-5-thiophen-2-yl-phenyl)-propenone (**Ex-11**, 472.2 mg, 1.3 mmol) and triethylamine (398.63 µL, 2.86 mmol) was stirred in 20 mL of anhydrous dichloromethane. The mixture was treated with mesyl chloride (100 µL, 1.3 mmol). The reaction mixture was stirred for 16 hours and heated gently for another 4 hours. The crude material was purified by silica gel chromatography (1:3 ethyl acetate/hexane) to give 337.0 mg (quantitative) of 1-[4-bis-(methanesulfonyl)aminophenyl]-3*E*-[(3,4-dimethoxy-5-(thien-2-yl)phenyl]-propenone. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 2H), 7.76 (d, 1H), 7.53 (m, 2H), 7.49 (d, 2H), 7.38 (m, 1H), 7.36 (d, 1H), 7.10 (m, 1H), 7.08 (m, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.42 (s, 6H).

A solution of 1-[4-bis-(methanesulfonyl)aminophenyl]-3*E*-[(3,4-dimethoxy-5-(thien-2-yl)phenyl]-propenone (378.86 mg, 0.73 mmol) from **Ex-14A** in tetrahydrofuran (6.6 mL) was treated with aqueous 1N NaOH (1.4 mL, 1.4 mmol). The reaction was stirred at room temperature for 1 h. The reaction was titrated with 1 N HCl to a pH of 6. The crude material was purified by silica gel chromatography (5% MeOH/CH_2Cl_2 with 1% acetic acid) to give 269.2 mg (83%) of the title compound as a solid, 83% yield, mp. 71 - 75 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 2H), 7.76 (d, 1H), 7.52 (m, 2H), 7.40 (d, 1H), 7.37 (m, 1H), 7.29 (d, 2H), 7.10 (m, 1H), 7.08 (m, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.12 (s, 1H), 3.09 (s, 3H). MS (Pos. Ion ES): calcd for $C_{22}H_{22}NO_5S_2$: *m/z* = 444 $[M+H]^+$, found: *m/z* = 444 $[M+H]^+$. HRMS m/z: calc. 444.0939, found 444.0953.

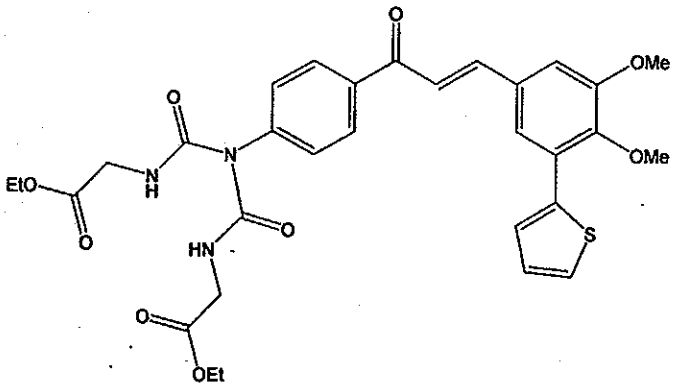
EXAMPLE 15



(3-{4-[3*E*-(4-Thiophen-2-yl-phenyl)-acryloyl]-phenyl}-ureido)-acetic acid ethyl ester

A solution of 1-(4-amino-phenyl)-3-(4-thiophen-2-yl-phenyl)-propenone (**Ex-12**, 250 mg, 0.80 mmol) and isocyanato-acetic acid ethyl ester (105.7 mg, 0.80 mmol) in toluene (15 mL) was refluxed for 16 hours. The reaction mixture was cooled to room temperature and the crude product precipitated out of solution. The material was suctioned filtered and dried on hi-vac to give 280.2 mg (79%) of the title compound as a yellow solid, mp 209-212°C. ^{1}H-NMR (DMSO-d6) δ 9.29 (br s, 1 H), 8.08 (d, 2H), 7.90 (m, 3H), 7.71 (d, 3H), 7.60 (m, 4H), 7.14 (t, 1H), 6.61 (t, 1H), 4.09 (q, 2H), 3.86 (dd, J= 2,6 Hz, 2H), 1.17 (t, 3H). MS *m/z* = 435 ([M+H]$^+$, 100%). HRMS m/z: calc. 435.1378, found 435.1375.

EXAMPLE 16

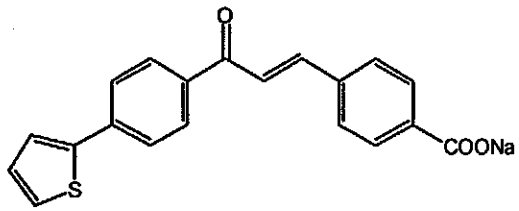


(3-[Ethoxycarbonylmethylaminocarbonyl]-3-{4-[3*E*-(3,4-dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-phenyl}-ureido)-acetic acid ethyl ester

A solution of 1-(4-aminophenyl)-3*E*-[(3,4-dimethoxy-5-(thien-2-yl)phenyl]-propenone (**Ex-11**, 500 mg, 1.37 mmol) and ethyl isocyanatoacetate (177 mg, 1.37 mmol) in anhydrous methylene chloride (20 mL) was stirred at room temperature for 5 hours. Due to no reaction, the reaction mixture was concentrated , diluted with toluene (20 mL), treated with ethyl isocyanatoacetate (177 mg, 1.37 mmol), and refluxed for 14 hours. The reaction was concentrated, diluted with

methylene chloride (50 mL), and washed with water (3 x 50 mL). The organic portion was collected, dried over sodium sulfate, and concentrated over silica gel. The crude material was purified by silica gel chromatography (50-75% ethyl acetate/hexanes) to give 178.0 mg (21%) of the title compound as a yellow solid, mp 83-86°C. ^{1}H-NMR ($CDCl_3$) δ 8.09 (d, 2 H), 7.76 (d, 1H), 7.55 (m, 2H), 7.65 (d, 2H), 7.40 (m, 2H), 7.30 (m, 2H), 7.11 (m, 2H), 4.17 (q, 4H), 4.01 (d, 4H), 3.97 (s, 3H), 3.88 (s, 3H). MS *m/z* = 646 ([M+Na]$^+$, 100%). Anal. calculated for $C_{31}H_{33}N_3O_9S$: C, 59.70, H, 5.33, S, 5.14; found C: 60.18, H: 5.38, S: 5.17.

EXAMPLE 17



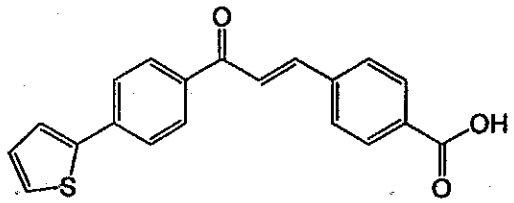
4-[3-{4-(thien-2-yl)-phenyl}-3-oxo-*E*-propenyl]-benzoic acid, sodium salt

Ex-17A: 4'-Bromoacetophenone (3.98 g, 20 mmol) was dissolved in ethylene glycol dimethyl ether and then the solution was degassed with nitrogen for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) (2.31 g, 2 mmol) was added, and the solution was further degassed for 10 minutes. Thiophene-2-boronic acid (3.07 g, 24 mmol) was added followed by the addition of sodium carbonate solution (2 M, 45 mL). The mixture was stirred at reflux under nitrogen overnight. Most of the solvent was removed, and water was added to the remainder. The solid was filtered out and recrystallized from ethanol and water to give 3.85 g of the desired 4'-(thien-2-yl)acetophenone as a solid, 95% yield. ^{1}H-NMR ($CDCl_3$) δ.7.97 (d, J = 9 Hz, 2H), 7.70 (d, J = 9 Hz, 2H), 7.44 (d, J = 4 Hz, 1H), 7.38 (d, J = 5 Hz, 1H), 7.11-7.14 (m, 1H), 2.62 (s, 3H). HMRS (EI) calcd. for $C_{12}H_{10}OS$: 202.0452; found: 202.0454.

4'-(Thien-2-yl)acetophenone obtained from **Ex-17A** (0.81 g, 4 mmol) and 4-carboxybenzaldehyde (0.6 g, 4 mmol) were dissolved in dimethylformamide (20 mL). Sodium hydroxide solution (5 M, 3.2 mL) was added over 30 minutes at room temperature, and the mixture was stirred for another 30 minutes at room temperature. The precipitate was filtered off and recrystallized from hot water to give the title compound as a yellow solid, 29% yield, m.p.

>260 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.17 (d, 2H), 7.89 (d, 1H), 7.87 (d, 2H), 7.81 (d, 2H), 7.76 (d, 2H), 7.72 (d, 1H), 7.69 (d, 1H), 7.64 (d, 1H), 7.17 (dd, 1H). Anal. calculated for $C_{20}H_{13}O_3NaS \cdot 1/2H_2O$: C, 65.74; H, 3.86; S, 8.78, found: C, 65.66; H, 4.04; S, 9.04.

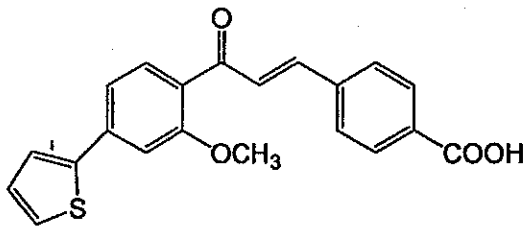
EXAMPLE 18



4-[3-{4-(thien-2-yl)-phenyl}-3-oxo-*E*-propenyl]-benzoic acid

The title compound was prepared by acidifying its sodium salt from **Ex-17**. Yellow solid, mp 260-265°C, 67% yield. ^{1}H-NMR (DMSO-d_6) δ 8.18 (d, J = 8Hz, 2H), 8.00 (d, J = 15 Hz, 1H), 7.91-7.94 (m, 4H), 7.82 (d, J = 8 Hz, 2H), 7.77-7.79 (m, 1H), 7.71(d, J = 3Hz, 1H), 7.66 (d, J =5 Hz, 1H), 7.16-7.19 (m, 1H), MS *m/z* = 334 ([M]$^+$, 100%). HRMS (EI) Calcd. for $C_{20}H_{14}O_3S$: 334.0664. Found: 334.0669.

EXAMPLE 19



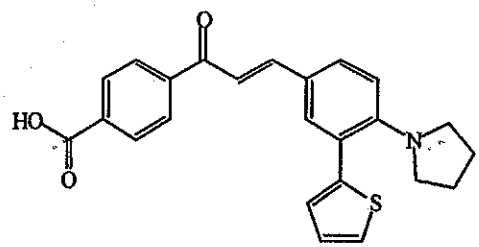
4-[3-(2-Methoxy-4-thiophen-2-yl-phenyl)-3-oxo-*E*-propenyl]-benzoic acid

Ex-19A: 1-(2-Methoxy-4-thiophen-2-yl-phenyl)-ethanone was prepared from 4-iodo-2-methoxyacetophenone in a similar manner as described in **Ex-17A**. ^{1}H-NMR ($CDCl_3$) δ 7.53 (d, J = 7 Hz, 1H), 7.37 (dd, J = 2, 5 Hz, 1H), 7.06 (dd, J = 4, 6 Hz, 1H), 6.98-7.00 (m, 1H), 6.88-6.95 (m, 2H), 3.84 (s, 3H), 2.10 (s, 3H).

The title compound was prepared by condensing 1-(2-methoxy-4-thiophen-2-yl-phenyl)-ethanone (**Ex-19A**) and 4-carboxybenzaldehyde in a similar manner as described in **Ex-17**

except an acidic workup. Yellow solid, mp 193-195°C. ^{1}H-NMR ($CDCl_3$) □ 7.70 (d, J = 8Hz, 2H), 7.38 (d, J = 8 Hz, 1H), 7.07-7.16 (m, 4H), 6.75-6.80 (m, 4H), 6.42 (d, J = 16 Hz, 1H), 3.67 (s, 3H), MS *m/z* = 364 ($[M]^+$, 100%). Anal. Calculated for $C_{21}H_{16}O_4S$: C, 69.21; H, 4.43; S, 8.80; found: C, 69.02; H, 4.56; S, 8.75.

EXAMPLE 20



4-[3*E*-(4-Pyrrolidin-1-yl-3-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

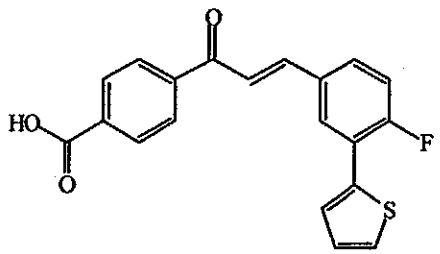
Ex-20A: A solution of 3-bromo-4-flouro-benzaldehyde (5.0 g, 24.6 mmol) and thiophene-2-boronic acid (4.7 g, 37.0 mmol) in ethylene glycol dimethyl ether (100 mL) was stirred at room temperature under nitrogen for 15 min. Then tetrakis(triphenylphosphine)-palladium(0) (2.8 g, 2.42 mmol) and a sodium carbonate solution (2 M, 33 mL) were added, and the resulting mixture was refluxed under nitrogen overnight. Upon cooling to room temperature the reaction was poured into water (100 mL) and extracted with ethyl acetate (2 X 100 mL). The organic phase was dried over magnesium sulfate, and the solvent was removed under reduced pressure. Silica gel chromatography (hexane/ethyl acetate, 1:1) gave 4.8 g (95%) of the desired 4-fluoro-3-(thiophen-2-yl)-benzaldehyde product as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.18 (dd, 1H, *J* = 7.3 and 2.4 Hz), 7.80 (m, 1H), 7.56 (dd, 1H, *J* = 3.7 and 1.7 Hz), 7.44 (d, 1H, *J* = 5.1 Hz), 7.36 (m, 1H), 7.16 (dd, 1H, *J* = 5.1 and 3.7 Hz).

Ex-20B: A solution of 4-fluoro-3-(thiophen-2-yl)-benzaldehyde (1.11 g, 5.38 mmol) from **Ex-20A** and pyrrolidine (13.0 g, 183.0 mmol) in dimethylformamide (30 mL) was treated with solid K_2CO_3 (1.7 g, 12.3 mmol), and the resulting mixture was stirred at reflux for 1 week. Upon cooling to room temperature, the reaction was poured into water (100 mL) and extracted with ethyl acetate (2 X 100 mL). The organic phase was dried over magnesium sulfate, and the solvent was removed under reduced pressure. Silica gel chromatography (hexane/ethyl acetate,

2:1) gave 400 mg (29%) of the desired 4-pyrrolidin-1-yl-3-(thiophen-2-yl)-benzaldehyde product as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.71-7.74 (m, 2H), 7.30 (dd, 1H, J = 5.1 and 1.6 Hz), 7.02 (dd, 1H, J = 5.1 and 3.7 Hz), 6.96 (m, 1H), 6.81 (d, 1H, J = 10.1 Hz), 3.15 (m, 4H), 1.84 (m, 4H).

4-Pyrrolidin-1-yl-3-(thiophen-2-yl)-benzaldehyde (400 mg, 1.55 mmol) from **Ex-20B** and 4-acetylbenzoic acid (255 mg, 1.55 mmol) were dissolved in dimethylformamide (30 mL). Sodium hydroxide solution (5 N, 1.25 mL) was added in one portion, and the mixture was stirred at room temperature overnight. The reaction was diluted with water (100 mL) and washed with ethyl acetate (100 mL). The aqueous phase was acidified with conc. HCl and extracted with ethyl acetate (2 X 100 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. Silica gel chromatography (100% ethyl acetate) followed by recrystallization from ethanol provided 80 mg (13%) of the title compound as a solid, m.p. 212-214°C with decomposition. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21 (d, 2H, J = 8.4 Hz), 7.06 (d, 2H, J = 8.4 Hz), 7.80 (d, 1H, J = 15.3 Hz), 7.58 (d, 1H, J = 1.9 Hz), 7.52 (dd, 1H, J = 8.5 and 1.9 Hz), 7.33 (m, 1H), 7.32 (d, 1H, 15.3 Hz), 7.01-7.06 (m, 2H), 6.82 (d, 1H, 7.9 Hz), 3.12 (m, 4H), 1.84 (m, 4H). MS m/z = 403 ($[M]^+$, 100%). HRMS (EI) Calcd. for $C_{24}H_{21}NO_3S$: 403.1242. Found: 403.1251.

EXAMPLE 21

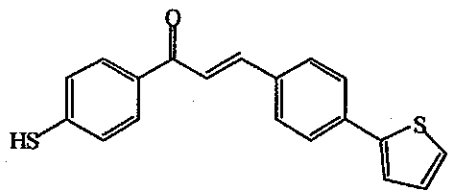


4-[3*E*-{4-Fluoro-3-(thiophen-2-yl)-phenyl}-acryloyl]-benzoic acid

4-Fluoro-3-thiophen-2-yl-benzaldehyde (1.0 g, 4.85 mmol, **from Ex-20A**) and 4-acetylbenzoic acid (0.80 g, 4.87 mmol) were dissolved in dimethylformamide (55 mL). Sodium hydroxide solution (5 N, 3.88 mL) was added in one portion, and the mixture was stirred at room temperature for 3 h. The reaction was diluted with water (100 mL) and washed with ethyl

acetate (100 mL). The aqueous phase was acidified with conc. HCl and extracted with ethyl acetate (2 X 100 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. Recrystallization from ethanol provided 0.90 g (53%) of the title compound as a solid, m.p. 242-244 °C. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 13.31 (bs, 1H), 8.32 (dd, 1H, J = 8.2 and 2.0 Hz), 8.24 (d, 2H, J = 8.2 Hz), 8.07 (d, 2H, J = 7.9 Hz), 7.98 (d, 1H, J = 16.1 Hz), 7.92 (m, 1H), 7.80 (d, 1H, J = 16.1 Hz), 7.69-7.73 (m, 2H), 7.41 (dd, 1H, 10.8 and 9.2 Hz), 7.20 (m, 1H). MS m/z = 352 ([M]$^+$, 50%), 343 (100%). HRMS (EI) Calcd. for $C_{20}H_{13}FO_3S$: 352.0569. Found: 352.0571.

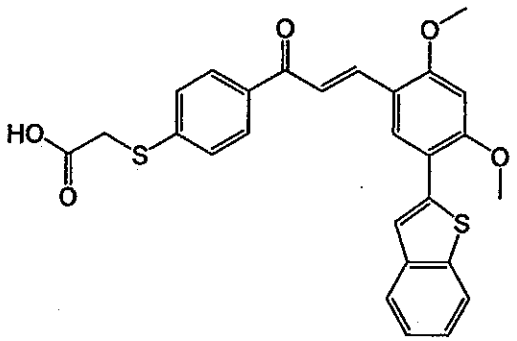
EXAMPLE 22



1-(4-Mercapto-phenyl)-3*E*-(4-thiophen-2-yl-phenyl)-propenone

To a solution of 4-mercaptoacetophenone (prepared according to European Patent Application 0271307) (0.57 g, 3.74 mmol) and 4-(thien-2-yl)-benzaldehyde (0.70 g, 3.74 mmol, **Ex. 2A**) in *N*,*N*-dimethylformamide (20 mL) was added a solution of sodium hydroxide (5 M, 3 mL). The solution was allowed to stir at room temperature for 3 h. The reaction mixture was then acidified with hydrochloric acid (0.5 M) to pH 3. The precipitate was collected by filtration, washed with water, and stirred in ethanol overnight. The resulting yellow solid was collected by filtration, washed with ethanol, and dried *in vacuo* to afford 0.68 g (56%) of the title compound as a solid, m.p. > 110 °C (dec). MS (direct probe) m/z = 322 (M^+). ^{1}H-NMR ($CDCl_3$) δ 7.98–8.01 (d, 1H), 7.90–7.93 (d, 1H), 7.79–7.84 (d, 2H), 7.61–7.66 (m, 3H), 7.33–7.53 (m, 4H), 7.10–7.25 (m, 2H).

EXAMPLE 23



{4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-phenylthio}-acetic acid

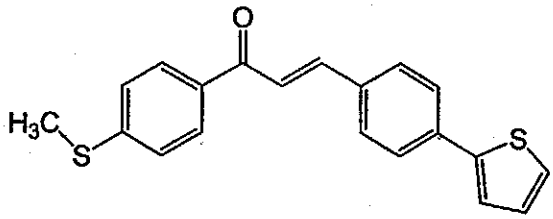
Ex-23A: To a solution of methyl bromoacetate (1.01 mL, 10.7 mmol) in potassium hydroxide (5M, 20 mL) was added benzenethiol (1.0 mL, 9.7 mmol). The reaction mixture was allowed to stir overnight at ambient temperature. The cloudy solution was then acidified to pH 3. The resulting solid was filtered, washed with water and dried *in vacuo* to obtain phenylthioacetic acid (0.55g). The aqueous filtrate was extracted with dichloromethane. The solution of dichloromethane was washed with brine, dried over sodium sulfate and concentrated to obtain additional phenylthioacetic acid (1.49g). ^{1}H NMR ($CDCl_3$) δ 743-7.40 (m, 2H), 7.34-7.23 (m, 3H), 3.67 (s, 2H).

Ex-23B: To a mixture of alumina chloride (5.5g, 41.0 mmol) in carbon disulfide (100mL) was added acetyl chloride (1.17 mL, 16.5 mmol) followed by addition of phenylthioacetic acid (**Ex-23A**, 1.38g, 8.2 mmol) and nitromethane (15 mL). The reaction mixture was allowed to stir overnight at ambient temperature and then was poured into ice containing sulfuric acid (6M). The insoluble solid was filtered, washed with water. After dried *in vacuo*, the solid was washed with toluene (2 x 60 mL), filtered and dried under reduced pressure to obtain (4-acetylphenylthio)acetic acid (1.28 g, 74%), m.p. 151-153 °C (Lit. 156-158 °C). ^{1}H NMR (DMSO-d_6) δ 12.80 (bs, 1H), 7.84 (d, J = 9 Hz, 2H), 7.36 (d, J = 9 Hz, 2H), 3.92 (s, 2H), 2.49 (s, 3H).

The title compound was prepared by condensing (4-acetylphenylthio)acetic acid (**Ex-23B**) and 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde (**Ex-3A**) in a similar manner as described

in **Ex-22**. Yellow solid, mp 136-138 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ 8.35 (s, 1H), 8.08 (d, J = 7.4 Hz, 2H), 8.03 (d, J = 16.3 Hz, 1H), 7.93-7.87 (m, 3H), 7.82 (d, J = 7.0 Hz, 1H), 7.42 (d, J = 7.9 Hz, 2H), 7.37-7.27 (m, 2H), 6.85 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 3.93 (s, 2H). MS *m/z* = 491 ([M+H]$^+$, 100%).

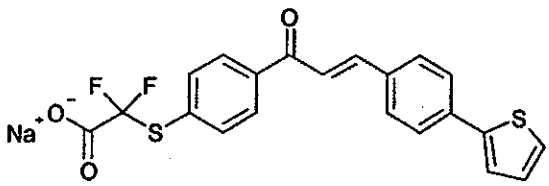
EXAMPLE 24



1-(4-Methylthiophenyl)-3*E*-(4-thiophen-2-yl-phenyl)-propenone

To a mixture of 1-(4-mercapto-phenyl)-3*E*-(4-thien-2-yl-phenyl)-proenone (**Ex-22**, 0.33g, 1.02 mmol) and potassium carbonate (0.54g, 3.9 mmol) in N,N-dimethylformamide (15 mL) was added iodomethane (0.32 mL, 5.1 mmol). The reaction mixture was allowed to stir at ambient temperature for 2 hours. The insoluble material was filtered. The solution was diluted with ethyl acetate. The solution of ethyl acetate was washed with hydrochloric acid (0.5 M), sodium carbonate (2M) and brine, dried over sodium sulfate, and concentrated. The crude product was purified by flash chromatography. Elution with ethyl acetate (33%, v/v, in hexane) gave the title compound (20 mg, 6%) as a yellow solid, mp 138-140 °C. ^{1}H-NMR ($CCDl_3$) δ 7.98 (d, J = 7.8 Hz, 2H), 7.89-7.86 (m, 1H), 7.83 (d, J = 15.3 Hz, 1H), 7.76 (s, 3H), 7.53 (d, J = 15.1 Hz, 1H), 7.41 (d, J = 3.7 Hz, 1H), 7.35-7.31 (m, 3H), 7.13-7.10 (s, 1H), 2.54 (m, 3H). MS *m/z* = 336 (M$^+$, 100%).

EXAMPLE 25

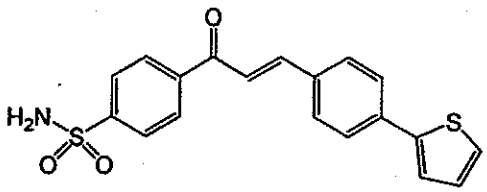


Difluoro-{4-[3*E*-(4-thiophen-2-yl-phenyl)-acryloyl]-phenylthio}-acetic acid, sodium salt

Ex-25A: To a solution of 4-mercaptoacetophenone (prepared according to published procedure, European Patent Application 0271307) (1.16g, 7.6 mmol) and ethyl bromodifluoroacetate (1.2 mL, 9.15 mmol) in N,N-dimethylformamide (20 mL) was added potassium carbonate (3.2g, 22.9 mmol). The reaction mixture was allowed to stir overnight at ambient temperature and then was diluted with ethyl acetate. The combined solution of ethyl acetate was subsequently washed with water, hydrochloric acid (0.5M), brine, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography. Elution with ethyl acetate (33%, v/v, in hexane) gave (4-acetyl-phenylthio)-difluoro-acetic acid ethyl ester (1.38g, 66%). ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H), 4.29 (q, J = 7 Hz, 2H), 2.62 (s, 3H), 1.29 (t, J = 7 Hz, 3H).

The title compound was prepared by condensing (4-acetyl-phenylthio)-difluoro-acetic acid ethyl ester (**Ex-25A**) and 4-(thien-2-yl)benzaldehyde (**Ex-2A**) in a similar manner as described in **Ex-22**. Yellow solid, 3% yield, mp 118-220 °C. ^{1}H-NMR ($CCDl_3$) δ 8.11 (d, J = 7.9 Hz, 2H), 7.95-7.90 (m, 3H), 7.75-7.70 (m, 3H), 7.66 (m, 3H), 7.59 (d, J = 5.0 Hz, 1H), 7.16-7.13 (m, 1H). MS *m/z* = 415 ([M – Na]$^+$, 50%), 321 (100%).

EXAMPLE 26

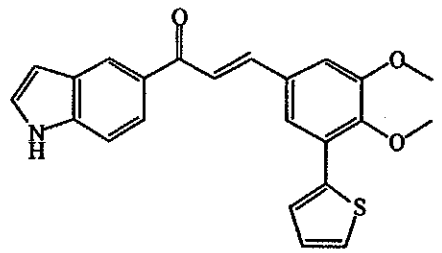


4-[3*E*-(4-Thiophen-2-yl-phenyl)-acryloyl]-benzenesulfonamide

Ex-26A: To a solution of 4-acetyl-benzenesulfonyl chloride (Hoffman, R.V. Org. Syn. VII, 508; 4.18g, 19.1 mmol) in acetone (30 mL) was added ammonia (28% in water, 8.2 mL, 57.3 mmol) dropwise at 0 °C. The reaction mixture was allowed to stir at 0 °C for 30 min. The precipitate was filtered and the residue was washed with water and dried *in vacuo* to afford 4-acetyl-benzenesulfonamide as a white solid (3.54g, 93%). ^{1}H NMR (DMSO-d_6) δ 8.10 (d, J = 9 Hz, 2H), 8.03 (d, J = 9 Hz, 2H), 4.86 (bs, 2H), 2.65 (s, 3H).

To a solution of 4-acetyl-benzsulfonamide (**Ex-26A**, 0.44g, 2.2 mmol) and 4-thiophen-2-yl-benaldehde (**Ex-2A**, 0.50g, 2.7 mmol) in DMF (18 mL) was added a solution of NaOH (5 M, 1.77 mL, 8.8 mmol) dropwise. The reaction mixture was allowed to stir at ambient temperature. The reaction was quenched after 2 hours with water. The precipitate was filtered, washed with water, dried *in vacuo* and purified by stirring in aqueous ethanol overnight. The title compound was collected as a yellow solid (0.45g, 55%), mp >245 °C. ^{1}H-NMR (DMSO-d_6) δ 8.22 (d, J = 8.6 Hz, 2H), 7.96-7.89 (m, 6H), 7.77-7.72 (m, 5H), 7.64 (d, J = 4.0 Hz, 1H), 7.60 (d, J = 4.6, 1H), 7.15 (m, 1H), 6.65 (bs, 1H). MS *m/z* = 369 ([M + H]$^+$, 100%).

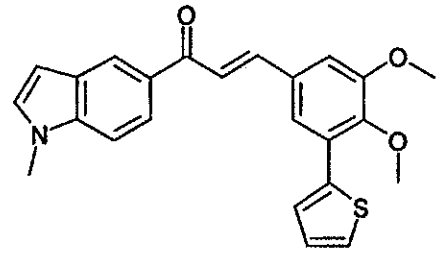
EXAMPLE 27



3*E*-(3,4-Dimethoxy-5-thiophen-2-yl-phenyl)-1-(1*H*-indol-5-yl)-propenone

To a solution of 1-(1*H*-indol-5-yl)-ethanone (Yang, Y., et al., *Heterocycles*, 1992, 34(6), 1169-1175) (0.26 g, 1.63 mmol) and 3,4-dimethoxy-5-(thien-2-yl)-benzaldehyde (0.45 g, 1.80 mmol, **Ex-1D**) in ethanol (30 mL) was added a solution of sodium hydroxide (50%, 0.65 mL, 16 mmol). The reaction mixture was allowed to stir overnight at room temperature. The solution was concentrated. The residue was treated with sulfuric acid (1 M), and the cloudy solution was extracted with dichloromethane. The combined dichloromethane extracts were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexane: 1/3 then 1/1) to give 0.17 g (26%) of the title compound as a yellow solid, m.p. 184.5-186 °C. MS (direct probe): *m/z* = 389 (M$^+$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.99 (d, 1H), 7.12–7.83 (m, 10H), 6.73 (s, 1H), 3.99 (s, 3H), 3.88 (s, 3H).

EXAMPLE 28

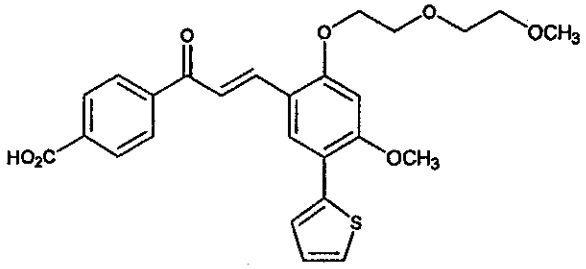


3*E*-(3,4-Dimethoxy-5-thiophen-2-yl-phenyl)-1-(1-methyl-1*H*-indol-5-yl)-propenone

Ex-28A: To a solution of 1-(1*H*-indol-5-yl)-ethanone (Yang, Y. et al, Heterocycles, 1992, 34(6), 1169-1175; 0.45g, 2.8 mmol) were added iodomethane (3 mL) and cesium carbonate (2.3g, 7.1 mmol). The reaction mixture was allowed to stir at 55 °C for 1.5 day during which additional iodomethane (11 mL) was added. The reaction was quenched with water. The aqueous solution was extracted with ether. The solution of ether was washed with saturated solution sodium bicarbonate, brine, dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography. Elution with ethyl acetate (33%, v/v, in hexane) gave 1-(1-methyl-1*H*-indol-5-yl)-ethanone (0.25g, 51%). ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1H), 7.91 (dd, J = 1.2, 8.1 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 3.2 Hz, 1H), 6.61 (d, J = 3.0, 1H), 3.82 (s, 3H), 2.66 (s, 3H).

The title compound was prepared by condensing 1-(1-methyl-1*H*-indol-5-yl)-ethanone (**Ex-28A**) and 3,4-dimethoxy-5-(thien-2-yl)benzaldehyde (**Ex-1D**) in a similar manner as described in **Ex-27**. Yellow solid, 43% yield, mp 70-71 °C. ^{1}H-NMR ($CDCl_3$) δ 8.41(s, 1H), 8.00 (dd, J = 1 Hz, 7 Hz, 1H), 7.80 (d, J = 15 Hz, 1H), 7.63 (d, J = 15.0 Hz, 1H), 7.58-7.55 (m, 2H), 7.43-7.40 (m, 2H), 7.15-7.12 (m, 3H), 6.66 (d, J = 3 Hz, 1H), 3.99 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H). Anal. ($C_{24}H_{21}NOS$•$0.25H_2O$) Calc. C 70.65, H 5.31, N 3.43, S 7.86, found C 70.64, H 5.35, N 3.43, S 7.90.

EXAMPLE 29



4-(3*E*-{4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic Acid

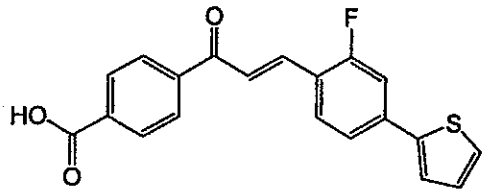
Ex-29A: 2-Hydroxy-4-methoxybenzaldehyde (6.0 g, 39 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C using an ice-water bath. Bromine (6.8 g, 43 mmol) in dichloromethane (2 mL) was added dropwise to the cooled solution and stirred for 2 h at 0 °C. The mixture was warmed to room temperature and stirred for an additional 1 h and the resulting yellow precipitate was collected. Recrystallization (ethyl acetate/hexanes) yielded 7.1 g (80%) of 5-bromo-2-hydroxy-4-methoxybenzaldehyde as white needles, m.p. 63-64 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.43 (s, 1 H), 9.69 (s, 1 H), 7.68 (s, 1 H), 6.48 (s, 1 H), 3.95 (s, 3 H). Anal. Calcd. for $C_8H_7BrO_3$: C, 41.59; H, 3.05. Found: C, 41.86; H, 3.05.

Ex-29B: 5-Bromo-2-hydroxy-4-methoxybenzaldehyde obtained from **Ex-29A** (1.5 g, 6.5 mmol) and thiophene-2-boronic acid (0.91 g, 7.1 mmol) were dissolved in tetrahydrofuran (15 mL). Nitrogen was bubbled into the solution for 10 min followed by the sequential addition of potassium fluoride (0.80 g, 14 mmol, spray-dried) and bis(tri-*t*-butylphosphine)palladium (0) (0.033 g, 0.065 mmol). The solution was immediately heated to 60 °C and aged for 1.5 h. Upon completion, as determined by HPLC, the reaction was diluted with water (25 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over sodium sulfate and concentrated to a brown solid. Silica gel chromatography (ethyl acetate/hexanes, 1:3) gave 1.46 g (97%) of 2-hydroxy-4-methoxy-5-thiophen-2-yl-benzaldehyde as a yellow solid, m.p. 118-119 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.48 (s, 1 H), 9.79 (s, 1 H), 7.72 (s, 1 H), 7.37 (dd, 1 H), 7.31 (dd, 1 H), 7.08 (dd, 1 H), 6.54 (s, 1 H), 3.98 (s, 3 H). Anal. Calcd. for $C_8H_7O_3S$: C, 61.52; H, 4.30; S, 13.69. Found: C, 61.12; H, 4.34; S, 13.56.

Ex-29C: To a solution of 2-hydroxy-4-methoxy-5-thiophen-2-yl-benzaldehyde from **Ex-29B** (0.10 g, 0.43 mmol) in *N,N*-dimethylformamide (3 mL) was added potassium carbonate (0.18 g, 1.3 mmol) and the resulting yellow slurry was heated to 80°C. Once at 80 °C, 1-bromo-2-(2-methoxyethoxy)ethane (0.24 g, 1.3 mmol) was added dropwise in three equal portions with stirring at 1 h intervals. After the last addition, the reaction was stirred for an additional 1 h at 80 °C and cooled to room temperature. The mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers was sequentially washed with a saturated ammonium chloride solution (1 x 15 mL), water (1 x 15 mL), and brine (1 x 15 mL), dried over sodium sulfate, and concentrated to a brown oil. Silica gel chromatography (ethyl acetate/hexanes, 4:1) afforded 0.13 g (87%) of 4-methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thiophen-2-yl-benzaldehyde as a pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1 H), 8.12 (s, 1 H), 7.44 (dd, 1 H), 7.30 (dd, 1 H), 7.07 (dd, 1 H), 6.57 (s, 1 H), 4.33 (t, 2 H), 4.00 (s, 3 H), 3.94 (t, 2 H), 3.74m, 2 H), 3.59 (m, 2 H), 3.40 (s, 3 H). HRMS (EI) Calcd. for $C_{17}H_{20}O_5S$: 336.1031. Found: 336.1027.

4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thiophen-2-yl-benzaldehyde obtained from **Ex-29C** (0.13 g, 0.37 mmol) and 4-acetylbenzoic acid (0.061 g, 0.37 mmol) were dissolved in a tetrahydrofuran-methanol solution (2 mL, 7:3). After complete dissolution, lithium methoxide (0.057 g, 1.5 mmol) was added and the resulting bright orange slurry was stirred in the dark at room temperature for 4 h. Upon completion, as determined by HPLC, the mixture was diluted with water (10 mL), acidified with a 1 N hydrochloric acid solution, and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was taken up in ethyl alcohol (3 mL) and warmed to 60 °C to obtain complete dissolution and allowed to cool to room temperature. The resulting precipitate was collected and dried *in vacuo* to yield 0.14 g (85%) of the title compound as a yellow solid, m.p. 145-146 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.22 (m, 3 H), 8.09 (d, 2 H), 8.01 (d, 2 H), 7.66 (dd, 1 H), 7.52 (d, 1 H), 7.13 (dd, 1 H), 6.88 (s, 1 H), 4.36 (t, 2 H), 4.00 (s, 3 H), 3.88 (t, 2 H), 3.65 (m, 2 H), 3.46 (m, 2 H), 3.22 (s, 3 H). Anal. Calcd. for $C_{26}H_{26}NO_7S$: C, 64.71; H, 5.43; S, 6.64. Found: C, 64.64; H, 5.44; S, 6.61.

EXAMPLE 30

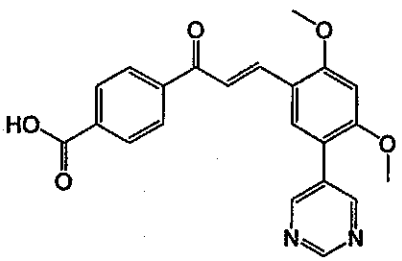


4-[3*E*-(2-Fluoro-4-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-30A: 2-Fluoro-4-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in **Ex-3A** from thiophene-2-boronic acid and 4-bromo-2-fluorobenzaldehide (93% yield). ^{1}H-NMR (300 MHz, d_6-DMSO): 10.13 (s, 1 H), 7.81 (d, 1 H, J = 8.0 Hz), 7.76 (m, 1 H), 7.67 (m, 2 H), 7.59 (dd, 1 H J = 8.0 and 2.1 Hz), 7.17 (dd, 1 H J = 5.2 and 3.7 Hz).

The title compound was prepared by condensing 2-fluoro-4-thiophen-2-yl-benzaldehyde (**Ex-30A**) and 4-acetylbezoic acid in a similar manner as described in **Ex-3**. Yellow solid, 71% yield, m.p. >260°C. ^{1}H-NMR (300 MHz, d_6-DMSO): 8.19 (d, 2 H, J = 8.4 Hz), 8.12 (d, 1 H, J = 8 Hz), 8.06 (d, 2 H, J = 8 Hz), 7.95 (d, 1 H, J = 16 Hz), 7.80 (d, 1 H, J = 16 Hz), 7.71 (d, 1 H, J = 3.5 Hz), 7.62 (m, 2 H), 7.56 (d, 1 H, J = 8 Hz), 7.15 (m, 1 H). MS m/z = 352 ([M]$^+$, 100%). HRMS (EI) Calcd. for $C_{20}H_{13}NO_3S$: 352.0569. Found: 352.0560.

EXAMPLE 31

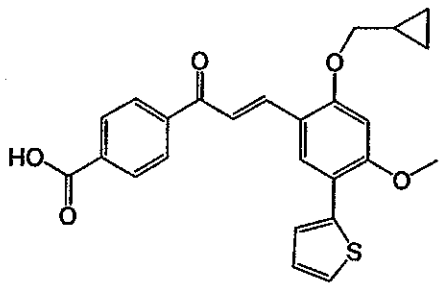


4-[3*E*-(2,4-Dimethoxy-5-pyrimidin-5-yl-phenyl)-acryloyl]-benzoic acid

Ex-31A: 2,4-Dimethoxy-5-pyrimidin-5-yl-benzaldehyde was prepared from 5-bromo-2,4-dimethoxybenzaldehyde and pyrimidine-5-boronic acid in a similar manner as described in **Ex-3A**, 98% yield. ^{1}H-NMR ($CDCl_3$) δ 10.37 (s, 1H), 9.15 (s, 1H), 8.87 (s, 2H) 7.86(s, 1H), 6.57 (s, 1H), 4.03 (s, 3H), 3.96 (s, 3H).

The title compound was prepared by condensing 2,4-dimethoxy-5-pyrimidin-5-yl-benzaldehyde (**Ex-31A**) and 4-acetylbezoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp >260°C, 26% yield. ^{1}H-NMR (DMSO-d_6) δ 9.11 (s, 1H), 8.96 (s, 2H), 8.13-8.16 (m, 3H), 8.01-8.09 (m, 3H), 7.90 (d, J = 15 Hz, 1H), 6.85(s, 1H), 3.99 (s, 3H), 3.91(s, 3H), MS *m/z* = 391 ([M+H]$^+$, 100%). HRMS (ES+) Calcd. for $C_{22}H_{18}N_2O_5$: 391.1294. Found: 391.1295.

EXAMPLE 32

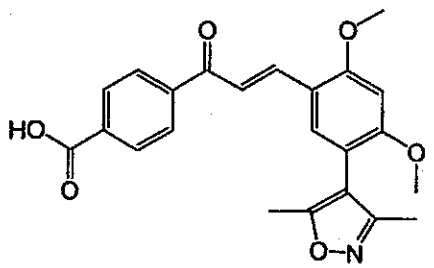


4-[3*E*-(2-Cyclopropylmethoxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-32A: 2-Cyclopropylmethoxy-4-methoxy-5-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in **Ex-29C** from 2-hydroxy-4-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex. 29B**) and chloromethyl-cyclopropane, 18% yield. ^{1}H-NMR ($CDCl_3$) δ 10.41 (s, 1 H), 8.24 (s, 1H), 7.43 (d, 1H), 7.29 (d, 1H), 7.06 (t, 1H), 6.45 (s, 1H), 3.95 (m, 5H), 1.31 (m, 1H), 0.68 (m, 2H), 0.40 (q, 2H).

The title compound was prepared by condensing 2-cyclopropylmethoxy-4-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-32B**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 187-191°C. ^{1}H-NMR (DMSO-d6) δ 8.22 (d, 2H), 8.19 (s, 1H), 7.01 (m, 4H), 7.62 (d, 1H), 7.47 (d, 1H), 7.09 (t, 1H), 6.76 (s, 1H), 4.06 (d, 2H), 3.94(s, 3H), 1.34 (m, 1H), 0.62 (q, 2H), 0.38 (q, 2H). MS *m/z* = 434 ([M]$^+$, 82%), 363 (100%). 10 %. Anal. for $C_{25}H_{22}O_5S$. HRMS m/z: calc. 435.1266, found 435.1266.

EXAMPLE 33

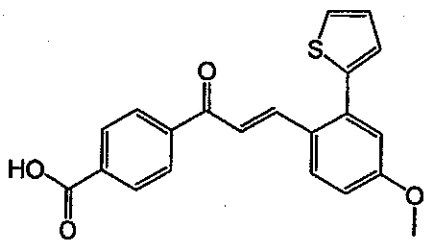


4-{3*E*-[5-(3,5-Dimethyl-isoxazol-4-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid

Ex-33A: 5-(3,5-Dimethyl-isoxazol-4-yl)-2,4-dimethoxy-benzaldehyde was prepared from 5-bromo-2,4-dimethoxybenzaldehyde and 3,5-dimethyl-isoxazole-4-boronic acid in a similar manner as described in **Ex-3A**, 75% yield. ^{1}H-NMR ($CDCl_3$) δ 10.34 (s, 1H), 7.63 (s, 1H), 6.52 (s, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 2.12(s, 6H).

The title compound was prepared by condensing 5-(3,5-dimethyl-isoxazol-4-yl)-2,4-dimethoxy-benzaldehyde (**Ex-33A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp >260°C, 7% yield. ^{1}H-NMR (DMSO-d_6) δ 8.15 (d, J = 8 Hz, 2H), 8.04 (d, J = 16 Hz, 1H), 8.02 (d, J = 8 Hz, 2H), 7.89 (s, 1H), 7.81(d, J = 16 Hz, 1H), 6.79(s, 1H), 4.00 (s, 3H), 3.97(s, 3H), 2.23 (s, 3H) 2.05 (s, 3H) MS *m/z* = 407 ([M]$^+$, 60%), 376 (100%). HMRS (EI) calcd. for $C_{23}H_{21}NO_6$: 407.1369; found: 407.1375.

EXAMPLE 34



4-[3*E*-(4-Methoxy-2-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

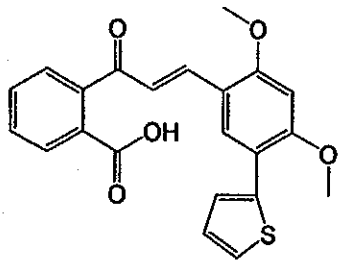
Ex-34A: A solution of 2-hydroxy-4-methoxy-benzaldehyde (5.0 g, 32.86 mmol) in dichloromethane (65 mL) was cooled to 0 °C and then pyridine (13.3 mL, 164.4 mmol) was added in 1 portion. Triflic anhydride (14.8 mL, 87.97 mmol) was then added over 2 h while

maintaining an internal temperature below 5 °C. The resulting solution was allowed to warm to room temperature overnight and then was slowly poured into ice water (100 mL). After diluting further with 1 N HCl (100 mL) the solution was extracted with dichloromethane (2 X 100 mL). The organic phase was washed with sat $NaHCO_3$ (100 mL) and dried over magnesium sulfate. The solvent was then removed under reduced pressure. Silica gel chromatography (hexane/ethyl acetate, 1:1) gave 1.65 g (18%) of the desired trifluoro-methanesulfonic acid 2-formyl-5-methoxy-phenyl ester. ^{1}H-NMR (300 MHz, $CDCl_3$): 10.12 (s, 1 H), 7.94 (dd, 1 H, J = 8.7 Hz), 7.03 (dd, 1 H, J = 8.7 and 2.4 Hz), 6.87 (d, 1 H, J = 2.4 Hz), 3.92 (s, 3 H).

Ex-34B: A solution of trifluoro-methanesulfonic acid 2-formyl-5-methoxy-phenyl ester (**Ex-34A**, 1.6 g, 5.63 mmol) in 1,4-dioxane (15 mL) was stirred at room temperature under nitrogen for 5 min. Thiophene-2-boronic acid (1.08 g, 8.44 mmol), tetrakis(triphenylphosphine)-palladium(0) (0.65 g, 0.56 mmol) and a potassium phosphate (2.2 g, 10.36 mmol) were then added and the resulting mixture was heated to 95 °C under nitrogen overnight. Upon cooling to room temperature the reaction was diluted with EtOAc (25 mL) and water (25 mL) and the layers were cut. The organic phase was concentrated under reduced pressure. Silica gel chromatography (hexane/ethyl acetate, 4:1) gave 1.1 g (90%) of the desired 4-methoxy-2-thiophen-2-yl-benzaldehyde product. ^{1}H-NMR (300 MHz, $CDCl_3$): 10.06 (s, 1H), 8.03 (m, 1H), 7.45 (m, 1H), 7.14 (m, 1H), 7.09 (m, 1H), 7.00 (m, 2 H), 3.91 (s, 3H).

The title compound was prepared by condensing 4-methoxy-2-thiophen-2-yl-benzaldehyde (**Ex-34A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 61% yield, m.p. 209-211°C. ^{1}H-NMR (300 MHz, d_6-DMSO): 8.14 (m, 3 H), 8.04 (d, 2 H, J = 9.2 Hz), 7.89 (d, 1 H, J = 15.5 Hz), 7.76 (d, 1 H, J = 15.5 Hz), 7.70 (d, 1 H, J = 5.0 Hz), 7.18 (dd, 1 H, J = 5.6 and 3.6 Hz), 7.11 (d, 1 H, J = 2.1 Hz), 7.05 (dd, 1 H, J = 8.8 and 1.8 Hz), 6.98 (d, 1 H, J = 1.8 Hz), 3.83 (s, 3 H). MS m/z = 364 ($[M]^+$, 100%). HRMS (EI) Calcd. for $C_{21}H_{16}O_4S$: 364.0769. Found: 364.0761.

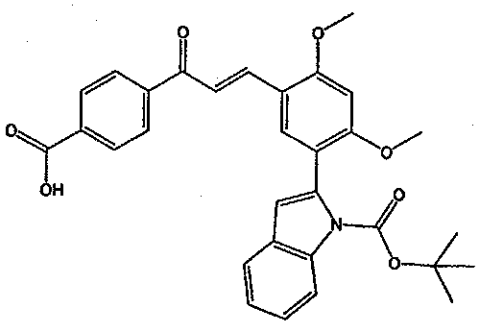
EXAMPLE 35



2-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

The title compound was prepared by condensing 2,4-dimethoxy-5-(thiophen-2-yl)-benzaldehyde (**Ex-6A**) and 2-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 47 % yield, mp 196-198°C. ^{1}H-NMR (DMSO-d6) δ 8.00 (s, 1H), 7.84 (d, 1H), 7.61 (m, 3H), 7.45 (m, 3H), 7.21 (d, 1H), 7.08 (t, 1H), 6.75 (s, 1H), 3.95 (s, 3H), 3.86 (s, 3H). MS *m/z* = 394 ([M]$^+$, 100%). Anal. calculated for C22H18O5S: C, 66.99, H, 4.60, S, 8.13; found C: 67.08, H: 4.17, S: 7.97.

EXAMPLE 36

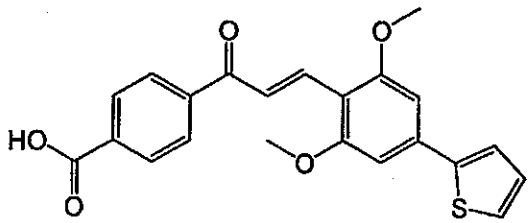


2-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-indole-1-carboxylic acid *tert*-butyl ester

Ex-36A: 2-(5-Formyl-2,4-dimethoxy-phenyl)-indole-1-carboxylic acid tert-butyl ester was prepared from 5-bromo-2,4-dimethoxybenzaldehyde and N-Boc-indole-2-boronic acid in a similar manner as described in **Ex-3A**. Yellow oil, 79% yield. ^{1}H-NMR (CDCl3) δ 10.36 (s, 1H), 8.15 (d, J = 8 Hz, 1H), 7.88 (s, 1H), 7.45 (d, J = 8 Hz, 3H), 7.27-7.35 (m, 1H), 7.19-7.27 (m, 1H), 6.52 (s, 1H), 6.47 (s, 1H), 4.00 (s, 3H), 3.86 (s, 3H), 1.42 (s, 9H).

The title compound was prepared by condensing 2-(5-formyl-2,4-dimethoxy-phenyl)-indole-1-carboxylic acid tert-butyl ester (**Ex-36A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 8% yield, mp 182-183°C. ^{1}H-NMR ($CDCl_3$) δ 8.21 (d, J = 8 Hz, 2H), 8.19 (d, J = 13 Hz, 1H), 8.16 (d, J = 7 Hz, 1H), 8.07 (d, J = 8 Hz, 2H), 7.69 (s, 1H), 7.54 (d, J = 7 Hz, 1H), 7.52 (d, J = 13 Hz, 1H), 7.29-7.35 (m, 1H), 7.23 (d, J = 7 Hz, 1H), 6.55 (s, 1H), 6.50 (s, 1H), 4.00 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H). MS *m/z* = 528 ([M+H]$^+$, 100%). Anal. calc. for $C_{31}H_{29}NO_7 \cdot H_2O$: C, 68.25; H, 5.73; N, 2.56; found: C, 68.63; H, 5.62; N, 2.45.

EXAMPLE 37

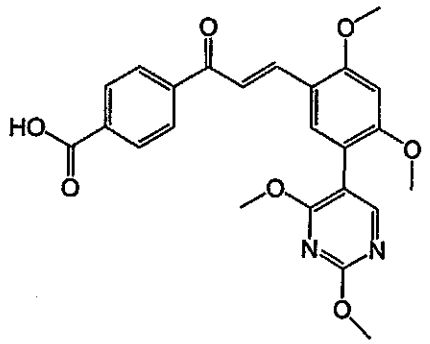


4-[3*E*-(2,6-Dimethoxy-4-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-37A: 2,6-Dimethoxy-4-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in **Ex-34A** and **Ex-34B**. 75% yield, m.p. 168-170°C. ^{1}H-NMR (300 MHz, $CDCl_3$): 10.48 (s, 1 H), 7.43 (dd, 1 H, *J* = 3.6 and 1.3 Hz), 7.41 (d, 1 H, *J* = 5.3 Hz), 7.13 (dd, 1 H, *J* = 5.3 and 3.6 Hz), 6.79 (s, 2 H), 3.96 (s, 6 H).

The title compound was prepared by condensing 2,6-dimethoxy-4-thiophen-2-yl-benzaldehyde (**Ex-37A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 79% yield, m.p. 256-258°C. ^{1}H-NMR (300 MHz, d_6-DMSO): 8.11 (d, 1 H, *J* = 15.9 Hz), 8.10 (m, 4 H), 8.05 (d, 1 H, *J* = 15.9 Hz), 7.73 (d, 1 H, *J* = 3.6 Hz), 7.61 (d, 1 H, *J* = 5.3 Hz), 7.16 (dd, 1 H, *J* = 5.3 and 3.6 Hz), 6.95 (s, 2 H), 3.98 (s, 6 H). MS *m/z* = 394 ([M]$^+$, 100%). HRMS (EI) Calcd. for $C_{22}H_{18}O_5S$: 394.0875. Found: 394.0877.

EXAMPLE 38

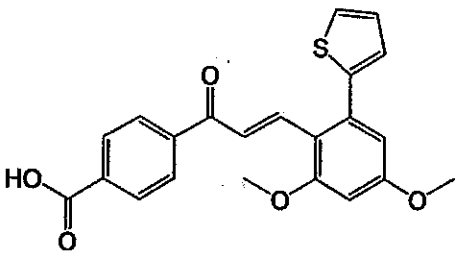


4-{3*E*-[5-(2,4-Dimethoxy-pyrimidin-5-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid

Ex-38A: 5-(2,4-Dimethoxy-pyrimidin-5-yl)-2,4-dimethoxy-benzaldehyde was prepared from 5-bromo-2,4-dimethoxybenzaldehyde and 2,4-Dimethoxy-pyrimidin-5-boronic acid in a similar manner as described in **Ex-3A**, 75% yield. ^{1}H-NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.13 (s, 1H), 7.74(s, 1H), 6.51 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 3.95(s, 3H), 3.88 (s, 3H).

The title compound was prepared by condensing 5-(2,4-dimethoxy-pyrimidin-5-yl)-2,4-dimethoxy-benzaldehyde (**Ex-38A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 203-205°C, 22% yield. ^{1}H-NMR (DMSO-d_6) δ 8.11-9.15 (m, 3H), 7.99-8.06 (m, 3H), 7.88 (s, 1H), 7.76 (d, J = 17 Hz, 1H), 6.76(s, 1H), 3.96(s, 3H), 3.90(s, 3H), 3.83 (s, 3H) 3.81 (s, 3H). MS *m/z* = 451 ($[M+H]^+$). HRMS (ES+) Calcd. for $C_{24}H_{22}N_2O_7$: 451.1505. Found: 451.1524.

EXAMPLE 39

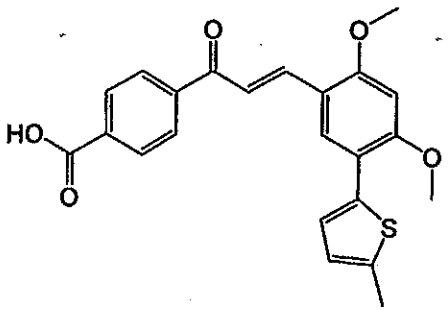


4-[3*E*-(2,4-Dimethoxy-6-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-39A: 2,4-Dimethoxy-6-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in **Ex-34A**, 40% yield. ^{1}H-NMR ($CDCl_3$) δ 10.02 (s, 1 H), 7.40 (d, 1H), 7.07 (m, 2H), 6.58 (d, 1H), 6.50 (d, 1H), 3.93 (s, 3H), 3.89 (s, 3H).

The title compound was prepared by condensing 2,4-dimethoxy-6-thiophen-2-yl-benzaldehyde (**Ex-39A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 61% yield, mp 231 °C (dec.). ^{1}H-NMR (DMSO-d6) δ 8.02 (d, 2 H), 7.93 (d, 2H), 7.73 (m, 3H), 7.15 (t, 1H), 7.07 (d, 1H), 6.72 (d, 1H), 6.62 (d, 1H). MS *m/z* = 394 ([M]$^+$, 6%), 245 (100%). HRMS m/z: calc. 395.0953, found 395.0949.

EXAMPLE 40

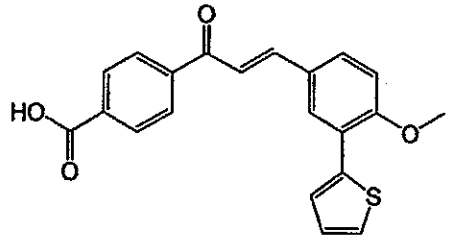


4-{3*E*-[2,4-Dimethoxy-5-(5-methyl-thiophen-2-yl)-phenyl]-acryloyl}-benzoic acid

Ex-40A: 2,4-Dimethoxy-5-(5-methyl-thiophen-2-yl)-benzaldehyde was prepared from 5-bromo-2,4-dimethoxybenzaldehyde and 5-methyl-thiophene-2-boronic acid in a similar manner as described in **Ex-3A**, 100% yield. ^{1}H-NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.05 (s, 1H), 7.22 (d, J = 4 Hz, 1 H), 6.72 (d, J = 4 Hz, 1 H), 6.49 (s, 1H), 4.00 (s, 3H), 3.97 (s, 3H), 2.50 (s, 3H). HMRS (EI) calcd. for $C_{14}H_{14}O_3S$: 262.0664; found: 262.0665.

The title compound was prepared by condensing 2,4-dimethoxy-5-(5-methyl-thiophen-2-yl)-benzaldehyde (**Ex-40A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 213-215°C, 27% yield. ^{1}H-NMR (DMSO-d_6) δ 8.18 (d, J = 7 Hz, 2H), 8.17 (s, 1H), 8.00-8.06 (m, 3H), 7.85 (d, J = 15Hz, 1H), 7.42(d, J = 4 Hz, 1H), 6.78(m, 2H), 3.96 (s, 3H), 3.95(s, 3H), 2.42 (s, 3H). MS *m/z* = 408 ([M]$^+$, 100%). HMRS (EI) calcd. for $C_{23}H_{20}O_5S$: 408.1031; found: 408.1023.

EXAMPLE 41

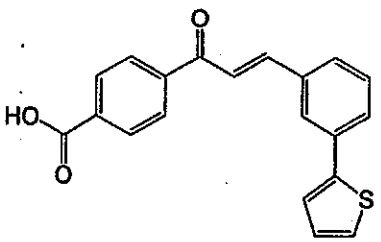


4-[3*E*-(4-Methoxy-3-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-41A: 4-Methoxy-3-(thiophen-2-yl)-benzaldehyde was prepared from 3-bromo-4-methoxybenzaldehyde and thiophene-2-boronic acid in a similar manner as described in **Ex-3A**. Orange oil, 96% yield. ^{1}H-NMR ($CDCl_3$) δ 9.94 (s, 1H), 8.16 (d, J = 1.8 Hz, 1H), 7.80 (dd, J = 2.4, 8.4 Hz, 1H), 7.57 (dd, J = 1.8, 3.6 Hz, 1H), 7.38 (d, J = 5.1 Hz, 1H), 7.12 (dd, J= 3.6, 5.1 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 4.02 (s, 3H). HRMS *m/z*: calc. 218.0402, found 218.0406.

The title compound was prepared by condensing 4-methoxy-3-(thiophen-2-yl)-benzaldehyde (**Ex-41A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 219-220°C, 71 % yield. ^{1}H-NMR (DMSO-D_6) δ 13.36 (br s, 1H), 8.25-8.31 (m, 3H), 8.11 (d, J = 8 Hz, 2H), 7.85-7.98 (m, 3H), 7.78-7.80 (m, 1H), 7.61 (d, J= 5 Hz, 1H), 7.25 (d, J = 9 Hz, 1H), 7.17 (dd, J = 4, 6 Hz, 1H), 3.99 (s, 3H). HRMS *m/z* = calc. 365.0848, found 365.0833.

EXAMPLE 42



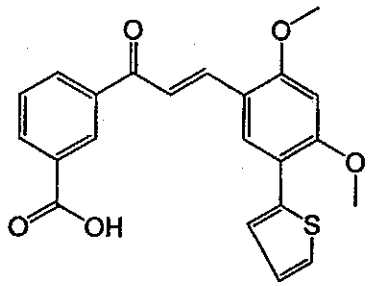
4-[3*E*-(3-Thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-42A: 3-(Thiophen-2-yl)-benzaldehyde was prepared from 3-bromobenzaldehyde and thiophene-2-boronic acid in a similar manner as described in **Ex-3A**. Orange oil, 93% yield. ^{1}H-NMR ($CDCl_3$) δ 10.06 (s, 1H), 8.10 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 7.2 Hz,

1H), 7.55 (dd, J = 7.2, 8.4 Hz, 1H), 7.40 (dd, J= 1.5, 3.6 Hz, 1H), 7.34 (dd, J = 1.5, 5.3 Hz, 1H), 7.11 (dd, J = 3.6, 5.3 Hz, 1H). HRMS *m/z*: calc. 188.0296, found 188.0293.

The title compound was prepared by condensing 3-(thiophen-2-yl)-benzaldehyde (**Ex-42A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 238°C (dec), 71% yield. ^{1}H-NMR (DMSO-D_6) δ 13.40 (bs, 1H), 8.29 (d, J = 8 Hz, 2H), 8.22 (s, 1H), 8.13 (d, J = 8 Hz, 2H), 8.04 (s, 1H), 7.87 (s, 1H), 7.83 (d, J = 8 Hz, 1H), 7.73 (d, J = 9 Hz, 1H), 7.69 (d, J = 4 Hz, 1H), 7.63 (d, J = 5 Hz, 1H), 7.52 (t, J = 8 Hz, 1H), 7,20 (dd, J = 4, 5 Hz, 1H). HRMS *m/z* = calc. 335.0742, found 335.0749.

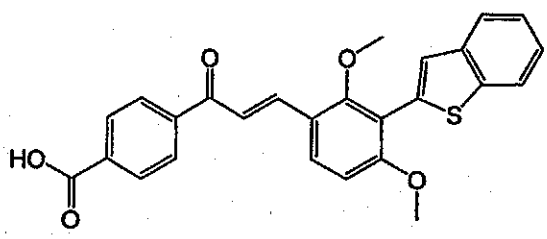
EXAMPLE 43



3-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

The title compound was prepared by condensing 2,4-dimethoxy-5-(thiophen-2-yl)-benzaldehyde (**Ex-6A**) and 3-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 65% yield, mp 179-182 °C. ^{1}H-NMR (DMSO-d6) δ 8.54 (s, 1 H), 8.39 (d, 1H), 8.25 (s, 1H), 8.15 (d, 1H), 8.04 (d, 1H), 7.90 (d, 1H), 7.67 (m, 2H), 7.48 (d, 1H), 7.09(t, 1H), 6.81 (s, 1H), 3.98 (s, 3H), 3.97 (s,3H). MS *m/z* = 394 ([M]$^+$, 72%), 363 (100%). Anal. calculated for C22H18O5S: C, 66.99, H, 4.60, S, 8.13; found C: 66.80, H: 4.60, S: 8.07.

EXAMPLE 44



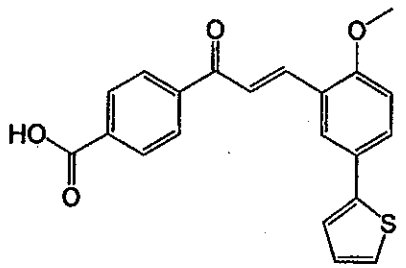
4-[3*E*-(3-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid

Ex-44A: 3-Benzo[*b*]thiophen-2-yl-2-hydroxy-4-methoxy-benzaldehyde was prepared through Suzuki coupling as described in Ex-3A using 3-bromo-2-hydroxy-4-methoxybenzaldehyde (obtained as a minor product from **Ex-29A**). ^{1}H-NMR ($CDCl_3$) δ 12.08 (s, 1H), 9.80 (s, 1H), 7.80-7.87 (m, 2H), 7.70 (s, 1H), 7.56 (d, J = 9 Hz, 1H), 7.31-7.35 (m, 2H), 6.71 (d, J = 9 Hz, 1H), 3.97 (s, 3H). HRMS *m/z*: calc. 284.0507, found 284.0502.

Ex-44B: 3-Benzo[*b*]thiophen-2-yl-2-hydroxy-4-methoxy-benzaldehyde (**Ex-44A**, 57.4 mg, 0.202 mmol) was dissolved in acetone (5 mL) and potassium carbonate (31 mg, 0.22 mmol) was added. Methyl iodide (25 uL, 0.40 mmol) was added and the solution was heated to reflux for 3.5 h. After cooling, the crude reaction mix was concentrated on the rotavap. The resulting residue was taken up in 10 mL of a 1:9 mix of saturated, aqueous NH_4Cl to water and extracted with EtOAc (2x15 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated to provide 58.5 mg of 3-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-benzaldehyde as an orange, oily residue which was used without further purification, 97% yield. ^{1}H-NMR ($CDCl_3$) δ 10.31 (s, 1H), 7.92 (d, J = 9 Hz, 1H), 7.81-7.88 (m, 2H), 7.56 (d, 1H), 7.33-7.39 (m, 2H), 6.88 (d, J = 9 Hz, 1H), 3.91 (s, 3H), 3.64 (s, 3H).

The title compound was prepared by condensing 3-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-benzaldehyde (**Ex-44B**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 237°C (dec.), 64% yield. ^{1}H-NMR (DMSO-d_6) δ 13.37 (bs, 1H), 8.20-8.25 (m, 3H), 8.11 (d, J = 8 Hz, 2H), 8.02 (d, J = 8 Hz, 1H), 7.96 (d, J = 9 Hz, 2H), 7.88-7.91 (m, 1H), 7.65 (s, 1H), 7.35-7.43 (m, 2H), 7.14 (d, J = 9 Hz, 1H), 3.90 (s, 3H), 3.53 (s, 3H). HRMS *m/z* = calc. 445.1110, found 445.1112.

EXAMPLE 45

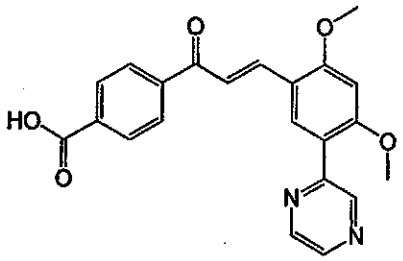


4-[3*E*-(2-Methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-45A: 2-Methoxy-5-(thiophen-2-yl)-benzaldehyde was prepared from 5-bromo-2-methoxybenzaldehyde and thiophene-2-boronic acid in a similar manner as described in **Ex-3A**. ^{1}H NMR ($CDCl_3$) δ 10.49 (s, 1H), 8.07 (d, J = 3 Hz, 1H), 7.79 (dd, J = 3, 9.0 Hz, 1H), 7.28-7.26 (m, 2H), 7.09-7.06 (m, 1H), 7.02 (d, J = 9 Hz, 1H), 3.97 (s, 3H).

The title compound was prepared by condensing 2-methoxy-5-(thiophen-2-yl)-benzaldehyde (**Ex-45A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 195-196 °C. ^{1}H-NMR (DMSO-d_6) δ 8.23-8.20 (m, 3H), 8.08-7.96 (m, 4H), 7.67 (dd, J = 2.1, 6.8 Hz, 1H), 7.55 (d, J = 3.8 Hz, 1H), 7.49 (d, J = 5.1 Hz, 1H), 7.16-7.11 (m, 2H), 3.90 (s, 3H). MS *m/z* = 364 (M^+, 100%).

EXAMPLE 46



4-[3*E*-(2,4-Dimethoxy-5-pyrazin-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-46A: 5-Bromo-2,4-dimethoxybenzaldehyde (4.92 g, 20.1 mmol) was dissolved in benzene (41 mL). Ethylene glycol (3 mL, 54 mmol) and p-toluenesulfonic acid (25 mg, 0.13 mmol) were added and the solution was refluxed with a Dean-Stark trap attached. After 6 h, the reaction was cooled and washed with water (1x20 mL), saturated, aqueous $NaHCO_3$ (1x20

mL), and water (1x20 mL). The organic phase was dried over sodium sulfate, filtered, concentrated, and dried to provide 5.32 g of 2-(5-bromo-2,4-dimethoxy-phenyl)-[1,3]dioxolane as a faint yellow oil which solidified upon standing (92% yield). ^{1}H-NMR ($CDCl_3$) δ 7.67 (s, 1H), 6.47 (s, 1H), 6.06 (s, 1H), 4.11-4.13 (m, 2H), 3.98-4.03 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H). HRMS (ES+) Calcd. for $C_{11}H_{13}BrO_4$: 289.0075. Found: 289.0077.

Ex-46B: 2-(5-Bromo-2,4-dimethoxy-phenyl)-[1,3]dioxolane (**Ex-46A**, 4.78 g, 10.5 mmol) was dissolved in dioxane (75 mL) and the solution was purged with nitrogen for 15 min. $Pd(OAc)_2$ (188 mg, 0.84 mmol), Et_3N (6.91 mL, 49.6 mmol), and 2-(dicyclohexylphosphino)biphenyl (1.16 g, 3.31 mmol) were added. 4,4,5,5-Tetramethyl-[1,3,2]dioxaborolane (3.6 mL, 24.8 mmol) was added slowly, accompanied by gas evolution and the darkening of the reaction solution. The solution was heated at reflux for 2.5 h and then cooled. Saturated, aqueous NH_4Cl (60 mL) and water (20 mL) were added and the solution extracted with EtOAc (1x100 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated to a dark oil. The oil was purified *via* silica gel chromatography (1:1 EtOAc/hexanes after a column pre-wash of 5% Et_3N in 1:1 EtOAc/hexanes) to provide 3.27 g of 2-(5-[1,3]dioxolan-2-yl-2,4-dimethoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane as a yellow solid (with some starting borolane present), 59% yield. ^{1}H-NMR ($CDCl_3$) δ 7.85 (s, 1H), 6.39 (s, 1H), 6.07 (s, 1H), 4.13-4.18 (m, 2H), 3.98-4.02 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 1.33 (s, 9H).

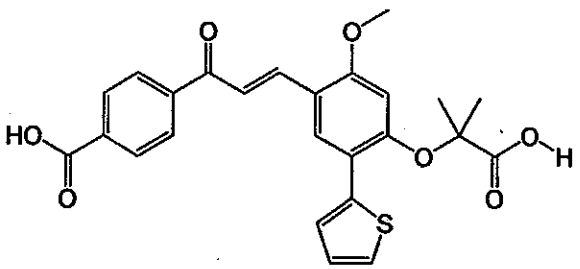
Ex-46C: 2-(5-[1,3]Dioxolan-2-yl-2,4-dimethoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**Ex-46B**, 2.22 g, 6.60 mmol, containing borolane impurity) was dissolved in DME (60 mL) and 2-iodopyrazine (0.59 mL, 6.0 mmol) was added. 2M aqueous Na_2CO_3 (17.8 mL, 35.6 mmol) was added and the mixture was purged with nitrogen for 20 min. Tetrakis(triphenylphosphine)palladium(0) (0.69 g, 0.60 mmol) was added and the mixture was heated at reflux for 2.5 h. After cooling, water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (2x30 mL). The organic phase was washed with brine (1x20 mL), dried over sodium sulfate, filtered, and concentrated. Purification of the resulting yellow-orange solids *via* silica chromatography (50-80% EtOAc/hexanes) provided 1.02 g of 2-(5-[1,3]dioxolan-2-yl-2,4-dimethoxy-phenyl)-pyrazine as a yellow solid (59% yield). ^{1}H-NMR

($CDCl_3$) δ 9.10 (d, J = 2 Hz, 1H), 8.61 (m, 1H), 8.39 (d, J = 3 Hz, 1H), 8.07 (s, 1H), 6.57 (s, 1H), 6.14 (s, 1H), 4.13-4.18 (m, 2H), 4.01-4.05 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H).

Ex-46D: 2-(5-[1,3]Dioxolan-2-yl-2,4-dimethoxy-phenyl)-pyrazine (1.02 g, 3.54 mmol) was dissolved in acetone and p-toluenesulfonic acid (100 mg, 0.53 mmol) and water (5 mL) were added. The solution was stirred for 3 h at room temperature, then concentrated on the rotavap. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (3x100 mL). The organic phase was washed with 25% saturated aqueous $NaHCO_3$, dried over sodium sulfate, filtered, and concentrated. Drying gave 0.30 g of 2,4-dimethoxy-5-pyrazin-2-yl-benzaldehyde as a yellow solid (18% yield). ^{1}H-NMR ($CDCl_3$) δ 10.35 (s, 1H), 9.06 (d, J = 2 Hz, 1H), 8.63-8.65 (m, 1H), 8.45 (d, J = 2 Hz, 1H), 8.39 (s, 1H), 6.56 (s, 1H), 4.03 (s, 3H), 4.01 (s, 3H). HRMS *m/z*: calc. 244.0848, found 244.0853.

The title compound was prepared by condensing 2,4-dimethoxy-5-pyrazin-2-yl-benzaldehyde (**Ex-46D**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 238°C (dec.), 4% yield. ^{1}H-NMR (DMSO-D_6) δ 9.04 (d, J = 2 Hz, 1H), 8.75-8.76 (m, 1H), 8.56 (d, J = 2 Hz, 1H), 8.32 (s, 1H), 8.19 (d, J = 9 Hz, 2H), 8.05-8.11 (m, 3H), 7.83 (d, J = 16 Hz, 1H), 6.90 (s, 1H), 4.05 (s, 3H), 4.00 (s,. 3H). HRMS *m/z* = calc. 391.1294, found 391.1313.

EXAMPLE 47



4-{3*E*-[4-(1-Carboxy-1-methyl-ethoxy)-2-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid

Ex-47A: 5-Bromo-4-hydroxy-2-methoxy-benzaldehyde was prepared in an analogous fashion as described in **Ex-29A** using 4-hydroxy-2-methoxybenzaldehyde. The crude solid was slurried in water to remove residual HBr and dried *in vacuo* to give the bromide as an off-white solid

(98%), mp 199-201 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.58 (s, 1H), 10.07 (s, 1H), 7.75 (s, 1H), 6.69 (s, 1H), 3.87 (s, 3H). MS (EI) *m/z* = 230 ([M]$^+$, 100%). Anal. Calcd. for $C_8H_7BrO_3 \cdot ¼H_2O$: C, 40.79; H, 3.21. Found: C, 40.66; H, 3.01.

Ex-47B: 4-Hydroxy-2-methoxy-5-thiophen-2-yl-benzaldehyde was prepared in an analogous fashion as described in **Ex-29B.** Silica gel chromatography (ethyl acetate/hexanes, 2:1) gave the expected product as a solid (85%), mp 200 °C (dec.). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.89 (s, 1H), 7.42 (dd, 1H, *J* = 4.8, 1.2 Hz), 7.14-7.19 (m, 2H), 6.59 (s, 1H), 6.14 (brs, 1H), 3.94 (s, 3H). MS (EI) *m/z*: 234 ([M]$^+$, 100%). Anal. Calcd. for $C_{12}H_{10}O_3S \cdot H_2O$: C, 57.13; H, 4.79; S, 12.71. Found:
C, 57.16; H, 4.47; S, 12.48.

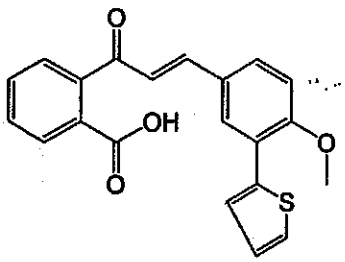
Ex-47C: 2-(4-Formyl-5-methoxy-2-thiophen-2-yl-phenoxy)-2-methyl-propionic acid ethyl ester was prepared in an analogous fashion as described in **Ex-29C** using ethyl 2-bromoisobutyrate. Silica gel chromatography (ethyl acetate/hexanes, 1:1) gave the expected product as a solid (82%), mp 111-113 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.14 (s, 1H), 7.45 (dd, 1H, *J* = 3.7, 1.3 Hz), 7.30 (dd, 1H, *J* = 5.2, 1.3 Hz), 7.07 (dd, 1H, *J* = 5.2, 3.7 Hz), 6.35 (s, 1H), 4.25 (q, 2H, *J* = 7.2 Hz), 3.85 (s, 3H), 1.76 (s, 6 H), 1.23 (t, 3H, *J* = 7.2 Hz). MS (EI) *m/z* = 348 ([M]$^+$, 100%). Anal. Calcd. for $C_{18}H_{20}O_5S$: C, 62.05; H, 5.79; S, 9.20. Found: C,
61.81; H, 5.81; S, 9.12.

Ex-47D: To a solution of 2-(4-formyl-5-methoxy-2-thiophen-2-yl-phenoxy)-2-methyl-propionic acid ethyl ester (0.29 g, 0.83 mmol) in a mixture of tetrahydrofuran, water and methanol (9 mL, 4:1:1) was added lithium hydroxide (0.10 g, 2.49 mmol) and the resulting yellow slurry was stirred at rt for 5 h. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (1 x 5 mL). The aqueous layer was acidified with a 1 N HCl solution and extracted with ethyl acetate (3 x 15 mL). The combined organic layers was dried over sodium sulfate and concentrated to afford 0.13 g (87%) of 2-(4-formyl-5-methoxy-2-thiophen-2-yl-phenoxy)-2-methyl-propionic acid as a pale green solid, mp 183-184 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.12 (s, 1H), 7.40 (d, 1H, *J* = 3.6 Hz), 7.32 (d, 1H, *J* = 4.8 Hz), 7.08

(dd, 1H, J = 4.8, 3.6 Hz), 6.47 (s, 1H), 3.86 (s, 3H), 1.78 (s, 6 H). MS (EI) m/z = 320 ($[M]^+$, 100%). Anal. Calcd. for $C_{16}H_{16}O_5S$: C, 59.99; H, 5.03; S, 10.01. Found: C, 60.04; H, 5.26; S, 9.70.

2-(4-Formyl-5-methoxy-2-thiophen-2-yl-phenoxy)-2-methyl-propionic acid (**Ex-47D**, 0.23 g, 0.72 mmol) and 4-acetylbenzoic acid (0.12 g, 0.72 mmol) were dissolved in a dimethylformamide-methanol solution (5 mL, 7:3). After complete dissolution, lithium methoxide (0.11 g, 2.9 mmol) was added and the resulting orange slurry was stirred in the dark at room temperature for 4 h. Upon completion, as determined by HPLC, the mixture was diluted with water (15 mL), acidified with a 1 N hydrochloric acid solution, and extracted with ethyl acetate (4 x 25 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was taken up in a tetrahydrofuran-heptane solution (5 mL, 10:1) and warmed to 60 °C to obtain complete dissolution and allowed to cool to room temperature. The resulting precipitate was collected on filter paper and dried *in vacuo* to yield 0.30 g (90%) of the title compound as a dark yellow solid, mp 135-137 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.23 (d, 2H, J = 8.4 Hz), 8.10 (d, 2H, J = 8.4 Hz), 7.99 (d, 2H, J = 15.6 Hz), 7.71 (d, 1H, J = 3.0 Hz), 7.54 (d, 1H, J = 5.1 Hz), 7.14 (dd, 1H, J = 5.1, 3.0 Hz), 6.49 (s, 1H), 3.85 (s, 3H), 1.69 (s, 6H). MS (ESI) m/z = 467 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{25}H_{28}O_8S$·EtOH: C, 63.27; H, 5.51; S, 6.26. Found: C, 63.40; H, 5.19; S, 6.38.

EXAMPLE 48

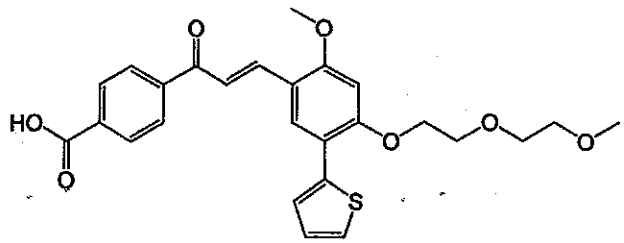


2-[3*E*-(4-Methoxy-3-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

The title compound was prepared by condensing 4-methoxy-3-(thiophen-2-yl)-benzaldehyde (**Ex-41A**) and 2-acetylbenzoic acid in a similar manner as described in **Ex-3**. Beige solid with green tint, mp 79-81°C, 44% yield. ^{1}H-NMR (DMSO-D_6) δ 8.07 (d, J = 2 Hz, 1H), 7.91 (d, J =

8 Hz, 1H), 7.73 (dd, J = 2, 4 Hz, 1H), 7.67-7.70 (m, 2H), 7.63 (dd, J = 2, 7 Hz, 1H), 7.57 (dd, J = 2, 5 Hz, 1H), 7.50 (d, J= 8 Hz, 1H), 7.22 (d, J = 2 Hz, 2H), 7.19 (d, J = 8 Hz, 1H), 7.12 (dd, J = 4, 5 Hz, 1H), 3.96 (s, 3H). HRMS *m/z* = calc. 365.0848, found 365.0853.

EXAMPLE 49



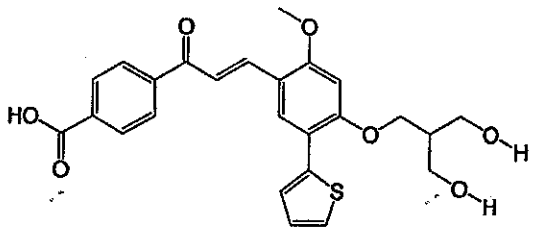
4-(3*E*-{2-Methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic acid

Ex-49A: To a solution of 4-hydroxy-2-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-47B**, 0.50 g, 2.14 mmol) and tri(ethylene glycol) monomethyl ether (0.38 g, 3.2 mmol) in tetrahydrofuran (20 mL) was added triphenylphosphine (0.84 g, 3.2 mmol) and the resulting mixture was cooled to 0 °C. Diethyl azodicarboxylate (0.55 g, 3.2 mmol) was then added drop wise, stirred at 0 °C for 30 min, and allowed to warm to rt. The solution was stirred for an additional 24 and concentrated under reduced pressure to a brown oil. Silica gel chromatography (ethyl acetate/hexanes, 8:1) afforded 0.31 g (45%) of the expected 2-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-5-thiophen-2-yl-benzaldehyde as a viscous clear oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.13 (s, 1H), 7.48 (d, 1H, *J* = 3.6 Hz), 7.30 (t, 1H, *J* = 5.1 Hz), 7.06 (dd, 1H, *J* = 5.1, 3.6 Hz), 6.56 (s, 1H), 4.34 (t, 2H, *J* = 5.1 Hz), 3.94 (t, 2H, *J* = 5.1 Hz), 3.96 (s, 3H), 3.72-3.75 (m, 2H), 3.56-3.59 (m, 2H), 3.39 (s, 3H). MS (ESI) *m/z* = 337 ($[M+H]^+$, 100%). HRMS (EI) Calcd. for $C_{17}H_{20}O_5S$: 336.1031. Found: 336.1028.

The title compound was prepared by condensing 2-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-5-thiophen-2-yl-benzaldehyde **(Ex-49A)** and 4-acetylbenzoic acid in a similar manner as described in **Ex-3.** Yellow solid, mp 174-175 °C, 61% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.23 (d, 2H, *J* = 8.1 Hz), 8.05-8.11 (m, 3H), 7.91 (d, 1H, *J* = 15.3 Hz), 7.72 (d, 1H, *J* = 2.7 Hz), 7.52 (d, 1H, *J* = 4.2 Hz), 7.11-7.15 (m, 1H), 6.86 (s, 1H), 4.39 (t, 2H, *J* = 3.9

Hz), 3.99 (s, 3H), 3.89 (t, 2H, J = 3.9 Hz), 3.64 (t, 2H, J = 3.9 Hz), 3.48 (t, 2H, J = 3.9 Hz), 3.25 (s, 3H). MS (ESI) m/z = 483 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{26}H_{26}O_7S$: C, 64.71; H, 5.43; S, 6.64. Found: C, 64.43; H, 5.34; S, 6.54.

EXAMPLE 50



4-{3*E*-[4-(3-Hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid

Ex-50A: To a solution of 3-(*tert*-butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propan-1-ol (25.0 g, 74.3 mmol) and triethylamine (22.6 g, 223 mmol) in dichloromethane (150 mL) at 0 °C. was added mesyl chloride (12.8 g, 111 mmol) and the resulting slurry was stirred at 0 °C for 15 min and allowed to warm to rt. The solution was stirred for an additional 3 h at rt and diluted with water (130 mL) and ethyl acetate (350 mL). The layers were separated and the aqueous was extracted with ethyl acetate (1 x 150mL). The combined organic extracts were washed with a saturated sodium bicarbonate (1 x 200 mL), a 50% sodium chloride solution (2 x 200 mL), dried over sodium sulfate and concentrated to afford 29.5 g (97%) of the expected methanesulfonic acid 3-(tert-butyl-dimethyl-silanyloxy)-2-(tert-butyl-dimethyl-silanyloxymethyl)-propyl ester as a yellow oil, 97% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.29 (d, 2H, J = 5.7 Hz), 3.61-3.68 (m, 4H), 2.99 (s, 3H), 2.04-2.11 (m, 1H), 0.88 (s, 18H), 0.049 (s, 12H). HRMS (ESI) Calcd. for $C_{17}H_{40}O_5SSi_2$: 413.2213. Found: 413.2226.

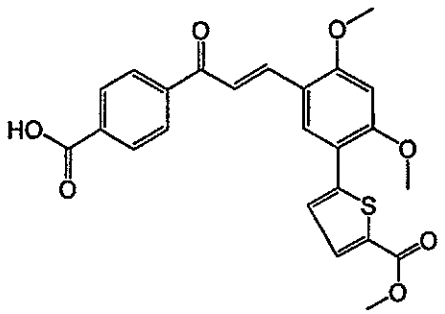
Ex-50B: 4-[3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propoxy]-2-methoxy-5-thiophen-2-yl-benzaldehyde was prepared in an analogous fashion as described in **EX-29C** using methanesulfonic acid 3-(tert-butyl-dimethyl-silanyloxy)-2-(tert-butyl-dimethyl-silanyloxymethyl)-propyl ester (**Ex-50A**). Silica gel chromatography (ethyl acetate/hexanes, 1:6) gave the expected product as a pale green solid, 90% yield. ^{1}H-NMR (300

MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.13 (s, 1H), 7.41 (dd, 1H, J = 3.6, 1.2 Hz), 7.28 (dd, 1H, J = 5.1, 1.2 Hz), 7.05 (dd, 1H, J = 5.1, 3.6 Hz), 6.54 (s, 1H), 4.22 (d, 2H, J = 5.7 Hz), 3.96 (s, 3H), 3.80 (d, 4H, J = 5.7 Hz), 2.33 (pentet, 1H, J = 5.7 Hz), 0.88 (s, 18H), 0.012 (s, 12H). MS (ESI) m/z = 551 ($[M+H]^+$, 100%). HRMS (EI) Calcd. for $C_{28}H_{46}O_5SSi_2$: 550.2604. Found: 550.2593.

Ex-50C: To a solution of 4-[3-(*tert*-butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propoxy]-2-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-50B**, 0.78 g, 1.41 mmol) in tetrahydrofuran (5 mL) was added tetrabutylammonium fluoride (1 M in tetrahydrofuran, 3.0 mL, 2.9 mmol) and the mixture was stirred at rt for 30 min. The reaction was diluted with ethyl acetate (50 mL) and washed with a 50% ammonium chloride solution (1 x 30 mL), water (2 x 30 mL), brine (1 x 30 mL), dried over sodium sulfate and concentrated to a crude yellow solid. Silica gel chromatography afforded 0.37 g (99%) of the expected 4-(3-hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thiophen-2-yl-benzaldehyde as a pale yellow solid, 90% yield, mp 144-145 °C.. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.10 (s, 1H), 7.38 (dd, 1H, J = 3.6, 1.5 Hz), 7.30 (dd, 1H, J = 5.1, 1.5 Hz), 7.07 (dd, 1H, J = 5.1, 3.6 Hz), 6.59 (s, 1H), 4.35 (d, 2H, J = 6.0 Hz), 4.02 (t, 4H, J = 4.8 Hz), 3.96 (s, 3H), 2.33 (pentet, 1H, J = 6.0 Hz), 1.89 (t, 2H, J = 4.8 Hz). MS (ESI) m/z = 323 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{16}H_{18}O_5S$: C, 59.61; H, 5.63; S, 9.95. Found: C, 59.34; H, 5.75; S, 9.82.

The title compound was prepared by condensing 4-(3-hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-50C**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 199-201 °C, 60% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.23 (d, 2H, J = 8.7 Hz), 8.06-8.11 (m, 3H), 7.93 (d, 1H, J = 15.0 Hz), 7.71 (d, 1H, J = 3.3 Hz), 7.54 (d, 1H, J = 5.1 Hz), 7.13-7.16 (m, 1H), 6.87 (s, 1H), 4.62 (brs, 2H), 4.27 (d, 2H, J = 5.1 Hz), 4.00 (s, 3H), 3.62 (brs, 4H), 2.11-2.15 (m, 1H). MS (ESI) m/z = 469 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{25}H_{24}O_7S \cdot ¼H_2O$: C, 63.48; H, 5.22; S, 6.78. Found: C, 63.45; H, 5.29; S, 6.61.

EXAMPLE 51

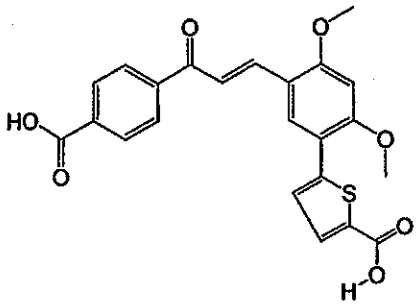


5-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-thiophene-2-carboxylic acid methyl ester

Ex-51A: 5-(5-Formyl-2,4-dimethoxy-phenyl)-thiophene-2-carboxylic acid methyl ester was prepared starting from 5-bromo-thiophene-2-carboxylic acid methyl ester in a similar manner as described in **Ex-46A** through **-46D**. Yellow solid, 18% yield. ^{1}H-NMR ($CDCl_3$) δ 10.32 (s, 1H), 8.16 (s, 1H), 7.74 (d, J = 4.4 Hz, 1H), 7.42 (d, J = 4.4 Hz, 1H), 6.51 (s, 1H), 4.05 (s, 3H), 3.98 (s, 3H), 3.90 (s, 3H). HRMS (ES+) Calcd. for $C_{15}H_{14}O_5S$: 307.0640. Found: 307.0630.

4-Acetylbenzoic acid (24 mg, 0.15 mmol) and 5-(5-formyl-2,4-dimethoxy-phenyl)-thiophene-2-carboxylic acid methyl ester (**Ex-51A**, 46 mg, 0.15 mmol) were dissolved in DMF (4 mL). Lithium methoxide, 1M in methanol (0.29 mL) was added and the solution stirred at room temperature overnight. The reaction solution was poured into cold 1N HCl (3 mL) and extracted with EtOAc (3x20 mL); the organic phase was washed with brine (1x10 mL), dried over sodium sulfate, filtered, and concentrated. The resulting orange residue was purified *via* silica gel chromatography (0-10% MeOH/CH_2Cl_2) to provide 89 mg of yellow solid which still contained DMF. The solid was slurried in EtOH for several hours, filtered, and dried to provide 31 mg of final product as a yellow solid (47% yield). ^{1}H-NMR (DMSO-d_6) δ 8.47 (s, 1H), 8.23 (d, J = 9 Hz, 2H), 8.01-8.11 (m, 4H), 7.89 (d, J = 4 Hz, 1H), 7.82 (d, J = 4 Hz, 1H), 6.90 (s, 1H), 4.09 (s, 3H), 4.03 (s, 3H), 3.84 (s, 3H). HRMS (ES+) Calcd. for $C_{24}H_{20}O_7S$: 453.1008. Found: 453.1020.

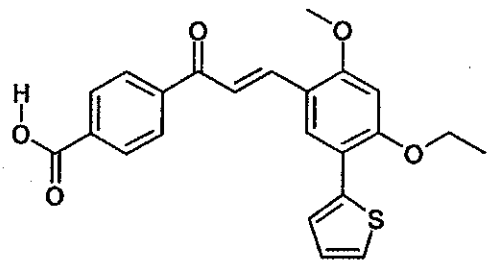
EXAMPLE 52



5-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-thiophene-2-carboxylic acid

The title compound was prepared through routine hydrolysis of 5-{5-[3-(4-Carboxy-phenyl)-3-oxo-propenyl]-2,4-dimethoxy-phenyl}-thiophene-2-carboxylic acid methyl ester (**Ex-51**). Orange solid, mp >260°C, 43% yield. ^{1}H-NMR (DMSO-d_6) δ 8.43 (s, 1H), 8.26 (d, J = 8 Hz, 2H), 8.01-8.12 (m, 4H), 7.82 (d, J = 4 Hz, 1H), 7.71 (d, J = 4 Hz, 1H), 6.89 (s, 1H), 4.08 (s, 3H), 4.03 (s, 3H).

EXAMPLE 53



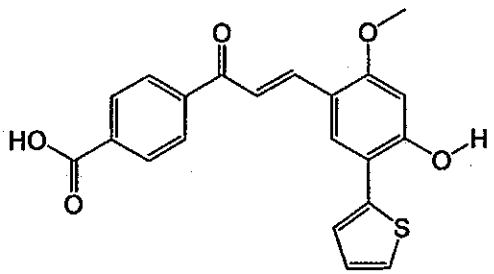
4-[3*E*-(4-Ethoxy-2-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-53A: Reaction of 4-hydroxy-2-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-47B**) and (2-ethoxymethyl-5-hydroxymethyl-[1,3]dioxolan-4-yl)methanol was preformed under the Mitsunobu condition using triphenylphosphine and diethyl azodicarboxylate in THF. However, the expected product, 4-(2-ethoxymethyl-5-hydroxymethyl-[1,3]dioxolan-4-ylmethoxy)-2-methoxy-5-thiophen-2-yl-benzaldehyde, was not obtained. Instead, 4-ethoxy-2-methoxy-5-thiophen-2-yl-benzaldehyde was formed *via* cleavage of the cyclic ethyl orthoformate group under the reaction conditions. Silica gel chromatography (ethyl acetate/hexanes, 1:2) gave 0.16

g (90%) of 4-ethoxy-2-methoxy-5-thiophen-2-yl-benzaldehyde, mp 101-103 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.15 (s, 1H), 7.48 (d, 1H, J = 3.6 Hz), 7.29 (d, 1H, J = 5.2 Hz), 7.07 (dd, 1H, J = 5.2, 3.6 Hz), 6.50 (s, 1H), 4.25 (q, 2H, J = 7.2 Hz), 3.97 (s, 3H), 1.59 (t, 3H, J = 7.2 Hz). MS (EI) m/z = 262 ([M]$^+$, 100%). HMRS (EI) Calcd. for $C_{14}H_{14}O_3S$: 262.0664. Found: 262.0667.

The title compound was prepared by condensing 4-ethoxy-2-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-53A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 210-212 °C, 76% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.23 (d, 2H, J = 9.0 Hz), 8.06-8.11 (m, 3H), 7.92 (d, 1H, J = 16.2 Hz), 7.71 (d, 1H, J = 3.9 Hz), 7.52 (d, 1H, J = 5.1 Hz), 7.13 (dd, 1H, J = 5.1, 3.9 Hz), 6.82 (s, 1H), 4.33 (q, 2H, J = 6.1 Hz), 3.99 (s, 3H), 1.48 (t, 3H, J = 6.1 Hz). MS (ESI) m/z = 409 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{23}H_{20}O_5S \cdot \frac{1}{2}H_2O$: C, 66.17; H, 5.07; S, 7.68. Found: C, 65.88; H, 5.24; S, 7.36.

EXAMPLE 54

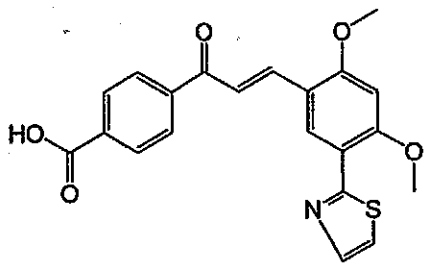


4-[3*E*-(4-Hydroxy-2-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

4-Hydroxy-2-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-47B**, 0.30 g, 0.86 mmol) and 4-acetylbenzoic acid (0.13 g, 0.86 mmol) were dissolved in a dimethylformamide-methanol solution (6 mL, 7:3). After complete dissolution, lithium methoxide (0.12 g, 3.3 mmol) was added and the resulting red slurry was stirred in the dark at room temperature for 18 h. The mixture was diluted with water (15 mL), acidified with a 1 N hydrochloric acid solution, and extracted with ethyl acetate (4 x 25 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was subjected to silica gel chromatography (CH_2Cl_2:MeOH, 20:1) to yield an orange solid containing residual amounts of starting acid. The solid was taken up in ethyl alcohol (5 mL) to remove acid impurity and the

resulting precipitate was collected on filter paper and dried *in vacuo* to yield 0.010 g (5%) of the title compound as an orange solid, mp 243 °C (dec). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.18-8.23 (m, 3H), 8.06-8.09 (m, 2H), 8.02 (s, 1H), 7.85 (d, 1H, J = 15.6 Hz), 7.68 (d, 1H, J = 3.6 Hz), 7.47 (d, 1H, J = 5.1 Hz), 7.11 (dd, 1H, J = 5.1, 3.6 Hz), 6.67 (s, 1H), 4.13 (s, 1H), 3.89 (s, 3H). MS (ESI) m/z = 381 ([M+H]$^+$, 100%). HRMS (ESI) Calcd. for $C_{21}H_{16}O_5S$: 381.0796. Found: 381.0800.

EXAMPLE 55

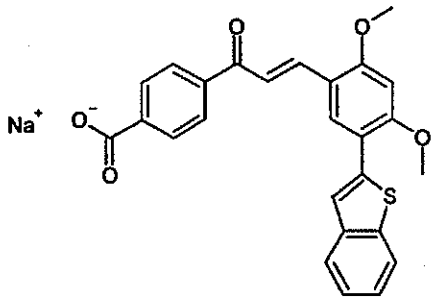


4-[3*E*-(2,4-Dimethoxy-5-thiazol-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-55A: 2,4-Dimethoxy-5-thiazol-2-yl-benzaldehyde was prepared from 2-bromothiazole in a similar manner as described in **Ex-46A** through **-46D**. Off-white solid, 83% yield. ^{1}H-NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.86 (s, 1H), 7.89 (d, J = 3.6 Hz, 1H), 7.36 (d, J = 3.6 Hz, 1H), 6.56 (s, 1H), 4.12 (s, 3H), 4.02 (s, 3H). HRMS *m/z*: calc. 249.0460, found 249.0461.

The title compound was prepared by condensing 2,4-dimethoxy-5-thiazol-2-yl-benzaldehyde (**Ex-55A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp >260°C, 65% yield. ^{1}H-NMR (DMSO-d_6) δ 13.33 (bs, 1H), 8.74 (s, 1H), 8.22 (d, J = 8 Hz, 2H), 8.04-8.12 (m, 3H), 7.95 (d, J = 2 Hz, 1H), 7.82 (d, J = 16 Hz, 1H), 7.76 (d, J = 3 Hz, 1H), 6.94 (s, 1H), 4.14 (s, 3H), 4.05 (s, 1H). HRMS *m/z* = calc. 396.0906, found 396.0903.

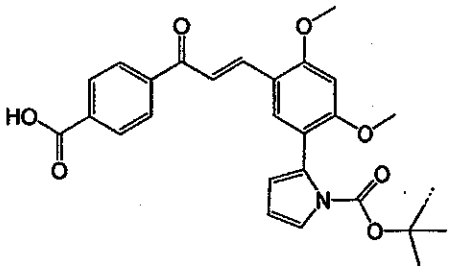
EXAMPLE 56



4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid, sodium salt

To a solution of 4-[3*E*-(5-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid (5.77g, 13.0 mmol) in tetrahydrofuran (50 mL) was added sodium methoxide (0.70g, 12.3 mmol). The reaction mixture was allowed to stir for 2 hours at ambient temperature. The precipitate was then filtered, washed with tetrahydrofuran and dried *in vacuo* to give the title compound (5.13g, 85%) as a yellow solid, mp > 235 °C. ^{1}H-NMR (DMSO-d_6) δ 8.35 (s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 8.00-7.89 (m, 4H), 7.82 (d, J = 7.6 Hz, 1H), 7.35-7.29 (m, 4H), 6.85 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H). MS *m/z* = 443 (M^+, 100%).

EXAMPLE 57



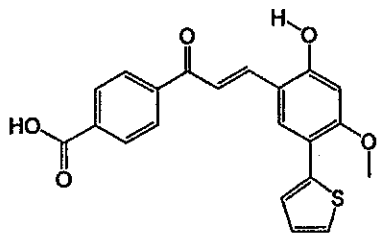
2-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-pyrrole-1-carboxylic acid *tert*-butyl ester

Ex-57A: 2-(5-Formyl-2,4-dimethoxy-phenyl)-pyrrole-1-carboxylic acid tert-butyl ester was prepared from pyrrole-1-carboxylic acid tert-butyl ester-2-boronic acid in a similar manner as described in **Ex-3A**, 81% yield. ^{1}H-NMR ($CDCl_3$) δ 10.32 (s, 1H), 7.76 (s, 1H), 7.31-7.33 (m,

1H), 6.43 (s, 1H), 6.22-6.24 (m, 1H), 6.14-6.16 (m, 1H), 3.98(s, 3H), 3.85 (s, 3H), 1.40 (s, 9H). HRMS (EI) Calcd. for $C_{18}H_{21}NO_5$: 331.1420. Found: 331.1421.

The title compound was prepared by condensing 2-(5-formyl-2,4-dimethoxy-phenyl)-pyrrole-1-carboxylic acid tert-butyl ester (**Ex-57A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 205-207°C, 6% yield. ^{1}H-NMR (DMSO-d_6) δ 8.19 (d, J = 5 Hz, 2H), 8.00-8.10 (m, 3H), 7.87 (s, 1H), 7.80 (d, J = 16 Hz, 1H), 7.27-7.28(m, 1H), 6.71(s, 1H), 6.22-6.23 (m, 1H), 6.14-6.16 (m, 1H), 3.96 (s, 3H), 3.79(s, 3H), 1.29 (s, 9H). MS *m/z* = 476 ([M-H]$^+$). HMRS (EI) calcd. for $C_{27}H_{27}NO_7$: 477.1788; found: 477.1793.

EXAMPLE 58

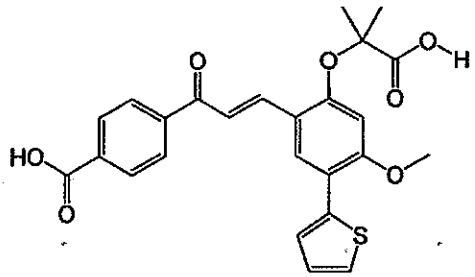


4-[3*E*-(2-Hydroxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

2-Hydroxy-4-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-29B**, 0.10 g, 0.43 mmol) and 4-acetylbenzoic acid (0.070 g, 0.43 mmol) were dissolved in a dimethylformamide-methanol solution (2.8 mL, 7:3). After complete dissolution, lithium methoxide (0.065 g, 1.7 mmol) was added and the resulting red slurry was stirred in the dark at room temperature for 18 h. The mixture was diluted with water (10 mL), acidified with a 1 N hydrochloric acid solution, and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was taken up in ethyl alcohol (5 mL) and warmed to 60 °C to obtain complete dissolution and allowed to cool to room temperature. Note: the compound appears to decompose with heating. The resulting precipitate was collected on filter paper and dried *in vacuo* to yield 0.025 g (15%) of the title compound as a dark yellow solid, mp 125 °C (dec). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.73 (s, 1 H), 8.18-8.22 (m, 3 H), 8.09 (d, 2 H, J = 8.1 Hz), 8.05 (s, 1 H), 7.87 (d, 1 H, J = 14.7 Hz), 7.60 (d, 1 H, J = 3.0 Hz), 7.49 (d, 1H, J = 4.2 Hz), 7.11 (dd, 1 H, J = 4.2, 3.0 Hz), 6.67 (s, 1 H), 3.90 (s, 3 H).

MS (ESI) *m/z* = 381 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{21}H_{16}O_5S$·EtOH: C, 64.77; H, 5.20; S, 7.52. Found: C, 64.68; H, 5.00; S, 7.77.

EXAMPLE 59



4-{3*E*-[2-(1-Carboxy-1-methyl-ethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid

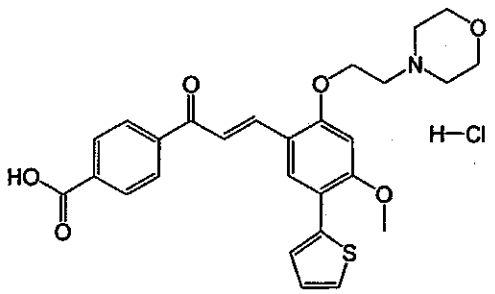
Ex-59A: 2-(2-Formyl-5-methoxy-4-thiophen-2-yl-phenoxy)-2-methyl-propionic acid ethyl ester was prepared in an analogous fashion as described in **Ex-29C** using ethyl 2-bromoisobutyrate. Silica gel chromatography (ethyl acetate/hexanes, 1:2) gave the expected product as a dark yellow solid (97%), mp 87-88 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.14 (s, 1H), 7.45 (dd, 1H, *J* = 3.6, 1.2 Hz), 7.30 (d, 1H, *J* = 5.4 Hz), 7.07 (dd, 1H, *J* = 5.1, 3.6 Hz), 6.42 (s, 1H), 4.25 (q, 2H, *J* = 6.9 Hz), 3.90 (s, 3H), 1.72 (s, 6H), 1.26 (t, 3H, *J* = 6.9 Hz). MS (ESI) *m/z* = 349 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{18}H_{20}O_5S$: C, 62.05; H, 5.79; S, 9.20. Found: C, 62.15; H, 5.82; S, 9.06.

Ex-59B: 2-(2-Formyl-5-methoxy-4-thiophen-2-yl-phenoxy)-2-methyl-propionic acid was prepared in an analogous fashion as described in **Ex-47D**. The crude solid was dried *in vacuo* to afford the product as a pale yellow solid (98%), mp 187-188 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.99 (s, 1H), 7.47 (dd, 1H, *J* = 3.6, 1.5 Hz), 7.37 (d, 1H, *J* = 4.8 Hz), 7.11 (dd, 1H, *J* = 4.8, 3.6 Hz), 6.67 (s, 1H), 4.00 (s, 3H), 1.75 (s, 6H). MS (ESI) *m/z* = 321 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{16}H_{16}O_5S$: C, 59.99; H, 5.03; S, 10.01. Found: C, 59.80; H, 5.12; S, 9.87.

2-(2-Formyl-5-methoxy-4-thiophen-2-yl-phenoxy)-2-methyl-propionic acid (**Ex-59B**, 0.12 g, 0.39 mmol) and 4-acetylbenzoic acid (0.064 g, 0.39 mmol) were dissolved in a

dimethylformamide-methanol solution (2.7 mL, 7:3). After complete dissolution, lithium methoxide (0.060 g, 1.6 mmol) was added and the resulting bright orange slurry was stirred in the dark at room temperature for 2 h. Upon completion, as determined by HPLC, the mixture was diluted with water (15 mL), acidified with a 1 N hydrochloric acid solution, and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was taken up in ethyl alcohol (5 mL) and warmed to 60 °C to obtain complete dissolution and allowed to cool to room temperature. The resulting precipitate was collected on filter paper and dried *in vacuo* to yield 0.15 g (85%) of the title compound as a dark yellow solid, mp 223-225 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.23 (d, 2H, J = 8.1 Hz), 8.10 (d, 2H, J = 8.1 Hz), 8.06 (s, 1H), 7.95 (d, 1H, J = 16.2 Hz), 7.69 (d, 1H, J = 3.0 Hz), 7.55 (d, 1H, J = 5.1 Hz), 7.14 (dd, 1H, J = 5.1, 3.0 Hz), 6.58 (s, 1H), 3.88 (s, 3H), 1.66 (s, 6H). MS (ESI) *m/z* = 467 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{25}H_{22}O_7S \cdot {}^1/_3H_2O$: C, 63.55; H, 4.84; S, 6.79. Found: C, 63.39; H, 5.02; S, 6.53.

EXAMPLE 60



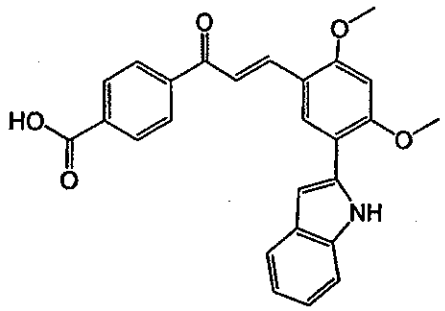
4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride

Ex-60A: 4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-benzaldehyde was prepared in an analogous fashion as described in **Ex-29C** using 4-(2-chloroethyl)morpholine. Silica gel chromatography (80 to 100% ethyl acetate/hexanes then 5% methanol/methylene chloride) gave of the expected product as a off-white solid (81%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.12 (s, 1H), 7.44 (dd, 1H, J = 3.6, 1.5 Hz), 7.30 (dd, 1H, J = 5.1, 1.5 Hz), 7.07 (dd, 1H, J = 5.1, 3.6 Hz), 6.53 (s, 1H), 4.27 (t, 2H, J = 6.3 Hz), 4.00 (s, 3H), 3.72-3.76 (m, 4H), 2.89

(t, 2H, J = 6.3 Hz), 2.60-2.63 (m, 4H). MS (ESI) m/z = 348 ($[M+H]^+$, 100%). HRMS (EI) Calcd. for $C_{18}H_{21}NO_4S$: 347.1191. Found: 347.1188.

4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-benzaldehyde (**Ex-60A**, 0.15 g, 0.43 mmol) and 4-acetylbenzoic acid (0.071 g, 0.43 mmol) were dissolved in a dimethylformamide-methanol solution (3.0 mL, 7:3). After complete dissolution, lithium methoxide (0.065 g, 1.7 mmol) was added and the resulting bright orange slurry was stirred in the dark at room temperature for 2 h. Upon completion, as determined by HPLC, the mixture was diluted with water (10 mL), acidified with a 1 N hydrochloric acid solution, and extracted with an ethyl acetate:tetrahydrofuran mixture (1:1, 6 x 20 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude solid was slurried in ethyl alcohol (5 mL) to remove residual impurities and the resulting solid was collected on filter paper and dried *in vacuo* to yield 0.21 g (98%) of the title compound as a dark yellow solid, mp: 255 °C (dec). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.26 (d, 2H, J = 8.7 Hz), 8.11 (d, 2H, J = 8.7 Hz), 8.08 (s, 1H), 7.95 (d, 1H, J = 15.9 Hz), 7.71 (d, 1H, J = 3.3 Hz), 7.55 (d, 1H, J = 4.5 Hz), 7.15 (dd, 1H, J = 4.5, 3.3 Hz), 6.94 (s, 1H), 4.68 (brs, 2H), 4.04 (s, 3H), 3.98 (brs, 2H), 3.81-3.88 (brm, 2H), 3.70 (brs, 2H), 3.54-3.58 (brm, 2H), 3.29 (brs, 2H). MS (ESI) m/z = 494 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{27}H_{28}ClNO_6S$: C, 61.18; H, 5.32; Cl, 6.69; N, 2.64; S, 6.05. Found: C, 61.18; H, 5.41; Cl, 6.16; N, 2.73; S, 5.87.

EXAMPLE 61



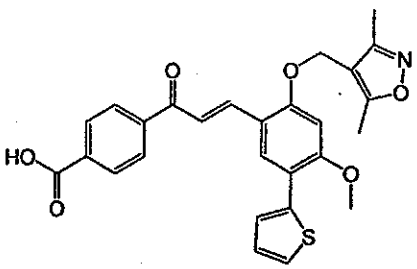
2 4-{3*E*-[5-(1H-Indol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid

Ex-61A: 2-(5-Formyl-2,4-dimethoxy-phenyl)-indole-1-carboxylic acid tert-butyl ester (**Ex-36A**, 2.0g, 5.2 mmol) was dissolved in 100 ml of THF, and Bu_4NF (6.86g, 26 mmol) was

added. The reaction mixture was stirred at room temperature overnight. No reaction occured at this condition. Then, Bu_4NF (6.86g, 26 mmol) was added to the mixture, and the mixture was stirred at reflux for 4 days. The reaction was about 50 % completion (HPLC). The reaction mixture was poured into CH_2Cl_2, and washed with water and brine. The organic phase was dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (EtOAc: Hex, 2:1) to give 0.45 g (30 %) of5-(1*H*-indol-2-yl)-2,4-dimethoxy-benzaldehyde. ^{1}H-NMR ($CDCl_3$) δ 10.37 (s, 1H), 9.25 (br, 1H), 8.28 (s, 1H), 7.63(d, J = 8 Hz, 1H), 7.39 (d, J = 8 Hz, 1H), 7.08-7.20 (m, 2H), 6.92(d, J = 2 Hz, 1H), 6.56 (s, 1H) 4.11(s, 3H), 4.00 (s, 3H). HMRS (EI) calcd. for $C_{17}H_{15}NO_3$: 281.1052; found: 281.1049.

The title compound was prepared by condensing 5-(1*H*-indol-2-yl)-2,4-dimethoxy-benzaldehyde (**Ex-61A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Red solid, mp 210-212°C, 66% yield. ^{1}H-NMR (Aceton-d_6) δ 10.53 (br, s, 1H), 8.32 (s, 1H), 8.14-8.21 (m, 5H), 7.89 (d, J = 15 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.38 (d, J = 7 Hz, 1H), 6.97-7.07(m, 3H), 6.87(s, 1H), 4.07 (s, 3H), 4.02(s, 3H), MS *m/z* = 427 ([M]$^+$). HMRS (EI) calcd. for $C_{26}H_{21}NO_5$: 427.1420; found: 427.1435.

EXAMPLE 62

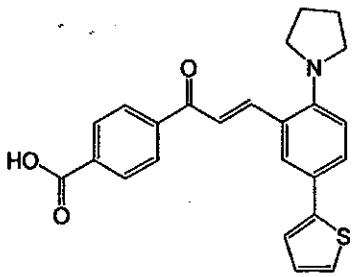


4-{3*E*-[2-(3,5-Dimethyl-isoxazol-4-ylmethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid

Ex-62A: 2-(3,5-Dimethyl-isoxazol-4-ylmethoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in Ex-29C using 4-chloromethyl-3,5-dimethyl-isoxazole. ^{1}H-NMR ($CDCl_3$) δ 10.26 (s, 1H), 8.14 (s, 1H), 7.45 (d, J = 6 Hz, 1H), 7.32 (d, J = 5 Hz, 1H), 7.07-710 (m, 1H), 6.58 (s, 1H), 4.96 (s, 2H), 4.04 (s, 3H), 2.46 (s, 3H), 2.32 (s, 3H).

The title compound was prepared by condensing 2-(3,5-dimethyl-isoxazol-4-ylmethoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-62A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 213-215°C. ^{1}H-NMR ($CDCl_3$) δ 8.20 (d, J = 9 Hz, 2H), 7.88-8.03 (m, 4H), 7.58 (d, J = 16 Hz, 1H), 7.44 (d, J = 4 Hz, 1H), 7.34(d, J = 5 Hz, 1H), 7.12(dd, J = 4, 5 Hz, 1H), 6.63 (s, 1H), 4.97(s, 2H), 4.01 (s, 3H), 2.46(s, 3H), 2.34 (s, 3H). MS *m/z* = 490 ([M+H]$^+$). HRMS (ES+) Calcd. for $C_{27}H_{22}NO_6S$: 490.1324. Found: 490.1321.

EXAMPLE 63

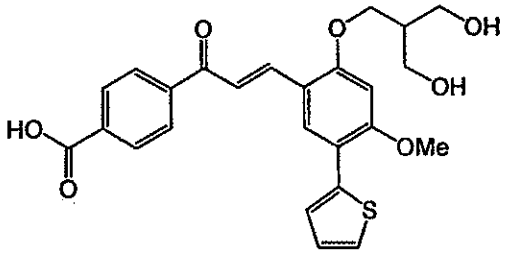


4-[3*E*-(2-Pyrrolidin-1-yl-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-63A: A solution of 2-fluoro-5-thiophen-2-yl-benzaldehyde (1.42g, 6.89 mmol) in pyrrolidine was refluxed (10 mL). After 4.5 days the reaction mixture was cooled and diluted with ethyl acetate. The solution of ethyl acetate was washed with hydrochloric acid (0.5M) sodium carbonate (2M) and saturated solution of sodium bicarbonate, dried over sodium sulfate, and concentrated. The crude product was purified by flash chromatography. Elution with ethyl acetate (20%, v/v, in hexane) afforded 2-pyrrolidin-1-yl-5-thiophen-2-yl-benzaldehyde (0.5g, 32%). ^{1}H NMR ($CDCl_3$) δ 10.14 (s, 1H), 7.94 (d, J = 2 Hz, 1H), 7.62 (dd, J = 2.7, 9 Hz, 1H), 7.22-7.20 (m, 2H), 7.07-7.04 (m, 1H), 6.86 (d, J = 9 Hz, 1H), 3.41 (m, 4H), 2.01 (m, 4H).

The title compound was prepared by condensing 2-pyrrolidin-1-yl-5-thiophen-2-yl-benzaldehyde (**Ex-63A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Red solid, mp 208-209 °C. ^{1}H-NMR (DMSO-d_6) δ 12.50 (bs, 1H), 8.22 (d, J = 8.5 Hz, 2H), 8.09-7.99 (m, 4H), 7.73 (d, J = 15.5 Hz, 1H), 7.52-7.41 (m, 3H), 7.10-7.07 (m, 1H), 6.93 (d, J = 9.0 Hz, 1H), 3.28 (m, 4H), 1.87 (m, 4H).

EXAMPLE 64



4-{3*E*-[2-(3-Hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid

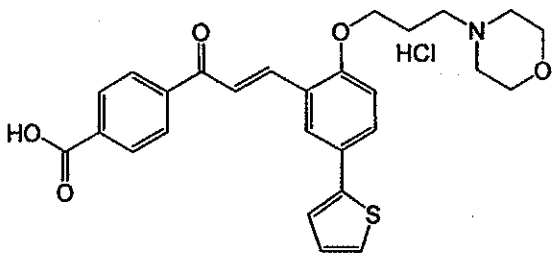
Ex-64A: To a solution of 2-hydroxy-4-methoxy-5-thiophen-2-yl-benzaldehyde (10.0 g, 42.7 mmol) in *N,N*-dimethylformamide (100 mL) was added potassium carbonate (11.8 g, 85.4 mmol) and the resulting yellow slurry was heated to 80 °C. Once at 80 °C, methanesulfonic acid 3-(tert-butyl-dimethyl-silanyloxy)-2-(tert-butyl-dimethyl-silanyloxymethyl)-propyl ester (**Ex-50A**, 19.5 g, 46.9 mmol) was added dropwise and the reaction was stirred for an additional 24 h at 80 °C and cooled to room temperature. The mixture was diluted with water (500 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers was sequentially washed with a saturated sodium bicarbonate solution (1 x 150 mL), water (1 x 150 mL), and brine (1 x 150 mL), dried over sodium sulfate, and concentrated to a brown oil. Silica gel chromatography (100% ethyl acetate to 10% ethyl acetate/hexanes) gave 19.0 g (81%) of 2-[3-(*tert*-butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propoxy]-4-methoxy-5-thiophen-2-yl-benzaldehyde as an off-white solid, mp 91-92 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.12 (s, 1H), 7.44 (dd, 1H, J = 3.6, 1.2 Hz), 7.29 (d, 1H, J = 5.1 Hz), 7.07 (dd, 1H, J = 5.1, 3.6 Hz), 6.54 (s, 1H), 4.19 (d, 2H, J = 6.0 Hz), 3.99 (s, 3H), 3.72-3.82 (m, 4H), 2.28 (pentet, 1H, J = 6.0 Hz), 0.88 (s, 18H), 0.048 (s, 12H). MS (EI) *m/z* = 550 ($[M]^+$, 100%). Anal. Calcd. for $C_{28}H_{46}O_5SSi_2$: C, 61.05; H, 8.42; S, 5.82. Found: C, 61.20; H, 8.74; S, 5.69.

Ex-64B: 2-(3-Hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde was prepared in an analogous fashion as described in **Ex-50C**. Silica gel chromatography (ethyl acetate/hexanes, 1:9) gave the expected product as an off-white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.03 (s, 1H), 7.43 (dd, 1H, J = 3.6, 1.2 Hz), 7.31 (d, 1H, J = 5.1 Hz),

7.08 (dd, 1H, J = 5.1, 3.6 Hz), 6.58 (s, 1H), 4.32 (d, 2H, J = 6.0 Hz), 4.01 (s, 3H), 3.95-3.99 (m, 4H), 2.51 (t, 2H, J = 5.1 Hz), 2.33 (pentet, 1H, J = 5.4 Hz). MS (EI) m/z = 322 ($[M]^+$, 100%). HRMS (EI) Calcd. for $C_{16}H_{18}O_5S$: 322.0875. Found: 322.0873.

The title compound was prepared by condensing 2-(3-hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-64B**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Light orange solid, mp 219-220 °C, 61% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.20 (d, 2H, J = 7.5 Hz), 8.05-8.11 (m, 3H), 7.93 (d, 1H, J = 16.2 Hz), 7.67 (d, 1H, J = 3.0 Hz), 7.52 (d, 1H, J = 5.1 Hz), 7.13 (dd, 1H, J = 5.1, 3.0 Hz), 6.88 (s, 1H), 4.66 (brs, 2H), 4.23 (d, 2H, J = 6.3 Hz), 4.01 (s, 3H), 3.55-3.66 (m, 4H), 2.09-2.14 (m, 1H). MS (ESI) m/z = 469 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{25}H_{24}O_7S \cdot H_2O$: C, 61.72; H, 5.39; S, 6.59. Found: C, 61.93; H, 5.30; S, 7.06.

EXAMPLE 65



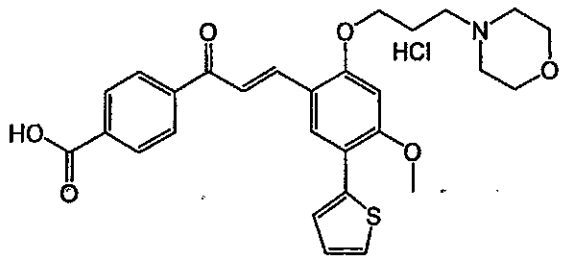
4-{3*E*-[2-(3-Morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride

Ex-65A: 2-(3-Morpholin-4-yl-propoxy)-5-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in **Ex-60A**, 80% yield. ^{1}H-NMR (DMSO-D6) δ 10.36 (s, 1 H), 7.90 (dd, J = 3, 5 Hz, 1H), 7.82 (d, 1H), 7.48 (d, 1H), 7.44 (d, 1H), 7.25 (d, 1H) , 7.09 (t, 1H), 4.18 (t, 2H), 3.53 (m, 4H), 3.28 (br s, 2H), 2.43 (m, 4H), 1.89 (q, 2H).

The title compound was prepared by condensing 2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-benzaldehyde (**Ex-65A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 67% yield, mp 234-236 °C. ^{1}H-NMR (DMSO-d6) δ 13.32 (br s, 1 H), 11.10 (br s, 1H), 8.21 (m, 3H), 8.02 (m, 3H), 7.67 (dd, J= 2,2 Hz, 1H), 7.56 (d, 1H), 7.50 (d, 1H), 7.14 (m,

2H), 4.21(t, 2H), 3.86 (m, 4H), 3.23 (m, 6H), 2.29 (q,2H). MS *m/z* = 478 ($[M+H]^+$, 100%). Anal. calculated for $C_{27}H_{28}ClNO_5S \cdot 3/2\ H_2O$: C, 59.94, H, 5.78, S, 5.93; found C: 60.20, H: 5.65, S: 5.94

EXAMPLE 66

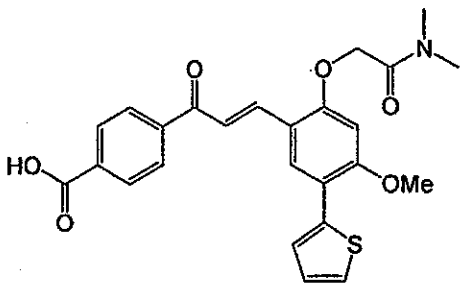


4-{3*E*-[4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride

Ex-66A: 4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in **Ex-60A**, 78% yield. ^{1}H-NMR (DMSO-D6) δ 10.21 (s, 1 H), 7.88 (s, 1H), 7.46 (m, 2H), 7.06 (t, 1H), 6.82 (s, 1H), 4.24 (t, 2H), 4.00 (s, 3H), 3.53 (m, 4H), 3.28 (m, 2H), 2.34 (m, 4H), 1.93 (q, 2H).

The title compound was prepared by condensing 4-methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-benzaldehyde (**Ex-66A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 72% yield, mp 188-191°C (dec). ^{1}H-NMR (DMSO-d6) δ 12.63 (br s, 1 H), 11.08 (br s, 1H), 8.33 (s, 1H), 8.22 (d, 2H), 8.05 (m, 3H), 7.89 (d, 1H), 7.65 (d, 1H), 7.49 (d, 1H), 7.10 (t, 1H), 6.84 (s, 1H), 4.30 (t, 2H), 3.98 (s, 3H), 3.84 (m, 4H), 3.21 (m,6H), 2.28 (q, 2H). MS *m/z* = 508 ($[M+H]^+$; 100%). Anal. calculated for $C_{28}H_{32}ClNO_7S \cdot H_2O$: C, 59.83, H, 5.74, S, 5.70; found C: 59.69, H: 5.80, S: 5.55.

EXAMPLE 67

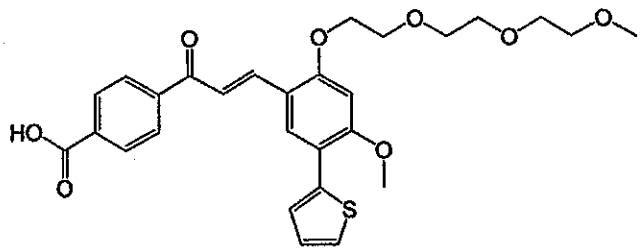


4-[3*E*-(2-Dimethylcarbamoylmethoxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-67A: 2-(2-Formyl-5-methoxy-4-thiophen-2-yl-phenoxy)-N,N-dimethyl-acetamide was prepared in an analogous fashion as described in **Ex-29C** using 2-chloro-*N*,*N*-dimethylacetamide. Methylene chloride was used in place of ethyl acetate for the work up procedure. The crude solid was slurried in ethyl acetate (25 mL) to remove residual impurities. The resulting solid was collected on filter paper and dried *in vacuo* to give the expected product as a pale yellow solid (85%), mp 197-198 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.13 (s, 1H), 7.44 (d, 1H, J = 3.6 Hz), 7.30 (dd, 1H, J = 5.1, 1.8 Hz), 7.07 (dd, 1H, J = 5.1, 3.6 Hz), 6.73 (s, 1H), 4.89 (s, 2H), 3.99 (s, 3H), 3.15 (s, 3H), 2.99 (s, 3H). MS (EI) *m/z* = 319 ($[M]^+$, 100%). Anal. Calcd. for $C_{16}H_{17}NO_4S \cdot {}^1/_5H_2O$: C, 59.50; H, 5.43; N, 4.34; S, 9.93. Found: C, 59.65; H, 5.42; N, 4.40; S, 9.69.

The title compound was prepared by condensing 2-(2-formyl-5-methoxy-4-thiophen-2-yl-phenoxy)-N,N-dimethyl-acetamide (**Ex-67A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 228-229 °C, 75% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.31 (d, 2H, J = 9.3 Hz), 8.22 (d, 2H, J = 13.3 Hz), 8.08 (d, 2H, J = 9.3 Hz), 7.95 (s, 1H), 7.65 (d, 1H, J = 2.7 Hz), 7.52 (d, 1H, J = 5.1 Hz), 7.13 (dd, 1H, J = 5.1, 2.7 Hz), 6.85 (s, 1H), 5.11 (s, 2H), 3.99 (s, 3H), 3.06 (s, 3H), 2.93 (s, 3H). MS (EI) *m/z* = 465 ($[M]^+$, 100%). HRMS (EI) Calcd. for $C_{25}H_{23}NO_6S$: 465.1246. Found: 465.1246.

EXAMPLE 68



4-[3*E*-(4-Methoxy-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

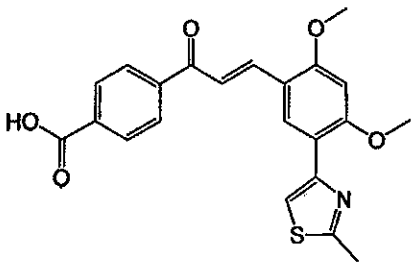
Ex-68A: Methanesulfonic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester was prepared in an analogous fashion as described in **Ex-50A** using di(ethylene glycol) methyl ether. The crude orange oil was dried *in vacuo* to give the expected product (oil) and was used without any further purification (99%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.37-4.40 (m, 2H), 3.76-3.78 (m, 2H), 3.61-3.70 (m, 6H), 3.53-3.57 (d, 2H), 3.38 (s, 3H), 3.08 (s, 3H). MS (ESI) *m/z* = 243 ($[M+H]^+$, 100%). HRMS (ESI) Calcd. for $C_8H_{18}O_6S$: 243.0902. Found: 243.0914.

Ex-68B: 4-Methoxy-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-5-thiophen-2-yl-benzaldehyde was prepared in an analogous fashion as as described in **Ex-29C** using methanesulfonic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester (**Ex-68A**). Silica gel chromatography (ethyl acetate/hexanes, 8:1) gave the expected product as a pale yellow oil (70%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.12 (s, 1H), 7.44 (d, 1H, J = 3.6 Hz), 7.30 (d, 1H, J = 5.4 Hz), 7.07 (dd, 1H, J = 5.4, 3.6 Hz), 6.57 (s, 1H), 4.31 (t, 2H, J = 4.8 Hz), 3.99 (s, 3H), 3.94 (t, 2H, J = 4.8 Hz), 3.74-3.78 (m, 2H), 3.62-3.69 (m, 4H), 3.53-3.56 (m, 2H), 3.37 (s, 3H). MS (EI) *m/z* = 380 ($[M]^+$, 100%). HRMS (ESI) Calcd. for $C_8H_{18}O_6S$: 243.0902. Found: 243.0914.

The title compound was prepared by condensing 4-methoxy-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-5-thiophen-2-yl-benzaldehyde (**Ex-68B**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 137-138 °C, 82% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.20-8.23 (m, 3H), 8.09 (d, 2H, J = 8.3 Hz), 8.01 (m, 2H), 7.66 (d, 1H, J = 3.6 Hz), 7.52 (d, 1H, J = 5.1 Hz), 7.13 (dd, 1H, J = 5.1, 3.6 Hz), 6.88 (s, 1H), 4.37 (t, 2H, J = 3.6

Hz), 4.01 (s, 3H), 3.89 (t, 2H, J = 3.6 Hz), 3.64-3.67 (m, 2H), 3.53-3.56 (m, 2H), 3.47-3.50 (m, 2H), 3.36-3.95 (m, 2H), 3.19 (s, 3H). MS (ESI) m/z = 527 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{28}H_{30}O_8S$: C, 63.86; H, 5.74; S, 6.09. Found: C, 64.08; H, 5.77; S, 6.09.

EXAMPLE 69



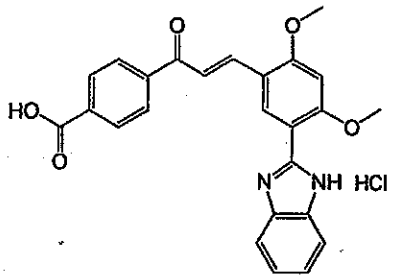
4-{3*E*-[2,4-Dimethoxy-5-(2-methyl-thiazol-4-yl)-phenyl]-acryloyl}-benzoic acid

Ex-69A: A solution of 2-bromo-1-(3,4-dimethoxy-phenyl)-ethanone (0.62g, 2.39 mmol) and thioacetamide (0.18g, 2.39 mmol) in ethanol (30 mL) was refluxed for 2 hours and the solvent was removed under reduced pressure. The product, 4-(3,4-dimethoxy-phenyl)-2-methyl-thiazole (0.56g, 100%) was obtained as a white solid and used without further purification. To a suspension of 4-(3,4-dimethoxy-phenyl)-2-methyl-thiazole obtained above (0.70g, 2.97 mmol) in dichloromethane (60 mL) at 0 °C was added dichloromethyl methyl ether (0.40 mL, 4.46 mmol) followed by addition of titanium tetrachloride (1.0 M solution in dichloromethane, 8.9 mL, 8.9 mmol) dropwise. The reaction mixture was allowed to stir overnight at ambient temperature and then poured into ice. The aqueous solution was extracted with dichloromethane. The solution of dichloromethane was washed with hydrochloric acid (0.5M), saturated solution of sodium bicarbonate and brine, dried over sodium sulfate and concentrated. The product, 2,4-dimethoxy-5-(2-methyl-thiazol-4-yl)-benzaldehyde, was obtained as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.67 (s, 1H), 7.56 (s, 1H), 6.52 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 2.75 (s, 3H).

The title compound was prepared by condensing 2,4-dimethoxy-5-(2-methyl-thiazol-4-yl)-benzaldehyde (**Ex-69A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 201-202 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ 8.47 (s, 1H), 8.14-7.97 (m, 5H),

7.76 (s, 1H), 7.65 (d, J = 15.8 Hz, 1H), 6.81 (s, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 2.69 (s, 3H). MS *m/z* = 409 (M^+, 70%), 378 ($[M - OCH_3]^+$, 100%).

EXAMPLE 70



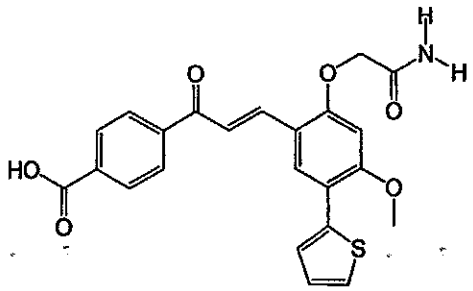
4-{3*E*-[5-(1*H*-Benzoimidazol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid

Ex-70A: A solution of benzene-1,2-diamine (2.60g, 24.1 mmol) and 2,4-dimethoxy-benzaldehyde (4.0g, 24.1 mmol) in ethanol (60 mL) containing catalytic amount of acetic acid was refluxed overnight. Solvent was then evaporated under reduced pressure. The residue oil was triturated in ethyl acetate to obtain 2-(2,4-dimethoxy-phenyl)-1*H*-benzoimidazole (0.76g, 12%). The crude product was used without further purification. To a solution of 2-(2,4-dimethoxy-phenyl)-1*H*-benzoimidazole obtained above (0.76g, 2.99 mmol) in dichloromethane (20 mL) was added dichloromethyl methyl ether (0.41 mL, 4.48 mmol) followed by addition of titanium tetrachloride (1.0M in dichloromethane, 9.0 mL, 9.0 mmol) at 0 °C. The reaction mixture was allowed to stir overnight at ambient temperature and then poured into ice. A solution of sodium hydroxide (5M) was added dropwise until the pH of the solution was about 12. The basic solution was extracted with dichloromethane. The combined solution of dichloromethane was subsequently washed with brine, dried over sodium carbonate and concentrated. The product, 5-(1*H*-benzoimidazol-2-yl)-2,4-dimethoxy-benzaldehyde (0.40g, 47%), was obtain and used without further purification. ^{1}H NMR ($CDCl_3$) δ 10.32 (s, 1H), 10.27 (bs, 1H), 9.03 (s, 1H), 7.83 (d, J = 9 Hz, 1H), 7.48-7.45 (m, 1H), 7.31-7.22 (m, 1H), 6.58 (s, 1H), 4.18 (s, 3H), 4.01 (s, 3H). MS *m/z* = 282 (M^+, 100%).

The title compound was prepared by condensing 5-(1*H*-benzoimidazol-2-yl)-2,4-dimethoxy-benzaldehyde (**Ex-70A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp > 240 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ 8.72 (s, 1H), 12.10 (s, 1H), 8.18 (d,

J = 8.4 Hz, 2H), 8.08-8.02 (m, 3H), 7.80 (d, J = 15.4 Hz, 1H), 7.59 (s, 2H), 7.17-7.13 (m, 2H), 6.89 (s, 1H), 4.10 (s, 3H), 4.03 (s, 3H). MS *m/z* = 429 ($[M + H]^+$, 100%).

EXAMPLE 71

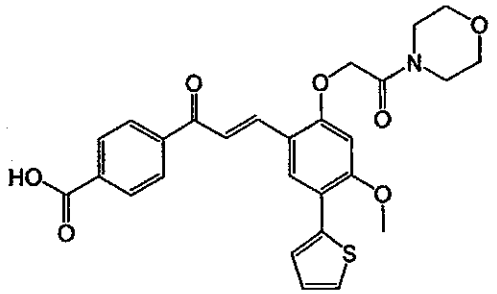


4-[3*E*-(2-Carbamoylmethoxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid

Ex-71A: 2-(2-Formyl-5-methoxy-4-thiophen-2-yl-phenoxy)-acetamide was prepared in an analogous fashion as described in **Ex-29C** using 2-bromoacetamide. Silica gel chromatography (ethyl acetate/hexanes, 8:1) gave the expected product as a pale yellow solid (75%), mp: 178-179 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.99 (s, 1H), 7.67 (brs, 1H), 7.44 (d, 1H, *J* = 3.6 Hz), 7.34 (d, 1H, *J* = 5.4 Hz), 7.10 (dd, 1H, *J* = 5.4, 3.6 Hz), 6.48 (s, 1H), 5.67 (brs, 1H), 4.64 (s, 2H), 4.02 (s, 3H). MS (EI) *m/z* = 291 ($[M]^+$, 100%). Anal. Calcd. for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.01. Found: C, 57.63; H, 4.50; N, 4.87; S, 11.03.

The title compound was prepared by condensing 2-(2-formyl-5-methoxy-4-thiophen-2-yl-phenoxy)-acetamide (**Ex-71A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 70% yield, mp 235 °C (dec.). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.26-8.30 (m, 3H), 8.08-8.11 (m, 4H), 7.67 (d, 1H, *J* = 2.7 Hz), 7.65 (brs, 1H), 7.53 (d, 1H, *J* = 4.0 Hz), 7.49 (brs, 1H), 7.13 (m, 1H), 6.77 (s, 1H), 4.75 (s, 2H), 3.97 (s, 3H). MS (EI) *m/z* = 437 ($[M]^+$, 100%). HRMS (EI) Calcd. for $C_{23}H_{19}NO_6S$: 437.0933. Found: 437.0924.

EXAMPLE 72

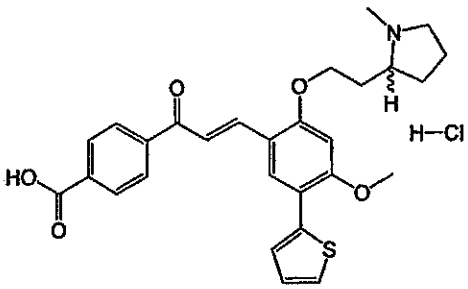


4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-2-oxo-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid

Ex-72A: 4-Methoxy-2-(2-morpholin-4-yl-2-oxo-ethoxy)-5-thiophen-2-yl-benzaldehyde was prepared in an analogous fashion as described in **Ex-29C** using 4-(2-chloroacetyl)morpholine. Silica gel chromatography (80% ethyl acetate/hexanes to 100% ethyl acetate) gave the expected product as a pale yellow solid, mp 200-201 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.12 (s, 1H), 7.44 (d, 1H, J = 3.6 Hz), 7.31 (d, 1H, J = 5.1 Hz), 7.08 (dd, 1H, J = 5.1, 3.6 Hz), 6.74 (s, 1H), 4.89 (s, 2H), 4.00 (s, 3H), 3.67 (brs, 8H). MS (ESI) m/z = 362 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88; S, 8.87. Found: C, 59.88; H, 5.36; N, 3.90; S, 8.75.

The title compound was prepared by condensing 4-methoxy-2-(2-morpholin-4-yl-2-oxo-ethoxy)-5-thiophen-2-yl-benzaldehyde (**Ex-72A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Orange solid, mp 231-233 °C, 70% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.28-8.35 (m, 3H), 8.21 (s, 1H), 8.07-8.11 (m, 3H), 7.66 (d, 1H, J = 3.3 Hz), 7.52 (d, 1H, J = 5.1 Hz), 7.13 (dd, 1H, J = 5.1, 3.3 Hz), 6.87 (s, 1H), 5.13 (s, 2H), 4.00 (s, 3H), 3.65 (brm, 4H), 3.54-3.55 (m, 4H). MS (EI) m/z = 507 ($[M]^+$, 100%). Anal. Calcd. for $C_{27}H_{25}NO_7S \cdot ½EtOH$: C, 63.55; H, 5.61; N, 2.60; S, 5.95. Found: C, 63.13; H, 5.55; N, 2.53; S, 5.84.

EXAMPLE 73



4-(3*E*-{4-Methoxy-2-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic acid, hydrochloride

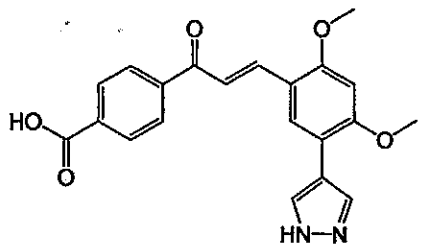
Ex-73A: Methanesulfonic acid 2-(1-methyl-pyrrolidin-2-yl)-ethyl ester was prepared in an analogous fashion as described in **Ex-50A** using (*S*)-(-)-1-methyl-2-pyrrolidinemethanol. The crude orange oil was dried *in vacuo* to give the expected product and was used without any further purification (40%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.99-5.04 (m, 1H), 4.41-4.51 (m, 1H), 4.19-4.29 (m, 1H), 3.88-3.94 (m, 1H), 3.49 (s, 3H), 3.17-3.29 (m, 1H), 2.95-3.05 (m, 1H), 2.74 (s, 3H), 2.41-2.58 (m, 3H), 1.98-2.08 (m, 2H). MS (EI) *m/z* = 207 ([M]$^+$, 100%). HRMS (EI) Calcd. for $C_{18}H_{19}NO_5S$: 207.0929. Found: 207.0922.

Ex-73B: 4-Methoxy-2-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-5-thiophen-2-yl-benzaldehyde was prepared in an analogous fashion as described in **Ex-29C** using Methanesulfonic acid 2-(1-methyl-pyrrolidin-2-yl)-ethyl ester (**Ex-73A**). Silica gel chromatography (10% methanol/methylene chloride to 15% methanol/methylene chloride) gave 0.50 g (70 %) of the expected product as a pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$, major isomer) δ 10.35 (s, 1H), 8.09 (s, 1H), 7.42-7.44 (m, 1H), 7.30 (d, 1H, *J* = 5.1 Hz), 7.06-7.09 (m, 1H), 6.49 (s, 1H), 4.80 (m, 1H), 4.20-4.26 (m, 1H), 3.98 (s, 3H), 2.64-2.84 (m, 2H), 2.47 (s, 3H), 1.80-2.33 (m, 7H). MS (EI) *m/z* = 345 ([M]$^+$, 100%). HRMS (EI) Calcd. for $C_{18}H_{19}NO_5S$: 345.1399. Found: 345.1401.

The title compound was prepared by condensing 4-methoxy-2-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-5-thiophen-2-yl-benzaldehyde **(Ex-73B)** and 4-acetylbenzoic acid in a similar manner as described in **Ex-3.** Dark Yellow solid, 52%, mp 206-208 °C.. ^{1}H-NMR (300 MHz, DMSO-

d_6, major isomer) δ 8.30 (s, 1H), 8.25 (d, 2H, J = 7.8 Hz), 8.07-8.12 (m, 3H), 7.94 (d, 1H, J = 15.6 Hz), 7.68 (d, 1H, J = 3.3 Hz), 7.52 (d, 1H, J = 5.1 Hz), 7.14 (dd, 1H, J = 5.1, 3.3 Hz), 6.86 (s, 1H), 5.05 (m, 1H), 4.34 (m, 1H), 4.00 (s, 3H), 3.40-3.46 (m, 2H), 2.81 (s, 3H), 2.40-2.44 (m, 1H), 2.16-2.27 (m, 2H), 1.81-2.00 (m, 4H). MS (ESI) m/z = 492 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{28}H_{30}ClNO_5S \cdot \frac{1}{2}H_2O$: C, 60.59; H, 5.99; N, 2.52; S, 5.78. Found: C, 60.70; H, 5.85; N, 2.64; S, 6.15.

EXAMPLE 74



4-{3*E*-[2,4-Dimethoxy-5-(1*H*-pyrazol-4-yl)-phenyl]-acryloyl}-benzoic acid

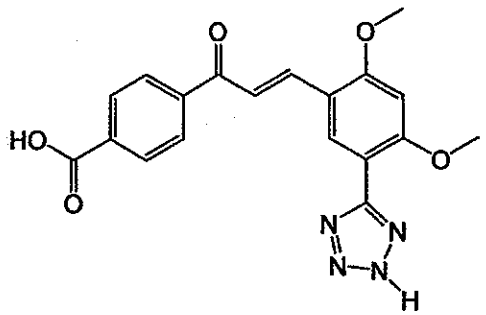
Ex-74A: A solution of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole (0.33g, 1.70 mmol) and di-*tert*-butyl dicarbonate (0.51g, 2.34 mmol) in dichloromethane (10 mL) was allowed to stir overnight at ambient temperature. The solution was then washed with saturated solution of sodium bicarbonate and brine, dried over sodium sulfate, and concentrated. The crude product of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazole-1-carboxylic acid *tert*-butyl ester (0.61g) was used in next step without further purification.

Ex-74B: To a mixture of 2,4-dimethoxy-5-bromo-benzaldehye (0.28g, 1.13 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazole-1-carboxylic acid tert-butyl ester (**Ex-76A**, 0.61g, 1.70 mmol), bis(tri-*tert*-butylphosphine)palladium (43 mg, 0.085 mmol) and potassium fluoride (0.24g, 4.08 mmol) was added degassed tetrahydrofuran (15 mL). The reaction mixture was heated at 60 °C for one day. Additional potassium fluoride (0.24g, 4.08 mmol) and water (20 μL) were added. The reaction mixture continued to stir at 60 °C for another 8 hours. The reaction was then quenched by water. The aqueous solution was extracted with ethyl acetate. The solution of ethyl acetate was washed with saturated solution of sodium bicarbonate, brine, dried over sodium sulfate and concentrated. The crude product was purified

by flash chromatography. Elution with ethyl acetate (50%, v/v, in hexane) afforded 4-(5-formyl-2,4-dimethoxy-phenyl)-pyrazole-1-carboxylic acid *tert*-butyl ester (0.15g, 40%) as white solid. ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 8.43 (s, 1H), 8.09 (s, 1H), 8.02 (s, 1H), 6.52 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 1.68 (s, 9H). MS *m/z* = 333 ($[M + H]^+$, 100%).

The title compound was prepared by condensing 2,4-dimethoxy-5-(1*H*-pyrazol-4-yl)-benzaldehyde (**Ex-74B**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3** including an acid work-up. Yellow solid, mp >250 °C. ^{1}H-NMR (DMSO-d_6) δ 12.42 (bs, 1H), 8.20-8.03 (m, 8H), 7.85 (d, J = 16.1 Hz), 6.74 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H). MS *m/z* = 379 ($[M + H]^+$, 100%).

EXAMPLE 75

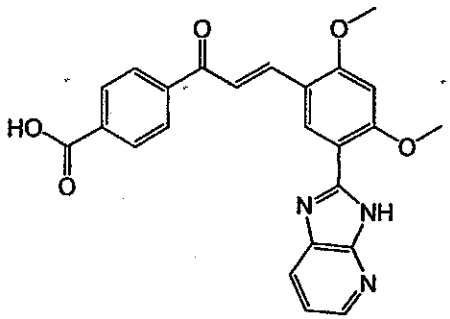


4-{3*E*-[2,4-Dimethoxy-5-(2*H*-tetrazol-5-yl)-phenyl]-acryloyl}-benzoic acid

Ex-75A: A solution of 2-(5-bromo-2,4-dimethoxy-phenyl)-[1,3]dioxolane (**Ex-46A**, 1.16 g, 4.9 mmol), sodium azide (641.3 mg, 9.86), and zinc bromide (552.2 mg, 2.46 mmol) in water (14 mL) and isopropanol (17 mL) were mixed and refluxed for 18 hours. The reaction mixture was quenched with 3N HCl (60 mL) and extracted with ethyl acetate (2 x 75 mL). The organic ws concentrated to a white solid. The solid was stirred in 0.25N NaOH (100 mL) for one hour. The suspension was filtered and the filtrate was collected and acidified with 1N HCl to a pH of 2. The aqueous solution was extracted with ethyl acetate:THF (40%). The organics were collected and concentrated to a crude brown solid of 2,4-dimethoxy-5-(2*H*-tetrazol-5-yl)-benzaldehyde (77.8 mg, 7%). ^{1}H-NMR (DMSO-d6) δ 10.09 (s, 1 H), 7.97 (s, 1H), 6.89 (s, 1H), 4.04 (s, 3H), 4.02 (s, 3H). MS *m/z* = 234 ($[M]^+$, 94%), 191 (100%).

The title compound was prepared by condensing 2,4-dimethoxy-5-(2*H*-tetrazol-5-yl)-benzaldehyde (**Ex-75A**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, 19% yield, mp 218 °C (dec). ^{1}H-NMR (DMSO-d6) δ 8.58 (s, 1 H), 8.20 (d, 2H), 8.03 (m, 3H), 7.85 (d, 1H), 6.90 (s, 1H), 4.04 (s, 3H), 4.02 (s, 3H). MS *m/z* = 422 ([M+CH_3CN+H]$^+$, 100%). HRMS m/z: calc. 381.1199, found 381.1184.

EXAMPLE 76



4-{3*E*-[5-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid

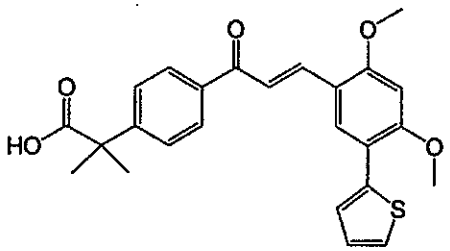
Ex-76A: To a suspension of 2, 4-dimethoxybenzoic acid (0.36 g, 2 mmol) and 8 ml of $POCl_3$ in a 50 ml of a round-bottom flask, 2,3-diaminopyridine (0.22 g, 2 mmol) was added. The mixture was heated to reflux for 4 hours and then cooled to room temperature. The reaction mixture was then concentrated to remove most of the $POCl_3$. The residue was carefully treated with 1N HCl at 0 °C using a water-ice bath, then neutralized with NaOH (50 %). The off-white solid was filtered to give 2-(2,4-dimethoxy-phenyl)-3*H*-imidazo[4,5-*b*]pyridine (0.44 g, 88%). ^{1}H-NMR (DMSO-d_6) δ 8.28-8.36 (m, 2H), 7.97 (d, J = 8 Hz, 1H), 7.21-7.25(m, 1H), 6.80 (s, 1H), 6.78 (d, J = 9 Hz, 1H), 4.05(s, 3H), 3.91 (s, 3H). HRMS (ES+) Calcd. for $C_{24}H_{19}N_3O_5$: 430.1403. Found: 430.1414.

Ex-76B: To a suspension of 2-(2,4-dimethoxy-phenyl)-3*H*-imidazo[4,5-*b*]pyridine (0.44 g, 1.7 mmol) in 20 ml of CH_2Cl_2, 1, 1-dichlorodimethyl ether (0.55 g, 4.8 mmol) was added. The mixture was cooled to 0 °C with a water-ice bath, and 7 ml (7 mmol) of $TiCl_4$ (1.0 m in CH_2Cl_2) was added dropwise. The mixture was stirred at 0 °C for 2 hrs, then room temperature for overnight. The reaction mixture was poured into ice-water and the precipitate was filtered to give 0.31 g (63%) of 5-(3*H*-imidazo[4,5-b]pyridin-2-yl)-2,4-dimethoxy-benzaldehyde as a

white solid. ^{1}H-NMR (DMSO-d_6) δ 10.22 (s, 1H), 8.67(s, 1H), 8.56 (d, J = 5 Hz, 1H), 8.44 (d, J = 8 Hz, 1H), 7.57-7.61(m, 1H), 6.97 (s, 1H), 4.19(s, 3H), 4.06 (s, 3H). HMRS (EI) calcd. for $C_{15}H_{13}N_3O_3$: 283.0957; found: 283.0952.

The title compound was prepared by condensing 5-(3*H*-imidazo[4,5-b]pyridin-2-yl)-2,4-dimethoxy-benzaldehyde (**Ex-76B**) and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, mp 222-224°C, 60% yield. ^{1}H-NMR (DMSO-d_6) δ 8.75 (s, 1H), 8.38-8.40 (m, 1H), 8.18 (d, J = 9Hz, 2H), 7.99-8.08(m, 4H), 7.83(d, J = 15 Hz, 1H), 7.28-7.33(m, 1H), 6.91 (s, 1H), 4.11(s, 3H), 4.04 (s, 3H). MS *m/z* = 430 ([M+H]$^+$).

EXAMPLE 77

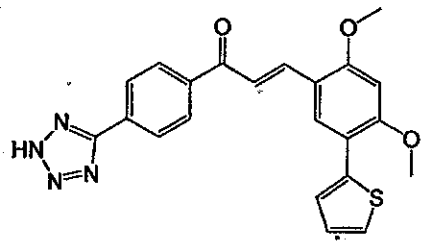


2-{4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-phenyl}-2-methyl-propionic acid

Ex-77A: To a mixture of aluminum chloride (2.8g, 20.8 mmol) in carbon disulfide (50 mL) was added acetyl chloride (0.74 mL, 10.4 mmol) followed by addition of 2-methyl-2-phenyl-propionic acid ethyl ester (1.0g, 5.2 mmol). The reaction mixture was refluxed for 2 hours and then poured into ice containing sulfuric acid (6M). The mixture was partitioned. The aqueous layer was extracted with ethyl acetate. The solution of ethyl acetate was washed with hydrochloric acid (0.5M), saturated solution of sodium bicarbonate and brine, dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography. Elution with ethyl acetate (33%, v/v, in hexane) gave 2-(4-acetyl-phenyl)-2-methyl-propionic acid ethyl ester (0.57g, 47%). ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 2.59 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H).

The title compound was prepared by condensing 2-(4-acetyl-phenyl)-2-methyl-propionic acid (**Ex-77A**) and 2,4-dimethoxy-5-thiophen-2-yl-benzaldehyde (**Ex-6A**) in a similar manner as described in **Ex-3**. White foam. ^{1}H-NMR ($CCDl_3$) δ 8.11-7.86 (m, 5H), 7.62-7.46 (m, 3H), 7.42 (d, J = 3.2 Hz, 1H), 7.31 (d, J = 5.3, 1H), 7.10-7.08 (m, 1H), 6.54 (s, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 1.67 (s, 3H), 1.65 (s, 3H). MS *m/z* = 436 (M^+, 55%), 405 ($[M-OCH_3]^+$, 100%).

EXAMPLE 78

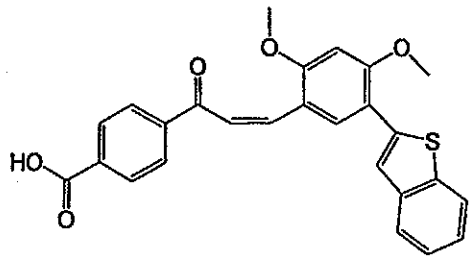


3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-1-[4-(2*H*-tetrazol-5-yl)-phenyl]-propenone

Ex-78A: A suspension of 4-acetylbenznitrile (2.9g, 20.0 mmol), sodium azide (1.43g, 22.0 mmol) and zinc bromide (4.5g, 20.0 mmol) in water (50 mL) was refluxed for one day. Additional water (40 mL), HCl (3M, 30 mL) and EtOAc (200 mL) were added subsequently. The mixture was stirred until no solid in the aqueous layer. The mixture was then portioned. The aqueous solution was further extracted with EtOAc (3 x 60 mL). The combined EtOAc was concentrated. The residue was treated with NaOH (0.25 M, 200 mL). After stirred for 50 min, insoluble material was filtered, washed with NaOH (1M). The filtrate was then acidified with HCl (conc.) to pH 3. The resulting white precipitate was filtered, washed with water and dried *in vacuo* to obtain 1-[4-(2*H*-tetrazol-5-yl)-phenyl]-ethanone as white solid. ^{1}H NMR (DMSO-d_6) δ 8.17-8.10 (m, 4H), 2.61 (s, 3H). MS *m/z* = 188 (M^+).

The title compound was prepared by condensing 1-[4-(2*H*-tetrazol-5-yl)-phenyl]-ethanone (**Ex-78A**) and 2,4-dimethoxy-5-thiophen-2-yl-benzaldehyde (**Ex-6A**) in a similar manner as described in **Ex-3**. Yellow solid, mp 235 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ 8.33 (d, J = 8.4 Hz, 2H), 8.26 (s, 1H), 8.20 (d, J = 8.9 Hz, 2H), 8.08 (d, J = 16.0 Hz, 1H), 7.93 (d, J = 15.0 Hz, 1H), 7.66-7.64 (m, 1H), 7.50-7.48 (m, 1H), 7.12-7.09 (m, 1H), 6.81 (s, 1H), 3.983 (s, 3H), 3.976 (s, 3H). MS *m/z* = 418 (M^+, 100%).

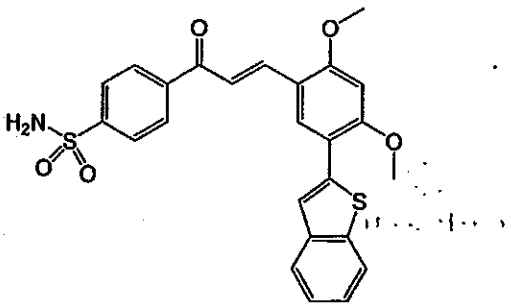
EXAMPLE 79



4-[3*Z*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid

A solution of 4-[3*E*-(5-benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid (**Ex-3**, 101.4 mg, 0.23 mmol) in ethyl acetate (889 ml) was stirred in a well lighted-area at room temperature for 36 hours. The solution was concentrated to a yellow solid. The crude material was purified on reversed-phase preprative plates (20 x 20 cm, RP-18 F_{254}, 1mm) eluted with MEOH/ACN/H_20 (45:45:10) to give 22.2 mg of the title compound, which was 86% the cis isomer by NMR analysis. ^{1}H-NMR (DMSO-D_6, major isomer) δ 7.98 (s, 4 H), 7.86 (m, 2H), 7.76 (d, J = 9 Hz 1H), 7.56 (s, 1H), 7.28 (m, 2H), 7.17 (d, J = 12 Hz, 1H), 6.78 (d, J= 12 Hz, 2H), 6.71 (s, 1H), 3.94 (s, 3H), 3.77 (s, 3H).

EXAMPLE 80

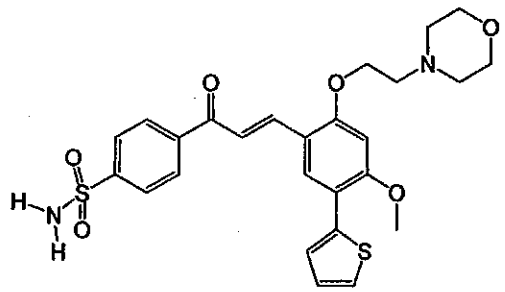


4-[3*E*-(5-Benzo[b]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzenesulfonamide

To a solution of 4-acetyl-benzsulfonamide (**Ex-26A**, 0.20g, 1.0 mmol) and 5-benzo[b]thiophene-2-yl-2,4-dimethoxyphenylbenzaldehyde (**Ex-3A**, 0.31g, 1.05 mmol) in DMF (5 mL) and methanol (2 mL) was added lithium methoxide (0.15g, 4.0 mmol). The reaction mixture was allowed to stir at ambient temperature. The reaction was quenched with

water (30 mL) after 2 hours. The aqueous solution was acidified to pH 4 with HCl (3 M) and extracted with ethyl acetate. The combined solution of ethyl acetate was subsequently washed with brine, dried (Na_2SO_4) and concentrated. The solid residue was stirred in ethanol (10 mL) for 1.5 hours, filtered, washed with aqueous ethanol (50%) and dried *in vacuo*. The title compound was obtained as a yellow solid (0.3g, 63%), mp 204-205 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ 8.35 (s, 1H), 8.27 (d, J = 7.7 Hz, 2H), 8.06 (d, J = 16.0 Hz, 1H), 7.97-7.92 (m, 4H), 7.88 (d, J = 6.6 Hz, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.53 (s, 2H), 7.37-7.27 (m, 2H), 6.85 (s, 1H), 4.09 (s, 3H), 4.03 (s, 3H).

EXAMPLE 81

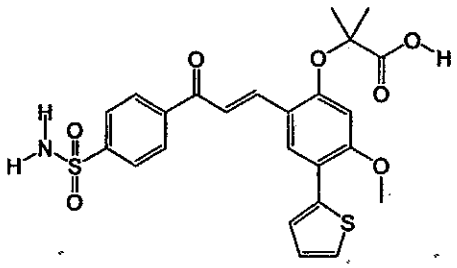


4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide

4-Acetyl-benzenesulfonamide **(Ex-26A)** (0.10 g, 0.29 mmol) and 4-acetylbenzenesulfonamide (0.057 g, 0.29 mmol) were dissolved in a dimethylformamide-methanol solution (2.0 mL, 7:3). After complete dissolution, lithium methoxide (0.044 g, 1.2 mmol) was added and the resulting orange slurry was stirred in the dark at room temperature for 4 h. Upon completion, as determined by HPLC, the mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was taken up in ethanol (2 mL) and warmed to 60 °C to obtain complete dissolution and allowed to cool to room temperature. The resulting precipitate was collected on filter paper and dried *in vacuo* to yield 0.13 g (82%) of the title compound as a yellow solid, mp 186-188 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.23-8.28 (m, 3H), 7.93-8.09 (m, 4H), 7.66 (d, 1H, J = 3.0 Hz), 7.56 (brs, 1H), 7.52 (d, 1H, J = 5.1 Hz), 7.13 (dd, 1H, J = 5.1, 3.0 Hz), 6.89 (s, 1H), 4.34 (t, 2H, J = 6 Hz), 4.01 (s, 3H), 3.54-3.58 (m, 4H), 2.83 (t, 2H, J = 6 Hz), 2.51-2.53 (m, 4H). MS (ESI) m/z = 529 ($[M+H]^+$, 100%). Anal. Calcd. for

$C_{26}H_{28}N_2O_6S_2$: C, 59.07; H, 5.34; N, 5.30; S, 12.13. Found: C, 58.90; H, 5.38; N, 5.37; S, 12.01.

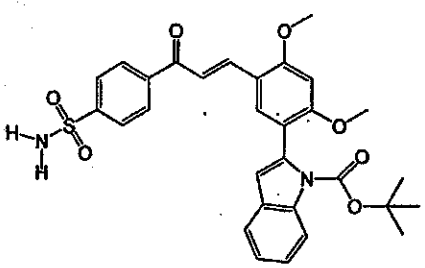
EXAMPLE 82



2-{5-Methoxy-2-[3-oxo-3-(4-aminosulfonyl-phenyl)-*E*-propenyl]-4-thiophen-2-yl-phenoxy}-2-methyl-propionic acid

The title compound was prepared by condensing 4-acetyl-benzenesulfonamide (**Ex-26A**) and 2-(2-formyl-5-methoxy-4-thiophen-2-yl-phenoxy)-2-methyl-propionic acid (**Ex-59B**) in a similar manner as described in **Ex-22**. Yellow solid, mp 164-165 °C, 85% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.21-8.28 (m, 3H), 7.96-8.12 (m, 4H), 7.67 (d, 1H, J = 3.0 Hz), 7.56 (brs, 3.0H), 7.14 (dd, 1H, J = 5.7, 3.0 Hz), 6.57 (s, 1H), 3.88 (s, 3H), 1.66 (s, 6H). MS (ESI) m/z = 502 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{24}H_{23}NO_7S_2$: C, 57.47; H, 4.62; N, 2.79; S, 12.79. Found: C, 57.70; H, 4.74; N, 2.85; S, 12.51.

EXAMPLE 83

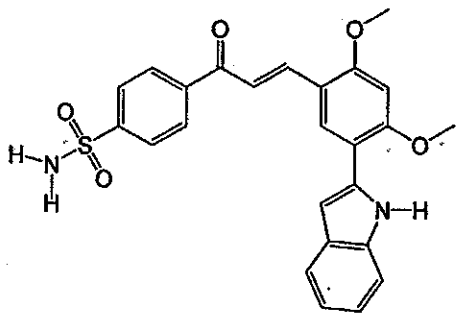


2-{2,4-Dimethoxy-5-[3-oxo-3-(4-aminosulfonyl-phenyl)-*E*-propenyl]-phenyl}-indole-1-carboxylic acid *tert*-butyl ester

The title compound was prepared by condensing 4-acetyl-benzenesulfonamide (**Ex-26A**) and 2-(5-formyl-2,4-dimethoxy-phenyl)-indole-1-carboxylic acid tert-butyl ester (**Ex-36A**) in a

similar manner as described in **Ex-22**. Yellow solid, 40% yield, mp 120 -122°C. ^{1}H-NMR ($CDCl_3$) δ 8.01-8.19 (m, 6H), 7.68 (s, 1H), 7.56 (d, J = 8 Hz, 1H), 7.46(d, J = 16 Hz, 1H), 7.21-7.35(m, 2H), 6.53 (d, J = 14 Hz, 2H), 5.01(s, 2H), 4.00 (s, 3H), 3.85(s, 3H), 1.42 (s, 9H). MS *m/z* = 563 ([M+H]$^+$). HRMS (ES+) Calcd. for $C_{30}H_{30}N_2O_7S$: 563.1852. Found: 563.1862.

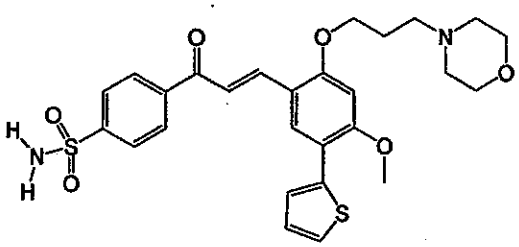
EXAMPLE 84



4-{3*E*-[5-(1*H*-Indol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzenesulfonamide

The title compound was prepared by condensing 4-acetyl-benzenesulfonamide (**Ex-26A**) and 5-(1*H*-indol-2-yl)-2,4-dimethoxy-benzaldehyde (**Ex-61A**) in a similar manner as described in **Ex-22**. Red solid, 70% yield, mp 185-187°C. ^{1}H-NMR (DMSO-d_6) δ 11.15 (br, s, 1H), 8.33(s, 1H), 8.24 (d, J = 8 Hz, 2H), 8.07 (d, J = 15 Hz, 1H), 7.98 (d, J = 8 Hz, 2H), 7.80(d, J = 15 Hz, 1H), 7.41-7.55(m, 4H), 7.03-7.08 (m, 1H), 6.93-6.99 (m, 2H), 6.83 (s, 1H), 4.04(s, 3H), 3.99(s, 3H). MS *m/z* = 463 ([M+H]$^+$). HRMS (ES+) Calcd. for $C_{25}H_{22}N_2O_5S$: 463.1327. Found: 463.1316.

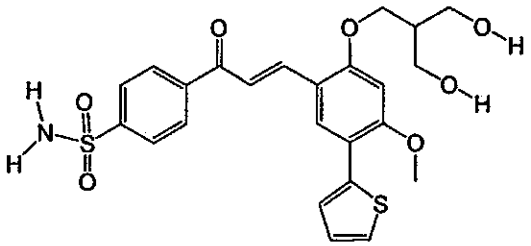
EXAMPLE 85



4-{3*E*-[4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide

The title compound was prepared by condensing 4-acetyl-benzenesulfonamide (**Ex-26A**) and 4-methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-benzaldehyde (**Ex-66A**) in a similar manner as described in **Ex-22**. Yellow solid, 48% yield, mp 193-196°C. ^{1}H-NMR (DMSO-d6) δ 8.24 (m, 3 H), 8.06 (s, 1H), 7.96 (d, 2H), 7.89 (d, 1H), 7.63 (d, 1H), 7.51 (m, 1H), 7.10 (dd, J = 3, 4 Hz, 1H), 6.81 (s, 1H), 4.23 (t, 2H), 3.98(s, 3H), 3.55 (t, 4H), 2.47 (m, 2H), 2.35(t, 4H) , 1.98(q, 2H). MS *m/z* = 542 ([M]$^+$, 38%), 100 (100%). Anal. calculated for $C_{27}H_{30}N_2O_6S_2 \cdot 3/5H_2O$: C, 58.59, H, 5.68, S, 11.59; found C: 58.59, H: 5.55, S: 11.40.

EXAMPLE 86

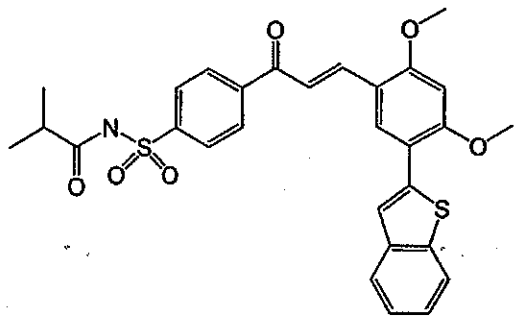


4-{3*E*-[2-(3-Hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide

2-(3-Hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-64B**) (8.0 g, 24.8 mmol) and 4-acetylbenzenesulfonamide (4.9 g, 24.8 mmol) were dissolved in a dimethylformamide-methanol solution (170 mL, 7:3). After complete dissolution, lithium methoxide (3.8 g, 99.2 mmol) was added and the resulting red-orange slurry was stirred in the dark at room temperature for 3 h. Upon completion, as determined by HPLC, the mixture was diluted with water (500 mL) and extracted with ethyl acetate (6 x 200 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was taken up in ethanol (150 mL) and warmed to 60 °C to obtain complete dissolution and allowed to cool to room temperature. The resulting precipitate was collected on filter paper and dried *in vacuo* to yield 7.0 g (60%) of the title compound as a light orange solid, mp 123-124 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.25-8.29 (m, 3H), 7.90-8.11 (m, 4H), 7.66 (d, 1H, J = 3.0 Hz), 7.56 (brs, 1H), 7.52 (d, 1H, J = 5.1 Hz), 7.13 (dd, 1H, J = 5.1, 3.0 Hz), 6.88 (s, 1H), 4.67 (t, 2H, J = 10.8 Hz), 4.24 (d, 2H, J = 6.0 Hz), 4.00 (s, 3H), 3.54-3.65 (m, 4H), 2.09-2.13 (m, 1H). MS

(ESI) *m/z* = 504 ([M+H]$^+$, 100%). Anal. Calcd. $C_{24}H_{25}NO_7S_2 \cdot H_2O$: C, 57.24; H, 5.00; N, 2.78; S, 12.73. Found: C, 56.72; H, 5.27; N, 2.71; S, 12.11.

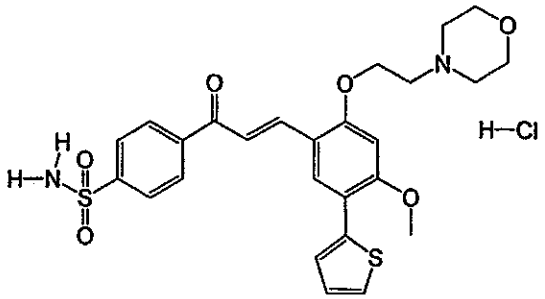
EXAMPLE 87



4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-*N*-isobutyryl-benzenesulfonamide

A solution of 4-[3*E*-(5-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzenesulfonamide (**Ex-80**, 0.15g, 0.31 mmol) in tetrahydrofuran (3 mL) was cooled to -78 °C and a solution of lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 0.63 mL, 0.63 mmol) was added dropwise. The solution was allowed to stir at this temperature for 1 hour and warm up to 0 °C. Isobutyric acid anhydride (0.31 mL, 1.88 mmol) was added at this temperature. The solution was allowed to stir at 0°C for 10 min and ambient temperature for 2 hours. The reaction then was quenched with water. The aqueous solution was extracted with ethyl acetate. The combined solution of ethyl acetate was washed with brine, dried over sodium sulfate and concentrated. The residual material was stirred in ethanol for 3 hours, filtered and dried *in vacuo* to give the title compound as a yellow solid (0.15g, 87%), mp > 240 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ 8.21 (d, J = 8.6 Hz, 2H), 8.13 (d, J = 8.7 Hz, 2H), 8.09 (s, 1H), 8.02 (bs, 1H), 7.94 (s, 1H), 7.85-7.78 (m, 2H), 7.68 (s, 1H), 7.55 (d, J = 16.9 Hz, 1H), 7.38-7.30 (m, 2H), 6.58 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 2.47-2.38 (m, 1H), 1.14 (d, J = 7.1 Hz, 6H). MS *m/z* = 549 (M$^+$, 100%).

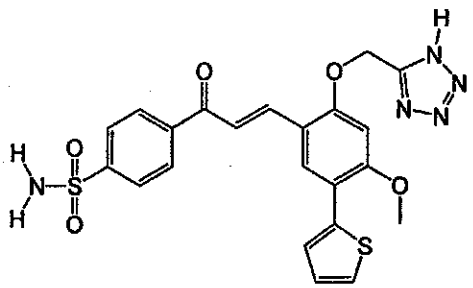
EXAMPLE 88



4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide, hydrochloride

Th 4-{3-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide (**Ex-81**, 0.065 g, 0.12 mmol) was dissolved in tetrahydrofuran (5 mL) and 3 N HCl (1 mL) was added drop wise to the solution. The resulting yellow slurry was stirred in the dark at room temperature for 30 min. The precipitate was collected and dried *in vacuo* to yield 0.054 g (78%) of the title compound as a yellow solid, mp 235 °C (dec). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.31-8.34 (m, 3H), 8.13 (d, 1H, J = 15.0 Hz), 7.92-8.01 (m, 3H), 7.70 (d, 1H, J = 4.0 Hz), 7.54 (m, 3H), 7.15-7.17 (m, 1H), 6.92 (s, 1H), 4.64 (brs, 2H), 4.03 (s, 5H), 3.72-3.79 (m, 4H), 3.56-3.60 (m, 4H). MS (ESI) m/z = 529 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{26}H_{29}ClN_2O_6S_2$: C, 55.26; H, 5.17; Cl, 6.27; N, 4.96; S, 11.35. Found: C, 55.31; H, 5.17; Cl, 6.32; N, 4.98; S, 11.20.

EXAMPLE 89



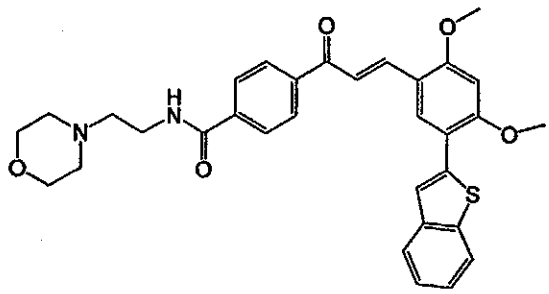
4-{3*E*-[4-Methoxy-2-(1*H*-tetrazol-5-ylmethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide

Ex-89A: (2-Acetyl-5-methoxy-4-thiophen-2-yl-phenoxy)-acetonitrile was prepared in an analogous fashion as described in **Ex-29C** using iodoacetonitrile. The crude solid was slurried in ethyl acetate (50 mL) to remove residual impurities. The resulting solid was collected on filter paper and dried *in vacuo* to give the expected product as an orange solid (70%), mp 175-176 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.17 (s, 1H), 7.48 (d, 1H, J = 3.6 Hz), 7.35 (d, 1H, J = 5.1 Hz), 7.10 (dd, 1H, J = 5.1, 3.6 Hz), 6.64 (s, 1H), 4.96 (s, 2H), 4.06 (s, 3H). MS (EI) m/z = 273 ($[M]^+$, 99%), 233 (100%). Anal. Calcd. for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.12; S, 11.73. Found: C, 61.65; H, 4.20; N, 5.16; S, 11.59.

Ex-89B: (2-Acetyl-5-methoxy-4-thiophen-2-yl-phenoxy)-acetonitrile (**Ex-89A**, 0.30 g, 1.1 mmol) was slurried in a mixture of water:isopropanol (3 mL, 2:1) to obtain a well-dispersed solution. Sodium azide (0.079 g, 1.2 mmol) followed by zinc bromide (0.25 g, 1.1 mmol) were added and the reaction was heated to reflux and vigorously stirred for 24 h. Additional solvent (1 mL, 1:1 water:isopropanol) was added after 10 h at reflux due to evaporation. The reaction was diluted with an ethyl acetate:tetrahydrofuran mixture (25 mL, 2:1) and a 3 N HCl solution (10 mL) and vigorously stirred until a homogenous solution was obtained (1 h). The layers were separated and the aqueous was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over sodium sulfate and concentrated to a dark green solid. Silica gel chromatography (15% methanol/methylene chloride containing 1% acetic acid) gave 0.22 g (65%) of 4-methoxy-2-(1H-tetrazol-5-ylmethoxy)-5-thiophen-2-yl-benzaldehyde as a pale green solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.97 (s, 1H), 7.52-7.56 (m, 2H), 7.10-7.12 (m, 2H), 5.81 (s, 2H), 4.05 (s, 3H). MS (ESI) m/z = 317 ($[M+H]^+$, 100%). HRMS (ESI) Calcd. for $C_{27}H_{25}NO_7S$: 317.0708. Found: 317.0712.

The title compound was prepared by condensing 4-acetyl-benzenesulfonamide (**Ex-26A**) and 4-methoxy-2-(1H-tetrazol-5-ylmethoxy)-5-thiophen-2-yl-benzaldehyde (**Ex-89A**) in a similar manner as described in **Ex-22**. Yellow solid, mp 163-164 °C (dec), 60% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.31-8.34 (m, 3H), 7.92-8.15 (m, 4H), 7.70 (d, 1H, J = 4.0 Hz), 7.54 (m, 3H), 7.15-7.17 (m, 1H), 6.92 (s, 1H), 4.64 (brs, 2H), 4.03 (s, 5H). MS (ESI) m/z = 498 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{22}H_{19}N_5O_5S_2 \cdot 1½H_2O$: C, 50.37; H, 4.23; N, 13.35; S, 12.23. Found: C, 50.48; H, 4.24; N, 12.95; S, 12.35.

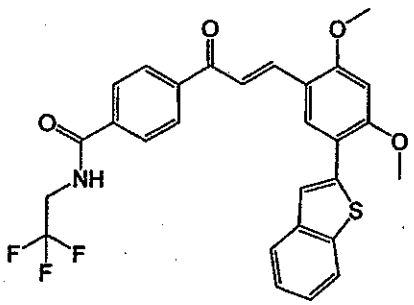
EXAMPLE 90



4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-N-(2-morpholin-4-yl-ethyl)-benzamide

To a solution of 4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid (**Ex-3**, 0.44 mg, 1 mmol) and 2-morpholin-4-yl-ethylamine (0.18 mL) in dichloromethane (20 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.38 g, 2 mmol) and the mixture was stirred at room temperature for four hours. It was poured into brine (100 mL) and extracted with dichloromethane (2 x 50 mL). The organic phase was dried and evaporated. Chromatography (dichloromethane/methanol 50:1) gave the title compound as a yellow solid (0.43 g, 77%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 16 Hz, 1H), 8.09 (d, J = 8 Hz, 2H), 7.95 (s, 1H), 7.90 (d, J = 8 Hz, 2H), 7..77-7.85 (m, 2H), 7.68 (s, 1H), 7.56 (d, J = 16 Hz, 1H), 7.29-7.40 (m, 2H), 6.80-6.85 (br s, 1H), 6.58 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 3.75 (t, J =5 Hz, 4H), 3.59 (quad, J = 5 Hz, 2H), 2.64 (t, J = 5 Hz, 2H), 2.53 (t, J = 5 Hz, 4H). Anal. calc. for $C_{32}H_{32}N_2O_5S{\cdot}H_2O$: C, 67.94; H, 5.88; N, 4.95; found: C, 68.12; H, 5.92; N, 4.96.

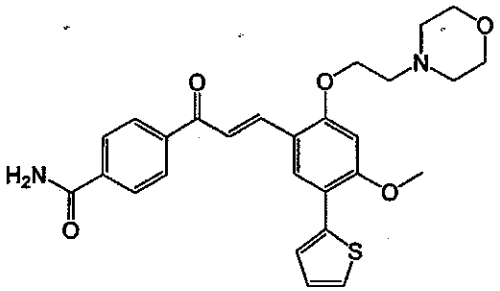
EXAMPLE 91



4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-N-(2,2,2-trifluoro-ethyl)-benzamide

The title compound was prepared in a similar manner as described in **Ex-90**. Yellow solid, 53% yield, mp 215-217°C. ^{1}H-NMR (Aceton-d_6) δ 8.46 (br, s, H), 8.12-8.24 (m, 4H), 8.06 (d, J = 8 Hz, 2H), 7.78-7.91 (m, 4H), 7.28-7.36(m, 2H), 6.92(s, 1H), 4.08 (s, 3H), 4.06(s, 3H), 2.79 (s, 2H). MS *m/z* = 526 ([M+H]$^+$). HRMS (ES+) Calcd. for $C_{28}H_{22}F_3NO_4S$: 526.1300. Found: 526.1324.

EXAMPLE 92



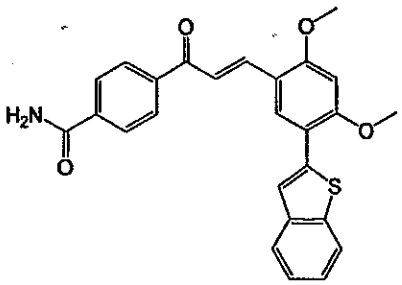
4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzamide

Ex-92A: To a solution of 4-acetyl-benzoic acid (0.5g, 3.05 mmol) in tetrahydrofuran (10 mL) was added carbonyldiimidazole (0.74g, 4.75 mmol). The solution was allowed to stir at ambient temperature for one hour and cooled to 0 °C followed by addition of ammonia (28% in water, 3 mL, 21 mmol). The solution was continued to stir at 0 °C for another one hour. The solvent was removed under reduced pressure. The residue was treated with water, filtered, washed with water, dried *in vacuo* to give 4-acetyl-benzamide (0.25g, 50%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.11 (bs, 1H), 8.00 (d, J = 9 Hz, 2H), 7.95 (d, J = 9 Hz, 2H), 7.53 (bs, 1H), 2.59 (s, 3H).

To a solution of 4-acetyl-benzamide (**Ex-92A**, 0.25g, 1.53 mmol) and 2-(2-morpholin-4-yl-ethoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-60A**, 0.53g, 1.53 mmol) in DMF (7 mL) and methanol (3 mL) was added lithium methoxide. The solution was allowed to stir at ambient temperature. The reaction was quenched with water after 2 hours. The aqueous solution was extracted with ethyl acetate. The combined extract was washed with $NaHCO_3$,

NH_4Cl, brine, dried (Na_2SO_4) and concentrated. The residue was stirred in ethanol overnight to afford the title compound as a yellow solid (0.43g, 57%), mp 183-184 °C. ^{1}H-NMR ($CDCl_3$) δ 8.09-8.04 (m, 3H), 7.93 (d, J = 8.3 Hz, 2H), 7.87 (s, 1H), 7.57 (d, J = 15.7 Hz, 1H), 7.42 (d, J = 3.9 Hz, 1H), 7.32 (d, 4.4 Hz, 1H), 7.11-7.08 (m, 1H), 6.55 (s, 1H), 6.25 (bs, 1H), 5.75 (bs, 1H), 4.25 (t, J = 5.9 Hz, 2H), 3.98 (s, 3H), 3.71 (t, J = 4.2 Hz, 4H), 2.92 (t, J = 5.7 Hz, 2H), 2.59 (t, J = 4.6 Hz, 4H). MS *m/z* = 493 ([M + H]$^+$, 100%).

EXAMPLE 93

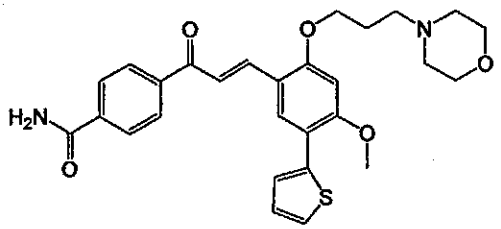


4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide

To a solution of 4-acetyl-benzamide (0.3g, 1.84 mmol) and 5-(benzo[*b*]thein-2yl)-2,4-dimethoxybenzaldehyde (0.55g, 1.84 mmol) in a mixture of *N,N*-dimethylformamide (7 mL) and methanol (3 mL) was added lithium methoxide (0.14g, 3.68 mmol). The reaction mixture was allowed to stir at ambient temperature for 9 hours. The resulting precipitate was collected by filtration, washed with methanol, dried *in vacuo* to obtain the title compound as a yellow solid (5.56g, 68%). Alternatively, to mixture of 4-[3*E*-(5-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid (**Ex-3**, 3.0 g, 6.75 mmol), 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (1.81 g, 9.45 mmol), 1-hydroxybenzotriazole hydrate (1.09g, 8.10 mmol) and ammonium chloride (1.81g, 33.7 mmol) in *N,N*-dimethylformamide (60 mL) was added triethylamine (2.4 mL, 16.9 mmol). The reaction mixture was allowed to stir overnight at ambient temperature. Any insoluble material was removed by filtration. The filtrate was diluted with ethyl acetate to 180 mL. The solution of ethyl acetate was washed with a saturated solution of sodium bicarbonate, brine, dried over sodium sulfate and concentrated to give the title compound as a yellow solid (2.82g, 94%), mp 240-241 °C. ^{1}H-NMR (DMSO-d_6) δ 8.37 (s, 1H), 8.19 (d, J = 7.8 Hz, 2H), 8.12 (d, J = 15.3

Hz, 1H), 8.04- 7.91 (m, 6H), 7.83 (d, J = 7.5 Hz, 1H), 7.55 (s, 1H), 7.36-7.30 (m, 2H), 6.87 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H). MS *m/z* = 444 ($[M+H]^+$, 100%).

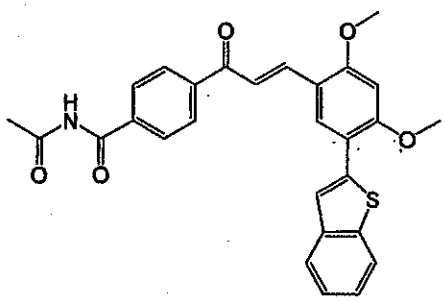
EXAMPLE 94



4-{3*E*-[4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzamide

The title compound was prepared by condensing 4-Acetyl-benzamide (**Ex-92A**) and 4-methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-benzaldehyde (**Ex-66A**) in a similar manner as described in **Ex-92**. Orange solid, mp 81-83°C. ^{1}H-NMR ($CDCl_3$) δ 8.08 (m, 3 H), 7.94 (d, 2H), 7.86 (s, 1H), 7.56 (d, 1H), 7.41 (d, 1H), 7.32 (d, 1H), 7.10 (m, 1H), 6.55 (s, 1H), 4.19 (t, 2H), 3.99(s, 3H), 3.72 (t, 4H), 2.59 (t, 2H), 2.12 (t, 4H) , 1.98(quintet, 2H). MS *m/z* = 506 ($[M]^+$, 34%), 100 (100%). 28 %. Anal. calculated for $C_{28}H_{30}N_2O_5S \cdot 2/5H_2O$: C, 65.45, H, 6.04, S, 6.24; found C: 65.30, H: 6.16, S: 6.17.

EXAMPLE 95

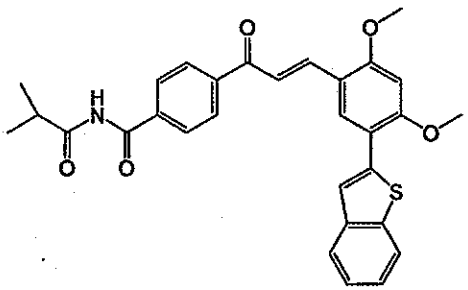


***N*-Acetyl-4-[3*E*-(5-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide**

A suspension of 4-[3*E*-(5-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide (**Ex-93**, 0.5g, 1.13 mmol) in THF (15 mL) was cooled to -78 °C followed by addition of lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.3 mL, 2.3 mmol). The mixture was stirred at this

temperature for 1 hour and warmed up to 0 °C. Acetic anhydride (0.48 mL, 6.8 mmol) was then added dropwise. After the addition was complete the reaction mixture was warmed up to ambient temperature and stirred for 2 hours. The reaction was quenched with water. The aqueous solution was extracted with ethyl acetate. The combined extract was washed with NH_4Cl, brine, dried and concentrated. The residue was purified by flash chromatography. Elution with 50% EtOAc/hexane gave the title compound as yellow solid (0.16g, 29%), mp 228-229 °C. ^{1}H-NMR ($CCDl_3$) δ 8.52 (s, 1H), 8.15-8.10 (m, 3H), 7.96 (d, J = 7.6 Hz, 2H), 7.85-7.77 (m, 2H), 7.67 (s, 1H), 7.55 (d, J = 16.7 Hz, 1H), 7.34-7.29 (m, 3H), 6.58 (s, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 2.65 (s, 3H). MS *m/z* = 485 (M^+, 100%).

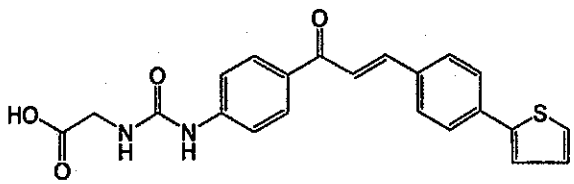
EXAMPLE 96



4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-*N*-isobutyryl-benzamide

The title compound was prepared in a similar manner as described in **Ex-95** from -[3*E*-(5-benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide (**Ex-93**) and isobutyric anhydride. Yellow solid, mp 208-209 °C. ^{1}H-NMR ($CCDl_3$) δ 8.14 (s, 1H), 8.15-8.10 (m, 3H), 7.96 (d, J = 7.2 Hz, 2H), 7.85-7.77 (m, 2H), 7.67 (s, 1H), 7.56 (d, J = 16.2 Hz, 1H), 7.38-7.29 (m, 3H), 6.59 (s, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 3.68-3.59 (m, 1H), 1.28 (d, J = 6.2 Hz, 6H). MS *m/z* = 513 (M^+, 93%), 425 (100%).

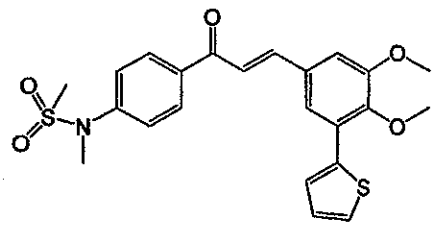
EXAMPLE 97



4(3*E*-{4-[3-(4-Thiophen-2-yl-phenyl)-acryloyl]-phenyl}-ureido)-acetic acid

A solution of (3-{4-[3-(4-thiophen-2-yl-phenyl)-acryloyl]-phenyl}-ureido)-acetic acid ethyl ester (**Ex-15**, 151.3 mg, 0.35 mmol) in THF:MeOH: H_2O (2:1:1, 6 mL) was treated with lithium monohydrate (73.2 mg, 1.74 mmol) and stirred for 4 hours. The reaction mixture was titrated with 5N HCl to a pH2. The mixture was extracted with ethyl acetate (30 mL). The organic phase was collected, dried over Na_2SO_4, and concentrated to a pure yellow solid (131.7 mg, 93%), mp 222-225°C. ^{1}H-NMR (DMSO-d6) δ 9.27 (br s, 1 H), 8.14 (d, 2H), 7.87 (m, 3H), 7.71 (d, 3H), 7.56 (m, 4H), 7.14 (t, 1H), 6.54 (t, 1H), 3.78 (d, 2H). MS *m/z* = 407 ($[M+H]^+$, 88%), 306 (100%). Anal. calculated for $C_{22}H_{18}N_2O_4S \cdot 1/2H_2O$: C, 63.60, H, 4.61, S, 7.72; found C: 63.23, H: 4.70, S: 7.66.

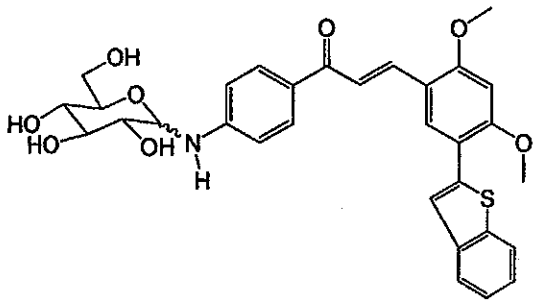
EXAMPLE 98



***N*-{4-[3*E*-(3,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-phenyl}-*N*-methyl-methanesulfonamide**

A solution of *N*-{4-[3*E*-(3,4-dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-phenyl}-methanesulfonamide (**Ex-14**, 90 mg, 0.20 mmol) in anhydrous DMF was treated with potassium carbonate (56.1 mg, 0.41). Methyl iodide (126.32 uL, 2.03 mmol) was added to the reaction mixture which was then refluxed for 1.5 hours under inert conditions. The reaction was diluted with water (25 mL) and extracted with diethyl ether (2 x 50 mL). The organic portion was dried over sodium sulfate, filtered, and concentrated to a yellow oil. The crude material was purified by silica gel chromatography (30-50% ethyl acetate/hexanes) to give 42 mg (45%) of the title compound as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ 8.06 (d, 2H), 7.59 (d, 1H), 7.54 (m, 4H), 7.42 (m, 2H), 7.12 (m, 2H), 3.97 (s, 3H), 3.88 (s, 3H), 3.40 (s, 3H), 2.89 (s,3H). MS *m/z* = 457 ($[M]^+$, 100%).

EXAMPLE 99

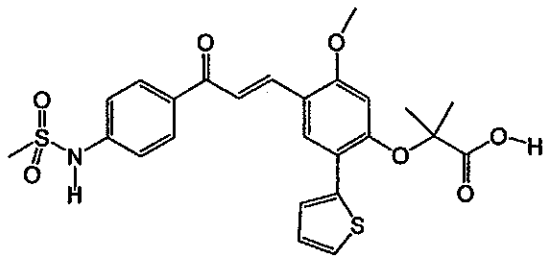


3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-1-[4-(D-glucopyranosylamino)-phenyl]-propenone

Ex-99A: D-Glucose (1.8 g, 10 mmol) and 4-aminoacetophenone (1.35 g, 10 mmol) were mixed in ethanol (50 ml), acetic acid (5 drops) was added, and the mixture was stirred at reflux for 2 hours. Water (2 ml) was added and the mixture became a homogeneous solution and was then stirred at reflux for 4 hours. Upon cooling to room temperature the precipitate was filtered out, rinsed with ethanol, and dried to give 4-(D-glucopyranosylamino)acetophenone as a white solid (1.21 g, 41%), mp 209-210°C (dec). ^{1}H-NMR (DMSO-D_6) δ 7.71 (d, J = 8 Hz, 2H), 7.06 (d, J = 8 Hz, 1H), 6.69 (d, J = 8 Hz, 2H), 4.98 (d, J = 4 Hz, 1H), 4.89 (d, J = 7 Hz, 2H), 4.38-4.45 (m, 2H), 3.55-3.64 (m, 1H), 3.30-3.46 (m, 1H), 3.00-3.30 (m, 4H), 2.38 (s, 3H). MS *m/z* = 297 ($[M]^+$, 15%), 148 (100%).

4-(D-Glucopyranosylamino)acetophenone (**Ex-99A**, 326 mg, 0.6 mmol) and (benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde (**Ex-3A**, 150 mg, 0.5 mmol) were mixed in DMF (10 ml) and methanol (5 ml). Lithium methoxide (120 mg) was added, and the mixture was stirred at room temperature for 18 hours. Lithium methoxide (120 mg) was added again and the mixture was stirred overnight. Saturated sodium chloride solution (50 ml) was added and the mixture was extracted with dichloromethane. Chromatography (dichloromethane/methanol 10:1) gave an oily yellow residue as the title compound (20 mg, 6%). ^{1}H-NMR (DMSO-D_6) δ 8.29 (s, 1H), 7.78-8.02 (m, 7H), 7.25-7.38 (m, 2H), 7.15 (d, 1H), 6.84 (s, 1H), 6.77 (d, 2H), 4.99 (d, 1H), 4.86-4.95 (m, 2H), 4.41-4.49 (m, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.00-3.45 (m 6H). MS *m/z* = 578 ($[M+H]^+$, 100%).

EXAMPLE 100



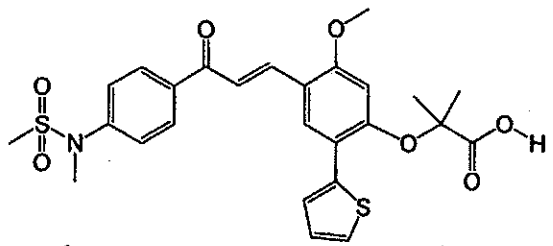
2-{4-[3-(4-Methanesulfonylamino-phenyl)-3-oxo-*E*-propenyl]-5-methoxy-2-thiophen-2-yl-phenoxy}-2-methyl-propionic acid

Ex-100A: A solution of 4-aminoacetophenone (5.0g, 37.0 mmol) and pyridine (3.0 mL) in anhydrous dichloromethane (300 mL) was treated with mesyl chloride (2.86 mL, 37.0 mmol). The reaction was stirred for 84 hours at room temperature under nitrogen, and then quenched with saturated NH_4Cl solution (100 mL). The organic phase was collected, washed with water (100 mL) and brine, dried over sodium sulfate, and concentrated over silica. The material was purified by silica gel chromatography (50 % ethyl acetate/hexanes) to give 4.72 g (60%) of *N*-(4-acetyl-phenyl)-methanesulfonamide as a yellowish oil. ^{1}H-NMR (DMSO-d6) δ 10.28 (s, 1 H), 7.90 (d, 1H), 7.24 (d, 1H), 3.06 (s, 3H), 2.48 (s,3H).

A solution of *N*-(4-acetyl-phenyl)-methanesulfonamide (**Ex-100A**, 279.6 mg, 1.31 mmol) and 2-(4-formyl-5-methoxy-2-thiophen-2-yl-phenoxy)-2-methyl-propionic acid (**Ex-47D**, 400 mg, 1.20 mmol) in DMF (5.25 mL) and MeOH (2.25 mL) was treated with lithium methoxide (182.2 mg, 4.8 mmol) and stirred for 5 hours at room temp. under nitrogen atmosphere. The reaction mixture was diluted with water (25 mL) which was then extracted with isopropyl acetate (2 x 50 mL). The aqueous portion was collected and acidified to a pH of 3 with 3N HCl. The aqueous solution was then extracted with isopropyl acetate (2 x 50 mL). The organic was collected, dried over sodium sulfate, and concentrated to a green solid. Attempted to recrystallize crude material from ethanol/hexanes; however, this mixture was concentrated and stirred with ethyl acetate (3 mL) to give 95.6 mg (14%) of the title compound as a yellow solid, mp 181-183°C. ^{1}H-NMR (DMSO-d6) δ 10.31 (br s, 1 H), 8.24 (s, 1H), 8.12 (d, 2H), 7.95 (d, 1H), 7.87 (d, 1H), 7.67 (d, 1H), 7.50 (d, 1H), 7.30 (d, 2H), 7.09 (t, 1H), 6.45 (s, 1H), 3.81 (s,

3H), 3.08 (s, 3H), 1.65 (s, 6H). MS *m/z* = 516 ([M+H]$^+$, 100%). HRMS m/z: calc. 516.1150, found 516.1165.

EXAMPLE 101



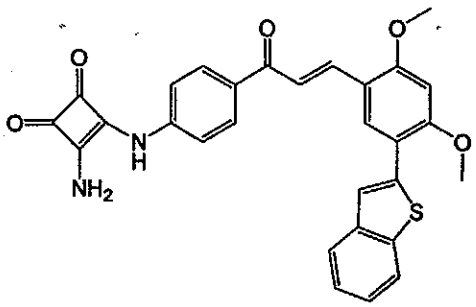
2-(4-{3-[4-(Methanesulfonyl-methyl-amino)-phenyl]-3-oxo-*E*-propenyl}-5-methoxy-2-thiophen-2-yl-phenoxy)-2-methyl-propionic acid

Ex-101A: A solution of *N*-(4-acetyl-phenyl)-methanesulfonamide (**Ex-100A**, 2.0g, 9.4 mmol) in anhydrous DMF (300 mL) was treated with potassium carbonate (2.59 g, 18.8 mmol), followed by the addition of methyl iodide (5.85 mL, 94 mmol). The reaction mixture refluxed for two hours and was then treated with more methyl iodide (5.85 mL, 94 mmol). The reaction refluxed for another two hours, and reaction completeness was confirmed by HPLC analysis. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (2 x 100mL).). The organic phase was collected, dried over sodium sulfate, and concentrated to a clear oil with residual DMF. Water (25 mL) was added to precipitate a white solid. The white solid was then filtered and dried by vacuum oven at 20 °C (-20 mm Hg) to give 1.37 g (64%) of N-(4-acetyl-phenyl)-N-methyl-methanesulfonamide. ^{1}H-NMR ($CDCl_3$) δ 7.88 (d, 2 H), 7.48 (d, 2H), 3.38 (s, 3H), 2.86 (s, 3H), 2.60 (s, 3H). HRMS m/z: calc. 530.1307, found 530.1313.

A solution of N-(4-acetyl-phenyl)-N-methyl-methanesulfonamide (**Ex-101A**, 298 mg, 1.31 mmol) and 2-(4-formyl-5-methoxy-2-thiophen-2-yl-phenoxy)-2-methyl-propionic acid (**Ex-47D**, 400 mg, 1.20 mmol) in DMF (5.25 mL) and MeOH (2.25 mL) was treated with lithium methoxide (182 mg, 4.8 mmol) and stirred for 6 hours at room temperature under nitrogen atmosphere. The reaction mixture was diluted with water (25 mL) which was then extracted with isopropyl acetate (2 x 50 mL). The aqueous portion was collected and acidified to a pH of 3 with 3N HCl. The aqueous solution was then extracted with isopropyl acetate (2 x 50 mL).

The organic was collected, dried over sodium sulfate, and concentrated to a yellow foam. The crude material was purified by silica gel chromatography (50% ethyl acetate/hexanes;10% MeOH/CH_2CL_2) to give 293 mg (42%) of the title compound as a yellow solid, mp 197-200°C. ^{1}H-NMR (DMSO-d6) δ 8.20 (s, 1 H), 8.12 (d, 2H), 8.00 (d, 1H), 7.83 (d, 1H), 7.66 (dd, J= 2,2 Hz, 1H), 7.53 (d, 2H), 7.44 (d, 1H), 7.06 (dd, J= 2, 4 Hz, 1H), 6.78 (s, 1H), 3.82 (s, 3H), 3.28 (s, 3H), 2.98 (s, 3H), 1.56 (s, 3H). MS *m/z* = 530 ([M+H]$^+$, 100%).

EXAMPLE 102



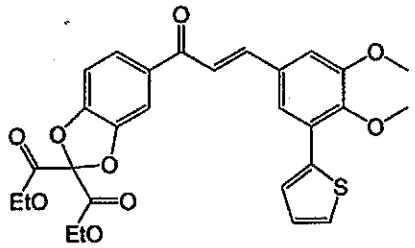
3-Amino-4-{4-[3*E*-(5-benzo[b]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-phenylamino}-cyclobut-3-ene-1,2-dione

Ex-102A: To a solution of 2.7g (20 mmol) of 4'-aminoacetophenone in 90 mL of ethanol, 4.5 g (20 mmol) of 3,4-dibutoxy-3-cyclobutene-1,2-dione (Aldrich) was added. The mixture was then heated to reflux overnight. A light yellow precipitate formed. To the reaction mixture, 20 mL (40 mmol) of ammonia (2.0 M in ethanol) was added, and the resultant mixture was stirred at room temperature for 2 hr. The light yellow solid was filtered and washed with ethanol to give 2.4 g (52%) of 3-(4-acetyl-phenylamino)-4-amino-cyclobut-3-ene-1,2-dione. ^{1}H-NMR (DMSO-d_6) δ 9.99 (br, 1H), 7.90 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 4.31 (br, 2H), 2.48 (s, 3H). HMRS (EI) calcd. for $C_{12}H_{10}N_2O_3$: 230.0691; found: 230.0691.

3-(4-Acetyl-phenylamino)-4-amino-cyclobut-3-ene-1,2-dione (**Ex-102A**, 0.46 g, 2 mmol), and 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde (**Ex-3A**, 0.596 g, 2mmol) were dissolved in DMF (10 mL) under nitrogen, and 4.0 ml (4 mmol) of LiOMe (1.0 M in MeOH) was added. The mixture was stirred under nitrogen at room temperature over night. The reaction mixture was poured into ice-water, acidified to pH1 with 3N HCl, extracted with dichloromethane. The

combined organic phase was then washed with brine and water, dried over $MgSO_4$, column chromatography (5 % MeOH in CH_2Cl_2) to give 57 mg (5.4 %) title compound as a yellow solid, mp > 260°C. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 8.36 (s, 1H), 8.18 (d, J = 8 Hz, 2H), 8.03 (d, J = 15 Hz, 1H), 7.82-7.95 (m, 4H), 7.57 (d, J = 8 Hz, 2H), 7.27-7.37 (m, 2H), 6.85 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 3.26 (s, 2H). MS *m/z* = 511[M+H]$^+$, (20%), 416 (100%). HRMS (ES+) Calcd. for $C_{29}H_{22}N_2O_5S$: 511.1327. Found: 511.1326.

EXAMPLE 103

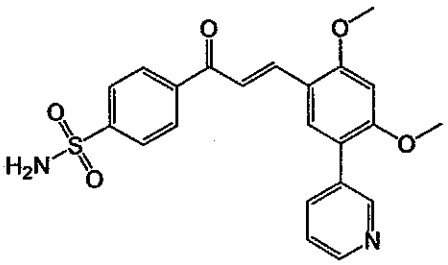


5-[3*E*-(3,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzo[1,3]dioxole-2,2-dicarboxylic acid, diethyl ester

Ex-103A: To a solution of KOH (1.25 M, 200 mL) were added 3,4-dihydroxy-acetophenone (2.0g, 13.1 mmol) and cetyltrimethylamonium chloride (25% in water, 17 mL, 13.1 mmol). The suspension was stirred at ambient temperature for 10 min followed by the addition of a suspension of 3,4-dimethoxy-5-thiophen-2yl-benzaldehyde (**Ex-6A**, 3.9g, 15.8 mmol) in ethanol (10 mL). The reaction mixture was allowed to stir at ambient temperature overnight and was acidified with concentrated HCl to pH 3, saturated with NaCl, extracted with CH_2Cl_2. The combined solution of CH_2Cl_2 was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography. Elution with 50% EtOAc/hexane gave 1-(3,4-dihydroxy-phenyl)-3*E*-(3,4-dimethoxy-5-thiophen-2-yl-phenyl)-propenone as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.88 (s, 1H), 7.83-7.81 (m, 2H), 7.76 (d, J = 2.4 Hz, 1H), 7.68-7.74 (m, 2H), 7.61-7.57 (m, 1H), 7.51 (s, 1H), 7.50 (d, J = 5.2 Hz, 1H), 7.13 (t, J = 4.5 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 3.92 (s, 3H), 3.77 (s, 3H). MS *m/z* = 382 (M$^+$, 100%).

1-(3,4-Dihydroxy-phenyl)-3*E*-(3,4-dimethoxy-5-thiophen-2-yl-phenyl)-propenone (106 mg), diethyl dibromomalonate (380 mg) and potassium carbonate (500 mg) was mixed in acetone (15 ml) and the mixture was stirred at room temperature over a weekend. It was poured into ethyl acetate (100 ml) and washed with water (100 ml). The organic layer was dried and evaporated. Chromatography (hexanes/ethyl acetate 4:1) gave an oily residue. Crystallization from hexanes and dichloromethane gave the title compound as a slightly yellow solid (70 mg), mp 125-126°C. ^{1}H-NMR (DMSO-d6) δ 7.76 (d, J = 15 Hz, 1H), 7.73 (dd, J = 2, 7 Hz, 1H), 7.64 (d, J = 2 Hz, 1H), 7.54 (d, J = 1 Hz, 1H), 7.53 (d, J = 2 Hz, 1H), 7.39 (d, J = 5 Hz, 1H), 7.38 (d, J = 15 Hz, 1H), 7.11 (dd, J = 2, 5 Hz, 1H), 7.08 (d, J = 1 Hz, 1H), 7.05 (d, J = 7 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 4.41 (quad, J = 7 Hz, 4H), 1.30 (t, J = 7 Hz, 6H).

EXAMPLE 104



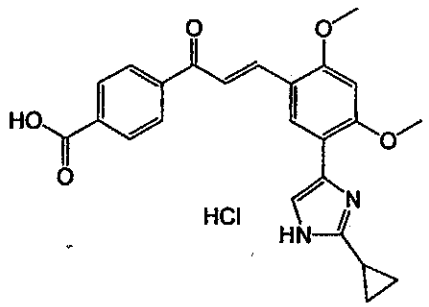
4-[3*E*-(2,4-Dimethoxy-5-pyridin-3-yl-phenyl)-acryloyl]-benzenesulfonamide

Ex-104A: 2,4-Dimethoxy-5-pyridin-3-yl-benzaldehyde was prepared in a similar manner as described in **Ex-3A** from pyridine-3-boronic acid and 5-bromo-2,4-dimethoxybenzaldehyde, 68% yield. ^{1}H-NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.71 (d, J = 1Hz, 1H), 8.51-8.53(m, 1H), 7.81 (s, 1H), 7.74-7.78 (m, 1H), 7.27-7.31 (m, 1H), 6.52 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H). HMRS (EI) calcd. for $C_{14}H_{13}NO_3$: 243.0895; found: 243.0888.

The title compound was prepared by condensing 2,4-dimethoxy-5-pyridin-3-yl-benzaldehyde (**Ex-104A**) and 4-acetyl-benzenesulfonamide (**Ex-26A**) in a similar manner as described in **Ex-22**. Yellow solid, 51% yield, mp 253-255°C. ^{1}H-NMR (DMSO-d6) δ 8.69 (d, J = 1Hz, 1H), 8.50 (d, J = 4 Hz, 1H), 8.25 (d, J = 9 Hz, 2H), 8.08 (d, J = 15Hz, 1H), 8.02 (s, 1H),7.84-7.94(m, 4H), 7.51 (s, 2H), 7.40-7.44 (m, 1H), 6.82(s, 1H), 3.98 (s, 3H), 3.88 (s, 3H). MS *m/z* =

424([M]$^+$, 45%), 393 (100 %). HMRS (EI) calcd. for $C_{22}H_{20}N_2O_5S$: 424.1093; found: 424.1100.

EXAMPLE 105



4-{3*E*-[5-(2-Cyclopropyl-1*H*-imidazol-4-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid, hydrochloride

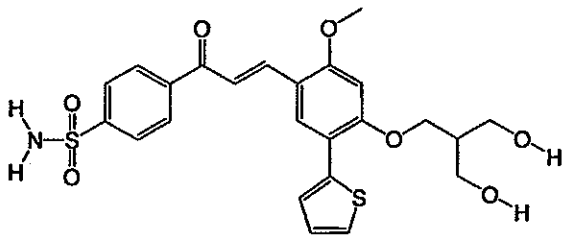
Ex-105A: A solution of 2-bromo-1-(3,4-dimethoxy-phenyl)-ethanone (0.3g, 1.16 mmol), cyclopropanecarboxamidine (0.14g, 1.16 mmol) and sodium hydroxide (0.18g, 4.5 mmol) in ethanol was refluxed overnight. The solvent was removed under reduced pressure, the residue taken up to water. The aqueous solution was then extracted with dichloromethane which was subsequently washed with brine, dried over sodium bicarbonate and concentrated. The crude product was purified by flash chromatography. Elution with ethyl acetate (50%, v/v, in hexane) then methanol (10%, v/v in dichloromethane) afforded 2-cyclopropyl-4-(2,4-dimethoxy-phenyl)-1*H*-imidazole as white solid (0.15g, 53%): ^{1}HNMR ($CDCl_3$) δ 9.50 (bs, 1H), 7.63 (s, 1H), 7.20 (s, 1H), 6.57-6.53 (m, 2H), 3.93 (s, 3H), 3.03 (s, 3H), 1.97-1.93 (m, 1H), 1.00-0.94 (m, 4H). MS *m/z* = 245 ([M + H]$^+$, 100%).

Ex-105B: To a solution of 2-cyclopropyl-4-(2,4-dimethoxy-phenyl)-1*H*-imidazole (0.51g, 2.09 mmol) was added dichloromethyl methyl ether (0.28 mL, 3.13 mmol) followed by addition of titanium tetrachloride (1.0M in dichloromethane, 8.4 mL, 8.4 mmol) dropwise at 0 °C. The solution was allowed to warm up to ambient temperature and stir for 4.5 hours. The reaction mixture was then poured into ice. The aqueous layer was adjusted to pH 12 and extracted with dichloromethane. The combined solution of dichloromethane was washed with saturated solution of sodium bicarbonate, brine, dried over sodium sulfate and concentrated to afford 5-

(2-cyclopropyl-1*H*-imidazol-4-yl)-2,4-dimethoxy-benzaldehyde which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 13.95 (bs, 1H), 10.22 (s, 1H), 8.09 (s, 1H), 7.70 (s, 1H), 6.88 (s, 1H), 4.04 (s, 3H), 4.00 (s, 3H), 2.25 (m, 1H), 1.20 (m, 4H). MS *m/z* = 245 ([M + H]$^+$, 100%).

The title compound was prepared by condensing 5-(2-cyclopropyl-1H-imidazol-4-yl)-2,4-dimethoxy-benzaldehyde **(Ex-105B)** and 4-acetylbenzoic acid in a similar manner as described in **Ex-3**. Yellow solid, m.p. > 240 °C. ^{1}H NMR (DMSO-d_6) δ 13.31 (bs, 1H), 8.29 (d, J = 8.9 Hz, 2H), 8.06-8.01 (m, 3H), 7.91 (s, 1H), 7.67 (s, 1H), 6.83 (s, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 1.29-1.22 (m, 4H). MS *m/z* = 419 ([M + H]$^+$, 100%).

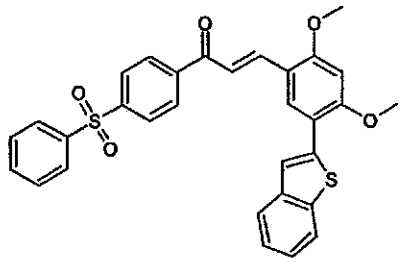
EXAMPLE 106



4-{3*E*-[4-(3-Hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide

The title compound was prepared by condensing 4-(3-hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thiophen-2-yl-benzaldehyde **(Ex-50C)** and 4-acetyl-benzenesulfonamide **(Ex-26A)** in a similar manner as described in **Ex-22.** Yellow solid, 72% yield, mp 191-192 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.29-8.32 (m, 3H), 8.09 (d, 1H, *J* = 16.0 Hz), 7.99 (d, 2H, *J* = 8.1 Hz), 7.92 (d, 1H, *J* = 16.0 Hz), 7.70 (d, 1H, *J* = 3.3 Hz), 7.53-7.56 (m, 3H), 7.14 (dd, 1H, *J* = 5.4, 3.3 Hz), 6.87 (s, 1H), 4.61 (t, 2H, *J* = 5.1 Hz), 4.28 (d, 2H, *J* = 5.1 Hz), 4.00 (s, 3H), 3.60-3.67 (m, 4H), 2.11-2.15 (m, 1H). MS (ESI) *m/z* = 504 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{24}H_{25}NO_7S_2 \cdot ½H_2O$: C, 56.23; H, 5.11; N, 2.73; S, 12.51. Found: C, 56.32; H, 5.06; N, 2.83; S, 12.55.

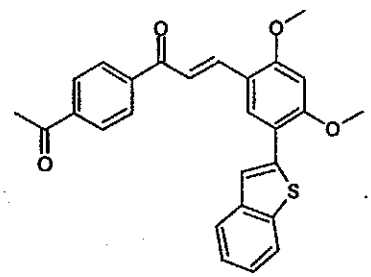
EXAMPLE 107



1-(4-Benzenesulfonyl-phenyl)-3*E*-(5-benzo[b]thiophen-2-yl-2,4-dimethoxy-phenyl)-propenone

The title compound was prepared by condensing 1-(4-benzenesulfonyl-phenyl)-ethanone with 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde (**Ex-3A**) in a similar manner as described in **Ex-3**, 5% yield. The product was purified using column chromatography. Yellow solid, mp 127-128°C. ^{1}H-NMR ($CDCl_3$) δ 8.05-8.11 (m, 5H), 7.97 (d, J = 7 Hz, 2H),7.91 (s, 1H), 7.76-7.84 (m, 2H), 7.66 (s, 1H), 7.46-7.60(m, 4H), 7.26-7.37(m, 2H), 6.56(s, 1H), 4.03 (s, 3H), 3.99 (s, 3H). MS *m/z* = 540 ([M]$^+$, 100%). HRMS (EI) Calcd. for $C_{13}H_{24}O_5S_2$: 540.1605. Found: 540.1074.

EXAMPLE 108

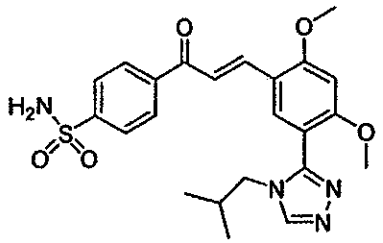


1-(4-Acetyl-phenyl)-3*E*-(5-benzo[b]thiophen-2-yl-2,4-dimethoxy-phenyl)-propenone

The title compound was prepared by condensing 1-(4-acetyl-phenyl)-ethanone with 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde (**Ex-3A**) in a similar manner as described in **Ex-3**. The product was purified using column chromatography. Yellow solid, 2% yield, mp 165-167°C. ^{1}H-NMR ($CDCl_3$) δ 8.06-8.12 (m, 5H), 7.92 (s, 1H), 7.75-7.82 (m, 2H), 7.65 (s,

1H), 7.55 (d, J = 15 Hz, 1H), 7.28-7.33(m, 2H), 6.56(s, 1H), 4.01 (s, 3H), 3.98 (s, 3H). MS *m/z* = 442 ([M]$^+$, 100%). HMRS (EI) calcd. for $C_{27}H_{22}O_4S$: 442.1239; found: 442.1229.

EXAMPLE 109



4-{3*E*-[5-(4-Isobutyl-4H-[1,2,4]triazol-3-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzenesulfonamide

Ex-109A: A solution of 2,4-dimethoxy-benzoic acid methyl ester (4.24g, 21.6 mmol) and hydrazine (3.4 mL, 108.1 mmol) in methanol (50 mL) was refluxed overnight. Solvent was removed under reduced pressure. The residue was re-dissolved in ethyl acetate. The solution of ethyl acetate was washed with saturated solution of sodium bicarbonate and brine, dried over sodium carbonate and concentrated to afford 2,4-dimethoxy-benzoic acid hydrazide (3.31g, 78%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.77 (bs, 1H), 8.15 (d, J = 8.8 Hz, 1H), 6.58 (dd, J = 8.8, 2.2 Hz, 1H), 6.46 (d, J = 2.2 Hz, 1H), 4.10 (bs, 2H), 3.91 (s, 3H), 3.83 (s, 3H).

Ex-109B: A solution of 2,4-dimethoxy-benzoic acid hydrazide (**Ex-109A**, 1.0g, 5.1 mmol) and isobutyl-isothiocyanate (0.70g, 6.1 mmol) in ethanol (30 mL) was refluxed for 8 hours. The precipitate was filtered, washed with ethanol, dried *in vacuo* to afford 1-(2,4-dimethoxy-benzoyl)amino-3-isobutyl-thiourea (1.43g). Additional product (0.1g, 96% overall) was obtained by concentrating the mother liquid. ^{1}H NMR ($CDCl_3$) δ 10.71 (bs, 1H), 9.23 (bs, 1H), 8.03 (d, J = 8.6 Hz, 1H), 6.98 (bs, 1H), 6.59 (dd, J = 8.6, 2.6 Hz, 1H), 6.51 (d, J = 2.6 Hz, 1H), 4.02 (s, 3H), 3.86 (s, 3H), 3.41 (dd, J = 6.4, 6.6 Hz, 2H), 1.96-1.87 (m, 1H), 0.91 (d, J = 6.5 Hz, 6H).

Ex-109C: A solution of 1-(2,4-dimethoxy-benzoyl)amino-3-isobutyl-thiourea (**Ex-109B**, 0.5g, 1.61 mmol) and sodium hydroxide (0.999M, 4.8 mL, 4.8 mmol) in ethanol (30 mL) was

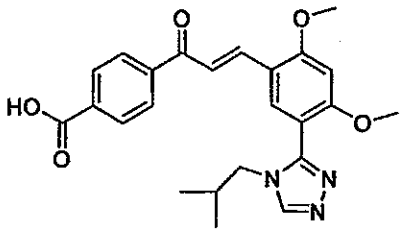
refluxed for one day. The solvent was removed under reduced pressure and the residue re-dissolved in ethyl acetate. The solution of ethyl acetate was washed with water and brine, dried over sodium sulfate, and concentrated to give 5-(2,4-dimethoxy-phenyl)-4-isobutyl-4*H*-[1,2,4]triazole-3-thiol (0.1g). Additional product (0.36g, 98% overall) was obtained by extracting the water wash with dichloromethane and a mixture of isopropyl alcohol (33%, v/v, in dichloromethane). ^{1}H NMR ($CDCl_3$) δ 10.82 (bs, 1H), 7.24 (d, J = 8.1 Hz, 1H), 6.56 (dd, J = 8.1, 2.4 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.72 (d, J = 6.7 Hz, 2H), 2.17-2.08 (m, 1H), 0.70 (d, J = 6.7 Hz, 6H).

Ex-109D: To a solution of 5-(2,4-dimethoxy-phenyl)-4-isobutyl-4*H*-[1,2,4]triazole-3-thiol (**Ex-109C**, 0.1g, 0.34 mmol) in ethanol (10 mL) was added wet Raney Ni (0.27g, 4.6 mmol). The suspension of ethanol was refluxed overnight and then passed through a bed of Hyflo Super Gel and diatomaceous earth. The filtrate was concentrated to afford 3-(2,4-dimethoxy-phenyl)-4-isobutyl-4*H*-[1,2,4]triazole (0.09g, 100%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 6.57 (dd, J = 7.8, 2.3 Hz, 1H), 6.51 (d, J = 2.3 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.62 (d, J = 7.5 Hz, 2H), 1.89-1.80 (m, 1H), 0.76 (d, J = 6.6 Hz, 6H).

Ex-109E: To a solution of 3-(2,4-dimethoxy-phenyl)-4-isobutyl-4*H*-[1,2,4]triazole (**Ex-109D**, 0.78g, 2.98 mmol) was added dichloromethyl methyl ether (0.4 mL, 4.48 mmol) followed by addition of titanium tetrachloride (1.0M in dichloromethane, 9.0 mL, 9.0 mmol) over 10 min at 0 °C. The reaction mixture was allowed to stir at 0 °C for 30 min and ambient temperature overnight. The reaction mixture was poured into ice. The aqueous solution was extracted with dichloromethane and isopropyl alcohol (33%, v/v, in dichloromethane). The combined dichloromethane and isopropyl alcohol were washed with brine, dried over sodium sulfate and concentrated. The aqueous solution was treated with sodium hydroxide to pH 12 and extracted again with isopropyl alcohol (33%, v/v, in dichloromethane) to give additional product. The crude product was purified by flash chromatography. Elution with methanol (10%, v/v, in dichloromethane) afford 5-(4-isobutyl-4*H*-[1,2,4]triazol-3-yl)-2,4-dimethoxy-benzaldehyde (0.24g, 28%): ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.17 (s, 1H), 7.90 (s, 1H), 6.51 (s, 1H), 4.00 (s, 3H), 3.87 (s, 3H), 3.58 (d, J = 7.2 Hz, 2H), 1.91-1.80 (m, 1H), 0.77 (d, J = 6.5 Hz, 6H).

To a solution of 4-acetyl-benzenesulfonamide (**Ex-26A**, 0.12g, 0.62 mmol) and 5-(4-isobutyl-4*H*-[1,2,4]triazol-3-yl)-2,4-dimethoxy-benzaldehyde (**Ex-109E**, 0.18g, 0.62 mmol) in N,N-dimethylformamide (9 mL) was added lithium methoxide (1.0M in methanol, 2.4 mL, 2.4 mmol). The solution was allowed to stir overnight. The reaction was quenched with water. The aqueous solution was washed ethyl acetate, acidified to pH 5, extracted with dichloromethane, isopropyl alcohol (33%, v/v, in dichloromethane). The combined dichloromethane and isopropyl alcohol was washed with brine, dried over sodium sulfate and concentrated. The crude product was then stirred in ethanol (50%, v/v, in acetone) to give the title compound as a light yellow solid: m.p. > 240 °C. ^{1}H NMR (DMSO-d_6) δ 8.60 (s, 1H), 8.26 (d, J = 8.1 Hz, 2H), 8.06 (d, J = 15.3 Hz, 1H), 8.07 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 15.3 Hz, 1H), 7.50 (s, 1H), 6.84 (s, 1H), 4.01 (s, 3H), 3.87 (s, 3H), 3.61 (d, J = 7.3 Hz, 2H), 1.81-1.74 (m, 1H), 0.67 (d, J = 16.7 Hz, 6H). MS *m/z* = 471 ([M + H]$^+$, 100%).

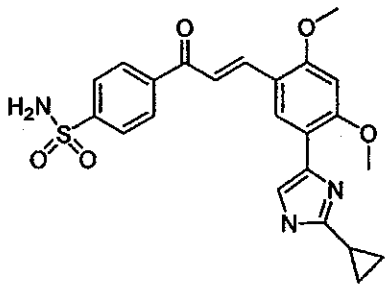
EXAMPLE 110



4-{3*E*-[5-(4-Isobutyl-4H-[1,2,4]triazol-3-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid

To a solution of 4-acetyl-benzoic acid (0.12g, 0.75 mmol) and 5-(4-isobutyl-4*H*-[1,2,4]triazol-3-yl)-2,4-dimethoxy-benzaldehyde (**Ex-109E**, 0.24g, 0.83 mmol) in N,N-dimethylformamide (6 mL) was added lithium methoxide (1.0M in methanol, 3.0 mL, 3.0 mmol). The solution was allowed to stir overnight and additional lithium methoxide (0.11g, 2.8 mmol). The reaction was quenched with water after 20 hours. The aqueous solution was washed ethyl acetate, acidified to pH 4. The precipitate was filtered, washed with ethanol and dried *in vacuo* to afford the title compound as a light yellow solid: m.p. >240 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 8.59 (s, 1H), 8.18 (d, J = 7.9 Hz, 2H), 8.07 (s, 1H), 8.04-8.01 (m, 3H), 7.85 (d, J = 15.7 Hz, 1H), 6.84 (s, 1H), 4.06 (s, 3H), 3.92 (s, 3H), 3.66 (d, J = 7.2 Hz, 2H), 1.87-1.74 (m, 1H), 0.72 (d, J = 6.7 Hz, 6H). MS *m/z* = 436 ([M + H]$^+$, 100%).

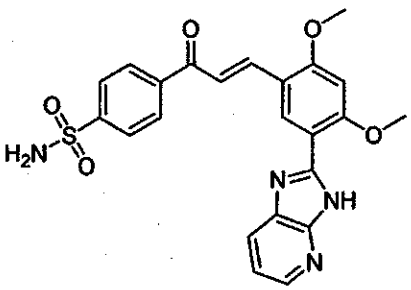
EXAMPLE 111



4-{3*E*-[5-(2-Cyclopropyl-1H-imidazol-4-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzenesulfonamide

To a solution of 4-acetyl-benzenesulfonamide (**Ex-26A**, 0.12g, 0.59 mmol) and 5-(2-cyclopropyl-1*H*-imidazol-4-yl)-2,4-dimethoxy-benzaldehyde (**Ex-105B**, 0.16g, 0.59 mmol) in N,N-dimethylformamide (16 mL) was added lithium methoxide (1.0M in methanol, 2.4 mL, 2.4 mmol). The reaction mixture was allowed to stir for 18 hours at ambient temperature. The reaction was quenched with water. The aqueous solution was extracted with dichloromethane. The combined dichloromethane was concentrated. The crude product was purified by flash chromatography. Elution with methanol (10%, v/v, in dichloromethane) gave the title compound as red solid: m.p. 156-160 °C. ^{1}H NMR (DMSO-d_6) δ 11.65 (bs, 1H), 8.32 (s, 1H), 8.19 (d, J = 9.0 Hz, 2H), 8.00 (d, J = 15.7 Hz, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.62-7.52 (m, 2H), 7.24 (bs, 1H), 6.73 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 1.98-1.94 (m, 1H), 0.88-0.85 (m, 4H). MS *m/z* = 454 ([M + H]$^+$, 100%).

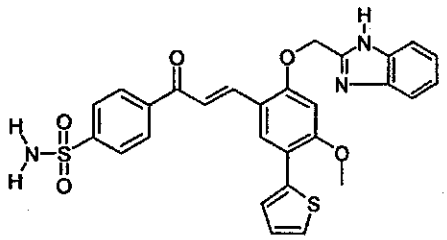
EXAMPLE 112



4-{3*E*-[5-(3*H*-Imidazo[4,5-b]pyridin-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzenesulfonamide

The title compound was prepared by condensing 5-(3*H*-imidazo[4,5-b]pyridin-2-yl)-2,4-dimethoxy-benzaldehyde (**Ex-76A**) with 4-acetyl-benzenesulfonamide (**Ex-26A**) in a similar manner as described in Ex-22. Yellow solid, 26% yield, mp >260°C. ^{1}H-NMR (DMSO-d6) δ 8.73 (s, 1H), 8.31 (dd, J = 1, 4 Hz, 1H), 8.26 (d, J = 8 Hz, 2H), 8.05(d, J = 16 Hz, 1H), 7.89-7.97 (m, 3H), 7.82(d, J = 16 Hz, 1H), 7.17-7.21(m, 1H), 6.89(s, 1H), 4.09 (s, 3H), 4.03 (s, 3H). MS *m/z* = 465([M+H]$^+$, 65%), 256 (100 %). HRMS (ES+) Calcd. for $C_{23}H_{20}N_4O_5S$: 465.1232. Found: 465.1240.

EXAMPLE 113



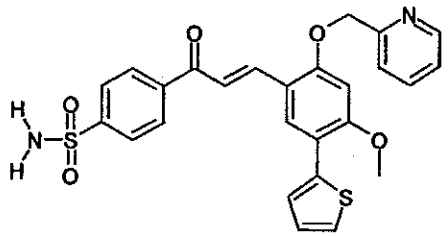
4-{3*E*-[2-(1*H*-Benzoimidazol-2-ylmethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide

Ex-113A: 2-(1*H*-Benzoimidazol-2-ylmethoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in **Ex-29C**. Off-white solid, 67% yield, mp 230 °C (dec). ^{1}H-NMR (300 MHz, DMSO-d_6) □ 10.44 (s, 1H), 8.00 (s, 1H), 7.79-7.84 (m, 2H), 7.49-7.57 (m, 4H), 7.16 (s, 1H), 7.12 (dd, 1H, *J* = 5.4, 3.6 Hz), 5.91 (s, 2H), 4.07 (s, 3H). MS (ESI) *m/z* = 365 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{20}H_{17}ClN_2O_3S \cdot {}^1/_3H_2O$: C, 59.04; H, 4.38; N, 6.88; S, 7.88. Found: C, 59.07; H, 4.25; N, 6.85; S, 7.77.

The title compound was prepared by condensing 2-(1*H*-benzoimidazol-2-ylmethoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-113A**) and 4-acetyl-benzenesulfonamide (**Ex-26A**) in a similar manner as described in **Ex-22**. Light orange solid, 56% yield, mp 235-237 °C (dec). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.19 (d, 2H, *J* = 8.4 Hz), 8.11 (d, 1H, *J* = 15.4 Hz), 7.98 (d, 1H, *J* = 15.4 Hz), 7.89 (d, 2H, *J* = 8.4 Hz), 7.66-7.70 (m, 3H), 7.53-7.55 (m, 3H), 7.22-7.27 (m, 2H), 7.12-7.15 (m, 2H), 5.59 (s, 2H), 4.01 (s, 3H). MS (ESI) *m/z* = 546

([M+H]$^+$, 100%). Anal. Calcd. for $C_{28}H_{23}N_3O_5S_2$: C, 61.64; H, 4.25; N, 7.70; S, 11.75. Found: C, 61.49; H, 4.47; N, 7.74; S, 11.58.

EXAMPLE 114

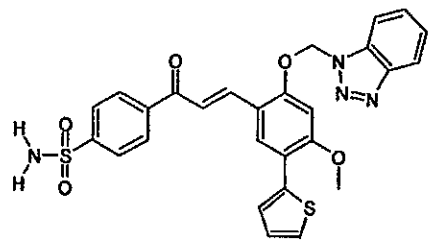


4-{3*E*-[4-Methoxy-2-(pyridin-2-ylmethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide

Ex-114A: 4-Methoxy-2-(pyridin-2-ylmethoxy)-5-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in **Ex-29C**. Yellow solid, 93% yield, mp 93-94 °C.. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.62 (d, 1H, J = 5.1 Hz), 8.13 (s, 1H), 7.77 (dt, 1H, J = 7.5, 1.5 Hz), 7.58 (d, 1H, J = 7.5 Hz), 7.44 (dd, 1H, J = 3.6, 1.5 Hz), 7.28-7.31 (m, 2H), 7.07 (dd, 1H, J = 5.4, 3.6 Hz), 6.64 (s, 1H), 5.39 (s, 2H), 3.94 (s, 3H). MS (ESI) *m/z* = 326 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30; S, 9.85. Found: C, 66.43; H, 4.72; N, 4.37; S, 9.81.

The title compound was prepared by condensing 4-methoxy-2-(pyridin-2-ylmethoxy)-5-thiophen-2-yl-benzaldehyde (**Ex-114A**) and 4-acetyl-benzenesulfonamide (**Ex-26A**) in a similar manner as described in **Ex-22**. Yellow solid, 90% yield, mp 188-189 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.66 (d, 1H, J = 3.6 Hz), 8.28 (s, 1H), 8.21 (d, 2H, J = 7.8 Hz), 8.11 (d, 1H, J = 15.4 Hz), 7.89-7.99 (m, 4H), 7.57-7.68 (m, 4H), 7.53 (dd, 1H, J = 5.4, 1.5 Hz), 7.41-7.45 (m, 1H), 7.13 (dd, 1H, J = 5.4, 3.6 Hz), 7.02 (s, 1H), 5.45 (s, 2H), 3.99 (s, 3H). MS (ESI) *m/z* = 507 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{26}H_{22}N_2O_5S_2 \cdot ½H_2O$: C, 60.57; H, 4.50; N, 5.43; S, 12.44. Found: C, 60.92; H, 4.54; N, 5.48; S, 12.32.

EXAMPLE 115

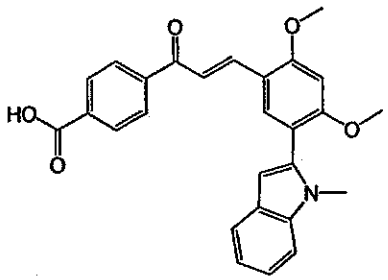


4-{3*E*-[2-(Benzotriazol-1-ylmethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide

Ex-115A: 2-(Benzotriazol-1-ylmethoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde was prepared in a similar manner as described in **Ex-29C**. Off-white solid, 92% yield, mp 137-138 °C.. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.10 (d, 1H, J = 8.1 Hz), 8.06 (s, 1H), 7.75 (d, 1H, J = 8.1 Hz), 7.57-7.62 (m, 1H), 7.40-7.48 (m, 2H), 7.30 (d, 1H, J = 5.1 Hz), 7.08 (s, 1H), 7.05 (dd, 1H, J = 5.1, 3.6 Hz), 6.74 (s, 2H), 4.01 (s, 3H). MS (ESI) m/z = 366 ($[M+H]^+$, 100%). Anal. Calcd. for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50; S, 8.78. Found: C, 62.69; H, 4.30; N, 11.52; S, 8.62.

The title compound was prepared by condensing 2-(benzotriazol-1-ylmethoxy)-4-methoxy-5-thiophen-2-yl-benzaldehyde (**Ex-115A**) and 4-acetyl-benzenesulfonamide (**Ex-26A**) in a similar manner as described in **Ex-22**. Light yellow solid, 56% yield, mp 255 °C (dec). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.09 (d, 3H, J = 9.4 Hz), 8.01 (d, 1H, J = 7.8 Hz), 7.93 (d, 2H, J = 7.8 Hz), 7.75 (d, 2H, J = 9.4 Hz), 7.56-7.69 (m, 4H), 7.42-7.47 (m, 1H), 7.38 (s, 1H), 7.13 (dd, 1H, J = 5.4, 3.6 Hz), 7.05 (s, 2H), 4.05 (s, 3H). MS (ESI) m/z = 547 ($[M+H]^+$, 100%). Anal. Calcd. $C_{27}H_{22}N_4O_5S_2$: C, 59.33; H, 4.06; N, 10.25; S, 11.73. Found: C, 59.45; H, 4.27; N, 9.92; S, 11.27.

EXAMPLE 116

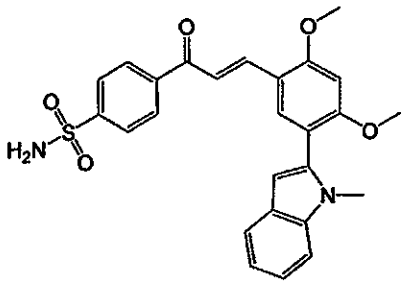


4-{3*E*-[2,4-Dimethoxy-5-(1-methyl-1*H*-indol-2-yl)-phenyl]-acryloyl}-benzoic acid

Ex-116A: To a solution of N-methyl indole (1.3 g, 10 mmol) in 50 ml THF, *t*-BuLi (1.7m in THF, 7.1 ml, 12 mmol) was slowly added at 0°C under nitrogen. The mixture was stirred at room temperature for 1 hr, BEt_3 (1.0 M in THF, 12 ml, 12 mmol) was added, and the mixture stirred for another 1 hr at room temperature. Then, $PdCl_2(PPh_3)_2$ (0.35 g, 0.5 mmol) and 5-bromo-2,4-dimethoxybenzaldehyde (3.7g, 15 mmol) were added, and the mixture was heated to about 60 °C for 30 minutes. The reaction mixture was poured into 50 ml 10% NaOH and treated with 30 % H_2O_2 and then stirred for 10 minutes. The mixture was extracted with EtOAc and combined organic phase was washed with H_2O and brine, dried over MgSO4, and absorbed to small amount of silica gel. Column chromatography (EtOAc: Hexane, 1:2) gave 0.72 g (25%) 2,4-dimethoxy-5-(1-methyl-1*H*-indol-2-yl)-benzaldehyde. ^{1}H-NMR ($CDCl_3$) δ 10.33 (s, 1H), 7.84 (s, 1H), 7.60 (d, J = 8 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.18-7.24 (m, 1H), 7.07-7.12(m, 1H), 6.53 (s, 1H), 6.46(s, 1H), 4.00 (s, 3H), 3.89 (s, 3H), 3.53 (s, 3H). HRMS (EI) Calcd. for $C_{18}H_{17}NO_3$: 295.1208. Found: 295.1202.

The title compound was prepared by condensing 4-acetylbenzoic acid and 2,4-dimethoxy-5-(1-methyl-1*H*-indol-2-yl)-benzaldehyde (**Ex-116A**) in a similar manner as described in **Ex-3**. Yellow solid, 87% yield, mp 157-160 °C. ^{1}H-NMR (DMSO-d6) δ 8.17 (d, J = 8 Hz, 2H), 8.08 (d, J = 15 Hz, 1H), 7.99-9.02 (m 3H), 7.83 (d, J = 15 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.42 (d, J = 8 Hz, 1H), 7.10-7.15 (m, 1H), 6.99-7.04(m, 1H), 6.85 (s, 1H), 6.42(s, 1H), 4.01 (s, 3H), 3.88 (s, 3H), 3.50 (s, 3H). MS *m/z* = 442 ($[M+H]^+$, 100%). HRMS (ES+) Calcd. for $C_{27}H_{23}NO_5$: 442.1654. Found: 442.1633.

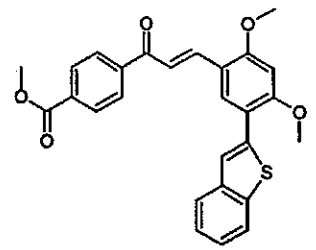
EXAMPLE 117



4-{3*E*-[2,4-Dimethoxy-5-(1-methyl-1*H*-indol-2-yl)-phenyl]-acryloyl}-benzenesulfonamide

The title compound was prepared by condensing 4-acetyl-benzenesulfonamide (**Ex-26A**) and 2,4-dimethoxy-5-(1-methyl-1*H*-indol-2-yl)-benzaldehyde (**Ex-116A**) in a similar manner as described in **Ex-3**. Yellow solid, 90% yield, mp 148-150°C. ^{1}H-NMR ($CDCl_3$) δ 8.17 (d, J = 16 Hz, 1H), 8.09 (d, J = 9 Hz, 2H), 8.01 (d, J = 9 Hz, 2H),7.68 (s, 1H), 7.64 (d, J = 8 Hz, 1H), 7.47 (d, J = 16 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.22-7.26 (m, 1H), 7.11-7.16(m, 1H), 6.58 (s, 1H), 6.50(s, 1H), 4.92 (br, 2H), 4.02 (s, 3H), 3.90 (s, 3H), 3.58 (s, 3H). MS *m/z* = 477 ($[M+H]^+$, 100%). HRMS (ES+) Calcd. for $C_{26}H_{24}NO_5S$: 477.1484. Found: 477.1487.

EXAMPLE 118

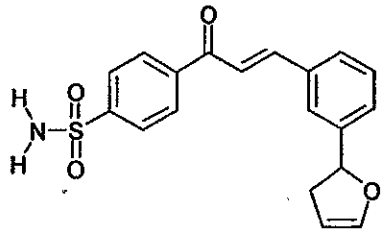


4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid methyl ester

The title compound was prpared by esterification of 4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid (**Ex-3**) with methanol in the presence of EDCI and DMAP. Yellow solid, 34% yield, m.p. 149-151°C. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.17 (d, 2 H, *J* = 6.7 Hz), 8.10 (d, 1 H, *J* = 15.8 Hz), 8.05 (d, 2 H, *J* = 6.7 Hz), 7.95 (s, 1 H), 7.82 (m, 2 H),

7.67 (s, 1 H), 7.57 (d, 1 H, J = 15.8 Hz), 7.33 (m, 2 H), 6.58 (s, 1 H), 4.04 (s, 3 H), 4.00 (s, 3 H), 3.97 (s, 3 H). MS m/z = 458 ($[M]^+$, 100%). HRMS (EI) Calcd. for $C_{27}H_{22}O_5S$: 458.1188. Found: 458.1196.

EXAMPLE 119



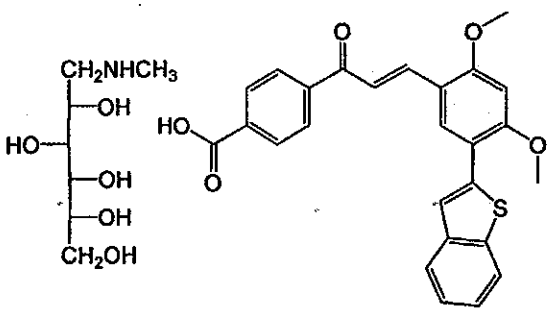
4-{3-[3*E*-(2,3-Dihydro-furan-2-yl)-phenyl]-acryloyl}-benzenesulfonamide

Ex-119A: 5-Bromobenzaldehyde (0.5 g, 2.7 mmol) and 2,3-dihydrofuran (0.56 g, 8.1 mmol) were dissolved in dioxane (5.0 mL). Nitrogen was bubbled into the solution for 15 min followed by the sequential addition of cesium carbonate (0.96 g, 2.9 mmol) and bis(tri-*t*-butylphosphine)palladium(0) (0.014 g, 0.027 mmol). The solution was immediately heated to 45 °C and aged for 24 h. Upon completion, as determined by HPLC, the reaction was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over sodium sulfate and concentrated to a brown oil. Silica gel chromatography (ethyl acetate/hexanes, 1:9) gave 0.18 g (40%) of 3-(2,3-dihydro-furan-2-yl)-benzaldehyde as a clear, colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.88 (s, 1H), 7.82 (d, 1H, J = 7.2 Hz), 7.62-7.64 (m, 1H), 7.53 (t, 1H, J = 7.2 Hz), 6.48 (q, 1H, J = Hz), 5.60 (dd, 1H, J = 8.1, 10.8 Hz), 4.98 (q, 1H, J = 3.3 Hz), 3.15 (ddt, 1H, J = 15.0, 8.1, 2.5 Hz), 2.59 (ddt, 1H, J = 15.0, 8.1, 2.5 Hz). MS (EI) m/z = 174 ($[M]^+$, 100%). HRMS (EI) Calcd. for $C_{11}H_{10}O_2$: 174.0681. Found: 174.0677.

The title compound was prepared by condensing 4-acetyl-benzenesulfonamide (**Ex-26A**) and **3-(2,3-dihydro-furan-2-yl)-benzaldehyde (Ex-119A)** in a similar manner as described in **Ex-3**. Tan solid, 40% yield, mp 152-153 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.31 (d, 2H, J = 7.5 Hz), 7.99 (d, 2H, J = 7.5 Hz), 7.95 (d, 1H, J = 15.8 Hz), 7.85 (brs, 3H), 7.78 (d, 1H, J = 15.8 Hz), 7.57 (brs, 1H), 7.44-7.52 (m, 2H), 6.62 (q, 1H, J = 2.4 Hz), 5.58 (dd, 1H, J = 8.7, 10.8

Hz), 5.59 (q, 1H, J = 2.4 Hz), 3.10 (ddt, 1H, J = 15.0, 8.1, 2.5 Hz), 2.54 (ddt, 1H, J = 15.0, 8.1, 2.5 Hz). MS (ESI) m/z = 356 ([M+H]$^+$, 100%). Anal. Calcd. for $C_{19}H_{17}NO_4S \cdot {}^1/_5H_2O$: C, 63.56; H, 4.89; N, 3.90; S, 8.93. Found: C, 63.64; H, 4.88; N, 4.00; S, 8.71.

EXAMPLE 120

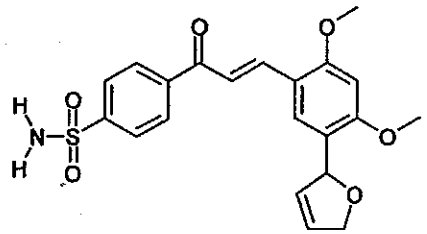


4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid, *N*-methyl-D-glucamine salt

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid of **Ex. 3** was then made into a meglumine salt by suspending the 4-[3*E*-(5-benzo[*b*]thien-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid (4.45 g, 10 mmol) and *N*-methyl-D-glucamine (1.95 g, 10 mmol) in THF (100 mL). The mixture was stirred at room temperature for 5 minutes. Then, ethanol (100 mL) was added. This mixture was stirred at room temperature for 30 minutes. THF (20 mL) and ethanol (20 mL) were added and the mixture was heated slightly until it became a solution. This solution was stirred for 30 minutes and evaporated to a yellow foam. Crystallization from methanol gave the desired 4-[3*E*-(5-benzo[*b*]thien-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid *N*-methyl-D-glucamine salt as a yellow solid (4 g, 63%), mp 75-80 °C (changing forms). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.14 (d, 2H), 8.02-8.10 (m, 3H), 7.94-7.98 (m, 3H), 7.86 (d, 1H), 7.36 (m, 2H), 6.89 (s, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 3.94 (m, 1H), 3.71 (d, 1H), 3.61 (m, 1H), 3.39-3.55 (m, 3H), 3.04 (m, 1 H), 2.95 (m, 1H), 2.54 (s, 3H). Anal. Calculated for $C_{33}H_{37}NO_{10}S \cdot 1.3H_2O$: C, 59.77; H, 6.02; N, 2.11; S, 4.84; found: C, 59.84; H, 5.75; N, 2.05; S, 4.70; Parent EIMS m/z = 443 (M$^+$).

Using the above procedure for producing the meglumine salt or procedures well known in the art, any of the compounds of the invention can be likewise made into a hydroxyl amine salt and in particular the meglumine salt.

EXAMPLE 121



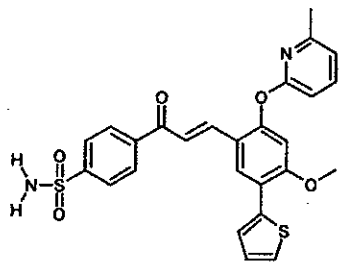
4-{3*E*-[5-(2,5-Dihydro-furan-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzenesulfonamide

Ex-121A: 5-Bromo-2,4-dimethoxybenzaldehyde (1.0 g, 4.0 mmol) and 2,3-dihydrofuran (0.85 g, 12.2 mmol) were dissolved in dioxane (10.0 mL). Nitrogen was bubbled into the solution for 15 min followed by the sequential addition of cesium carbonate (1.4 g, 4.5 mmol) and bis(tri-*t*-butylphosphine)palladium (0) (0.021 g, 0.041 mmol). The solution was immediately heated to 45 °C and aged for 72 h. Additional equivalents of cesium carbonate (0.70 g, 2.1 mmol), 2,3-dihydrofuran (0.85 g, 12.2 mmol), and Pd catalyst (0.0021 g, 0.0041 mmol) were added after 24 h and 48 h to drive the reaction to completion. Upon completion, as determined by HPLC, the reaction was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over sodium sulfate and concentrated to an orange oil. Silica gel chromatography (ethyl acetate/hexanes, 1:2) afforded 0.32 g (50%) of 5-(2,5-dihydro-furan-2-yl)-2,4-dimethoxy-benzaldehyde as a pale yellow solid, mp 84-85 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.79 (s, 1H), 6.42 (s, 1H), 5.99-6.06 (m, 2H), 5.89-5.92 (m, 1H), 4.80-4.87 (m, 1H), 4.71-4.77 (m, 1H), 3.95 (s, 3H), 3.92 (s, 3H). MS (EI) *m/z* = 234 ($[M]^+$, 100%). Anal. Calcd. $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.49; H, 6.08.

5-(2,5-Dihydro-furan-2-yl)-2,4-dimethoxy-benzaldehyde (**Ex-121A**, 0.10 g, 0.43 mmol) and 4-acetylbenzenesulfonamide (**Ex-26A**, 0.085 g, 0.43 mmol) were dissolved in a dimethylformamide-methanol solution (2.9 mL, 7:3). After complete dissolution, lithium methoxide (0.065 g, 1.7 mmol) was added and the resulting orange slurry was stirred in the

dark at room temperature for 4 h. Upon completion, as determined by HPLC, the mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was taken up in ethanol (2 mL) and warmed to 60 °C to obtain complete dissolution and allowed to cool to room temperature. The resulting precipitate was collected on filter paper and dried *in vacuo* to yield 0.13 g (70%) of the title compound as a yellow solid, mp 194-195 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.23 (d, 2H, J = 8.2 Hz), 8.03 (d, 1H, J = 15.3 Hz), 7.97 (d, 2H, J = 8.2 Hz), 7.69 (s, 1H), 7.65 (d, 1H, J = 15.3 Hz), 7.55 (brs, 2H), 6.73 (s, 1H), 6.06-6.09 (m, 1H), 5.90-5.98 (m, 2H), 4.86-4.92 (m, 1H), 4.63-4.68 (m, 1H), 3.96 (s, 3H), 3.92 (s, 3H). MS (ESI) *m/z* = 416 ([M+H]$^+$, 100%). Anal. Calcd. $C_{21}H_{21}NO_6S$: C, 60.71; H, 5.09; N, 3.37; S, 7.72. Found: C, 60.95; H, 5.24; N, 3.46; S, 7.72.

EXAMPLE 122



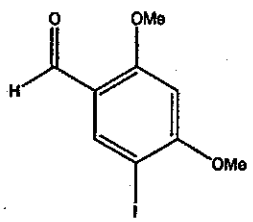
4-{3*E*-[4-Methoxy-2-(6-methyl-pyridin-2-yloxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzenesulfonamide

Ex-122A: To a solution of 2-hydroxy-4-methoxy-5-thiophen-2-yl-benzaldehyde (0.68 g, 2.9 mmol) and 2-bromo-6-methylpyridine (0.25 g, 1.4 mmol) in toluene (1.0 mL) was added ethyl acetate (0.0063 g, 0.072 mmol, 1-naphthoic acid (0.50 g, 2.9 mmol), 5Å molecular sieves (0.36 g), cesium carbonate (0.94 g, 2.9 mmol), and copper(I) triflate-benzene complex (0.020 g, 0.036 mmol). The phenoxide crashed out of solution upon addition of cesium carbonate and additional toluene (1 mL) was added to facilitate stirring. The heterogeneous solution was immediately heated to 110 °C and aged for 24 h. Upon completion, as determined by HPLC, the reaction was diluted with a 5% sodium hydroxide solution (10 mL) and ethyl acetate (10 mL) and stirred for 30 min. The layers were separated and the aqueous layer was extracted with

ethyl acetate (5 x 20 mL). The combined organic extracts were washed with a 50% brine solution (1 x 25 mL), brine (1 x 25 mL), dried over sodium sulfate and concentrated to an dark brown semi-solid. Silica gel chromatography (ethyl acetate/hexanes, 1:4) afforded 0.30 g (65%) of 4-methoxy-2-(6-methyl-pyridin-2-yloxy)-5-thiophen-2-yl-benzaldehydeas a light orange solid, mp 140-141 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.23 (s, 1H), 7.64 (dd, 1H, J = 7.8, 7.2 Hz), 7.52 (d, 1H, J = 3.3 Hz), 7.35 (d, 1H, J = 5.1 Hz), 7.10 (dd, 1H, J = 5.1, 3.3 Hz), 6.94 (d, 1H, J = 7.2 Hz), 6.78 (d, 1H, J = 7.8 Hz), 6.75 (s, 1H), 3.92 (s, 3H), 2.44 (s, 3H). HRMS (EI) Calcd. for $C_{18}H_{15}NO_3S$: 325.0773. Found: 325.0775. Anal. Calcd. $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30; S, 9.85. Found: C, 60.00; H, 4.58; N, 4.05; S, 9.84.

4-Methoxy-2-(6-methyl-pyridin-2-yloxy)-5-thiophen-2-yl-benzaldehyde (**Ex-122A**, 0.20 g, 0.62 mmol) and 4-acetylbenzenesulfonamide (**Ex-26A**, 0.12 g, 0.62 mmol) were dissolved in a dimethylformamide-methanol solution (4.2 mL, 7:3). After complete dissolution, lithium methoxide (0.093 g, 2.5 mmol) was added and the resulting orange slurry was stirred in the dark at room temperature for 3 h. Upon completion, as determined by HPLC, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was taken up in ethanol (2 mL) and warmed to 60 °C to obtain complete dissolution and allowed to cool to room temperature. The resulting precipitate was collected on filter paper and dried *in vacuo* to yield 0.25 g (82%) of the title compound as a yellow solid, mp 164-165 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.24 (d, 2H, J = 8.1 Hz), 7.98 (d, 1H, J = 15.3 Hz), 7.96 (d, 2H, J = 8.1 Hz), 7.78-7.85 (m, 2H), 7.77 (d, 1H, J = 15.3 Hz), 7.62 (d, 1H, J = 5.1 Hz), 7.57 (s, 2H), 7.19 (dd, 1H, J = 5.1, 3.6 Hz), 7.04 (d, 1H, J = 7.5 Hz), 6.99 (s, 1H), 6.91 (d, 1H, J = 8.4 Hz), 3.90 (s, 3H), 2.33 (s, 3H). Anal. Calcd. $C_{26}H_{22}N_2O_5S_2$: C, 61.64; H, 4.38; N, 5.53; S, 12.66. Found: C, 61.88; H, 4.47; N, 5.59; S, 12.62.

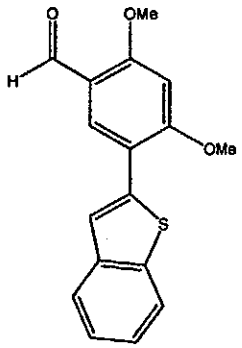
EXAMPLE 123



5-Iodo-2,4-dimethoxy-benzaldehyde

To a solution of 2,4-dimethoxy-benzaldehyde (20.0g, 120.4 mmol) in methanol (550 mL) was added a solution of iodine monochloride (23.52g, 144.9 mmol) in methanol (60 mL) dropwise over 20 min. The solution was allowed to stir at ambient temperature for 3 hours and then poured into a solution of hydrochloric acid (0.5 M, 600 mL). The resulting precipitate was collected by filtration, washed with water, and dried *in vacuo*. The crude product was further recrystallized from a mixture of tetrahydrofuran and heptane (1:1, v/v) to give the tiltle compound as a white solid (30.62g, 87.5%), m.p. 170-172 °C. ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 8.22 (s, 1H), 6.39 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H).

EXAMPLE 124

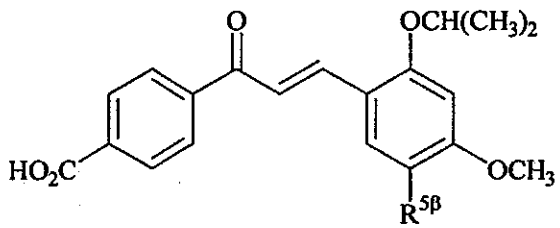


5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-benzaldehyde

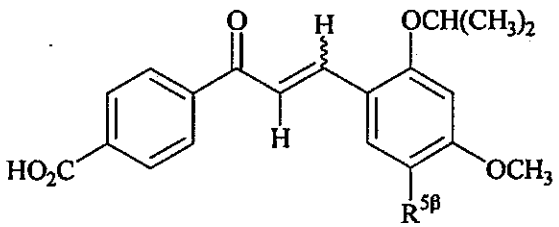
Ex-123A: Potassium fluoride (0.42g, 7.2 mmol), 5-iodo-2,4-dimethoxy-benzaldehyde (**Ex-123**, 1.0g, 3.42 mmol), 2-benzo[*b*]thiophene boronic acid (0.67g, 3.77 mmol), degased tetrahydrofuran (10 mL), tris(dibenzylideneacetone)dipalladium (19mg, 0.02 mmol), and tri-*tert*-butylphosphine (100mg, 0.05 mmol) were sequentially charged into a flask equipped with a condenser and nitrogen inlet adapter. The reaction mixture was heated at 60 °C for one hour under nitrogen. HPLC analysis indicated of 100% conversion of 5-iodo-2,4-dimethoxy-benzaldehyde (**Ex-123**) to the titlé compound prepared through another route (**Ex-3A**).

Using one or more of the preceding methods, additional substituted 1-[2,2-bis(hydroxymethyl)-benzo[1,3]dioxol-5-yl]-3-[(heteroaryl or heterocyclic)phenyl]-2-propen-1-ones, 4-[3-{(heteroaryl or heterocyclic)phenyl}acryloyl]-benzoic acids, 1-[(amino)phenyl]-3-[(heteroaryl or heterocyclic)phenyl]-2-propen-1-ones, 4-[3-{(heteroaryl or heterocyclic)-phenyl}-3-oxo-propenyl]-benzoic acids, 1-(1*H*-indol-5-yl)-3-{(heteroaryl or heterocyclic)-phenyl}-propen-2-ones, 1-[(heteroaryl or heterocyclic)phenyl]-3-phenyl-2-propen-1-ones, and substituted 3-[(heteroaryl or heterocyclic)phenyl]-1-phenyl-2-propen-1-ones can be prepared by one skilled in the art using similar methods, as shown in Example Tables 1 through 33.

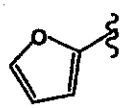
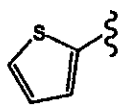
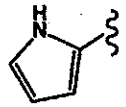
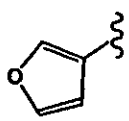
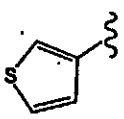
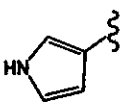
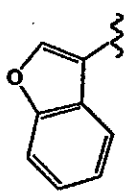
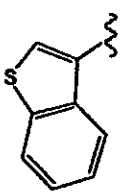
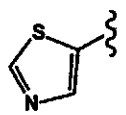
Example Table 1. Substituted 4-[3-{2-Isopropoxy-4-methoxy-(5-heteroaryl or 5-heterocyclic)phenyl}-acryloyl]-benzoic Acids.

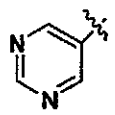
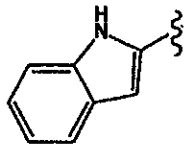
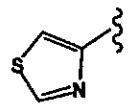
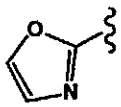
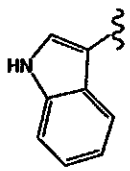
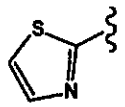
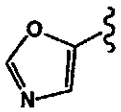
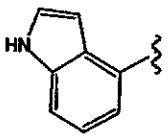
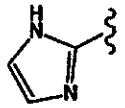
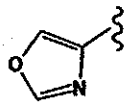
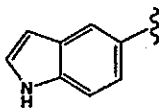
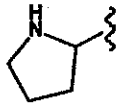
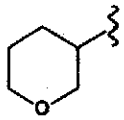
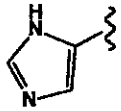
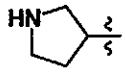
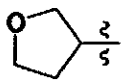
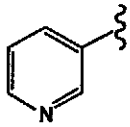
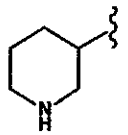
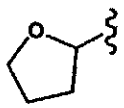
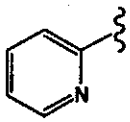
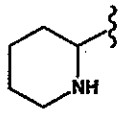
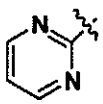
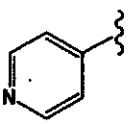
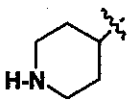
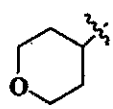
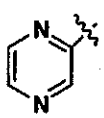
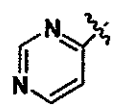
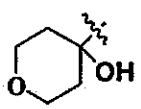
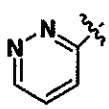
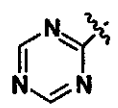
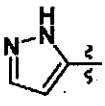
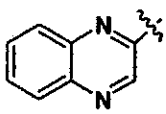
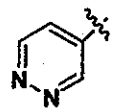


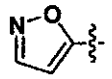
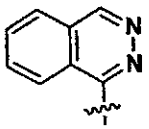
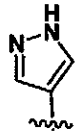
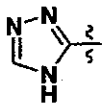
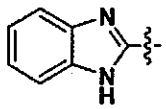
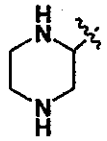
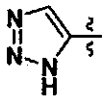
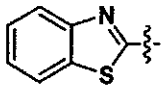
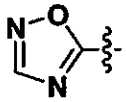
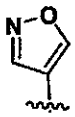
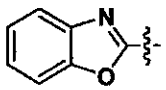
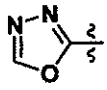
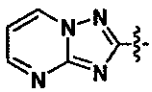
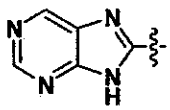
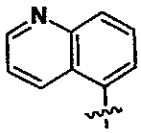
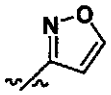
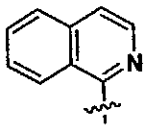
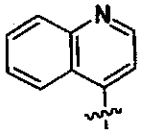
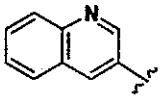
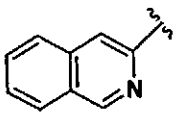
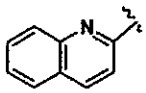
A



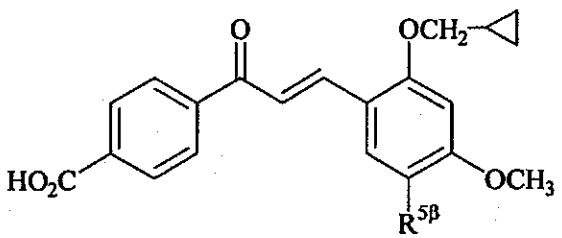
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
200A 200B		201A 201B		202A 202B	
203A 203B		204A 204B		205A 205B	
206A 206B		207A 207B		208A 208B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
209A 209B		210A 210B		211A 211B	
212A 212B		213A 213B		214A 214B	
215A 215B		216A 216B		217A 217B	
218A 218B		219A 219B		220A 220B	
221A 221B		222A 222B		223A 223B	
224A 224B		225A 225B		226A 226B	
227A 227B		228A 228B		229A 229B	
230A 230B		231A 231B		232A 232B	
233A 233B		234A 234B		235A 235B	
236A 236B		237A 237B		238A 238B	
239A 239B		240A 240B		241A 241B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
242A 242B		243A 243B		244A 244B	
245A 245B		246A 246B		247A 247B	
248A 248B		249A 249B		250A 250B	
251A 251B		252A 252B		253A 253B	
254A 254B		255A 255B		256A 256B	
257A 257B		258A 258B		259A 259B	
260A 260B		261A 261B		262A 262B	

Example Table 12. Substituted 4-[3-{2-Cyclopropylmethoxy-4-methoxy-(5-heteroaryl or 5-heterocyclic)phenyl}-acryloyl]-benzoic Acids.



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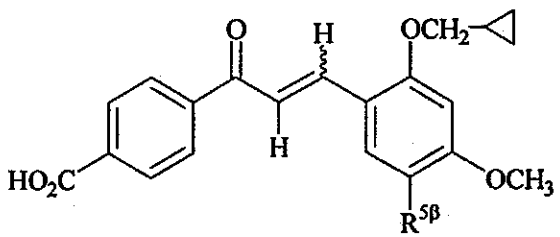

B

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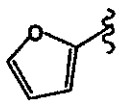
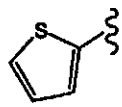
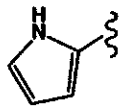
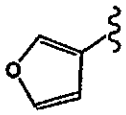
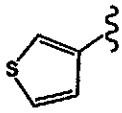
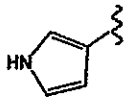
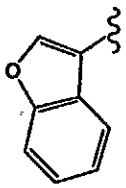
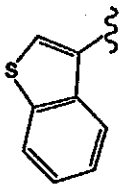
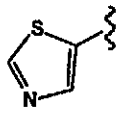
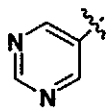
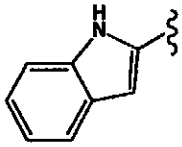
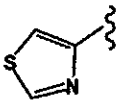
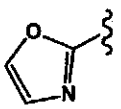
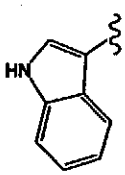
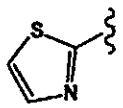
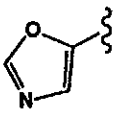
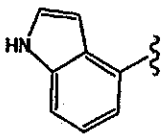
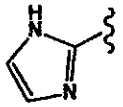
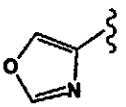
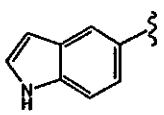
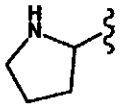
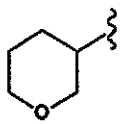
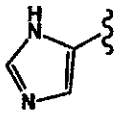
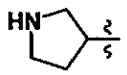
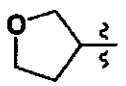
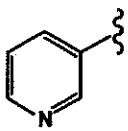
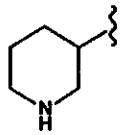
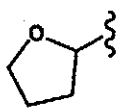
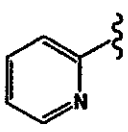
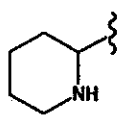
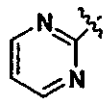
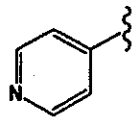
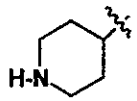
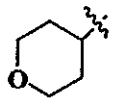
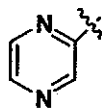
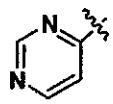
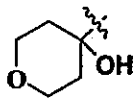
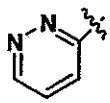
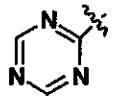
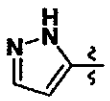
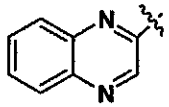
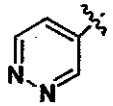
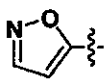
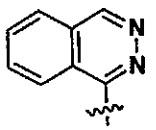
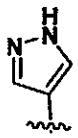
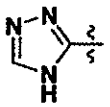
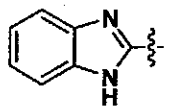
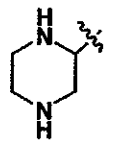
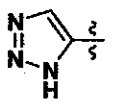
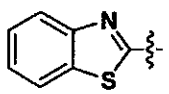
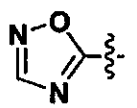
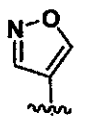
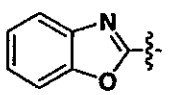
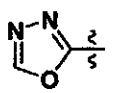
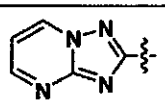
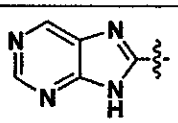
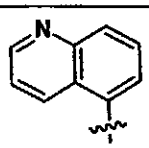
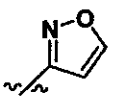
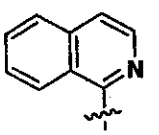
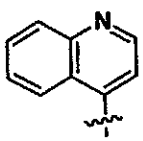
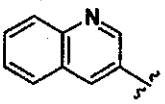
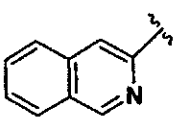
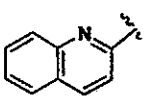
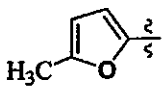
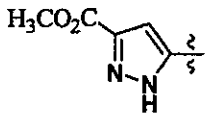
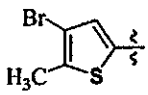
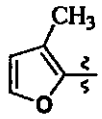
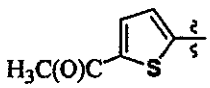
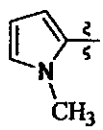
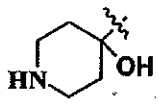
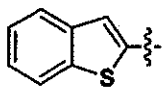
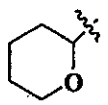
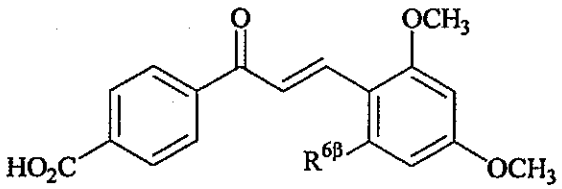
263A 263B		264A 264B		265A 265B	
266A 266B		267A 267B		268A 268B	
269A 269B		270A 270B		271A 271B	
272A 272B		273A 273B		274A 274B	
275A 275B		276A 276B		277A 277B	
278A 278B		279A 279B		280A 280B	
281A 281B		282A 282B		283A 283B	
284A 284B		285A 285B		286A 286B	
287A 287B		288A 288B		289A 289B	
290A 290B		291A 291B		292A 292B	

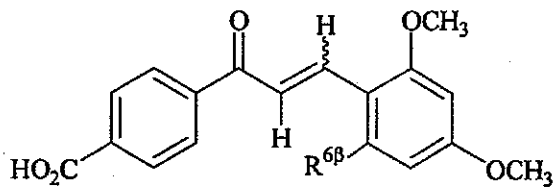
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
293A 293B		294A 294B		295A 295B	
296A 296B		297A 297B		298A 298B	
299A 299B		300A 300B		301A 301B	
302A 302B		303A 303B		304A 304B	
305A 305B		306A 306B		307A 307B	
308A 308B		309A 309B		310A 310B	
311A 311B		312A 312B		313A 313B	
314A 314B		315A 315B		316A 316B	
317A 317B		318A 318B		319A 319B	
320A 320B		321A 321B		322A 322B	
323A 323B		324A 324B		325A 325B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
326A 326B		327A 327B		328A 328B	
329A 329B		330A 330B		331A 331B	
332A 332B		333A 333B		334A 334B	

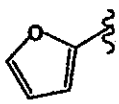
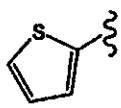
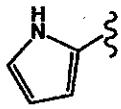
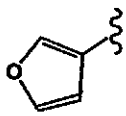
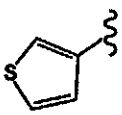
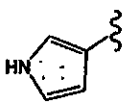
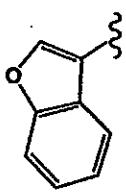
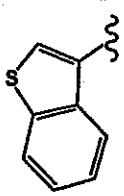
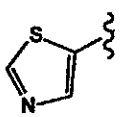
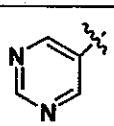
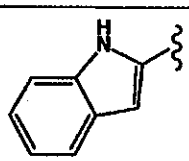
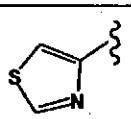
Example Table 3. Substituted 4-[3-{2,4-dimethoxy-(6-Heteroaryl or 6-heterocyclic)phenyl}-acryloyl]-benzoic Acids.

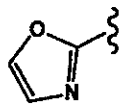
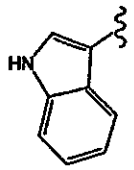
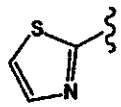
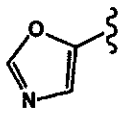
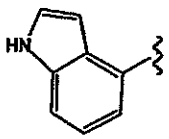
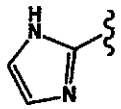
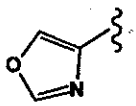
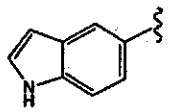
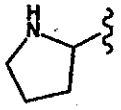
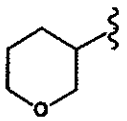
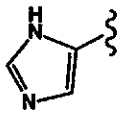
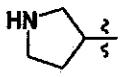
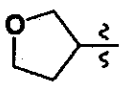
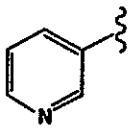
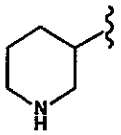
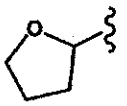
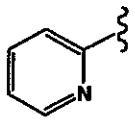
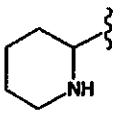
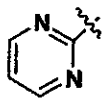
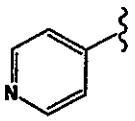
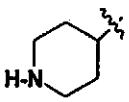
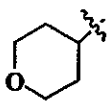
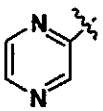
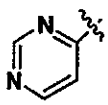
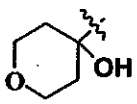
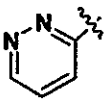
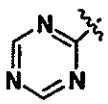
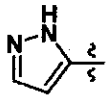
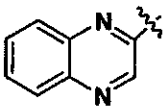
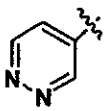
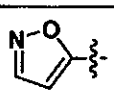
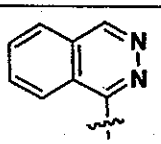
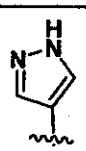


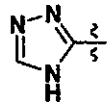
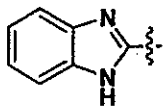
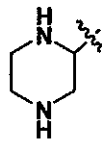
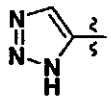
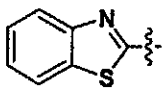
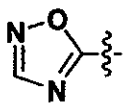
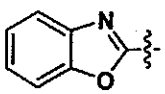
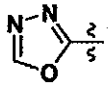
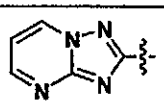
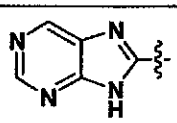
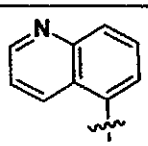
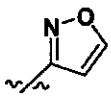
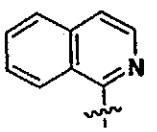
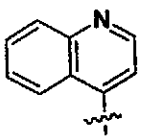
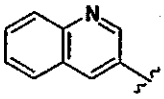
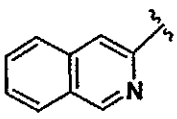
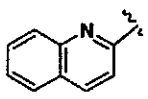
A



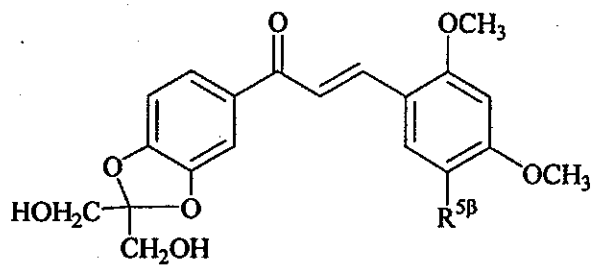
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
335A 335B		336A 336B		337A 337B	
338A 338B		339A 339B		340A 340B	
341A 341B		342A 342B		343A 343B	
344A 344B		345A 345B		346A 346B	

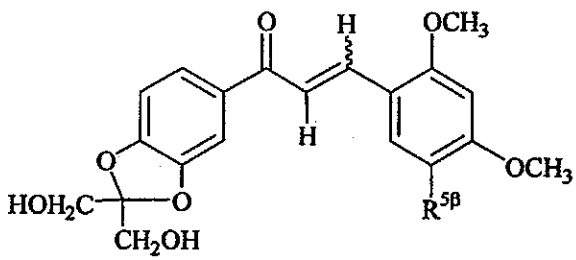
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
347A 347B		348A 348B		349A 349B	
350A 350B		351A 351B		352A 352B	
353A 353B		354A 354B		355A 355B	
356A 356B		357A 357B		358A 358B	
359A 359B		360A 360B		361A 361B	
362A 362B		363A 363B		364A 364B	
365A 365B		366A 366B		367A 367B	
368A 368B		369A 369B		370A 370B	
371A 371B		372A 372B		373A 373B	
374A 374B		375A 375B		376A 376B	
377A 377B		378A 378B		379A 379B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
380A 380B		381A 381B		382A 382B	
383A 383B		384A 384B		385A 385B	
386A 386B		387A 387B		388A 388B	
389A 389B		390A 390B		391A 391B	
392A 392B		393A 393B		394A 394B	
395A 395B		396A 396B		397A 397B	

Example Table 4. Substituted 1-(2,2-Bis-hydroxymethyl-benzo[1,3]dioxol-5-yl)-3-[2,4-dimethoxy-(5-heteroaryl or 5-heterocylic)phenyl]-2-propen-1-ones.

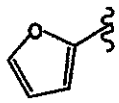
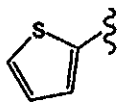
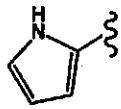
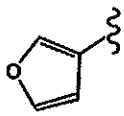
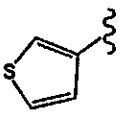
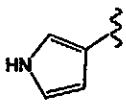
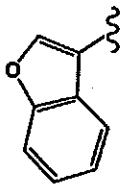
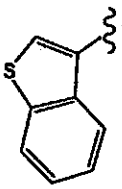
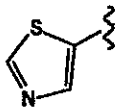
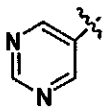
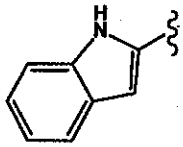
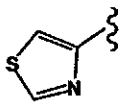
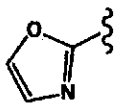
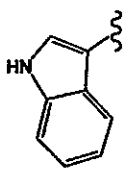
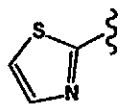
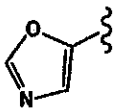
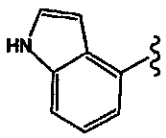
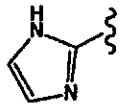
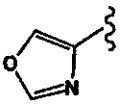
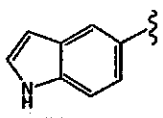
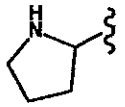
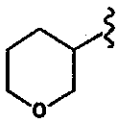
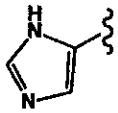
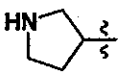
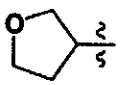
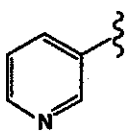
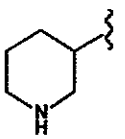
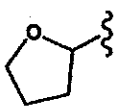
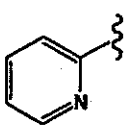
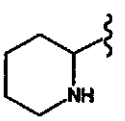


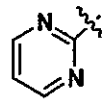
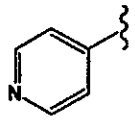
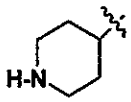
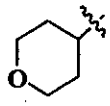
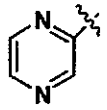
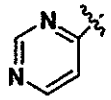
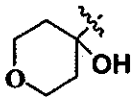
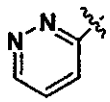
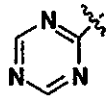
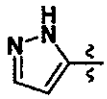
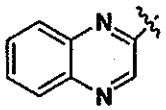
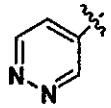
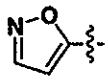
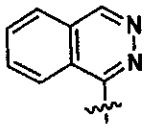
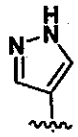
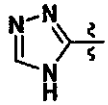
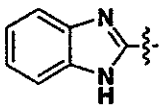
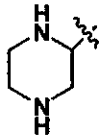
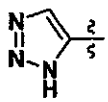
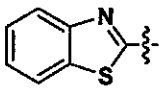
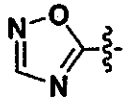
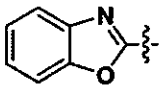
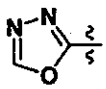
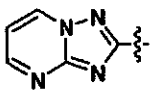
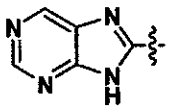
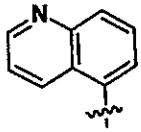
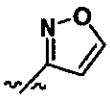
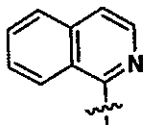
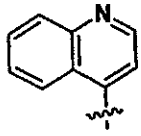
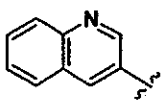
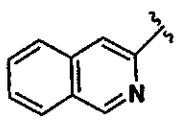
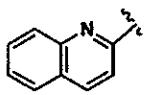
A

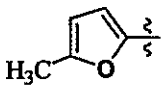
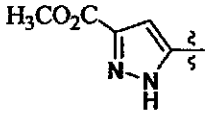
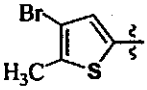
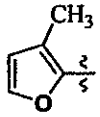
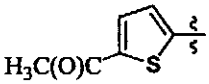
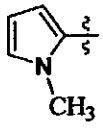
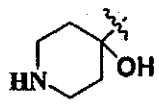
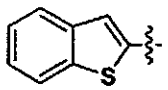
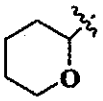


B

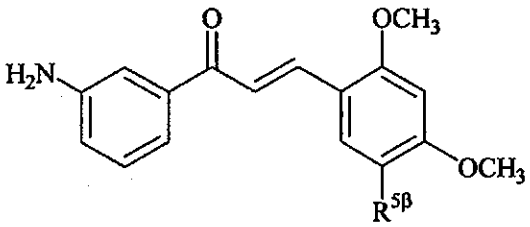
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
398A 398B		399A 399B		400A 400B	
401A 401B		402A 402B		403A 403B	
404A 404B		405A 405B		406A 406B	
407A 407B		408A 408B		409A 409B	
410A 410B		411A 411B		412A 412B	
413A 413B		414A 414B		415A 415B	
416A 416B		417A 417B		418A 418B	
419A 419B		420A 420B		421A 421B	
422A 422B		423A 423B		424A 424B	
425A 425B		426A 426B		427A 427B	

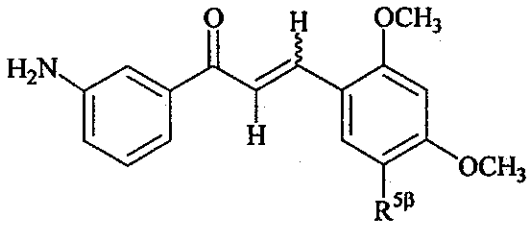
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
428A 428B		429A 429B		430A 430B	
431A 431B		432A 432B		433A 433B	
434A 434B		435A 435B		436A 436B	
437A 437B		438A 438B		439A 439B	
440A 440B		441A 441B		442A 442B	
443A 443B		444A 444B		445A 445B	
446A 446B		447A 447B		448A 448B	
449A 449B		450A 450B		451A 451B	
452A 452B		453A 453B		454A 454B	
455A 455B		456A 456B		457A 457B	
458A 458B		459A 459B		460A 460B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
461A 461B		462A 462B		463A 463B	
464A 464B		465A 465B		466A 466B	
467A 467B		468A 468B		469A 469B	

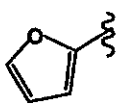
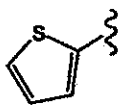
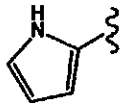
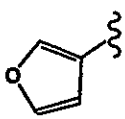
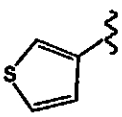
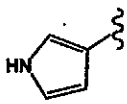
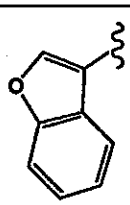
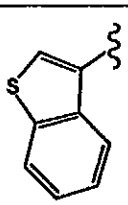
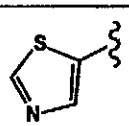
Example Table 5. Substituted 1-(3-Aminophenyl)-3-[2,4-dimethoxy-(5-heteroaryl or 5-heterocylic)phenyl]-2-propen-1-ones.

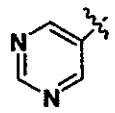
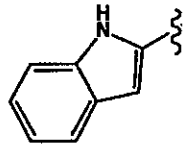
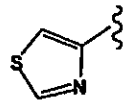
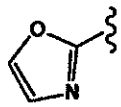
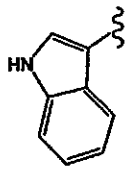
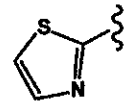
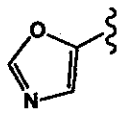
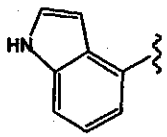
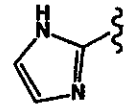
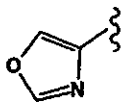
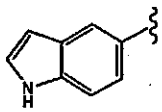
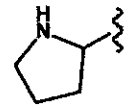
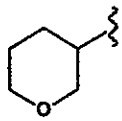
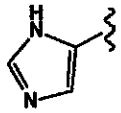
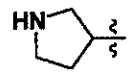
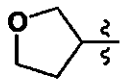
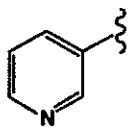
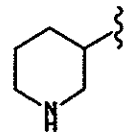
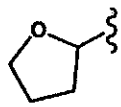
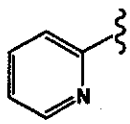
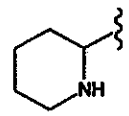
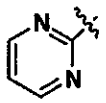
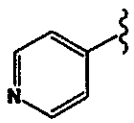
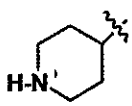
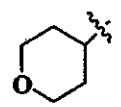
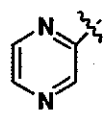
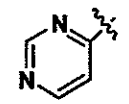
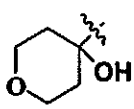
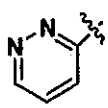
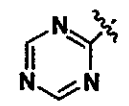
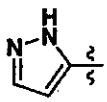
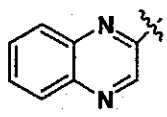
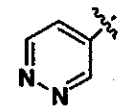


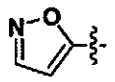
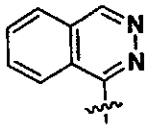
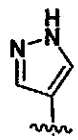
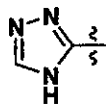
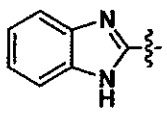
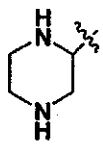
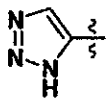
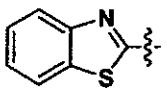
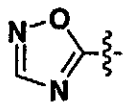
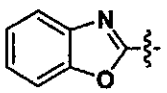
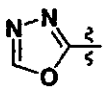
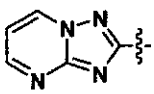
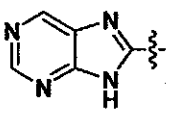
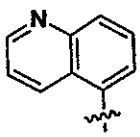
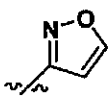
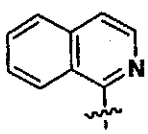
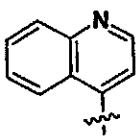
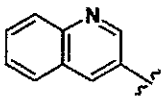
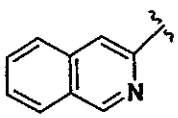
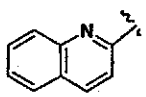
A



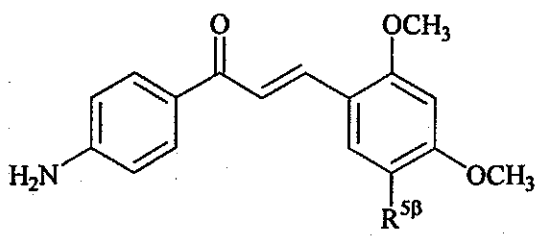
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
470A 470B		471A 471B		472A 472B	
473A 473B		474A 474B		475A 475B	
476A 476B		477A 477B		478A 478B	

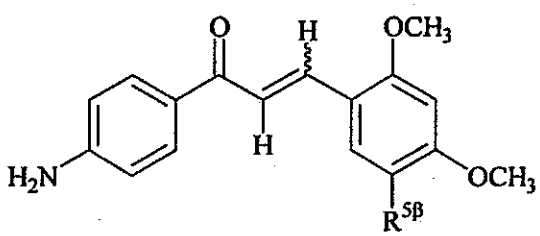
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
479A 479B		480A 480B		481A 481B	
482A 482B		483A 483B		484A 484B	
485A 485B		486A 486B		487A 487B	
488A 488B		489A 489B		490A 490B	
491A 491B		492A 492B		493A 493B	
494A 494B		495A 496B		496A 496B	
497A 497B		498A 498B		499A 499B	
500A 500B		501A 501B		502A 502B	
503A 503B		504A 504B		505A 505B	
506A 506B		507A 507B		508A 508B	
509A 509B		510A 510B		511A 511B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
512A 512B		513A 513B		514A 514B	
515A 515B		516A 516B		517A 517B	
518A 518B		519A 519B		520A 520B	
521A 521B		522A 522B		523A 523B	
524A 524B		525A 525B		526A 526B	
527A 527B		528A 528B		529A 529B	
530A 530B		531A 531B		532A 532B	

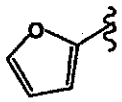
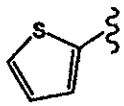
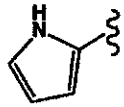
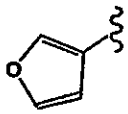
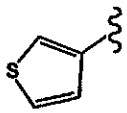
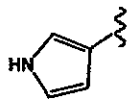
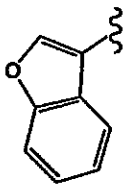
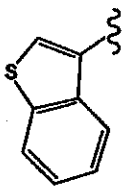
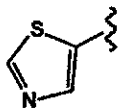
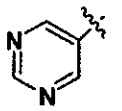
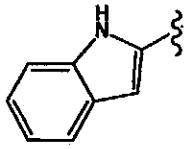
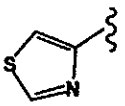
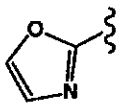
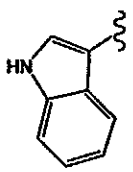
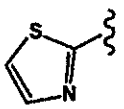
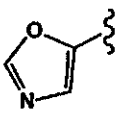
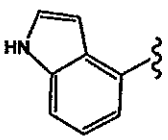
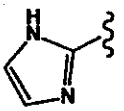
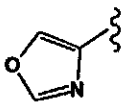
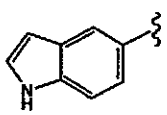
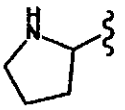
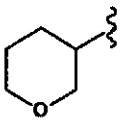
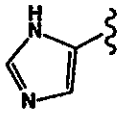
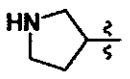
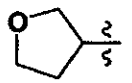
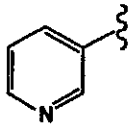
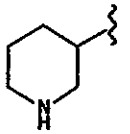
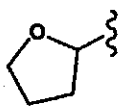
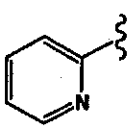
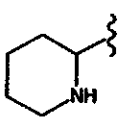
Example Table 6. Substituted 1-(4-Aminophenyl)-3-[2,4-dimethoxy-(5-heteroaryl or 5-heterocylic)phenyl]-2-propen-1-ones.



A



B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
533A 533B		534A 534B		535A 535B	
536A 536B		537A 537B		538A 538B	
539A 539B		540A 540B		541A 541B	
542A 542B		543A 543B		544A 544B	
545A 545B		546A 546B		547A 547B	
548A 548B		549A 549B		550A 550B	
551A 551B		552A 552B		553A 553B	
554A 554B		555A 555B		556A 556B	
557A 557B		558A 558B		559A 559B	
560A 560B		561A 561B		562A 562B	

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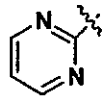
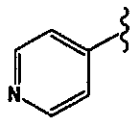
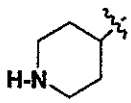
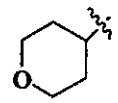
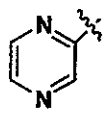
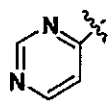
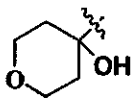
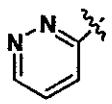
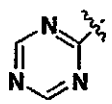
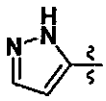
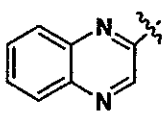
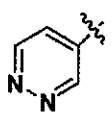
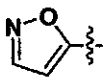
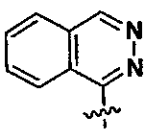
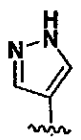
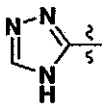
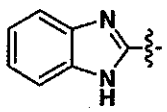
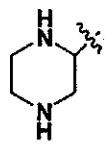
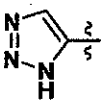
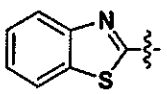
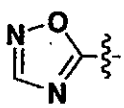
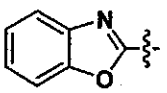
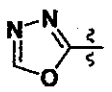
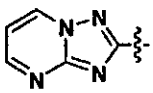
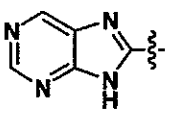
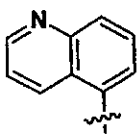
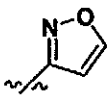
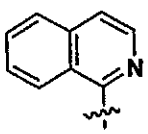
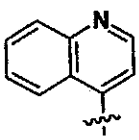
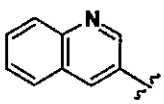
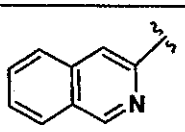
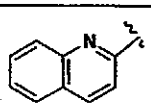
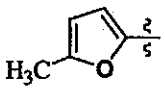
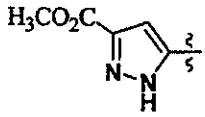
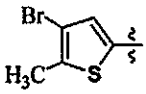
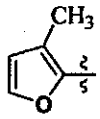
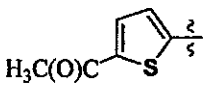
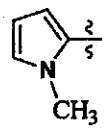
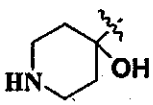
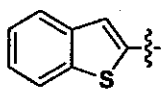
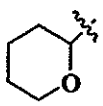
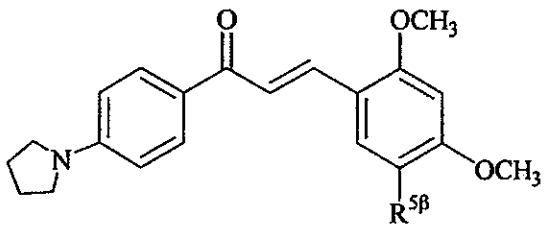
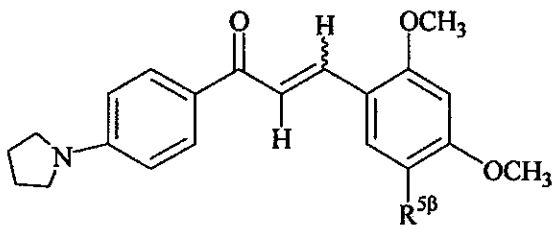
563A 563B		564A 564B		565A 565B	
566A 566B		567A 567B		568A 568B	
569A 569B		570A 570B		571A 571B	
572A 572B		573A 573B		574A 574B	
575A 575B		576A 576B		577A 577B	
578A 578B		579A 579B		580A 580B	
581A 581B		582A 582B		583A 583B	
584A 584B		585A 585B		586A 586B	
587A 587B		588A 588B		589A 589B	
590A 590B		591A 591B		592A 592B	
593A 593B		594A 594B		595A 595B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
596A 596B		597A 597B		598A 598B	
599A 599B		600A 600B		601A 601B	
602A 602B		603A 603B		604A 604B	

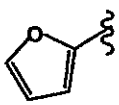
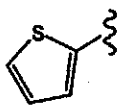
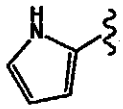
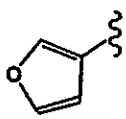
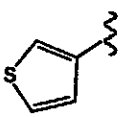
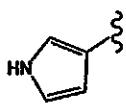
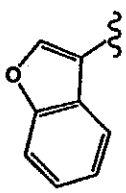
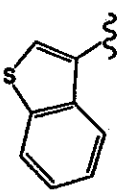
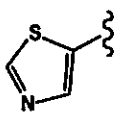
Example Table 7. Substituted 1-{4-(Pyrrolidin-1-yl)phenyl}-3-[2,4-dimethoxy-(5-heteroaryl or 5-heterocylic)phenyl]-2-propen-1-ones.

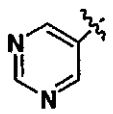
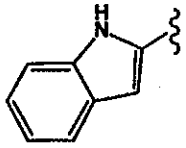
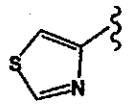
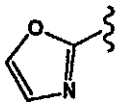
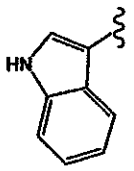
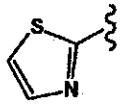
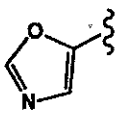
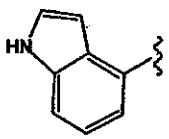
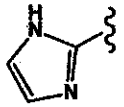
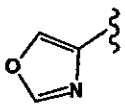
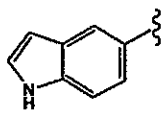
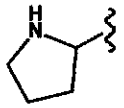
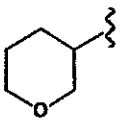
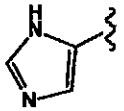
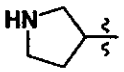
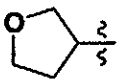
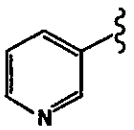
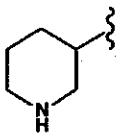
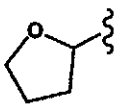
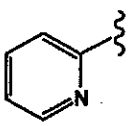
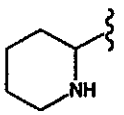
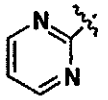
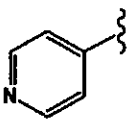
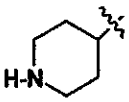
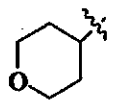
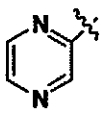
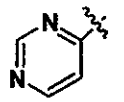
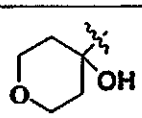
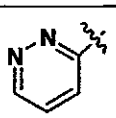
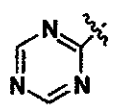
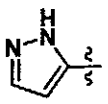
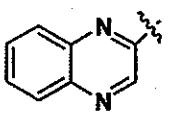
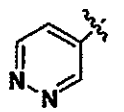


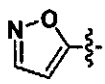
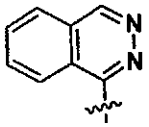
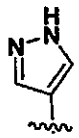
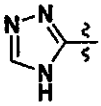
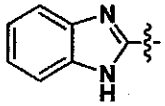
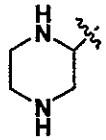
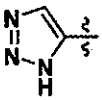
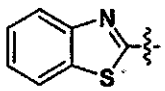
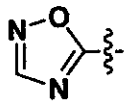
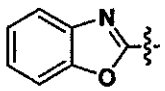
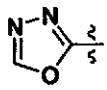
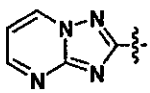
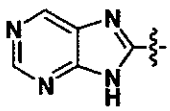
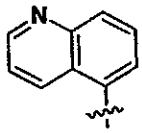
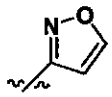
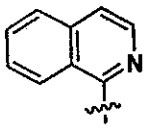
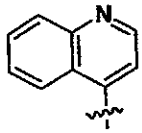
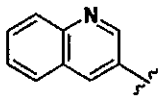
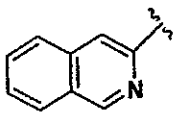
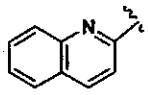
A



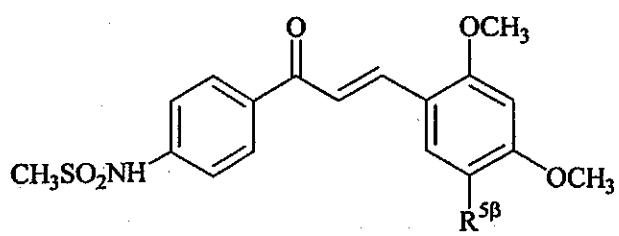
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
605A 605B		606A 606B		607A 607B	
608A 608B		609A 609B		610A 610B	
611A 611B		612A 612B		613A 613B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
614A 614B		615A 615B		616A 616B	
617A 617B		618A 618B		619A 619B	
620A 620B		621A 621B		622A 622B	
623A 623B		624A 624B		625A 625B	
626A 626B		627A 627B		628A 628B	
629A 629B		630A 630B		631A 631B	
632A 632B		633A 633B		634A 634B	
635A 635B		636A 636B		637A 637B	
638A 638B		639A 639B		640A 640B	
641A 641B		642A 642B		643A 643B	
644A 644B		645A 645B		646A 646B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
647A 647B		648A 648B		649A 649B	
650A 650B		651A 651B		652A 652B	
653A 653B		654A 654B		655A 655B	
656A 656B		657A 657B		658A 658B	
659A 659B		660A 660B		661A 661B	
662A 662B		663A 663B		664A 664B	
665A 665B		666A 666B		667A 667B	

Example Table 8. Substituted 1-{4-(Methanesulfonylamino)phenyl}-3-[2,4-dimethoxy-(5-heteroaryl or 5-heterocylic)phenyl]-2-propen-1-ones.



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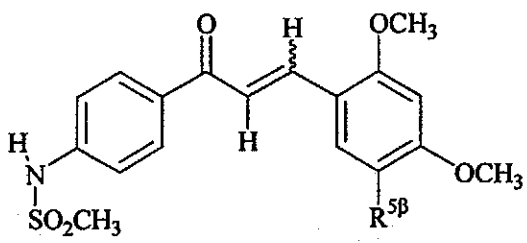

B

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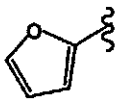
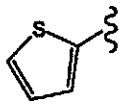
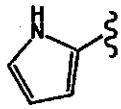
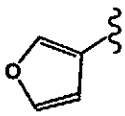
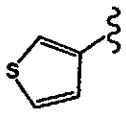
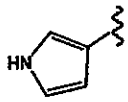
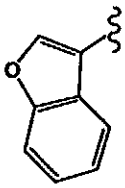
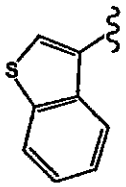
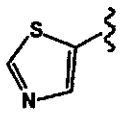
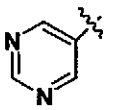
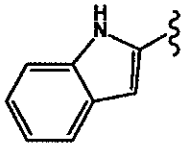
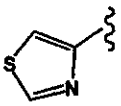
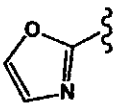
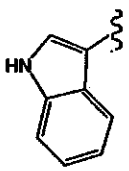
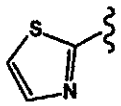
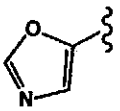
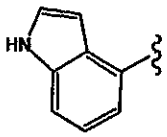
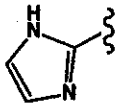
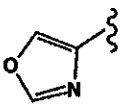
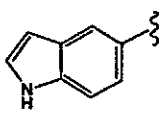
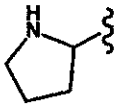
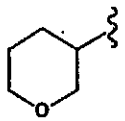
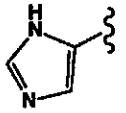
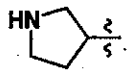
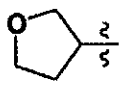
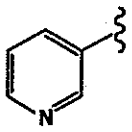
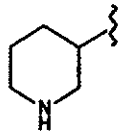
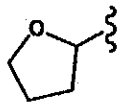
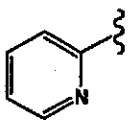
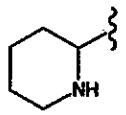
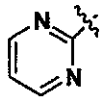
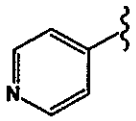
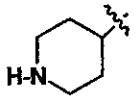
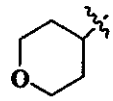
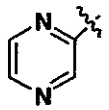
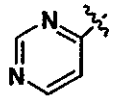
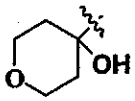
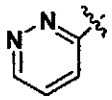
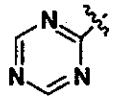
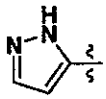
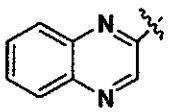
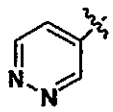
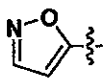
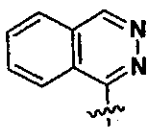
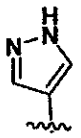
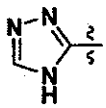
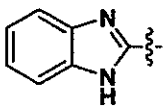
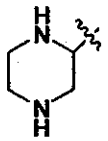
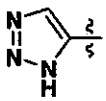
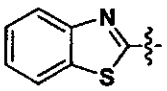
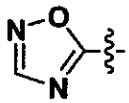
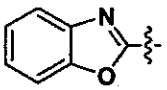
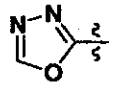
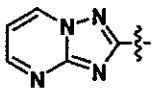
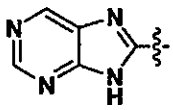
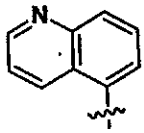
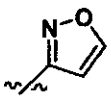
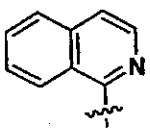
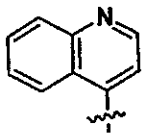
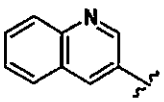
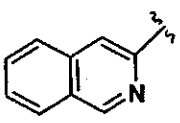
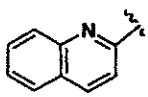
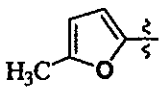
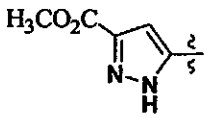
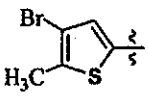
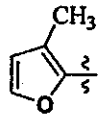
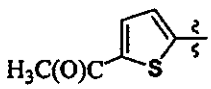
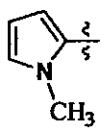
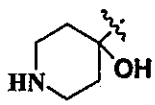
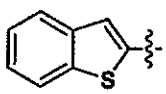
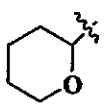
668A 668B		669A 669B		670A 670B	
671A 671B		672A 672B		673A 673B	
674A 674B		675A 675B		676A 676B	
677A 677B		678A 678B		679A 679B	
680A 680B		681A 681B		682A 682B	
683A 683B		684A 684B		685A 685B	
686A 686B		687A 687B		688A 688B	
689A 689B		690A 690B		691A 691B	
692A 692B		693A 693B		694A 694B	
695A 695B		696A 696B		697A 697B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
698A 698B		699A 699B		700A 700B	
701A 701B		702A 702B		703A 703B	
704A 704B		705A 705B		706A 706B	
707A 707B		708A 708B		709A 709B	
710A 710B		711A 711B		712A 712B	
713A 713B		714A 714B		715A 715B	
716A 716B		717A 717B		718A 718B	
719A 719B		720A 720B		721A 721B	
722A 722B		723A 723B		724A 724B	
725A 725B		726A 726B		727A 727B	
728A 728B		729A 729B		730A 730B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
731A 731B		732A 732B		733A 733B	
734A 734B		735A 735B		736A 736B	
737A 737B		738A 738B		739A 739B	

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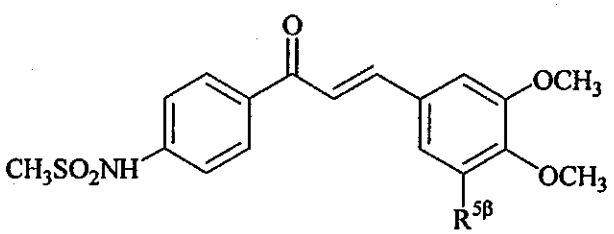
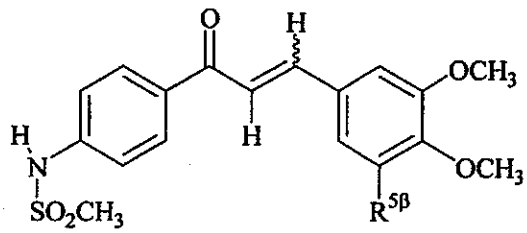
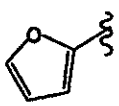
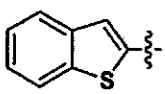
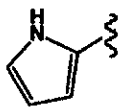
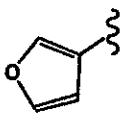
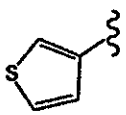
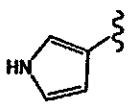
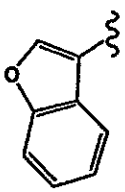
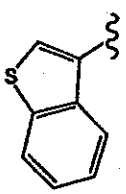
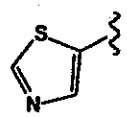
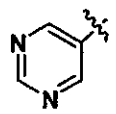
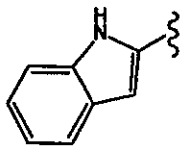
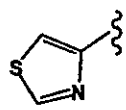
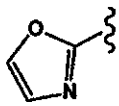
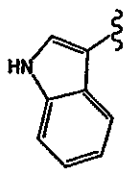
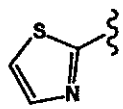
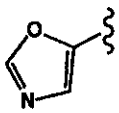
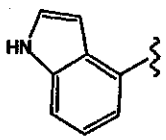
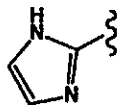
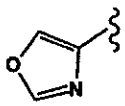
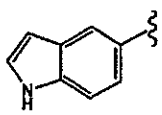
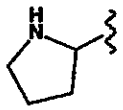
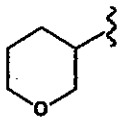
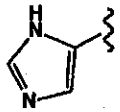
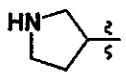
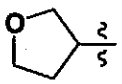
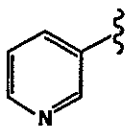
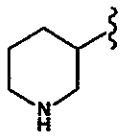
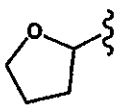
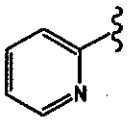
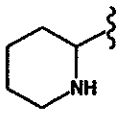
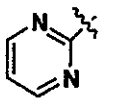
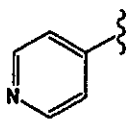
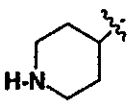
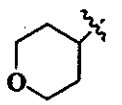
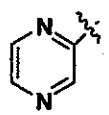
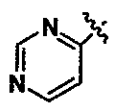
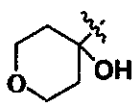
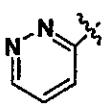
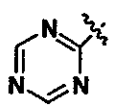
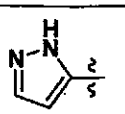
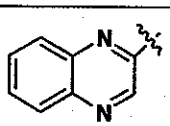
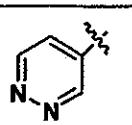


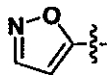
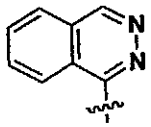
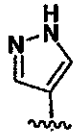
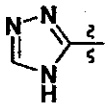
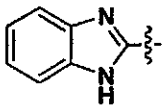
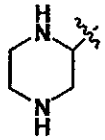
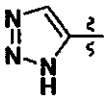
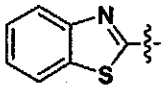
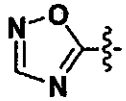
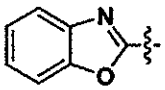
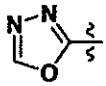
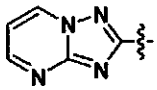
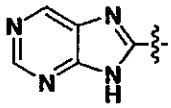
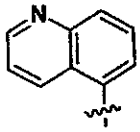
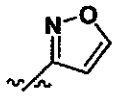
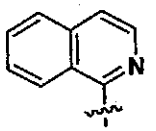
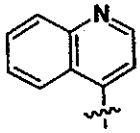
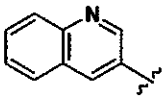
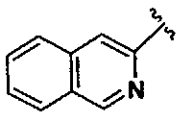
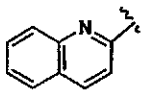
A



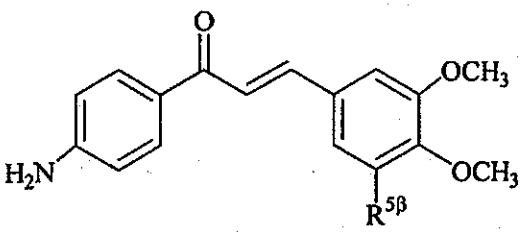
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
740A 740B		741A 741B		742A 742B	
743A 743B		744A 744B		745A 745B	
746A 746B		747A 747B		748A 748B	

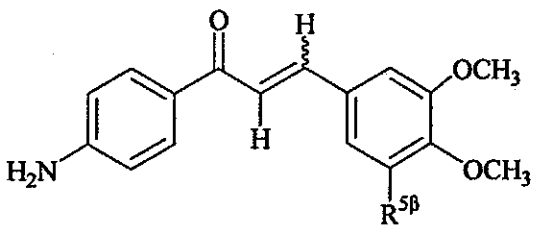
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
749A 749B		750A 750B		751A 751B	
752A 752B		753A 753B		754A 754B	
755A 755B		756A 756B		757A 757B	
758A 758B		759A 759B		760A 760B	
761A 761B		762A 762B		763A 763B	
764A 764B		765A 765B		766A 766B	
767A 767B		768A 768B		769A 769B	
770A 770B		771A 771B		772A 772B	
773A 773B		774A 774B		775A 775B	
776A 776B		777A 777B		778A 778B	
779A 779B		780A 780B		781A 781B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
782A 782B		783A 783B		784A 784B	
785A 785B		786A 786B		787A 787B	
788A 788B		789A 789B		790A 790B	
791A 791B		792A 792B		793A 793B	
794A 794B		795A 795B		796A 796B	
797A 797B		798A 798B		799A 799B	
800A 800B		801A 801B		802A 802B	

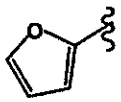
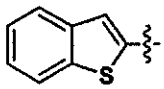
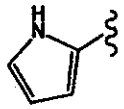
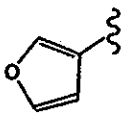
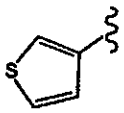
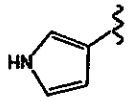
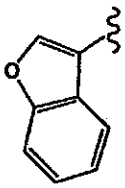
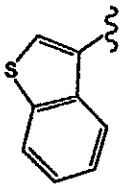
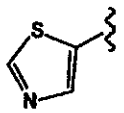
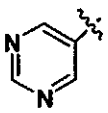
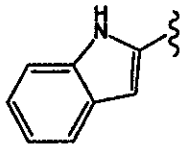
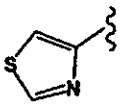
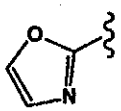
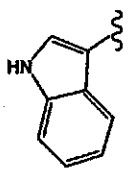
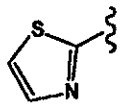
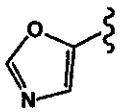
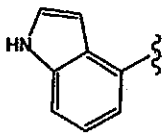
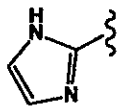
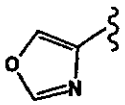
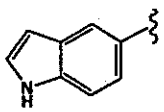
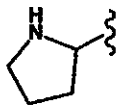
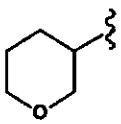
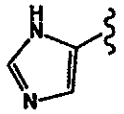
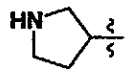
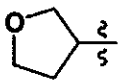
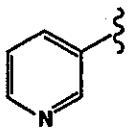
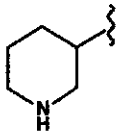
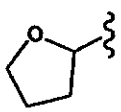
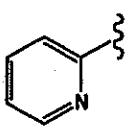
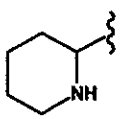
Example Table 10. Substituted 1-{4-(Amino)phenyl}-3-[3,4-dimethoxy-(5-heteroaryl or 5-heterocylic)phenyl]-2-propen-1-ones.



A



B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
803A 803B		804A 804B		805A 805B	
806A 806B		807A 807B		808A 808B	
809A 809B		810A 810B		811A 811B	
812A 812B		813A 813B		814A 814B	
815A 815B		816A 816B		817A 817B	
818A 818B		819A 819B		820A 820B	
821A 821B		822A 822B		823A 823B	
824A 824B		825A 825B		826A 826B	
827A 827B		828A 828B		829A 829B	
830A 830B		831A 831B		832A 832B	

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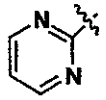
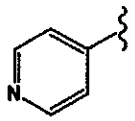
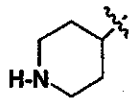
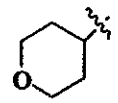
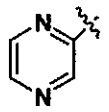
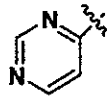
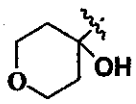
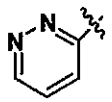
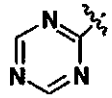
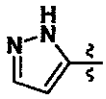
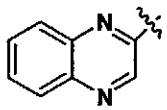
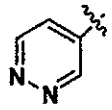
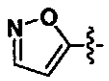
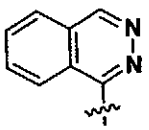
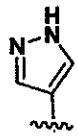
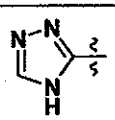
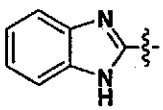
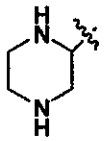
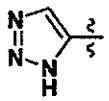
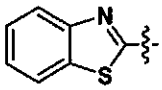
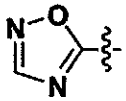
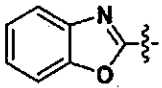
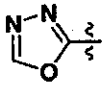
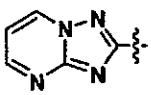
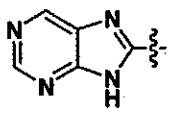
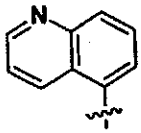
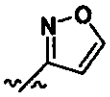
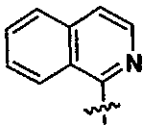
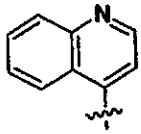
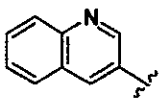
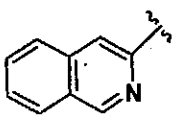
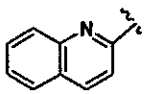
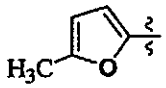
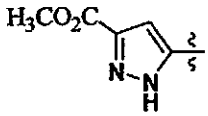
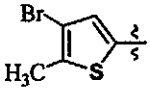
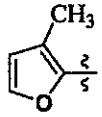
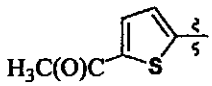
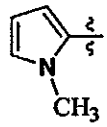
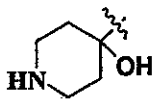
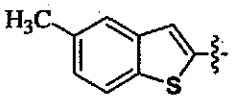
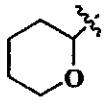
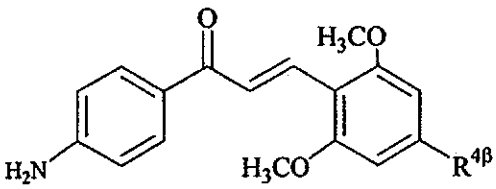
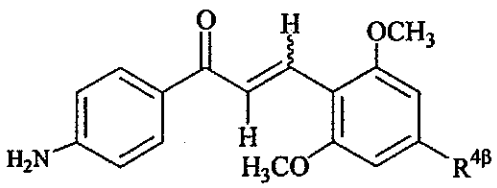
833A 833B		834A 834B		835A 835B	
836A 836B		837A 837B		838A 838B	
839A 839B		840A 840B		841A 841B	
842A 842B		843A 843B		844A 844B	
845A 845B		846A 846B		847A 847B	
848A 848B		849A 849B		850A 850B	
851A 851B		852A 852B		853A 853B	
854A 854B		855A 855B		856A 856B	
857A 857B		858A 858B		859A 859B	
860A 860B		861A 861B		862A 862B	
863A 863B		864A 864B		865A 865B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
866A 866B		867A 867B		868A 868B	
869A 869B		870A 870B		871A 871B	
872A 872B		873A 873B		874A 874B	

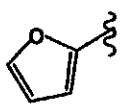
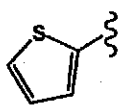
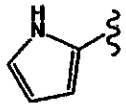
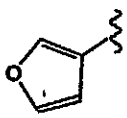
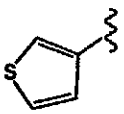
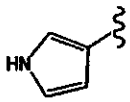
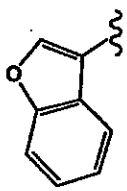
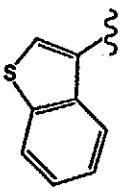
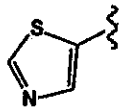
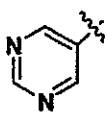
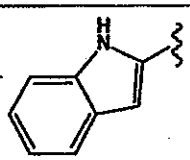
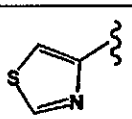
Example Table 11. Substituted 1-{4-(Amino)phenyl}-3-[2,6-dimethoxy-(4-heteroaryl or 4-heterocylic)-phenyl]-2-propen-1-ones.

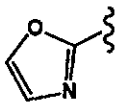
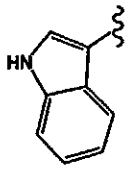
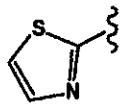
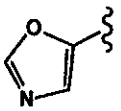
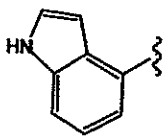
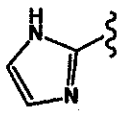
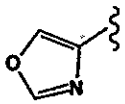
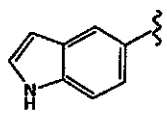
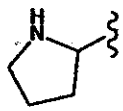
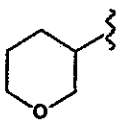
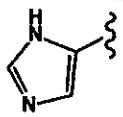
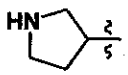
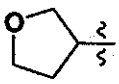
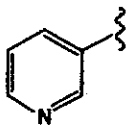
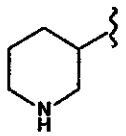
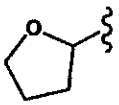
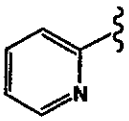
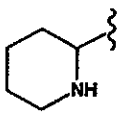
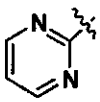
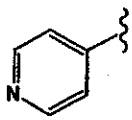
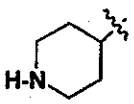
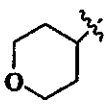
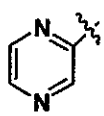
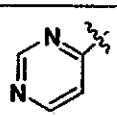
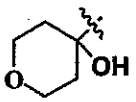
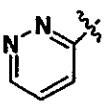
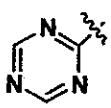
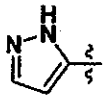
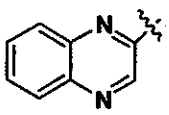
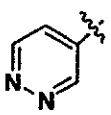


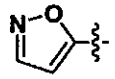
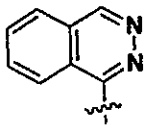
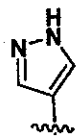
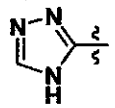
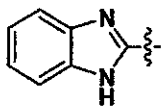
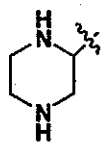
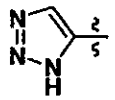
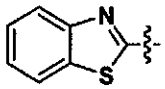
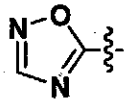
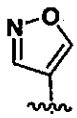
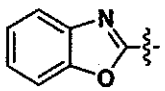
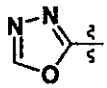
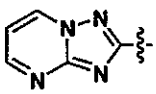
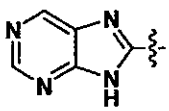
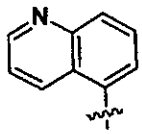
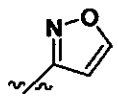
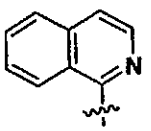
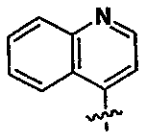
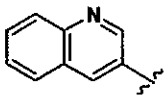
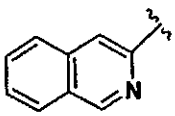
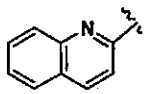
A



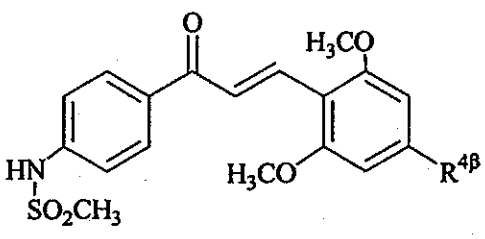
B

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
875A 875B		876A 876B		877A 877B	
878A 878B		879A 879B		880A 880B	
881A 881B		882A 882B		883A 883B	
884A 884B		885A 885B		886A 886B	

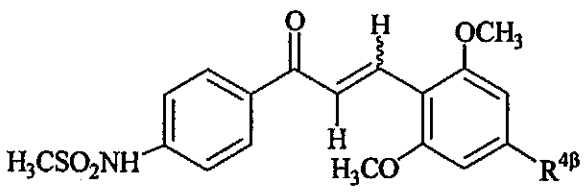
Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
887A 887B		888A 888B		889A 889B	
890A 890B		891A 891B		892A 892B	
893A 893B		894A 894B		895A 895B	
896A 896B		897A 897B		898A 898B	
899A 899B		900A 900B		901A 901B	
902A 902B		903A 903B		904A 904B	
905A 905B		906A 906B		907A 907B	
908A 908B		909A 909B		910A 910B	
911A 911B		912A 912B		913A 913B	
914A 914B		915A 915B		916A 916B	

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
917A 917B		918A 918B		919A 919B	
920A 920B		921A 921B		922A 922B	
923A 923B		924A 924B		925A 925B	
926A 926B		927A 927B		928A 928B	
929A 929B		930A 930B		931A 931B	
932A 932B		933A 933B		934A 934B	
935A 935B		936A 936B		937A 937B	

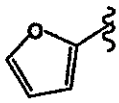
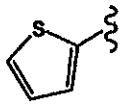
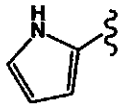
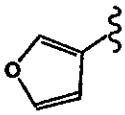
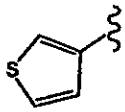
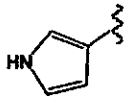
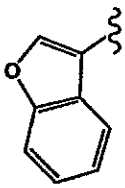
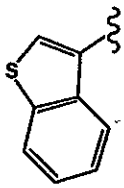
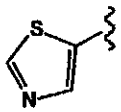
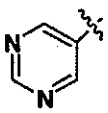
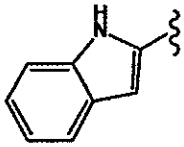
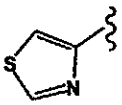
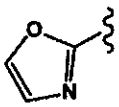
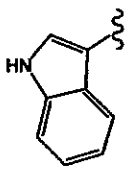
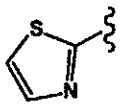
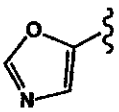
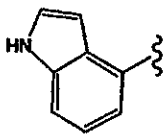
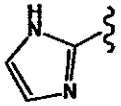
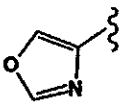
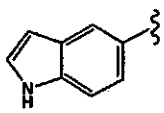
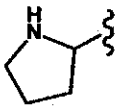
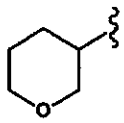
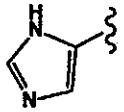
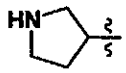
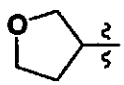
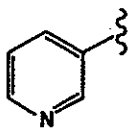
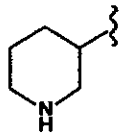
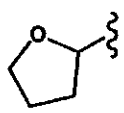
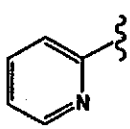
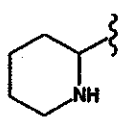
Example Table 12. Substituted 1-{4-(Methanesulfonylamino)phenyl}-3-[2,6-dimethoxy-(4-heteroaryl or 4-heterocylic)phenyl]-2-propen-1-ones.

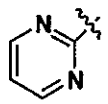
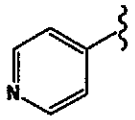
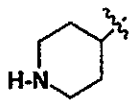
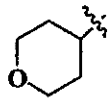
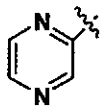
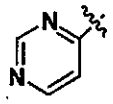
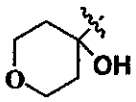
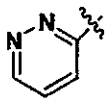
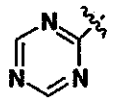
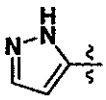
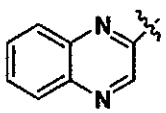
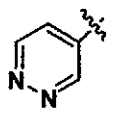
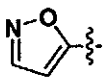
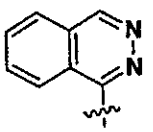
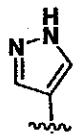
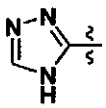
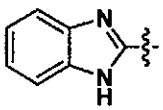
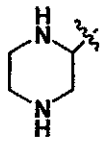
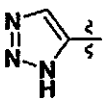
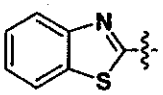
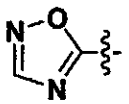
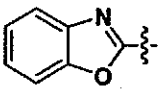
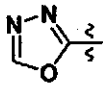
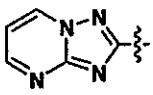
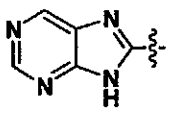
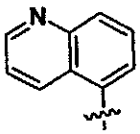
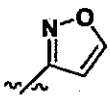
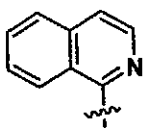
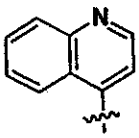
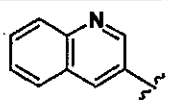
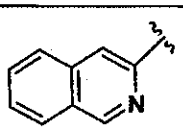
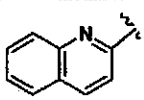


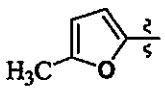
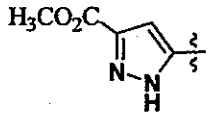
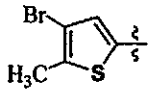
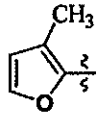
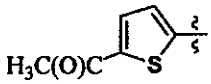
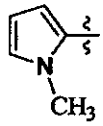
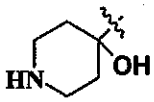
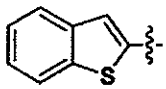
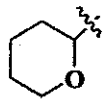
A



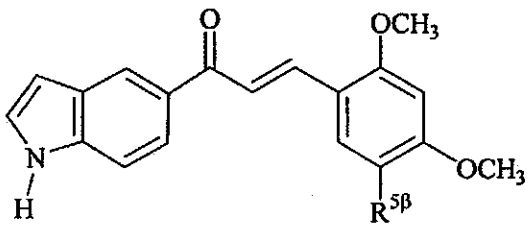
B

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
938A 938B		939A 939B		940A 940B	
941A 941B		942A 942B		943A 943B	
944A 944B		945A 945B		946A 946B	
947A 947B		948A 948B		949A 949B	
950A 950B		951A 951B		952A 952B	
953A 953B		954A 954B		955A 955B	
956A 956B		957A 957B		958A 958B	
959A 959B		960A 960B		961A 961B	
962A 962B		963A 963B		964A 964B	
965A 965B		966A 966B		967A 967B	

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
968A 968B		969A 969B		970A 970B	
971A 971B		972A 972B		973A 973B	
974A 974B		975A 975B		976A 976B	
977A 977B		978A 978B		979A 979B	
980A 980B		981A 981B		982A 982B	
983A 983B		984A 984B		985A 985B	
986A 986B		987A 987B		988A 988B	
989A 989B		990A 990B		991A 991B	
992A 992B		993A 993B		994A 994B	
995A 995B		996A 996B		997A 997B	
998A 998B		999A 999B		1000A 1000B	

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
1001A 1001B		1002A 1002B		1003A 1003B	
1004A 1004B		1005A 1005B		1006A 1006B	
1007A 1007B		1008A 1008B		1009A 1009B	

Example Table 13. Substituted 1-(1*H*-Indol-5-yl)-3-{2,4-dimethoxy-5-(heteroaryl or heterocyclic)phenyl}-propen-2-ones.



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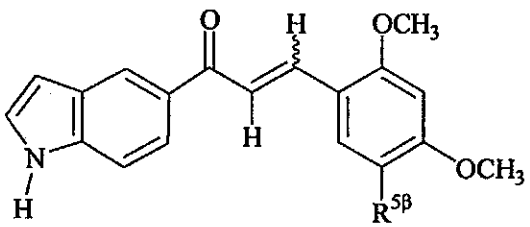
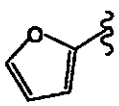
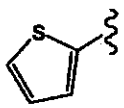
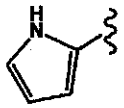
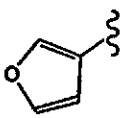
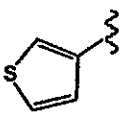
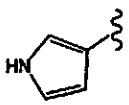
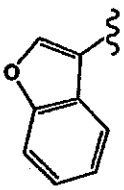
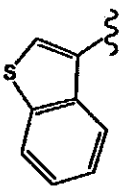
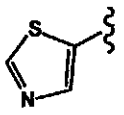
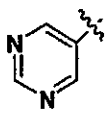
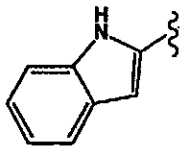
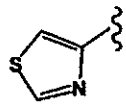
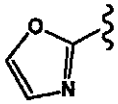
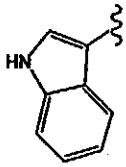
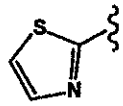
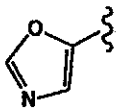
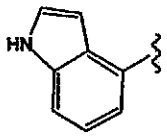
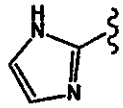
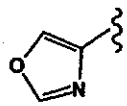
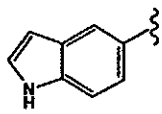
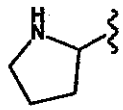
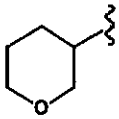
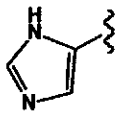
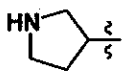
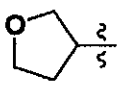
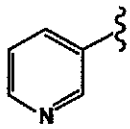
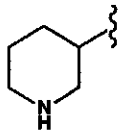
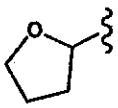
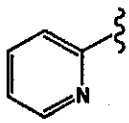
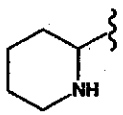
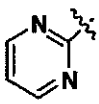
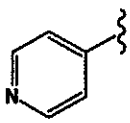
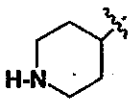
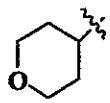
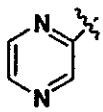
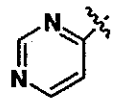
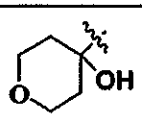
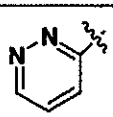
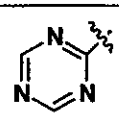
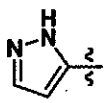
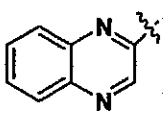
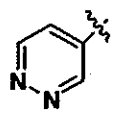
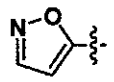
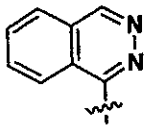
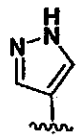
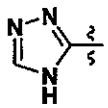
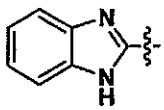
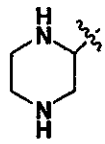
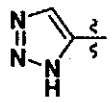
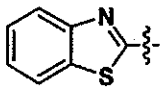
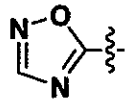
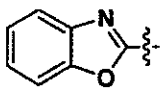
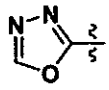
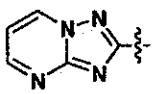
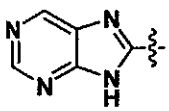
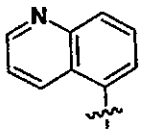
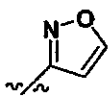
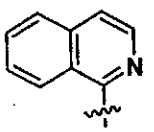
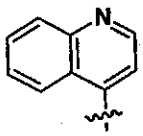
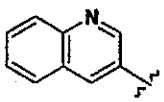
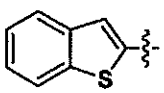
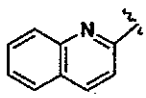


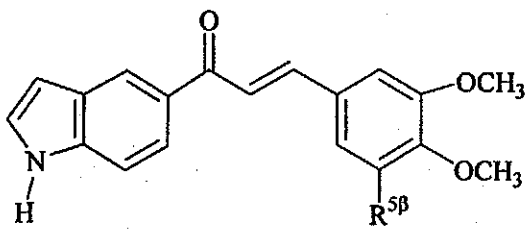
B .

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1010A 1010B		1011A 1011B		1012A 1012B	
1013A 1013B		1014A 1014B		1015A 1015B	
1016A 1016B		1017A 1017B		1018A 1018B	

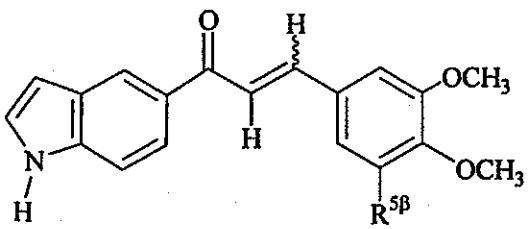
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1019A 1019B		1020A 1020B		1021A 1021B	
1022A 1022B		1023A 1023B		1024A 1024B	
1025A 1025B		1026A 1026B		1027A 1027B	
1028A 1028B		1029A 1029B		1030A 1030B	
1031A 1031B		1032A 1032B		1033A 1033B	
1034A 1034B		1035A 1035B		1036A 1036B	
1037A 1037B		1038A 1038B		1039A 1039B	
1040A 1040B		1041A 1041B		1042A 1042B	
1043A 1043B		1044A 1044B		1045A 1045B	
1046A 1046B		1047A 1047B		1048A 1048B	
1049A 1049B		1050A 1050B		1051A 1051B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1052A 1052B		1053A 1053B		1054A 1054B	
1055A 1055B		1056A 1056B		1057A 1057B	
1058A 1058B		1059A 1059B		1060A 1060B	
1061A 1061B		1062A 1062B		1063A 1063B	
1064A 1064B		1065A 1065B		1066A 1066B	
1067A 1067B		1068A 1068B		1069A 1069B	
1070A 1070B		1071A 1071B		1072A 1072B	

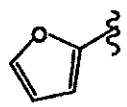
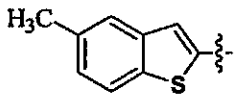
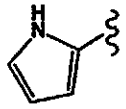
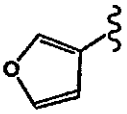
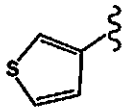
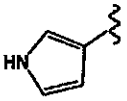
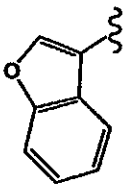
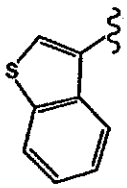
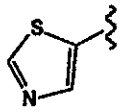
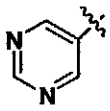
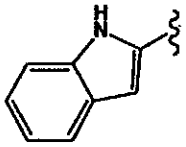
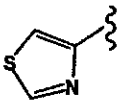
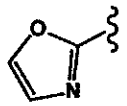
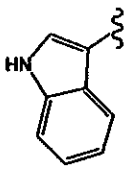
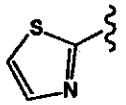
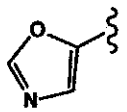
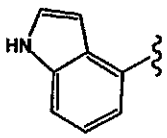
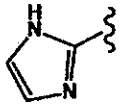
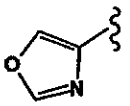
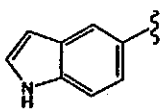
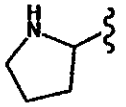
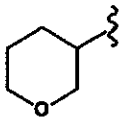
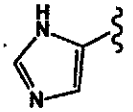
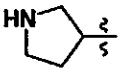
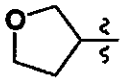
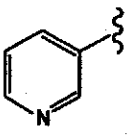
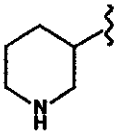
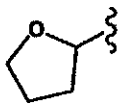
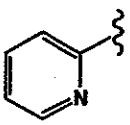
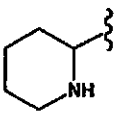
Example Table 14. Substituted 1-(1*H*-Indol-5-yl)-3-{3,4-dimethoxy-5-(heteroaryl or heterocyclic)phenyl}-propen-2-ones.

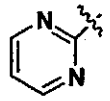
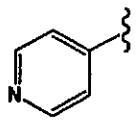
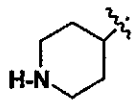
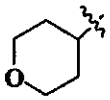
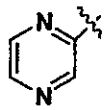
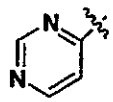
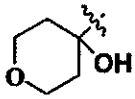
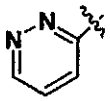
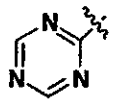
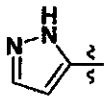
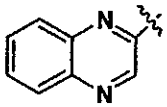
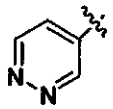
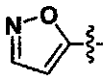
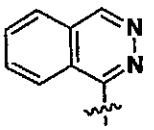
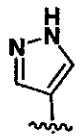
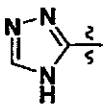
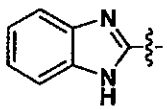
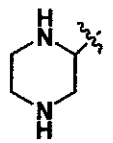
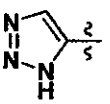
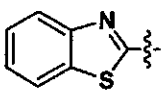
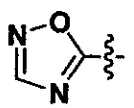
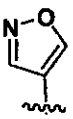
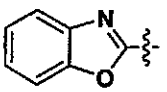
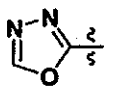
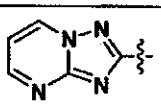
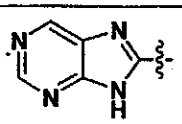
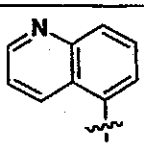
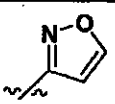
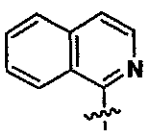
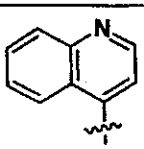
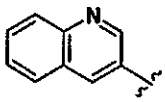
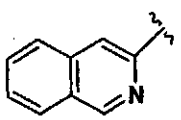
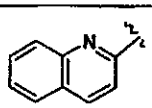


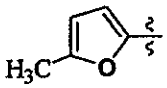
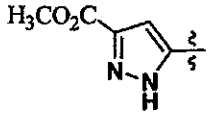
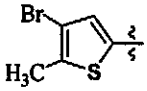
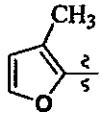
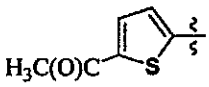
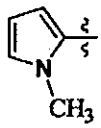
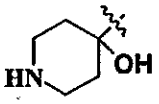
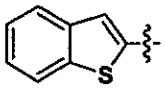
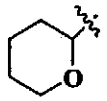
A



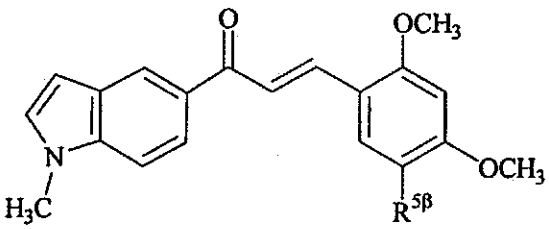
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1073A 1073B		1074A 1074B		1075A 1075B	
1076A 1076B		1077A 1077B		1078A 1078B	
1079A 1079B		1080A 1080B		1081A 1081B	
1082A 1082B		1083A 1083B		1084A 1084B	
1085A 1085B		1086A 1086B		1087A 1087B	
1088A 1088B		1089A 1089B		1090A 1090B	
1091A 1091B		1092A 1092B		1093A 1093B	
1094A 1094B		1095A 1095B		1096A 1096B	
1097A 1097B		1098A 1098B		1099A 1099B	
1100A 1100B		1101A 1101B		1102A 1102B	

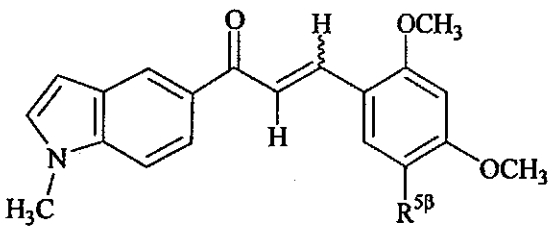
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1103A 1103B		1104A 1104B		1105A 1105B	
1106A 1106B		1107A 1107B		1108A 1108B	
1109A 1109B		1110A 1110B		1111A 1111B	
1112A 1112B		1113A 1113B		1114A 1114B	
1115A 1115B		1116A 1116B		1117A 1117B	
1118A 1118B		1119A 1119B		1120A 1120B	
1121A 1121B		1122A 1122B		1123A 1123B	
1124A 1124B		1125A 1125B		1126A 1126B	
1127A 1127B		1128A 1128B		1129A 1129B	
1130A 1130B		1131A 1131B		1132A 1132B	
1133A 1133B		1134A 1134B		1135A 1135B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1136A 1136B		1137A 1137B		1138A 1138B	
1139A 1139B		1140A 1140B		1141A 1141B	
1142A 1142B		1143A 1143B		1144A 1144B	

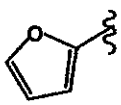
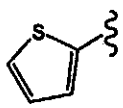
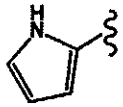
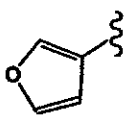
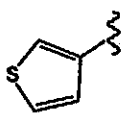
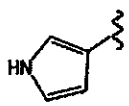
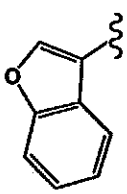
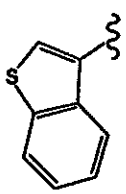
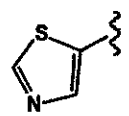
Example Table 15. Substituted 1-(1*H*-1-Methyl-indol-5-yl)-3-{2,4-dimethoxy-5-(heteroaryl or heterocyclic)phenyl}-propen-2-ones.

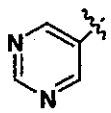
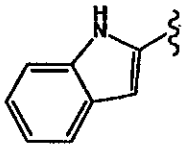
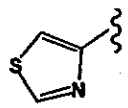
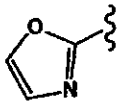
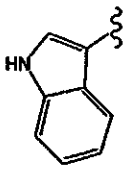
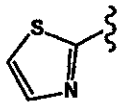
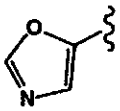
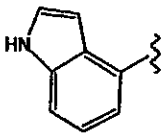
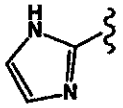
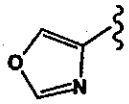
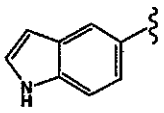
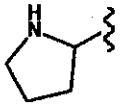
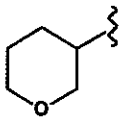
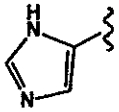
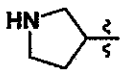
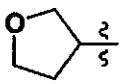
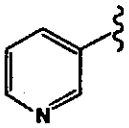
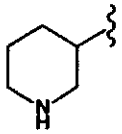
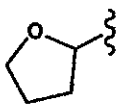
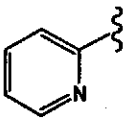
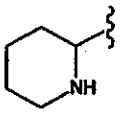
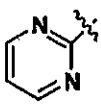
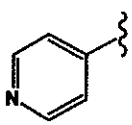
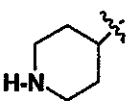
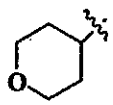
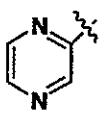
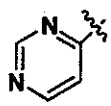
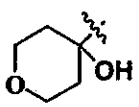
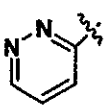
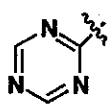
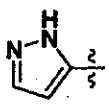
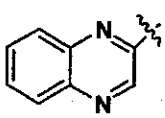
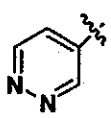


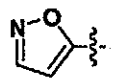
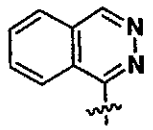
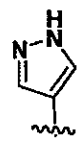
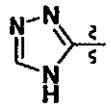
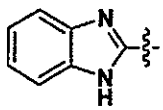
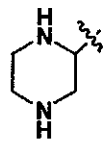
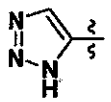
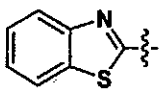
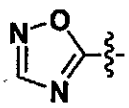
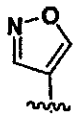
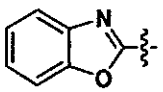
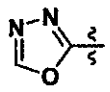
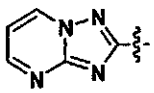
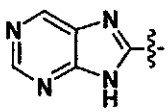
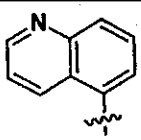
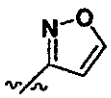
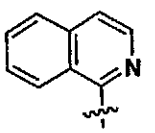
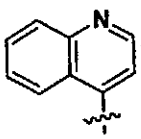
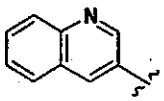
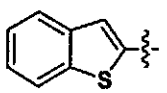
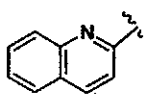
A



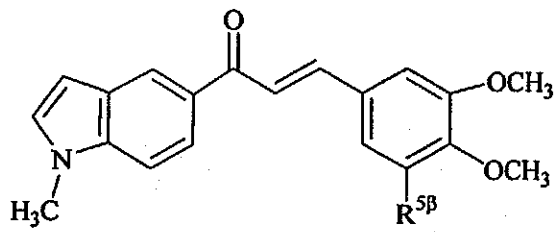
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1145A 1145B		1146A 1146B		1147A 1147B	
1148A 1148B		1149A 1149B		1150A 1150B	
1151A 1151B		1152A 1152B		1153A 1153B	

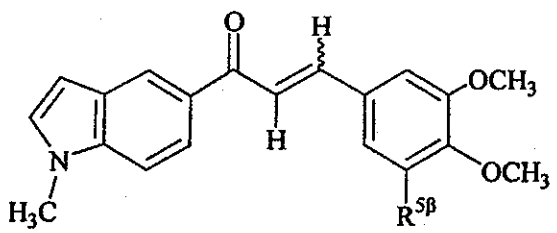
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1154A 1154B		1155A 1155B		1156A 1156B	
1157A 1157B		1158A 1158B		1159A 1159B	
1160A 1160B		1161A 1161B		1162A 1162B	
1163A 1163B		1164A 1164B		1165A 1165B	
1166A 1166B		1167A 1167B		1168A 1168B	
1169A 1169B		1170A 1170B		1171A 1171B	
1172A 1172B		1173A 1173B		1174A 1174B	
1175A 1175B		1176A 1176B		1177A 1177B	
1178A 1178B		1179A 1179B		1180A 1180B	
1181A 1181B		1182A 1182B		1183A 1183B	
1184A 1184B		1185A 1185B		1186A 1186B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1187A 1187B		1188A 1188B		1189A 1189B	
1190A 1190B		1191A 1191B		1192A 1192B	
1193A 1193B		1194A 1194B		1195A 1195B	
1196A 1196B		1197A 1197B		1198A 1198B	
1199A 1199B		1200A 1200B		1201A 1201B	
1202A 1202B		1203A 1203B		1204A 1204B	
1205A 1205B		1206A 1206B		1207A 1207B	

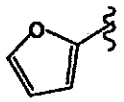
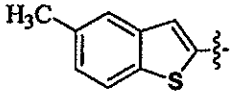
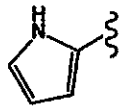
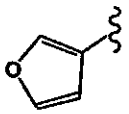
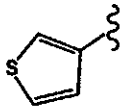
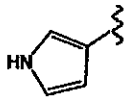
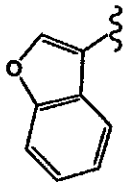
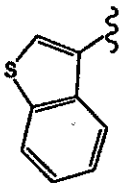
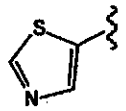
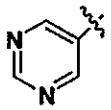
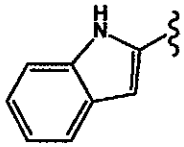
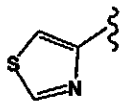
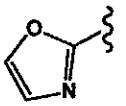
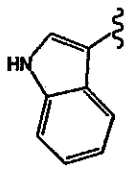
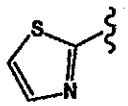
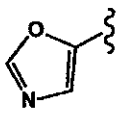
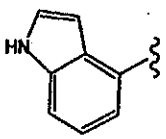
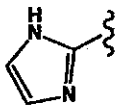
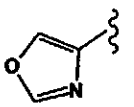
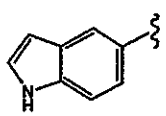
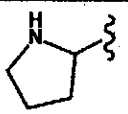
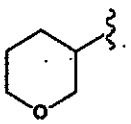
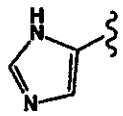
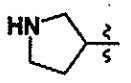
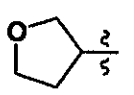
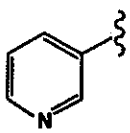
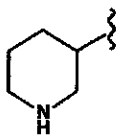
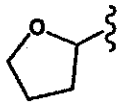
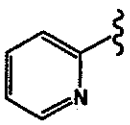
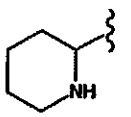
Example Table 17. Substituted 1-(1*H*-1-Methyl-indol-5-yl)-3-{3,4-dimethoxy-5-(heteroaryl or heterocyclic)phenyl}-propen-2-ones.

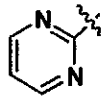
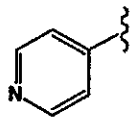
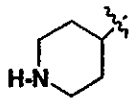
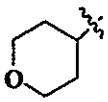
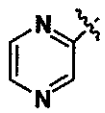
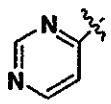
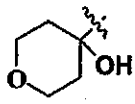
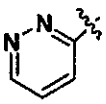
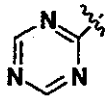
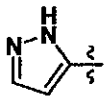
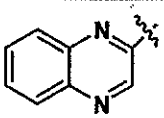
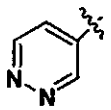
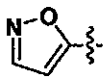
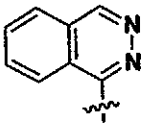
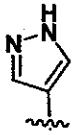
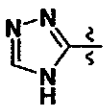
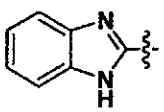
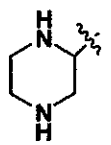
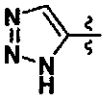
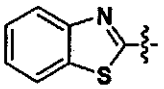
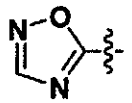
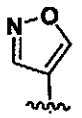
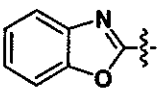
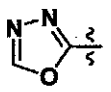
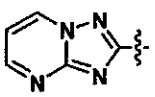
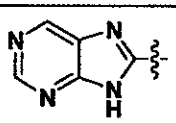
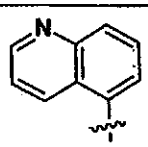
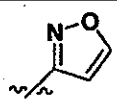
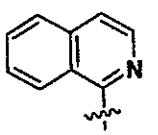
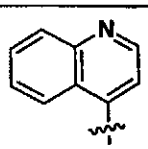
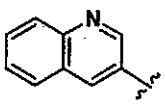
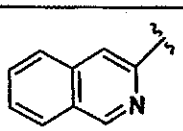
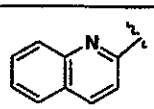


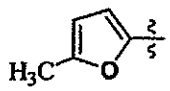
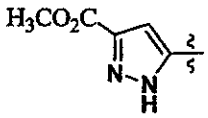
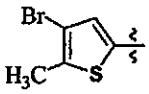
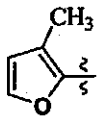
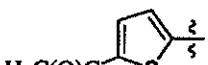
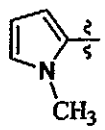
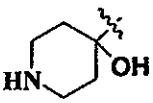
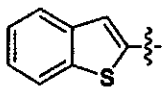
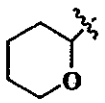
A



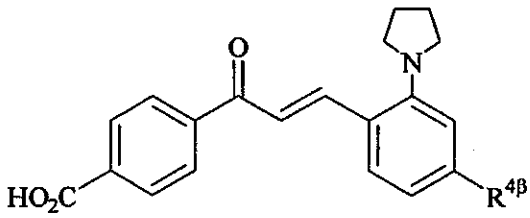
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1208A 1208B		1209A 1209B		1210A 1210B	
1211A 1211B		1212A 1212B		1213A 1213B	
1214A 1214B		1215A 1215B		1216A 1216B	
1217A 1217B		1218A 1218B		1219A 1219B	
1220A 1220B		1221A 1221B		1222A 1222B	
1223A 1223B		1224A 1224B		1225A 1225B	
1226A 1226B		1227A 1227B		1228A 1228B	
1229A 1229B		1230A 1230B		1231A 1231B	
1232A 1232B		1233A 1233B		1234A 1234B	
1235A 1235B		1236A 1236B		1237A 1237B	

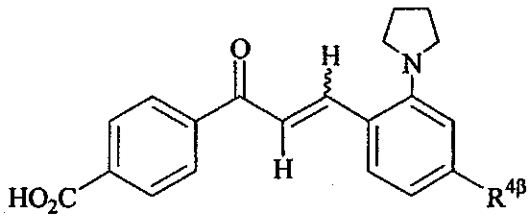
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1238A 1238B		1239A 1239B		1240A 1240B	
1241A 1241B		1242A 1242B		1243A 1243B	
1244A 1244B		1245A 1245B		1246A 1246B	
1247A 1247B		1248A 1248B		1249A 1249B	
1250A 1250B		1251A 1251B		1252A 1252B	
1253A 1253B		1254A 1254B		1255A 1255B	
1256A 1256B		1257A 1257B		1258A 1258B	
1259A 1259B		1260A 1260B		1261A 1261B	
1262A 1262B		1263A 1263B		1264A 1264B	
1265A 1265B		1266A 1266B		1267A 1267B	
1268A 1268B		1269A 1269B		1270A 1270B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1271A 1271B		1272A 1272B		1273A 1273B	
1274A 1274B		1275A 1275B		1276A 1276B	
1277A 1277B		1278A 1278B		1279A 1279B	

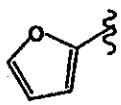
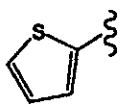
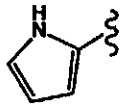
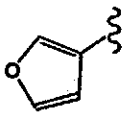
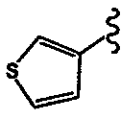
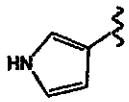
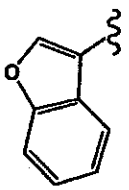
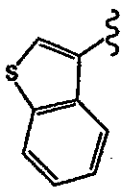
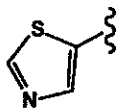
Example Table 17. Substituted 4-[3-{2-(Pyrrolidin-1-yl)-(4-heteroaryl or 4-heterocyclic)-phenyl}-acryloyl]-benzoic Acids.

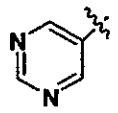
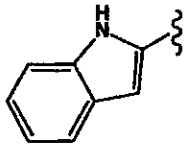
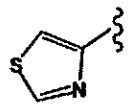
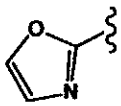
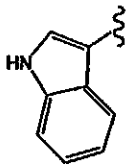
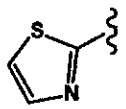
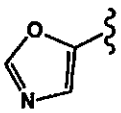
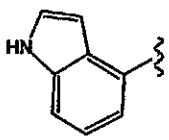
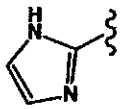
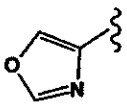
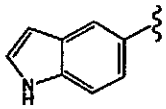
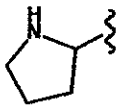
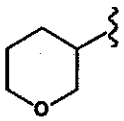
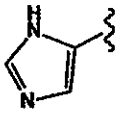
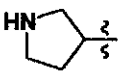
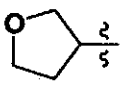
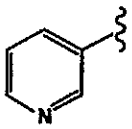
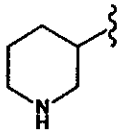
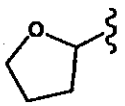
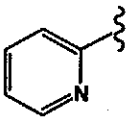
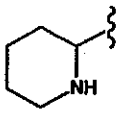
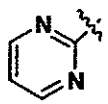
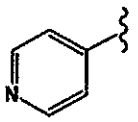
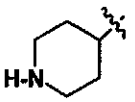
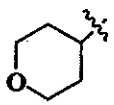
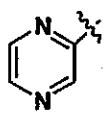
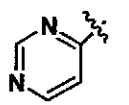
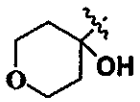
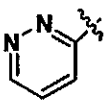
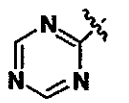
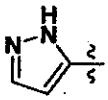
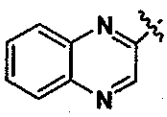
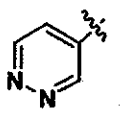


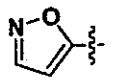
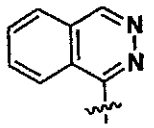
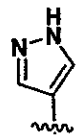
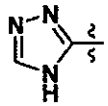
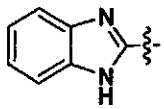
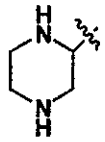
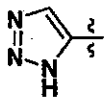
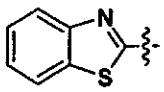
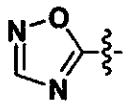
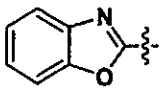
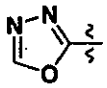
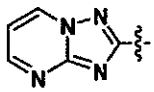
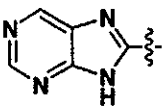
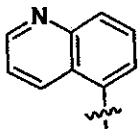
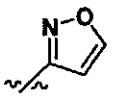
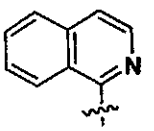
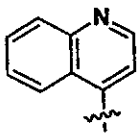
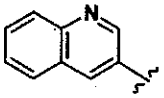
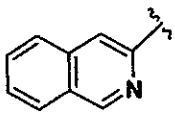
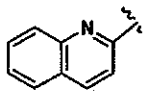
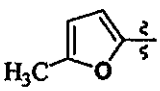
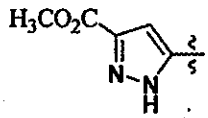
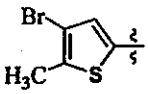
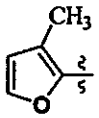
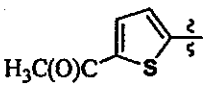
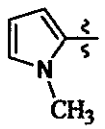
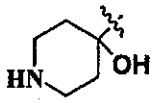
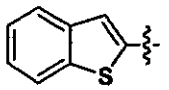
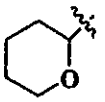
A



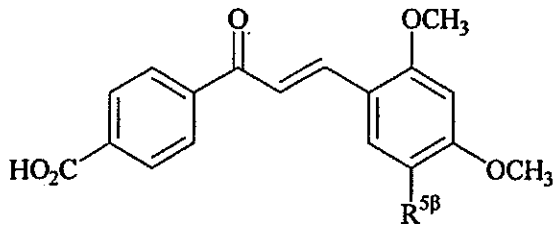
B

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
1280A 1280B		1281A 1281B		1282A 1282B	
1283A 1283B		1284A 1284B		1285A 1285B	
1286A 1286B		1287A 1287B		1288A 1288B	

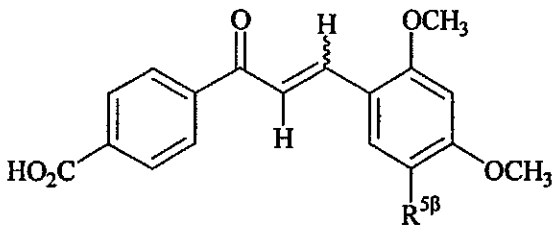
Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
1289A 1289B		1290A 1290A		1291A 1291B	
1292A 1292B		1293A 1293B		1294A 1294B	
1295A 1295B		1296A 1296B		1297A 1297B	
1298A 1298B		1299A 1299B		1300A 1300B	
1301A 1301B		1302A 1302B		1303A 1303B	
1304A 1304B		1305A 1305B		1306A 1306B	
1307A 1307B		1308A 1308B		1309A 1309B	
1310A 1310B		1311A 1311B		1312A 1312B	
1313A 1313B		1314A 1314B		1315A 1315B	
1316A 1316B		1317A 1317B		1318A 1318B	
1319A 1319B		1320A 1320B		1321A 1321B	

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
1322A 1322B		1323A 1323B		1324A 1324B	
1325A 1325B		1326A 1326B		1327A 1327B	
1328A 1328B		1329A 1329B		1330A 1330B	
1331A 1331B		1332A 1332B		1333A 1333B	
1334A 1334B		1335A 1335B		1336A 1336B	
1337A 1337B		1338A 1338B		1339A 1339B	
1340A 1340B		1341A 1341B		1342A 1342B	
1343A 1343B		1344A 1344B		1345A 1345B	
1346A 1346B		1347A 1347B		1348A 1348B	
1349A 1349B		1350A 1350B		1351A 1351B	

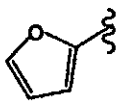
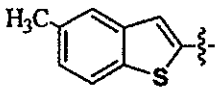
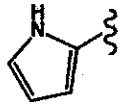
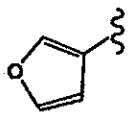
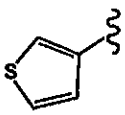
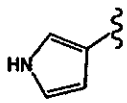
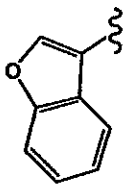
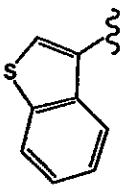
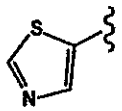
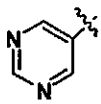
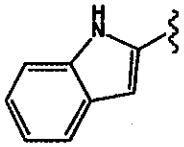
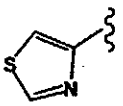
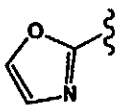
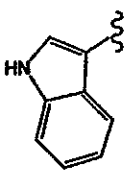
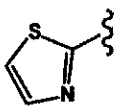
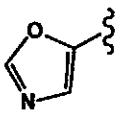
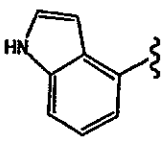
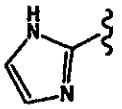
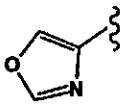
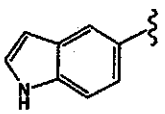
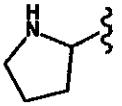
Example Table 18. Substituted 4-[3-{(5-Heteroaryl or 5-heterocyclic)-2,4-dimethoxyphenyl}-acryloyl]-benzoic Acids.

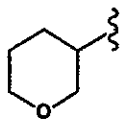
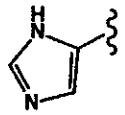
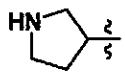
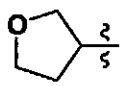
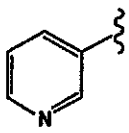
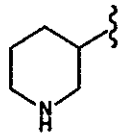
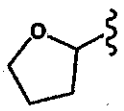
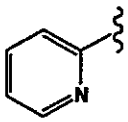
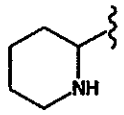
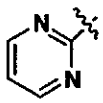
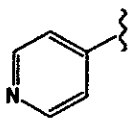
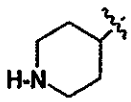
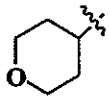
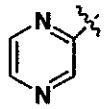
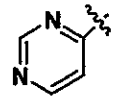
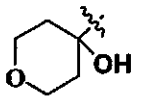
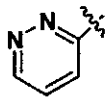
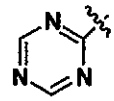
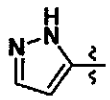
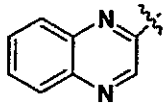
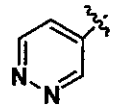
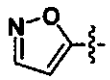
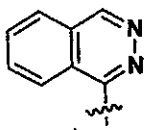
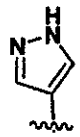
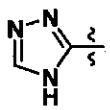
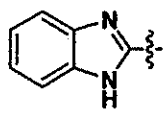
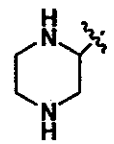
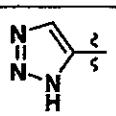
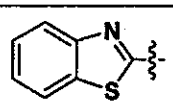
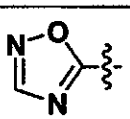
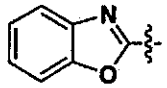
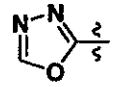


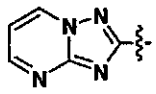
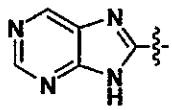
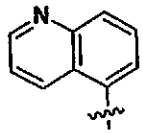
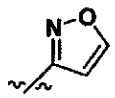
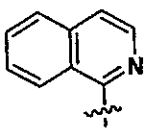
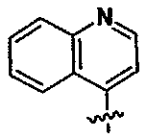
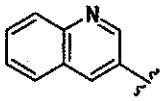
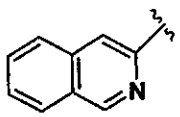
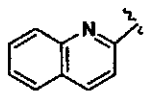
A



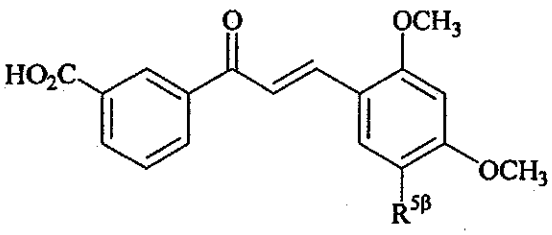
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1352A 1352B		1353A 1353B		1354A 1354B	
1355A 1355B		1356A 1356B		1357A 1357B	
1358A 1358B		1359A 1359B		1360A 1360B	
1361A 1361B		1362A 1362B		1363A 1363B	
1364A 1364B		1365A 1365B		1366A 1366B	
1367A 1367B		1368A 1368B		1369A 1369B	
1370A 1370B		1371A 1371B		1372A 1372B	

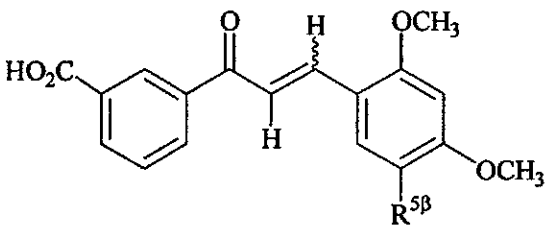
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1373A 1373B		1374A 1374B		1375A 1375B	
1376A 1376B		1377A 1377B		1378A 1378B	
1379A 1379B		1380A 1380B		1381A 1381B	
1382A 1382B		1383A 1383B		1384A 1384B	
1385A 1385B		1386A 1386B		1387A 1387B	
1388A 1388B		1389A 1389B		1390A 1390B	
1391A 1391B		1392A 1392B		1393A 1393B	
1394A 1394B		1395A 1395B		1396A 1396B	
1397A 1397B		1398A 1398B		1399A 1399B	
1400A 1400B		1401A 1401B		1402A 1402B	
1403A 1403B		1404A 1404B		1405A 1405B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1406A 1406B		1407A 1407B		1408A 1408B	
1409A 1409B		1410A 1410B		1411A 1411B	
1412A 1412B		1413A 1413B		1414A 1414B	

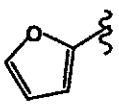
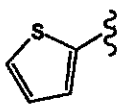
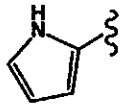
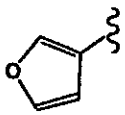
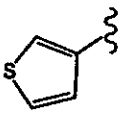
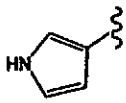
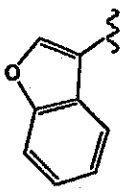
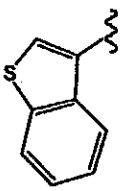
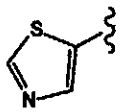
Example Table 19. Substituted 3-[3-{(5-Heteroaryl or 5-heterocyclic)-2,4-dimethoxyphenyl}-acryloyl]-benzoic Acids.

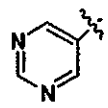
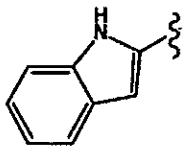
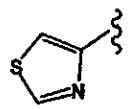
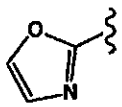
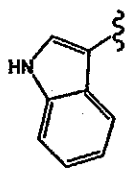
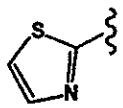
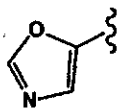
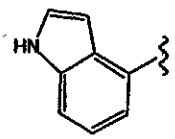
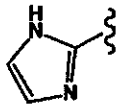
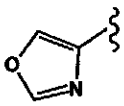
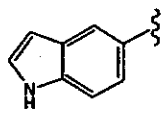
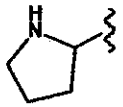
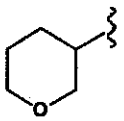
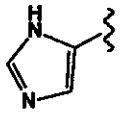
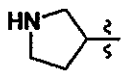
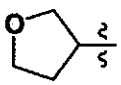
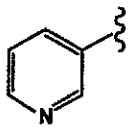
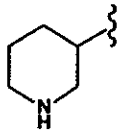
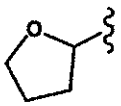
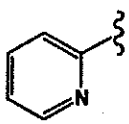
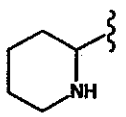
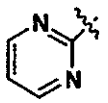
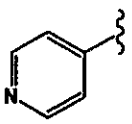
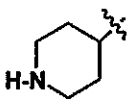
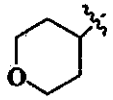
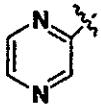
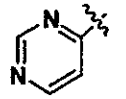
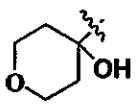
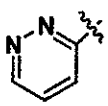
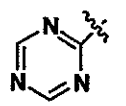
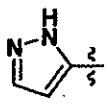
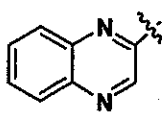
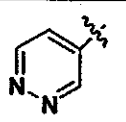


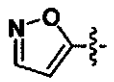
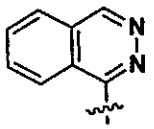
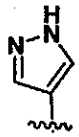
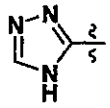
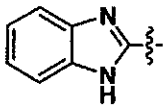
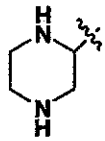
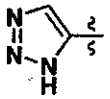
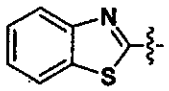
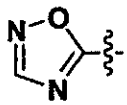
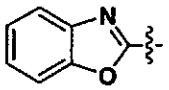
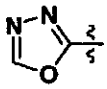
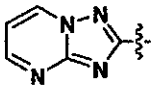
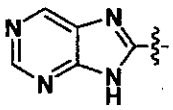
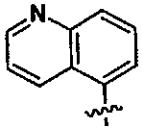
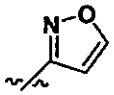
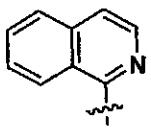
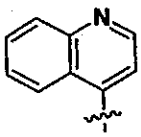
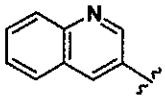
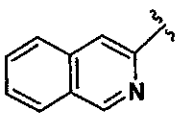
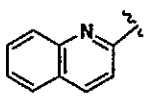
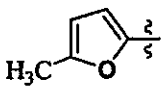
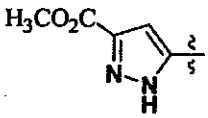
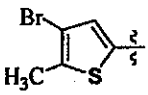
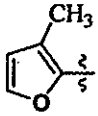
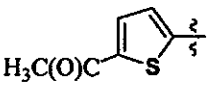
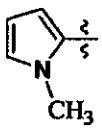
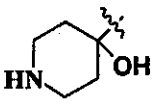
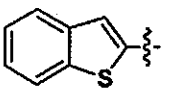
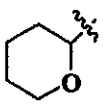
A



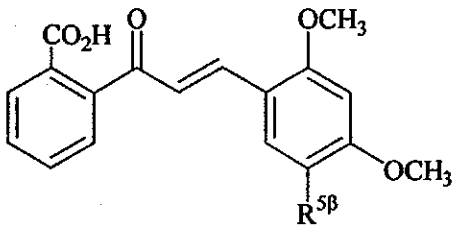
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1415A 1415B		1416A 1416B		1417A 1417B	
1418A 1418B		1419A 1419B		1420A 1420B	
1421A 1421B		1422A 1422B		1423A 1423B	

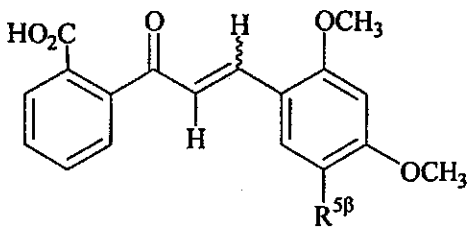
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1424A 1424B		1425A 1425B		1426A 1426B	
1427A 1427B		1428A 1428B		1429A 1429B	
1430A 1430B		1431A 1431B		1432A 1432B	
1433A 1433B		1434A 1434B		1435A 1435B	
1436A 1436B		1437A 1437B		1438A 1438B	
1439A 1439B		1440A 1440B		1441A 1441B	
1442A 1442B		1443A 1443B		1444A 1444B	
1445A 1445B		1446A 1446B		1447A 1447B	
1448A 1448B		1449A 1449B		1450A 1450B	
1451A 1451B		1452A 1452B		1453A 1453B	
1454A 1454B		1455A 1455B		1456A 1456B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1457A 1457B		1458A 1458B		1459A 1459B	
1460A 1460B		1461A 1461B		1462A 1462B	
1463A 1463B		1464A 1464B		1465A 1465B	
1466A 1466B		1467A 1467B		1468A 1468B	
1469A 1469B		1470A 1470B		1471A 1471B	
1473A 1473B		1474A 1474B		1475A 1475B	
1476A 1476B		1477A 1477B		1478A 1478B	
1479A 1479B		1480A 1480B		1481A 1481B	
1482A 1482B		1483A 1483B		1484A 1484B	
1485A 1485B		1486A 1486B		1487A 1487B	

Example Table 20. Substituted 2-[3-{(5-Heteroaryl or 5-heterocyclic)-2,4-dimethoxyphenyl}-acryloyl]-benzoic Acids.



A



B

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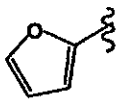
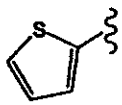
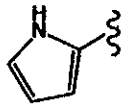
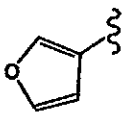
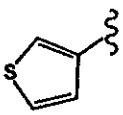
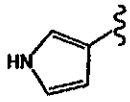
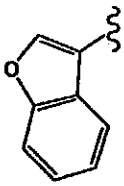
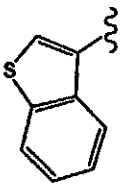
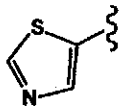
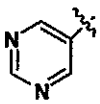
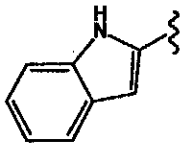
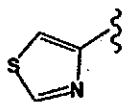
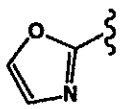
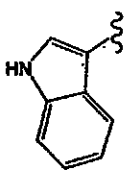
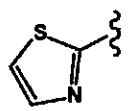
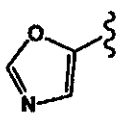
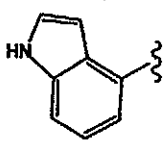
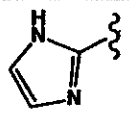
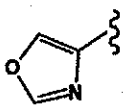
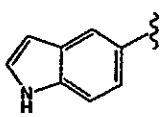
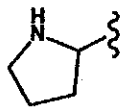
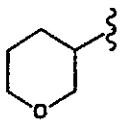
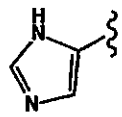
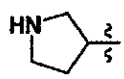
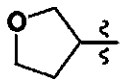
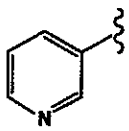
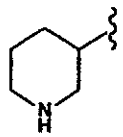
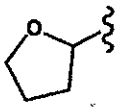
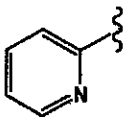
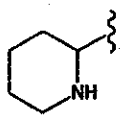
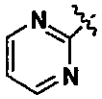
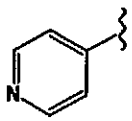
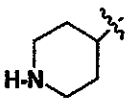
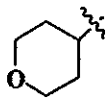
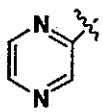
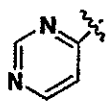
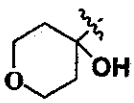
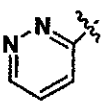
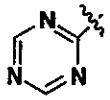
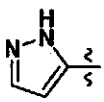
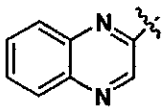
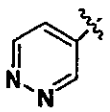
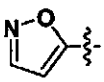
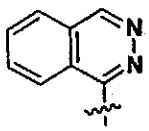
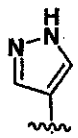
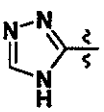
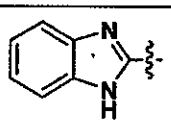
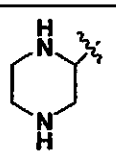
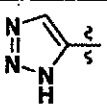
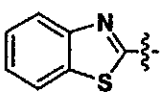
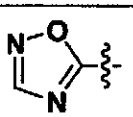
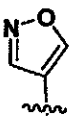
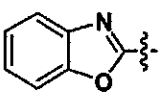
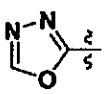
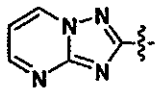
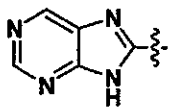
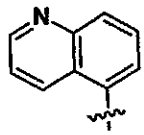
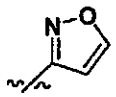
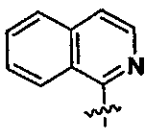
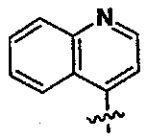
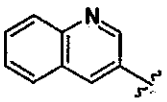
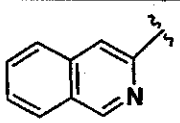
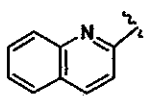
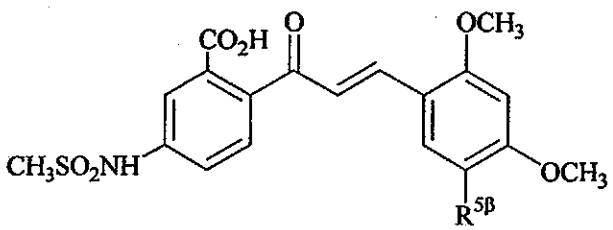
1488A 1488B		1489A 1489B		1490A 1490B	
1491A 1491B		1492A 1492B		1493A 1493B	
1494A 1494B		1495A 1495B		1496A 1496B	
1497A 1497B		1498A 1498B		1499A 1499B	
1500A 1500B		1501A 1501B		1502A 1502B	
1503A 1503B		1504A 1504B		1505A 1505B	
1506A 1506B		1507A 1507B		1508A 1508B	

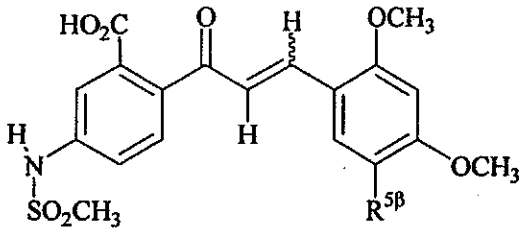
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1509A 1509B		1510A 1510B		1511A 1511B	
1512A 1512B		1513A 1513B		1514A 1514B	
1515A 1515B		1516A 1516B		1517A 1517B	
1518A 1518B		1519A 1519B		1520A 1520B	
1521A 1521B		1522A 1522B		1523A 1523B	
1524A 1524B		1525A 1525B		1526A 1526B	
1527A 1527B		1528A 1528B		1529A 1529B	
1530A 1530B		1531A 1531B		1532A 1532B	
1533A 1533B		1534A 1534B		1535A 1535B	
1536A 1536B		1537A 1537B		1538A 1538B	
1539A 1539B		1540A 1540B		1541A 1541B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1542A 1542B		1543A 1543B		1544A 1544B	
1545A 1545B		1546A 1546B		1547A 1547B	
1548A 1548B		1549A 1549B		1550A 1550B	

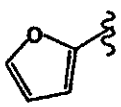
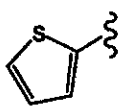
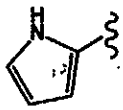
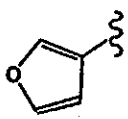
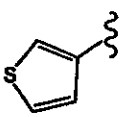
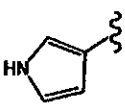
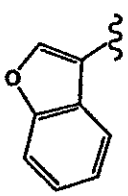
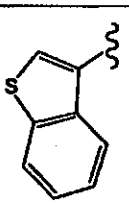
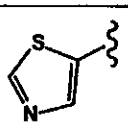
Example Table 21. Substituted 2-[3-{(5-Heteroaryl or 5-heterocyclic)-2,4-dimethoxyphenyl}-acryloyl]-5-methanesulfonylamino-benzoic Acids.

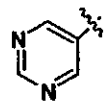
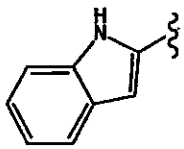
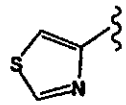
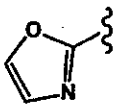
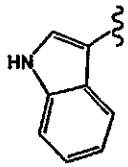
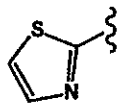
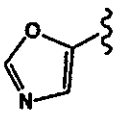
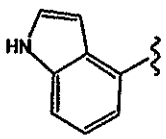
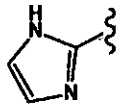
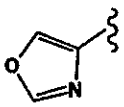
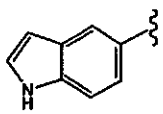
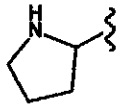
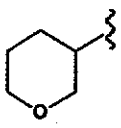
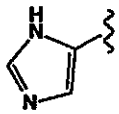
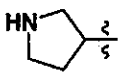
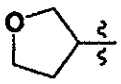
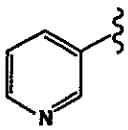
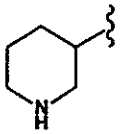
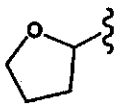
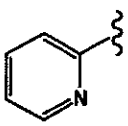
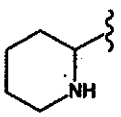
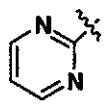
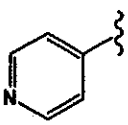
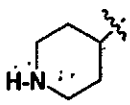
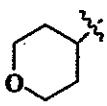
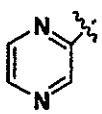
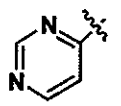
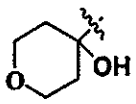
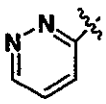
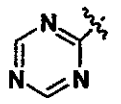
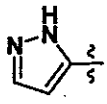
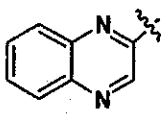
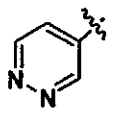


A



B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1551A 1551B		1552A 1552B		1553A 1553B	
1554A 1554B		1555A 1555B		1556A 1556B	
1557A 1557B		1558A 1558B		1559A 1559B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1560A 1560B		1561A 1561B		1562A 1562B	
1563A 1563B		1564A 1564B		1565A 1565B	
1566A 1566B		1567A 1567B		1568A 1568B	
1569A 1569B		1570A 1570B		1571A 1571B	
1572A 1572B		1573A 1573B		1574A 1574B	
1575A 1575B		1576A 1576B		1577A 1577B	
1578A 1578B		1579A 1579B		1580A 1580B	
1581A 1581B		1582A 1582B		1583A 1583B	
1584A 1584B		1585A 1585B		1586A 1586B	
1587A 1587B		1588A 1588B		1589A 1589B	
1590A 1590B		1591A 1591B		1592A 1592B	

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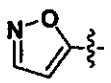
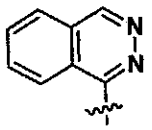
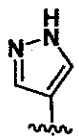
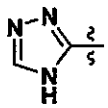
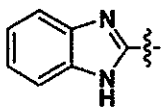
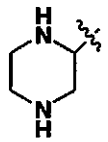
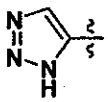
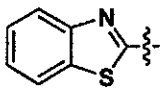
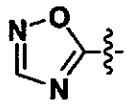
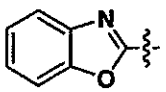
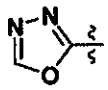
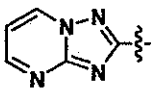
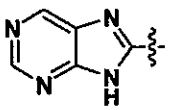
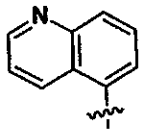
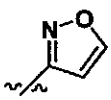
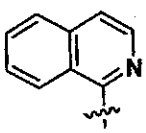
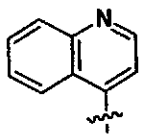
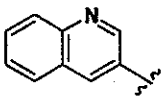
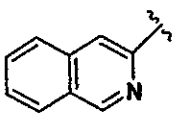
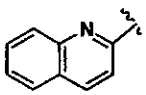
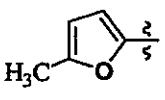
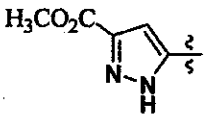
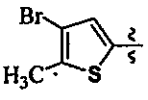
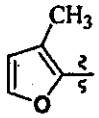
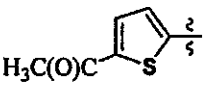
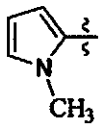
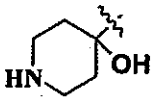
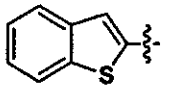
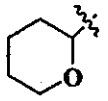
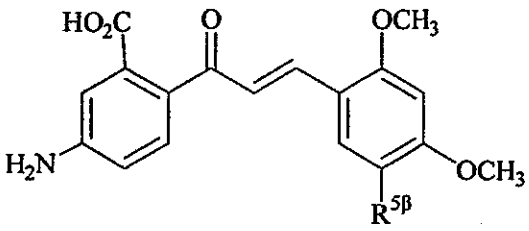
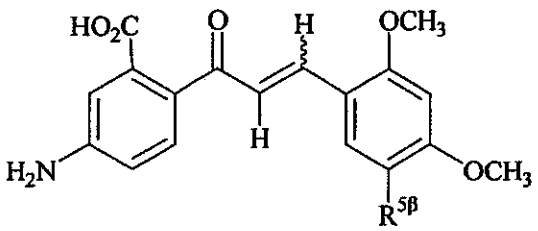
1593A 1593B		1594A 1594B		1595A 1595B	
1596A 1596B		1597A 1597B		1598A 1598B	
1599A 1599B		1600A 1600B		1601A 1601B	
1602A 1602B		1603A 1603B		1604A 1604B	
1605A 1605B		1606A 1606B		1607A 1607B	
1608A 1608B		1609A 1609B		1610A 1610B	
1611A 1611B		1612A 1612B		1613A 1613B	
1614A 1614B		1615A 1615B		1616A 1616B	
1617A 1617B		1618A 1618B		1619A 1619B	
1620A 1620B		1621A 1621B		1622A 1622B	

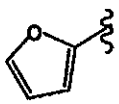
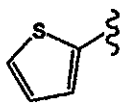
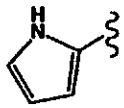
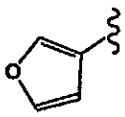
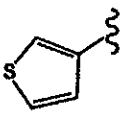
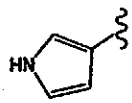
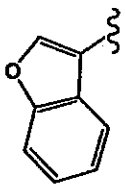
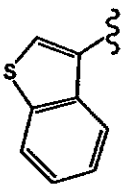
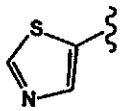
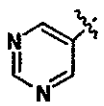
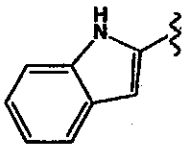
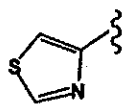
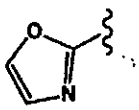
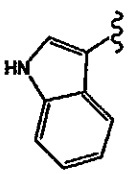
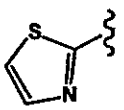
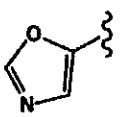
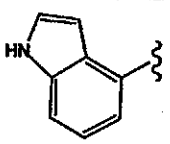
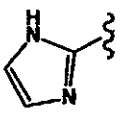
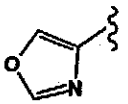
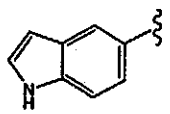
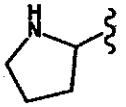
Example Table 22. Substituted 5-Amino-2-[3-{(5-heteroaryl or 5-heterocyclic)-2,4-dimethoxy-phenyl}- acryloyl]- benzoic Acids.



A



B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1623A 1623B		1624A 1624B		1625A 1625B	
1626A 1626B		1627A 1627B		1628A 1628B	
1629A 1629B		1630A 1630B		1631A 1631B	
1632A 1632B		1633A 1633B		1634A 1634B	
1635A 1635B		1636A 1636B		1637A 1637B	
1638A 1638B		1639A 1639B		1640A 1640B	
1641A 1641B		1642A 1642B		1643A 1643B	

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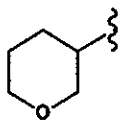
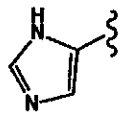
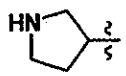
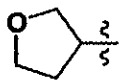
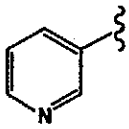
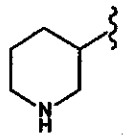
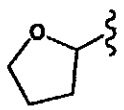
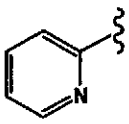
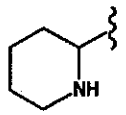
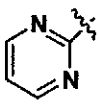
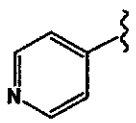
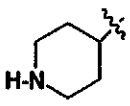
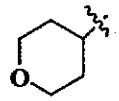
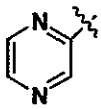
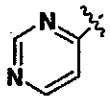
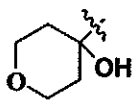
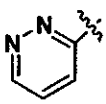
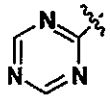
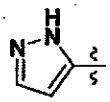
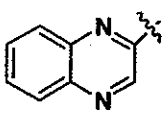
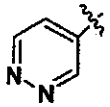
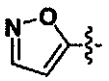
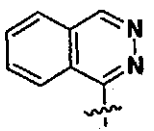
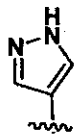
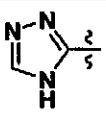
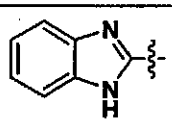
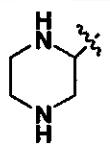
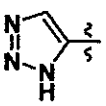
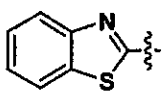
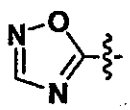
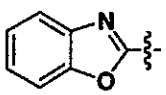
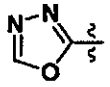
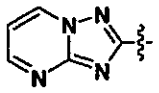
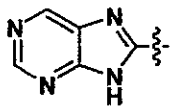
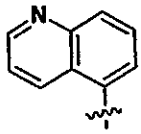
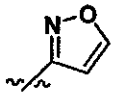
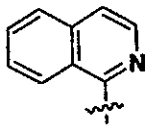
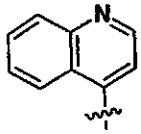
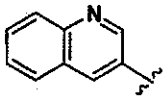
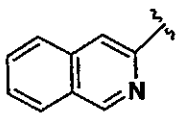
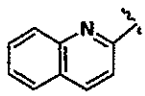
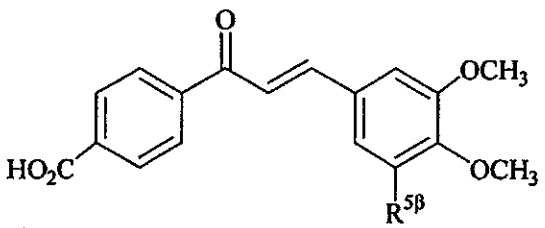
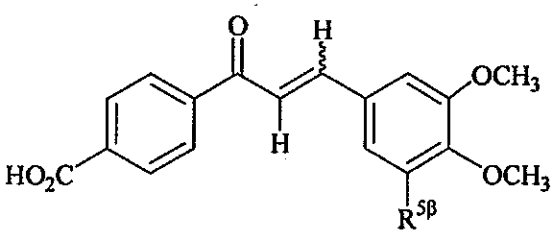
1644A 1644B		1645A 1645B		1646A 1646B	
1647A 1647B		1648A 1648B		1649A 1649B	
1650A 1650B		1651A 1651B		1652A 1652B	
1653A 1653B		1654A 1654B		1655A 1655B	
1656A 1656B		1657A 1657B		1658A 1658B	
1659A 1659B		1660A 1660B		1661A 1661B	
1662A 1662B		1663A 1663B		1664A 1664B	
1665A 1665B		1666A 1666B		1667A 1667B	
1668A 1668B		1669A 1669B		1670A 1670B	
1671A 1671B		1672A 1672B		1673A 1673B	
1674A 1674B		1675A 1675B		1676A 1676B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1677A 1677B		1678A 1678B		1679A 1679B	
1680A 1680B		1681A 1681B		1682A 1682B	
1683A 1683B		1684A 1684B		1685A 1685B	

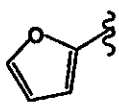
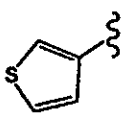
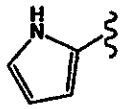
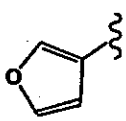
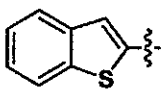
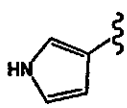
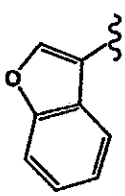
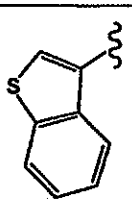
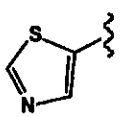
Example Table 23. Substituted 4-[3-{(5-Heteroaryl or 5-heterocyclic)-3,4-dimethoxyphenyl}-acryloyl]-benzoic Acids.

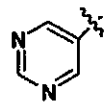
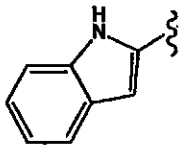
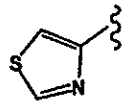
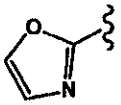
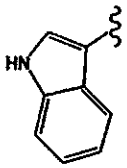
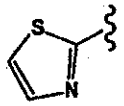
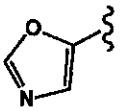
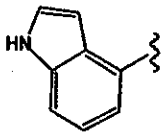
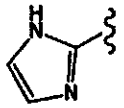
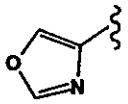
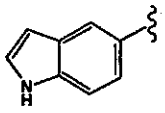
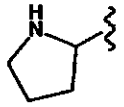
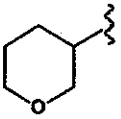
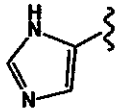
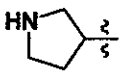
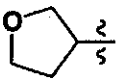
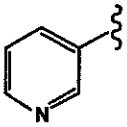
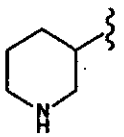
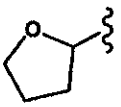
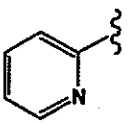
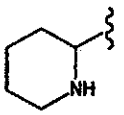
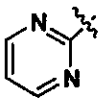
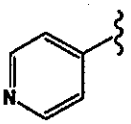
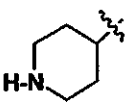
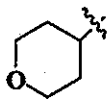
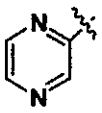
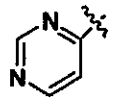
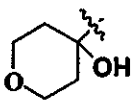
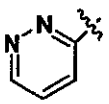
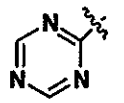
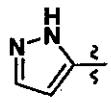
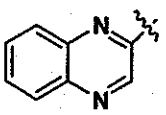
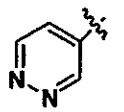


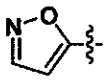
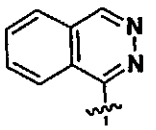
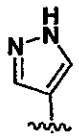
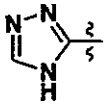
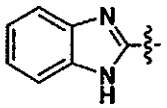
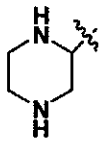
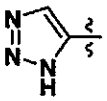
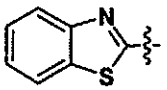
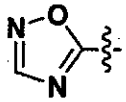
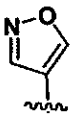
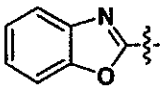
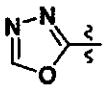
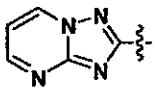
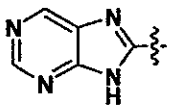
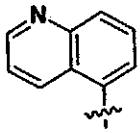
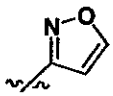
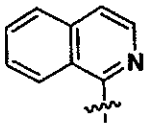
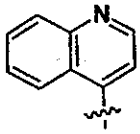
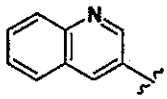
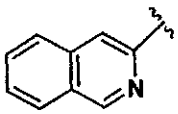
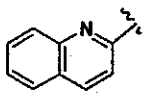
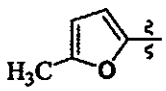
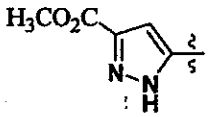
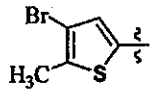
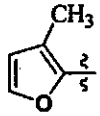
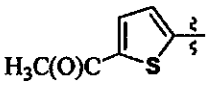
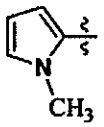
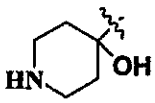
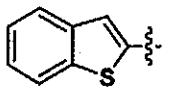
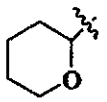
A



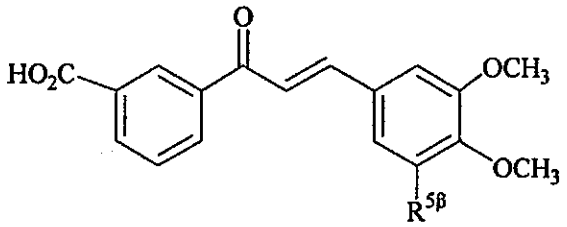
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1686A 1686B		1687A 1687B		1688A 1688B	
1689A 1689B		1690A 1690A		1691A 1691B	
1692A 1692B		1693A 1693B		1694A 1694B	

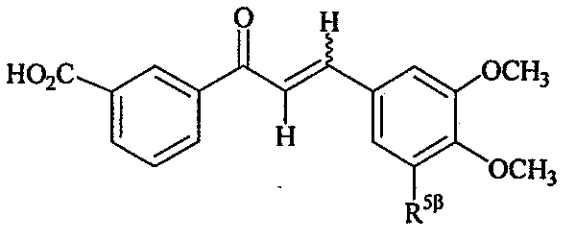
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1695A 1695B		1696A 1696B		1697A 1697B	
1698A 1698B		1699A 1699B		1700A 1700B	
1701A 1701B		1702A 1702B		1703A 1703B	
1704A 1704B		1705A 1705B		1706A 1706B	
1707A 1707B		1708A 1708B		1709A 1709B	
1710A 1710B		1711A 1711B		1712A 1712B	
1713A 1713B		1714A 1714B		1715A 1715B	
1716A 1716B		1717A 1717B		1718A 1718B	
1719A 1719B		1720A 1720B		1721A 1721B	
1722A 1722B		1723A 1723B		1724A 1724B	
1725A 1725B		1726A 1726B		1727A 1727B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1728A 1728B		1729A 1729B		1730A 1730B	
1731A 1731B		1732A 1732B		1733A 1733B	
1734A 1734B		1735A 1735B		1736A 1736B	
1737A 1737B		1738A 1738B		1739A 1739B	
1740A 1740B		1741A 1741B		1742A 1742B	
1743A 1743B		1744A 1744B		1745A 1745B	
1746A 1746B		1747A 1747B		1748A 1748B	
1749A 1749B		1750A 1750B		1751A 1751B	
1752A 1752B		1753A 1753B		1754A 1754B	
1755A 1755B		1756A 1756B		1757A 1757B	

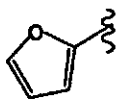
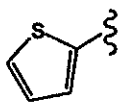
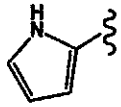
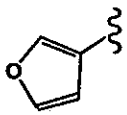
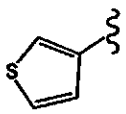
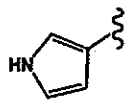
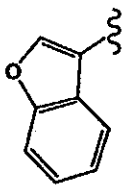
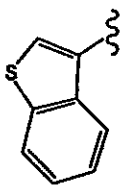
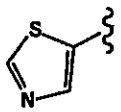
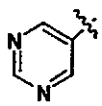
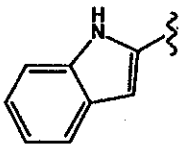
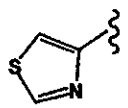
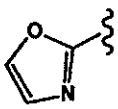
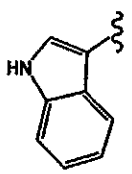
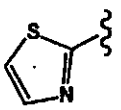
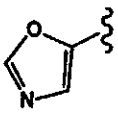
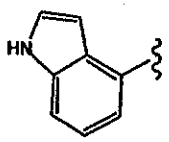
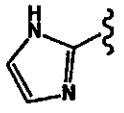
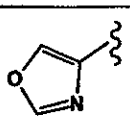
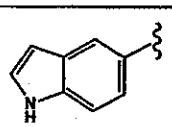
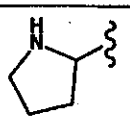
Example Table 24. Substituted 3-[3-{(5-Heteroaryl or 5-heterocyclic)-3,4-dimethoxyphenyl}-acryloyl]-benzoic Acids.

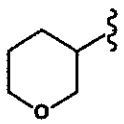
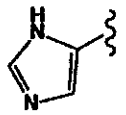
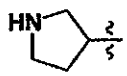
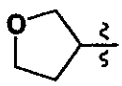
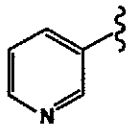
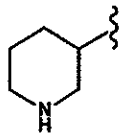
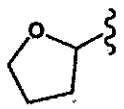
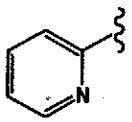
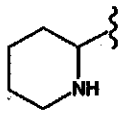
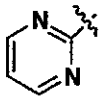
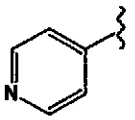
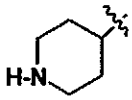
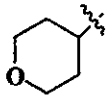
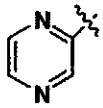
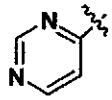
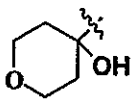
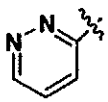
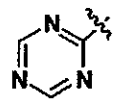
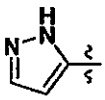
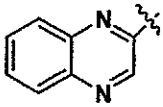
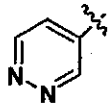
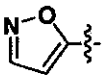
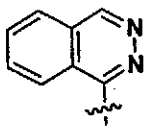
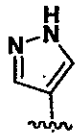
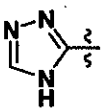
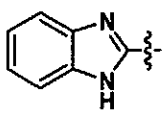
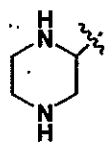
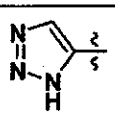
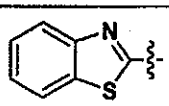
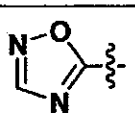
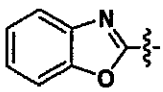
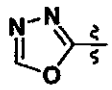


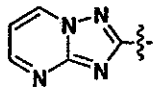
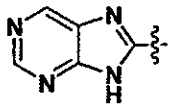
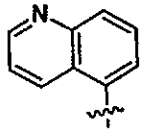
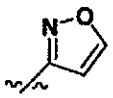
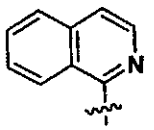
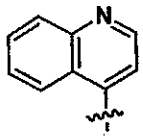
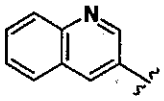
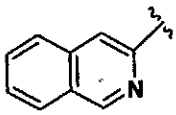
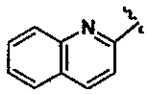
A



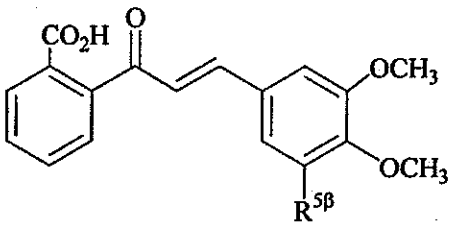
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1758A 1758B		1759A 1759B		1760A 1760B	
1761A 1761B		1762A 1762B		1763A 1763B	
1764A 1764B		1765A 1765B		1766A 1766B	
1767A 1767B		1768A 1768B		1769A 1769B	
1770A 1770B		1771A 1771B		1772A 1772B	
1773A 1773B		1774A 1774B		1775A 1775B	
1776A 1776B		1777A 1777B		1778A 1778B	

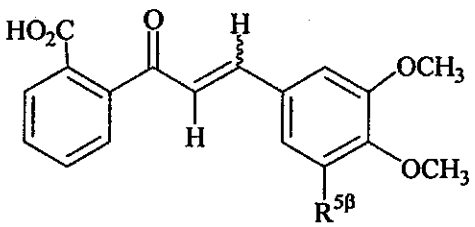
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1779A 1779B		1780A 1780B		1781A 1781B	
1782A 1782B		1783A 1783B		1784A 1784B	
1785A 1785B		1786A 1786B		1787A 1787B	
1788A 1788B		1789A 1789B		1790A 1790B	
1791A 1791B		1792A 1792B		1793A 1793B	
1794A 1794B		1795A 1795B		1796A 1796B	
1797A 1797B		1798A 1798B		1799A 1799B	
1800A 1800B		1801A 1801B		1802A 1802B	
1803A 1803B		1804A 1804B		1805A 1805B	
1806A 1806B		1807A 1807B		1808A 1808B	
1809A 1809B		1810A 1810B		1811A 1811B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1812A 1812B		1813A 1813B		1814A 1814B	
1815A 1815B		1816A 1816B		1817A 1817B	
1818A 1818B		1819A 1819B		1820A 1820B	

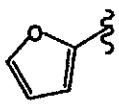
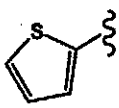
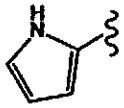
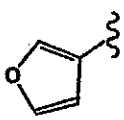
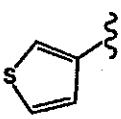
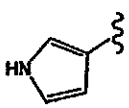
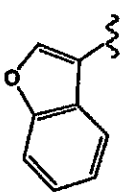
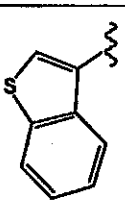
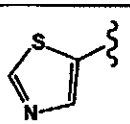
Example Table 25. Substituted 2-[3-{(5-Heteroaryl or 5-heterocyclic)-3,4-dimethoxyphenyl}-acryloyl]-benzoic Acids.



A



B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1821A 1821B		1822A 1822B		1823A 1823B	
1824A 1824B		1825A 1825B		1826A 1826B	
1827A 1827B		1828A 1828B		1829A 1829B	

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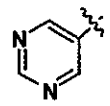
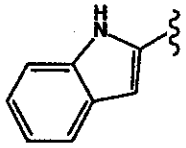
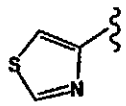
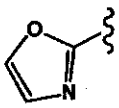
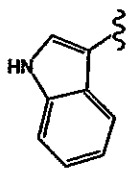
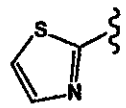
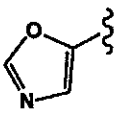
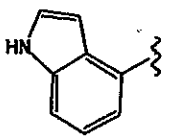
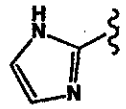
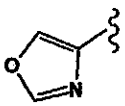
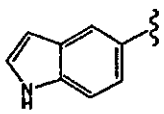
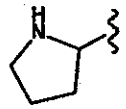
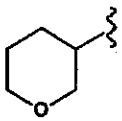
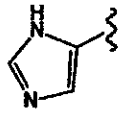
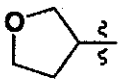
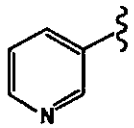
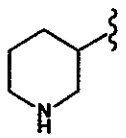
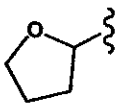
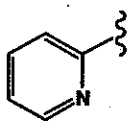
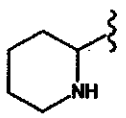
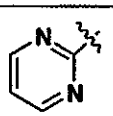
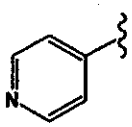
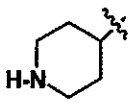
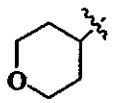
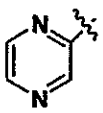
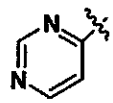
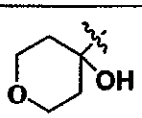
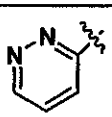
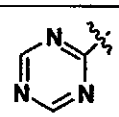
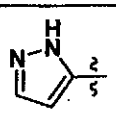
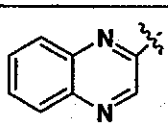
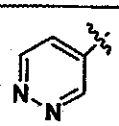
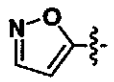
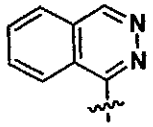
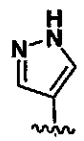
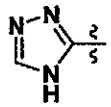
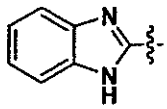
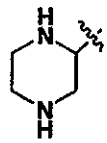
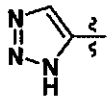
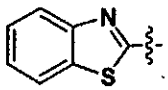
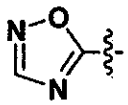
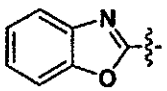
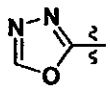
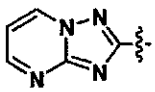
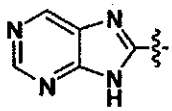
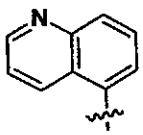
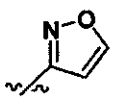
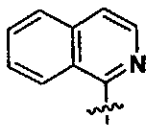
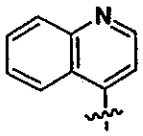
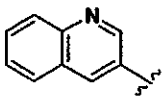
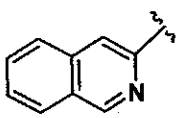
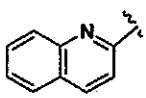
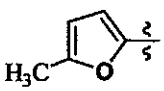
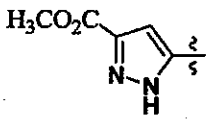
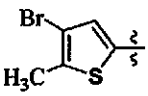
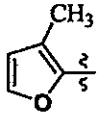
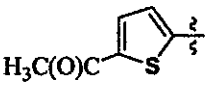
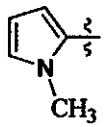
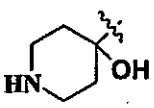
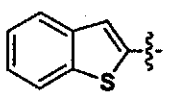
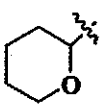
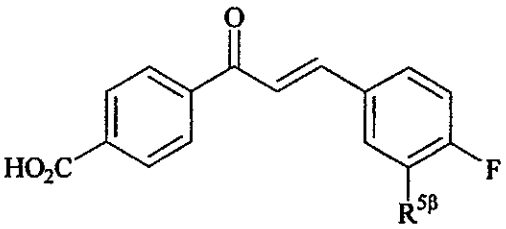
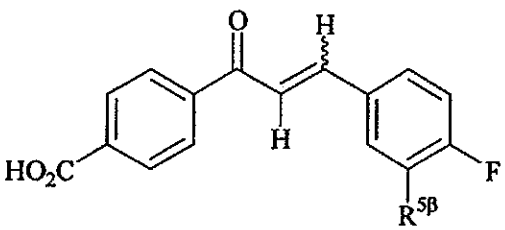
1830A 1830B		1831A 1831B		1832A 1832B	
1833A 1833B		1834A 1834B		1835A 1835B	
1836A 1836B		1837A 1837B		1838A 1838B	
1839A 1839B		1840A 1840B		1841A 1841B	
1842A 1842B		1843A 1843B		1844A 1844B	
1845A 1845B		1846A 1846B		1847A 1847B	
1848A 1848B		1849A 1849B		1850A 1850B	
1851A 1851B		1852A 1852B		1853A 1853B	
1854A 1854B		1855A 1855B		1856A 1856B	
1857A 1857B		1858A 1858B		1859A 1859B	
1860A 1860B		1861A 1861B		1862A 1862B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1863A 1863B		1864A 1864B		1865A 1865B	
1866A 1866B		1867A 1867B		1868A 1868B	
1869A 1869B		1870A 1870B		1871A 1871B	
1872A 1872B		1873A 1873B		1874A 1874B	
1875A 1875B		1876A 1876B		1877A 1877B	
1878A 1878B		1879A 1879B		1880A 1880B	
1881A 1881B		1882A 1882B		1883A 1883B	
1884A 1884B		1885A 1885B		1886A 1886B	
1887A 1887B		1888A 1888B		1889A 1889B	
1890A 1890B		1891A 1891B		1892A 1892B	

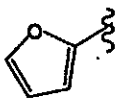
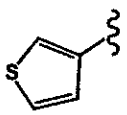
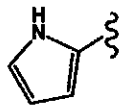
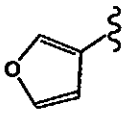
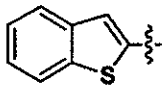
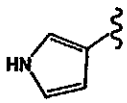
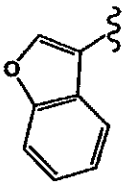
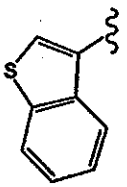
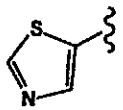
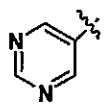
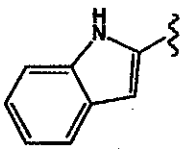
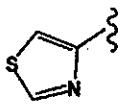
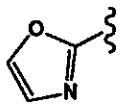
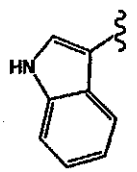
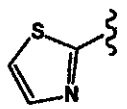
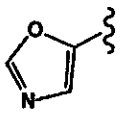
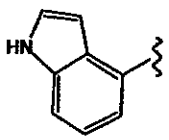
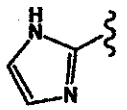
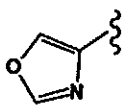
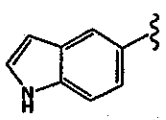
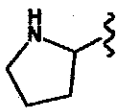
Example Table 26. Substituted 4-[3-{(5-Heteroaryl or 5-heterocyclic)-4-fluorophenyl}-acryloyl]-benzoic Acids.

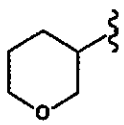
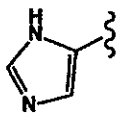
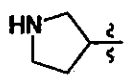
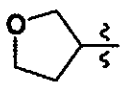
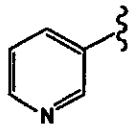
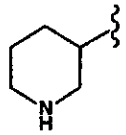
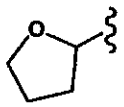
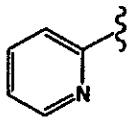
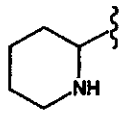
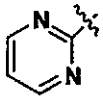
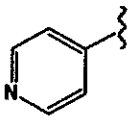
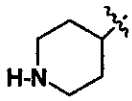
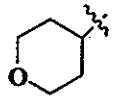
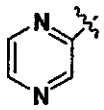
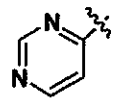
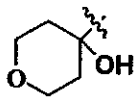
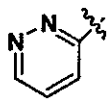
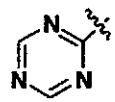
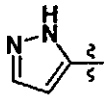
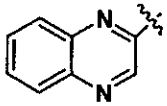
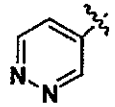
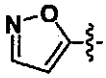
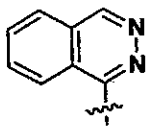
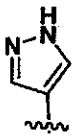
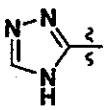
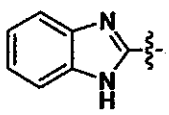
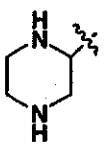
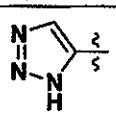
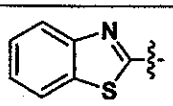
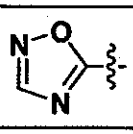
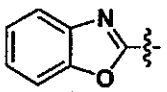
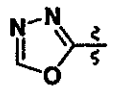


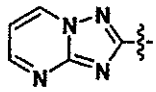
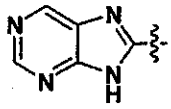
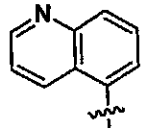
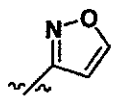
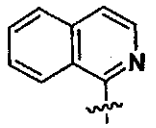
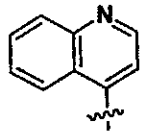
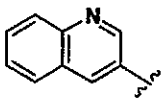
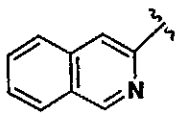
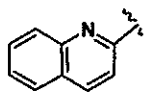
A



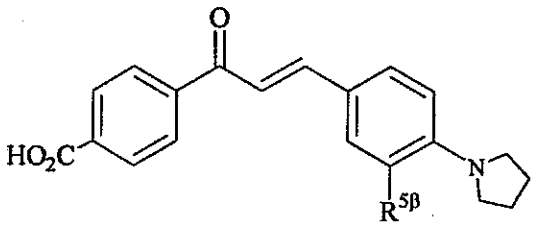
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1893A 1893B		1894A 1894B		1895A 1895B	
1896A 1896B		1897A 1897B		1898A 1898B	
1899A 1899B		1900A 1900B		1901A 1901B	
1902A 1902B		1903A 1903B		1904A 1904B	
1905A 1905B		1906A 1906B		1907A 1907B	
1908A 1908B		1909A 1909B		1910A 1910B	
1911A 1911B		1912A 1912B		1913A 1913B	

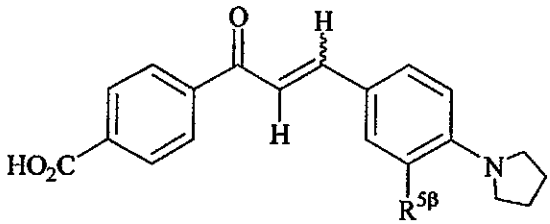
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1914A 1914B		1915A 1915B		1916A 1916B	
1917A 1917B		1918A 1918B		1919A 1919B	
1920A 1920B		1921A 1921B		1922A 1922B	
1923A 1923B		1924A 1924B		1925A 1925B	
1926A 1926B		1927A 1927B		1928A 1928B	
1929A 1929B		1930A 1930B		1931A 1931B	
1932A 1932B		1933A 1933B		1934A 1934B	
1935A 1935B		1936A 1936B		1937A 1937B	
1938A 1938B		1939A 1939B		1940A 1940B	
1941A 1941B		1942A 1942B		1943A 1943B	
1944A 1944B		1945A 1945B		1946A 1946B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1947A 1947B		1948A 1948B		1949A 1949B	
1950A 1950B		1951A 1951B		1952A 1952B	
1953A 1953B		1954A 1954B		1955A 1955B	

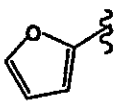
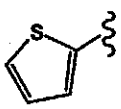
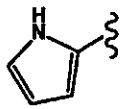
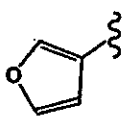
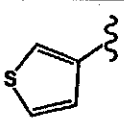
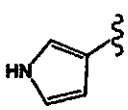
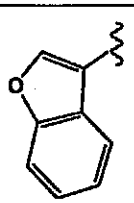
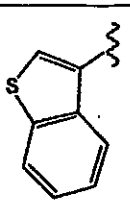
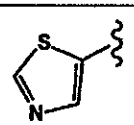
Example Table 27. Substituted 4-[3-{(3-Heteroaryl or 3-heterocyclic)-4-(pyrrolidin-1-yl)-phenyl}acryloyl]-benzoic Acids.

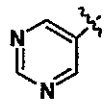
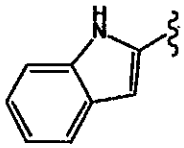
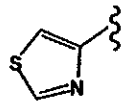
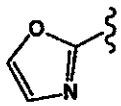
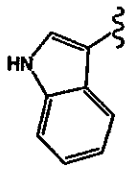
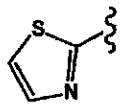
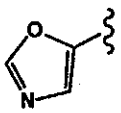
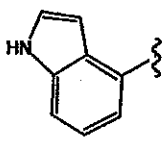
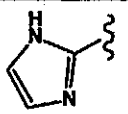
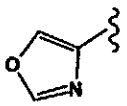
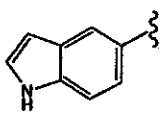
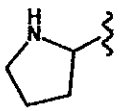
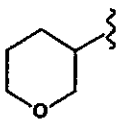
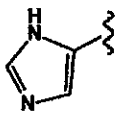
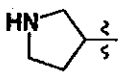
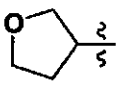
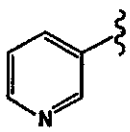
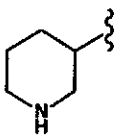
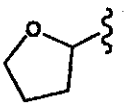
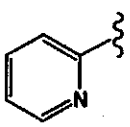
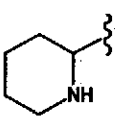
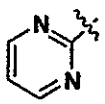
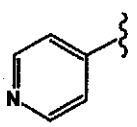
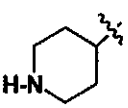
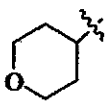
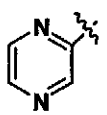
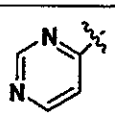
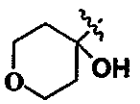
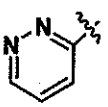
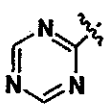
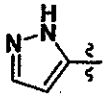
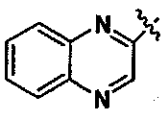
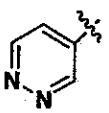


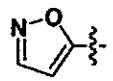
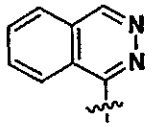
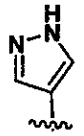
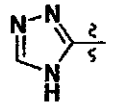
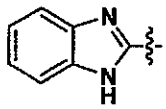
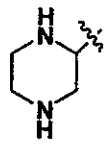
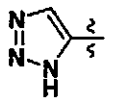
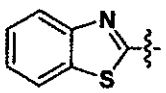
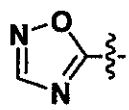
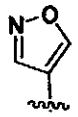
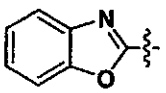
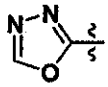
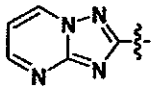
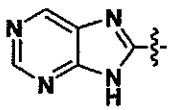
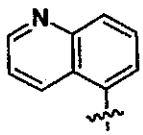
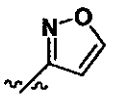
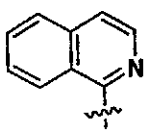
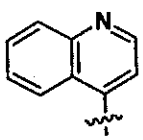
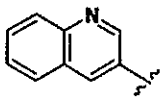
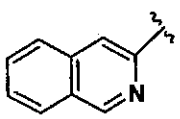
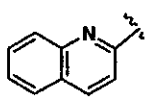
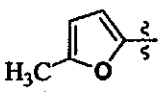
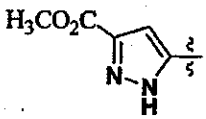
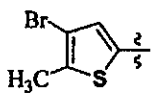
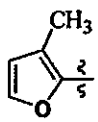
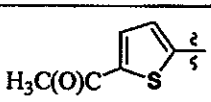
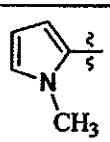
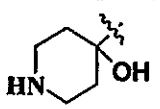
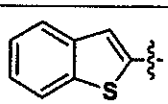
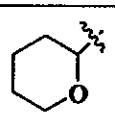
A



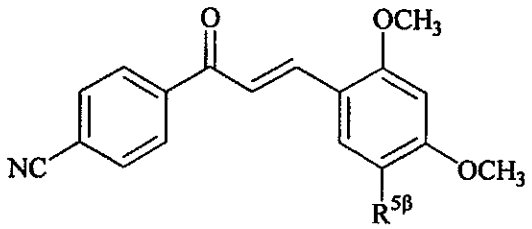
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1956A 1956B		1957A 1957B		1958A 1958B	
1959A 1959B		1960A 1960B		1961A 1961B	
1962A 1962B		1963A 1963B		1964A 1964B	

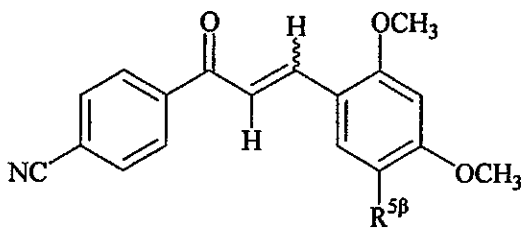
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1965A 1965B		1966A 1966B		1967A 1967B	
1968A 1968B		1969A 1969B		1970A 1970B	
1971A 1971B		1972A 1972B		1973A 1973B	
1974A 1974B		1975A 1975B		1976A 1976B	
1977A 1977B		1978A 1978B		1979A 1979B	
1980A 1980B		1981A 1981B		1982A 1982B	
1983A 1983B		1984A 1984B		1985A 1985B	
1986A 1986B		1987A 1987B		1988A 1988B	
1989A 1989B		1990A 1990B		1991A 1991B	
1992A 1992B		1993A 1993B		1994A 1994B	
1995A 1995B		1996A 1996B		1997A 1997B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
1998A 1998B		1999A 1999B		2000A 2000B	
2001A 2001B		2002A 2002B		2003A 2003B	
2004A 2004B		2005A 2005B		2006A 2006B	
2007A 2007B		2008A 2008B		2009A 2009B	
2010A 2010B		2011A 2011B		2012A 2012B	
2013A 2013B		2014A 2014B		2015A 2015B	
2016A 2016B		2017A 2017B		2018A 2018B	
2019A 2019B		2020A 2020B		2021A 2021B	
2022A 2022B		2023A 2023B		2024A 2024B	
2025A 2025B		2026A 2026B		2027A 2027B	

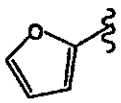
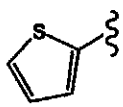
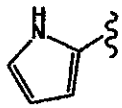
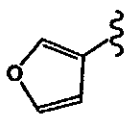
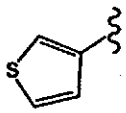
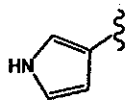
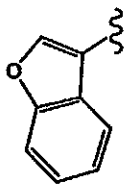
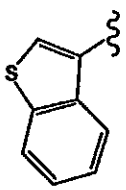
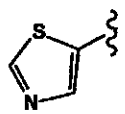
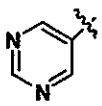
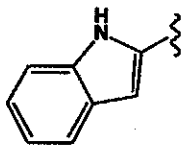
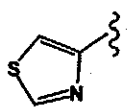
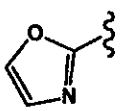
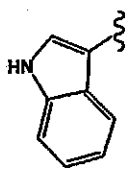
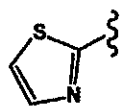
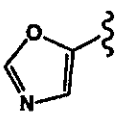
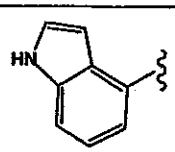
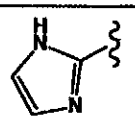
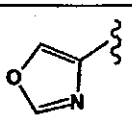
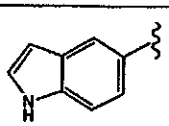
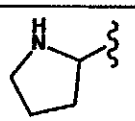
Example Table 28. Substituted 4-[3-{(5-Heteroaryl or 5-heterocyclic)-2,4-dimethoxyphenyl}-acryloyl]benzonitriles.

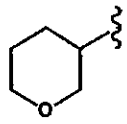
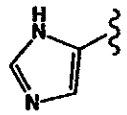
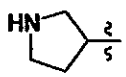
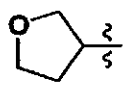
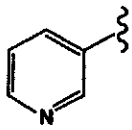
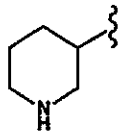
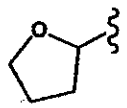
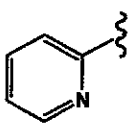
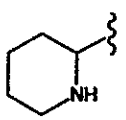
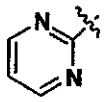
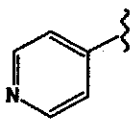
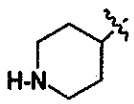
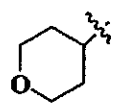
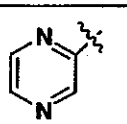
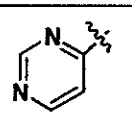
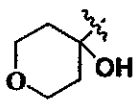
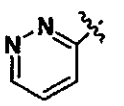
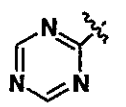
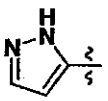
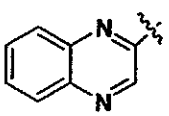
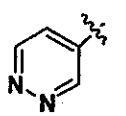
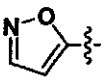
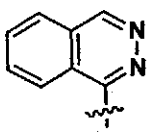
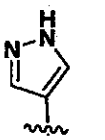
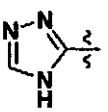
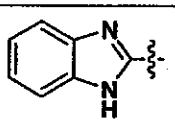
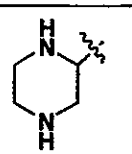
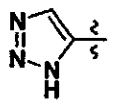
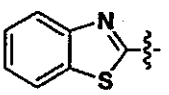
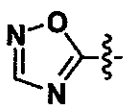
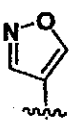
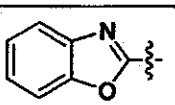
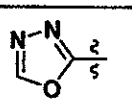


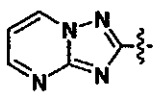
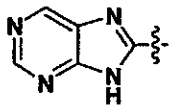
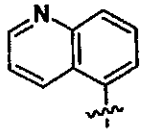
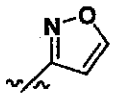
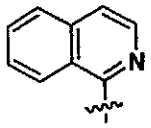
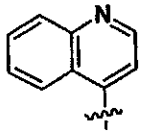
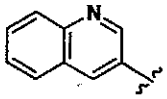
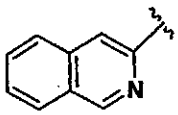
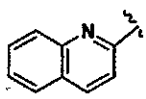
A



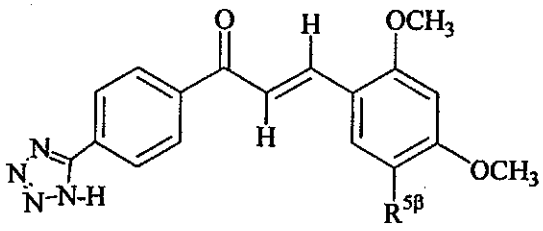
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
2028A 2028B		2029A 2029B		2030A 2030B	
2031A 2031B		2032A 2032B		2033A 2033B	
2034A 2034B		2035A 2035B		2036A 2036B	
2037A 2037B		2038A 2038B		2039A 2039B	
2040A 2040B		2041A 2041B		2042A 2042B	
2043A 2043B		2044A 2044B		2045A 2045B	
2046A 2046B		2047A 2047B		2048A 2048B	

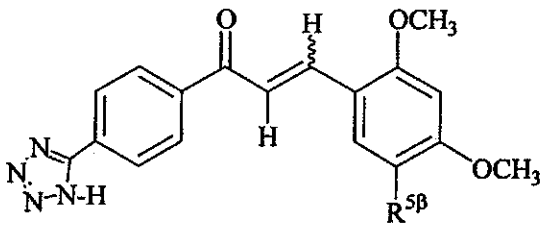
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
2049A 2049B		2050A 2050B		2051A 2051B	
2052A 2052B		2053A 2053B		2054A 2054B	
2055A 2055B		2056A 2056B		2057A 2057B	
2058A 2058B		2059A 2059B		2060A 2060B	
2061A 2061B		2062A 2062B		2063A 2063B	
2064A 2064B		2065A 2065B		2066A 2066B	
2067A 2067B		2068A 2068B		2069A 2069B	
2070A 2070B		2071A 2071B		2072A 2072B	
2073A 2073B		2074A 2074B		2075A 2075B	
2076A 2076B		2077A 2077B		2078A 2078B	
2079A 2079B		2080A 2080B		2081A 2081B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
2082A 2082B		2083A 2083B		2084A 2084B	
2085A 2085B		2086A 2086B		2087A 2087B	
2088A 2088B		2089A 2089B		2090A 2090B	

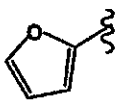
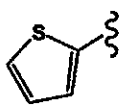
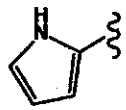
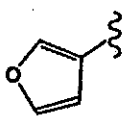
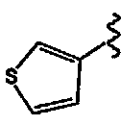
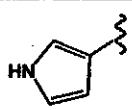
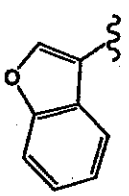
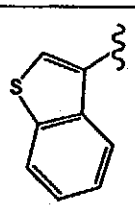
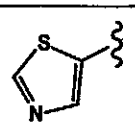
Example Table 29. Substituted 3-[2,4-Dimethoxy-(5-heteroaryl or 5-heterocyclic)phenyl]-1-[4-(2*H*-tetrazol-5-yl)phenyl]-2-propen-1-ones.

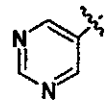
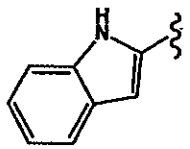
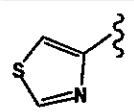
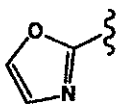
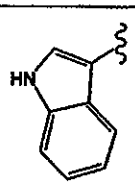
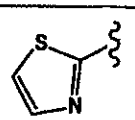
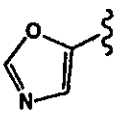
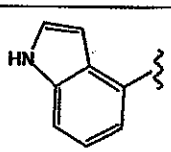
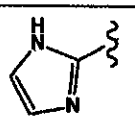
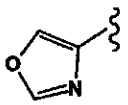
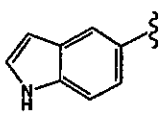
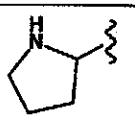
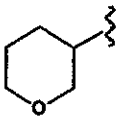
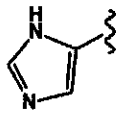
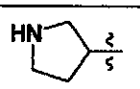
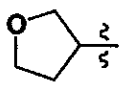
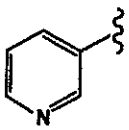
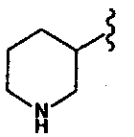
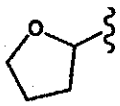
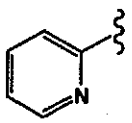
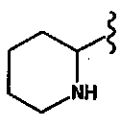
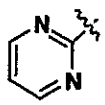
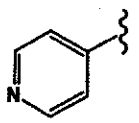
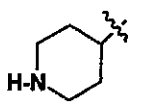
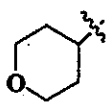
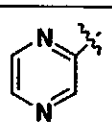
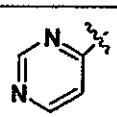
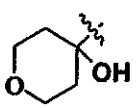
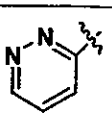
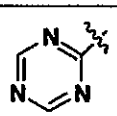
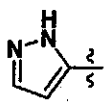
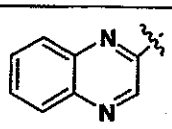
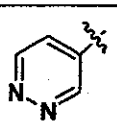


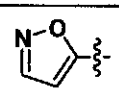
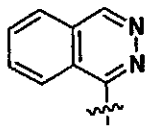
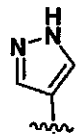
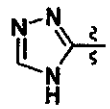
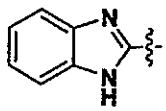
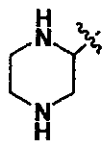
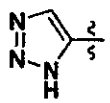
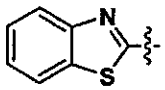
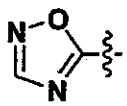
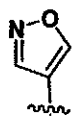
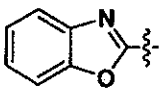
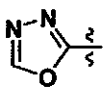
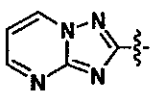
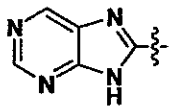
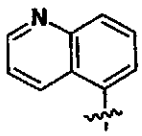
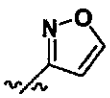
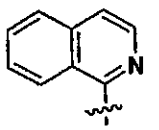
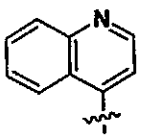
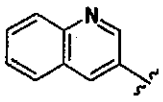
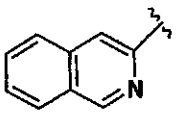
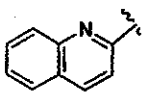
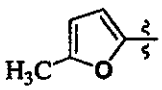
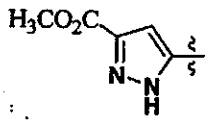
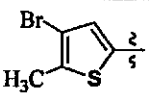
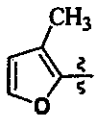
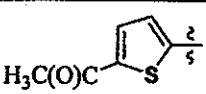
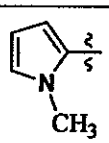
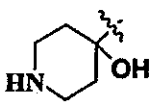
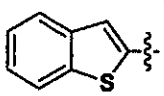
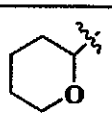
A



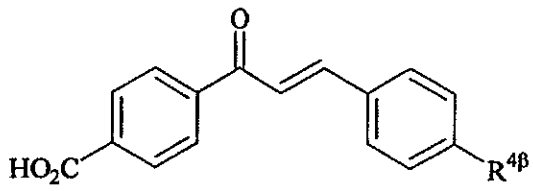
B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
2091A 2091B		2092A 2092B		2093A 2093B	
2094A 2094B		2095A 2095B		2096A 2096B	
2097A 2097B		2098A 2098B		2099A 2099B	

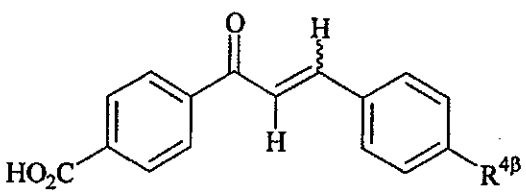
Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
2100A 2100B		2101A 2101B		2102A 2102B	
2103A 2103B		2104A 2104B		2105A 2105B	
2106A 2106B		2107A 2107B		2108A 2108B	
2109A 2109B		2110A 2110B		2111A 2111B	
2112A 2112B		2113A 2113B		2114A 2114B	
2115A 2115B		2116A 2116B		2117A 2117B	
2118A 2118B		2119A 2119B		2120A 2120B	
2121A 2121B		2122A 2122B		2123A 2123B	
2124A 2124B		2125A 2125B		2126A 2126B	
2127A 2127B		2128A 2128B		2129A 2129B	
2130A 2130B		2131A 2131B		2132A 2132B	

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
2133A 2133B		2134A 2134B		2135A 2135B	
2136A 2136B		2137A 2137B		2138A 2138B	
2139A 2139B		2140A 2140B		2141A 2141B	
2142A 2142B		2143A 2143B		2144A 2144B	
2145A 2146B		2146A 2146B		2147A 2147B	
2148A 2148B		2149A 2149B		2150A 2150B	
2151A 2151B		2152A 2152B		2153A 2153B	
2154A 2154B		2155A 2155B		2156A 2156B	
2157A 2157B		2158A 2158B		2159A 2159B	
2160A 2160B		2161A 2161B		2162A 2162B	

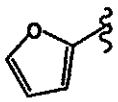
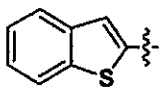
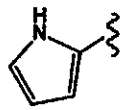
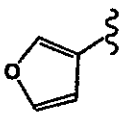
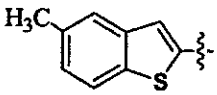
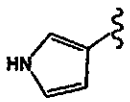
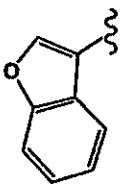
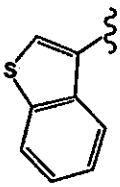
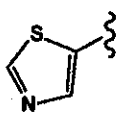
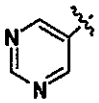
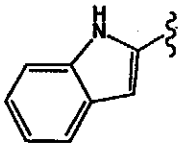
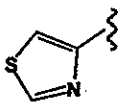
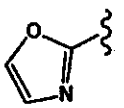
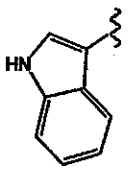
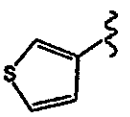
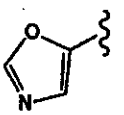
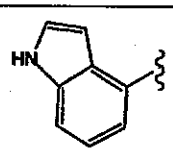
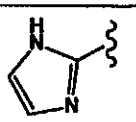
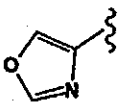
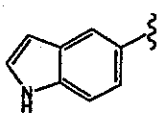
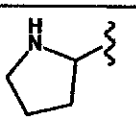
Example Table 30. Substituted 4-[3-{(4-Heteroaryl or 4-heterocyclic)phenyl}-acryloyl]-benzoic Acids.

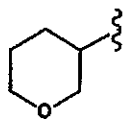
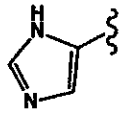
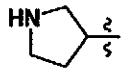
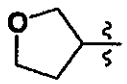
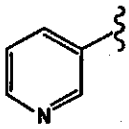
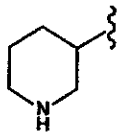
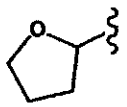
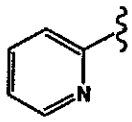
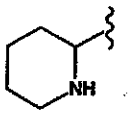
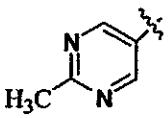
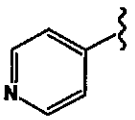
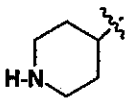
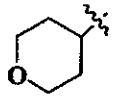
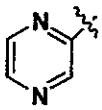
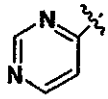
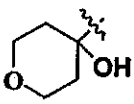
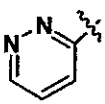
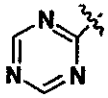
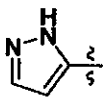
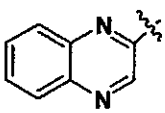
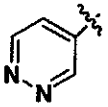
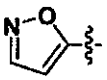
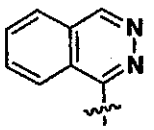
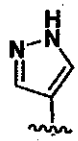
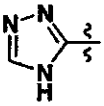
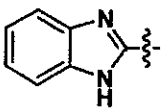
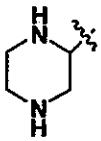
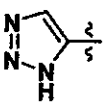
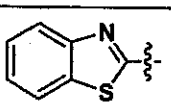
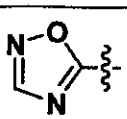
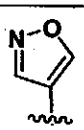
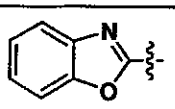
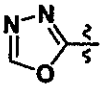


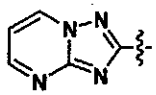
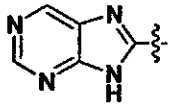
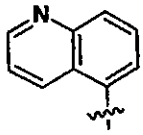
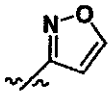
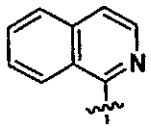
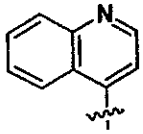
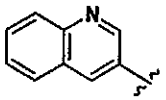
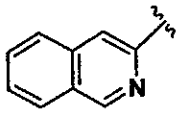
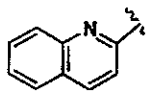
A



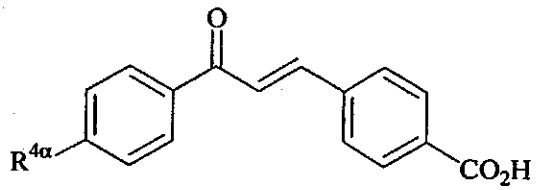
B

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
2163A 2163B		2164A 2164B		2165A 2165B	
2166A 2166B		2167A 2167B		2168A 2168B	
2169A 2169B		2170A 2170B		2171A 2171B	
2172A 2172B		2173A 2173B		2174A 2174B	
2175A 2175B		2176A 2176B		2177A 2177B	
2178A 2178B		2179A 2179B		2180A 2180B	
2181A 2181B		2182A 2182B		2183A 2183B	

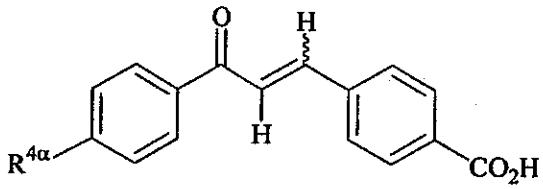
Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
2184A 2184B		2185A 2185B		2186A 2186B	
2187A 2187B		2188A 2188B		2189A 2189B	
2190A 2190B		2191A 2191B		2192A 2192B	
2193A 2193B		2194A 2194B		2195A 2195B	
2196A 2196B		2197A 2197B		2198A 2198B	
2199A 2199B		2200A 2200B		2201A 2201B	
2202A 2202B		2203A 2203B		2204A 2204B	
2205A 2205B		2206A 2206B		2207A 2207B	
2208A 2208B		2209A 2209B		2210A 2210B	
2211A 2211B		2212A 2212B		2213A 2213B	
2214A 2214B		2215A 2215B		2216A 2216B	

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
2217A 2217B		2218A 2218B		2219A 2219B	
2220A 2220B		2221A 2221B		2222A 2222B	
2223A 2223B		2224A 2224B		2225A 2225B	

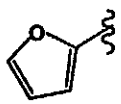
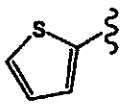
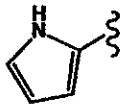
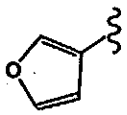
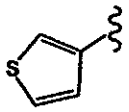
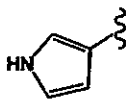
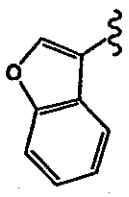
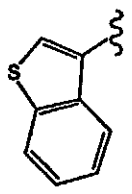
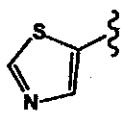
Example Table 31. Substituted 4-[3-{(4-Heteroaryl or 4-heterocyclic)phenyl}-3-oxo-propenyl]-benzoic Acids.

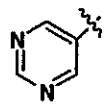
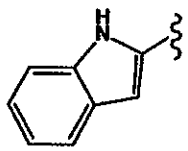
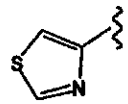
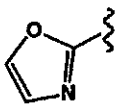
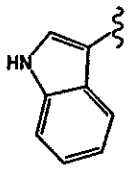
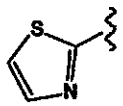
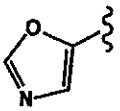
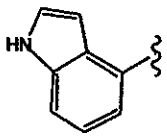
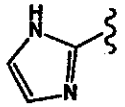
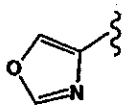
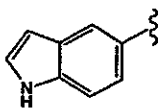
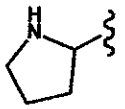
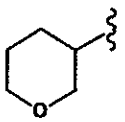
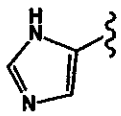
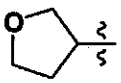
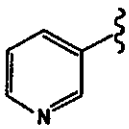
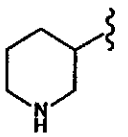
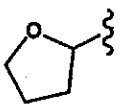
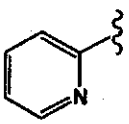
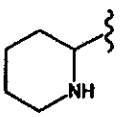
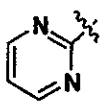
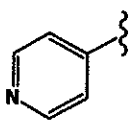
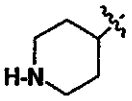
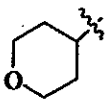
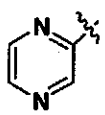
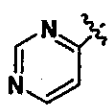
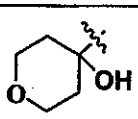
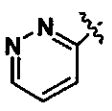
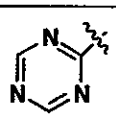
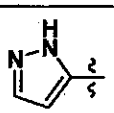
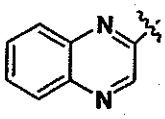
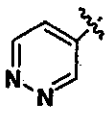


A



B

Ex. No.	$R^{4\alpha}$	Ex. No.	$R^{4\alpha}$	Ex. No.	$R^{4\alpha}$
2226A 2226B		2227A 2227B		2228A 2228B	
2229A 2229B		2230A 2230B		2231A 2231B	
2232A 2232B		2233A 2233B		2234A 2234B	

Ex. No.	$R^{4\alpha}$	Ex. No.	$R^{4\alpha}$	Ex. No.	$R^{4\alpha}$
2235A 2235B		2236A 2236B		2237A 2237B	
2238A 2238B		2239A 2239B		2240A 2240B	
2241A 2241B		2242A 2242B		2243A 2243B	
2244A 2244B		2245A 2245B		2246A 2246B	
2247A 2247B		2248A 2248B		2249A 2249B	
2250A 2250B		2251A 2251B		2252A 2252B	
2253A 2253B		2254A 2254B		2255A 2255B	
2256A 2256B		2257A 2257B		2258A 2258B	
2259A 2259B		2260A 2260B		2261A 2261B	
2262A 2262B		2263A 2263B		2264A 2264B	
2265A 2265B		2266A 2266B		2267A 2267B	

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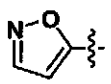
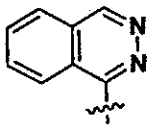
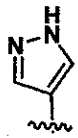
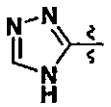
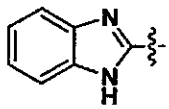
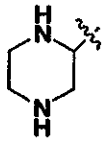
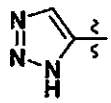
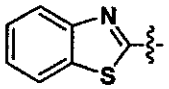
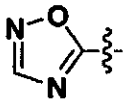
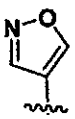
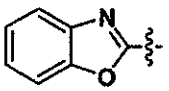
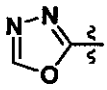
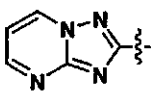
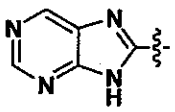
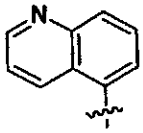
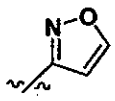
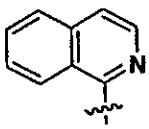
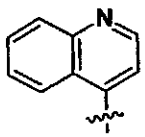
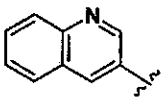
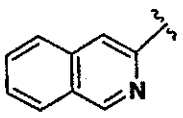
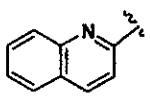
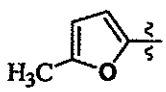
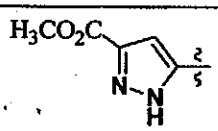
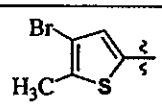
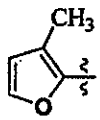
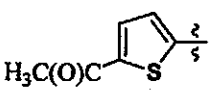
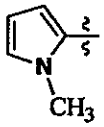
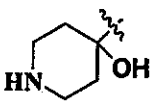
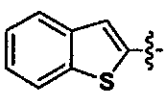
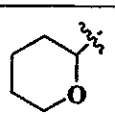
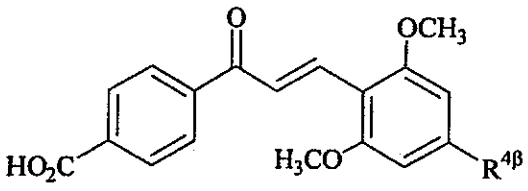
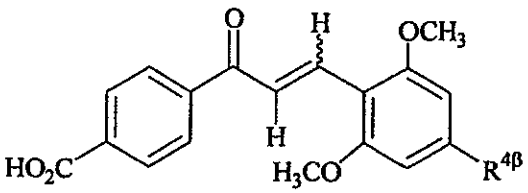
2268A 2268B		2269A 2269B		2270A 2270B	
2271A 2271B		2272A 2272B		2273A 2273B	
2274A 2274B		2275A 2275B		2276A 2276B	
2277A 2277B		2278A 2278B		2279A 2279B	
2280A 2280B		2281A 2281B		2282A 2282B	
2283A 2283B		2284A 2284B		2285A 2285B	
2286A 2286B		2287A 2287B		2288A 2288B	
2289A 2289B		2290A 2290B		2291A 2291B	
2292A 2292B		2293A 2293B		2294A 2294B	
2295A 2295B		2296A 2296B		2297A 2297B	

Example Table 32. Substituted 4-[3-{(4-Heteroaryl or 4-heterocyclic)-2,6-dimethoxyphenyl}-acryloyl]-benzoic Acids.



A



B

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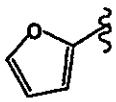
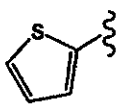
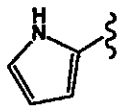
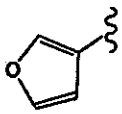
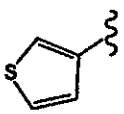
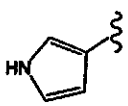
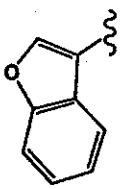
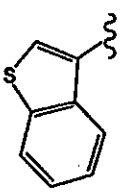
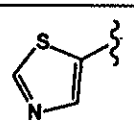
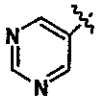
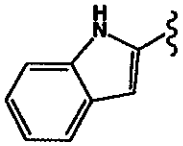
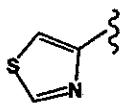
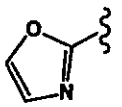
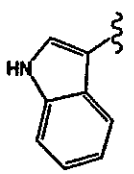
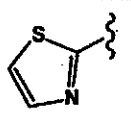
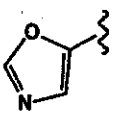
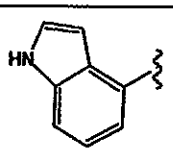
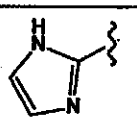
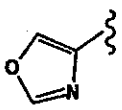
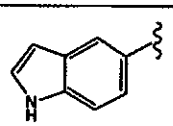
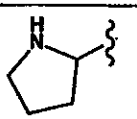
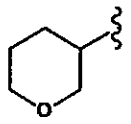
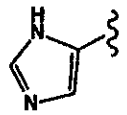
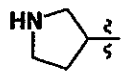
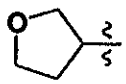
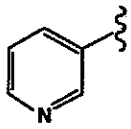
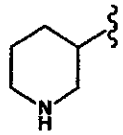
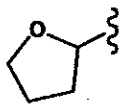
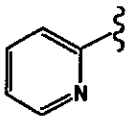
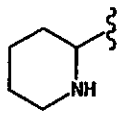
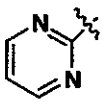
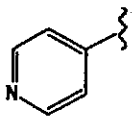
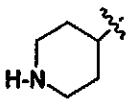
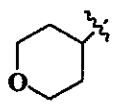
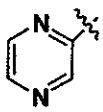
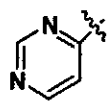
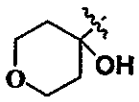
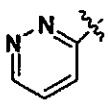
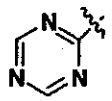
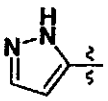
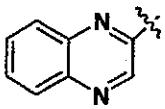
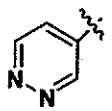
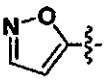
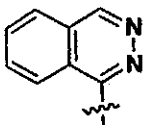
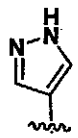
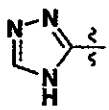
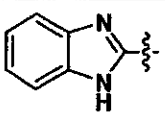
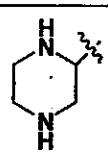
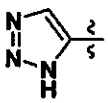
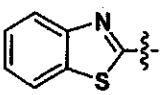
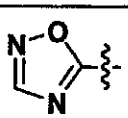
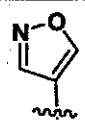
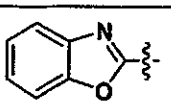
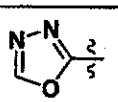
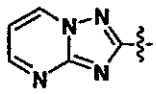
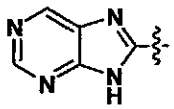
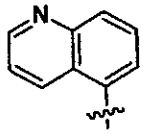
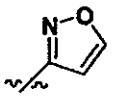
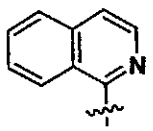
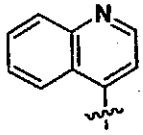
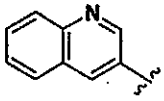
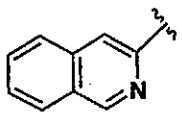
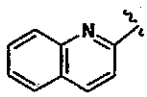
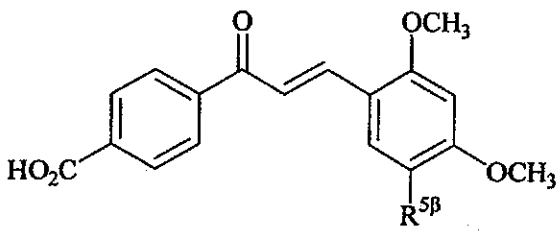
2298A 2298B		2299A 2299B		2300A 2300B	
2301A 2301B		2302A 2302B		2303A 2303B	
2304A 2304B		2305A 2305B		2306A 2306B	
2307A 2307B		2308A 2308B		2309A 2309B	
2310A 2310B		2311A 2311B		2312A 2312B	
2313A 2313B		2314A 2314B		2315A 2315B	
2316A 2316B		2317A 2317B		2318A 2318B	

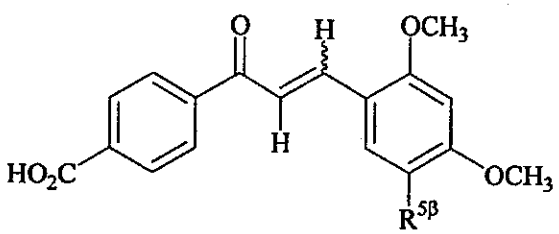
Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
2319A 2319B		2320A 2320B		2321A 2321B	
2322A 2322B		2323A 2323B		2324A 2324B	
2325A 2325B		2326A 2326B		2327A 2327B	
2328A 2328B		2329A 2329B		2330A 2330B	
2331A 2331B		2332A 2332B		2333A 2333B	
2334A 2334B		2335A 2335B		2336A 2336B	
2337A 2337B		2338A 2338B		2339A 2339B	
2340A 2340B		2341A 2341B		2342A 2342B	
2343A 2343B		2344A 2344B		2345A 2345B	
2346A 2346B		2347A 2347B		2348A 2348B	
2349A 2349B		2350A 2350B		2351A 2351B	

Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$	Ex. No.	$R^{4\beta}$
2352A 2352B		2353A 2353B		2354A 2354B	
2355A 2355B		2356A 2356B		2357A 2357B	
2358A 2358B		2359A 2359B		2360A 2360B	

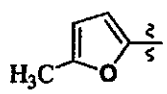
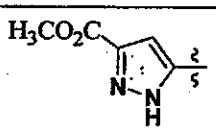
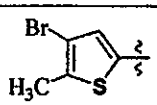
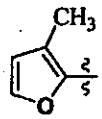
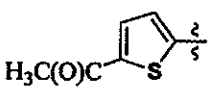
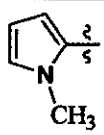
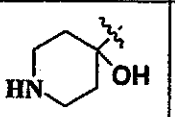
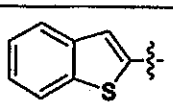
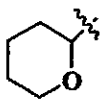
Example Table 33. Substituted 4-[3-{(5-Heteroaryl or 5-heterocyclic)-2,4-dimethoxyphenyl}-acryloyl]-benzoic Acids.



A



B

Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$	Ex. No.	$R^{5\beta}$
2361A 2361B		2362A 2362B		2363A 2363B	
2364A 2364B		2365A 2365B		2366A 2366B	
2367A 2367B		2368A 2368B		2369A 2369B	

Stereoisomerism and Polymorphism

It is appreciated that compounds of the present invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, diastereomeric, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

Examples of methods to obtain optically active materials are known in the art, and include at least the following.

i) physical separation of crystals - a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals of the separate enantiomers exist, i.e., the material is a conglomerate, and the crystals are visually distinct;

ii) simultaneous crystallization - a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;

iii) enzymatic resolutions - a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme;

iv) enzymatic asymmetric synthesis - a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer;

v) chemical asymmetric synthesis - a synthetic technique whereby the desired enantiomer is synthesized from an achiral precursor under

conditions that produce asymmetry (i.e., chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;

vi) diastereomer separations - a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

vii) first- and second-order asymmetric transformations - a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

viii) kinetic resolutions - this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

ix) enantiospecific synthesis from non-racemic precursors - a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

x) chiral liquid chromatography - a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase. The stationary phase can

be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

xi) chiral gas chromatography - a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

xii) extraction with chiral solvents - a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent;

xiii) transport across chiral membranes - a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane which allows only one enantiomer of the racemate to pass through.

Pharmaceutically Acceptable Salt Formulations

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically acceptable salt may be appropriate. The term **"pharmaceutically acceptable salts"** or **"complexes"** refers to salts or complexes that retain the desired biological activity of the compounds of the present invention and exhibit minimal undesired toxicological effects.

Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids, which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate and α-glycerophosphate. Suitable inorganic salts may also be formed, including, sulfate, nitrate, bicarbonate and carbonate salts. Alternatively, the pharmaceutically acceptable

salts may be made with sufficiently basic compounds such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Nonlimiting examples of such salts are (a) acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalcturonic acid; (b) base addition salts formed with metal cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium, sodium, potassium, and the like, or with a cation formed from ammonia, N,N-dibenzylethylenediamine, D-glucosamine, tetraethylammonium, or ethylenediamine; or (c) combinations of (a) and (b); e.g., a zinc tannate salt or the like. Also included in this definition are pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^+A^-$, wherein R is as defined above and A is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

Particular FDA-approved salts can be conveniently divided between anions and cations (Approved Drug Products with Therapeutic Equivalence Evaluations (1994) U.S. Department of Health and Human Services, Public Health Service, FDA, Center for Drug Evaluation and Research, Rockville, Md; L.D. Bighley, S.M. Berge and D.C. Monkhouse, Salt Forms of Drugs and Absorption, *Encyclopedia of Pharmaceutical Technology*, Vol. 13, J. Swarbridk and J. Boylan, eds., Marcel Dekker, NY (1996)). Among the approved anions include aceglumate, acephyllinate, acetamidobenzoate, acetate, acetylasparaginate, acetylaspartate, adipate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, benzoate, besylate, bicarbonate, bisulfate, bitartrate, borate, bromide, camphorate, camsylate, carbonate, chloride, chlorophenoxyacetate, citrate,closylate, cromesilate, cyclamate, dehydrocholate, dihydrochloride, dimalonate, edentate, edisylate, estolate, esylate, ethylbromide, ethylsulfate,

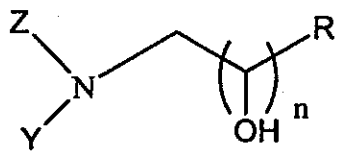
fendizoate, fosfatex, fumarate, gluceptate, gluconate, glucuronate, glutamate, glycerophosphate, glysinate, glycollylarsinilate, glycyrrhizate, hippurate, hemisulfate, hexylresorcinate, hybenzate, hydrobromide, hydrochloride, hydroiodid, hydroxybenzenesulfonate, hydroxybenzoate, hydroxynaphthoate, hyclate, iodide, isethionate, lactate, lactobionate, lysine, malate, maleate, mesylate, methylbromide, methyliodide, methylnitrate, methylsulfate, monophosadenine, mucate, napadisylate, napsylate, nicotinate, nitrate, oleate, orotate, oxalate, oxoglurate, pamoate, pantothenate, pectinate, phenylethylbarbiturate, phosphate, pacrate, plicrilix, polistirex, polygalacturonate, propionate, pyridoxylphosphate, saccharinate, salicylate, stearate, succinate, stearylsulfate, subacetate, succinate, sulfate, sulfosalicylate, tannate, tartrate, teprosilate, terephthalate, teoclate, thiocyante, tidiacicate, timonacicate, tosylate, triethiodide, triethiodide, undecanoate, and xinafoate. The approved cations include ammonium, benethamine, benzathine, betaine, calcium, carnitine, clemizole, chlorcyclizine, choline, dibenylamine, diethanolamine, diethylamine, diethylammonium diolamine, eglumine, erbumine, ethylenediamine, heptaminol, hydrabamine, hydroxyethylpyrrolidone, imadazole, meglumine, olamine, piperazine, 4-phenylcyclohexylamine, procaine, pyridoxine, triethanolamine, and tromethamine. Metallic cations include, aluminum, bismuth, calcium lithium, magnesium, neodymium, potassium, rubidium, sodium, strontium and zinc.

A particular class of salts can be classified as organic amine salts. The organic amines used to form these salts can be primary amines, secondary amines or tertiary amines, and the substituents on the amine can be straight, branched or cyclic groups, including ringed structures formed by attachment of two or more of the amine substituents. Of particular interest are organic amines that are substituted by one or more hydroxyalkyl groups, including alditol or carbohydrate moieties. These hydroxy substituted organic amines can be cyclic or acyclic, both classes of which can be primary amines, secondary amines or tertiary amines. A common class of cyclic hydroxy substituted amines are the amino sugars.

Carbohydrate moieties that can comprise one or more substituents in the amine salt include those made from substituted and unsubstituted monosaccharides, disaccharides, oligosaccharides, and polysaccharides. The saccharide can be an aldose or ketose, and may comprise 3, 4, 5, 6, or 7 carbons. In one embodiment the carbohydrates are monosaccharides.

In another embodiment the carbohydrates are pyranose and furanose sugars. Non limiting examples of pyranose and furanose moieties that can be part of the organic amine salt include threose, ribulose, ketose, gentiobiose, aldose, aldotetrose, aldopentose, aldohexose, ketohexose, ketotetrose, ketopentose, erythrose, threose, ribose, deoxyribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, glactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, dextrose, maltose, lactose, sucrose, cellulose, aldose, amylose, palatinose, trehalose, turanose, cellobiose, amylopectin, glucosamine, mannosamine, fucose, phamnose, glucuronate, gluconate, glucono-lactone, muramic acid, abequose, rhamnose, gluconic acid, glucuronic acid, and galactosamine. The carbohydrate moiety can optionally be deoxygenated at any corresponding C-position, and/or substituted with one or more moieties such as hydrogen, halo, haloalkyl, carboxyl, acyl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, thioester, thioether, oxime, hydrazine, carbamate, phosphonic acid, phosphonate, or any other viable functional group that does not inhibit the pharmacological activity of this compound. Exemplary substituents include amine and halo, particularly fluorine. The substituent or carbohydrate can be either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference. In one embodiment the monosaccharide is a furanose such as (L or D)-ribose.

Of particular interest among the acyclic organic amines are a class represented by the formula



wherein Y and Z are independently hydrogen or lower alkyl or, may be taken together to form a ring, R is hydrogen, alkyl or hydroxyloweralkyl, and n is 1, 2, 3, 4, or 5. Among these hydroxyl amines are a particular class characterized when n is 4. A representative of this group

is meglumine, represented when Y is hydrogen, Z is methyl and R is methoxy. Meglumine is also known in the art as N-methylglucamine, N-MG, and 1-deoxy-1-(methylamino)-D-glucitol.

The invention also includes pharmaceutically acceptable prodrugs of the compounds. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound.

Any of the compounds described herein can be administered as a prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the compound. A number of prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the compound will increase the stability of the chalcone. Examples of substituent groups that can replace one or more hydrogens on the compound are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, *Antiviral Research*, **27** (1995) 1-17. Any of these can be used in combination with the disclosed compounds to achieve a desired effect.

The compounds can be used to treat inflammatory disorders that are mediated by VCAM-1 including, but not limited to arthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation late and chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosis, inflammatory bowel diseases, autoimmune diabetes, diabetic retinopathy, diabetic nephropathy, diabetic vasculopathy, rhinitis, ischemia-reperfusion injury, post-angioplasty restenosis, chronic obstructive pulmonary disease (COPD), glomerulonephritis, Graves disease, gastrointestinal allergies, conjunctivitis, atherosclerosis, coronary artery disease, angina and small artery disease.

The compounds disclosed herein can be used in the treatment of inflammatory skin diseases that are mediated by VCAM-1, and in particular, human endothelial disorders that are mediated by VCAM-1, which include, but are not limited to, psoriasis, dermatitis, including

eczematous dermatitis, and Kaposi's sarcoma, as well as proliferative disorders of smooth muscle cells.

In yet another embodiment, the compounds disclosed herein can be selected to treat anti-inflammatory conditions that are mediated by mononuclear leucocytes.

In yet another embodiment, the compounds of the present invention can be selected for the prevention or treatment of tissue or organ transplant rejection. Treatment and prevention of organ or tissue transplant rejection includes, but are not limited to treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, spleen, small bowel, or corneal transplants. They are also indicated for the prevention or treatment of graft-versus-host disease, which sometimes occurs following bone marrow transplantation.

In an alternative embodiment, the compounds described herein are useful in both the primary and adjunctive medical treatment of cardiovascular disease. The compounds are used in primary treatment of, for example, coronary disease states including atherosclerosis, post-angioplasty restenosis, coronary artery diseases and angina. The compounds can be administered to treat small vessel disease that is not treatable by surgery or angioplasty, or other vessel disease in which surgery is not an option. The compounds can also be used to stabilize patients prior to revascularization therapy.

In another aspect the invention provides pharmaceutical compositions for the treatment of diseases or disorders mediated by VCAM-1 wherein such compositions comprise a VCAM-1 inhibiting amount of a chalcone derivatives of the invention or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable carrier.

In another aspect the invention provides a method for treating a disease or disorder mediated by VCAM-1 comprising administering to a patient a VCAM-1 inhibiting effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

In another aspect the invention provides a method for treating cardiovascular and inflammatory disorders in a patient in need thereof comprising administering to said patient an VCAM-1 inhibiting effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

In another aspect the invention provides a method and composition for treating asthma or arthritis in a patient in need thereof comprising administering to said patient an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

The compounds of the present invention can be used to treat any disorder that is mediated by VCAM-1. VCAM-1 is upregulated in a wide variety of disease states, including but not limited to arthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation late and chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosis, inflammatory bowel diseases, autoimmune diabetes, diabetic retinopathy, diabetic nephropathy, diabetic vasculopathy, rhinitis, ischemia-reperfusion injury, post-angioplasty restenosis, chronic obstructive pulmonary disease (COPD), glomerulonephritis, Graves disease, gastrointestinal allergies, atherosclerosis, coronary artery disease, angina, small artery disease, and conjunctivitis.

Nonlimiting examples of arthritis include rheumatoid (such as soft-tissue rheumatism and non-articular rheumatism, fibromyalgia, fibrositis, muscular rheumatism, myofascil pain, humeral epicondylitis, frozen shoulder, Tietze's syndrome, fascitis, tendinitis, tenosynovitis, bursitis), juvenile chronic, spondyloarthropaties (ankylosing spondylitis), osteoarthritis, hyperuricemia and arthritis associated with acute gout, chronic gout and systemic lupus erythematosus.

Human endothelial disorders mediated by VCAM-1 include psoriasis, eczematous dermatitis, Kaposi's sarcoma, as well as proliferative disorders of smooth muscle cells.

In yet another embodiment, the compounds disclosed herein can be selected to treat anti-inflammatory conditions that are mediated by mononuclear leucocytes.

In one embodiment, the compounds of the present invention are selected for the prevention or treatment of tissue or organ transplant rejection. Treatment and prevention of organ or tissue transplant rejection includes, but are not limited to treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, spleen, small bowel, or corneal transplants. The compounds can also be used in the prevention or treatment of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation.

In an alternative embodiment, the compounds described herein are useful in both the primary and adjunctive medical treatment of cardiovascular disease. The compounds are used in primary treatment of, for example, coronary disease states including atherosclerosis, post-angioplasty restenosis, coronary artery diseases and angina. The compounds can be administered to treat small vessel disease that is not treatable by surgery or angioplasty, or other vessel disease in which surgery is not an option. The compounds can also be used to stabilize patients prior to revascularization therapy.

In addition to inhibiting the expression of VCAM-1, some of the compounds of the invenion have the additional properties of inhibiting monocyte chemoattractant protein-1 (MCP-1) and/or smooth muscle proliferation. MCP-1 is a chemoattractant protein produced by endothelial cells, smooth muscle cells as well as macrophages. MCP-1 promotes integrin activation on endothelial cells thereby facilitating adhesion of leukocytes to VCAM-1, and MCP-1 is a chemoattractant for monocytes. MCP-1 has been shown to play a role in leukocyte recruitment in a number of chronic inflammatory diseases including atherosclerosis, rheumatoid arthritis, and asthma. Its expression is upregulated in these diseases and as such inhibition of MCP-1 expression represents a desirable property of anti-inflammatory therapeutics. Furthermore, smooth muscle cell hyperplasia and resulting tissue remodeling and decreased organ function is yet another characteristic of many chronic inflammatory diseases including atherosclerosis, chronic transplant rejection and asthma. Inhibition of the hyperproliferation of smooth muscle cells is another desirable property for therapeutic compounds.

Combination and Alternation Therapy

Any of the compounds disclosed herein can be administered in combination or alternation with a second biologically active agent to increase its effectiveness against the target disorder.

In combination therapy, effective dosages of two or more agents are administered together, whereas during alternation therapy an effective dosage of each agent is administered serially. The dosages will depend on absorption, inactivation and excretion rates of the drug as

well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

The efficacy of a drug can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, agent that induces a different biological pathway from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the condition.

Any method of alternation can be used that provides treatment to the patient. Nonlimiting examples of alternation patterns include 1-6 weeks of administration of an effective amount of one agent followed by 1-6 weeks of administration of an effective amount of a second agent. The alternation schedule can include periods of no treatment. Combination therapy generally includes the simultaneous administration of an effective ratio of dosages of two or more active agents.

Illustrative examples of specific agents that can be used in combination or alternation with the compounds of the present invention are described below in regard to asthma and arthritis. The agents set out below or others can alternatively be used to treat a host suffering from any of the other disorders listed above or that are mediated by VCAM-1 or MCP-1. Illustrative second biologically active agents for the treatment of cardiovascular disease are also provided below.

Asthma

In one embodiment, the compounds of the present invention are administered in combination or alternation with heparin, frusemide, ranitidine, an agent that effects respiratory function, such as DNAase, or immunosuppressive agents, IV gamma globulin, troleandomycin, cyclosporin (Neoral), methotrexate, FK-506, gold compounds such as Myochrysine (gold sodium thiomalate), platelet activating factor (PAF) antagonists such as thromboxane

inhibitors, leukotriene-D_4-receptor antagonists such as Accolate (zafirlukast), Ziflo (zileuton), leukotriene C_1 or C_2 antagonists and inhibitors of leukotriene synthesis such as zileuton for the treatment of asthma, or an inducible nitric oxide synthase inhibitor.

In another embodiment, the active compound is administered in combination or alternation with one or more other prophylactic agent(s). Examples of prophylactic agents that can be used in alternation or combination therapy include but are not limited to sodium cromoglycate, Intal (cromolyn sodium, Nasalcrom, Opticrom, Crolom, Ophthalmic Crolom), Tilade (nedocromil, nedocromil sodium) and ketotifen.

In another embodiment, the active compound is administered in combination or alternation with one or more other β_2-adrenergic agonist(s) (β agonists). Examples of β_2-adrenergic agonists (β agonists) that can be used in alternation or combination therapy include but are not limited to albuterol (salbutamol, Proventil, Ventolin), terbutaline, Maxair (pirbuterol), Serevent (salmeterol), epinephrine, metaproterenol (Alupent, Metaprel), Brethine (Bricanyl, Brethaire, terbutaline sulfate), Tornalate (bitolterol), isoprenaline, ipratropium bromide, bambuterol hydrochloride, bitolterol meslyate, broxaterol, carbuterol hydrochloride, clenbuterol hydrochloride, clorprenaline hydrochloride, efirmoterol fumarate, ephedra (source of alkaloids), ephedrine (ephedrine hydrochloride, ephedrine sulfate), etafedrine hydrochloride, ethylnoradrenaline hydrochloride, fenoterol hydrochloride, hexoprenaline hydrochloride, isoetharine hydrochloride, isoprenaline, mabuterol, methoxyphenamine hydrochloride, methylephedrine hydrochloride, orciprenaline sulphate, phenylephrine acid tartrate, phenylpropanolamine (phenylpropanolamine polistirex, phenylpropanolamine sulphate), pirbuterol acetate, procaterol hydrochloride, protokylol hydrochloride, psuedoephedrine (psuedoephedrine polixtirex, psuedoephedrine tannate, psuedoephedrine hydrochloride, psuedoephedrine sulphate), reproterol hydrochloride, rimiterol hydrobromide, ritodrine hydrochloride, salmeterol xinafoate, terbutaline sulphate, tretoquinol hydrate and tulobuterol hydrochloride.

In another embodiment, the active compound is administered in combination or alternation with one or more other corticosteriod(s). Examples of corticosteriods that can be used in alternation or combination therapy include but are not limited to glucocorticoids (GC), Aerobid (Aerobid-M, flunisolide), Azmacort (triamcinolone acetonide), Beclovet (Vanceril,

beclomethasone dipropionate), Flovent (fluticasone), Pulmicort (budesonide), prednisolone, hydrocortisone, adrenaline, Alclometasone Dipropionate, Aldosterone, Amcinonide, Beclomethasone Dipropionate, Bendacort, Betamethasone (Betamethasone Acetate, Betamethasone Benzoate, Betamethasone Dipropionate, Betamethasone Sodium Phosphate, Betamethasone Valerate), Budesonide, Ciclomethasone, Ciprocinonide, Clobetasol Propionate, Clobetasone Butyrate, Clocortolone Pivalate, Cloprednol, Cortisone Acetate, Cortivazol, Deflazacort, Deoxycortone Acetate (Deoxycortone Pivalate), Deprodone, Desonide, Desoxymethasone, Dexamethasone (Dexamethasone Acetate, Dexamethasone Isonicotinate, Dexamethasone Phosphate, Dexamethasone Sodium Metasulphobenzoate, Dexamethasone Sodium Phosphate), Dichlorisone Acetate, Diflorasone Diacetate, Diflucortolone Valerate, Difluprednate, Domoprednate, Endrysone, Fluazacort, Fluclorolone Acetonide, Fludrocortisone Acetate, Flumethasone (Flumethasone Pivalate), Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortin Butyl, Fluocortolone (Fluocortolone Hexanoate, Fluocortolone Pivalate), Fluorometholone (Fluorometholone Acetate), Fluprednidene Acetate, Fluprednisolone, Flurandrenolone, Fluticasone Propionate, Formocortal, Halcinonide, Halobetasol Propionate, Halometasone, Hydrocortamate Hydrochloride, Hydrocortisone (Hydrocortisone Acetate, Hydrocortisone Butyrate, Hydrocortisone Cypionate, Hydrocortisone Hemisuccinate, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Hydrocortisone Valerate), Medrysone, Meprednisone, Methylprednisolone (Methylprednisolone Acetate, Methylprednisolone, Hemisuccinate, Methylprednisolone Sodium Succinate), Mometasone Furoate, Paramethasone Acetate, Prednicarbate, Prednisolamate Hydrochloride, Prednisolone (Prednisolone Acetate, Prednisolone Hemisuccinate, Prednisolone Hexanoate, Prednisolone Pivalate, Prednisolone Sodium Metasulphobenzoate, Prednisolone Sodium Phosphate, Prednisolone Sodium Succinate, Prednisolone Steaglate, Prednisolone Tebutate), Prednisone (Prednisone Acetate), Prednylidene, Procinonide, Rimexolone, Suprarenal Cortex, Tixocortol Pivalate, Triamcinolone (Triamcinolone Acetonide, Triamcinolone Diacetate and Triamcinolone Hexacetonide).

In another embodiment, the active compound is administered in combination or alternation with one or more other antihistimine(s) (H_1 receptor antagonists). Examples of antihistimines (H_1 receptor antagonists) that can be used in alternation or combination therapy include alkylamines, ethanolamines ethylenediamines, piperazines, piperidines or

phenothiazines. Some non-limiting examples of antihistimes are Chlortrimeton (Teldrin, chlorpheniramine), Atrohist (brompheniramine, Bromarest, Bromfed, Dimetane), Actidil (triprolidine), Dexchlor (Poladex, Polaramine, dexchlorpheniramine), Benadryl (diphenhydramine), Tavist (clemastine), Dimetabs (dimenhydrinate, Dramamine, Marmine), PBZ (tripelennamine), pyrilamine, Marezine (cyclizine), Zyrtec (cetirizine), hydroxyzine, Antivert (meclizine, Bonine), Allegra (fexofenadine), Hismanal (astemizole), Claritin (loratadine), Seldane (terfenadine), Periactin (cyproheptadine), Nolamine (phenindamine, Nolahist), Phenameth (promethazine, Phenergan), Tacaryl (methdilazine) and Temaril (trimeprazine).

Alternatively, the compound of the present invention is administered in combination or alternation with

(a) xanthines and methylxanthines, such as Theo-24 (theophylline, Slo-Phylline, Uniphyllin, Slobid, Theo-Dur), Choledyl (oxitriphylline), aminophylline;

(b) anticholinergic agents (antimuscarinic agents) such as belladonna alkaloids, Atrovent (ipratropium bromide), atropine, oxitropium bromide;

(c) phosphodiesterase inhibitors such as zardaverine;

(d) calcium antagonists such as nifedipine; or

(e) potassium activators such as cromakalim for the treatment of asthma.

Arthritic disorders

In one embodiment, the compound of the present invention can also be administered in combination or alternation with apazone, amitriptyline, chymopapain, collegenase, cyclobenzaprine, diazepam, fluoxetine, pyridoxine, ademetionine, diacerein, glucosamine, hylan (hyaluronate), misoprostol, paracetamol, superoxide dismutase mimics, TNFα receptor antagonists, TNFα antibodies, P38 Kinase inhibitors, tricyclic antidepressents, cJun kinase inhibitors or immunosuppressive agents, IV gamma globulin, troleandomycin, cyclosporin (Neoral), methotrexate, FK-506, gold compounds such as Myochrysine (gold sodium thiomalate), platelet activating factor (PAF) antagonists such as thromboxane inhibitors, and inducible nitric oxide sythase inhibitors.

In another embodiment, the active compound is administered in combination or alternation with one or more other corticosteriod(s). Examples of corticosteriods that can be used in alternation or combination therapy include but are not limited to glucocorticoids (GC), Aerobid (Aerobid-M, flunisolide), Azmacort (triamcinolone acetonide), Beclovet (Vanceril, beclomethasone dipropionate), Flovent (fluticasone), Pulmicort (budesonide), prednisolone, hydrocortisone, adrenaline, Alclometasone Dipropionate, Aldosterone, Amcinonide, Beclomethasone Dipropionate, Bendacort, Betamethasone (Betamethasone Acetate, Betamethasone Benzoate, Betamethasone Dipropionate, Betamethasone Sodium Phosphate, Betamethasone Valerate), Budesonide, Ciclomethasone, Ciprocinonide, Clobetasol Propionate, Clobetasone Butyrate, Clocortolone Pivalate, Cloprednol, Cortisone Acetate, Cortivazol, Deflazacort, Deoxycortone Acetate (Deoxycortone Pivalate), Deprodone, Desonide, Desoxymethasone, Dexamethasone (Dexamethasone Acetate, Dexamethasone Isonicotinate, Dexamethasone Phosphate, Dexamethasone Sodium Metasulphobenzoate, Dexamethasone Sodium Phosphate), Dichlorisone Acetate, Diflorasone Diacetate, Diflucortolone Valerate, Difluprednate, Domoprednate, Endrysone, Fluazacort, Fluclorolone Acetonide, Fludrocortisone Acetate, Flumethasone (Flumethasone Pivalate), Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortin Butyl, Fluocortolone (Fluocortolone Hexanoate, Fluocortolone Pivalate), Fluorometholone (Fluorometholone Acetate), Fluprednidene Acetate, Fluprednisolone, Flurandrenolone, Fluticasone Propionate, Formocortal, Halcinonide, Halobetasol Propionate, Halometasone, Hydrocortamate Hydrochloride, Hydrocortisone (Hydrocortisone Acetate, Hydrocortisone Butyrate, Hydrocortisone Cypionate, Hydrocortisone Hemisuccinate, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Hydrocortisone Valerate), Medrysone, Meprednisone, Methylprednisolone (Methylprednisolone Acetate, Methylprednisolone, Hemisuccinate, Methylprednisolone Sodium Succinate), Mometasone Furoate, Paramethasone Acetate, Prednicarbate, Prednisolamate Hydrochloride, Prednisolone (Prednisolone Acetate, Prednisolone Hemisuccinate, Prednisolone Hexanoate, Prednisolone Pivalate, Prednisolone Sodium Metasulphobenzoate, Prednisolone Sodium Phosphate, Prednisolone Sodium Succinate, Prednisolone Steaglate, Prednisolone Tebutate), Prednisone (Prednisone Acetate), Prednylidene, Procinonide, Rimexolone, Suprarenal Cortex, Tixocortol Pivalate, Triamcinolone (Triamcinolone Acetonide, Triamcinolone Diacetate and Triamcinolone Hexacetonide).

In another embodiment, the active compound is administered in combination or alternation with one or more other non-steroidal anti-inflammatory drug(s) (NSAIDS). Examples of NSAIDS that can be used in alternation or combination therapy are carboxylic acids, propionic acids, fenamates, acetic acids, pyrazolones, oxicans, alkanones, gold compounds and others that inhibit prostaglandin synthesis, preferably by selectively inhibiting cylcooxygenase-2 (COX-2). Some nonlimiting examples of COX-2 inhibitors are Celebrex (celecoxib), Bextra (valdecoxib), Dynastat (parecoxib sodium) and Vioxx (rofacoxib). Some non-limiting examples of NSAIDS are aspirin (acetylsalicylic acid), Dolobid (diflunisal), Disalcid (salsalate, salicylsalicylate), Trisilate (choline magnesium trisalicylate), sodium salicylate, Cuprimine (penicillamine), Tolectin (tolmetin), ibuprofen (Motrin, Advil, Nuprin Rufen), Naprosyn (naproxen, Anaprox, naproxen sodium), Nalfon (fenoprofen), Orudis (ketoprofen), Ansaid (flurbiprofen), Daypro (oxaprozin), meclofenamate (meclofanamic acid, Meclomen), mefenamic acid, Indocin (indomethacin), Clinoril (sulindac), tolmetin, Voltaren (diclofenac), Lodine (etodolac), ketorolac, Butazolidin (phenylbutazone), Tandearil (oxyphenbutazone), piroxicam (Feldene), Relafen (nabumetone), Myochrysine (gold sodium thiomalate), Ridaura (auranofin), Solganal (aurothioglucose), acetaminophen, colchicine, Zyloprim (allopurinol), Benemid (probenecid), Anturane (sufinpyrizone), Plaquenil (hydroxychloroquine), Aceclofenac, Acemetacin, Acetanilide, Actarit, Alclofenac, Alminoprofen, Aloxiprin, Aluminium Aspirin, Amfenac Sodium, Amidopyrine, Aminopropylone, Ammonium Salicylate, Ampiroxicam, Amyl Salicylate, Anirolac, Aspirin, Auranofin, Aurothioglucose, Aurotioprol, Azapropazone, Bendazac (Bendazac Lysine), Benorylate, Benoxaprofen, Benzpiperylone, Benzydamine, Hydrochloride, Bornyl Salicylate, Bromfenac Sodium, Bufexamac, Bumadizone Calcium, Butibufen Sodium, Capsaicin, Carbaspirin Calcium, Carprofen, Chlorthenoxazin, Choline Magnesium Trisalicylate, Choline Salicylate, Cinmetacin, Clofexamide, Clofezone, Clometacin, Clonixin, Cloracetadol, Cymene, Diacerein, Diclofenac (Diclofenac Diethylammonium Salt, Diclofenac Potassium, Diclofenac Sodium), Diethylamine Salicylate, Diethylsalicylamide, Difenpiramide, Diflunisal, Dipyrone, Droxicam, Epirizole, Etenzamide, Etersalate, Ethyl Salicylate, Etodolac, Etofenamate, Felbinac, Fenbufen, Fenclofenac, Fenoprofen Calcium, Fentiazac, Fepradinol, Feprazone, Floctafenine, Flufenamic, Flunoxaprofen, Flurbiprofen (Flurbiprofen Sodium), Fosfosal, Furprofen, Glafenine, Glucametacin, Glycol Salicylate, Gold Keratinate, Harpagophytum

Procumbens, Ibufenac, Ibuprofen, Ibuproxam, Imidazole Salicylate, Indomethacin (Indomethacin Sodium), Indoprofen, Isamifazone, Isonixin, Isoxicam, Kebuzone, Ketoprofen, Ketorolac Trometamol, Lithium Salicylate, Lonazolac Calcium, Lornoxicam, Loxoprofen Sodium, Lysine Aspirin, Magnesium Salicylate, Meclofenamae Sodium, Mefenamic Acid, Meloxicam, Methyl Butetisalicylate, Methyl Gentisate, Methyl Salicylate, Metiazinic Acid, Metifenazone, Mofebutazone, Mofezolac, Morazone Hydrochloride, Morniflumate, Morpholine Salicylate, Nabumetone, Naproxen (Naproxen Sodium), Nifenazone, Niflumic Acid, Nimesulide, Oxametacin, Oxaprozin, Oxindanac, Oxyphenbutazone, Parsalmide, Phenybutazone, Phenyramidol Hydrochloride, Picenadol Hydrochloride, Picolamine Salicylate, Piketoprofen, Pirazolac, Piroxicam, Pirprofen, Pranoprofen, Pranosal, Proglumetacin Maleate, Proquazone, Protizinic Acid, Ramifenazone, Salacetamide, Salamidacetic Acid, Salicylamide, Salix, Salol, Salsalate, Sodium Aurothiomalate, Sodium Gentisate, Sodium Salicylate, Sodium Thiosalicylate, Sulindac, Superoxide Dismutase (Orgotein, Pegorgotein, Sudismase), Suprofen, Suxibuzone, Tenidap Sodium, Tenoxicam, Tetrydamine, Thurfyl Salicylate, Tiaprofenic, Tiaramide Hydrochloride, Tinoridine Hydrochloride, Tolfenamic Acid, Tometin Sodium, Triethanolamine Salicylate, Ufenamate, Zaltoprofen, Zidometacin and Zomepirac Sodium.

Cardiovascular Disease

Compounds useful for combining with the compounds of the present invention for the treatment of cardiovascular disease encompass a wide range of therapeutic compounds.

Ileal bile acid transporter (IBAT) inhibitors, for example, are useful in the present invention, and are disclosed in patent application no. PCT/US95/10863, herein incorporated by reference. More IBAT inhibitors are described in PCT/US97/04076, herein incorporated by reference. Still further IBAT inhibitors useful in the present invention are described in U.S. Application Serial No. 08/816,065, herein incorporated by reference. More IBAT inhibitor compounds useful in the present invention are described in WO 98/40375, and WO 00/38725, herein incorporated by reference. Additional IBAT inhibitor compounds useful in the present invention are described in U.S. Application Serial No. 08/816,065, herein incorporated by reference.

In another aspect, the second biologically active agent is a statin. Statins lower cholesterol by inhibiting of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, a

key enzyme in the cholesterol biosynthetic pathway. The statins decrease liver cholesterol biosynthesis, which increases the production of LDL receptors thereby decreasing plasma total and LDL cholesterol (Grundy, S. M. *New Engl. J. Med. 319*, 24 (1988); Endo, A. *J. Lipid Res. 33*, 1569 (1992)). Depending on the agent and the dose used, statins may decrease plasma triglyceride levels and may increase HDLc. Currently the statins on the market are lovastatin (Merck), simvastatin (Merck), pravastatin (Sankyo and Squibb) and fluvastatin (Sandoz). A fifth statin, atorvastatin (Parke-Davis/Pfizer), is the most recent entrant into the statin market. Any of these statins or thers can be used in combination with the chalcones of the present invention.

MTP inhibitor compounds useful in the combinations and methods of the present invention comprise a wide variety of structures and functionalities. Some of the MTP inhibitor compounds of particular interest for use in the present invention are disclosed in WO 00/38725, the disclosure from which is incorporated by reference. Descriptions of these therapeutic compounds can be found in Science, 282, 23 October 1998, pp. 751-754, herein incorporated by reference.

Cholesterol absorption antagonist compounds useful in the combinations and methods of the present invention comprise a wide variety of structures and functionalities. Some of the cholesterol absorption antagonist compounds of particular interest for use in the present invention are described in U.S. Patent No. 5,767,115, herein incorporated by reference. Further cholesterol absorption antagonist compounds of particular interest for use in the present invention, and methods for making such cholesterol absorption antagonist compounds are described in U.S. Patent No. 5,631,365, herein incorporated by reference.

A number of phytosterols suitable for the combination therapies of the present invention are described by Ling and Jones in "Dietary Phytosterols: A Review of Metabolism, Benefits and Side Effects," Life Sciences, 57 (3), 195-206 (1995). Without limitation, some phytosterols of particular use in the combination of the present invention are Clofibrate, Fenofibrate, Ciprofibrate, Bezafibrate, Gemfibrozil. The structures of the foregoing compounds can be found in WO 00/38725.

Phytosterols are also referred to generally by Nes (Physiology and Biochemistry of Sterols, American Oil Chemists' Society, Champaign, Ill., 1991, Table 7-2). Especially

preferred among the phytosterols for use in the combinations of the present invention are saturated phytosterols or stanols. Additional stanols are also described by Nes (Id.) and are useful in the combination of the present invention. In the combination of the present invention, the phytosterol preferably comprises a stanol. In one preferred embodiment the stanol is campestanol. In another preferred embodiment the stanol is cholestanol. In another preferred embodiment the stanol is clionastanol. In another preferred embodiment the stanol is coprostanol. In another preferred embodiment the stanol is 22,23-dihydrobrassicastanol. In another embodiment the stanol is epicholestanol. In another preferred embodiment the stanol is fucostanol. In another preferred embodiment the stanol is stigmastanol.

Another embodiment the present invention encompasses a therapeutic combination of a compound of the present invention and an HDLc elevating agent. In one aspect, the second HDLc elevating agent can be a CETP inhibitor. Individual CETP inhibitor compounds useful in the present invention are separately described in WO 00/38725, the disclosure of which is herein incorporated by reference. Other individual CETP inhibitor compounds useful in the present invention are separately described in WO 99/14174, EP818448, WO 99/15504, WO 99/14215, WO 98/04528, and WO 00/17166, the disclosures of which are herein incorporated by reference. Other individual CETP inhibitor compounds useful in the present invention are separately described in WO 00/18724, WO 00/18723, and WO 00/18721, the disclosures of which are herein incorporated by reference. Other individual CETP inhibitor compounds useful in the present invention are separately described in WO 98/35937 as well as U.S. Patent Nos. 6,313,142, 6,310,075, 6,197,786, 6,147,090, 6,147,089, 6,140,343, and 6,140,343, the disclosures of which is herein incorporated by reference.

In another aspect, the second biologically active agent can be a fibric acid derivative. Fibric acid derivatives useful in the combinations and methods of the present invention comprise a wide variety of structures and functionalities which have been reported and published in the art.

In another embodiment the present invention encompasses a therapeutic combination of a compound of the present invention and an antihypertensive agent. Hypertension is defined as persistently high blood pressure. In another embodiment, the chalcone is administered in

combination with an ACE inhibitor, a beta andrenergic blocker, alpha andrenergic blocker, angiotensin II receptor antagonist, vasodilator and diuretic.

Pharmaceutical Compositions

Any host organism, including a pateint, mammal, and specifically a human, suffering from any of the above-described conditions can be treated by the administration of a composition comprising an effective amount of the compound of the invention or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier or diluent.

The composition can be administered in any desired manner, including oral, topical, parenteral, intravenous, intradermal, intra-articular, intra-synovial, intrathecal, intra-arterial, intracardiac, intramuscular, subcutaneous, intraorbital, intracapsular, intraspinal, intrasternal, topical, transdermal patch, via rectal, vaginal or urethral suppository, peritoneal, percutaneous, nasal spray, surgical implant, internal surgical paint, infusion pump, or via catheter. In one embodiment, the agent and carrier are administered in a slow release formulation such as an implant, bolus, microparticle, microsphere, nanoparticle or nanosphere. For standard information on pharmaceutical formulations, see Ansel, et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Sixth Edition, Williams & Wilkins (1995).

An effective dose for any of the herein described conditions can be readily determined by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to: the species of patient; its size, age, and general health; the specific disease involved; the degree of involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication. Typical systemic dosages for all of the herein described conditions are those ranging from 0.1 mg/kg to 500 mg/kg of body weight per day as a single daily dose or divided daily doses. Preferred dosages for the described conditions range from 5-1500 mg per day. A more particularly preferred dosage for the desired conditions ranges from

25-750 mg per day. Typical dosages for topical application are those ranging from 0.001 to 100% by weight of the active compound.

The compound is administered for a sufficient time period to alleviate the undesired symptoms and the clinical signs associated with the condition being treated.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutic amount of compound *in vivo* in the absence of serious toxic effects.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

A preferred mode of administration of the active compound for systemic delivery is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound or its salts can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action. The compounds can also be administered in combination with nonsteroidal antiinflammatories such as ibuprofen, indomethacin, fenoprofen, mefenamic acid, flufenamic acid, sulindac. The compound can also be administered with corticosteriods.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS).

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters and polylactic acid. Methods for preparation of

such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the compound is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

Suitable vehicles or carriers for topical application can be prepared by conventional techniques, such as lotions, suspensions, ointments, creams, gels, tinctures, sprays, powders, pastes, slow-release transdermal patches, suppositories for application to rectal, vaginal, nasal or oral mucosa. In addition to the other materials listed above for systemic administration, thickening agents, emollients and stabilizers can be used to prepare topical compositions. Examples of thickening agents include petrolatum, beeswax, xanthan gum, or polyethylene, humectants such as sorbitol, emollients such as mineral oil, lanolin and its derivatives, or squalene.

Any of the compounds described herein for combination or alternation therapy can be administered as any derivative that upon administration to the recipient, is capable of providing directly or indirectly, the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as "physiologically acceptable salts"), and a compound which has been alkylated or acylated at an appropriate position. The modifications can affect the biological activity of the compound, in some cases increasing the activity over the parent compound. This can easily be assessed by preparing the derivative and testing its anti-inflammatory activity according to known methods.

Biological Activity of Active Compounds

The ability of a compound described herein to inhibit the expression of VCAM-1 or in the treatment of diseases in a host can be assessed using any known method, including that described in detail below.

In Vitro MCP-1 Activity Assay

Cultured human endothelial cells were seeded in 96-well plates. On the following day cells were stimulated with TNF-α (1ng/ml) in the presence or absence of compounds dissolved in DMSO. To establish a dose curve and an IC_{50}, multiple concentrations in 2- to 5-fold increments were used. Cells were exposed to TNF-α and compounds for approximately 16 hours. The next day the cells were visually examined via light microscopy to score for visual signs of toxicity. Cell culture media, diluted 1:10, was analyzed by an MCP-1 immunoassay kit (R & D Systems). This assay is a sandwich immunoassay using immobilized anti-MCP-1 antibody in 96-well plate to capture secreted MCP-1 in cell culture media. Captured MCP-1 was subsequently detected with a horse radish peroxidase-conjugated anti-MCP-1 antibody for color development. Compound 3 expressed an IC_{50} values of >10(the amount of compound (μM) required to achieve a 50% reduction compared to control (cells stimulated with TNF-α only)).

In Vitro VCAM-1 Assay

Cell Culture and compound dosing: Cultured primary human aortic (HAEC) or pulmonary (HPAEC) endothelial cells were obtained from Clonetics, Inc., and were used below passage 9. Cells were seeded in 96 well plates such that they would reach 90-95% confluency by the following day. On the following day the cells were stimulated with TNF-α (1ng/ml) in the presence or absence of compounds dissolved in DMSO such that the final concentration of DMSO is 0.25% or less. To establish a dose curve for each compound, four concentrations in 2- to 5-fold increments were used. Cells were exposed to TNF-α and compounds for approximately 16 hours. The next day the cells were examined under microscope to score for visual signs of toxicity or cell stress.

Following 16hr exposure to TNF-α and compound the media was discarded and the cells were washed once with Hanks Balanced Salt Solution (HBSS)/ Phosphate buffered saline (PBS) (1:1). Primary antibodies against VCAM-1 (0.25μg/ml in HBSS/ PBS + 5% FBS) were added and incubated for 30-60 minutes at 37°C. Cells were washed with HBSS/PBS three times, and secondary antibody Horse Radish Peroxidase (HRP)-conjugated goat anti-mouse IgG (1:500 in HBSS/PBS + 5% FBS) were added and incubated for 30 minutes at 37°C. Cells were washed with HBSS/ PBS four time and TMB substrate were added and incubated at room temperature in the dark until there was adequate development of blue color. The length of time of incubation was typically 5-15 minutes. 2N sulfuric acid was added to stop the color development and the data was collected by reading the absorbance on a BioRad ELISA plate reader at OD 450nm. The results are expressed as IC_{50} values (the concentration (micromolar) of compound required to inhibit 50% of the maximal response of the control sample stimulated by TNF-α only). Compounds exhibiting IC_{50}'s of less than 5 micromolar are tabulated in Biological Table 1.

Biological Table 1

Example Number	VCAM-1 IC50 (μM)	Example Number	VCAM-1 IC50 (μM)	Example Number	VCAM-1 IC50 (μM)	Example Number	VCAM-1 IC50 (μM)
1	<1	31	>10	61	<1	91	<5
2	<5	32	<5	62	<5	92	<1
3	<1	33	<5	63	<10	93	<1
4	<10	34	>10	64	>10	94	<1
5	<1	35	>10	65	<1	95	<1
6	<1	36	<5	66	<1	96	<5
7	<1	37	>10	67	<10	97	NE
8	<1	38	<10	68	<5	98	<5

9	<5	39	>10	69	<5	99	>10
10	<5	40	<1	70	<5	100	>10
11	<5	41	<5	71	NE	101	>10
12	<5	42	<5	72	0	102	>10
13	<5	43	<5	73	0	103	>10
14	<1	44	<1	74	>10	104	NE
15	>10	45	<5	75	>10	105	NE
16	<5	46	<10	76	>10	106	<10
17	<5	47	>10	77	<5	107	NE
18	<5	48	<10	78	<10	108	<10
19	<1	49	<10	79	<1	109	NE
20	>10	50	>10	80	<5	110	>10
21	<5	51	<5	81	<1	111	>10
22	>10	52	>10	82	NE	112	NE
23	<1	53	<5	83	<1	113	<5
24	>10	54	<10	84	<5	114	<5
25	>10	55	<5	85	<1	115	<5
26	>10	56	<1	86	<5	116	
27	<5	57	<5	87	<1	117	<5
28	<5	58	>10	88		118	<10
29	<1	59	NE	89	NE	119	
30	<1	60	<1	90	<1	120	<1

Rheumatoid Arthritis Protocol

Male Lewis rats (150-175g) from Charles River Laboratories were anesthetized on day 0 with 3-5% isoflurane anesthesia while the tail base was shaved and adjuvant mixture was injected. Fifty μL of adjuvant (10 mg/ml M. butyricum in mineral oil) was injected subcutaneously into two sites at the tail base. Paw swelling was monitored using a plethysmometer (UGO Basile), after shaving each leg to the level of the Achilles tendon to mark the level of immersion. A baseline paw measurement for both hindpaws was taken between d2-d5 and a second measurement was taken on day 7-8. Onset of paw swelling occurred rapidly between d9-11 and daily measurements were performed every weekday between d9 and day 15. Compounds of the invention and vehicles were dosed either prophylactically (d1-14), or therapeutically (d9-14) after swelling was confirmed. Solutions were injected subcutaneously or given orally by gavage 1-2 times per day. From day 0, rats were weighed every 2-3 days and overall health was monitored. Plasma drug levels, if desired, were measured in tail-vein derived blood samples taken on day 14. On day 15, blood samples were obtained by cardiac puncture, rats were euthanized with CO_2 , selected organs removed and both hindpaws were amputated and placed in 10% buffered formalin for histopathological analysis. See Biological Table 2.

Biological Table 2

Compound Example Number	% Inhibition 60 mg/Kg/day, sq, bid, d1-14
3	96
6	77
29	82
60	62*

* 75 mg/kg/day, sq,bid, d1-14

Asthma Protocol

Balb/C mice (6-8 weeks old) are sensitized to ovalbumin (ova) (8 ug ova absorbed in 3.3 mg Alum inject) on days 0 and 5. On day 12, the mice were aerosol challenged with 0.5% ovalbumin dissolved in sterile saline for 1 hr in the AM, and then again in the PM (at least 4 hr apart). On day 14, the mice were anesthetized with ketamine/xylazine/acepromazine cocktail, exsanguinated, and then euthanized. Following blood collection, bronchoaveolar lavage was performed on each animal. Total cell counts were conducted on the lavage fluid, which was subsequently diluted with cell media 1:1. Slides of the lavage fluid were made by spinning the samples with a cytospin centrifuge. Slides were airdried and stained with x. Cell differentials of the lavage fluid were completed at the conclusion of the study. All compounds except Example 2 were well tolerated with no body weight loss throughout the course of the study. Statistical analysis involved ANOVA and Tukey-Kramer post hoc tests. Compounds were administered except where noted by subcutaneous injection once daily from day 0-13. The formulations used contained various mixtures of the following excipients (pharmasolve, cremophor RH 40, tween 80, PEG 300). See Biological Table 3

Biological Table 3

Compound Example Number	% Inhibition sc, daily dosing at 100 mg/kg from day 0-13
3	79
6	81
86	48
36	71
60	36
29	24

Effect of serum IgE levels in ovalbumin sensitized Balb/c mice

Peripheral blood samples were collected from ovalbumin (Calbiochem) or vehicle (2% Cremophor/Bicarbonate) treated Balb/c mice (Charles River) with or without administration of test compound (100mg/kg/d, from day 0 to day 14). Serum was obtained by centrifugation and transferred into Microtainer serum tubes and frozen at -80^{0}C. Mouse IgE ELISA Quantitation Kit (Bethyl Laboratories, Inc. Montgomery, TX or PharMingen, San Diego, CA) was applied to measure the IgE levels of serum samples. Immuno-reactions were performed as Kit protocol with IgE standard and serum samples in duplicates. The results were read in a microplate reader (Bio-Rad Model 550) at 450nm and the amounts of IgE were calculated according to the standard curve. The limit of detection in our experiments was 7ng/ml. Compound 3 administrated at 100mg/kg/d from day 0 to day 14, reduced serum IgE levels by 38% in ovalbumin sensitized Balb/c mice compared with vehicle treated mice.

Effect of levels of IL-13, IL-5, IL-4, IFN-gamma and IL-2 mRNA in mouse lungs of Balb/c mice with ovalbumin sensitization and challenge

Lung tissues were collected from ovalbumin (Calbiochem) or vehicle (2% Cremophor/Bicarbonate) sensitized Balb/c mice (Charles River) with or without treatment of test compound (100mg/kg/d, from day 0 to day 14). Total RNA samples were isolated by the Trizol method (Life Technologies, Grand Island, NY) and quantitatively measured by UV spectrophotometer, as well as qualitatively examined by ethidum bromide stained gel electrophoresis. First strand cDNA templates were generated with oligo (dT) by Reverse Transcription Kit (Invitrogen, Carlsbad, CA). The initial amounts of mRNA of each samples were quantitatively determined by running a SYBR Green (Qiagen, Valencia, CA) based real-time PCR (programmed as: initial denaturation at 95°C for 15 minutes, denaturation at 95°C for 15 seconds, annealing and elongation at 51±1 °C for 1 minute for total 40 cycles) with a specific pair of primers (IDT Corporation, Coralville, IA) and control primers for GAPDH in iCycler IQ Optical System (Hercules, CA). The data were statistically analyzed by ANOVA

and t-tests with multiple comparisons of means (n = 5 and P < 0.05 were considered significant). Compound 3 administrated at 100mg/kg/d, significantly inhibited ovalbumin induced levels of IL-13, IL-5 and IL-4 mRNA in the lung of Balb/c mice by 82%, 98% and 68% respectively; without significantly affecting IFN-gamma and IL-2 compared with vehicle treated mice.

List of Primers used in above experiments:

Primer Name	Forward Sequence	Reverse Sequence	Annealing Temperature
GAPDH	CTA CCC CCA ATG TGT CC	CTG CTT CAC CAC CTT CTT	52.2
IL-13	AAF AFF AGA GCA AAT GAA AG	CTG TGT AAC CTT CCC AAC A	51.3
IL-4	TGA ATG AGT CCA AGT CCA	AGC ATG GTG GCT CAG TA	51.2
IL5	AGC TCT GTT GAC AAG CAA T	CCC TGA AAG ATT TCT CCA ATG	52.4
IL-2	GTC GAC TTT CTG AGG AGA TG	ATG TGT TGT AAG CAG GAG GT	53.2
IFN-γ	TTC TGT CTC CTC AAC TAT TTC T	CAA TCA CAG TCT TGG CTA AT	51.3

Smooth Muscle Cell Proliferation Protocol

Human Aortic Smooth Mucle Cells (HAoSMC) were obtained from Clonetics, Inc. and were used below passage 10. Cells were seeded in 24-well plates. When cells were 80% confluent, they were made quiescent by adding media containing 0.2% serum (as compared to 5% serum in normal culture media) for 48 hours. The cells were, then, stimulated by 5% serum in the presence or absence of compounds dissolved in DMSO. To establish a dose curve and IC_{50} for each compound, multiple concentrations in the range of 20 to 0.05 μM were used. Rapamycin (at 1 and 0.1μM) was used as a positive control for the assay. After a 20 hour incubation with or without test compounds, 3H-thymidine (0.5μCi/ well) was added to the cells for 4 hours of labeling. Washed cells were then lysed in NaOH and the amount of 3H-thymidine incorporation was determined. Cytotoxicity of the drug was measured by use of the CytolTox 96 assay kit (Promega, Madison, WI). Compound 3 had an IC_{50} of 0.5 μM.

Effect of Test Compounds on LPS-Stimulated IL-1β

Human peripheral blood mononuclear cells were treated with or without Compound 3 for 1 hour, then stimulated with LPS (1-2 μg/ml) for 3 hours. Condition media was collected and IL-1β measured using an ELISA kit. Compound 3 demonstrated a dose dependent inhibition of LPS-stimulated IL-1β secretion. See Biological Table 4

Biological Table 4

Amount of Compound 3 (μM)	Percent IL-1β Secreted
1.25	>40
2.5	>10
5	>5
10	>1

Reduction of Plasma TNF-α levels and lung VCAM-1 mRNA levels in LPS-Challenged Mice.

Balb/C mice (6-8 weeks) were injected with LPS (1 mg/kg; 5 mls/kg) and sacrificed 2hr later. Blood was collected for plasma TNF-α levels and lungs for measurement of VCAM-1 mRNA levels by quantitative RT-PCR. Compound 3 administered subcutaneously at a dose of 100 mg/kg/d, 2hr prior to LPS injection, inhibited TNF-α production by 80% and VCAM-1 expression by 60% compared with vehicle controls.

Disease Modifying Anti-Rheumatic Drug (DMARD) activity in Rat Adjuvant Arthritis

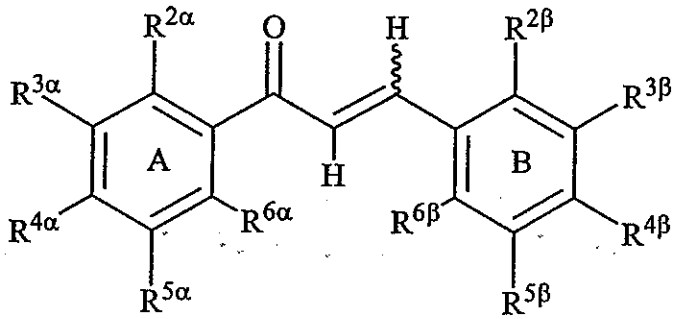
Compound 3 at twice daily subcutaneous doses of 60, 40 and 20 mg/kg/d was found to inhibit bone erosion in the ankle joint by histopathological analysis when administered prophylactically in the rat adjuvant arthritis model. The evaluation was carried out with hematoxylin and eosin stained ankle cross sections by a certified veterinary pathologist. When dosed prophylactically at doses of 100, 50 and 25 mg/kg/d, b.i.d., s.c., Compound 3 was also

found to inhibit splenomegaly. Splenomegaly tracks with bone erosion in the adjuvant arthritis model and is thought to be a predictor of DMARDs activity.

Modifications and variations of the present invention relating to compounds and methods of treating diseases will be obvious to those skilled in the art from the foregoing detailed description of the invention. Such modifications and variations are intended to come within the scope of the appended claims.

CLAIMS:

1. A compound of Formula I



(I)

or its pharmaceutically acceptable salt or ester, wherein:

the wavy line indicates that the compound can be in the form of the E- or Z- isomer;

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl, hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$,

$-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $-SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, sulfonic acid, sulfonate, sulfate, sulfinic acid, sulfenic acid, cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, $-PO_2H_2$, $-PO_3H_2$, $-P(R^2)O_2H$, and phosphate, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 12-membered monocyclic, bicylic, tricyclic or benzofused ring;

wherein lower alkyl refers to a C1 to C4 alkyl group;

wherein one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$, or one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ must be a carbon-carbon linked heterocyclic or heteroaryl;

wherein when one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

wherein when one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ is a carbon-carbon linked heterocyclic or heteroaryl, only one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ can be $-OCH_3$;

with the proviso that $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; or

at least one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$ or one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$ must be selected from the group consisting of cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$,

$-SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

2. The compound of Claim 1 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, R^1, R^2, R^7, and R^8 are as defined in claim 1; and

with the proviso that $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; and

at least one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, or one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$ must be selected from the group consisting of cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$,

$-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$.

3. The compound of Claim 1 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$, $R^{6\beta}$, R^1, R^2, R^7, and R^8 are as defined in claim 1; and

wherein one of $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$; and

with the proviso that $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; and

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, or $R^{6\alpha}$ must be selected from the group consisting of cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $-SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$.

4. The compound of Claim 3 or its pharmaceutically acceptable salt or ester, wherein:

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; or

$R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; and

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$.

5. The compound of Claim 4 or its pharmaceutically acceptable salt or ester, wherein:

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$.

6. The compound of Claim 5 or its pharmaceutically acceptable salt or ester, wherein:

at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, carboxy,

$-C(O)OR^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6.

7. The compound of Claim 6 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, nitro, alkyl, lower alkyl, alkenyl, alkynyl, carbocycle, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkylthioalkyl, cycloalkylthioalkyl, arylthio lower alkyl, aralkyl lower thioalkyl, heteroarylthio lower alkyl, heteroaralkyl lower thioalkyl, heterocyclicthio lower alkyl, heterocyclicalkyl lower thioalkyl, lower alkyl S(O)-lower alkyl, lower alkyl-$S(O)_2$-lower alkyl, arylsulfinyl lower alkyl, arylsulfonyl lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl, hydroxyl, hydroxyalkyl, alditol, carbohydrate, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, acylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, thiol, alkylthio, cycloalkylthio, cycloalkylalkylthio, haloalkylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, heterocyclicthio, heterocyclicalkylthio, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $-SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$,

$-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, and $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

8. The compound of Claim 7 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, $-C(O)R^2$, $R^2C(O)$alkyl, aminoalkyl, cycloalkylaminoalkyl, arylamino lower alkyl, heteroarylamino lower alkyl, heterocyclicamino lower alkyl, hydroxyl, hydroxyalkyl, polyol alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, haloalkoxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy,

$-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, heterocyclicamino, heterocyclicalkylamino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-N(R^2)C(O)R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NHC(O)NR^7R^8$, $-NHC(O)N(R^2)_2$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $-SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2R^2$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(CH_3)_2C(O)OH$, and $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^1 is independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, aryl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

wherein all R^1, R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, alkenyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

9. The compound of Claim 8 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, lower alkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, heterocyclicamino lower alkyl, hydroxyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, cycloalkyloxy, cycloalkylalkoxy, heteroarylalkoxy, heteroaryl lower alkoxy, heterocyclicoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, dialkylamino, $N(R^2)_2$, $-NR^7R^8$, carboxy, $-C(O)OR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(CH_3)_2C(O)OH$, and $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, all of which can be optionally substituted by one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, lower alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, and heterocyclicalkyl, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently selected from the group consisting of alkyl, alkenyl and aryl and linked together forming a 4- to 8-membered monocyclic or benzofused ring;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

10. The compound of Claim 9 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, heteroaryl, heteroaryl lower alkyl, heterocyclic, heterocyclic lower alkyl, alkoxy, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, polyoxyalkylene, heteroaryl lower alkoxy, heterocyclicalkoxy, heterocyclic lower alkoxy, carboxy, $-C(O)OR^2$, $-C(O)N(R^2)_2$, and $-C(O)NR^7R^8$, all of which can be optionally substituted

by one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, hydroxy, hydroxyalkyl, heterocyclic, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is independently selected from the group consisting of alkyl, and lower alkyl, wherein all may be substituted by one or more selected from the group consisting of halo, lower alkyl, $-NR^7R^8$, alkoxy, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 5- to 7-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from carboxy or $-C(O)OR^2$;

wherein all R^2, R^7 and R^8 substituents can be optionally substituted with one or more selected from the group consisting of halo, lower alkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$.

11. The compound of Claim 10 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, heterocyclic lower alkoxy, and carboxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

12. The compound of Claim 11 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and –$C(O)N(R^2)_2$;

R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl;

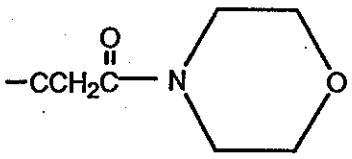
with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

13. The compound of Claim 12 or its pharmaceutically acceptable salt or ester, wherein:

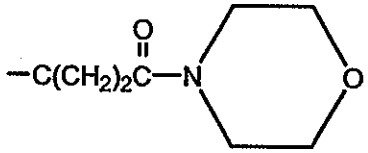
$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, lower alkoxy, -$(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, -NR^7R^8, -$C(O)NR^7R^8$, and -$C(O)N(R^2)_2$;

14. The compound of Claim 13 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, fluorine, chlorine, methoxy, ethoxy, propoxy, 3-(1-morpholino) propoxy, 2-(1-morpholino) ethoxy, $CH_3O(CH_2)_2O(CH_2)_2$-,



, and



;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be selected from the group consisting of thiophen-2-yl, thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, indol-2-yl, indol-3-yl, pyrrol-2-yl, pyrrol-3-yl, 1-methyl-indol-2-yl, 1-methyl-indol-3-yl, N-Boc-indol-2-yl, N-Boc-indol-3-yl,

N-Boc-pyrrol-2-yl, and N-Boc-pyrrol-3-yl.

15. The compound of Claim 14 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, methoxy, 3-(1-morpholino) propoxy, 2-(1-morpholino) ethoxy, and$CH_3O(CH_2)_2O(CH_2)_2$;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be selected from the group consisting of thiophen-2-yl, benzo[b]thiophen-2-yl, indol-2-yl, 1-methyl-indol-2-yl, N-Boc-indol-2-yl, N-Boc-pyrrol-2-yl, and N-Boc-pyrrol-3-yl.

16. The compound of Claim 15 selected from the group consisting of:

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid;

4-[3*E*-(4-Pyrimidin-5-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(4-Thiazol-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

2-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(3,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

2-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid, sodium salt;

4-[3*E*-(4-Thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3-{4-(thien-2-yl)-phenyl}-3-oxo-*E*-propenyl]-benzoic acid, sodium salt;

4-[3-{4-(thien-2-yl)-phenyl}-3-oxo-*E*-propenyl]-benzoic acid;

4-[3-(2-Methoxy-4-thiophen-2-yl-phenyl)-3-oxo-*E*-propenyl]-benzoic acid;

4-[3*E*-(4-Pyrrolidin-1-yl-3-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-{4-Fluoro-3-(thiophen-2-yl)-phenyl}-acryloyl]-benzoic acid;

4-(3*E*-{4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic acid;

4-[3*E*-(2-Fluoro-4-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-pyrimidin-5-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2-Cyclopropylmethoxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[5-(3,5-Dimethyl-isoxazol-4-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(4-Methoxy-2-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

2-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

2-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-indole-1-carboxylic acid *tert*-butyl ester;

4-[3*E*-(2,6-Dimethoxy-4-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[5-(2,4-Dimethoxy-pyrimidin-5-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-6-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[2,4-Dimethoxy-5-(5-methyl-thiophen-2-yl)-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(4-Methoxy-3-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(3-Thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

3-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(3-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2-Methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-pyrazin-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[4-(1-Carboxy-1-methyl-ethoxy)-2-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

2-[3*E*-(4-Methoxy-3-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-(3*E*-{2-Methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic acid;

4-{3*E*-[4-(3-Hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

5-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-thiophene-2-carboxylic acid methyl ester;

5-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-thiophene-2-carboxylic acid;

4-[3*E*-(4-Ethoxy-2-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(4-Hydroxy-2-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-thiazol-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid, sodium salt;

2-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-pyrrole-1-carboxylic acid *tert*-butyl ester;

4-[3*E*-(2-Hydroxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[2-(1-Carboxy-1-methyl-ethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride;

2 4-{3*E*-[5-(1H-Indol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[2-(3,5-Dimethyl-isoxazol-4-ylmethoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(2-Pyrrolidin-1-yl-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[2-(3-Hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[2-(3-Morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride;

4-{3*E*-[4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, hydrochloride;

4-[3*E*-(2-Dimethylcarbamoylmethoxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-[3*E*-(4-Methoxy-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[2,4-Dimethoxy-5-(2-methyl-thiazol-4-yl)-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[5-(1*H*-Benzoimidazol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-[3*E*-(2-Carbamoylmethoxy-4-methoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-2-oxo-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid;

4-(3*E*-{4-Methoxy-2-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic acid, hydrochloride;

4-{3*E*-[2,4-Dimethoxy-5-(1*H*-pyrazol-4-yl)-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[2,4-Dimethoxy-5-(2*H*-tetrazol-5-yl)-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[5-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

2-{4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-phenyl}-2-methyl-propionic acid;

4-{3*E*-[5-(2-Cyclopropyl-1*H*-imidazol-4-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid, hydrochloride;

4-{3*E*-[5-(4-Isobutyl-4H-[1,2,4]triazol-3-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic acid;

4-{3*E*-[2,4-Dimethoxy-5-(1-methyl-1*H*-indol-2-yl)-phenyl]-acryloyl}-benzoic acid; and

4-[3*E*-(5-Benzo[*b*]thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid ethyl ester, or its pharmaceutically acceptable salt.

17. The compound of Claim 16 selected from the group consisting of:

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid;

4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid;

4-(3*E*-{4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic acid; and

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, or its pharmaceutically acceptable salt or ester.

18. The compound of Claim 17 wherein the compound is

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid

or its pharmaceutically acceptable salt or ester.

19. The compound of Claim 17 wherein the compound is 4-[3*E*-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid, or its pharmaceutically acceptable salt or ester.

20. The compound of Claim 17 wherein the compound is 4-(3*E*-{4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thiophen-2-yl-phenyl}-acryloyl)-benzoic acid; or its pharmaceutically acceptable salt or ester.

21. The compound of Claim 17 wherein the compound is 4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thiophen-2-yl-phenyl]-acryloyl}-benzoic acid, or its pharmaceutically acceptable salt or ester.

22. The compound of Claim 5 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, and $R^{6\alpha}$ are independently selected from the group consisting of hydrogen and carboxy;

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, halogen, heteroaryl, heterocyclic, lower alkoxy, $-(O(CH_2)_2)_{1-3}$-O-lower alkyl, heteroaryl lower alkoxy, and heterocyclic lower alkoxy, all of which can be optionally substituted by one or more selected from the group consisting of hydroxy, hydroxyalkyl, $-NR^7R^8$, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$;

R^2 is lower alkyl;

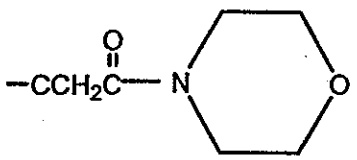
R^7 and R^8 are independently alkyl, and linked together forming a 6-membered monocyclic or benzofused ring;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic;

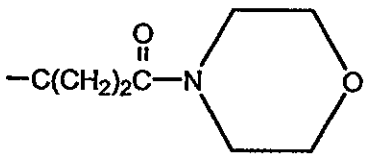
with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be carboxy.

23. The compound of Claim 22 or its pharmaceutically acceptable salt or ester, wherein:

$R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ are independently selected from the group consisting of hydrogen, fluorine, chlorine, methoxy, ethoxy, propoxy, 3-(1-morpholino) propoxy, 2-(1-morpholino) ethoxy, $CH_3O(CH_2)_2O(CH_2)_2$-,



, and



;

wherein one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked tetrahydrofuran-2-yl or dihydrofuran-2-yl.

24. The compound of Claim 5 or its pharmaceutically acceptable salt or ester, wherein:

at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, and $-C(O)NHSO_2R^2$.

25. The compound of Claim 5 or its pharmaceutically acceptable salt or ester, wherein:

at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCH_2C(O)OH$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $-SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, and $-SO_2NHC(O)NR^7R^8$.

26. The compound of Claim 5 or its pharmaceutically acceptable salt or ester, wherein:

at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of amino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$.

27. The compound of Claim 5 or its pharmaceutically acceptable salt or ester, wherein:

at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, and $-OC(R^1)_2C(O)NR^7R^8$.

28. The compound of Claim 3 or its pharmaceutically acceptable salt or ester, wherein:

one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together, or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$

taken together form a heterocyclic or heteroaryl optionally substituted by one or more alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or aminoalkyl and optionally substituted with one or more selected from the group consisting of hydroxy, alkyl, carboxy, hydroxyalkyl, carboxyalkyl, amino, cyano, alkoxy, alkoxycarbonyl, acyl, oxo, $-NR^7R^8$, and halo; and with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$, $-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$.

29. The compound of Claim 3 or its pharmaceutically acceptable salt or ester, wherein:

one of $R^{4\beta}$, $R^{5\beta}$ or $R^{6\beta}$ must be a carbon-carbon linked heterocyclic or heteroaryl, and only one of $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$ or $R^{6\alpha}$ can be $-OCH_3$;

with the proviso that $R^{2\alpha}$ and $R^{3\alpha}$ taken together or $R^{3\alpha}$ and $R^{4\alpha}$ taken together or $R^{4\alpha}$ and $R^{5\alpha}$ taken together or $R^{2\beta}$ and $R^{3\beta}$ taken together or $R^{3\beta}$ and $R^{4\beta}$ taken together or $R^{4\beta}$ and $R^{5\beta}$ taken together form a 5- or 6-membered ring containing one nitrogen, which may optionally be substituted with one or more selected from the group consisting of halo, alkyl, lower alkyl, cycloalkyl, acyl, hydroxy, hydroxyalkyl, heterocyclic, amino, aminoalkyl, $-NR^7R^8$, alkoxy, oxo, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, $-C(O)NR^7R^8$, and $-C(O)N(R^2)_2$; provided that $R^{2\alpha}$, $R^{3\alpha}$, $R^{4\alpha}$, $R^{5\alpha}$, $R^{6\alpha}$, $R^{2\beta}$, $R^{3\beta}$, $R^{4\beta}$, $R^{5\beta}$ and $R^{6\beta}$ cannot be $-OC(R^1)_2C(O)OH$; and with the proviso that at least one of $R^{2\alpha}$, $R^{3\alpha}$, or $R^{4\alpha}$ must be selected from the group consisting of cyano, carboxy, $-C(O)OR^2$, $-C(O)NH_2$, $-C(O)NHR^2$, $-C(O)N(R^2)_2$, $-C(O)NR^7R^8$,

$-C(O)NHC(O)NHR^2$, $-C(O)NHC(O)N(R^2)_2$, $-C(O)NHC(O)NR^7R^8$, $-C(O)NHSO_2NHR^2$, $-C(O)NHSO_2N(R^2)$, $-C(O)NHSO_2NR^7R^8$, $-C(O)NHC(O)R^2$, $-C(O)NHSO_2R^2$, $-C(CH_3)_2C(O)OH$, $-(CH_2)_yC(O)OH$, wherein y is 1, 2, 3, 4, 5, or 6, thiol, $-SC(R^1)_2C(O)OH$, $-SC(R^1)_2C(O)OR^2$, $-SCF_2C(O)OH$, $-SO_2NH_2$, $-SO_2NHR_2$, $-SO_2N(R^2)_2$, $SO_2NR^7R^8$, $-SO_2NHC(O)R^2$, $-SR_2$, $-SO_2NHC(O)NHR^2$, $-SO_2NHC(O)N(R^2)_2$, $-SO_2NHC(O)NR^7R^8$, $-OC(R^1)_2C(O)OH$, $-OC(R^1)_2C(O)OR^2$, $-OC(R^1)_2C(O)NH_2$, $-OC(R^1)_2C(O)NHR^2$, $-OC(R^1)_2C(O)N(R^2)_2$, $-OC(R^1)_2C(O)NR^7R^8$, amino, $-NHR^2$, $-N(R^2)_2$, $-NR^7R^8$, $-NHC(R^1)_2C(O)OH$, $-NHC(R^1)_2C(O)OR^2$, $-NHC(O)R^2$, $-N(R^2)C(O)R^2$, $-NHC(O)OR^2$, $-NHC(O)SR^2$, $-NHSO_2NHR^2$, $-NHSO_2R^2$, $-NHSO_2NR^7R^8$, $-N(C(O)NHR^2)_2$, $-NR^2SO_2R^2$, $-NHC(O)NHR^2$, $-NHC(O)NR^7R^8$, and $-NHC(O)N(R^2)_2$.

30. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29, together with one or more pharmaceutically acceptable carrier.

31. A use of a compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29 in the manufacture of a medicament for the treatment or prophylaxis of an inflammatory disorder.

32. The use of claim 31, wherein the disorder is arthritis.

33. The use of claim 31, wherein the disorder is rheumatoid arthritis.

34. The use of claim 31, wherein the disorder is asthma.

35. The use of claim 31, wherein the treatment is disease modifying for the treatment of rheumatoid arthritis.

36. The use of claim 31, wherein the disorder is allergic rhinitis.

37. The use of claim 31, wherein the disorder is chronic obstructive pulmonary disease.

38. The use of claim 31, wherein the disorder is atherosclerosis.

39. The use of claim 31, wherein the disorder is restenosis.

40. A use for a compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29 in the manufacture of a medicament for inhibiting the expression of VCAM-1.