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(54) Titre : UTILISATION DE THIADIAZOLES COMME LIGANDS DES RECEPTEURS AUX CHIMIOKINES CXC ET CC
(54) Title: THIADIAZOLES AS CXC- AND CC- CHEMOKINE RECEPTOR LIGANDS

(IA)

(57) Abrégé/Abstract:
Disclosed are novel compounds of Formula (IA) and the pharmaceutically acceptable salts and solvates thereof. Examples of groups comprising Substituent A include heteroaryl, aryl, heterocycloalkyl, cycloalkyl, aryl, alkynyl, alkenyl, aminoalkyl, alkyl or amino. Examples of groups comprising Substituent B include aryl and heteroaryl. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenisis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and ischemia reperfusion injury, pain (e.g., acute pain, acute and chronic inflammatory pain, and neuropathic pain) using a compound of Formula (IA).

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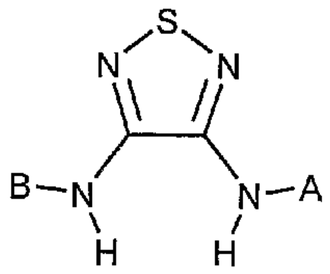

(IA)

(57) Abstract: Disclosed are novel compounds of Formula (IA) and the pharmaceutically acceptable salts and solvates thereof. Examples of groups comprising Substituent A include heteroaryl, aryl, heterocycloalkyl, cycloalkyl, aryl, alkynyl, alkenyl, aminoalkyl, alkyl or amino. Examples of groups comprising Substituent B include aryl and heteroaryl. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenisis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and ischemia reperfusion injury, pain (*e.g.*, acute pain, acute and chronic inflammatory pain, and neuropathic pain) using a compound of Formula (IA).

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THIADIAZOLES AS CXC- AND CC- CHEMOKINE RECEPTOR LIGANDS

FIELD OF THE INVENTION

The present invention relates to novel substituted thiadiazole compounds, pharmaceutical compositions containing the compounds, and the use of the compounds and formulations in treating CXC and CC-chemokine-mediated diseases.

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T-cells, eosinophils, basophils, neutrophils and endothelial cells to sites of inflammation and tumor growth. There are two main classes of chemokines, the CXC-chemokines and the CC- chemokines. The class depends on whether the first two cysteines are separated by a single amino acid (CXC-chemokines) or are adjacent (CC-chemokines). The CXC-chemokines include, but are not limited to, interleukin-8 (IL-8), neutrophil-activating protein-1 (NAP-1), neutrophil-activating protein-2 (NAP-2), GROα, GROβ, GROγ, ENA-78, GCP-2, IP-10, MIG and PF4. CC chemokines include, but are not limited to, RANTES, MIP -1α, MIP-2β, monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3, CCL19, CCL21 and eotaxin. Individual members of the chemokine families are known to be bound by at least one chemokine receptor, with CXC-chemokines generally bound by members of the CXCR class of receptors, and CC-chemokines by members of the CCR class of receptors. For example, IL-8 is bound by the CXCR-1 and CXCR-2 receptors.

Since CXC-chemokines promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory disorders including psoriasis and rheumatoid arthritis. Baggiolini

et al., FEBS Lett. 307, 97 (1992); Miller et al., Crit. Rev. Immunol. 12, 17 (1992); Oppenheim et al., Annu. Fev. Immunol. 9, 617 (1991); Seitz et al., J. Clin. Invest. 87, 463 (1991); Miller et al., Am. Rev. Respir. Dis. 146, 427 (1992); Donnely et al., Lancet 341, 643 (1993).

ELRCXC chemokines including IL-8, GROα, GROβ, GROγ, NAP-2, and ENA-78 (Strieter et al. 1995 JBC 270 p. 27348-57) have also been implicated in the induction of tumor angiogenesis (new blood vessel growth). All of these chemokines are believed to exert their actions by binding to the 7 transmembrane G-protein coupled receptor CXCR2 (also known as IL-8RB), while IL-8 also binds CXCR1 (also known as IL-8RA). Thus, their angiogenic activity is due to their binding to and activation of CXCR2, and possible CXCR1 for IL-8, expressed on the surface of vascular endothelial cells (ECs) in surrounding vessels.

Many different types of tumors have been shown to produce ELRCXC chemokines and their production has been correlated with a more aggressive phenotype (Inoue et al. 2000 Clin Cancer Res 6 p. 2104-2119) and poor prognosis (Yoneda et. al. 1998 J Nat Cancer Inst 90 p. 447-454). Chemokines are potent chemotactic factors and the ELRCXC chemokines have been shown to induce EC chemotaxis. Thus, these chemokines probably induce chemotaxis of endothelial cells toward their site of production in the tumor. This may be a critical step in the induction of angiogenesis by the tumor. Inhibitors of CXCR2 or dual inhibitors of CXCR2 and CXCR1 will inhibit the angiogenic activity of the ELRCXC chemokines and therefore block the growth of the tumor. This anti-tumor activity has been demonstrated for antibodies to IL-8 (Arenberg et al. 1996 J Clin Invest 97 p. 2792-2802), ENA-78 (Arenberg et al. 1998 J Clin Invest 102 p. 465-72), and GROα (Haghnegahdar et al. J. Leukoc Biology 2000 67 p. 53-62).

Many tumor cells have also been shown to express CXCR2 and thus tumor cells may also stimulate their own growth when they secrete ELRCXC chemokines. Thus, along with decreasing angiogenesis, inhibitors of CXCR2 may directly inhibit the growth of tumor cells.

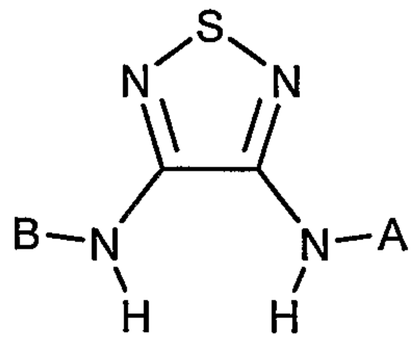
Hence, the CXC-chemokine receptors represent promising targets for the development of novel anti-inflammatory and anti-tumor agents.

There remains a need for compounds that are capable of modulating activity at CXC-chemokine receptors. For example, conditions associated with an increase in

IL-8 production (which is responsible for chemotaxis of neutrophil and T-cell subsets into the inflammatory site and growth of tumors) would benefit by compounds that are inhibitors of IL-8 receptor binding.

SUMMARY OF THE INVENTION

This invention provides novel compounds of formula IA:



(IA)

and the pharmaceutically acceptable salts (e.g., sodium or calcium) thereof, wherein A and B are defined below.

This invention also provides a method of treating a chemokine mediated disease or condition in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound (usually 1) of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating a CXCR1 and/or CXCR2 mediated disease or condition in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound (usually 1) of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating a CCR7 mediated disease or condition in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound (usually 1) of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating Kaposi's sarcoma, melanoma, gastric carcinoma, and non-small cell carcinoma in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating melanoma, gastric carcinoma, and non-small cell carcinoma in a patient in need of such treatment comprising

administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one anticancer agent selected from the group consisting of: (a) microtubule affecting agents, (b) antineoplastic agents, (c) anti-angiogenesis agents, or (d) VEGF receptor kinase inhibitors, (e) antibodies against the VEGF receptor, (f) interferon, and g) radiation. The compound of formula IA can be administered concurrently or sequentially with the anticancer agent.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one (usually 1) antineoplastic agent selected from the group consisting of: gemcitabine, paclitaxel (Taxol®), 5-Fluorourcil (5-FU), cyclophosphamide (Cytoxan®), temozolomide, and Vincristine.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, concurrently or sequentially with microtubule affecting agent, e.g., paclitaxel.

This invention also provides a method treating cancer in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of: (a) at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, concurrently or sequentially with (b) at least one (usually 1) agent selected from the group consisting of: (1) antineoplastic agents, (2) microtubule affecting agents, and (3) anti-angiogenesis agents.

This invention also provides a method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating angiogenic ocular disease (e.g., ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization) in a patient

in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating a chemokine mediated (e.g., CXCR1 and/or CXCR2, or CCR7) disease or condition selected from the group consisting of: pain (e.g., acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain), acute inflammation, chronic inflammation, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, ischemia reperfusion injury, renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction (i.e., graft vs. host disease), allograft rejections (e.g., acute allograft rejection, and chronic allograft rejection), malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral ischemia, cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus (i.e., Kaposi's sarcoma), meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute pancreatitis, chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred, corneal neovascularization, polymyositis, vasculitis, acne, gastric ulcers, duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness (i.e., airway hyperreactivity), bronchiectasis, bronchiolitis, bronchiolitis obliterans (i.e., bronchiolitis obliterans syndrome), chronic bronchitis, cor pulmonae, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds,

gout, alcoholic liver disease, lupus, burn therapy (i.e., the treatment of burns), periodontitis, cancer, transplant reperfusion injury, early transplantation rejection (e.g., acute allograft rejection), airway hyperreactivity, allergic contact dermatitis, allergic rhinitis, alopecia areata, antiphospholipid syndromes, aplastic anemia, autoimmune deafness (including, for example, Meniere's disease), autoimmune hemolytic syndromes, autoimmune hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, bullous pemphigoid, chronic allograft vasculopathy, chronic inflammatory demyelinating polyneuropathy, cirrhosis, cor pneumoniae, cryoglobulinemia, dermatomyositis, diabetes, drug-induced autoimmunity, epidermolysis bullosa acquisita, endometriosis, fibrotic diseases, gastritis, Goodpasture's syndrome, Graves' disease, Gullain-Barre disease, Hashimoto's thyroiditis, hepatitis-associated autoimmunity, HIV-related autoimmune syndromes and hematologic disorders, hypophytis, idiopathic thrombocytic pupura, interstitial cystitis, juvenile arthritis, Langerhans' cell histiocytitis, lichen planus, metal-induced autoimmunity, myasthenia gravis, myelodysplastic syndromes, myocarditis (including viral myocarditis), myositis, Neuropathies (including, for example, IgA neuropathy, membranous neuropathy and idiopathic neuropathy), nephritic syndrome, optic neuritis, pancreatitis, paroxysmal nocturnal hemoglobulinemia, pemphigus, polymyalgia, post-infectious autoimmunity, primary biliary cirrhosis, reactive arthritis, ankylosing spondylitis, Raynaud's phenomenon, Reiter's syndrome, reperfusion injury, scleritis, scleroderma, secondary hematologic manifestation of autoimmune diseases (such as, for example, anemias), silicone implant associated autoimmune disease, Sjogren's syndrome, systemic lupus erythematosus, thrombocytopenia, transverse myelitis, tubulointerstitial nephritis, uveitis, vasculitis syndromes (such as, for example, giant cell arteritis, Behcet's disease and Wegener's granulomatosis), and Vitiligo in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound (usually 1) of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating a CXCR1 and/or a CXCR2 mediated disease or condition selected from the group consisting of: pain (e.g., acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain), acute inflammation, chronic inflammation, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel

disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, ischemia reperfusion injury, renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction (i.e., graft vs. host disease), allograft rejections (e.g., acute allograft rejection, and chronic allograft rejection), malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral ischemia, cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus (i.e., Kaposi's sarcoma), meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute pancreatitis, chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred, corneal neovascularization, polymyositis, vasculitis, acne, gastric ulcers, duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness (i.e., airway hyperreactivity), bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy (i.e., the treatment of burns), periodontitis, cancer, transplant reperfusion injury, early transplantation rejection (e.g., acute allograft rejection) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound (usually 1) of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating a CCR7 mediated disease or condition selected from the group consisting of: pain (e.g., acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain), acute inflammation, chronic inflammation, acute allograft rejection, acute respiratory distress

syndrome, adult respiratory disease, airway hyperreactivity, allergic contact dermatitis, allergic rhinitis, alopecia areata, alzheimer's disease, angiogenic ocular disease, antiphospholipid syndromes, aplastic anemia, asthma, atherosclerosis, atopic dermatitis, autoimmune deafness (including, for example, Meniere's disease), autoimmune hemolytic syndromes, autoimmune hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, bronchiolitis, bronchiolitis obliterans syndrome, bullous pemphigoid, burn therapy (i.e., the treatment of burns), cancer, cerebral ischemia, cardiac ischemia, chronic allograft rejection, chronic allograft vasculopathy, chronic bronchitis, chronic inflammatory demyelinating polyneuropathy, chronic sinusitis, cirrhosis, CNS vasculitis, COPD, Cor pneumoniae, Crohn's disease, cryoglobulinemia, crystal-induced arthritis, delayed-type hypersensitivity reactions, dermatomyositis, diabetes, diabetic retinopathy, drug-induced autoimmunity, dyspnea, emphysema, epidermolysis bullosa acquisita, endometriosis, fibrotic diseases, gastritis, glomerulonephritis, Goodpasture's syndrome, graft vs host disease, Graves' disease, Gullain-Barre disease, Hashimoto's thyroiditis, hepatitis-associated autoimmunity, HIV-related autoimmune syndromes and hematologic disorders, hyperoxia-induced inflammation, hypercapnea, hyperinflation, hypophytis, hypoxia, idiopathic thrombocytic pupura, inflammatory bowel diseases, interstitial cystitis, interstitial pneumonitis, juvenile arthritis, Langerhans' cell histiocytitis, lichen planus, metal-induced autoimmunity, multiple sclerosis, myasthenia gravis, myelodysplastic syndromes, myocarditis including viral myocarditis, myositis, neuropathies (including, for example, IgA neuropathy, membranous neuropathy and idiopathic neuropathy), nephritic syndrome, ocular inflammation, optic neuritis, osteoarthritis, pancreatitis, paroxysmal nocturnal hemoglobulinemia, pemphigus, polymyalgia, polymyositis, post-infectious autoimmunity, pulmonary fibrosis, primary biliary cirrhosis, psoriasis, pruritis, rheumatoid arthritis, reactive arthritis, ankylosing spondylitis, psoriatic arthritis, Raynaud's phenomenon, Reiter's syndrome, ischemia injury, restenosis, sarcoidosis, scleritis, scleroderma, secondary hematologic manifestation of autoimmune diseases (such as, for example, anemias), silicone implant associated autoimmune disease, Sjogren's syndrome, systemic lupus erythematosus, thrombocytopenia, thrombosis, transverse myelitis, tubulointerstitial nephritis, ulcerative colitis, uveitis, vasculitis and vasculitis syndromes (such as, for example, giant cell arteritis, Behcet's disease and

Wegener's granulomatosis), and vitiligo in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound (usually 1) of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating a chemokine (e.g., a CXC, or a CC chemokine) mediated disease or condition in a patient in need of such treatment comprising administering to said patient at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one (usually 1) other medicament (e.g., a drug, agent or therapeutic) useful for the treatment of chemokine mediated diseases.

This invention also provides a method of treating a chemokine mediated disease or condition in a patient in need of such treatment comprising administering to said patient at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one (usually 1) other medicament (e.g., a drug, agent or therapeutic) selected from the group consisting of:

a) disease modifying antirheumatic drugs;
b) nonsteroidal anitinflammatory drugs;
c) COX-2 selective inhibitors;
d) COX-1 inhibitors;
e) immunosuppressives;
f) steroids;
g) biological response modifiers; and
h) other anti-inflammatory agents or therapeutics useful for the treatment of chemokine mediated diseases.

This invention also provides a method of treating a pulmonary disease (e.g., COPD, asthma or cystic fibrosis) in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one compound (usually 1) of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one (usually 1) compound selected from the group consisting of: glucocorticoids, 5-lipoxygenase inhibitors, β-2 adrenoceptor agonists, muscarinic M1 antagonists, muscarinic M3 antagonists, muscarinic M2 agonists, NK3 antagonists, LTB4 antagonists, cysteinyl leukotriene antagonists, bronchodilators, PDE4 inhibitors, PDE inhibitors, elastase inhibitors, MMP inhibitors, phospholipase A2 inhibitors, phospholipase D inhibitors, histamine H1 antagonists, histamine H3

antagonists, dopamine agonists, adenosine A2 agonists, NK1 and NK2 antagonists, GABA-b agonists, nociceptin agonists, expectorants, mucolytic agents, decongestants, antioxidants, anti-IL-8 anti-bodies, anti-IL-5 antibodies, anti-IgE antibodies, anti-TNF antibodies, IL-10, adhesion molecule inhibitors, and growth hormones.

This invention also provides a method of treating multiple sclerosis in a patient in need of such treatment comprising administering to said patient, a therapeutically effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one compound selected from the group consisting of glatiramer acetate, glucocorticoids, methotrexate, azothioprine, mitoxantrone, chemokine inhibitors, and CB2-selective agents.

This invention also provides a method of treating multiple sclerosis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one compound selected from the group consisting of: methotrexate, cyclosporin, leflunimide, sulfasalazine, β-methasone, β-interferon, glatiramer acetate, and prednisone.

This invention also provides a method of treating rheumatoid arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating rheumatoid arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one compound selected from the group consisting of COX-2 inhibitors, COX inhibitors, immunosuppressives (e.g., methotrexate, cyclosporin, leflunimide and sulfasalazine), steroids (e.g., betamethasone, cortisone and dexamethasone), PDE IV inhibitors, anti-TNF-α compounds, MMP inhibitors, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, and other classes of compounds indicated for the treatment of rheumatoid arthritis.

This invention also provides a method of treating stroke and ischemia reperfusion injury in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one compound (usually 1) of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one compound selected from the group consisting of thrombolitics (e.g., tenecteplase, TPA, alteplase), antiplatelet agents (e.g., gpIIb/IIIa), antagonists (e.g., abciximab and eftiifbatide), anticoagulants (e.g., heparin), and other compounds indicated for the treatment of rheumatoid arthritis.

This invention also provides a method of treating stroke and ischemia reperfusion injury in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one compound selected from the group consisting of tenecteplase, TPA, alteplase, abciximab, eftiifbatide, and heparin.

This invention also provides a method of treating psoriasis in a patient in need of such treatment comprising administering to said patient a thereapeutically effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, in combination with at least one compound selected from the group consisting of immunosuppressives (e.g., methotrexate, cyclosporin, leflunimide and sulfasalazine), steroids (e.g., β-methasone) and anti-TNF-α compounds (e.g., etonercept and infliximab).

This invention also provides a method of treating COPD in a patient in need of such treatment comprising administering to said patient a therapeutically effective

amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating osteoarthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof, and administering a therapeutically effective amount of at least one medicament selected from the group consisting of: NSAIDs, COXIB inhibitors, anti-depressants, and anti-convulsants.

This invention also provides a method of treating acute pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating acute inflammatory pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating chronic inflammatory pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a method of treating neropathic pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

This invention also provides a pharmaceutical composition comprising at least one (e.g., 1-3, usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising at least one (e.g., 1-3, usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, and at least one (e.g., 1-3, usually 1) other agent, medicament, antibody and/or inhibitor disclosed above, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

When any variable occurs more than one time in any moiety, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless indicated otherwise, the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. For example, the definition of "alkyl" also applies to the "alkyl" portion of "alkoxy".

"An effective amount" means a therapeutically acceptable amount (i.e., that amount which provides the desired therapeutic effective).

"At least one" means one or more (e.g., 1-3, 1-2, or 1).

"Bu" represents butyl.

"Bn" represents benzyl.

"Composition" includes a product comprising the specified ingredients in the specified amounts, as well as any product that results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

"Et" represents ethyl.

"In combination with" as used to describe the administration of a compound of formula IA with other medicaments in the methods of treatment of this invention, means that the compounds of formula IA and the other medicaments are administered

sequentially or concurrently in separate dosage forms, or are administered concurrently in the same dosage form.

"Mammal" includes a human being, and preferably means a human being.

"Patient" includes both human and other mammals, preferably human.

"Ph", as used in the structures herein, represents phenyl.

"Pr" represents propyl.

"Prodrug" represents compounds that are rapidly transformed *in vivo* to the compound of formula IA, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

"Alkyl" means a straight or branched saturated hydrocarbon chain having 1 to 20 carbon atoms, preferably 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms.

"Alkoxy" means an alkyl-O- group wherein alkyl is as defined above. Non-limiting examples of alkoxy groups include: methoxy, ethoxy, n-propoxy, iso-propoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Alkenyl" means a straight or branched aliphatic hydrocarbon group having at least one carbon-carbon double bond, and 2 to 20 carbon atoms, preferably 2 to 12 carbon atoms, and more preferably 2 to 6 carbon atoms. Non-limiting examples of alkenyl groups include: ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means a straight or branched aliphatic hydrocarbon group having at least one carbon-carbon triple bond, and 2 to 15 carbon atoms, preferably 2 to 12 carbon atoms, and more preferably 2 to 4 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system, wherein at least one ring is aromatic, comprising about 6 to about 14 carbon atoms, and preferably about 6 to about 10 carbon atoms. Non-limiting examples of suitable aryl groups include: phenyl, naphthyl, indenyl, tetrahydronaphthyl, indanyl, anthracenyl, and fluorenyl.

"Arylalkyl" means an aryl group, as defined above, bound to an alkyl group, as defined above, wherein the alkyl group is bound to the parent moiety. Non-limiting examples of suitable arylalkyl groups include benzyl, phenethyl and naphthleneylmethyl.

"Bn" represents benzyl.

"Cycloalkyl" means saturated carbocyclic rings having 3 to 10 (e.g., 3 to 7) carbon atoms, preferably 5 to 10 carbon atoms, and more preferably 5 to 7 carbon atoms, and having one to three rings. Non-limiting examples of cycloalkyl groups include: cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

"Cycloalkylalkyl" means a cycloalkyl group bound to the parent moiety through an alkyl group. Non–limiting examples include: cyclopropylmethyl and cyclohexylmethyl.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising 3 to 10 carbon atoms, and preferably 5 to 10 carbon atoms, and having at least one carbon-carbon double bond. Preferred cycloalkenyl rings have 5 to 7 carbon atoms. Non-limiting examples of cycloalkyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, and norbornenyl.

"Et" represents ethyl.

"Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

"Haloalkyl" means an alkyl group as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

"Heterocyclyl" or "heterocyclic" or "heterocycloalkyl" means a non-aromatic saturated monocyclic or multicyclic ring system (i.e., a saturated carbocyclic ring or ring system) comprising 3 to 10 ring atoms (e.g., 3 to 7 ring atoms), preferably 5 to 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls have 5 to 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom, respectively, is present as a ring atom. The nitrogen or sulfur atom of the heterocyclyl

can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocyclyl rings include: piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

The term heterocyclic acidic functional group is intended to include groups such as, pyrrole, imidazole, triazole, tetrazole, and the like.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising 5 to 14 ring atoms, preferably 5 to 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain 5 to 6 ring atoms. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of heteroaryls include: pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, and benzothiazolyl.

“Heteroarylalkyl” means a heteroaryl group, as defined above, bound to an alkyl group, as defined above, where the bond to the parent moiety is through the alkyl group.

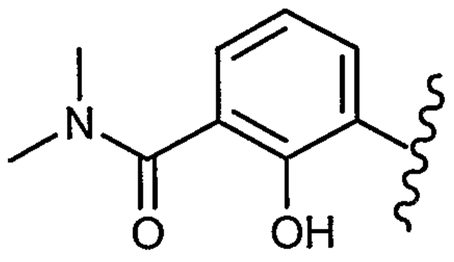
"Solvate" means a physical association of a compound of this invention with one or more solvent molecules; This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding; In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid; "Solvate" encompasses both solution-phase and isolatable solvates; Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like; "Hydrate" is a solvate wherein the solvent molecule is H_2O.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two)

pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

N-oxides can form on a tertiary nitrogen present in an R substituent, or on =N- in a heteroaryl ring substituent and are included in the compounds of formula IA.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom. For example: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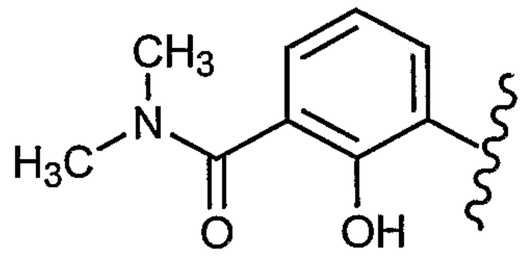
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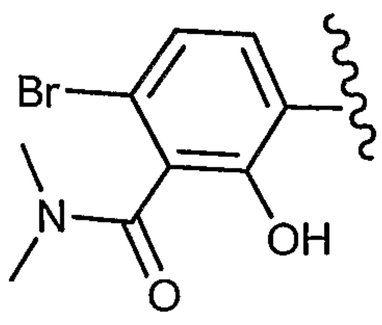
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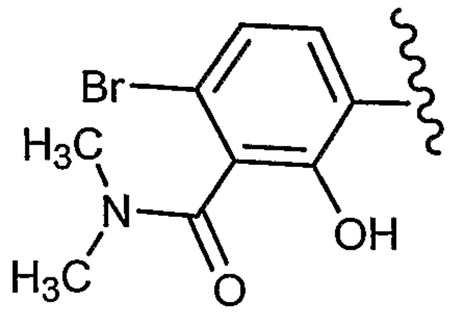
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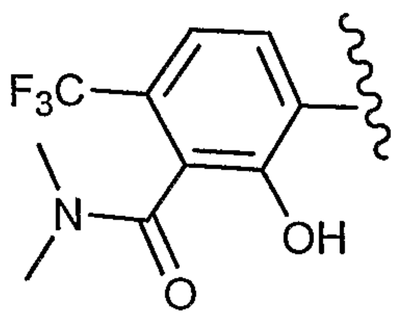
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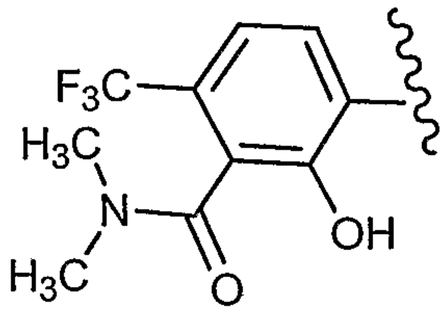
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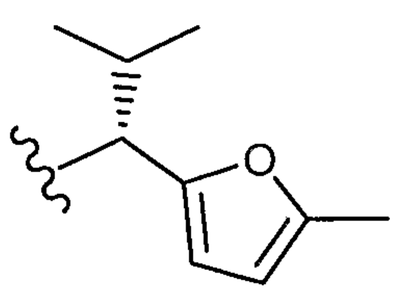
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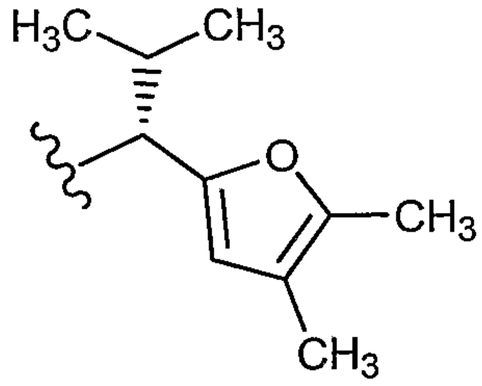
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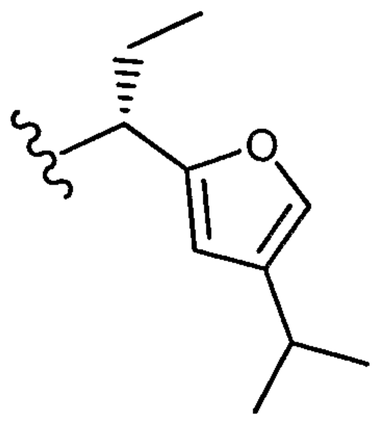

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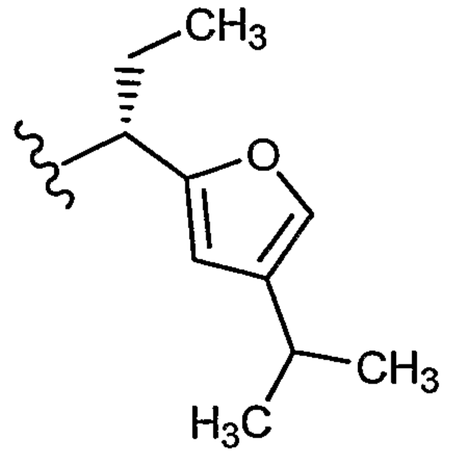

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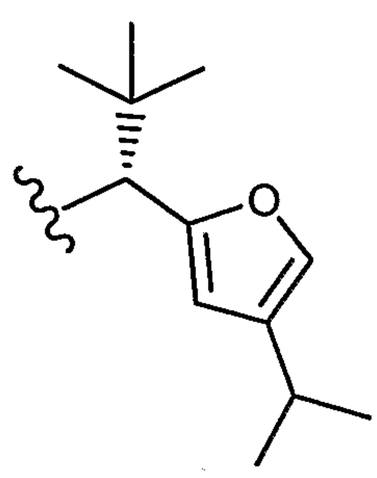

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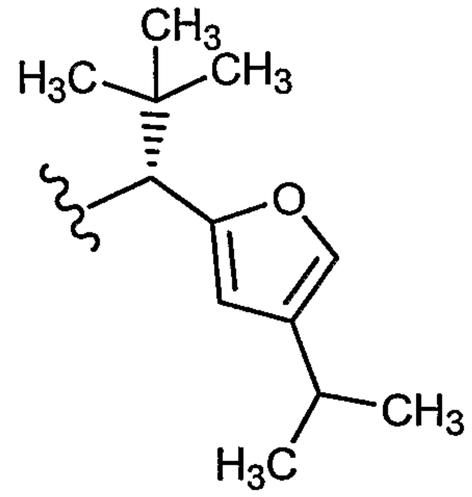

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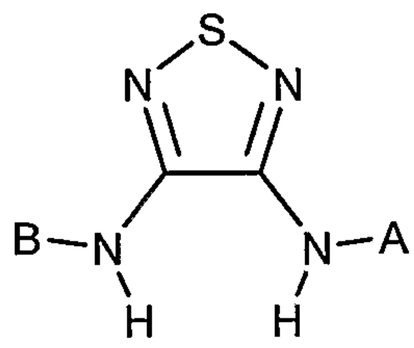
The compounds of this invention are represented by formula IA:

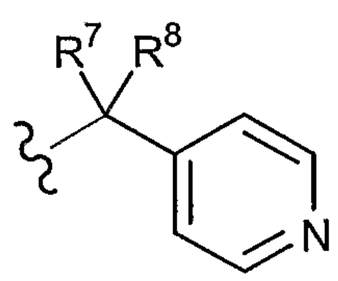


(IA)

and the pharmaceutically acceptable salts (e.g., sodium or calcium salt) thereof, wherein:

A is selected from the group consisting of:

(1)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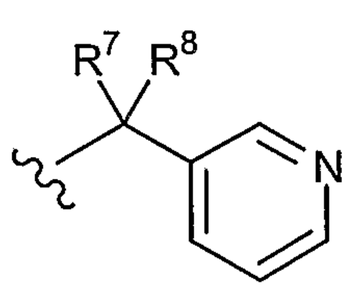
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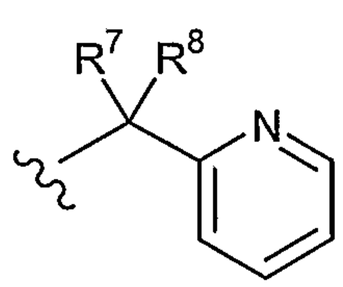
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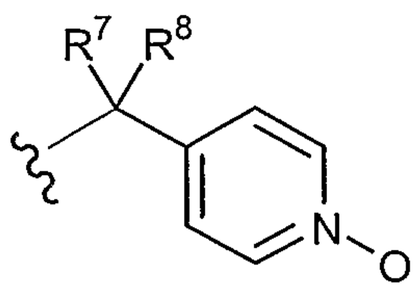
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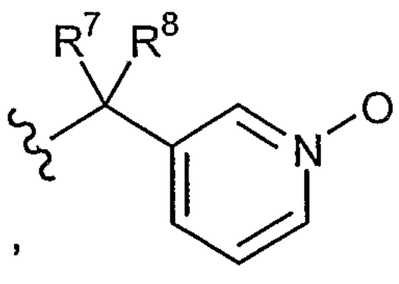
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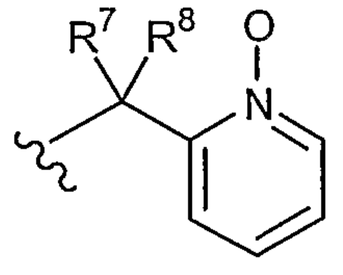
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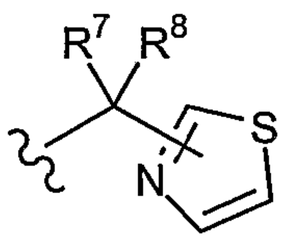
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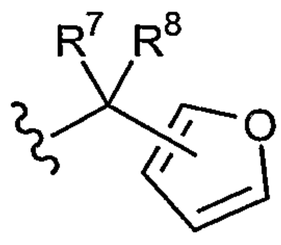
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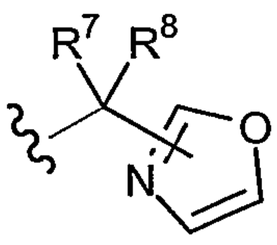
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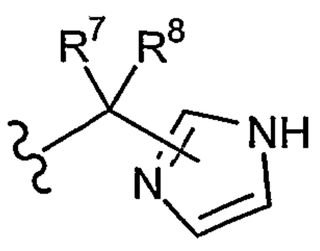
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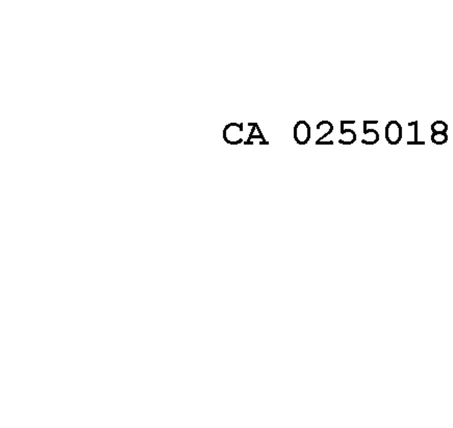
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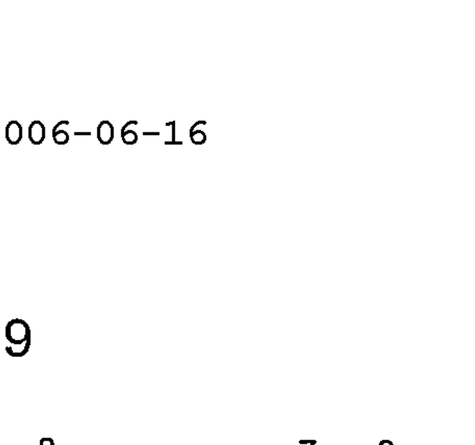
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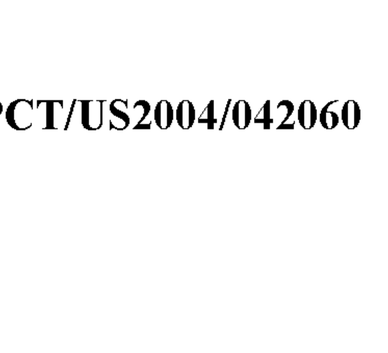
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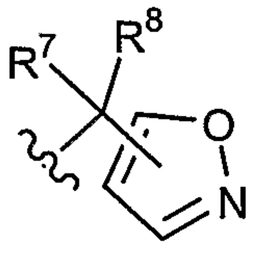
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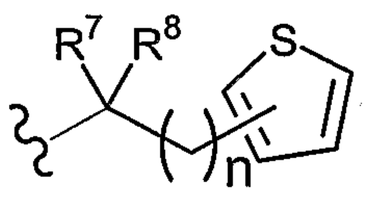
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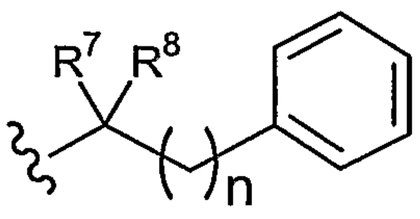
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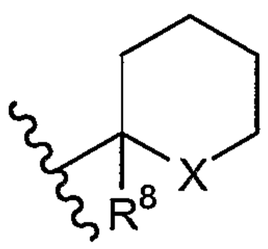
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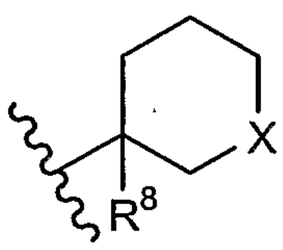
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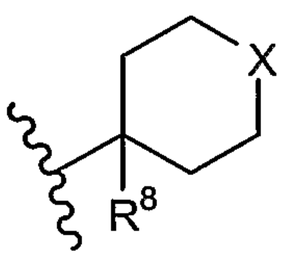
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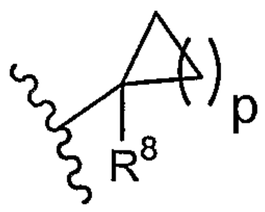
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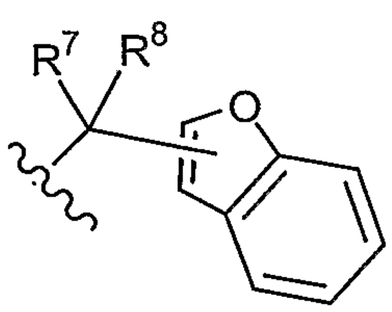
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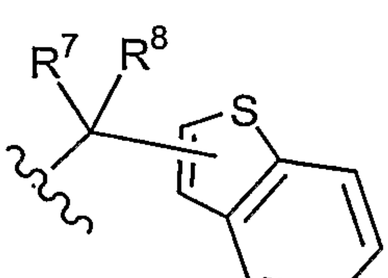
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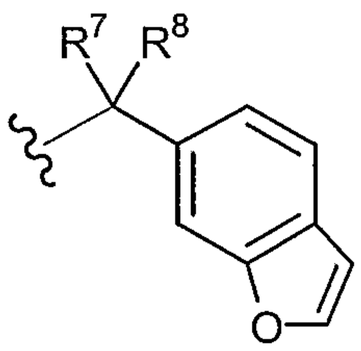
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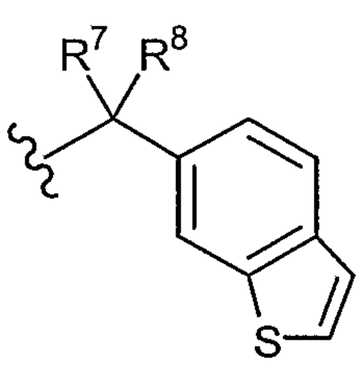
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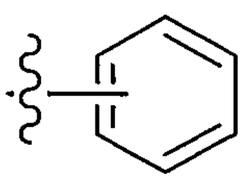
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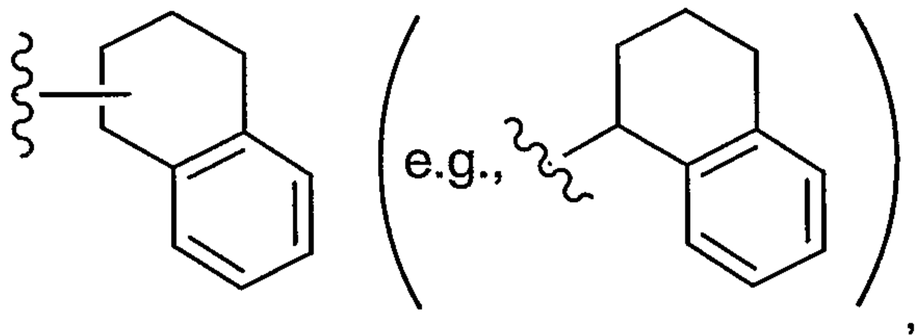
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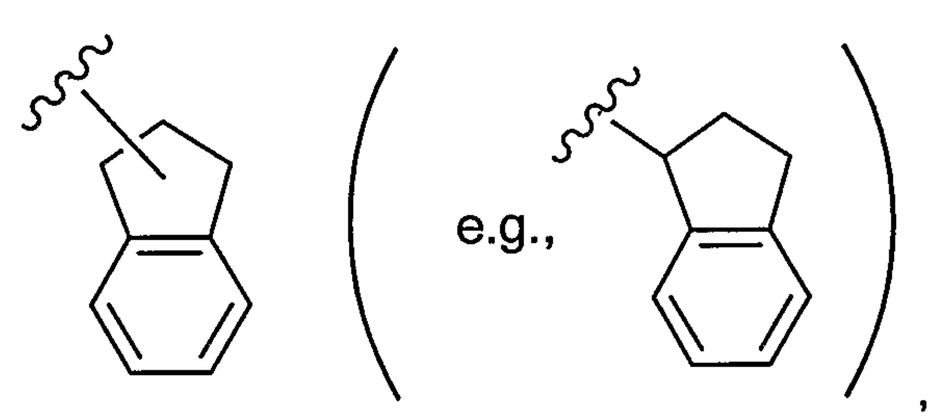
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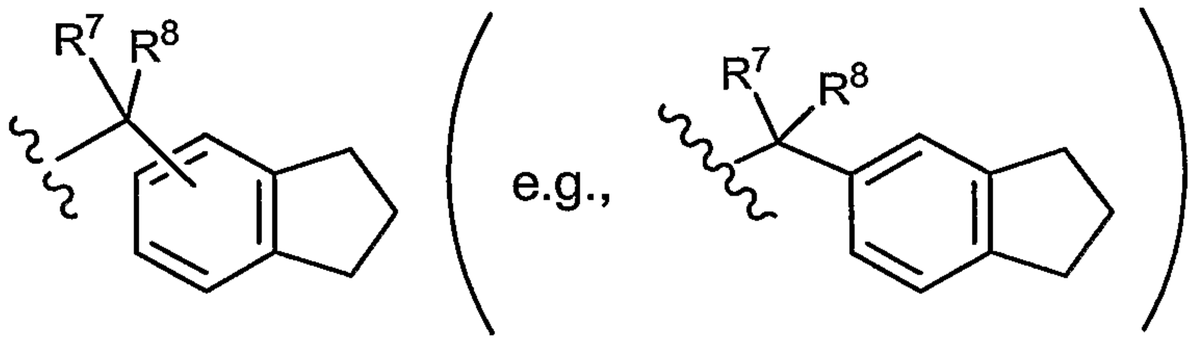
R7
R8
e.g.,
R7
R8

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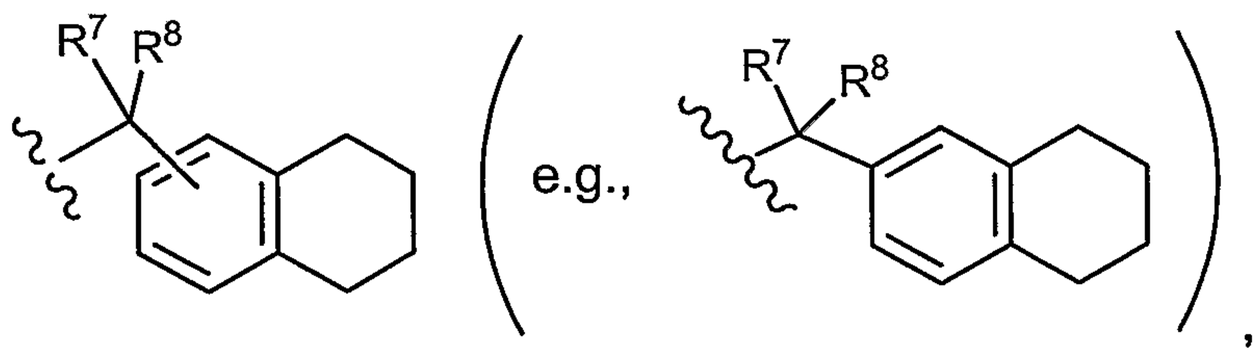
R7
R8
e.g.,
R7
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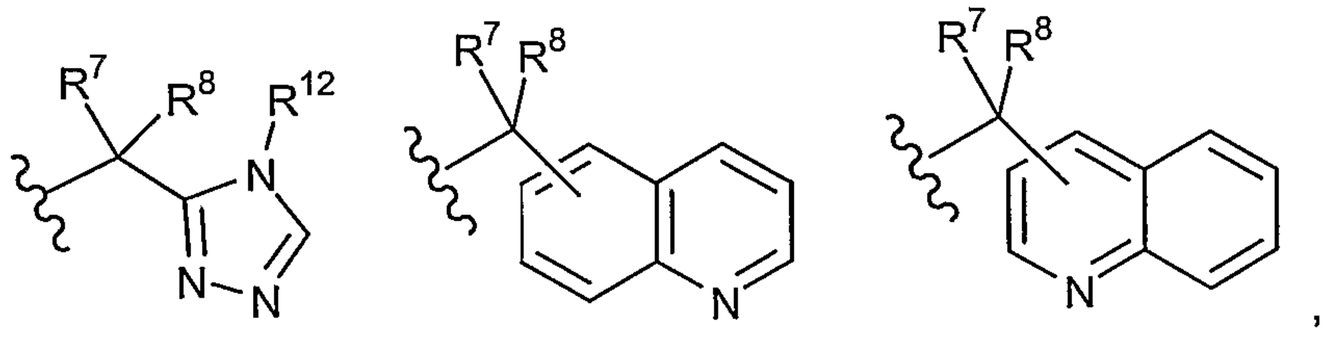
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R8
R12
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R7
R8
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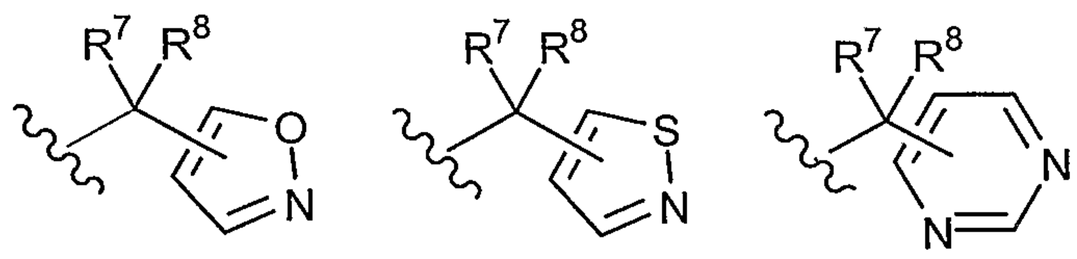
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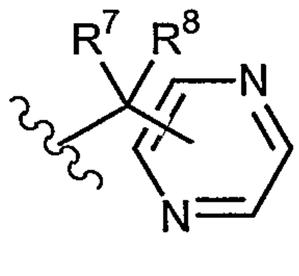
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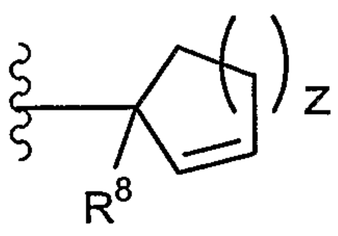
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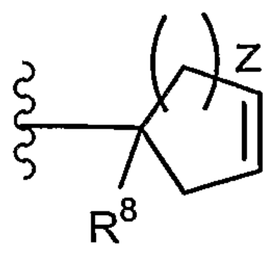
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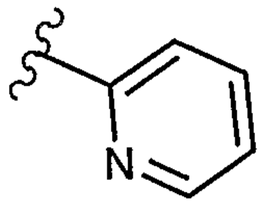
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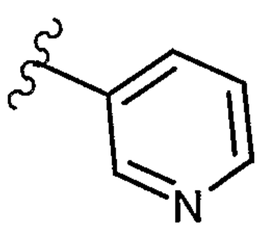
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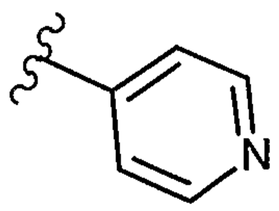
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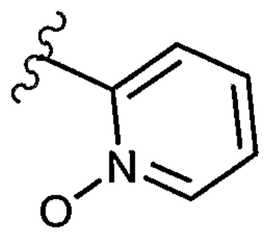
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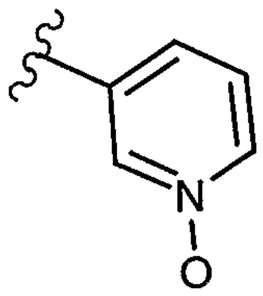
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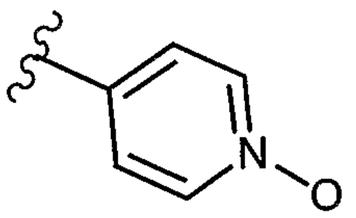
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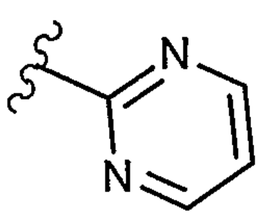
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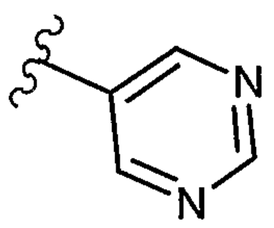
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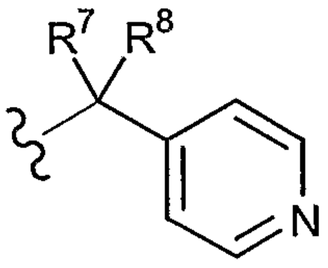
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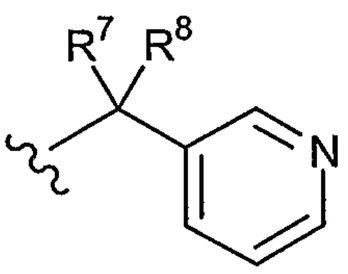
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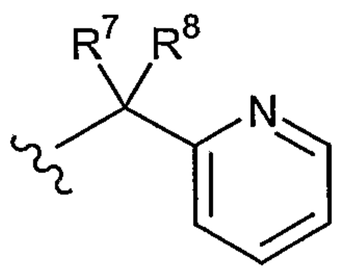
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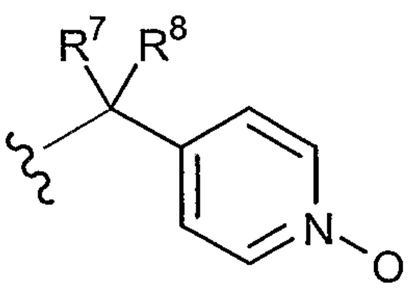
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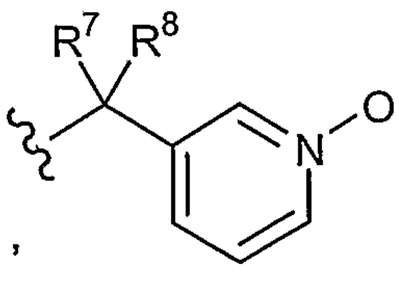
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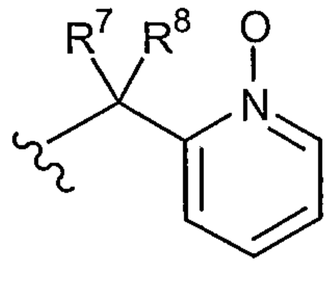
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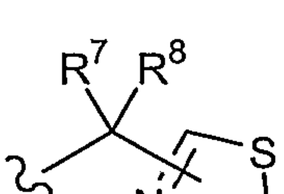
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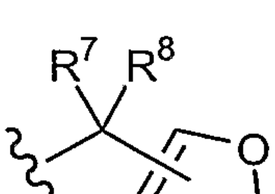
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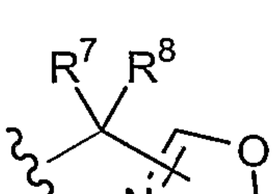
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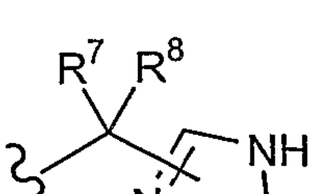
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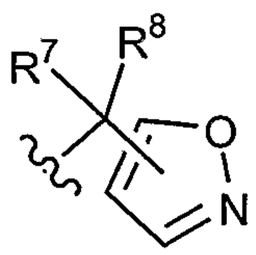
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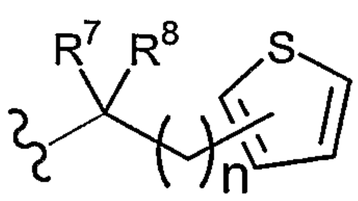
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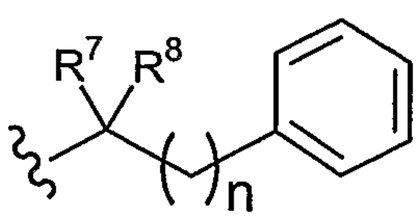
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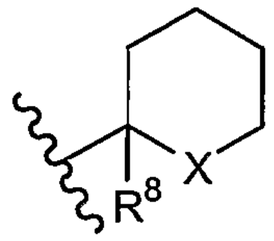
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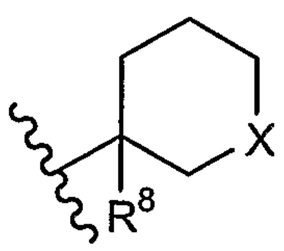
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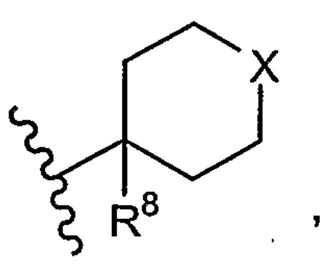
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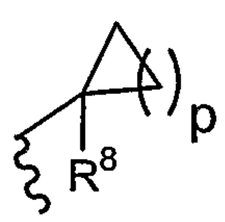
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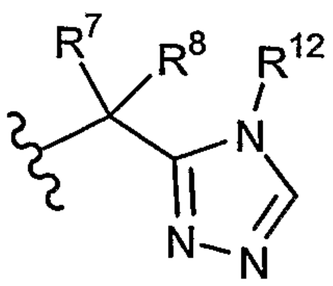
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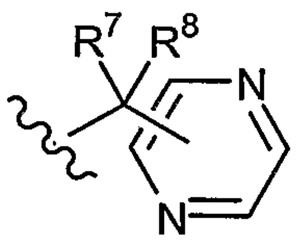
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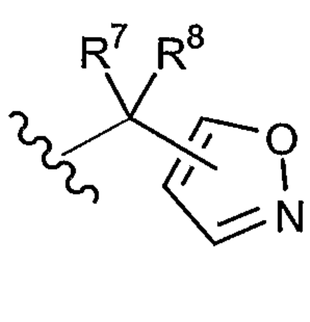
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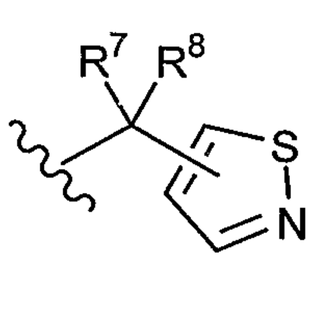
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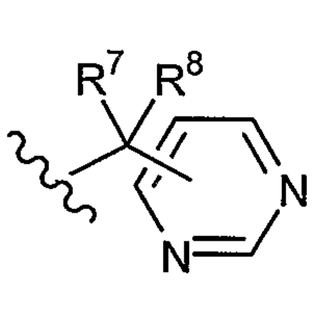
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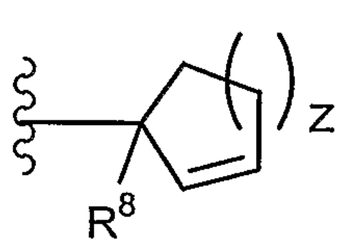
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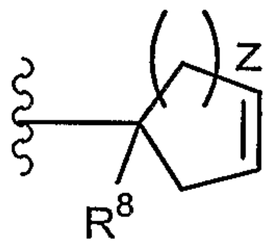
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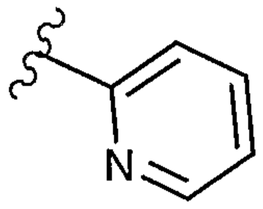
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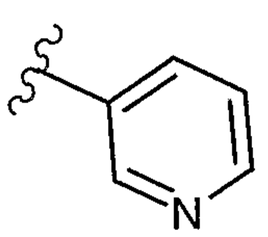
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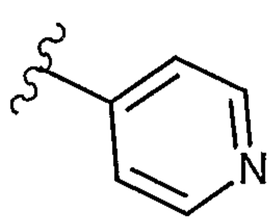
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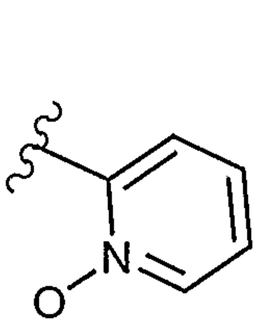
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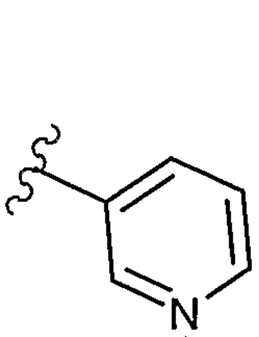
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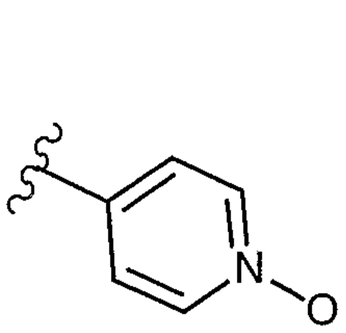
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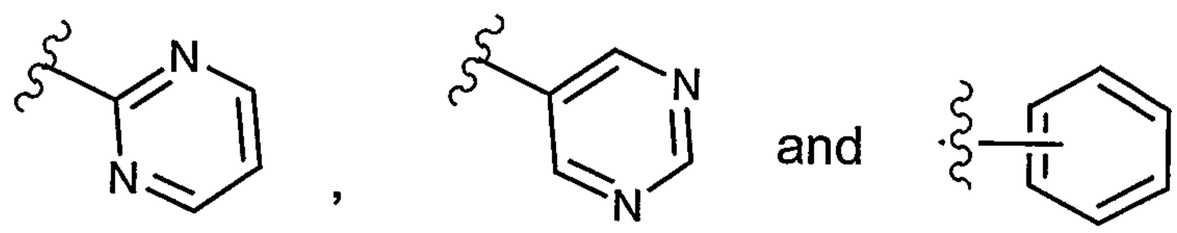
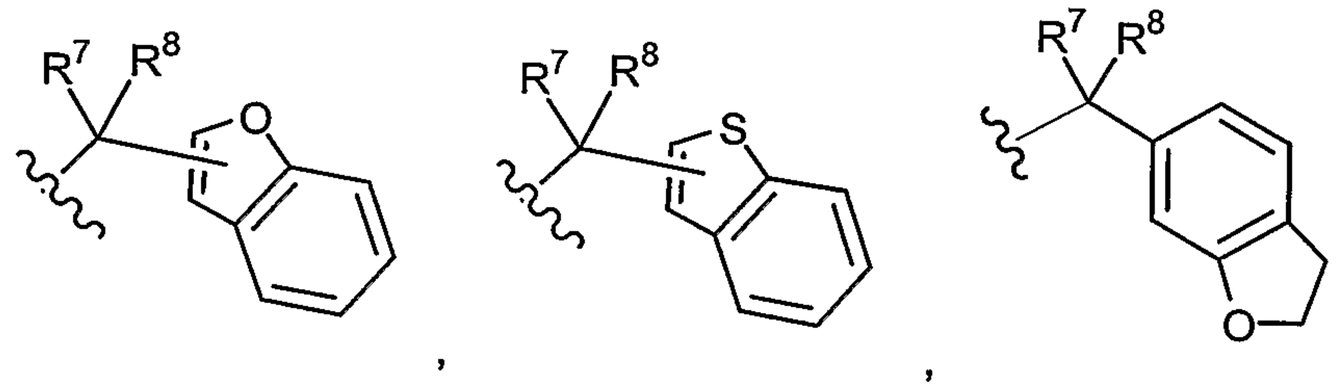
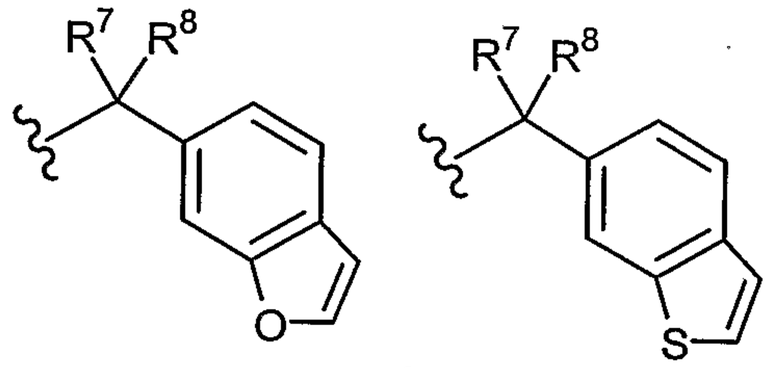
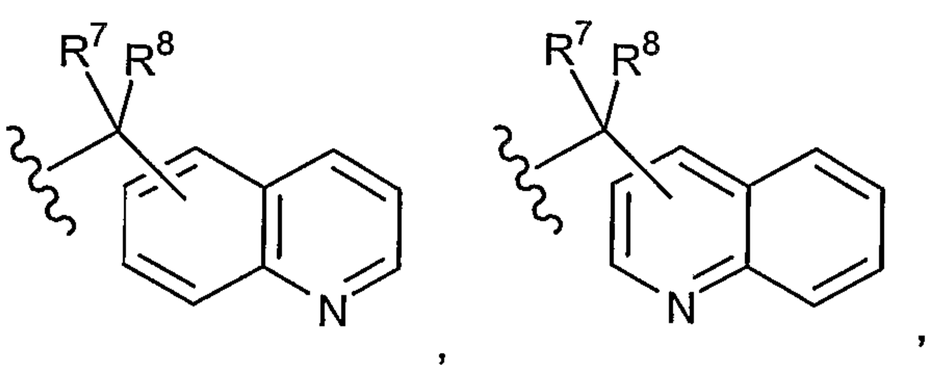


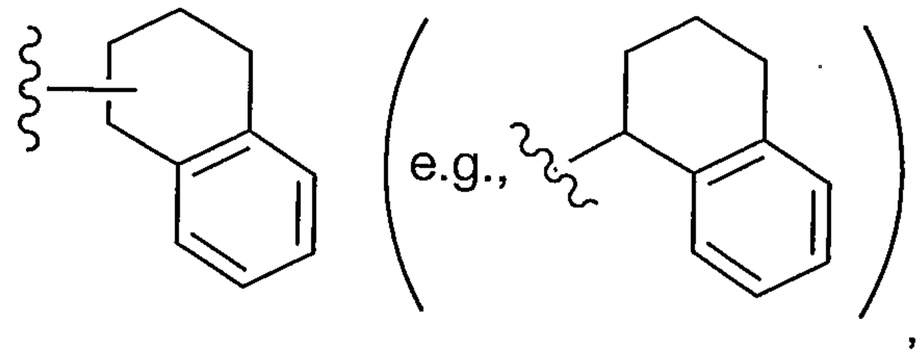
wherein the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

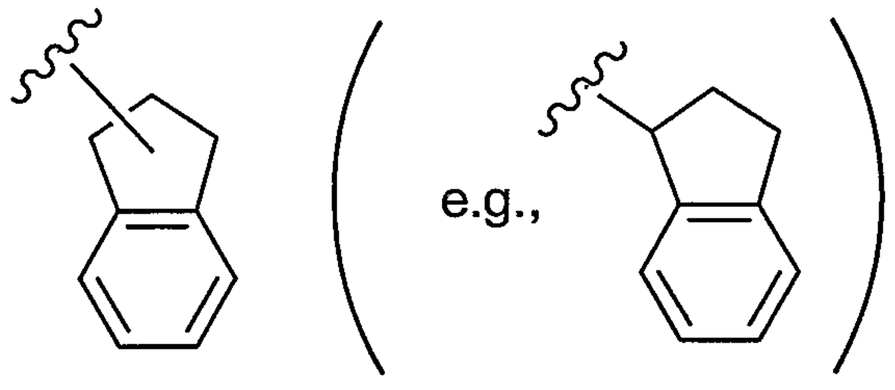
(3)

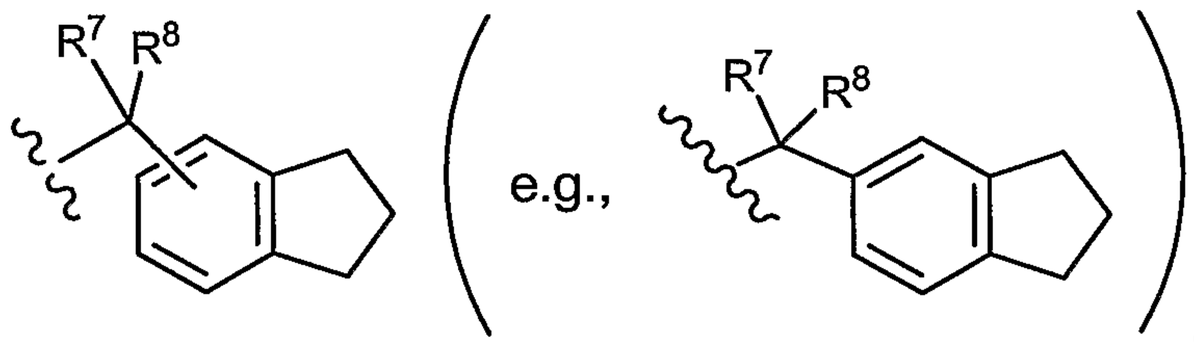


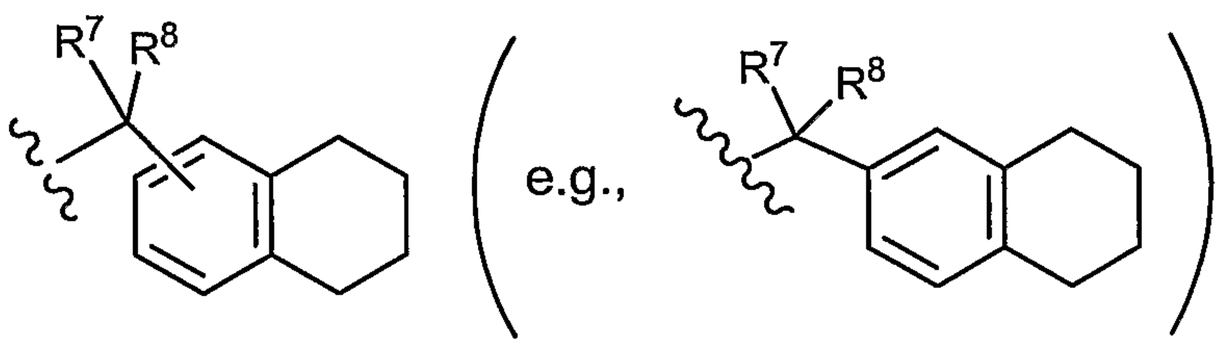






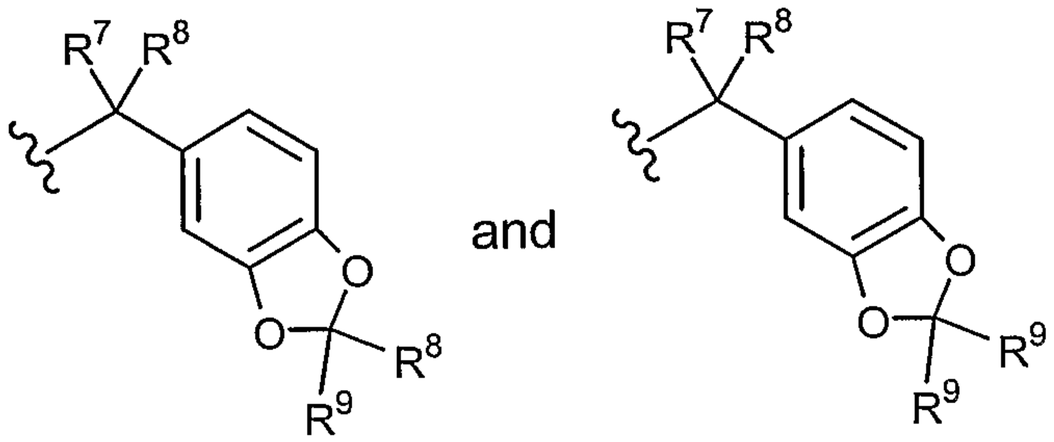






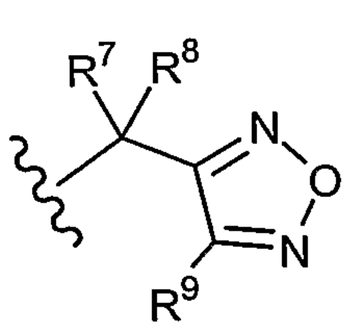
wherein one or both of the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

(4)



wherein the above phenyl rings of said A groups are substituted with 1 to 3 substituents each independently selected from the group consisting of: R^9 groups; and

(5)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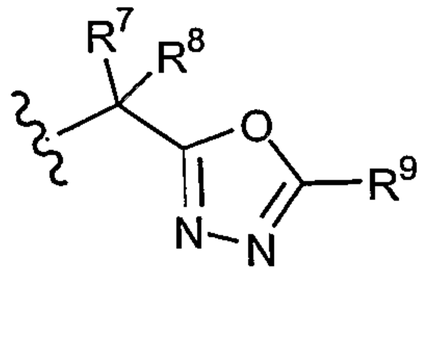
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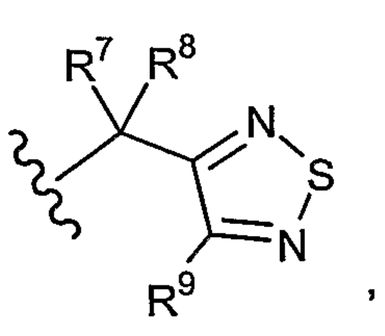
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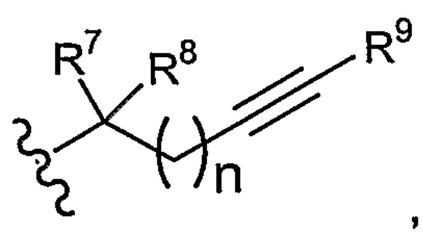
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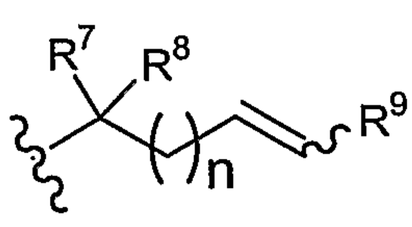
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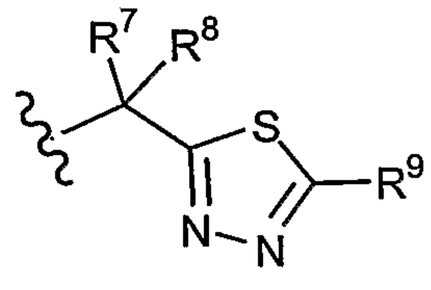
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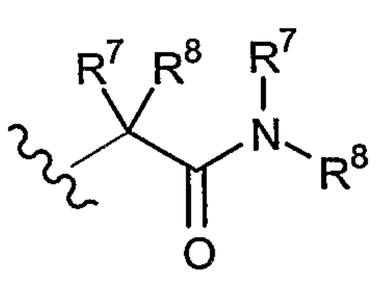
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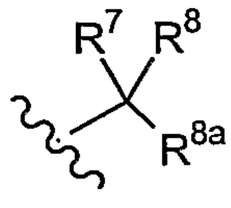
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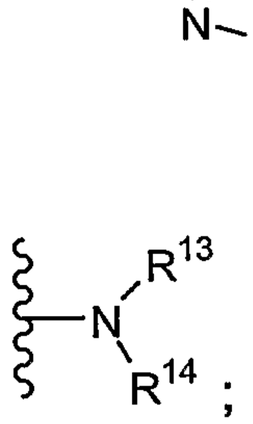
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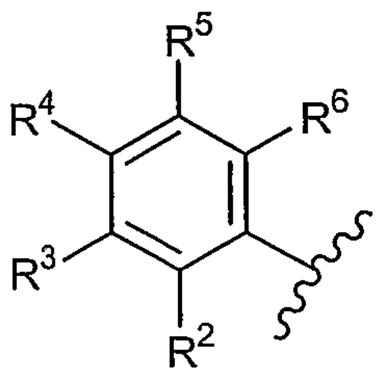
B is selected from the group consisting of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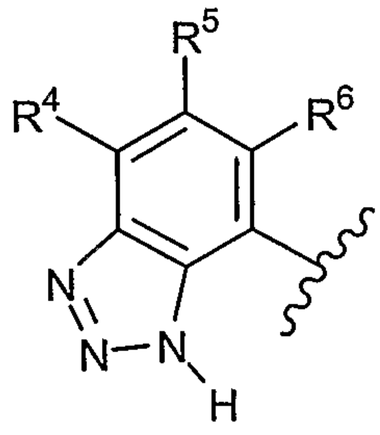
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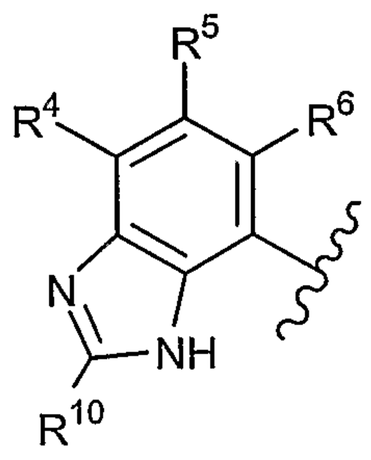
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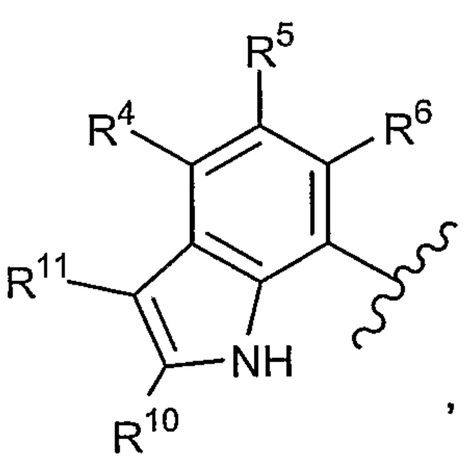
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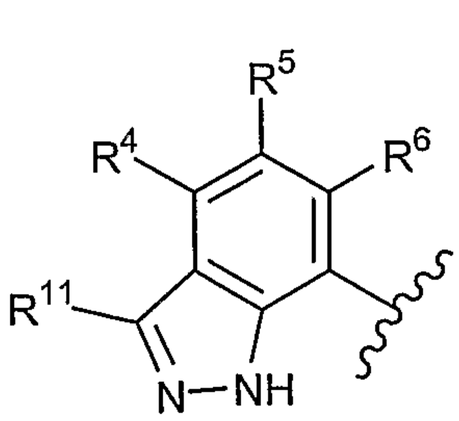
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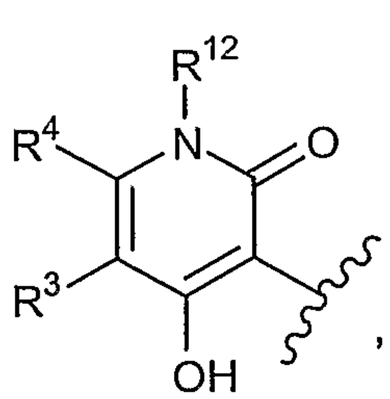
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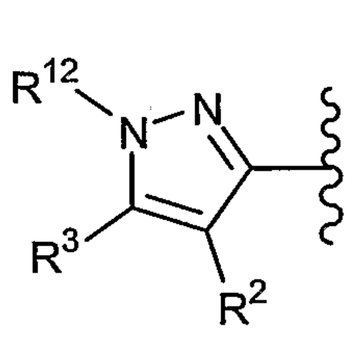
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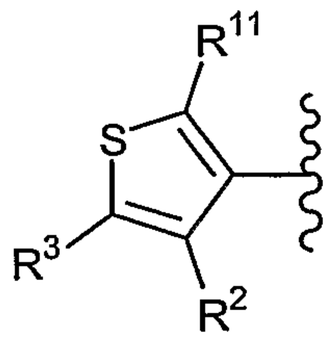
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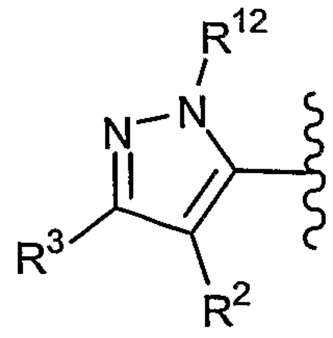
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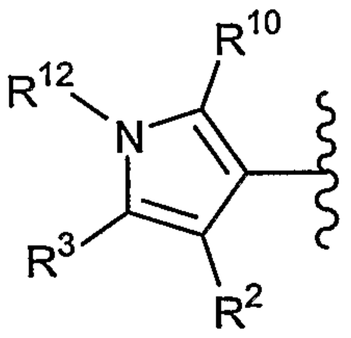
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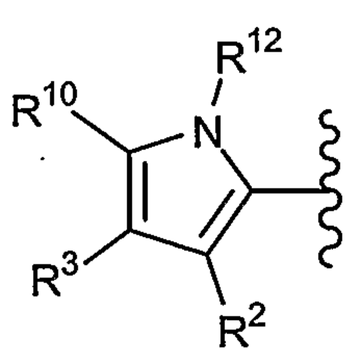
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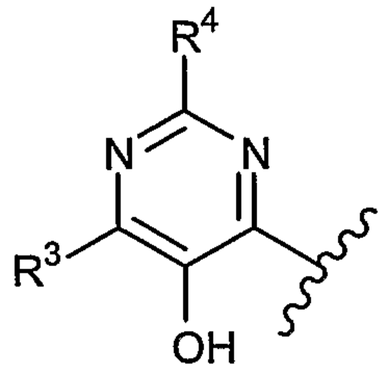
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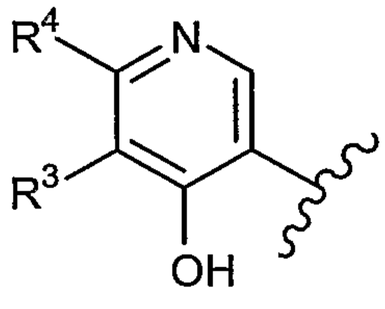
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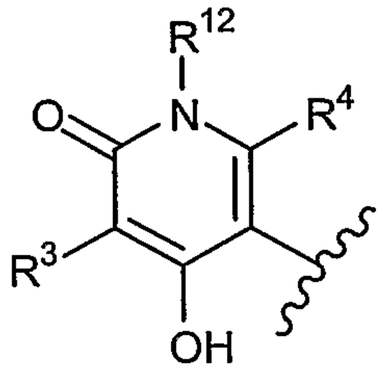
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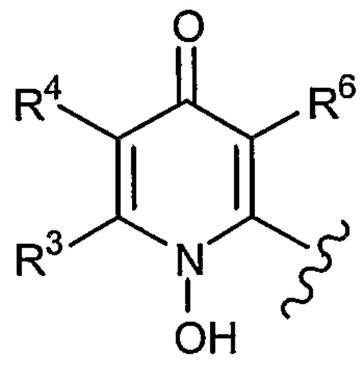
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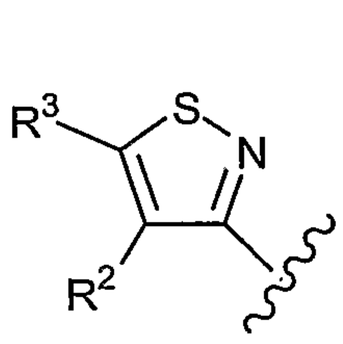
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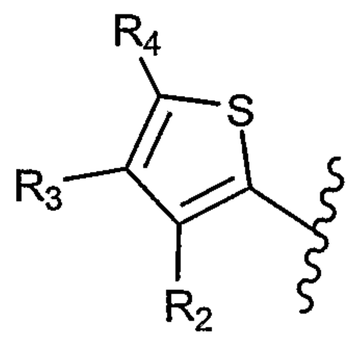
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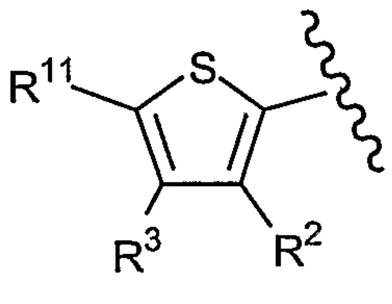

;

n is 0 to 6;

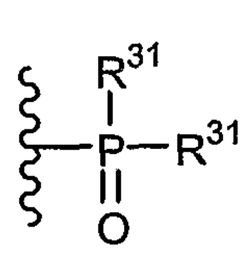
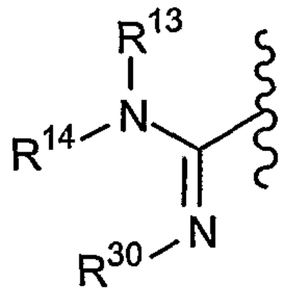
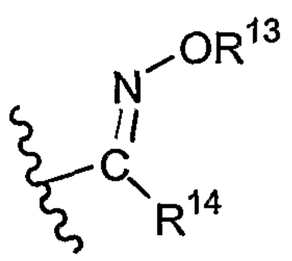
p is 1 to 5;

X is O, NR^{18}, or S;

Z is 1 to 3;

R^2 is selected from the group consisting of: hydrogen, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, - $S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

each R^3 and R^4 is independently selected from the group consisting of: hydrogen, cyano, halogen, alkyl, cycloalkyl substituted with 1 to 4 alkyl groups (preferably C_1 to C_6 alkyl groups) wherein each alkyl group is independently selected, unsubstituted cycloalkyl, alkoxy, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,


, 
and 
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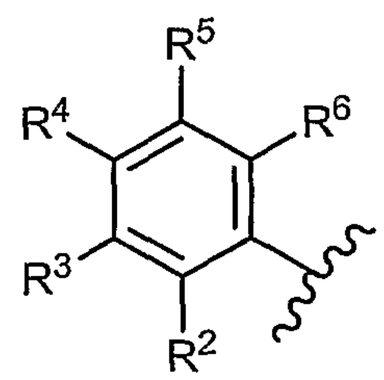
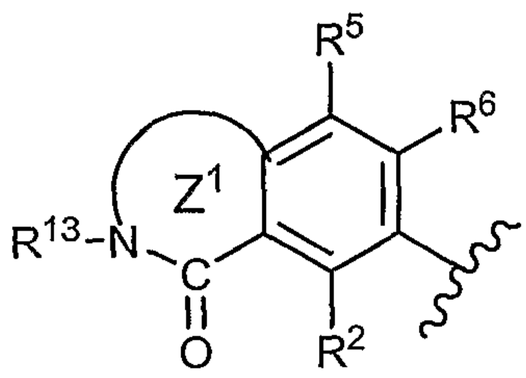
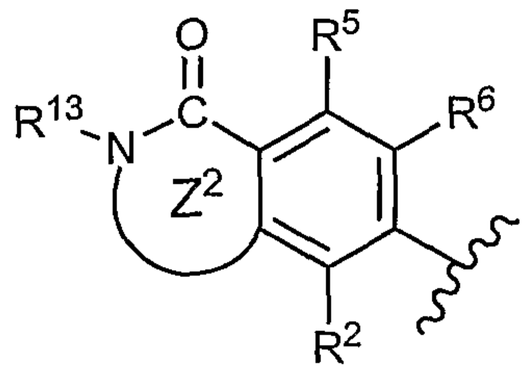
wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups; or

R^3 is and R^4 taken together with the carbons atoms to which they are bonded to in the the phenyl B substituent

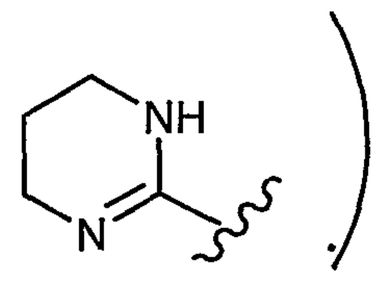


form a fused ring of the formula:

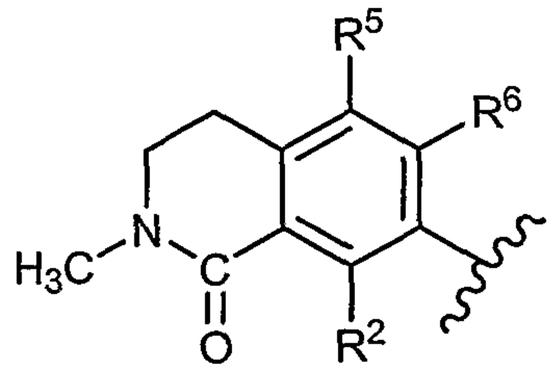
 or 

(preferably Z^1) wherein Z^1 or Z^2 is an unsubstituted or substituted saturated heterocyclic ring (preferably a 4 to 7 membered heterocyclic ring), said ring Z^1 or Z^2 optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on said ring Z^1 or Z^2, and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$, $-NHC(O)OR^{15}$, halogen, and a

heterocycloalkenyl group (i.e., a heterocyclic group that has at least one, and preferably one, double bond in a ring, e.g.,



examples of the fused ring moiety include, but are not limited to:



;

each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; and wherein there are one or more (e.g., 1 to 6) substituents on said substituted R^7 and R^8 groups, wherein each substitutent is independently selected from the group consisting of:

a) halogen,
b) $-CF_3$,
c) $-COR^{13}$,
d) $-OR^{13}$,
e) $-NR^{13}R^{14}$,
f) $-NO_2$,

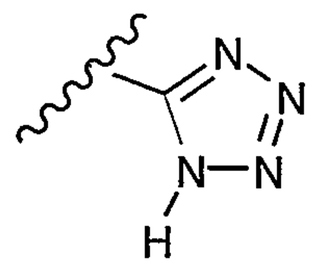
g) –CN,
h) $–SO_2OR^{13}$,
i) $–Si(alkyl)_3$, wherein each alkyl is independently selected,
j) $–Si(aryl)_3$, wherein each alkyl is independently selected,
k) $–(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
l) $–CO_2R^{13}$,
m) $–C(O)NR^{13}R^{14}$,
n) $–SO_2NR^{13}R^{14}$,
o) $–SO_2R^{13}$,
p) $–OC(O)R^{13}$,
q) $–OC(O)NR^{13}R^{14}$,
r) $–NR^{13}C(O)R^{14}$, and
s) $–NR^{13}CO_2R^{14}$;

(fluoroalkyl is one non-limiting example of an alkyl group that is substituted with halogen);

R^{8a} is selected from the group consisting of: hydrogen, alkyl, cycloalkyl and cycloalkylalkyl;

each R^9 is independently selected from the group consisting of:

a) $-R^{13}$,
b) halogen,
c) $-CF_3$,
d) $–COR^{13}$,
e) $–OR^{13}$,
f) $–NR^{13}R^{14}$,
g) $-NO_2$,
h) –CN,
i) $-SO_2R^{13}$,
j) $-SO_2NR^{13}R^{14}$,
k) $–NR^{13}COR^{14}$,
l) $–CONR^{13}R^{14}$,
m) $–NR^{13}CO_2R^{14}$,
n) $-CO_2R^{13}$,
o)



p) alkyl substituted with one or more (e.g., one) –OH groups (e.g., $-(CH_2)_qOH$, wherein q is 1-6, usually 1 to 2, and preferably 1),

q) alkyl substituted with one or more (e.g., one) $-NR^{13}R^{14}$ group (e.g., $-(CH_2)_qNR^{13}R^{14}$, wherein q is 1-6, usually 1 to 2, and preferably 1), and

r) $-N(R^{13})SO_2R^{14}$ (e.g., R^{13} is H and R^{14} is alkyl, such as methyl);

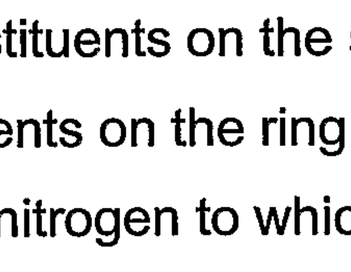
each R^{10} and R^{11} is independently selected from the group consisting of R^{13}, (e.g., hydrogen and alkyl (e.g., C_1 to C_6 alkyl, such as methyl)), halogen, $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$ and cyano;

R^{12} is selected from the group consisting of: hydrogen, $-C(O)OR^{13}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6 substituents on the substituted R^{12} groups and each substituent is independently selected from the group consisting of: R^9 groups;

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted cyanoalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cyanocycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl (wherein "heterocyloalkyl" means heterocyclic); wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, $-CF_3$, -OH, alkoxy, aryl, arylalkyl, fluroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, $-N(R^{40})_2$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_tNR^{15}R^{16}$, $-C(O)R^{15}$, halogen, $-NHC(O)NR^{15}R^{16}$ and $-SO_2R^{15}$ provided that R^{15} is not H; and provided that for the substituted cyanoalkyl and the substituted

cyanocycloalkyl moieties the carbon atom to which the cyano (CN) group is bound to does not also have bound to said carbon atom a substituent selected from the group consisting of: -OH, alkoxy, -N(R^{40})$_2$, halogen and -NHC(O)N$R^{15}R^{16}$; or

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups -C(O)N$R^{13}R^{14}$ and -SO_2N$R^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered heterocyclic ring), said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., there is 1 to 3 substituents on the ring formed when the R^{13} and R^{14} groups are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: CN, alkyl, cyanoalkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cyanocycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, -C(O)OR^{15}, -C(O)N$R^{15}R^{16}$, -SO_tN$R^{15}R^{16}$, -C(O)R^{15}, -SO_2R^{15} (provided that R^{15} is not H), -NHC(O)N$R^{15}R^{16}$, -NHC(O)OR^{15}, halogen, and a heterocycloalkenyl group (i.e., a heterocyclic group that has at least one, and preferably one, double bond in a ring, e.g.,

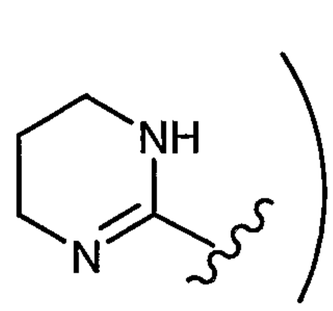


;

and provided that the carbon atom to which the cyano (CN) group is bound to does not also have bound to said carbon atom a substituent selected from the group consisting of: hydroxy, alkoxy, amino, halogen, -NHC(O)N$R^{15}R^{16}$ and -NHC(O)OR^{15};

(or in another embodiment, (1) each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl (wherein “heterocyloalkyl” means heterocyclic); wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, -CF_3, -OH, alkoxy, aryl, arylalkyl, fluroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, -N(R^{40})$_2$,

-C(O)OR^{15}, -C(O)NR^{15}R^{16}, -S(O)$_t$NR^{15}R^{16}, -C(O)R^{15}, -SO$_2$R^{15} provided that R^{15} is not H, halogen, and -NHC(O)NR^{15}R^{16}; or (2) R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups -C(O)NR^{13}R^{14} and -SO$_2$NR^{13}R^{14} form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered heterocyclic ring), said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., there is 1 to 3 substituents on the ring formed when the R^{13} and R^{14} groups are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, -C(O)OR^{15}, -C(O)NR^{15}R^{16}, -SO$_t$NR^{15}R^{16}, -C(O)R^{15}, -SO$_2$R^{15} provided that R^{15} is not H, -NHC(O)NR^{15}R^{16}, -NHC(O)OR^{15}, halogen, and a heterocycloalkenyl group (i.e., a heterocyclic group that has at least one, and preferably one, double bond in a ring, e.g.,



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each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: -SO$_2$alkyl, -SO$_2$aryl, -SO$_2$cycloalkyl, and -SO$_2$heteroaryl;

R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, -C(O)R^{19}, -SO$_2$R^{19} and -C(O)NR^{19}R^{20};

each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl;

R^{30} is selected from the group consisting of: alkyl, cycloalkyl, -CN, -NO$_2$, or -SO$_2$R^{15} provided that R^{15} is not H;

each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6 substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and -CF$_3$;

each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

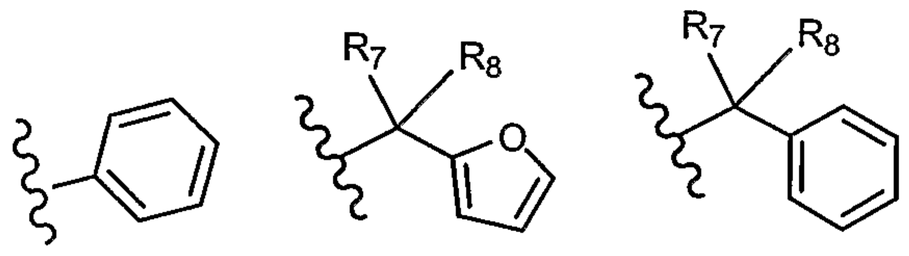
t is 0, 1 or 2.

For compounds of formula IA, when R^3 is $-SO_{(t)}NR^{13}R^{14}$ (e.g., $-SO_2NR^{13}R^{14}$), preferably R^{13} and R^{14} are independently selected from the group consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl). Examples include, but are not limited to (1) $-SO_2NH_2$ and (2) $-SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} are the same or different alkyl group (e.g., methyl, ethyl, isopropyl and t-butyl), e.g., the same alkyl group, such as, for example $-SO_2N(CH_3)_2$.

For compounds of formula IA, when R^3 is $-C(O)NR^{13}R^{14}$, preferably R^{13} and R^{14} are independently selected from the group consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl). Examples include, but are not limited to $-C(O)NR^{13}R^{14}$ wherein each R^{13} and R^{14} are the same or different alkyl group, e.g., the same alkyl group, such as, for example $-C(O)N(CH_3)_2$.

For the compounds of formula IA substituent A is preferably selected from the group consisting of:

(1) unsubstituted or substituted: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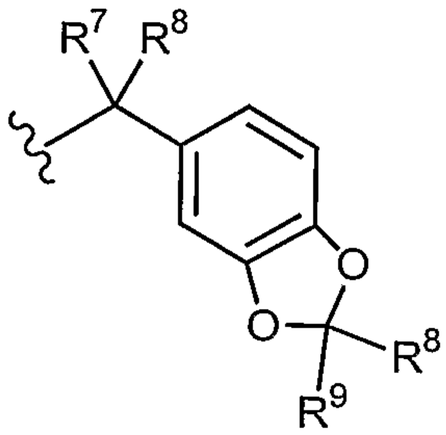
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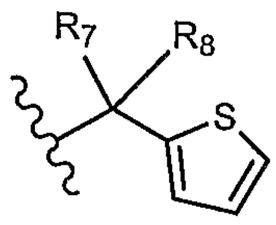
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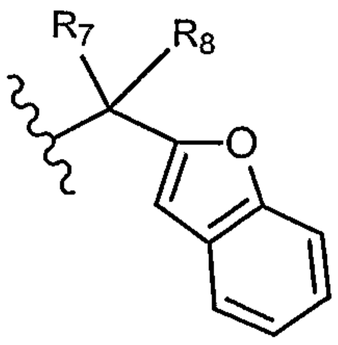
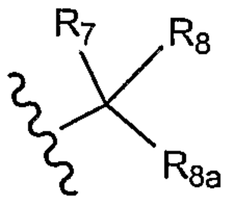
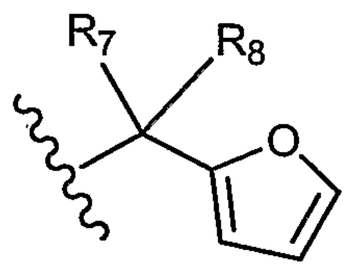

; and

(2)



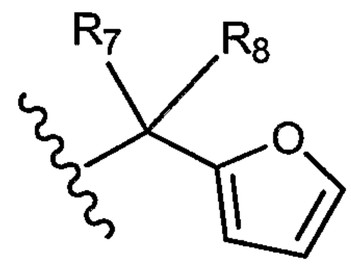
wherein all substitutents are as defined for formula IA.

For the compounds of formula IA substituent A is most preferably:



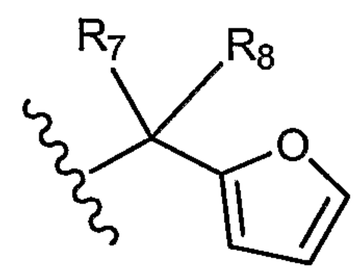
wherein the furan ring is unsubstituted or substituted with 1 or 2 alkyl groups (e.g., C_1 to C_3 alkyl groups) wherein each alkyl group is independently selected, R^7 is selected from the group consisting of: $-CF_3$, alkyl (e.g., C_1 to C_4 alkyl) and cycloalkyl (e.g., cyclopropyl), and R^8 is H. More preferably the furan ring is substituted.

For the compounds of formula IA substituent A is even more preferably:



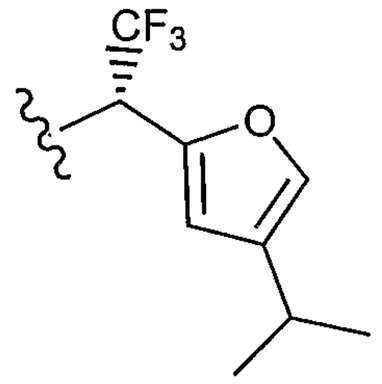
wherein the furan ring is unsubstituted or substituted with 1 or 2 alkyl groups independently selected from the group consisting of methyl, ethyl and isoprpyl, R^7 is selected from the group consisting of: $-CF_3$, ethyl, isopropyl, t-butyl and cyclopropyl, and R^8 is H. Still more preferably the furan ring is substituted.

For the compounds of formula IA substituent A is even yet more preferably:



wherein the furan ring is substituted with 1 or 2 alkyl groups independently selected from the group consisting of methyl, ethyl and isopropyl, R^7 is selected from the group consisting of: ethyl, isopropyl and t-butyl, and R^8 is H.

Examples of substituent A in formula IA include, but are not limited to:



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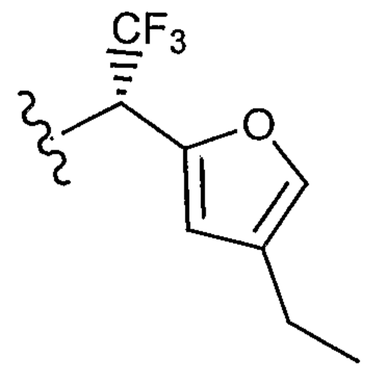

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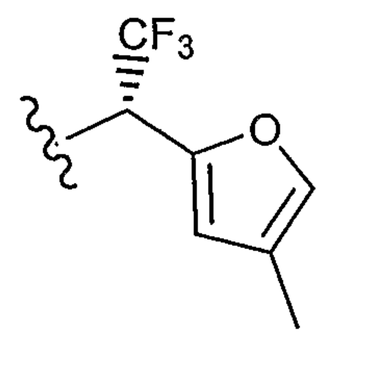

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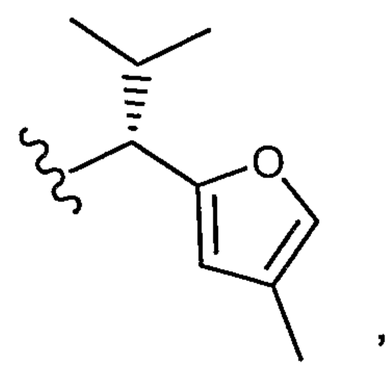

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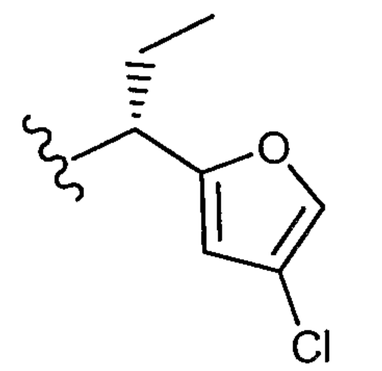

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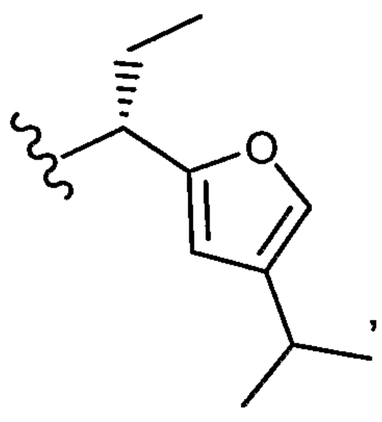
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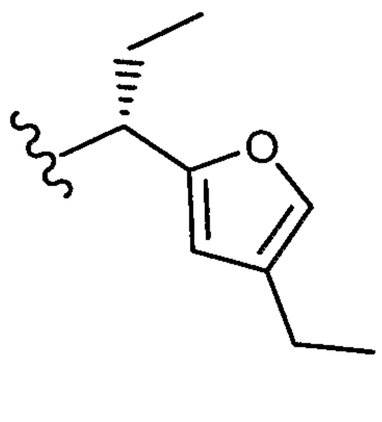
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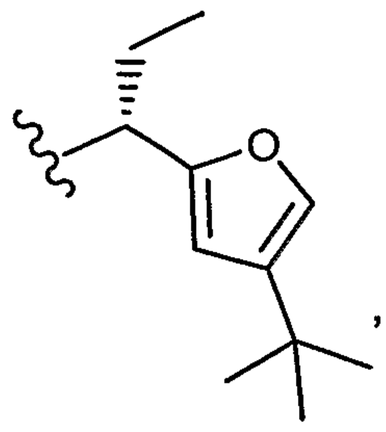
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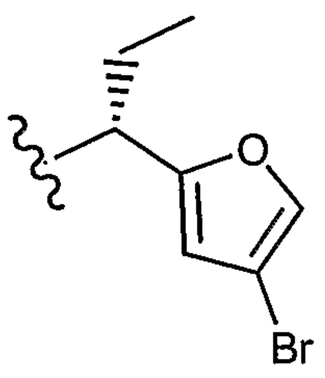
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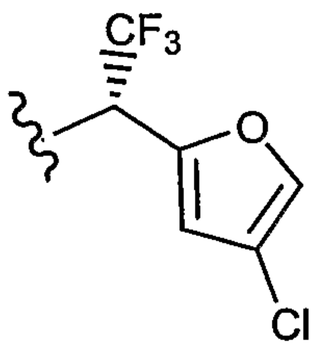
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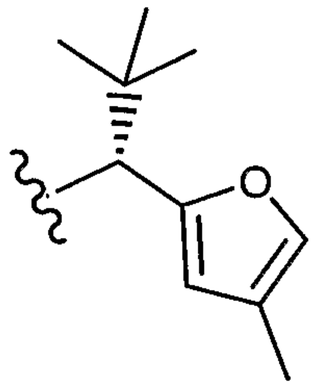
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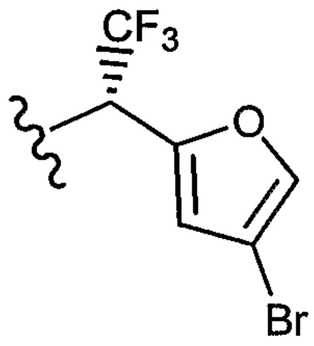
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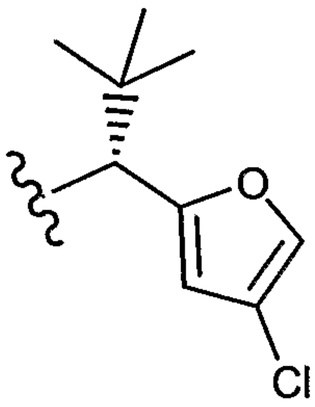
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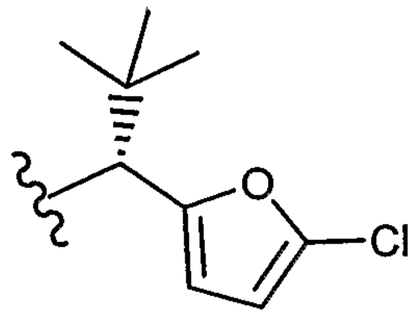
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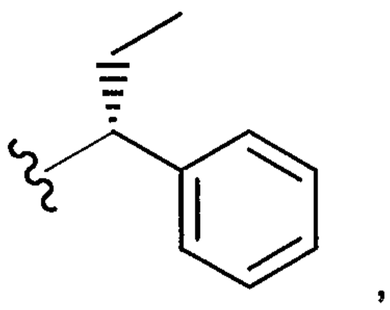
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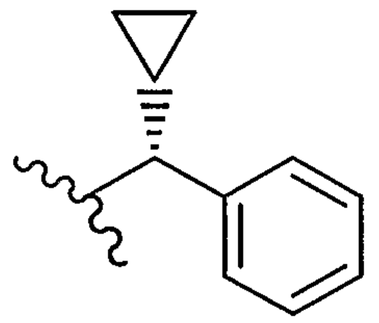
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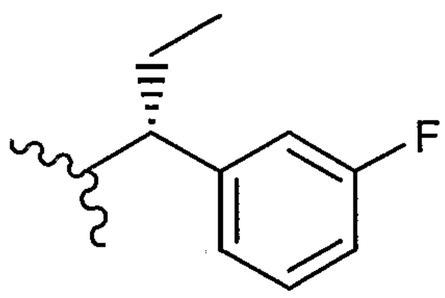
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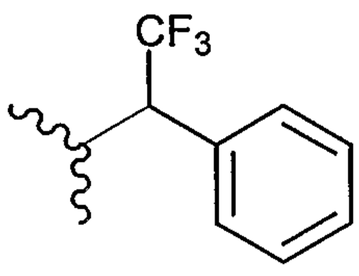
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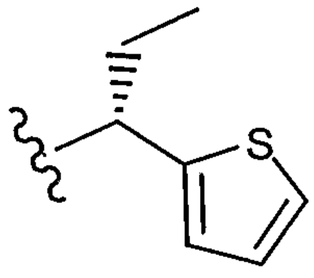
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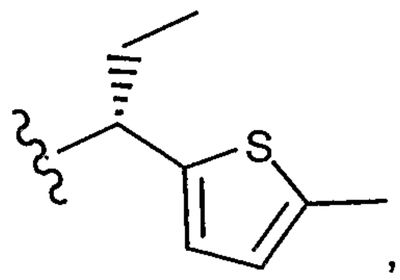
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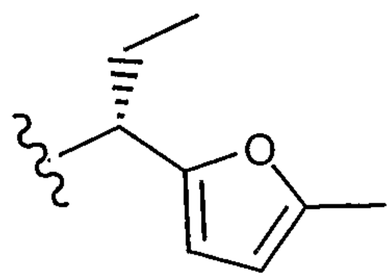
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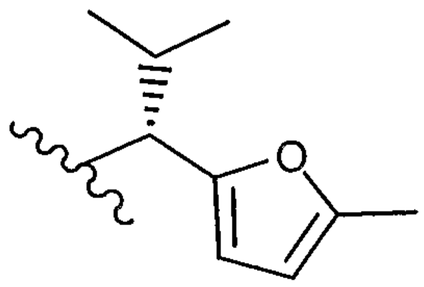
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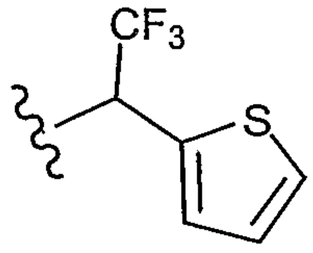
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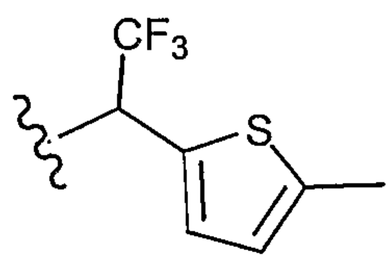
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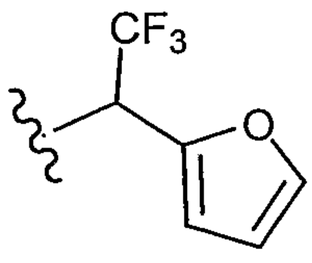
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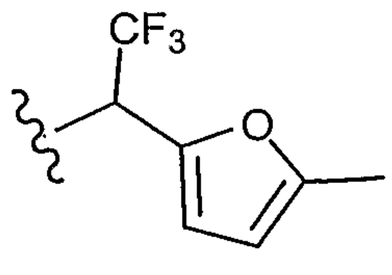
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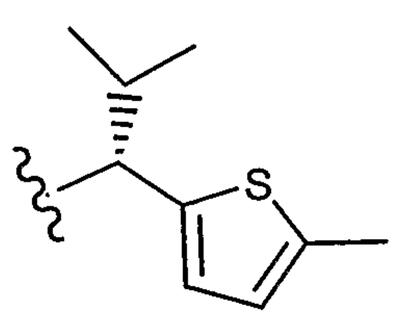
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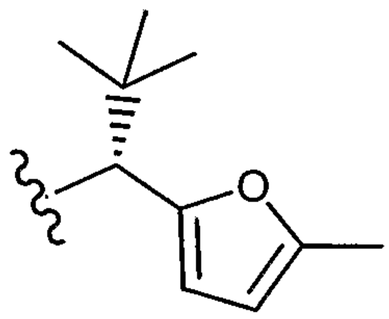
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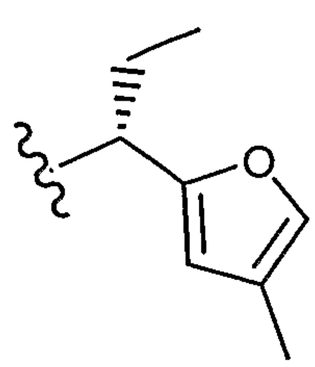
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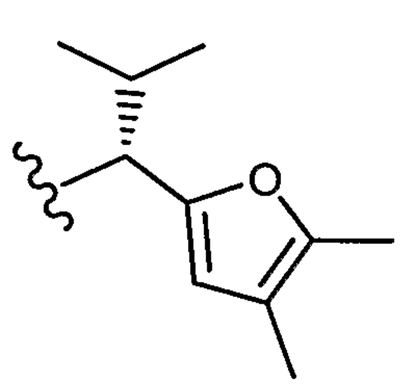
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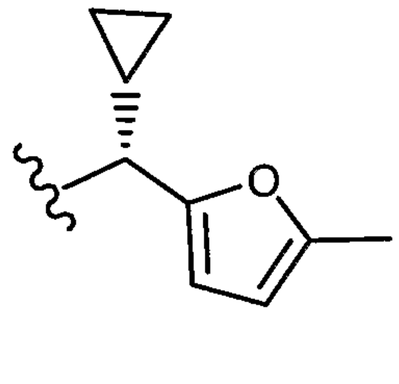
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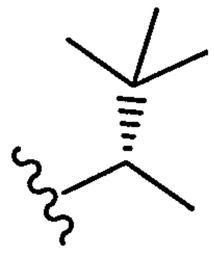
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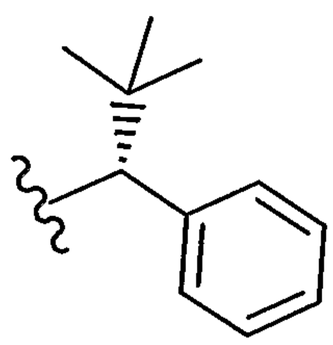
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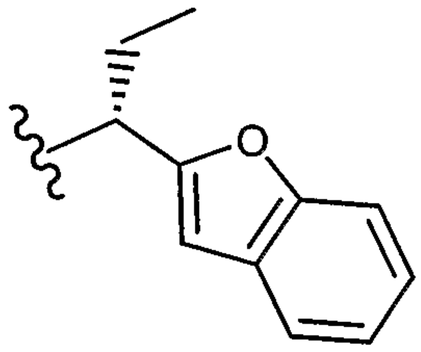
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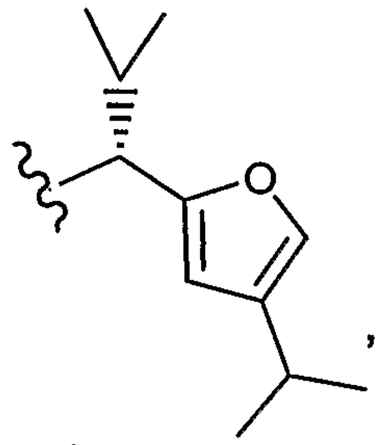
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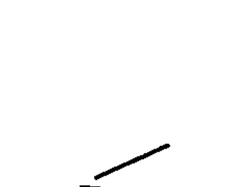
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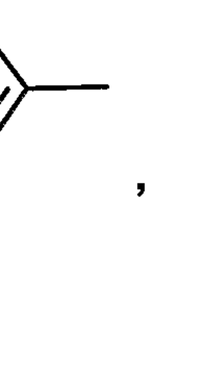
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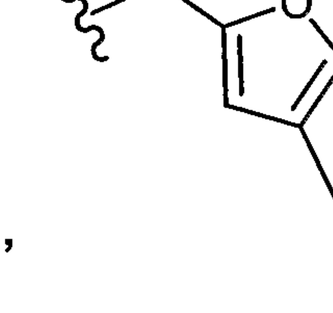
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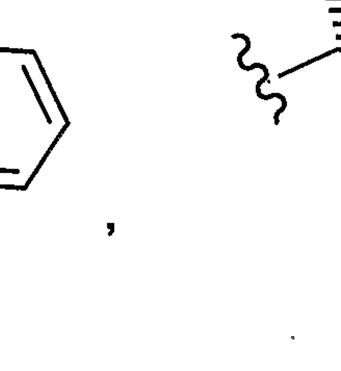
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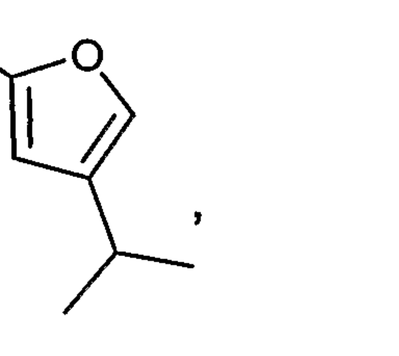
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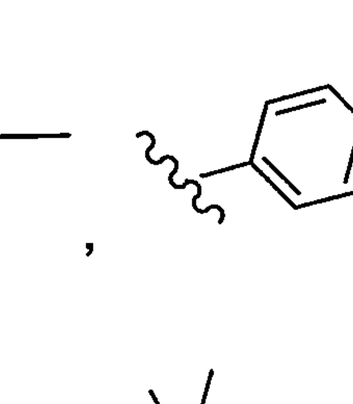
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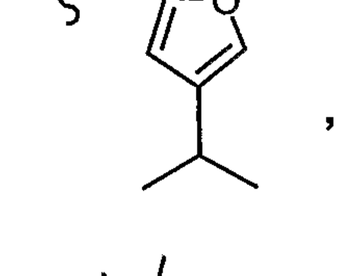
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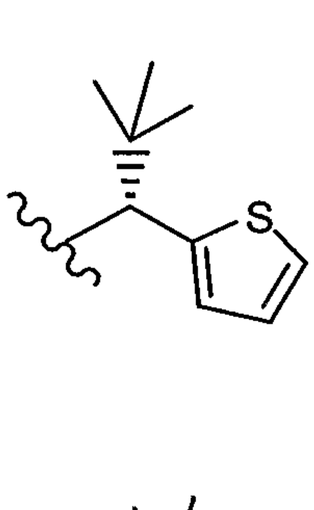
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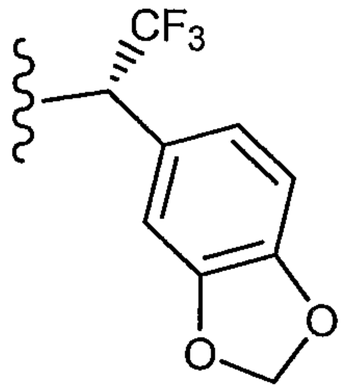
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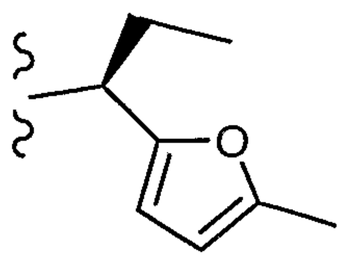
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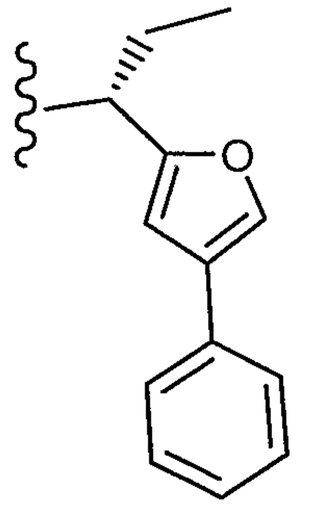
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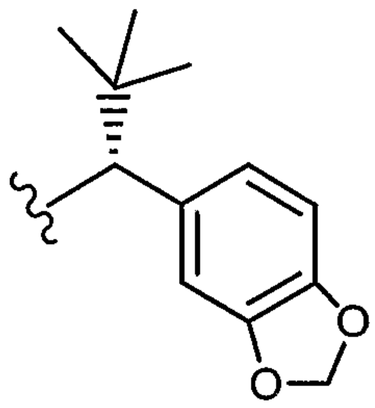
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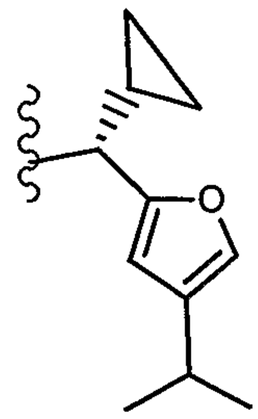
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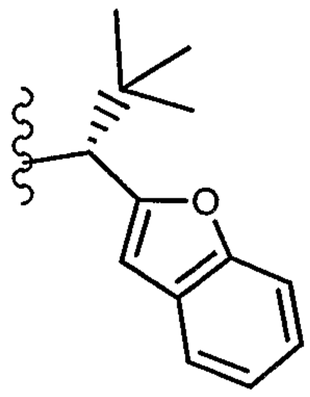

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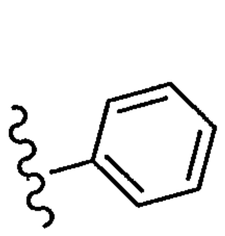
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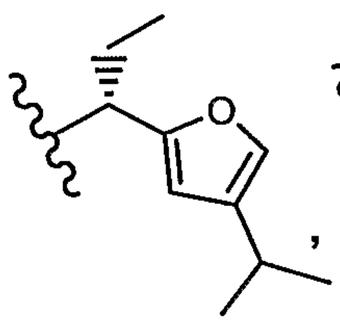
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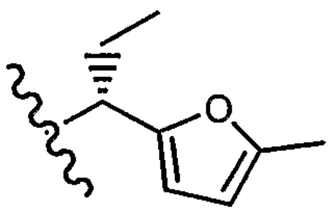
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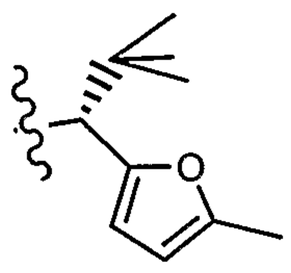
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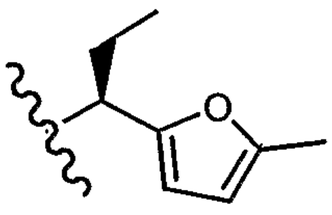
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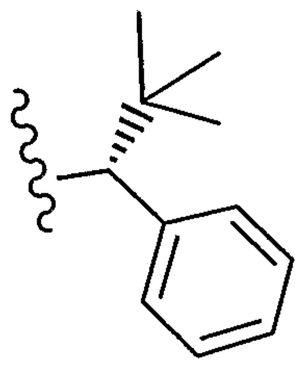
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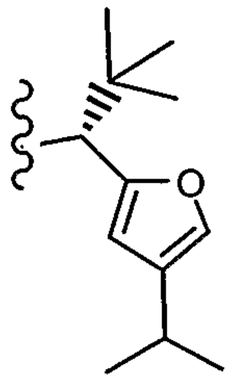
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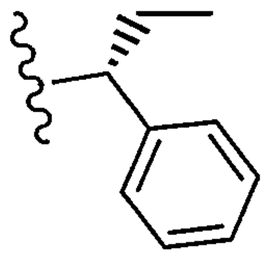
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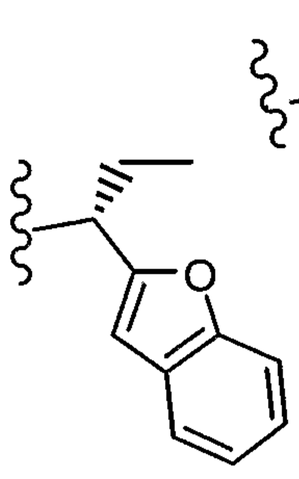
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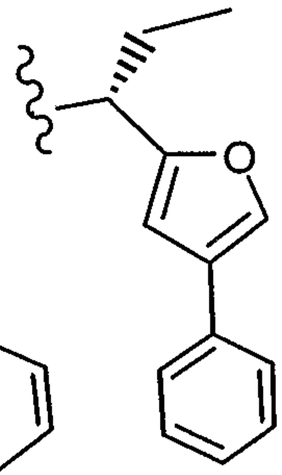
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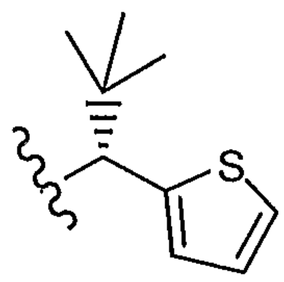
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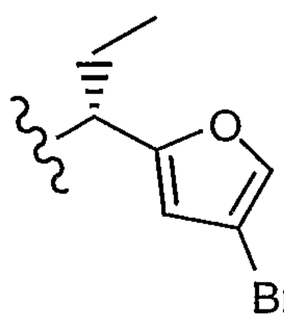
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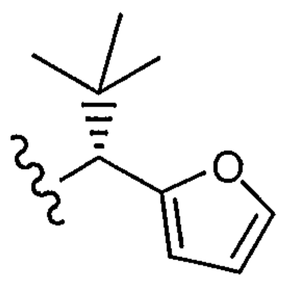
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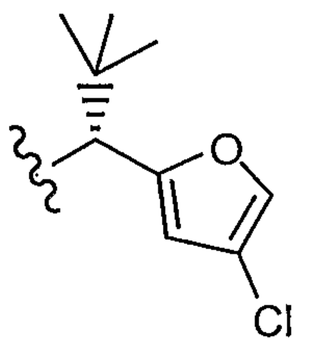
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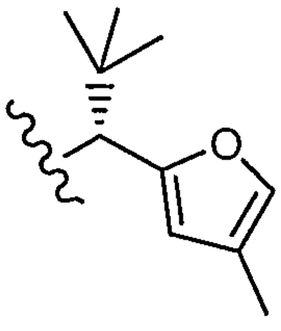
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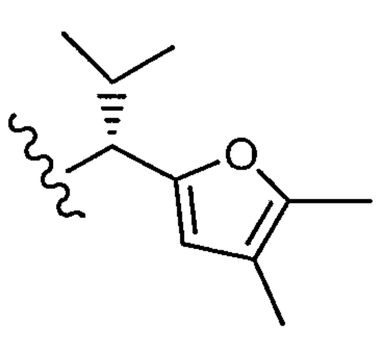
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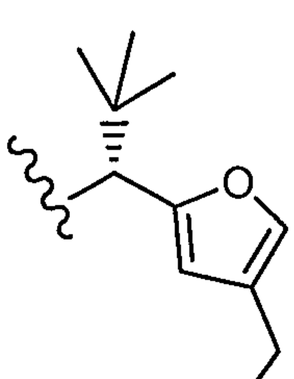
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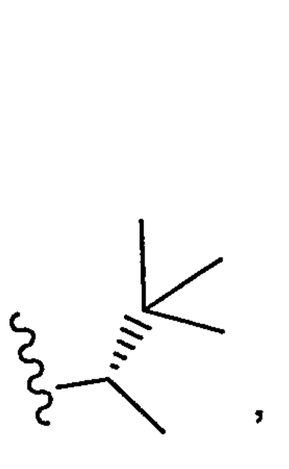
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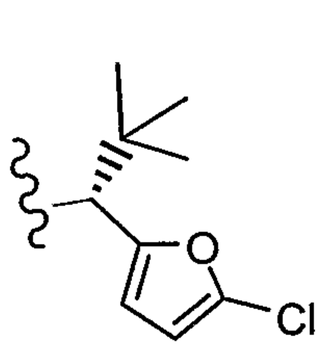
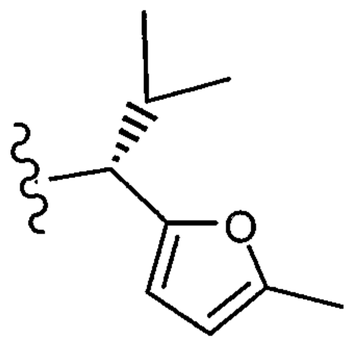
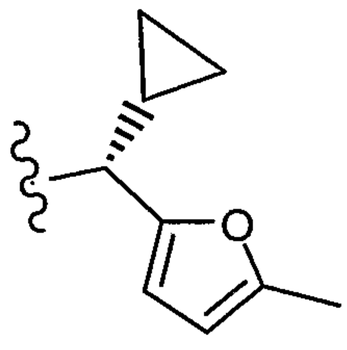
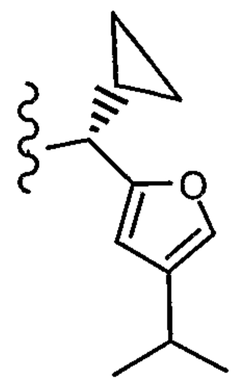
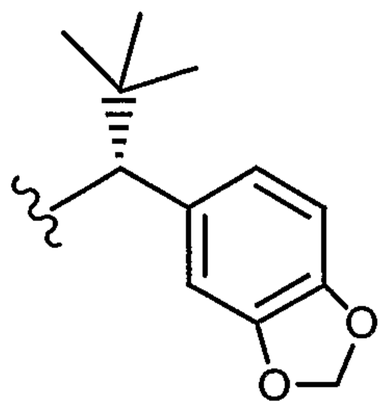
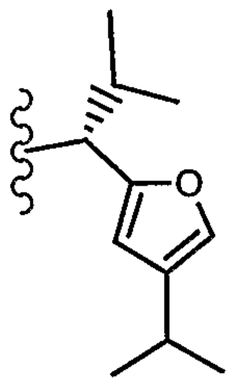
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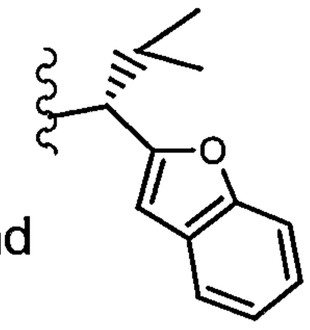

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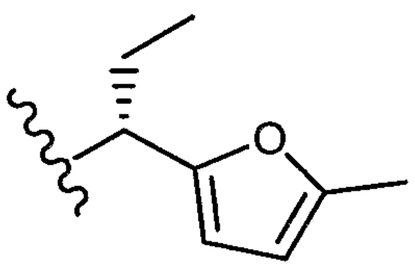
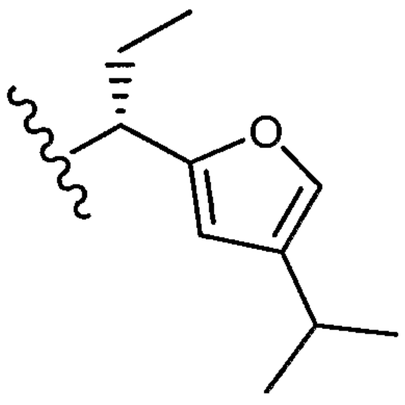
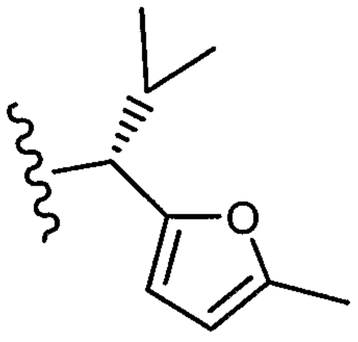
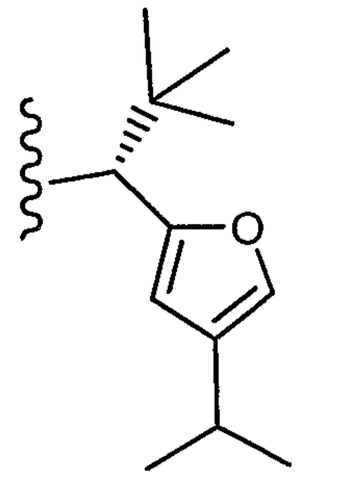
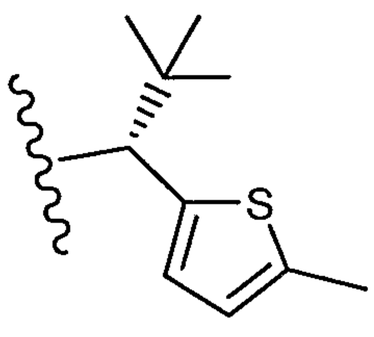
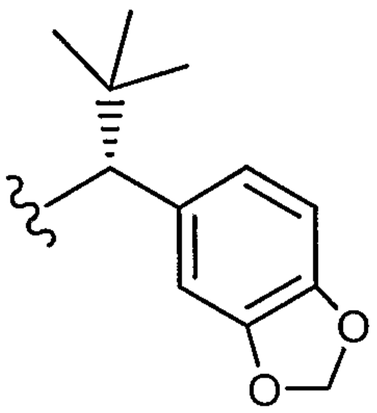
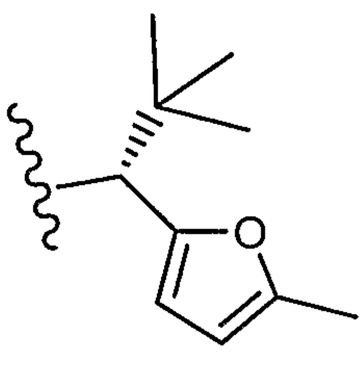
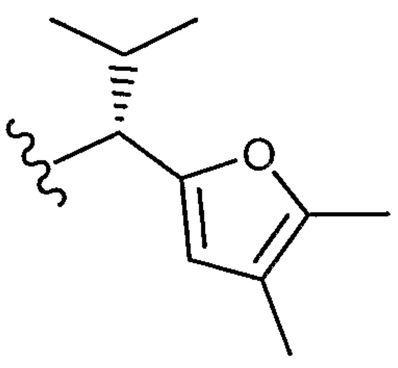
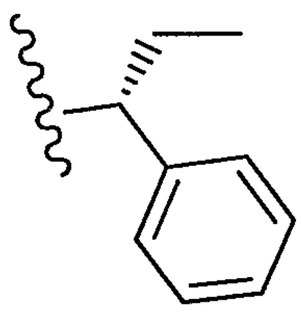
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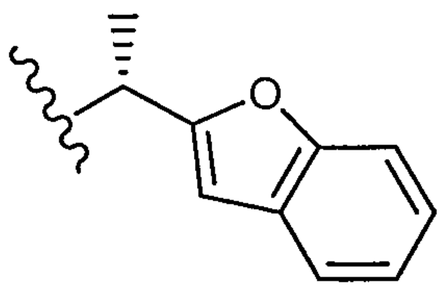
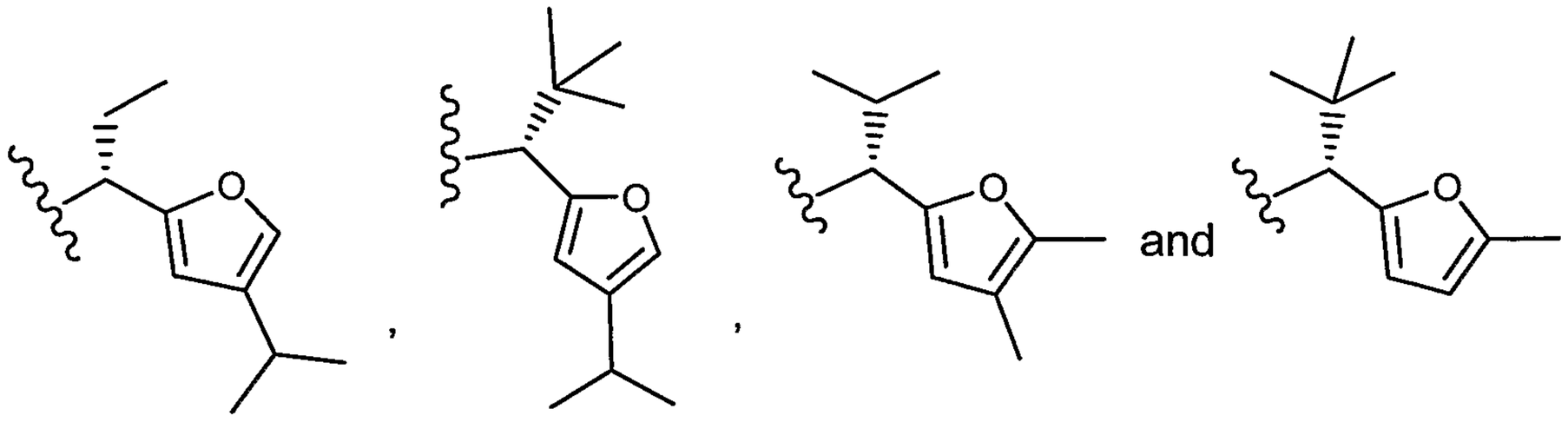
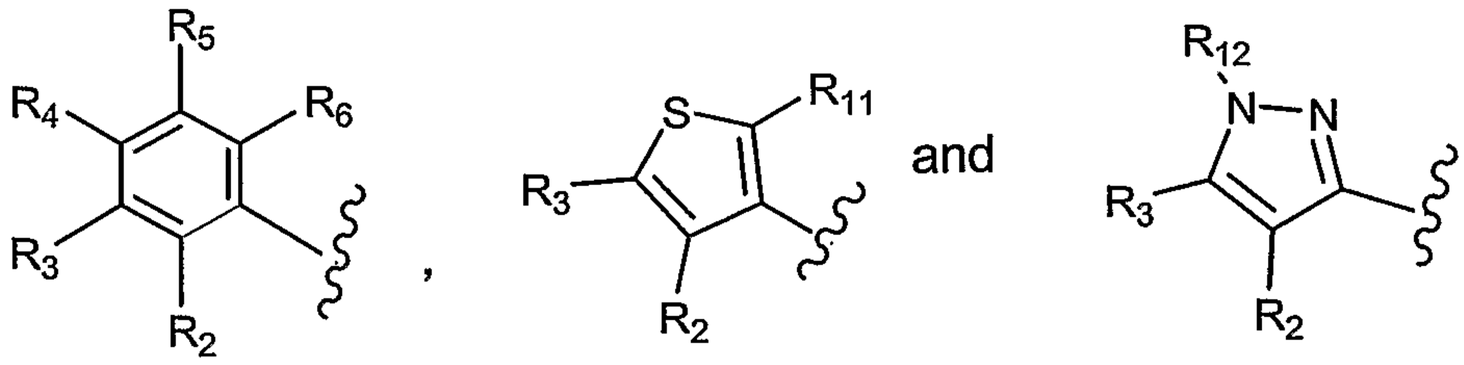


Substituent A in formula IA is even more preferably selected from the group consisting of:

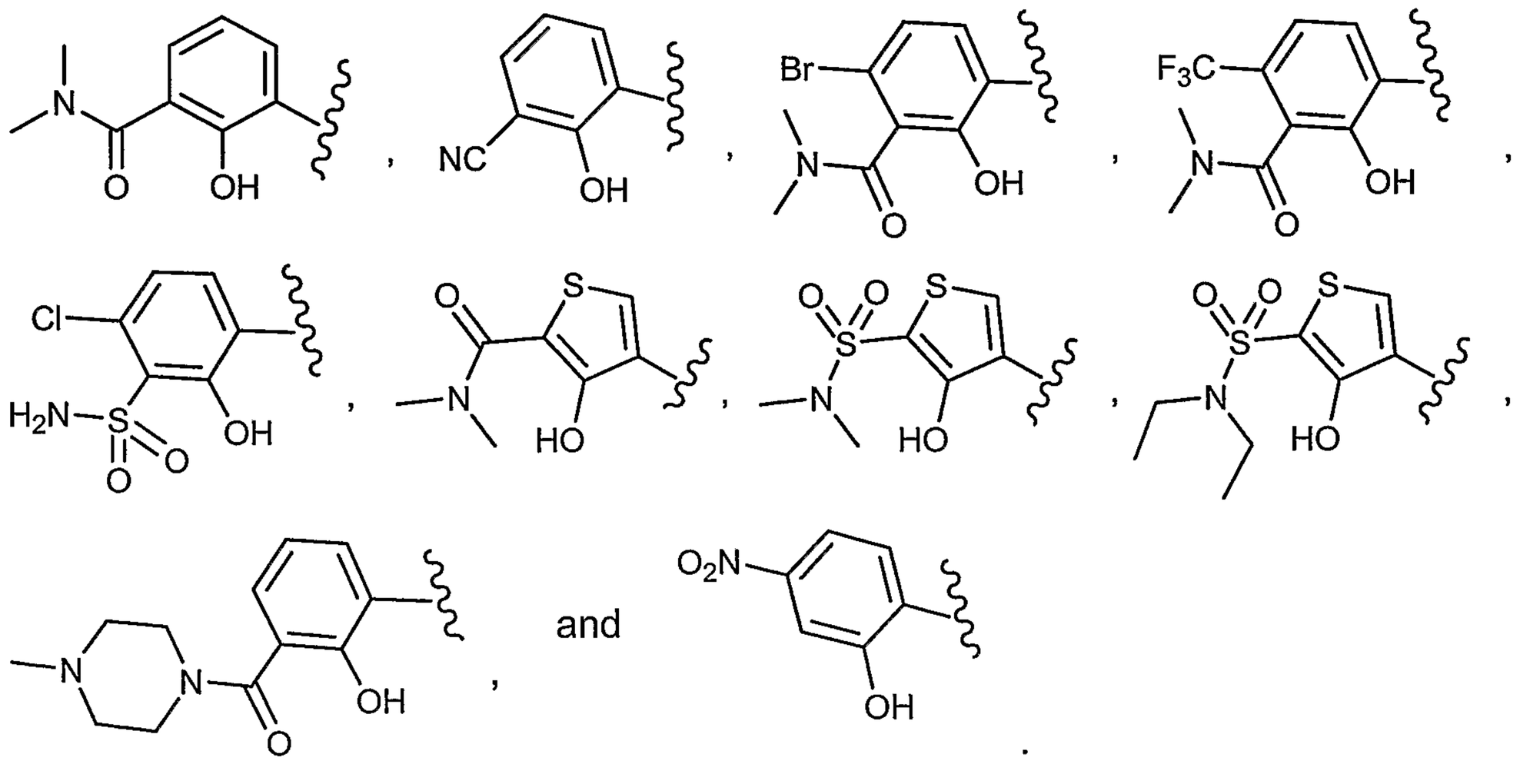


Substituent B in formula IA is preferably selected from the group consisting of:



wherein all substituents are as defined for formula IA.

Substituent B in formula IA is most preferably selected from the group consisting of:



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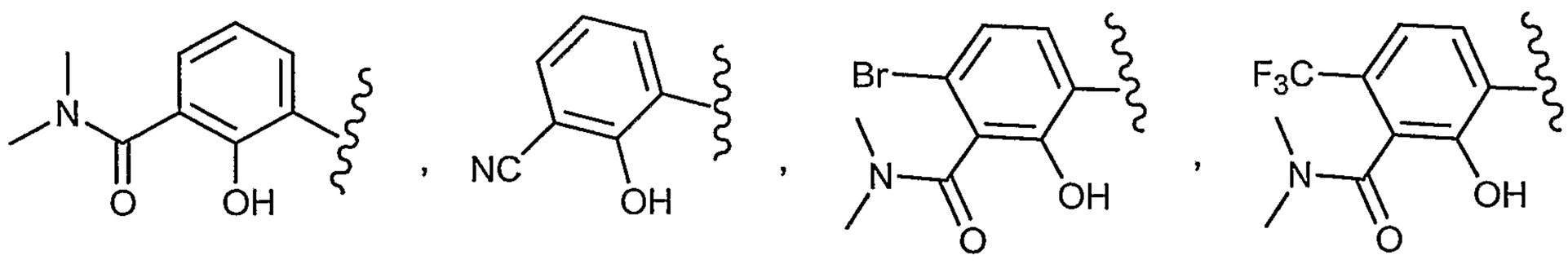
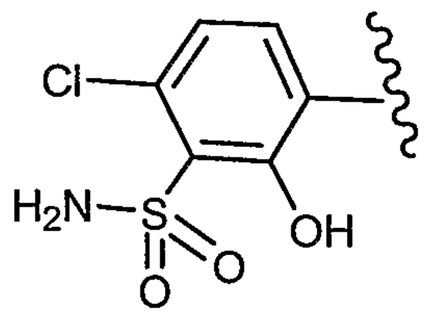


and  .

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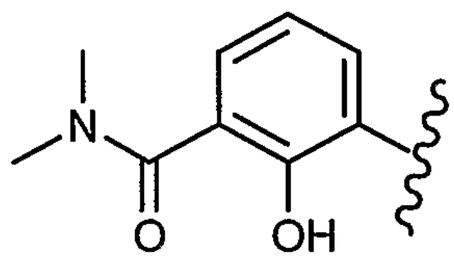
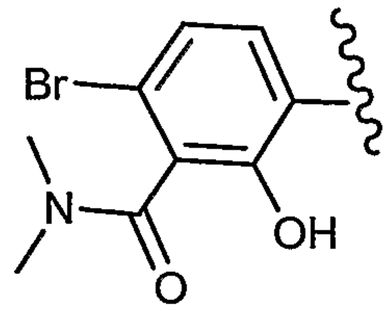
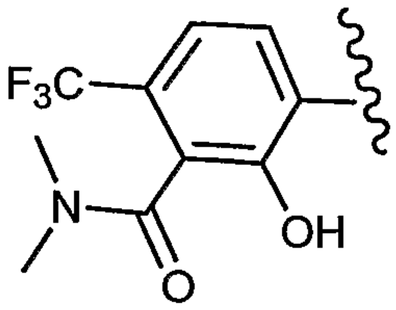
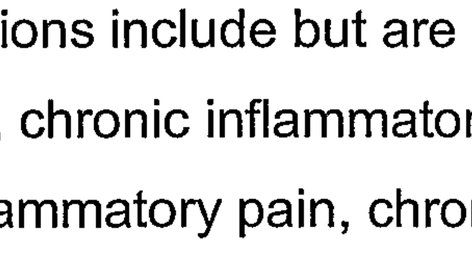
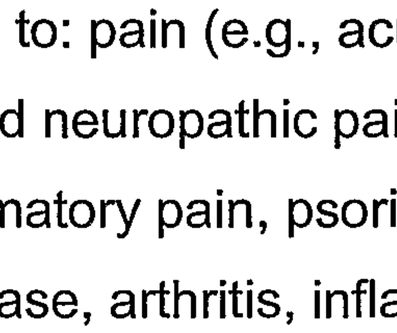
 ,  and  .

Substituent B in Formula IA is still even more preferably selected from the group consisting of:

 and  .

An embodiment of the present invention is directed to a method of treating an chemokine mediated disease in a patient in need of such treatment (e.g., a mammal, preferably a human being) comprising administering to said patient a therapeutically effective amount of at least one (e.g., 1-3, and usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof.

Examples of chemokine mediated (e.g., CXCR1 and/or CXCR2, or CCR7) diseases or conditions include but are not limited to: pain (e.g., acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain), rheumatoid arthritis, acute inflammatory pain, chronic inflammatory pain, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, ischemia reperfusion injury, renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction (i.e., graft vs. host disease), allograft rejections (e.g., acute allograft rejection, and chronic allograft rejection), malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral ischemia, cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma

associated virus (i.e., Kaposi's sarcoma), meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute pancreatitis, chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred, corneal neovascularization, polymyositis, vasculitis, acne, gastric ulcers, duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness (i.e., airway hyperreactivity), bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy (i.e., the treatment of burns), periodontitis, cancer, transplant reperfusion injury, early transplantation rejection (e.g., acute allograft rejection), airway hyperreactivity, allergic contact dermatitis, allergic rhinitis, alopecia areata, antiphospholipid syndromes, aplastic anemia, autoimmune deafness (including, for example, Meniere's disease), autoimmune hemolytic syndromes, autoimmune hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, bullous pemphigoid, chronic allograft vasculopathy, chronic inflammatory demyelinating polyneuropathy, cirrhosis, cor pneumoniae, cryoglobulinemia, dermatomyositis, diabetes, drug-induced autoimmunity, epidermolysis bullosa acquisita, endometriosis, fibrotic diseases, gastritis, Goodpasture's syndrome, Graves' disease, Gullain-Barre disease, Hashimoto's thyroiditis, hepatitis-associated autoimmunity, HIV-related autoimmune syndromes and hematologic disorders, hypophytis, idiopathic thrombocytic pupura, interstitial cystitis, juvenile arthritis, Langerhans' cell histiocytitis, lichen planus, metal-induced autoimmunity, myasthenia gravis, myelodysplastic syndromes, myocarditis (including viral myocarditis), myositis, Neuropathies (including, for example, IgA neuropathy, membranous neuropathy and idiopathic neuropathy), nephritic syndrome,

optic neuritis, pancreatitis, paroxysmal nocturnal hemoglobulinemia, pemphigus, polymyalgia, post-infectious autoimmunity, primary biliary cirrhosis, reactive arthritis, ankylosing spondylitis, Raynaud's phenomenon, Reiter's syndrome, reperfusion injury, scleritis, scleroderma, secondary hematologic manifestation of autoimmune diseases (such as, for example, anemias), silicone implant associated autoimmune disease, Sjogren's syndrome, systemic lupus erythematosus, thrombocytopenia, transverse myelitis, tubulointerstitial nephritis, uveitis, vasculitis syndromes (such as, for example, giant cell arteritis, Behcet's disease and Wegener's granulomatosis), and Vitiligo.

Examples of CXCR1 and/or CXCR2 mediated diseases or conditions include but are not limited to: pain (e.g., acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain), acute inflammation, chronic inflammation, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, ischemia reperfusion injury, renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction (i.e., graft vs. host disease), allograft rejections (e.g., acute allograft rejection, and chronic allograft rejection), malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral ischemia, cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus (i.e., Kaposi's sarcoma), meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute pancreatitis, chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred, corneal neovascularization, polymyositis, vasculitis, acne, gastric ulcers, duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness (i.e., airway hyperreactivity), bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia,

surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy (i.e., the treatment of burns), periodontitis, cancer, transplant reperfusion injury, early transplantation rejection (e.g., acute allograft rejection).

Examples of CCR7 mediated diseases or conditions include, but are not limited to: pain (e.g., acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain), acute inflammation, chronic inflammation, acute allograft rejection, acute respiratory distress syndrome, adult respiratory disease, airway hyperreactivity, allergic contact dermatitis, allergic rhinitis, alopecia areata, alzheimer's disease, angiogenic ocular disease, antiphospholipid syndromes, aplastic anemia, asthma, atherosclerosis, atopic dermatitis, autoimmune deafness (including, for example, Meniere's disease), autoimmune hemolytic syndromes, autoimmune hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, bronchiolitis, bronchiolitis obliterans syndrome, bullous pemphigoid, burn therapy (i.e., the treatment of burns), cancer, cerebral ischemia, cardiac ischemia, chronic allograft rejection, chronic allograft vasculopathy, chronic bronchitis, chronic inflammatory demyelinating polyneuropathy, chronic sinusitis, cirrhosis, CNS vasculitis, COPD, Cor pneumoniae, Crohn's disease, cryoglobulinemia, crystal-induced arthritis, delayed-type hypersensitivity reactions, dermatomyositis, diabetes, diabetic retinopathy, drug-induced autoimmunity, dyspnea, emphysema, epidermolysis bullosa acquisita, endometriosis, fibrotic diseases, gastritis, glomerulonephritis, Goodpasture's syndrome, graft vs host disease, Graves' disease, Gullain-Barre disease, Hashimoto's thyroiditis, hepatitis-associated autoimmunity, HIV-related autoimmune syndromes and hematologic disorders, hyperoxia-induced inflammation, hypercapnea, hyperinflation, hypophytis, hypoxia, idiopathic thrombocytic pupura, inflammatory bowel diseases, interstitial cystitis, interstitial pneumonitis, juvenile arthritis, Langerhans' cell histiocytitis, lichen planus, metal-induced autoimmunity, multiple sclerosis, myasthenia gravis, myelodysplastic syndromes, myocarditis including viral myocarditis, myositis, neuropathies (including, for example, IgA neuropathy, membranous neuropathy and idiopathic neuropathy), nephritic syndrome, ocular inflammation, optic neuritis, osteoarthritis, pancreatitis,

paroxysmal nocturnal hemoglobulinemia, pemphigus, polymyalgia, polymyositis, post-infectious autoimmunity, pulmonary fibrosis, primary biliary cirrhosis, psoriasis, pruritis, rheumatoid arthritis, reactive arthritis, ankylosing spondylitis, psoriatic arthritis, Raynaud's phenomenon, Reiter's syndrome, reperfusion injury, restenosis, sarcoidosis, scleritis, scleroderma, secondary hematologic manifestation of autoimmune diseases (such as, for example, anemias), silicone implant associated autoimmune disease, Sjogren's syndrome, systemic lupus erythematosus, thrombocytopenia, thrombosis, transverse myelitis, tubulointerstitial nephritis, ulcerative colitis, uveitis, vasculitis and vasculitis syndromes (such as, for example, giant cell arteritis, Behcet's disease and Wegener's granulomatosis), and vitiligo.

Another embodiment of this invention is directed to a method of treating a CXCR1 and/or CXCR2 mediated disease or condition, as described above, in a patient in need of such treatment comprising administering to said patient an effective amount of a compound selected from the group consisting of the final compounds of Examples 1-11, 19, 20, 24-28, 31 and 32 and the pharmaceutically acceptable salts thereof.

Another embodiment of this invention is directed to a method of treating a CCR7 mediated disease or condition, as described above, in a patient in need of such treatment comprising administering to said patient an effective amount of a compound selected from the group consisting of the final compounds of Examples 6, 31 and 32, and the pharmaceutically acceptable salts thereof.

In another embodiment this invention is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of this invention, or a pharmaceutically acceptable salt thereof. Examples of pain include, but are not limited to, the pain associated with: allodynia, ankylosing spondylitis, appendicitis, autoimmune disorders, bacterial infections, Behcet's syndrome, broken bones, bronchitis, burns, bursitis, cancer including metastatic cancer, candidiasis, cardiovascular conditions, casualgia, chemical injury, childbirth (e.g., labor), chronic regional neuropathies, Crohn's disease, colorectal cancer, connective tissue injuries, conjunctivitis, COPD, decreased intracranial pressure, dental procedures, dermatitis, diabetes, diabetic neuropathy, dysesthesia, dysmenorrhea, eczema, emphysema, fever, fibromyalgia, gastric ulcer, gastritis, giant cell arteritis, gingivitis, gout, gouty

arthritis, headache, headache pain resulting from lumbar puncture, headaches including migraine headache, herpes simplex virus infections, HIV, Hodgkin's disease, hyperalgesia, hypersensitivity, inflammatory bowel disease, increased intracranial pressure, irritable bowel syndrome, ischemia, juvenile arthritis, kidney stones, lumbar spondylanhrosis, lower back, upper back and lumbrosacral conditions, lumbar spondylarthrosis, menstrual cramps, migraines, minor injuries, multiple sclerosis, myasthenia gravis, myocarditis, muscle strains, musculoskeletal conditions, myocardial ischemia, nephritic syndrome, nerve root avulsion, neuritis, nutritional deficiency, ocular and corneal conditions, ocular photophobia, ophthalmic diseases, osteoarthritis, otic surgery, otitis externa, otitis media, periarteritis nodosa, peripheral neuropathies, phantom limb pain, polymyositis, post-herpetic neuralgia, post-operative/surgical recovery, post-thoracotomy, psoriatic arthritis, pulmonary fibrosis, pulmonary edema, radiculopathy, reactive arthritis, reflex sympathetic dystrophy, retinitis, retinopathies, rheumatic fever, rheumatoid arthritis, sarcoidosis, sciatica, scleroderma, sickle cell anemia, sinus headaches, sinusitis, spinal cord injury, spondyloarthropathies, sprains, stroke, swimmer's ear, tendonitis, tension headaches, thalamic syndrome, thrombosis, thyroiditis, toxins, traumatic injury, trigeminal neuralgia, ulcerative colitis, urogenital conditions, uveitis, vaginitis, vascular diseases, vasculitis, viral infections and/or wound healing.

In another embodiment this invention is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of this invention, or the pharmaceutically acceptable salts thereof, and administering to said patient a therapeutically effective amount of at least one medicament selected from the group consisting of: NSAIDs, COXIB inhibitors, anti-depressants and anti-convulsants. Examples of the pain treatable are described above.

In another embodiment this invention is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of this invention, or the pharmaceutically acceptable salts thereof, and administering to said patient a therapeutically effective amount of at least one NSAIDs. Examples of the pain treatable are described above.

In another embodiment this invention is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of this invention, or the pharmaceutically acceptable salts thereof, and administering to said patient a therapeutically effective amount of at least one COXIB inhibitor. Examples of the pain treatable are described above.

In another embodiment this invention is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of this invention, or the pharmaceutically acceptable salts thereof, and administering to said patient a therapeutically effective amount of at least one anti-depressant. Examples of the pain treatable are described above.

In another embodiment this invention is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of this invention, or the harmaceutically acceptable salts thereof, and administering to said patient a therapeutically effective amount of at least one anti-convulsant. Examples of the pain treatable are described above.

In general the compounds of this invention used to treat pain will have CXCR2 antagonistic activity.

NSAIDs are well known to those skilled in the art and can be used in their known dosages and dosage regimens. Examples of NSAIDs include but are not limited to: piroxicam, ketoprofen, naproxen, indomethacin, and ibuprofen

COXIB inhibitors are well known to those skilled in the art and can be used in their known dosages and dosage regimens. Examples of COXIB inhibitors include but are not limited to: rofecoxib and celecoxib.

Anti-depressants are well known to those skilled in the art and can be used in their known dosages and dosage regimens. Examples of anti-depressants include but are not limited to: amitriptyline and nortriptyline.

Anti-convulsants are well known to those skilled in the art and can be used in their known dosages and dosage regimens. Examples of Anti-convulsants include but are not limited to: gabapentin, carbamazepine, pregabalin, and lamotragine.

Another embodiment of this invention is directed to a method of treating Kaposi's sarcoma, melanoma, gastric carcinoma, and non-small cell carcinoma in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof.

Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell carcinoma in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is directed to a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering to said patient, concurrently or sequentially, a therapeutically effective amount of (a) at least one (e.g., 1-3, and usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof, and (b) at least one (e.g., 1, 2 or 3) anticancer agent selected from the group consisting of: (1) microtubule affecting agents, (2) antineoplastic agents, (3) anti-angiogenesis agents, (4) VEGF receptor kinase inhibitors, (5) antibodies against the VEGF receptor, (6) interferon, and (7) radiation.

In further embodiments of this invention that are directed to the treatment of cancer, at least one (e.g., 1-3, and usually one) compound of formula IA, or a pharmaceutically acceptable salt thereof, is administered in combination with at least one (e.g., 1 or 2, or 1) antineoplastic agent selected from the group consisting of: gemcitabine, paclitaxel (Taxol®), 5-Fluorouracil (5-FU), cyclophosphamide (Cytoxan®), temozolomide, taxotere and Vincristine.

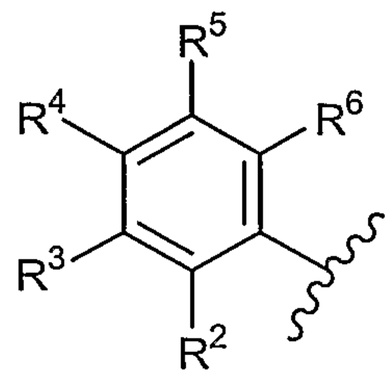
In another embodiment the present invention provides a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering, concurrently or sequentially, an effective amount of (a) at least one (e.g., 1-3, usually 1) compound of formula IA, or a pharmaceutically acceptable salt thereof, and (b) at least one (e.g., 1-3, usually 1) microtubule affecting agent (*e.g.,* paclitaxel).

In the method of treating a pulmonary disease (e.g., COPD, asthma, or cystic fibrosis), at least one (usually 1) compound of formula IA, or a pharmaceutically

acceptable salt thereof, is administered in combination with at least one compound selected from the group consisting of: glucocorticoids, 5-lipoxygenase inhibitors, β-2 adrenoceptor agonists, muscarinic M1 antagonists, muscarinic M3 antagonists, muscarinic M2 agonists, NK3 antagonists, LTB4 antagonists, cysteinyl leukotriene antagonists, bronchodilators, PDE4 inhibitors, PDE inhibitors, elastase inhibitors, MMP inhibitors, phospholipase A2 inhibitors, phospholipase D inhibitors, histamine H1 antagonists, histamine H3 antagonists, dopamine agonists, adenosine A2 agonists, NK1 and NK2 antagonists, GABA-b agonists, nociceptin agonists, expectorants, mucolytic agents, decongestants, antioxidants, anti-IL-8 anti-bodies, anti-IL-5 antibodies, anti-IgE antibodies, anti-TNF antibodies, IL-10, adhesion molecule inhibitors, and growth hormones. Agents that belong to these classes include, but are not limited to, beclomethasone, mometasone, ciclesonide, budesonide, fluticasone, albuterol, salmeterol, formoterol, loratadine, desloratadine, tiotropium bromide, MSI-ipratropium bromide, montelukast, theophilline, cilomilast, roflumilast, cromolyn, ZD-4407, talnetant, LTB-019, revatropate, pumafentrine, CP-955, AR-C-89855, BAY-19-8004, GW-328267, QAB-149, DNK-333, YM-40461 and TH-9506 or pharmaceutically acceptable formulations thereof.

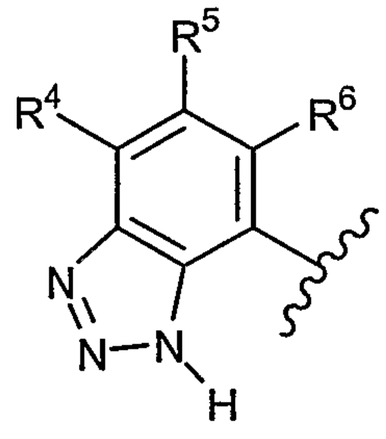
Representative embodiments of the novel compounds of this invention are described below. The embodiments have been numbered for purposes of reference thereto.

Embodiment No. 1 is directed to the novel compounds of formula IA wherein B is:



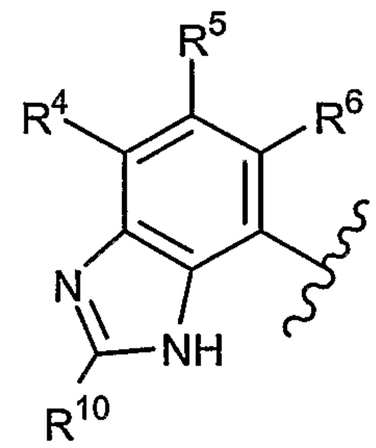
and all other substitutents are as defined for of formula IA.

Embodiment No. 2 is directed to the novel compounds of formula IA wherein B is:



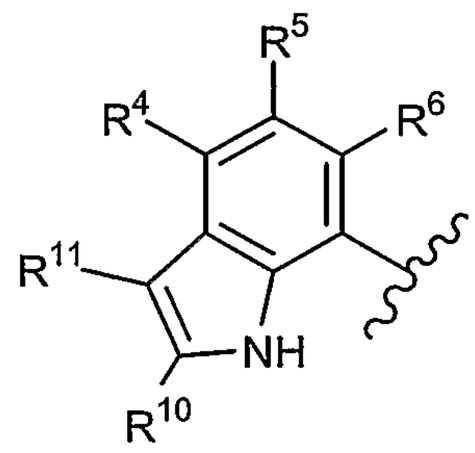
and all other substitutents are as defined for of formula IA.

Embodiment No. 3 is directed to the novel compounds of formula IA wherein B is:



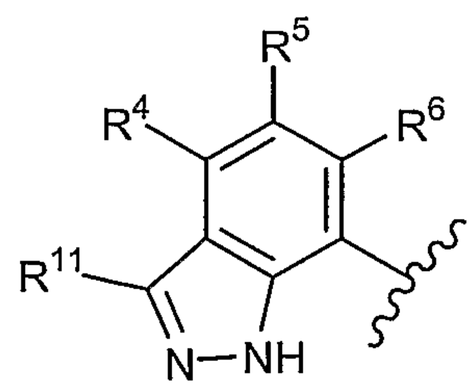
and all other substitutents are as defined for of formula IA.

Embodiment No. 4 is directed to the novel compounds of formula IA wherein B is:



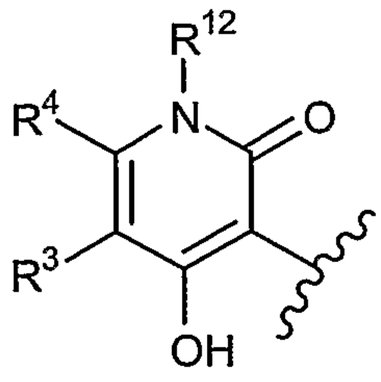
and all other substitutents are as defined for of formula IA.

Embodiment No. 5 is directed to the novel compounds of formula IA wherein B is:



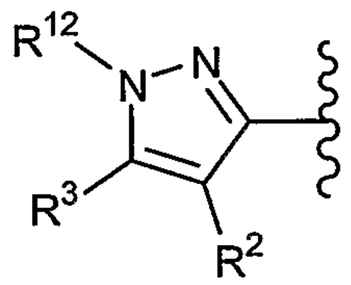
and all other substitutents are as defined for of formula IA.

Embodiment No. 6 is directed to the novel compounds of formula IA wherein B is:



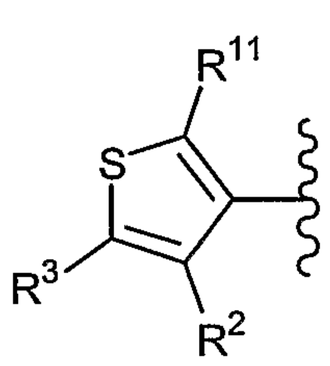
and all other substitutents are as defined for of formula IA.

Embodiment No. 7 is directed to the novel compounds of formula IA wherein B is:



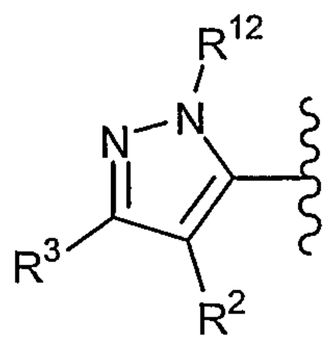
and all other substitutents are as defined for of formula IA.

Embodiment No. 8 is directed to the novel compounds of formula IA wherein B is:



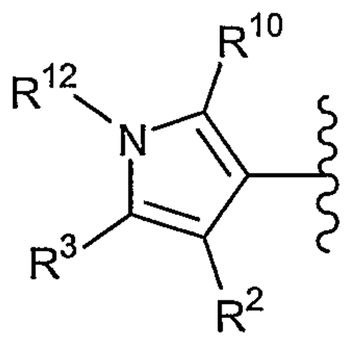
and all other substitutents are as defined for of formula IA.

Embodiment No. 9 is directed to the novel compounds of formula IA wherein B is:



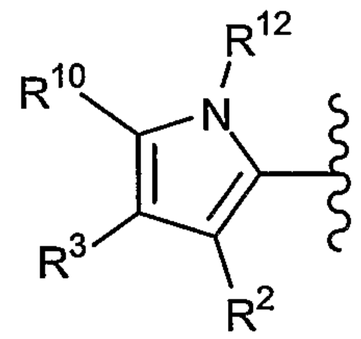
and all other substitutents are as defined for of formula IA.

Embodiment No. 10 is directed to the novel compounds of formula IA wherein B is:



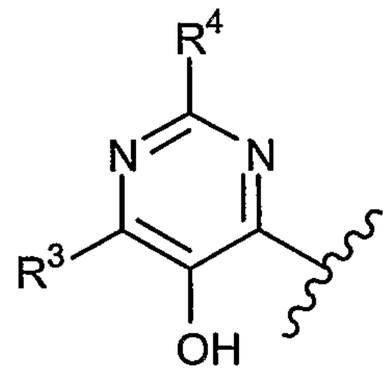
and all other substitutents are as defined for of formula IA.

Embodiment No. 11 is directed to the novel compounds of formula IA wherein B is:



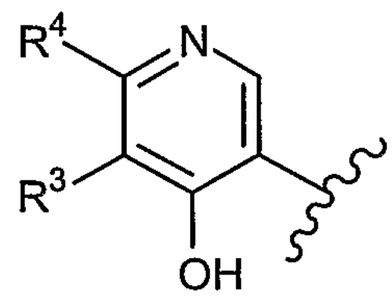
and all other substitutents are as defined for of formula IA.

Embodiment No. 12 is directed to the novel compounds of formula IA wherein B is:



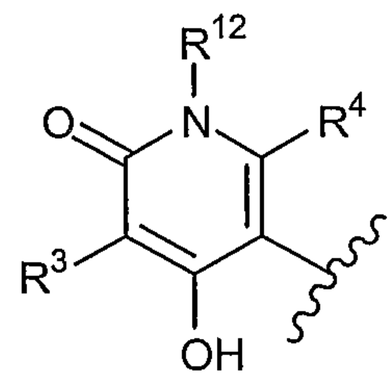
and all other substitutents are as defined for of formula IA.

Embodiment No. 13 is directed to the novel compounds of formula IA wherein B is:



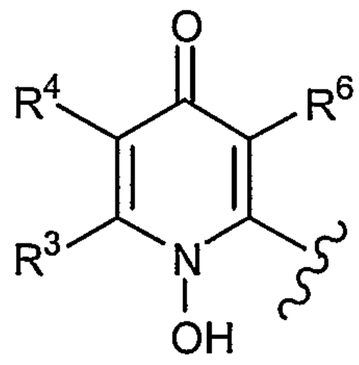
and all other substitutents are as defined for of formula IA.

Embodiment No. 14 is directed to the novel compounds of formula IA wherein B is:



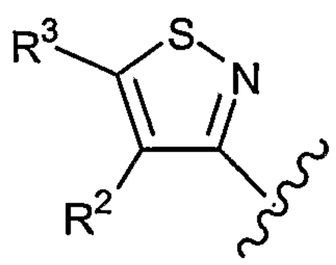
and all other substitutents are as defined for of formula IA.

Embodiment No. 15 is directed to the novel compounds of formula IA wherein B is:



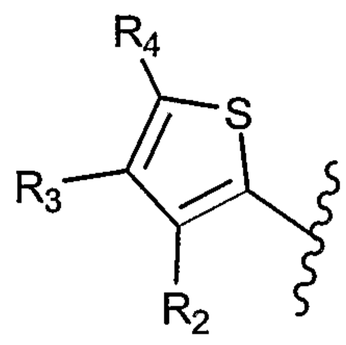
and all other substitutents are as defined for of formula IA.

Embodiment No. 16 is directed to the novel compounds of formula IA wherein B is:



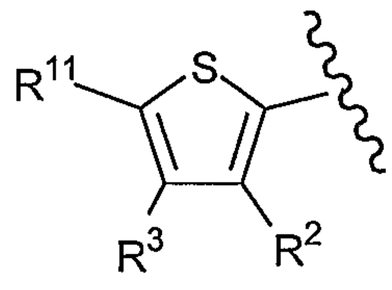
and all other substitutents are as defined for of formula IA.

Embodiment No. 17 is directed to the novel compounds of formula IA wherein B is:



and all other substitutents are as defined for of formula IA.

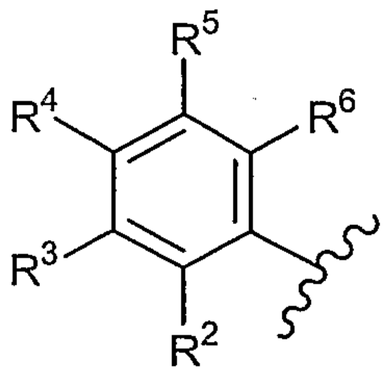
Embodiment No. 18 is directed to the novel compounds of formula IA wherein B is:



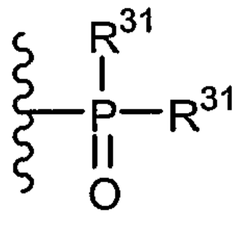
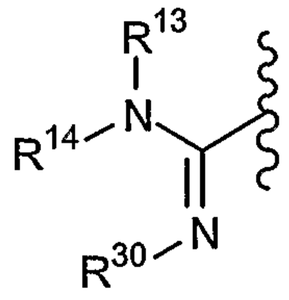
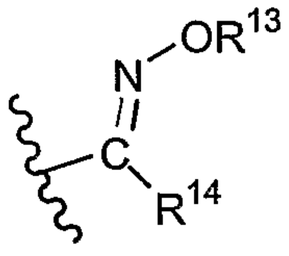
and all other substitutents are as defined for of formula IA.

Embodiment No. 19 is directed to compounds of formula IA wherein B is selected from the group consisting of:

(1)

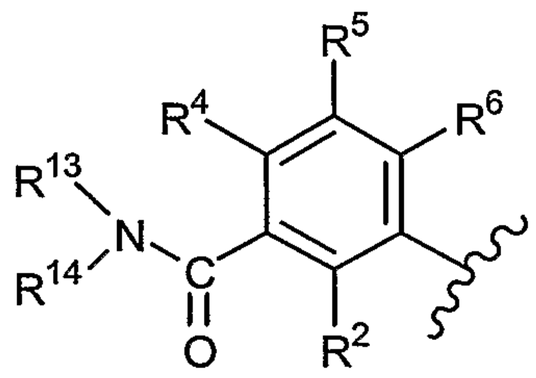


and R^3 for this B group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



and


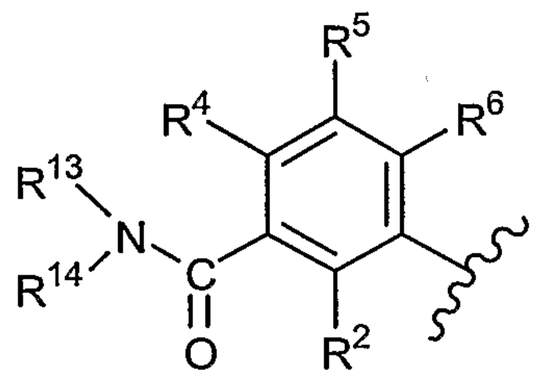
and all other substituents are as defined for formula IA.

Embodiment No. 20 is directed to compounds of formula IA wherein B is:



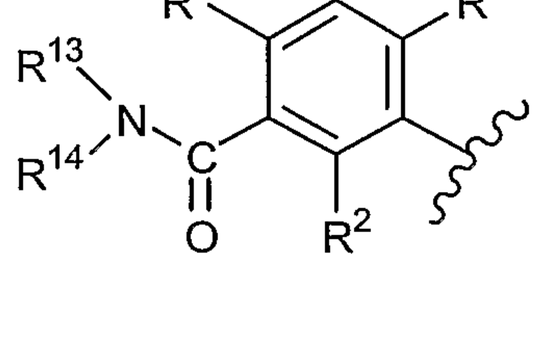
and all other substituents are as defined in formula IA.

Embodiment No. 21 is directed to compounds of formula IA wherein B is



R^{13} and R^{14} are independently selected from the group consisting of H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), and all other substituents are as defined in formula IA.

Embodiment No. 22 is directed to compounds of formula IA wherein B is



wherein:

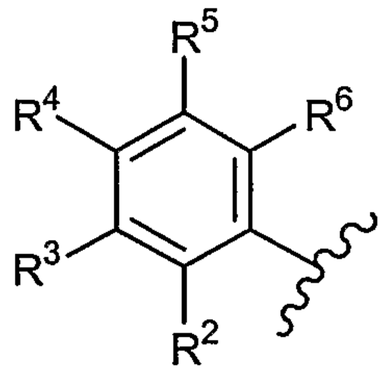
(1) R^2 is –OH and all other substituents are as defined in formula IA, or

(2) R^2 is–OH, and R^{13} and R^{14} are independently selected from the group, consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), or

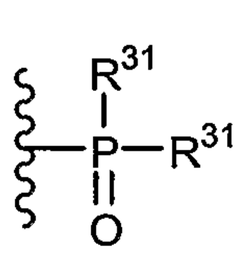
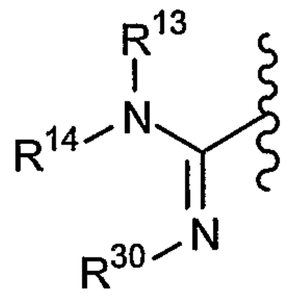
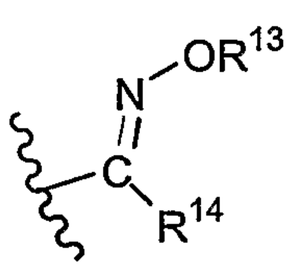
(3) R^2 is–OH, and R^{13} and R^{14} are the same or different and alkyl group (e.g., methyl, ethyl, isopropyl and t-butyl), for example the same alkyl group, for example methyl, and

(4) and all other substituents are as defined in formula IA.

Embodiment No. 23 is directed to compounds of formula IA wherein B is

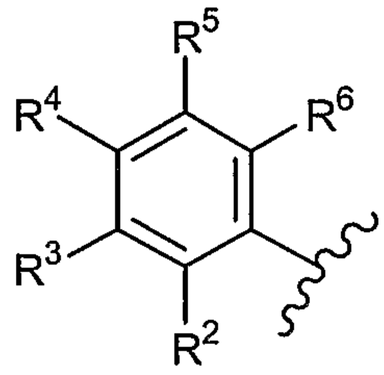


R^3 is selected from the group consisting of:

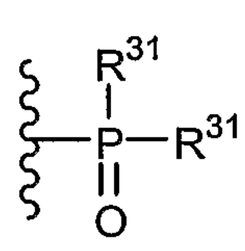
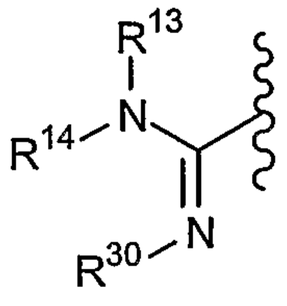
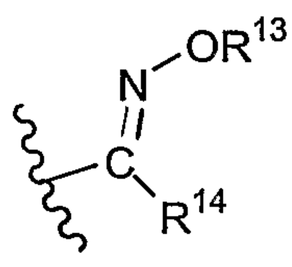

, 
and 

and all other substituents are as defined in formula IA.

Embodiment No. 24 is directed to compounds of formula IA wherein B is

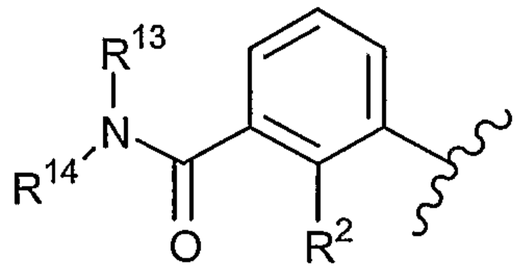


R^3 is selected from the group consisting of:


, 
and 
,

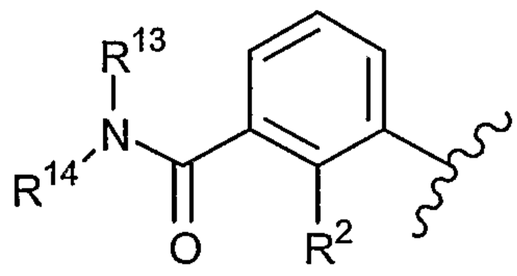
R^2 is –OH, and all other substituents are as defined in formula IA.

Embodiment No. 25 is directed to compounds of formula IA wherein B is:



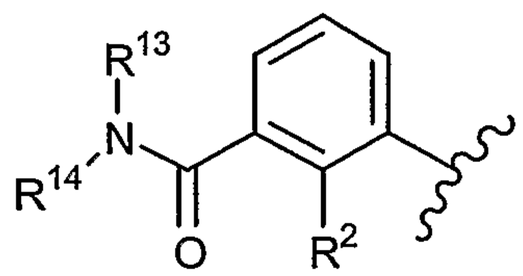
and all other substituents are as defined in formula IA.

Embodiment No. 26 is directed to compounds of formula IA wherein B is:



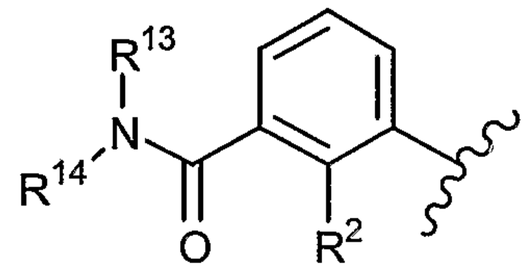
R^2 is –OH, and all other substituents are as defined in formula IA.

Embodiment No. 27 is directed to compounds of formula IA wherein B is:



R^2 is as defined for compounds of formula IA, R^{13} and R^{14} are independently selected from the group consisting of H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), and all other substituents areas defined for compounds of formula IA. For example, R^{13} and R^{14} are the same or different alkyl group. Also, for example, R^{13} and R^{14} are the same alkyl group. Also, for example, R^{13} and R^{14} are methyl.

Embodiment No. 28 is directed to the novel compounds of formula IA wherein B is:



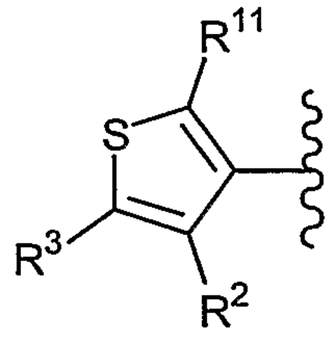
R^2 is –OH, R^{13} and R^{14} are independently selected from the group consisting of H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), and all other substituents areas defined for compounds of formula IA. For example, R^{13} and R^{14} are the same or different alkyl group. Also, for example, R^{13} and R^{14} are the same alkyl group. Also, for example, R^{13} and R^{14} are methyl.

Embodiment No. 29 is directed to novel compounds of formula IA wherein B is as described in Embodiment No. 23, R^4 is H, R^5 is H, R^6 is H, and all other substituents are as defined for compounds of formula IA.

Embodiment No. 30 is directed to novel compounds of formula IA wherein B is as described in Embodiment No. 24, R^4 is H, R^5 is H, R^6 is H, and all other substituents areas defined for compounds of formula IA.

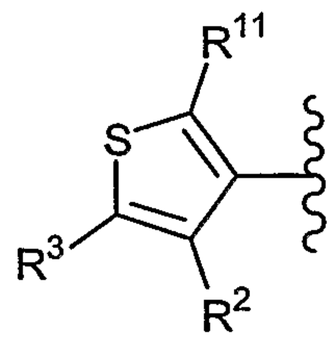
Embodiment No. 31 is directed to novel compounds of formula IA wherein B is as described in Embodiments Nos. 21, 22, 25 and 26, except that R^{13} and R^{14} are each methyl, and all other substituents are as defined in formula IA.

Embodiment No. 32 is directed to compounds of formula IA wherein B is:



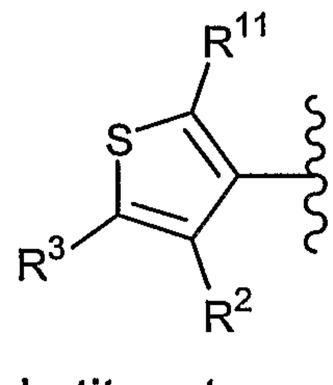
R^{11} is H or methyl (preferably H), and all other substituents are as defined in formula IA.

Embodiment No. 33 is directed to compounds of formula IA wherein B is:



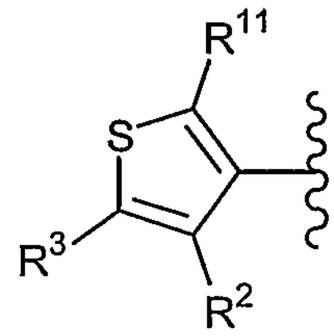
R^2 is –OH, and all other substituents are as defined in formula IA.

Embodiment No. 34 is directed to compounds of formula IA wherein B is:



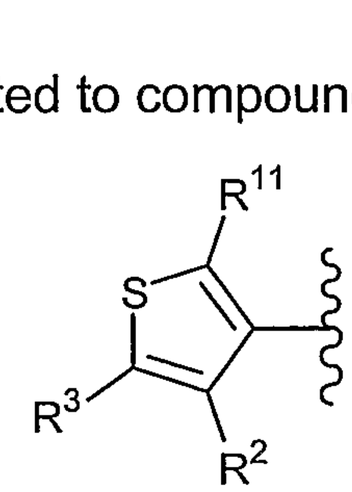
R^3 is $-C(O)NR^{13}R^{14}$, and all other substituents are as defined in formula IA.

Embodiment No. 35 is directed to compounds of formula IA wherein B is:



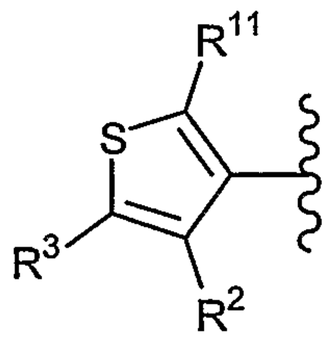
R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

Embodiment No. 36 is directed to compounds of formula IA wherein B is:



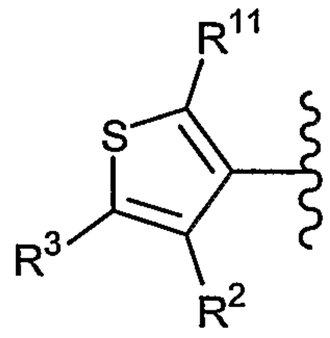
R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, and all other substituents are as defined in formula IA.

Embodiment No. 37 of this invention is directed to compounds of formula IA wherein B is:



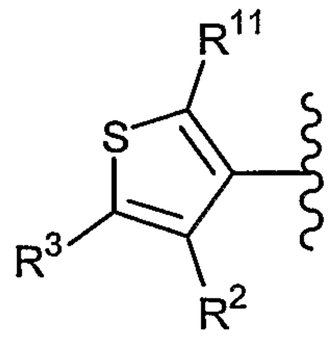
R^2 is –OH, and R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

Embodiment No. 38 is directed to compounds of formula IA wherein B is:



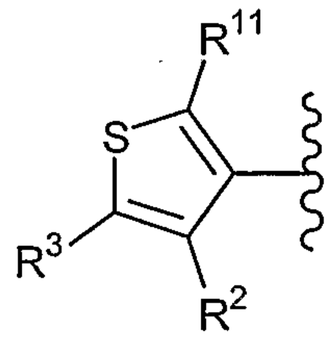
R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H or methyl (preferably H), and all other substituents are as defined in formula IA.

Embodiment No. 39 is directed to compounds of formula IA wherein B is:

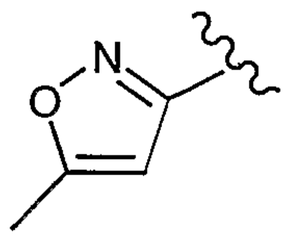


R^2 is –OH, R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H or methyl (preferably H), and all other substituents are as defined in formula IA.

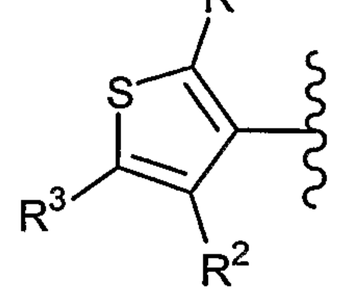
Embodiment No. 40 is directed to compounds of formula IA wherein B is:



R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H or methyl (preferably H), and R^{13} and R^{14} are independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), unsubstituted cycloalkyl, substituted cycloalkyl, unsubstituted heteroaryl and substituted heteroaryl, and all other substituents are as defined in formula IA. For example, one of R^{13} or R^{14} is alkyl (e.g., methyl). An example of a substituted heteroaryl group is

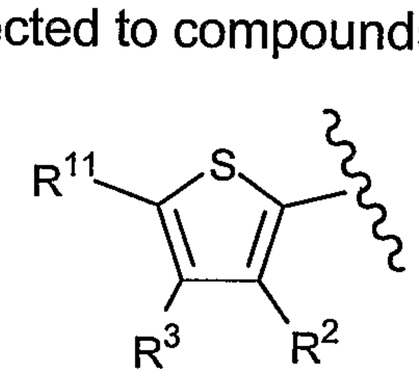


Embodiment No. 41 is directed to compounds of formula IA wherein B is:



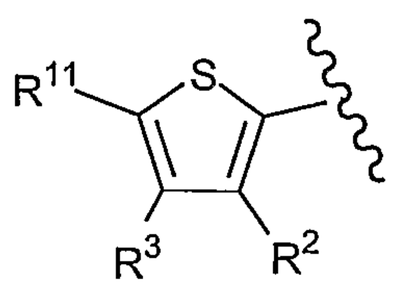
R^2 is –OH, R^3 is $–S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H or methyl (preferably H), and R^{13} and R^{14} are independently selected from the group consisting of:H, alkyl (e.g., methyl, ethyl, isopropyl, and t-butyl), unsubstituted cycloalkyl, and substituted cycloalkyl, and all other substituents are as defined in formula IA. For example R^3 is (1) $–SO_2NH_2$ or (2) $–SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} are the same or different alkyl group (e.g., methyl, ethyl, isopropyl and t-butyl), e.g., the same alkyl group, such as, for example $–SO_2N(CH_3)_2$.

Embodiment No. 42 is directed to compounds of formula IA wherein B is:



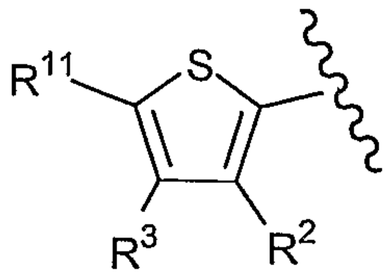
R^{11} is H, and all other substituents are as defined in formula IA.

Embodiment No. 43 is directed to compounds of formula IA wherein B is:



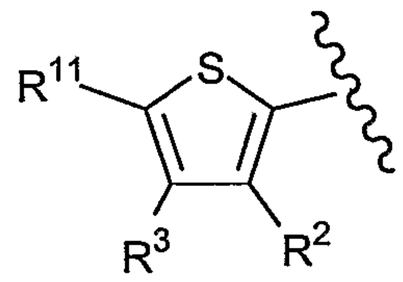
R^2 is –OH, and all other substituents are as defined in formula IA.

Embodiment No. 44 is directed to compounds of formula IA wherein B is:



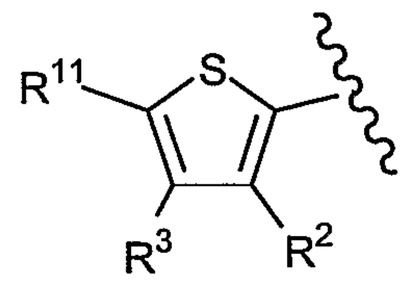
R^3 is $–C(O)NR^{13}R^{14}$, and all other substituents are as defined in formula IA.

Embodiment No. 45 is directed to compounds of formula IA wherein B is:



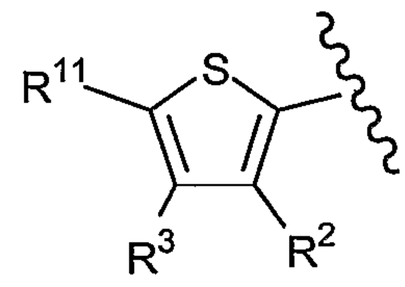
R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

Embodiment No. 46 is directed to compounds of formula IA wherein B is:



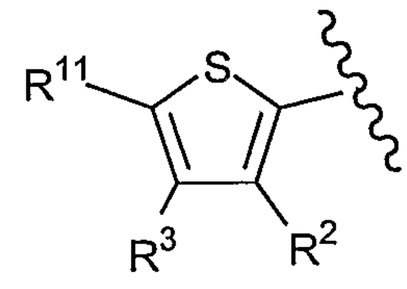
R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, and all other substituents are as defined in formula IA.

Embodiment No. 47 of this invention is directed to compounds of formula IA wherein B is:



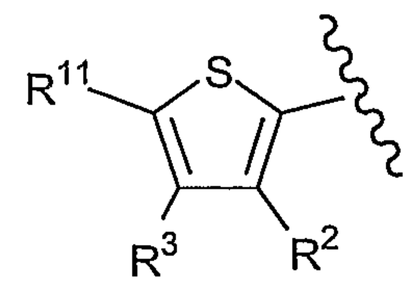
R^2 is –OH, and R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

Embodiment No. 48 is directed to compounds of formula IA wherein B is:



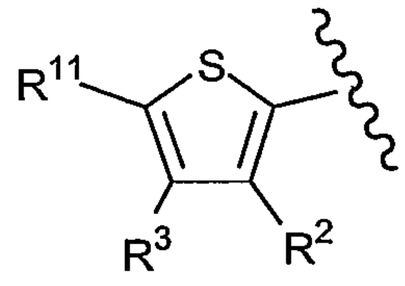
R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H, and all other substituents are as defined in formula IA.

Embodiment No. 49 is directed to compounds of formula IA wherein B is:

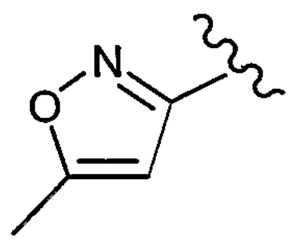


R^2 is –OH, R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H, and all other substituents are as defined in formula IA.

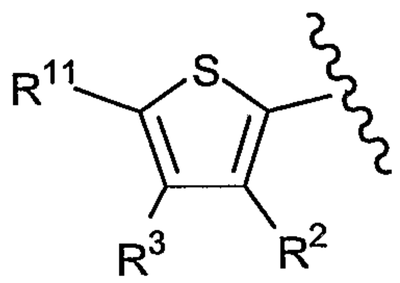
Embodiment No. 50 is directed to compounds of formula IA wherein B is:



R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H, and R^{13} and R^{14} are independently selected from the group consisting of: alkyl, unsubstituted heteroaryl and substituted heteroaryl, and all other substituents are as defined in formula IA. For example, one of R^{13} or R^{14} is alkyl (e.g., methyl). An example of a substituted heteroaryl group is

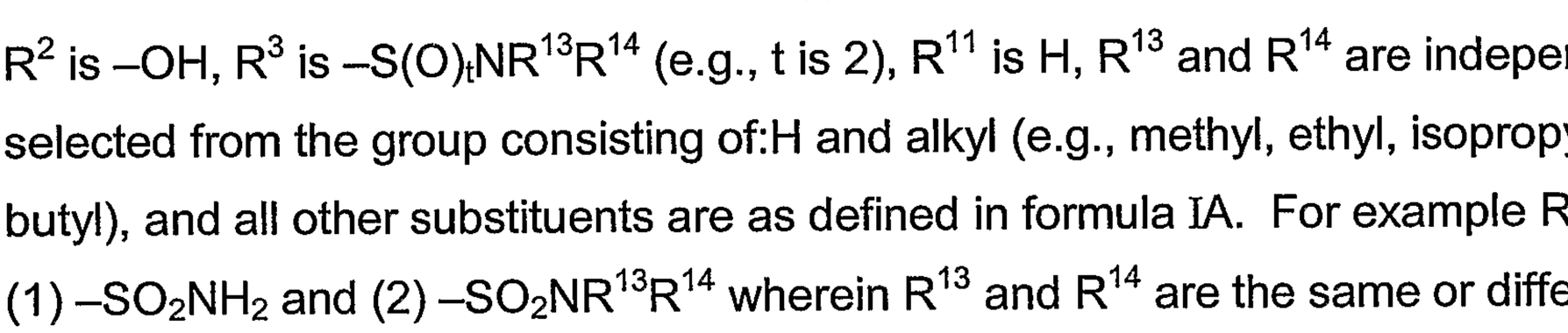


Embodiment No. 51 is directed to compounds of formula IA wherein B is:

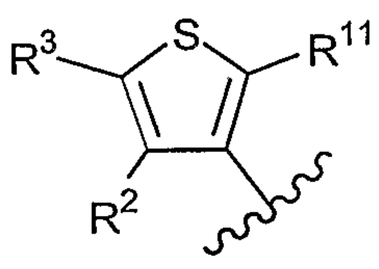


R^2 is –OH, R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H, R^{13} and R^{14} are independently selected from the group consisting of:H and alkyl (e.g., methyl, ethyl, isopropyl, and t-butyl), and all other substituents are as defined in formula IA. For example R^3 is (1) $-SO_2NH_2$ and (2) $-SO_2NR^{13}R^{14}$ wherein R^{13} and R^{14} are the same or different alkyl group (e.g., methyl, ethyl, isopropyl and t-butyl), e.g., the same alkyl group, such as, for example $-SO_2N(CH_3)_2$.

Embodiment No. 52 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:

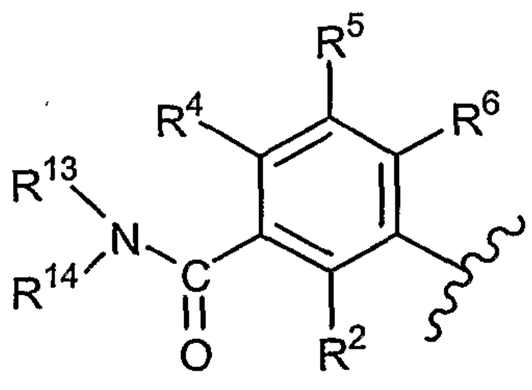
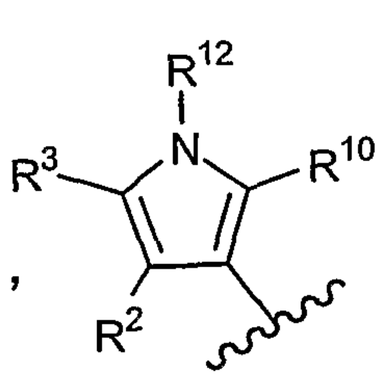
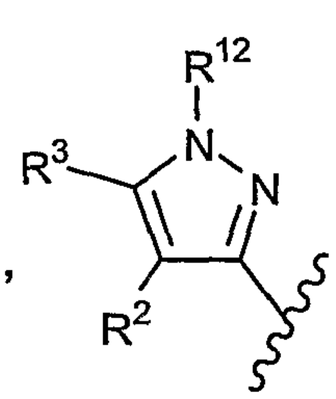
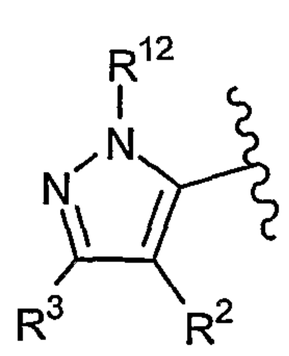


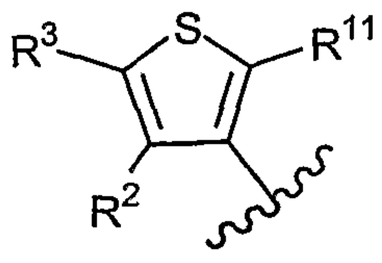
and



wherein R^2 to R^6 and R^{10} to R^{14} are as defined above for the compounds of formula IA.

Embodiment No. 53 is directed to compounds of formula IA wherein substituent B in formula is selected from the group consisting of:

and 

wherein

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ or and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-C(O)NR^{13}R^{14}$, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$, halogen, and $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano;

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

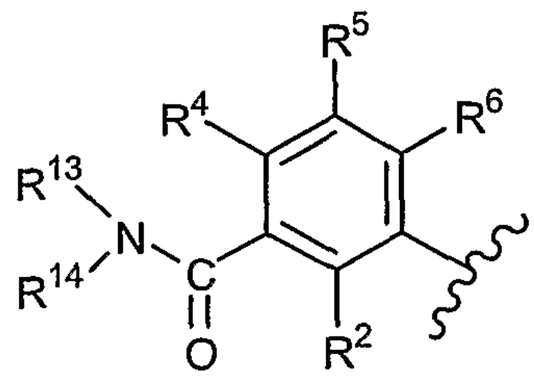
each R^{10} and R^{11} is independently selected from the group consisting of: R^{13}, hydrogen, halogen, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$,$-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, and cyano;

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl and isopropyl; or

R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-SO_tNR^{13}R^{14}$, $-NHSO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$; wherein each R^{19} and R^{20} is independently

selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

Embodiment No. 54 is directed to compounds of formula IA wherein substituent B in formula selected from the group consisting of:



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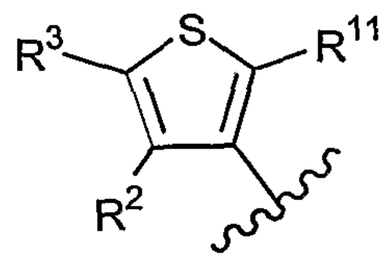


wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

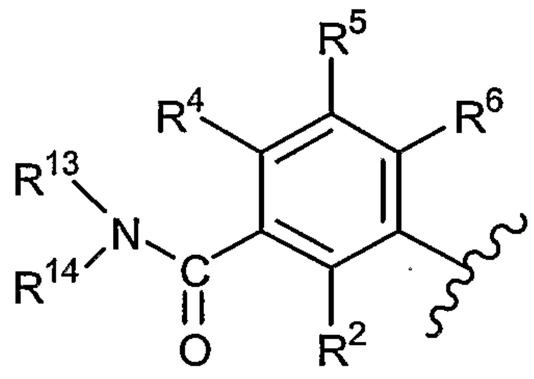
R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl and isopropyl; or

R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-SO_tNR^{13}R^{14}$, $-NHSO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally

having one additional heteroatom selected from O, S or NR^{18} wherein R^{18} is selected from H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$, wherein each R^{19} and R^{20} is independently selected from alkyl, aryl and heteroaryl, wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

Embodiment No. 55 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



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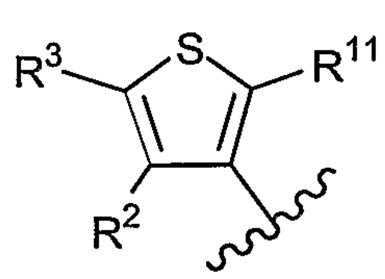


wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$ $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, and $-SO_2R^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

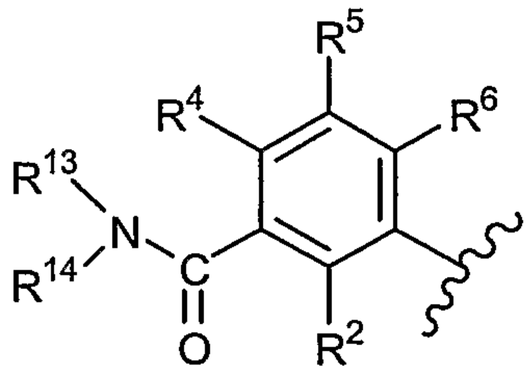
R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl and ethyl.

Embodiment No. 56 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



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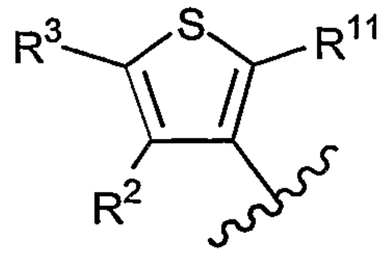


wherein:

R^2 is –OH;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;

R^4 is selected form the group consisting of: H, $-CH_3$ and $-CF_3$;

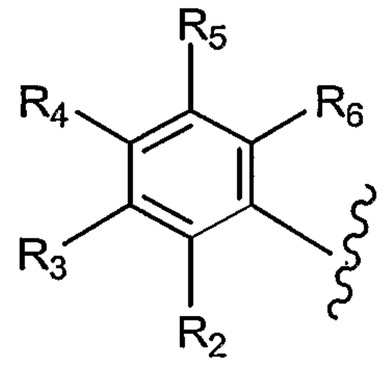
R^5 is selected from the group consisting of: H and cyano;

R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$;

R^{11} is H; and

R^{13} and R^{14} are independently selected from the group consisting of H and methyl (e.g., for $-SO_2NR^{13}R^{14}$ both R^{13} and R^{14} are H, or both R^{13} and R^{14} are methyl, also, for example, for $-CONR^{13}R^{14}$ both R^{13} and R^{14} are methyl).

Embodiment No. 57 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



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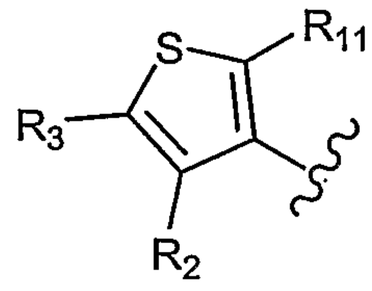

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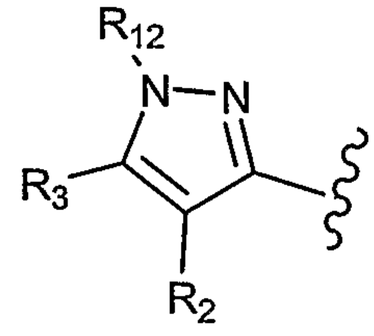
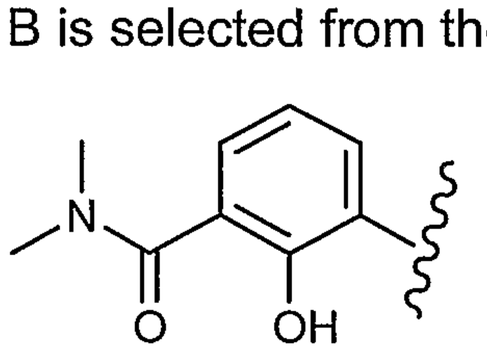


wherein all substituents are as defined for formula IA.

Embodiment No. 58 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



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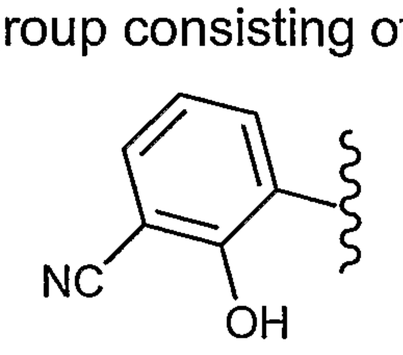

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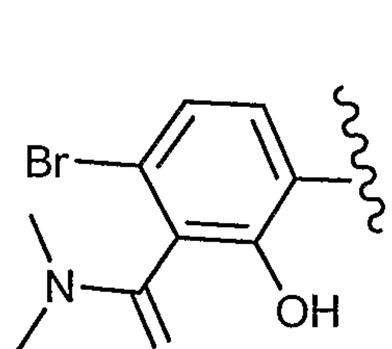

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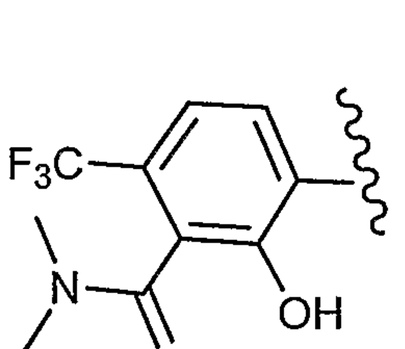

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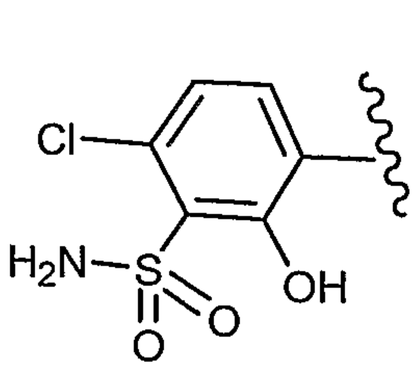

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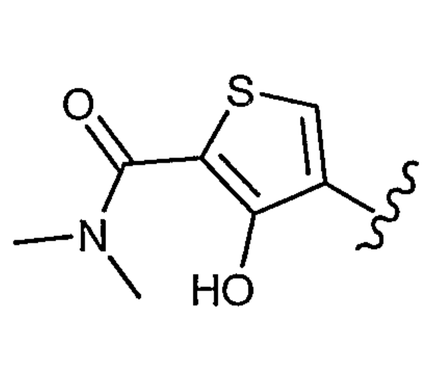

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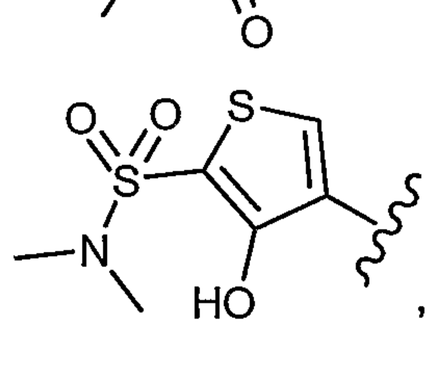

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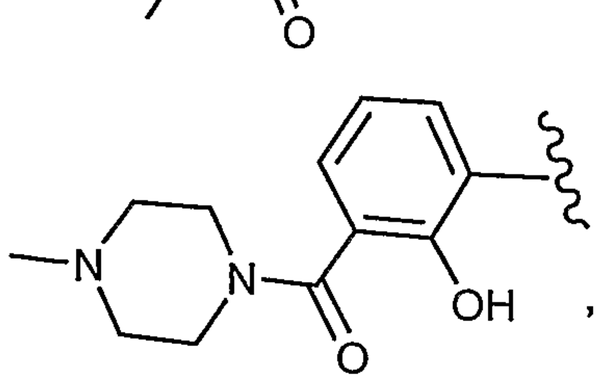

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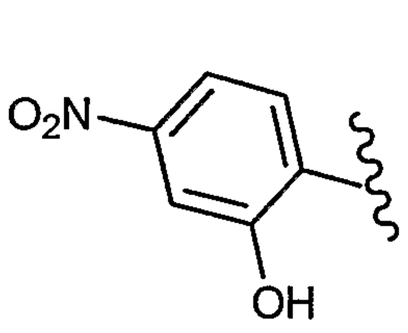
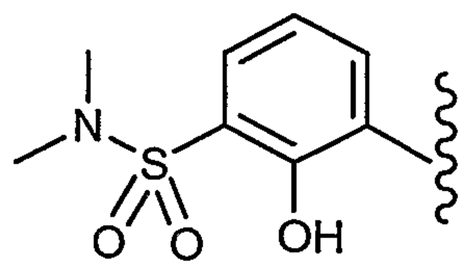
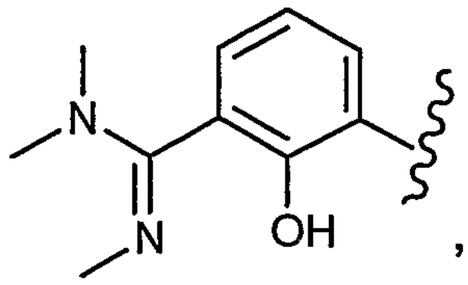
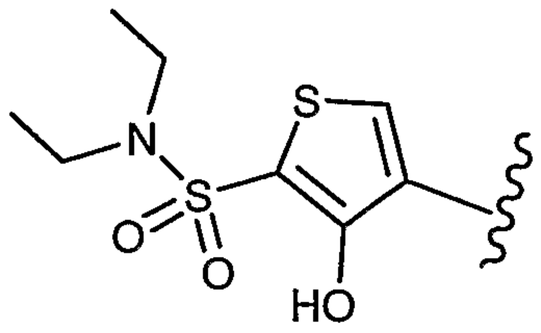
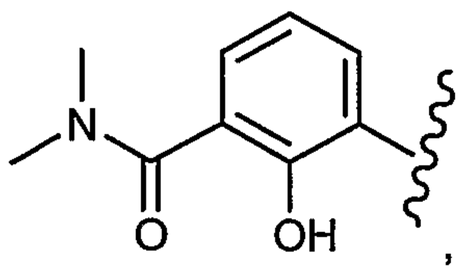
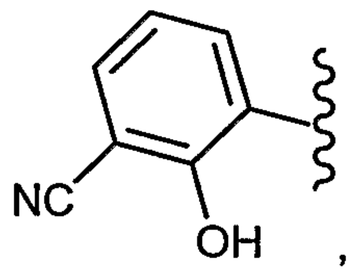
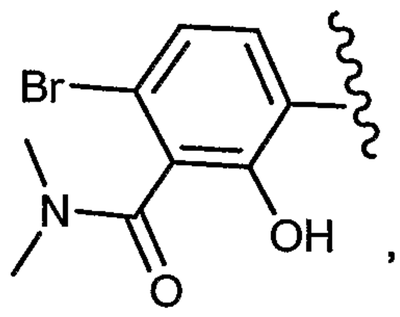
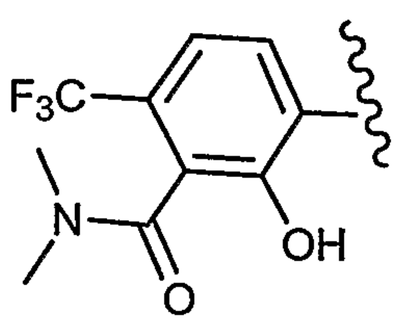
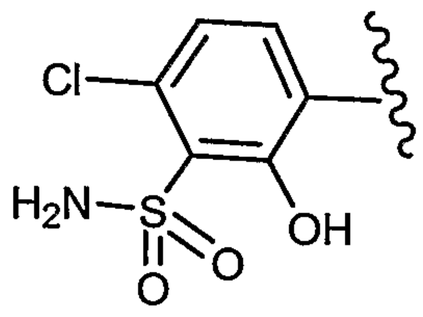
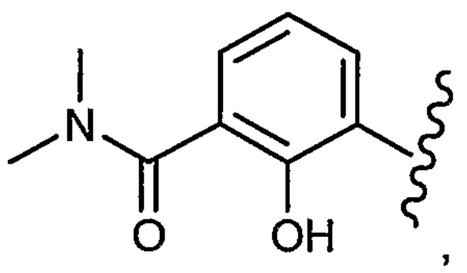
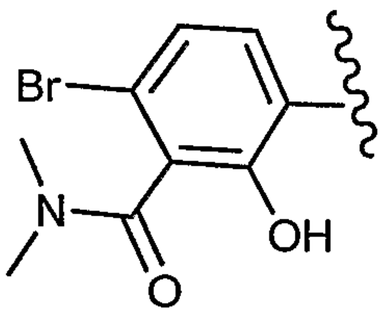
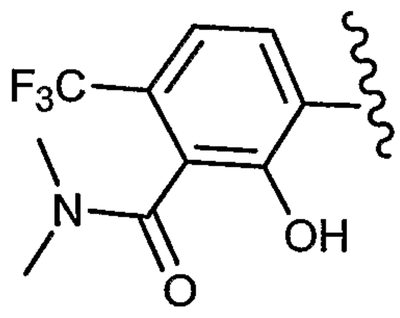





Embodiment No. 59 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:

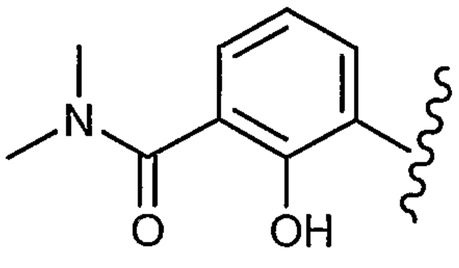
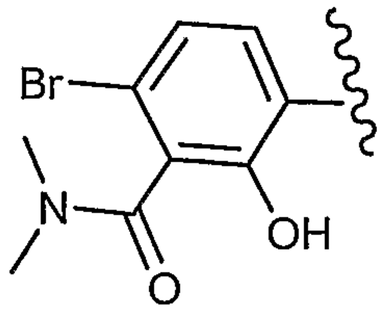





and 

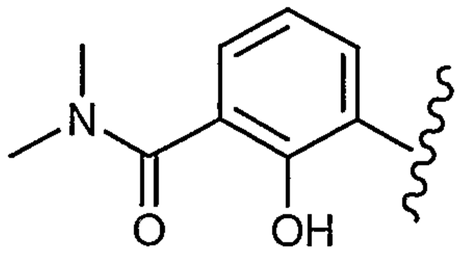
Embodiment No. 60 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



and 

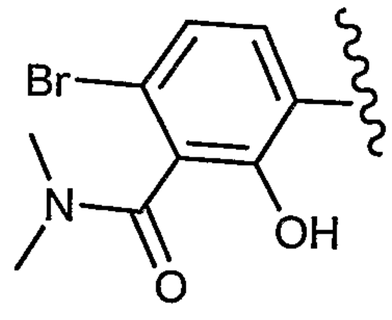
Embodiment No. 61 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:


and 

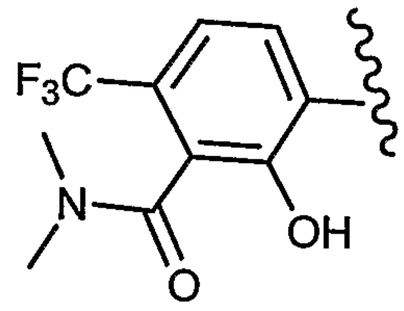
Embodiment No. 62 is directed to compounds of formula IA wherein substituent B is:



Embodiment No. 63 is directed to compounds of formula IA wherein substituent B is:

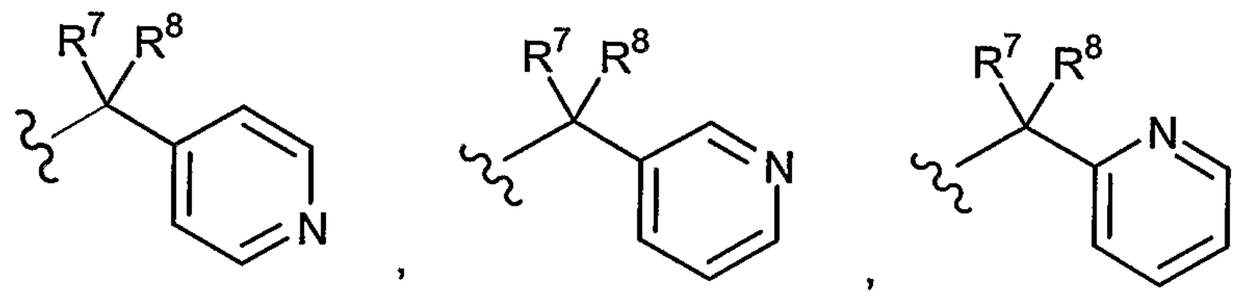


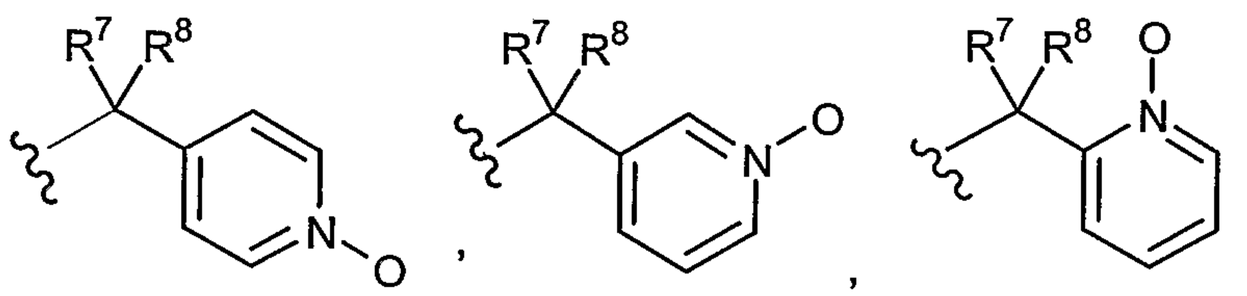
Embodiment No. 64 is directed to compounds of formula IA wherein substituent B is:

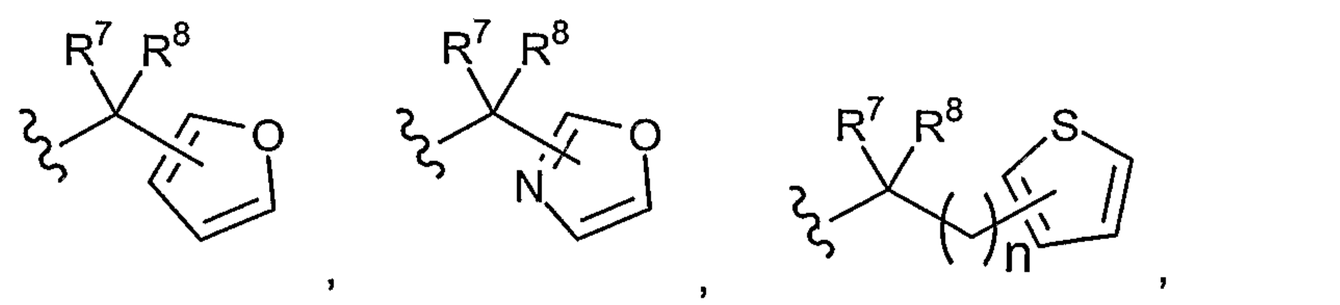


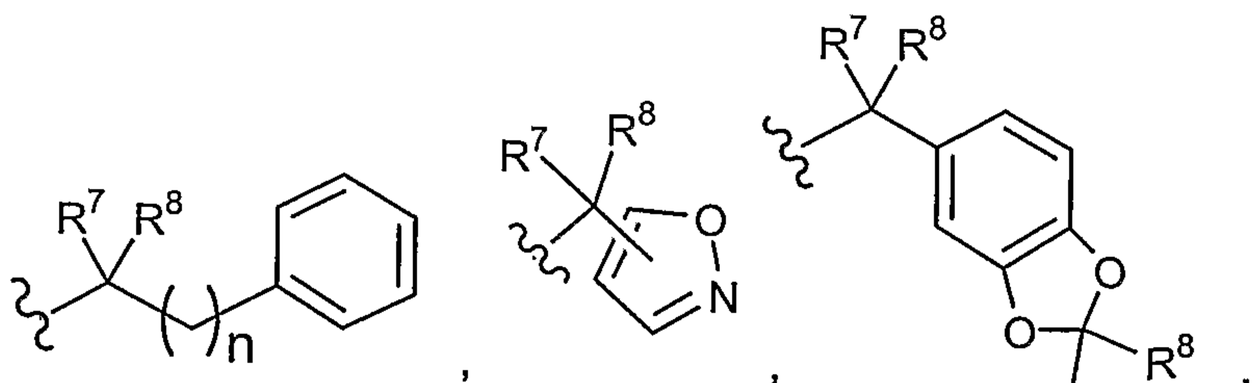
Embodiment No. 65 is directed to compounds of formula IA wherein: substituent A is selected from the group consisting of:

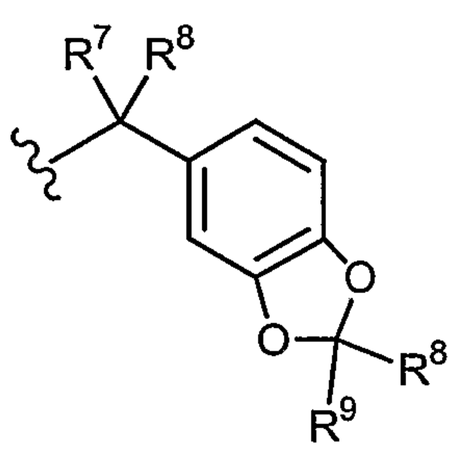
(a)







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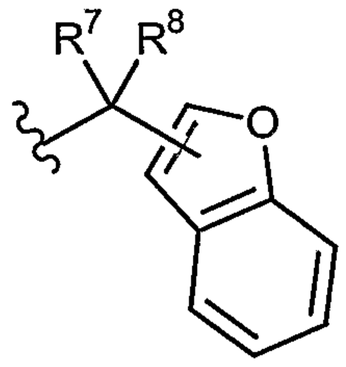
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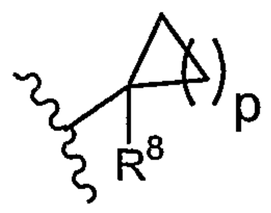
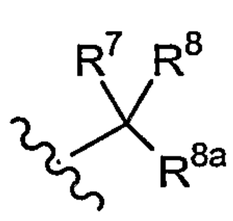


wherein the above rings are unsubstituted or substituted, as described for formula IA: and

(b)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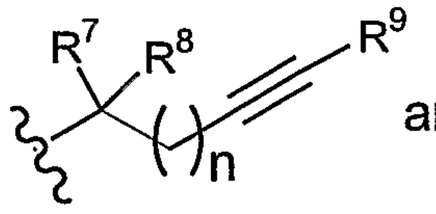
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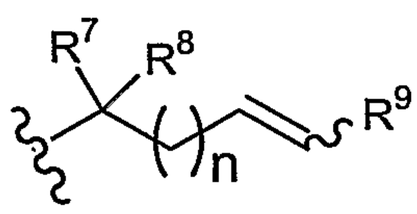
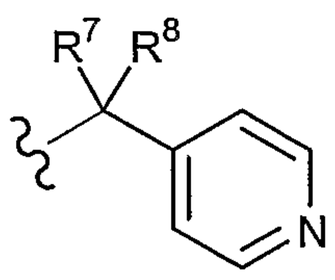

, and

wherein in (a) and (b): each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, and cycloalkenyl, wherein said substituents on said R^7 and R^8 substituted groups are selected from the group consisting of: a) cyano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$, i) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, and k) halogen; and R^{8a} and R^9 are as defined in formula IA.

Embodiment No. 66 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:

(a)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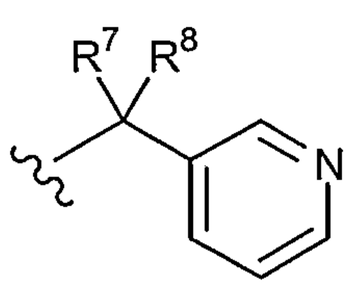
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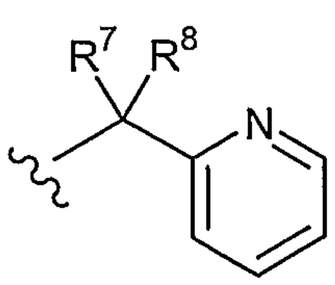
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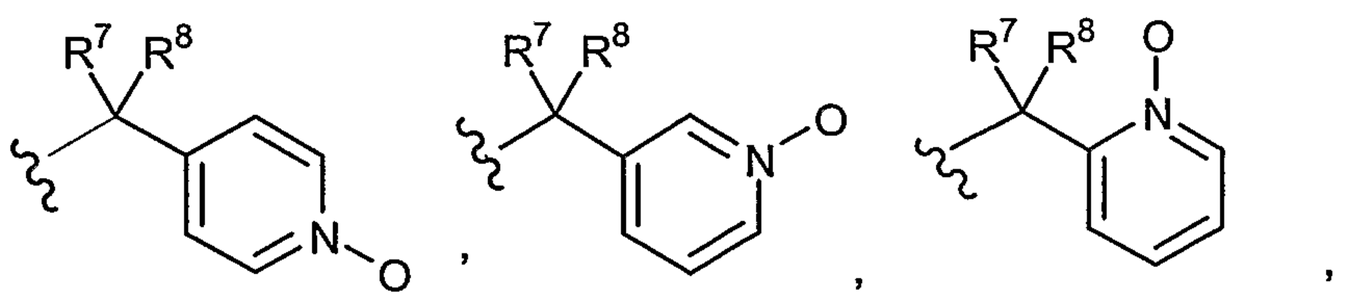
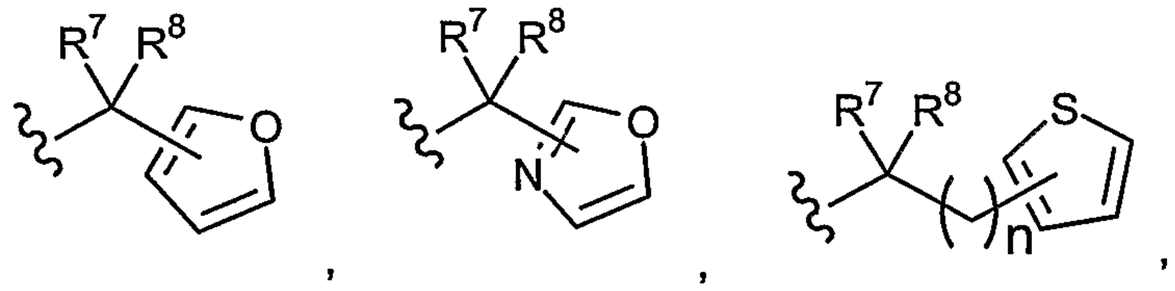
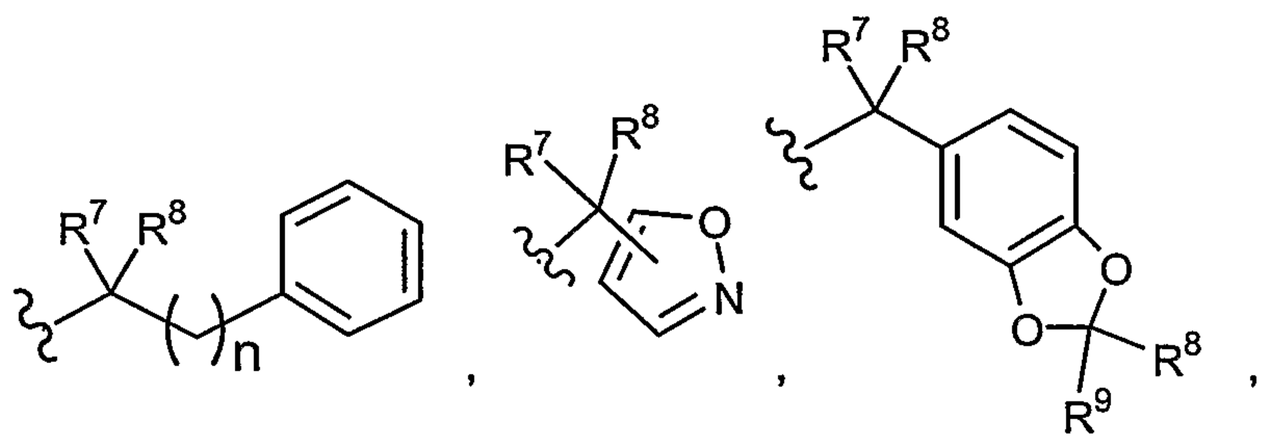
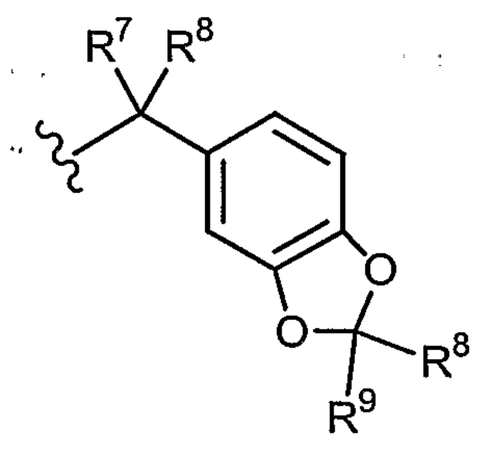
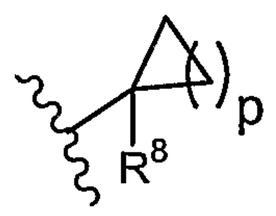






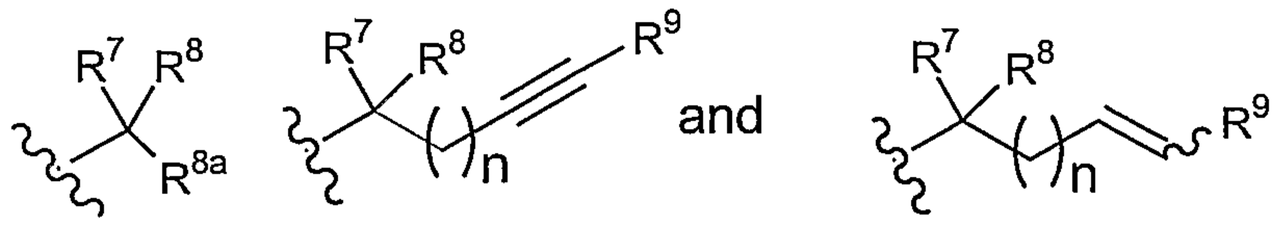


and



wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; and

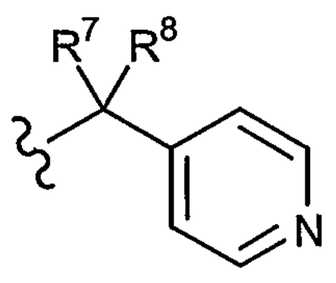
(b)



wherein each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); wherein R^{8a} is as defined in formula IA, and wherein R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl).

Embodiment No. 67 is directed to the novel compounds of formula IA wherein substituent A is selected from the group consisting of:

(a)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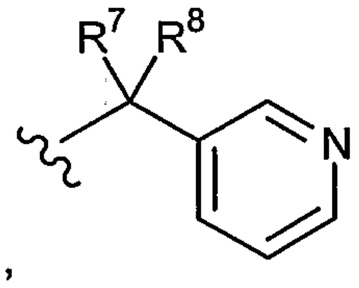
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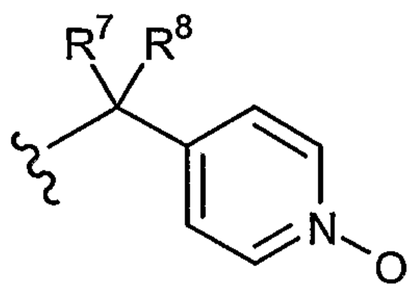
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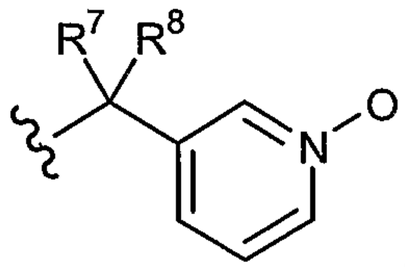
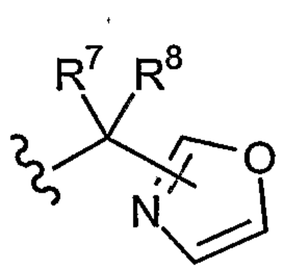

,

,

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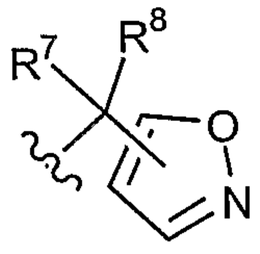
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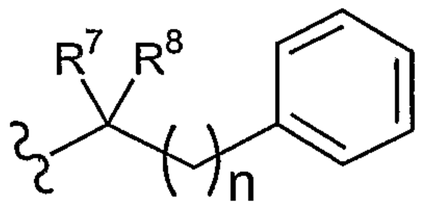
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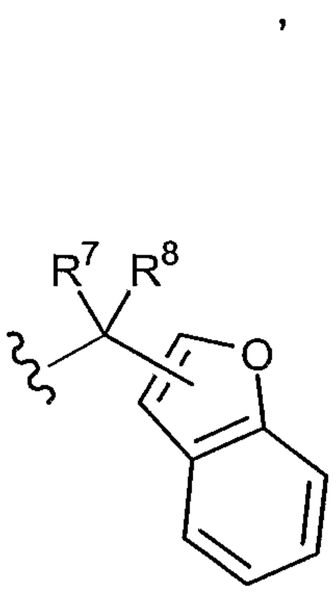
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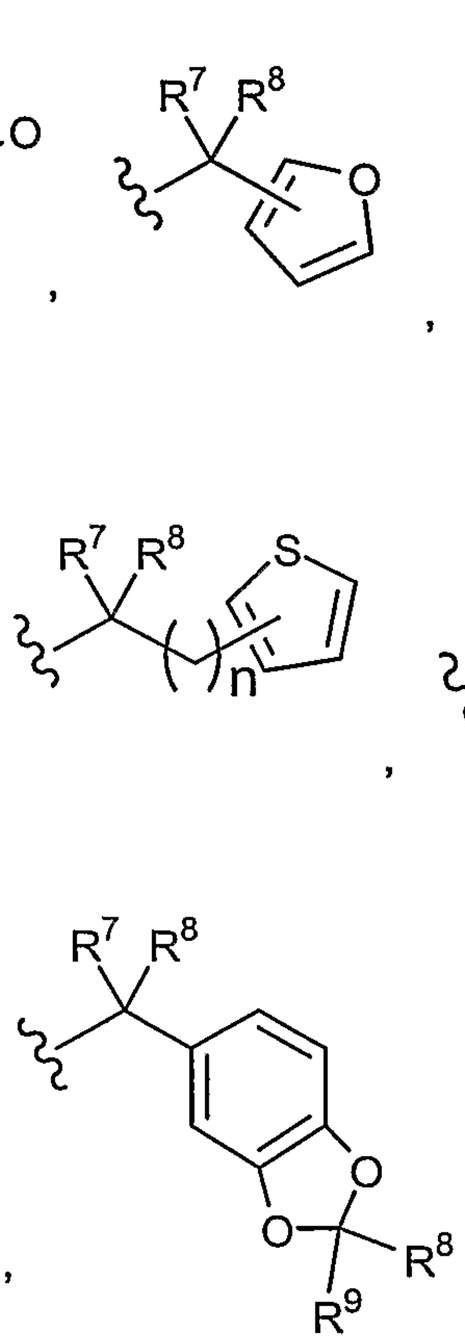
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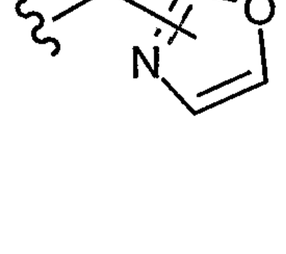
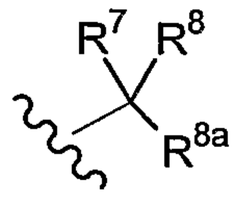

and

wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, fluoroalkyl, alkyl and cycloalkyl; R^8 is selected form the group consisting of: H, alkyl, $-CF_2CH_3$ and $-CF_3$; and R^9 is selected from the group consisting of: H, F, Cl, Br, alkyl or $-CF_3$; and

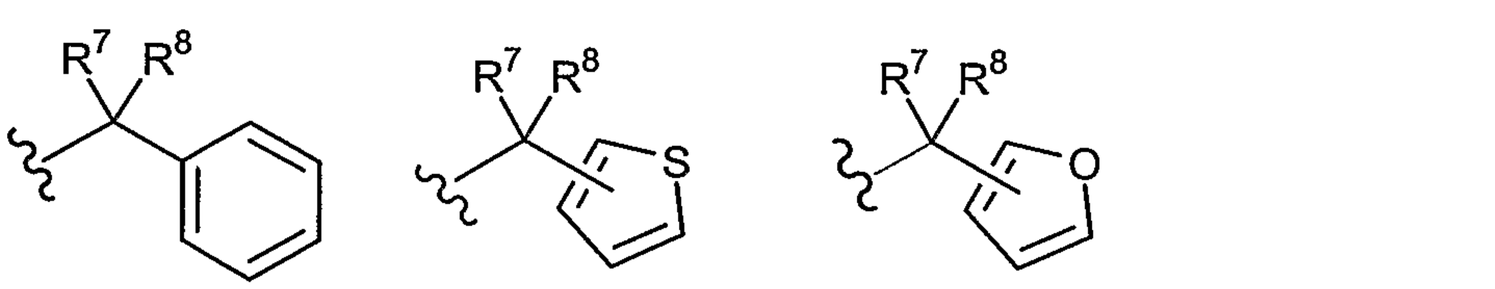
(b)



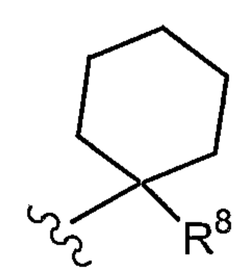
wherein R^7 is selected from the group consisting of: H, fluoroalkyl, alkyl and cycloalkyl; R^8 is selected form the group consisting of: H, alkyl, $-CF_2CH_3$ and $-CF_3$; and R^{8a} is as defined for formula IA.

Embodiment No. 68 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:

(a)

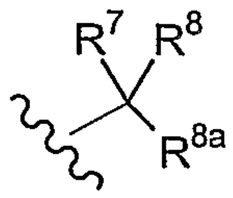


and



wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

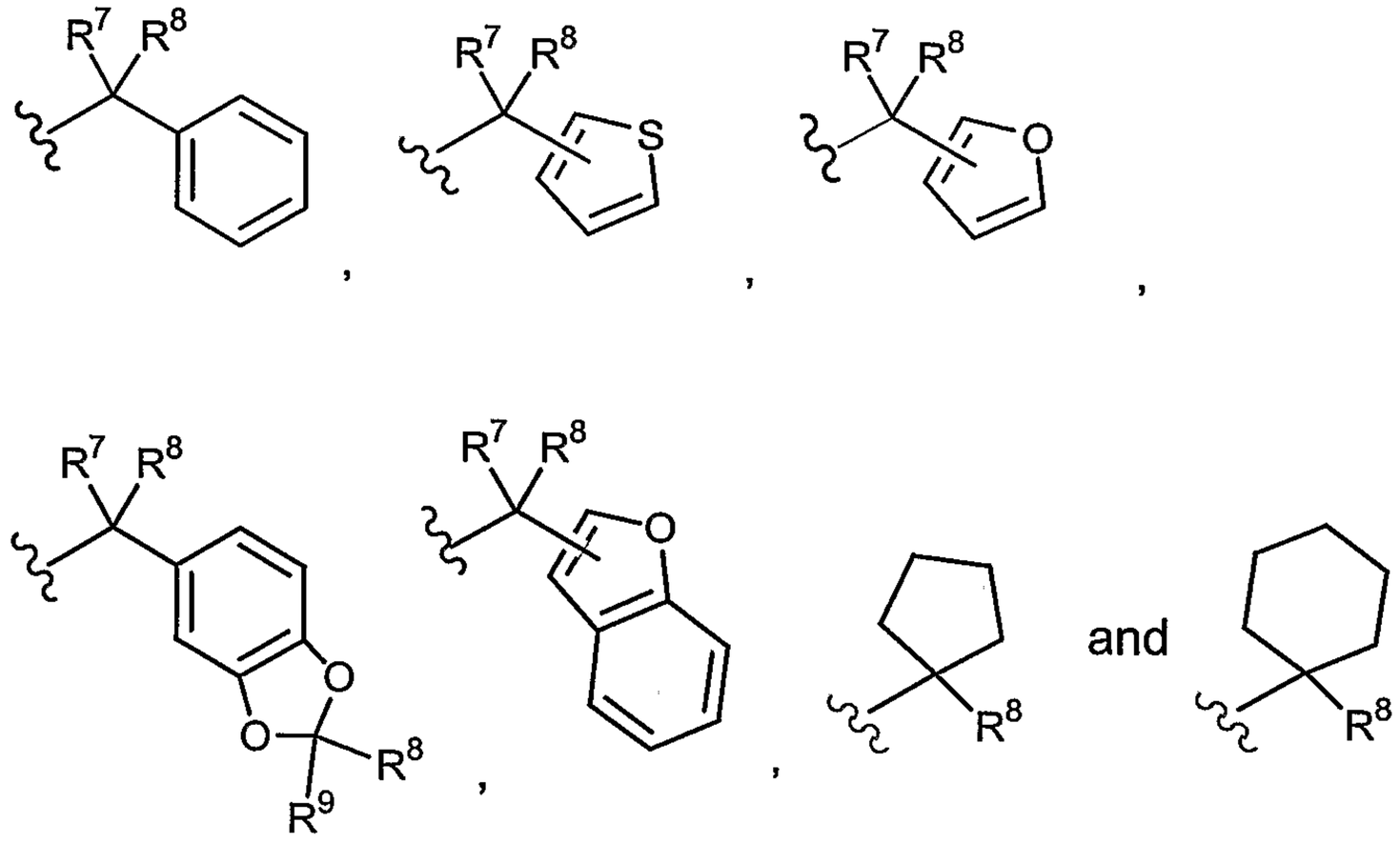
(b)



wherein R^7 is selected from the group consisting of: H, -CF_3, -CF_2CH_3, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA.

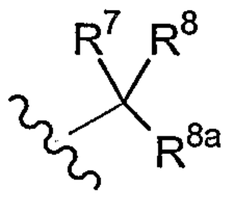
Embodiment No. 69 is directed compounds of formula IA wherein substituent A is selected from the group consisting of:

(a)



wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: F, Cl, Br, alkyl, cycloalkyl, and –CF_3; R^7 is selected from the group consisting of: H, -CF_3, -CF_2CH_3, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

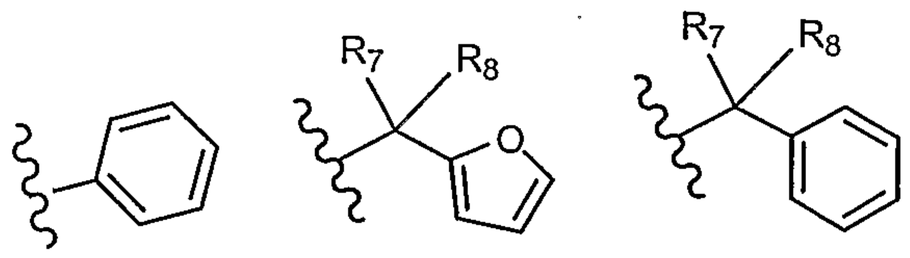
(b)

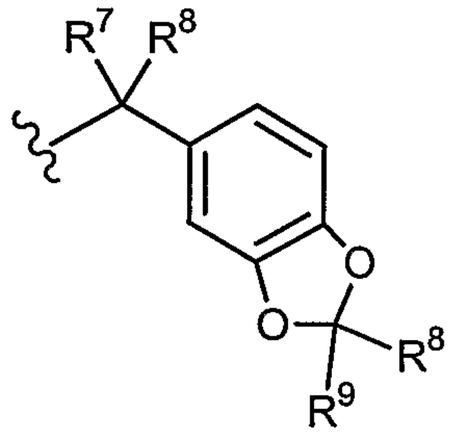
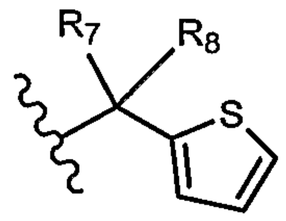


wherein R^7 is selected from the group consisting of: H, -CF_3, -CF_2CH_3, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA;

Embodiment No. 70 is directed compounds of formula IA wherein substituent A is selected from the group consisting of:

(1) unsubstituted or substituted:

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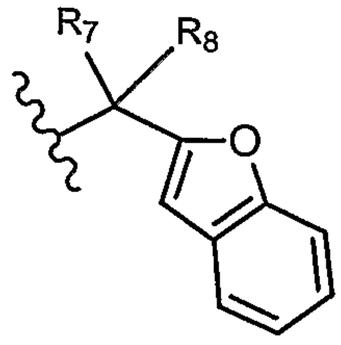
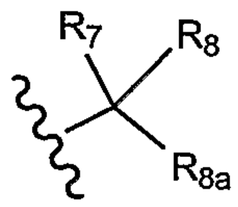
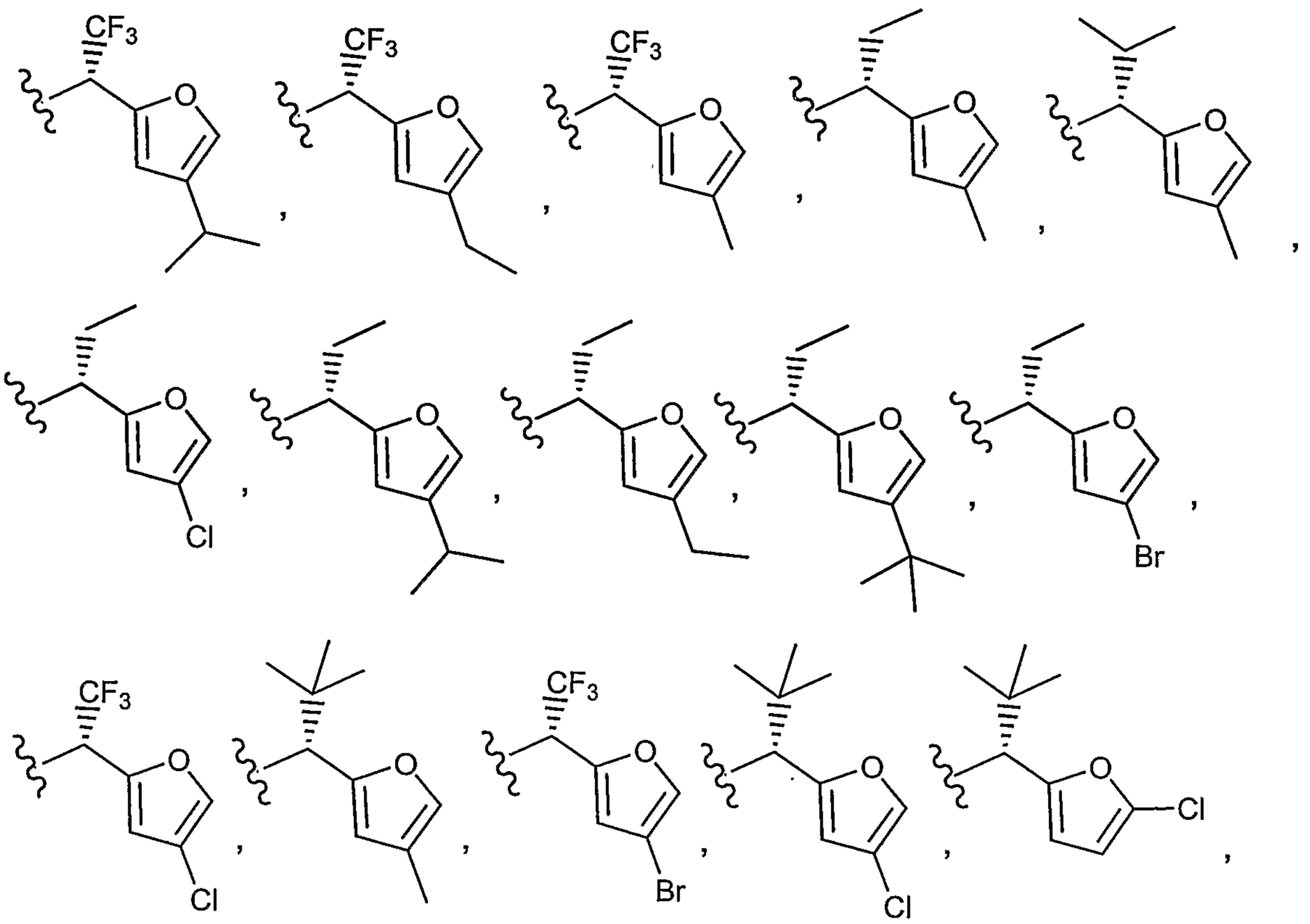
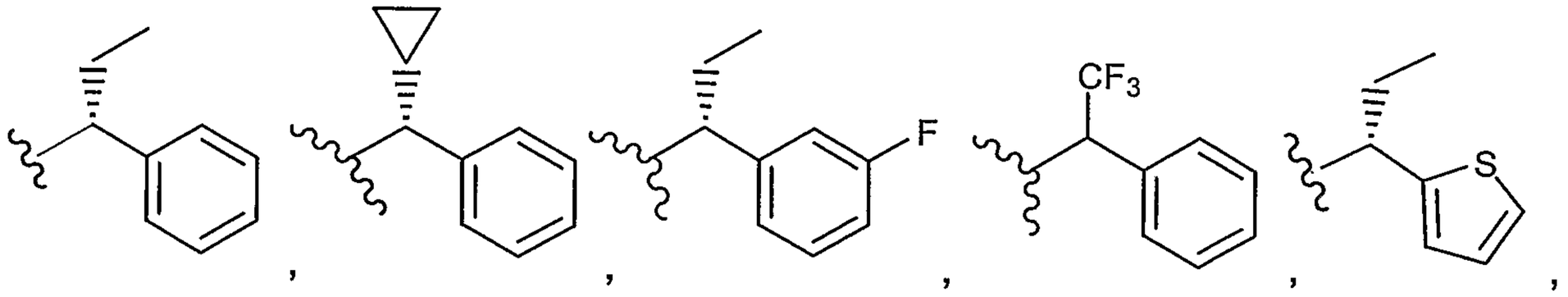

; and

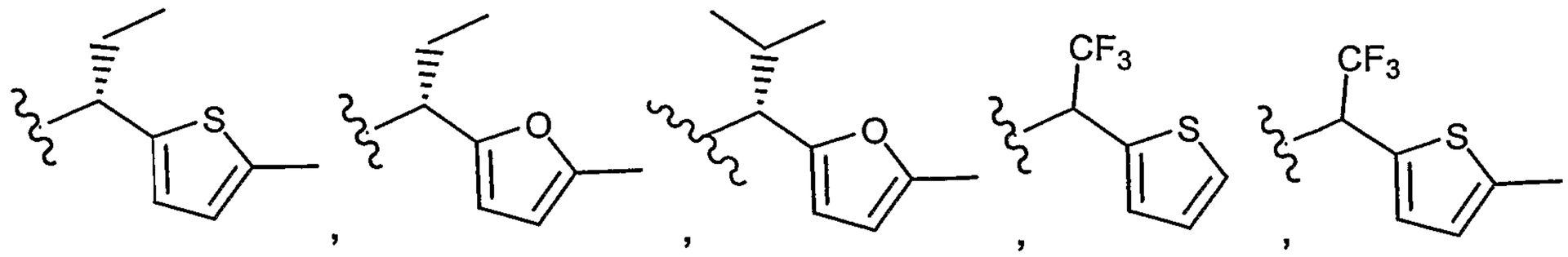
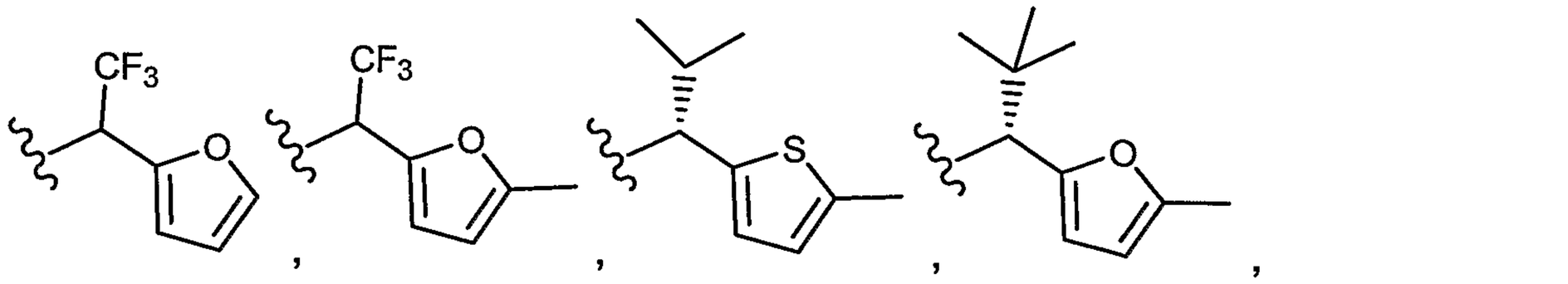
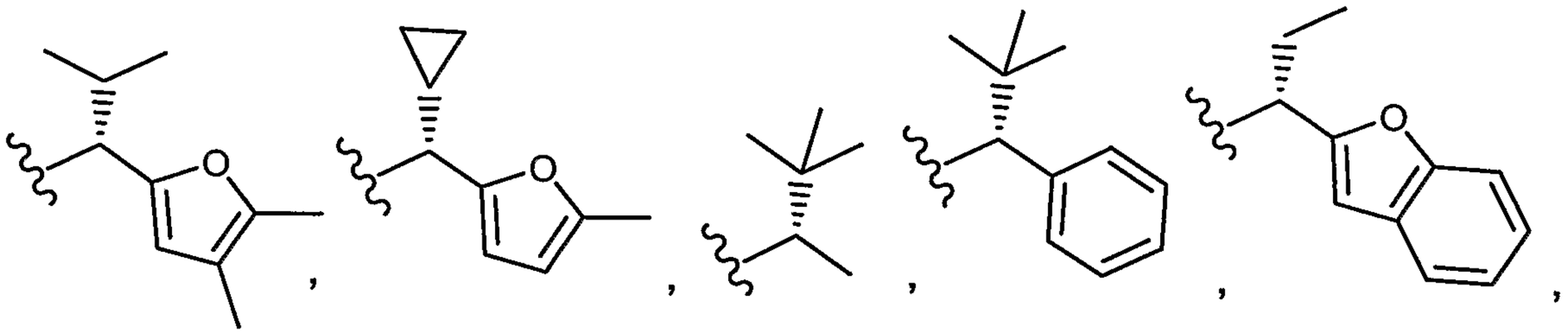
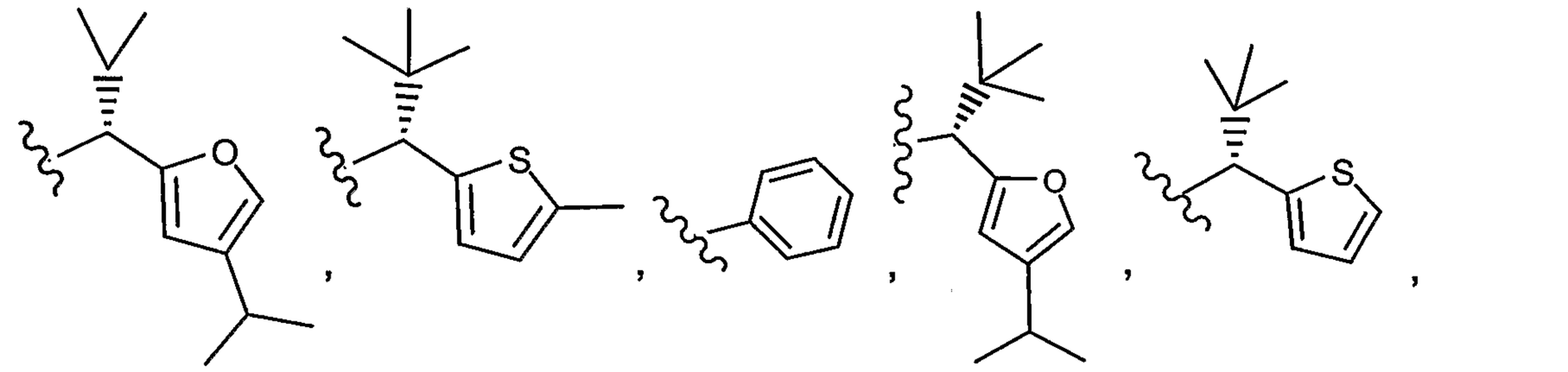
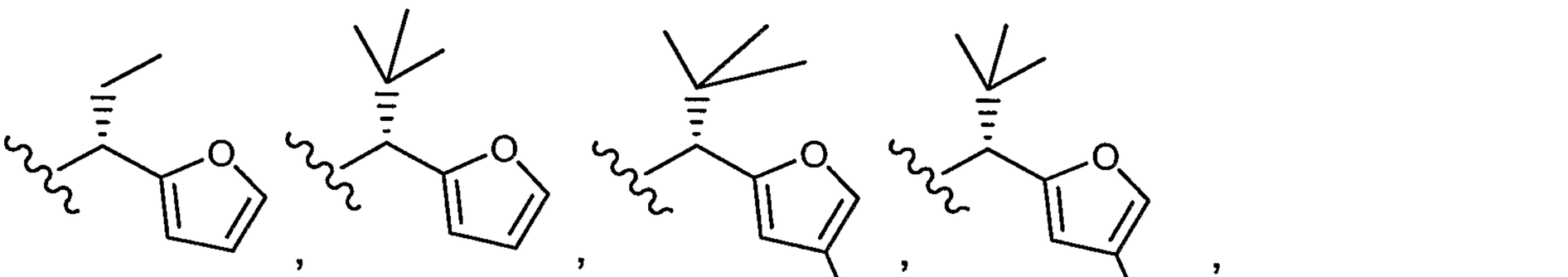
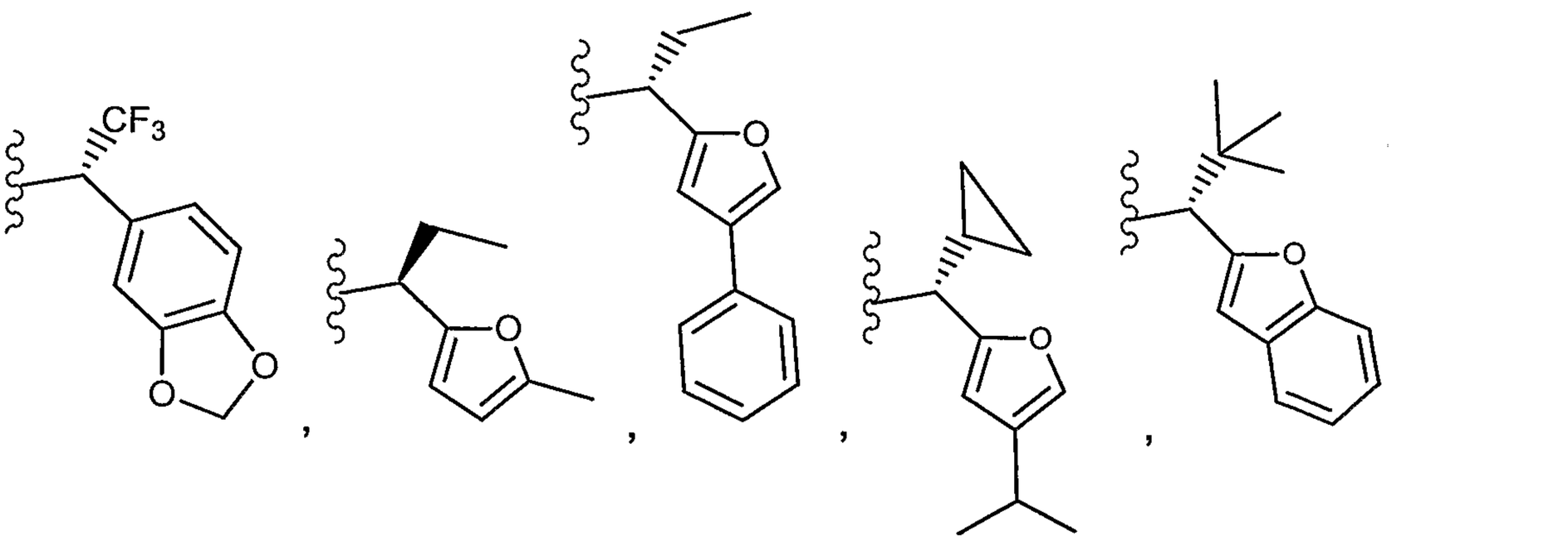
(2)



wherein all substitutents are as defined for formula IA.

Embodiment No. 71 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:

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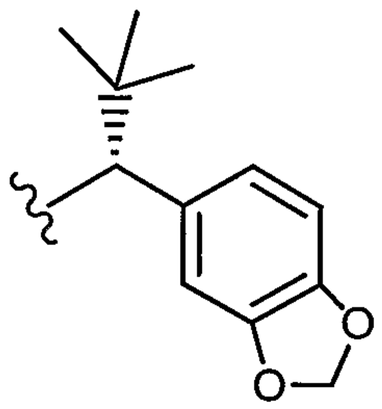
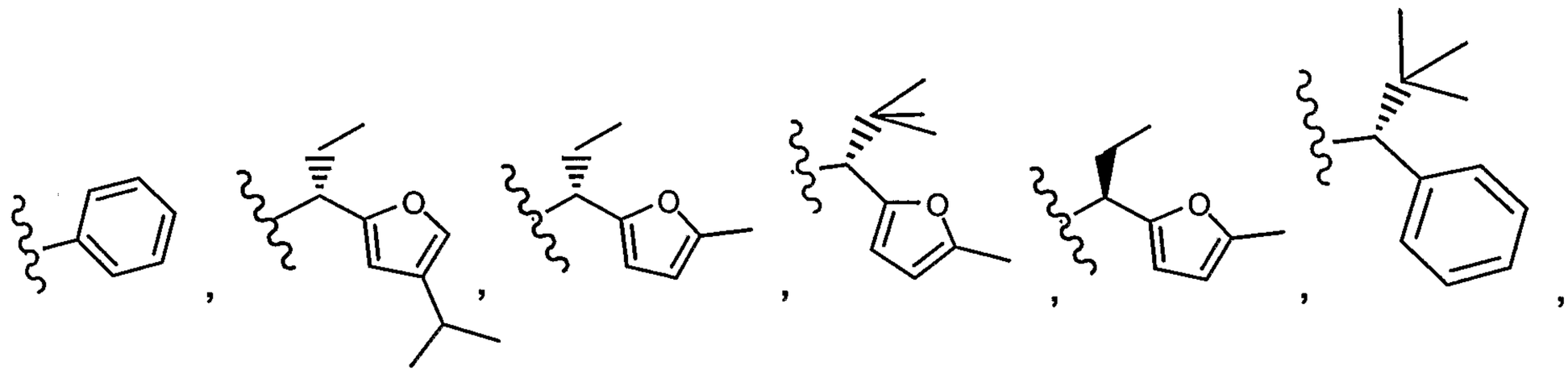
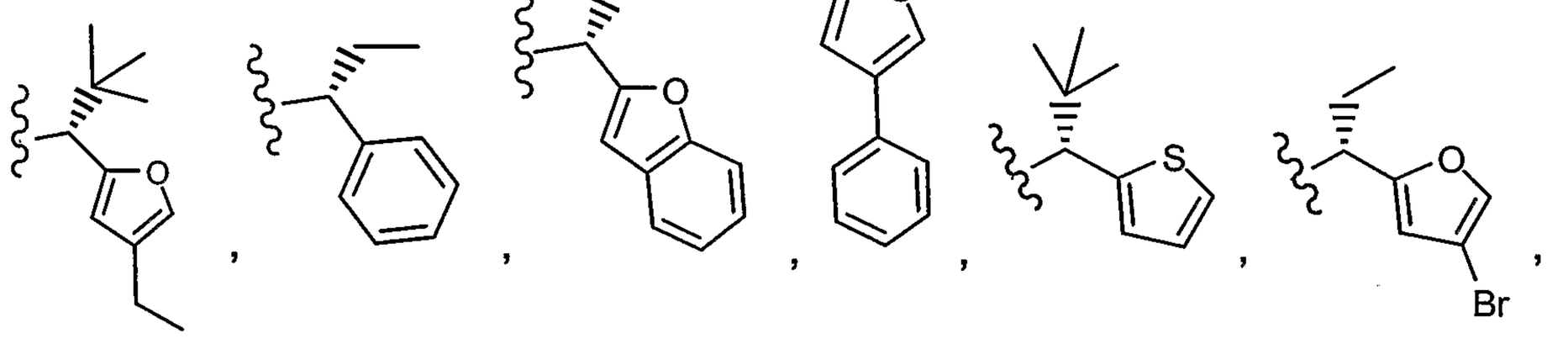
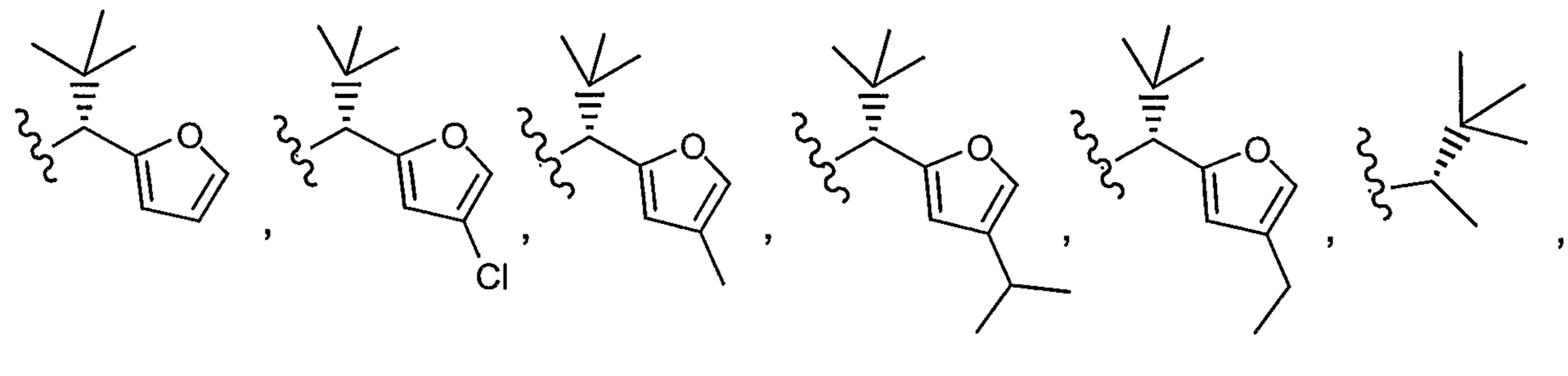
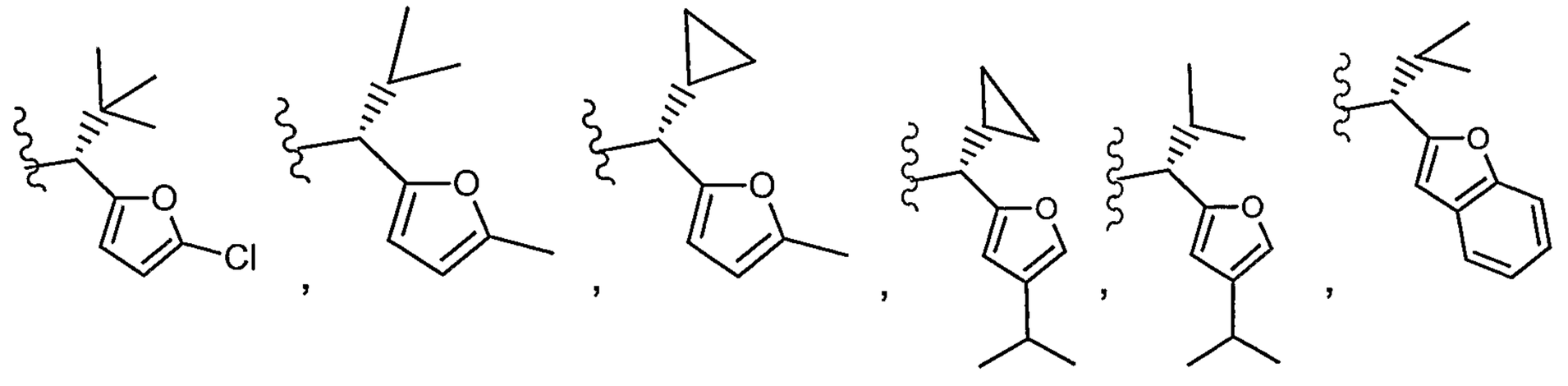
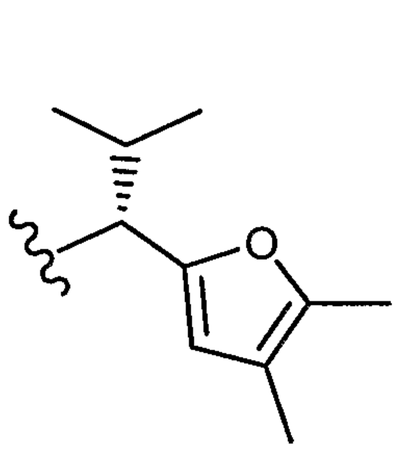
and  .

Embodiment No. 72 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of: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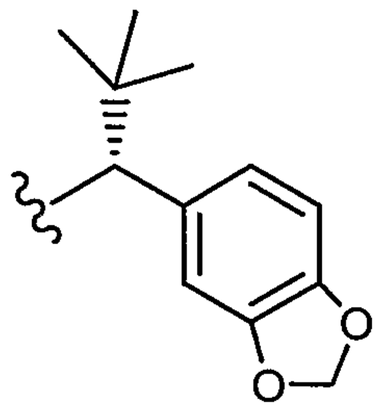
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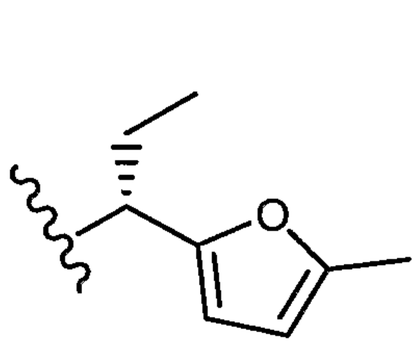
Embodiment No. 73 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of: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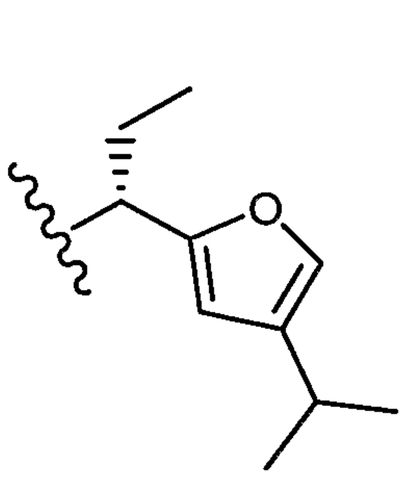
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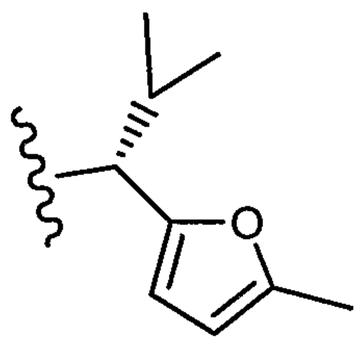
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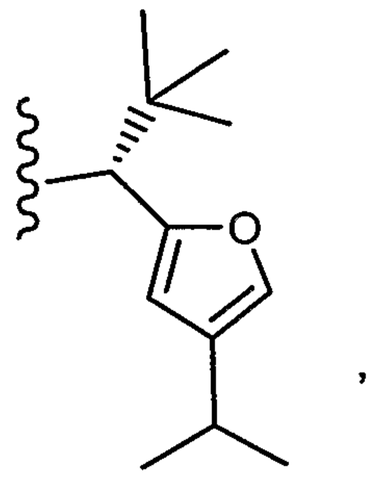
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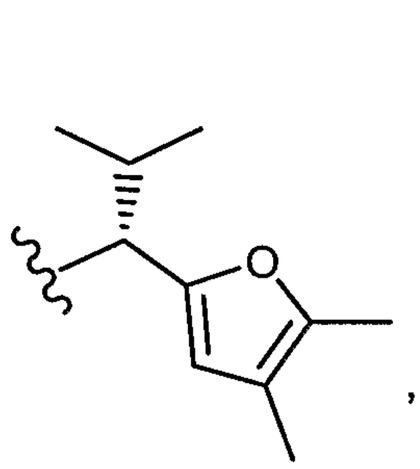
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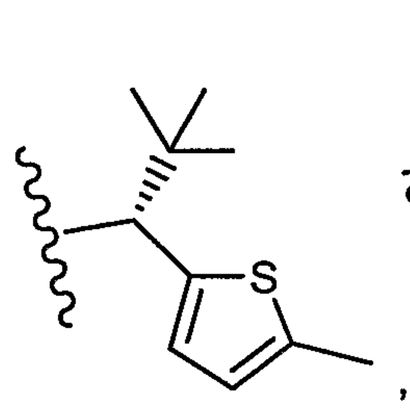
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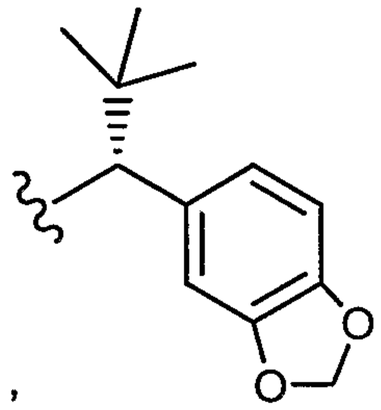
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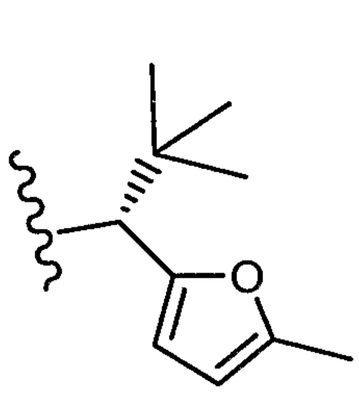
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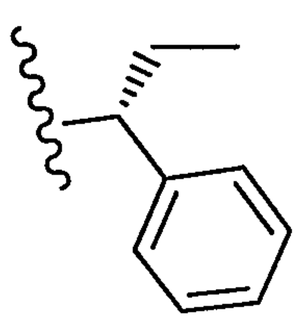
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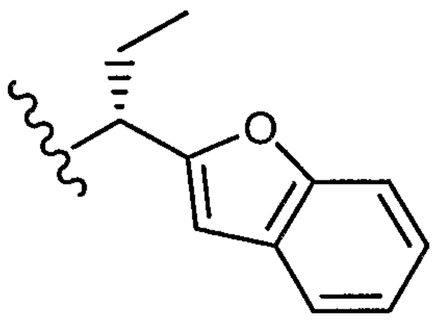
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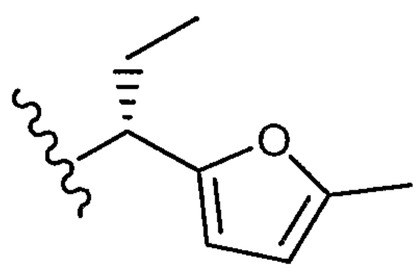
Embodiment No. 74 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of: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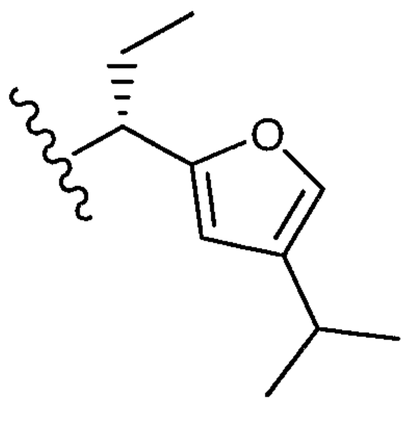
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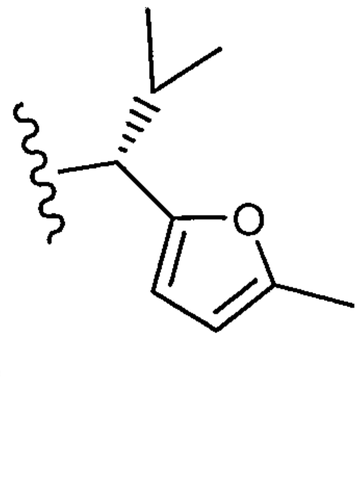
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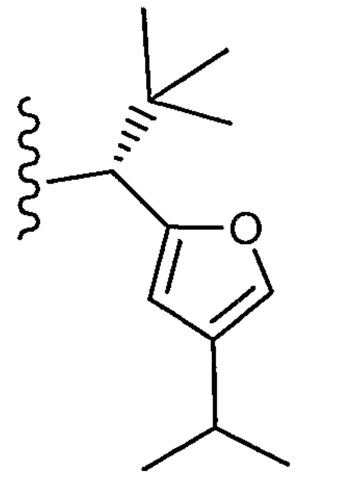
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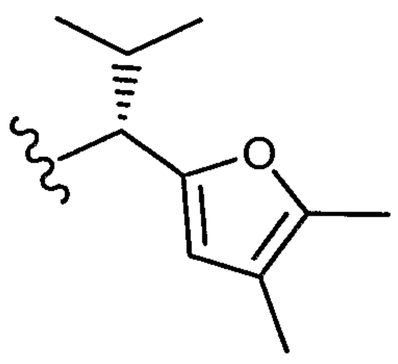
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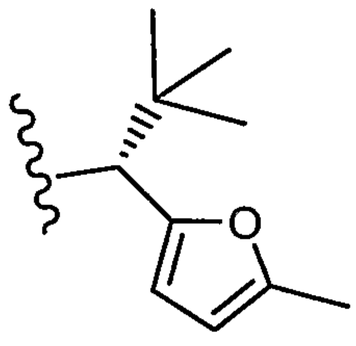
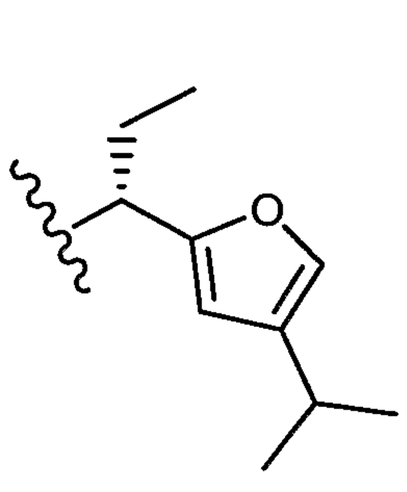


Embodiment No. 75 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of: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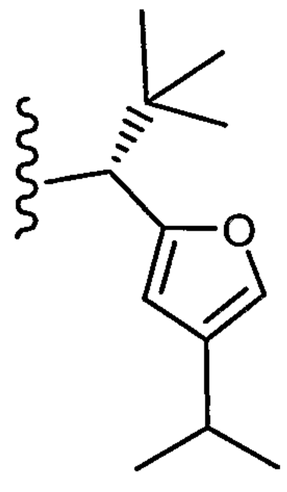
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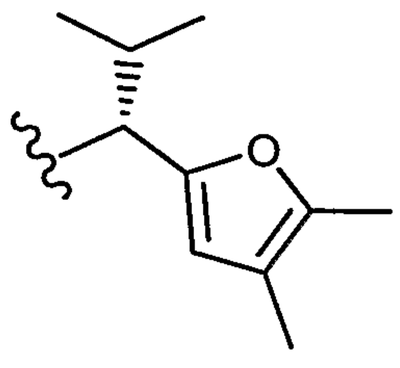
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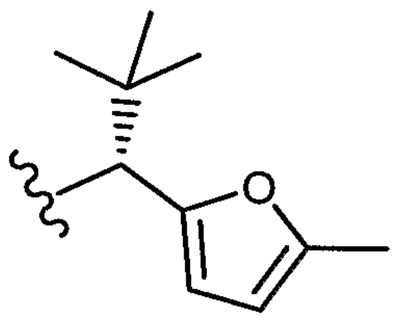
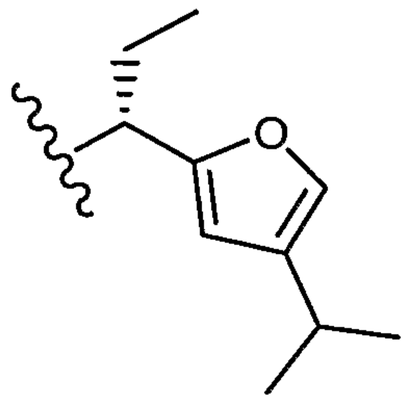
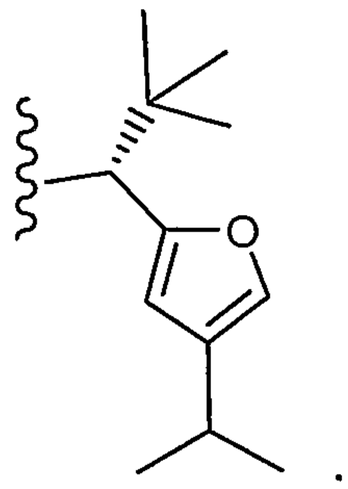


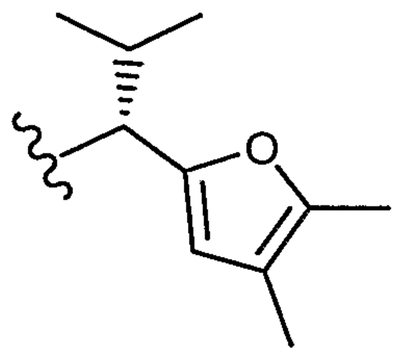
Embodiment No. 76 is directed to compounds of formula IA wherein substituent A is:



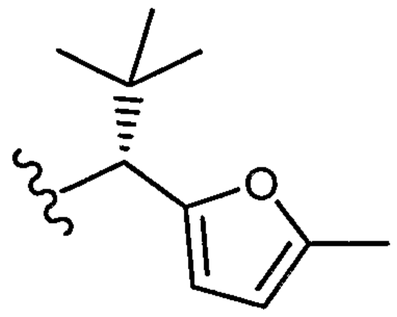
Embodiment No. 77 is directed to compounds of formula IA wherein substituent A is:



Embodiment No. 78 is directed to compounds of formula IA wherein substituent A is:

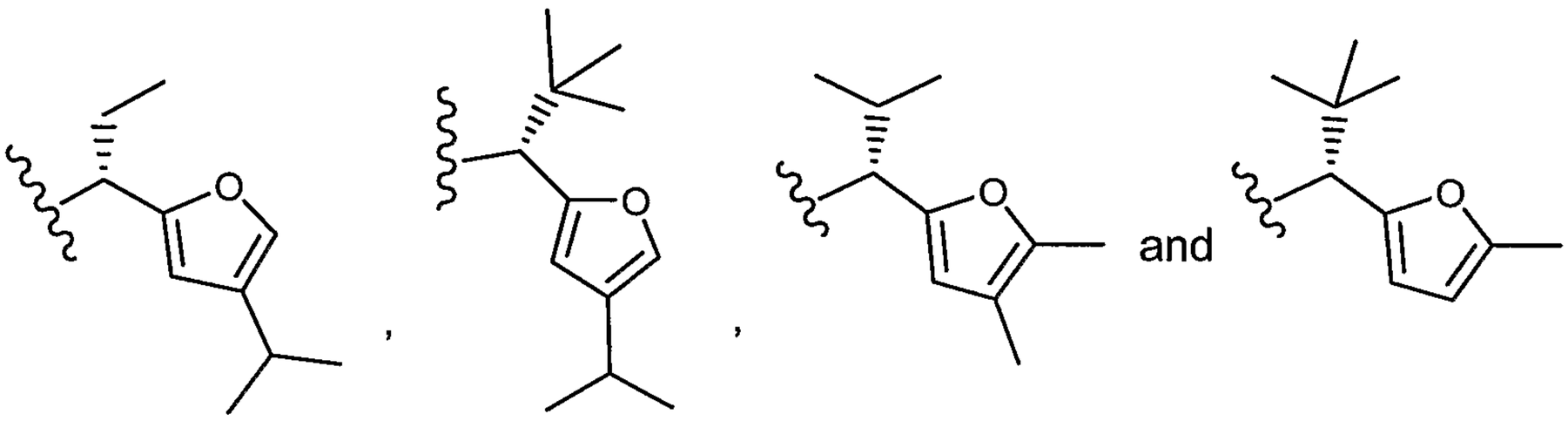


Embodiment No. 79 is directed to compounds of formula IA wherein substituent A is:

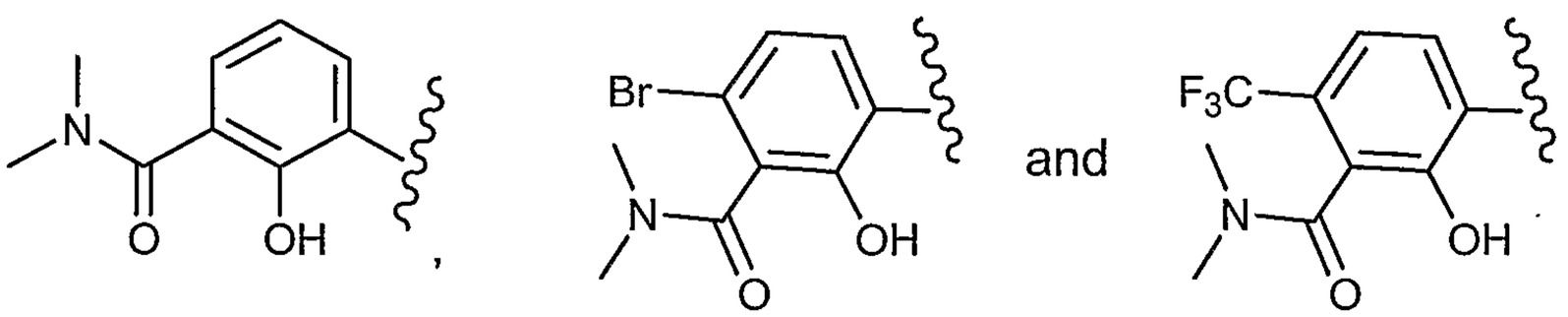


.

Embodiment No. 80 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:

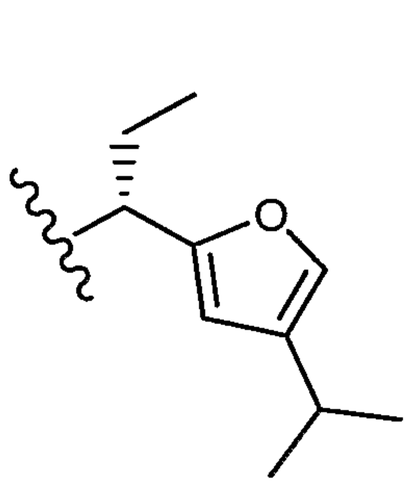


and substituent B is selected from the group consisting of:



.

Embodiment No. 81 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of: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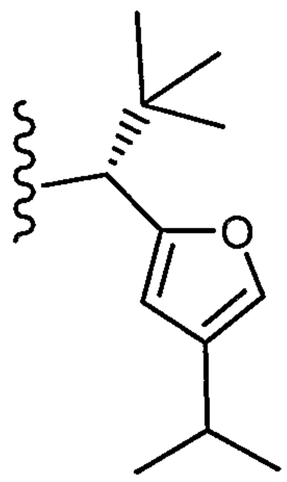
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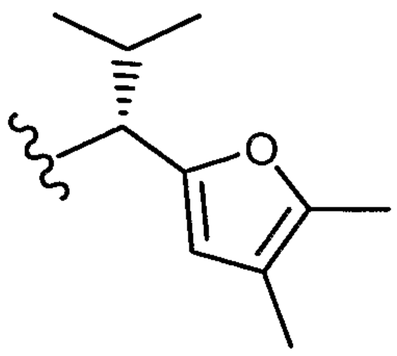
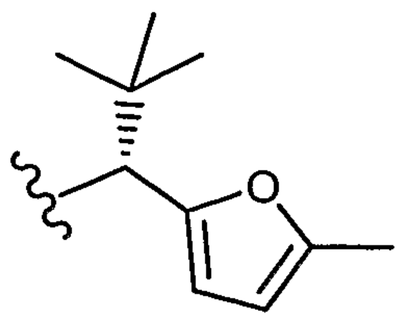
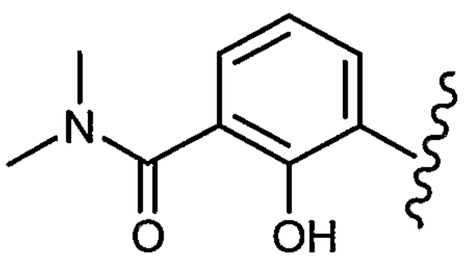

and

,

and substituent B is selected from the group consisting of: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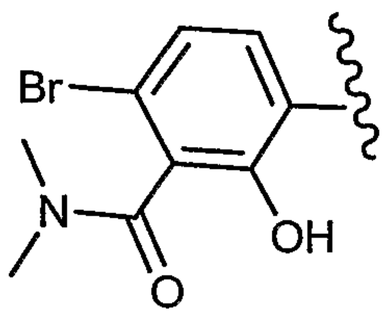
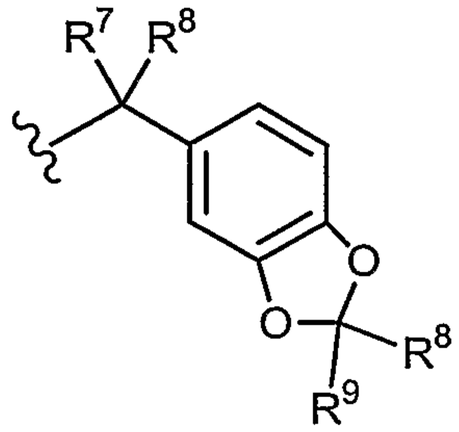

.

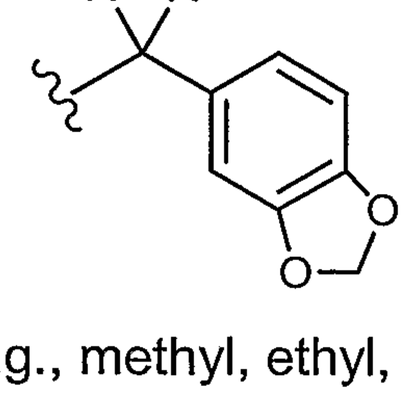
Embodiment No. 82 is directed to novel compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64, and A is as defined in any one of the Embodiment Nos. 65 to 79.

Embodiment No. 83 is directed to compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64, and A is:



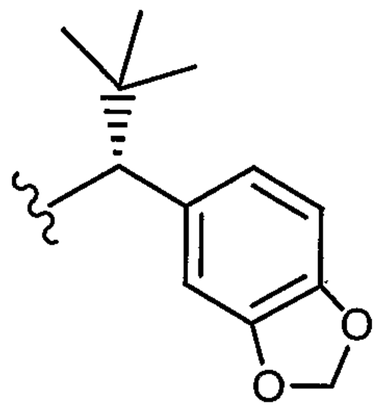
and all other substituents are as defined for formula IA.

Embodiment No. 84 is directed to compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64, and A is:



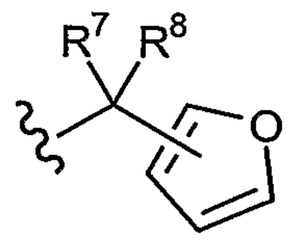
wherein R^7 is H, and R^8 is alkyl (e.g., methyl, ethyl, isopropyl, cyclopropyl and t-butyl), and all other substituents are as defined for formula IA.

Embodiment No. 85 is directed to compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64, and A is:



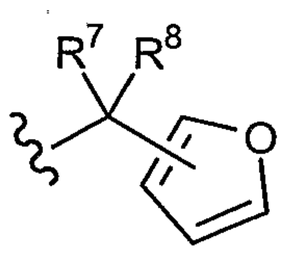
and all other substituents are as defined for formula IA.

Embodiment No. 86 is directed to compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64, and A is:



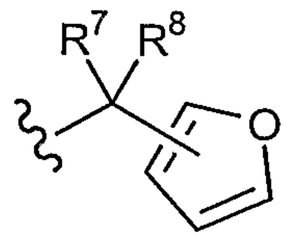
wherein the furan ring is unsubstituted or substituted as described in the definition of A for formula IA, and all other substituents are as defined for formula IA.

Embodiment No. 87 is directed to compounds of formula IA wherein B is described in any one of the Embodiment Nos. 1 to 64, and A is



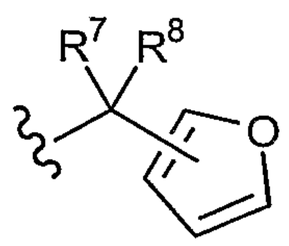
wherein the furan ring is substituted and all other substituents are as defined for formula IA.

Embodiment No. 88 is directed to compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64,and A is



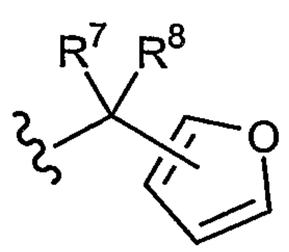
wherein the furan ring is substituted with at least one (e.g., 1 to 3, or 1 to 2) alkyl group and all other substituents are as defined for formula IA.

Embodiment No. 89 is directed to compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64, A is



wherein the furan ring is substituted with one alkyl group and all other substituents are as defined for formula IA.

Embodiment No. 90 is directed to compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64, and A is



wherein the furan ring is substituted with one C_1 to C_3 alkyl group (e.g., methyl or isopropyl), and all other substituents are as defined for formula IA.

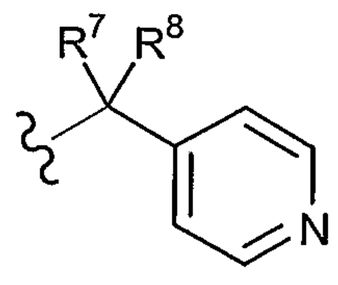
Embodiment No. 91 is directed to novel compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64, and A is as defined in any one of the Embodiment Nos. 86 to 90, except that R^7 and R^8 are the same or different and each is selected from the group consisting of: H and alkyl.

Embodiment No. 92 is directed to novel compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 64, and A is as defined in any one of the Embodiment Nos. 86 to 90, except that R^7 is H, and R^8 is alkyl (e.g., ethyl or t-butyl).

Embodiment No. 93 is directed to compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

(a)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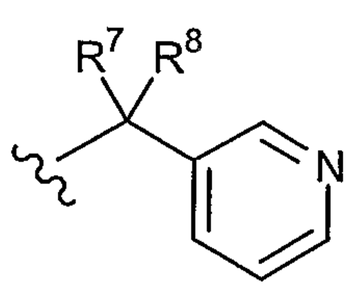
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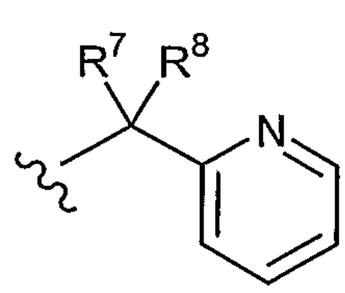
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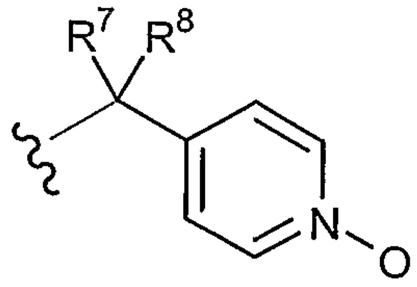
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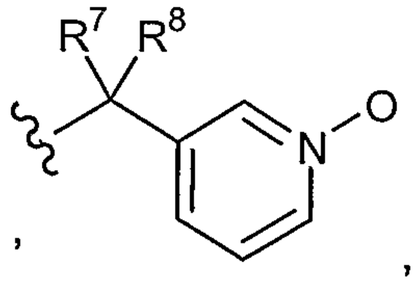
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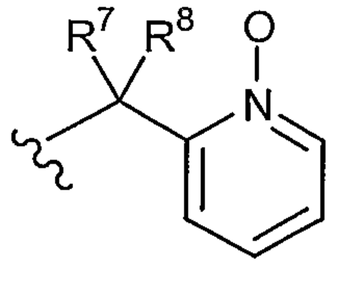
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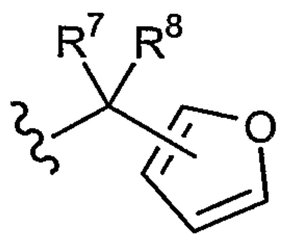
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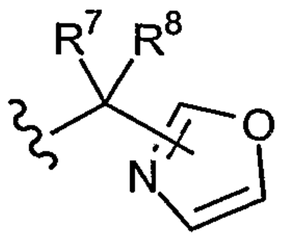
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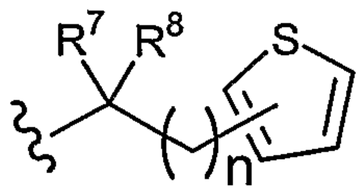
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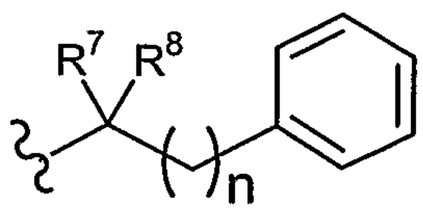
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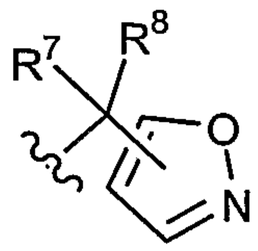
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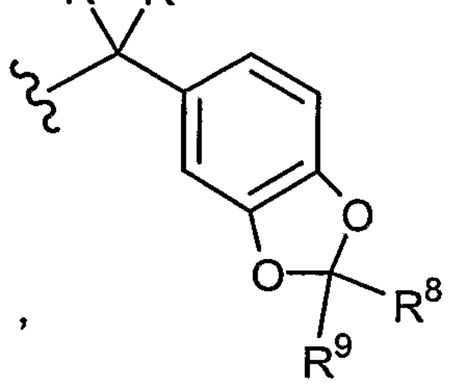
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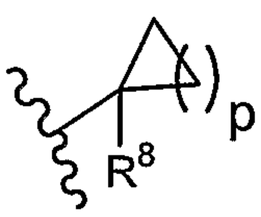
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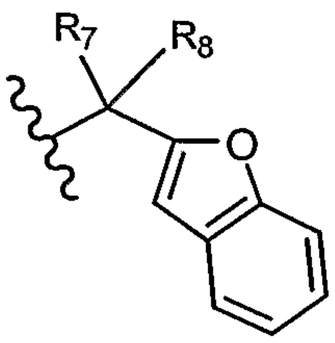
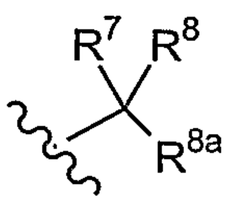


wherein the above rings are unsubstituted or substituted, as described for formula IA: and

(b)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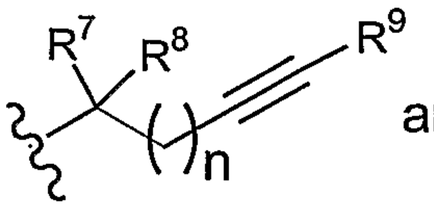
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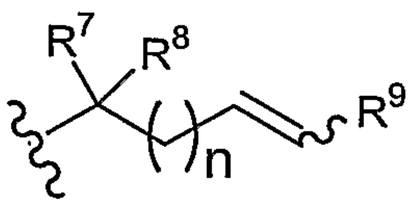
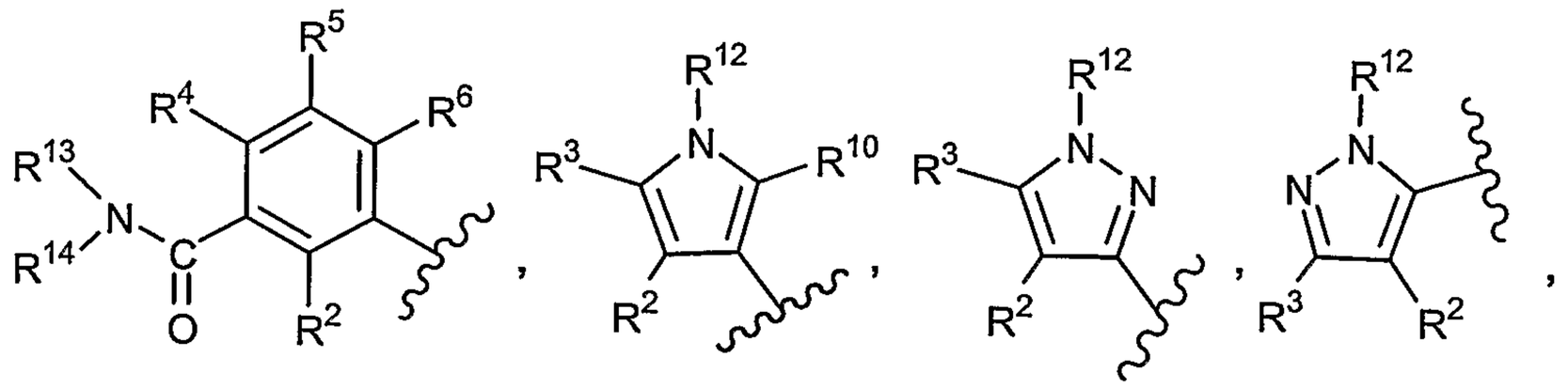

, and

wherein in (a) and (b) above: each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, and cycloalkenyl, wherein said substituents on said R^7 and R^8 substituted groups are selected from the group consisting of: a) cyano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$, i) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, and k) halogen; and R^{8a} and R^9 are as defined in formula IA; and

(2) substituent B in formula IA is selected from the group consisting of:



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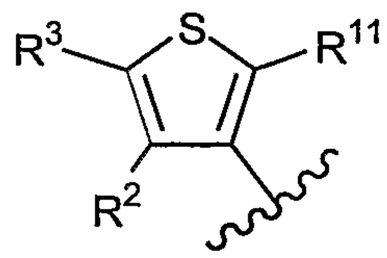
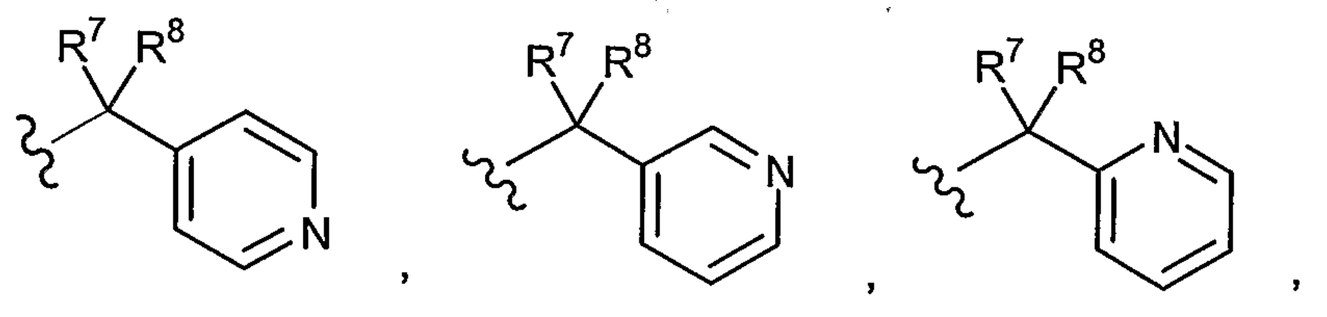


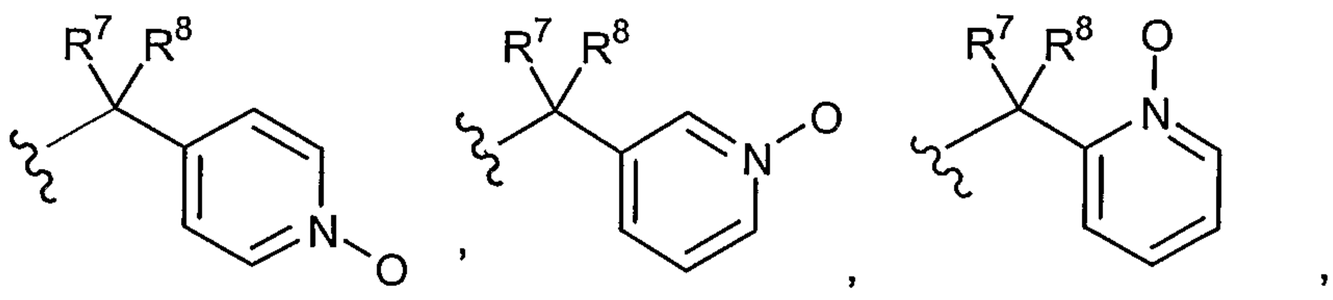
wherein R^2 to R^6 and R^{10} to R^{14} are as defined above for the novel compounds of formula IA .

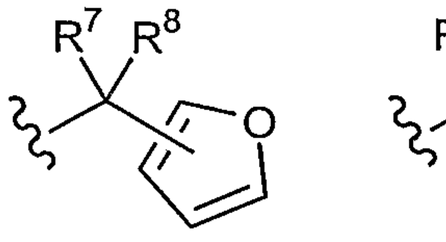
Embodiment No. 94 is directed to compounds of formula IA wherein:

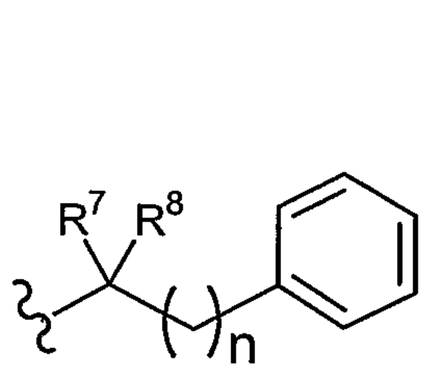
(1) substituent A in formula IA is selected from the group consisting of:

(a)





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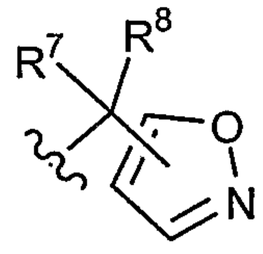
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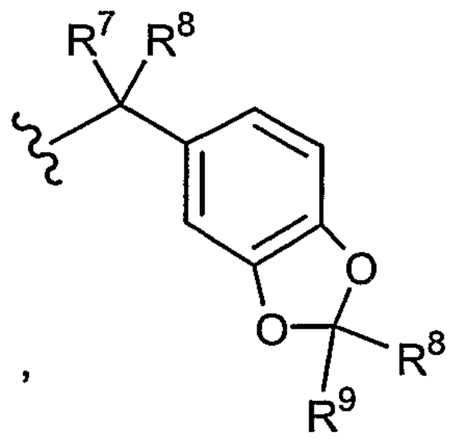
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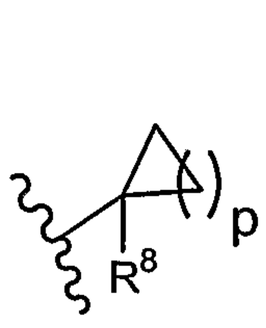
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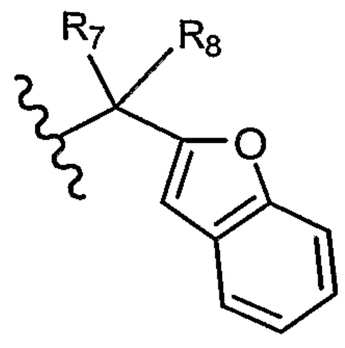
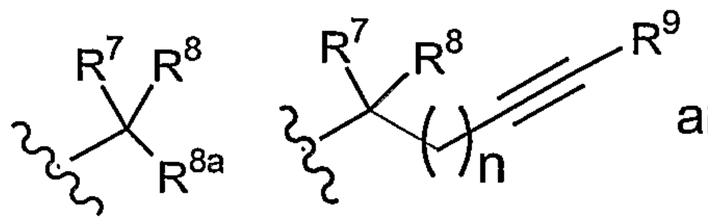
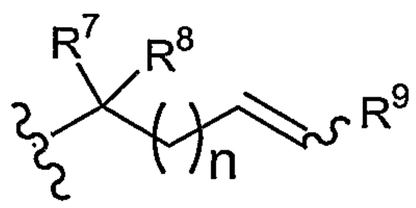


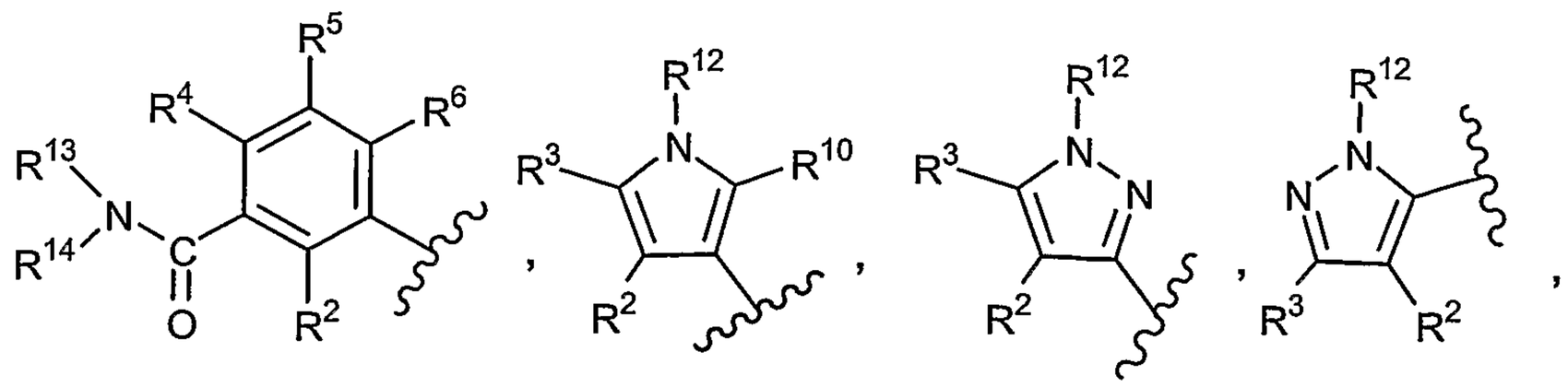
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; and

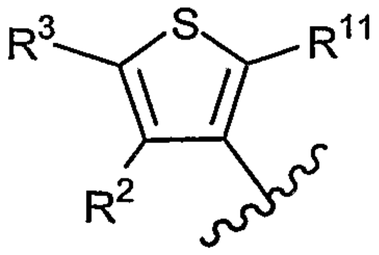
(b)


and


wherein each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); wherein R^{8a} is as defined in formula IA, and wherein R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and

(2) substituent B in formula IA is selected from the group consisting of:



and 

wherein

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ or and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-C(O)NR^{13}R^{14}$, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$, halogen, and $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano;

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

each R^{10} and R^{11} is independently selected from the group consisting of: R^{13}, hydrogen, halogen, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$,$-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, and cyano;

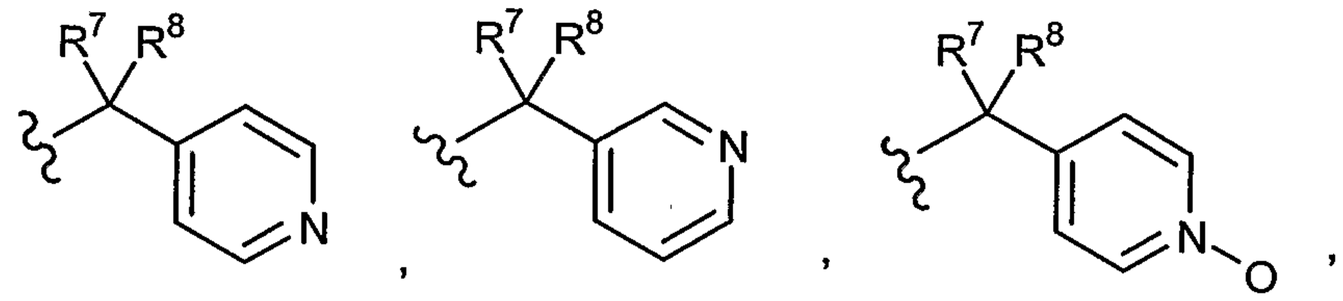
each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl and isopropyl; or

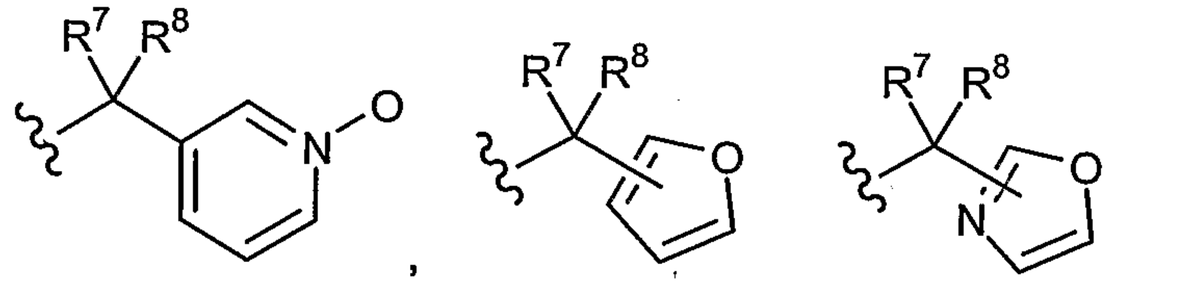
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-SO_tNR^{13}R^{14}$, $-NHSO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$; wherein each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they

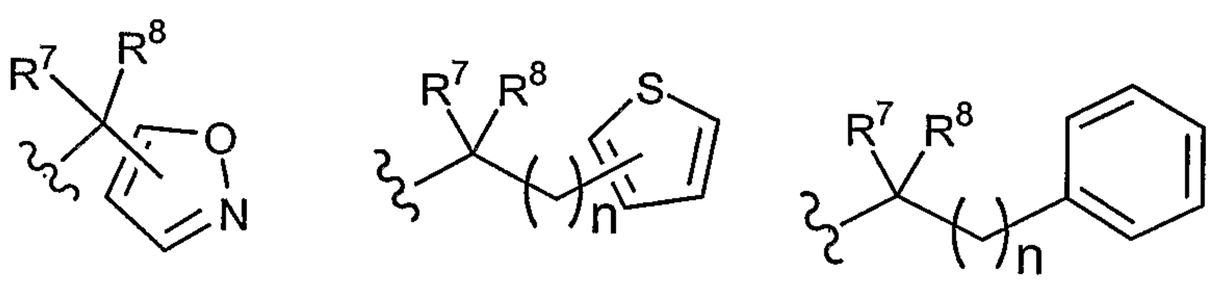
are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

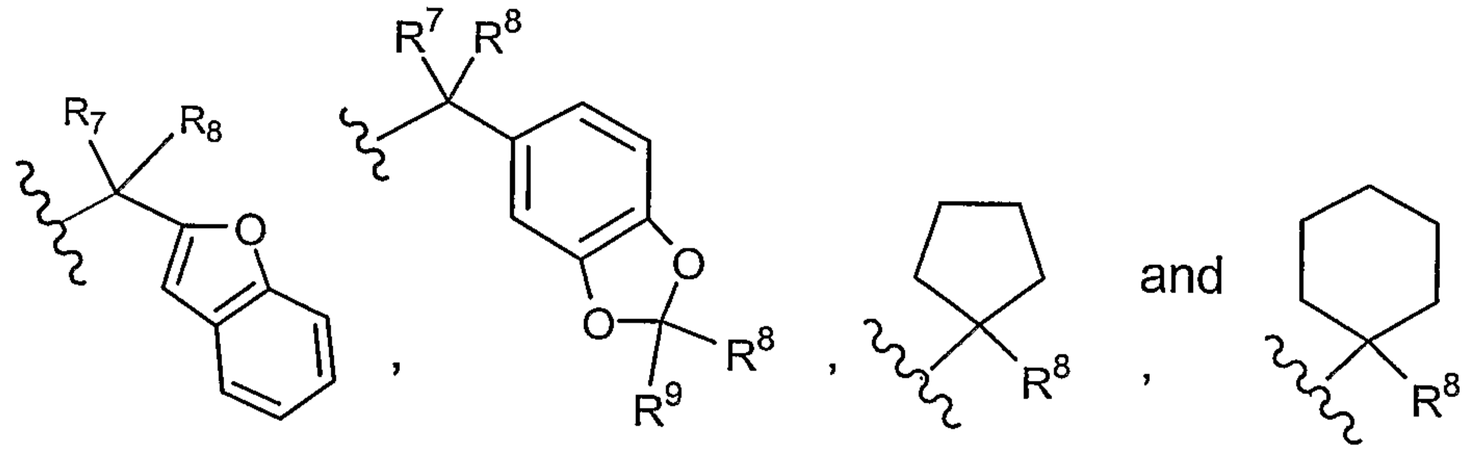
Embodiment No. 95 is directed to compounds of formula IA wherein substituent A in formula IA is even more preferably selected from the group consisting of:

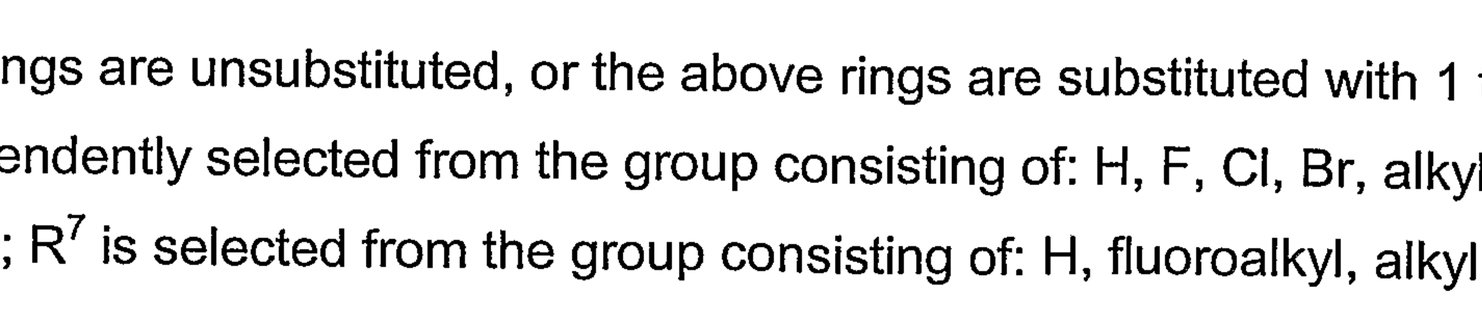
(a)







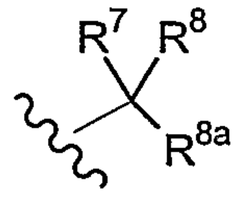




wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, fluoroalkyl, alkyl

and cycloalkyl; R^8 is selected form the group consisting of: H, alkyl, $-CF_2CH_3$ and $-CF_3$; and R^9 is selected from the group consisting of: H, F, Cl, Br, alkyl or $-CF_3$; and

(b)

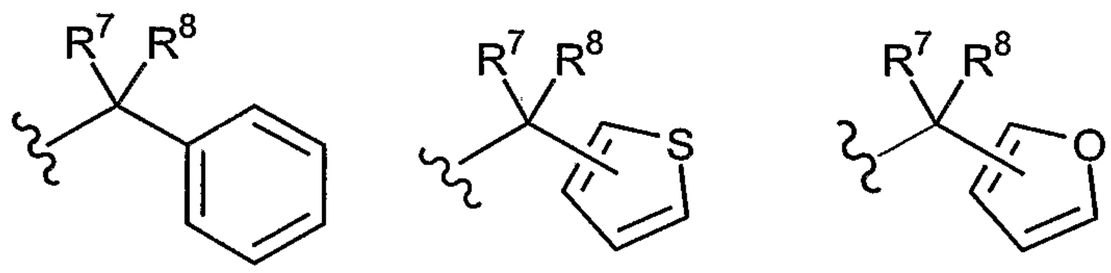


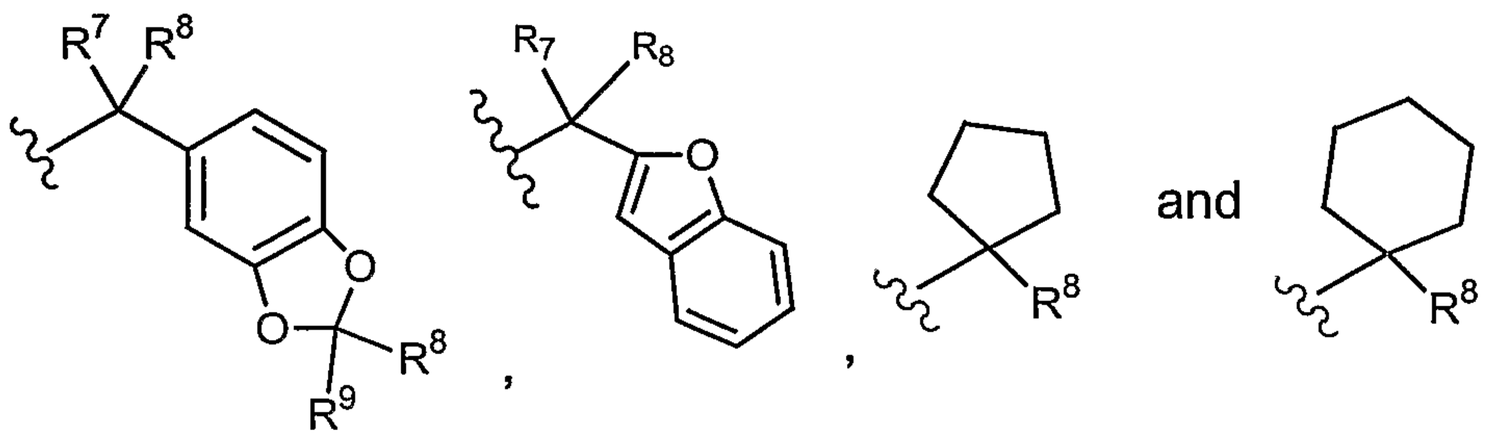
wherein R^7 is selected from the group consisting of: H, fluoroalkyl, alkyl and cycloalkyl; R^8 is selected form the group consisting of: H, alkyl, $-CF_2CH_3$ and $-CF_3$; and R^{8a} is as defined for formula IA.

Embodiment No. 96 is directed to compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

(a)

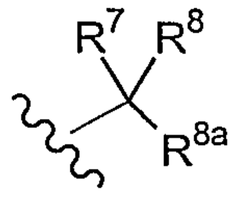




and

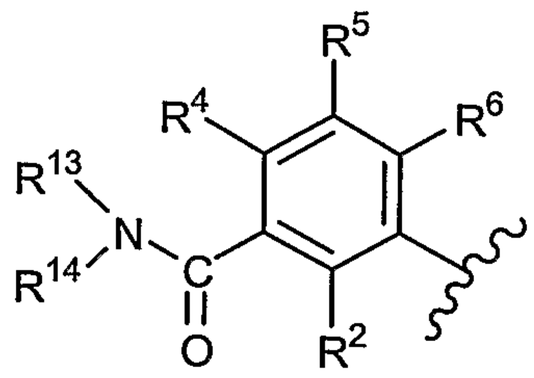
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)



wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA.

(2) substituent B in formula IA is selected from the group consisting of:



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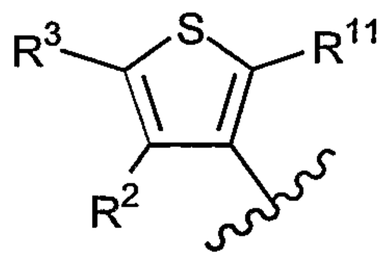


wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, alkyl (e.g., $-CH_3$ and ethyl), $-CF_3$, and halogen;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl and isopropyl; or

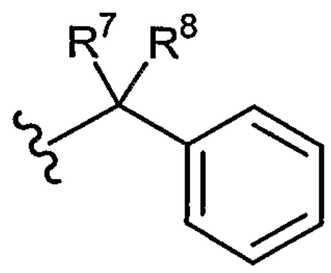
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-SO_tNR^{13}R^{14}$, $-NHSO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from O, S or NR^{18} wherein R^{18} is selected from H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$, wherein each R^{19} and R^{20} is independently selected from alkyl, aryl and heteroaryl, wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$,

$-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

Embodiment No. 97 is directed to compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

(a)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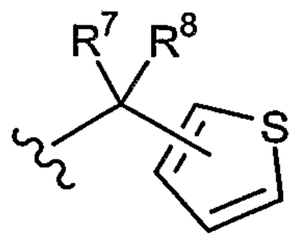
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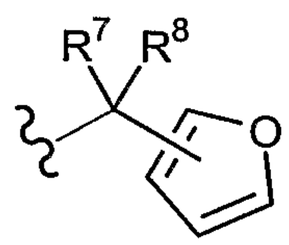
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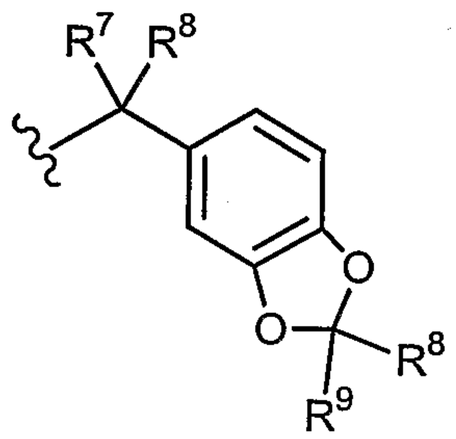
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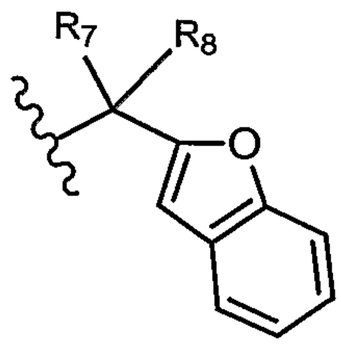
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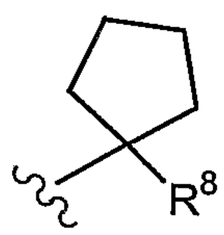
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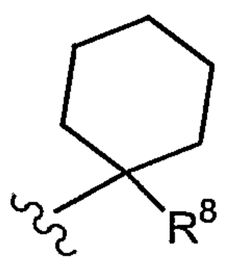
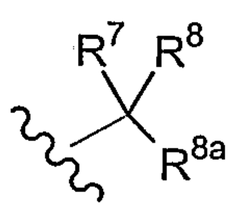


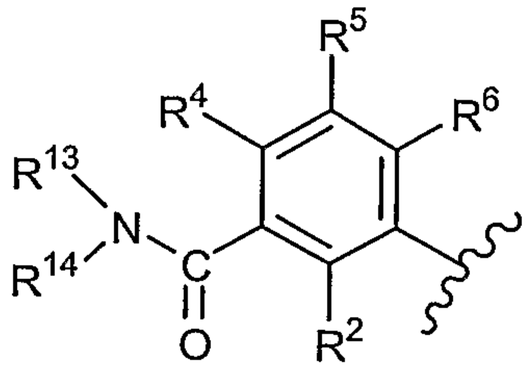
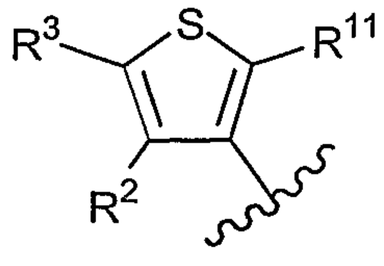
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)



wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA;

(2) substituent B in formula IA is selected from the group consisting of:


and


wherein:

R^2 is selected from the group consisting of: H, OH, -NHC(O)R^{13} and -NHSO_2R^{13};

R^3 is selected from the group consisting of: -C(O)N$R^{13}R^{14}$ -SO_2N$R^{13}R^{14}$, -NO_2, cyano, and -SO_2R^{13};

R^4 is selected from the group consisting of: H, -NO_2, cyano, alkyl (e.g., -CH_3 and ethyl), -CF_3 and halogen;

R^5 is selected from the group consisting of: H, -CF_3, -NO_2, halogen and cyano; and

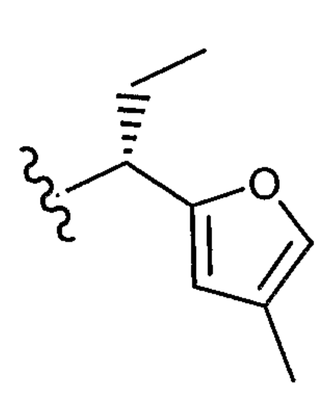
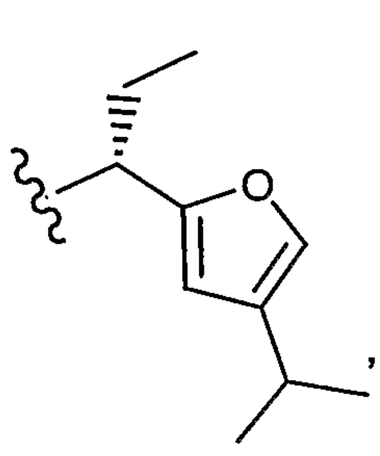
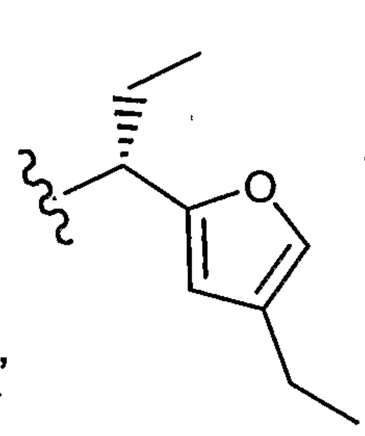
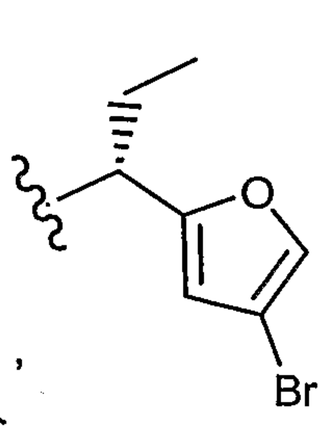
R^6 is selected from the group consisting of: H, alkyl and -CF_3;

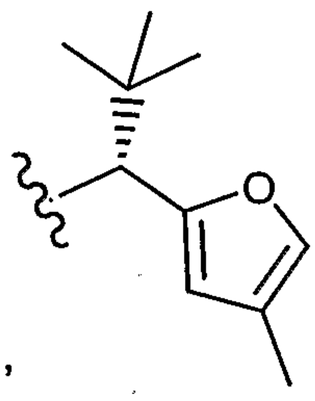
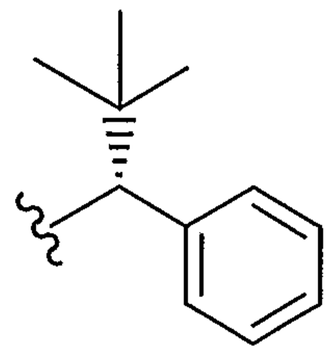
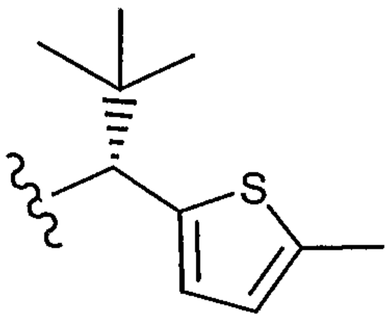
R^{11} is selected from the group consisting of: H, halogen and alkyl; and

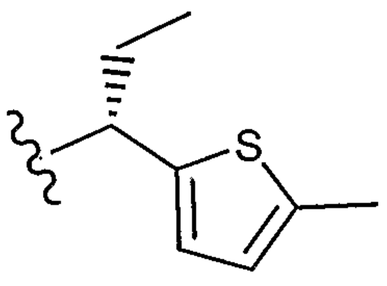
each R^{13} and R^{14} is independently selected from the group consisting of: H and unsubstituted alkyl (e.g., methyl and ethyl).

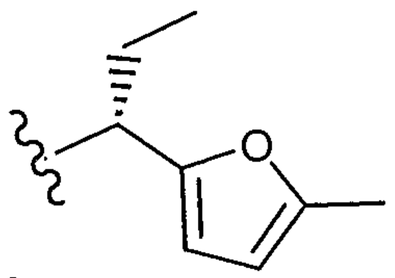
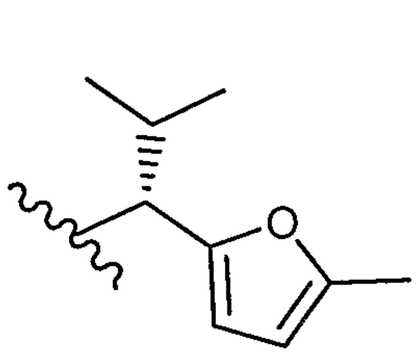
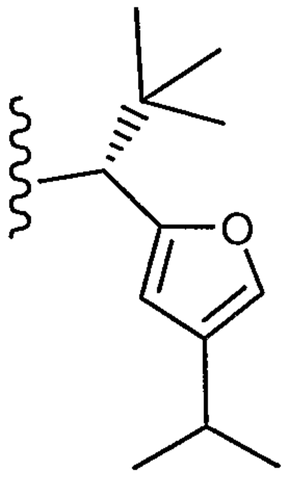
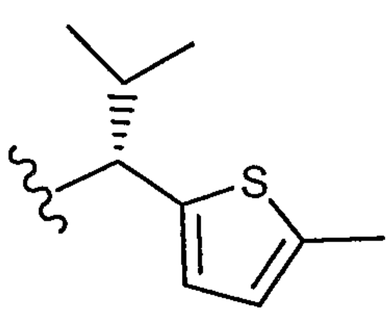
Embodiment No. 98 is directed to compounds of formula IA wherein:

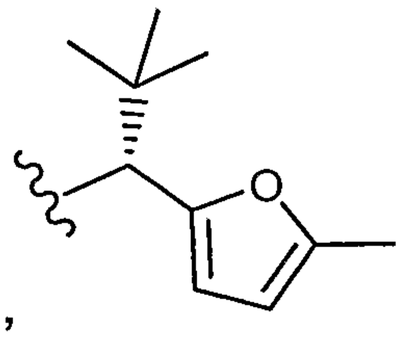
(1) substituent A in formula IA is selected from the group consisting of:

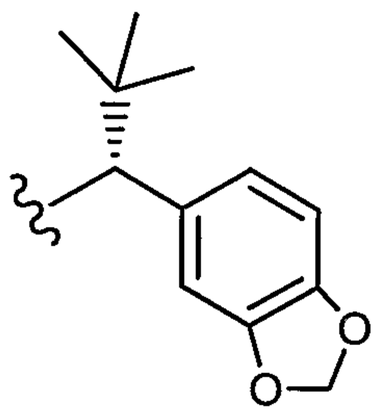
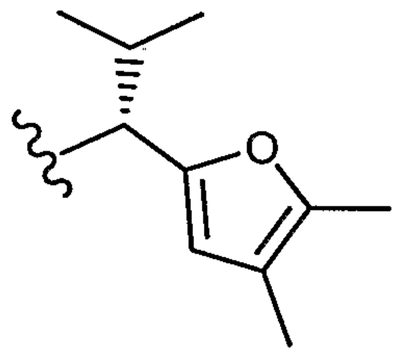
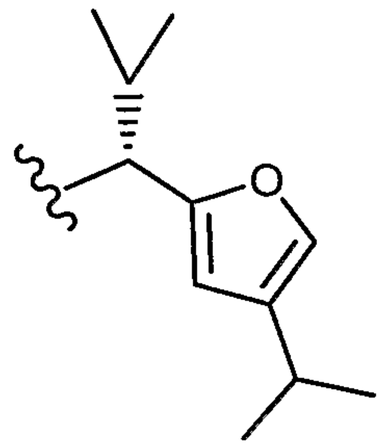





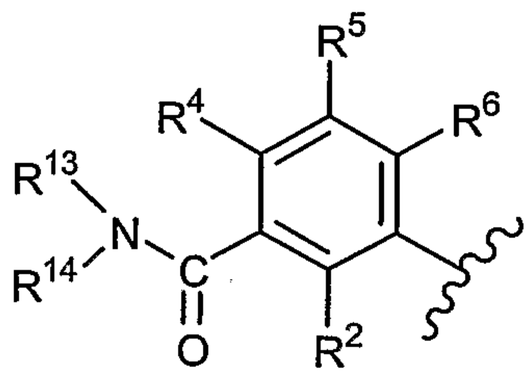
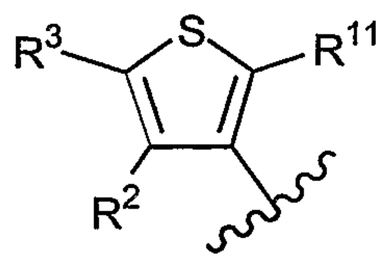





,  and  ; and

(2) substituent B in formula IA is selected from the group consisting of:

 and 

wherein:

R^2 is –OH;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;

R^4 is selected form the group consisting of: H, Br, $-CH_3$, ethyl and $-CF_3$;

R^5 is selected from the group consisting of: H and cyano;

R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$;

R^{11} is H; and

R^{13} and R^{14} are independently selected from the group consisting of H and methyl (e.g., for $-SO_2NR^{13}R^{14}$ both R^{13} and R^{14} are H, or both R^{13} and R^{14} are methyl, also, for example, for $-CONR^{13}R^{14}$ both R^{13} and R^{14} are methyl).

Embodiment No. 99 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 70 and substituent B is as defined in Embodiment No. 57.

Embodiment No. 100 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 70 and substituent B is as defined in Embodiment No. 58.

Embodiment No. 101 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 70 and substituent B is as defined in Embodiment No. 59.

Embodiment No. 102 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 71 and substituent B is as defined in Embodiment No. 57.

Embodiment No. 103 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 71 and substituent B is as defined in Embodiment No. 58.

Embodiment No. 104 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 71 and substituent B is as defined in Embodiment No. 59.

Embodiment No. 105 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 72 and substituent B is as defined in Embodiment No. 57.

Embodiment No. 106 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 72 and substituent B is as defined in Embodiment No. 58.

Embodiment No. 107 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 72 and substituent B is as defined in Embodiment No. 59.

Embodiment No. 108 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 73 and substituent B is as defined in Embodiment No. 57.

Embodiment No. 109 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 73 and substituent B is as defined in Embodiment No. 58.

Embodiment No. 110 is directed to compounds of formula IA wherein substituent A is as defined in Embodiment No. 73 and substituent B is as defined in Embodiment No. 59.

Embodiment No. 111 is directed to any one of the Embodiment Nos. 1 to 110 wherein the compound of formula IA is a pharmaceutically acceptable salt.

Embodiment No. 112 is directed to any one of the Embodiment Nos. 1 to 110 wherein the compound of formula IA is a sodium salt.

Embodiment No. 113 is directed to any one of the Embodiment Nos. 1 to 110 wherein the compound of formula IA is a calcium salt.

Embodiment No. 114 is directed to a pharmaceutically acceptable salt of any one of the representative compounds of this invention that are described below.

Embodiment No. 115 is directed to a sodium salt of any one of the representative compounds described below.

Embodiment No. 116 is directed to a calcium salt of any one of the representative compounds described below.

Embodiment No. 117 is directed to a pharmaceutical composition comprising at least one (e.g., 1 to 3, usually 1) compound of formula IA as described in any one of Embodiment Nos. 1 to 116 in combination with a pharmaceutically acceptable carrier (or diluent). When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 118 is directed to a method of treating any one of the diseases or conditions described herein (i.e., the chemokine mediated diseases or conditions) comprising administering to a patient in need of such treatment an effective amount (e.g., a therapeutically effective amount) of a compound of formula IA as described in any one of the Embodiment Nos. 1 to 116.

Embodiment No. 119 is directed to a method of treating any one of the diseases or conditions described herein (i.e., the chemokine mediated diseases or conditions) comprising administering to a patient in need of such treatment an effective amount (e.g., a therapeutically effective amount) of the pharmaceutical composition described in Embodiment No. 117.

Embodiment No. 120 is directed to a method of treating rheumatoid arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 121 is directed to a method of treating rheumatoid arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment No. 117.

Embodiment No. 122 is directed to a method of treating rheumatoid arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually 1) compound from any of

Embodiment Nos. 1 to 116 in combination with at least one compound selected from the group consisting of COX-2 inhibitors, COX inhibitors, immunosuppressives (e.g., methotrexate, cyclosporin, leflunimide and sulfasalazine), steroids (e.g., betamethasone, cortisone and dexamethasone), PDE IV inhibitors, anti-TNF-α compounds, MMP inhibitors, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, and other classes of compounds indicated for the treatment of rheumatoid arthritis. When more than one compound of Embodiment Nos. 1 to 116 is used, each compound is independently selected from said Embodiment Numbers.

Embodiment No. 123 is directed to a method of treating rheumatoid arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment 117 in combination with at least one compound selected from the group consisting of COX-2 inhibitors, COX inhibitors, immunosuppressives (e.g., methotrexate, cyclosporin, leflunimide and sulfasalazine), steroids (e.g., betamethasone, cortisone and dexamethasone), PDE IV inhibitors, anti-TNF-α compounds, MMP inhibitors, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, and other classes of compounds indicated for the treatment of rheumatoid arthritis.

Embodiment No. 124 is directed to a method of treating COPD in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 125 is directed to a method of treating COPD in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment 117.

Embodiment No. 126 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 127 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment 117.

Embodiment No. 128 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116, and administering a therapeutically effective amount of at least one medicament selected from the group consisting of NSAIDs, COXIB inhibitors, anti-depressants and anti-convulsants. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 129 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment 117, and administering a therapeutically effective amount of at least one medicament selected from the group consisting of NSAIDs, COXIB inhibitors, anti-depressants and anti-convulsants.

Embodiment No. 130 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116, and administering a therapeutically effective amount of at least one NSAID. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 131 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment 117, and administering a therapeutically effective amount of at least one NSAID.

Embodiment No. 132 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116, and administering a therapeutically effective amount of at least one COXIB inhibitor. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 133 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment 117, and administering a therapeutically effective amount of at least one COXIB inhibitor.

Embodiment No. 134 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116, and administering a therapeutically effective amount of at least one anti-depressant. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 135 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment 117, and administering a therapeutically effective amount of at least one anti-depressant.

Embodiment No. 136 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116, and administering a therapeutically effective amount of at least one anti-convulsant. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 137 is directed to a method of treating pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment 117, and administering a therapeutically effective amount of at least one anti-convusant.

Embodiment No. 138 is directed to a method of treating pain in any one of Embodiment Nos. 128-131 wherein said NSAID is selected from the group consisting of: piroxicam, ketoprofen, naproxen, indomethacin, and ibuprofen.

Embodiment No. 139 is directed to a method of treating pain in any one of Embodiment Nos. 128, 129, 132 and 133 wherein said COXIB inhibitor is selected from the group consisting of: rofecoxib and celecoxib.

Embodiment No. 140 is directed to a method of treating pain in any one of Embodiment Nos. 128, 129, 134 and 135 wherein said anti-depressant is selected from the group consisting of: amitriptyline and nortriptyline.

Embodiment No. 141 is directed to a method of treating pain in any one of Embodiment Nos. 128, 129, 136 and 137 wherein said anti-convulsant is selected from the group consisting of: gabapentin, carbamazepine, pregabalin, and lamotragine.

Embodiment No. 142 is directed to a method of treating pain described by any one of Embodiment Nos. 126 to 141 wherein the pain treated is pain associated with: allodynia, ankylosing spondylitis, appendicitis, autoimmune disorders, bacterial infections, Behcet's syndrome, broken bones, bronchitis, burns, bursitis, cancer including metastatic cancer, candidiasis, cardiovascular conditions, casualgia, chemical injury, childbirth (e.g., labor), chronic regional neuropathies, Crohn's disease, colorectal cancer, connective tissue injuries, conjunctivitis, COPD, decreased intracranial pressure, dental procedures, dermatitis, diabetes, diabetic neuropathy, dysesthesia, dysmenorrhea, eczema, emphysema, fever, fibromyalgia, gastric ulcer, gastritis, giant cell arteritis, gingivitis, gout, gouty arthritis, headache, headache pain resulting from lumbar puncture, headaches including migraine headache, herpes simplex virus infections, HIV, Hodgkin's disease, hyperalgesia, hypersensitivity, inflammatory bowel disease, increased intracranial pressure, irritable bowel syndrome, ischemia, juvenile arthritis, kidney stones, lumbar spondylanhrosis, lower back, upper back and lumbrosacral conditions, lumbar spondylarthrosis, menstrual cramps, migraines, minor injuries, multiple sclerosis, myasthenia gravis, myocarditis, muscle strains, musculoskeletal conditions, myocardial ischemia, nephritic syndrome, nerve root avulsion, neuritis, nutritional deficiency, ocular and corneal conditions, ocular photophobia, ophthalmic diseases, osteoarthritis, otic surgery, otitis externa, otitis media, periarteritis nodosa, peripheral neuropathies, phantom limb pain, polymyositis, post-herpetic neuralgia, post-operative/surgical recovery, post-thoracotomy, psoriatic arthritis, pulmonary fibrosis, pulmonary edema, radiculopathy, reactive arthritis, reflex sympathetic dystrophy, retinitis, retinopathies, rheumatic fever, rheumatoid arthritis, sarcoidosis, sciatica, scleroderma, sickle cell anemia, sinus headaches, sinusitis, spinal cord injury, spondyloarthropathies, sprains, stroke, swimmer's ear, tendonitis, tension headaches, thalamic syndrome, thrombosis, thyroiditis, toxins, traumatic injury, trigeminal neuralgia, ulcerative colitis, urogenital conditions, uveitis, vaginitis, vascular diseases, vasculitis, viral infections and/or wound healing.

Embodiment No. 143 is directed to a method of treating acute pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 144 is directed to a method of treating acute pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment No. 117.

Embodiment No. 145 is directed to a method of treating acute inflammatory pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 146 is directed to a method of treating acute inflammatory pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment No. 117.

Embodiment No. 147 is directed to a method of treating chronic inflammatory pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 148 is directed to a method of treating chronic inflammatory pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment No. 117.

Embodiment No. 149 is directed to a method of treating neuropathic pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 150 is directed to a method of treating neuropathic pain in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment No. 117.

Embodiment No. 151 is directed to a method of treating pain as described in any of Embodiment Nos. 128 to 141 wherein said pain is acute pain.

Embodiment No. 152 is directed to a method of treating pain as described in any of Embodiment Nos. 128 to 141 wherein said pain is acute inflammatory pain.

Embodiment No. 153 is directed to a method of treating pain as described in any of Embodiment Nos. 128 to 141 wherein said pain is chronic inflammatory pain.

Embodiment No. 154 is directed to a method of treating pain as described in any of Embodiment Nos. 128 to 141 wherein said pain is neuropathic pain.

Embodiment No. 155 is directed to a method of treating arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 156 is directed to a method of treating arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment No. 117.

Embodiment No. 157 is directed to a method of treating osteoarthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound from any of Embodiment Nos. 1 to 116. When more than one compound is used each compound is independently selected from the group consisting of Embodiment Nos. 1 to 116.

Embodiment No. 158 is directed to a method of treating osteoarthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition described in Embodiment No. 117.

Representative compounds include the final compounds of Examples 1, 2-4, 6-35, 100-105, 107, 108, 110, 111, 112, 114-116, 118-132, 134-145, 148, 180, 182,

183, 185, 186, 188, 300-389, 500-639, 700-787, and 900-987, or the pharmaceutically acceptable salts thereof.

Preferred compounds of the invention are the final compounds of Examples 1, 6, 8, 110, 111, 112, 114, 122, 120, 123, 124, 127, 128, 129, 130, 131, 139, 142, 144, 145, 300, 305, 306, 307, 313, 316, 317, 318, 323, 324, 327, 328, 329, 330, 334, 335, 338, 339, 340, 349, 350, 351, 359, 360, 361, 362, 364, 370, 372, 373, 374, 381, 544, 545, 546, 548, 558, 559, 560, 561, 562, 572, 573, 587,601,616, 708,718, 719, 721, 732, 754, 774, 784, 928, 930, 931, 939, 942, 941, 950, 952, or the pharmaceutically acceptable salts thereof.

More preferred compounds of the invention are the final compounds of Examples 1, 6, 8, 110, 111, 112, 114, 122, 120, 123, 124, 129, 130, 131, 142, 144, 145, 300, 305, 306, 307, 313, 316, 317, 318, 323, 324, 327, 328, 329, 334, 335, 338, 339, 340, 349, 350, 351, 359, 360, 361, 362, 364, 370, 372, 373, 374, 381, 544, 545, 546, 548, 558, 559, 560, 561, 562, 572, 708,718, 719, 721, 732, 754, 774, 784, 928, 930, 931, 939, 942, 941, 950, 952, or the pharmaceutically acceptable salts thereof.

Most preferred compounds of the invention are the final compounds of Examples 1, 6, 8, 114, 120, 123, 129, 131, 300, 305, 306, 307, 316, 317, 318, 323, 327, 328, 329, 334, 359, 360, 361, 370, 372, 373, 374, 544, 545, 546, 548, 558, 559, 560, 561, 562, 928, 930, 931, 939, 942, 941, 950, 952, or the pharmaceutically acceptable salts thereof.

Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers, diastereoisomers and atropisomers). The invention contemplates all such stereoisomers both in pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional methods.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the

present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

Certain compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of formula IA can exist in unsolvated and solvated forms (or compounds of formula IA can optionally be converted to a solvate), including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such

as water, ethanol and the like, are equivalent to the unsolvated forms for the purposes of this invention.

Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

This invention also includes Prodrugs of the novel compounds of this invention. The term "prodrug," as used herein, represents compounds that are rapidly transformed *in vivo* to the parent compound (i.e., a compound of formula IA), for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

This invention also includes the compounds of this invention in isolated and pure form.

This invention also includes polymorphic forms of the compounds of this invention. The polymorphic forms of the compounds of formula IA, and of the salts, solvates and prodrugs of the compounds of formula IA, are intended to be included in the present invention.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets,

powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD..

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal composition can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For

convenience, the total dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000 mg/day, in two to four divided doses.

Classes of compounds that can be used as the chemotherapeutic agent (antineoplastic agent) include: alkylating agents, antimetabolites, natural products and their derivatives, hormones and steroids (including synthetic analogs), and synthetics. Examples of compounds within these classes are given below.

Alkylating agents (including nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): Uracil mustard, Chlormethine, Cyclophosphamide (Cytoxan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Antimetabolites (including folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine.

Natural products and their derivatives (including vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins): Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, paclitaxel (paclitaxel is commercially available as Taxol® and is described in more detail below in the subsection entitled “Microtubule Affecting Agents”), Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, Interferons (especially IFN-a), Etoposide, and Teniposide.

Hormones and steroids (including synthetic analogs): 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Tamoxifen, Methylprednisolone, Methyl-testosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone,

Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, Zoladex.

Synthetics (including inorganic complexes such as platinum coordination complexes): Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, and Hexamethylmelamine.

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., Physician's Desk Reference, 57th edition, 2003, Thompson PDR at Montvale, NJ 07645-1742, USA; the disclosure of which is incorporated herein by reference thereto.

As used herein, a microtubule affecting agent is a compound that interferes with cellular mitosis, *i.e.,* having an anti-mitotic effect, by affecting microtubule formation and/or action. Such agents can be, for instance, microtubule stabilizing agents or agents that disrupt microtubule formation.

Microtubule affecting agents useful in the invention are well known to those of skill in the art and include, but are not limited to allocolchicine (NSC 406042), Halichondrin B (NSC 609395), colchicine (NSC 757), colchicine derivatives (e.g., NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin (NSC 332598), paclitaxel (Taxol®, NSC 125973), Taxol® derivatives (*e.g.,* derivatives (*e.g.,* NSC 608832), thiocolchicine (NSC 361792), trityl cysteine (NSC 83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574), epothilone A, epothilone, and discodermolide (*see* Service, (1996) *Science*, 274:2009) estramustine, nocodazole, MAP4, and the like. Examples of such agents are also described in the scientific and patent literature, see, *e.g.,* Bulinski (1997) *J. Cell Sci.* 110:3055-3064; Panda (1997) *Proc. Natl. Acad. Sci.* USA 94:10560-10564; Muhlradt (1997) Cancer Res. 57:3344-3346; Nicolaou (1997) *Nature* 387:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; Panda (1996) *J. Biol. Chem*. 271:29807-29812.

Particularly preferred agents are compounds with paclitaxel-like activity. These include, but are not limited to paclitaxel and paclitaxel derivatives (paclitaxel-like compounds) and analogues. Paclitaxel and its derivatives are available commercially. In addition, methods of making paclitaxel and paclitaxel derivatives and analogues are

well known to those of skill in the art (*see, e.g.,* U.S. Patent Nos: 5,569,729; 5,565,478; 5,530,020; 5,527,924; 5,508,447; 5,489,589; 5,488,116; 5,484,809; 5,478,854; 5,478,736; 5,475,120; 5,468,769; 5,461,169; 5,440,057; 5,422,364; 5,411,984; 5,405,972; and 5,296,506).

More specifically, the term "paclitaxel" as used herein refers to the drug commercially available as Taxol® (NSC number: 125973). Taxol® inhibits eukaryotic cell replication by enhancing polymerization of tubulin moieties into stabilized microtubule bundles that are unable to reorganize into the proper structures for mitosis. Of the many available chemotherapeutic drugs, paclitaxel has generated interest because of its efficacy in clinical trials against drug-refractory tumors, including ovarian and mammary gland tumors (Hawkins (1992) *Oncology*, 6: 17-23, Horwitz (1992) *Trends Pharmacol. Sci.* 13: 134-146, Rowinsky (1990) *J. Natl. Canc. Inst.* 82: 1247-1259).

Additional microtubule affecting agents can be assessed using one of many such assays known in the art, *e.g.,* a semiautomated assay which measures the tubulin-polymerizing activity of paclitaxel analogs in combination with a cellular assay to measure the potential of these compounds to block cells in mitosis (see *Lopes* (1997) *Cancer Chemother. Pharmacol.* 41:37-47).

Generally, activity of a test compound is determined by contacting a cell with that compound and determining whether or not the cell cycle is disrupted, in particular, through the inhibition of a mitotic event. Such inhibition may be mediated by disruption of the mitotic apparatus, *e.g.,* disruption of normal spindle formation. Cells in which mitosis is interrupted may be characterized by altered morphology (*e.g.,* microtubule compaction, increased chromosome number, etc.).

Compounds with possible tubulin polymerization activity can be screened *in vitro*. In a preferred embodiment, the compounds are screened against cultured WR21 cells (derived from line 69-2 wap-ras mice) for inhibition of proliferation and/or for altered cellular morphology, in particular for microtubule compaction. *In vivo* screening of positive-testing compounds can then be performed using nude mice bearing the WR21 tumor cells. Detailed protocols for this screening method are described by Porter (1995) *Lab. Anim. Sci.,* 45(2):145-150.

Other methods of screening compounds for desired activity are well known to those of skill in the art. Typically such assays involve assays for inhibition of

microtubule assembly and/or disassembly. Assays for microtubule assembly are described, for example, by Gaskin *et al.* (1974) *J. Molec. Biol.,* 89: 737-758. U.S. Patent No. 5,569,720 also provides *in vitro* and *in vivo* assays for compounds with paclitaxel-like activity.

Methods for the safe and effective administration of the above-mentioned microtubule affecting agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated herein by reference thereto.

The amount and frequency of administration of the compounds of formula IA and the chemotherapeutic agents and/or radiation therapy will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the disease being treated. A dosage regimen of the compound of formula IA can be oral administration of from 10 mg to 2000 mg/day, preferably 10 to 1000 mg/day, more preferably 50 to 600 mg/day, in two to four (preferably two) divided doses, to block tumor growth. Intermittant therapy (*e.g.*, one week out of three weeks or three out of four weeks) may also be used.

The chemotherapeutic agent and/or radiation therapy can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent and/or radiation therapy can be varied depending on the disease being treated and the known effects of the chemotherapeutic agent and/or radiation therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents (i.e., antineoplastic agent or radiation) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

In the methods of this invention, a compound of formula IA is administered concurrently or sequentially with a chemotherapeutic agent and/or radiation. Thus, it is not necessary that, for example, the chemotherapeutic agent and the compound of

formula IA, or the radiation and the compound of formula IA, should be administered simultaneously or essentially simultaneously. The advantage of a simultaneous or essentially simultaneous administration is well within the determination of the skilled clinician.

Also, in general, the compound of formula IA and the chemotherapeutic agent do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the compound of formula IA may be administered orally to generate and maintain good blood levels thereof, while the chemotherapeutic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician .

The particular choice of a compound of formula IA, and chemo-therapeutic agent and/or radiation will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the appropriate treatment protocol.

The compound of formula IA, and chemotherapeutic agent and/or radiation may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the proliferative disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (i.e., within a single treatment protocol) with the compound of formula or IA.

If the compound of formula IA, and the chemotherapeutic agent and/or radiation are not administered simultaneously or essentially simultaneously, then the initial order of administration of the compound of formula IA, and the chemotherapeutic agent and/or radiation, may not be important. Thus, the compound of formula IA may be administered first, followed by the administration of the chemotherapeutic agent and/or radiation; or the chemo-therapeutic agent and/or radiation may be administered first, followed by the administration of the compound of formula IA . This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of

repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient.

For example, the chemotherapeutic agent and/or radiation may be administered first, especially if it is a cytotoxic agent, and then the treatment continued with the administration of the compound of formula IA followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or radiation, and so on until the treatment protocol is complete.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (therapeutic agent--*i.e.*, the compound of formula IA, chemotherapeutic agent or radiation) of the treatment according to the individual patient's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radio-logical studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

BIOLOGICAL EXAMPLES

The compounds of the present invention are useful in the treatment of CXC-chemokine mediated conditions and diseases. This utility is manifested in their ability to inhibit IL-8 and GRO-α chemokine as demonstrated by the following *in vitro* assays.

Receptor Binding Assays:

CXCR1 SPA Assay

For each well of a 96 well plate, a reaction mixture of 10 μg hCXCR1-CHO overexpressing membranes (Biosignal) and 200 μg/well WGA-SPA beads (Amersham) in 100 μl was prepared in CXCR1 assay buffer (25 mM HEPES, pH 7.8, 2 mM $CaCl_2$, 1mM $MgCl_2$, 125 mM NaCl, 0.1% BSA) (Sigma). A 0.4 nM stock of

ligand, [125I]-IL-8 (NEN) was prepared in the CXCR1 assay buffer. 20X stock solutions of test compounds were prepared in DMSO (Sigma). A 6 X stock solution of IL-8 (R&D) was prepared in CXCR2 assay buffer. The above solutions were added to a 96-well assay plate (PerkinElmer) as follows: 10 μl test compound or DMSO, 40 μl CXCR1 assay buffer or IL-8 stock, 100 μl of reaction mixture, 50 μl of ligand stock (Final [Ligand] = 0.1 nM). The assay plates were shaken for 5 minutes on plate shaker, then incubated for 8 hours before cpm/well were determined in Microbeta Trilux counter (PerkinElmer). % Inhibition of Total binding-NSB (250 nM IL-8) was determined for IC_{50} values.

Alternative CXCR1 SPA Assay

Protocol using CXCR1-expressing membranes from Biosignal Packard

For each 50 μl reaction, a working stock of 0.25 μg/μl hCXCR1-CHO over-expressing membranes with a specific activity of 0.05 pmol/mg (Biosignal Packard) and 25 μg/μl WGA-SPA beads (Perkin Elmer Life Sciences) was prepared in CXCR1 assay buffer (25 mM HEPES, pH 7.8, 0.1 mM $CaCl_2$, 1mM $MgCl_2$, 100 mM NaCl) (Sigma). This mixture was incubated on ice for 30 minutes and then centrifuged at 2500 rpm for 5 minutes. The beads and membranes were resuspended in CXCR1 assay buffer to the same concentrations as in the original mixture. A 0.125 nM stock of ligand, [^{125}I]-IL-8 (Perkin Elmer Life Sciences), was prepared in the CXCR1 assay buffer. Test compounds were first serially diluted by half-logs in DMSO (Sigma) and then diluted 20-fold in CXCR1 assay buffer. The above solutions were added to a Corning NBS (non-binding surface) 96-well assay plate as follows: 20 μl test compound or 5% DMSO (final [DMSO] = 2%), 20 μl of membranes and SPA bead mixture (Final [membrane] = 5 μg/reaction; Final [SPA bead] = 500 μg/reaction), 10 μl of ligand stock (Final [^{125}I-IL-8] = 0.025 nM). The assay plates were incubated for 4 hours before cpm/well were determined in a Microbeta Trilux counter (Perkin Elmer Life Sciences). IC_{50} values were quantified using nonlinear regression analysis in GraphPad Prism.

Alternative CXCR1 SPA Assay

Protocol using CXCR1-expressing membranes from Euroscreen

For each 50 μl reaction, a working stock of 0.025 μg/μl hCXCR1-CHO over-expressing membranes with a specific activity of 3.47 pmol/mg (Euroscreen) and 5 μg/μl WGA-SPA beads (Perkin Elmer Life Sciences) was prepared in CXCR1 assay buffer (25 mM HEPES, pH 7.8, 2.0 mM $CaCl_2$, 1mM $MgCl_2$, 125 mM NaCl) (Sigma). This mixture was incubated on ice for 5 minutes. A 0.125 nM stock of ligand, [^{125}I]-IL-8 (Perkin Elmer Life Sciences), was prepared in the CXCR1 assay buffer. Test compounds were first serially diluted by half-logs in DMSO (Sigma) and then diluted 13.3-fold in CXCR1 assay buffer. The above solutions were added to a Corning NBS (non-binding surface) 96-well assay plate as follows: 20 μl test compound or 7.5% DMSO (final [DMSO] = 3%), 20 μl of membranes and SPA bead mixture (Final [membrane] = 0.5 μg/reaction; Final [SPA bead] = 100 μg/reaction), 10 μl of ligand stock (Final [^{125}I-IL-8] = 0.025 nM). The assay plates were incubated for 4 hours before cpm/well were determined in a Microbeta Trilux counter (Perkin Elmer Life Sciences). IC_{50} values were quantified using nonlinear regression analysis in GraphPad Prism.

For the CXCR1 assay, the compounds of Examples 1 to 35 had a K_i within the range of 91 nM to 23,000 nM. The compound of Example 6 had a K_i of 91 nM, and the compound of Example 1 had a K_i of 808 nM.

CXCR2 SPA Assay

For each well of a 96 well plate, a reaction mixture of 4 μg hCXCR2-CHO overexpressing membranes (Biosignal) and 200 μg/well WGA-SPA beads (Amersham) in 100 μl was prepared in CXCR2 assay buffer (25 mM HEPES, pH 7.4, 2 mM $CaCl_2$, 1mM $MgCl_2$). A 0.4 nM stock of ligand, [125I]-IL-8 (NEN), was prepared in the CXCR2 assay buffer. 20X stock solutions of test compounds were prepared in DMSO (Sigma). A 6 X stock solution of GRO-α (R&D) was prepared in CXCR2 assay buffer. The above solutions were added to a 96-well assay plate (PerkinElmer or Corning) as follows: 10 μl test compound or DMSO, 40 ul CXCR2 assay buffer or GRO- α stock, 100 μl of reaction mixture, 50 μl of ligand stock (Final [Ligand] = 0.1 nM). When 40 X stock solutions of test compounds in DMSO were prepared, then

the above protocol was used except instead 5 μl test compound or DMSO and 45 μl CXCR2 assay buffer were used. The assay plates were shaken for 5 minutes on a plate shaker, then incubated for 2-8 hours before cpm/well were determined in Microbeta Trilux counter (PerkinElmer). % Inhibition of total binding minus non-specific binding (250 nM Gro-α or 50 μM antagonist) was determined and IC50 values calculated. Compounds of this invention had an IC_{50} of <5μM.

Alternative CXCR2 SPA Assay

Protocol using the CXCR2 50 μl assay

For each 50 μl reaction, a working stock of 0.031 μg/μl hCXCR2-CHO over-expressing membranes with a specific activity of 0.4 pmol/mg (Biosignal Packard) and 2.5 μg/μl WGA-SPA beads (Perkin Elmer Life Sciences) was prepared in CXCR2 assay buffer (25 mM HEPES, pH 7.4, 2.0 mM $CaCl_2$, 1 mM $MgCl_2$) (Sigma). This mixture was incubated on ice for 5 minutes. A 0.50 nM stock of ligand, [^{125}I]-IL-8 (Perkin Elmer Life Sciences), was prepared in the CXCR2 assay buffer. Test compounds were first serially diluted by half-logs in DMSO (Sigma) and then diluted 13.3-fold in CXCR2 assay buffer. The above solutions were added to a Corning NBS (non-binding surface) 96-well assay plate as follows: 20 μl test compound or 7.5% DMSO (final [DMSO] = 3%), 20 μl of membranes and SPA bead mixture (final [membrane] = 0.625 μg/reaction; final [SPA bead] = 50 μg/reaction), 10 μl of ligand stock (final [^{125}I-IL-8] = 0.10 nM). The assay plates were incubated for 2 hours before cpm/well were determined in a Microbeta Trilux counter (Perkin Elmer Life Sciences). IC_{50} values were quantified using nonlinear regression analysis in GraphPad Prism.

Alternative CXCR2 SPA Assay

Protocol using the CXCR2 200 μl assay

For each 200 μl reaction, a working stock of 0.02 μg/μl hCXCR2-CHO over-expressing membranes with a specific activity of 0.6 pmol/mg (Biosignal Packard) and 2 μg/μl WGA-SPA beads (Perkin Elmer Life Sciences) was prepared in CXCR2 assay buffer (25 mM HEPES, pH 7.4, 2.0 mM $CaCl_2$, 1 mM $MgCl_2$) (Sigma). This mixture was incubated on ice for 5 minutes. A 0.40 nM stock of ligand, [^{125}I]-IL-8 (Perkin Elmer Life Sciences), was prepared in the CXCR2 assay buffer. Test compounds were first serially diluted by half-logs in DMSO (Sigma) and then diluted 20-fold in

CXCR2 assay buffer. The above solutions were added to a Corning NBS (non-binding surface) 96-well assay plate as follows: 50 μl test compound or 10% DMSO (final [DMSO] = 2.5%), 100 μl of membranes and SPA bead mixture (final [membrane] = 2 μg/reaction; final [SPA bead] = 200 μg/reaction), 50 μl of ligand stock (final [^{125}I-IL-8] = 0.10 nM). The assay plates were incubated for 2 hours before cpm/well were determined in a Microbeta Trilux counter (Perkin Elmer Life Sciences). IC_{50} values were quantified using nonlinear regression analysis in GraphPad Prism.

For the CXCR2 assay, the compounds of Examples 1 to 35 had a K_i within the range of 7.5 nM to 1,900 nM. The compound of Example 6 had a K_i of 14 nM, and the compound of Example 1 had a K_i of 28 nM.

Calcium Fluorescence Assay (FLIPR)

HEK 293 cells stably transfected with hCXCR2 and Gαι/q were plated at 10,000 cells per well in a Poly-D-Lysine Black/Clear plate (Becton Dickinson) and incubated 48 hours at 5% CO_2, 37°C. The cultures were then incubated with 4 mM fluo-4, AM (Molecular Probes) in Dye Loading Buffer (1% FBS, HBSS w. Ca & Mg, 20 mM HEPES (Cellgro), 2.5 mM Probenicid (Sigma) for 1 hour. The cultures were washed with wash buffer (HBSS w Ca, & Mg, 20 mM HEPES, Probenicid (2.5 mM)) three times, then 100 μl/well wash buffer was added.

During incubation, compounds were prepared as 4X stocks in 0.4% DMSO (Sigma) and wash buffer and added to their respective wells in the first addition plate. IL-8 or GRO-α (R&D Systems) concentrations were prepared 4X in wash buffer + 0.1% BSA and added to their respective wells in second addition plate.

Culture plate and both addition plates were then placed in the FLIPR imaging system to determine change in calcium fluorescence upon addition of compound and then ligand. Briefly, 50 μl of compound solutions or DMSO solution was added to respective wells and change in calcium fluorescence measured by the FLIPR for 1 minute. After a 3 minute incubation within the instrument, 50 μl of ligand was then added and the change in calcium fluorescence measured by the FLIPR instrument for I minute. The area under each stimulation curve was determined and values used to determine % Stimulation by compound (agonist) and % Inhibition of Total Calcium response to ligand (0.3 nM IL-8 or GRO-α) for IC50 values of the test compounds.

Chemotaxis assays for 293-CXCR2

A chemotaxis assay is setup using Fluorblok inserts (Falcon) for 293-CXCR2 cells (HEK-293 cells overexpressing human CXCR2). The standard protocol used at present is as follows:

1. Inserts are coated with collagenIV (2ug/ml) for 2 hrs at 37°C.
2. The collagen is removed and inserts are allowed to air dry overnight.
3. Cells are labeled with 10uM calcein AM (Molecular Probes) for 2 hrs. Labeling is done in complete media with 2% FBS.
4. Dilutions of compound are made in minimal media (0.1% BSA) and placed inside the insert which is positioned inside the well of a 24 well plate. Within the well is IL-8 at a concentration of 0.25nM in minimal media. Cells are washed and resuspended in minimal media and placed inside the insert at a concentration of 50,000 cells per insert.
5. Plate is incubated for 2hrs and inserts are removed and placed in a new 24 well. Fluorescence is detected at excitation=485 nM and emission=530 nM.

Cytotoxicity Assays

A cytotoxicity assay for CXCR2 compounds is conducted on 293-CXCR2 cells. Concentrations of compounds are tested for toxicity at high concentrations to determine if they may be used for further evaluation in binding and cell based assays. The protocol is as follows:

1. 293-CXCR2 cells are plated overnight at a concentration of 5000 cells per well in complete media.
2. Dilutions of compound are made in minimal media w/0.1% BSA. Complete media is poured off and the dilutions of compound are added. Plates are incubated for 4, 24 and 48hrs. Cells are labeled with 10uM calcein AM for 15 minutes to determine cell viability. Detection method is the same as above.

Soft Agar Assay

10,000 SKMEL-5 cells/well are placed in a mixture of 1.2% agar and complete media with various dilutions of compound. Final concentration of agar is 0.6%. After 21 days viable cell colonies are stained with a solution of MTT (1mg/ml in PBS). Plates are then scanned to determine colony number and size. IC_{50} is determined by comparing total area vs. compound concentration.

CCR7 membrane preparation.

Ba/F3-CCR7 membranes were prepared as previously described (Hipkin et al., *J. Biol. Chem.*, 272, 1997, 13869-76). Cells were pelleted by centrifugation, incubated in homogenization buffer (10 mM Tris-HCl, 5 mM EDTA, 3 mM EGTA, pH 7.6) and 1 μM PMSF for 30 min. on ice. The cells were then lysed with a Dounce homogenizer using stirrer type RZR3 polytron homogenizer (Caframo, Wiarton, Ont.) with 12 strokes at 900 RPM. The intact cells and nuclei were removed by centrifugation at 500Xg for 5 min. The cell membranes in the supernatant were then pelleted by centrifugation at 100,000Xg for 30 min. The membranes were then resuspended in glygly buffer (20 mM glycylglycine, 1 mM $MgCl_2$, 250 mM sucrose, pH 7.2), aliquoted, quick frozen and stored at -80°C.

CCR7 [^{35}S]GTPγS exchange assay.

The exchange of guanosine 5'-[γ–^{35}S]triphospate ([^{35}S]GTPγS, triethylammonium salt; specific activity = 1250 Ci/mmol; NEN Boston, MA) was measured using a scintillation proximity assay (SPA) as previously described (Cox, et. al., *Mol. Pharmacol.,* 59, 2001, 707-15). For each assay point, 2 μg of membrane was preincubated for 30 min at room temperature with 200 μg wheat germ agglutinin-coated SPA beads (WGA-SPA; Amersham, Arlington Heights, IL) in SPA binding buffer (50 mM HEPES, 10 mM $MgCl_2$, 1 mM EDTA, 100 mM NaCl, 0.1% BSA, pH 7.6). The beads and membranes were transferred to a 96-well Isoplate (Wallac, Gaithersburg, MD) and incubated with 10 μM guanosine 5'-diphosphate (GDP) in the presence or absence of 2 nM MIP-3β and/or compounds for 60 min at room temperature. The incubation continued for another 60 min. following the addition of 0.1 nM [^{35}S]GTPγS. Membrane-bound [^{35}S]GTPγS was measured using a 1450 Microbeta Trilux counter (Wallac, Gaithersburg, MD).

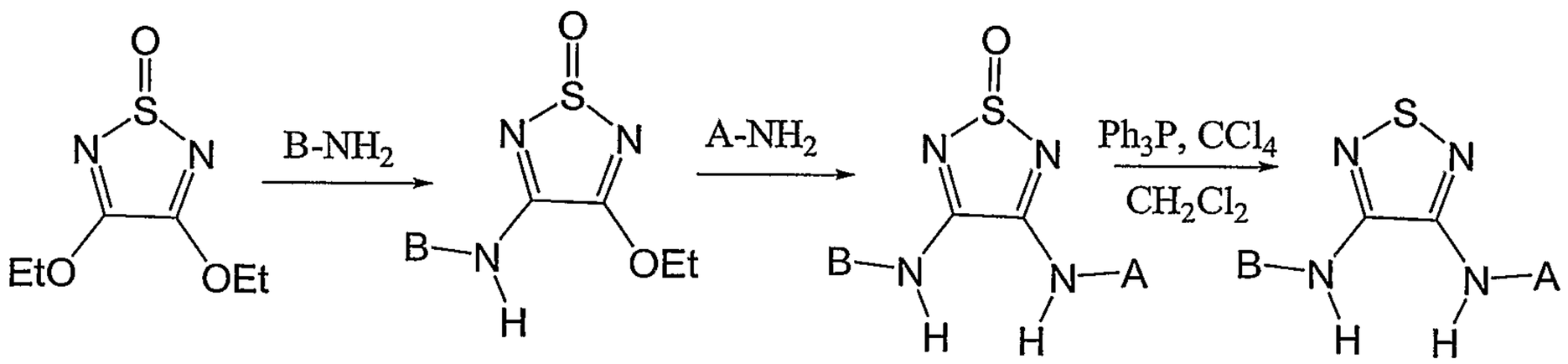
The compounds of Examples 1 to 35 had an EC_{50} within the range of 22 nM to 120μM. The compound of Example 6 had an EC_{50} of 22 nM, and the compound of Example 3 had an EC_{50} of 880 nM.

Rat Carrageenan-Induced Thermal Hyperalgesia

Male Sprague-Dawley rats (Charles River Laboratories; 150-200gm) can be maintained under normal housing and lighting conditions, with food and water supplied *ad libitum*. Each animal can be tested for its baseline paw withdrawal response to a heat source by placement of the animal into a plantar testing unit (Ugo Basile, Italy), in which a light source is moved under its paw and the time of withdrawal is measured. The animals can then be dosed orally with a compound of this invention, and then can be injected intraplantarly with 2-3 mg lambda carrageenan (FMC Colloids) in 100 ul of saline while under isofurane anesthesia. Three hours later, the animals can be re-measured for their withdrawal response to the heat source. Plantar tissue can also be analyzed for myeloperoxidase levels as a surrogate for neutrophil infiltration.

Compounds of formula IA may be produced by processes known to those skilled in the art, in the following reaction schemes, and in the preparations and examples below.

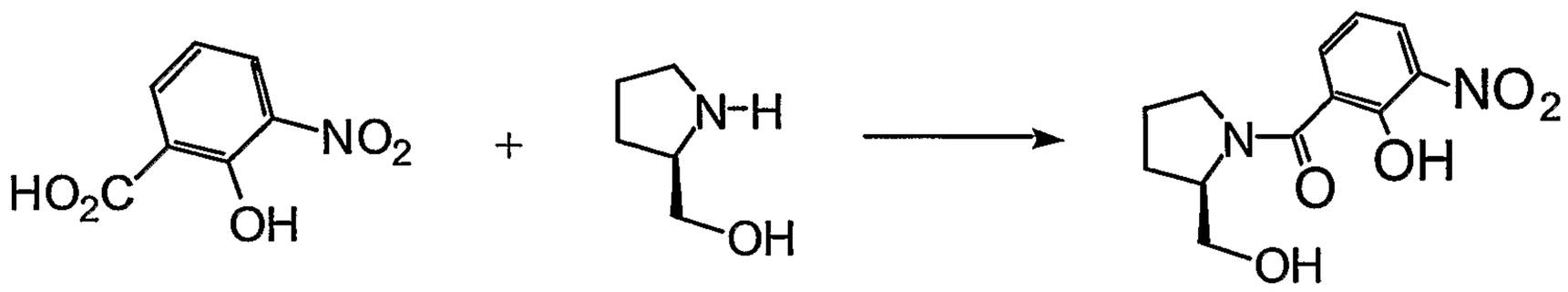
A general procedure for the preparation of compounds of formula IA is as follows:



Compounds of this invention are prepared by condensing an amine (either A-NH_2 or B-NH_2) with the known diethoxy thiadiazole mono-oxide prepared according to the literature to give the monoethoxy thiadizoleoxide intermediate. Subsequent condensation of this intermediate with the commercially available or prepared amine (either A-NH_2 or B-NH_2) provides the desired 3,4-diamino mono oxide intermediate, which is reduced with triphenylphosphine and carbon tetrachloride in dichloromethane to produce the final thiadiazole chemokine antagonist.

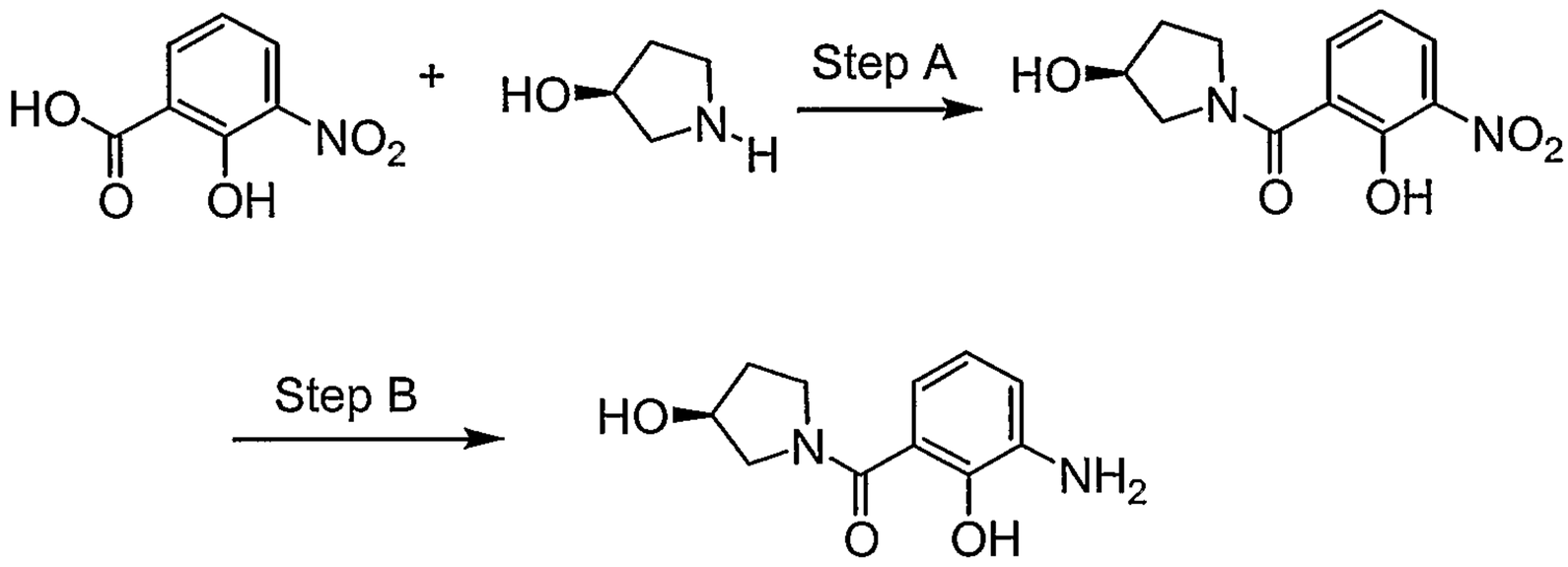
The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures may be apparent to those skilled in the art.

PREPARATIVE EXAMPLE 1



3-Nitrosalicylic acid (500 mg, 2.7 mmol), DCC (563 mg) and ethyl acetate (10 mL) were combined and stirred for 10 min. *(R)* -(-)-2-pyrrolidinemethanol (0.27 mL) was added and the resulting suspension was stirred at room temperature overnight. The solid was filtered and the filtrate washed with 1N NaOH. The aqueous phase was acidified and extracted with EtOAc. The resulting organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by preparative plate chromatography (silica gel, 5% $MeOH/CH_2Cl_2$ saturated with AcOH) gave the product (338 mg, 46%, $MH^+ = 267$).

PREPARATIVE EXAMPLE 2



Step A

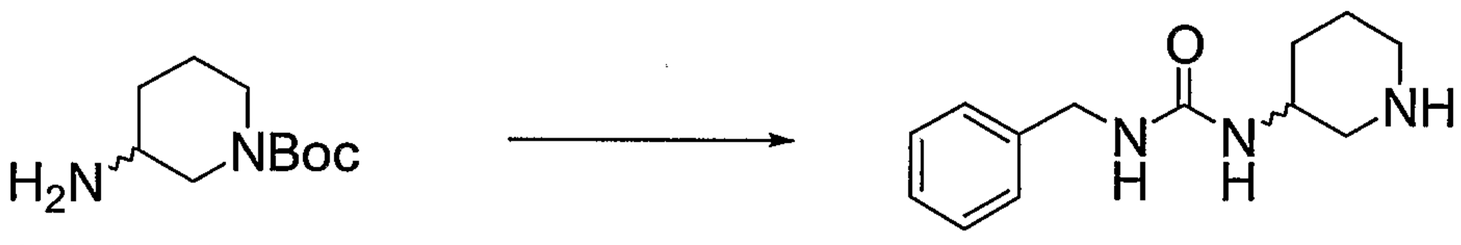
3-Nitrosalicylic acid (9.2 g), bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP, 23 g) and N,N-diisopropylethylamine (DIEA, 26 mL) in anhydrous CH_2Cl_2 (125 mL) were combined and stirred at 25°C for 30 min. *(R)* -(+)-3-pyrrolidinol (8.7 g) in CH_2Cl_2 (25 mL) was added over 25 min and the resulting suspension was stirred at room temperature overnight. The mixture was extracted

with 1M NaOH (aq) and the organic phase was discarded. The aqueous phase was acidified with 1M HCl (aq), extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product (7 g) which was used without further purification.

Step B

The crude product from Step A above was stirred with 10% Pd/C (0.7 g) in MeOH (100 mL) under a hydrogen gas atmosphere overnight. The reaction mixture was filtered through celite, the filtrate concentrated *in vacuo,* and the resulting residue purified by column chromatography (silica gel, 10% MeOH/CH_2Cl_2 saturated with NH_4OH) to give the product (2.5 g, 41%, MH+=223).

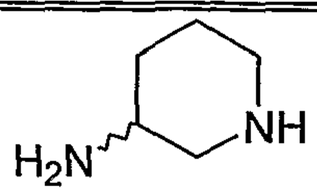
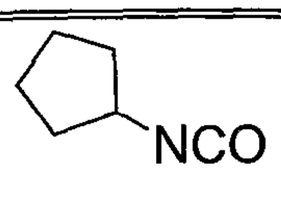
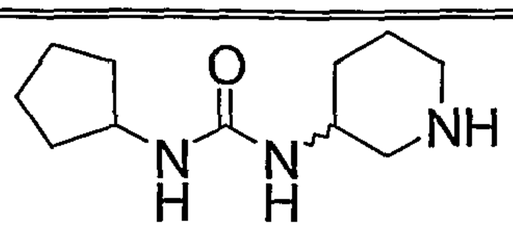
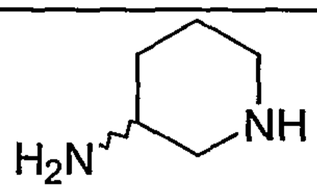
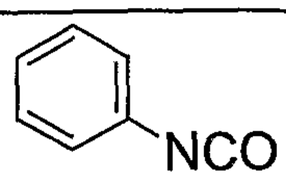
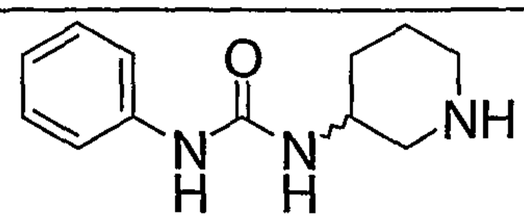
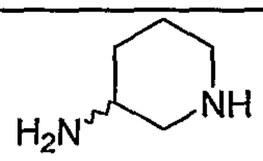
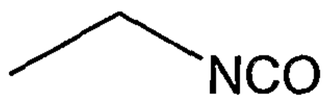
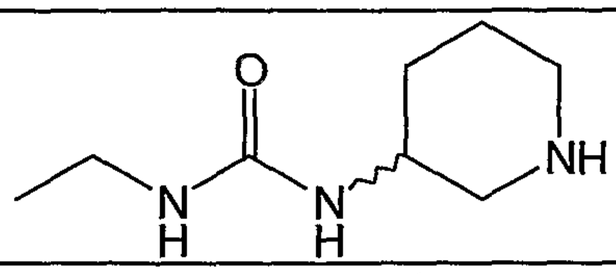
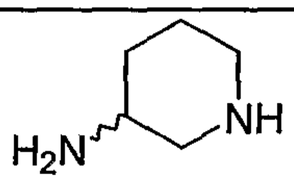
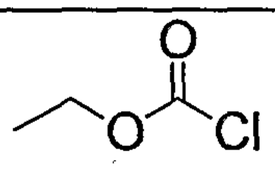
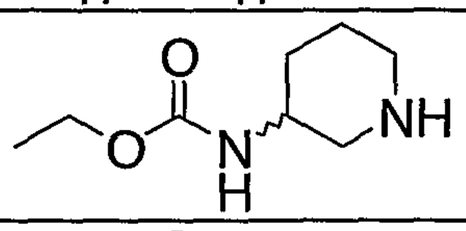
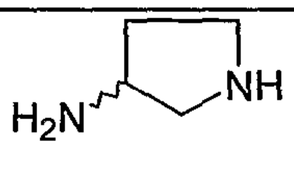
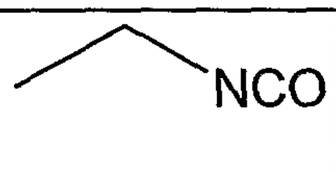
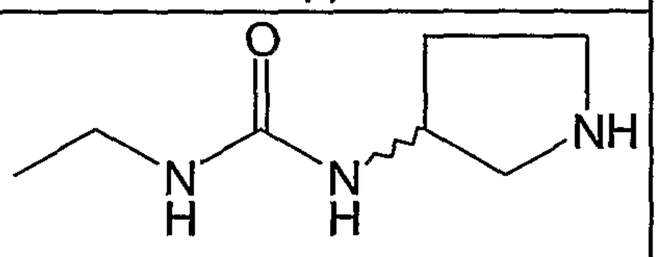
PREPARATIVE EXAMPLE 2.1



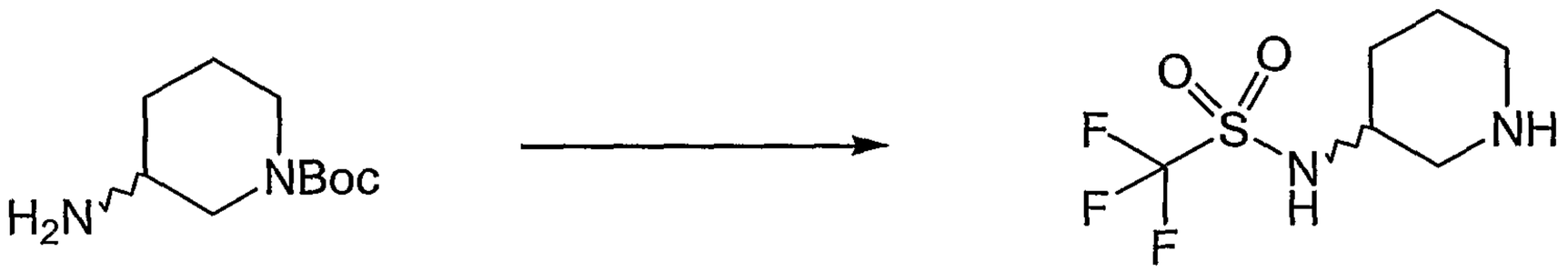
To N-BOC-3-(amino)piperidine (0.5 g) dissolved in CH_2Cl_2 (10 mL) was added benzylisocyanate (3 mmol). After stirring for 2 hrs, amine scavenger resin (1.9 mmol) was added and the mixture was stirred overnight, filtered, the resin back-washed with CH_2Cl_2 and methanol, and the organics concentrated *in vacuo*. Stirring of the crude material in 4*N* HCl/dioxane (40 mL) for 2.5 hrs before concentrating *in vacuo* gave the title compound (41%, MH+=369).

PREPARATIVE EXAMPLE 2.2 – 2.6

Following the procedures set forth in Preparative Example 2.1 but using the isocyanate (or chloroformate) indicated in the Table below, the amines were obtained and used without further purification.

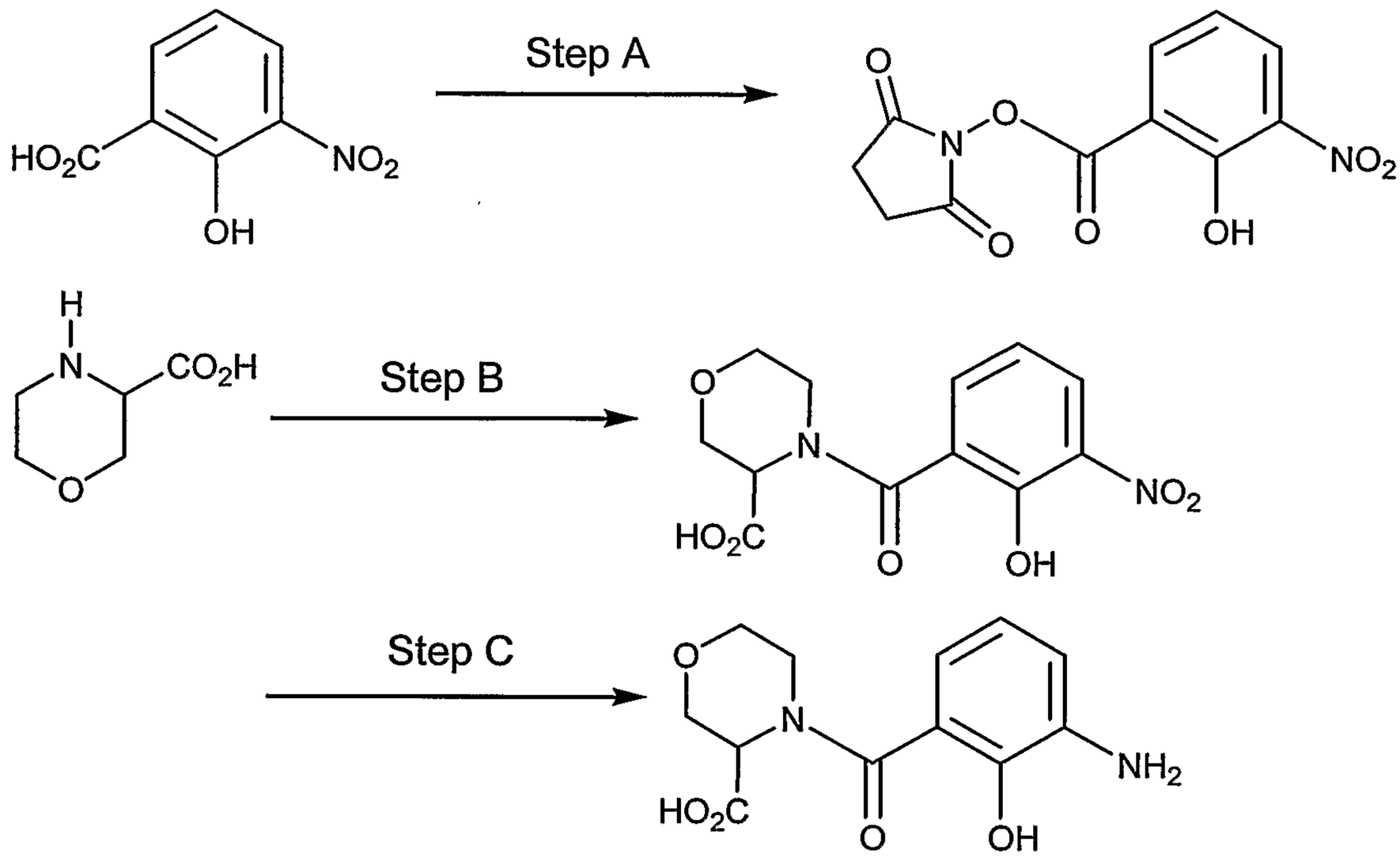
Prep Ex.	Amine	Isocyanate	Amine
2.2			
2.3			
2.4			
2.5			
2.6			

PREPARATIVE EXAMPLE 2.7



To N-BOC-3-(amino)piperidine (5 mmol) dissolved in CH_2Cl_2 (30 mL) was added trifluoromethanesulfonic anhydride (5 mmol) and the mixture was stirred overnight. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 (10 mL) and treated with trifluoroacetic acid (10 mL). After stirring for 2 hr, the mixture was concentrated *in vacuo* to give the title compound (43%, MH+=233.1).

PREPARATIVE EXAMPLE 2.8



Step A

3-Nitrosalicylic acid (5 mmol) and N-hydroxysuccinimide (5 mmol) were added to a solution of 2% DMF/CH_2Cl_2, followed by DCC (5 mmol). After stirring for 2 hr, the mixture was filtered and concentrated *in vacuo* and the residue used directly in Step B.

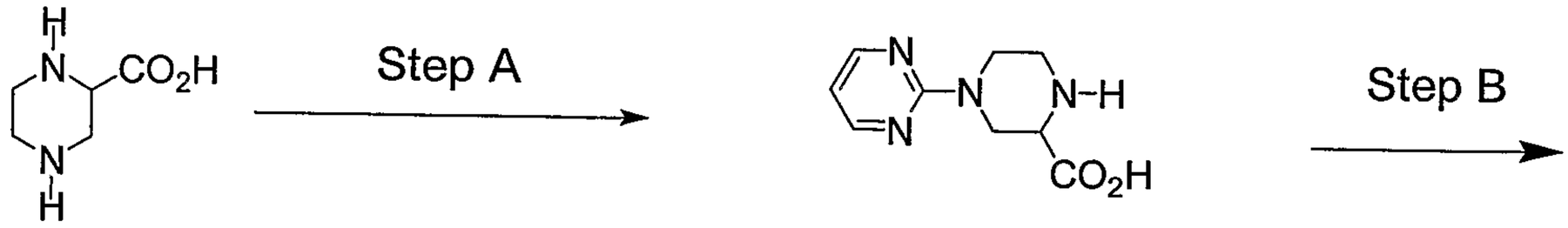
Step B

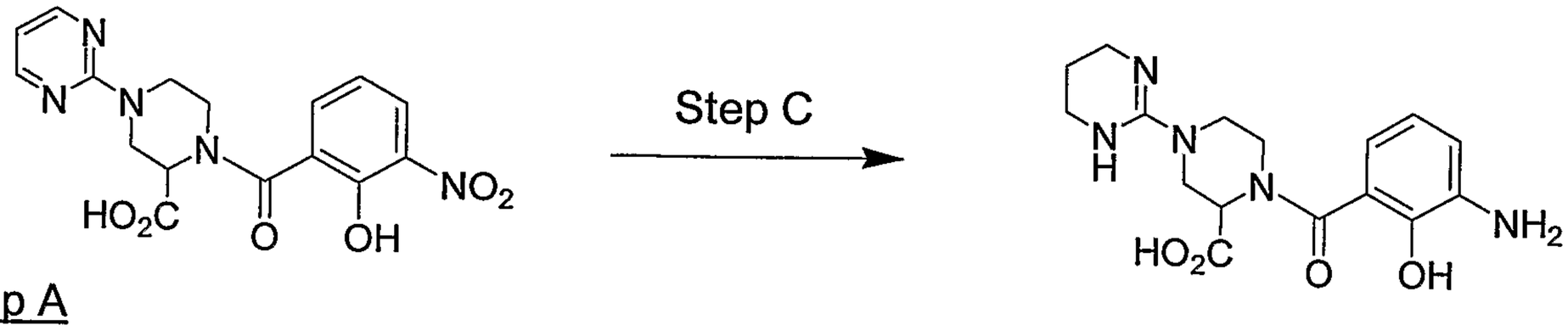
The product from Step A above was suspended in DMF and to this was added morpholino-2-carboxylic acid HCl (5 mmol) in CH_2Cl_2 (10 mL)/DMF (5 mL) and diisopropylethylamine (10 mmol). The mixture was stirred overnight, filtered, basified with 1*N* NaOH (50 mL), washed with CH_2Cl_2, acidified with 5*N* HCl and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the desired compound which was used directly in Step C (MH+=296).

Step C

Following a similar procedure as in Preparative Example 2 Step B, but using the product from Step B above, the title compound was obtained (23%, MH+=267).

PREPARATIVE EXAMPLE 2.9





Step A

2-Piperazinecarboxylic acid and 2-chloro-1,3-pyrimidine were stirred with triethylamine and MeOH. After stirring overnight at reflux, the mixture was filtered and concentrated *in vacuo* to give the desired compound which was used directly in Step B (MH+ = 209).

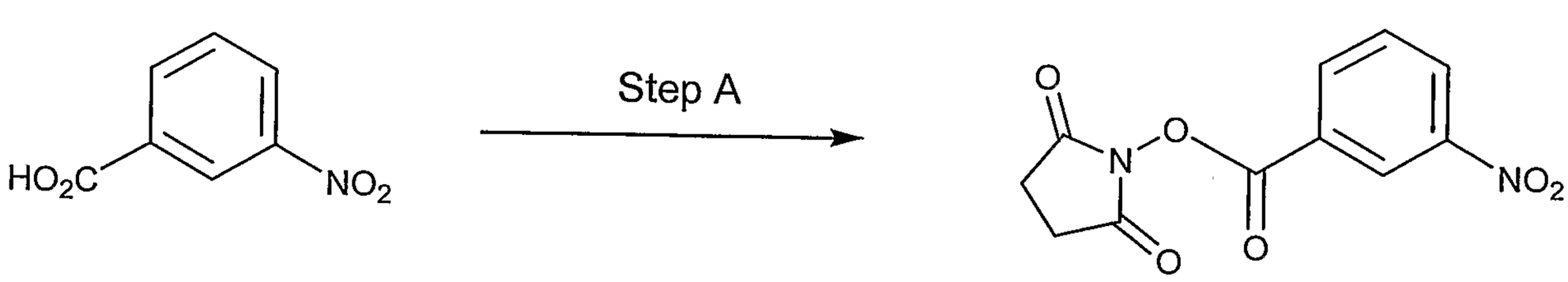
Step B

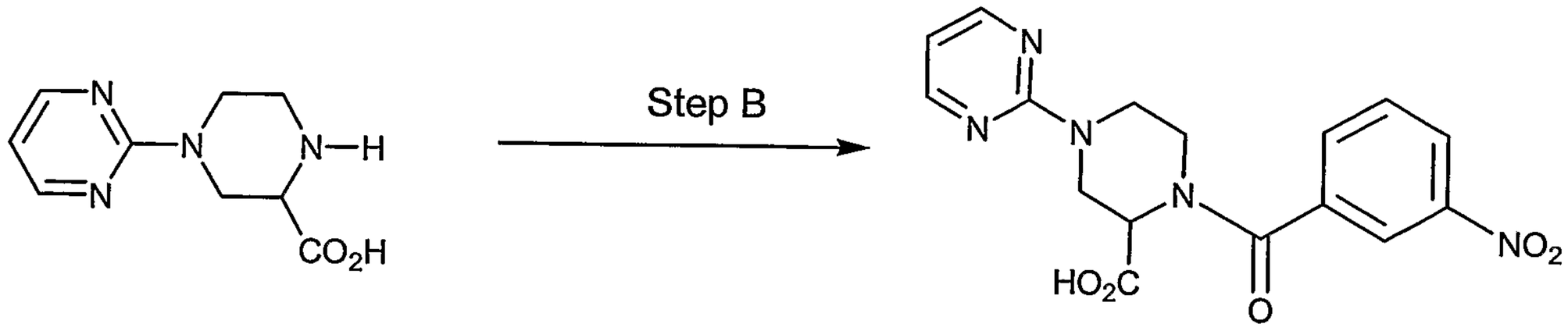
Following a similar procedure as Preparative Example 2.8, Step B except using the product from Preparative Example 2.9 Step A above, the desired compound was obtained (41%, MH+ = 374).

Step C

Following a similar procedure as in Preparative Example 2, Step B, but using the product from Step B above, the desired compound was obtained (99%, MH+=344).

PREPARATIVE EXAMPLE 2.10





Step A

Following a similar procedure as Preparative Example 2.8, Step A except using 3-nitrobenzoic acid, the desired compound was obtained and used directly in Step B.

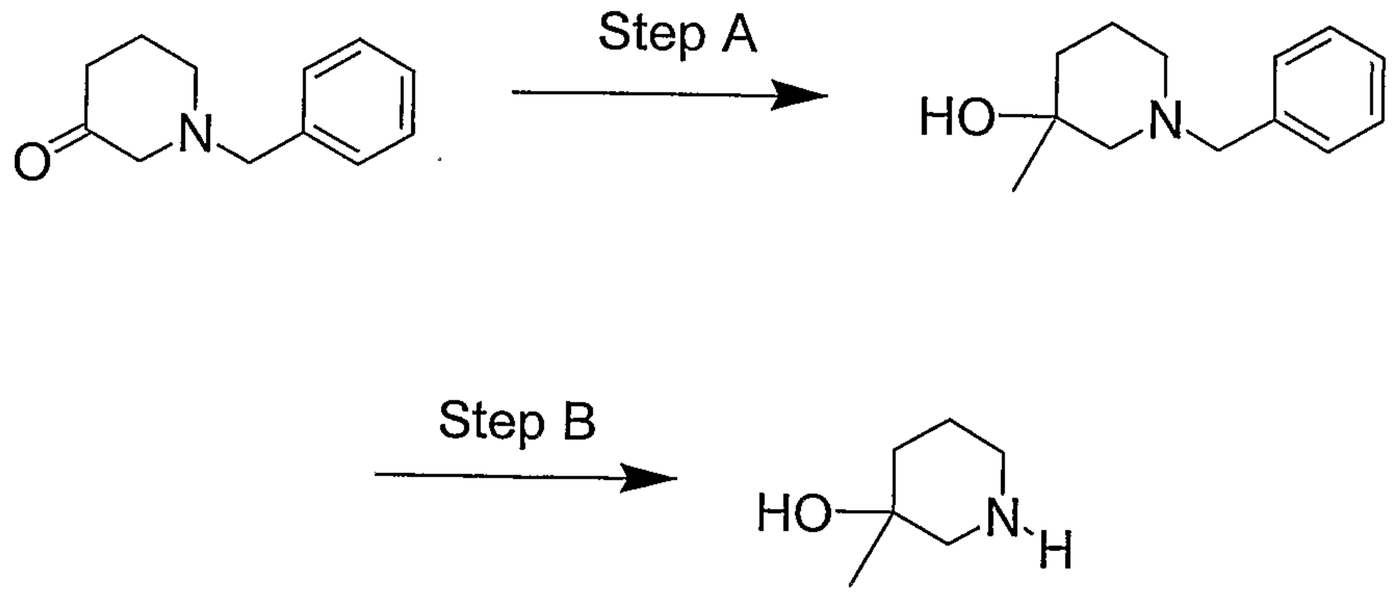
Step B

Following a similar procedure as Preparative Example 2.8, Step B except using the products from Preparative Example 2.9, Step A and Preparative Example 2.10, Step A, the desired compound was obtained (86%).

Step C

Following a similar procedure as in Preparative Example 2, Step B, but using the product from Step B above, the desired compound was obtained (67%, MH+=331).

PREPARATIVE EXAMPLE 2.11



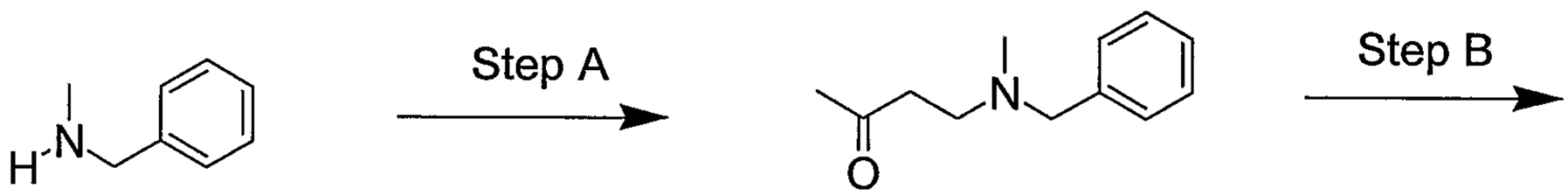
Step A

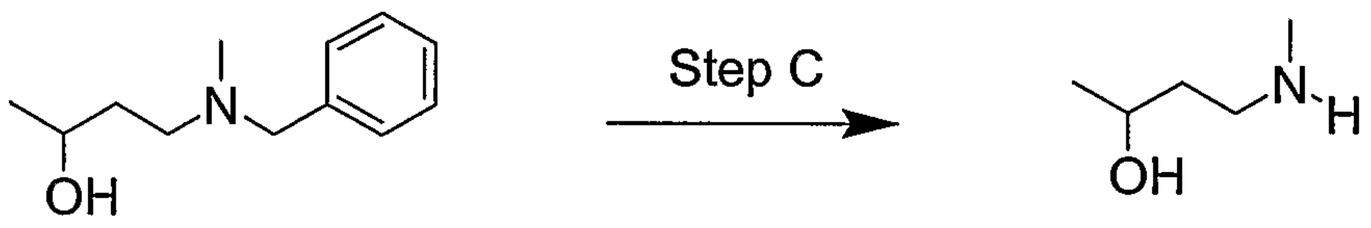
N-Benzylpiperidone (2 g, HCl salt, hydrate) was stirred with THF (20 mL), concentrated to dryness, and placed under high vac. The residue was diluted in THF (20 mL), and methyllithium was added (2.5 eq of 1.6*N* in Et_2O) via syringe. After stirring for 3 hr, the mixture was concentrated *in vacuo*, diluted with water, extracted with CH_2Cl_2, and dried over Na_2SO_4. Filtration and concentrating *in vacuo* gave the desired product (50%, MH+ = 205).

Step B

Following a similar procedure as in Preparative Example 2, Step B, but using the product from Step A above, the title compound was obtained (95%, MH+=116).

PREPARATIVE EXAMPLE 2.12





Step A

To N-benzyl-N-methylamine (20 mmol) dissolved in acetone (50 mL) was added concentrated HCl (20 mmol), paraformaldehyde (30 mmol) and 2-propanol (2 mL). After stirring at reflux overnight, the mixture was concentrated *in vacuo*, diluted with water, basified to pH 14 and extracted with ether. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the desired product (98%) which was used directly in Step B.

Step B

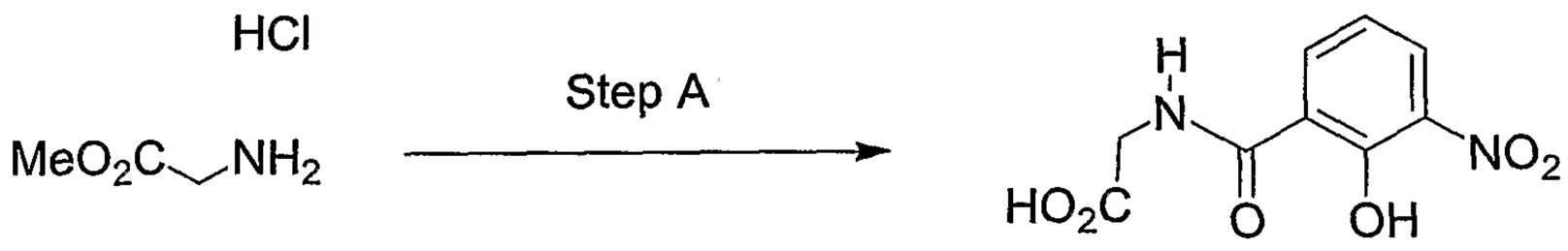
The product from Step A above (500 mg) was dissolved in MeOH (20 mL) and to this was added $NaBH_4$ (50 mg). After stirring for 10 min, the solution was

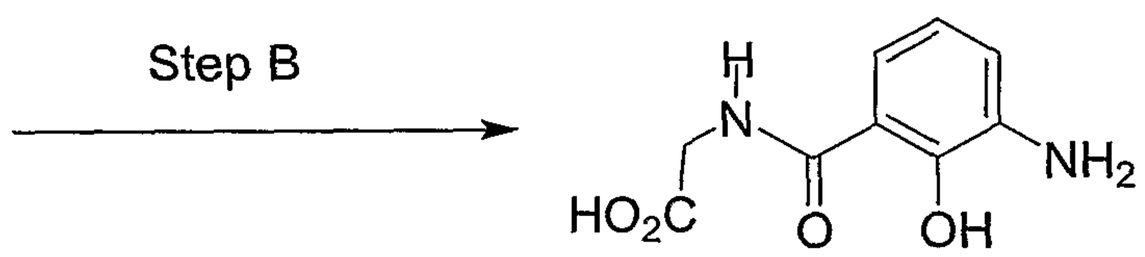
concentrated *in vacuo* to give the desired compound which was used directly in Step C without purification.

Step C

The product from Step B above was diluted with MeOH (20 mL) and to this was added AcOH (0.1 mL), a catalytic amount of Pd/C (10%) and the mixture stirred under H_2 atmosphere (balloon) overnight. The mixture was filtered, 4N HCl in dioxane (1 mL) was added, and the mixture was concentrated *in vacuo* to give the desired compound that was used directly without purification.

PREPARATIVE EXAMPLE 2.13





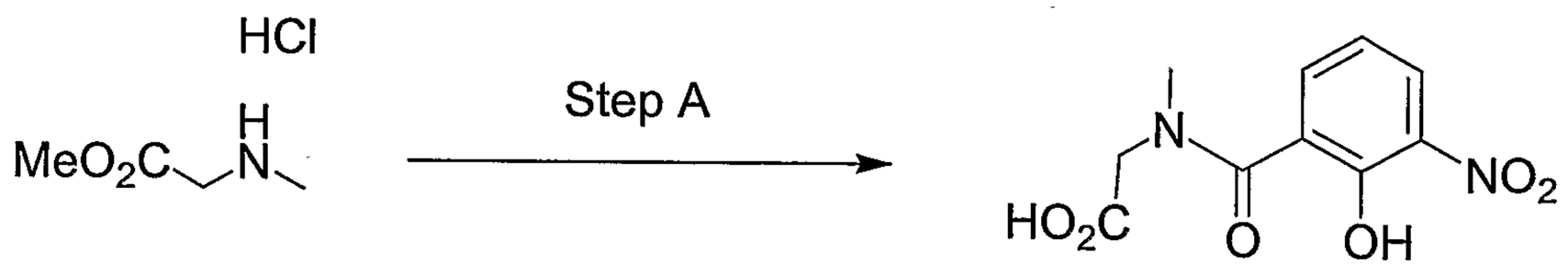
Step A

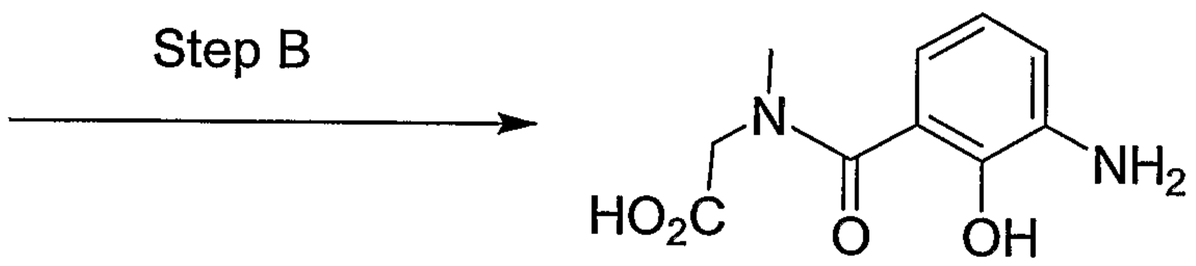
Following a similar procedure as Preparative Example 2, Step A except using methyl glycinate, the desired ester was obtained. The mixture was poured into 200 mL of 1*N* NaOH, then extracted with dichloromethane. The pH was adjusted to 1 and NaCl was added until saturation. After several hours, the resulting precipitate was filtered and washed with cold water to give the desired product (42%).

Step B

Following a similar procedure as in Preparative Example 2 Step B, but using the product from Step A above, the title compound was obtained (95%).

PREPARATIVE EXAMPLE 2.14





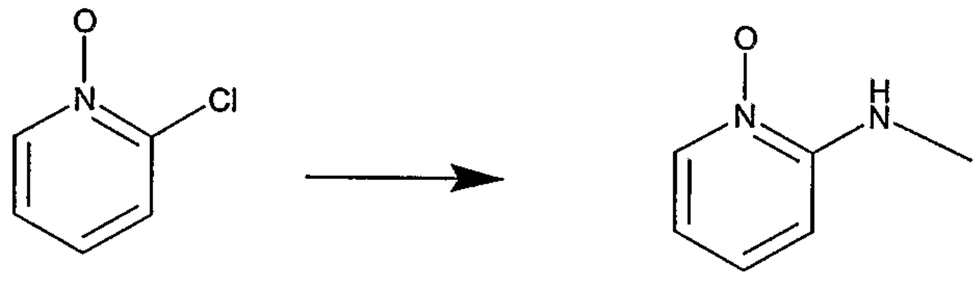
Step A

Following a similar procedure as in Preparative Example 2.13, Step A except using methyl N-methylglycinate, the desired product was obtained (18%).

Step B

Following a similar procedure as in Preparative Example 2, Step B, but using the product from Step A above, the title compound was obtained (95%, MH+ = 225).

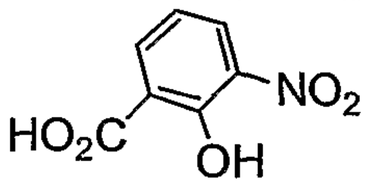
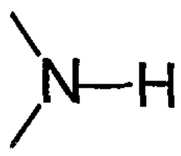
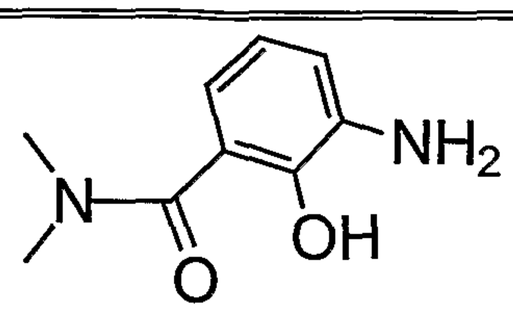
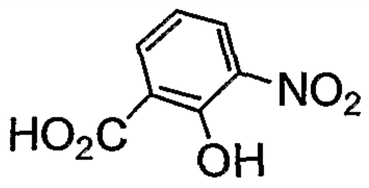
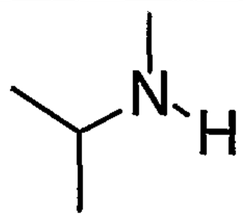
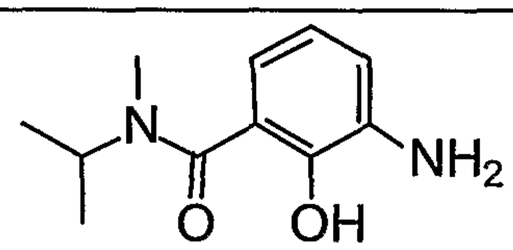
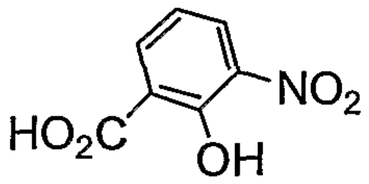
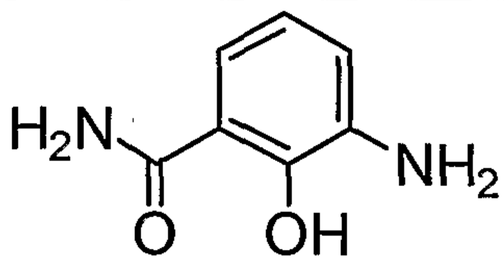
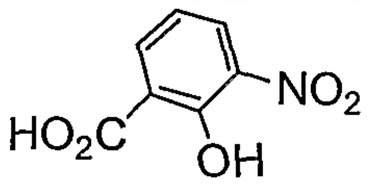
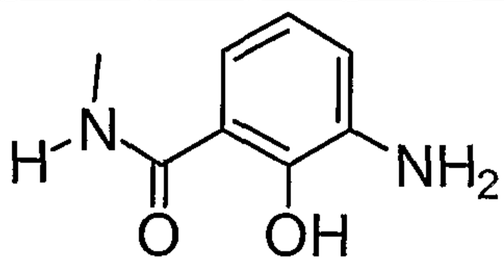
PREPARATIVE EXAMPLE 2.16

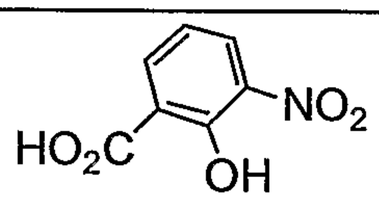
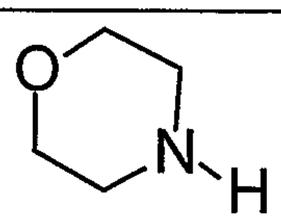
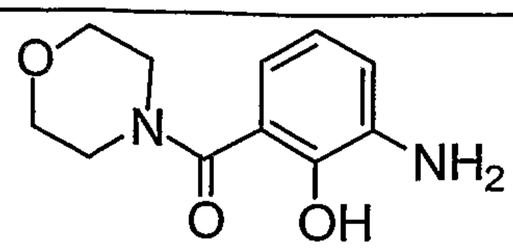
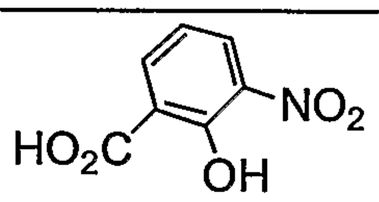
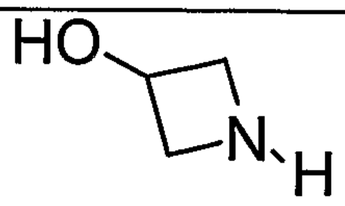
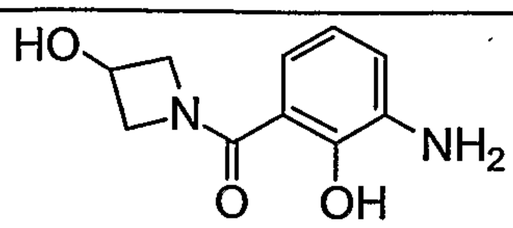
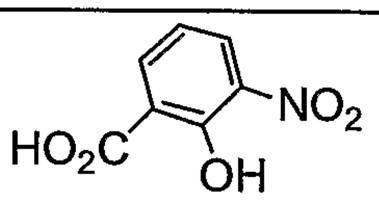
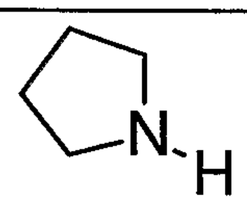
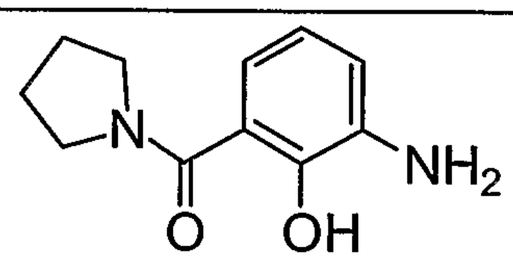
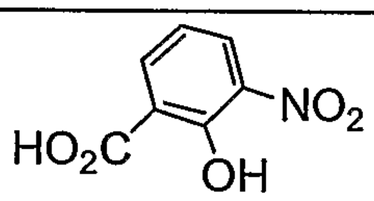
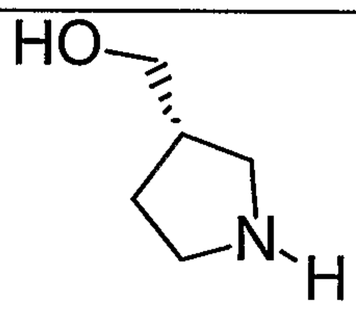
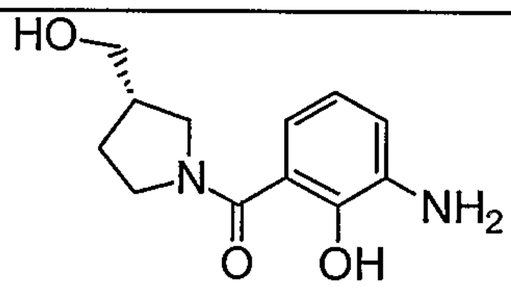
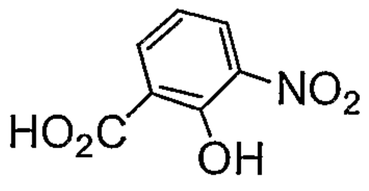
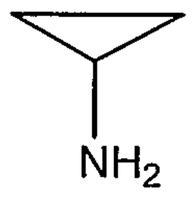
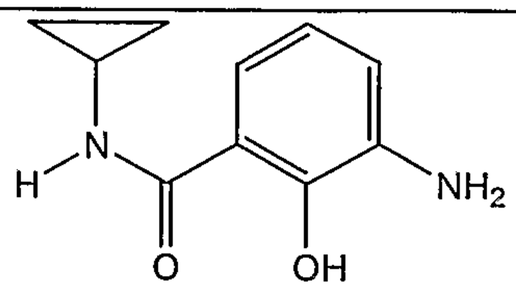


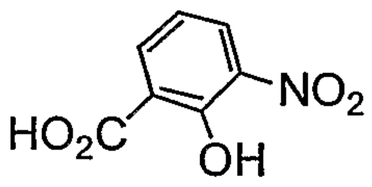
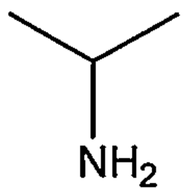
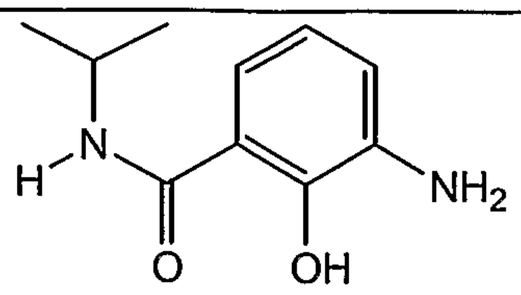
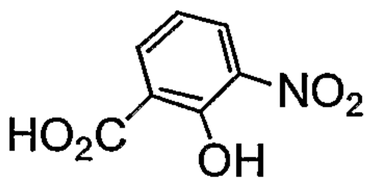
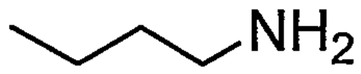
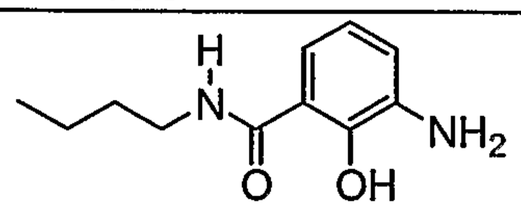
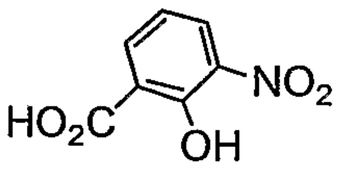
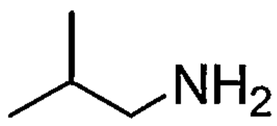
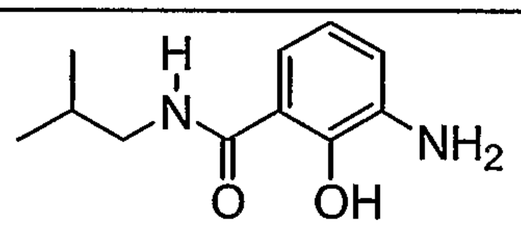
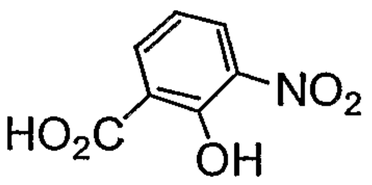
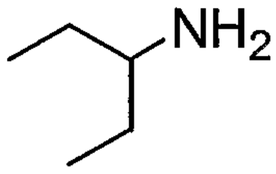
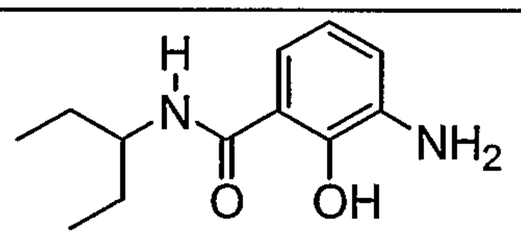
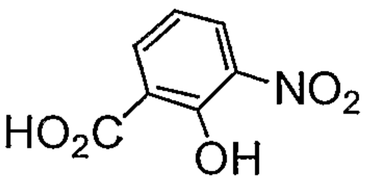
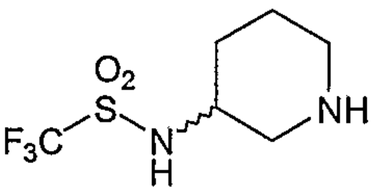
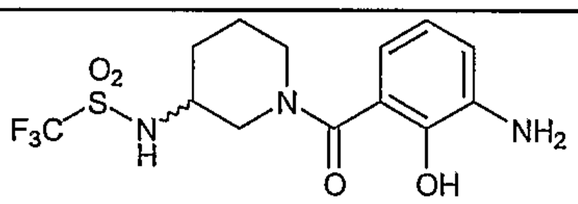
The above n-oxide (2g) was combined with H_2NMe/H_2O ($15cm^3$) and heated to 140^0C overnight. Potassium carbonate (1.3g) added and the mixture concentrated *in vacuo*. Extraction with EtOH and concentration of the filtrate *in vacuo* gave 1.56g of crude amine (MH+=125).

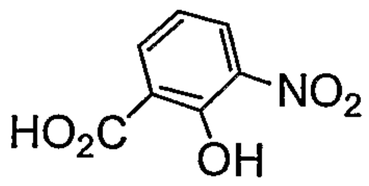
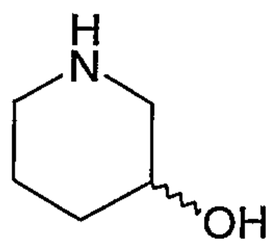
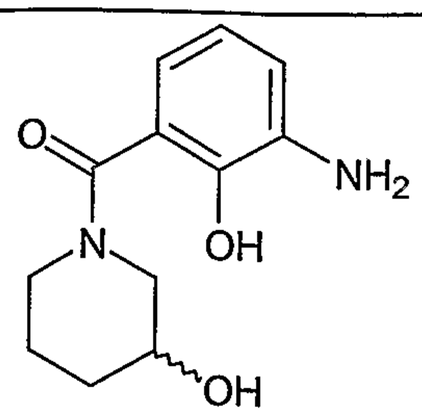
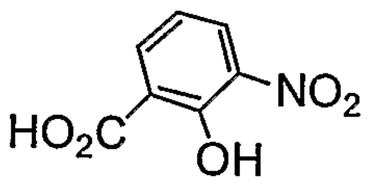
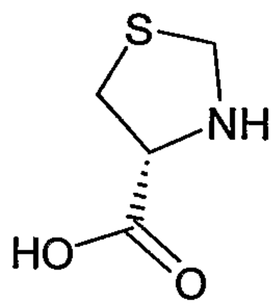
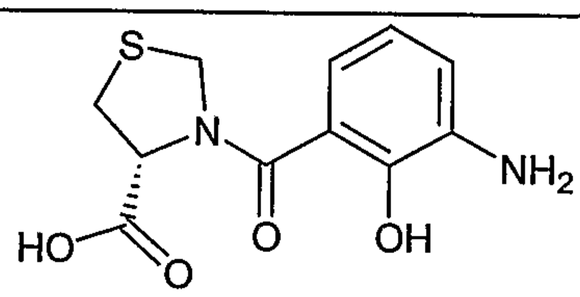
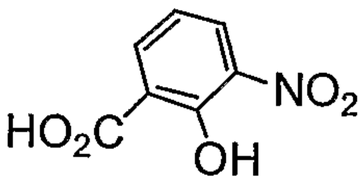
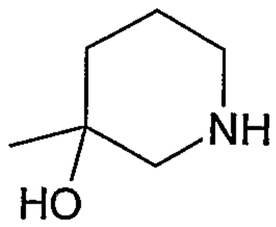
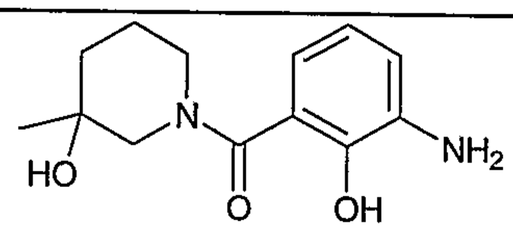
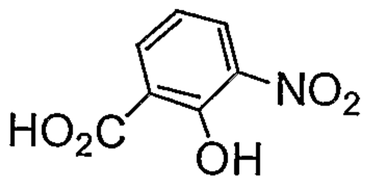
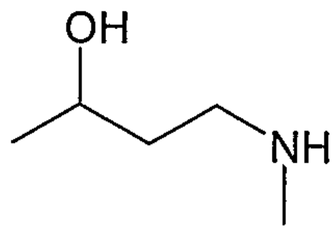
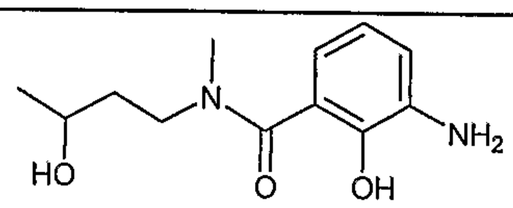
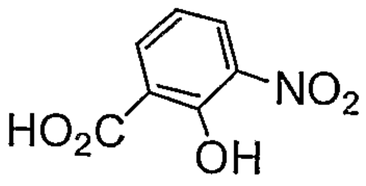
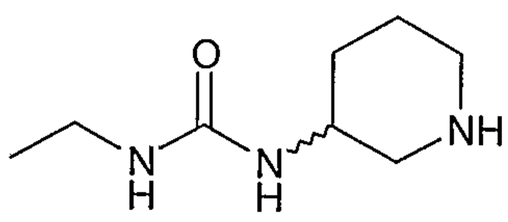
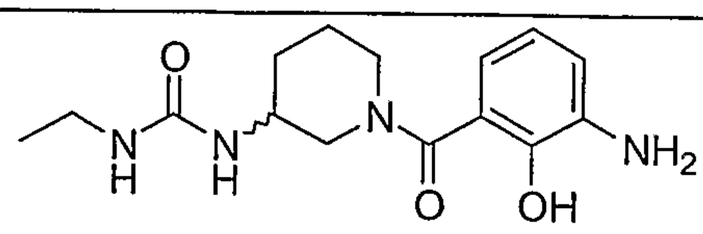
PREPARATIVE EXAMPLE 3-10.50

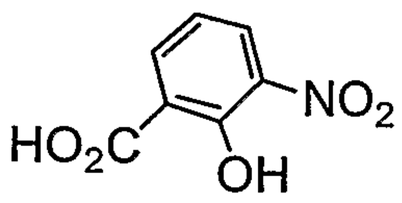
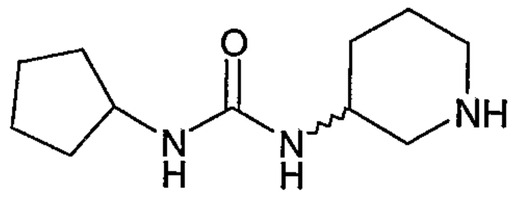
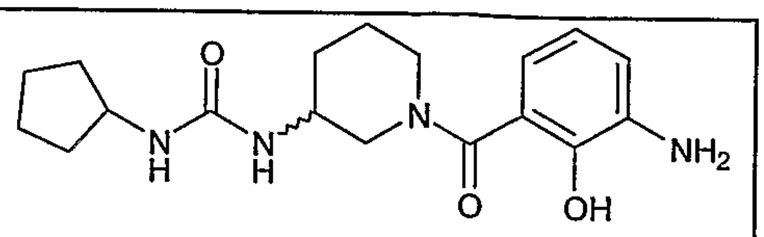
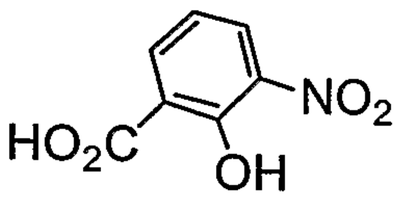
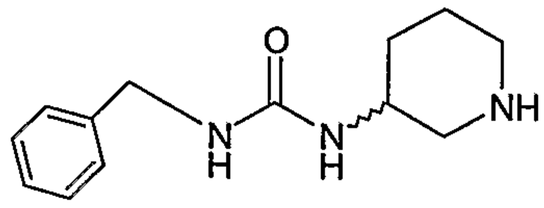
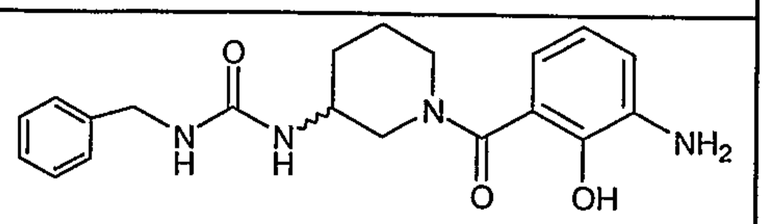
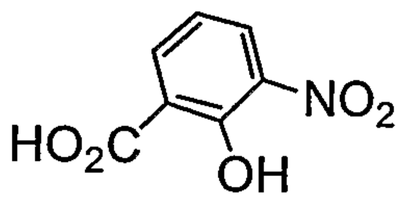
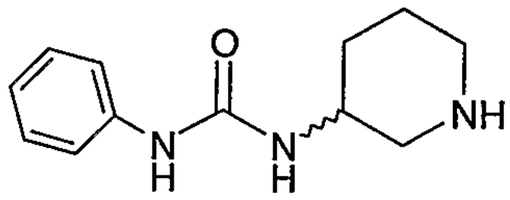
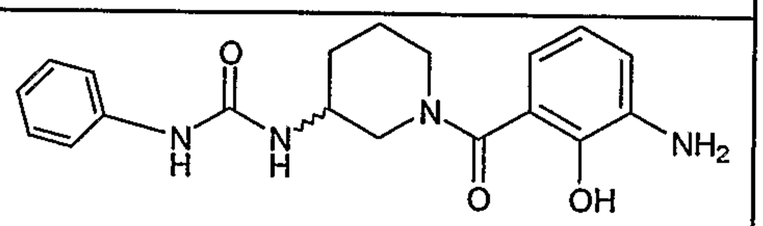
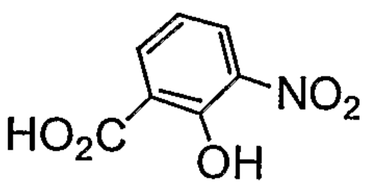
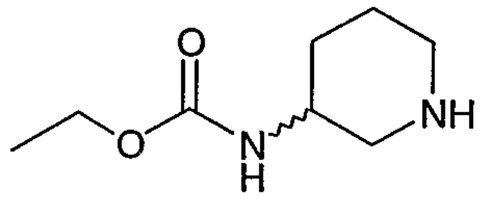
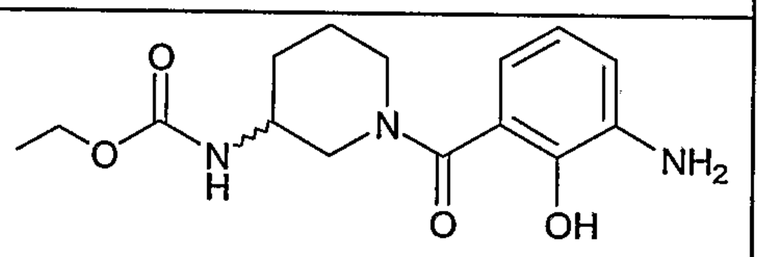
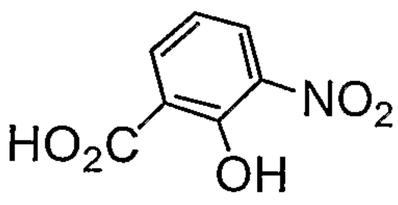
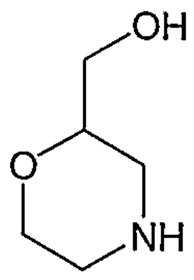
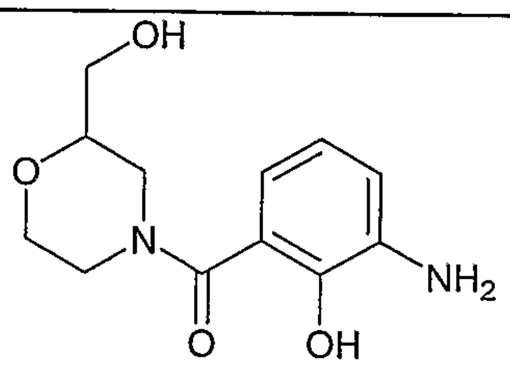
Following the procedures set forth in Preparative Examples 1-2 but using the carboxylic acid, amine, and coupling agent [DCC (Prep. Ex. 1) or PyBrop (Prep. Ex. 2)] listed in the Table below, the indicated amide products were obtained and used without further purification.

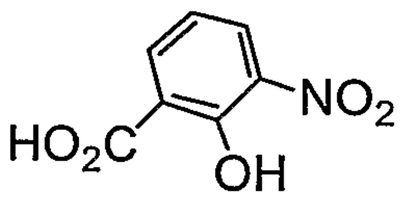
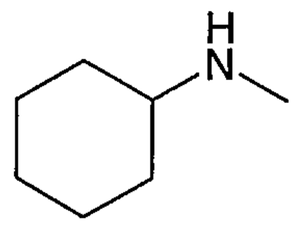
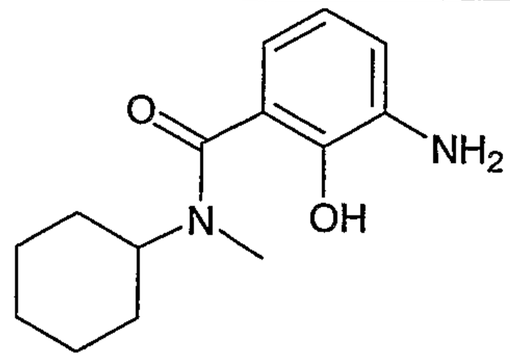
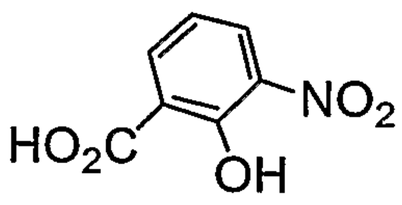
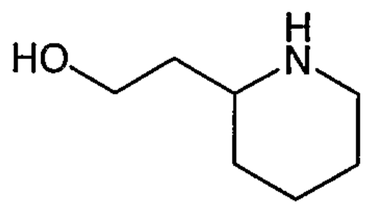
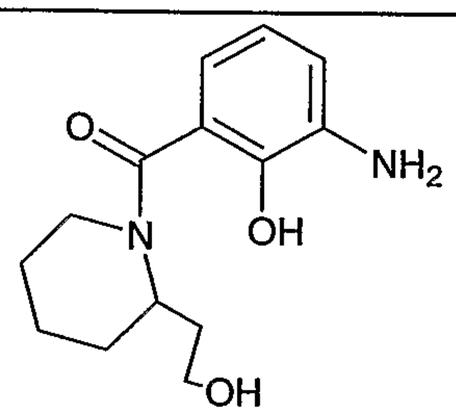
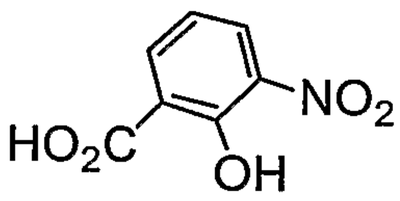
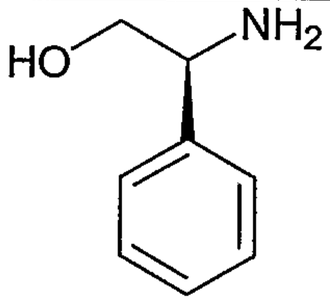
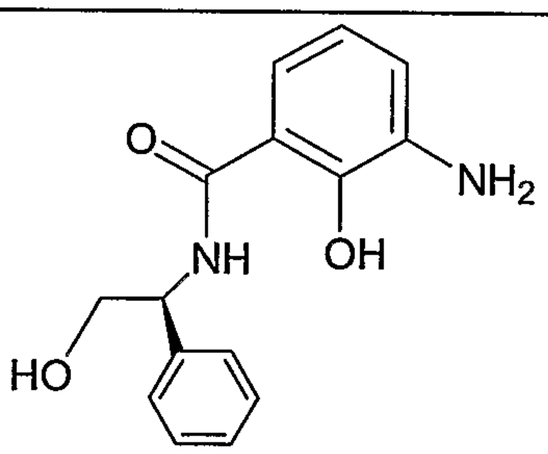
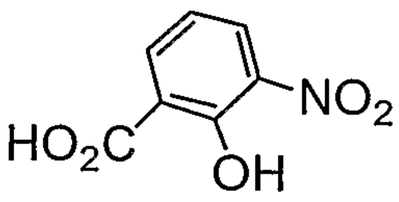
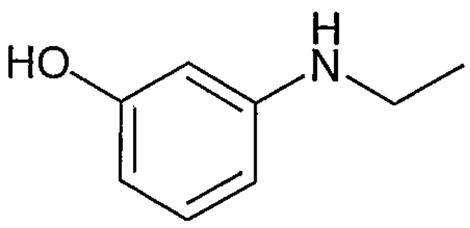
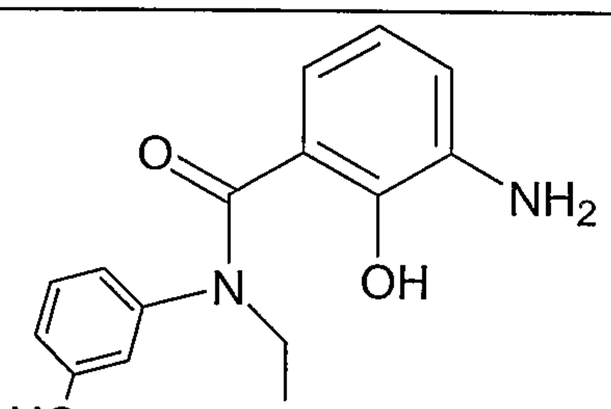
Prep Ex.	Carboxylic acid	Amine	Product 1. Coupling Agent 2. %yield 3. MH^+
3			 1. PyBrop 2. 87, 86 3. 181
4			 1. PyBroP 2. 49 3. 209
5		NH_3	 1. PyBroP 2. 95 3. 153
6		$—NH_2$	 1. PyBroP 2. 83 3. 167

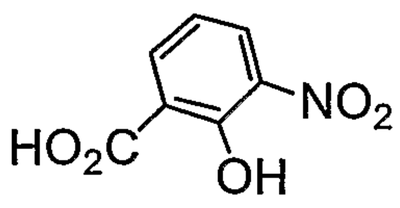
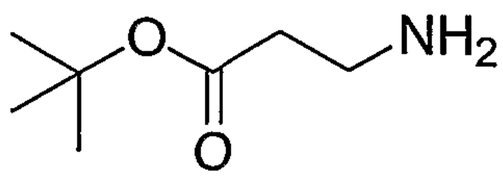
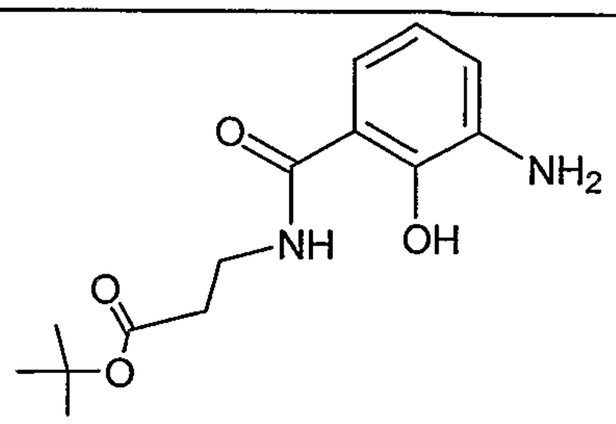
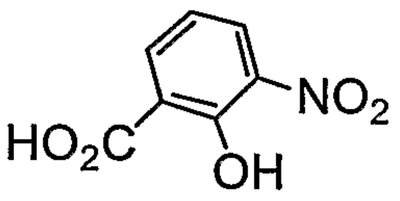
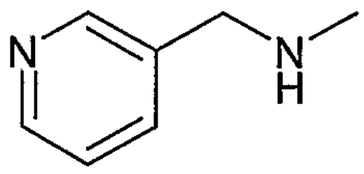
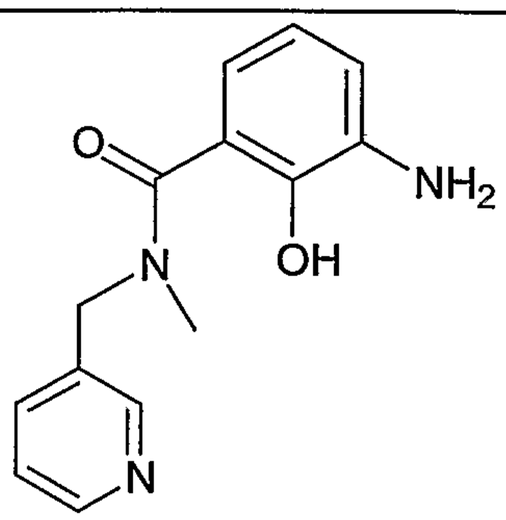
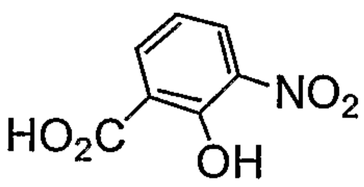
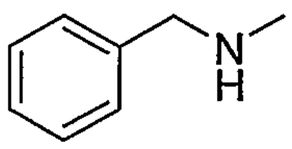
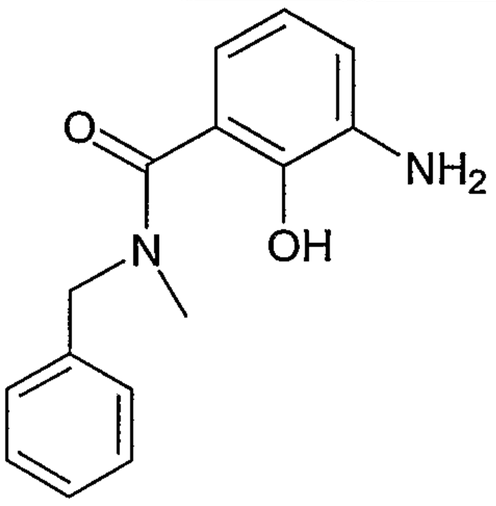
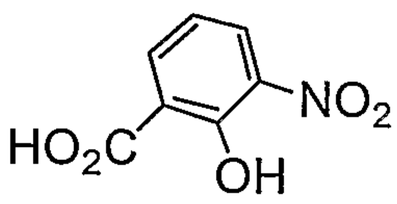
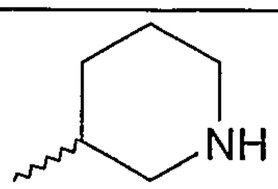
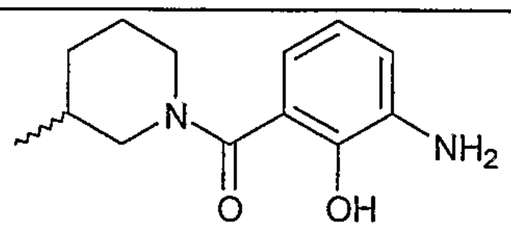
7			 1. PyBroP 2. 76 3. 223
8			 1. PyBroP 2. 65, 53 3. 209
9			 1. PyBroP 2. 59, 69 3. 207
10			 1. PyBroP 2. 49, 86 3. 237
10.1			 1. PyBroP 2. 30,88 3. 193

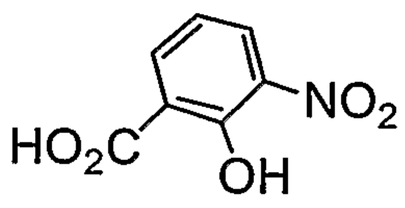
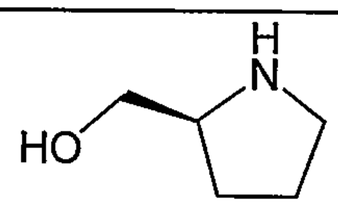
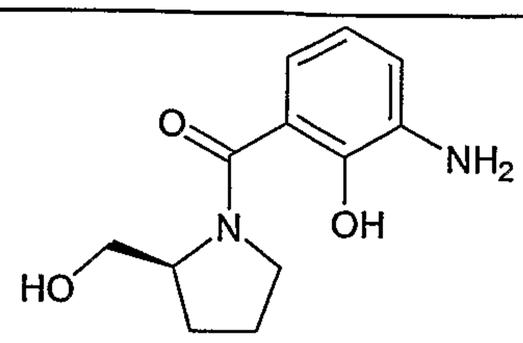
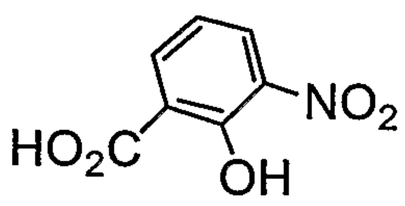
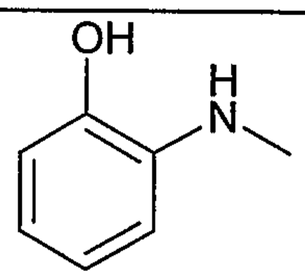
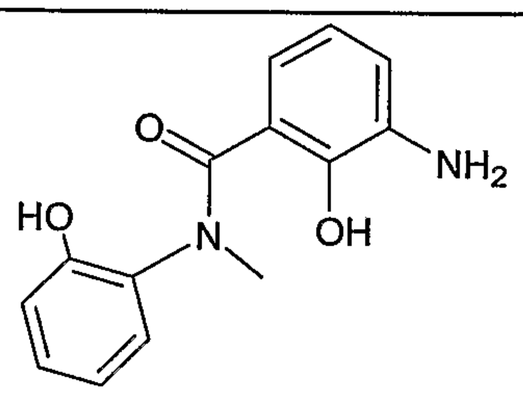
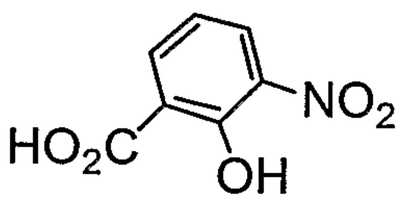
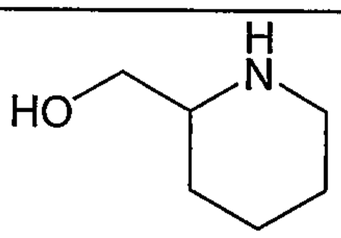
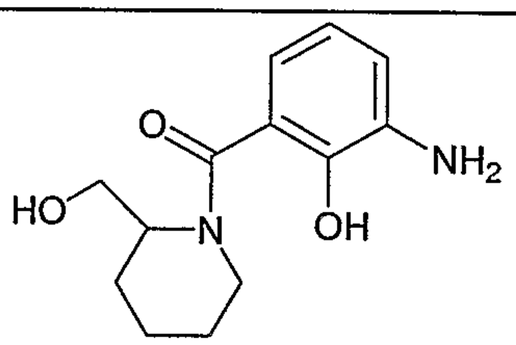
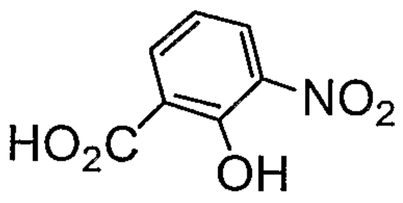
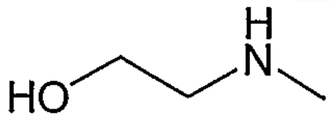
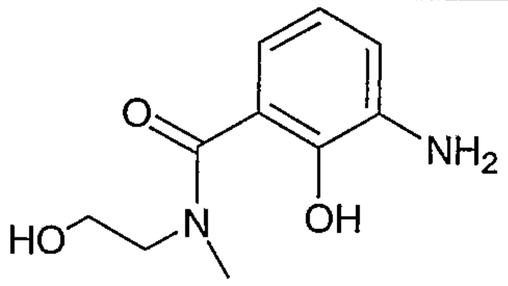
10.2			 1. PyBroP 2. 26,87 3. 195
10.3			 1. PyBroP 2. 38 3. 209
10.4			 1. PyBroP 2. 29 3. 209
10.5			 1. PyBroP 2. 38 3. 223
10.6		2.7 	 1. PyBroP 2. 32,99 3. 367.9

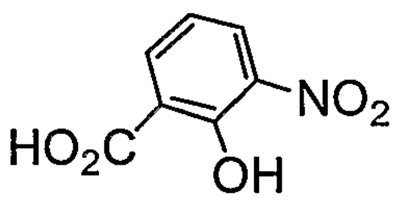
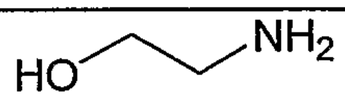
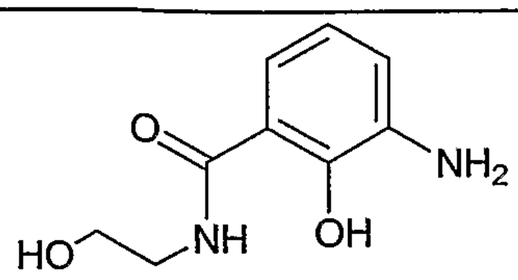
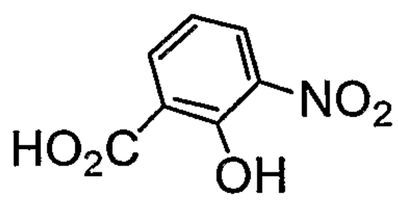
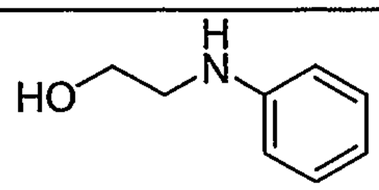
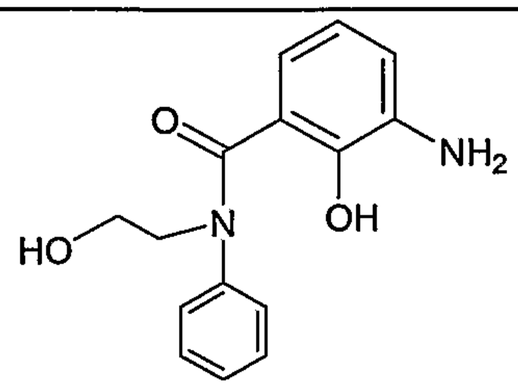
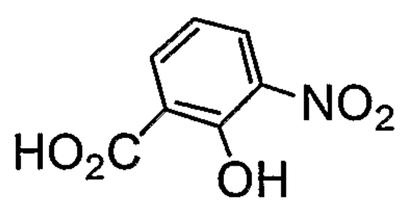
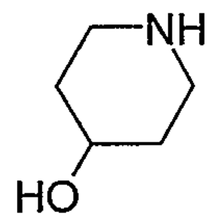
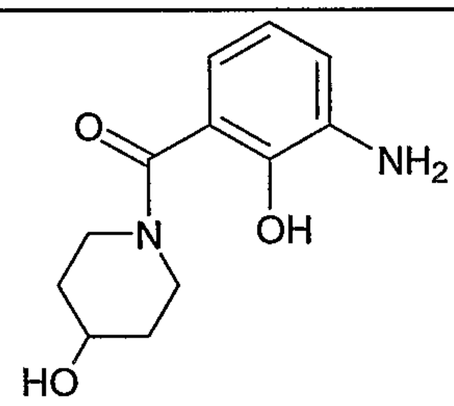
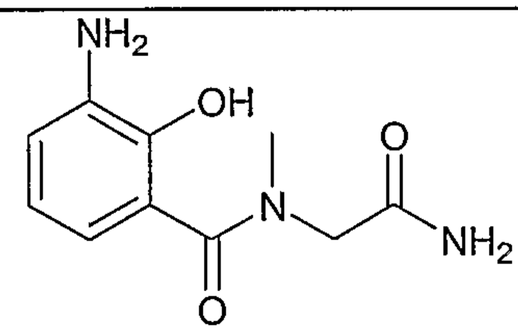
10.7			 1. PyBroP 2. 35,99 3. 237
10.8			 1. DCC 2. 30,99 3. 269
10.9		2.11 	 1. PyBroP 2. 58,95 3. 233.1
10.10		2.12 	 1. PyBroP 2. 42,95 3. 238.9
10.13		2.4 	 1. PyBroP 2. 51,95 3. 307

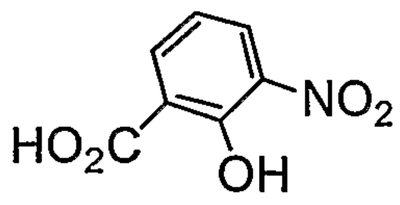
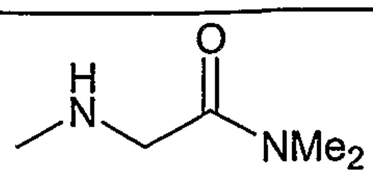
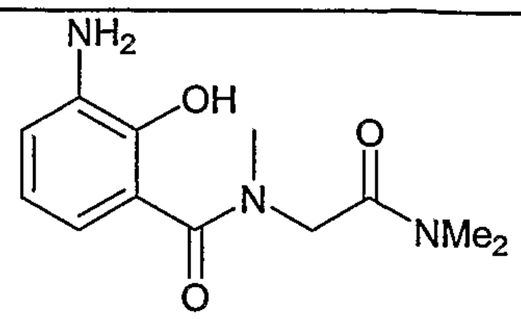
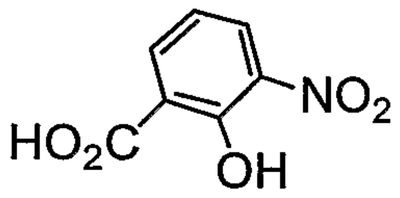
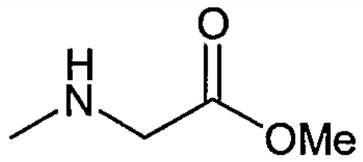
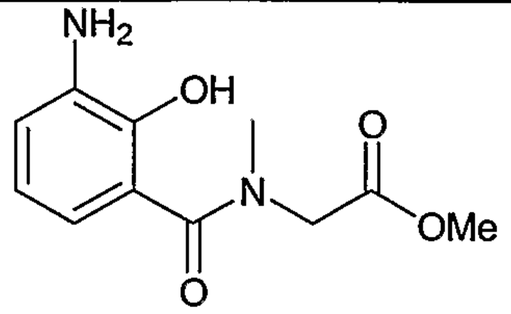
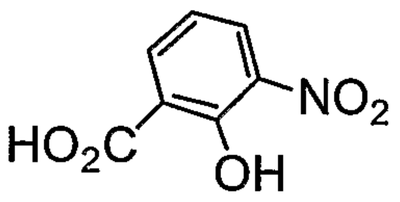
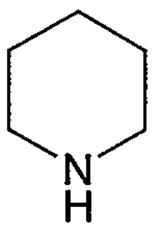
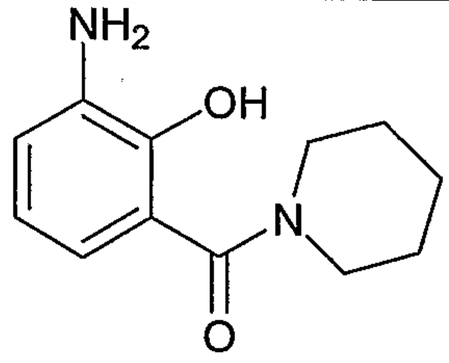
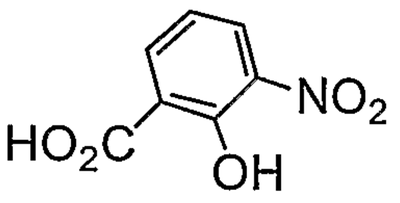
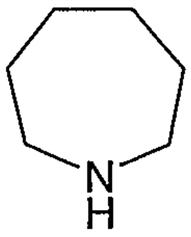
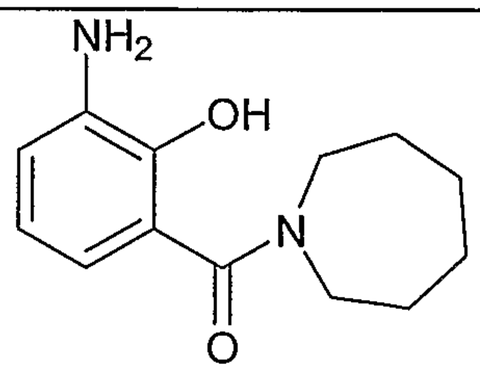
10.14		2.2 	 1. PyBroP 2. 55 3. 347
10.15		2.1 	 1. PyBroP 2. 41 3. 369.1
10.16		2.3 	 1. PyBroP 2. 56 3. 354.9
10.17		2.5 	 1. PyBroP 2. 56 3. 308
10.18		12.4 	 1. PyBroP 2. 10,95 3. 252.9

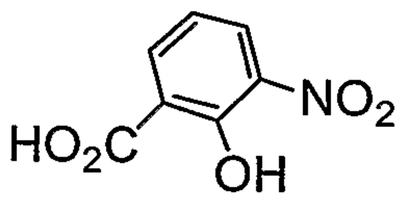
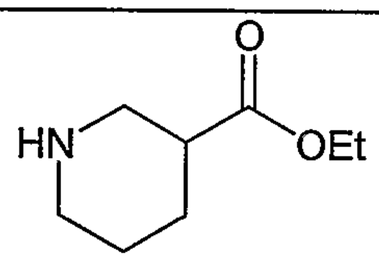
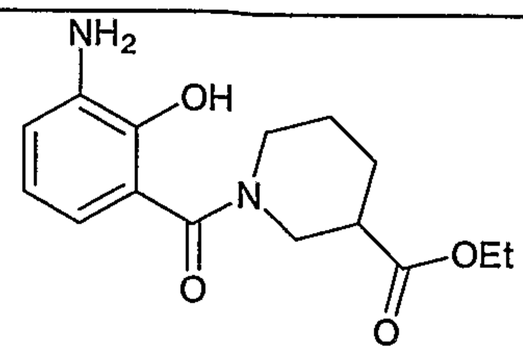
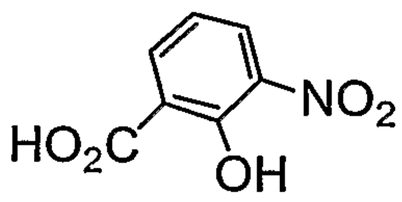
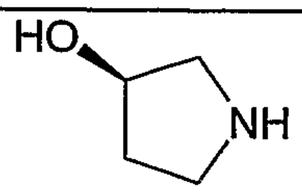
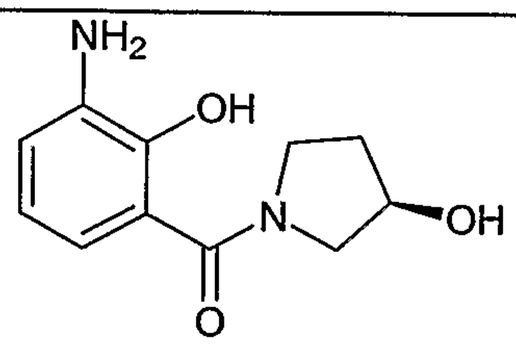
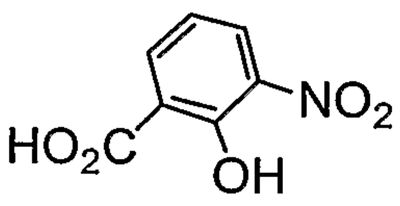
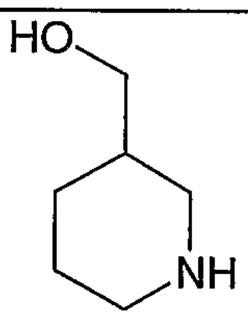
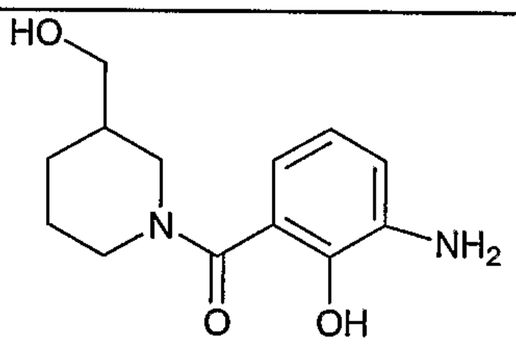
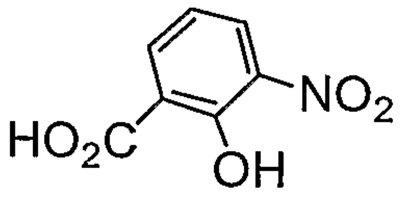
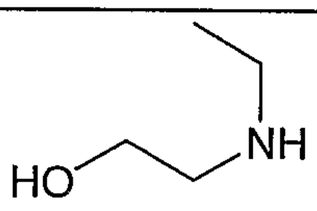
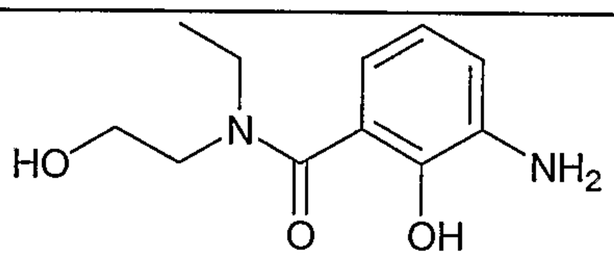
10.19			 1. PyBroP 2. 42,95 3. 249
10.20			 1. PyBroP 2. 15,95 3. 264.9
10.21			 1. PyBroP 2. 64,95 3. 273
10.22			 1. PyBroP 2. 45,95 3. 273

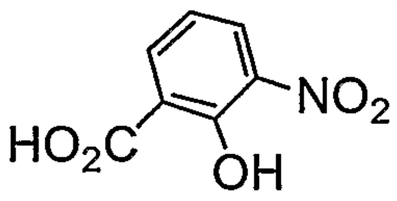
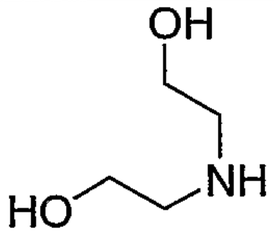
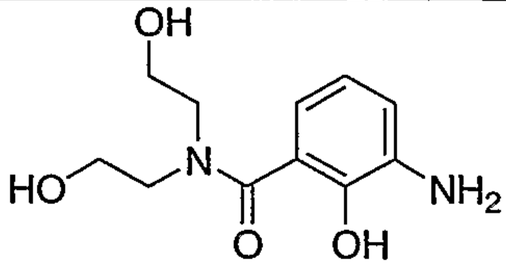
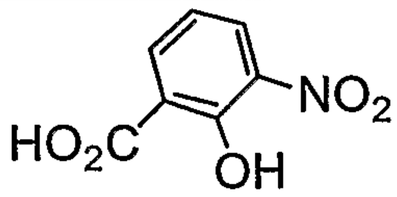
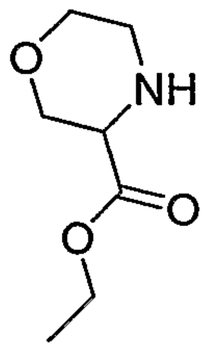
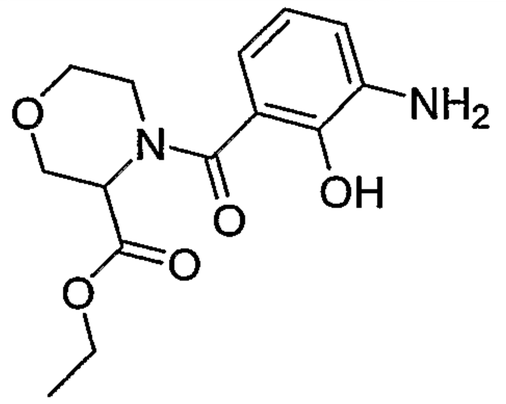
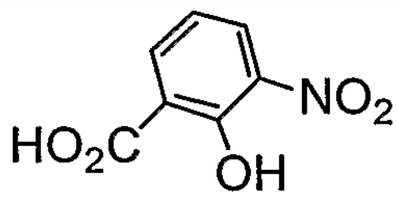
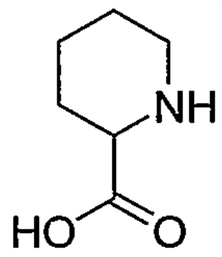
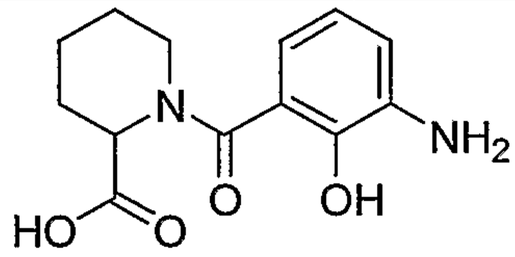
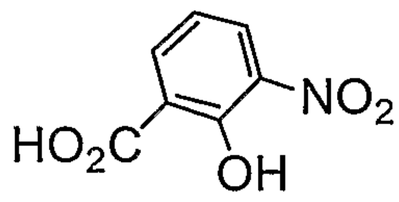
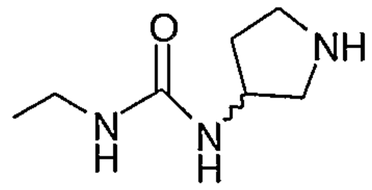
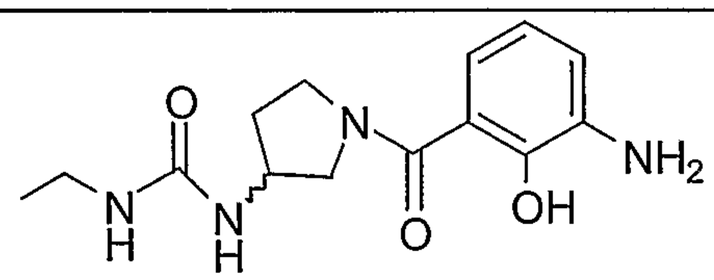
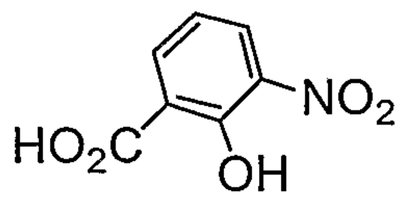
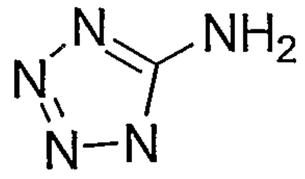
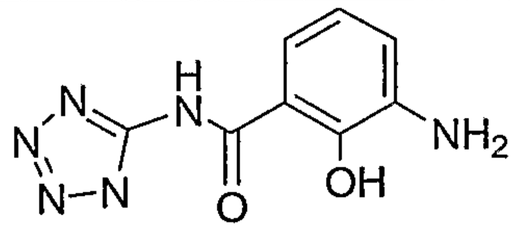
10.23			 1. PyBroP 2. 44,95 3. 281
10.24			 1. PyBroP 2. 41,95 3. 281.1
10.25			 1. PyBroP 2. 48,95 3. 257
10.26			 1. DCC 2. 15,99 3. 235

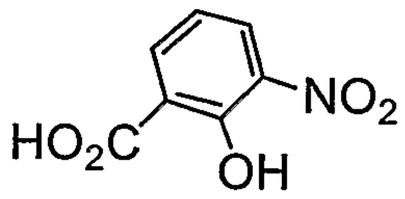
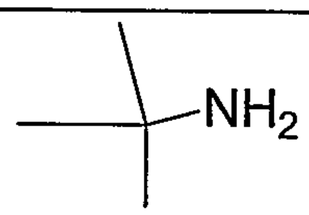
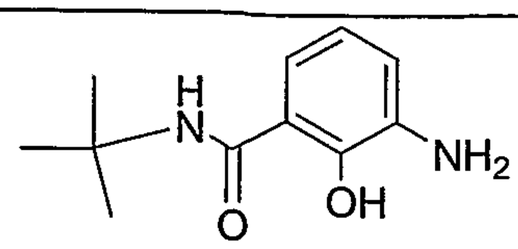
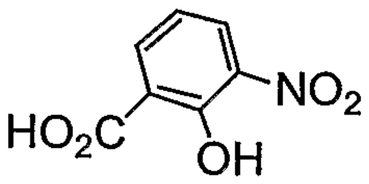
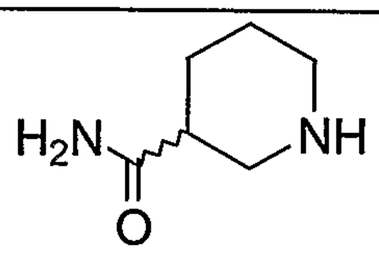
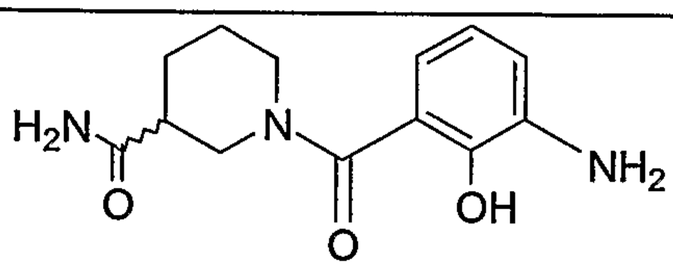
10.28			 1. PyBroP 2. 52,95 3. 237.1
10.29			 1. PyBroP 2. 31,95 3. 259.1
10.30			 1. PyBroP 2. 54,95 3. 250.9
10.31			 1. PyBroP 2. 64,95 3. 210.9

10.32			 1. PyBroP 2. 47,95 3. 197
10.33			 1. PyBroP 2. 47,95 3. 273
10.34			 1. PyBroP 2. 51,95 3. 237.1
10.35			 1. PyBroP 2. 60,90 3. 224

10.36			 1. PyBroP 2. 65,99 3. 252
10.37			 1. PyBroP 2. 58,99 3. 239
10.38			 1. PyBroP 2. 35,99 3. 221.1
10.39			 1. PyBroP 2. 42,99 3. 235.2

10.40			 1. DCC 2. 32,99 3. 293.1
10.41			 1. PyBroP 2. 45,99 3. 223.1
10.42			 1. PyBroP 2. 55,81 3. 251.1
10.43			 1. PyBroP 2. 68,66 3. 224.9

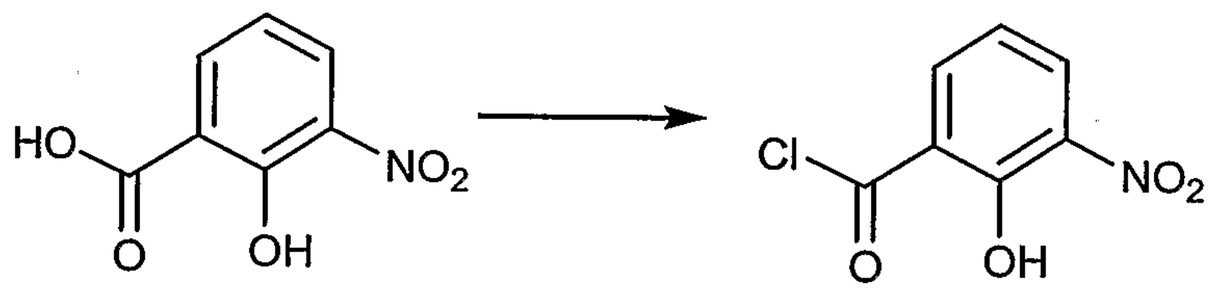
10.44			 1. PyBroP 2. 68,66 3. 241.1
10.45		12.3 	 1. PyBroP 2. 44,40 3. 295
10.46			 1. DCC 2. 37,81 3. 265
10.47		2.6 	 1. PyBroP 2. 71,95 3. 293.1
10.48			 1. PyBroP 2. 35,99 3. 220.9

10.49			 1. DCC 2. 16,99 3. 209.0
10.50			 1. DCC 2. 18,99 3. 264.0

PREPARATIVE EXAMPLE 10.55

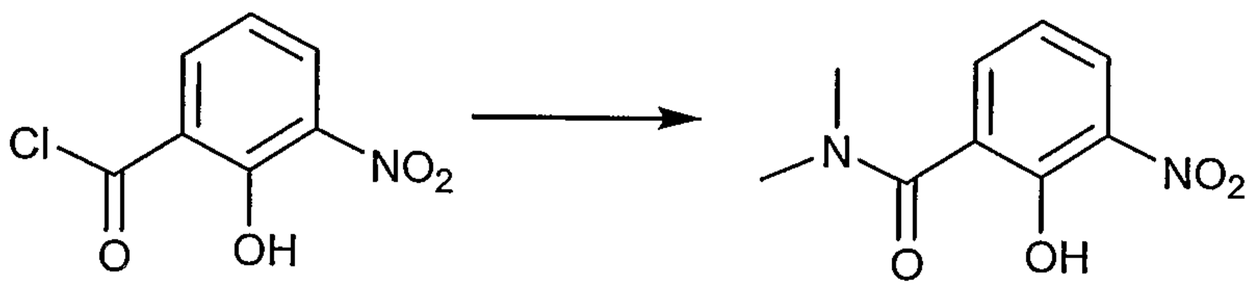
Alternative Procedure for Preparative Example 3

Step A



To the nitrosalicylic acid (3 g) dissolved dichloromethane (150 mL) at room temperature was added oxalyl chloride (4.3 mL) and DMF (0.01 eq.). After stirring for one day the mixture was concentrated in a vacuum to give a semi solid which was used directly in step B.

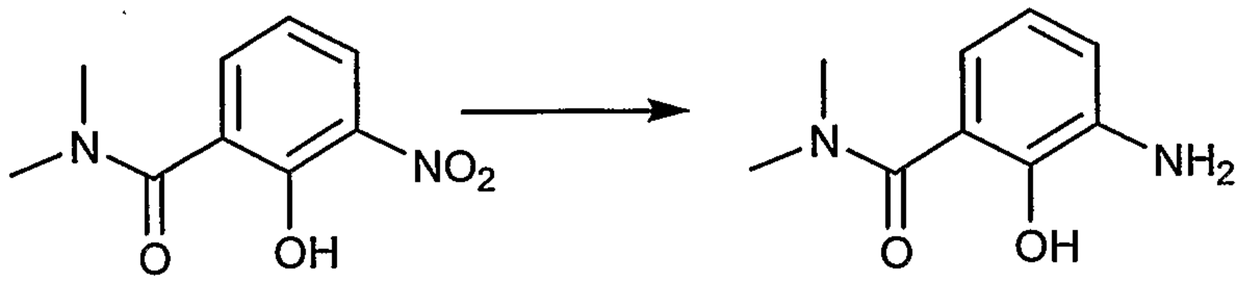
Step B



To the material from step A diluted in dichloromethane (50 mL) and cooled to 0° C was added dimethyl amine in THF (2*N* solution, 24.6 mL) and triethylamine (4 eq.). After stirring for 24 hours at room temperature the mixture was concentrated in vacuo, diluted with 1M sodium hydroxide (30 mL) and after a half hour was washed

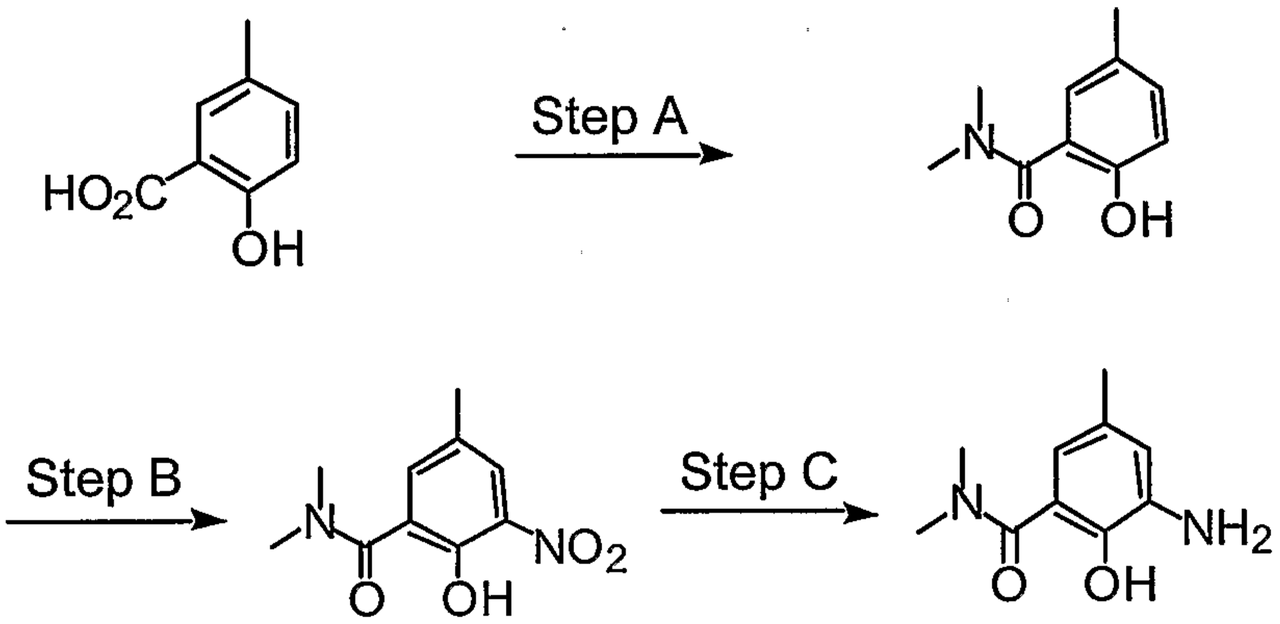
with dichloromethane. The aqueous phase was acidified with 6M HCl (aq), extracted with dichloromethane and the organic phase was washed with water, dried over Na_2SO_4 and concentrated to give the title compound (3.2 g, 93%).

Step C



A mixture of the product from step B above (6 g), 10% Pd/C (0.6 g), and EtOH (80 mL) was stirred in a parr shaker under hydrogen (40 psi) at room temperature for 2 days. Filtration through celite and concentration *in vacuo* afforded the title product (5.1 g, 99%, MH^+ = 181).

PREPARATIVE EXAMPLE 11



Step A

Following a similar procedure as in Preparative Example 1 except using dimethylamine (2*M* in THF, 33 mL) and 5-methylsalicylic acid (5 g), the desired product was prepared (6.5 g).

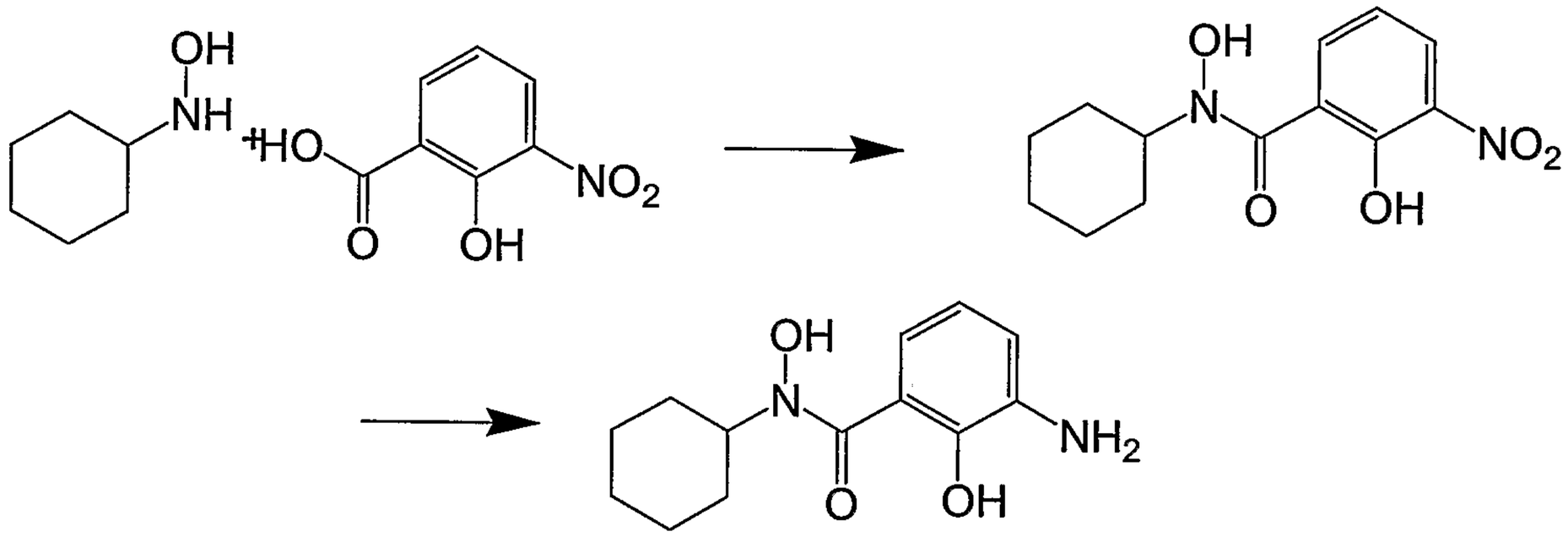
Step B

Nitric acid (0.8 mL) in H_2SO_4 was added to a cooled (-20°C) suspension of the product from Step A above (3 g) in H_2SO_4 (25 mL). The mixture was treated with 50% NaOH (aq) dropwise, extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the product as a crude solid (2.1 g, 44%, MH^+ = 225).

Step C

The product was prepared in the same manner as described in Step B of Preparative Example 2 (0.7 g, 99%, MH^+ = 195).

PREPARATIVE EXAMPLE 11.1



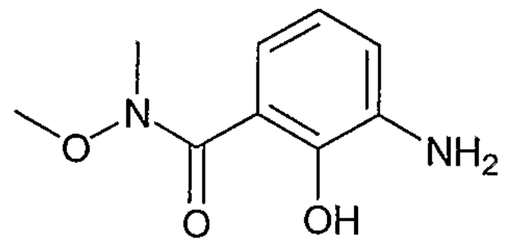
Step A

The above amine was reacted with the acid using the procedure set forth in Preparative Example 2, Step A to yield the desired amide (54%).

Step B

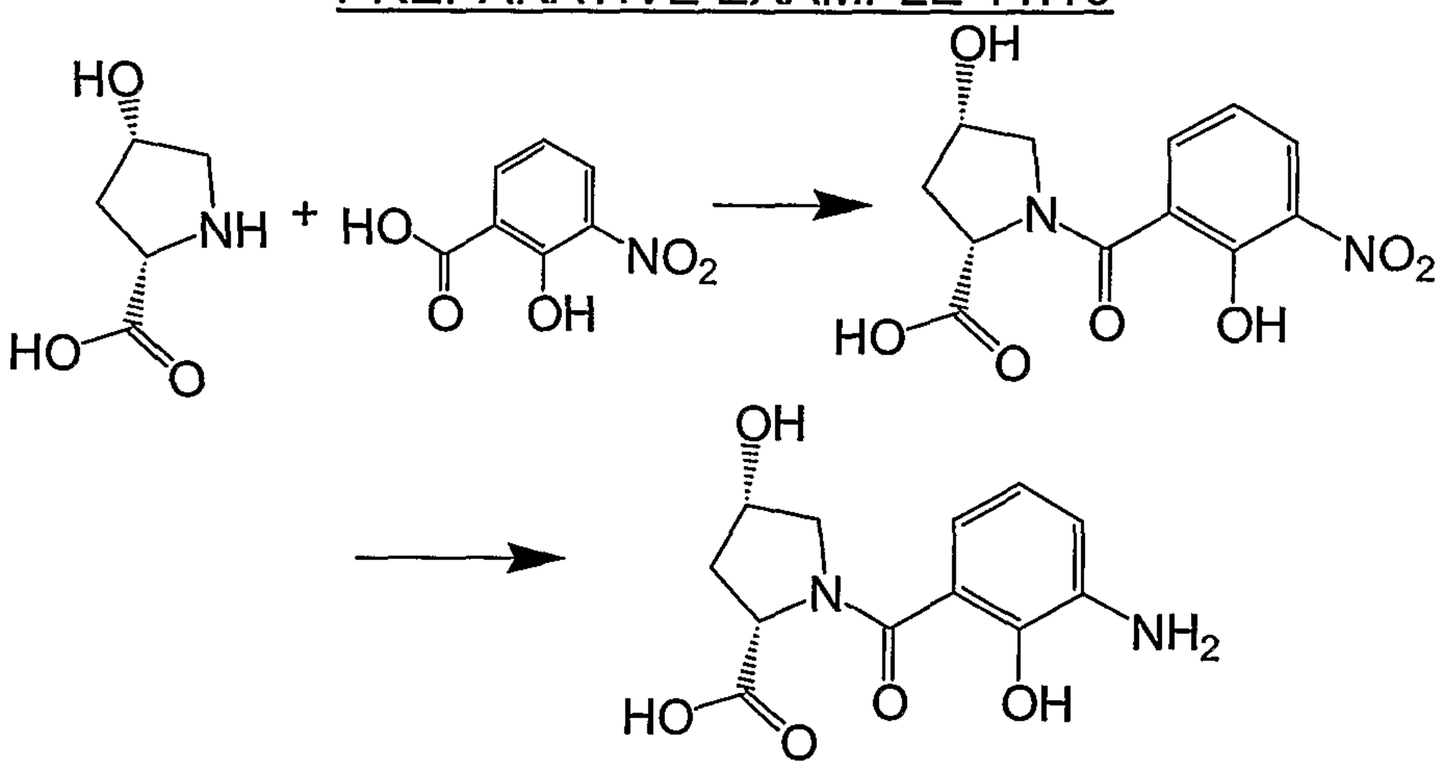
$Na_2S_2O_4$ (1.22g) was dissolved in water (4ml) followed by the addition of NH_3/H_2O (300ul). The solution ws then added to the product from Step A (200 mg) in dioxane (4ml) and stirred for 30min. The crude material was purified via flash column chromatography (CH_2Cl_2/MeOH, 20:1) to give 100mg of product (56%, MH+=251).

PREPARATIVE EXAMPLE 11.2



Following the procedures set forth in Preparative Example 11.1, Steps A and B, but using N-methylmethoxylamine, the title compound was obtained (86%, MH+=181).

PREPARATIVE EXAMPLE 11.10



Step A

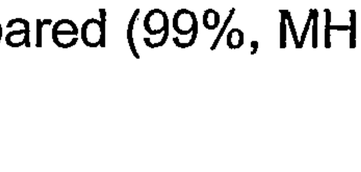
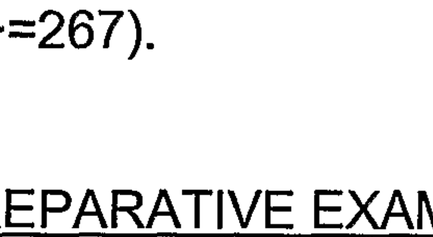
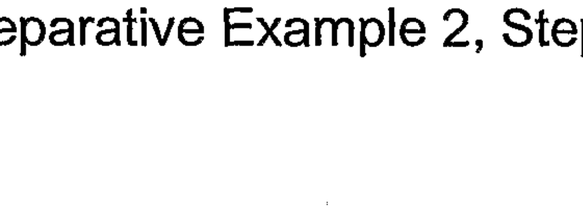
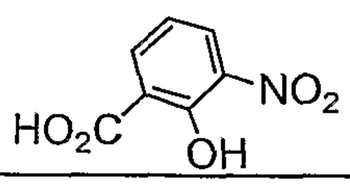
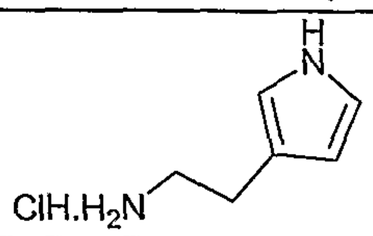
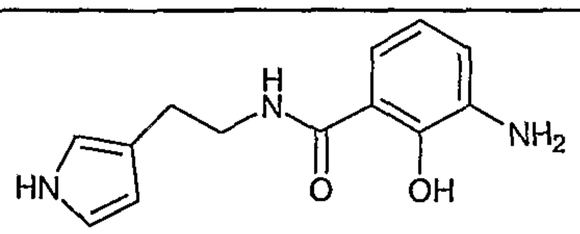
Following the procedure set forth in Preparative Example 1, but using N-hydroxysuccinimide and 2% DMF in CH_2Cl_2, the desired amide was obtained (33%, MH+=297).

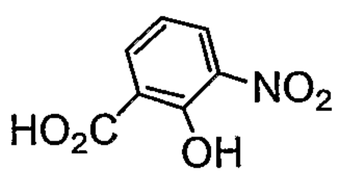
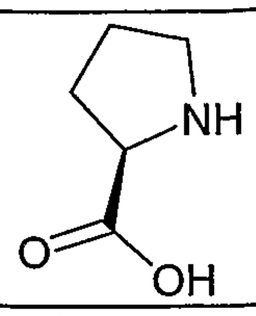
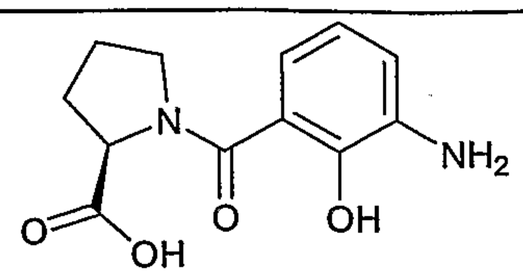
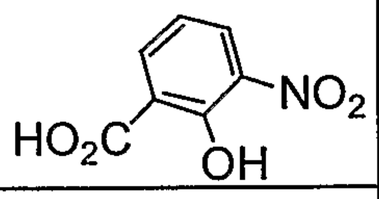
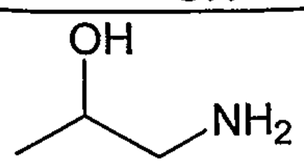
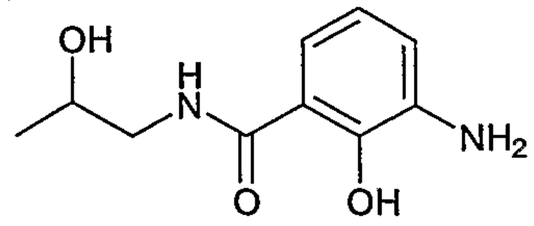
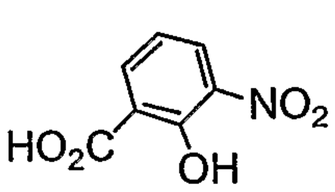
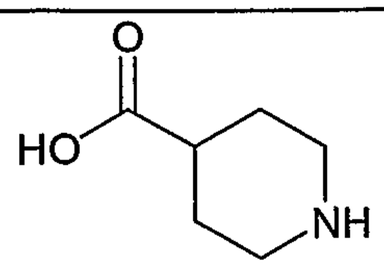
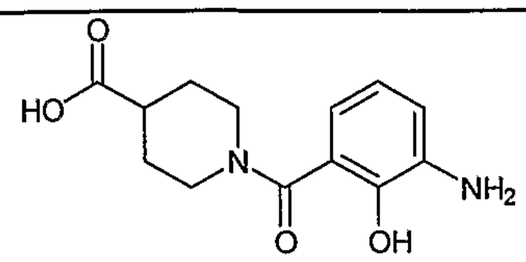
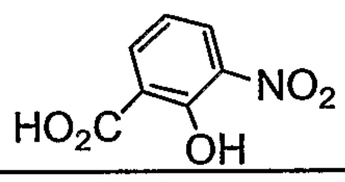
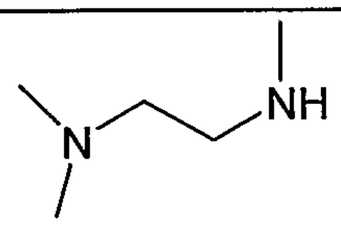
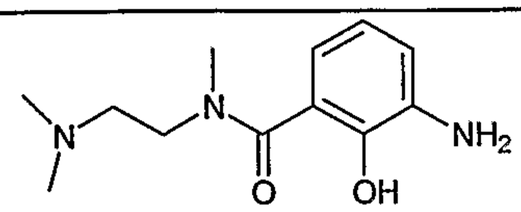
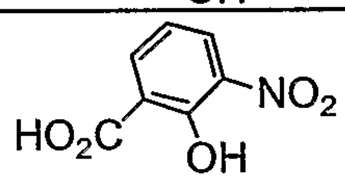
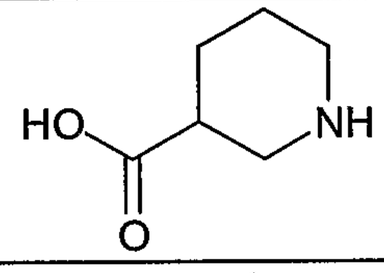
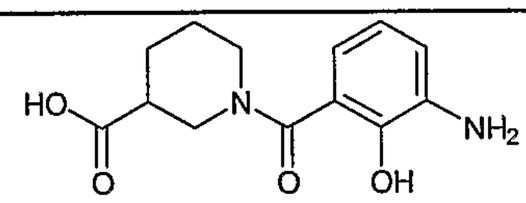
Step B

Following the procedure set forth in Preparative Example 2, Step B, the amine was prepared (99%, MH+=267).

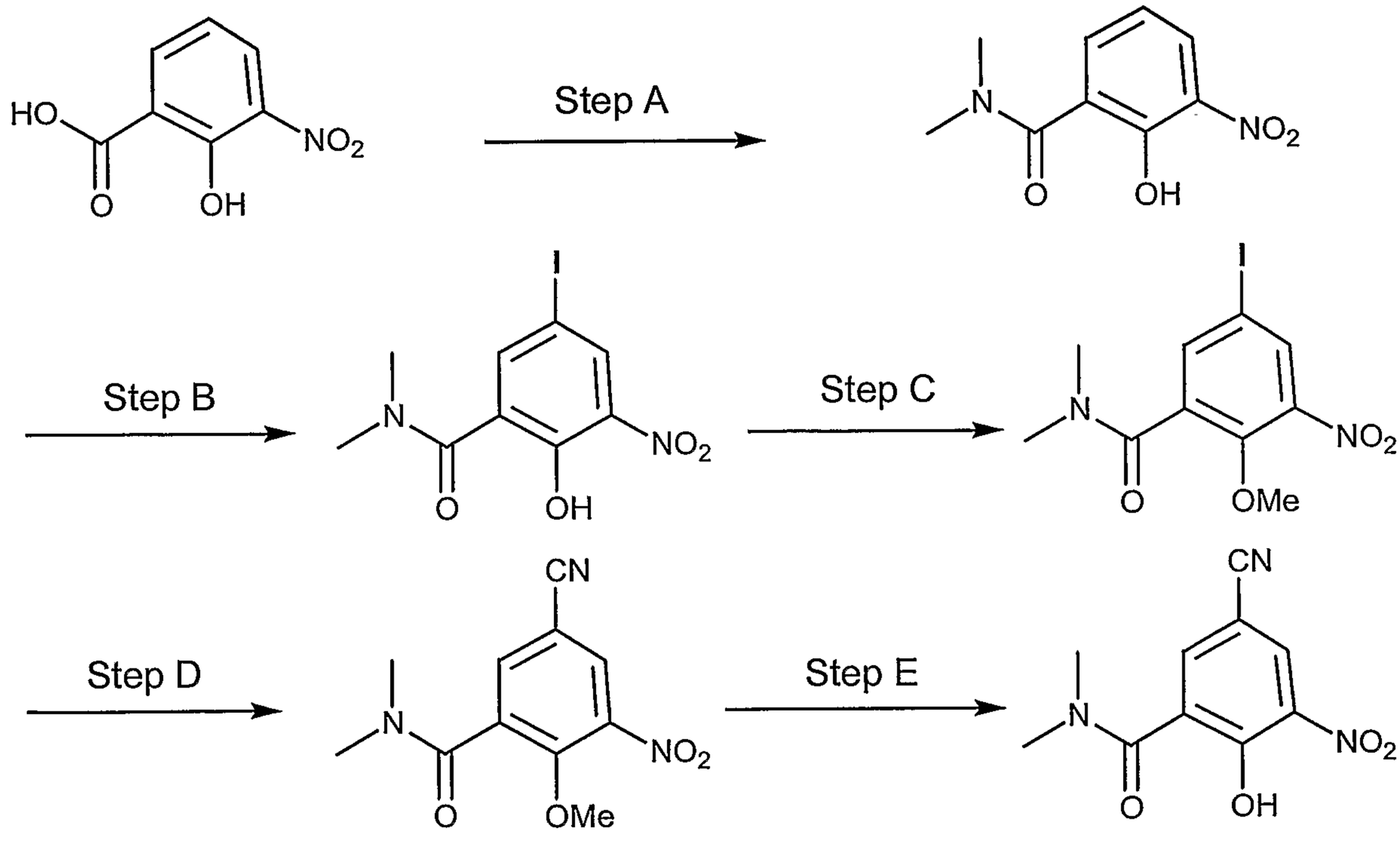
PREPARATIVE EXAMPLE 11.11 – 11.18

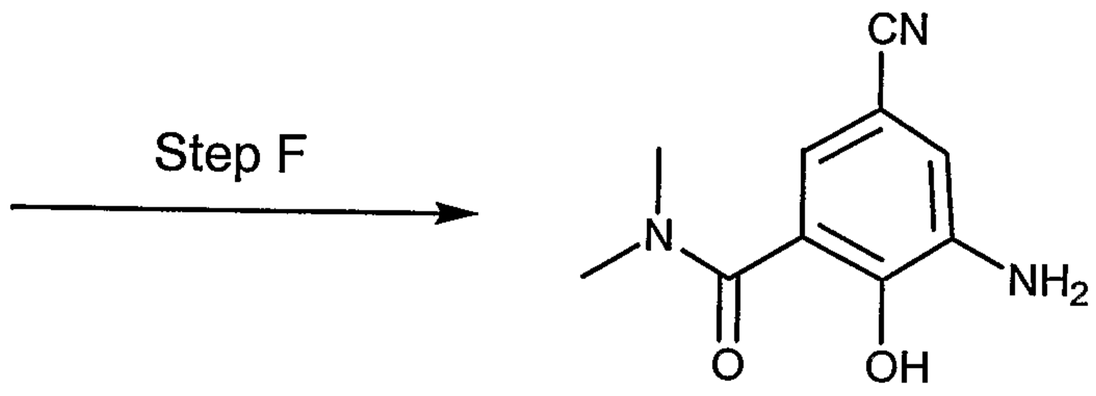
Following the procedures set forth in Preparative Examples 11.11 but using the carboxylic acid, amine, and coupling agent DCC indicated, the indicated amide products were obtained and used without further purification.

Prep Ex.	Carboxylic acid	Amine	Product	1. % Yield 2. MH^+
11.11				1. 45,92 2. 310.0
11.12				1. 45,95 2. 247.2

11.13				1. 85,85 2. 251.1
11.14				1. 99,92 2. 211.1
11.15				1. 48,84 2. 265
11.16				1. 78,91 2. 238.1
11.17				1. 67,90 2. 265.1
11.18				1. 28,99 2. 267

PREPARATIVE EXAMPLE 12





Step A

Following a similar procedure as described in Preparative Example 2 Step A except using dimethylamine in place of R-(+)-3-pyrrolidinol, the desired product was prepared.

Step B

The product from step A above (8 g) was combined with iodine (9.7 g), silver sulfate (11.9 g), EtOH (200 mL) and water (20 mL) and stirred overnight. Filtration, concentration of the filtrate, re-dissolution in CH_2Cl_2 and washing with 1*M* HCl (aq) gave an organic solution which was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the product (7.3 g, 57%, MH^+ = 337).

Step C

The product from Step B above (3.1 g) was combined with DMF(50 mL) and MeI (0.6 mL). NaH (60% in mineral oil, 0.4 g) was added portionwise and the mixture was stirred overnight. Concentration *in vacuo* afforded a residue which was diluted with CH_2Cl_2, washed with 1*M* NaOH (aq), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification through a silica gel column (EtOAc/Hex, 1:1) gave the desired compound (1.3 g, 41%, MH^+ = 351).

Step D

The product from Step D above (200 mg), $Zn(CN)_2$ (132 mg), $Pd(PPh_3)_4$ (130 mg) and DMF (5 mL) were heated at 80°C for 48 hrs, then cooled to room temperature and diluted with EtOAc and 2M NH_4OH. After shaking well, the organic extract was dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by preparative plate chromatography (Silica, EtOAc/Hex, 1:1) to give the desired compound (62 mg, 44%, MH^+ = 250).

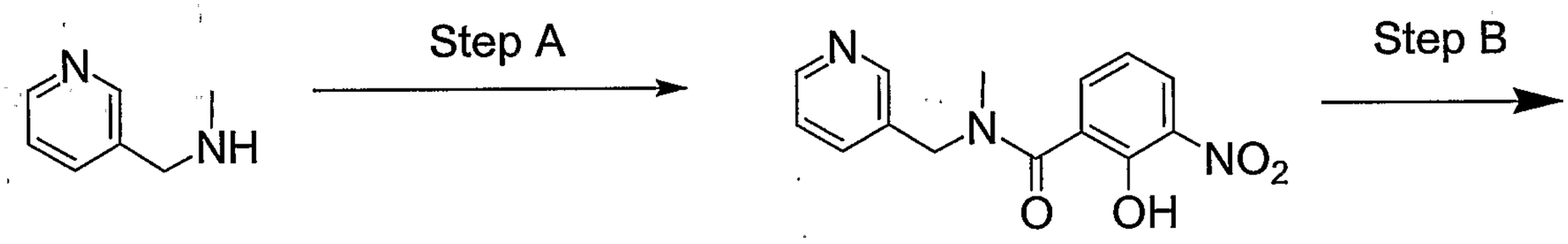
Step E

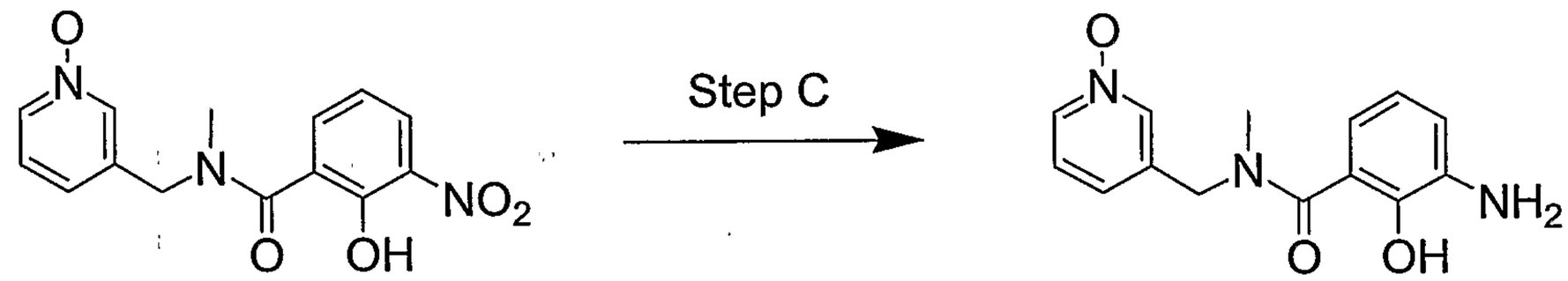
BBr_3 (1.3 mL, 1*M* in CH_2Cl_2) was added to a CH_2Cl_2 solution (5 mL) of the product from step D above (160 mg) and stirred for 30 min. The mixture was diluted with water, extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give the desired compound (158 mg, MH^+ = 236).

Step F

A mixture of the product from step E above (160 mg), platinum oxide (83%, 19 mg), and EtOH (20 mL) was stirred under hydrogen (25-40 psi) for 1.5 hr. Filtration through celite and concentration *in vacuo* afforded the product (165 mg, MH^+ = 206).

PREPARATIVE EXAMPLE 12.1





Step A

Following a similar procedure as in Preparative Example 2, Step A except using 3-(methylaminomethyl)pyridine and 3-nitrosalicylic acid, the desired compound was prepared (41%).

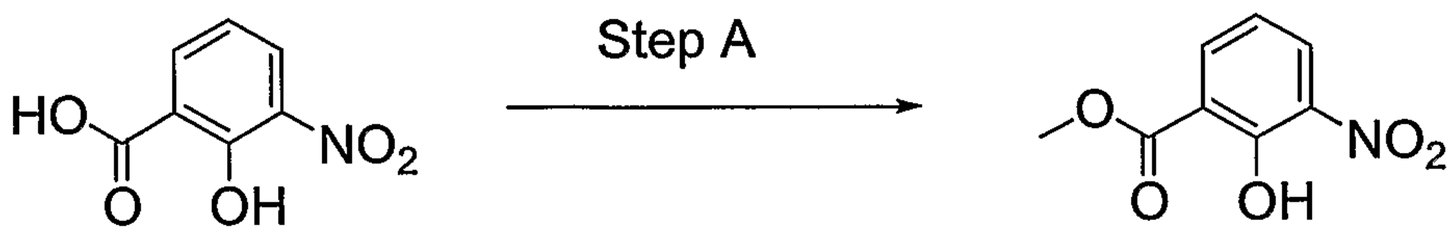
Step B

The compound from Step A above (0.3 g) was diluted with chloroform (15 mL) and stirred with *m*CPBA (0.4 g) for 2 hr. Purification by column chromatography (silica, 10% MeOH/CH_2Cl_2) gave the pyridyl N-oxide (0.32 g, 100%, MH^+ = 303.9).

Step C

Following a similar procedure as in Preparative Example 11.1, Step B, but using the product from Step B above, the desired compound was obtained (15%, MH+=274).

PREPARATIVE EXAMPLE 12.2



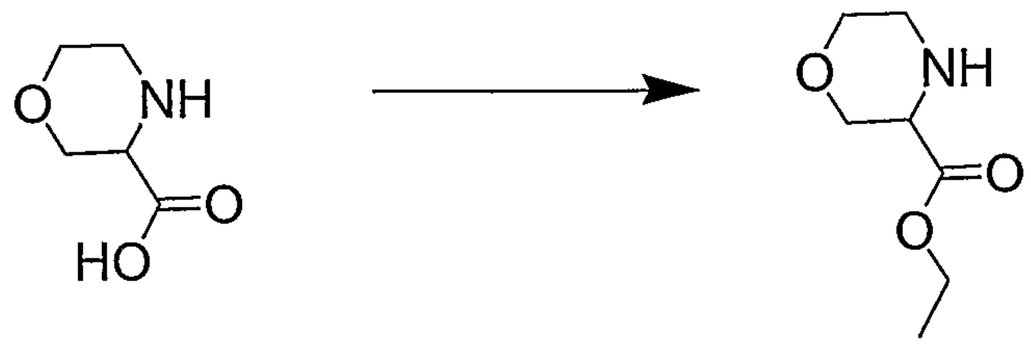
Step A

3-Nitrosalicylic acid (4 g) in MeOH (100 mL) and concentrated H_2SO_4 (1 mL) were stirred at reflux overnight, concentrated *in vacuo*, diluted with CH_2Cl_2, and dried over Na_2SO_4. Purification by column chromatography (silica, 5% MeOH/CH_2Cl_2) gave the methyl ester (2.8 g, 65%).

Step B

Following a similar procedure as in Preparative Example 2, Step B, but using the product from Step A above, the desired compound was obtained (95%, MH+=167.9).

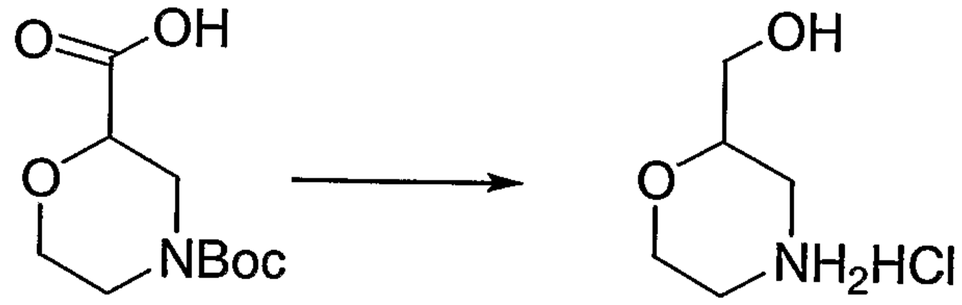
PREPARATIVE EXAMPLE 12.3



To morpholine-2-carboxilic acid (200mg) in EtOH (40mL) at 0°C was added acetyl chloride (3mL) and the mixture was stirred at reflux overnight. Concentration *in*

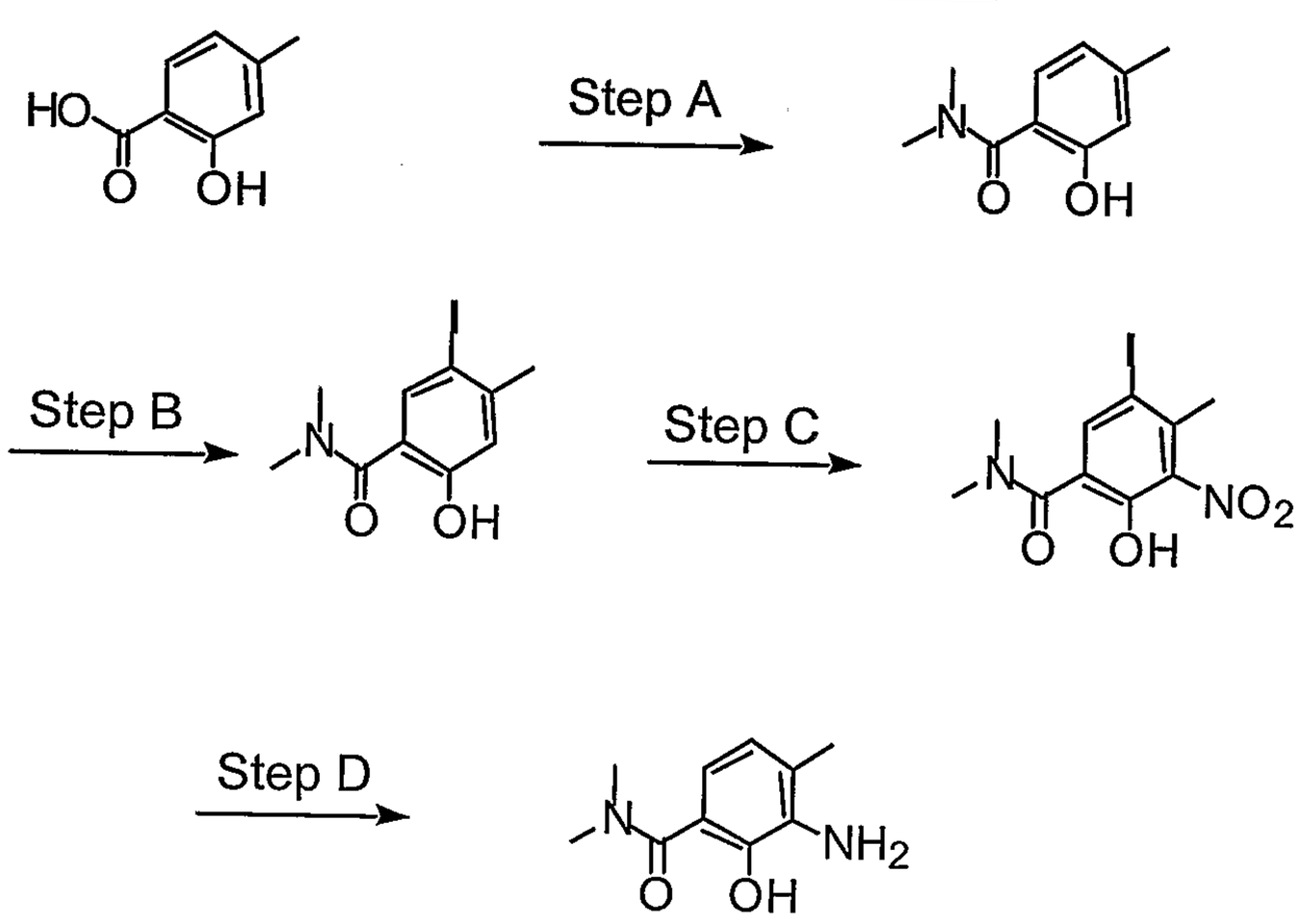
vacuo, dilution with CH_2Cl_2 and washing with $NaHCO_3$ (aq) gave the title compound (99%, MH^+ = 160.1).

PREPARATIVE EXAMPLE 12.4



To N-Boc morpholine-2-carboxylic acid (2g) in THF (5ml) at 0°C was added a solution of borane.THF complex (1N, 10.38ml) and the mixture was stirred for 30min at 0°C, and for 2hr at room temperature. Water (200ml) was added to the reaction and the mixture extracted with CH_2Cl_2, dried with Na_2SO_4, and concentrated *in vacuo* to give 490mg of product (26%). The product was then stirred in 4N HCl/dioxane to give the amine salt.

PREPARATIVE EXAMPLE 13



Step A

Following a similar procedure as in Preparative Example 1 except using dimethylamine (2*M* in THF, 50 mL) and 4-methylsalicylic acid (15 g), the desired compound was prepared (6.3 g, 35%) .

Step B

The product from Step A above (1.5 g) was combined with iodine (2.1 g), $NaHCO_3$ (1.1 g), EtOH (40 mL) and water (10 mL) and stirred overnight. Filtration, concentration of the filtrate, re-dissolution in CH_2Cl_2 and washing with 1*M* HCl (aq) gave an organic solution which was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 0.5-0.7% MeOH/CH_2Cl_2) gave the product (0.5 g, 20%, MH^+ = 306).

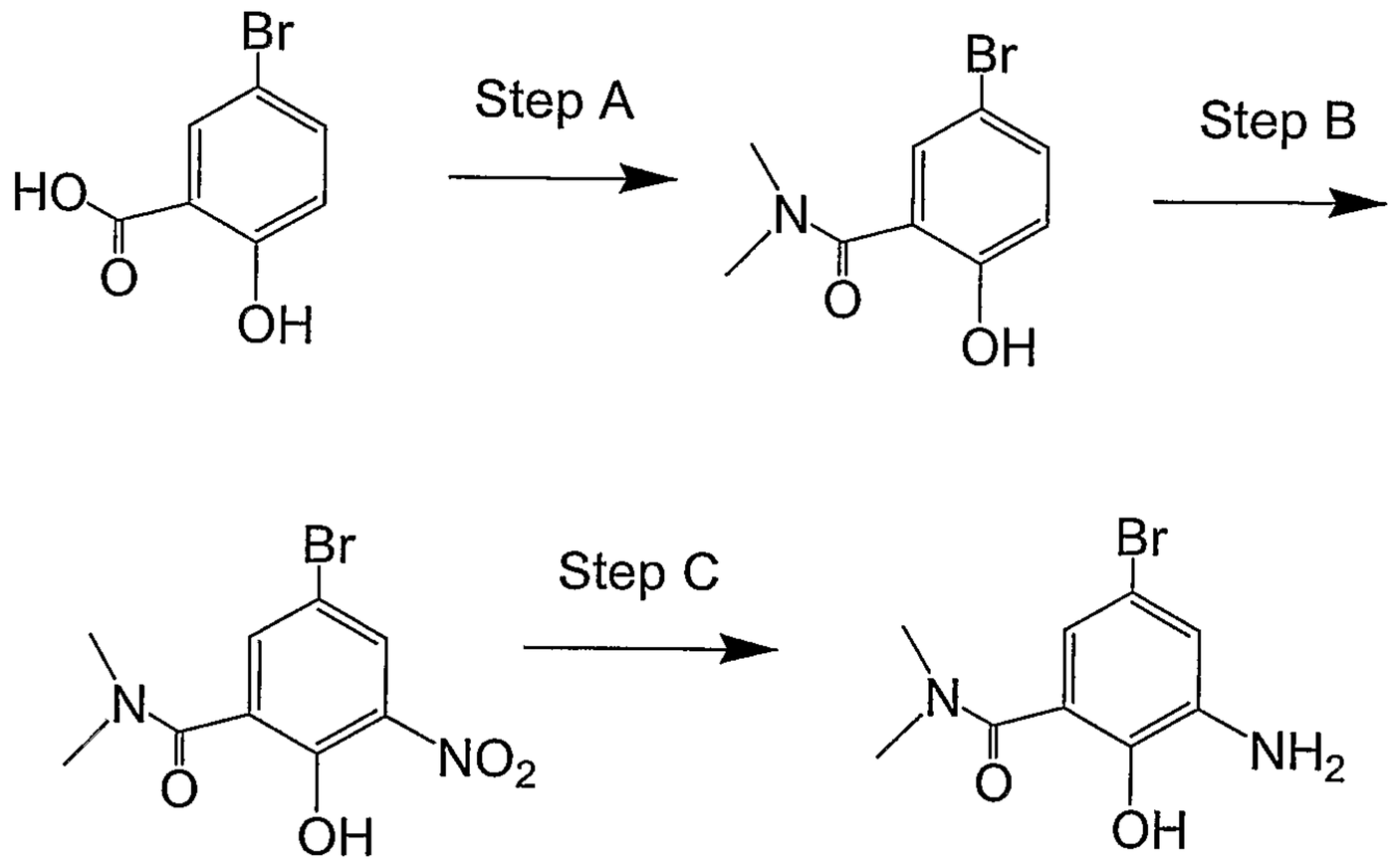
Step C

Nitric acid (3.8 mL) in AcOH (10 mL) was added to the product from Step B above (0.8 g) and the mixture was stirred for 40 min. The mixture was diluted with water and extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the product as an orange solid (0.8 g, 92%, MH^+ = 351).

Step D

A mixture of the product from step C above (800 mg), 10% Pd/C (100 mg), and EtOH/MeOH (40 mL) was stirred in a parr shaker under hydrogen (45 psi) for 1.5 hr. Filtration through celite and concentration *in vacuo* afforded the title product after purification by preparative plate chromatography (Silica, 10% MeOH/CH_2Cl_2, saturated with NH_4OH) to give the product (92 mg, 22%, MH^+ = 195).

PREPARATIVE EXAMPLE 13.1



Step A

Following a similar procedure as in Preparative Example 2, Step A except using dimethylamine (2M in THF, 23 ml) and 5-bromosalicylic acid (5g), the desired compound was prepared (4.2g, 75%, MH+=244).

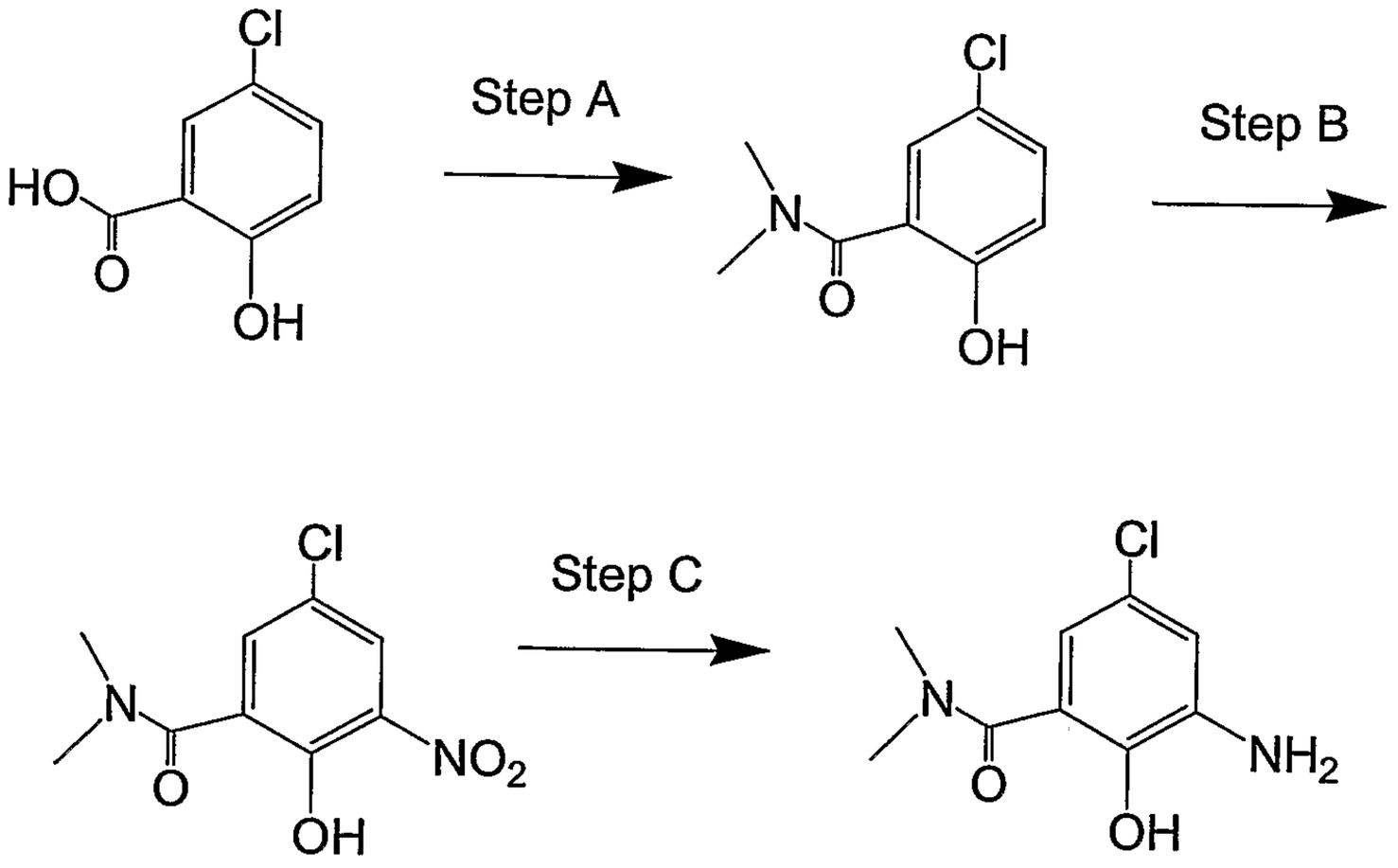
Step B

Nitric acid (10ml) in AcOH (100ml) was added to the product from Step A above (2g) and the mixture was stirred for 20 min. The mixture was diluted with water and extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the product as a yellow solid (1.9g, 80%, MH+=289).

Step C

The product from Step B above (1.9g) was partially dissolved in EtOH (50ml). Conc HCl in EtOH (5ml in 40ml), followed by $SnCl_2.2H_2O$ (5.74g) was added and stirred at room temperature overnight. The crude reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the product as a solid (185mg, 9%, MH+=259).

PREPARATIVE EXAMPLE 13.2



Step A

Following a similar procedure as in Preparative Example 2, Step A, except using dimethylamine (2M in THF, 29 ml) and 5-chlorosalicylic acid (5g), the desired compound was prepared (4.5g, 78%, MH+=200).

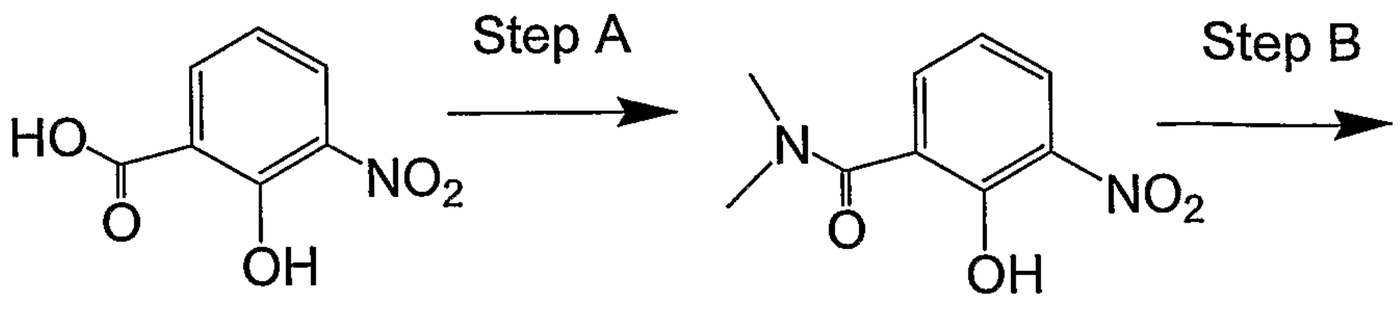
Step B

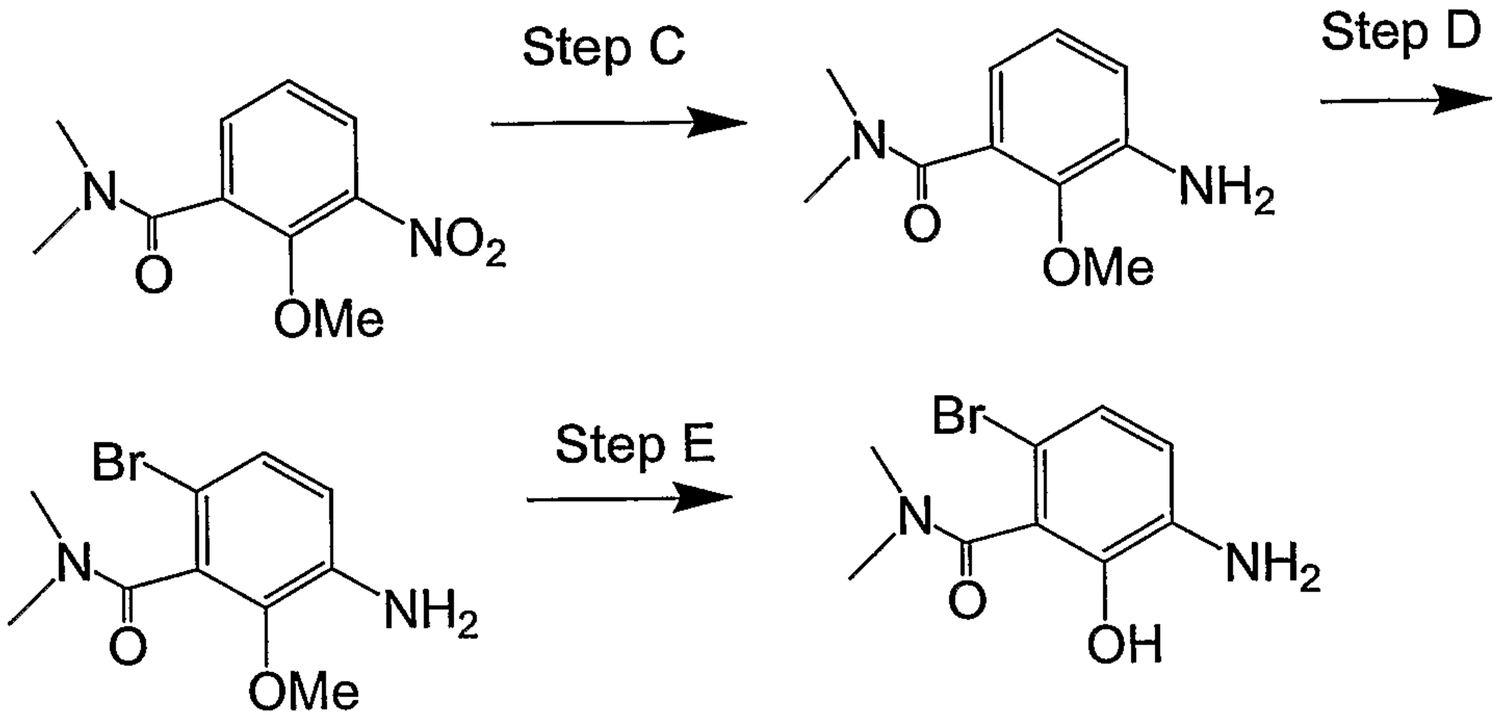
Nitric acid (10ml) in AcOH (100ml) was added to the product from Step A above (2g) and the mixture was stirred for 20 min. The mixture was diluted with water and extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the product as a solid (2.2g, 88%, MH+=245).

Step C

The product from Step B above (2.2g) was partially dissolved in EtOH(50ml). Conc HCl in EtOH (5ml in 40ml), followed by $SnCl_2.2H_2O$ (7.01g) was added and stirred at room temperature overnight. The crude reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 and neutralized with NaOH. The entire emulsion was filtered though celite, the layers were separated and the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a solid (540mg, 22%, MH+=215).

PREPARATIVE EXAMPLE 13.3





Step A

3-Nitrosalicylic acid (10g), PyBroP (20.52g), and DIEA (28ml) in anhydrous CH_2Cl_2 (200ml) were combined and stirred at room temperature for 10 min. Dimethylamine (2M in THF, 55ml) was added and let the reaction stir over the weekend. The mixture was extracted with 1N NaOH (aq) and the organic phase was discarded. The aqueous phase was acidified with 1N HCl (aq), extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The oil was taken up in ether and a solid crashed out, triterated in ether to give 4.45g of a solid (39%, MH+=211).

Step B

The product from Step A (2.99g), K_2CO_3 (9.82g), and iodomethane (8.84ml) were combined in acetone and heated to reflux overnight. The reaction was filtered and concentrated *in vacuo*. The oil was taken up in CH_2Cl_2 and washed with 1N NaOH, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give 3.3g of an oil (99%, MH+=225).

Step C

The crude product from Step B (3.3g) was stirred with 10% Pd/C (350mg) in EtOH (50ml) under a hydrogen gas atmosphere at 20psi overnight. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to give 2.34 g of a solid (85%, MH+=195).

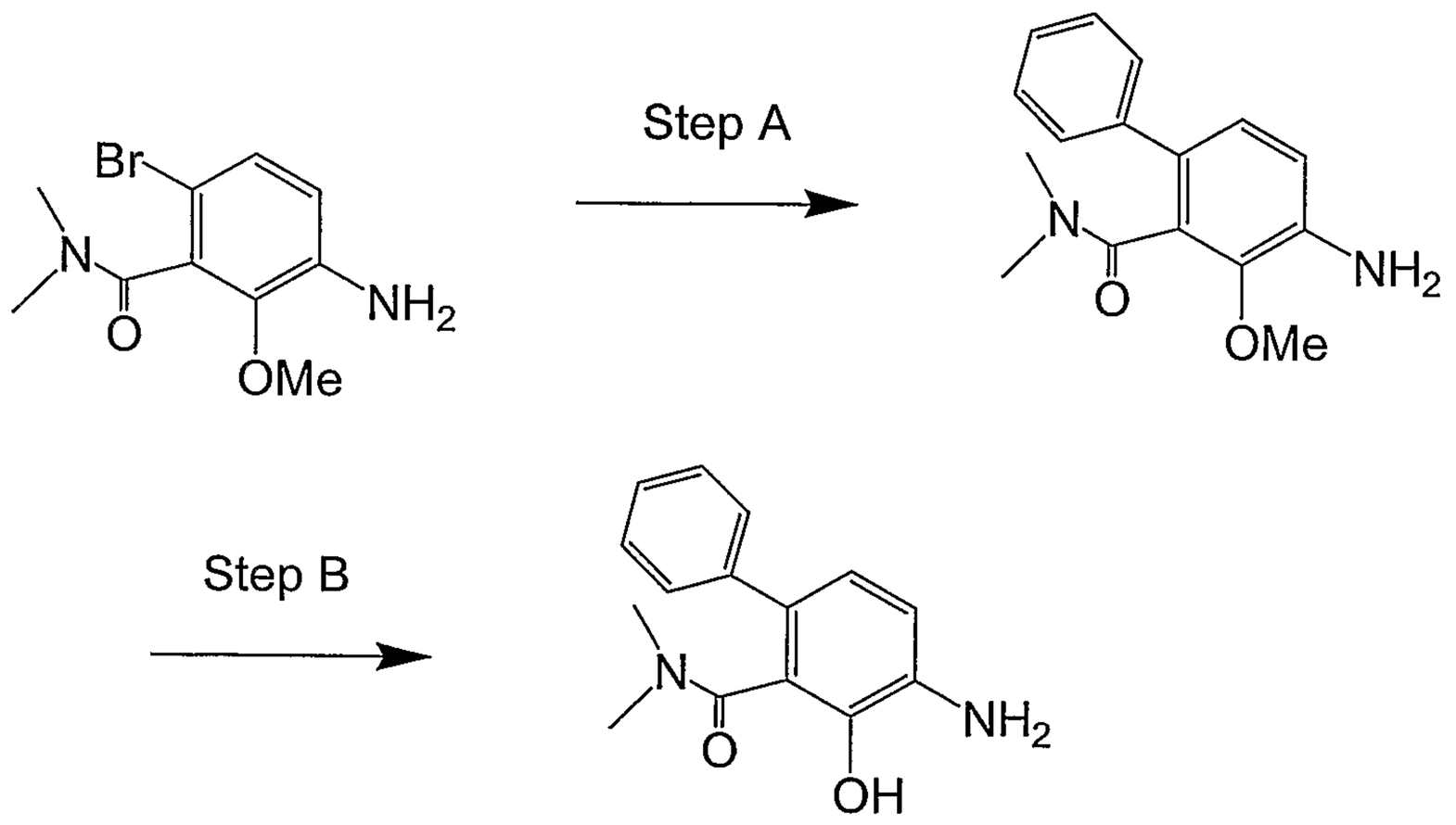
Step D

The product from Step C (469mg) was dissolved in AcOH (6ml). 1.95M Br_2 in AcOH (1.23ml) was added dropwise to the reaction and the mixture was stirred at room temperature for 1 hour. 50% NaOH was added to the reaction at 0°C and the mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by preparative plate chromatography (Silica, 5% MeOH/ CH_2Cl_2) to give the desired product (298mg, 23%, MH+=273).

Step E

BBr_3 (2.14ml, 1M in CH_2Cl_2) was added to a CH_2Cl_2 solution (8ml) of the product from Step D above (290mg) and stirred overnight. A solid formed and was filtered, taken up in MeOH/ CH_2Cl_2 and purified by preparative plate chromatography (Silica, 5% MeOH/ CH_2Cl_2) to give the desired product (137mg, 49%, MH+=259).

PREPARATIVE EXAMPLE 13.4



Step A

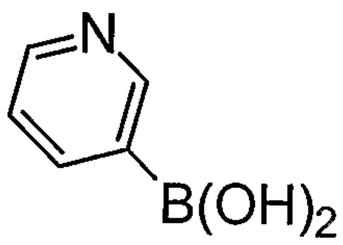
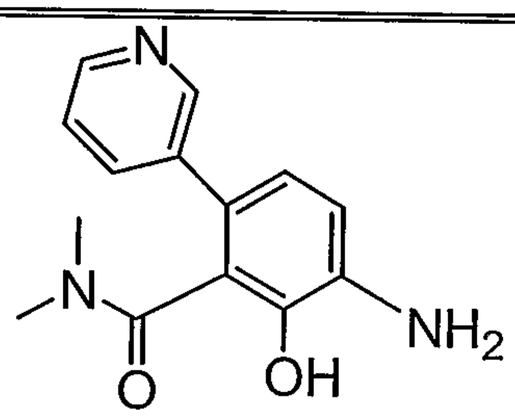
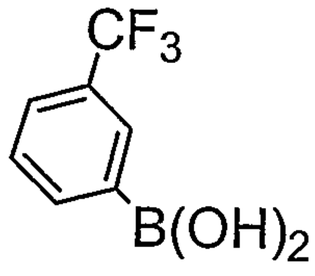
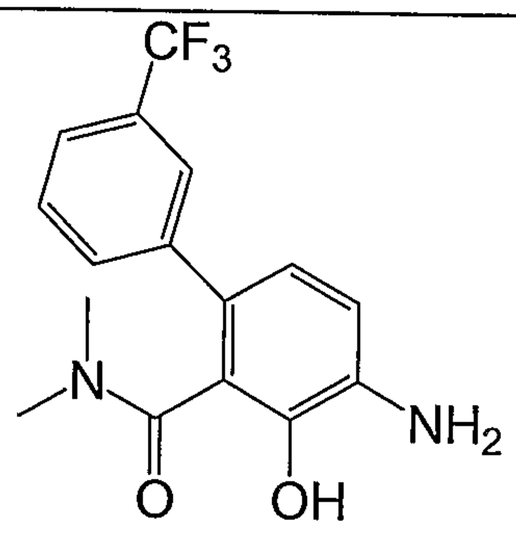
To the product from Preparative Example 13.3 Step D (200mg) was added phenylboronic acid (98mg), $PdCl_2(PPh_3)_2$ (51mg), and Na_2CO_3 (155mg) in THF/H_2O (4ml/1ml). The solution was heated at 80°C overnight. EtOAc was added to reaction and washed with 1N NaOH. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by preparative plate chromatography (5% MeOH/ CH_2Cl_2) to give 128mg of an oil (65%, MH+=271).

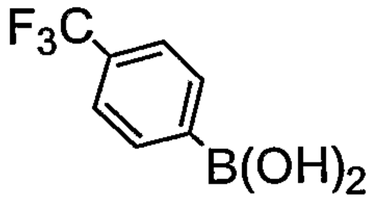
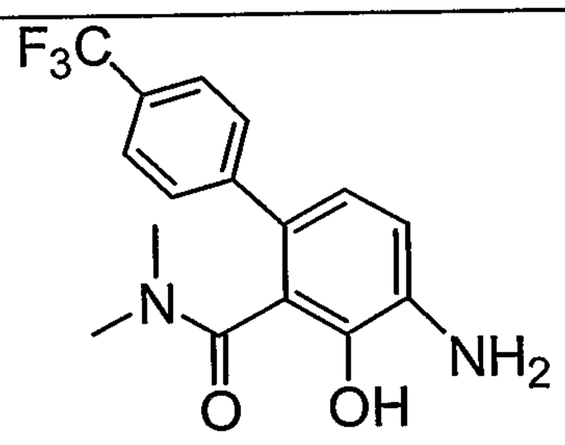
Step B

Following a similar procedure as in Preparative Example 13.3 Step E and using the product from Step A above, the desired compound was prepared (0.1 g, 69%, MH+=257.1).

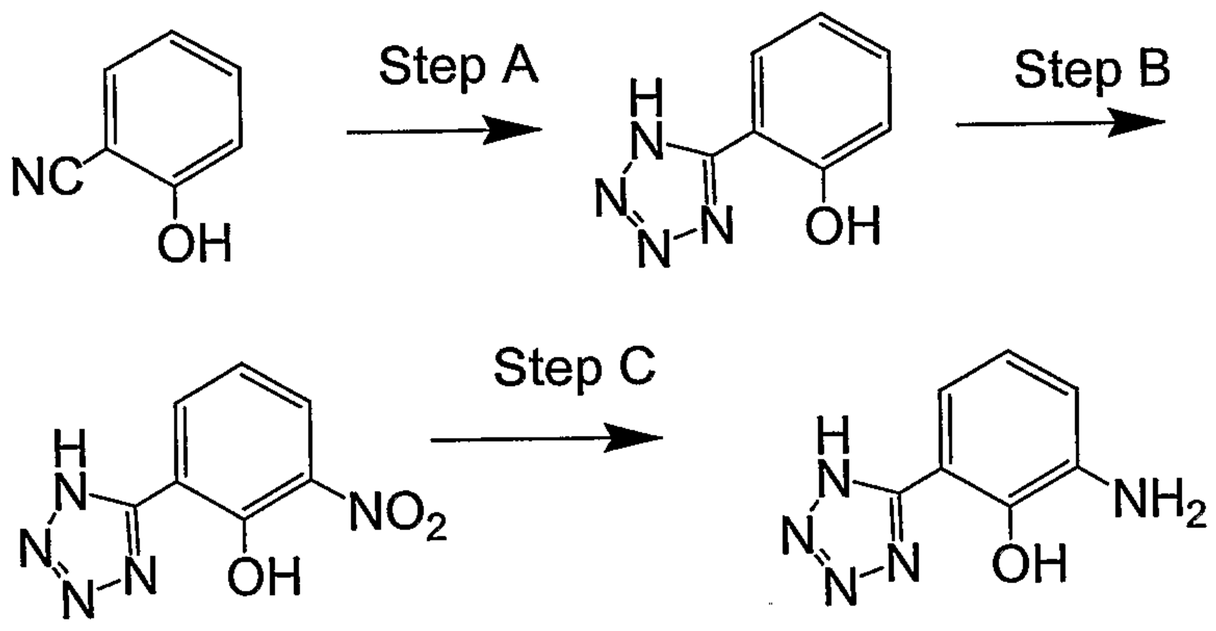
PREPARATIVE EXAMPLE 13.5-13.7

Following the procedures set forth in Preparative Example13.4 but using the boronic acid from the Preparative Example indicated in the Table below, the amine products were obtained.

Prep Ex.	Boronic Acid	Product	1. Yield (%) 2. MH^+
13.5			1. 15% 2. 258
13.6			1. 32% 2. 325

13.7			1. 18% 2. 325

PREPARATIVE EXAMPLE 13.8



Step A

2-Cyanophenol (500mg), sodium azide (819mg), and triethylamine hydrochloride (1.73g) were combined in anhydrous toluene and heated to 99°C overnight. After the reaction cooled down, product was extracted with H_2O. Aqueous layer was acidified with conc. HCl dropwise giving a precipitate, which was filtered to give the product (597mg, 87%, MH+=163).

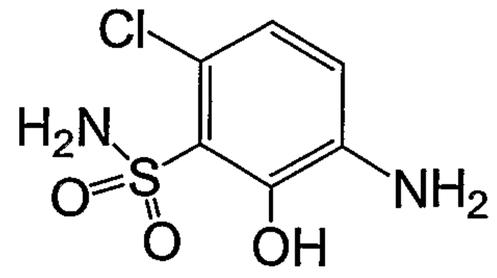
Step B

Nitric acid (0.034ml) in AcOH (5ml) was added to the product from Step A above (100mg) in AcOH and the mixture was allowed to stir for 1hr. CH_2Cl_2 and H_2O were added to reaction. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Trituration in ether gave the product as a solid (12mg, 9%, MH+=208).

Step C

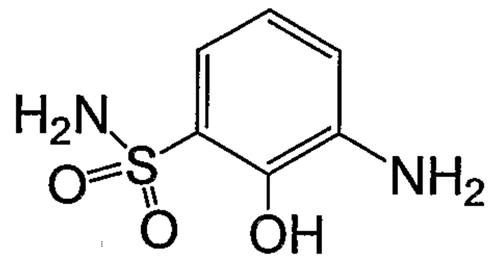
The product from step C (56mg) was stirred with 10% Pd/C (20mg) in EtOH/MeOH (15ml) under a hydrogen gas atmosphere overnight. The reaction mixture was filtered through celite, the filtrate was concentrated *in vacuo* to give 29mg of a solid (62%, MH+=178).

PREPARATIVE EXAMPLE 13.9



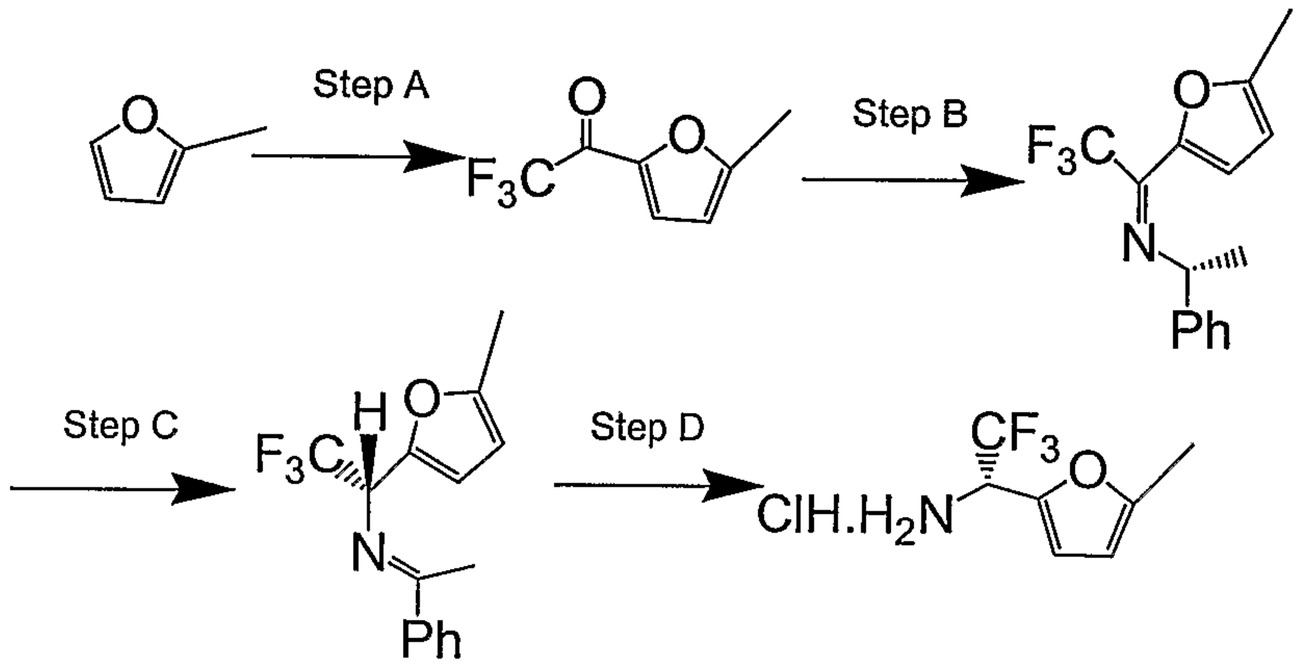
The amine was prepared following the procedure disclosed in WO 01/68570, the disclosure of which is incorporated herein by reference thereto.

PREPARATIVE EXAMPLE 13.10



The amine was prepared following the procedure disclosed in WO 01/68570, the disclosure of which is incorporated herein by reference thereto.

PREPARATIVE EXAMPLE 13.11



Step A

Following the procedure described in Preparative Example 88.2, Step A, the ketone was prepared (6.4g, 36%).

Step B

To a solution of ketone (1g) and 2-*R*-methylbenzylamine (0.73ml) in anhydrous toluene (20ml) was added 1N $TiCl_4$ in toluene (3ml) at room temperature for 1.5hrs.

The precipitate was filtered and the filtrate was concentrated *in vacuo* and purified via flash column chromatography (Hex/EtOAc, 18/1) to give 800mg of product (71%).

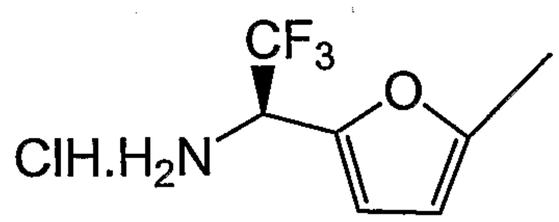
Step C

The imine from above (760mg) and DBU (800ul) were stirred without solvent for 4hr. The crude reaction was concentrated *in vacuo* and purified via flash column chromatography (Hex/EtOAc, 8/1) to give 600mg of product (79%).

Step D

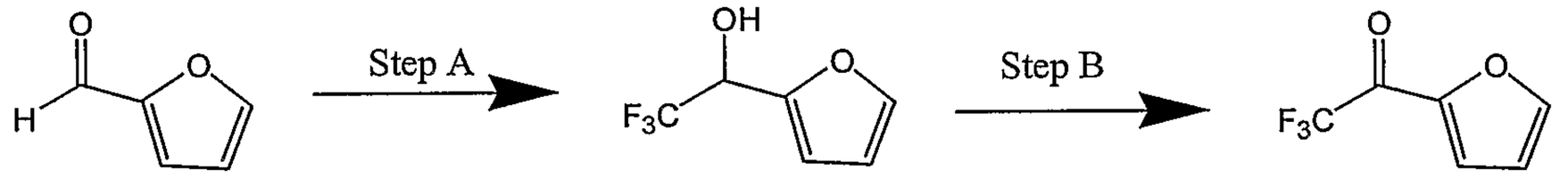
The imine from Step C (560mg) was dissolved in ether (8ml). 3N HCl (5ml) added and let stir at room temperature overnight. The ether layer was separated and concentrated *in vacuo* to give 400mg of the amine hydrochloride product (93%).

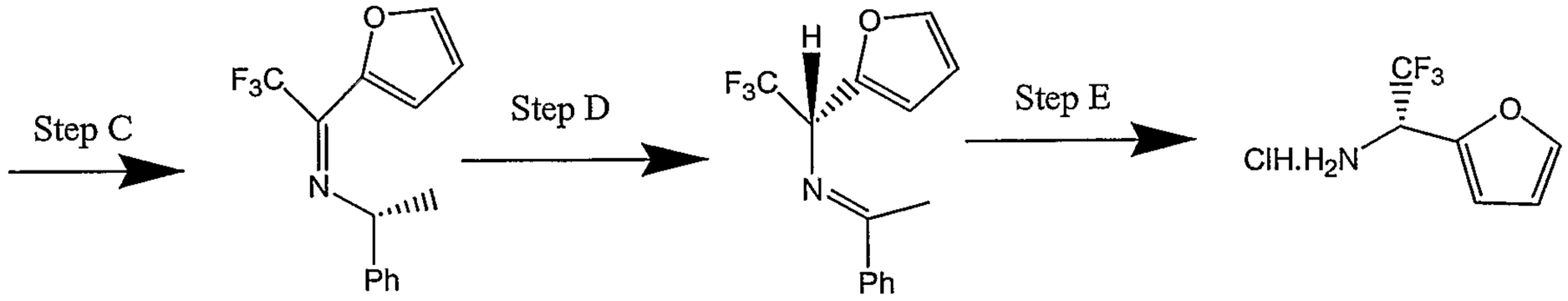
PREPARATIVE EXAMPLE 13.12



The title compound was prepared similarly as in Preparative Example 13.11, but using the 2-*S*-methylbenzylamine instead of 2-*R*-methylbenzylamine (69%).

PREPARATIVE EXAMPLE 13.13





Step A

At room temperature, CsF (60mg) was added to a mixture of furfuraldehyde (1.3ml) and TMS-CF_3 (2.5g) and stirred at room temperature (24 h) and refluxed for another 12h. 3N HCl (40ml) was added and after 4hr, the mixture was extracted with

ether, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the product (2.6g, 100%).

Step B

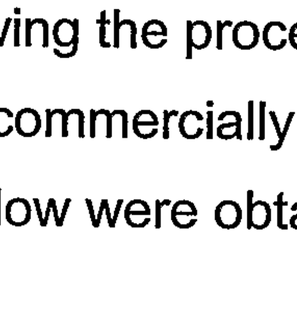
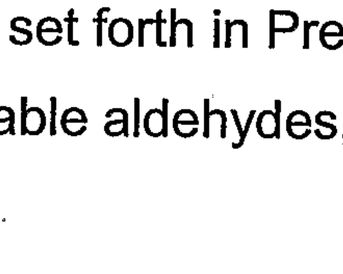
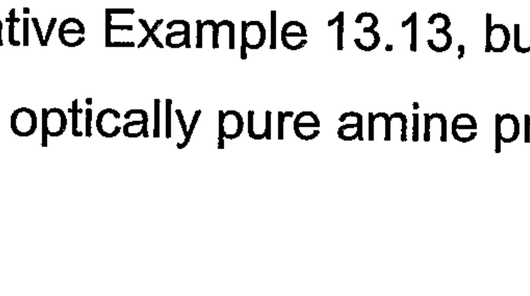
To a solution of alcohol from above (2.6g) in CH_2Cl_2 at room temperature was added Dess-Martin reagent (10g) portionwise and 1 drop of water. After stirring for 3hr at room temperature, 10% $Na_2S_2O_3$ (60ml) was added and after stirring overnight, the solid was filtered off and the filtrate was extracted with CH_2Cl_2. The organic layer was washed with saturated sodium bicarbonate, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Ether/hexane (1:2; 30ml) was added to the residue, filtered, and filtrate concentrated *in vacuo* to give the product (2g, 78%).

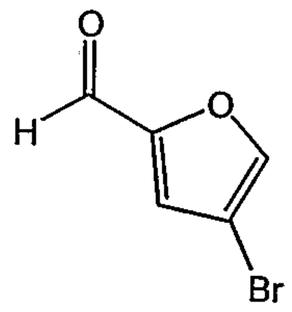
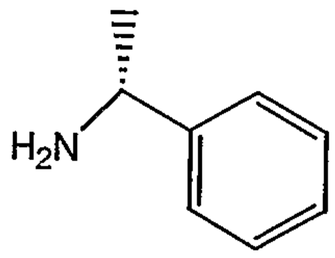
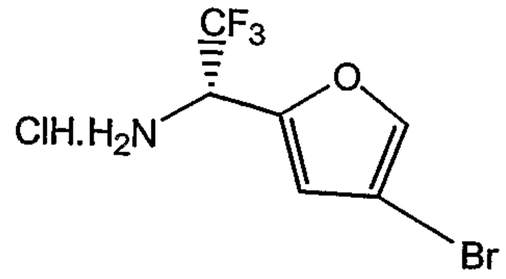
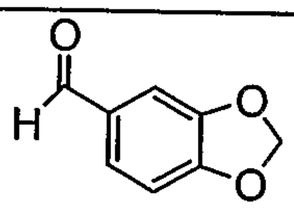
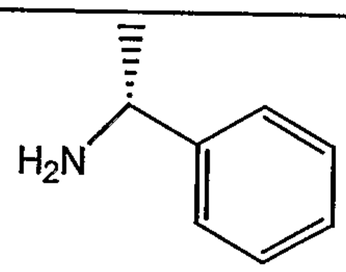
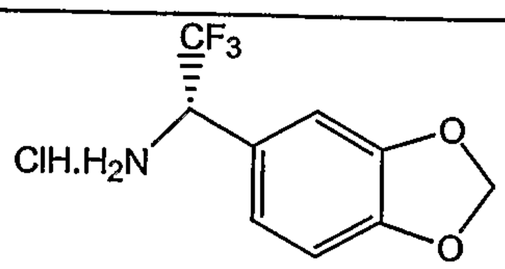
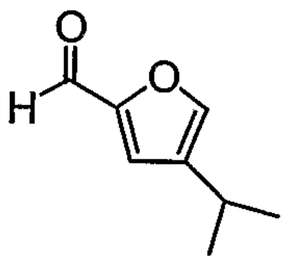
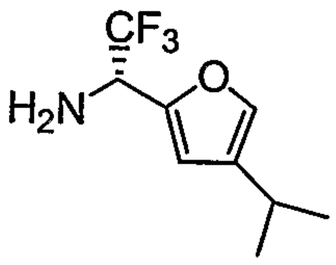
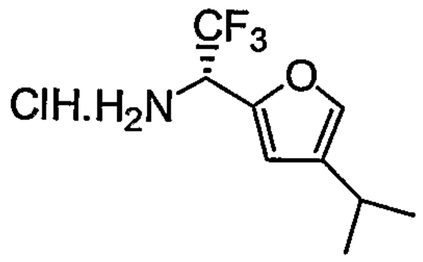
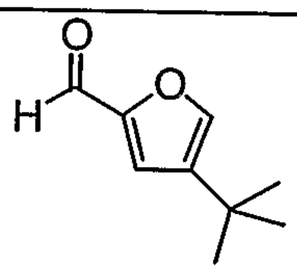
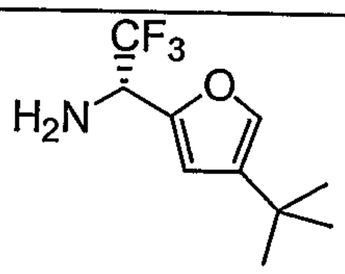
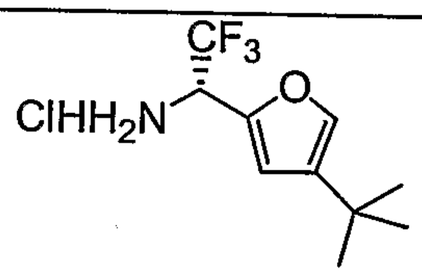
Step C

Following the procedures described in Preparative Example 13.11, Steps B, C and D, the amine salt was prepared.

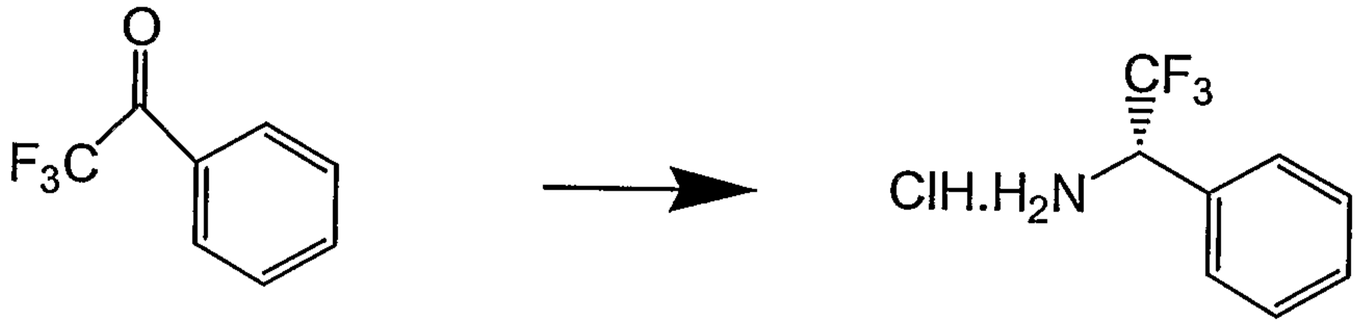
PREPARATIVE EXAMPLES 13.15-13.17

Following the procedure set forth in Preparative Example 13.13, but using the prepared or commercially available aldehydes, the optically pure amine products in the Table below were obtained.

Prep Ex.	Aldehyde	Amine	Product	Yield (%)
13.15	34.12 			20

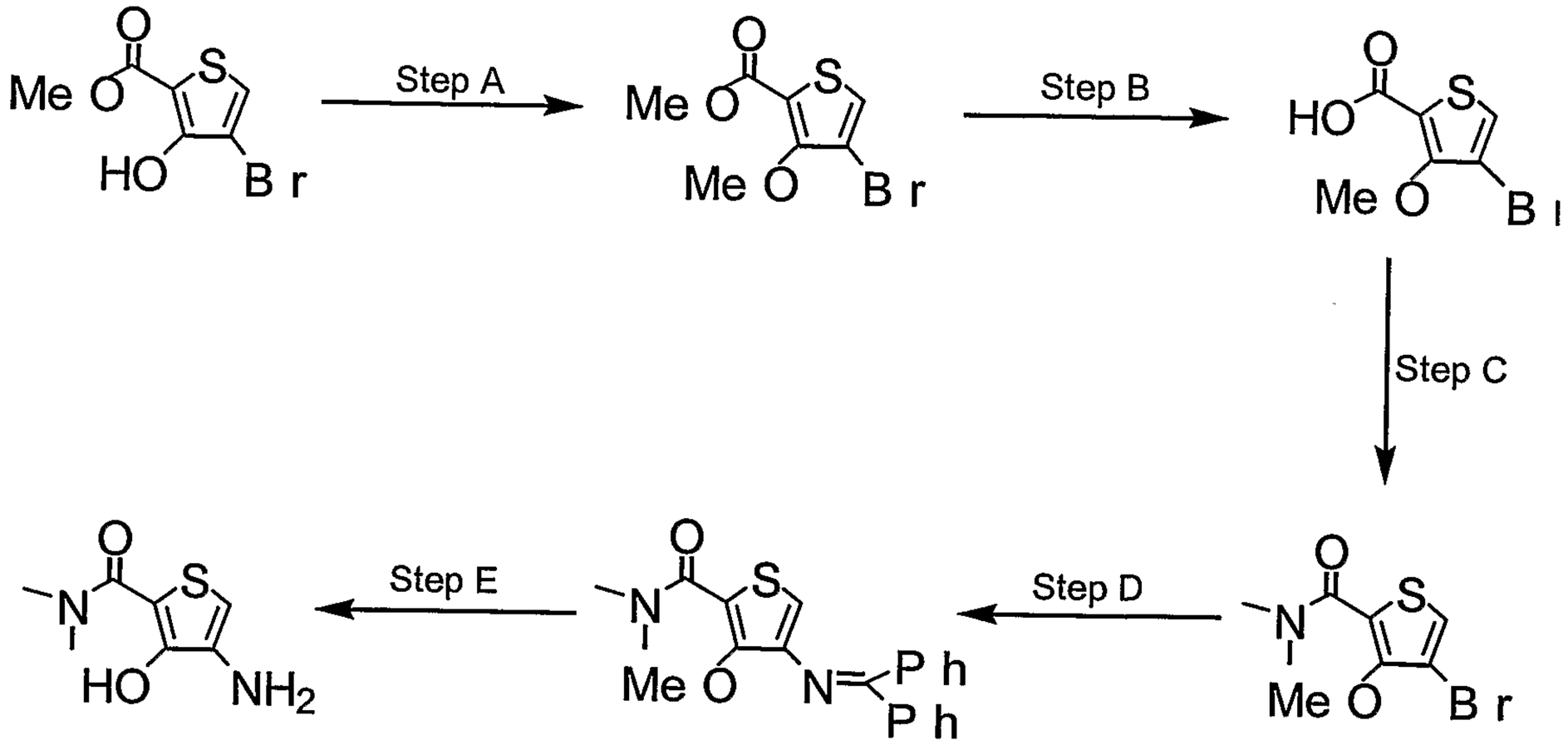
13.16				31
13.17				66
13.17A	34.8 			38
13.17B				31

PREPARATIVE EXAMPLE 13.18



The title compound was prepared from trifluorophenylketone according to the procedures described in Preparative Example 13.11, Steps B, C, and D (68%).

PREPARATIVE EXAMPLE 13.19



Step A

Methyl-3-hydroxy-4-bromo-2-thiophenecarboxylate (10.0 g, 42.2 mmol) was dissolved in 250 mL of acetone. Potassium carbonate (30.0 g, 217.4 mmol) was added followed by a solution of iodomethane (14.5 mL, 233.0 mmol). The mixture was heated to reflux and continued for 6 h. After cooled to room temperature, the mixture was filtered, the solid material was rinsed with acetone (~200 mL). The filtrate and rinsing were concentrated under reduced pressure to a solid, further dried on high vacuum, yielding 13.7 g (100%) of methyl-3-methoxy-4-bromo-2-thiophenecarboxylate (MH^+ = 251.0).

Step B

Methyl-3-methoxy-4-bromo-2-thiophenecarboxylate (13.7 g), available from step A, was dissolved in 75 mL of THF, and added with a 1.0 M sodium hydroxide aqueous solution (65 mL, 65.0 mmol). The mixture was stirred at room temperature for 24 h. A 1.0 M hydrogen chloride aqueous solution was added dropwise to the mixture until pH was approximately 2. The acidic mixture was extracted with CH_2Cl_2 (100 mL x 2, 50 mL). The combined organic extracts were washed with brine (40 mL), dried with Na_2SO_4, and concentrated under reduced pressure to a solid, 10.0 g (100%, over two steps) of 3-methoxy-4-bromo-2-thiophenecarboxylic acid (MH^+ = 237.0).

Step C

To a stirred solution of 3-methoxy-4-bromo-2-thiophenecarboxylic acid (6.5 g, 27.4 mmol) in 140 mL of CH_2Cl_2, obtained from step B, was added bromo-tripyrrolidinophosphonium hexafluorophosphate (PyBrop, 12.8 g, 27.5 mmol), a 2.0 M solution of dimethyl amine in THF (34.5mL, 69.0 mmol), and diisopropylethyl amine (12.0 mL, 68.7 mmol). After 3 d, the mixture was diluted with 100 mL of CH_2Cl_2, and washed with a 1.0 M sodium hydroxide aqueous solution (30 mL x 3) and brine (30 mL). The organic solution was dried with Na_2SO_4, filtered, and concentrated to an oil. This crude oil product was purified by flash column chromatography, eluting with CH_2Cl_2-hexanes (1:1, v/v). Removal of solvents afforded a solid, further dried on high vacuum, yielding 6.76 g (93 %) of *N*, *N'*-dimethyl-3-methoxy-4-bromo-2-thiophenecarboxamide (MH^+ = 265.0, M+2 = 266.1).

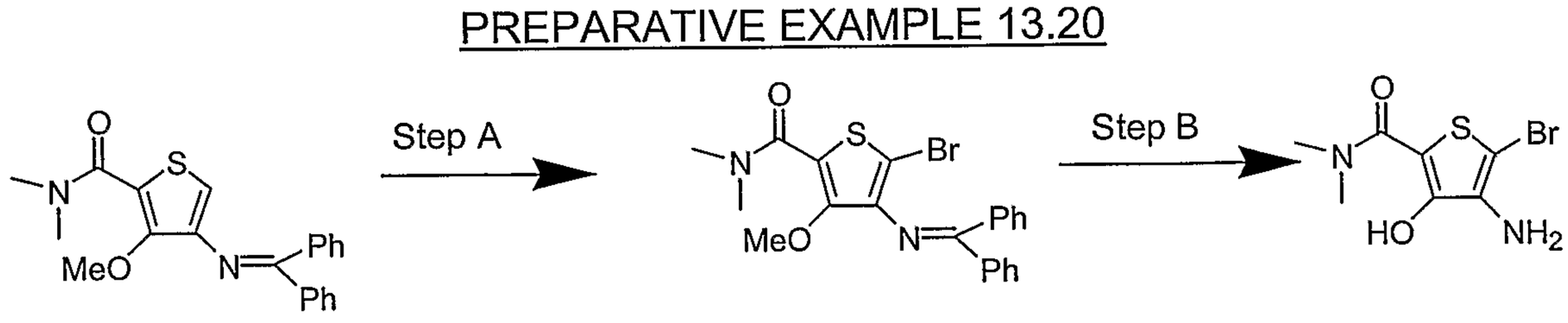
Step D

An oven dried three-neck round bottom flask was equipped with a refluxing condenser, charged sequentially with palladium acetate (95 mg, 0.42 mmol), (*R*)-BINAP (353 mg, 0.57 mmol), cesium carbonate (9.2 g, 28.33 mmol), and *N*, *N'*-dimethyl-3-methoxy-4-bromo-2-thiophenecarboxamide (3.74 g, 14.2 mmol, from step C). The solid mixture was flushed with nitrogen. Toluene (95 mL) was added to the solid mixture followed by benzophenone imine (3.6 mL, 21.5 mmol). The mixture was heated to reflux and continued for 10 h. A second batch of palladium acetate (95 mg, 0.42 mmol) and (*R*)-BINAP (353 mg, 0.57 mmol) in 5 mL of toluene was added. Refluxing was continued for 14 h. The third batch of palladium acetate (30 mg, 0.13 mmol) and (*R*)-BINAP (88 mg, 0.14 mmol) was added, and reaction continued at 110°C for 24 h. The mixture was cooled to room temperature, diluted with ether (50 mL), filtered through a layer of Celite, rinsing with ether. The filtrate and rinsing were concentrated under reduced pressure to an oil, which was purified twice by flash column chromatography using CH_2Cl_2 and CH_2Cl_2-MeOH (200:1) as eluents. Removal of solvents afforded 4.1 g (79 %) of the amido-thiophene diphenylimine product as a solid (MH^+ = 365.1).

Step E

To a stirred solution of thiophene imine (5.09 g, 13.97 mmol), obtained from step D, in 140 mL of CH_2Cl_2 at –78°C was added dropwise a 1.0 M solution of boron tribromide in CH_2Cl_2. The mixture was stirred for 3 h while the temperature of the cooling bath was increased slowly from –78°C to –15°C. 100 mL of H_2O was added, the mixture was stirred at room temperature for 30 min, then the two layers were separated. The organic layer (as A) was extracted with H_2O (30 mL x 2). The aqueous layer and aqueous extracts were combined, washed with CH_2Cl_2 (30 mL), and adjusted to pH ~ 8 using a saturated $NaHCO_3$ aqueous solution. The neutralized aqueous solution was extracted with CH_2Cl_2 (100 mL x 3), the extracts were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to a light yellow solid, 1.49 g of *N*, *N'*-dimethyl-3-hydroxy-4-amino-2-thiophenecarboxamide (first crop). The previous separated organic layer A and organic washing were combined, stirred with 30 mL of a 1.0 M HCl aqueous solution for 1 h. The two layers were separated, the aqueous layer was washed with CH_2Cl_2 (30 mL) and adjusted to pH ~8 using a saturated $NaHCO_3$ aqueous solution, and the separated organic layer and organic washing were combined as organic layer B. The neutralized aqueous solution was extracted with CH_2Cl_2 (30 mL x 4), the extracts were washed with brine, dried by Na_2SO_4, and concentrated under reduced pressure to give 0.48g of a solid as the second crop of the titled product. Organic layer B from above was washed with brine, and concentrated to an oil, which was separated by preparative TLC (CH_2Cl_2-MeOH = 50:1) to afford 0.45 g of a solid as the third crop of the titled product. The overall yield of the product, *N*, *N'*-dimethyl-3-hydroxy-4-amino-2-thiophenecarboxamide, is 2.32 g (89%) (MH^+ = 187.0).

PREPARATIVE EXAMPLE 13.20



Step A

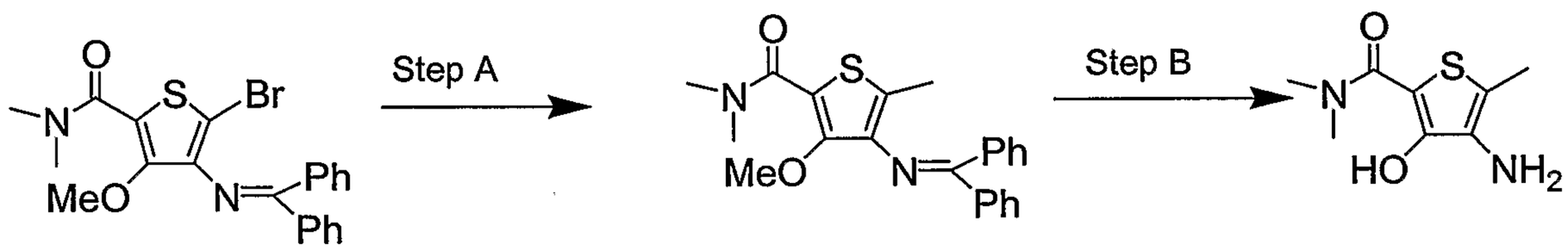
To the product from Preparative Example 13.19 Step D (1.56g) in CH_2Cl_2 (55ml) was added potassium carbonate (1.8g) followed by dropwise addition of

bromine (0.45ml). After 5hr of mixing, water (100ml) was added to the reaction and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, which was then washed with brine, saturated sodium bicarbonate, and brine again. The organic layer was dried with Na_2SO_4, and concentrated *in vacuo*. The residue was purified via flash column chromatography (CH_2Cl_2) to yield 1.6g of product (83%).

Step B

The product from above was reacted in the procedure set forth in Preparative Example 13.19 Step C to give the amine.

PREPARATIVE EXAMPLE 13.21



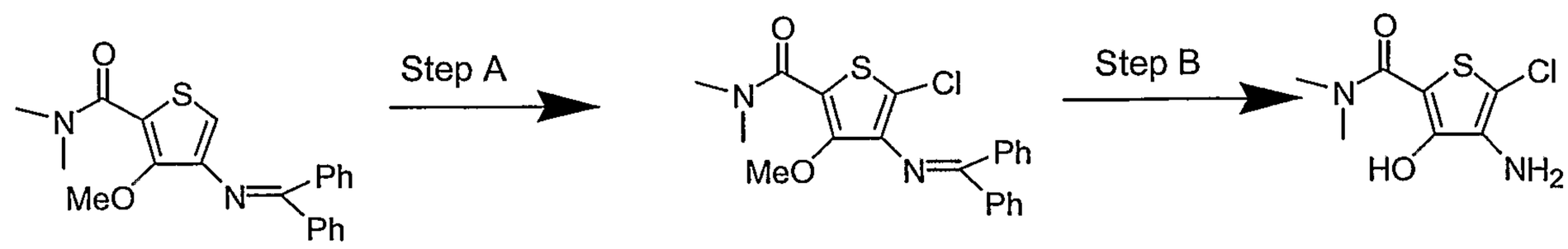
Step A

To the product from Preparative Example 13.20, Step A (300mg) in THF (7ml) at -78 °C was added a solution of n-BuLi (1.6M in hexanes, 0.54ml). After 1hr, iodomethane (0.42ml) was added dropwise. After 3 hrs of stirring at -78 °C, the reaction was warmed to room temperature overnight. Saturated ammonium chloride and water were added to the reaction and extracted with CH_2Cl_2. The organic layer was washed with saturated sodium bicarbonate and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by preparative plate chromatography (CH_2Cl_2-MeOH = 70:1 to 50:1) to afford the product (111mg, 43%).

Step B

The product from above was reacted in the procedure set forth in Preparative Example 13.19, Step E to give the amine.

PREPARATIVE EXAMPLE 13.22



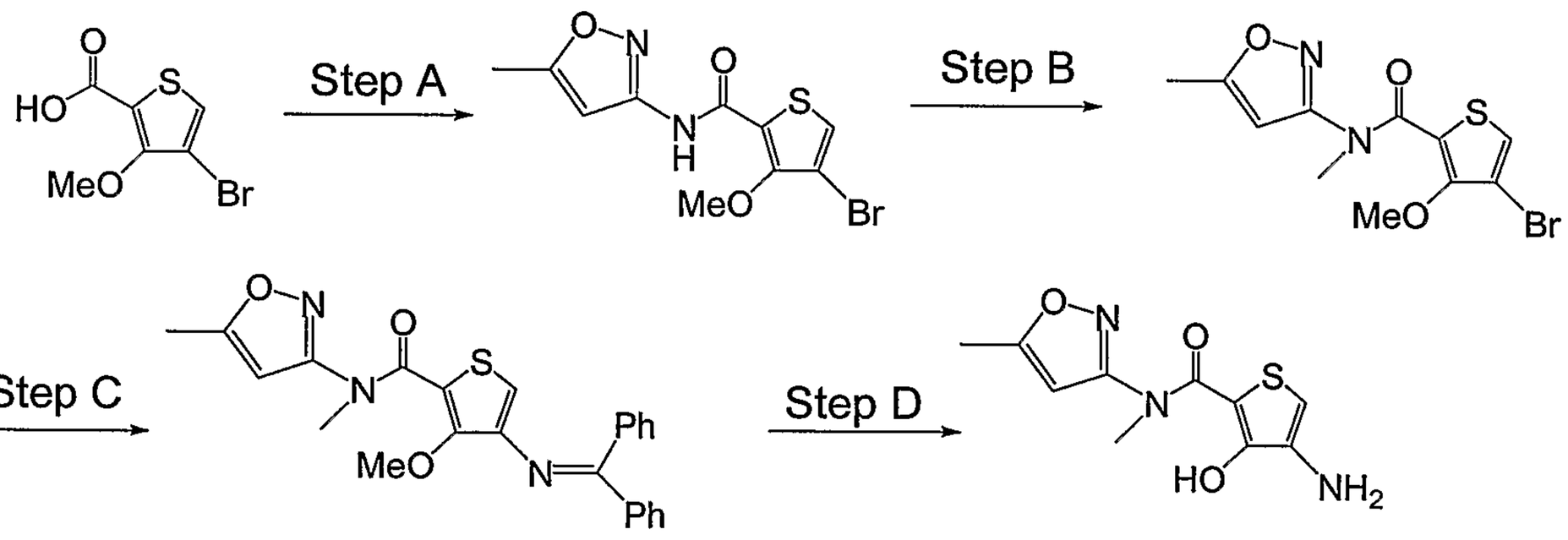
Step A

To the product from Preparative Example 13.19 (400mg), Step D in CH_2Cl_2-pyridine (14ml) was added N-chlorosuccinimide (220mg). The mixture was stirred for 5hr and then diluted with CH_2Cl_2 and washed with water, saturated sodium bicarbonate and brine, and concentrated *in vacuo*. The crude product was purified via preparative plate chromatography (CH_2Cl_2-MeOH = 50:1) to give 180mg of product (64%).

Step B

The product from above (274mg) was reacted in the procedure set forth in Preparative Example 13.19, Step E to give the amine (89mg, 58%).

PREPARATIVE EXAMPLE 13.23



Step A

To a stirred solution of acid (630mg) from Preparative Example 13.19, Step B in CH_2Cl_2 (25ml) was added oxalyl chloride (235ul) followed by a catalytic amount of DMF (10ul). The mixture was stirred for 1hr, then potassium carbonate (1.8g) was added followed by 3-amino-5-methylisoxazole (443mg). The reaction stirred overnight and was quenched with water (25ml). Layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by preparative plate chromatography (CH_2Cl_2) to afford the product (580mg, 78%, MH+=317,319).

Step B

The acid from the above (750mg) step was reacted following the procedure set forth in Preparative Example 13.3, Step B to yield 625mg of product (80%, MH+=331).

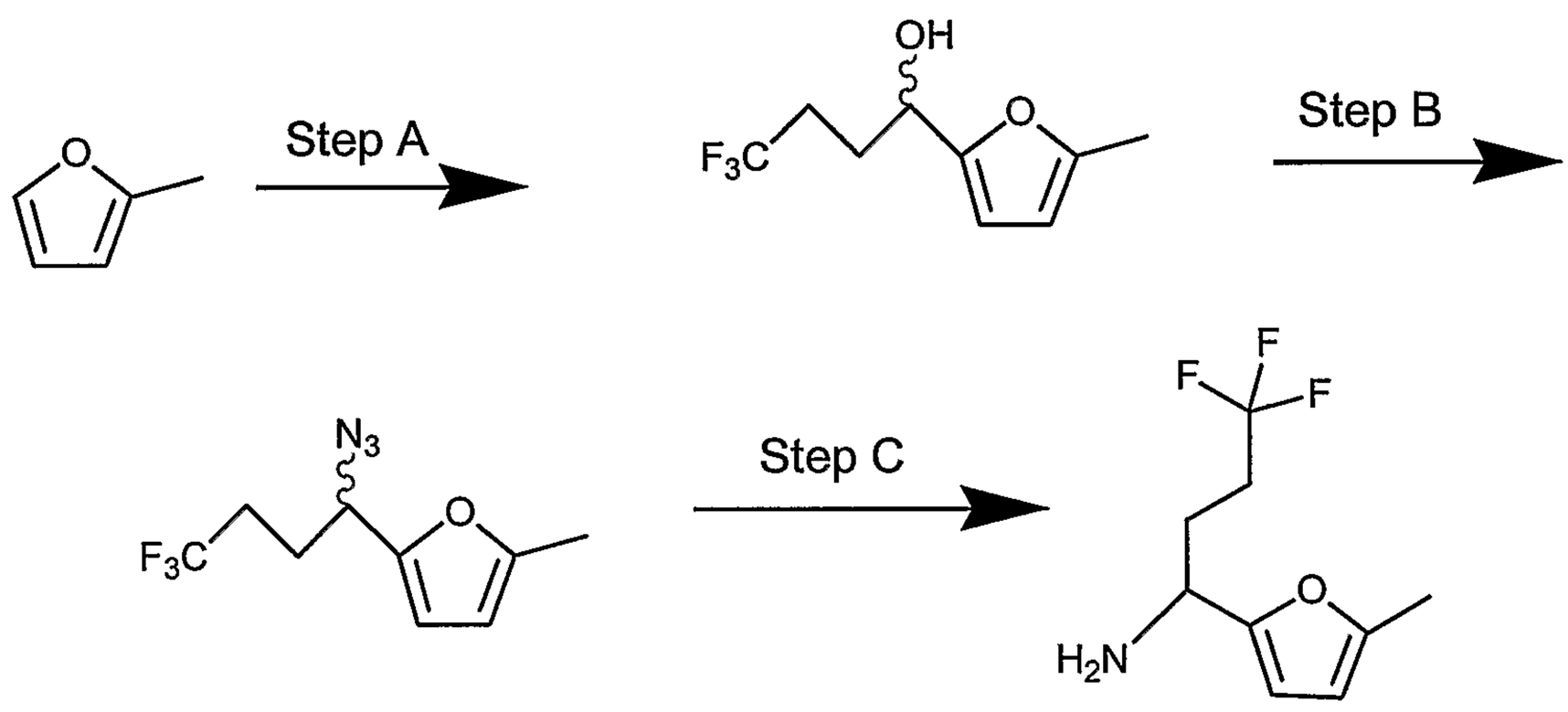
Step C

The product from above was reacted following the procedure set forth in Preparative Example 13.19, Step D to yield 365mg of product (53%)

Step D

The product from above was reacted following the procedure set forth in Preparative Example 13.19, Step E to give the amine product (MH+=254).

PREPARATIVE EXAMPLE 13.25



Step A

To a solution of 2-methylfuran (1g) in ether (30ml) was added n-BuLi (5.32ml) at –78°C. The reaction was warmed to room temperature and then refluxed at 38 °C for 1hr. The reaction was cooled back down to –78°C where the furyl lithium was quenched with trifluorobutyraldehyde and let stir at room temperature overnight. Saturated ammonium chloride added and extracted with ether. Purified via flash column chromatography to yield pure product (2g, 80%)

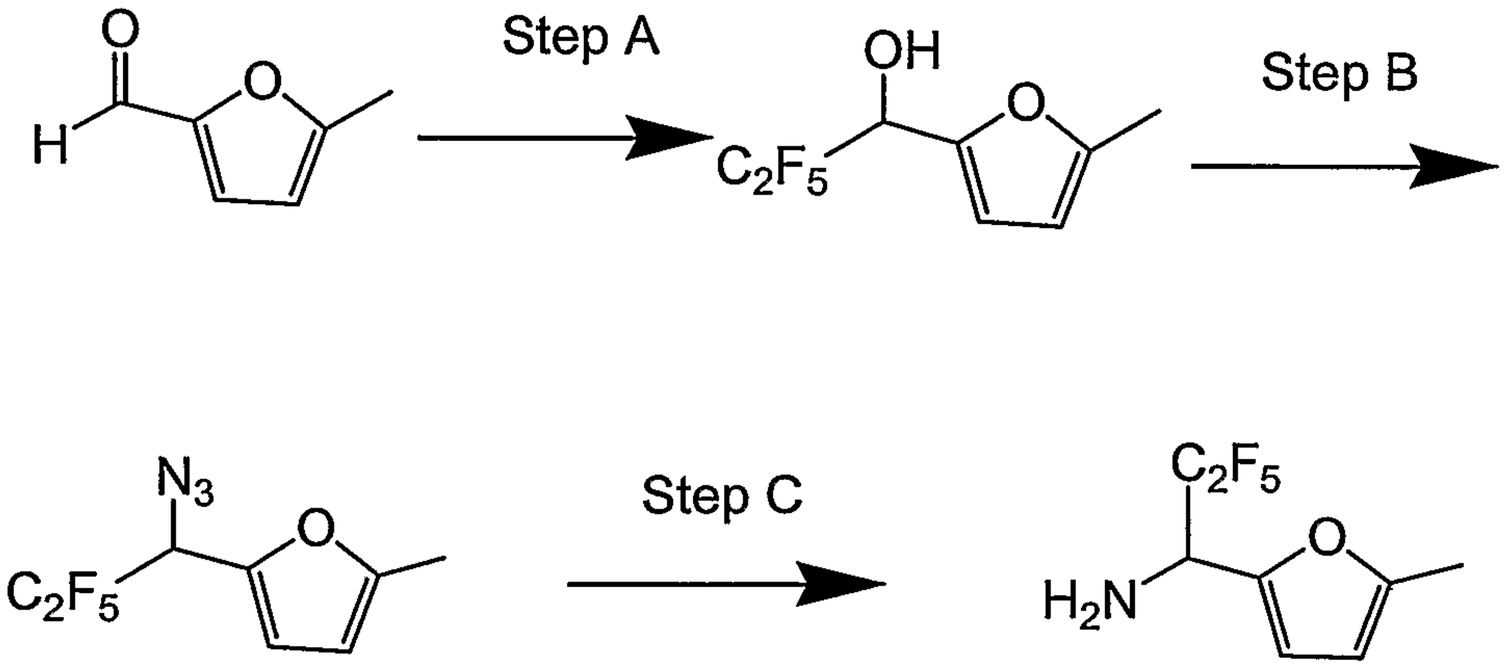
Step B

The azide was prepared using the procedure from Preparative Example 75.75, Step B and the alcohol (1g) from above and carried on crude to Step C below.

Step C

The amine was prepared using the procedure from Preparative Example 75.75, Step C to yield 400mg of an oil (53%).

PREPARATIVE EXAMPLE 13.26



Step A

Perfluoroiodide (3.6ml) was condensed at –78°C. Ether (125ml) was added followed by the methyllithium.lithiumbromide complex (1.5M in ether, 18.4ml). After 15min, a solution of 5-methylfuraldehyde (2.5ml) in ether was added dropwise. The reaction was warmed to -45 °C and let stir for 2hr. Saturated ammonium chloride (30ml) and water (30ml) were added and let stir at room temperature for 1hr. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated *in vacuo* to give 5.86g of product (100%).

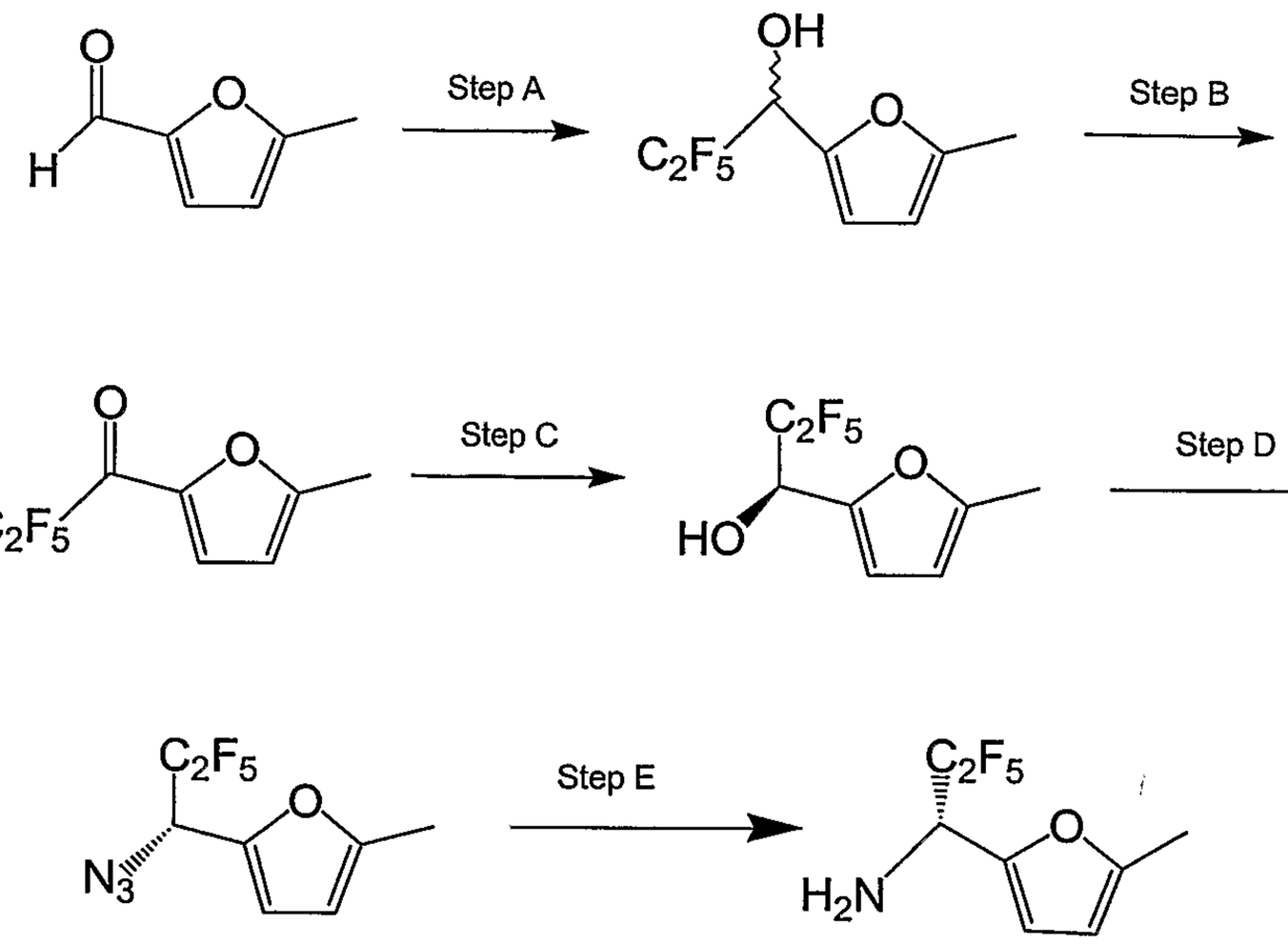
Step B

The alcohol from above was reacted to form the azide using the procedure set forth in Preparative Example 75.75 Step B.

Step C

The azide from above was reacted to form the racemic amine using the procedure set forth in Preparative Example 75.75 Step C.

PREPARATIVE EXAMPLE 13.27



Step A

Following the procedure set forth in Preparative Example 13.26, Step A, the alcohol was prepared (100%).

Step B

To a solution of the alcohol (500mg) from step A above in CH_2Cl_2 (20ml) was added N-methyl-morpholine monohydrate (575mg) and a catalytic amount of tetrapropyl ammonium perruthenate (76mg). After 3hr, the mixture was diluted with hexane (10ml) and filtered through a silica pad, rinsing with hexane: CH_2Cl_2 (200ml). The filtrate was concentrated *in vacuo* to give 350mg of product (70.7%)

Step C

The ketone (1.19g) from Step B was dissolved in THF (9.5ml) and cooled to 0 °C. A solution of S-methyl oxazoborolidine (1M in toluene, 1ml) followed by a solution of borane complexed with dimethylsulfide (9.5ml, 2M in THF) was added to the solution. The mixture was stirred at 0 °C for 30min and continued at room temperature for 5hr. The mixture was cooled back down to 0 °C and methanol (15ml) was added dropwise to the mixture. After 30min, the mixture was concentrated *in vacuo* to give an oily residue.

The residue was dissolved in CH_2Cl_2 and washed with 1N HCl, water, and brine. Dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was

purified via flash column chromatography (Hex/ CH_2Cl_2, 1:1) to afford 1.14g of an oil (67%).

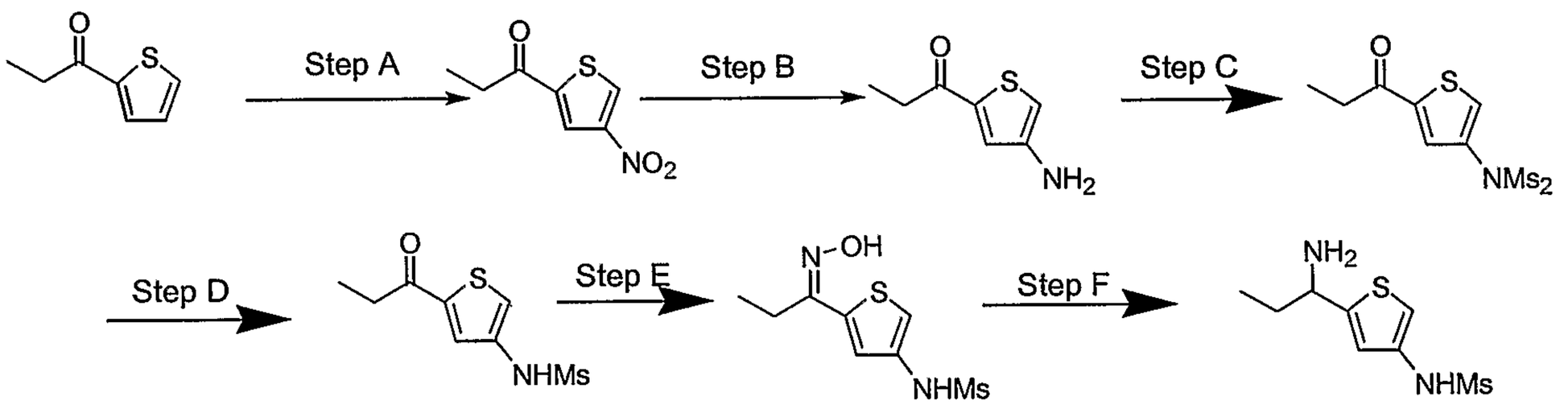
Step D

The alcohol (1.14g) from above was reacted to form the azide using the procedure set forth in Preparative Example 75.75 Step B.

Step E

The azide (1.11g) from above was stirred with 10% Pd/C (280mg) in EtOH (40ml) under a hydrogen gas atmosphere overnight. The reaction was filtered through celite, the filtrate was concentrated *in vacuo* to give 700mg of product (70%).

PREPARATIVE EXAMPLE 13.28



Ms represents methanesulfonyl

Step A

To a stirred solution of 1-(2-thienyl)-1-propanone (3g) in acetic anhydride (6ml) at 0°C was added dropwise a solution of fuming nitric acid in acetic acid (2ml in 10ml). After 30min, the reaction was warmed to room temperature and let stir for 5hrs where a solid precipitated out. Ice was added to the reaction and the solid was filtered. The solid was purified by flash column chromatography (Hex/ CH_2Cl_2, 3:1 and 2:1) to yield 800mg of desired product (20%).

Step B

The above nitro-thiophene compound (278mg) was reduced using the procedure set forth in Preparative Example 2, Step B to give 54mg of product (23%).

Step C

The above amine (395mg), TEA (1ml) and methanesulfonylchloride (0.5ml) were combined in CH_2Cl_2 (35ml) and stirred at room temperature for 1hr. The reaction was quenched with saturated sodium bicarbonate (15ml). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford product (854mg, 100%).

Step D

To the above product (854mg) in THF (25ml) was added dropwise a solution of tetrabutylammonium fluoride (1M in THF, 2.8ml). The mixture was stirred overnight, then diluted with CH_2Cl_2 (30ml), washed with ammonium chloride and brine, dried over over Na_2SO_4, filtered and concentrated *in vacuo* to afford product (2.36g, >100%).

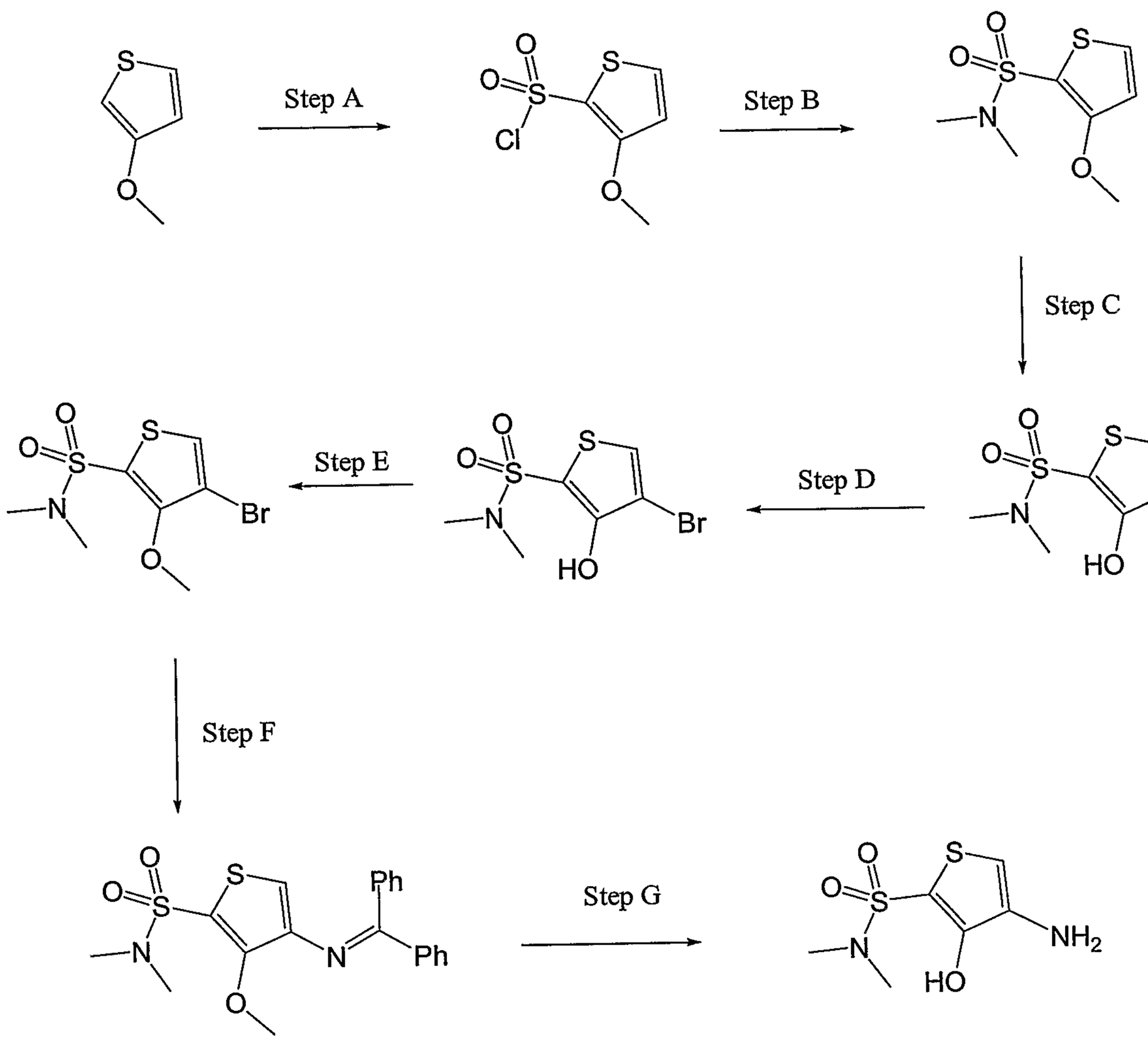
Step E

The ketone (2.36g) above was reacted via the procedure set forth in Preparative Example 88.2, Step B to yield 547mg of product (86.6%).

Step F

To the product from step E (310mg) in dimethoxyethane (12ml) was added dropwise a solution of LAH (1M in ether, 3.8ml). The mixture was heated to reflux overnight. The reaction was cooled to room temperature, SiO_2 was added as well as water (1ml) dropwise and let stir for 15min. The mixture was filtered and the filtrate was concentratred *in vacuo*. The crude product was purified by preparative plate chromatography (MeOH/ CH_2Cl_2, 15:1) to give the amine product (40mg, 14%).

PREPARATIVE EXAMPLE 13.29



Step A

To a solution of 3-methoxythiophene (3 g) in dichloromethane (175 mL) at –78°C was added chlorosulfonic acid (8.5 mL) dropwise. The mixture was stirred for 15 min at –78°C and 1.5 h at room temp. Afterwards, the mixture was poured carefully into crushed ice, and extracted with dichloromethane. The extracts were washed with brine, dried over magnesium sulfate, filtered through a 1-in silica gel pad. The filtrate was concentrated in vacuo to give the desired compound (4.2 g).

Step B

The product from Step A above (4.5 g) was dissolved in dichloromethane (140 mL) and added with triethylamine (8.8 mL) followed by diethyl amine in THF (2*M*, 21 mL). The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine and saturated bicarbonate (aq) and brine again, dried over

sodium sulfate, filtered through a 1-in silica gel pad. The filtrate was concentrated in vacuo to give the desired compound (4.4 g).

Step C

The product from Step B above (4.3 g) was dissolved in dichloromethane (125 mL) and cooled in a -78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 24.3 mL) was added. The mixture was stirred for 4 h while the temperature was increased slowly from -78°C to 10°C. H_2O was added, the two layers were separated, and the aqueous layer was extracted with dichloro- methane. The combined organic layer and extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 3.96 g of the desired hydroxy-compound.

Step D

The product from step C above (3.96 g) was dissolved in 125 mL of dichloromethane, and added with potassium carbonate (6.6 g) followed by bromine (2 mL). The mixture was stirred for 5 h at room temperature, quenched with 100 mL of H_2O. The aqueous mixture was addjusted to pH ~ 5 using a 0.5N hydrogen chloride aqueous solution, and extracted with dichloromethane. The extracts were washed with a 10 % $Na_2S_2O_3$ aqueous solution and brine, dried over sodium sulfate, and filtered through a celite pad. The filtrate was concentrated in vacuo to afford 4.2 g of the desired bromo-compound.

Step E

The product from Step D (4.2 g) was dissolved in 100 mL of acetone and added with potassium carbonate (10 g) followed by iodomethane (9 mL). The mixture was heated to reflux and continued for 3.5 h. After cooled to room temperature, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo to a dark brown residue, which was purified by flash column chromatography eluting with dichloromethane-hexanes (1:1, v/v) to give 2.7 g of the desired product.

Step F

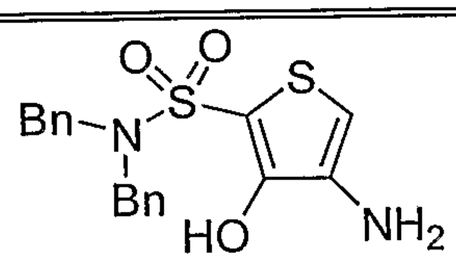
The product from step E (2.7 g) was converted to the desired imine compound (3 g), following the similar procedure to that of Preparative Example 13.19 step D.

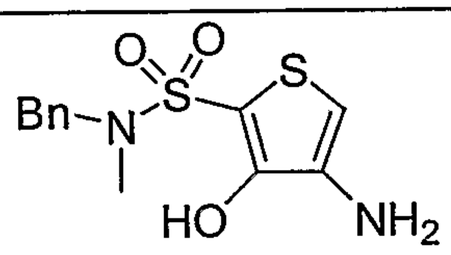
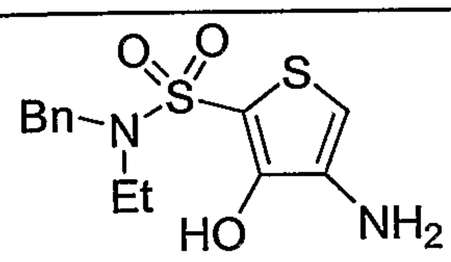
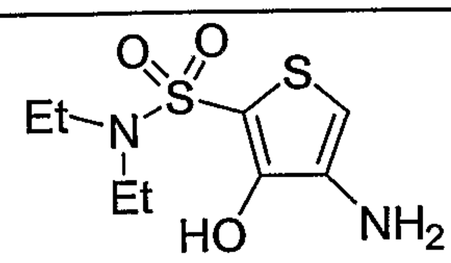
Step G

The imine product from step F (3 g) was dissolved in 80 mL of dichloromethane and cooled in a –78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 9.2 mL) was added dropwise. The mixture was stirred for 4.25 h from -78°C to 5°C. H_2O (50 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane. The organic layer and extracts were combined, washed with brine, and concentrated to an oily residue. The residue was dissolved in 80 mL of methanol, stirred with sodium acetate (1.5 g) and hydroxyamine hydrochloride (0.95 g) at room temperature for 2 h. The mixture was poured into an aqueous mixture of sodium hydroxide (1.0 M aq, 50 mL) and ether (100 mL). The two layers were separated. The aqueous layer was washed with ether three times. The combined ether washings were re-extracted with H_2O once. The aqueous layers were combined, washed once with dichloromethane, adjusted to pH ~ 6 using 3.0 M and 0.5 M hydrogen chloride aqueous solutions, and extracted with dichloromethane. The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 1.2 g of desired amine compound.

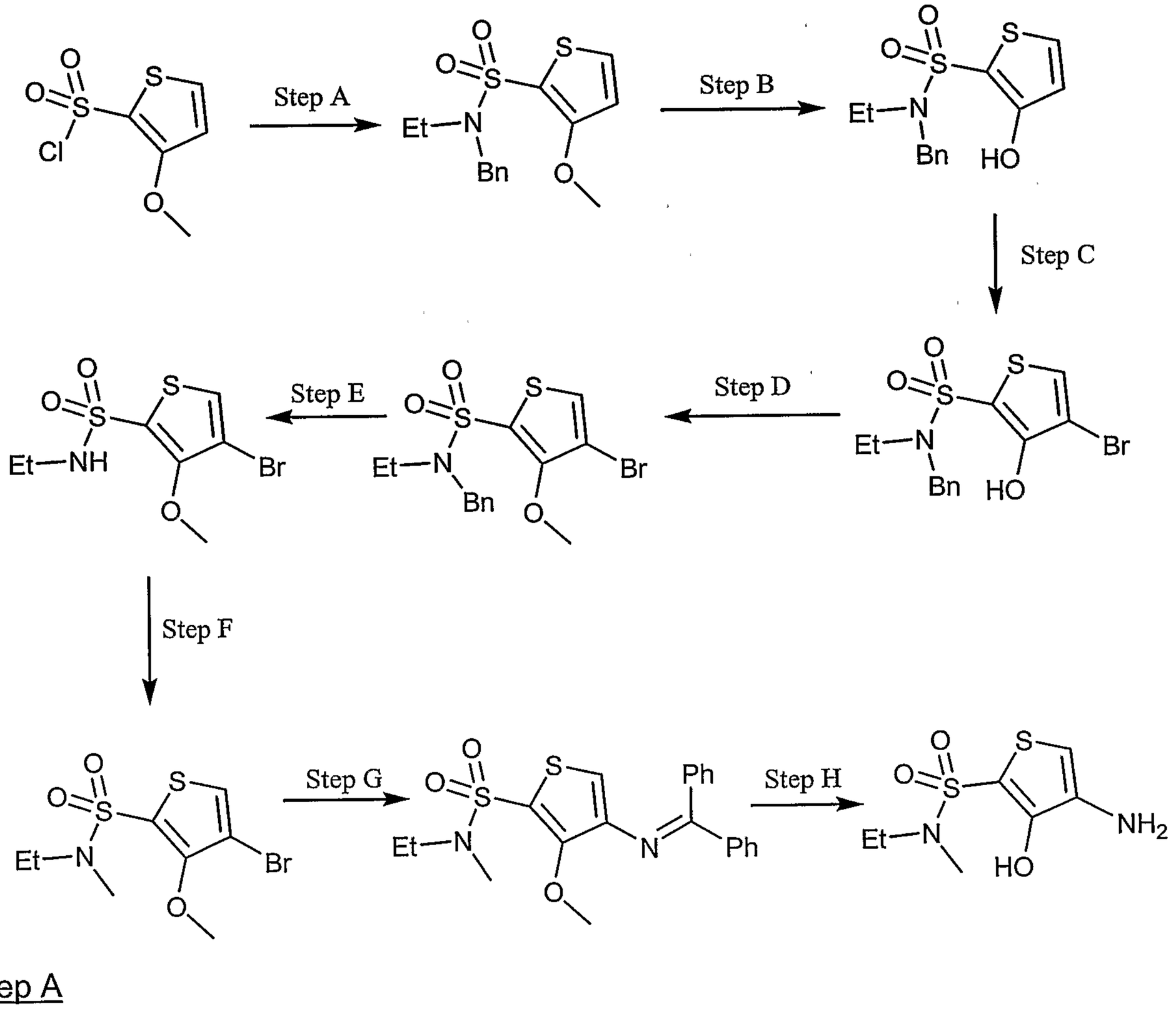
PREPARATIVE EXAMPLES 13.30-13.32-A

Following the procedures set forth in Example 13.29, but using commercially available amines, hydroxy-amino-thiophene products in the Table below were obtained.

Prep Ex.	Amine	Product	Yield (%) MH^+
13.30	$(Bn)_2NH$		10% 375.1

13.31	Me(Bn)NH		14% 299.0
13.32	Et(Bn)NH		22%
13.32A	$(Et)_2NH$		25%

PREPARATIVE EXAMPLE 13.33



Step A

2-Chlorosulfonyl-3-methoxy-thiophene (4.0 g, 18.8 mmol), the product from Step A of Preparative Example 13.29 was converted to 3-methoxy-2-

ethylbenzylsulfonyl-thiophene (5.5 g, 94%, MH^+ = 312.1) by using ethylbenzyl-amine, following the procedure set forth in Preparative Example 13.29, Step B.

Step B

The product from Step A above (5.5 g, 17.70 mmol) was demethylated following the procedure set forth in Preparative Example 13.29, Step C. The alcohol product was obtained in 4.55 g (87%, MH^+ = 298.0).

Step C

The product from Step B above (4.55 g, 15.30 mmol) was brominated using the procedure set forth in Preparative Example 13.29, Step D. The corresponding bromide was obtained in 4.85 g (84%).

Step D

The bromo-alcohol from Step C above (4.84 g, 12.86 mmol) was methylated using the procedure set forth in Preparative Example 13.29, Step E. The product was obtained in 4.82 g (96%).

Step E

The product from Step D above (4.82 g, 12.36 mmol) was stirred with concentrated sulfuric acid (5 mL) at room temperature ro 3 h. Ice water (30 mL) was added to the mixture followed by CH_2Cl_2 (50 mL). The aqueous mixture was adjusted to pH ~ 6 using a 1.0 M NaOH aqueous solution. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to a dark brown oil, which was purified by flash column chromatography, eluting with CH_2Cl_2-hexanes (1:1, v/v). Removal of solvents afforded 3.03 g (82%) of the debenzylated product (M^+ = 300.0, M+2 = 302.0).

Step F

The product from Step E (1.34 g, 4.45 mmol) was methylated using the procedure set forth in Preparative Example 13.29, Step E. The desired product was obtained in 1.36 g (97%, M^+ = 314.1, M+2 = 316.0).

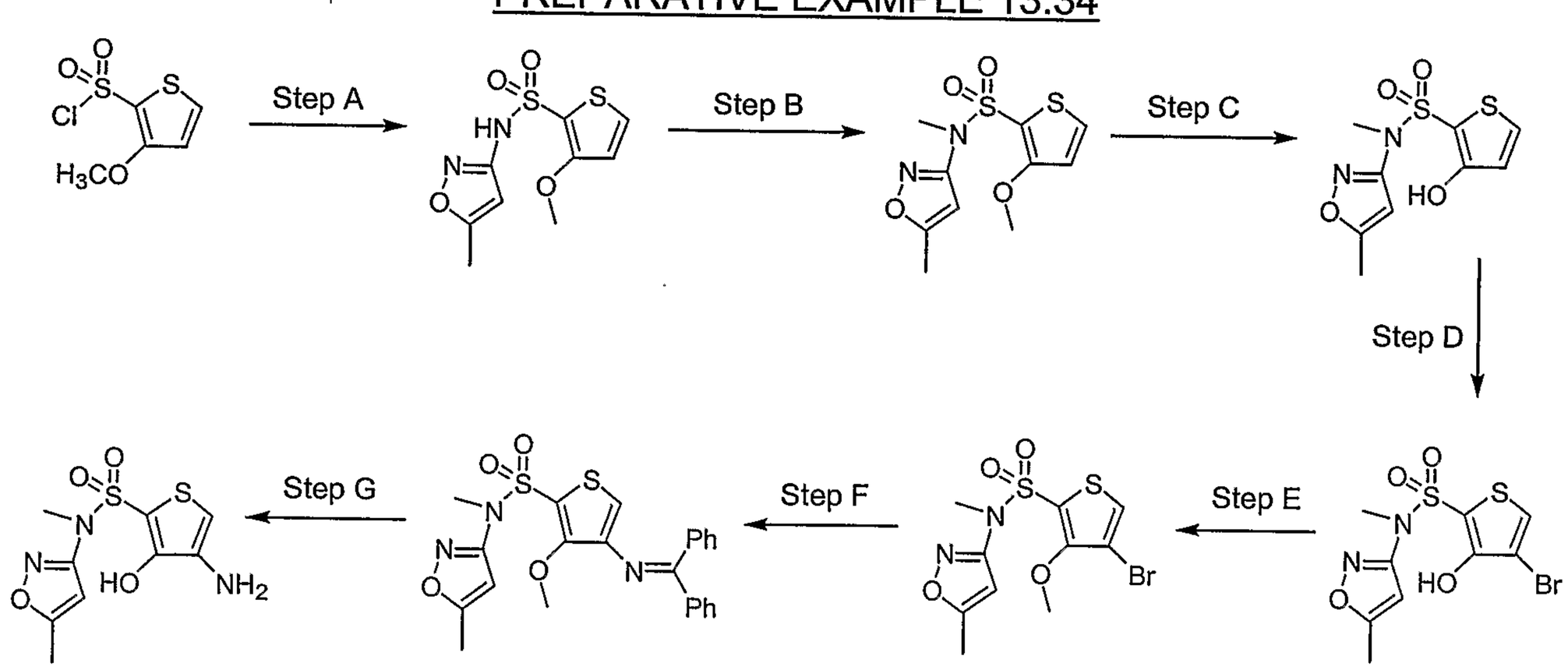
Step G

The product from Step F (1.36 g, 4.33 mmol) was converted to imine product (1.06 g, 55%, MH^+ = 415.1) using the procedure set forth in Preparative Example 13.29, Step F.

Step H

The imine product from Step G (1.06 g, 2.56 mmol) was converted to the desired hydroxy-amino thiophene compound (0.26 g, 43%) using the procedure set forth in Preparative Example 13.29, Step G.

PREPARATIVE EXAMPLE 13.34



Step A

2-Chlorosulfonyl-3-methoxy-thiophene (3.8 g, 17.87 mmol), the product from step A of Preparative Example 13. 29, was dissolved in 100 mL of CH_2Cl_2 and 20 mL of pyridine. 3-Amino-5-methyl-isoxazole (3.5 g, 35.68 mmol) was added. The mixture was stirred for 20 h at room temperature, diluted with 100 mL of CH_2Cl_2, and washed with a 0.5 N HCl aqueous solution (50 mL x 2), H_2O (50 mL), and brine (50 mL). The organic solution was dried with Na_2SO_4, and conentrated in vacuo to a brown oil. This oil was dissolved in 100 mL of CH_2Cl_2, washed again with a 0.5 M HCl aqueous

solution (30 mL x 3) and brine. After dried over Na_2SO_4, the organic solution was concentrated in vacuo to a yellow solid, 4.48 g (91%, MH^+= 275.0) of the desired product.

Step B

The product from Step A above (4.48 g, 16.33 mmol) was dissolved in acetone (100 mL), added with potassium carbonate (5.63 g, 40.80 mmol) and iodomethane (10.1 mL, 163.84 mmol). The mixture was stirred at room temperature for 1.5 h, diluted with 100 mL of hexanes and 50 mL of CH2Cl2, and filtered through a 1-in silica gel pad, rinsing with CH2Cl2. The filtrate was concentrated under reduced pressure to give 4.23 g (90%, MH^+= 289.0) of the desired product as a light yellow solid.

Step C

To a stirred suspension of sodium hydride (130 mg, 95%, 5.4 mmol) in 8 mL of *N*, *N'*-dimethylforamide at room temperature was added ethanethiol (0.45 mL, 6.0 mmol) dropwise. After 5 min, the mixture became a clear solution, and was added to a stirred solution of the product obtained from Step B above (0.45 g, 1.56 mmol) in 2 mL of *N*, *N'*-dimethylforamide in a round bottom flask. The flask was sealed with a ground glass stopper, and the mixture was heated at 90-95°C for 4 h. After cooled to room temperature, the mixture was poured into 20 mL of a 1.0 M NaOH aqueous solution, further rinsed with 20 mL of H_2O. The aqueous mixture was washed with diethyl ether (30 mL x 2), adjusted to PH ~5 using a 0.5 M HCl aqueous solution, and extracted with CH_2Cl_2 (50 mL x4). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to a dark yellow solution. This was dissolved in 50 mL of ethyl acetate, washed with H_2O (30 mL x2) and brine (30 mL), dried over Na_2SO_4. Evaporation of solvent gave 0.422 g of the alcohol product (99%, MH^+ = 275.0).

Step D

The alcohol obtained from Step C above (0.467 g, 1.70 mmol) was brominated using the procedure set forth in Preparative Example 13.29, Step D, to afford the corresponding bromide in 0.607 g (100%).

Step E

The bromide obtained from Step D above (0.607 g, 1.72 mmol) was methylated using the procedure set forth in Preparative Example 13.29, Step E, to give the desired product in 0.408 g (65%, M^+ = 367, M+2 = 369.1).

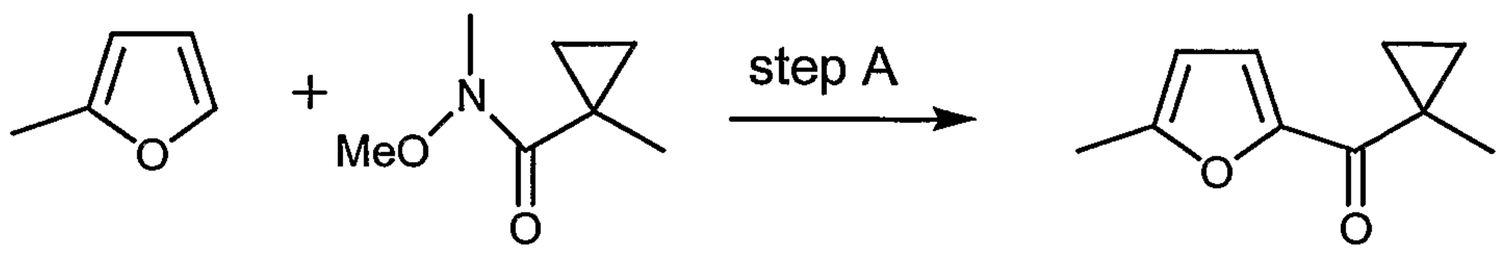
Step F

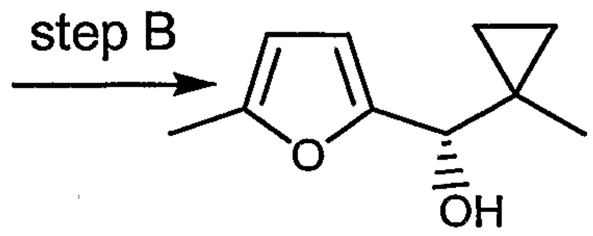
The product (0.405 g, 1.103 mmol) from Step E above was converted to the imine compound (0.29 g, 56%) using the procedure set forth in Preparative Example 13.29, Step F.

Step G

The imine product obtained from Step F above (0.29 g, 0.61 mmol) was demethylated using the procedure set forth in Step C above to give the corresponding alcohol as a dark yellow oil, which was dissolved in 5 mL methanol and added with sodium acetate (0.12 g, 1.46 mmol) and hydroxyamine hydrochloride (0.075 g, 1.08 mmol). The resulting mixture was stirred at room temperature for 3 h, and poured into 10 mL of 1.0 M NaOH aqueous solution. 30 mL of H_2O was used as rinsing and combined to the aqueous layer. The aqueous mixture was washed with diethyl ether (40 mL x 3), adjusted to pH ~ 6 using a 1.0 M HCl aqueous solution, and extracted with ethyl acetate (40 mL x 3). The organic extracts were washed with H_2O (20 mL x2), brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo to give 0.112 g of the desired hydroxy-amino thiophene sulfonamide (64%, MH^+ = 290).

PREPARATIVE EXAMPLE 13.35





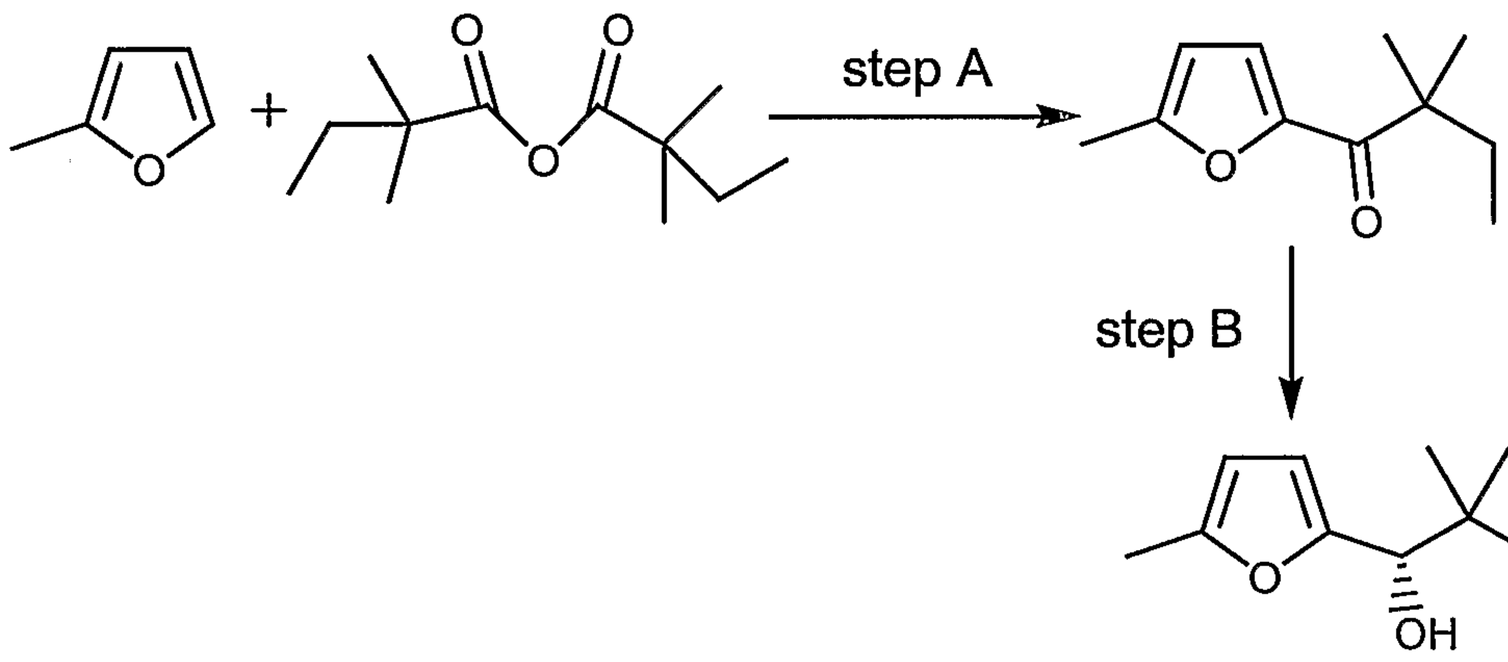
Step A

To a solution of 2-methyl furan (1.72g) in ether was added BuLi (8.38mL) at –78^{0}C and stirred at room temperature for half an hour. The reaction mixture again cooled to –78^{0}C and quenched with cyclopropyl amide **1** and stirred for two hours at –78^{0}C and slowly warmed to room temperature. The reaction mixture stirred for three hours at room temperature and quenched with the addition of saturated ammonium chloride solution. The mixture was taken to a separatory funnel, washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was purified by using column chromatography to afford the ketone 3.0g (87%) as a pale yellow oil.

Step B

To a solution of ketone (1.0g) in THF (5.0mL) at 0^0C was added R-methyl oxazoborolidine (1.2Ml, 1M in toluene) dropwise followed by addition of a solution of borane complexed with dimethyl sulfide (1.85mL, 2M in THF). The reaction mixture was stirred for 30minutes at 0^0C and than at room temperature for one hour. The reaction mixture was cooled to 0^0C and MeOH was added carefully. The mixture was stirred for 20 minutes and was concentrated under reduced pressure. The residue was extracted with ether, washed with water, 1M HCl (10mL), saturated sodium bicarbonate (10.0mL) water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and removal of solvent afforded the crude alcohol which was purified by silica gel chromatography to afford the pure alcohol 0.91g (91%) as yellow oil.

PREPARATIVE EXAMPLE 13.36



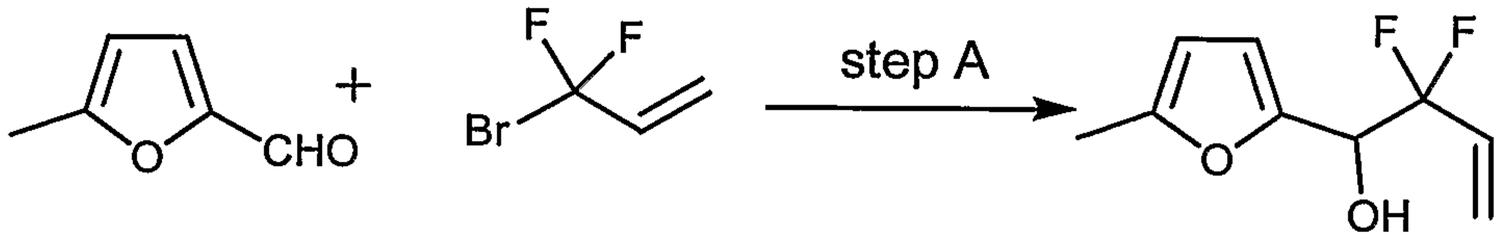
Step A

An equimolar mixture of 2-methylfuran (1.0g) and anhydride (2.6g) was mixed with $SnCl_4$ (0.05mL) and heated at 100^0C for 3 hours. After cooling the reaction mixture, water (10mL) was added, followed by saturated sodium carbonate solution until it becomes alkaline. The reaction mixture was extracted with ether several times and the combined ether layer was washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was purified by using silica gel chromatography to afford the ketone 0.9g (43%) as a yellow oil.

Step B

The step B alcohol was obtained following a similar procedure set forth in the preparative example 13.35 Step B.

PREPARATIVE EXAMPLE 13.37

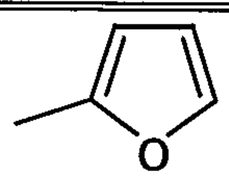
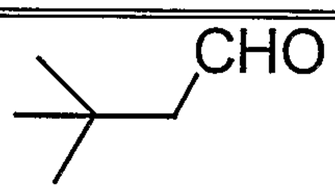
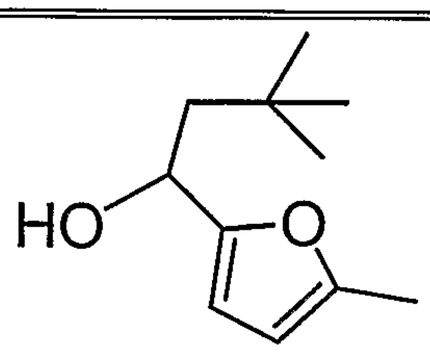
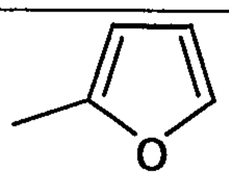
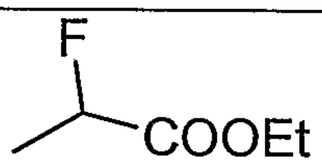
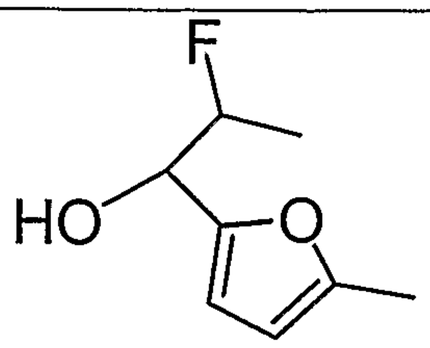


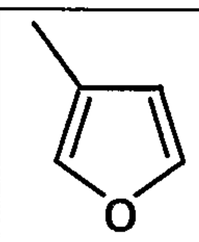
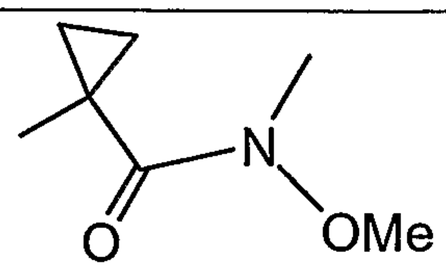
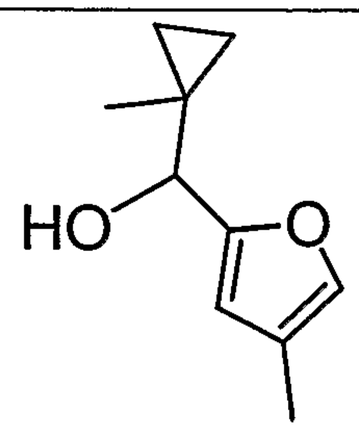
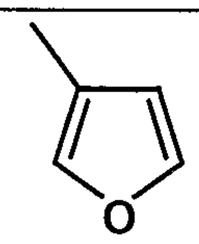
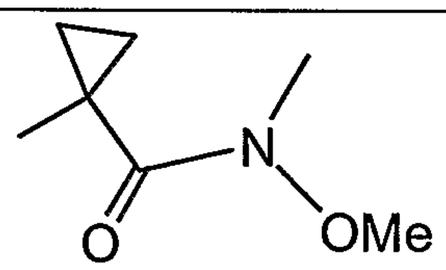
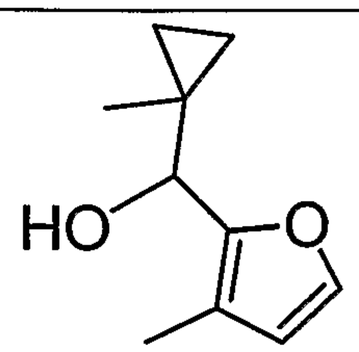
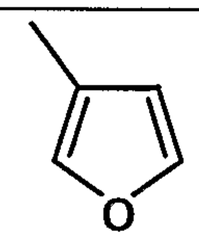
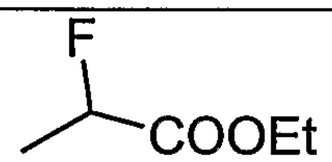
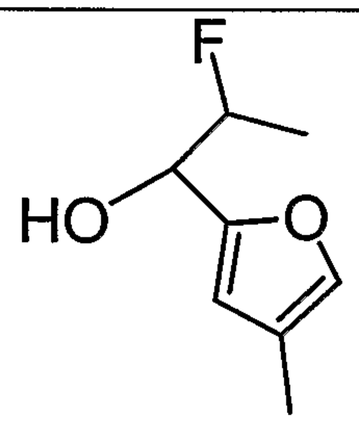
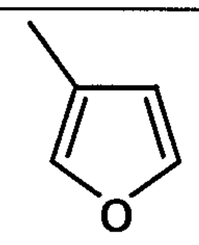
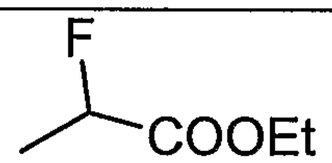
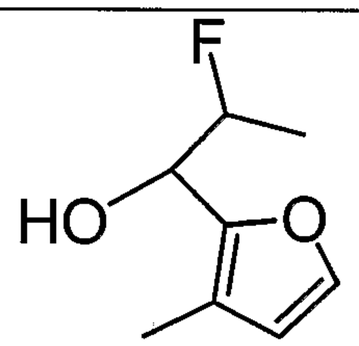
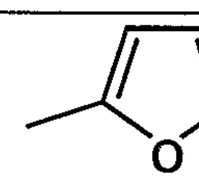
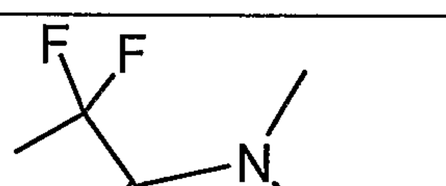
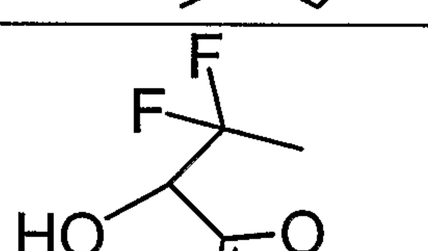
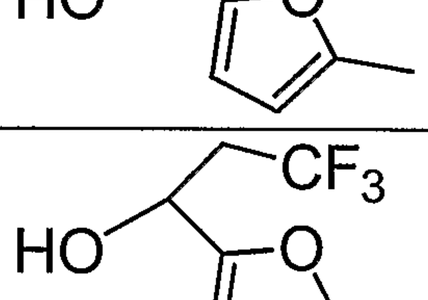
Step A

To a solution of 5-methyl furan-2-aldehyde (1.0g) and 3-bromo-3,3-difluoropropene (2.24g) in DMF (30mL) was added indium powder (1.66g) and lithium iodide (50.0mg). The reaction mixture was stirred over night, diluted with water and extracted with ether. The ether layer was washed with water, brine and purified by silicagel chromatography to afford the pure alcohol 2.8g (92%).

PREPARATIVE EXAMPLES 13.38-13.45

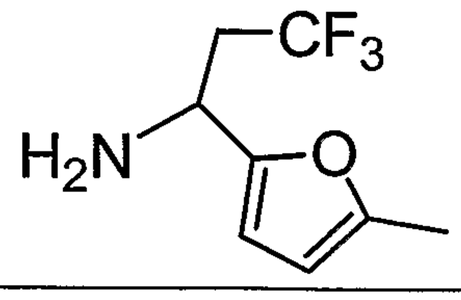
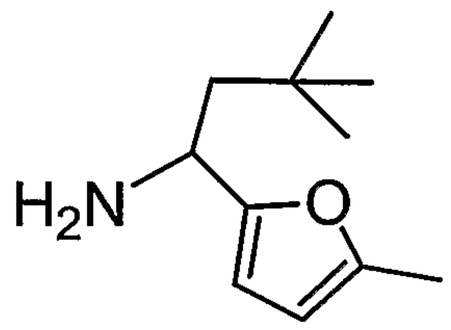
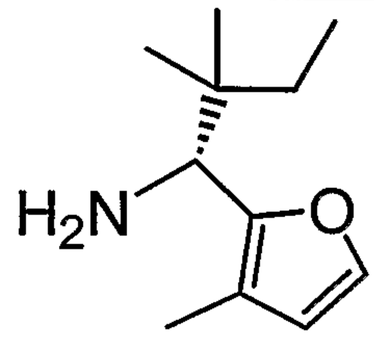
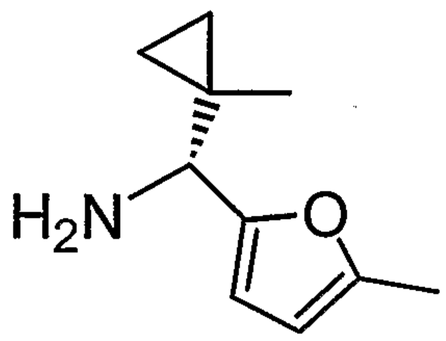
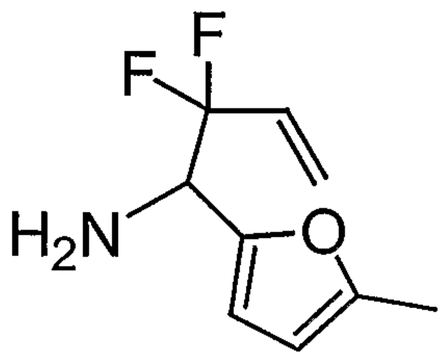
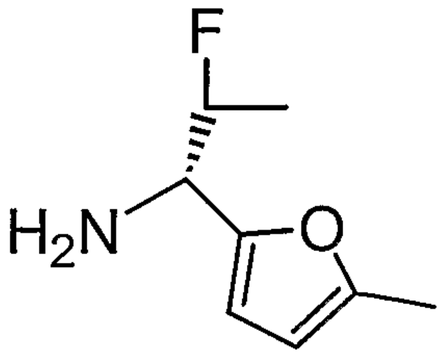
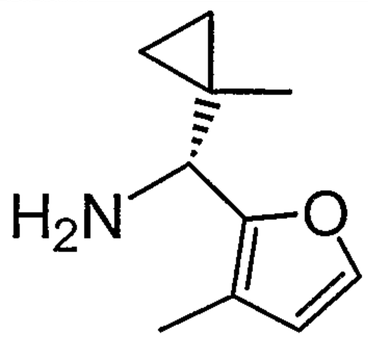
Following a similar procedure set forth in Preparative Examples 13.25 and 13.35, and using the indicated Furan and Electrophile, the following Alcohols in the Table below were prepared.

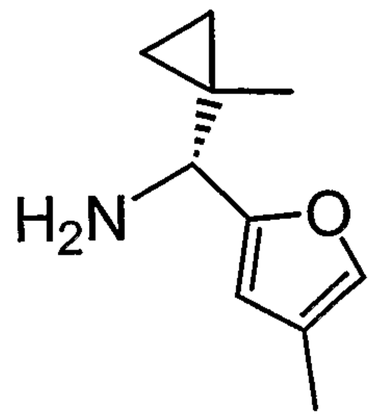
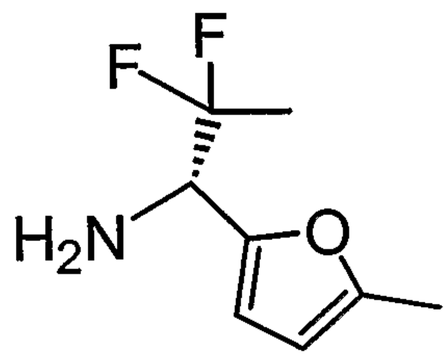
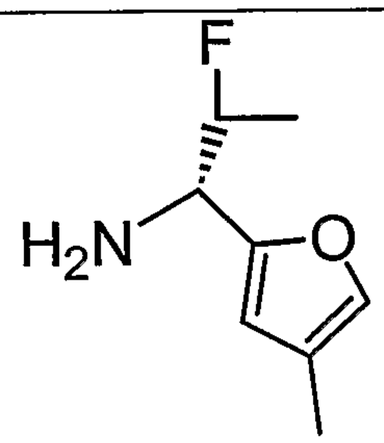
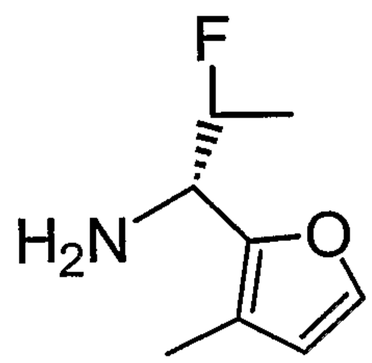
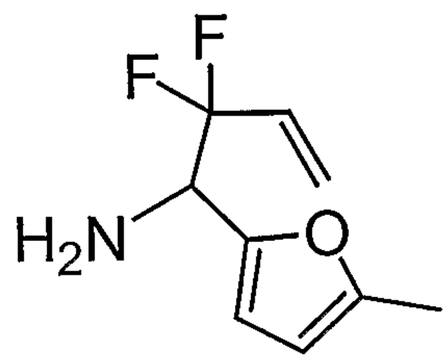
Prep. ex	Furan	Electrophile	Alcohol	Yield
13.38				86%
13.39				69%

13.40				84%
13.41				82%
13.42				60%
13.43				65%
13.44				82%
13.45				89%

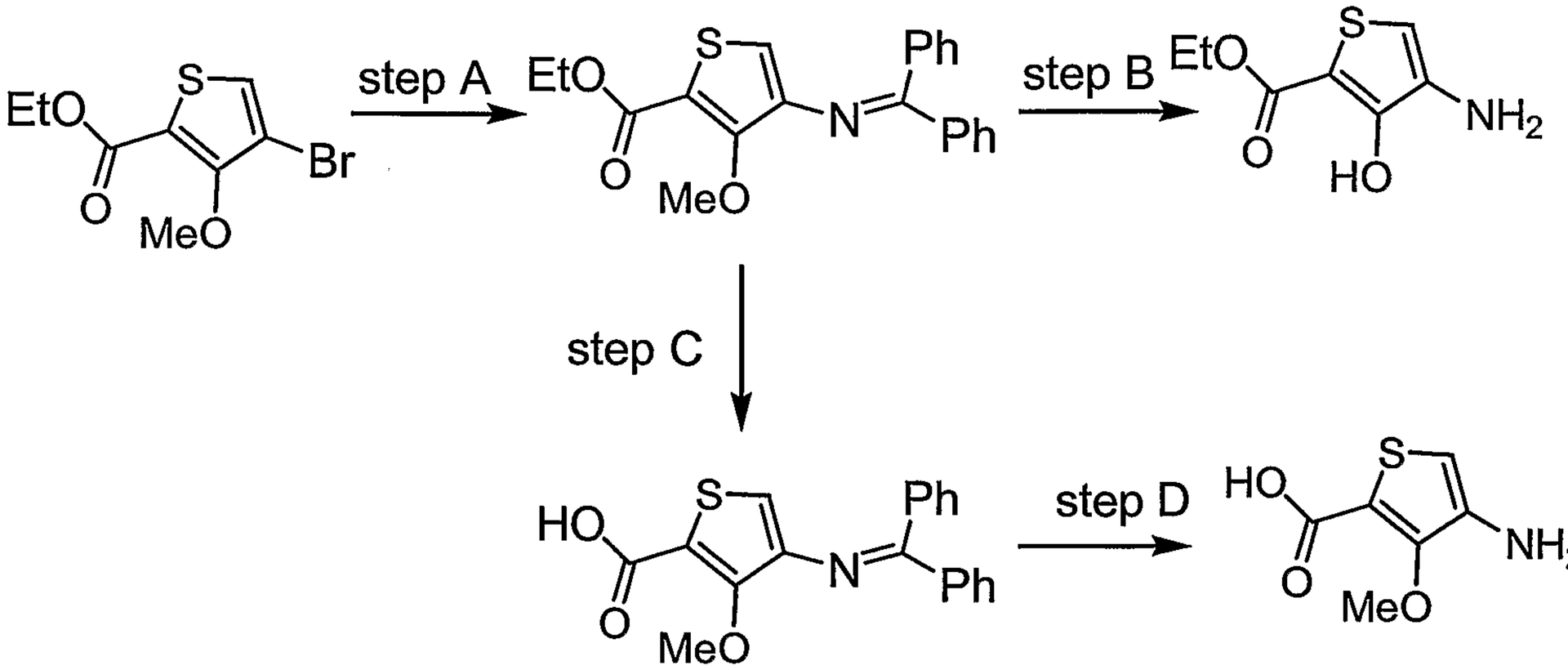
PREPARATIVE EXAMPLES 13.50-13.61

Following a similar procedure set forth in Preparative Examples 13.25, and using the indicated Alcohol, the following Amines in the Table below were prepared.

PREP. EX.	ALCOHOL	AMINE	% YIELD
13.50	13.45		28%
13.51	13.38		58%
13.52	13.36		69%
13.53	13.35		81%
13.54	13.37		82%
13.55	13.39		45%
13.56	13.41		57%

13.57	13.40		58%
13.58	13.44		54%
13.59	13.42		53%
13.60	13.43		50%
13.61	13.37		82%

PREPARATIVE EXAMPLE 13.70



Step A

The imine was prepared following the procedure set forth in the preparative example 13.19 from the known bromoester (1.0g) as a yellow solid, Step A to yield 1.1g (79%).

Step B

The Step A product (0.6g) was reacted following the procedure set forth in the preparative example 13.19 to give the amine product 0.19g (64%).

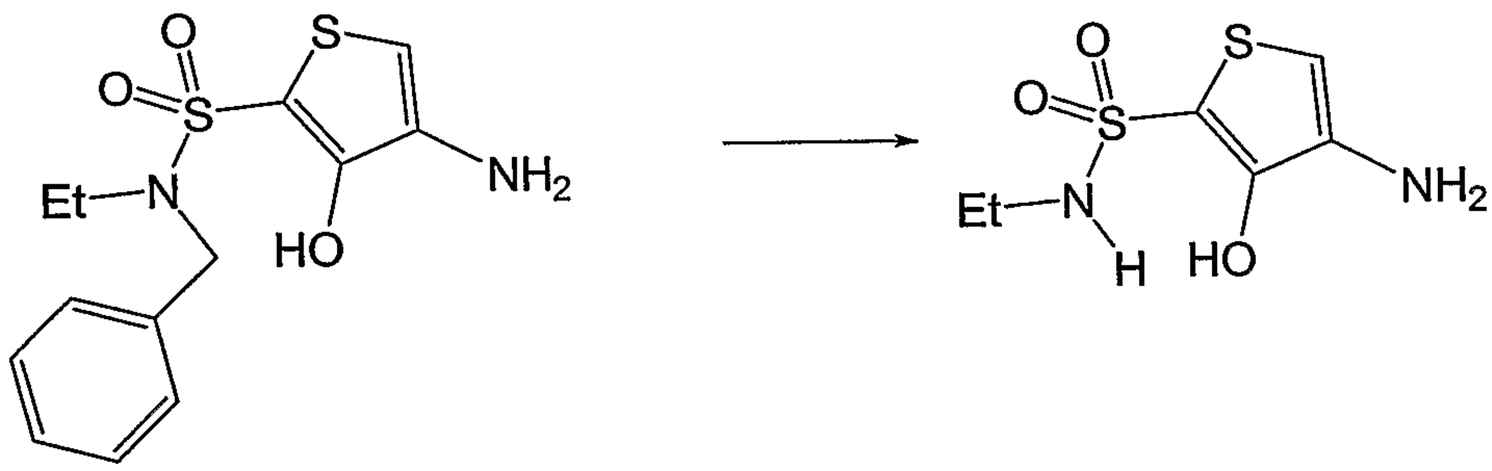
Step C

The Step B product (1.0g) was reacted following the procedure set forth in the preparative example 13.19 to give the acid as yellow solid 0.9g (94%)

Step D

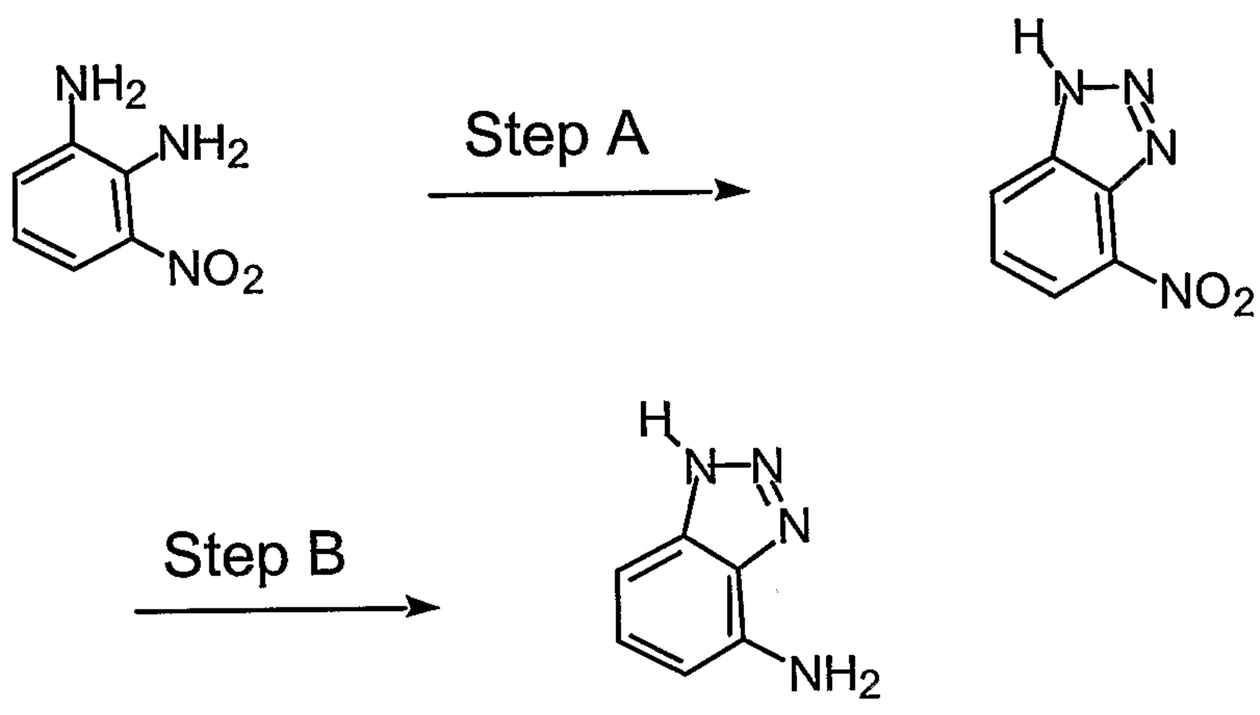
The Step C product (0.35g) was reacted following the procedure set forth in the preparative example 13.19 to give the amino acid as yellow solid 0.167g (93%).

PREPARATIVE EXAMPLE 13.71



Following a similar procedure set forth in Preparative Example 13.33 Step E, but using the product from Preparative Example 13.32, the title compound was obtained (121 mg, 69% yield, MH+ = 223.0).

PREPARATIVE EXAMPLE 14



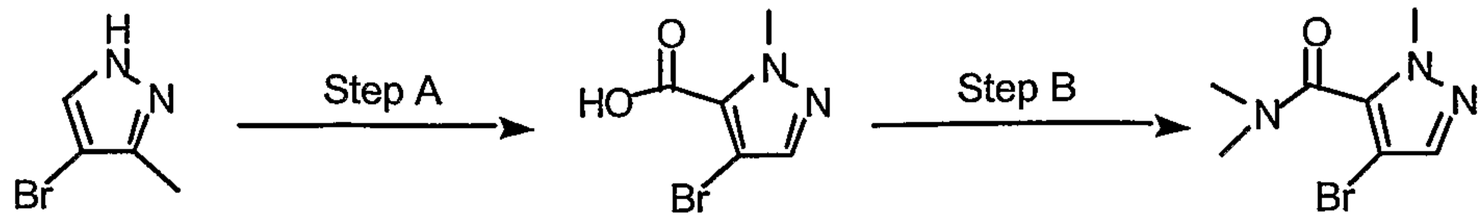
Step A

3-Nitro-1,2-phenylenediamine(10 g), sodium nitrite (5.4 g) and acetic acid (20 mL) were heated at 60°C overnight, then concentrated *in vacuo*, diluted with water and extracted with EtOAc. The product precipitated from the organic phase (5.7 g) as a solid and used directly in step B.

Step B

The product from Step A above (2.8 g) was stirred with 10% Pd/C (0.3 g) in MeOH (75 mL) under a hydrogen gas atmosphere overnight. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo,* to give the product (2.2 g, MH+=135).

PREPARATIVE EXAMPLE 15



Step A

N-methyl-4-bromopyrazole-3-carboxylic acid was prepared according to known methods, see: Yu. A. M.; Andreeva, M. A.; Perevalov, V. P.; Stepanov, V. I.; Dubrovskaya, V. A.; and Seraya, V. I. in *Zh. Obs. Khim,* (Journal of General Chemistry of the USSR) 1982, 52, 2592 (and the references cited therein) the disclosure of whichis incorporated hereinby reference thereto.

Step B

To a solution of N-methyl-4-bromopyrazole-3-carboxylic acid (2.0 g), available from step A, in 65 mL of anhydrous DMF was added bromotripyrrolidinophosphonium hexafluorophosphate (PyBrop, 4.60 g), dimethyl amine (10 mL, 2.0 M in THF) and diisopropylethyl amine (5.2 mL) at 25 °C. The mixture was stirred for 26 h, and concentrated under reduced pressure to an oily residue. This residue was treated with a 1.0 M NaOH aqueous solution, and extracted with ethyl acetate (50 mL x 4). The organic extracts were combined, washed with brine, and dried with anhydrous Na_2SO_4. Removal of solvents yielded an oil, which was purified by preparative thin layer chromatography, eluting with CH_2Cl_2-MeOH (20:1), to give 1.09 g of the amide product (48%, MH^+ = 232.0).

Step C

To a solution of the amide (0.67 g), obtained from step B, in 8 mL of concentrated sulfuric acid at 0 °C was added potassium nitrate (1.16 g) in small portions. The cooling bath was removed and the mixture was heated at 110 °C for 6 h. After cooling to 25 °C, the mixture was poured into 80 mL of H_2O, and an additional

20 mL of H_2O was used as a rinse. The aqueous mixture was extracted with CH_2Cl_2 (100 mL x 4). The combined extracts were washed with brine (50 mL), sat. $NaHCO_3$ aqueous solution (50 mL), brine (50 mL), and dried with Na_2SO_4. Evaporation of solvent gave an oil, which solidified on standing. The crude product was purified by flash column chromatography, eluting with CH_2Cl_2-MeOH (1:0, 50:1 and 40:1). Removal of solvents afforded 0.521 g (65%) of the product as a solid (MH^+ = 277.1)

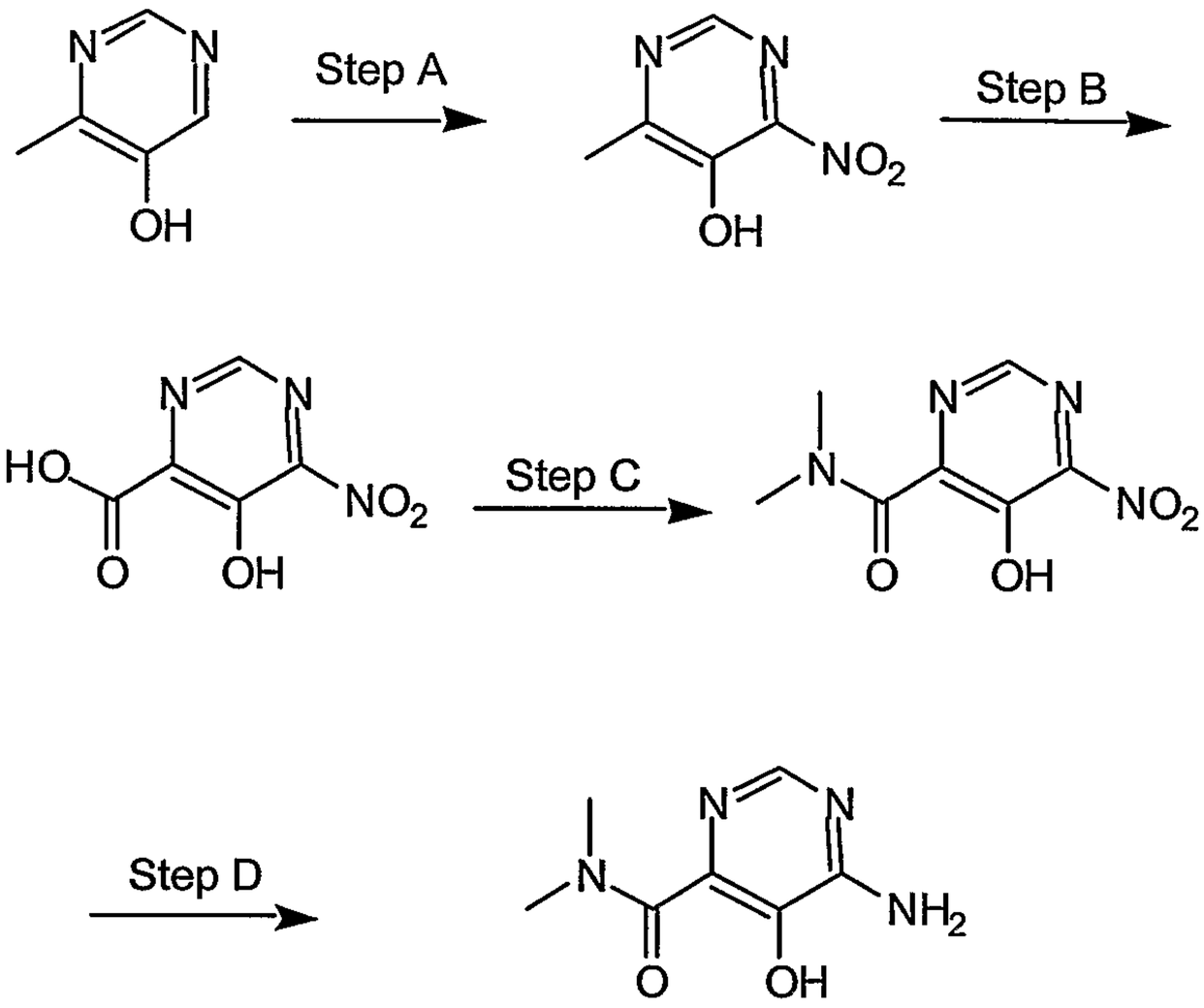
Step D

The product (61 mg) obtained from step C was dissolved in 3 mL of THF. To this solution at – 78 °C was added dropwise along the inside wall of the flask a 1.6 M solution of *n*-butyl lithium in hexane. After 45 min, a solution of methyl borate (0.1 mL) in THF (1.0 mL) was added. After 1.5 h, a solution of acetic acid in THF (0.25 mL, 1:10 v/v) was added to the cold mixture. Stirring was continued for 10 min, and a 30 wt % aqueous hydrogen peroxide solution (0.1 mL) was added. An additional portion of hydrogen peroxide aqueous solution (0.05 mL) was added 20 min later. The cooling bath was removed, and the mixture was stirred at 25 °C for 36 h. The mixture was poured into 30 mL of H_2O, and the aqueous mixture was extracted with ethyl acetate (30 mL x 4). The extracts were combined, washed with brine (10 mL), 5% $NaHCO_3$ aqueous solution (10 mL) and brine (10 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to a residue, which was then purified by preparative thin layer chromatography eluting with CH_2Cl_2-MeOH (20:1) to give the hydroxylated product (5 mg, 10%, MH^+ = 215.3).

Step E

By treating the hydroxylated product of Step E with H_2 under the conditions of 10% palladium on carbon in ethanol, one would obtain the desired hydroxyl-amino compound.

PREPARATIVE EXAMPLE 16



Step A

Following a similar procedure used in Preparative Example 13, Step C except using the known compound, 4-methyl-pyrimidin-5-ol, the product can be prepared.

Step B

Following a similar oxidation procedure used in Preparative Example 15, Step A except using the compound from Step A above, the product can be prepared.

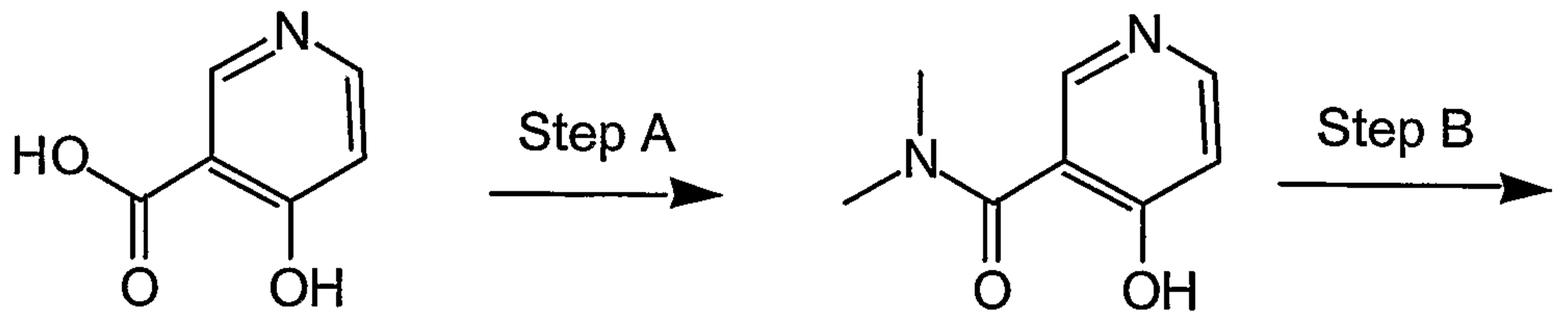
Step C

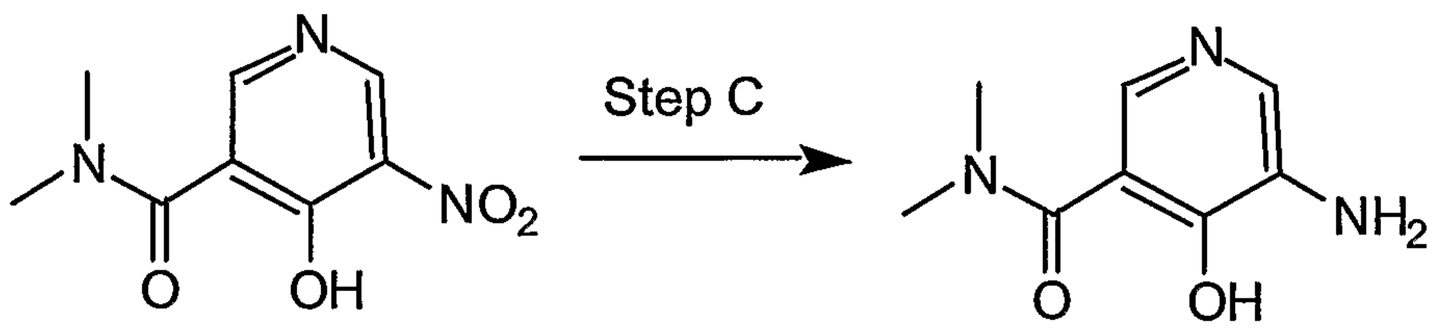
Following a similar procedure used in Preparative Example 11, Step A except using the compound from Step B above, the product can be prepared.

Step D

Following a similar procedure used in Preparative Example 12, Step F except using the compound from Step C above, the product can be prepared.

PREPARATIVE EXAMPLE 17





Step A

Following a similar procedure used in Preparative Example 11, Step A except using the known 4-hydroxynicotinic acid, the product can be prepared.

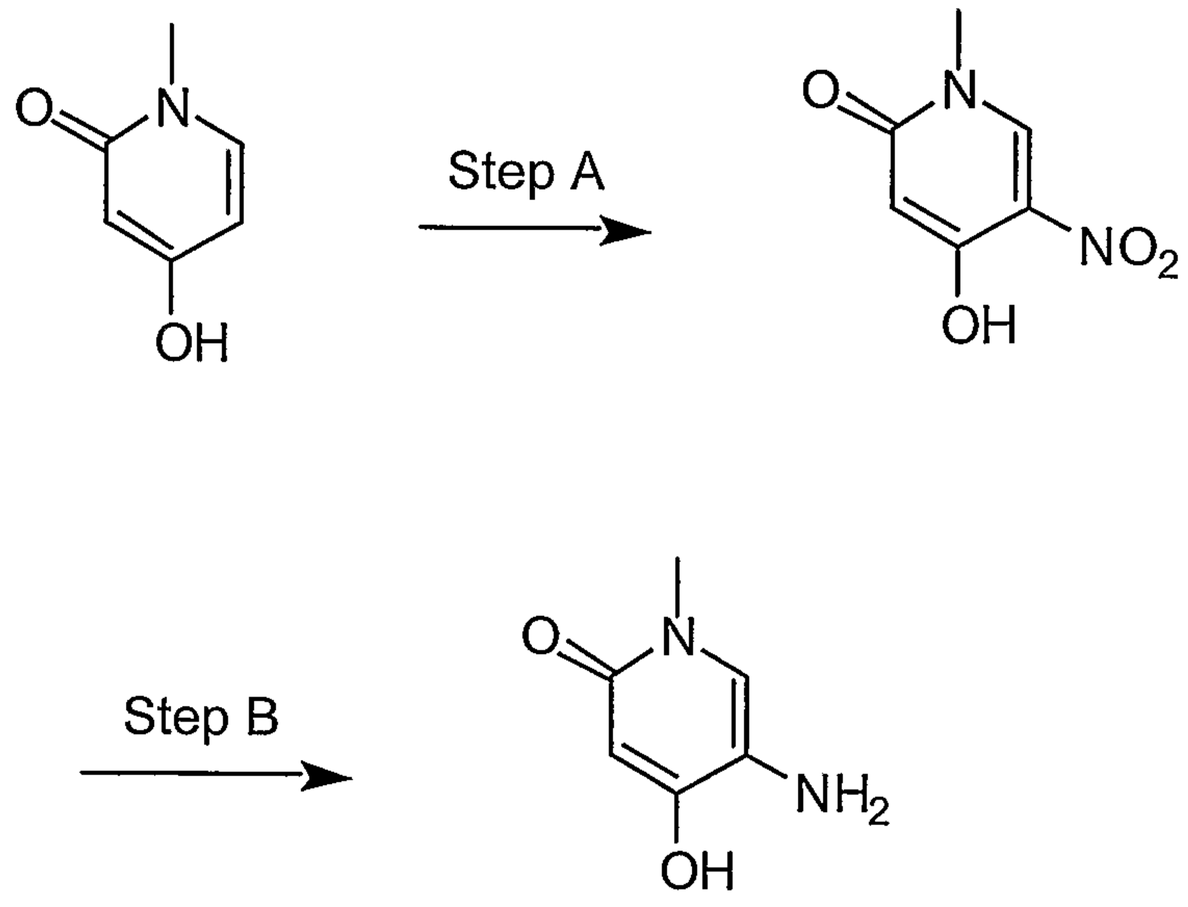
Step B

Following a similar procedure used in Preparative Example 13, Step C except using the compound from Step A above, the product can be prepared.

Step C

Following a similar procedure used in Preparative Example 12, Step F except using the compound from Step C above, the product can be prepared.

PREPARATIVE EXAMPLE 18



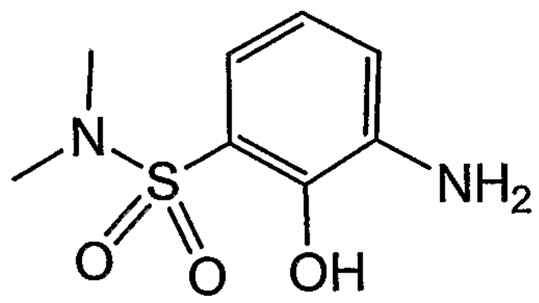
Step A

Following a similar procedure used in Preparative Example 13, Step C except using the compound from Step A above, the product can be prepared.

Step B

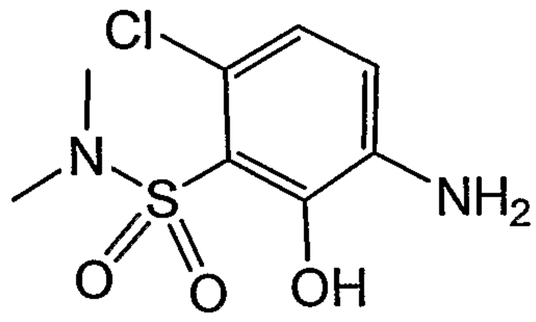
Stirring the compound from Step A above, a suitable Pt or Pd catalyst and EtOH under hydrogen atmosphere (1-4 atm) the product can be prepared.

PREPARATIVE EXAMPLE 19



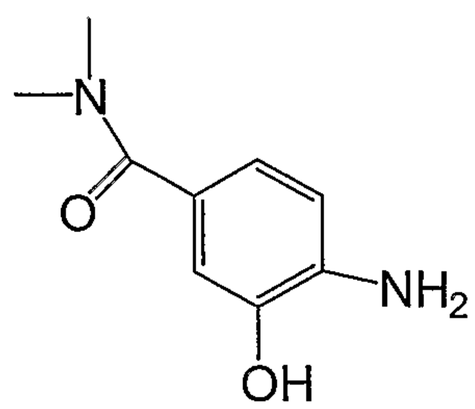
The amine was prepared following WO 01/68570, the disclosure of whichis incorporated herein by reference thereto.

PREPARATIVE EXAMPLE 19.1



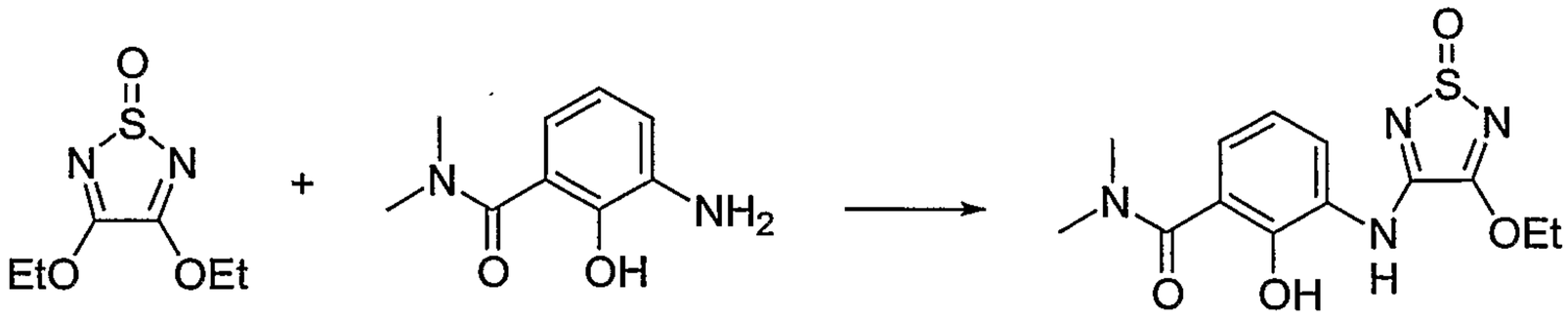
The amine was prepared following WO 01/68570, the disclosure of which is incorporated herein by reference thereto.

PREPARTIVE EXAMPLE 20



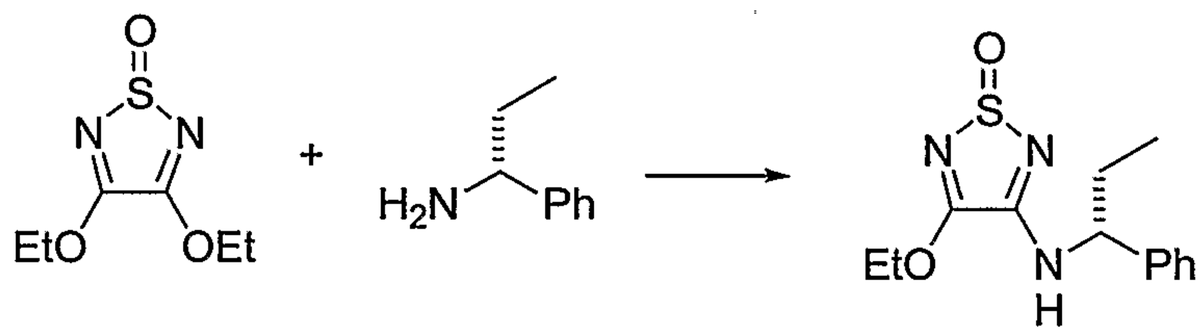
The title compound was prepared according to the procedure set forth in Preparative Example 1, but instead using 4-nitrosalycilic acid (57%, MH+=181).

PREPARATIVE EXAMPLE 22.1



3,4-Diethoxy-1,2-5-thiadiazole-1,1-oxide (226mg, 1.4mmol) (prepared according to known methods, see: *J. Am. Chem. Soc.*, **1982**, p. 1375, the disclosure of which is incorporated herein by reference thereto) was added to 3-amino-2-hydroxy-N,N-dimethylbenzamide (252mg, 1.4mmol) in methanol (15mL). The reaction mixture was stirred overnight. The desired product precipitated and was recovered by filtration. Concentration of the mother liquor to half volume afforded a second batch of precipitated product. Combined batches afforded 293mg (65% yield) of product with sufficient purity to be used in subsequent steps. MH^+ = 346.9.

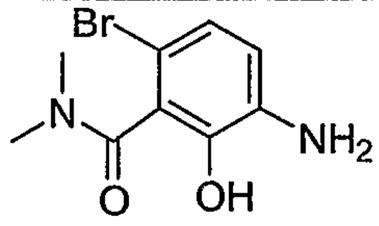
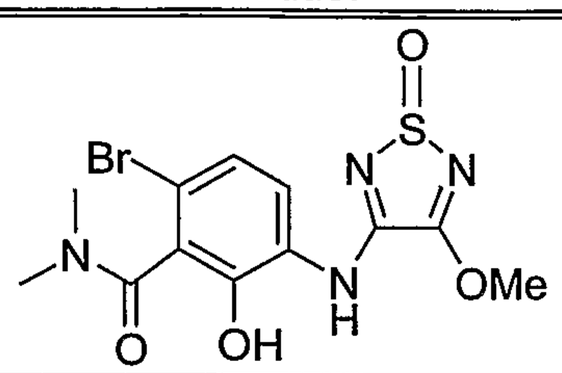
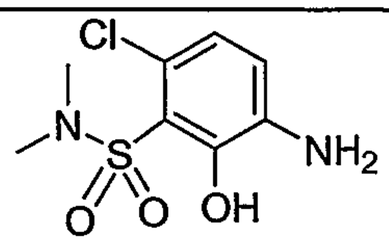
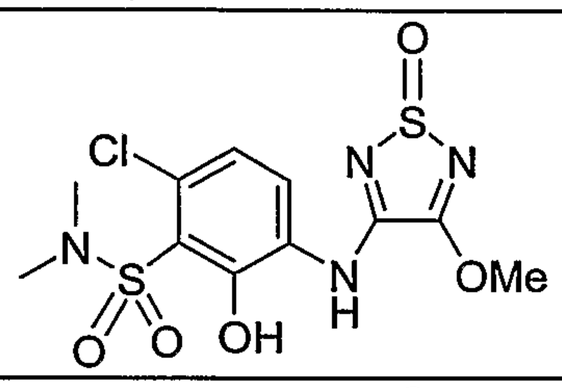
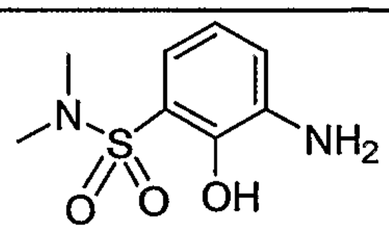
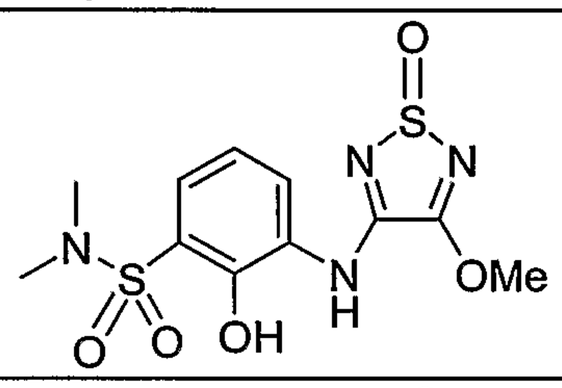
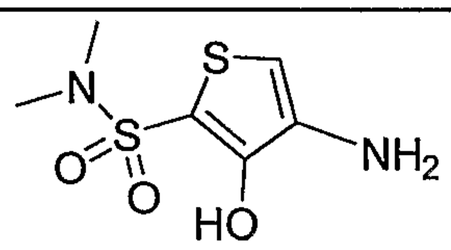
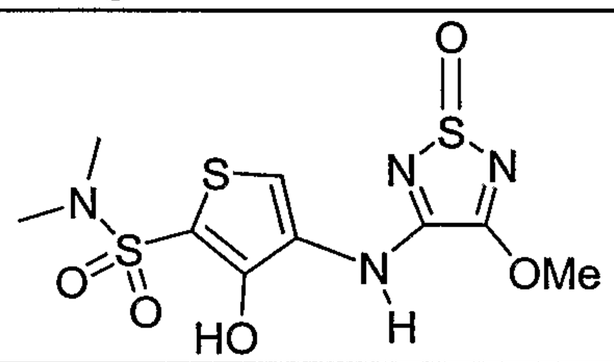
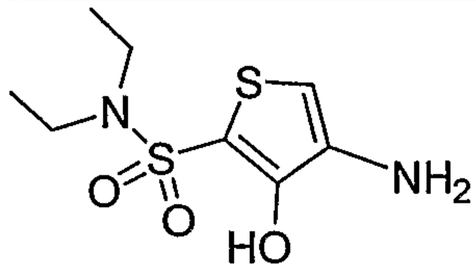
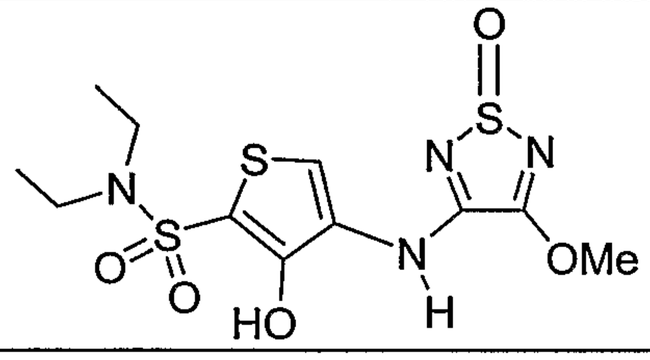
PREPARATIVE EXAMPLE 22.2



3,4-Diethoxy-1,2-5-thiadiazole-1,1-oxide (226mg, 1.4mmol) (prepared according to known methods, see: *J. Am. Chem. Soc.*, **1982**, p. 1375, the disclosure of which is incorporated herein by reference thereto) was added to *R*-2-phenylpropylamine (0.195mL, 1.4mmol) in methanol (15mL). The reaction mixture was stirred overnight. Evaporation of solvent afforded an amorphous solid (390mg, 99%) of sufficient purity for use in subsequent steps. MH^+ = 279.9.

PREPARATIVE EXAMPLES 22.3-22.7

Following a similar procedure set forth in Preparative Example 22.1 but using the commercially available (or prepared amine) indicated in the Table below, the following thiadiazoleoxide intermediates could be obtained.

Ex.	Amine	Product
22.3		
22.4		
22.5		
22.6		
22.7		

PREPARATIVE EXAMPLES 22.8-22.38

Following a similar procedure as that set forth in Preparative Example 22.1 but using the commercially available (or prepared amine) indicated in the Table below, the following thiadiazoleoxide intermediates could be obtained.

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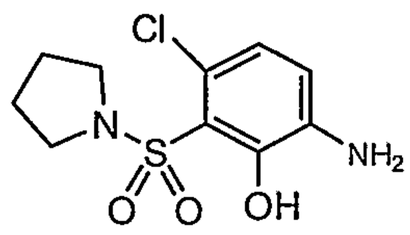
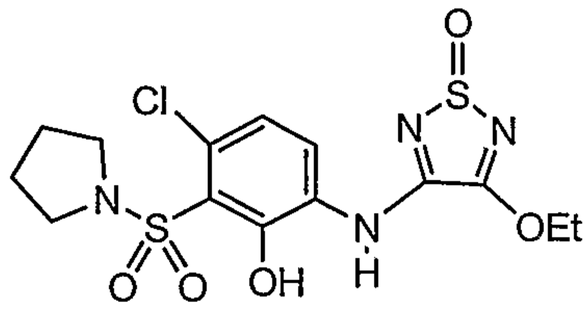
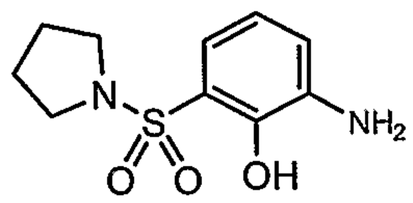
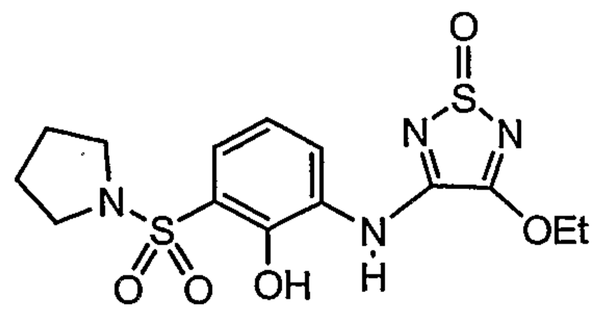
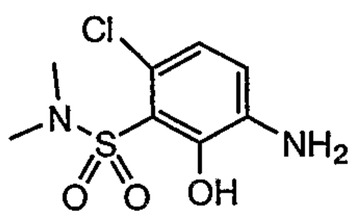
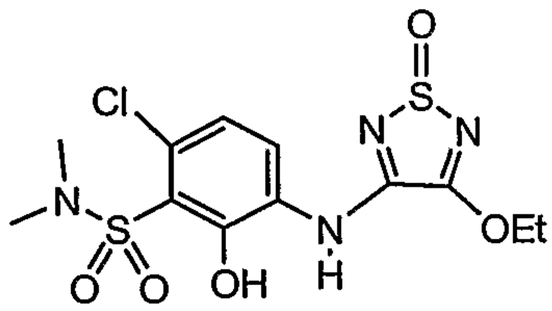
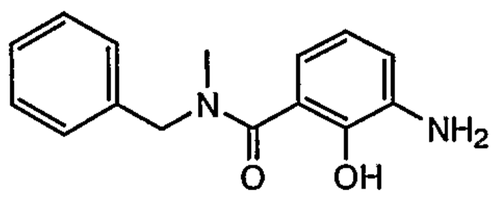
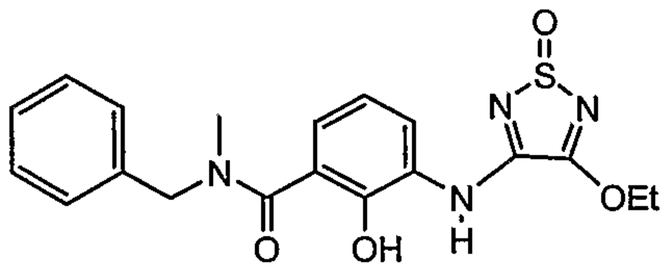
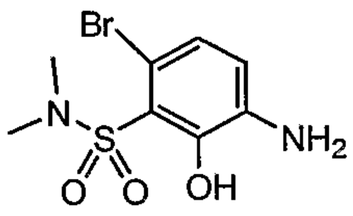
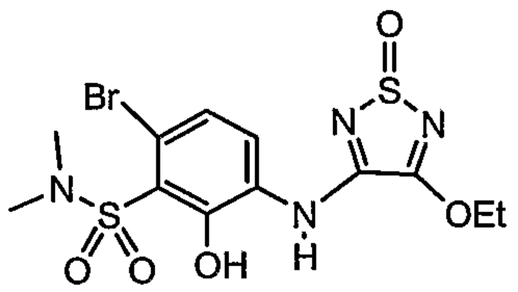
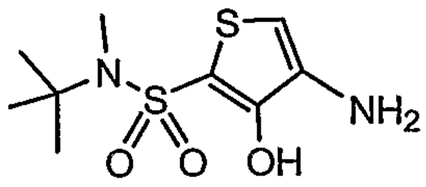
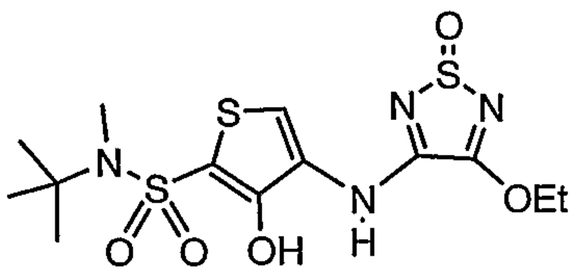
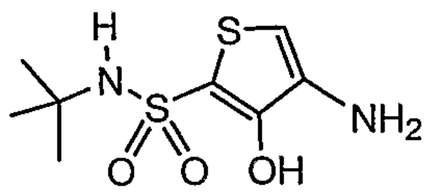
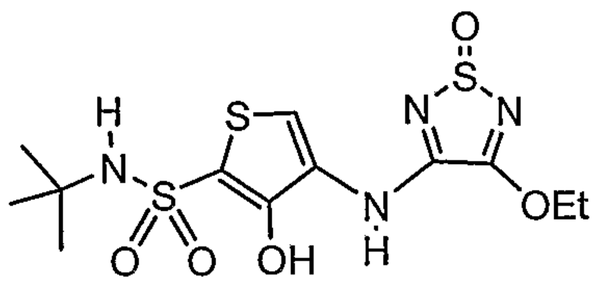
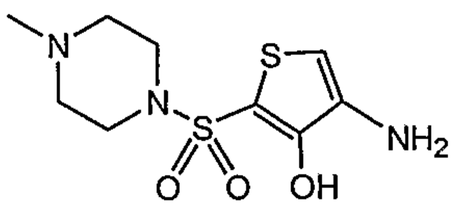
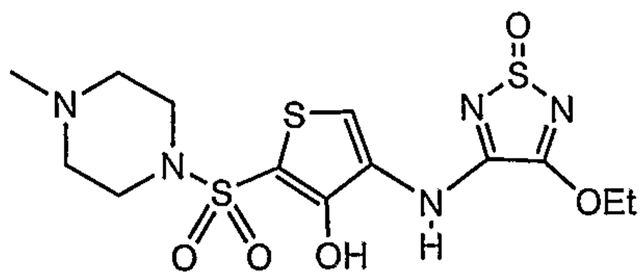
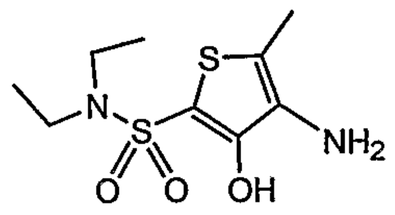
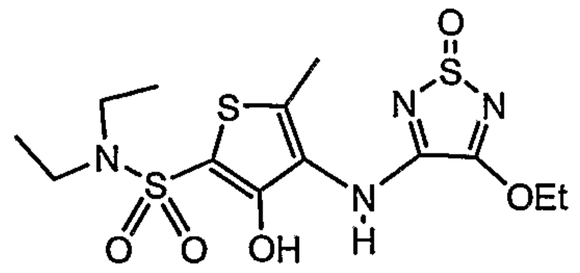
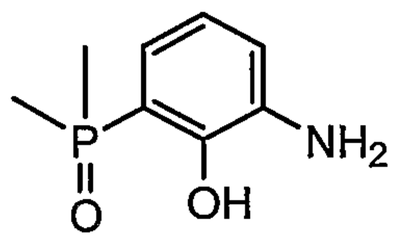
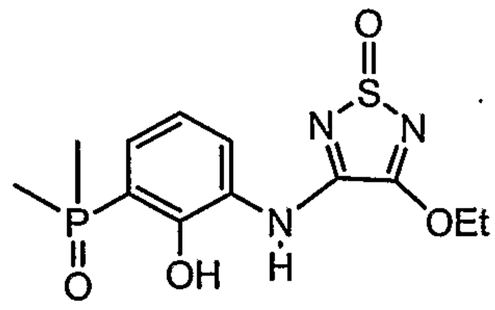
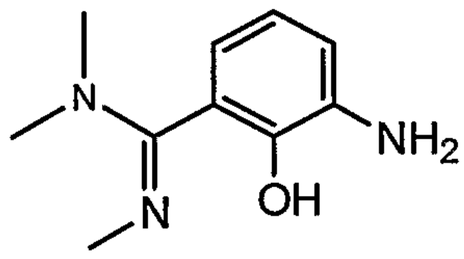
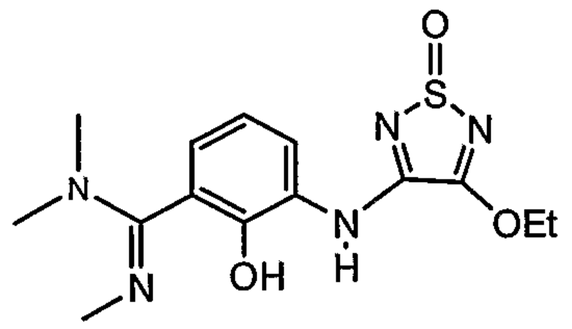
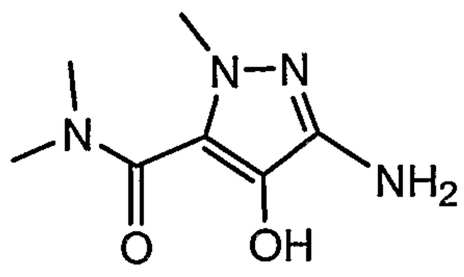
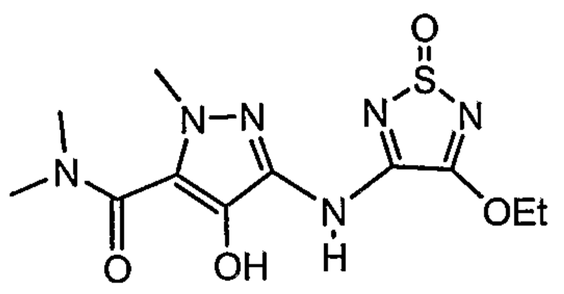
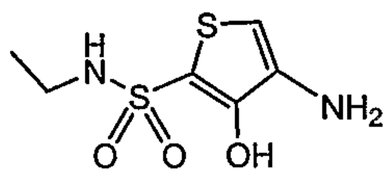
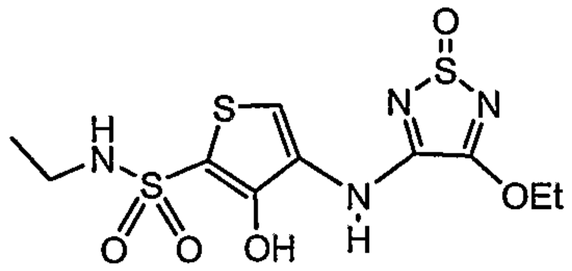
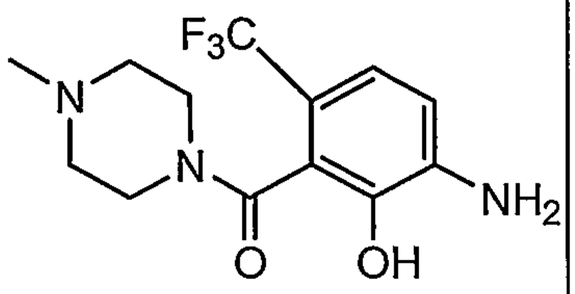
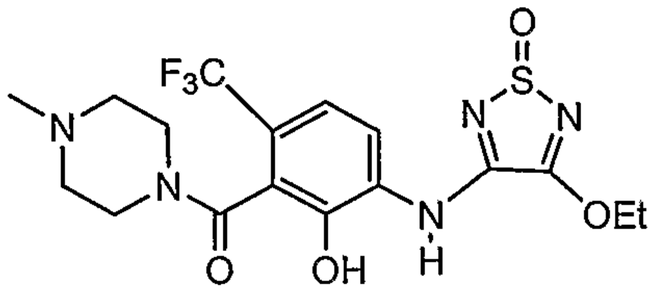
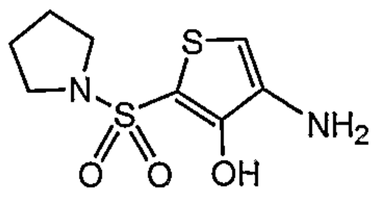
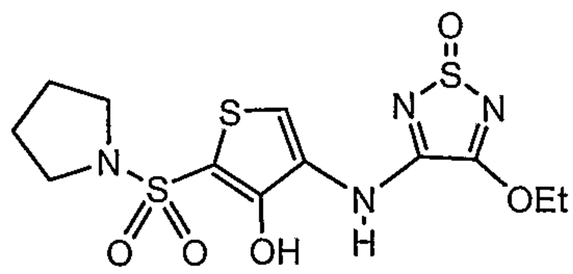
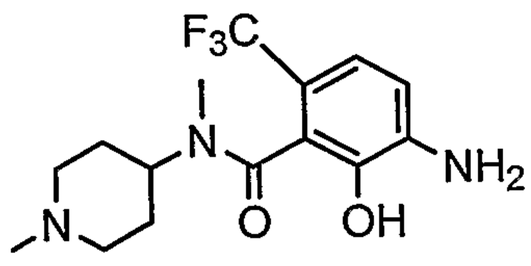
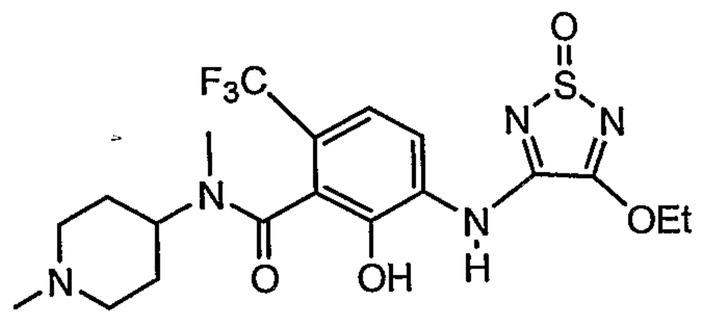
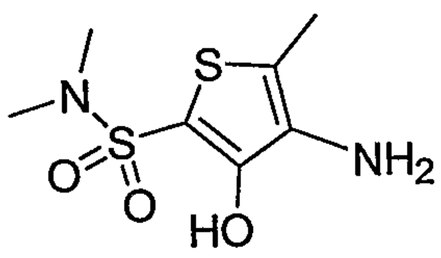
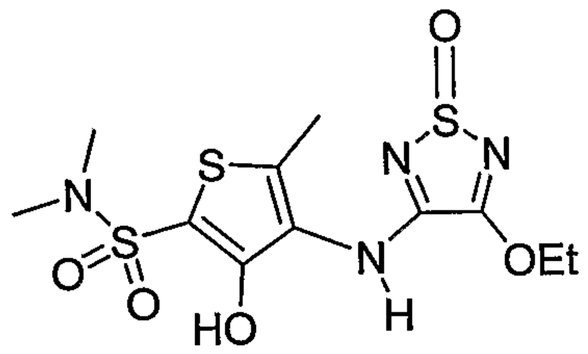
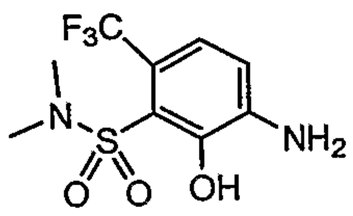
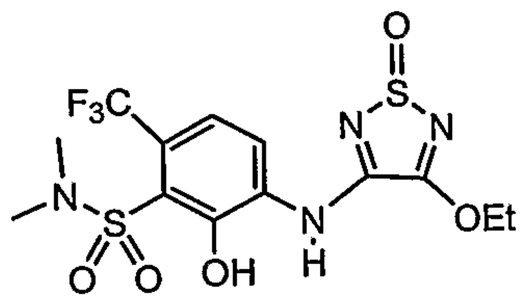
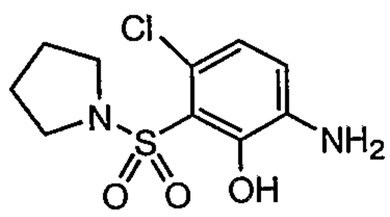
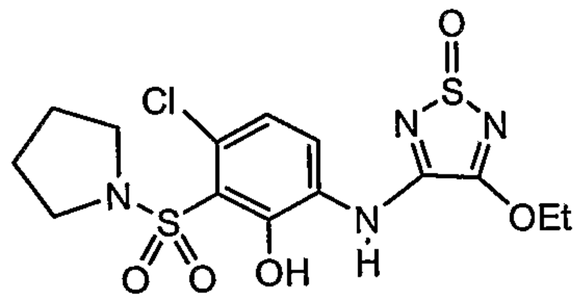
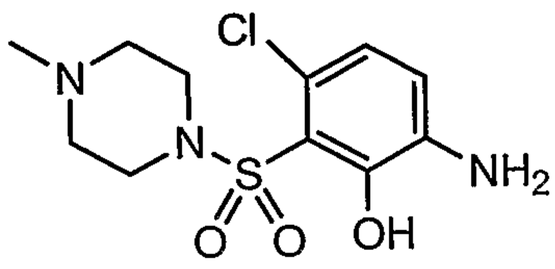
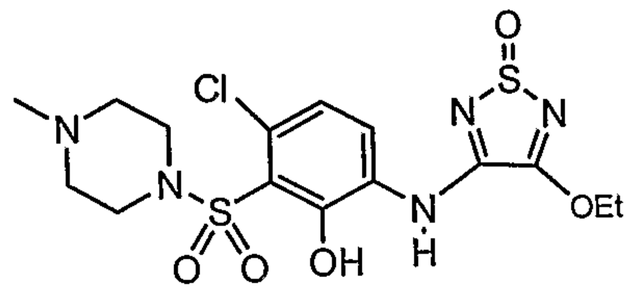
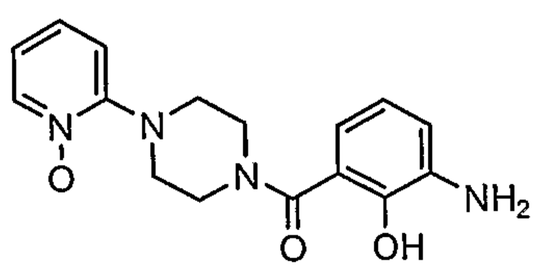
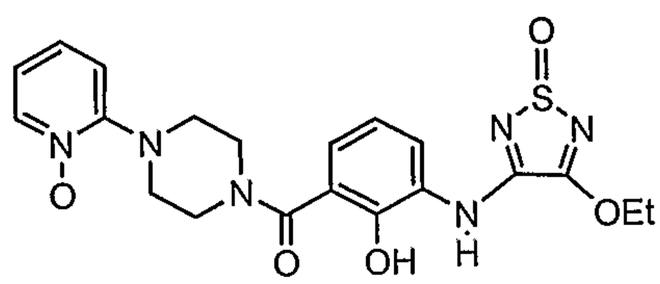
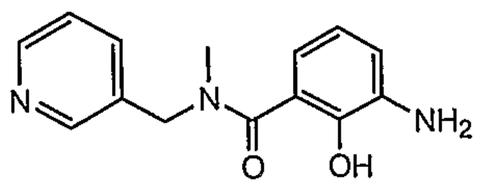
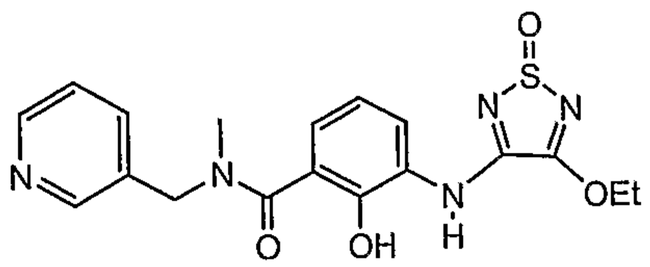
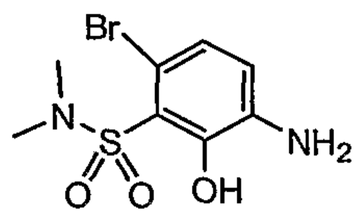
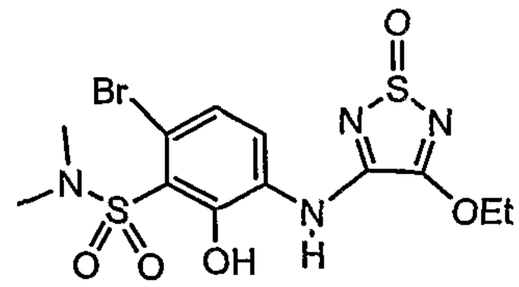
22.8		

22.9		
22.10		
22.16		
22.17		
22.19		
22.20		
22.21		

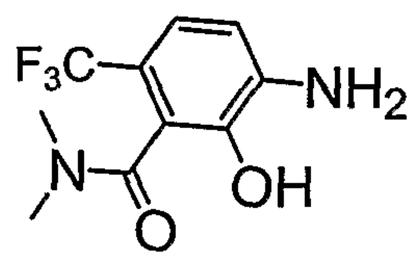
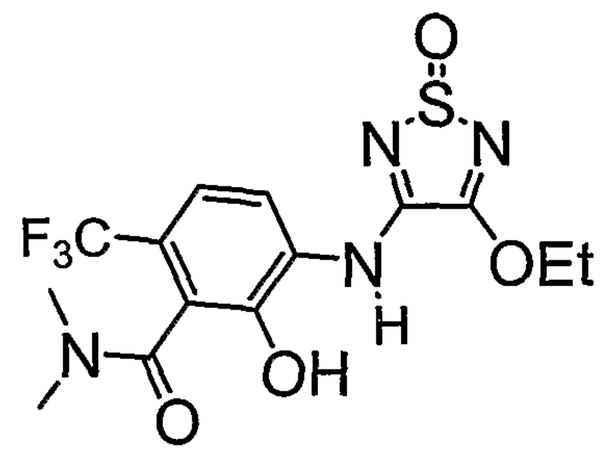
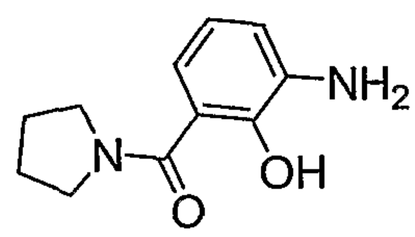
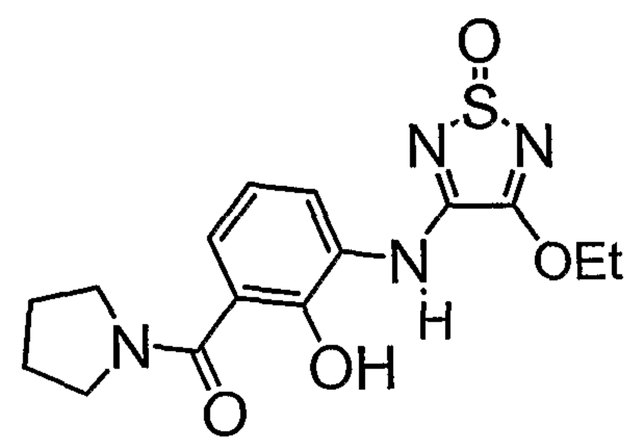
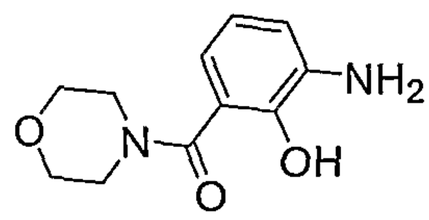
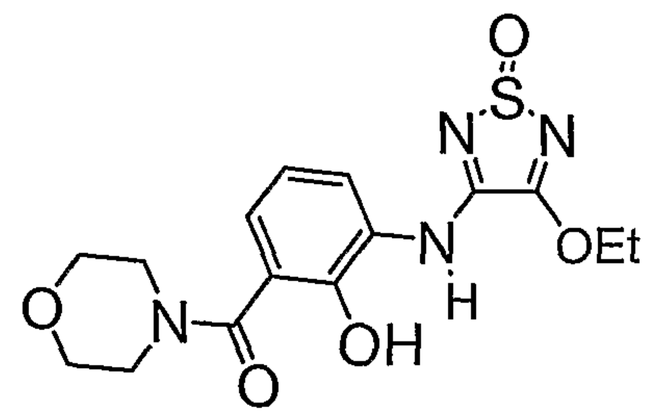
22.22		
22.23		
22.24		
22.25		
22.26		
22.27		
22.28		

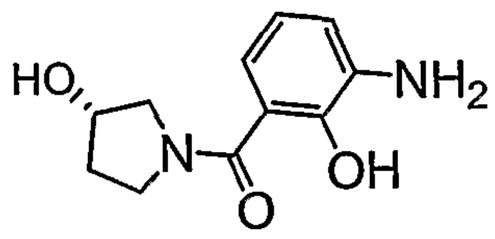
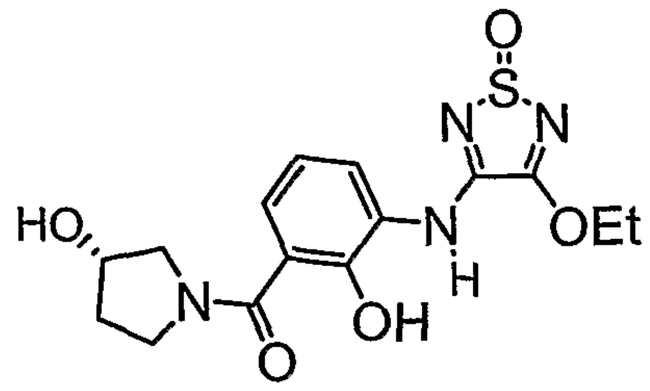
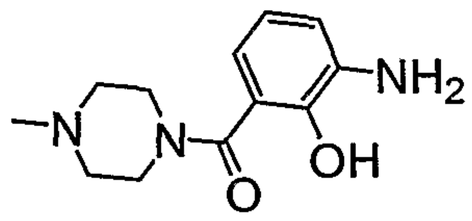
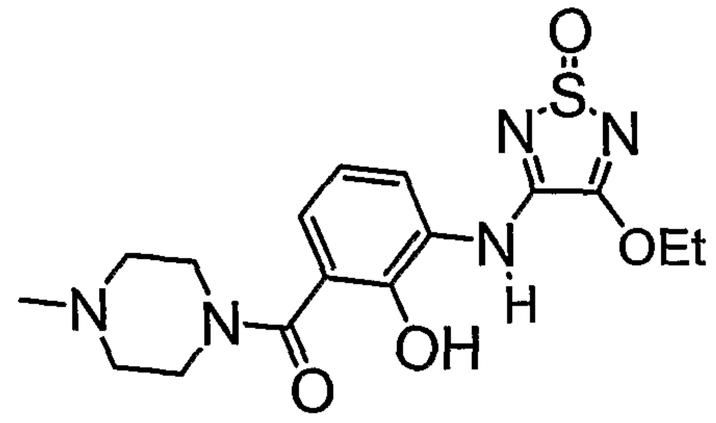
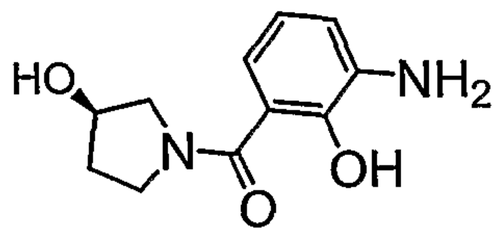
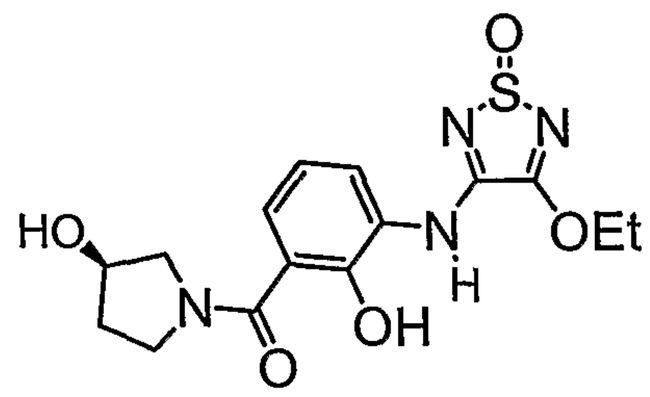
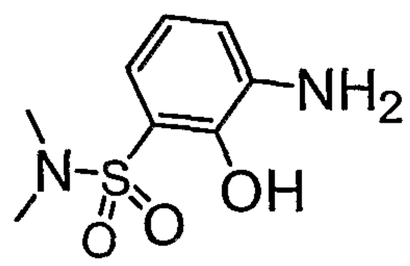
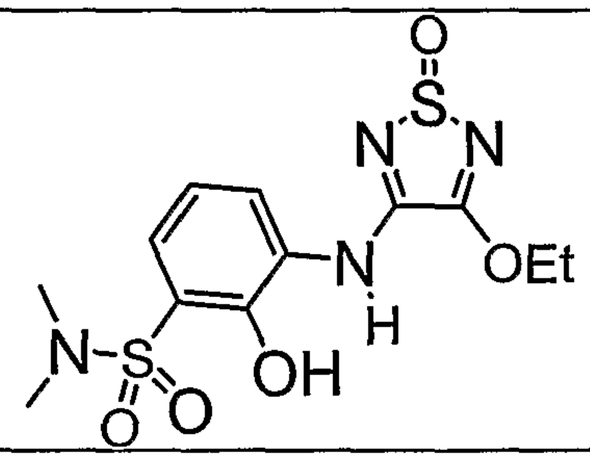
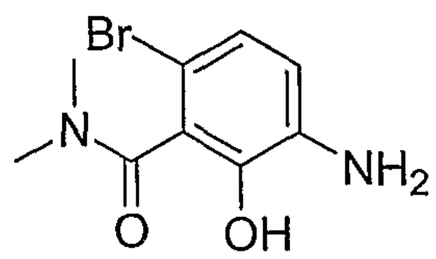
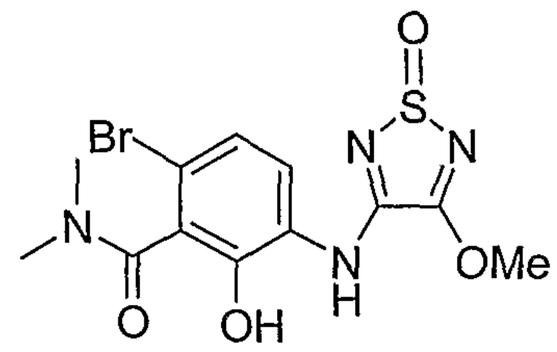
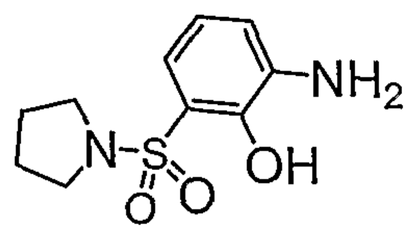
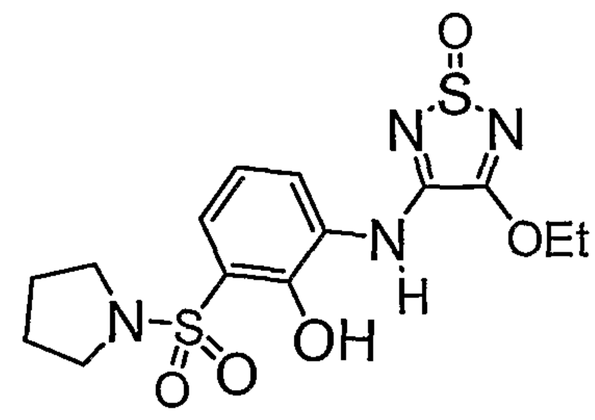
22.29		
22.30		
22.31		
22.32		
22.34		
22.36		
22.37		

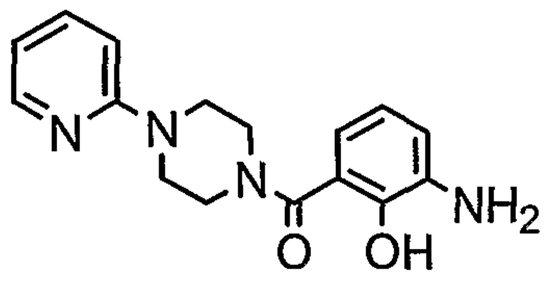
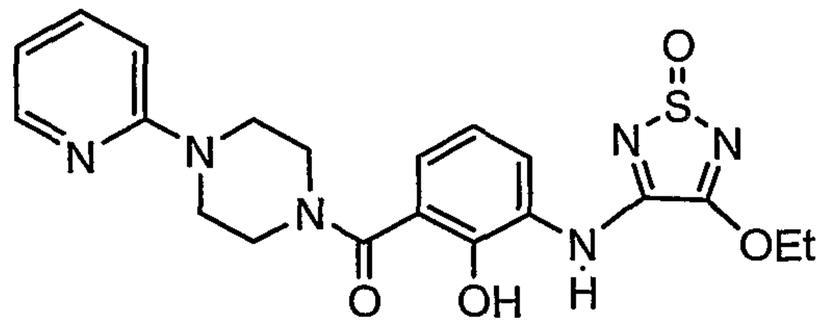
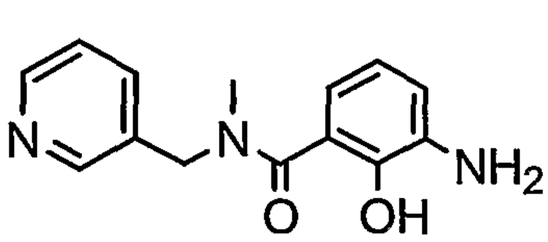
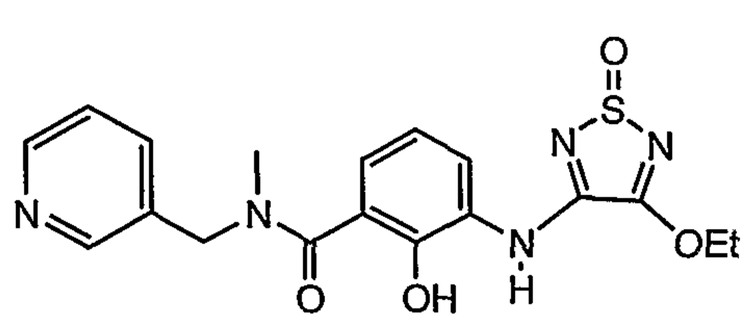
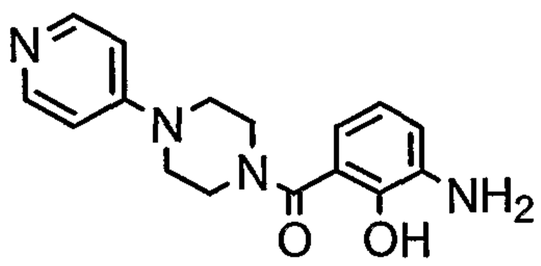
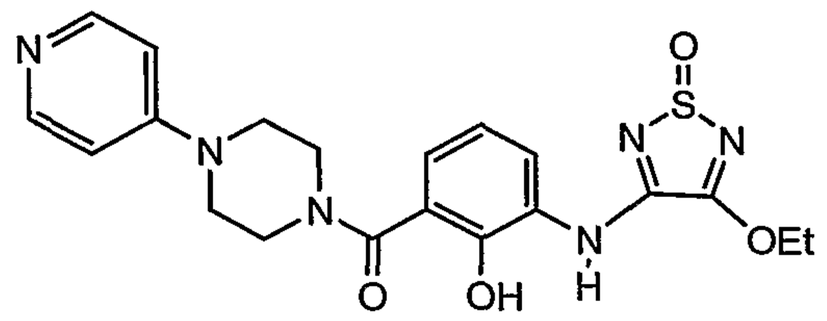
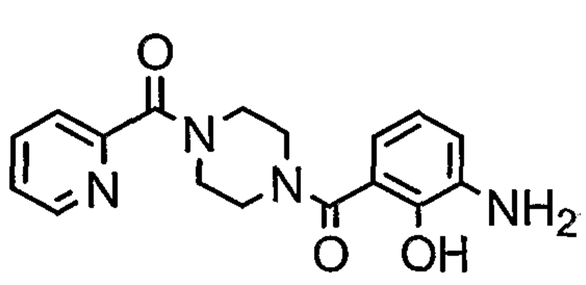
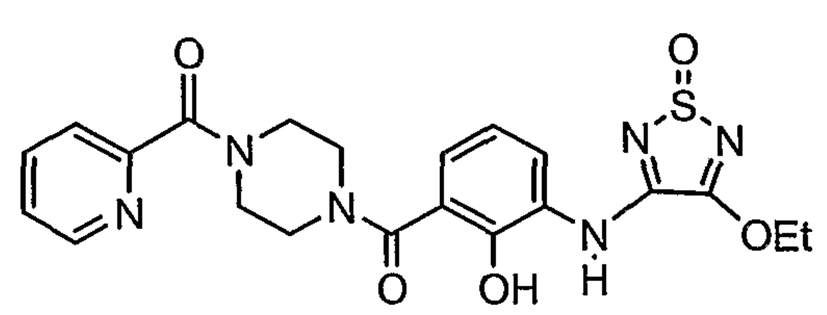
22.38		

PREPARATIVE EXAMPLES 22.39-22.51

Following a similar procedure set forth in Preparative Example 22.1 but using the commercially available (or prepared amine) indicated in the Table below, the following thiadiazoleoxide intermediates could be obtained.

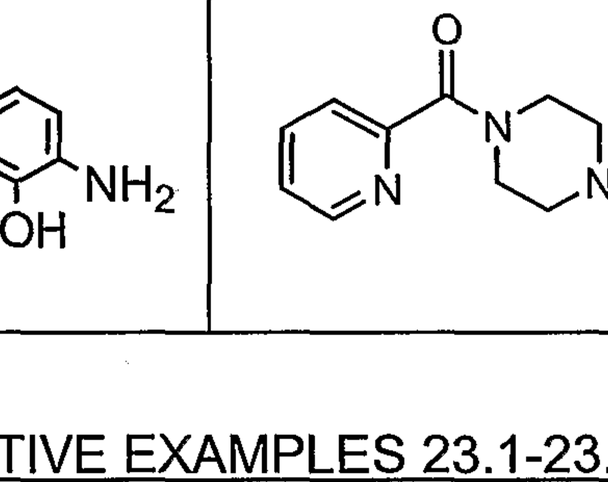
Ex.	Amine	Product
22.39		
22.40		
22.41		

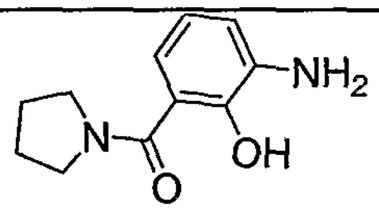
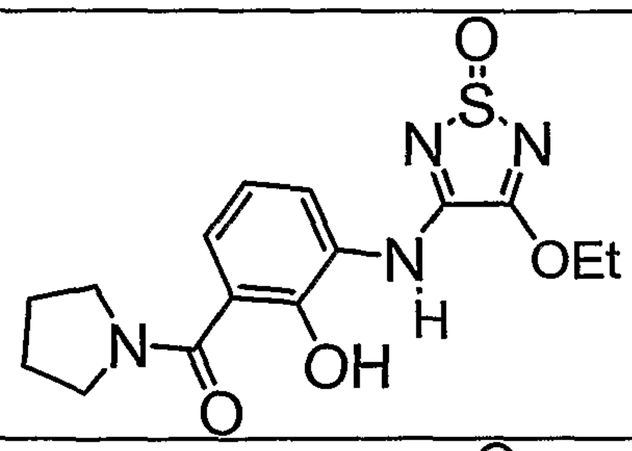
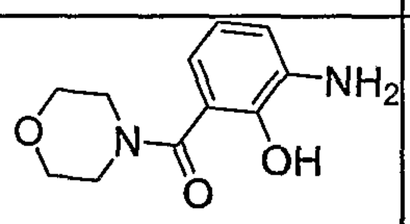
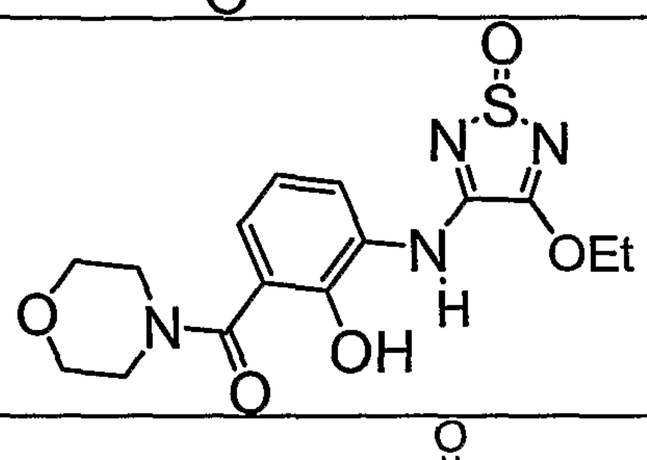
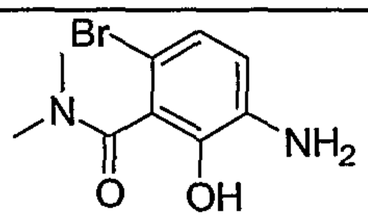
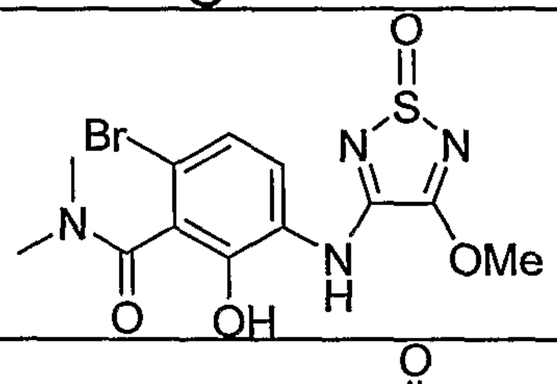
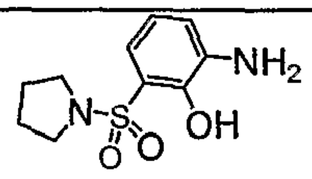
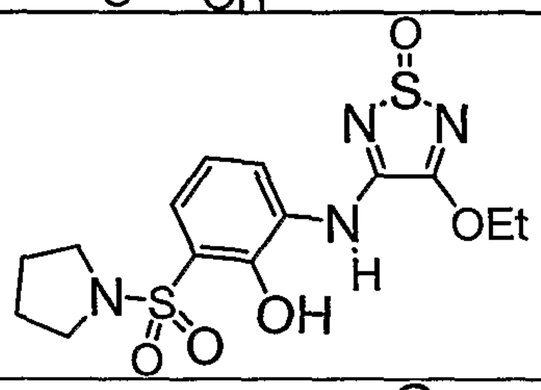
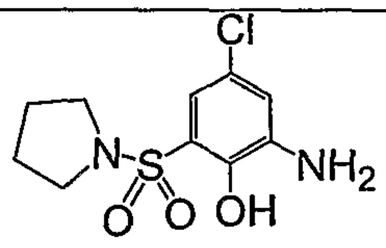
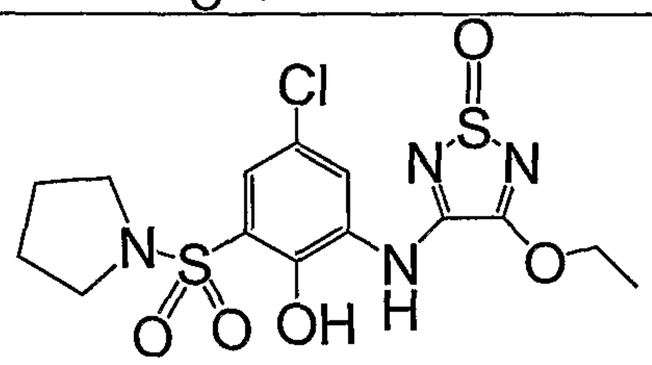
22.42		
22.43		
22.44		
22.45		
22.46		
22.47		

22.48		
22.49		
22.50		
22.51		

PREPARATIVE EXAMPLES 23.1-23.10

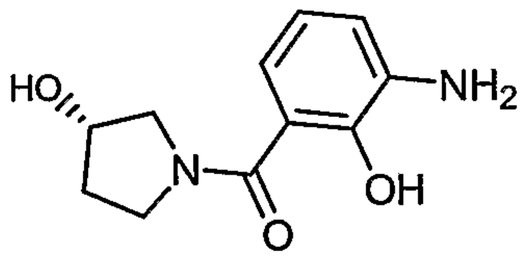
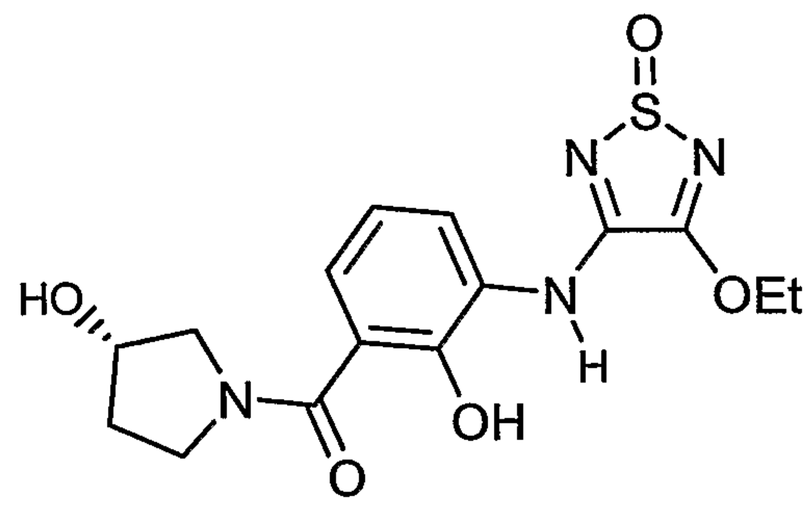
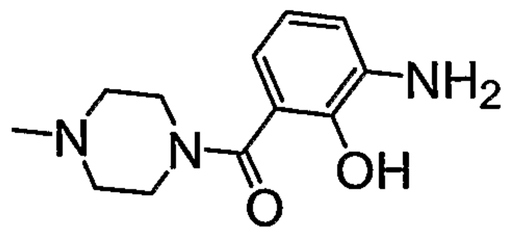
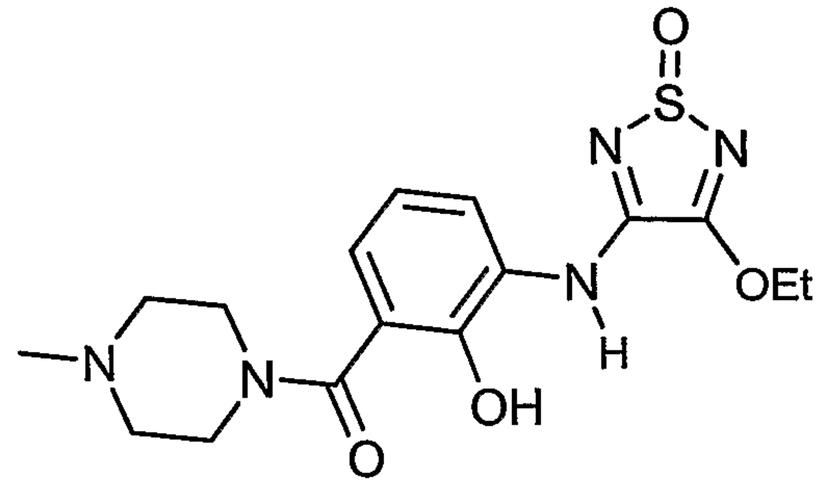
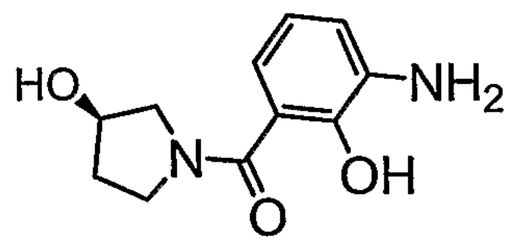
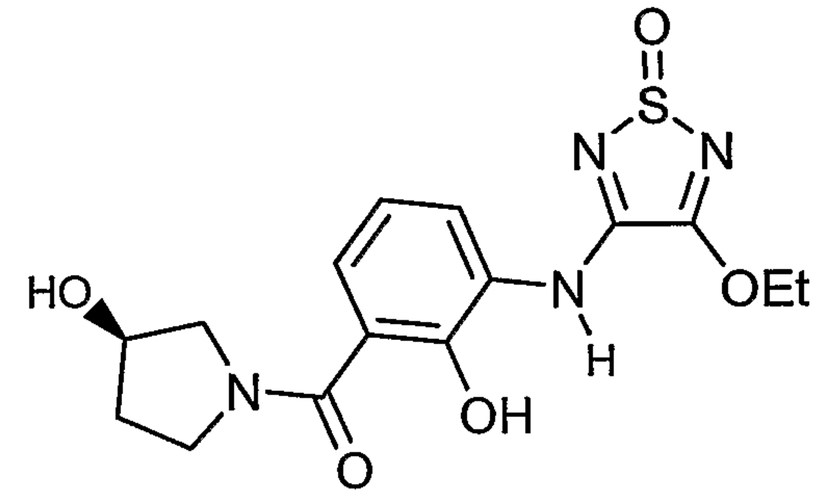
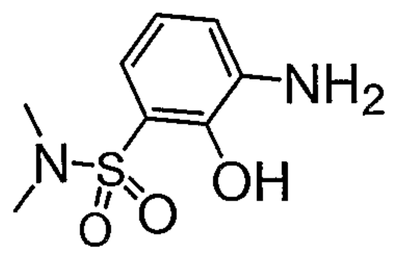
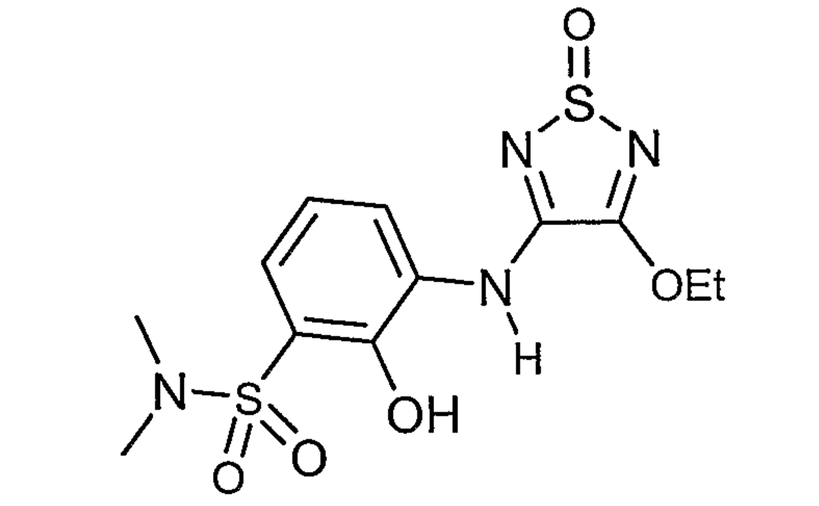
Following a similar procedure set forth in Preparative Example 22 but using the commercially available (or prepared amine) from the Preparative Example indicated in the Table below, the following thiadiazoleoxide intermediates were obtained.

Prep Ex	Amine	Product	1. Yield 2. MH+
23.1			1. 99% 2. 379

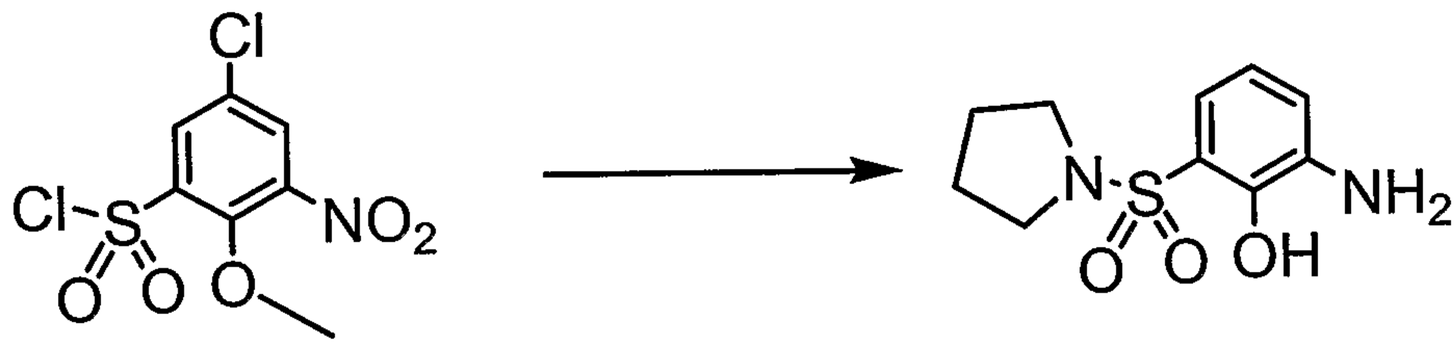
23.2			used crude
23.3			used crude
23.8			1. 85% 2. 390.0
23.9			1. 25%
23.10			1. 83% 2. 277.1

PREPARATIVE EXAMPLES 23.4-23.2

Following a similar procedure set forth in Preparative Example 22 but using the commercially available (or prepared amine) from the Preparative Example indicated in the Table below, the following thiadiazoleoxide intermediates could be obtained.

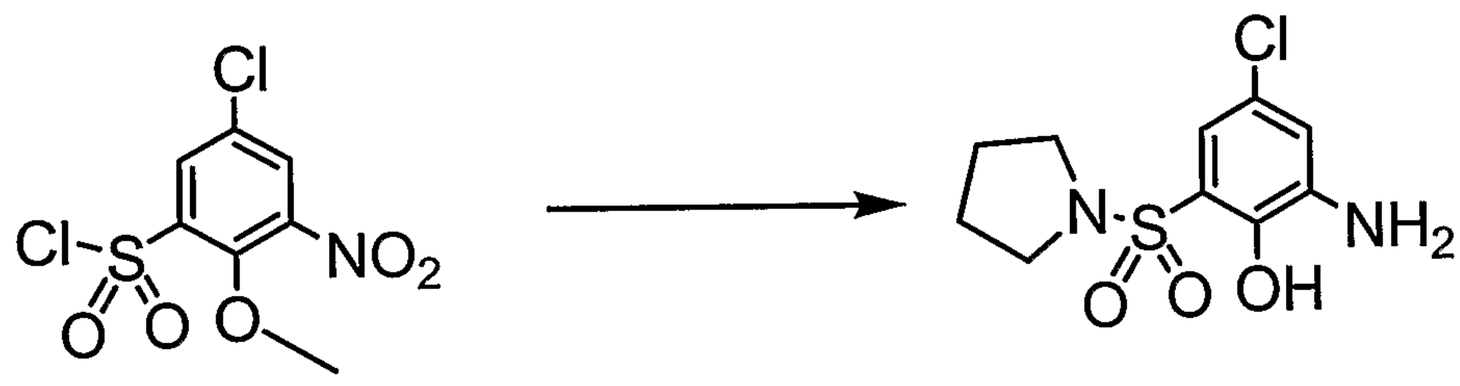
Prep Ex	Amine	Product
23.4		
23.5		
23.6		
23.7		

PREPARATIVE EXAMPLE 23.10A



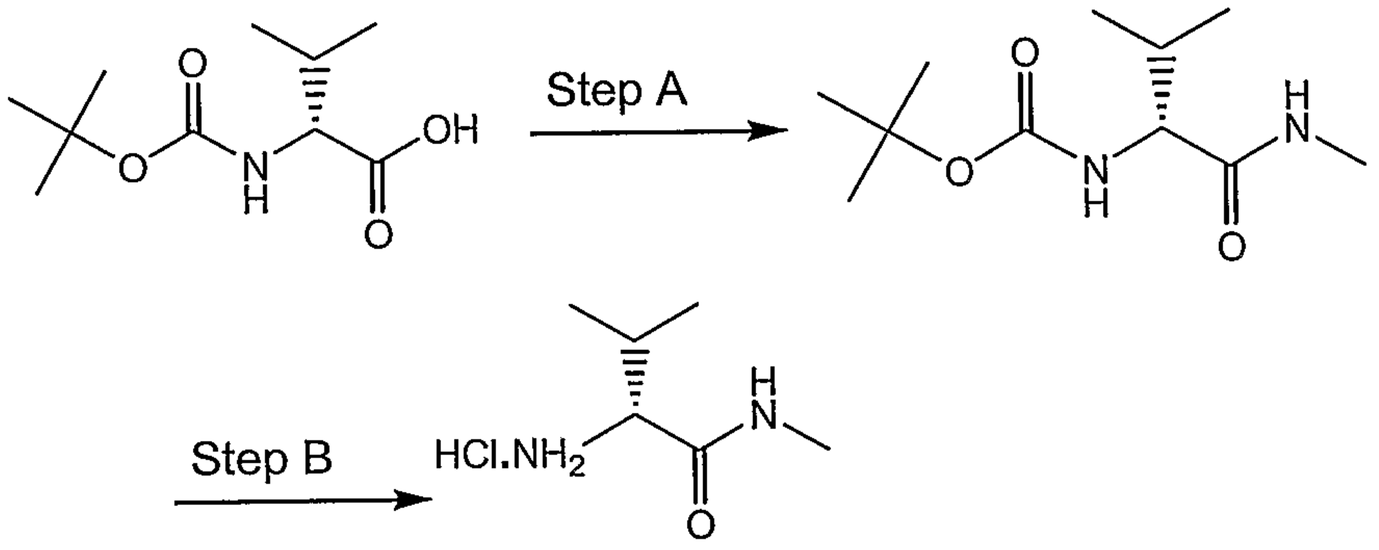
Following a similar procedure as that used in the Preparative Example 1302 Steps A-C, except using pyrrolidine in Step A instead of diethyl amine and 50psi hydrogen pressure in the hydrogenation Step C, the title compound was obtained (80%, 1.0g, MH^+ = 243.1)

PREPARATIVE EXAMPLE 23.10B



Following the same procedure set forth in the Preparative Example 23.10A, except by using 30psi hydrogen pressure in the hydrogenation Step C, the title compound was obtained (83%, 1.2g, MH^+ = 277.1).

PREPARATIVE EXAMPLE 24



Step A

To a solution of *N*-protected amino acid (1.5 g, 6.9 mmol) in CH_2Cl_2 (25 mL) at room temperature was added DIPEA (3.6 mL, 20.7 mmol), and PyBrop (3.4 g, 6.9 mmol) followed by $MeNH_2$ (6.9 mL, 13.8 mmol, 2.0 M in CH_2Cl_2). The resulting

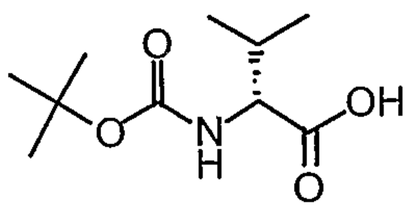
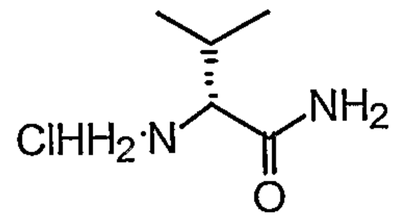
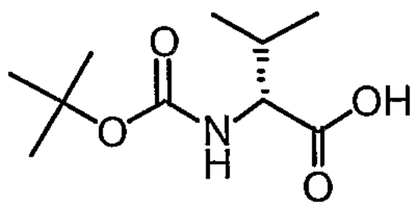
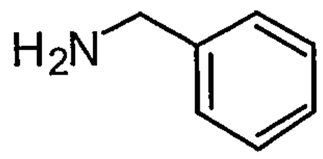
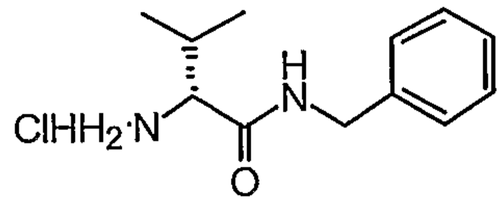
solution was stirred for 18 h at room temperature (until TLC analysis deemed the reaction to be complete). The resulting mixture was washed sequentially with 10% citric acid (3 x 20 mL), sat. aq. $NaHCO_3$ (3 x 20 mL), and brine (3 x 20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with CH_2Cl_2/MeOH (40:1) to afford 1.0 g (63% yield) of a solid.

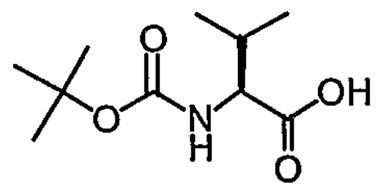
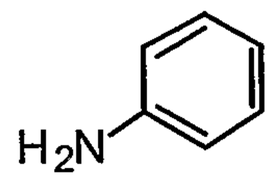
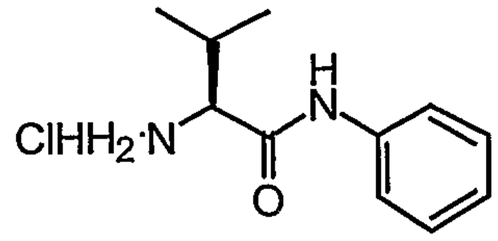
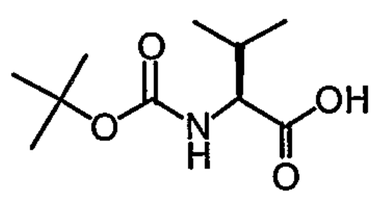
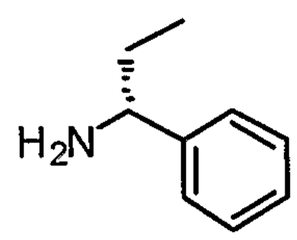
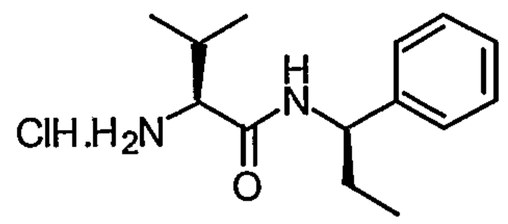
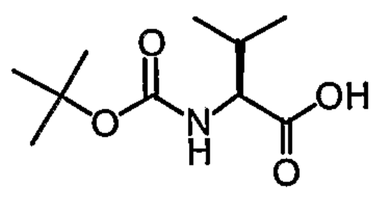
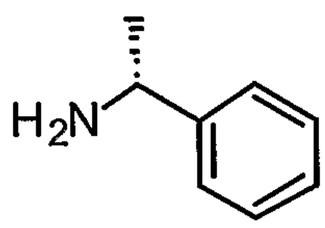
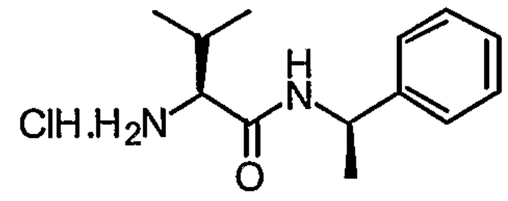
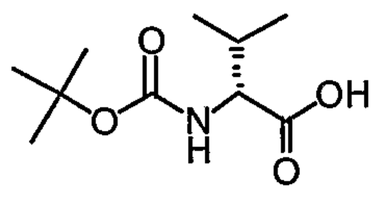
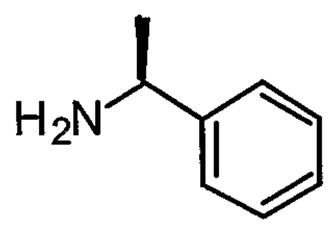
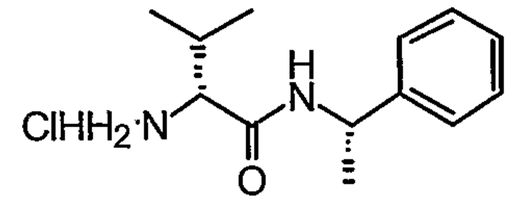
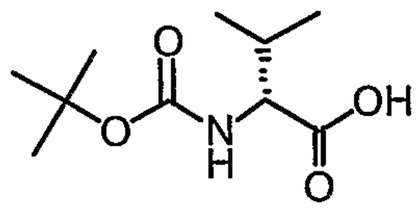
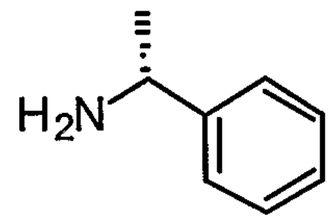
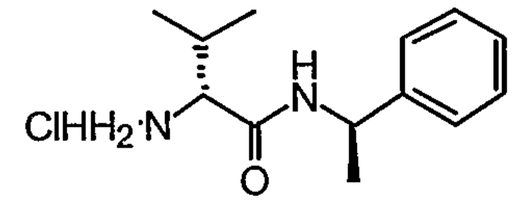
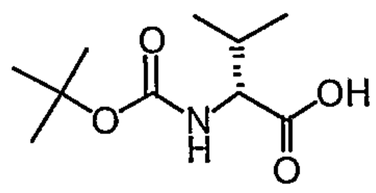
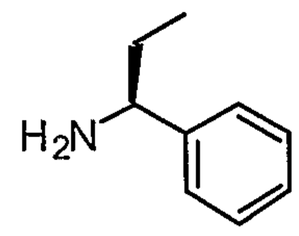
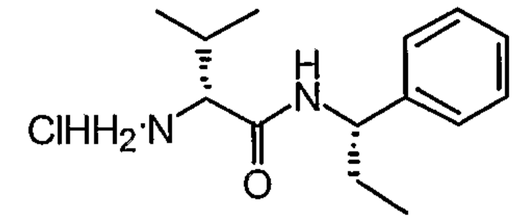
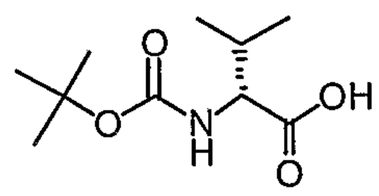
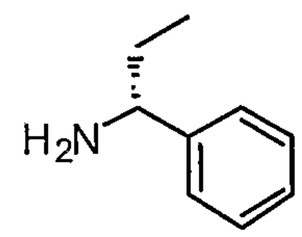
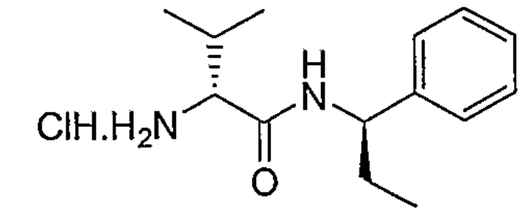
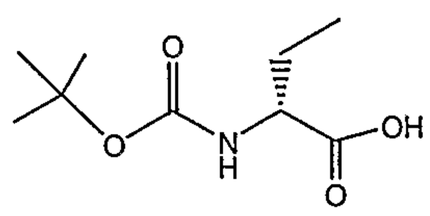
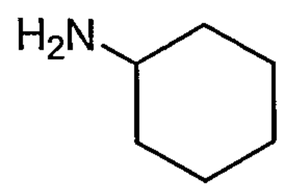
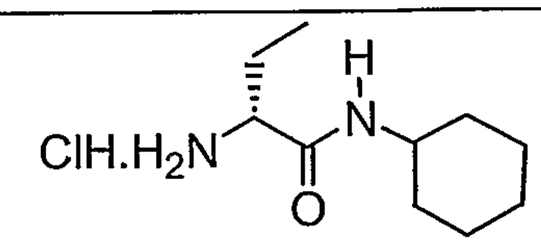
Step B

To a round bottom charged with the *N*-protected amide (1.0 g, 4.35 mmol) (from Step A) was added 4N HCl/dioxane (10 mL) and the mixture was stirred at room temperature for 2 h. The mixture was diluted with Et_2O (20 mL) and concentrated under reduced pressure. The crude product was treated with Et_2O (2 x 20 mL) and concentrated under reduced pressure to afford 0.72 g (~100 % yield) of crude product as the HCl salt. This material was taken on without further purification or characterization.

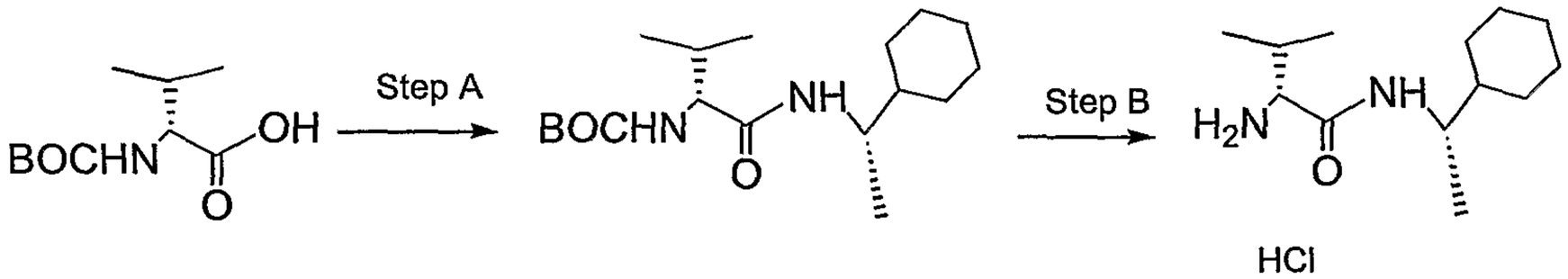
PREPARATIVE EXAMPLES 25-33.1

Following the procedure set forth in Preparative Example 24 but using the commercially available *N*-protected amino acids and amines in the Table below, the amine hydrochloride products were obtained.

Prep Ex.	Amino acid	Amine	Product	Yield (%)
25		NH_3		70
26				71

27				66
28				65
29				90
30				68
31				68
32				97
33				97
33.1				20

PREPARATIVE EXAMPLE 33.2



Step A

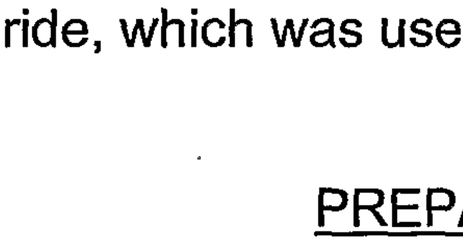
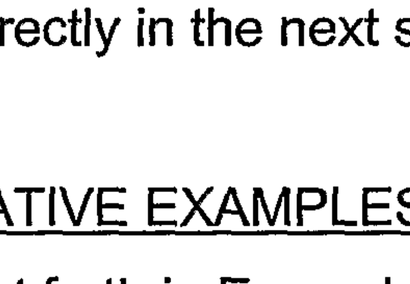
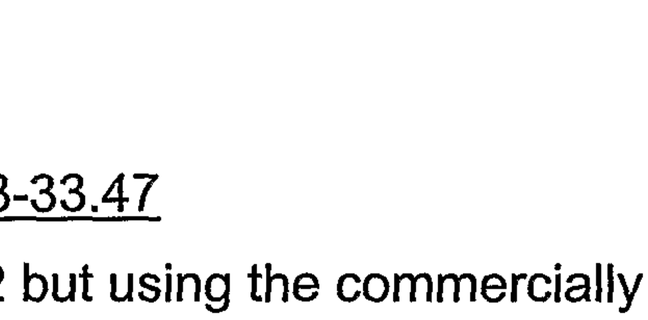
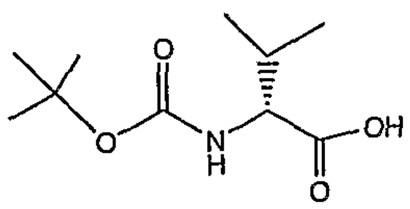
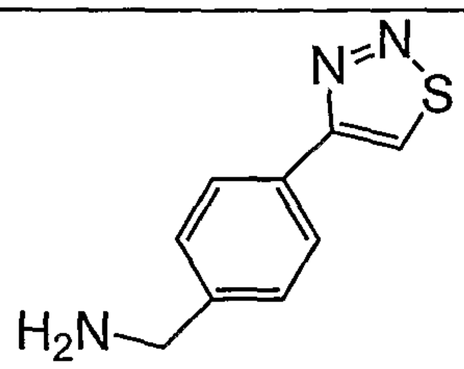
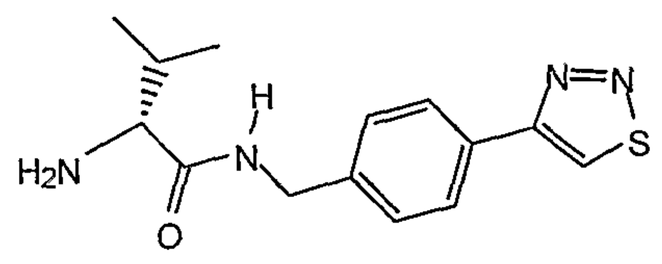
BOC-valine (45mg) and PS-carbodiimide (200mg) were suspended in CH_2Cl_2 (4ml). After addition of the CH_2Cl_2-amine solution (0.138N, 1ml), the mixture was shaken overnight. The solution was filtered and the resin was washed with more CH_2Cl_2, and the filtrate was concentrated *in vacuo* to yield the product, which was carried on directly in Step B.

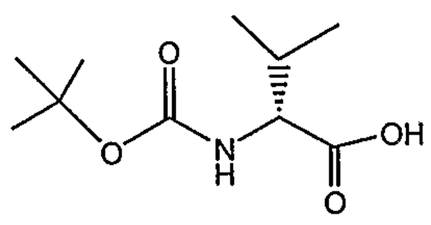
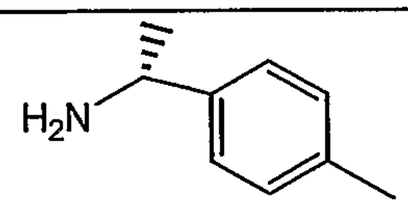
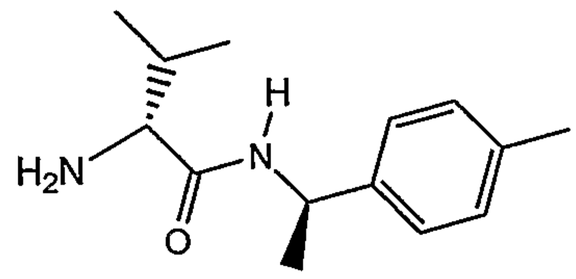
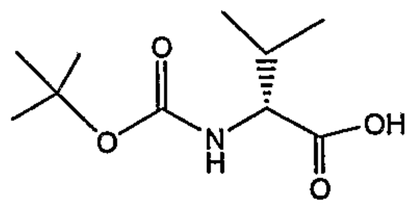
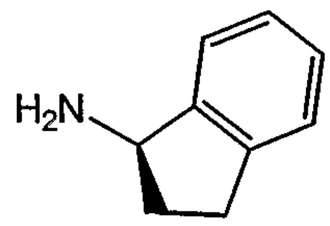
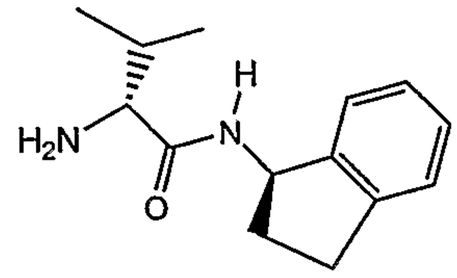
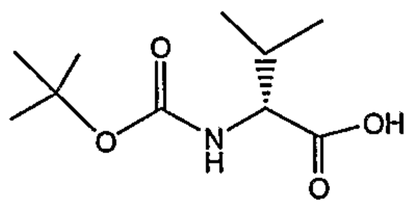
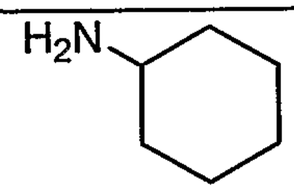
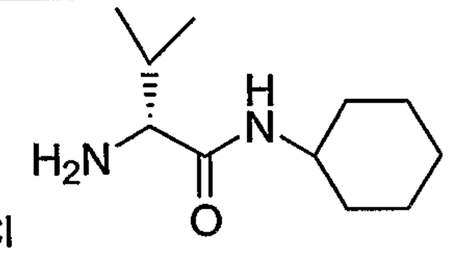
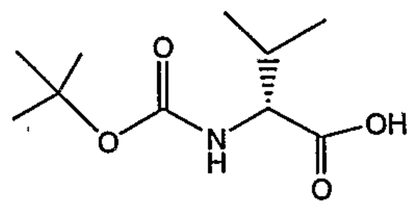
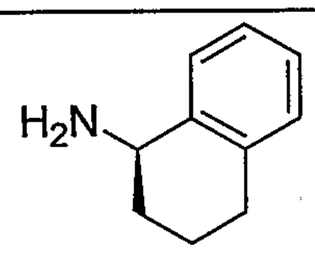
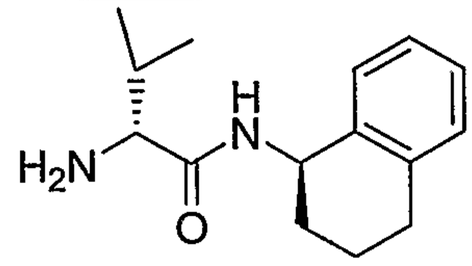
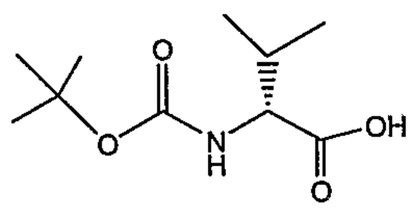
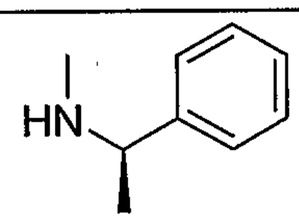
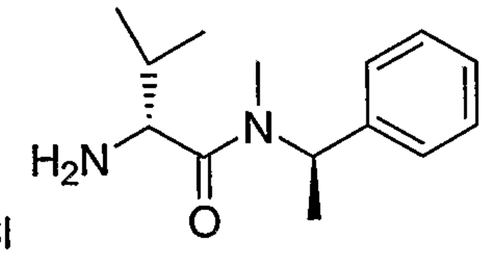
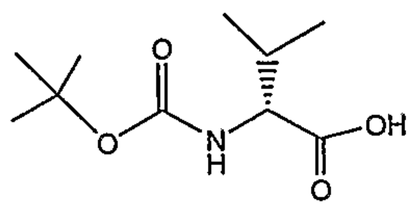
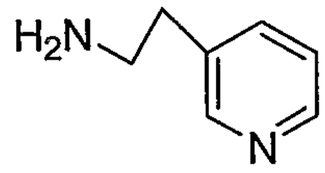
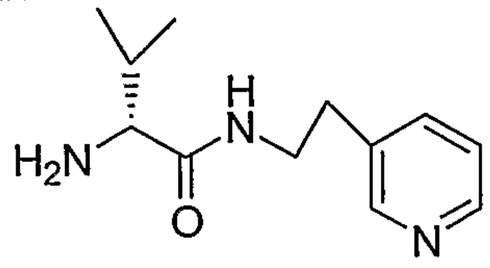
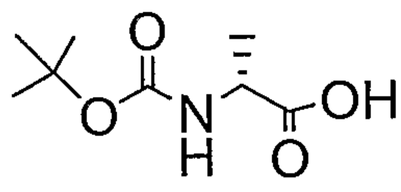
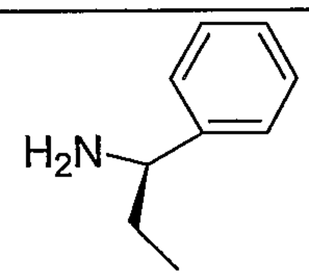
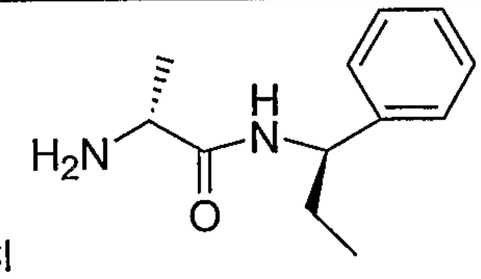
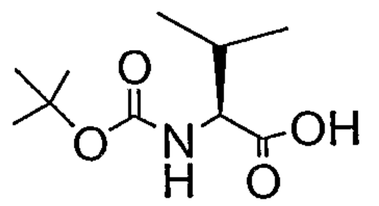
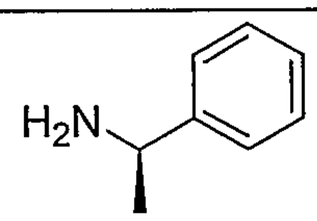
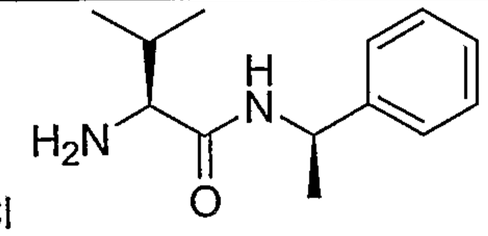
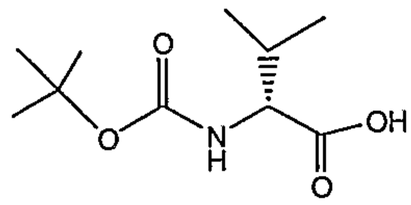
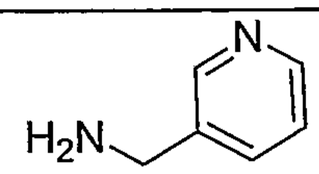
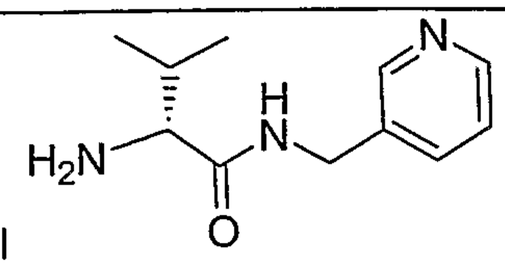
Step B

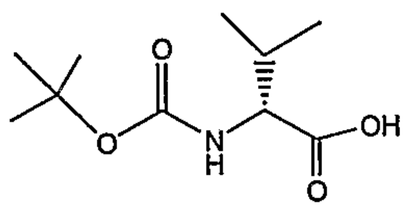
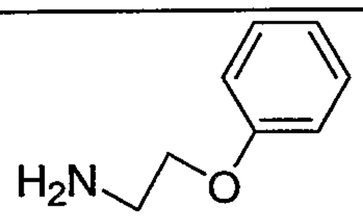
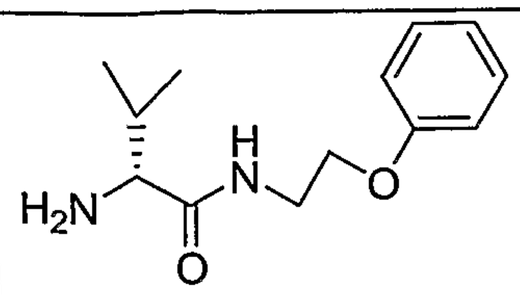
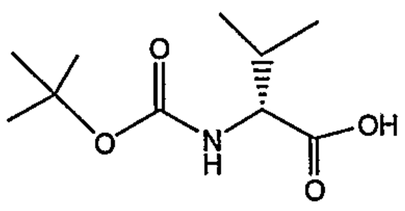
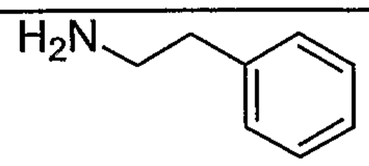
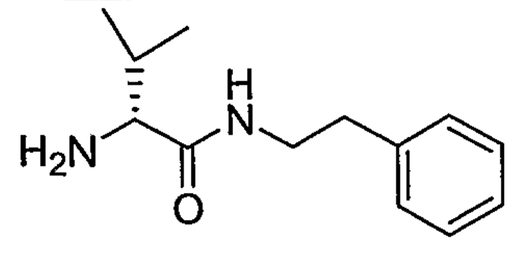
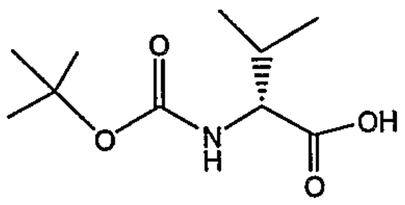
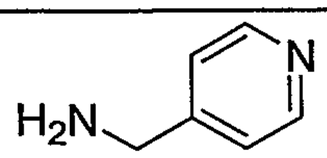
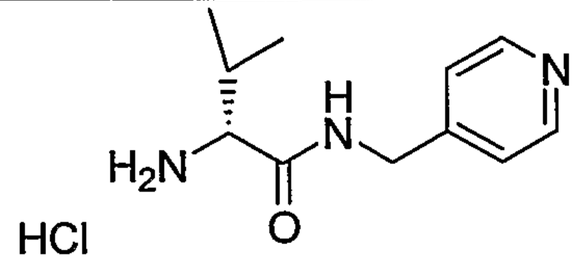
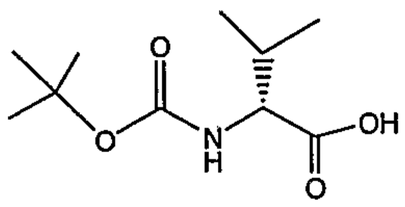
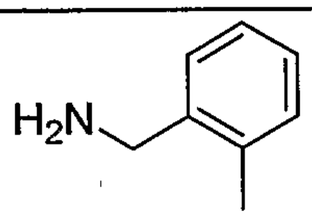
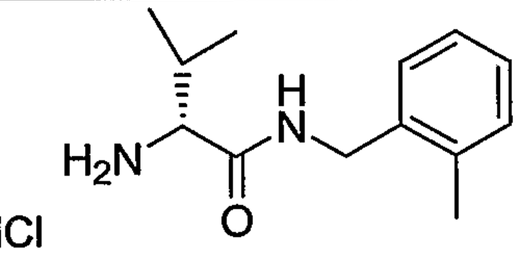
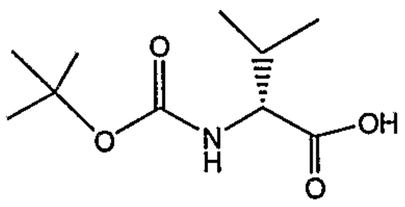
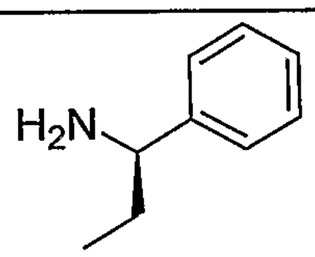
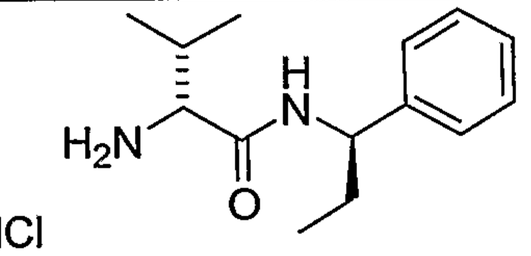
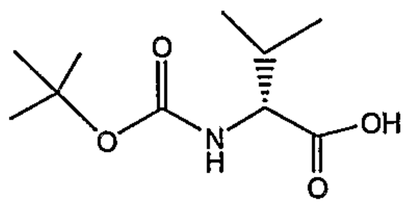
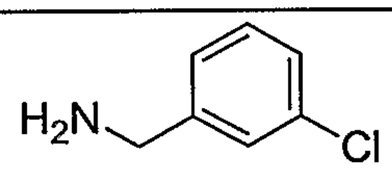
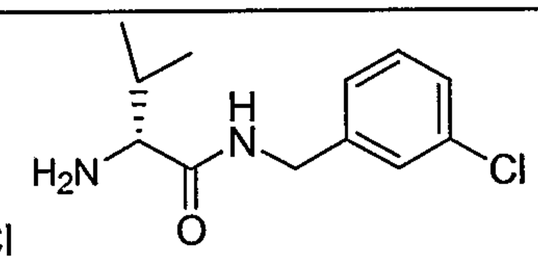
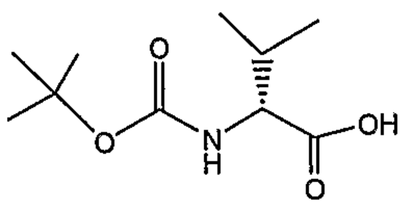
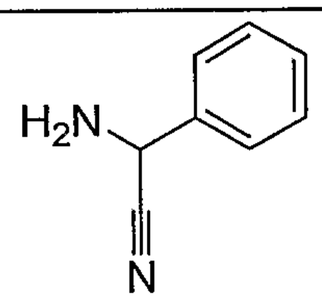
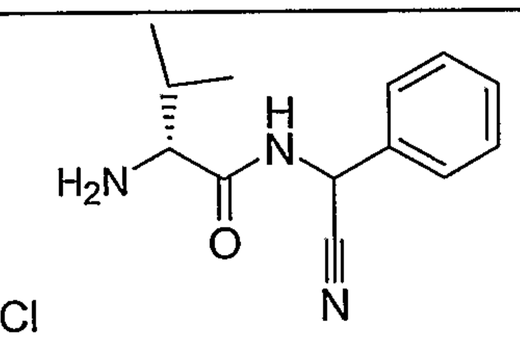
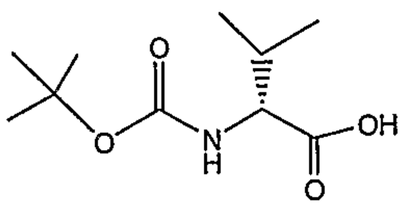
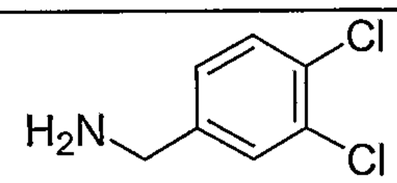
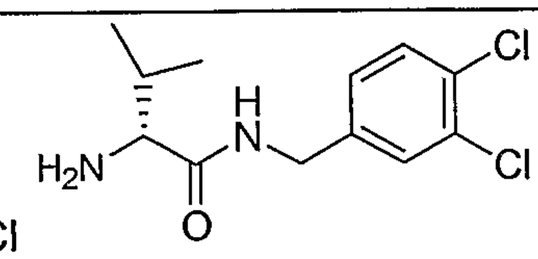
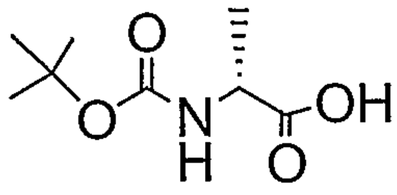
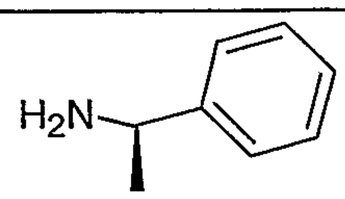
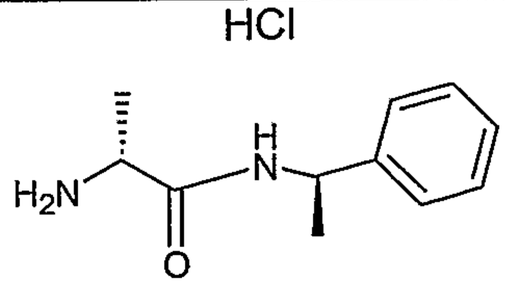
The crude material from Step A was dissolved in 4N HCl/dioxane (2.5ml) and stirred for 2h. The reaction was concentrated *in vacuo* to yield the desired amine hydrochloride, which was used directly in the next step.

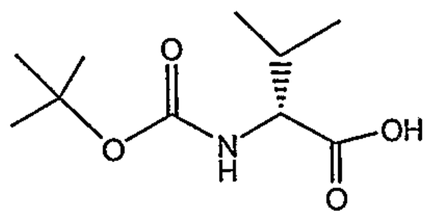
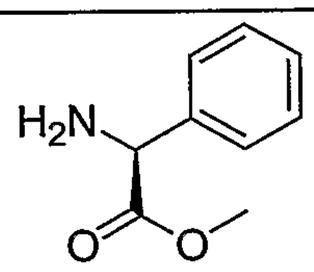
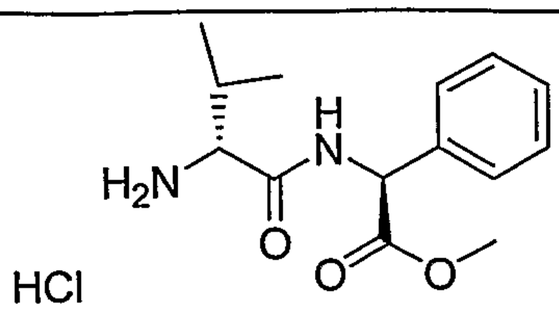
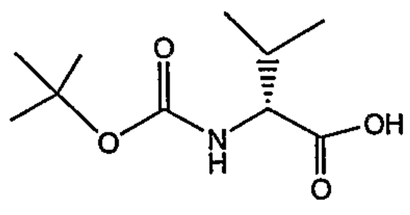
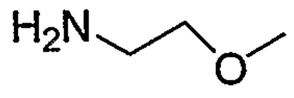
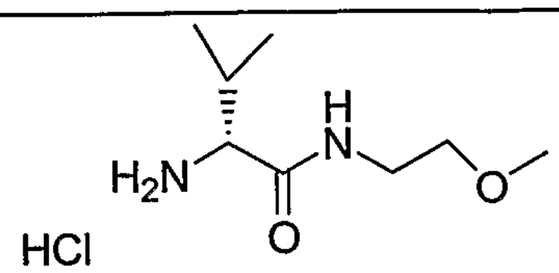
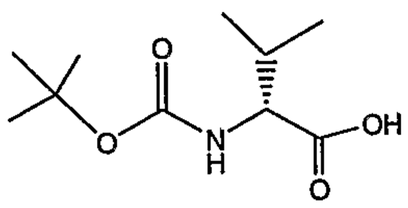
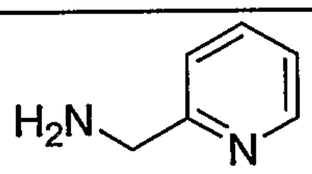
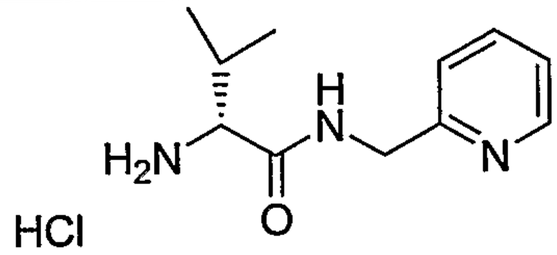
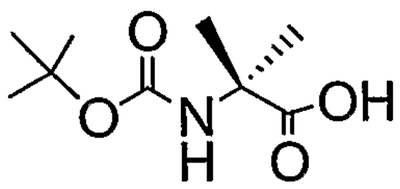
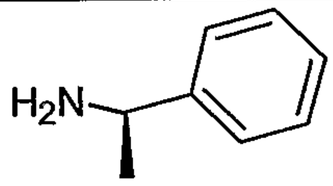
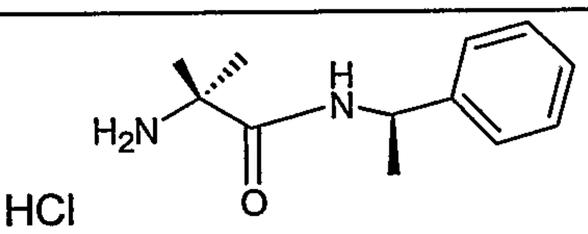
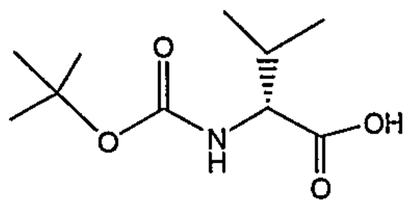
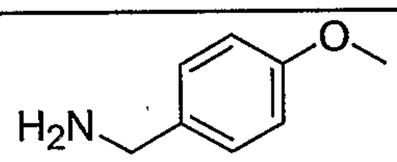
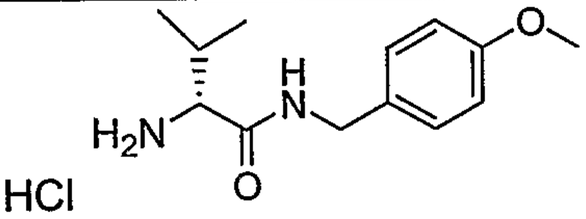
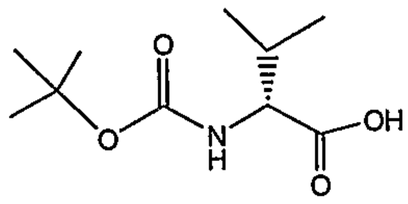
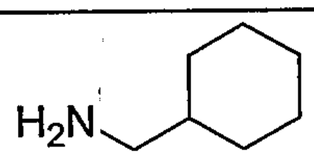
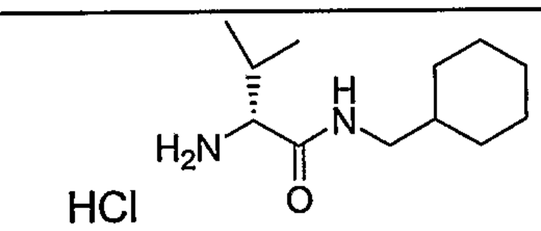
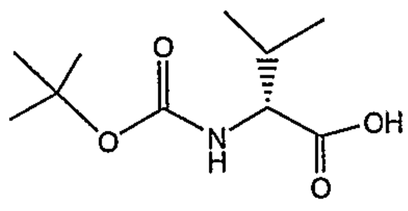
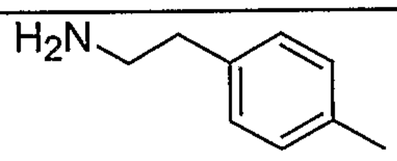
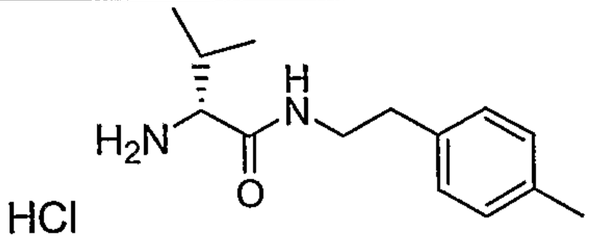
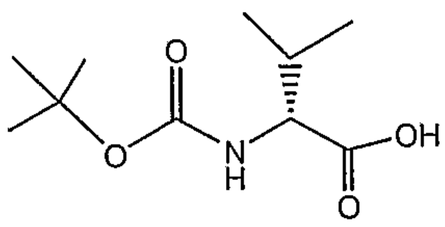
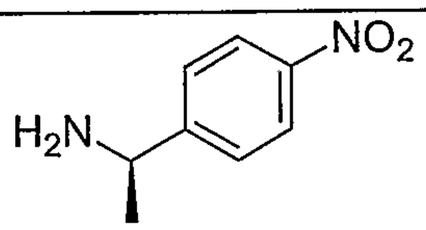
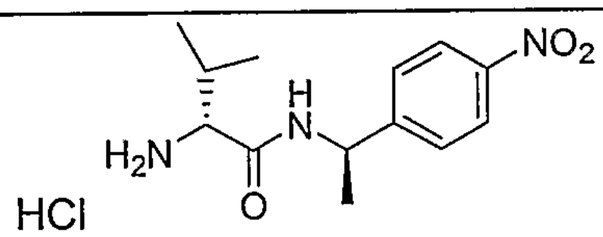
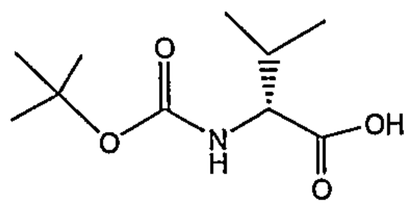
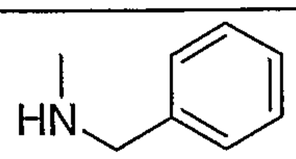
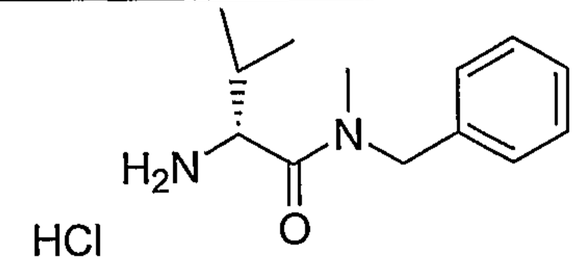
PREPARATIVE EXAMPLES 33.3-33.47

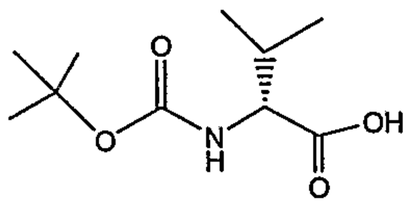
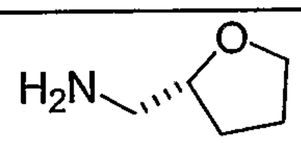
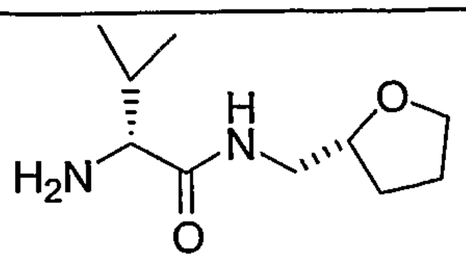
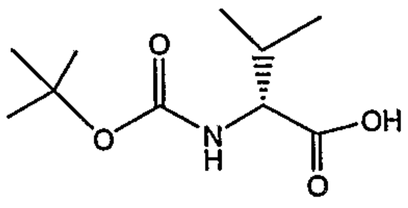
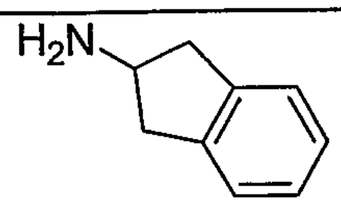
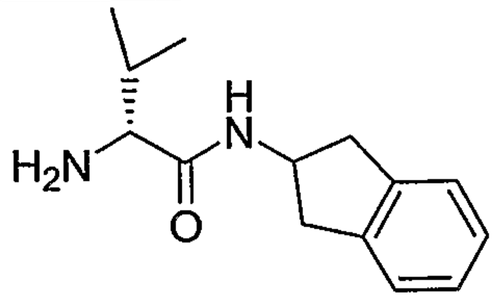
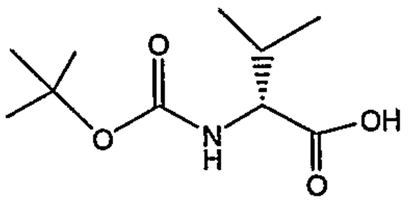
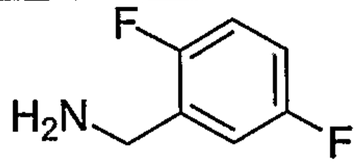
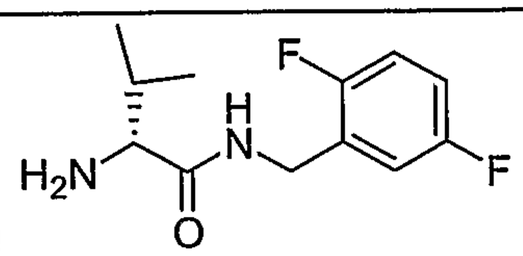
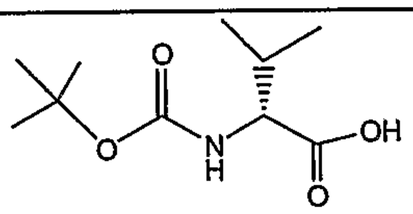
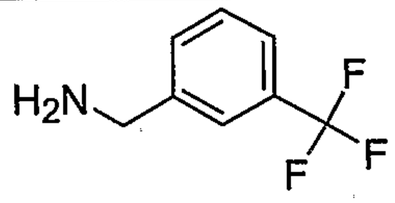
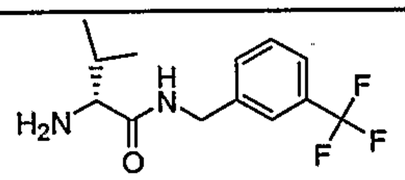
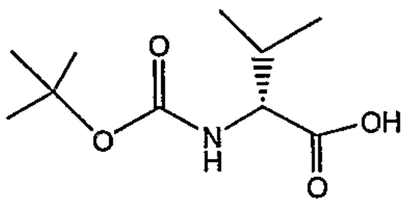
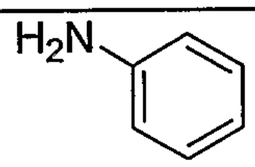
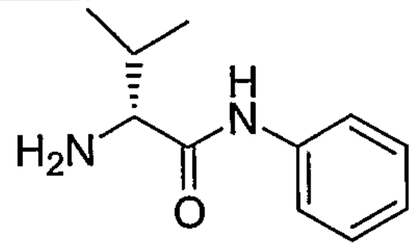
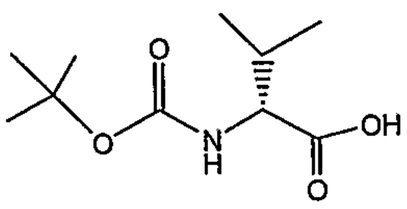
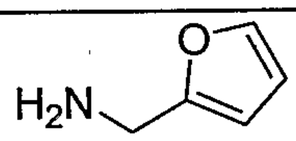
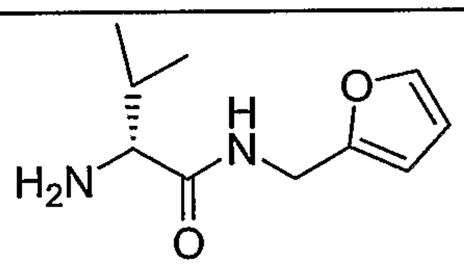
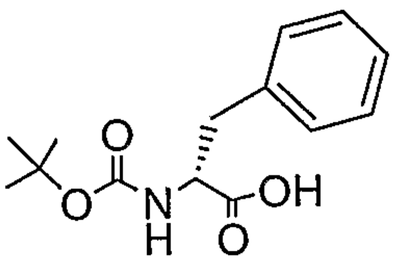
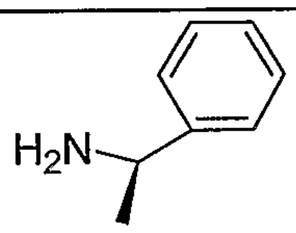
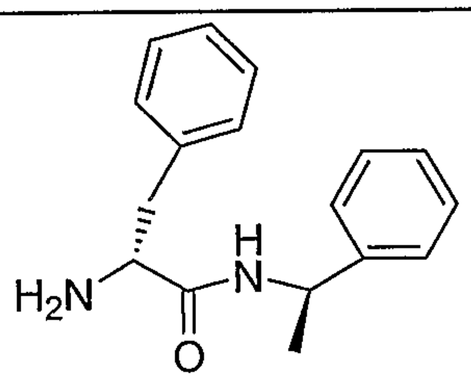
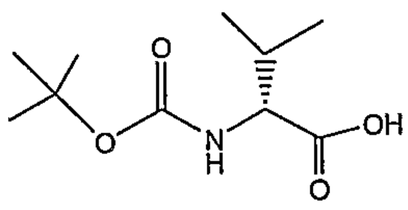
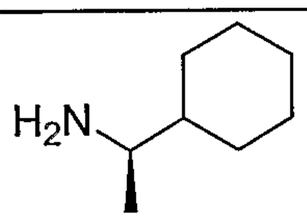
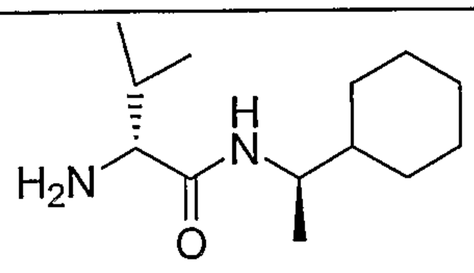
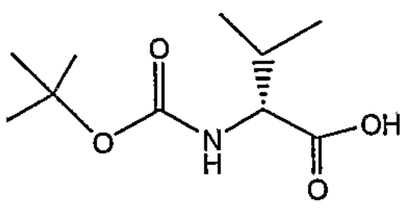
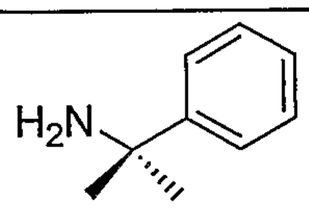
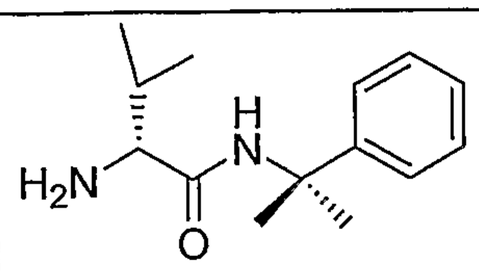
Following the procedure set forth in Example 33.2 but using the commercially available N-protected amino acids in the Table below, the amine hydrochloride products were obtained.

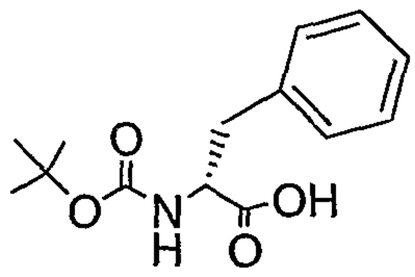
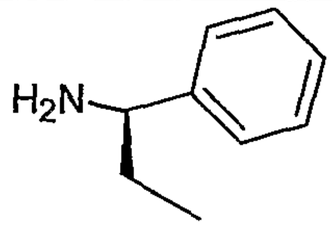
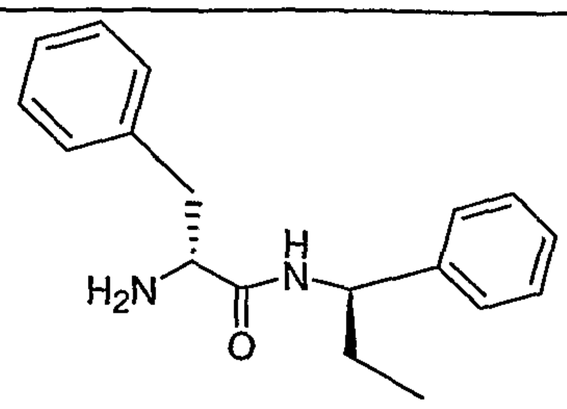
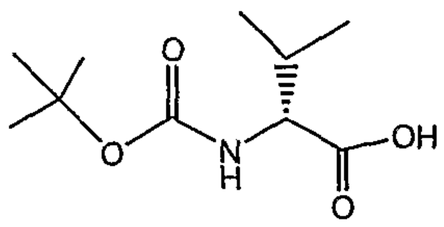
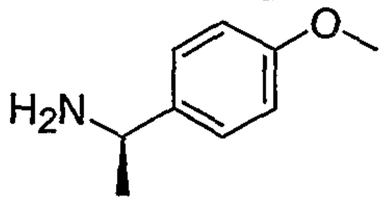
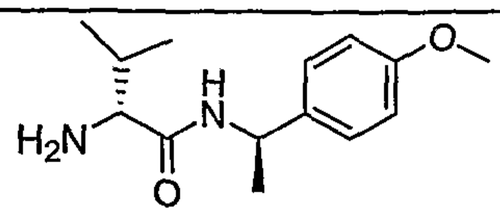
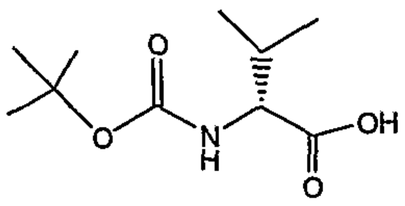
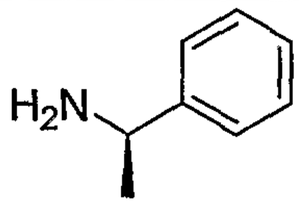
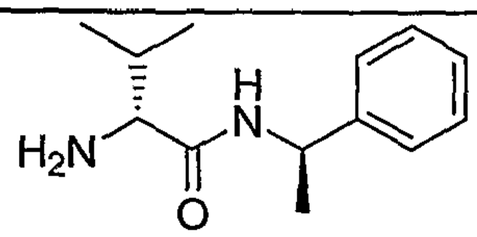
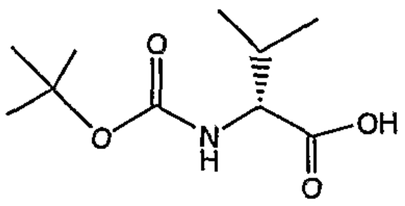
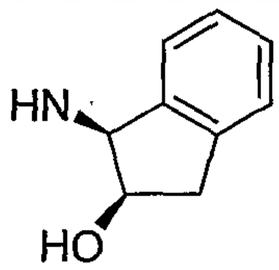
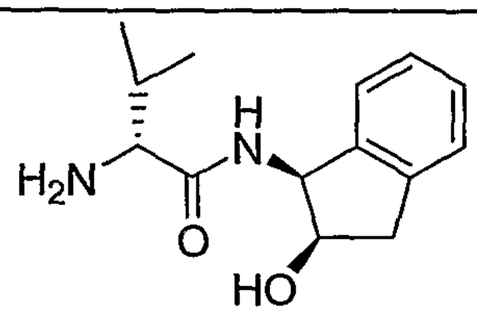
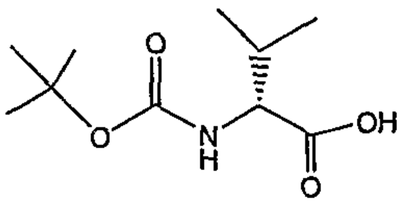
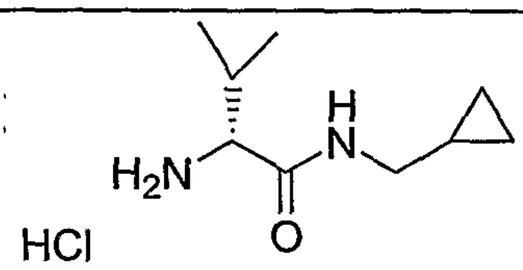
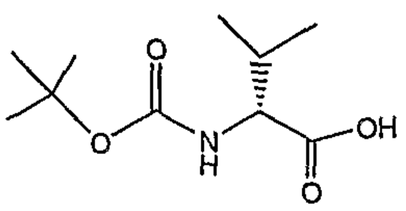
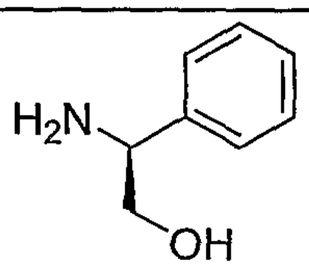
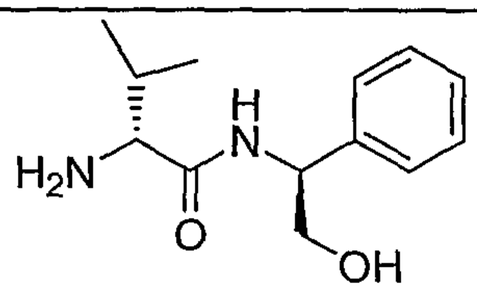
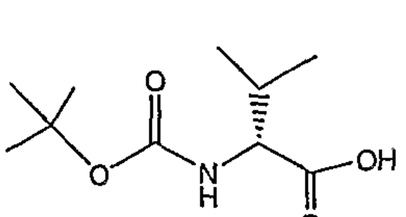
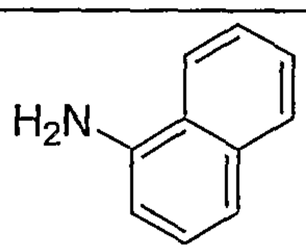
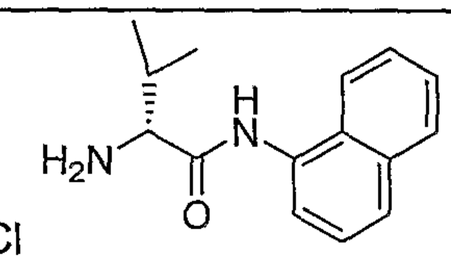
Prep Ex.	Amino acid	Amine	Product
33.3			HCl 
33.4			HCl 

33.5			HCl 
33.6			
33.7			 HCl
33.8			 HCl
33.9			 HCl
33.10			 HCl
33.11			 HCl
33.12			 HCl
33.13			 HCl

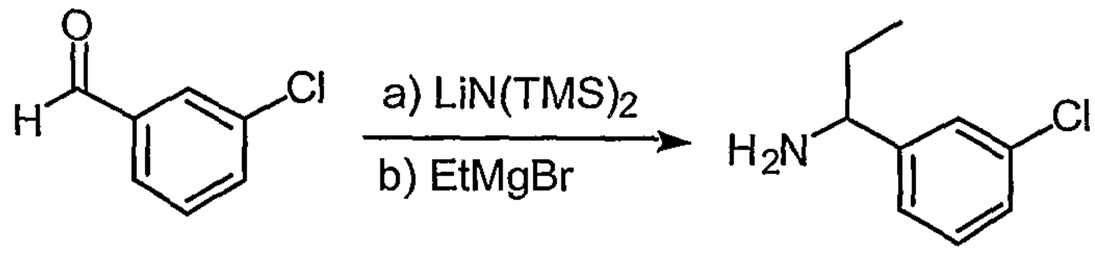
33.14			
33.15			
33.16			
33.17			
33.18			
33.19			
33.20			
33.21			
33.22			

33.23			
33.24			
33.25			
33.26			
33.27			
33.28			
33.29			
33.30			
33.31			

33.32			
33.33			
33.34			
33.35			
33.36			
33.37			
33.38			
33.39			
33.40			

33.41			 HCl
33.42			 HCl
33.43			 HCl
33.44			 HCl
33.45			 HCl
33.46			 HCl
33.47			 HCl

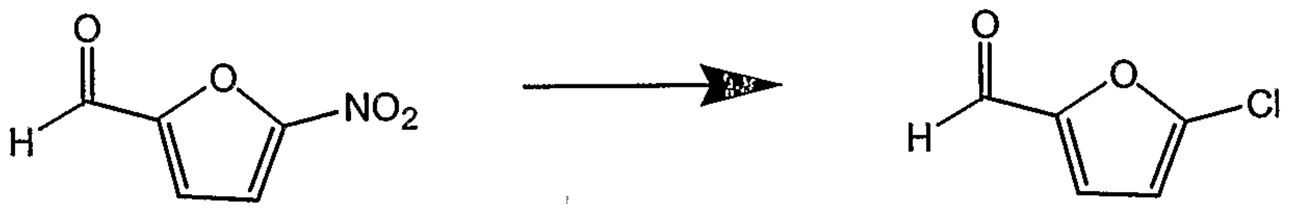
Preparative Example 34



To a solution of 3-chlorobenzaldehyde (2.0 g, 14.2 mmol) in THF (5 mL) at 0 °C was added $LiN(TMS)_2$ (17.0 ml, 1.0 M in THF) dropwise and the resulting solution was

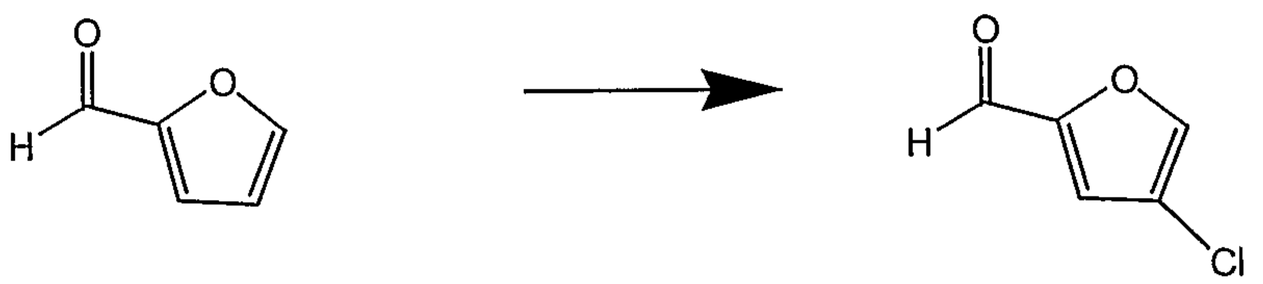
stirred for 20 min. EtMgBr (6.0 mL, 3.0 M in Et_2O) was added dropwise and the mixture was refluxed for 24 h. The mixture was cooled to room temperature, poured into saturated aqueous NH_4Cl (50 mL), and then extracted with CH_2Cl_2 (3 x 50 volumes). The organic layers were combined, concentrated under reduced pressure. The crude residue was stirred with 3 M HCl (25 mL) for 30 min and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the organic layers were discarded. The aqueous layer was cooled to 0 °C and treated with solid NaOH pellets until pH = 10 was attained. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the organic layers were combined. The organic layer was washed with brine (1 x 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford 1.6 g (66% yield) of the crude amine as an oil (MH^+ 170). This material was determined to be >90% pure and was used without further purification.

PREPARATIVE EXAMPLE 34.1



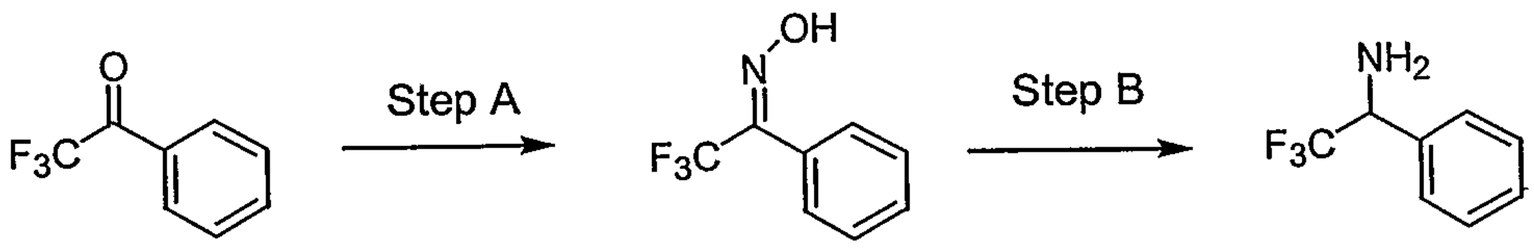
The aldehyde (3.5g) and conc. HCl (20ml) were combined and stirred overnight at 40^0C. The reaction mixture was poured into cold water and extracted with ether, washed with satd. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give 1.76g of product (55%)

PREPARATIVE EXAMPLE 34.2



Chlorine was bubbled into 100ml of CH_2Cl_2 at 10^0C. The aldehyde (3.73ml) was charged with 50ml of $CHCl_3$ and then cooled to 0^0C. $AlCl_3$ was added portionwise, followed by the chlorine solution and let stir at room temperature overnight. The reaction was poured into 150ml of ice and 50ml of 3N HCl and stirred for 30min. Organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (Hex/EtOAc 40/1) to yield 1.5g of pure product.

PREPARATIVE EXAMPLE 34.3



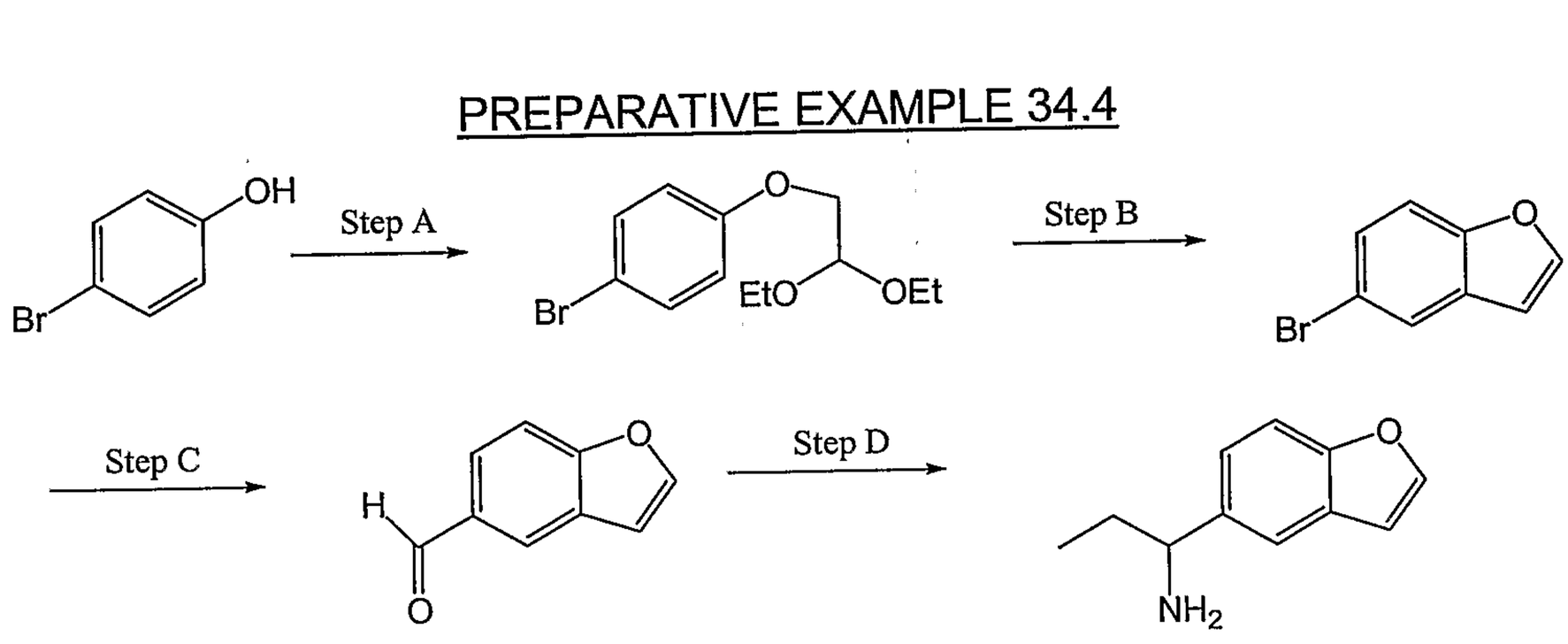
Step A

The ketone (3.25g) was reacted following the procedure set forth in Preparative Example 88.2, Step B to give the oxime (3.5g, 99%).

Step B

The product from step A (1.2g) was stirred with AcOH (3ml) and Pd/C (10%, 300mg) in EtOH (40ml) under a hydrogen atmosphere overnight. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The crude material dissolved in ether and washed with 2N NaOH, organic washed with brine, dried with Na_2SO_4, and concentrated *in vacuo* to give product (960mg, 86%).

PREPARATIVE EXAMPLE 34.4



Step A

To a suspension of NaH (1.45g) in DMF (25ml) under a nitrogen atmosphere was added *p*-bromophenol (5g) at 0^0C. After stirring for 20min, $BrCH_2CH(OEt)_2$ (5.3ml) was added and the reaction was heated to reflux overnight. The solution was cooled and poured into ice water (80ml) and extracted with ether. The ether layer was washed with 1N NaOH and brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 8.4g of crude product (100%)

Step B

To a solution of the product from Step A (8.4g) in benzene (50ml) was added polyphosphoric acid (10g). The mixture was heated at reflux for 4 hrs. The reaction was cooled to 0^0C and poured into ice water (80ml) and extracted with ether. The ether layer was washed with saturated sodium bicarbonate and brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 4.9g of crude product (85%)

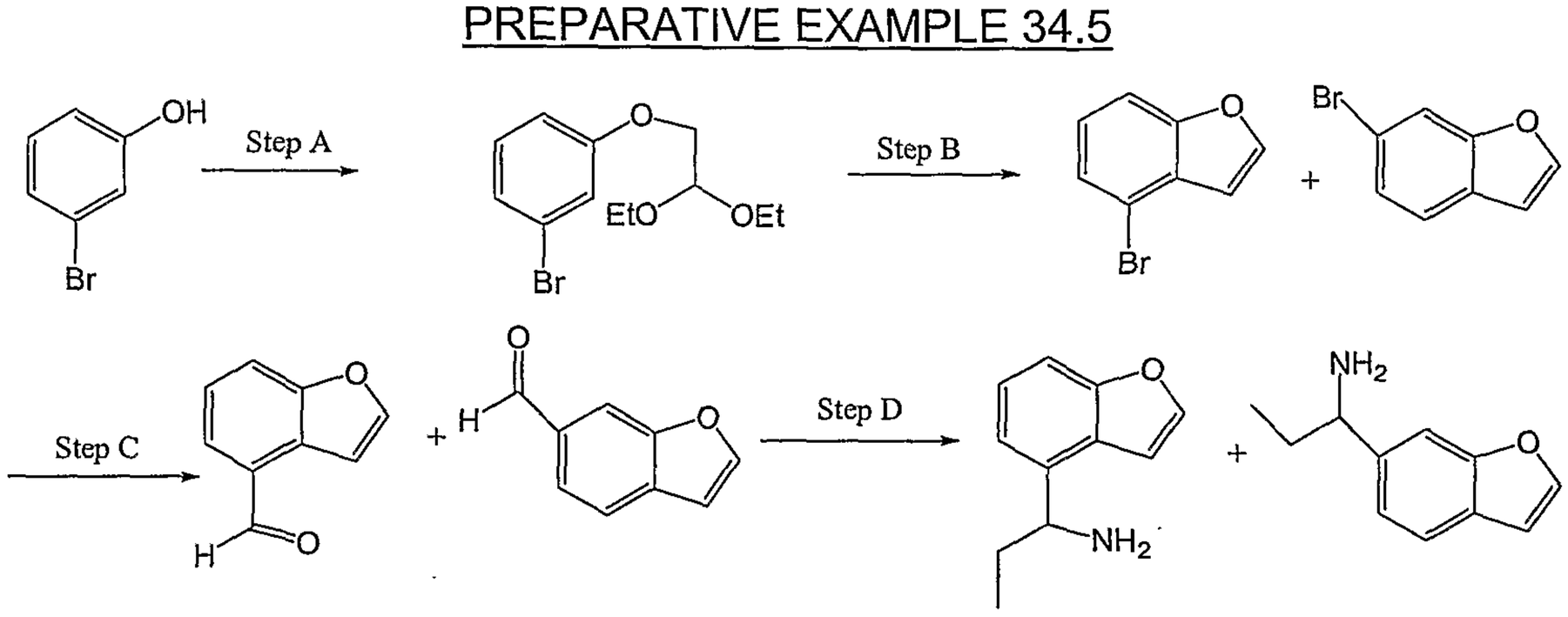
Step C

To a solution of the product from Step B (2g) in ether (20ml) at -78^{0}C was added t-BuLi dropwise. After stirring for 20min, DMF (950mg) was added dropwise and the mixture was stirred at -25^{0}C for 3hrs and then warmed to room temperature overnight. Saturated ammonium chloride was added and the solution was extracted with ether. The ether layer was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 980mg of crude product (67%).

Step D

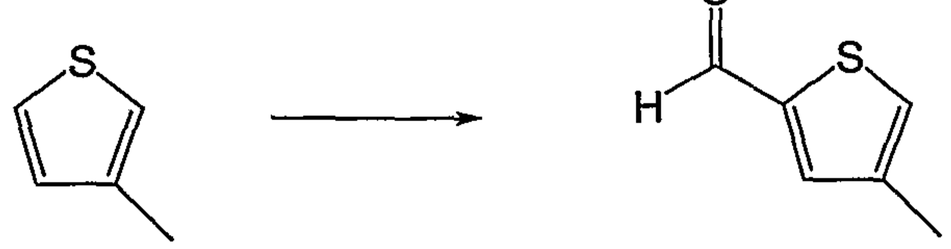
To a solution of aldehyde (400g) in ether (10ml) was added $LiN(TMS)_2$ (1M in THF, 3.3ml) at 0^0C dropwise. The solution was stirred at 0^0C for 30min and EtMgBr (3M in THF, 1.83ml) was added dropwise. The reaction was refluxed overnight, cooed to 0^0C, quenched with saturated ammonium chloride and extracted with ether. The ether was stirred with 3N HCl (20ml), then the aqueous layer was basified with NaOH pellets and extracted with ether. The ether layer was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 220mg of product (46%).

PREPARATIVE EXAMPLE 34.5



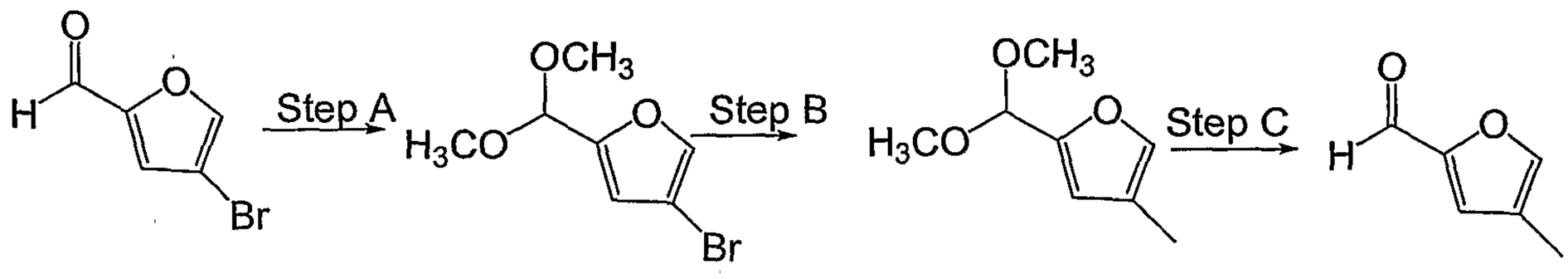
Following the procedures set forth in Preparative Example 34.4 Steps A through D, but using *m*-bromophenol (8g), both amines were formed and separated by preparative plate chromatography (63-65%, MH+=175).

PREPARATIVE EXAMPLE 34.6



To a solution of 3-methyl-thiophene (5g) in ether (50ml) was added dropwise a solution of n-BuLi (1.6M in hexane, 32ml). The mixture was stirred for 1.5hr at room temperature. DMF (5.1ml) was then added and let stir overnight. The mixture was poured into saturated ammonium chloride and extracted with ether. The ether layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (EtOAc/Hex 20:1) to afford 5.27g of an oil (84%).

PREPARATIVE EXAMPLE 34.7



Step A

To a solution of 4-bromo-2-furaldehyde (4g) in MeOH (75ml) was added trimethyl- orthoformate (3.8ml). A catalytic amount of *p*-toluene sulfonic acid (195mg) and the mixture was heated to reflux for 3.5hr. The reaction was cooled down and potassium carbonate was added. The mixture was filtered through a silica gel pad. The filtrate was concentrated *in vacuo*, dissolved in CH_2Cl_2 and filtered. The filtrate was again concentrated *in vacuo* to give 4.03g of product (80%).

Step B

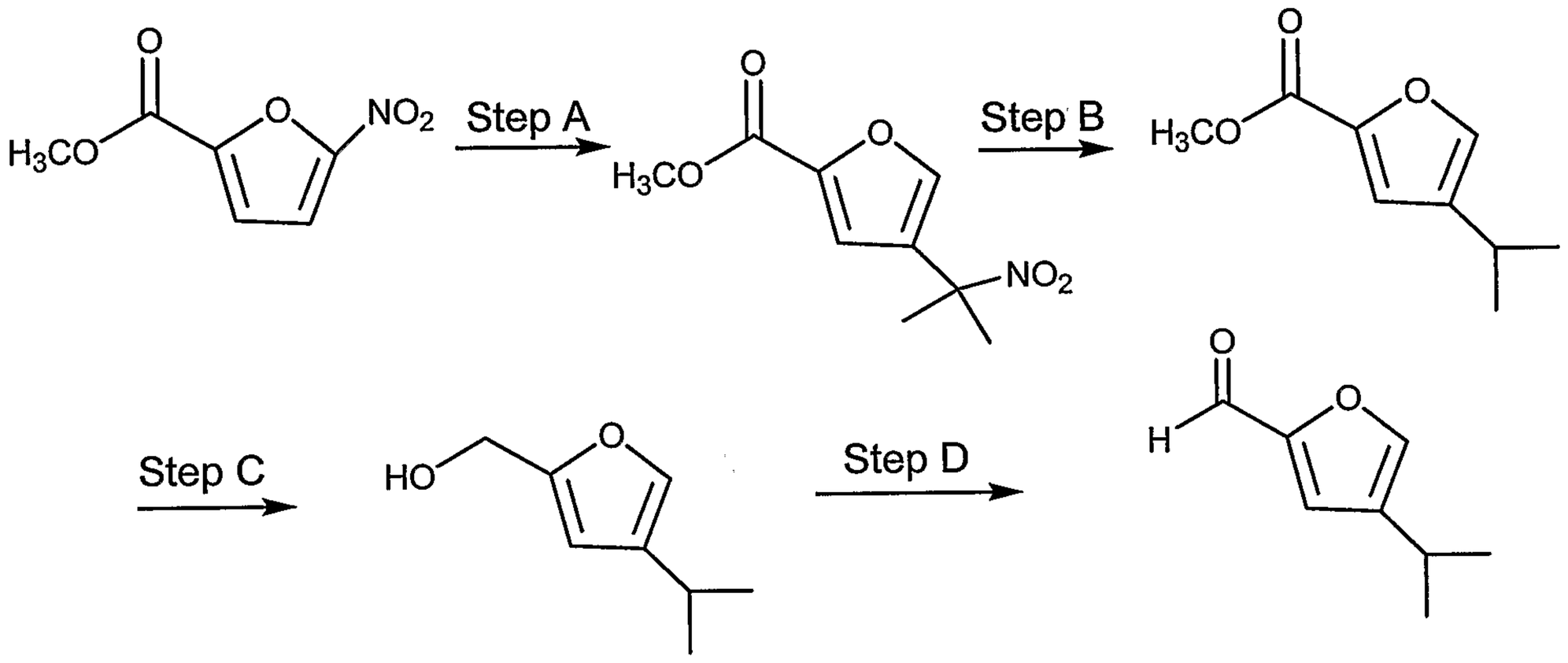
To a solution of the product from Step A (2.02g) in THF (80ml) at -78^{0}C was added dropwise a solution of n-BuLi (2.5M in hexanes, 4.4ml) and stirred for 1.5hr. A solution of iodomethane (1.7ml) was added and let stir for 2.5hrs at -60^{0}C. The

cooling bath was removed and saturated ammonium chloride was added and let stir for 10min. The layers were separated and the organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuo* to afford 1.34g of crude product.

Step C

The product from Step B (1.43g) was dissolved in acetone (50ml) and treated with a catalytic amount of p-toluene sulfonic acid (80mg). The mixture was heated to reflux for 2hr. The reaction was cooled down and solid potassium carbonate was added. The mixture was filtered through a silica gel pad and the filtrate was concentrated *in vacuo* to give 1.246g of crude product.

PREPARATIVE EXAMPLE 34.8



Step A

To a stirred solution of potassium t-butoxide (2.5g) in HMPA (20ml) was added 2-nitropropane (2ml) dropwise. After 5min, a solution of methyl-5-nitro-2-furoate (3.2g) in HMPA (8ml) was added to the mixture and stirred for 16hr. Water was added and the aqueous mixture was extracted with EtOAc. The EtOAc layer was washed with water, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (Hex/EtOAc, 6:1) to yield 3.6g of product (90%).

Step B

To a solution of the product from Step A (3.6g) in toluene (16ml) was added tributyltin hydride (5.4ml) followed by AIBN (555mg). The mixture was heated to 85^0C for 3.5hr. After cooling, the mixture was separated by flash column chromatography (Hex/EtOAc, 7:1) to afford 2.06g of product (73%).

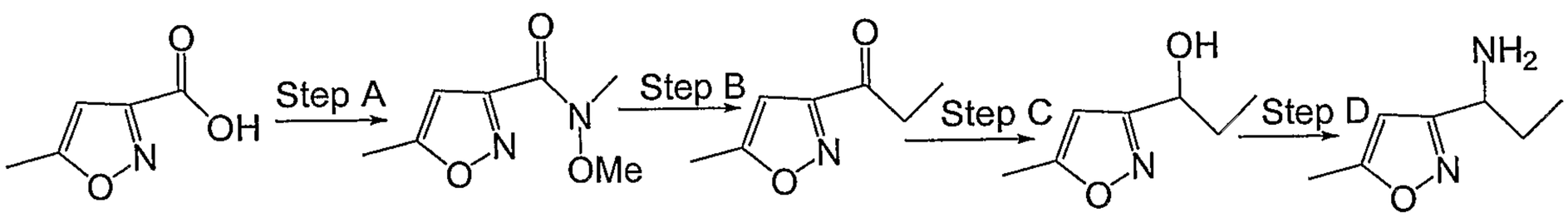
Step C

To a solution of product from Step B (2.05g) in THF (60ml) at 0^0C was added a solution of LAH (1M in ether, 12.8ml). The reaction was stirred at room temperature for 30min. Water and 1M NaOH was added until a precipitate formed, diluted with EtOAc, stirred for 30min and then filtered through a celite pad. The organic filtrate was concentrated *in vacuo* to give 1.56g of product (93%).

Step D

To a solution of product from Step C (2.15g) in CH_2Cl_2 (100ml) was added Dess-Martin oxidant (7.26g) in CH_2Cl_2 (45ml) and stirred for 30min. The mixture was diluted with ether (200ml). The organic layer was washed with 1N NaOH, water and brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give oil and solid. The material was extracted with ether and filtered. Some solid crystallized out from the filtrate, filtered again, and the filtrate was concentrated *in vacuo* to give 2.19g of product.

PREPARATIVE EXAMPLE 34.9



Step A

To a solution of carboxylic acid (5g) in CH_2Cl_2 (400ml) at 0^0C was added $N(OCH_3)CH_3.HCl$ (11.5g), DEC (15.1g), HOBt (5.3g) and NMM (43ml) and stirred for 14hr. The mixture was diluted with CH_2Cl_2 (100ml) and the organic layer was washed with 10% HCl, saturated sodium bicarbonate and brine, dried with Na_2SO_4, and concentrated *in vacuo* to afford 5.74g of crude product (85%).

Step B

To a solution of iodoethane (0.56ml) in ether (5ml) at -78^{0}C was added a solution of t-BuLi (1.7M in pentane, 8.3ml) dropwise. The mixture was warmed to room temperature for 1hr and transferred to a 100ml round bottom charged with the product from Step A (1g) in THF (12ml) at -78^{0}C. The mixture was stirred at -78^{0}C for 1hr and at 0^{0}C for an additional 2hr. 1M HCl was added dropwise followed by CH_2Cl_2. The layers were separated and the organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuo* to afford 620mg of product (76%).

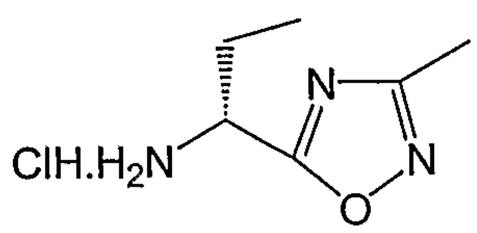
Step C

To a solution of the product from Step B (620mg) in THF/MeOH (10:1) at 0^{0}C was added $NaBH_4$ (250mg) in one portion. The mixture was stirred overnight at 0^{0}C, concentrated *in vacuo* and the crude material was dissolved in CH_2Cl_2 and washed with 1N NaOH and brine, dried with Na_2SO_4, and concentrated *in vacuo* to afford 510mg of product.

Step D

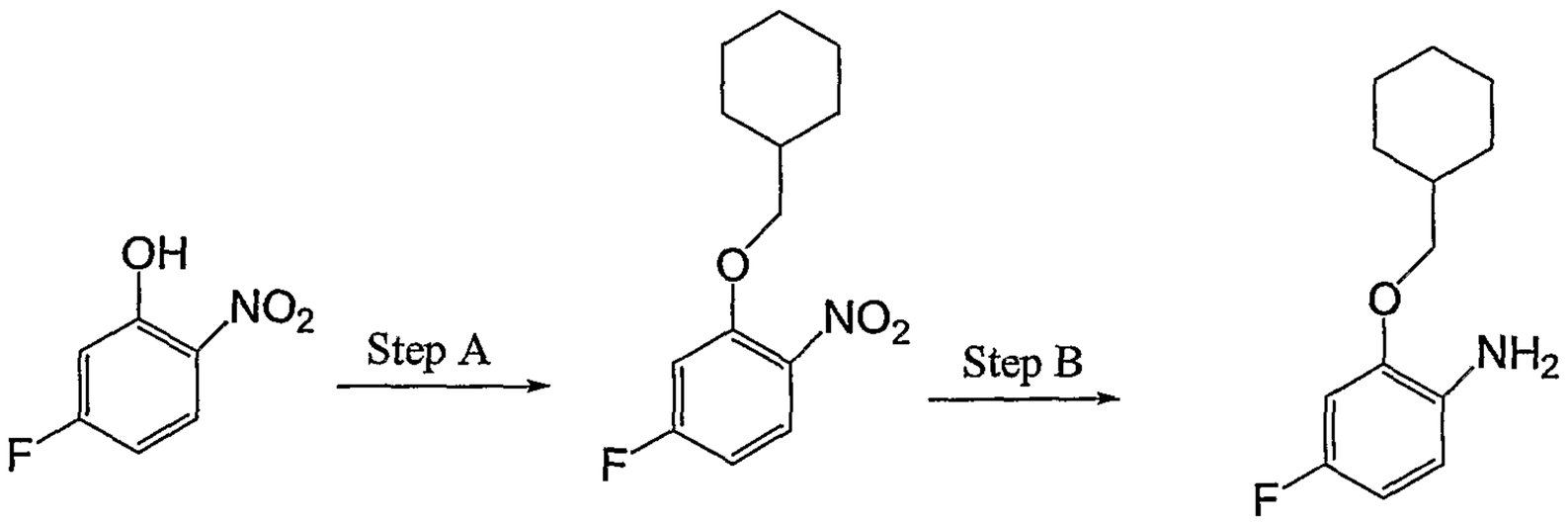
The above material was reacted in the procedures set forth in Preparative Example 75.75 Steps B and C to yield 170mg of amine product (28%).

PREPARATIVE EXAMPLE 34.10



The above amine was made analogous to the procedures set forth in Patent WO96/22997 p.56 (the disclosure of which is incorporated herein by reference thereto), but using ethylglycine instead of benzylglycine in the DCC coupling.

PREPARATIVE EXAMPLE 34.11



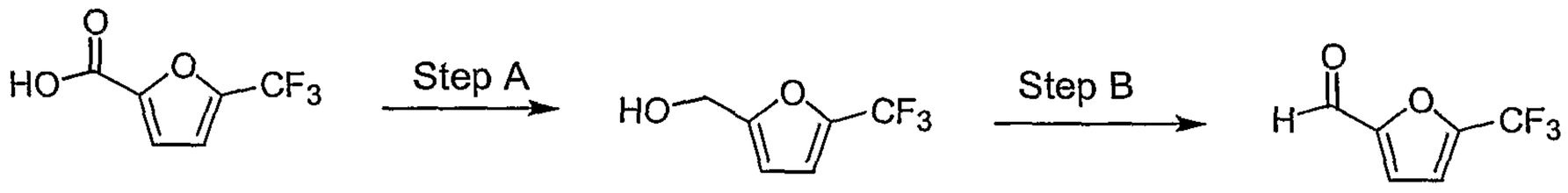
Step A

To the nitro compound (3.14g) and cyclohexylmethanol (1.14g) in THF (50ml) was added PPH_3 (4.72g) and cooled to 0^0C. Diisopropylazadicarboxylate (3.15ml) was added dropwise and let stir overnight. The reaction was concentrated *in vacuo* and purified via flash column chromatography (Hex/EtOAc, 30:1) to give product (3.3g), which was carried on directly to the next step.

Step B

To the product from step A (3.3g) in EtOH (50ml) was added 10% Pd/C (1.7g) under a hydrogen atmosphere at 55psi and let stir overnight. The reaction was filtered through celite and concentrated *in vacuo* to give 3.2g of product.

PREPARATIVE EXAMPLE 34.12



Step A

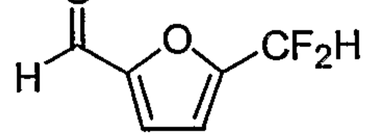
A solution of acid (2g) in ether (20ml) was added dropwise to a suspension of $LiAlH_4$ (350mg) in ether (15ml) at 0^0C. The solution was refluxed for 3hr and stirred at room temperature ovenright. 5% KOH was added and reaction was filtered, extracted with ether, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give the product (1.46g, 79%, MH+=166).

Step B

To a solution of alcohol from above (1.46g) in CH_2Cl_2 at room temperature was added Dess-Martin reagent (5.6g) portionwise and one drop of water and let stir over

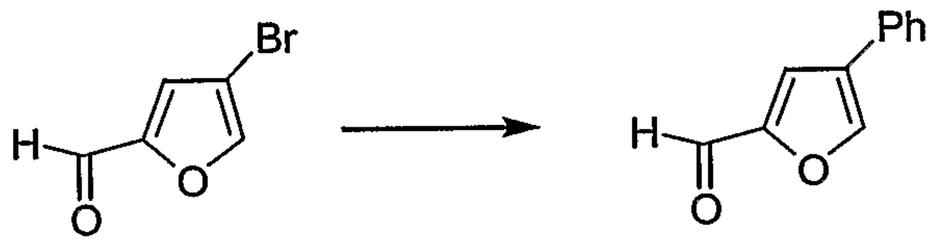
the weekend at room temperature. 10% $Na_2S_2O_3$ was added and stirred for 20min, extracted with CH_2Cl_2, washed with saturated sodium bicarbonate, dried with Na_2SO_4, and concentrated *in vacuo* to afford 1.1g of product (76%).

PREPARATIVE EXAMPLE 34.13



The above compound was prepared according to the procedure set forth in EP 0 555 153 A1 (the disclosure of which is incorporated herein by reference thereto).

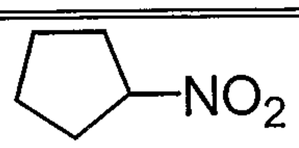
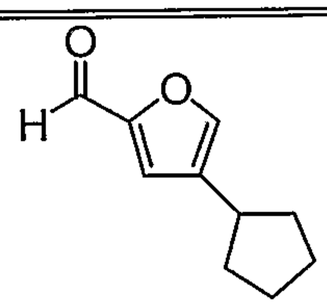
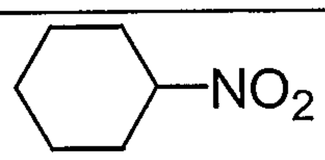
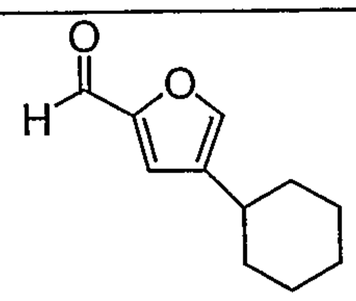
PREPARATIVE EXAMPLE 34.14



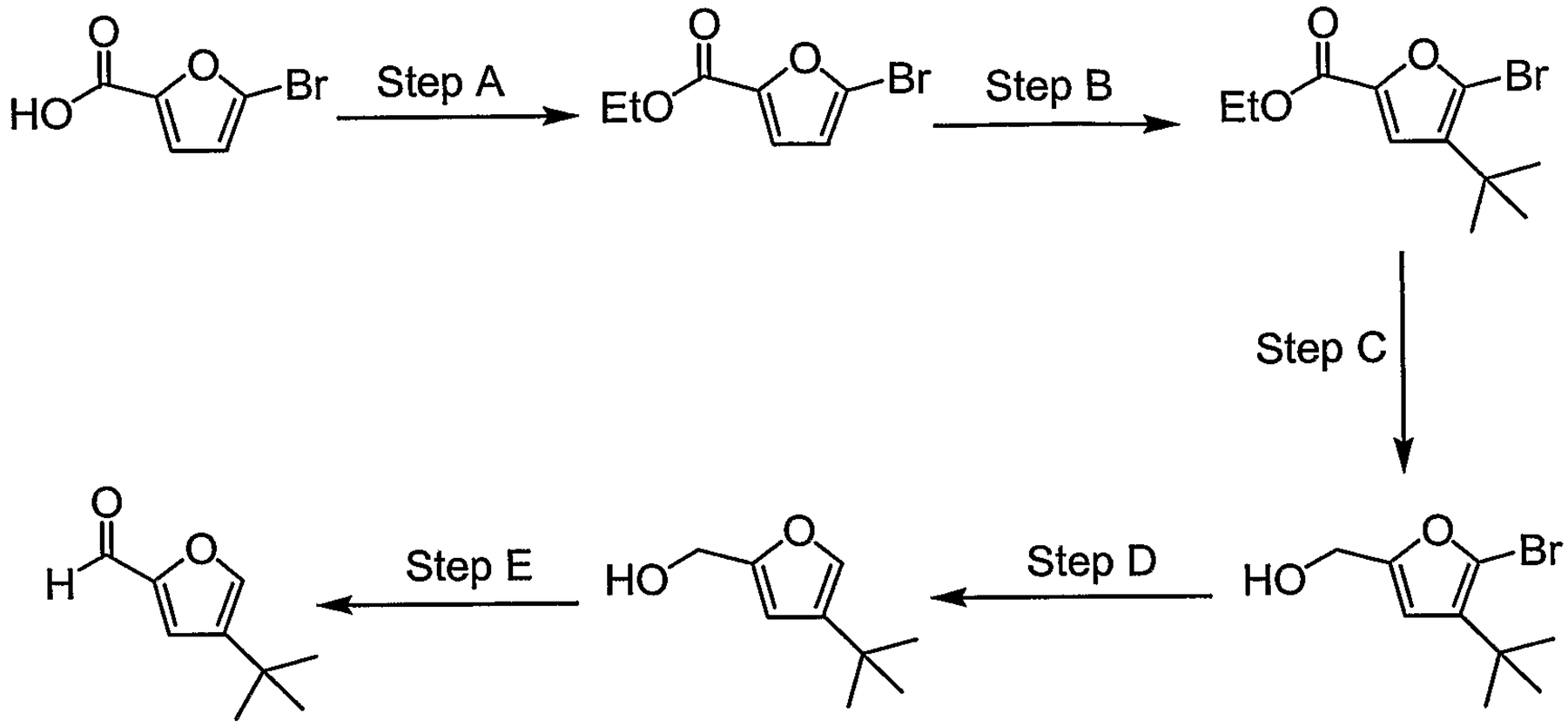
The aldehyde (500mg) from above was reacted following the procedure set forth in the Preparative Example 13.4, Step A to yield 372mg of product (76%).

PREPARATIVE EXAMPLE 34.15-34.16

Following the procedures set forth in Preparative Example 34.8 but using the nitroalkanes indicated in the table below, the aldehydes were prepared.

PREP. Ex.	NITROALKANE	ALDEHYDE	YIELD (%)
34.15			17
34.16			21

PREPARATIVE EXAMPLE 34.17



Step A

To a stirred suspension of 5-bromo-2-furoic acid (15.0 g, 78.54 mmol) in 225 mL of CH_2Cl_2 at room temperature was added oxalyl chloride followed by a catalytic amount of *N,N'*-dimethylforamide. After 1 h, ethanol (20 mL) was added followed by triethylamine (22 mL). Reaction was continued for 15 h. The mixture was concentrated under reduced pressure to a residue, which was extracted with excess volume of hexanes, and hexanes-CH_2Cl_2 (3:1, v/v). The extracts were filtered, the filtrated was concentrated to a yellow oil, dried on high vacuum, yielding 17.2 g (93%) of the desired ester.

Step B

The ester product obtained from Step A above (17.2 g, 73.18 mmol) was converted to 2-ethyl-4-tertbutyl-5-bromo-furoate (7.9 g, 37%) using the literature procedure: *J. Am. Chem.Soc.,* **1939**, *61*, 473-478 (the disclosure of which is incorporated herein by reference thereto).

Step C

The ester product obtained from Step B above (7.9 g, 27.13 mol) was reduced to the alcohol (6.32 g) using the procedure set forth in Preparative Example 34.8, Step C.

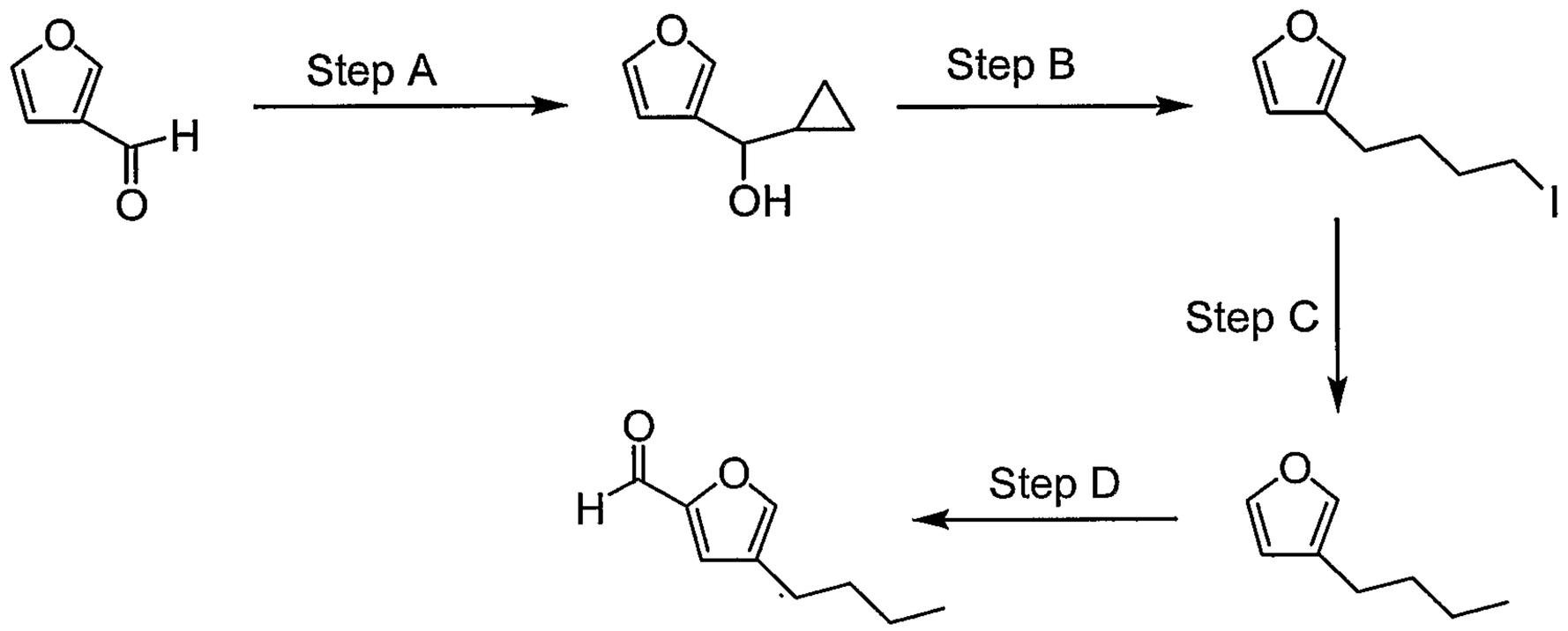
Step D

The product obtained from Step C above (6.32 g) was dissolved in 140 mL of THF and cooled in a –78°C bath. A 2.5 M solution of n-butyllithium in hexanes (22 mL, 55.0 mmol) was added dropwise along the side wall of the flask. After 15 min, H_2O (~70 mL) was added. Cooling bath was removed, the mixture was stirred for an additional 1h. Brine (50 mL) and CH_2Cl_2 (300 mL) were added, the two layers were separated, the aqueous layer was extracted with CH_2Cl_2 (100 mL), and the combined organic layers ere dried by Na_2SO_4. Evaporation of solvents afforded 5.33 g (crude) of the debrominated product as a reddish brown oil.

Step E

The alcohol product obtained from Step D above (5.33g) was oxidized to the corresponding aldehyde (3.06 g, 74% over three steps) using the procedure set forth in Preparative Example 34.8, Step D.

PREPARATIVE EXAMPLE 34.18



Step A

To a stirred solution of cyclopropyl bromide (4.0 mL, 50 mmol) in 120 mL of ether at –78°C was added dropwise a 1.7M solution of t-butyllithium in pentane (44.5 mL, 75.7 mmol). After 10 min, cooling bath was removed, stirring was continued for 1.5 h. The mixture was cooled again in a –78°C bath, and 3-furaldehyde (3.5 mL, 41.9 mmol) was added. Reaction was continued for 1 h, and quenched with a saturated NH4Cl aqueous solution. The aqueous mixture was extracted with CH_2Cl_2 (100 mL x 3). The organic extracts were washed with brine, dried by Na_2SO_4, filtered, and concentrated in vacuo to give 5.3 g (91%) of the alcohol product as a yellow oil.

Step B

Chloro trimethylsilane (27.2 mL, 214.2 mmol) was added dropwise to a vigorously stirred suspension of sodium iodide (32 g, 213.5 mmol) in 100 mL of acetonitrile. After 5 min, a solution of the alcohol obtained from Step A above (4.93 g, 35.68 mmol) in 100 mL of acetonitrile was added dropwise. Stirring was continued for 5 min. H_2O (100 mL) was added, the layers were separated, and the aqueous layer was extracted with ether (100 mL x 2). The organic layers were combined, washed with a 10 % $Na_2S_2O_3$ aqueous solution and brine, and dried over Na_2SO_4. Evaporation of solvents gave a dark brown oil, which was filtered through a 5-in silica gel column, eluting with CH_2Cl_2-hexanes (1:3.5, v/v). Removal of solvents afforded 4.22 g (47%) of the iodo product as a light yellow oil.

Step C

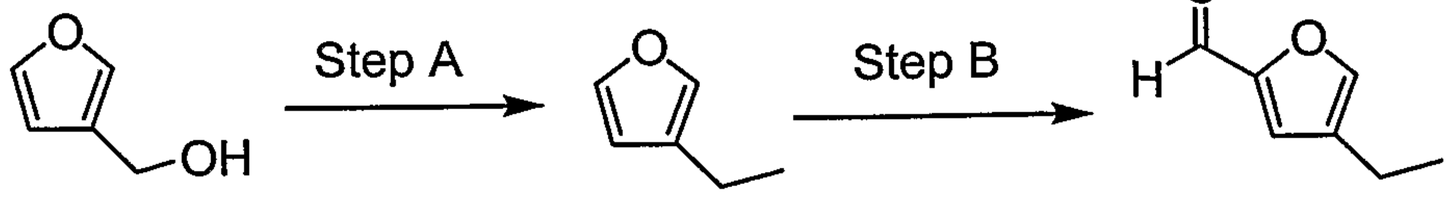
The iodo-product obtained from Step B above (2.2 g, 8.8 mmol) was dissolved in 60 mL of ether, and stirred in a –78°C bath. A 1.7 M solution of t-butyllithium in pentane (10.4 mL, 17.7 mmol) was added dropwise. After 20 min, cooling bath was removed. Reaction was continued for 2.5 h, and quenched with H_2O (20 mL). The aqueous mixture was stirred overnight and separated. The aqueous layer was extracted with ether (30 mL). The combined organic layers were washed with brine, dried by Na_2SO_4, and filtered through a Celite pad. Removal of solvent gave 1.10 g (100%) of 3-butylfuran as a reddish-yellow oil.

Step D

3-Butylfuran (1.1 g, 8.8 mmol), obtained from Step C above, was dissolved in 60 mL of ether, and stirred in a –78°C bath. A 1.7 M solution of t-butyllithium in pentane (6.0 mL, 10.2 mmol) was added dropwise along the side wall of the flask. The mixture was stirred for 3 h from –78°C to 0°C, and continued for 1 h at room temperature. A solution of *N,N'*-dimethylforamide (1.1 mL, 14.23 mmol) was added. Reaction was continued overnight, and quenched with a saturated NH_4Cl aqueous solution. The two layers were separated, the aqueous layer was extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated to an oil, which was purified by preparative TLC (CH_2Cl_2-

hexanes = 1 :1.5, v/v) to give 0.48 g (36%) of the aldehyde (contaminated by some 3-butyl-2-furaldehyde).

PREPARATIVE EXAMPLE 34.19



Step A

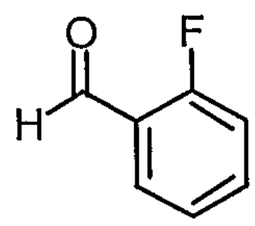
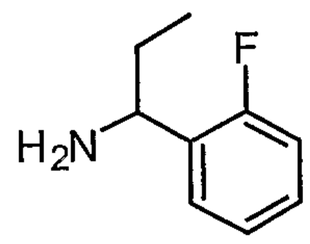
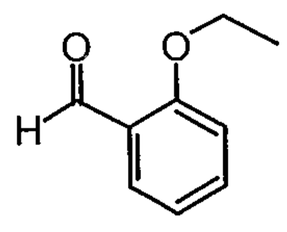
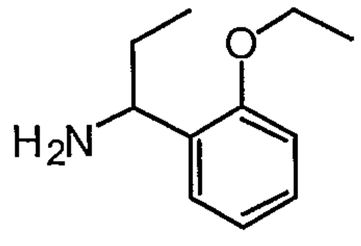
3-Ethylfuran was prepared from 3-hydroxymethylfuran according to literature procedure: *J. Org. Chem.*, **1983**, *48*, 1106-1107 (the disclosure of which is incorporated herein by reference thereto).

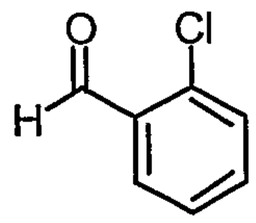
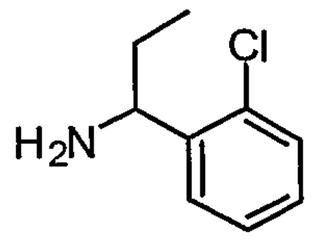
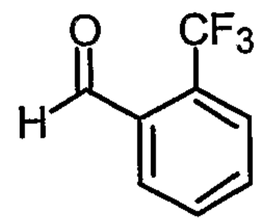
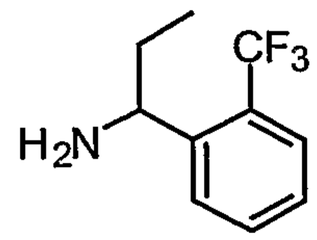
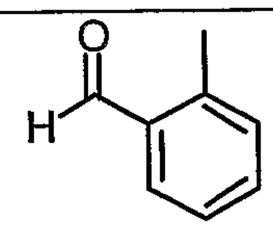
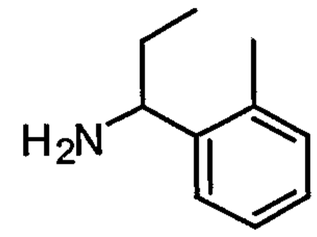
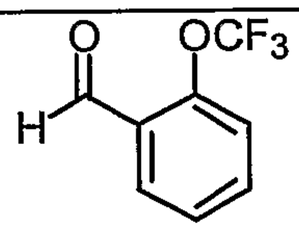
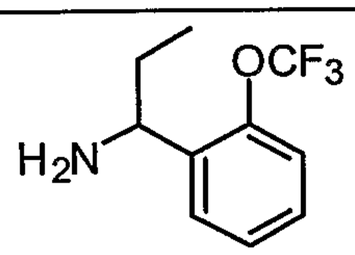
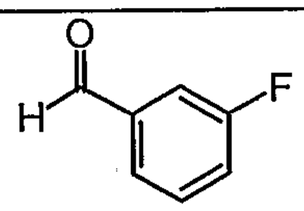
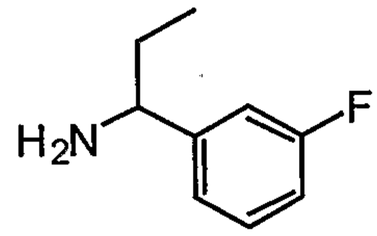
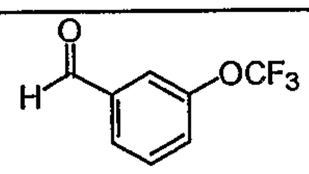
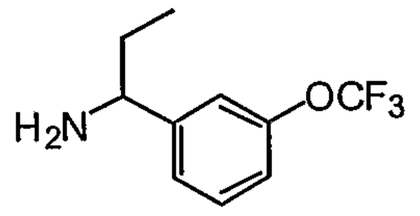
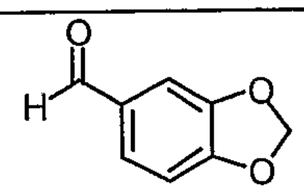
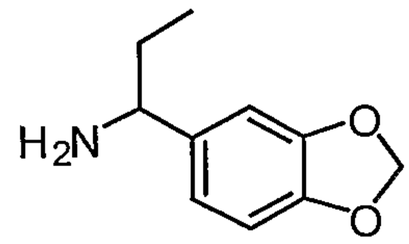
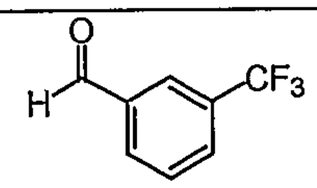
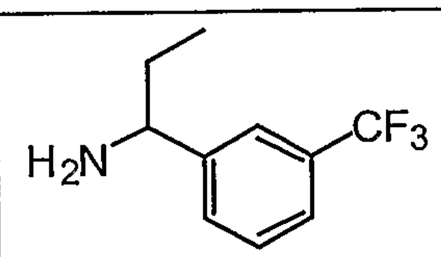
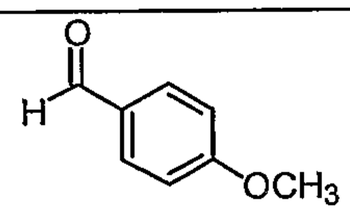
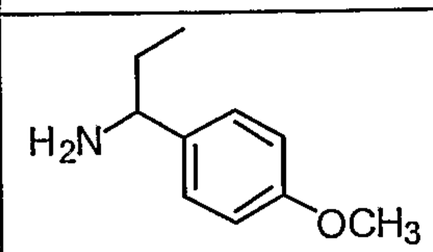
Step B

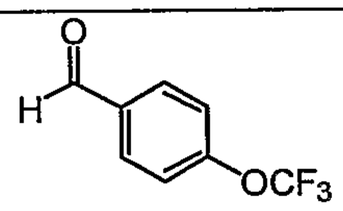
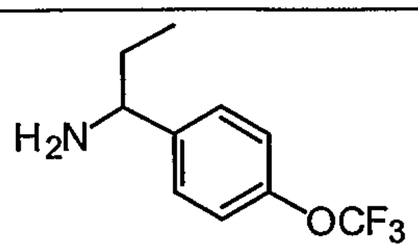
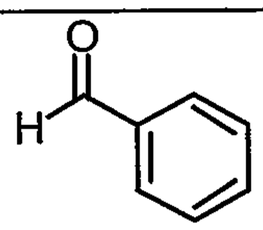
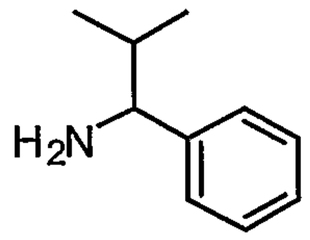
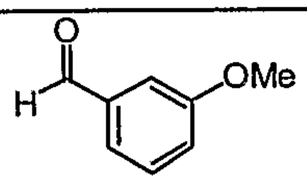
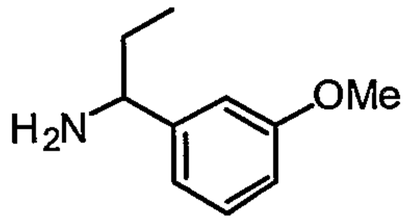
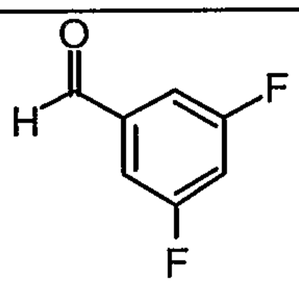
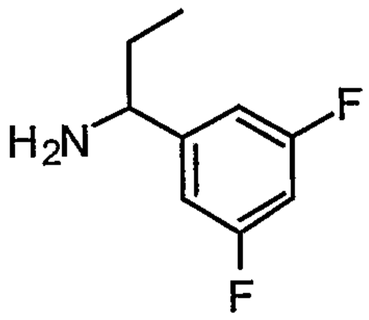
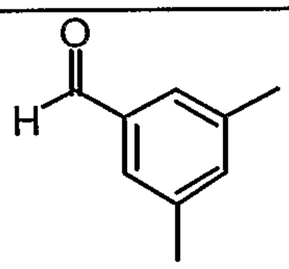
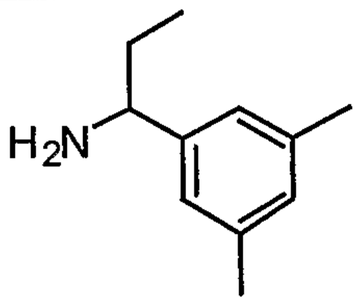
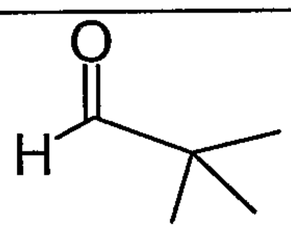
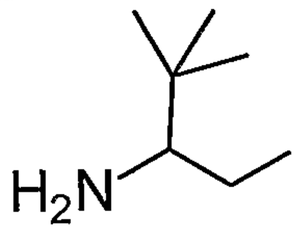
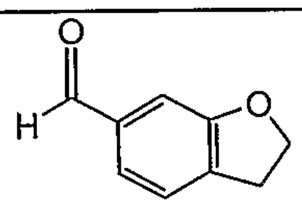
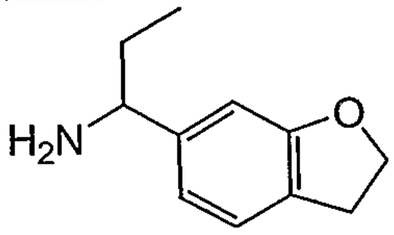
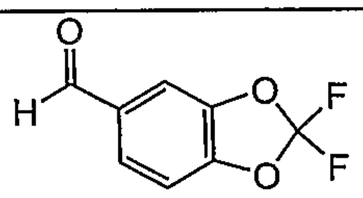
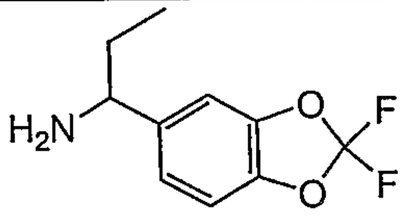
3-Ethylfuran obtained from Step A above was converted to 4-ethyl-2-furaldehyde using the procedure set forth in Preparative Example 34.32, Step D.

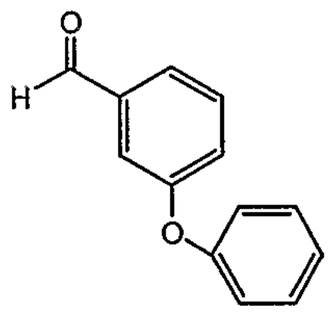
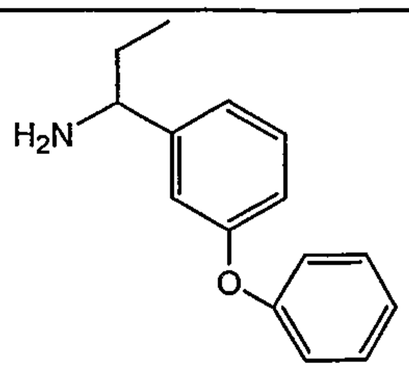
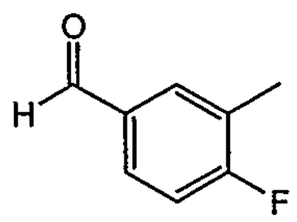
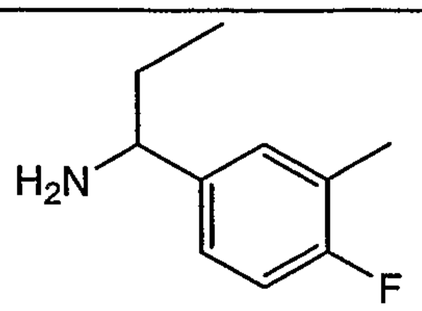
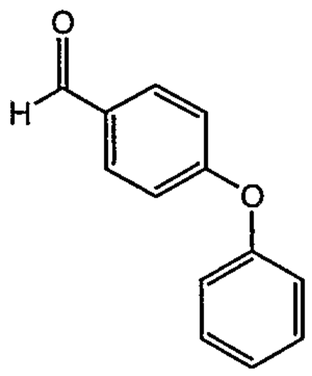
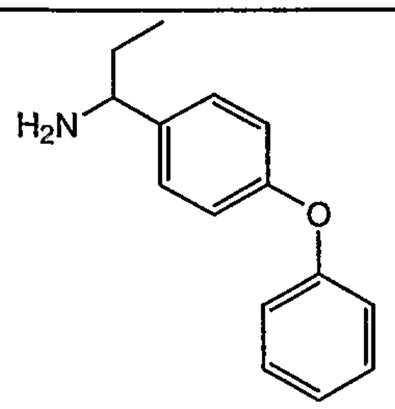
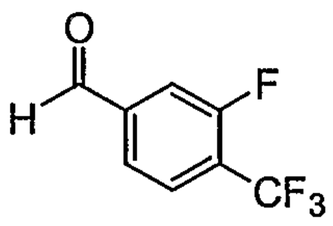
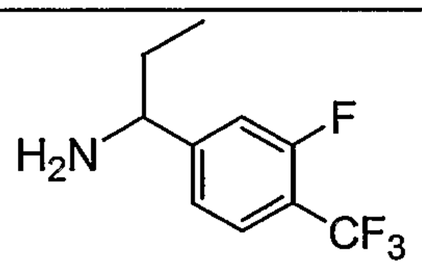
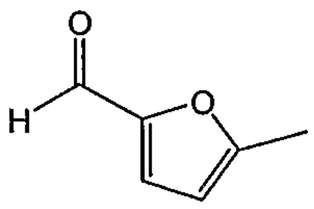
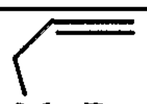
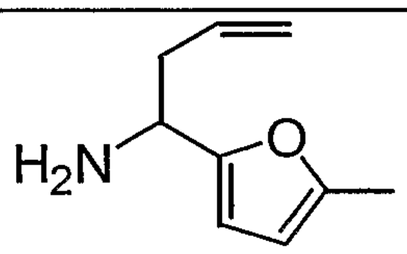
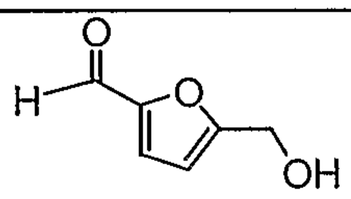
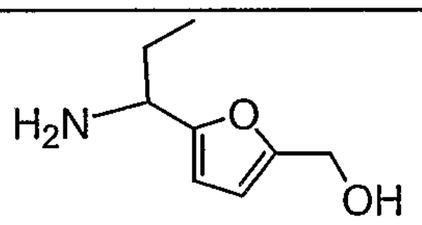
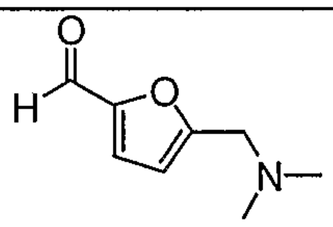
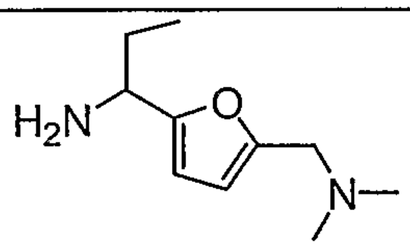
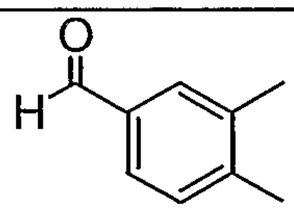
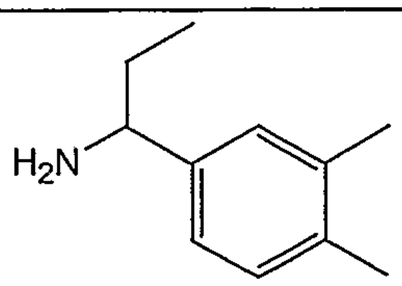
PREPARATIVE EXAMPLES 35-51.21

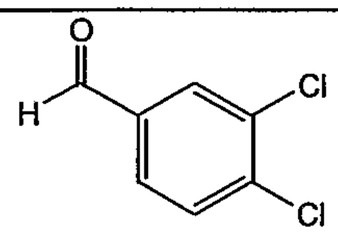
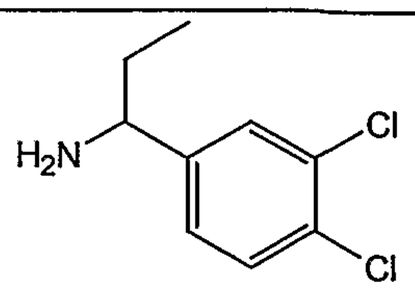
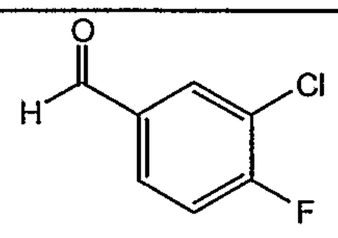
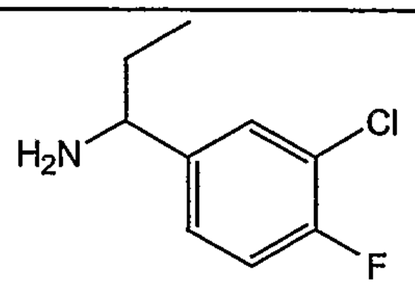
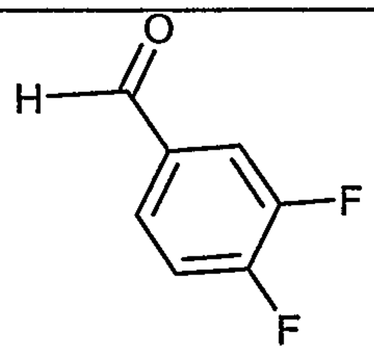
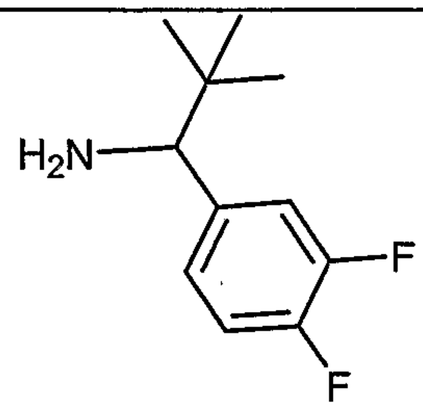
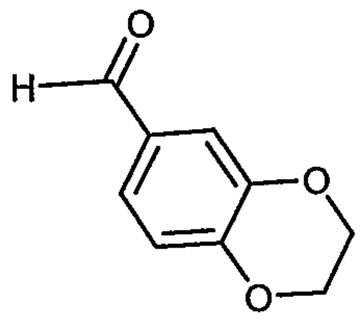
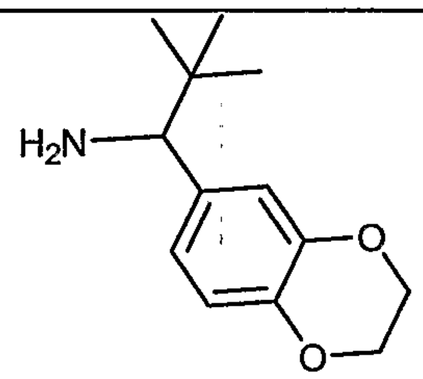
Following the procedure set forth in Preparative Example 34 but using the commercially available aldehydes and Grignard reagents listed in the Table below, the amine products below were obtained.

Prep Ex.	Aldehyde	Grignard Reagent	Amine	1.Yield 2. MH^+
35		EtMgBr		1. 65% 2. 154
36		EtMgBr		1. 75% 2. 180

37		EtMgBr		1. 78% 2. 170
38		EtMgBr		1. 34% 2. 204
39		EtMgBr		1. 68% 2. 150
40		EtMgBr		1. 40% 2. 220
41		EtMgBr		1. 73% 2. 154
42		EtMgBr		1. 52% 2. 220
43		EtMgBr		1. 55% 2. 180
44		EtMgBr		1. 20% 2. 204
45		EtMgBr		1. 80% 2. 166

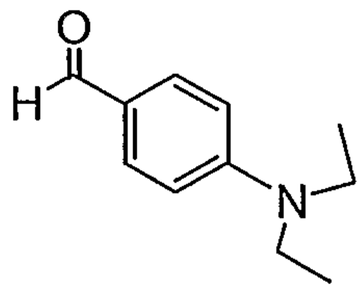
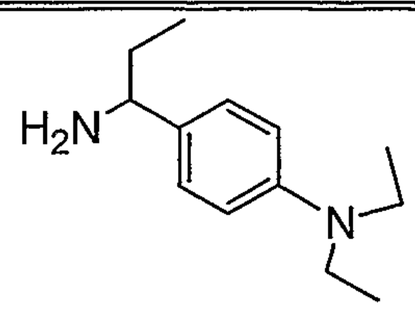
46		EtMgBr		1. 35% 2. 220
47		*i*-PrMgBr		1. 20% 2. 150
48		EtMgBr		1. 77% 2. $[M-NH_2]^+$ = 149
49		EtMgBr		1. 77% 2. 172
50		EtMgBr		1. 78% 2. $[M-NH_2]^+$ = 147
51		EtLi		1. 10% 2. 116
51.2		EtMgBr		1. 37% 2. 161
51.3		EtMgBr		1. 63% 2. 216

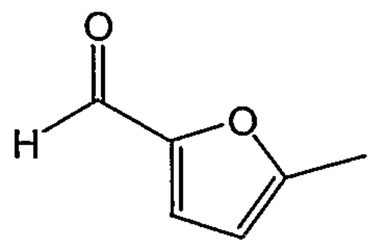
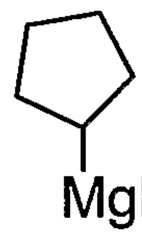
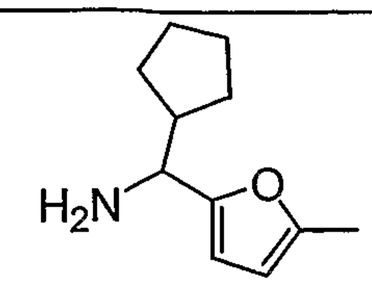
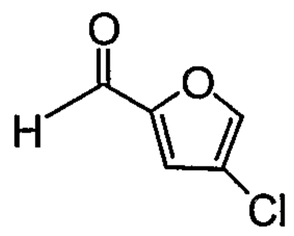
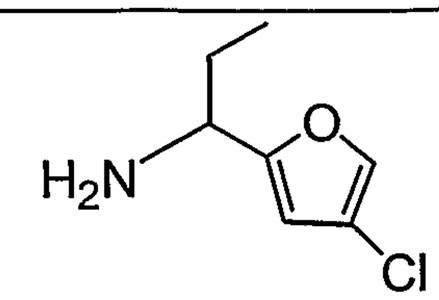
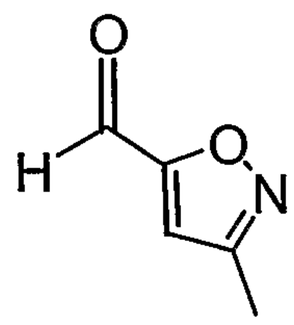
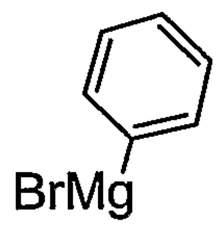
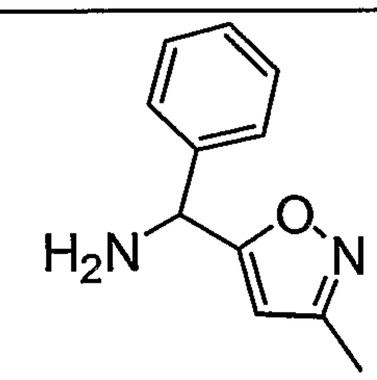
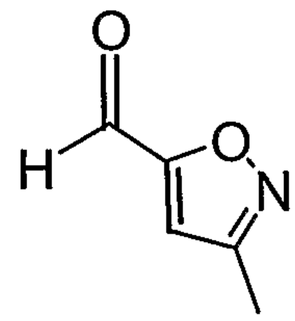
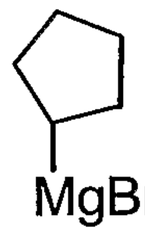
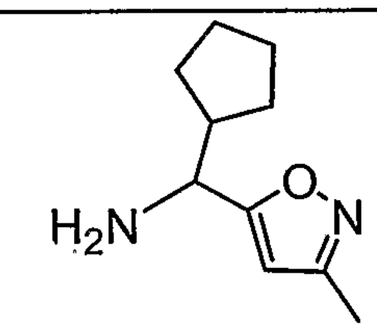
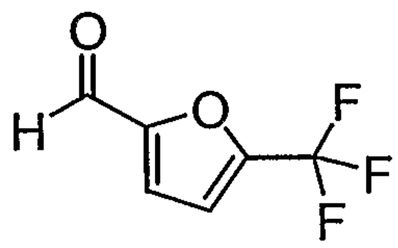
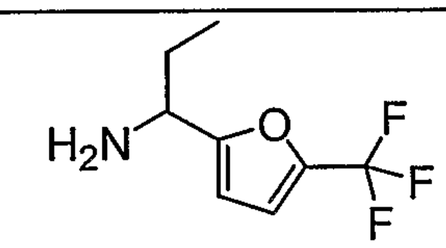
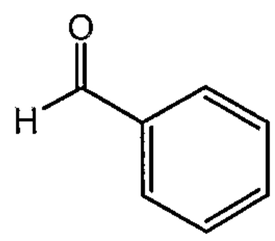
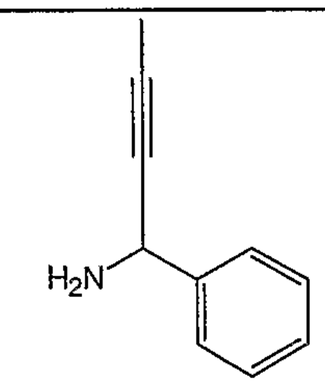
51.4		EtMgBr		1. 71% 2. 228
51.5		EtMgBr		1. 89% 2. 168
51.6		EtMgBr		1. 20% 2. 228
51.8		EtMgBr		1. 36% 2. 222
51.10				1. 95% 2. 152.1
51.11		EtMgBr		1. 61% 2. 138.1 MH^+-H_2O
51.12		EtMgBr		1. 70% 2. 184.1
51.18		EtMgBr		1. 42% 2. 147 $[M-NH_2]^+$

51.19		EtMgBr		1. 67% 2. 204
51.20		EtMgBr		1. 33% 2. 188
51.21		t-BuLi		1. 7%
51.22		t-BuLi		1. 20% 2. 205 (M-NH_2)$^+$

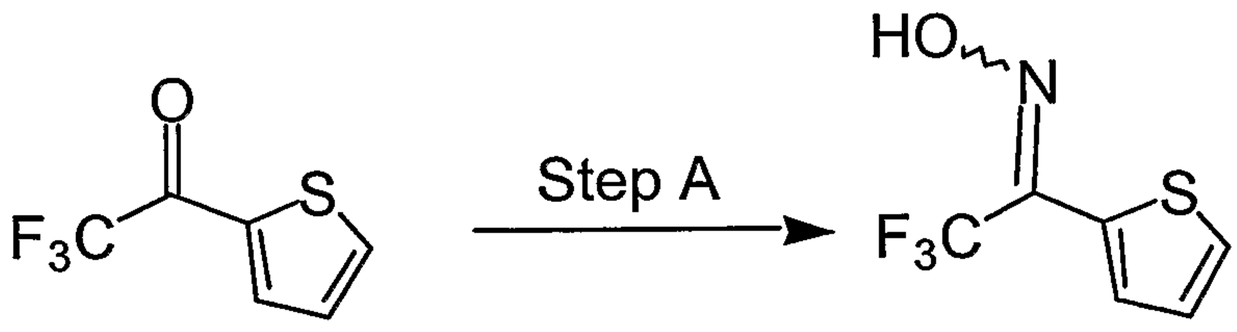
PREPARATIVE EXAMPLES 51.25 - 51.31

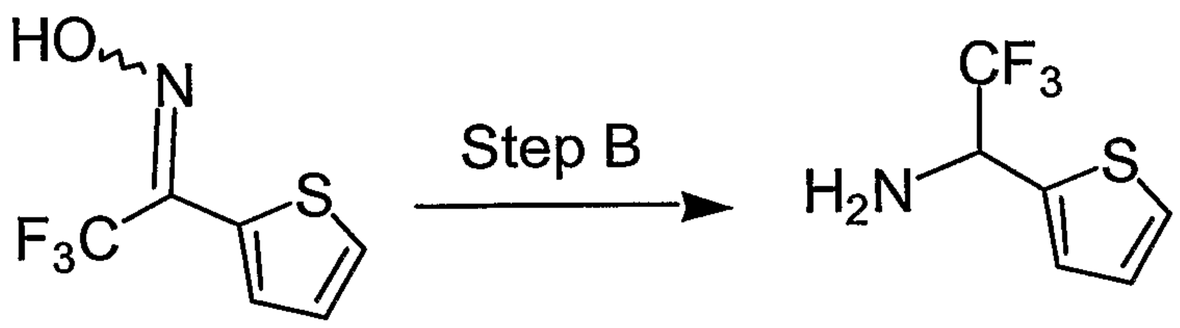
Following the procedure set forth in Example 34 but using the commercially available aldehydes and Grignard reagents listed in the Table below, the amine products were obtained.

Prep Ex.	Aldehyde	Grignard Reagent	Amine	Yield (%)
51.25		EtMgBr		20

51.26				77
51.27	(34.2) 	EtMgBr		51
51.28	(78.1) 			56
51.29	(78.1) 			54
51.30	(34.12) 	EtMgBr		80
51.31				10

PREPARATIVE EXAMPLE 52





Step A

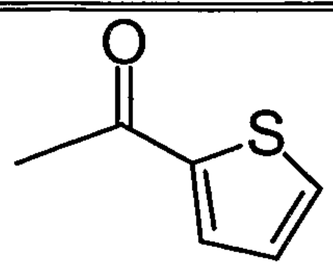
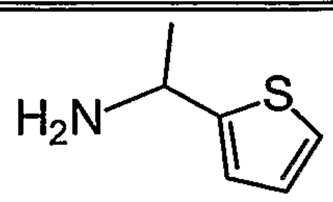
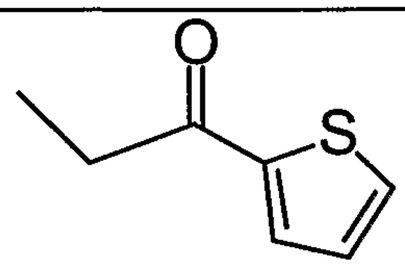
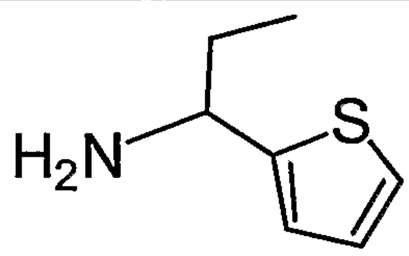
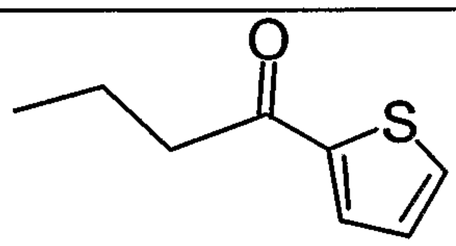
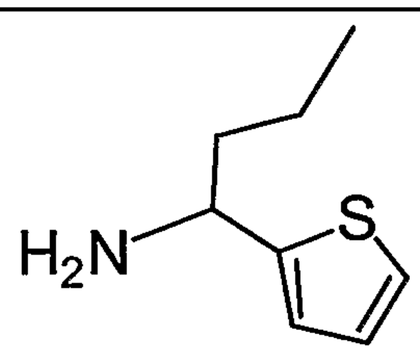
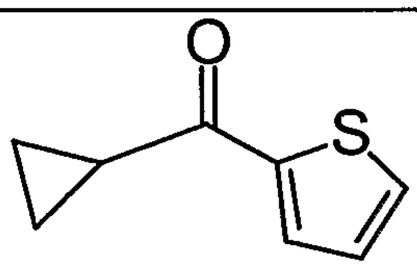
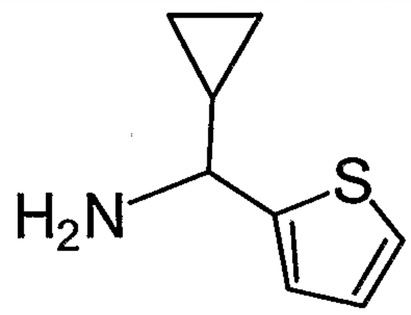
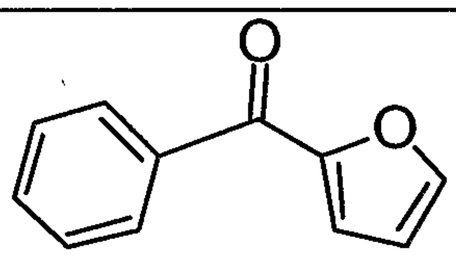
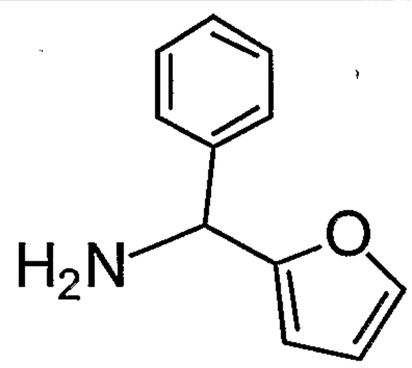
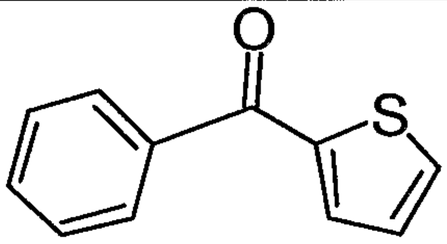
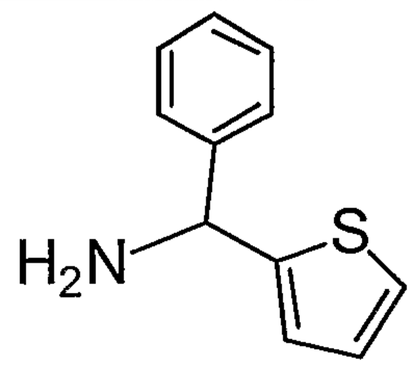
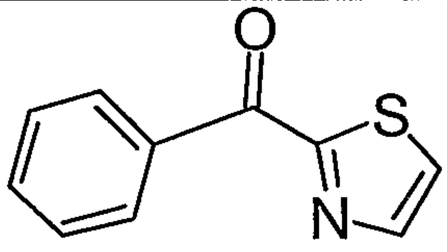
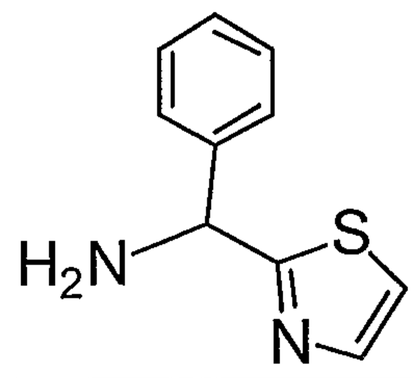
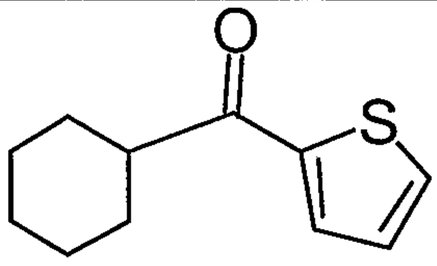
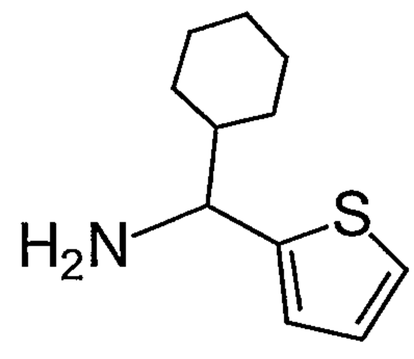
A mixture of 2-(trifluoroacetyl)thiophene (2 mL, 15.6 mmol), hydroxylamine hydrochloride (2.2 g, 2 eq), diisopropylethylamine (5.5 mL, 2 eq) and MeOH (50 mL) was stirred at reflux for 48-72 hrs, then concentrated *in vacuo*. The residue was diluted with EtOAc, washed with 10% KH_2PO_4 and dried over Na_2SO_4 (anhydrous). Filtration and concentration afforded the desired oxime (2.9 g, 96%) which was used directly in Step B without further purification.

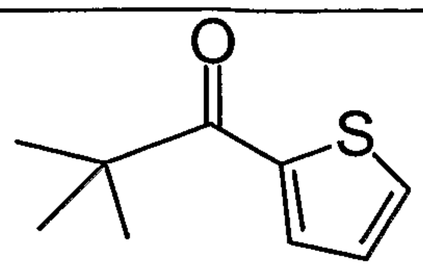
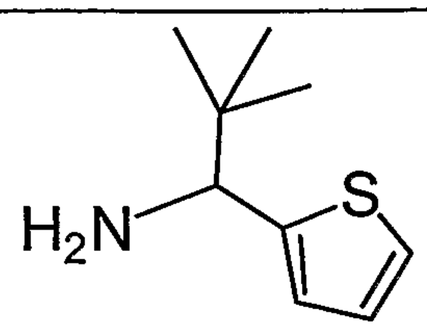
Step B

To a mixture of the product from Step A above in TFA (20 mL) was added Zn powder (3 g, 3 eq) portionwise over 30 min and stirred at room temperature overnight. The solid was filtered and the mixture reduced *in vacuo*. Aqueous NaOH (2 *M*) was added and the mixture was extracted several times with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to afford the desired product (1.4 g, 50%).

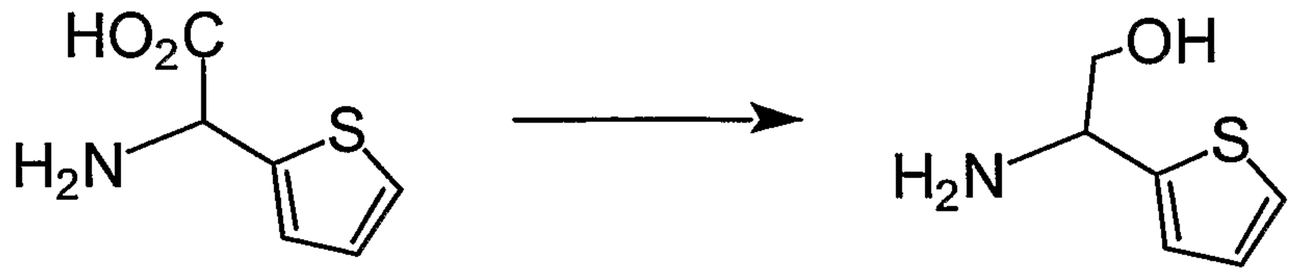
PREPARATIVE EXAMPLES 53-61

Following the procedure set forth in Preparative Example 52 but using the commercially available ketones listed in the Table below, the following amines were obtained.

Prep Example	Ketone	Amine	1.Yield (%) 2. MH^+
53			1. 11 2. 128
54			1. 33 2. 142
55			1. 49 2. 156
56			1. 5 2. 154
57			1. 47 2. 174
58			1. 71 2. 190
59			1. 78 2. 191
60			1. 80 2. 190

61			1. 9 2. 156

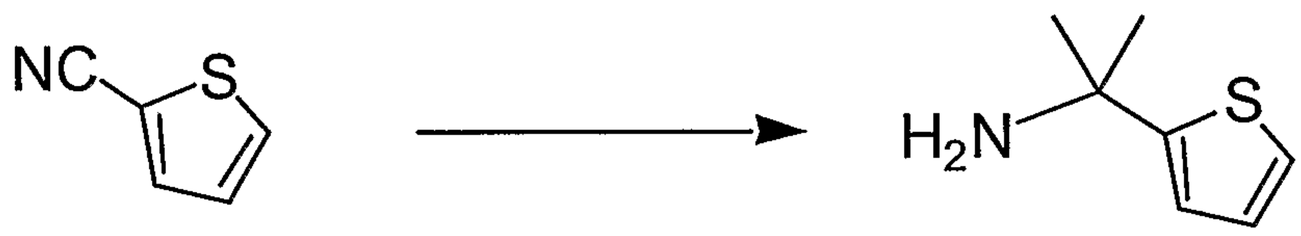
PREPARATIVE EXAMPLE 62



To a cooled (0-5°C) suspension of L-α-(2-thienyl)glycine (0.5 g) and $LiBH_4$ (2*M* in THF, 3.8 mL) in anhydrous THF (10 mL) was slowly added a THF (5 mL) solution of iodine (0.8 g). After stirring at room temperature for 15 min, the mixture was stirred at relux overnight. After cooling to room temperature, MeOH was added dropwise until gas evolution ceased and after 30 min, the mixture was evaporated. The oily residue was stirred in 20 mL KOH for 4 hrs, diluted with brine and extracted with EtOAc.

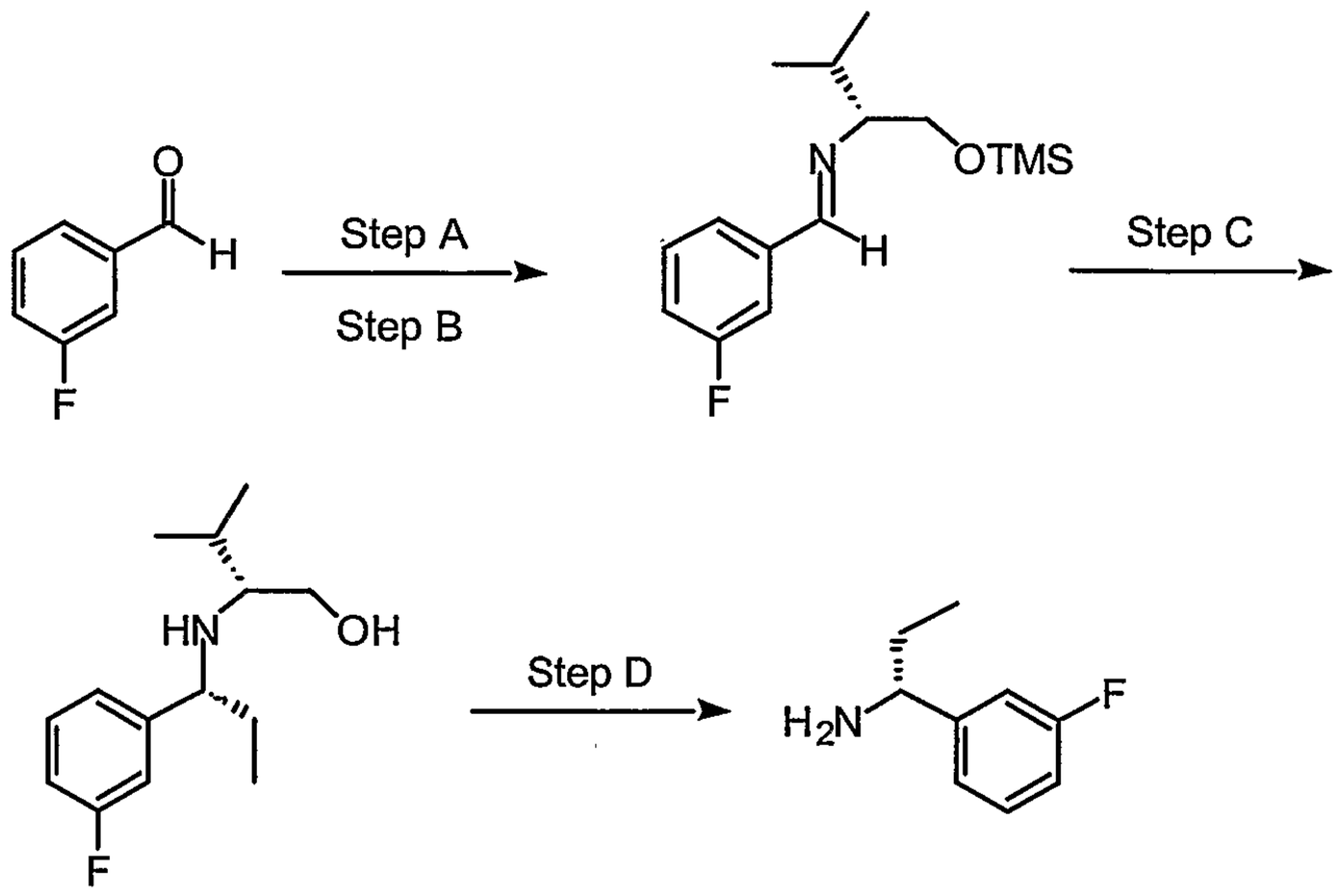
The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude mixture. Purification by flash column chromatography (50% EtOAc/ CH_2Cl_2, silica) afforded the product (0.3 g, 63%, MH^+ = 144).

PREPARATIVE EXAMPLE 63



$CeCl_3$-$7H_2O$ was dried at 140-150°C for 22 hr. To this solid was added THF (80 mL, anhydrous) and after stirring for 2 hr, the suspension was cooled to –78°C and to it was added methyl lithium over 30 min. After stirring for an additional 30 min 2-thiophenecarbonitrile dissolved in anhydrous THF (4.5 mL) was added and the resulting mixture stirred for an additional 4.5 hr at –78°C. Concentrated aqueous NH_3 (25 mL) was added and the mixture was warmed to room temperature and filtered through celite. The filtrate was extracted with dichloromethane, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford a crude mixture. Purification by flash column chromatography (5% MeOH, CH_2Cl_2, silica) afforded the desired product (1.2 g, 62%).

PREPARATIVE EXAMPLE 64



Step A

To a solution of (D)-valinol (4.16 g, 40.3 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added $MgSO_4$ (20 g) followed by dropwise addition of 3-fluorobenzaldehyde (5.0 g, 40.3 mmol). The heterogenous solution was stirred at 0°C for 2h and was allowed to warm to room temperature and stir overnight (14h). The mixture was filtered and the drying agent was washed with CH_2Cl_2 (2 x 10 mL). The filtrate was concentrated under reduced pressure to afford 8.4 g (100%) of an oil which was taken onto the next step without further purification.

Step B

To a solution of the imine (8.4 g, 40.2 mmol) from Step A in CH_2Cl_2 (60 mL) at room temperature was added Et_3N (6.2 mL, 44.5 mmol) followed by dropwise addition of TMSCl (5.7 mL, 44.5 mmol). The mixture was stirred for 6h at room temperature whereupon the ppt that had formed was filtered off and washed with CH_2Cl_2 (2 x 10 mL). The combined filtrate was concentrated under reduced pressure and was taken up in Et_2O/hexane (1:1/150 mL). The precipitate was filtered off and the filtrate was concentrated under reduced pressure to afford 10.1 g (89%) of the protected imine as an oil. This material was taken onto the next step without further purification.

Step C

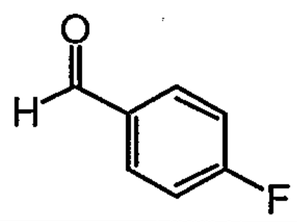
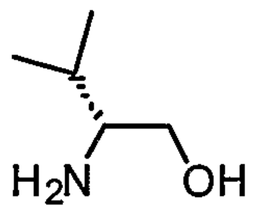
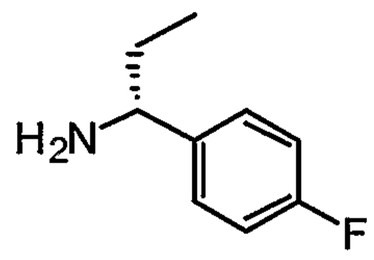
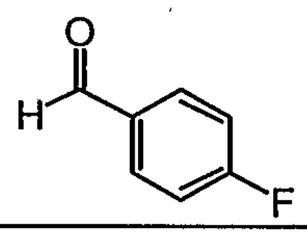
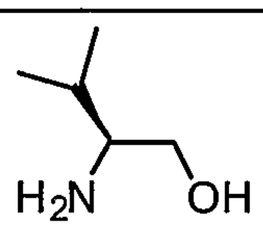
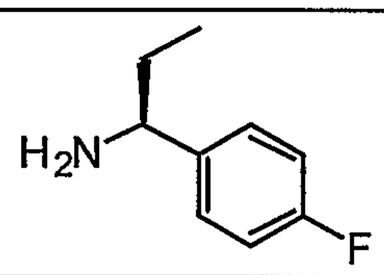
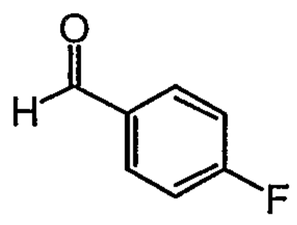
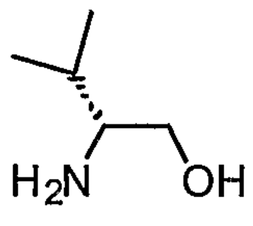
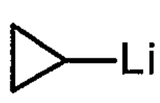
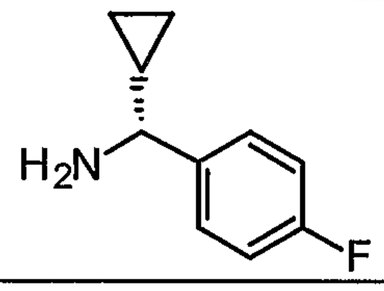
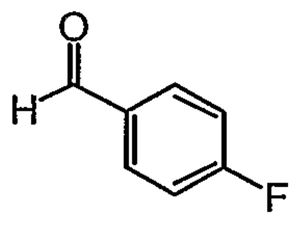
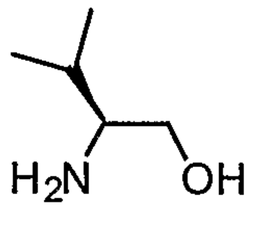
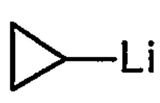
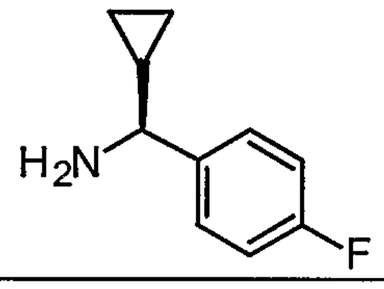
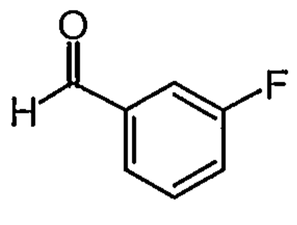
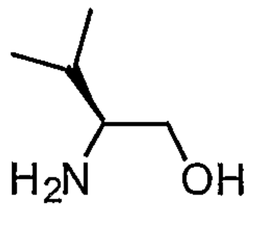
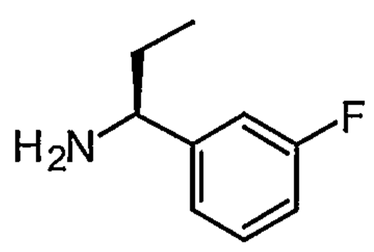
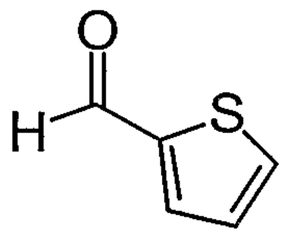
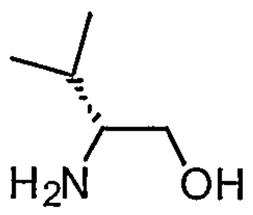
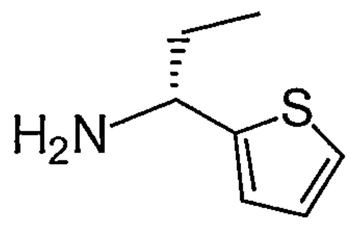
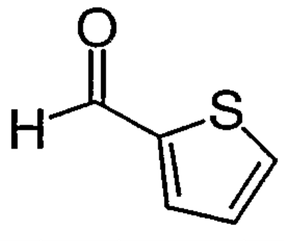
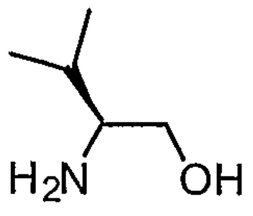
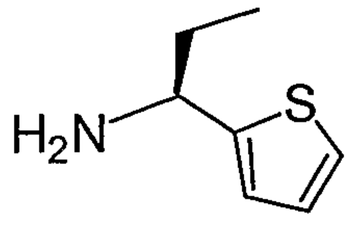
To a solution of EtI (4.0 g, 25.6 mmol) in Et_2O (40 mL) at –78 °C was added t-BuLi (30.1 mL, 51.2 mmol, 1.7 M in pentane) and the mixture was stirred for 10 min. The mixture was warmed to room temperature, stirred for 1 h, and was recooled to –40 °C. A solution of the imine (6.0 g, 21.4 mmol) from Step B in Et_2O (30 mL) was added dropwise via addition funnel to afford a bright orange mixture. The reaction mixture was stirred for 1.5 h at –40 °C then 3M HCl (50 mL) was added and the mixture was allowed to warm to room temperature. Water (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL) and the organic layers were combined and discarded. The aqueous layer was cooled to 0 °C and carefully treated with solid NaOH pellets until pH = 12 was attained. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined layers were washed with brine (1 x 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 4.8 g (94% yield) of the amine as an oil. This material was taken on crude to the next step without further purification.

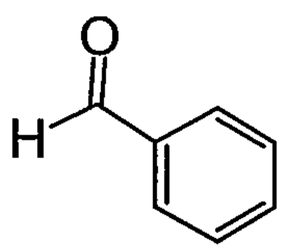
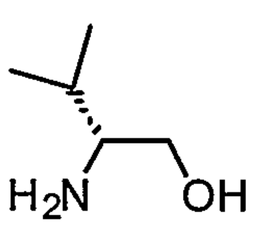
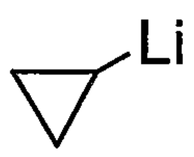
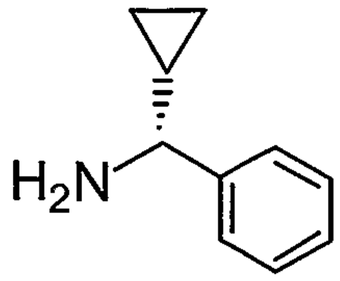
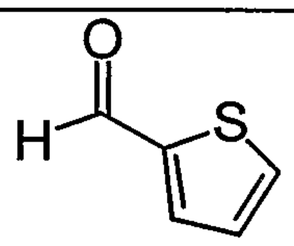
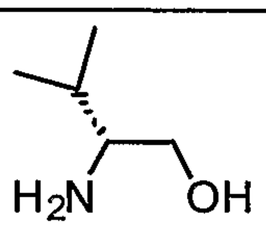
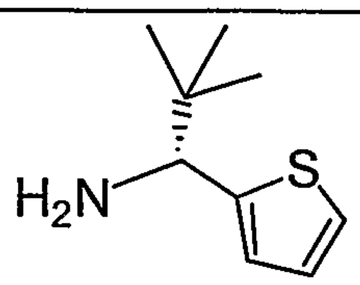
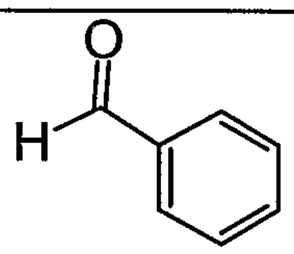
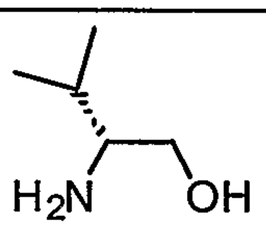
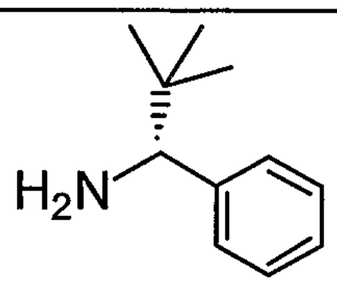
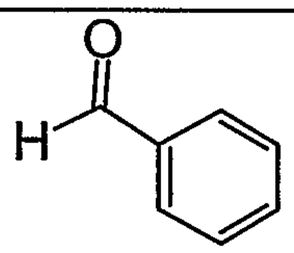
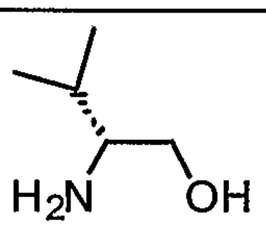
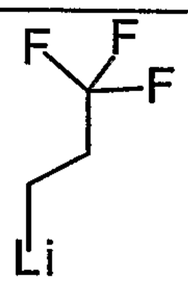
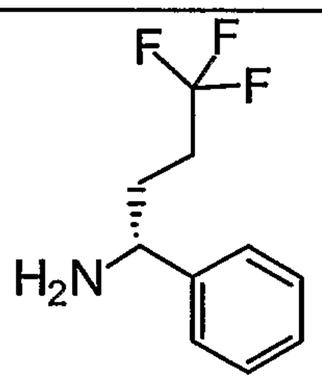
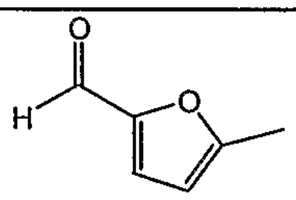
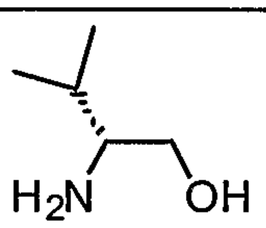
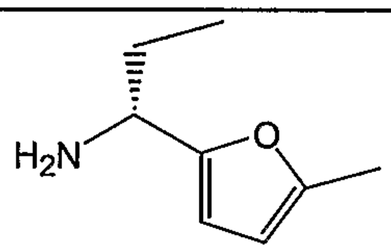
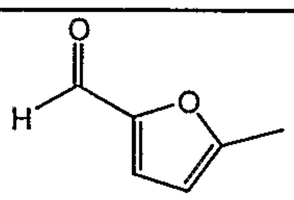
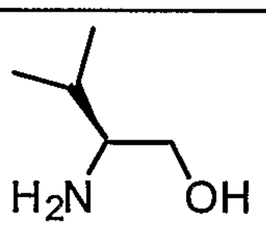
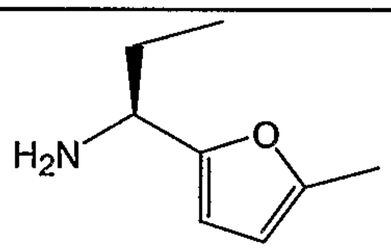
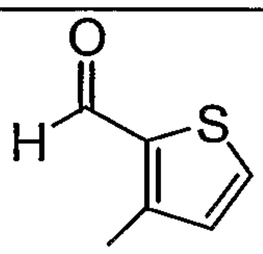
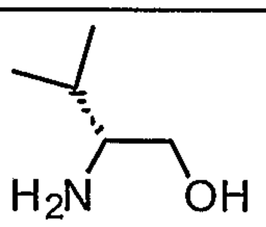
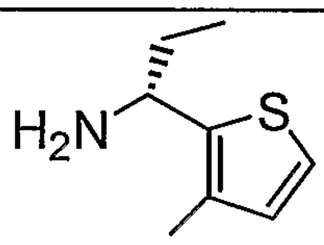
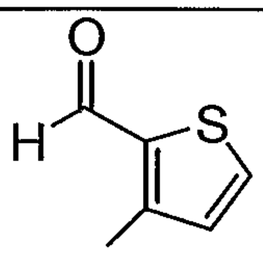
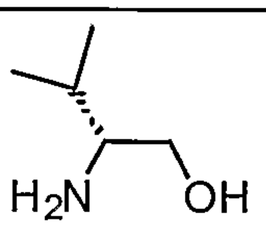
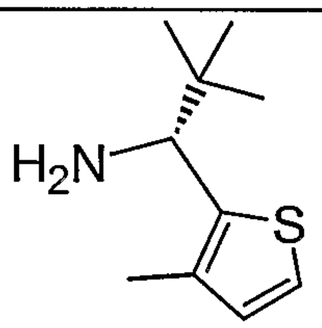
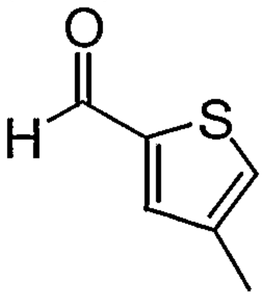
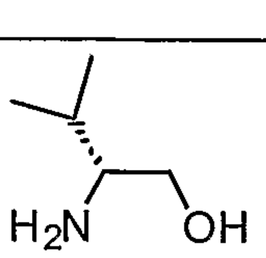
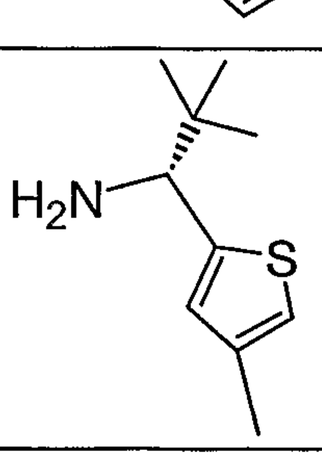
Step D

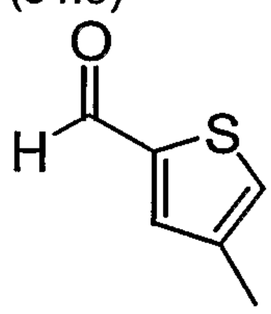
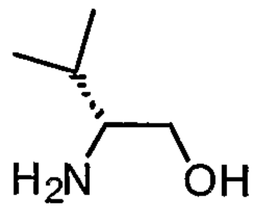
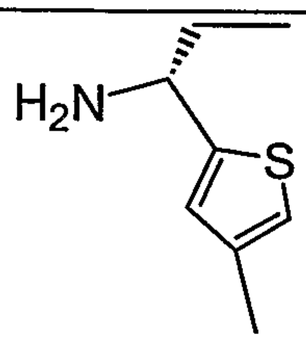
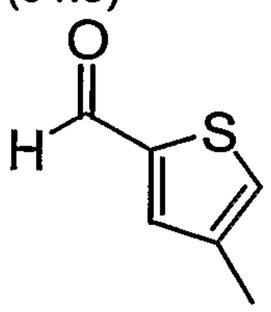
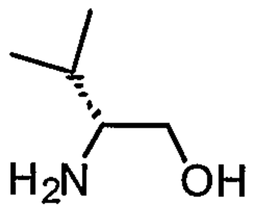
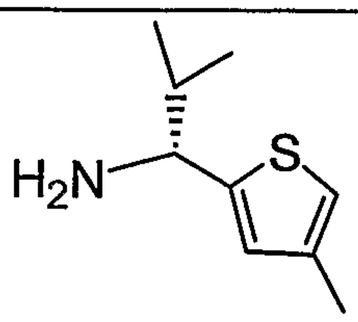
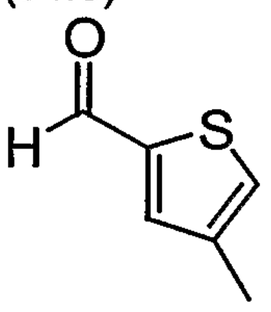
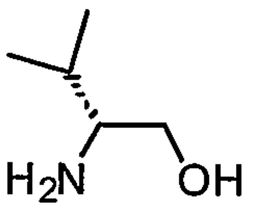
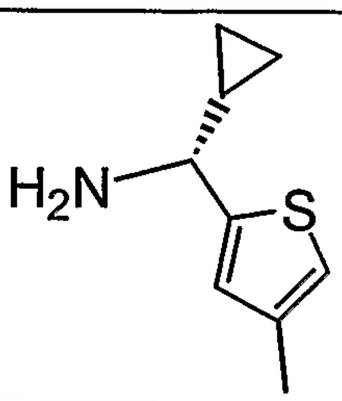
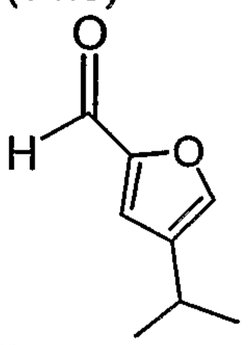
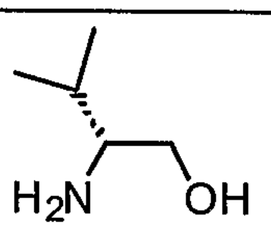
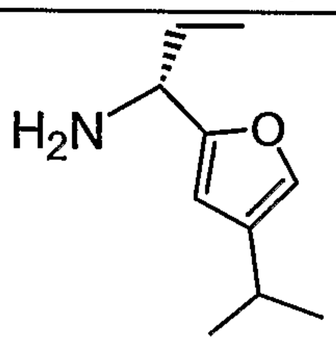
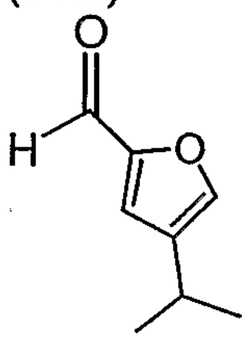
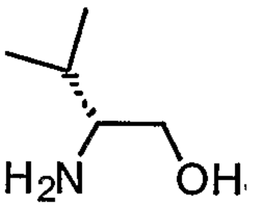
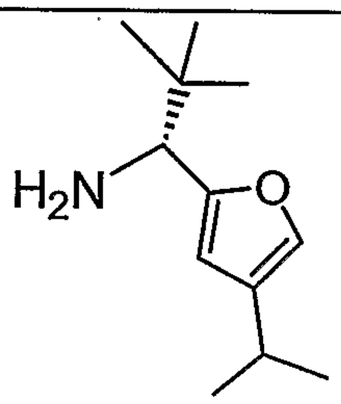
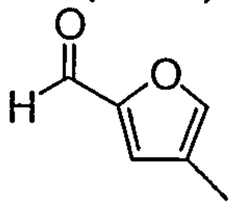
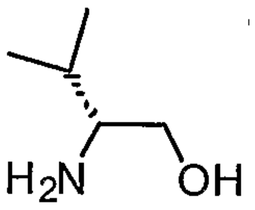
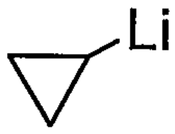
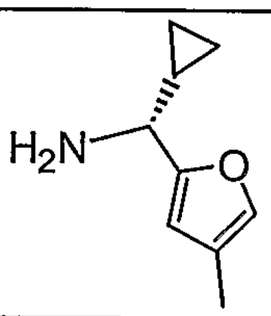
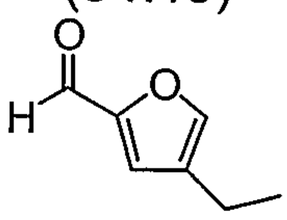
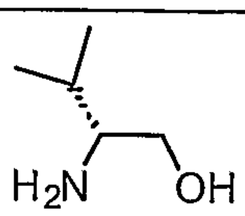
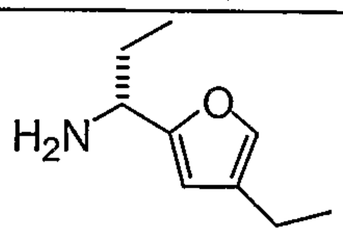
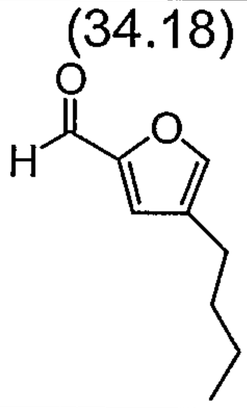
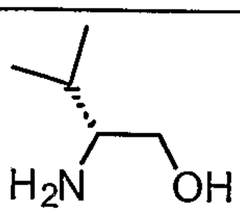
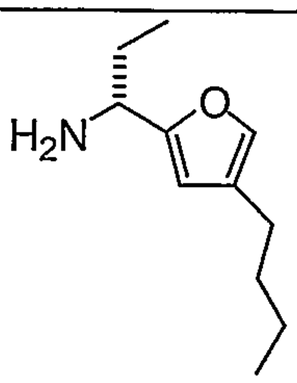
To a solution of amine (4.5 g, 18.8 mmol) from Step C in MeOH (80 mL) at room temperature was added $MeNH_2$ (25 mL, 40% in water) followed by addition of a solution of H_5IO_6 (14.0 g, 61.4 mmol) in H_2O (25 mL). The heterogenous mixture was stirred for 1.5 h (until the reaction was complete by TLC) and the precipitate was filtered off. The resulting filtrate was diluted with water (50 mL) and the mixture was extracted with Et_2O (4 x 60 mL). The combined organic layers were concentrated to a volume of ~30 mL whereupon 3M HCl (75 mL) was added. The mixture was stirred overnight (12h at room temperature) after which the mixture was concentrated to remove the volatiles. The aqueous layer was extracted with Et_2O (3 x 40 mL) and the organic layers were discarded. The aqueous layer was cooled to 0 °C and was carefully treated with solid NaOH pellets until pH ~12 was reached. The aqueous layer was extracted with Et_2O (3 x 60 mL) and the combined organic layers were dried ($MgSO_4$). The organic layer was concentrated under reduced pressure to afford 2.8 g (97% yield) of the desired amine as an oil [MH^+ 154]. This compound was proven to be >85% pure by ^1H NMR and was used crude in the subsequent coupling step.

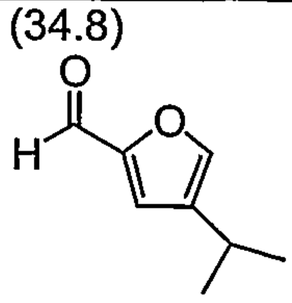
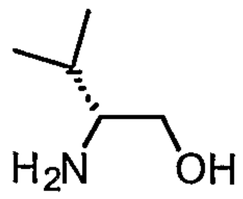
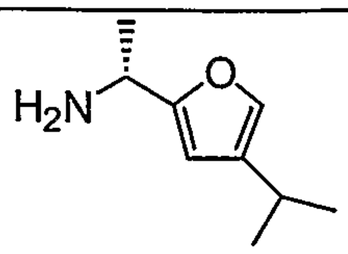
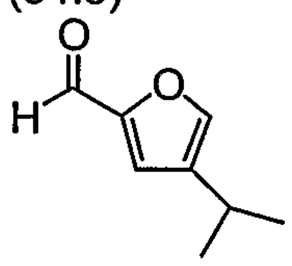
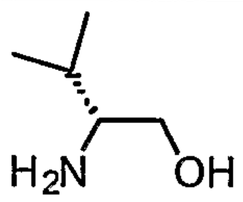
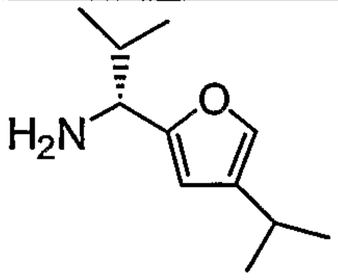
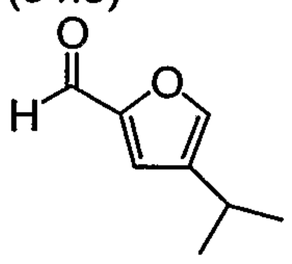
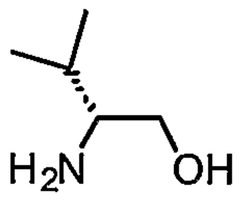
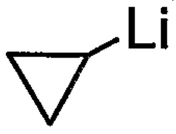
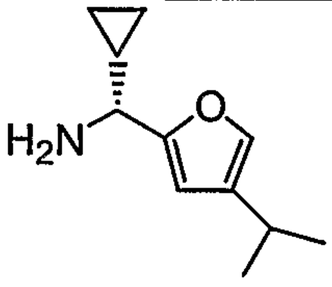
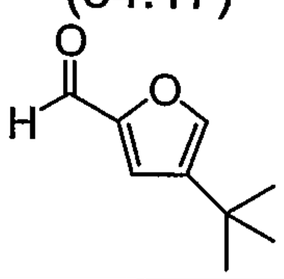
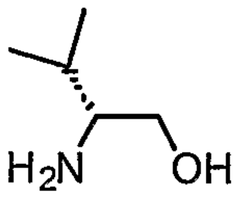
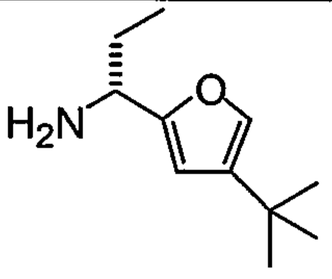
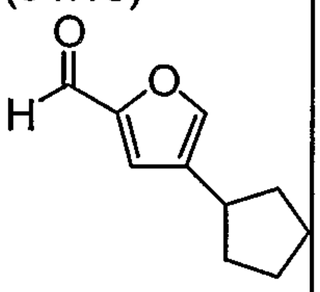
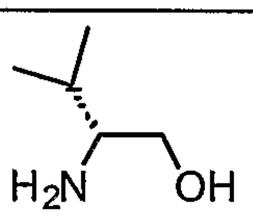
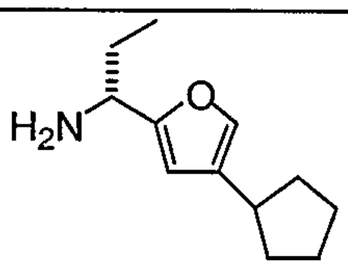
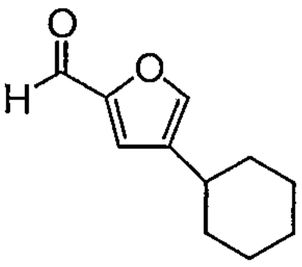
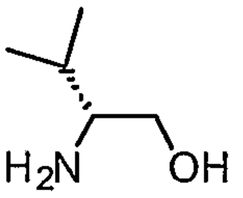
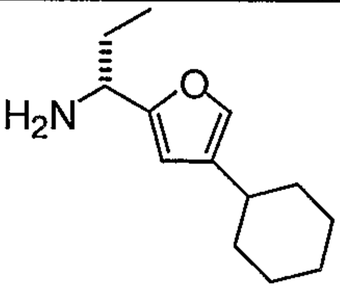
PREPARATIVE EXAMPLES 65-75.10J

Following the procedure set forth in Preparative Example 64 but using the prepared or commercially available aldehydes, amino alcohols, and organolithium reagents in the Table below, the optically pure amine products in the Table below were obtained.

Prep Ex.	Aldehyde	Amino Alcohol	Organo lithium	Product	1.Yield (%) 2. MH^+
65			EtLi		1. 62 2. 154
66			EtLi		1. 70 2. 154
67					1. 54 2. 166
68					1. 67 2. 166
69			EtLi		1. 67 2. 154
70			EtLi		1. 42 2. 142
71			EtLi		1. 36 2. 142

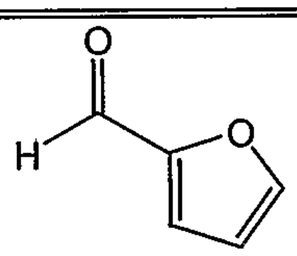
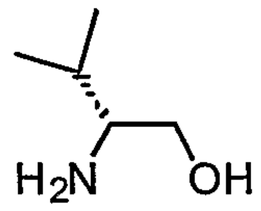
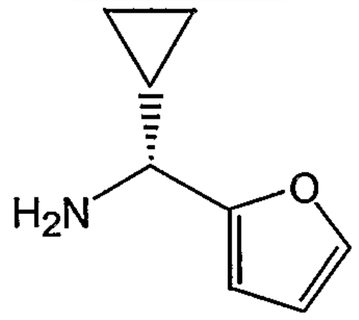
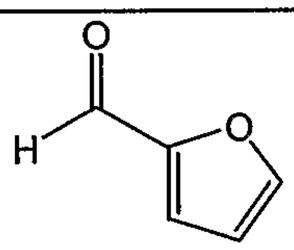
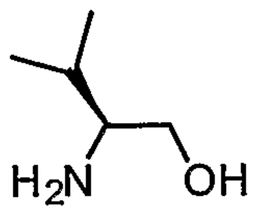
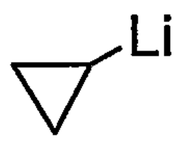
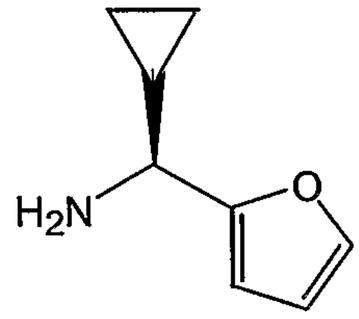
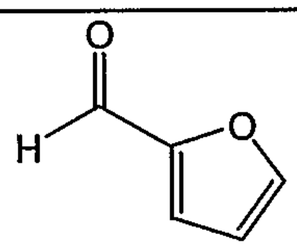
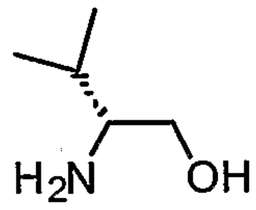
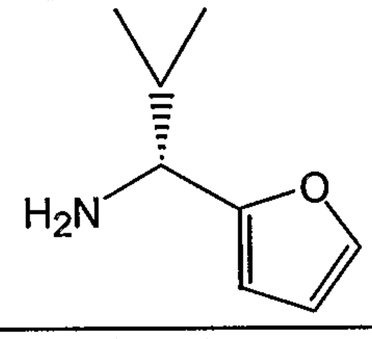
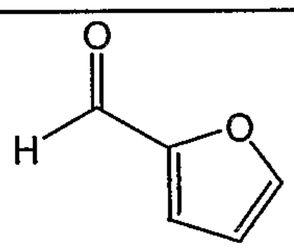
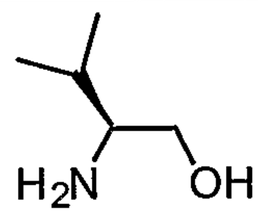
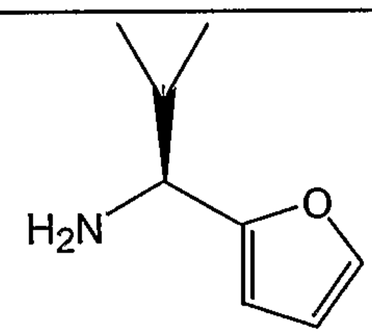
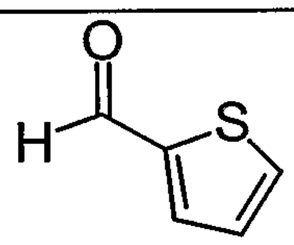
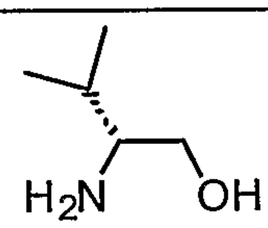
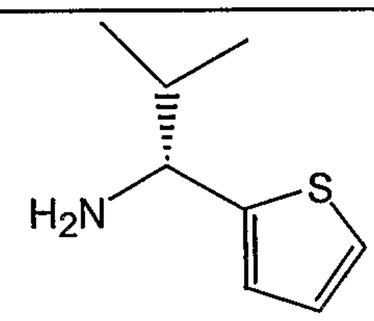
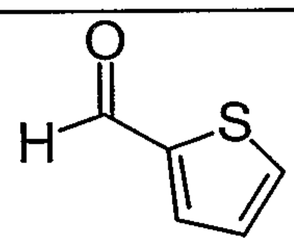
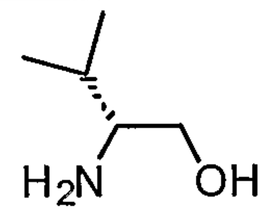
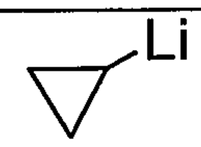
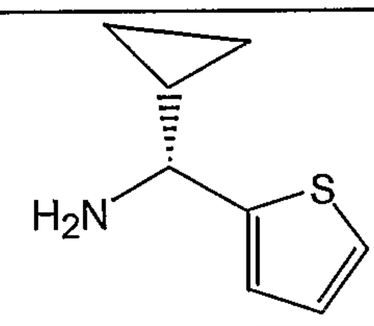
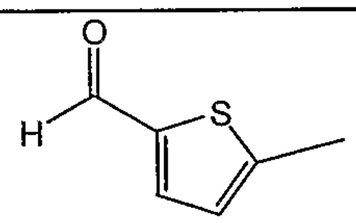
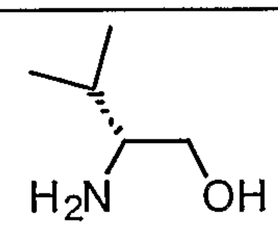
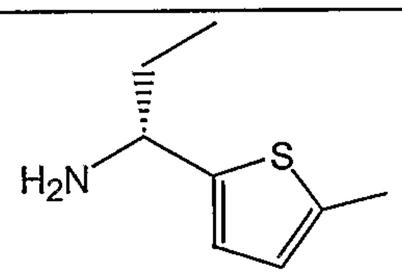
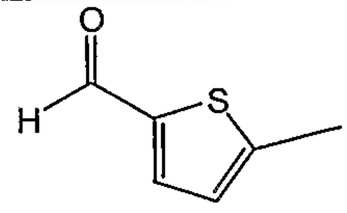
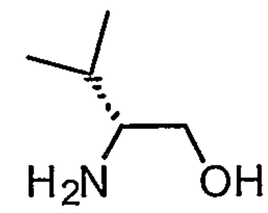
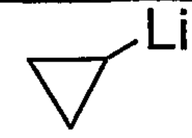
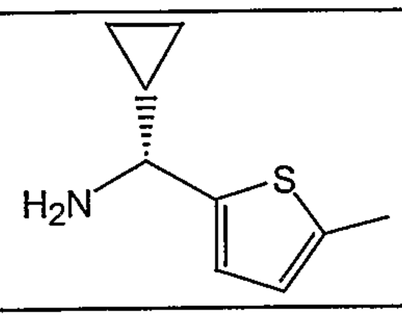
72					1. 62 2. 148
73			t-BuLi		1. 27 2. 256
74			t-BuLi		1. 15 2. 164
75					1. 7 2. 204
75.1			EtLi		1. 65 2. 123 $[M-NH_2]^+$
75.2			EtLi		1. 62 2. 123 $[M-NH_2]^+$
75.3			EtLi		1. 93 2. 139 $[M-NH_2]^+$
75.4			tBuLi		1. 50 2. 167 $[M-NH_2]^+$
75.5	(34.6) 		tBuLi		1. 48 2. 167 $[M-NH_2]^+$

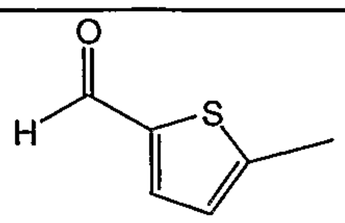
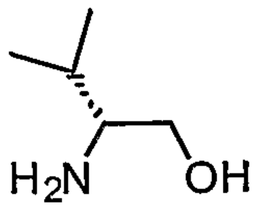
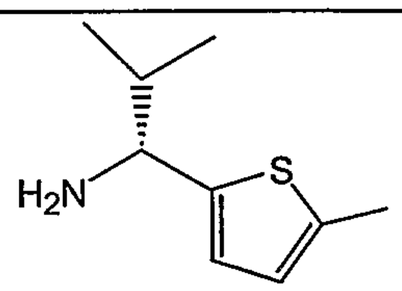
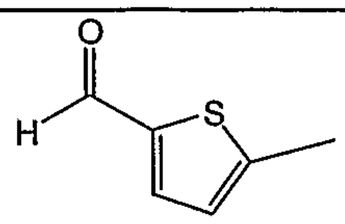
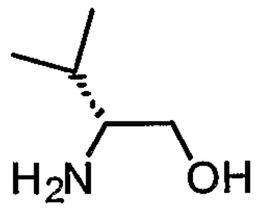
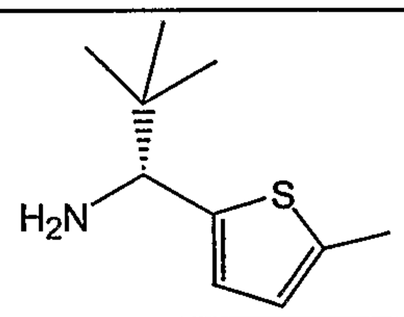
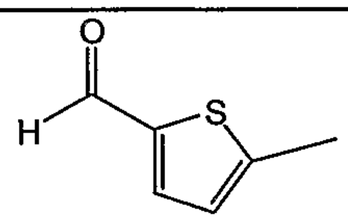
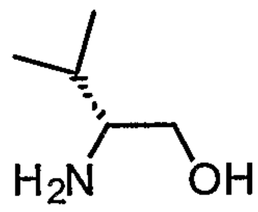
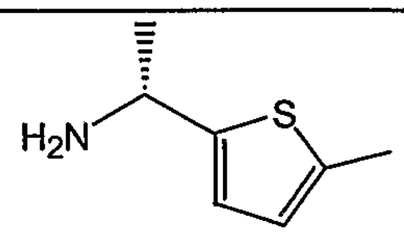
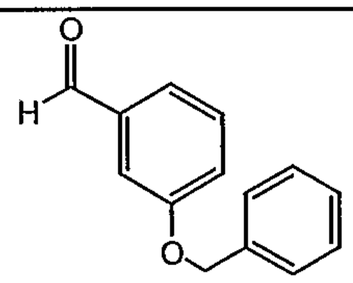
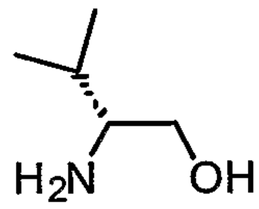
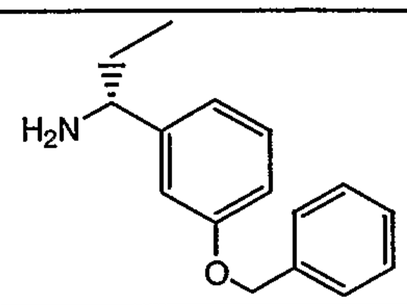
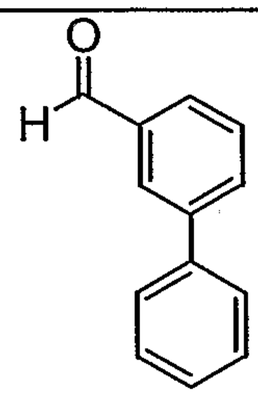
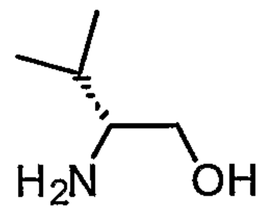
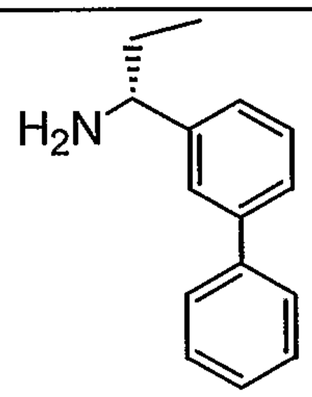
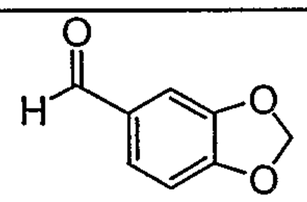
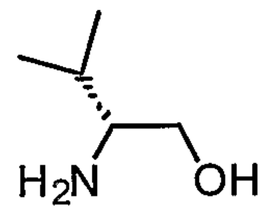
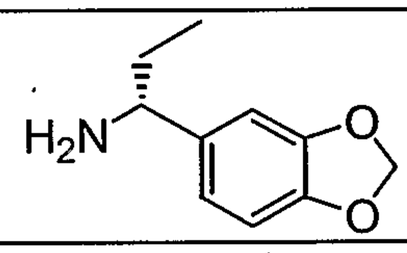
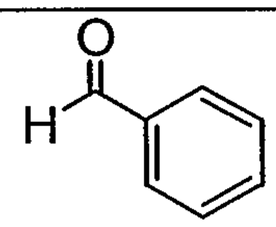
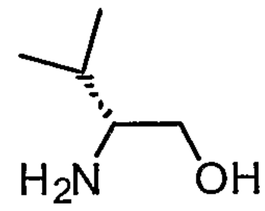
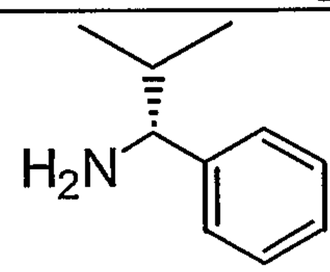
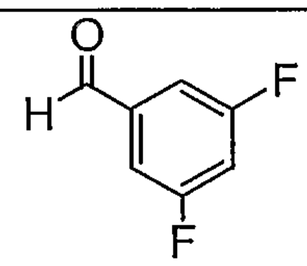
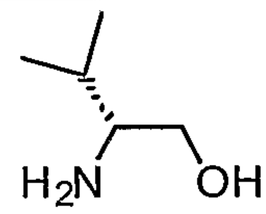
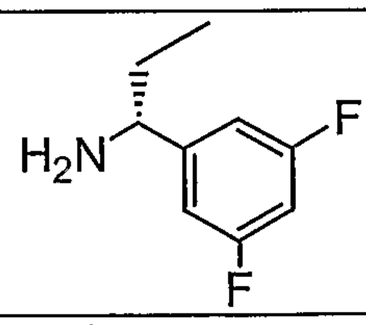
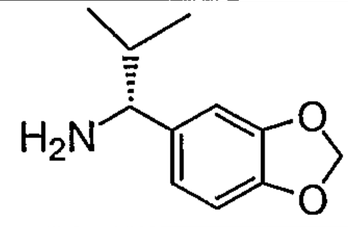
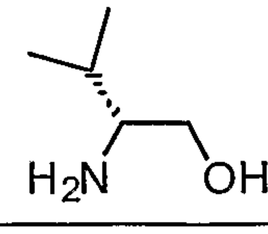
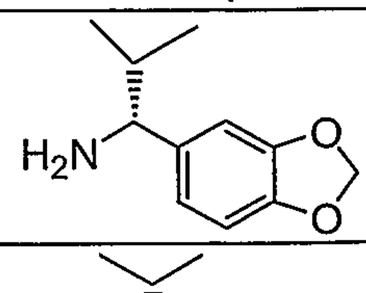
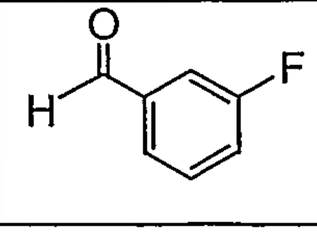
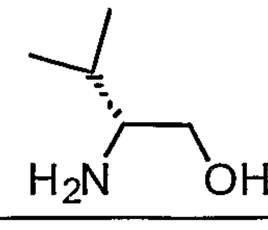
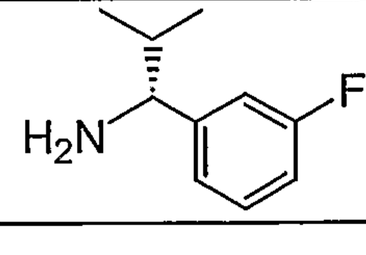
75.6	(34.6) 		EtLi		1. 97 2. 139 $[M-NH_2]^+$
75.7	(34.6) 		iPrLi		1. 87 2. 153 $[M-NH_2]^+$
75.8	(34.6) 				1. 94 2. 151 $[M-NH_2]^+$
75.9	(34.8) 		EtLi		1. 75 2. 151 $[M-NH_2]^+$
75.10	(34.8) 		tBuLi		1. 30 2. 179 $[M-NH_2]^+$
75.10A	(34.7) 				1. 61 2. 135 $[M-NH_2]^+$
75.10B	(34.19) 		EtLi		1. 24 2. 154
75.10C	(34.18) 		EtLi		1. 32 2. 165 $[M-NH_2]^+$

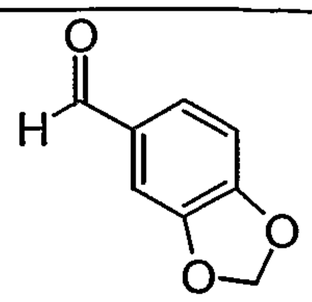
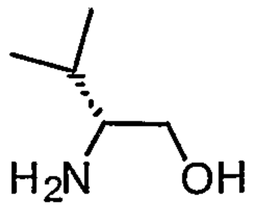
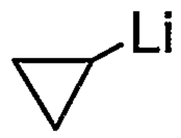
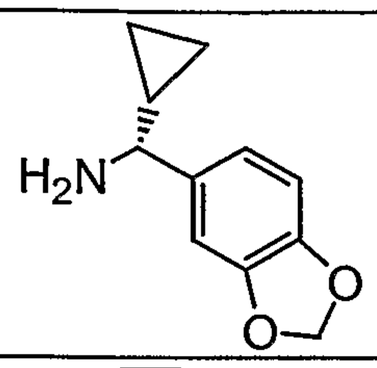
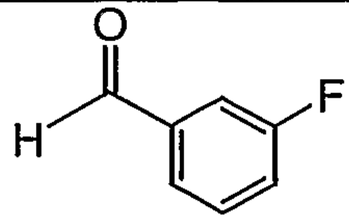
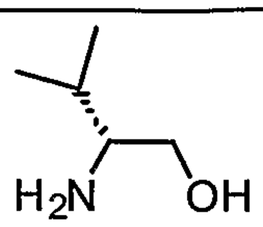
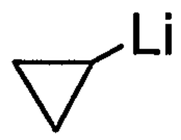
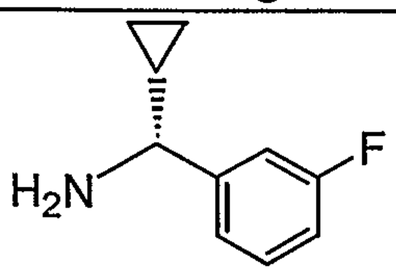
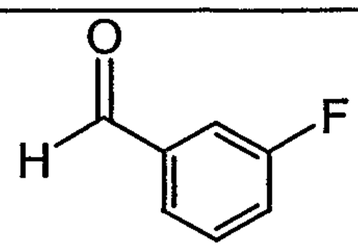
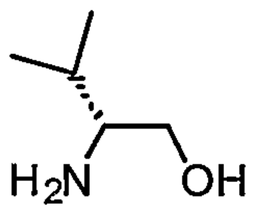
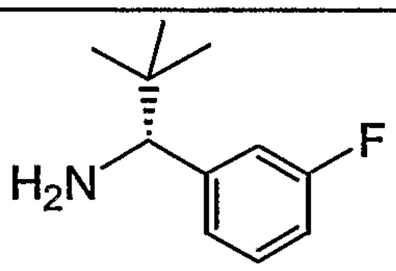
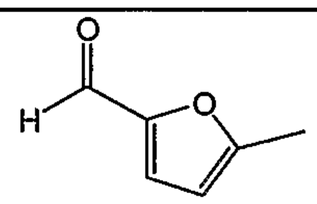
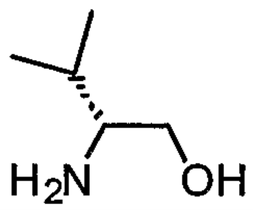
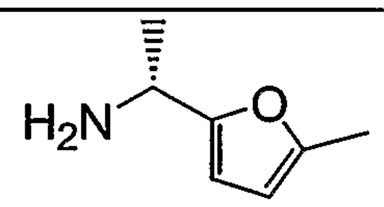
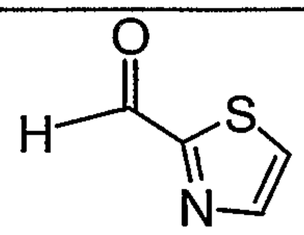
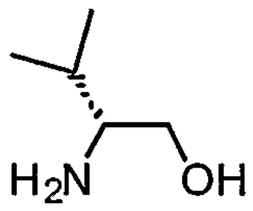
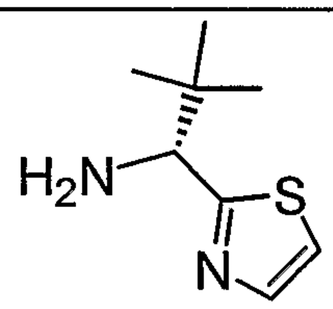
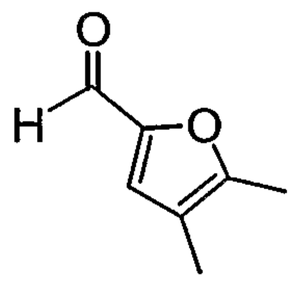
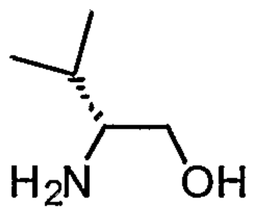
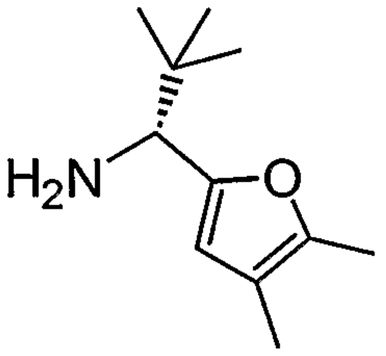
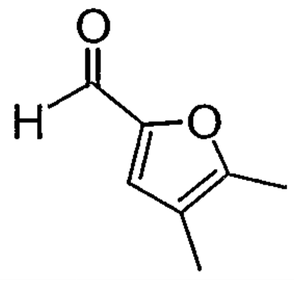
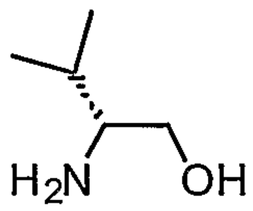
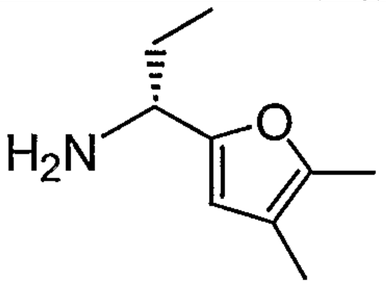
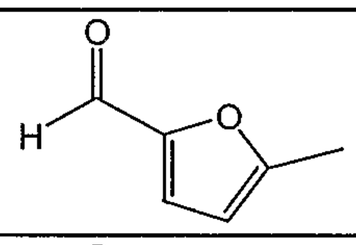
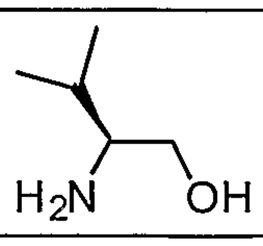
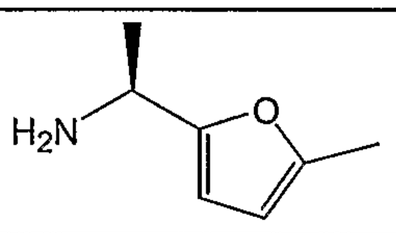
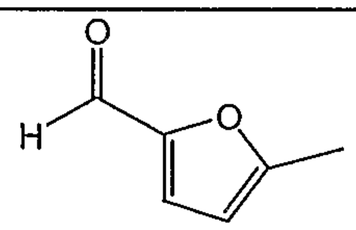
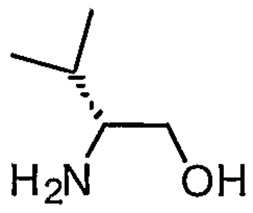
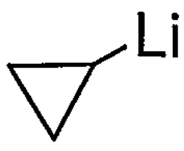
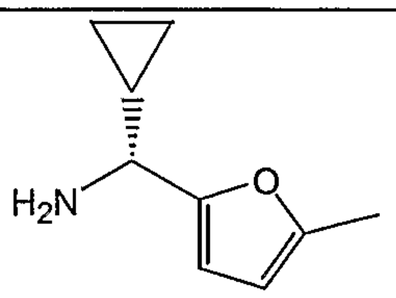
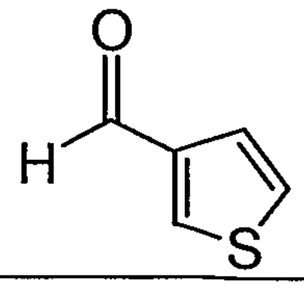
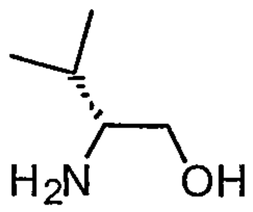
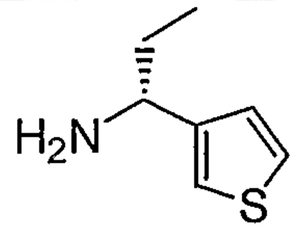
75.10D	(34.8) 		MeLi		1. 47 2. 137 $[M-NH_2]^+$
75.10E	(34.8) 		iPrLi		1. 30 2. 165 $[M-NH_2]^+$
75.10F	(34.8) 				1. 67 2. 163.0 $[M-NH_2]^+$
75.10G	(34.17) 		EtLi		1. 24 2. 165 $[M-NH_2]^+$
75.10H	(34.15) 		EtLi		1. 70 2. 194
75.10J	(34.16) 		EtLi		1. 54 2. 208

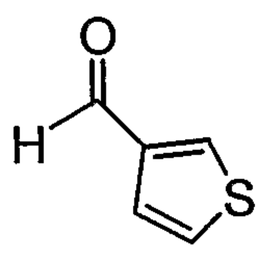
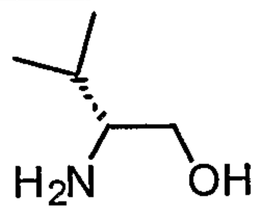
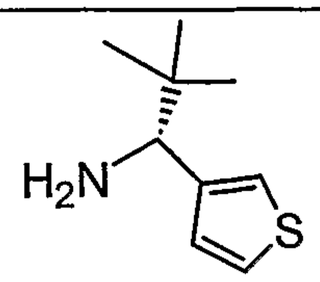
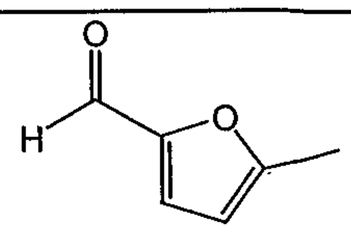
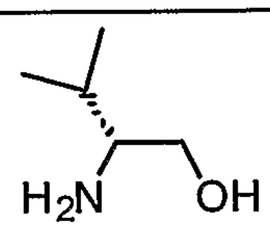
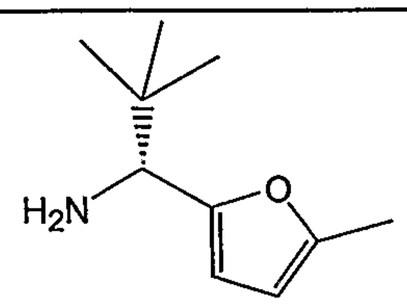
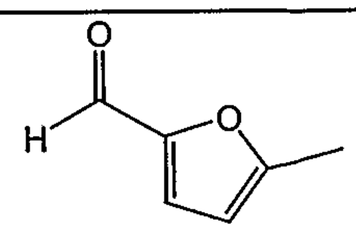
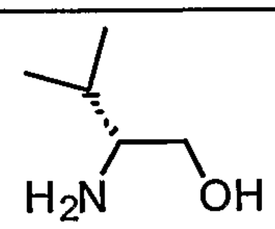
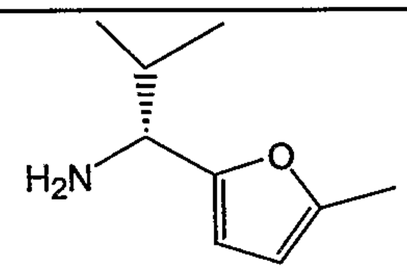
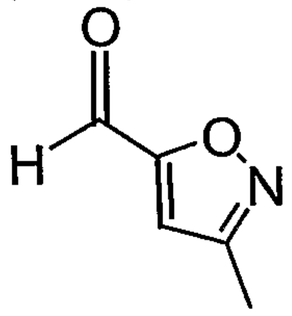
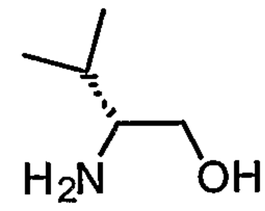
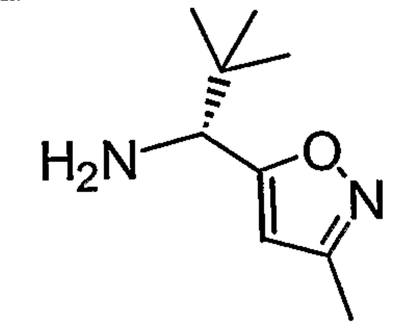
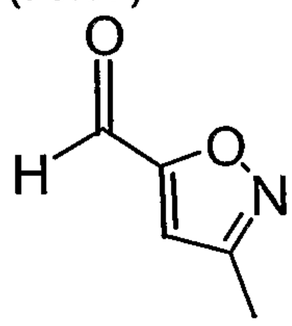
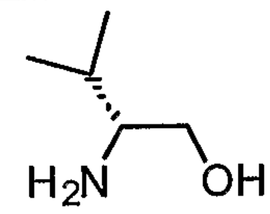
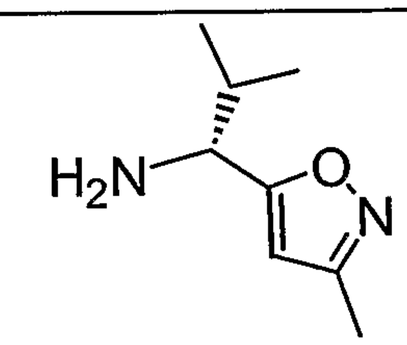
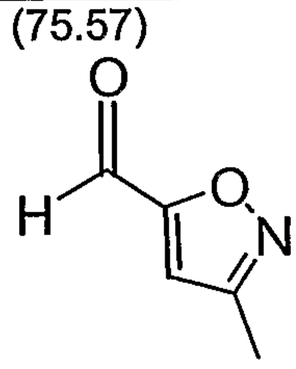
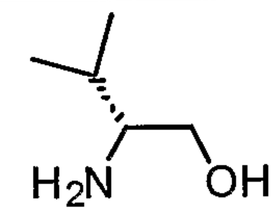
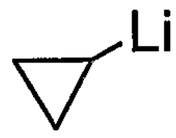
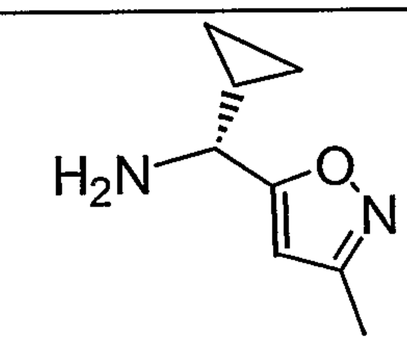
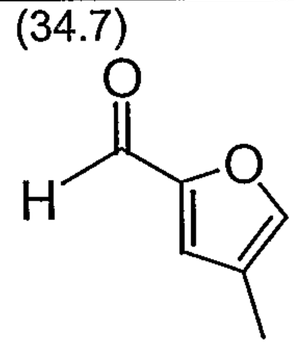
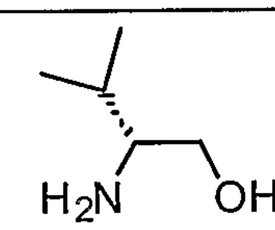
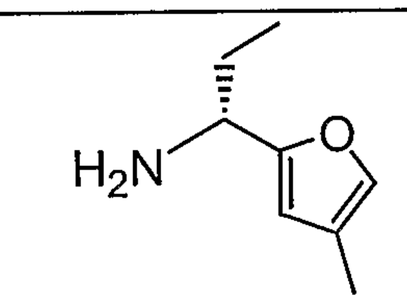
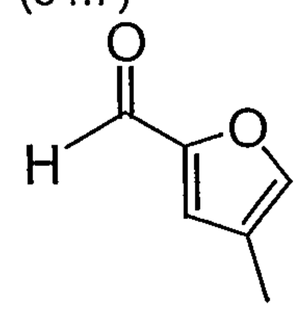
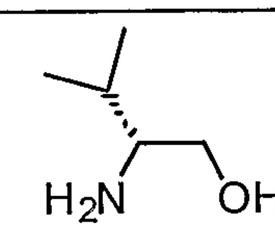
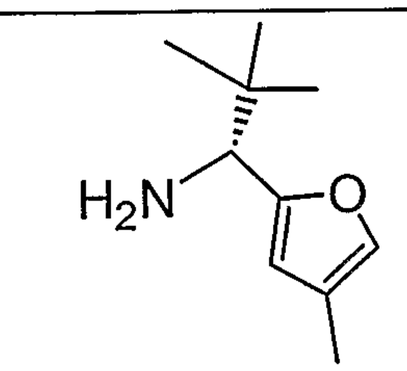
PREPARATIVE EXAMPLES 75.11-75.59

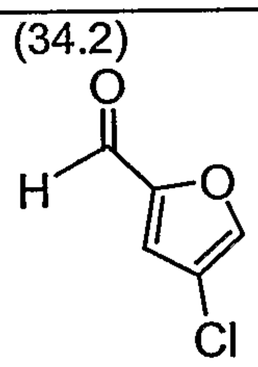
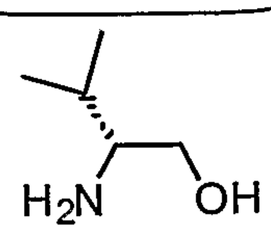
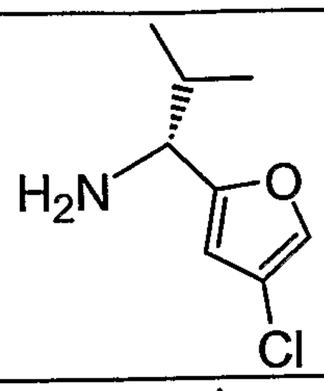
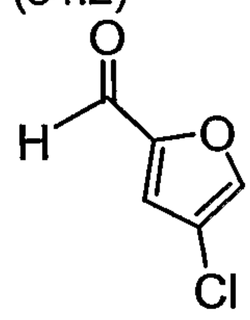
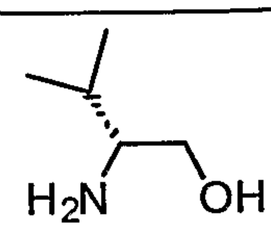
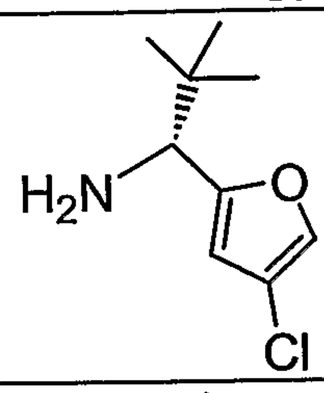
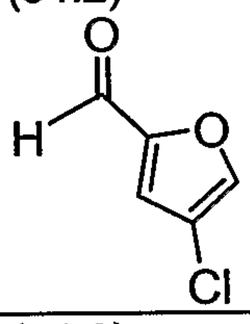
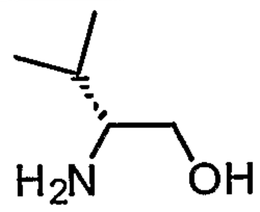
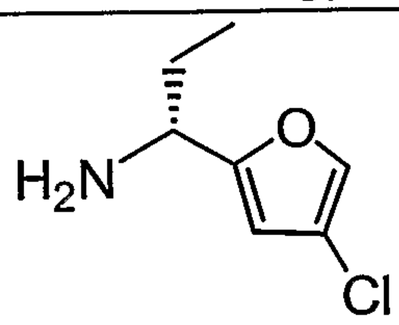
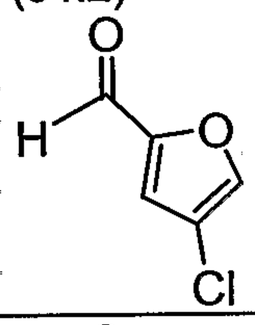
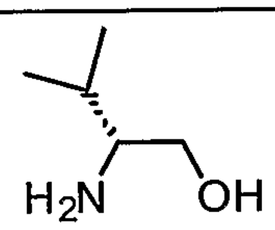
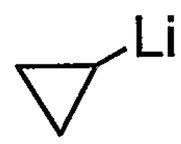
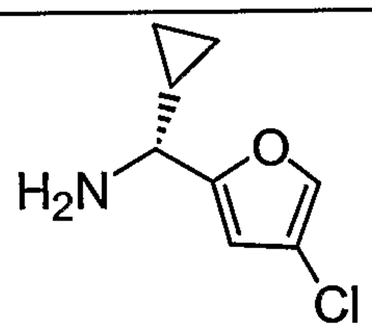
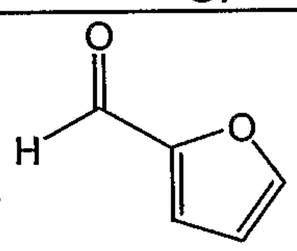
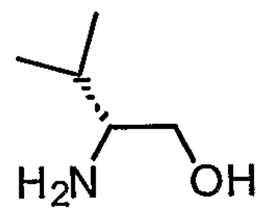
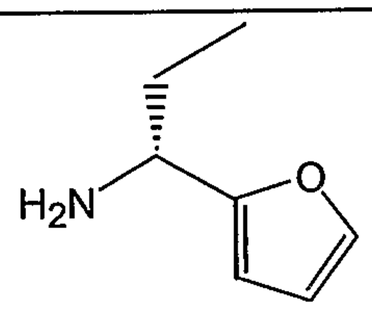
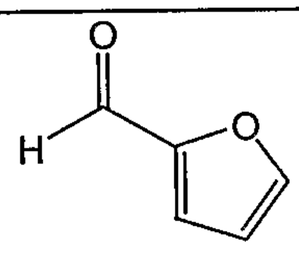
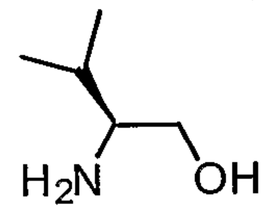
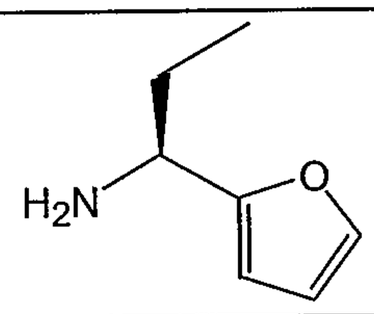
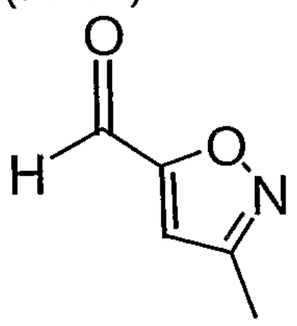
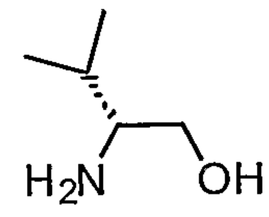
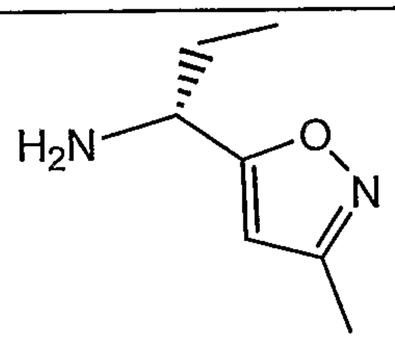
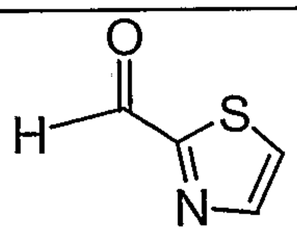
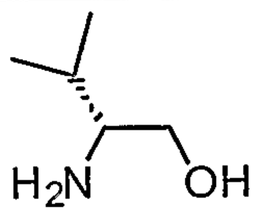
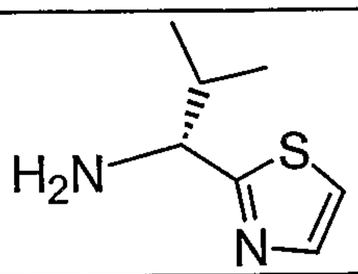
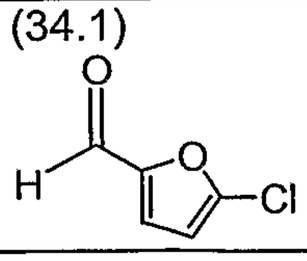
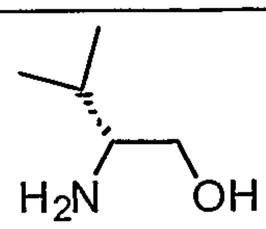
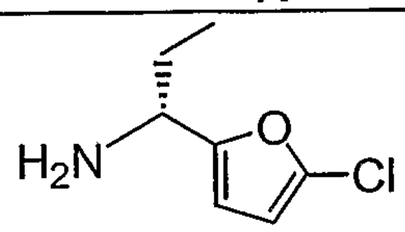
Following the procedure set forth in Preparative Example 64 but using the prepared or commercially available aldehydes, amino alcohols, and organolithium reagents in the Table below and carrying the amine on crude, the optically pure amine products in the Table below were obtained.

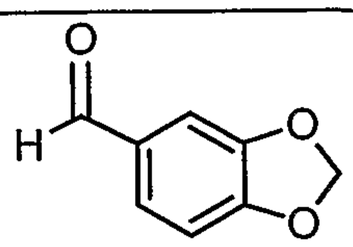
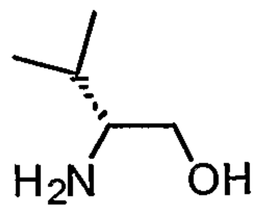
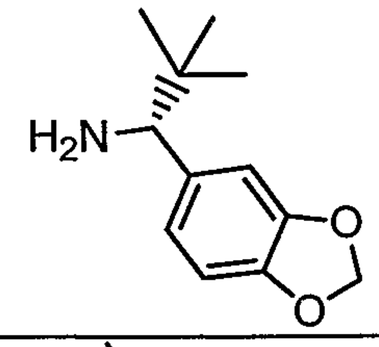
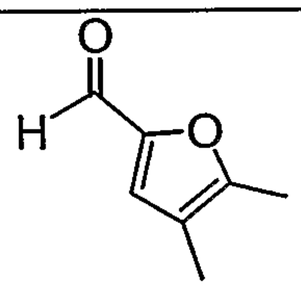
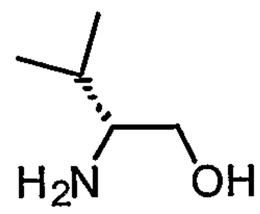
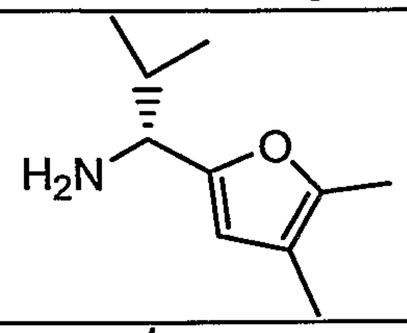
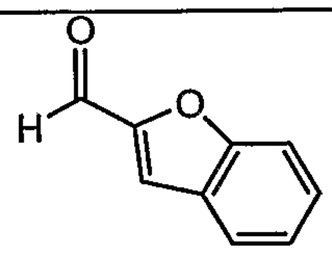
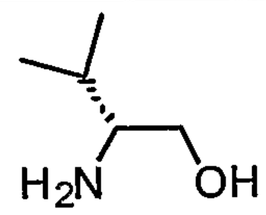
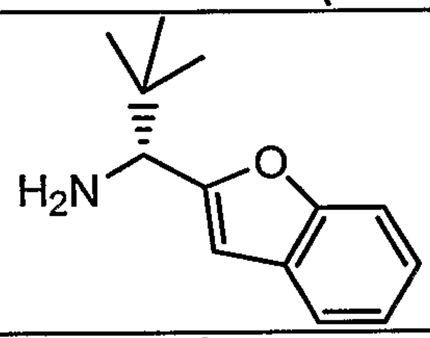
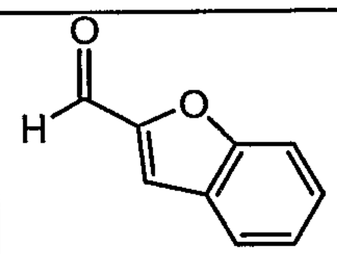
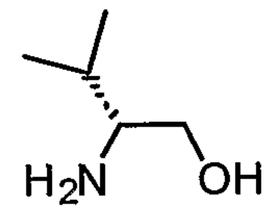
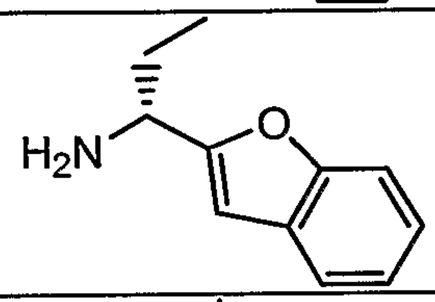
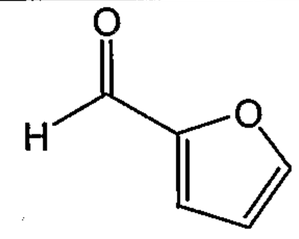
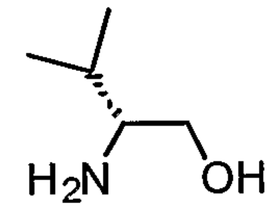
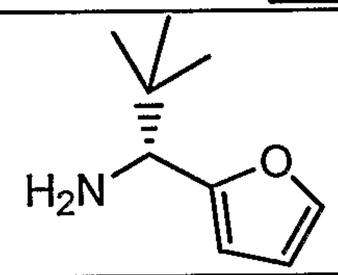
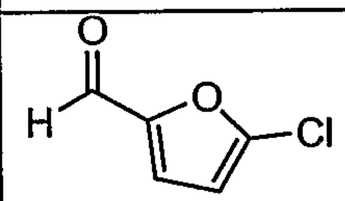
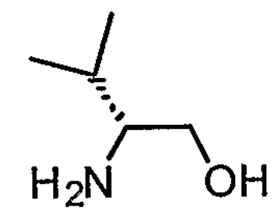
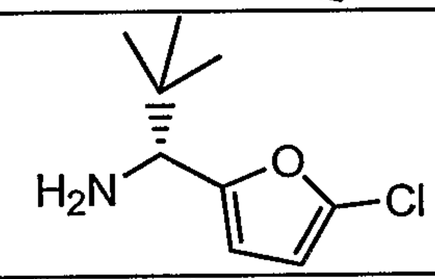
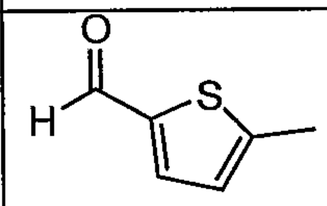
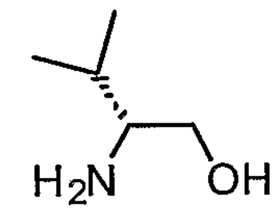
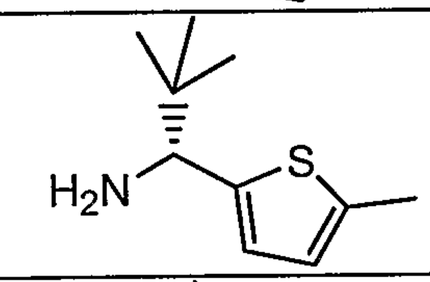
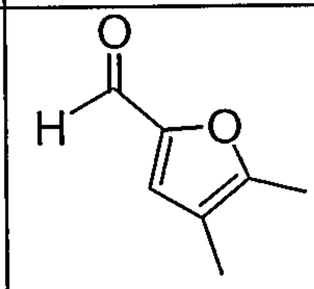
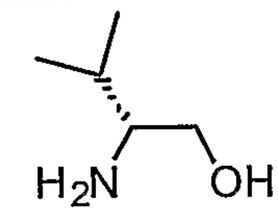
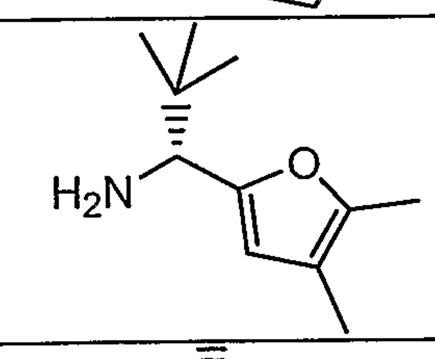
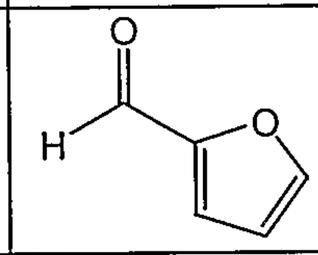
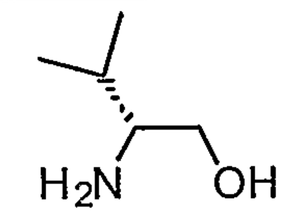
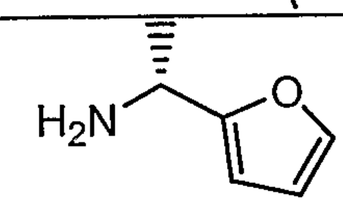
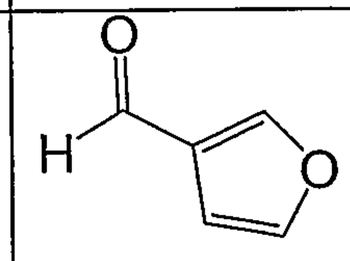
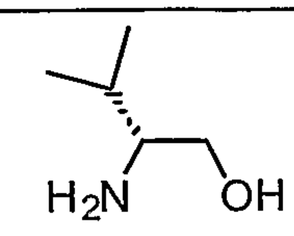
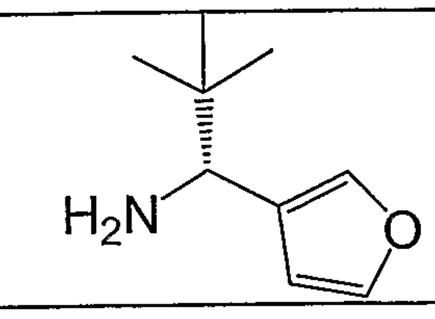
Prep Ex.	Aldehyde	Amino Alcohol	Organo lithium	Product	Yield (%)
75.11					52
75.12					50
75.13			iPrLi		57
75.14			iPrLi		54
75.15			iPrLi		58
75.16					61
75.17			EtLi		72
75.18					68

75.19			iPrLi		77
75.20			t-BuLi		15
75.21			MeLi		50
75.22			EtLi		23
75.24			EtLi		20
75.27			EtLi		65
75.28			iPrLi		61
75.29			EtLi		90
75.30			iPrLi		62
75.31			iPrLi		43

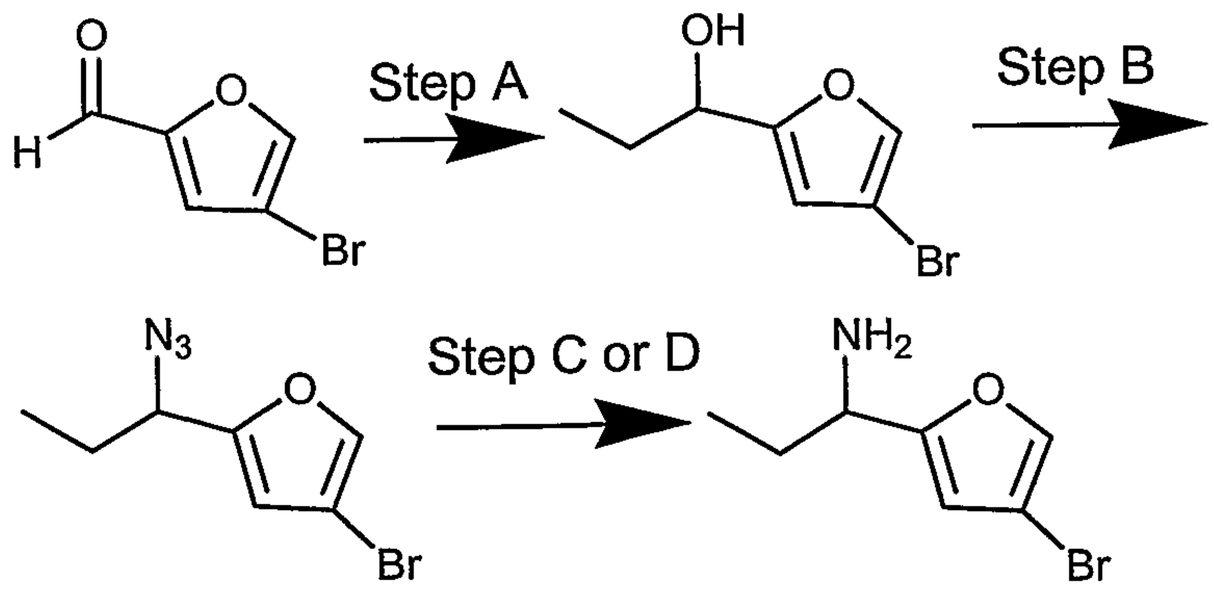
75.32					50
75.33					50
75.34			tBuLi		51
75.35			MeLi		51
75.36			tBuLi		57
75.37			tBuLi		60
75.38			EtLi		73
75.39			MeLi		48
75.41					52
75.42			EtLi		40

75.43			tBuLi		20
75.44			t-BuLi		79
75.45			iPrLi		55
75.46	(75.57) 		tBuLi		39
75.47	(75.57) 		iPrLi		55
75.48	(75.57) 				34
75.49	(34.7) 		EtLi		61
75.50	(34.7) 		tBuLi		25

75.51	(34.2) 		iPrLi		33
75.52	(34.2) 		tBuLi		30
75.53	(34.2) 		EtLi		39
75.54	(34.2) 				38
75.55			EtLi		64
75.56			EtLi		46
75.57	(75.57) 		EtLi		62
75.58			iPrLi		24
75.59	(34.1) 		EtLi		70

75.60			t-BuLi		60
75.61			iPrLi		60
75.62			t-BuLi		57
75.63			EtLi		94
75.64			t-BuLi		46
75.65			t-BuLi		60
75.66			t-BuLi		15
75.67			t-BuLi		60
75.68			MeLi		60
75.69			t-BuLi		12

PREPARATIVE EXAMPLE 75.75



Step A

To a solution of aldehyde (2.5g) in ether (50ml) at 0°C was added EtMgBr (4.56ml) dropwise. The heterogenous mixture was stirred for 2hr at 0°C and then poured into a beaker of saturated ammonium chloride (25ml), ice and CH_2Cl_2 (30ml). After the biphasic mixture stirred for 10min, the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the product (2.41g, 95%)

Step B

To a solution of alcohol from Step A above (1g) in toluene at room temperature was added DPPA. The mixture was cooled to 0°C and DBU was added and let stir for 12hr at room temperature. The layers were separated and the organic layer was washed with water, 1N HCl and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purified by preparative plate chromatography (hexane/EtOAc 20/1) to give the product (840mg, 75%).

Step C

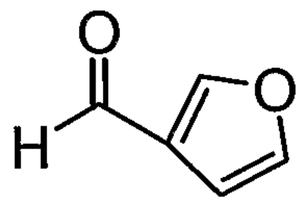
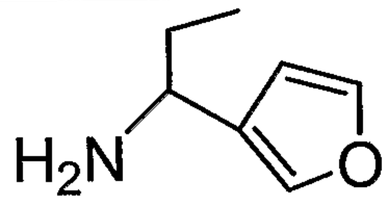
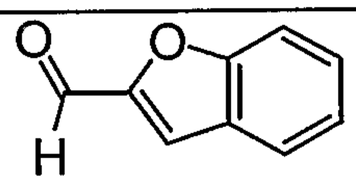
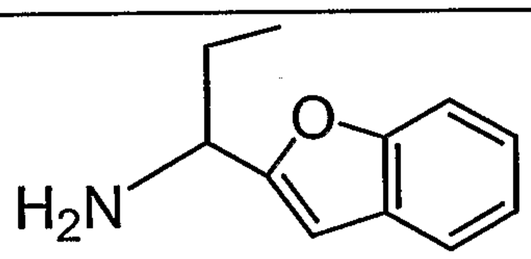
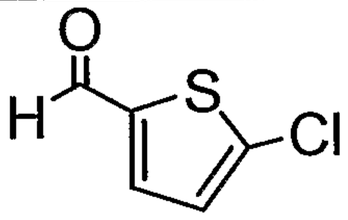
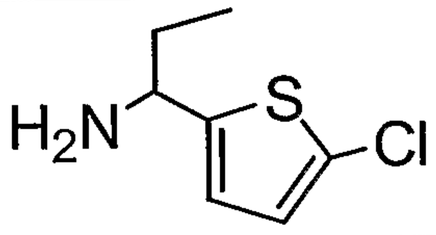
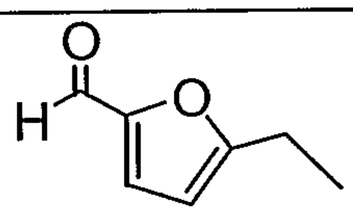
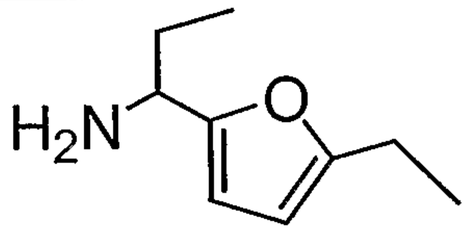
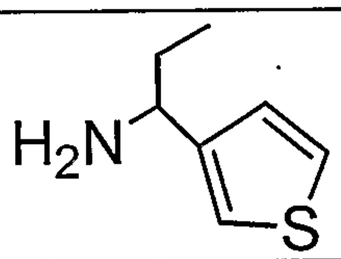
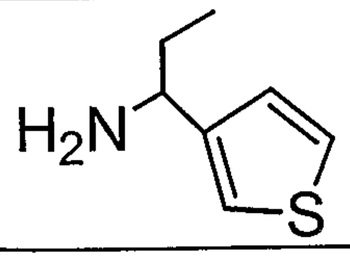
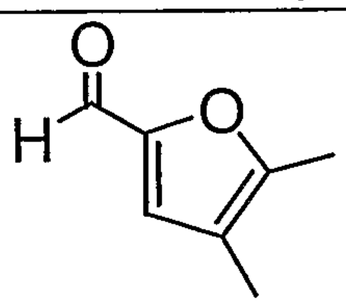
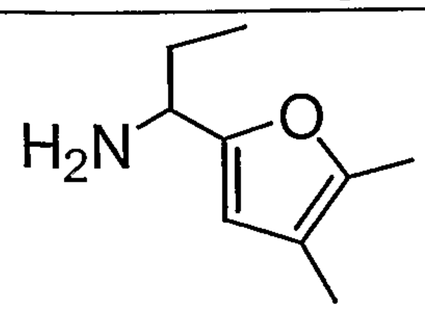
To a solution of azide (730mg) from Step B above in THF (7ml) was added PPh_3 (1g). The heterogenous solution was stirred for 12hr, whereupon water (1.5ml) was added. The mixture was refluxed overnight, cooled to room temperature and concentrated *in vacuo*. Ether and 1N HCl were added to the residue. The aqueous layer was cooled to 0°C, basified with NaOH pellets and extracted with ether. The ether layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the product (405mg, 62%).

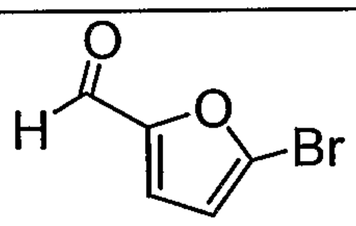
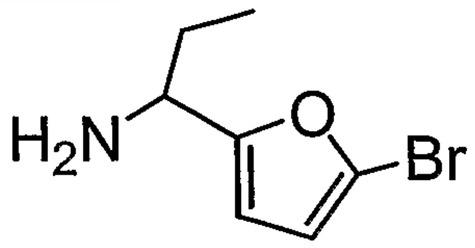
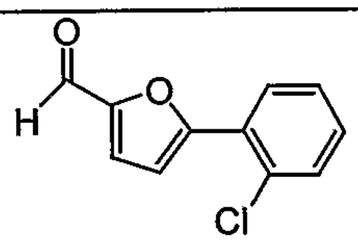
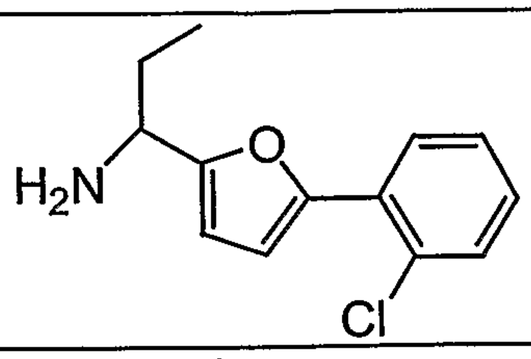
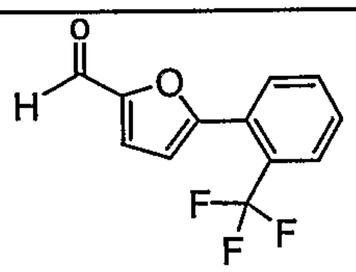
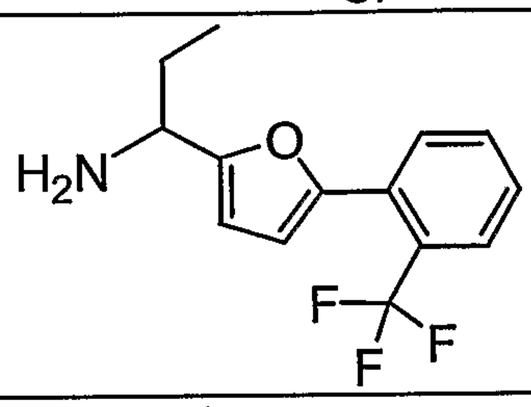
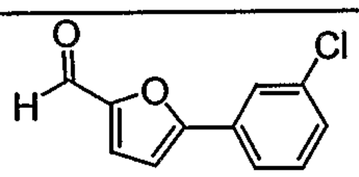
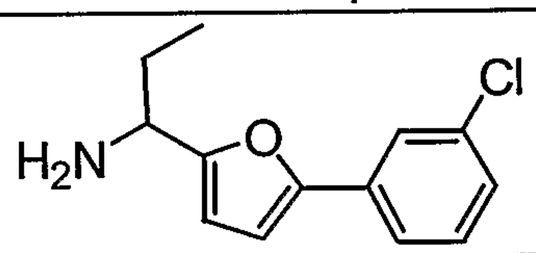
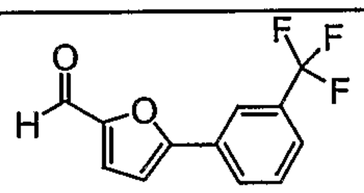
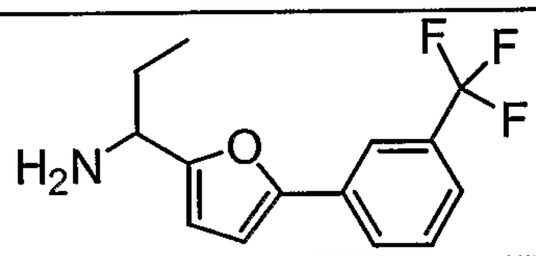
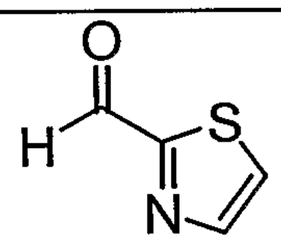
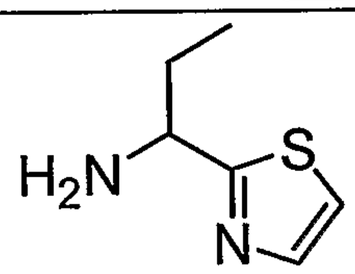
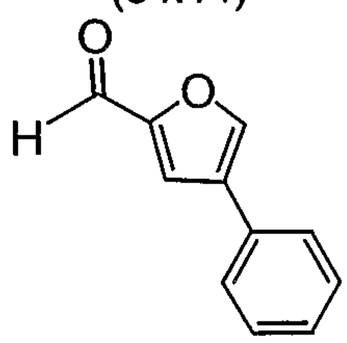
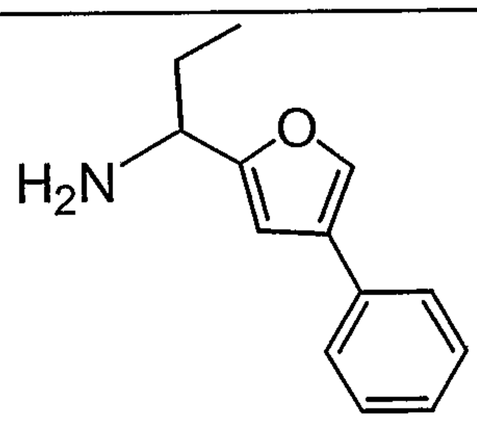
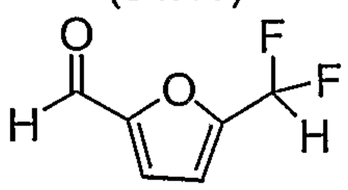
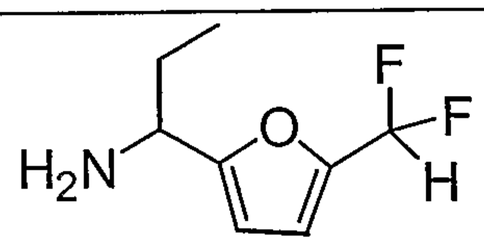
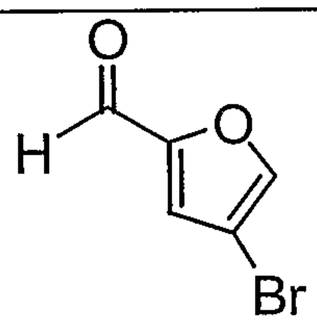
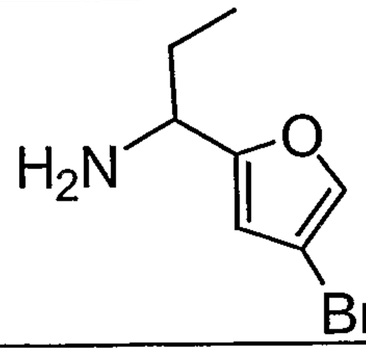
Step D

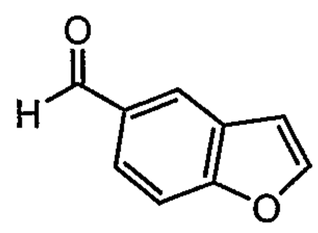
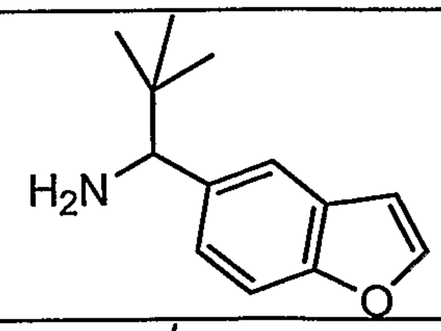
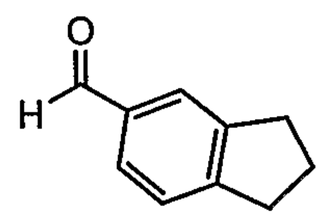
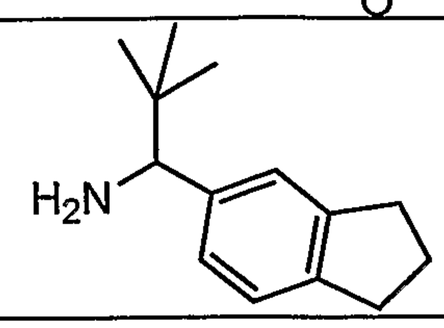
To a solution of azide in THF at -10°C was added $LiAlH_4$ portionwise. The heterogenous solution was stirred at room temperature for 1hr and then refluxed for 4hr. The solution was cooled to 0°C and water, 2M NaOH and ether were added to the reaction. The mixture was filtered through a celite pad. The filtrate was treated with 3N HCl. The aqueous layer was cooled to 0°C, basified with NaOH pellots and extracted with ether. The ether layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the product.

PREPARATIVE EXAMPLE 75.76-75.90

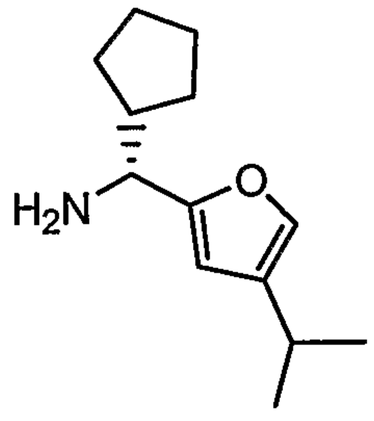
Following a similar procedure set forth in Preparative Example 75.75, and using the reduction procedure indicated, the following amines were obtained.

Prep Ex.	Aldehyde	Reducing Step	Product	% Yield
75.76		D		43
75.77		C		36
75.78		D		32
75.79		C		42
75.80		D		56
75.81		D		35

75.82		C		13
75.83		C		42
75.84		C		39
75.85		C		26
75.86		C		25
75.87		C		14
75.88	(34.14) 	C		49
75.89	(34.13) 	C		34
75.90		C		44

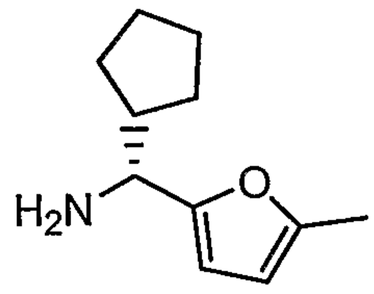
75.92		C		74
75.93		C		81

Preparative Example 75.200



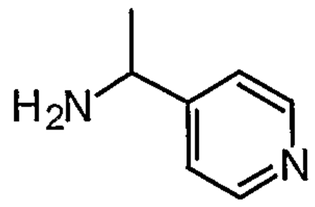
If one were to follow a similar procedure as that in Preparative Example 64, but using the aldehyde from Preparative Example 1004A and cyclopentyllithium instead of ethyllithium, the title aldehyde could be prepared.

Preparative Example 75.201



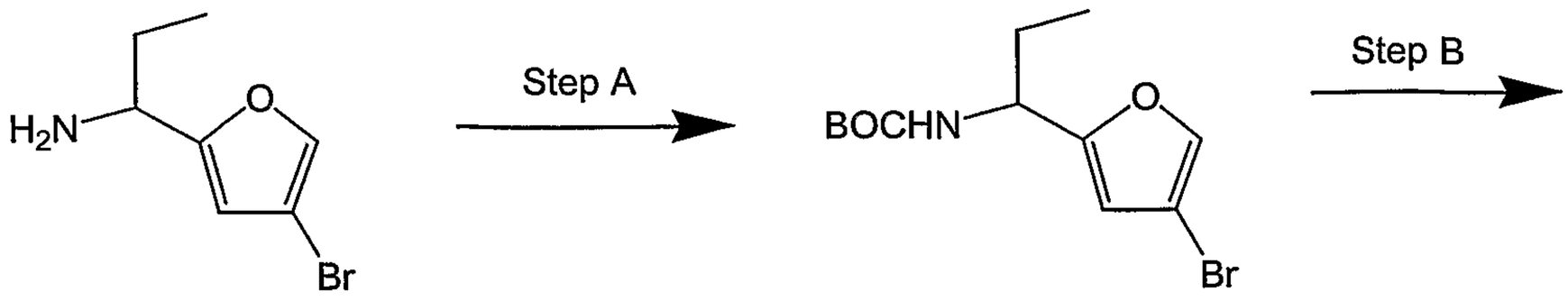
If one were to follow a similar procedure as in Preparative Example 75.200, but using 5-methylfuranaldehyde instead of the aldehyde from Preparative Example 1004A, the title aldehyde could be prepared.

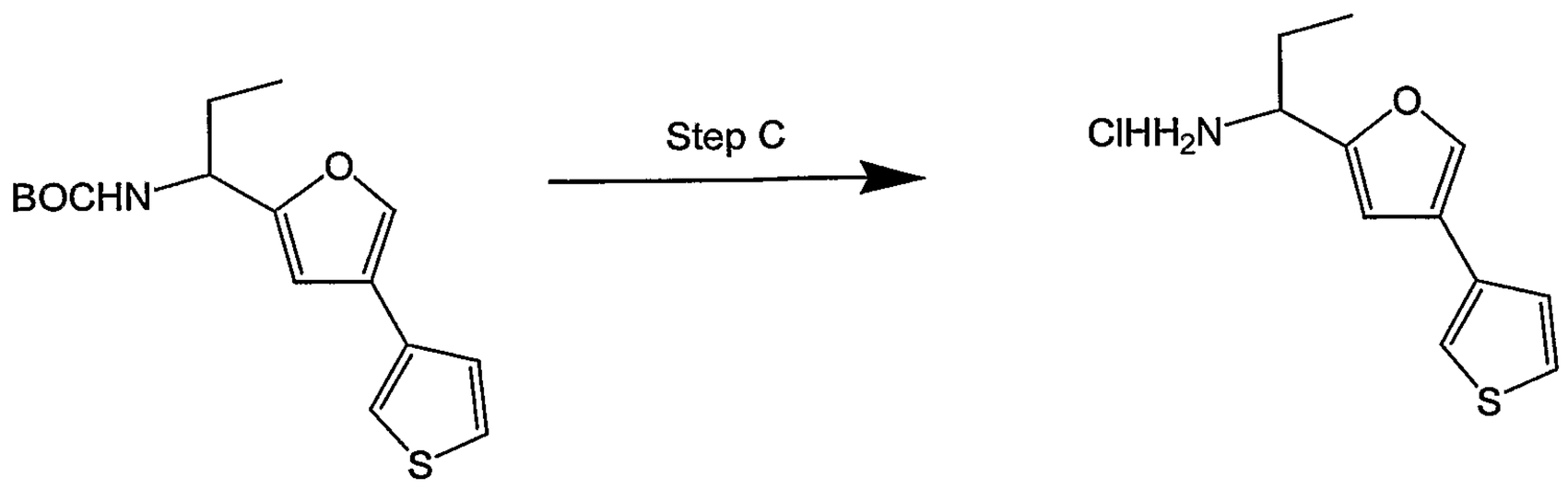
PREPARATIVE EXAMPLE 76



The desired compound was prepared according to methods previously described in *J. Med. Chem.* 1996, *39*, 3319-3323 (the disclosure of which is incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 76.1





Step A

To a solution of amine from Preparative Example 75.90 (2.22g) in CH_2Cl_2 (50ml) at 0°C was added TEA (3.03ml) followed by BOC_2O (2.85g). The heterogenous mixture was allowed to stir at room temperature overnight. 10% Citric acid was added to the reaction and the layers were separated. The organic layer was washed with saturated sodium bicarbonate, brine and dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (Hex/EtOAc 10:1) to afford 2.7g of an oil (81%).

Step B

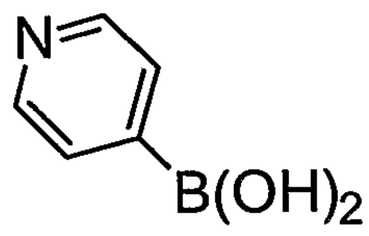
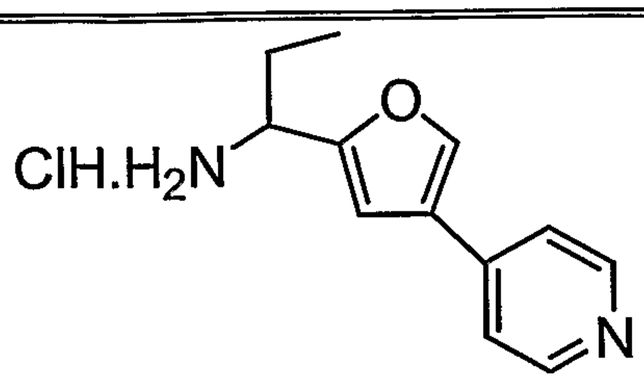
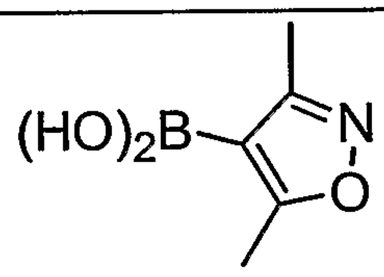
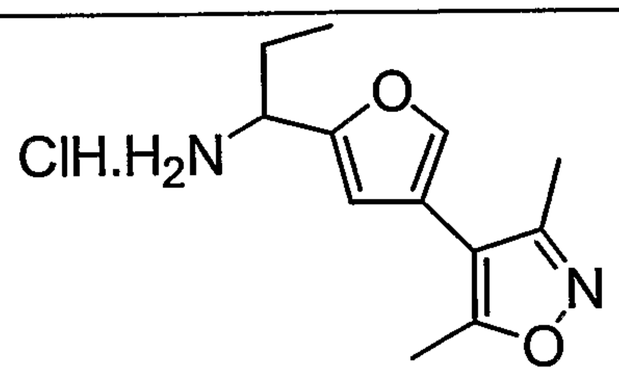
Following the procedure from Preparative Example 13.4, Step A, but using the product from Step A above (450mg) and 3-thiophene boronic acid (284mg), the product was prepared (325mg, 71%).

Step C

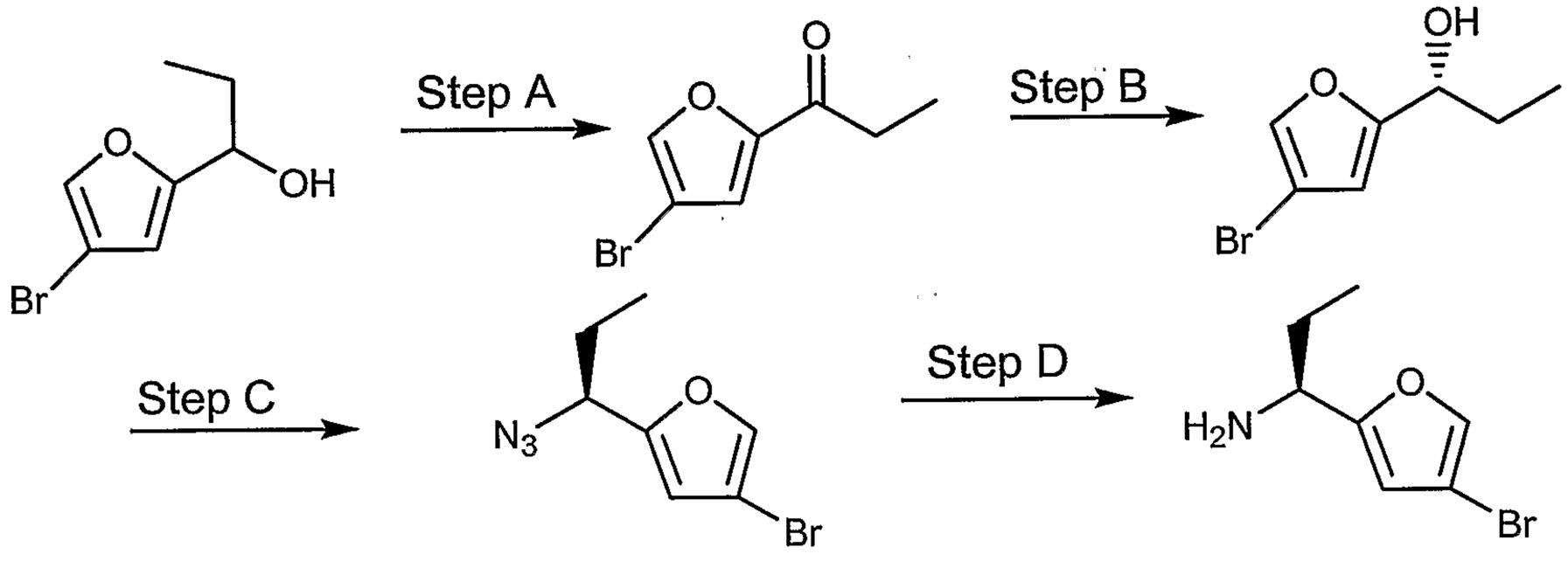
To the product from Step B (325g) was added 4M HCl in dioxane (1.31ml) and let stir for 1hr. The reaction was concentrated *in vacuo* and taken up in CH_2Cl_2 and concentrated *in vacuo* again. This procedure was repeated 5 times to afford a semisolid (89%).

PREPARATIVE EXAMPLE 76.2-76.3

Following the procedures set forth in Preparative Example 76.1, but using the commercially available boronic acids, the indicated amines were prepared.

Prep Ex.	Boronic Acid	Product	Yield (%)
76.2			70
76.3			35

PREPARATIVE EXAMPLE 76.10



Step A

The product from Preparative Example 75.75, Step A (2.5g) was reacted via the Preparative Example 13.11, Step B to give the ketone (1.93g, 78%).

Step B

To a solution of ketone from Step A above (500mg) in THF (5ml) at 0°C was added S-2-methyl-CBS-oxazaborolidine (0.98ml) dropwise followed by $BH_3.Me_2S$ (1.48ml). The mixture was stirred at 0°C for 2hr and was allowed to warm to room temperature and stir overnight. The mixture was cooled to 0°C and treated with MeOH (10ml). After stirring for 20min, the reaction was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with 1M HCl, saturated sodium

bicarbonate, water and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by preparative plate chromatography (Hex/EtOAc 4:1) to afford 650mg of an oil (89%).

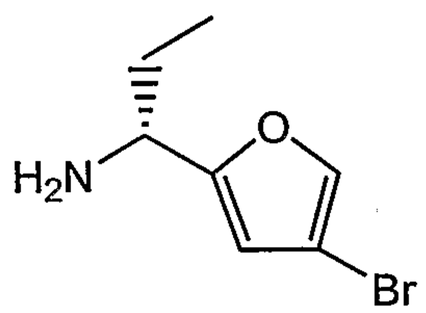
Step C

The chiral alcohol from Step B above was reacted via the Preparative Example 75.75 Step B to give the azide.

Step D

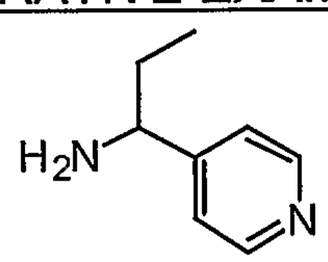
The azide from Step C above was reacted via the Preparative Example 75.75 Step C to give the amine product.

PREPARATIVE EXAMPLE 76.11



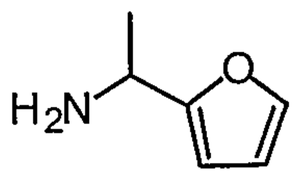
The desired compound was prepared as in Preparative Example 76.10, but using the R-2-methyloxazaborolidine in step B.

PREPARATIVE EXAMPLE 77



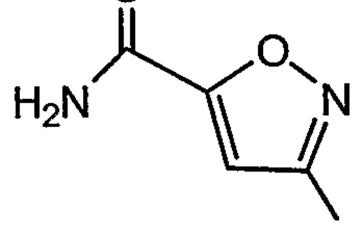
The desired compound was prepared according to methods previously described in *J. Med. Chem.* 1996, *39*, 3319-3323 (the disclosure of which is incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 78



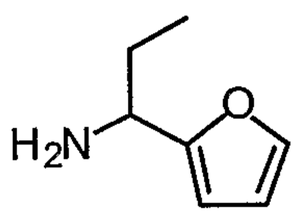
The desired compound was prepared according to methods previously described in *Chem. Pharm. Bull.* 1991, *39*, 181-183 (the disclosure of which is incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 78.1



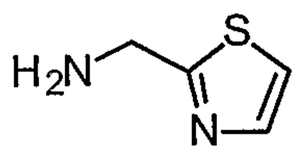
The desired compound was prepared according to methods previously described in J. Organometallic Chem. 1998, 567, 31-37 (the disclosure of which is incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 79



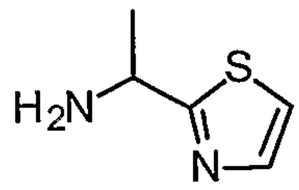
The desired compound was prepared according to methods previously described in *Chem. Pharm. Bull.* 1991, *39*, 181-183 (the disclosure of which is incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 80



The desired compound was prepared according to methods previously described in (a) *Synthesis* **1987**, 998-1001, (b) *Synthesis* **1996**, 641-646, and (c) *J. Med. Chem.* **1991**, *34*, 2176-2186 (the disclosures of each reference being incorporated herein by reference thereto).

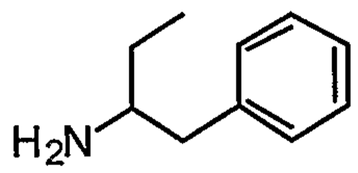
PREPARATIVE EXAMPLE 81



The desired compound was prepared according to methods previously described in (a) *Synthesis* **1987**, 998-1001, (b) *Synthesis* **1996**, 641-646 and

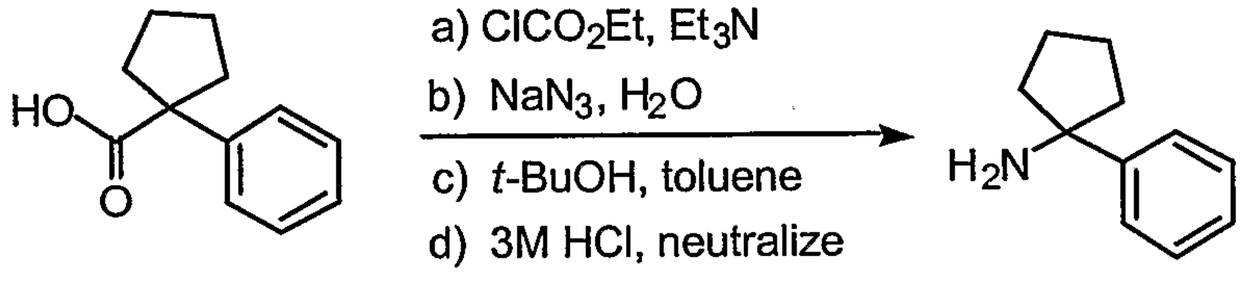
(c) *J. Med. Chem.* **1991**, *34*, 2176-2186 (the disclosures of each reference being incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 82



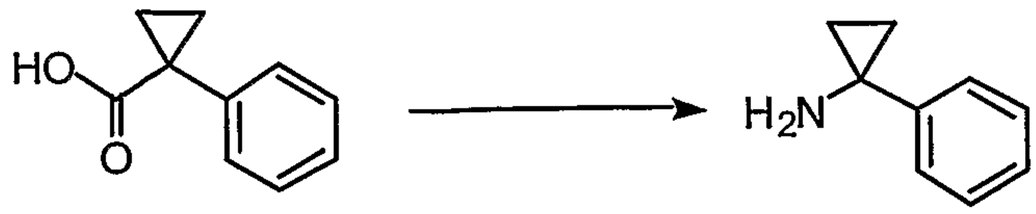
The desired compound was prepared according to methods previously described in *J. Med. Chem.* **1988**, *31*, 2176-2186 (the disclosure of which is incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 83



To a solution of carboxylic acid (1.5 g, 7.89 mmol) in H_2O/acetone (1:10/12 mL total) at 0°C was added Et_3N (1.43 mL, 10.3 mmol) followed by addition of ethyl chloroformate (0.83 mL, 8.68 mmol). The resulting mixture was stirred for 30 min after which a solution of NaN_3 (0.77g, 11.8 mmol) in H_2O (2 mL) was added dropwise. The resultant heterogenous mixture was stirred for 1 h at 0°C, then cold water (5 mL) and Et_2O (10 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, toluene (20 mL) was added, and the organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to a volume of 20 mL. *t*-BuOH (5 mL) was added and the mixture was refluxed for 12h. The mixture was concentrated under reduced pressure and the crude residue was taken up in 3M HCl (30 mL) and was heated at reflux for 12h. The mixture was cooled to room temperature and extracted with Et_2O (3 x 15 mL). The aqueous layer was cooled to 0 °C and solid NaOH pellets were added until pH ~12 was reached. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford 0.78 g (61% yield) of an oil [MH^+ 162]. This material was used without further purification.

PREPARATIVE EXAMPLE 84

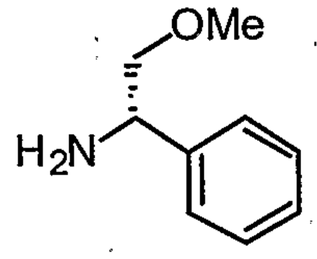


The corresponding cyclopropyl analog was prepared according to the procedure outlined in Preparative Example 83.

PREPARATIVE EXAMPLE 85

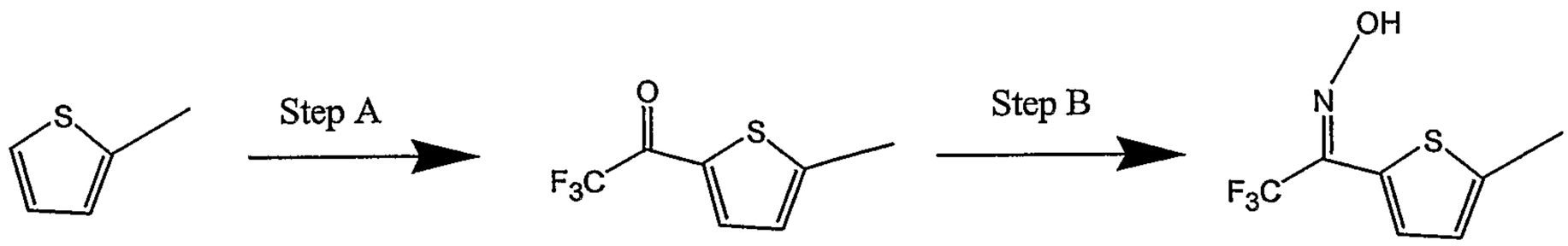
The corresponding cyclohexyl analog was prepared according to the procedure outlined in Preparative Example 83.

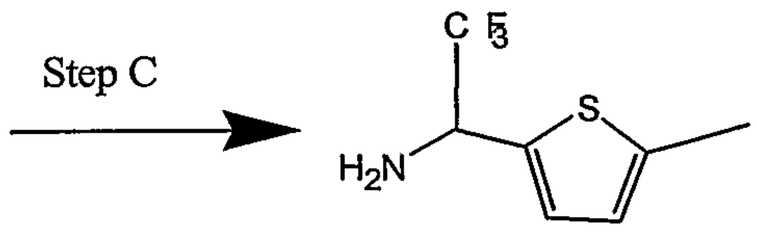
PREPARATIVE EXAMPLE 86



The desired compound was prepared according to methods previously described in *J. Org. Chem.* **1978**, *43*, 892-898 (the disclosure of which is incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 88.2





Step A

2-Methylthiophene (3g) was dissolved in THF and cooled to -40^{0}C. N-butyllithium (2.5M in hexane, 12.24ml) added dropwise and let stir at -40^{0}C for 30min. CuBr.$(CH_3)_2S$ (6.29g) added and let warm to -25^{0}C where the trifluoroaceticanhydride (4.32ml) was added. The reaction was stirred at -15^{0}C over the weekend. The reaction was quenched with saturated ammonium chloride and extracted with EtOAc. The organic layer washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 4.59g of an oil (78%).

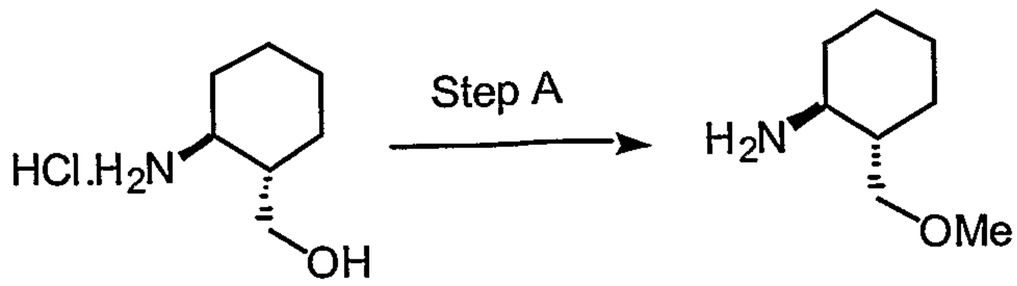
Step B

The product from Step A (4.58g), hydroxylamine hydrochloride (3g), sodium acetate (4.4g), EtOH (75ml) and H_2O (7.5ml) were combined and heated to 75^{0}C overnight. The reaction was concentrated *in vacuo* , taken up 1N HCl, extracted with ether, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 4.58g of the product (93%, MH+=210).

Step C

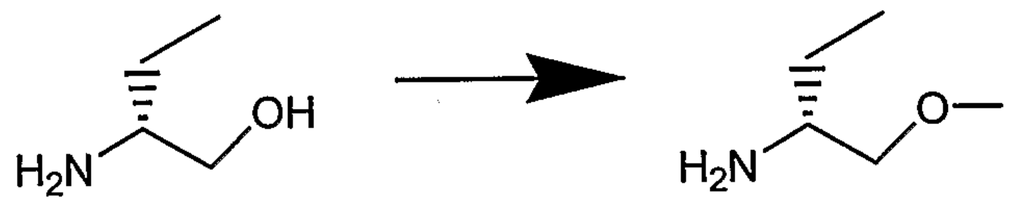
The product from Step B above (4.5g) was dissolved in TFA (40ml) and cooled to 0^{0}C. Zn powder (4.2g) was added portionwise and let reaction warm to room temperature and stir overnight. The reaction was concentrated *in vacuo*, taken up in 1N NaOH, extracted with ether, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 3.43g of the product (80%).

PREPARATIVE EXAMPLE 89



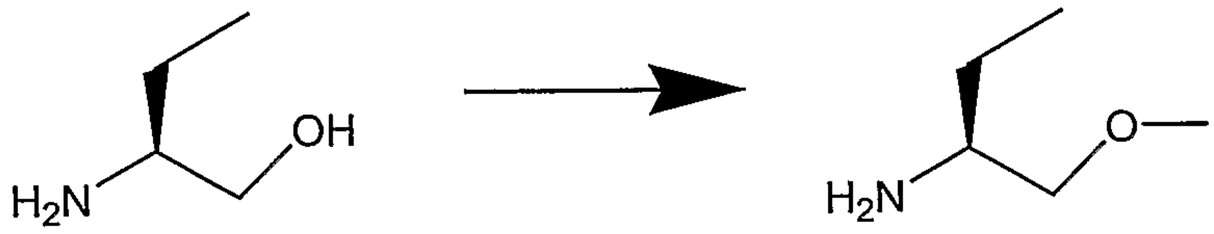
To a solution of KH (0.45 g, 11.3 mmol) in THF (15 mL) at room temperature was added amine hydrochloride (0.85 g, 5.1 mmol) portionwise to afford a heterogenous reaction mixture. The mixture was allowed to stand overnight (12h) and MeI (0.32 mL, 5.1 mmol) was added dropwise. The mixture was stirred for 6h after which the mixture was carefully poured into cold brine (125 mL). The mixture was extracted with Et_2O (3 x 25 mL) and the organic layers were combined. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the crude product as an oil. This material was carried on crude to the coupling step without further purification or characterization.

PREPARATIVE EXAMPLE 89.1



To a solution of KH (1.1g) in THF (20ml) at room temperature was added (R)-2-amino-1-butanol 48ml) dropwise to afford a heterogenous mixture. The mixture was allowed to stand overnight (18hr) and then MeI (1.59ml) was added dropwise. The mixture was stirred for 4hr after which brine was added. Extracted with ether, dried with K_2CO_3, filtered and concentrated *in vacuo* to afford 1.75g of an oil.

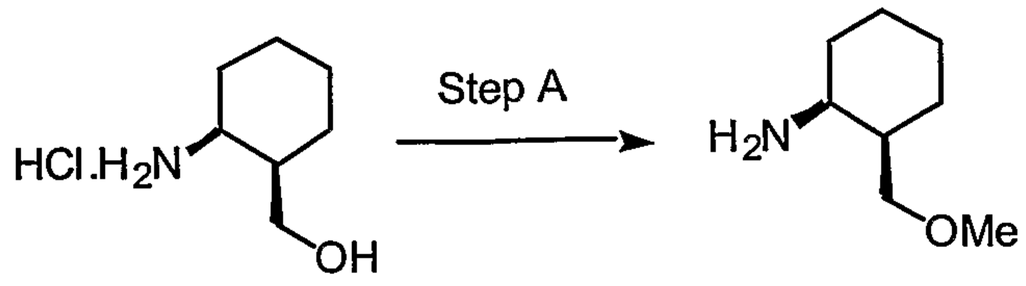
PREPARATIVE EXAMPLE 89.2



To a solution of KH (1.1g) in THF (20ml) at room temperature was added (S)-2-amino-1-butanol 48ml) dropwise to afford a heterogenous mixture. The mixture was allowed to stand overnight (18hr) and then MeI (1.59ml) was added dropwise.

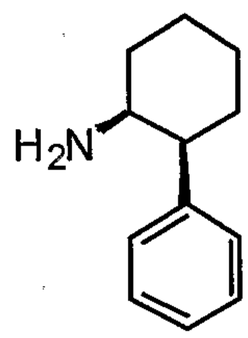
The mixture was stirred for 4hr after which brine was added. Extracted with ether, dried with K_2CO_3, filtered and concentrated *in vacuo* to afford 1.75g of an oil.

PREPARATIVE EXAMPLE 90



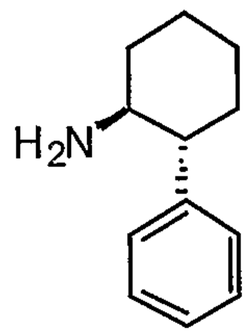
The corresponding *cis* analog was prepared in an analogous fashion utilizing the procedure described in Preparative Example 89. This material was also used without further purification.

PREPARATIVE EXAMPLE 91



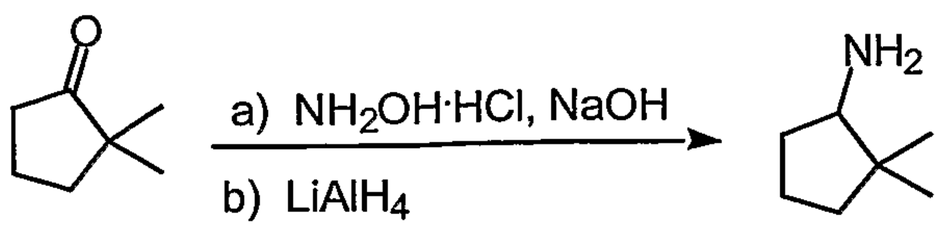
The desired compound was prepared according to methods previously described in *J. Org. Chem.* **1987**, *52*, 4437-4444 (the disclosure of which is incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 92



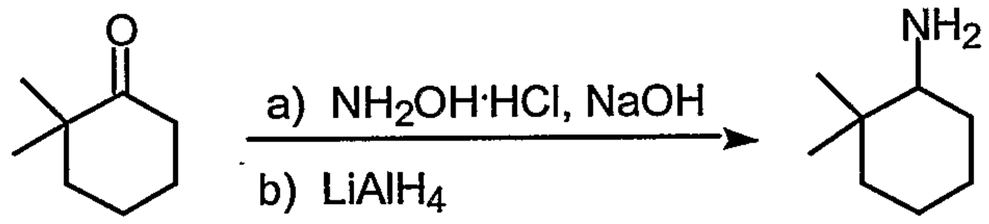
The desired compound was prepared according to methods previously described in *Bull. Chem. Soc. Jpn*. **1962**, *35*, 11-16 (the disclosure of which is incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 93



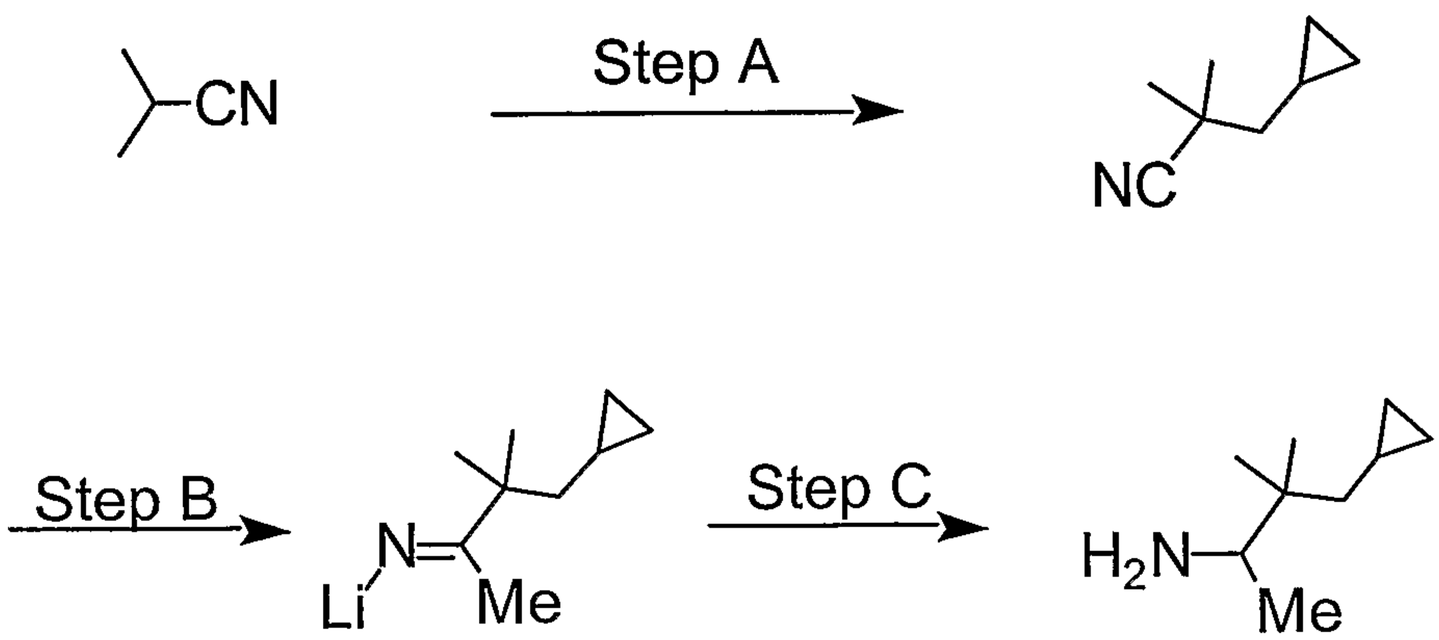
The desired amine was prepared from the corresponding ketone according to standard methods previously described in (a) *Synthesis* **1987**, 998-1001, (b) *Synthesis* **1996**, 641-646 and (c) *J. Med. Chem.* **1991**, *34*, 2176-2186 (the disclosures of each being incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 94



The desired amine was prepared from the corresponding ketone according to standard methods previously described in(a) *Synthesis* **1987**, 998-1001, (b) *Synthesis* **1996**, 641-646 and (c) *J. Med. Chem.* **1991**, *34*, 2176-2186 (the disclosures of each being incorporated herein by reference thereto).

PREPARATIVE EXAMPLE 95



Step A

Lithium hexamethyldisilylazide (34 mL, 1*M* in THF) was added dropwise to a –78°C THF (20 mL) solution of isobutyronitrile (2.8 mL). After 40 min, cyclopropyl-methylbromide (5 g) was added and the mixture warmed to and stirred at 25°C overnight. After cooling to 0°C, 1*M* HCl (aq) was added and the mixture was

extracted with diethyl ether, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* at 0°C to give the desired product (4.5 g).

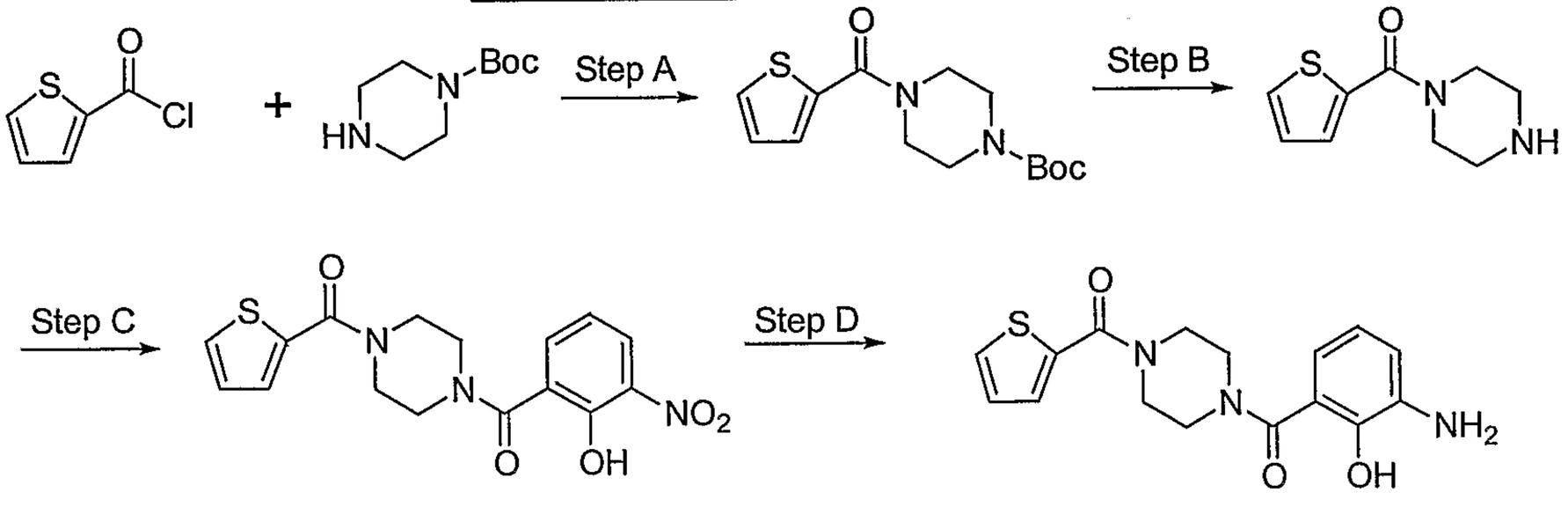
Step B

Methyl Lithium (17 mL, 1.4 *M* in Et_2O) was added to the product from Step A above (1.5 g) in Et_2O (anhydrous) at 0°C. The mixture was stirred at 0-25°C overnight, then diluted with 3*M* HCl (aq), extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* at 0°C and used directly in Step C.

Step C

The product from Step B above was added to a slurry of $NaBH_4$ (1.4 g) in isopropanol (50 mL) at 0°C, then the mixture was stirred at reflux for 8 hr and at room temperature for 48 hrs. Water was added and the mixture was stirred for 30 min, then extracted with diethyl ether, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 and extracted with 3M HCl. The organic phase was discarded and the aqueous phase was basified with NaOH (aq) and extracted with CH_2Cl_2. Drying over anhydrous Na_2SO_4, filtering, and concentration *in vacuo* gave the desired compound (0.5 g).

PREPARATIVE EXAMPLE 96



Step A

2-Thiophenecarbonyl chloride (2.0mL, 18.7mmol) was dissolved in 100mL dichloromethane. After addition of diisopropylethylamine (4.1mL, 23.4mmol) and Boc-piperazine (3.66g, 19.7mmol), the mixture was stirred for 4h at room temperature. The resulting mixture was put into water (500mL) and acidified with 3N HCl to pH~1. Extraction with dichloromethane (2x100mL) and drying over sodium sulfate resulted in sufficiently pure product that was used in the next step without any further purification.

^{1}H NMR (300MHz, d_6-DMSO) 1.60 (s, 9H), 3.29 (dd, 4H), 3.69 (dd, 4H), 7.23 (dd, 1H), 7.49 (d, 1H), 7.79 (d, 1H).

Step B

The crude material from Step A was dissolved in trifluoroacetic acid/dichloromethane (75mL, 4/1). After stirring for 2h, the reaction mixture was put into 1N sodium hydroxide (400mL). Extraction with dichloromethane (2x100mL) and drying over sodium sulfate resulted in sufficiently pure product that was used in Step C without any further purification. ^{1}H NMR (300MHz, d_6-DMSO) 2.81 (dd, 4H), 3.63 (dd, 4H), 7.21 (dd, 1H), 7.46 (d, 1H), 7.82 (d, 1H).

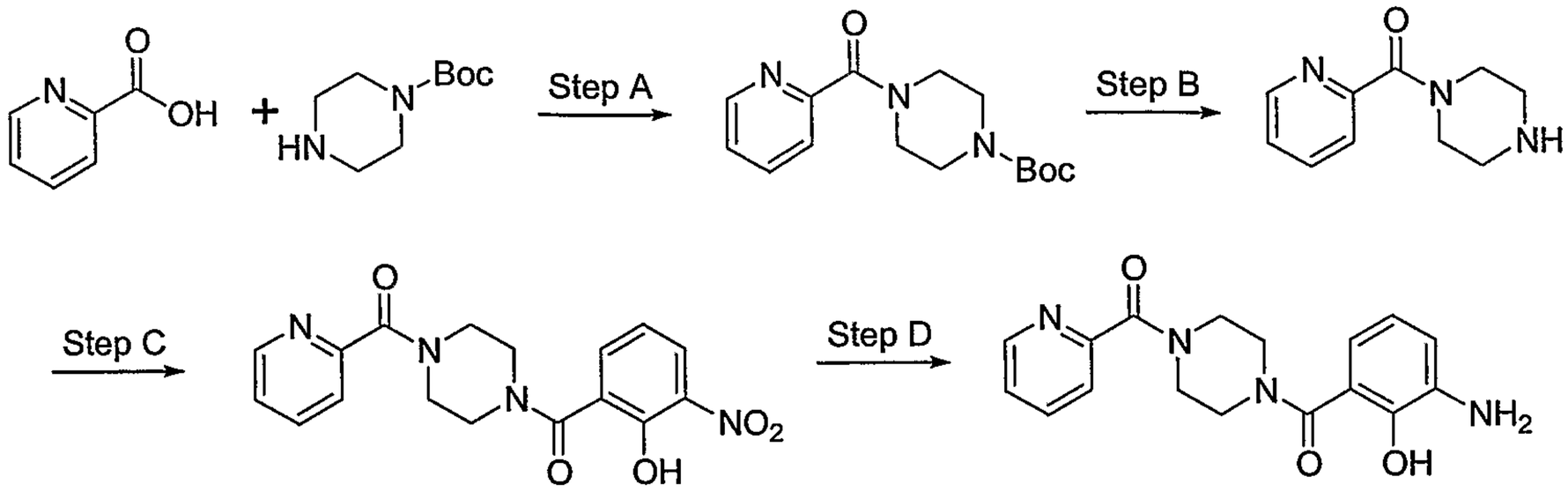
Step C

The crude material (3.50g, 17.8mmol) from Step B was dissolved in dichloromethane (100mL). After addition of diisopropylethylamine (18.7mL, 107mmol), 3-nitrosalicylic acid (3.3g, 18.0mmol), and PyBrOP (10.4g, 22.3mmol), the resulting mixture was stirred over night at room temperature before being put into 1N sodium hydroxide (200mL). Extraction with dichloromethane (2x200mL) removed all PyBrOP by-products. The aqueous phase was acidified with 3N HCl and subsequently extracted with dichloromethane (3x 100mL). The combined organic phases of the acidic extraction were dried over sodium sulfate, concentrated, and finally purified by column chromatography (dichloromethane/methanol = 10/1) to yield the desired product (2.31g, 34 % over 3 steps). ^{1}H NMR (300MHz, d_6-DMSO) 3.30-3.90 (m, 8H), 7.10-8.20 (m, double signals due to E/Z-isomers, 6H), 10.82 (s, 1H).

Step D

The nitro-compound (2.3g, 6.4mmol) from Step C was dissolved in methanol (50mL) and stirred with 10% Pd/C under a hydrogen gas atmosphere over night. The reaction mixture was filtered through Celite and washed thoroughly with methanol. Finally, the filtrate was concentrated *in vacuo* and purified by column chromatography (dichloromethane/methanol = 10/1) to yield the desired product (1.78g, 84%). ^{1}H NMR (300MHz, d_6-DMSO) 3.30-3.90 (m, 8H), 7.22 (m, 2H), 7.55 (d, 1H), 7.71 (d, 1H), 7.88 (d, 1H), 8.15 (d, 1H), 10.85 (bs, 1H).

PREPARATIVE EXAMPLE 97



Step A

Picolinic acid (3.0g, 24.3mmol) was suspended in $SOCl_2$ (15mL). After addition of dimethylformamide (5 drops), the reaction mixture was stirred for 4 hours. Evaporation of the solvent yielded the corresponding acid chloride as HCl-salt. Without any further purification, the solid was suspended in 120mL dichloromethane. After addition of diisopropylethylamine (12.7mL, 73mmol) and Boc-piparazine (4.8g, 25.5mmol), the reaction was stirred over night at room temperature. The resulting mixture was put into water (500mL) and extracted with dichloromethane (2x100mL). Drying over sodium sulfate resulted in sufficiently pure product that was used in Step B without any further purification. ^{1}H NMR (300MHz, d_6-DMSO) 1.63 (s, 9H), 3.21 (dd, 4H), 3.61 (dd, 4H), 7.57 (dd, 1H), 7.63 (d, 1H), 7.98 (dd, 1H), 8.70 (d, 1H).

Step B

The crude material from Step A was dissolved in trifluoroacetic acid/dichloromethane (75mL, 4/1). After stirring for 2days, the reaction mixture was put into 1N sodium hydroxide (400mL). Extraction with dichloromethane (2x100mL) and drying over sodium sulfate resulted in sufficiently pure product that was used in Step C without any further purification. ^{1}H NMR (300MHz, d_6-DMSO) 2.77 (dd, 2H), 2.83 (dd, 1H), 3.38 (dd, 2H), 3.64 (dd, 1H), 7.58 (dd, 1H), 7.62 (d, 1H), 8.00 (dd, 1H), 8.67 (d, 1H).

Step C

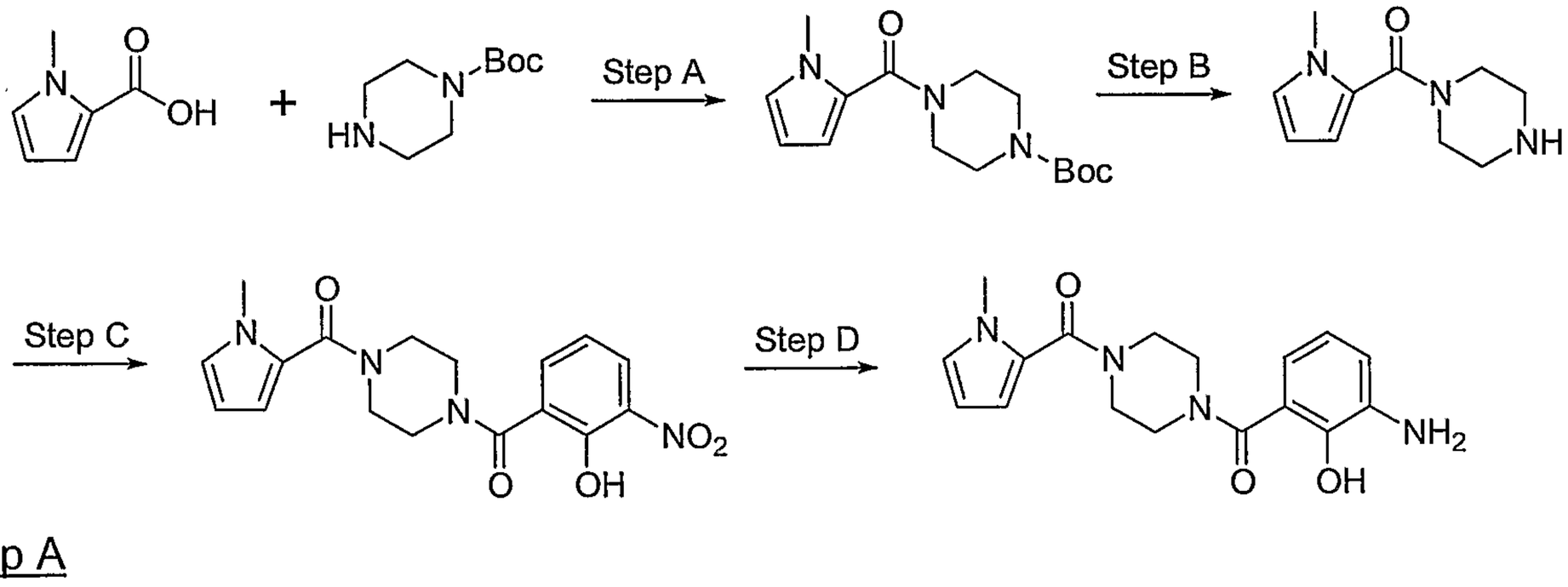
The crude material (1.35g, 7.06mmol) from Step B was dissolved in dichloromethane (50mL). After addition of diisopropylethylamine (3.7mL, 21.2mmol), 3-nitrosalicylic acid (1.36g, 7.41mmol), and PyBrOP (3.62g, 7.77mmol), the resulting mixture was stirred over night at room temperature before being put into 1N sodium

hydroxide (300mL). Extraction with dichloromethane (2x100mL) removed any PyBrOP products. The aqueous phase was acidified with 3N HCl. Adjustment of the pH with saturated sodium carbonate solution to almost neutral crushed the desired compound out of solution. The aqueous phase was subsequently extracted with dichloromethane (3x 100mL). The combined organic layers of the neutral extraction were dried over sodium sulfate, concentrated, and finally purified by column chromatography (dichloromethane/methanol = 20/1) to yield the desired product (1.35g, 16% over 3 steps). ^{1}H NMR (300MHz, d_6-DMSO) 3.30-3.95 (m, 8H), 7.22 (m, 1H), 7.61 (m, 1H), 7.73 (d, 2H), 8.03 (m, 1H), 8.17 (m, 1H), 8.69 (m, 1H), 10.82 (s, 1H).

Step D

The nitro-compound (1.35g, 3.79mmol) from Step C was dissolved in methanol (60mL) and stirred with 10% Pd/C under a hydrogen gas atmosphere over night. The reaction mixture was filtered through Celite and washed thoroughly with methanol. Finally, the filtrate was concentrated *in vacuo* and purified by column chromatography (dichloromethane/methanol = 20/1) to yield the desired product (1.10g, 89 %). ^{1}H NMR (300MHz, d_6-DMSO) 3.50-3.85 (m, 8H), 6.47 (dd 1H), 6.74 (m, 2H), 7.59 (dd, 1H), 7.71 (d, 1H), 8.04 (dd, 1H), 8.68 (d, 1H).

PREPARATIVE EXAMPLE 98



Step A

1-Methyl-2-pyrrolecarboxylic acid (2.5g, 20.0mmol) was dissolved in dichloromethane (50mL). After addition of PyBrOP (16.3g, 35.0mmol), diisopropylethylamine (14.0mL, 73.0mmol) and Boc-piparazine (5.5g, 30.0mmol), the reaction was stirred over night at room temperature before being put into 1N sodium

hydroxide (200mL). Extraction with dichloromethane (2x100mL) removed all PyBrOP by-products. The aqueous phase was acidified with 3N HCl. Adjustment of the pH with saturated sodium carbonate solution to almost neutral precipitated the desired compound. The aqueous phase was subsequently extracted with dichloromethane (3x 100mL). The combined organic phases of the neutral extraction were dried over sodium sulfate. Removal of the solvent resulted in sufficiently pure product that was used in Step B without any further purification. ^{1}H NMR (300MHz, d_6-DMSO) 1.59 (s, 9H) 3.21 (dd, 4H), 3.61 (dd, 4H), 3.74 (s, 3H), 6.11 (dd, 1H), 6.33 (d, 1H), 7.01 (d, 1H).

Step B

The crude material from Step A was dissolved in trifluoroacetic acid/dichloromethane (75mL, 4/1). After stirring for 3h, the reaction mixture was put into 1N sodium hydroxide (400mL). Extraction with dichloromethane (3x100mL) and drying over sodium sulfate resulted in sufficiently pure product that was used in Step C without any further purification. ^{1}H NMR (300MHz, d_6-DMSO) 2.79 (dd, 4H), 3.62 (dd, 4H), 3.76 (s, 3H), 6.11 (dd, 1H), 6.37 (d, 1H), 6.96 (d, 1H).

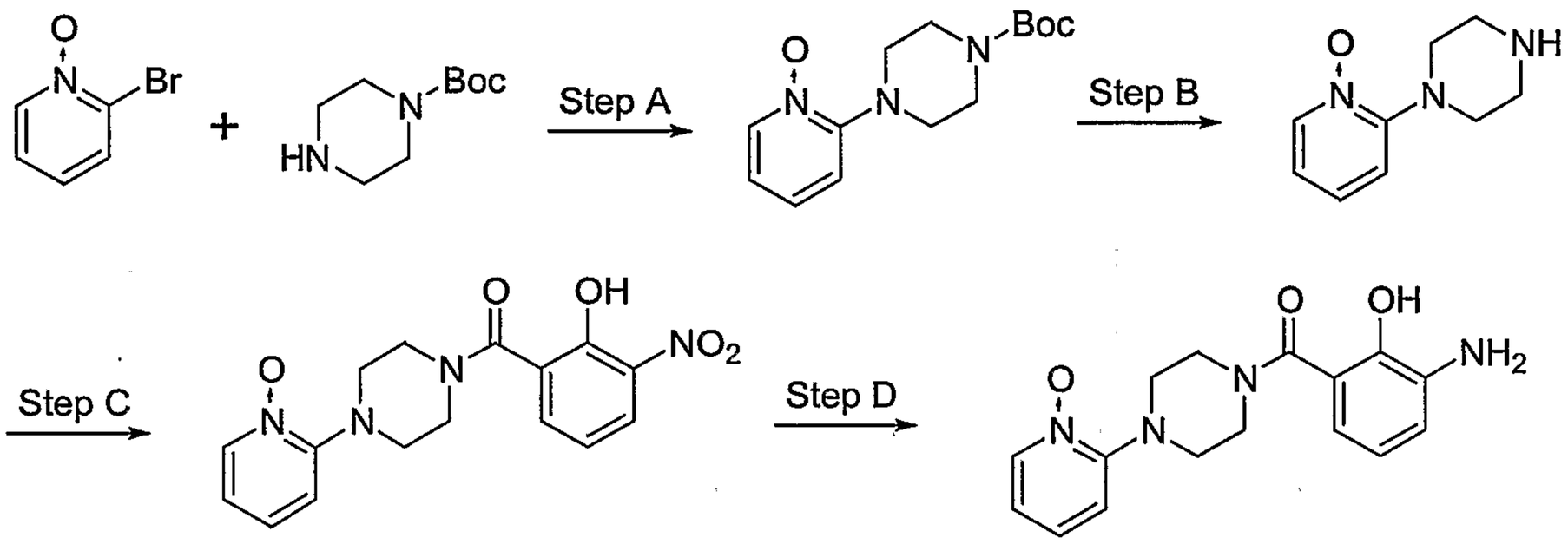
Step C

The crude material (3.15g, 16.3mmol) from Step B was dissolved in dichloromethane (100mL). After addition of diisopropylethylamine (8.5mL, 49.0mmol), 3-nitrosalicylic acid (3.13g, 17.1mmol), and PyBrOP (9.11g, 19.6mmol), the resulting mixture was stirred over night at room temperature before being put into 1N sodium hydroxide (400mL). Extraction with dichloromethane (2x100mL) removed all PyBrOP products. The aqueous phase was then carefully acidified with 3N HCl until the color of the solution changes from orange to yellow and the desired compound crashed out of solution. The aqueous phase was subsequently extracted with dichloromethane (3x 100mL). The combined organic layers of the acidic extraction were dried over sodium sulfate and concentrated *in vacuo* to yield the desired product. ^{1}H NMR (300MHz, d_6-DMSO) 3.35-3.85 (m, 8H), 3.79 (s, 3H), 6.13 (dd, 1H), 6.45 (d, 1H), 7.01 (s, 1H), 7.22 (dd, 1H), 7.70 (d, 1H), 8.16 (d, 1H), 10.83 (s, 2H).

Step D

The crude nitro-compound from Step C was suspended in methanol (60mL) and stirred with 10% Pd/C under a hydrogen gas atmosphere over night. The reaction mixture was filtered through Celite and washed thoroughly with methanol. The filtrate was concentrated *in vacuo* and purified by column chromatography (dichloromethane/methanol = 10/1) to yield the desired product (2.61g, 40 % for 4 steps). ^{1}H NMR (300MHz, d_6-DMSO) 3.45-4.80 (m, 8H), 3.79 (s, 3H), 6.17 (dd, 1H), 6.45 (m, 2H), 6.78 (m, 2H), 7.01 (d, 1H).

PREPARATIVE EXAMPLE 99



Step A

2-Bromopyridine N-oxide hydrochloride (1.13g, 5.37mmol) and Boc-piperazine (1.50g, 8.06mmol) were heated to 80° C in pyridine (10mL) over night. The reaction mixture was put into water (300mL) and then extracted with dichloromethane (2x100mL). The combined organic phases were dried over sodium sulfate, concentrated, and finally purified by column chromatography (dichloromethane/methanol = 10/1) to yield the desired product (500mg, 33 %). ^{1}H NMR (300MHz, d-$CDCl_3$) 1.60 (s, 9H), 3.46 (dd, 4H), 3.78 (dd, 4H), 6.99 (m, 2H), 7.37 (dd, 1H), 8.33 (d, 1H).

Step B

The purified product (500mg, 1.79mmol) was stirred for 30 min with 4N HCl/dioxane (15mL). Evaporation of the solvent yielded the crude amine (465mg) as multiple HCl-salt which was used in Step C without any further purification. ^{1}H NMR (300MHz, d_6-DMSO) 3.38 (m, 4H), 4.81 (m, 4H), 7.34 (dd, 1H), 7.55 (d, 1H), 7.86 (dd, 1H), 8.55 (d, 1H).

Step C

The crude material (370mg, 1.48mmol) from Step B was suspended in dichloromethane (20mL). After addition of diisopropylethylamine (2.6mL, 14.8mmol), 3-nitrosalicylic acid (406mg, 2.22mmol), and PyBrOP (1.21g, 2.59mmol), the mixture was stirred over night at room temperature before being put into 1N sodium hydroxide (50mL). Extraction with dichloromethane (2x50mL) removed all PyBrOP products. The aqueous phase was then carefully acidified (pH ~ 4-5) with 3N HCl and extracted with dichloromethane (3x 50mL). The combined organic layers of the acidic extraction were dried over sodium sulfate, concentrated *in vacuo* and purified by column chromatography (dichloromethane/methanol = 10/1) to yield the desired product (330mg, 65%).

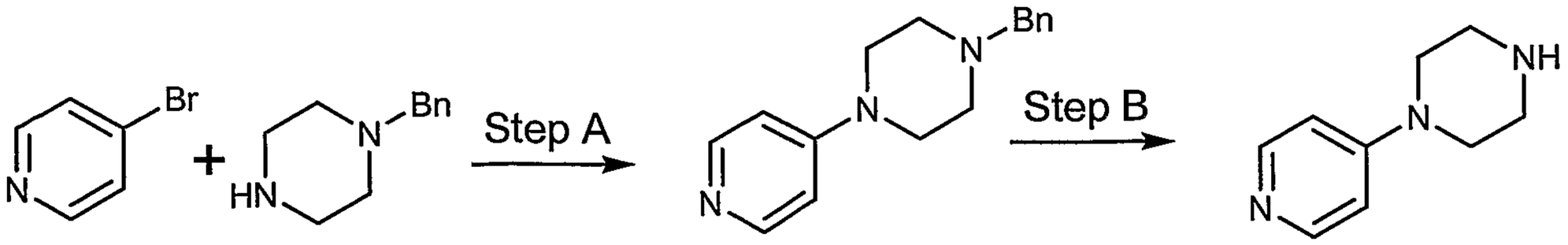
LCMS calculated: 344.1, found: $(M+1)^+$ 345.1

Step D

Sodium hydrosulfite (1.05g) was dissolved in water (3.0mL) to yield a 1.5N solution. Addition of dioxane (3.0mL) was followed by injection of conc. ammonium hydroxide (0.60mL, yields a 1.0N concentration). After addition of the nitro-compound (100mg, 0.29mmol), the reaction mixture was stirred for 0.5h. Subsequently, the solvent was removed and the residue suspended in dichloromethane/methanol (10/1). Filtration through Celite removed most of the salts. Final purification by column chromatography (dichloromethane/methanol = 5/1) yielded the desired product (68mg, 75%).

LCMS calculated: 314.14, found: $(M+1)^+$ 315.1

PREPARATIVE EXAMPLE 100



Step A

4-Bromopyridine hydrochloride (3.0g, 15.4mmol) was dissolved in water (15mL). After addition of N-benzylpiperazine (14.8mL, 85.0mmol) and 500mg copper sulfate, the reaction mixture was heated overnight to 140° C. The resulting product was extracted with ether (5x75mL), dried over sodium sulfate and concentrated. Final purification by column chromatography (dichloromethane/methanol/NH_4OH = 10/1/0.1) yielded the desired product (2.16g, 55%). ^1H NMR (300MHz, d-$CDCl_3$) 2.68 (dd, 4H), 3.45 (dd, 4H), 6.76 (d, 2H), 7.40 (m, 5H), 8.38 (d, 2H).

Step B

The benzylamine (2.16g, 8.54mmol) from Step A, ammonium formate (2.71g, 43.0mmol) and Pd(C) (10%, 1.0g) was suspended in methanol (50mL) and refluxed for 3h. The palladium was filtered off and the filtrate was concentrated. The sufficiently pure product was used in Step C without any further purification. ^1H NMR (300MHz, d-$CDCl_3$) 2.48 (bs, 1H), 3.13 (dd, 4H), 3.41 (dd, 4H), 7.78 (d, 2H), 8.39 (d, 2H).

Step C

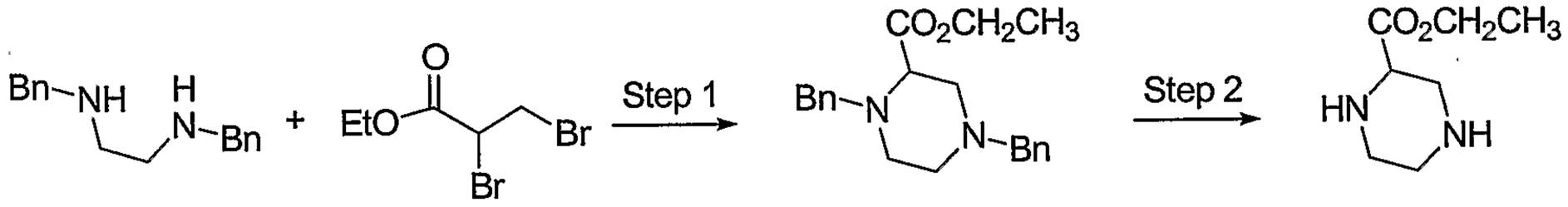
The crude material (1.15g, 7.06mmol) from Step B was dissolved in dichloromethane (50mL). After addition of diisopropylethylamine (4.7mL, 42.4mmol), 3-nitrosalicylic acid (1.94g, 10.6mmol), and PyBrOP (5.78g, 12.3mmol), the resulting mixture was stirred over night at room temperature before being put into 1N sodium hydroxide (300mL). Extraction with dichloromethane (2x100mL) removed all PyBrOP products. The aqueous phase was carefully acidified to pH ~ 5-6 with 3N HCl and

extracted with dichloromethane (3x 100mL). The combined organic layers of the neutral extraction were dried over sodium sulfate, concentrated, and finally purified by column chromatography (dichloromethane/methanol/NH_4OH = 10/1/0.1) to yield the desired product (850mg, 37% for 2 steps).

Step D

The nitro-compound (850mg, 2.59mmol) from Step C was dissolved in methanol (40mL) and stirred with 10% Pd/C under a hydrogen gas atmosphere over night. The reaction mixture was filtered through Celite and washed thoroughly with methanol. Finally, the filtrate was concentrated *in vacuo* and purified by column chromatography (dichloromethane/methanol/
NH_4OH = 10/1/0.1) to yield the desired product (650g, 84 %). ^1H NMR (300MHz, d_6-DMSO) 3.40-3.75 (bm, 8H), 6.49 (dd, 1H), 6.76 (m, 2H), 6.93 (d, 2H), 8.28 (d, 2H).

PREPARATIVE EXAMPLE 101



Step 1

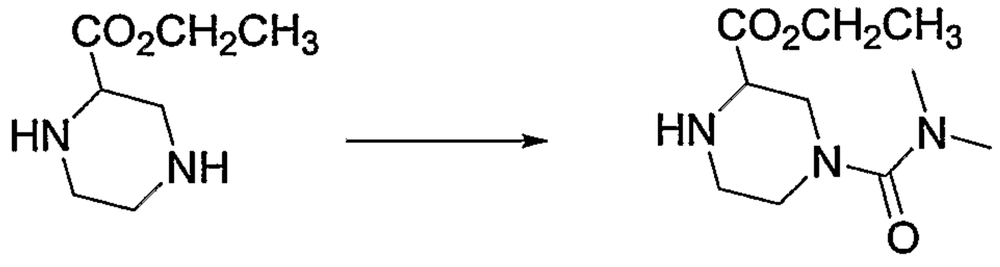
N,N'-Dibenzyl-ethane-1,2-diamine (20mL, 0.0813mol), triethylamine (22.66mL, 0.1626mol) and benzene (100mL) were combined in a round bottom flask. A solution of 2,3-dibromo-propionic acid ethyl ester (11.82mL, 0.0813mol) in benzene (50mL) was added dropwise. The solution was refluxed over night and monitored by TLC (20% ethyl acetate/hexane). The reaction was cooled to room temperature, then filtered and washed with benzene. The filtrate was concentrated then purified by column chromatography (15% ethyl acetate/hexane). The product was isolated as an oil (25.42g, 0.0752mol, 92%). MS: calculated: 338.20, found: 339.2
^1H NMR (300 MHz, $CDCl_3$) 1.23 (t, 3H), 2.48 (m, 3H), 2.62 (m, 1H), 2.73 (m, 1H), 3.07 (m, 1H), 3.30 (m, 1H), 3.42 (d, 1H), 3.56 (m, 2H), 3.91 (d, 1H), 4.17 (m, 2H), 7.27 (m, 10H).

Step 2

In a Parr shaker vessel, the ester (25.43g, 0.075mol) and methanol (125mL) were combined. The vessel was purged with argon and palladium catalyst (5% on carbon, 2.5g) was added. The system was shaken under an atmosphere of hydrogen overnight. TLC (20% ethyl acetate/hexane) indicated that reaction was complete. The reaction mixture was filtered through a pad of Celite and washed with methanol. The filtrate was concentrated and the product isolated as a solid (11.7g, 0.074mol, 98%).

MS: calculated: 158.11, found:159.2 ^{1}H NMR (300 MHz, $CDCl_3$) 1.27 (t, 3H), 2.70 (m, 4H), 2.96 (m, 1H), 3.13 (dd, 1H), 3.43 (dd, 1H), 4.18 (m, 2H).

PREPARATIVE EXAMPLE 102



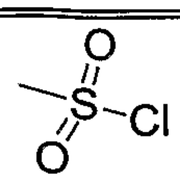
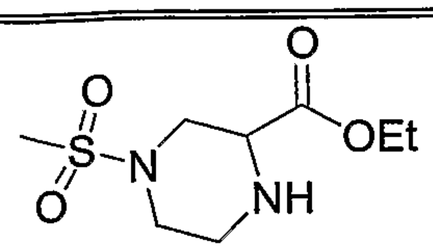
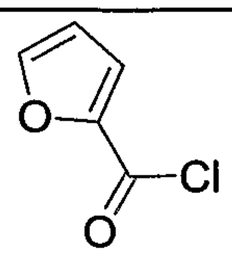
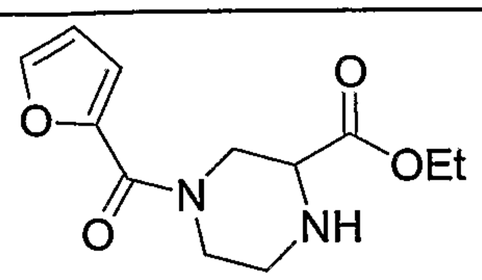
Piperazine-2-carboxylic acid ethyl ester (3.11g, 0.0197mol), diisopropylethylamine (5.15mL, 0.0296mol) and methylene chloride (200mL) were combined in a round bottom flask. While stirring at room temperature, a solution of N,N-dimethylcarbamoyl chloride (1.81mL, 0.0197mol) in methylene chloride (20mL) was added dropwise. The reaction was stirred for one hour. After this time the reaction was concentrated and carried on to the next step without further purification. (99% yield).

MS: calculated: 229.14, found:230.1

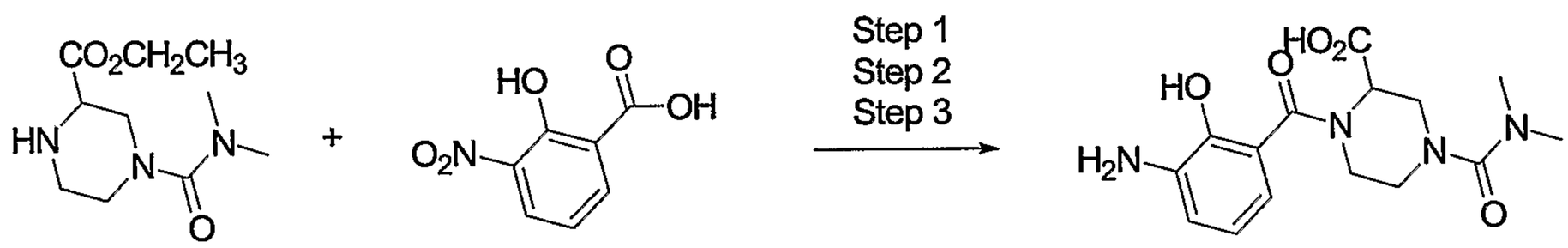
^{1}H NMR (300 MHz, $CDCl_3$) 1.30 (t, 3H), 2.85 (s, 6H), 3.10 (m, 3H), 3.31 (m, 2H), 3.60 (m, 2H), 4.21 (q, 2H).

PREPARATIVE EXAMPLE 103-104

Following the procedure described for Preparative Example 102, the Products listed in the table below were prepared using the commercially available chloride shown and piperazine-2-carboxylic acid ethyl ester from Preparative Example 101.

Example	Chloride	Product	1.Yield (%) 2. $(M+1)^+$
103			1. 99 2. 237.1
104			1. 62 2. 253.1

PREPARATIVE EXAMPLE 105



Step 1

3-Nitrosalicylic acid (3.61g, 0.0197g), DCC (2.03g, 0.0099mol) and ethyl acetate (130mL) were combined in a round bottom flask and stirred for 15min. 4-Dimethylcarbamoyl-piperazine-2-carboxylic acid ethyl ester (4.51g, 0.0197g) was added, and the reaction was stirred for 72 hours. The reaction mixture was concentrated then dissolved in dichloromethane. The organic phase was washed once with 0.1N sodium hydroxide. The aqueous phase was back extracted once with dichloromethane. The aqueous phase was acidified and wash three times with ethyl acetate. The aqueous phase was concentrated and purified by column chromatography (5% methanol/DCM).

MS: calculated: 394.15, found:395.0

^{1}H NMR (300 MHz, $CDCl_3$) 1.32 (t, 3H), 2.86 (m, 7H), 3.15 (m, 1H), 3.51 (m, 4H), 4.24 (m, 3H), 7.15 (m, 1H), 7.66 (m, 1H), 8.20 (m, 1H), 10.86 (bs, 1H).

Step 2

4-Dimethylcarbamoyl-1-(2-hydroxy-3-nitro-benzoyl)-piperazine-2-carboxylic acid ethyl ester (0.80g, 0.002mol) and methanol (50mL) were combined in a round bottom flask. The system was purged with argon. To the solution was added 5% palladium on carbon (~100mg). The flask was purged with hydrogen and stirred

overnight. The reaction was filtered through a pad of celite and washed with methanol. The material was concentrated then purified by column chromatography (6% methanol/DCM). Isolated product (0.74g, 0.002mol, 100%).

MS: calculated: 364.17, found:365.1

^{1}H NMR (300 MHz, $CDCl_3$) 1.27 (t, 3H), 2.85 (m, 8H), 3.18 (1H), 3.45 (m, 3H), 4.19 (m, 3H), 3.90 (m, 3H)

Step 3

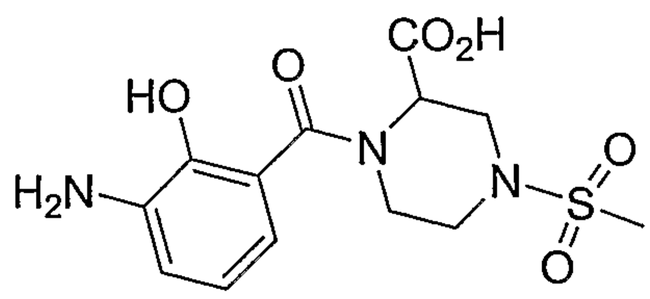
1-(3-Amino-2-hydroxy-benzoyl)-4-dimethylcarbamoyl-piperazine-2-carboxylic acid ethyl ester (0.74g, 0.002mol) was suspended in a solution of dioxane (10mL) and water (10mL). Lithium hydroxide (0.26g, 0.0061mol) was added and the mixture stirred for two hours. The solution was acidified to pH=6 with 3N HCl then extracted with butanol. The extracts were combined, dried over sodium sulfate and concentrated.

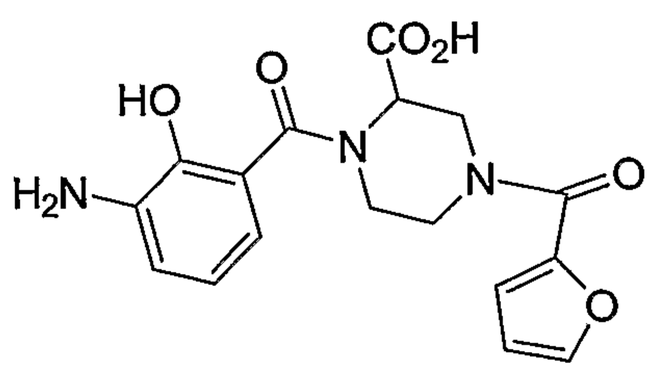
MS: calculated: 336.14, found:337.1

^{1}H NMR (300 MHz, CD_3OD) 2.86 (m, 7H), 3.23 (m, 3H), 3.54 (m, 3H), 6.92 (m, 2H), 7.23 (m, 1H).

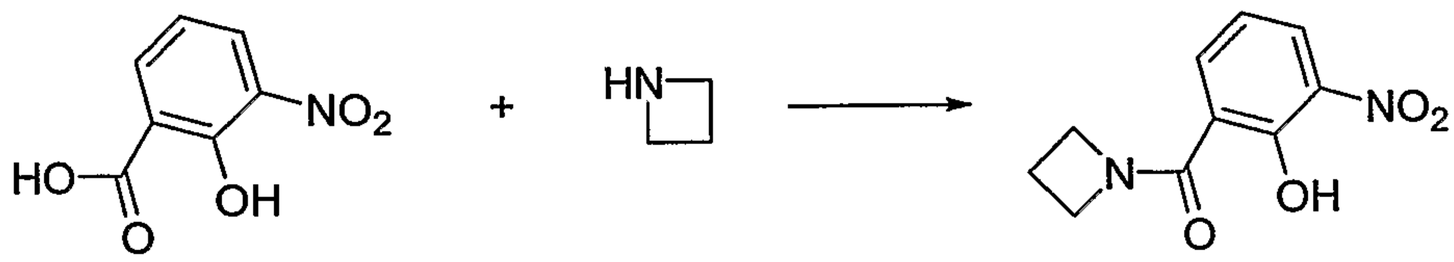
PREPARATIVE EXAMPLE 106-107

Following the procedure described for Example 105, the Products listed in the table below were prepared using the amine from the Preparative Example indicated and 3-nitrosalacylic acid.

Example	Aniline	Product	1.Yield (%) 2. $(M+1)^+$ 3. Note
106	103		1. 91 2. Not observed 3. Rainey nickel used in Step 2

107	104		1. 24 2. 360.0 3. For Step 1 used PyBrop/ DIEA in DCM

PREPARATIVE EXAMPLE 108

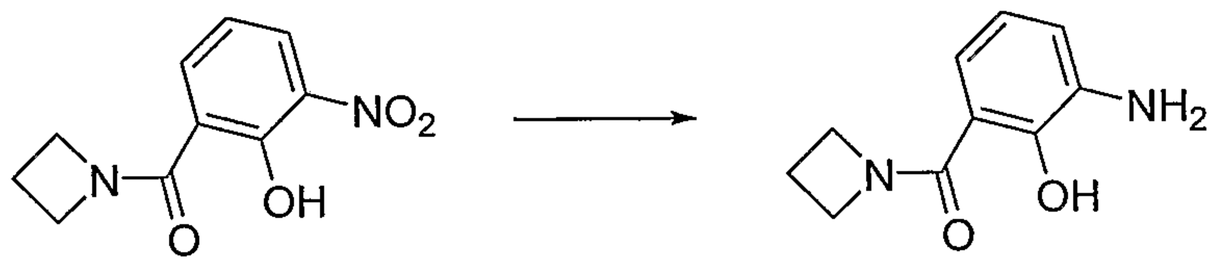


Step A

3-Nitrosalicylic acid (1.0g, 5.5mmol) was dissolved in ethyl acetate (20mL). 1,3-Dicyclohexylcarbodiimide (0.568g, 2.8mmol) was added and the mixture was stirred for approximately 10 minutes and cooled to 0°C. During this time a precipitate formed. Azetidine (0.39mL, 5.8mmol) was added and the reaction was stirred overnight and allowed to warm to room temperature. After this time the reaction was cooled to 0°C and filtered. The collected solid was washed with chilled ethyl acetate. The filtrate was concentrated and purified by column chromatography (80% EtOAc/Hex) to give the product (476mg, 39.0%).

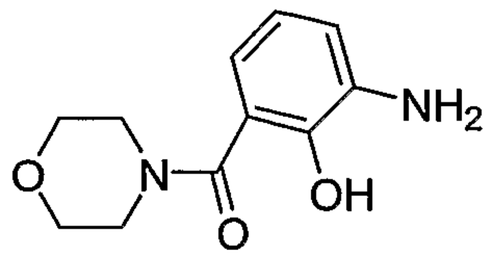
^{1}H NMR (300 MHz, $CDCl_3$) δ2.40(m, 2H), 4.38(m, 4H), 6.97(m, 1H), 7.62(d, 1H), 8.12(d, 1H), 12.88(m, 1H) ppm.

Step B



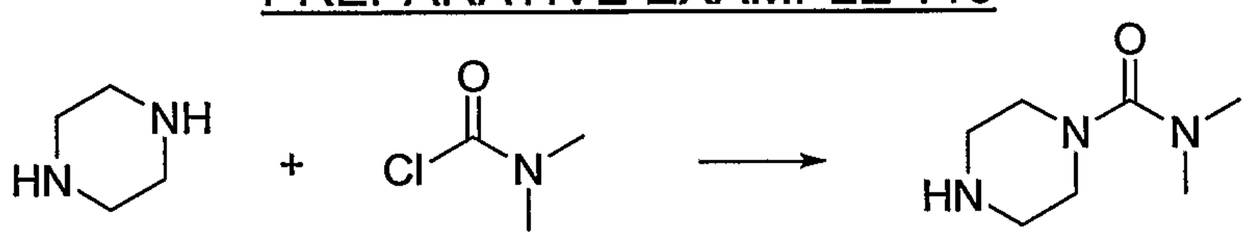
The nitro compound (0.48g, 2.1mmol) from Preparative Example 32 Step A was dissolved in methanol (25ml) and stirred with 10% Pd/C under a hydrogen gas atmosphere overnight. The reaction mixture was filtered through celite, the filtrate concentrated *in vacuo* to give the product (344mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ2.52(m, 2H), 4.57(bs, 4H), 6.75(m, 1H), 6.90(m, 2H), 12.71(bs, 1H) ppm.

PREPARATIVE EXAMPLE109



In essentially the same manner as described in Preparative Example 108 above, the morpholino-amine product was obtained.

PREPARATIVE EXAMPLE 110

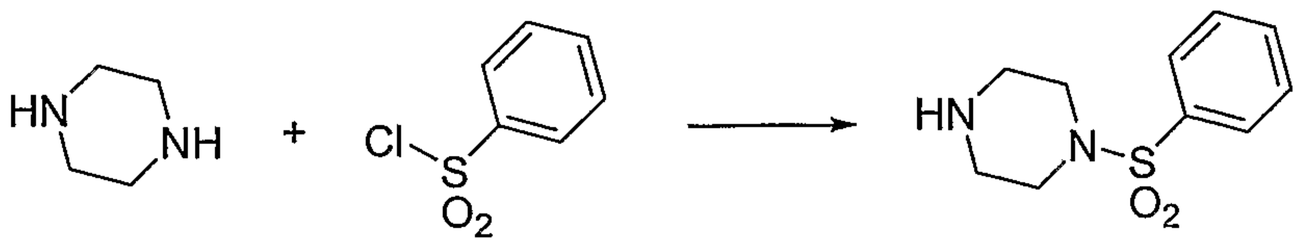


Piperazine (4.9g, 0.057mol) was dissolved in dichloromethane (100mL). N,N'-Dimethylcarbamoyl chloride (1.0mL, 0.011mol) was added dropwise to the solution at room temperature. The reaction was stirred for one hour. After this time 1N potassium hydroxide (200mL) was added. The layers were separated and the aqueous layer was extracted three times with dichloromethane. The organic fractions were combined and dried over sodium sulfate. Filtration and concentration provided the product, without further purification, as an oil (1.16g, 13%).

^{1}H NMR ($CDCl_3$, 300 MHz) 1.95 (s, 1H), 2.83 (s, 6H), 2.86 (m, 4H), 3.20 (m, 4H).

MS: calculated: 157.12, found: 158.1.

PREPARATIVE EXAMPLE 111



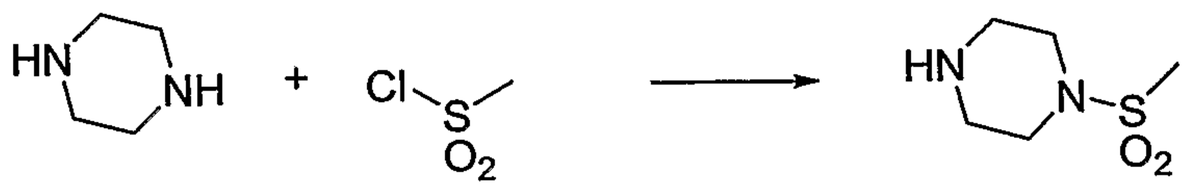
Piperazine (4.9g, 0.057mol) was dissolved in 1N HCl (100mL). A solution of phenylsulfonylchloride (1.45mL, 0.011mol) in acetonitrile (25mL) was added dropwise to the solution at room temperature. The reaction was stirred for 30 minutes. After this time the reaction was extracted two times with ethyl acetate. The solution was then made basic with 1N potassium hydroxide and extracted three times with dichloromethane. The dichloromethane fractions were combined and dried over

magnesium sulfate. Filtration and concentration provided the product, without further purification, as a solid (1.22g, 9.4%).

^{1}H NMR ($CDCl_3$, 300 MHz) 2.94 (m, 8H), 7.56 (m, 3H), 7.76 (m, 2H).

MS: calculated: 226.08, found: 227.1.

PREPARATIVE EXAMPLE 112

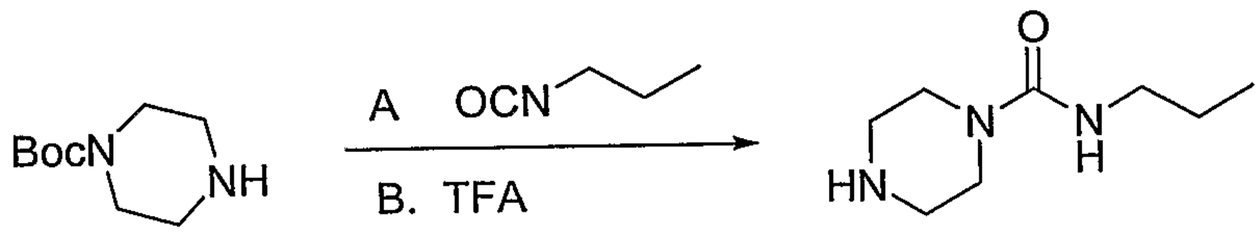


Piperazine (4.9g, 0.057mol) was dissolved in dichloromethane (100mL). Methanesulfonyl chloride (0.85mL, 0.011mol) was added dropwise to the solution at room temperature. The reaction was stirred for 30 minutes. After this time 1N potassium hydroxide (200mL) was added. The layers were separated and the aqueous layer was extracted three times with dichloromethane. The organic fractions were combined and dried over sodium sulfate. Filtration and concentration provided the product, without further purification, as a solid (1.07g, 11%).

^{1}H NMR ($CDCl_3$, 300 MHz) 1.75 (s, 1H), 2.78 (s, 3H), 2.97 (m, 4H), 3.20 (m, 4H).

MS: calculated: 164.06, found: 165.1.

PREPARATIVE EXAMPLE 113



Step A

Boc-Piperazine (3.0g, 0.0161mol) was dissolved in dichloromethane (100mL). Propylisocyanate (1.51mL, 0.0161mol) was added to the solution at room temperature. The reaction was stirred for over night. After this time the reaction was diluted with 1N potassium hydroxide (200mL) and extracted six times with dichloromethane. The organic fractions were combined and dried over magnesium sulfate. Filtration and concentration provided the product as a solid.

Step B

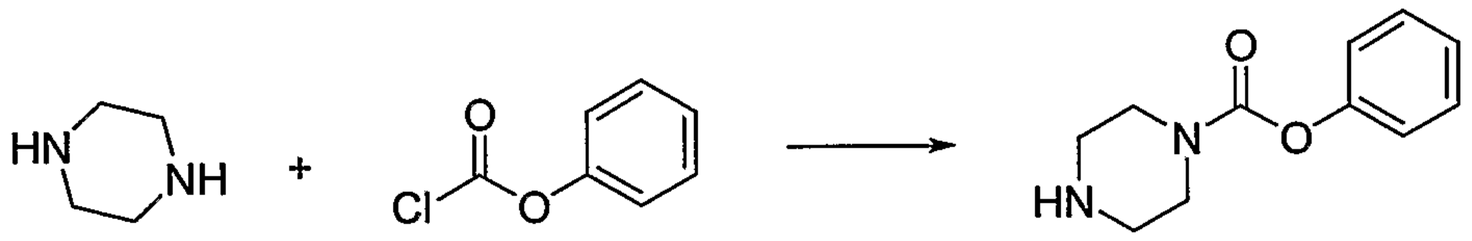
The product of Step A above, was dissolved in a 30% trifluoroacetic acid/dichloromethane solution and stirred overnight. After this time a 1N potassium

hydroxide solution (200 mL) was added to the reaction. The aqueous layer was extracted a total of six times with dichloromethane. The organic fractions were combined and dried over sodium sulfate. Filtration and concentration provided the product (1.37g, 50%).

^{1}H NMR ($CDCl_3$, 300 MHz) 0.92 (t, 3H), 1.52 (m, 2H), 2.89 (m, 4H), 3.01 (s, 1H), 3.18 (m, 2H), 3.37 (m, 4H), 4.61 (bs, 1H).

MS: calculated: 171.14, found: 172.0.

PREPARATIVE EXAMPLE 114



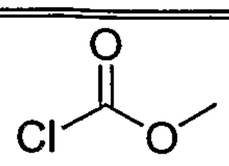
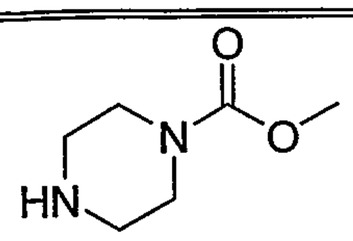
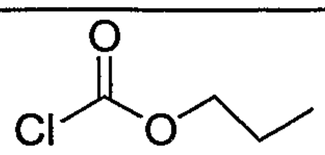
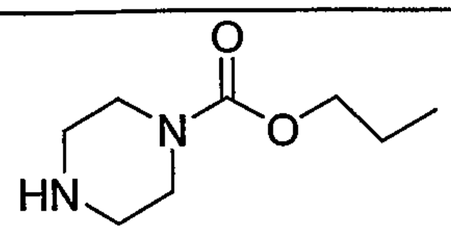
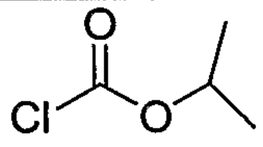
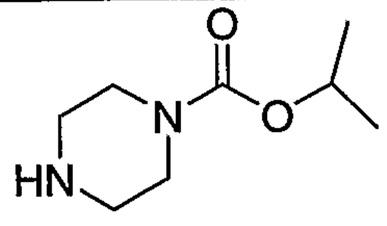
Piperazine (4.9g, 0.0569mol) was dissolved in 1N HCl (70mL). A solution of phenylchloroformate (1.43mL, 0.0114mol) in acetonitrile (25mL) was added dropwise to the solution at room temperature. The reaction was stirred for 30 minutes. After this time the reaction was extracted two times with ethyl acetate. The solution was then made basic with 1N potassium hydroxide and extracted three times with dichloromethane. The dichloromethane fractions were combined and dried over magnesium sulfate. Filtration and concentration provided the product, without further purification, as a solid (2.12g, 18%).

^{1}H NMR ($CDCl_3$, 300 MHz) 1.78 (s, 1H), 2.91 (m, 4H), 3.59 (m, 4H), 7.11 (2H), 7.19 (m, 1H), 7.36 (m, 2H).

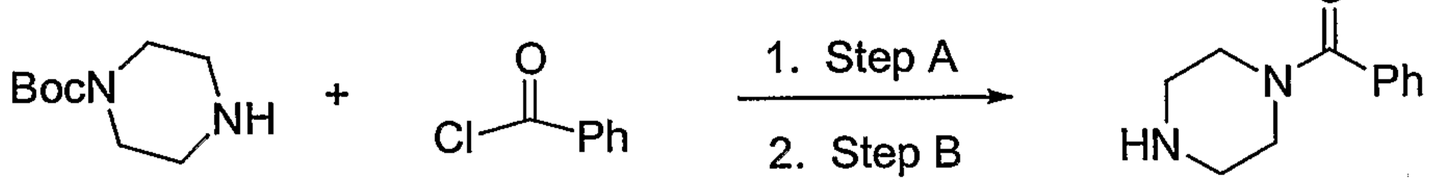
MS: calculated: 206.24, found: 207.1.

PREPARATIVE EXAMPLE 115-117

Following the procedure described for Example 112, the Products listed in the table below were prepared using the commercially available chloroformate shown and piperazine.

Example	Chloroformate	Product	1.Yield (%) 2. $(M+1)^+$
115			1. 54 2. 144.9
116			1. 17 2. 173.0
117			1. 69 2. 173.0

PREPARATIVE EXAMPLE 118



Step A

Boc-Piperazine (3.01g, 0.0161mol) was dissolved in dichloromethane (100mL) along with diisopropylethylamine (5.61mL, 0.0322mol). Benzoylchloride (1.87mL, 0.0161mol) was added dropwise to the solution at room temperature. The reaction was stirred for several hours. After this time the reaction was concentrated and the product was purified by column chromatography (10% MeOH/DCM). Boc-Protected product was isolated as a solid (5.21g).

^{1}H NMR ($CDCl_3$, 300 MHz) 1.47 (s, 9H), 3.45 (m, 8H), 7.41 (m, 5H).

MS: calculated: 290.16, found: 290.8.

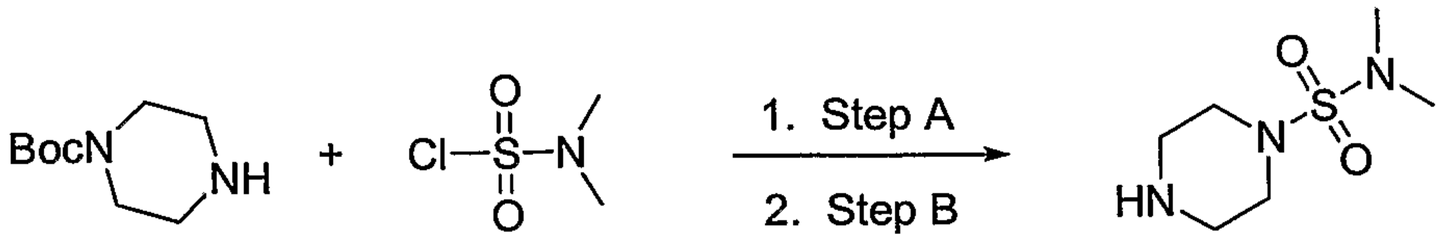
Step B

The product from Step A above, was dissolved in a 50% trifluoroacetic acid/dichloromethane solution and stirred overnight. After this time the reaction was diluted with 1N potassium hydroxide (200mL) and the organic layer was separated. The aqueous phase was then extracted six times with dichloromethane. The organic fractions were combined and dried over magnesium sulfate. Filtration and concentration provided product (2.93g).

^{1}H NMR ($CDCl_3$, 300 MHz) 1.92 (s, 1H), 2.87 (m, 4H), 3.52 (m, 4H), 7.39 (s, 5H).

MS: calculated: 190.11, found: 191.1.

PREPARATIVE EXAMPLE 119



Step A

Boc-Piperazine (3.0g, 0.0161mol) was dissolved in dichloromethane (100mL) along with diisopropylethylamine (3.1mL, 0.0177mol). N,N'-dimethylsulfamoyl chloride (1.73mL, 0.0161mol) was added dropwise to the solution at room temperature. The reaction was stirred for several hours. After this time the reaction was diluted with water (100mL). The layers were separated and the aqueous layer was extracted six times with dichloromethane. The organic fractions were combined and dried over magnesium sulfate. Filtration and concentration provided the product, without further purification, as a solid (4.53g).

^{1}H NMR ($CDCl_3$, 300 MHz) 1.47 (s, 9H), 2.84 (s, 6H), 3.21 (m, 4H), 3.48 (m, 4H).

MS: calculated: 293.14, found: 194.1 $(M\text{-}Boc)^+$.

Step B

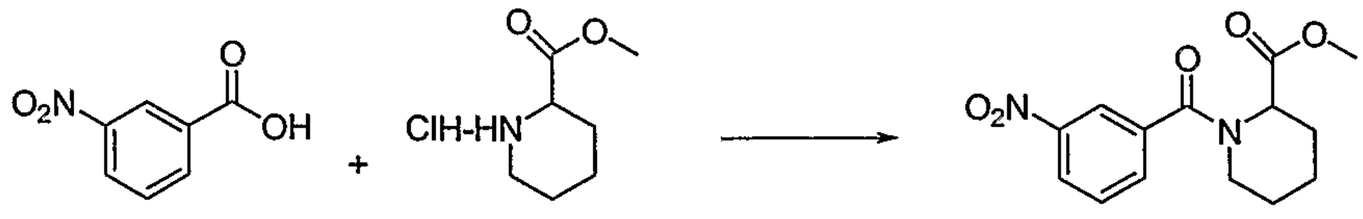
The product from Step A above, was dissolved in a 30% trifluoroacetic acid/dichloromethane solution and stirred overnight. After this time the reaction was diluted with water and 1N potassium hydroxide was used to make the aqueous layer slightly basic. The aqueous layer was extracted a total of seven times with dichloromethane. The organic fractions were combined and dried over sodium sulfate. Filtration and concentration provided the product (2.96g).

^{1}H NMR ($CDCl_3$, 300 MHz) 2.03 (s, 1H), 2.83 (s, 6H), 2.92 (m, 4H), 3.23 (m, 4H).

MS: calculated: 193.09, found: 194.1.

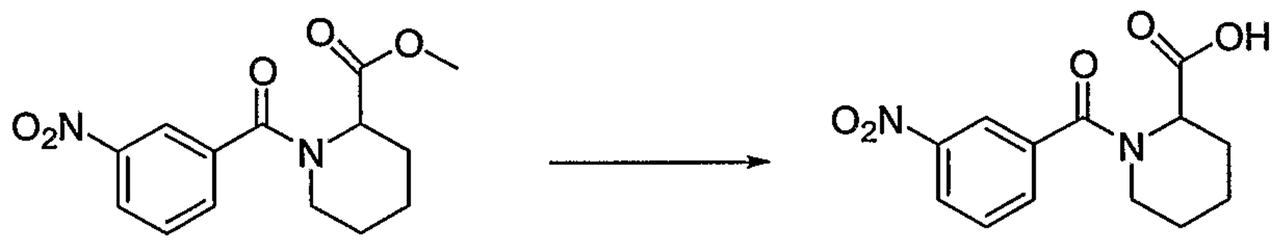
PREPARATIVE EXAMPLE 120

Step A



In essentially the same manner as that described in Preparative Example 105, Step 1, using 3-nitrobenzoic acid instead of 3-nitrosalicylic acid, the methyl ester product was prepared.

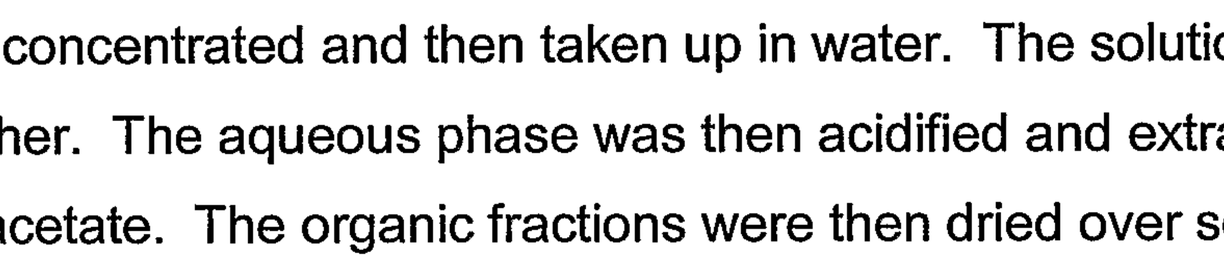
Step B



The methyl ester (1.79g, 6.1mmol) from Step A above, was dissolved in dioxane/water (20mL/15mL) at room temperature. Lithium hydroxide (0.258g, 6.2mmol) was added to the solution. After a few hours more lithium hydroxide was added (0.128g, 3.0mmol) and the reaction was stirred for another hour. After this time the reaction was concentrated and then taken up in water. The solution was extracted two times with ether. The aqueous phase was then acidified and extracted three times with ethyl acetate. The organic fractions were then dried over sodium sulfate, filtered and concentrated. Product was isolated by column chromatography (95% EtOAc/Hex, 0.05% HOAc) to give the product (1.66 g, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) 1.49(m, 2H), 1.68(m, 1H), 1.82(m, 2H), 2.44(m, 1H) 3.32(m, 1H), 3.58(m, 1H), 5.57(m, 1H), 7.65(m, 1H), 7.80(m, 1H), 8.32(m, 2H), 10.04(bs, 1Hppm).

Step C



The nitro compound was dissolved in an excess of methanol (20mL) and covered by a blanket of argon. 5% Palladium on carbon was added (catalytic) and a hydrogen balloon was attached to the flask. The atmosphere of the system was

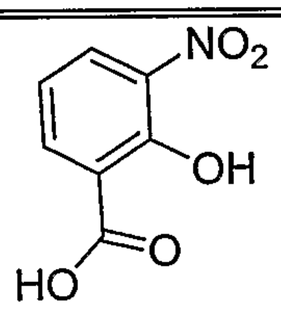
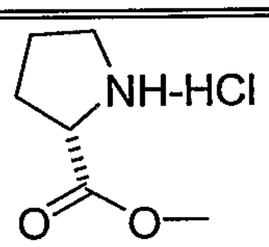
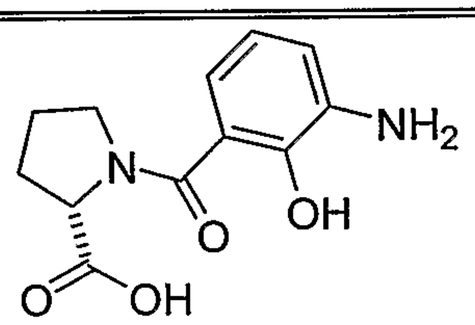
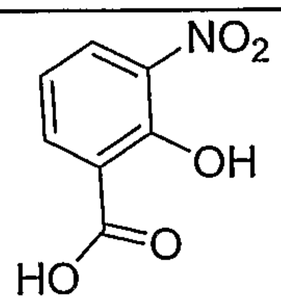
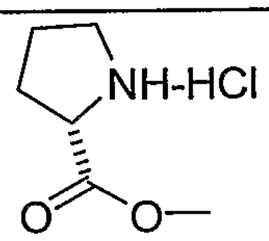
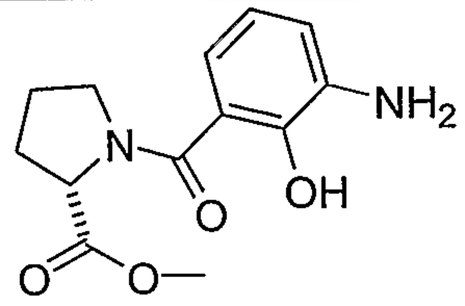
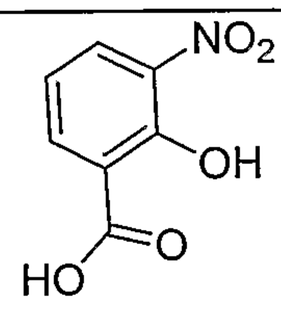
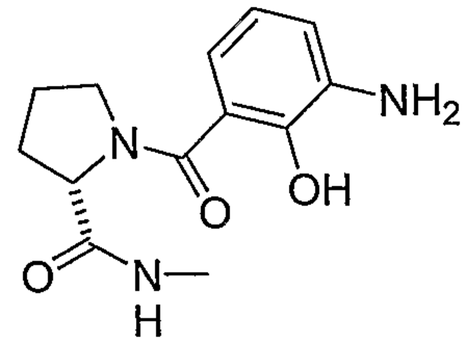
purged under vacuum and replaced with hydrogen. This step was repeated for a total of three times. The reaction was then stirred under hydrogen overnight. After this time the balloon was removed and the solution was filtered through celite followed by several rinses with methanol. The filtrate was concentrated and dried on the vacuum line to provide the desired aniline product (1.33 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) 1.40(m, 2H), 1.50(m, 1H), 1.68(m, 2H), 2.33(m, 1H) 3.18(m, 1H), 3.62(m, 1H), 5.39(m, 1H), 6.12(bs, 2H), 6.75(m, 2H), 7.12(m, 1H)ppm.

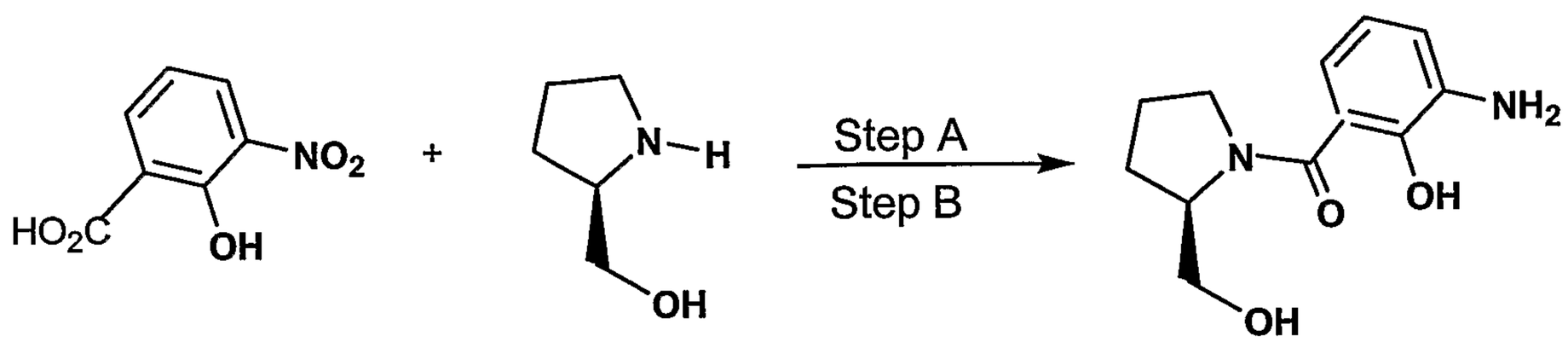
Mass Spectra, calculated: 248, found: 249.1 $(M+1)^+$

PREPARATIVE EXAMPLES 121-123

Following the procedure described in Preparative Example 120, but using the commercially available amine and benzoic acid indicated, the intermediate products in the table below were obtained.

Prep Ex	Carboxylic Acid	Amine	Product	1.Yield (%) 2. $(M+1)^+$ 3. Note
121				1. 21 2. 251.0
122				1. 21 2. 265.0 3. Skipped step B
123				1. 15 2. 264.0 3. Skipped step B

PREPARATIVE EXAMPLE 124



Step A

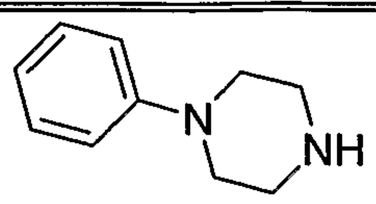
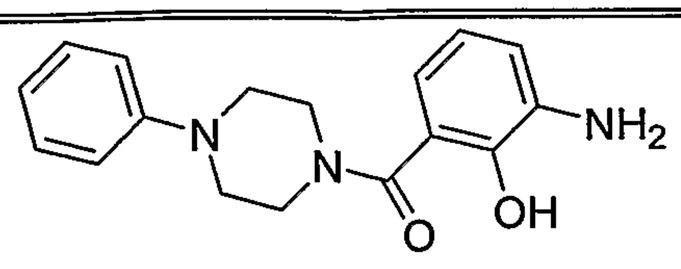
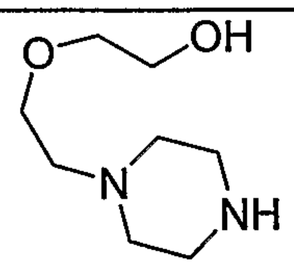
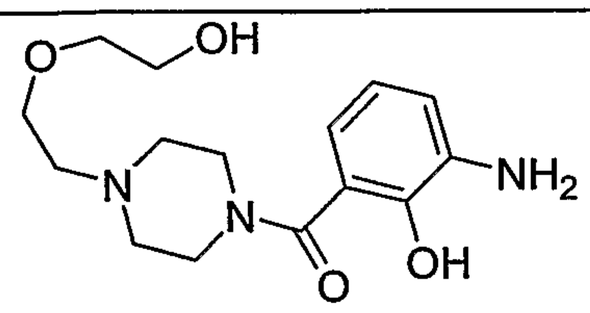
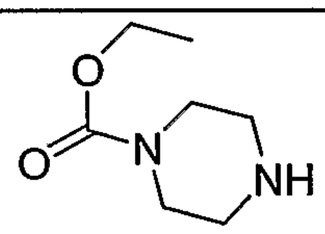
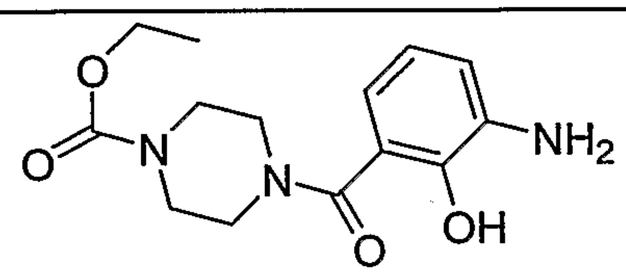
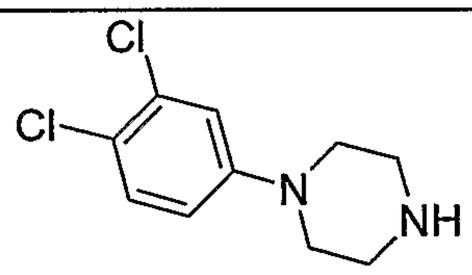
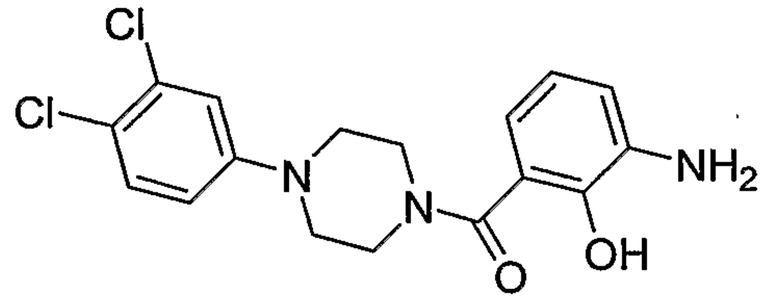
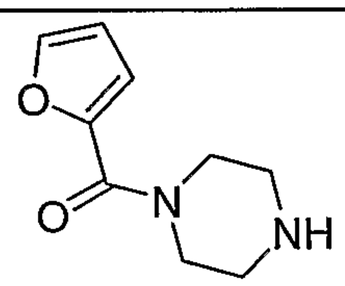
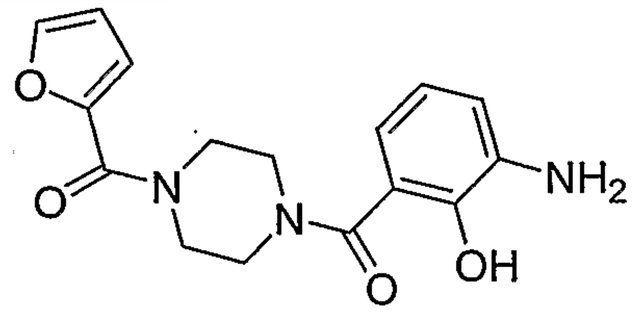
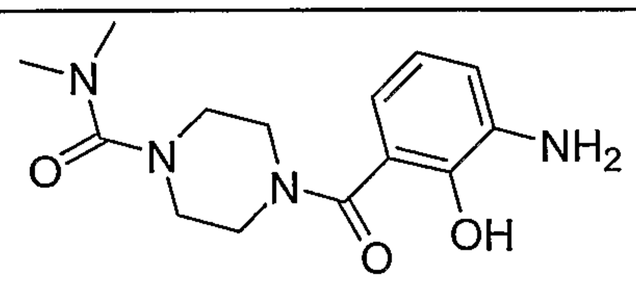
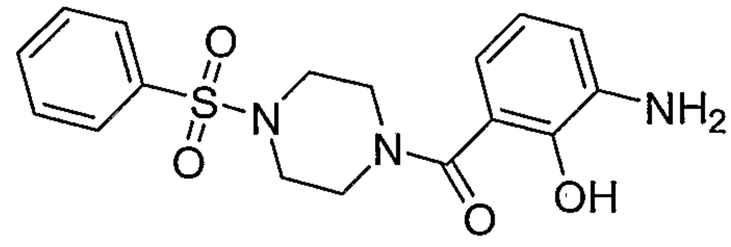
3-Nitrosalicylic acid (500 mg, 2.7 mmol), 1,3-dicyclohexylcarbodiimide (DCC) (563 mg) and ethyl acetate (10 mL) were combined and stirred for 10 min. (*R*)-(-)-2-pyrrolidinemethanol (0.27 mL) was added and the resulting suspension was stirred at room temperature overnight. The solid was filtered off and the filtrate was either concentrated down and directly purified or washed with 1N NaOH. The aqueous phase was acidified and extracted with EtOAc. The resulting organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by preparative plate chromatography (silica gel, 5% MeOH/CH_2Cl_2 saturated with AcOH) gave the desired compound (338 mg, 46%, MH^+ = 267).

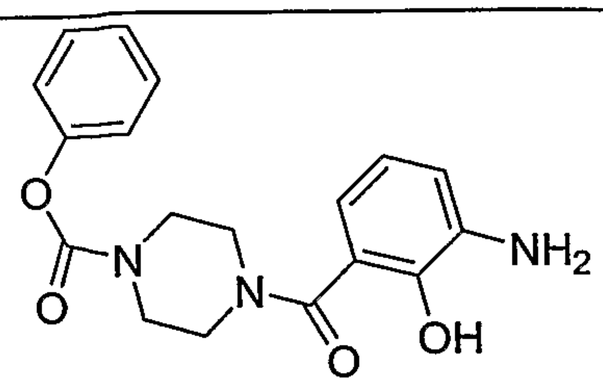
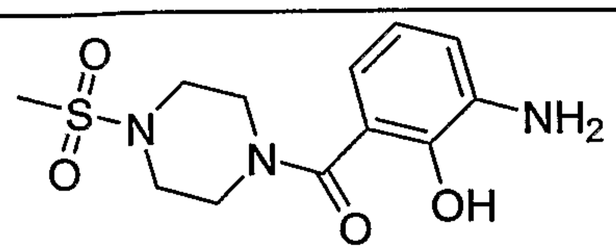
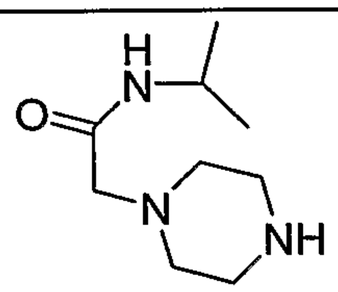
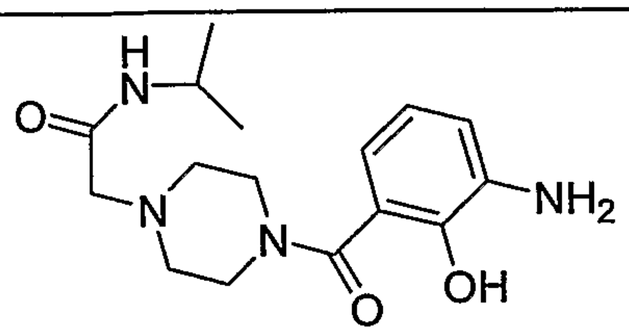
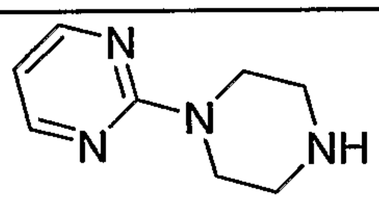
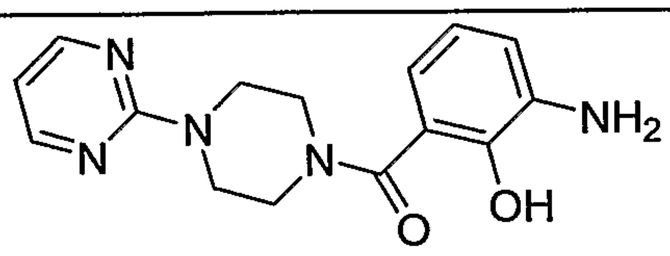
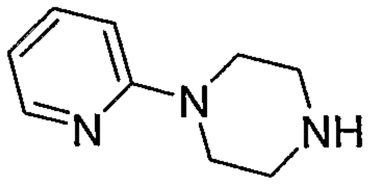
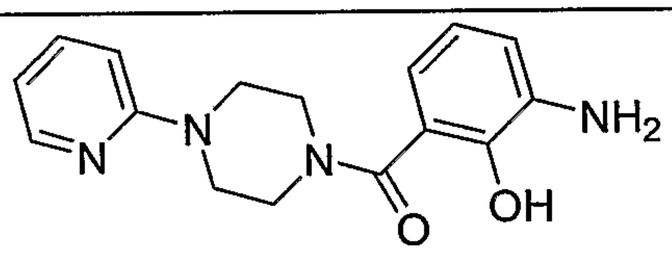
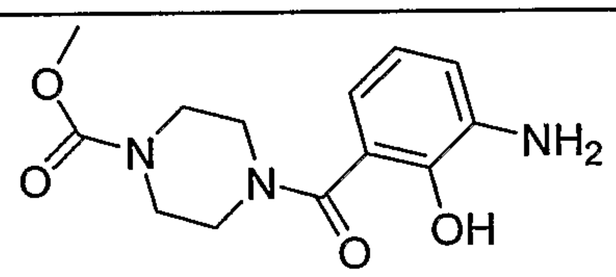
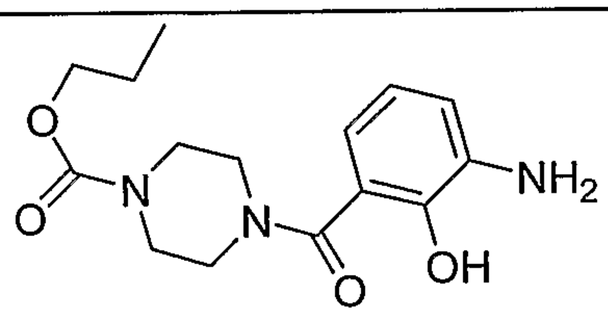
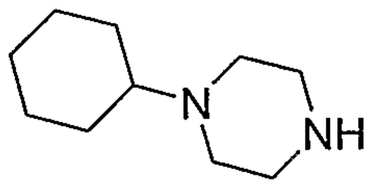
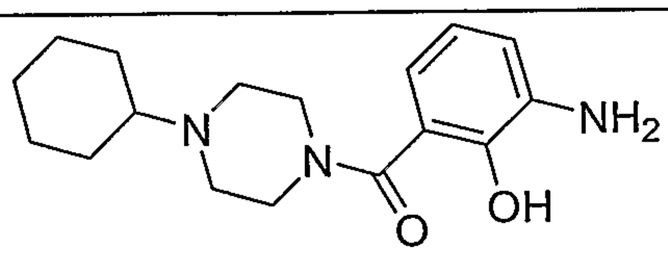
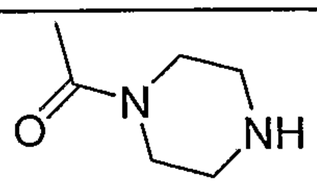
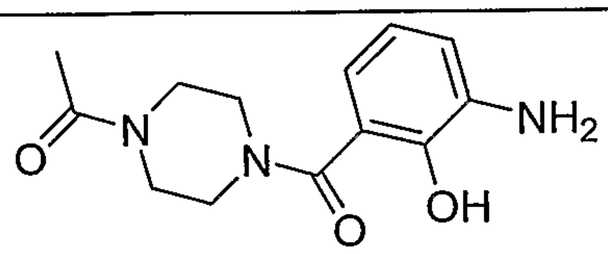
Step B

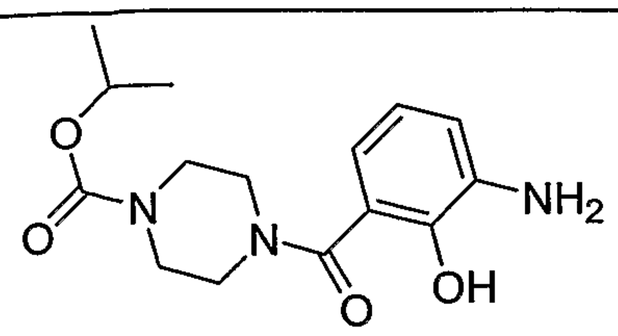
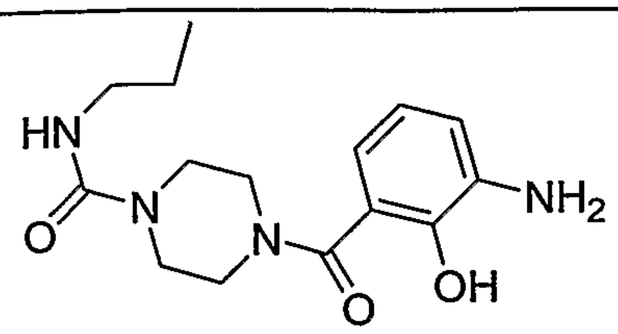
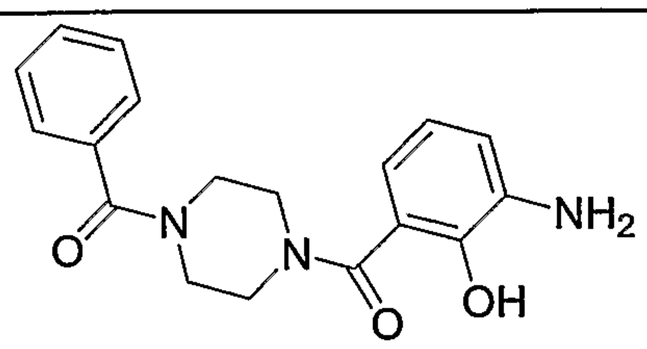
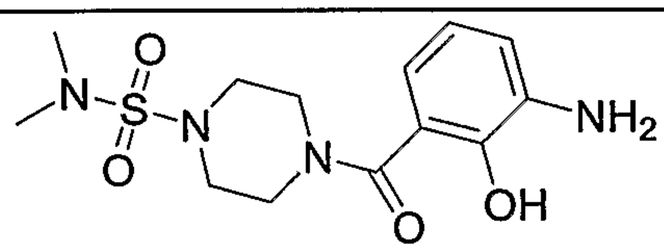
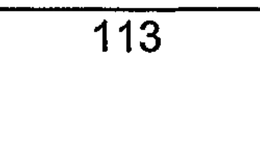
The product from Step A above was stirred with 10% Pd/C under a hydrogen gas atmosphere overnight. The reaction mixture was filtered through celite, the filtrate concentrated *in vacuo,* and the resulting residue purified by column chromatography (silica gel, 4% MeOH/CH_2Cl_2 saturated with NH_4OH) to give the product (129mg, 43%, MH+=237).

PREPARATIVE EXAMPLES 125-145

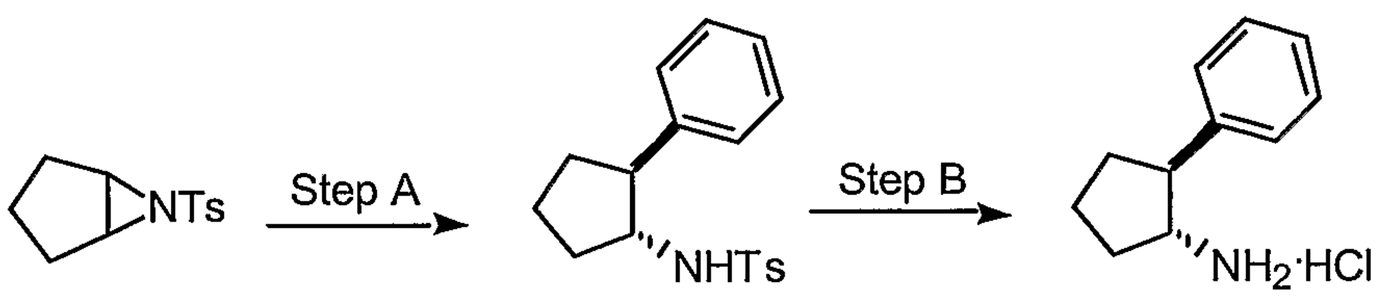
Following the procedure described for Preparative Example 124, but using the commercially available amine or the amine from the Preparative Example indicated and 3-nitrosalicylic acid, the products in the table below were obtained.

Prep Ex	Amine Comm. Avail./ From Prep.Ex.	Product	1.Yield(%) 2. $(M+1)^+$
125			1. 37 2. 298.1
126			1. 31 2. 310.1
127			1. 68 2. 294.1
128			1. 54 2. 365.9
129			1. 45 2. 316.1
130	110		1. 59 2. 293.1
131	111		1. 32 2. 362.0

132	114		1. 36 2. 342.0
133	112		1. 65 2. 300.0
134			1. 48 2. 321.1
135			1. 50 2. 300.1
136			1. 56 2. 299.2
137	115		1. 79 2. 280.1
138	116		1. 64 2. 307.1
139			1. 73 2. 304.2
140			1. 34 2. 264.0

141	117		1. 40 2. 307.1
142	113		1. 91 2. 307.1
143	118		1. 9.0 2. 326.0
144	119		1. 42 2. 329.0
145			1. 6.5 2. 236.1

PREPARATIVE EXAMPLE 146



Step A

To a solution of tosylaziridine (*J. Am. Chem. Soc.* **1998**, *120*, 6844-6845, the disclosure of which is incorporated herein by refernce thereto) (0.5 g, 2.1 mmol) and $Cu(acac)_2$ (55 mg, 0.21 mmol) in THF (5 mL) at 0 °C was added PhMgBr (3.5 ml, 3.0 M in THF) diluted with THF (8 mL) dropwise over 20 min. The resulting solution was allowed to gradually warm to rt and was stirred for 12h. Sat. aq. NH_4Cl (5 mL), was added and the mixture was extracted with Et_2O (3 x 15 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by preparative TLC eluting with

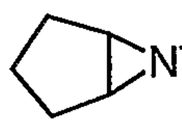
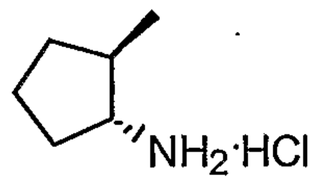
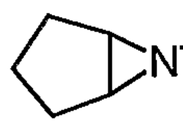
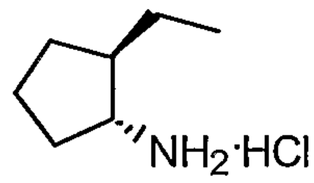
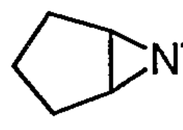
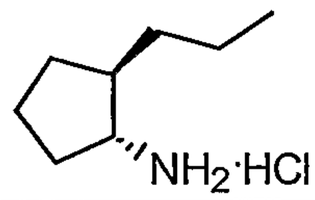
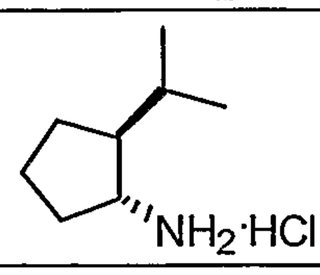
hexane/EtOAc (4:1) to afford 0.57 g (86% yield) of a solid. The purified tosylamine was taken on directly to the next step.

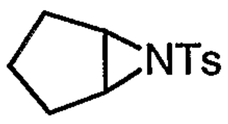
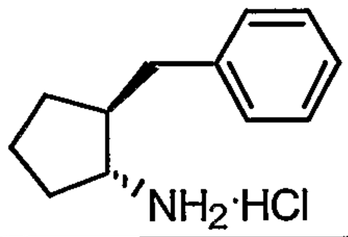
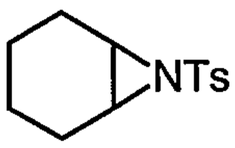
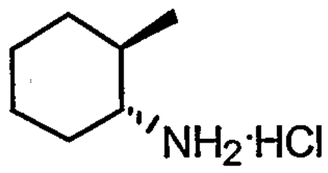
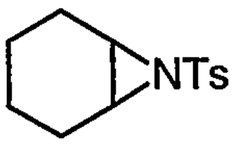
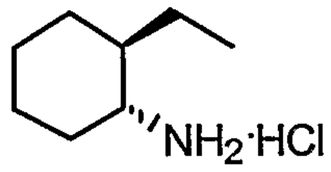
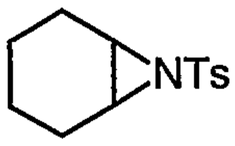
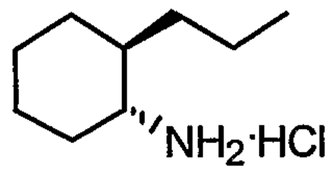
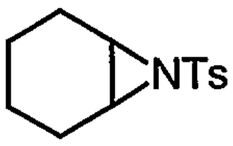
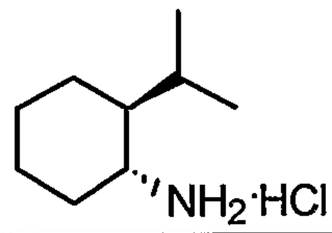
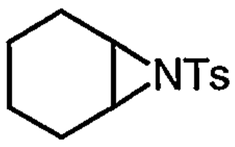
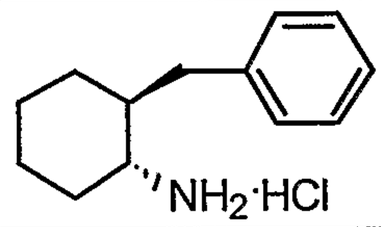
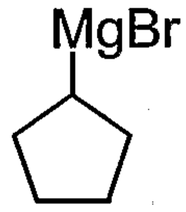
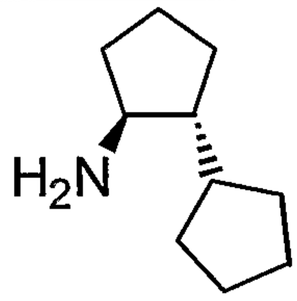
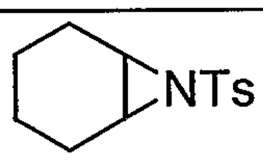
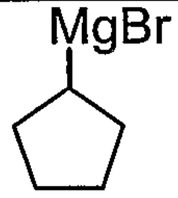
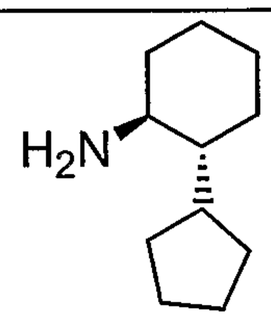
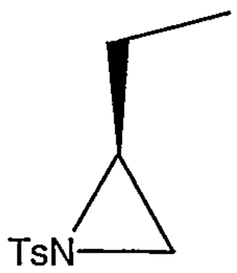
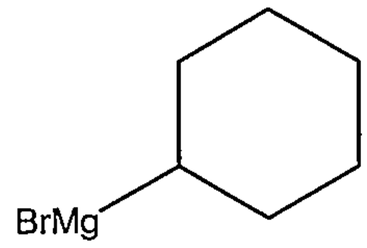
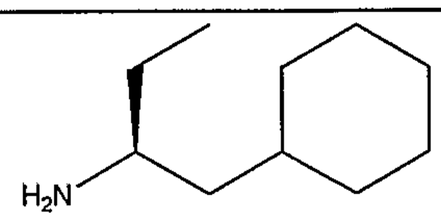
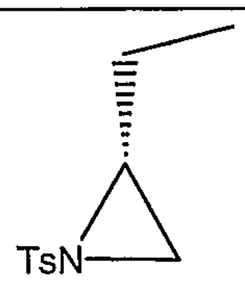
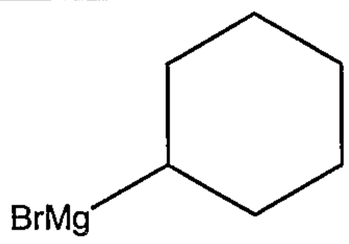
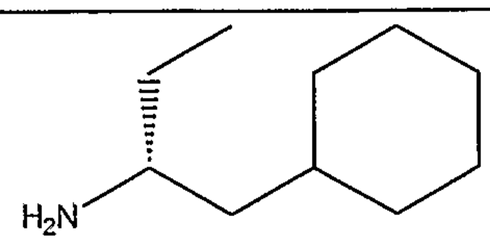
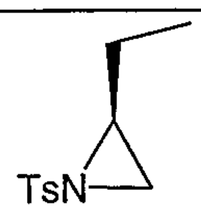
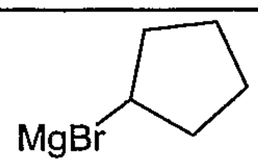
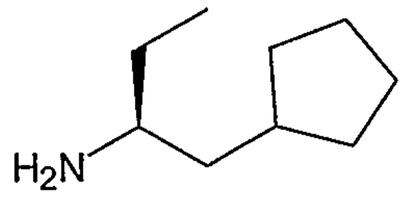
Step B

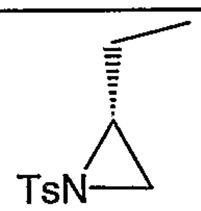
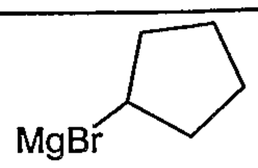
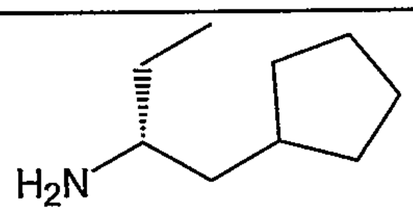
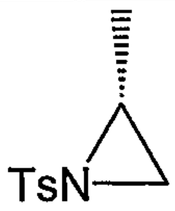
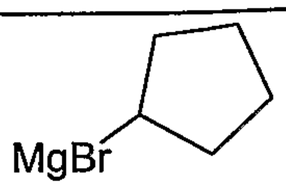
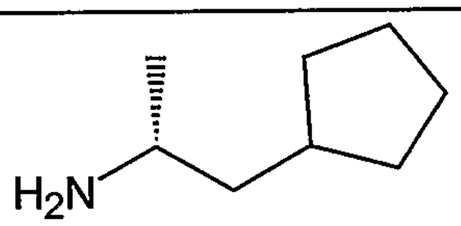
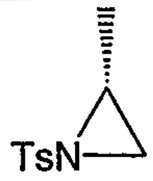
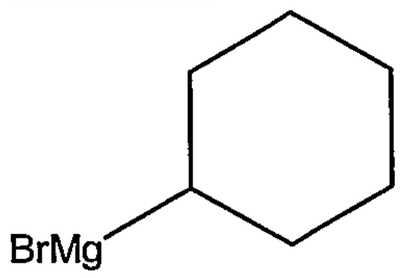
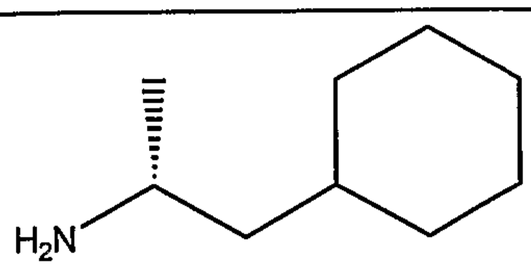
To a solution of tosylamine (0.55 g, 1.75 mmol) in NH_3 (20 mL) at –78 °C was added sodium (0.40 g, 17.4 mmol). The resulting solution was stirred at –78 °C for 2 h whereupon the mixture was treated with solid NH_4Cl and allowed to warm to rt. Once the NH_3 had boiled off, the mixture was partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x10 mL). The organic layers were combined,), dried ($NaSO_4$), and concentrated under reduced pressure to a volume of ~20 mL. 4N HCl in dioxane (5 mL) was added and the mixture was stirred for 5 min. The mixture was concentrated under reduced pressure and the resultant crude residue was recrystallized from $EtOH/Et_2O$ to afford 0.30 g (87% yield) of a solid.

PREPARATIVE EXAMPLES 147-156.10

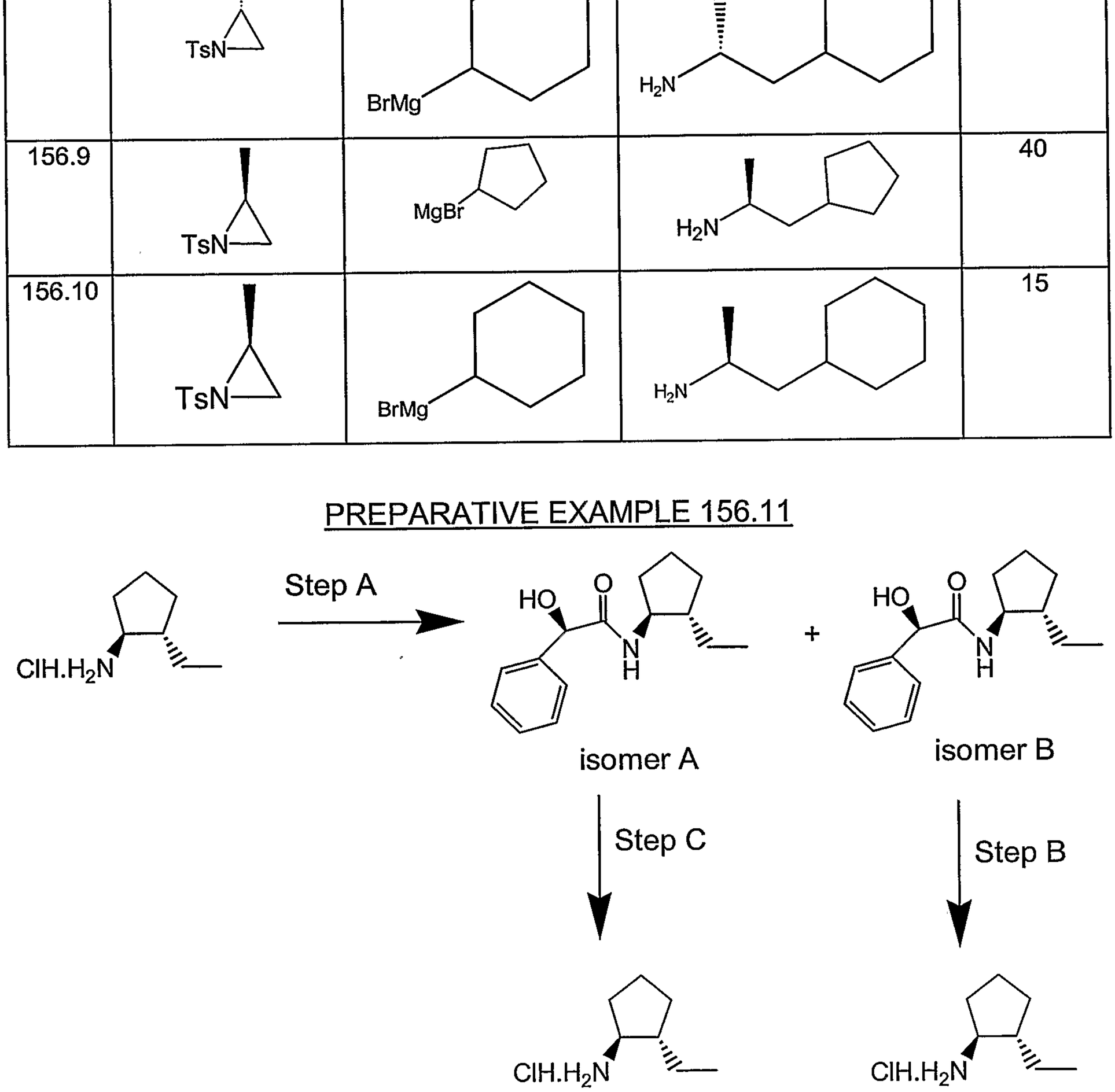
Following the procedure set forth in Preparative Example 146 but using the requisite tosylaziridines and Grignard reagents listed in the Table below, the following racemic amine hydrochloride products were obtained.

Prep Ex.	Tosyl aziridine	Grignard Reagent	Amine hydrochloride	Yield (%)
147		MeMgBr		1. 19%
148		EtMgBr		1. 56%
149		*n*-PrMgBr		1. 70%
150		*i*-PrMgCl		1. 41%

151		BnMgCl		1. 61%
152		MeMgBr		1. 61%
153		EtMgBr		1. 66%
154		*n*-PrMgBr		1. 80%
155		*i*-PrMgBr		1. 27%
156		BnMgCl		1. 79%
156.1				52
156.2				49
156.3				61
156.4				57
156.5				64

156.6				64
156.7				45
156.8				23
156.9				40
156.10				15

PREPARATIVE EXAMPLE 156.11



Step A

To a solution of the amine (118mg) from Preparative Example 148 in CH_2Cl_2 (10ml) was added triethylamine (120ul), R-Mandelic Acid (164mg), DCC (213mg) and DMAP (8.8mg)and let stir for 40hr. The mixture was diluted with CH_2Cl_2 and washed

with saturated ammonium chloride, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by preparative plate chromatography (Hex/EtOAc 4:1) to afford both isomers (A, 86mg, 45%) (B, 90mg, 48%).

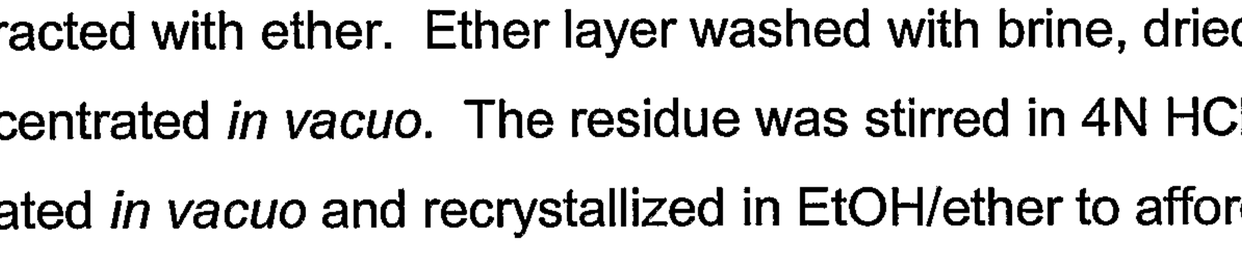
Step B

To isomer B (90mg) from above in dioxane (5ml) was added 6M H_2SO_4 (5ml). The reaction was heated to 80°C over the weekend. 2M NaOH added to basify the reaction and extracted with ether. Ether layer washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was stirred in 4N HCl in dioxane for 30min, concentrated *in vacuo* and recrystallized in EtOH/ether to afford 55mg of product (98%).

Step C

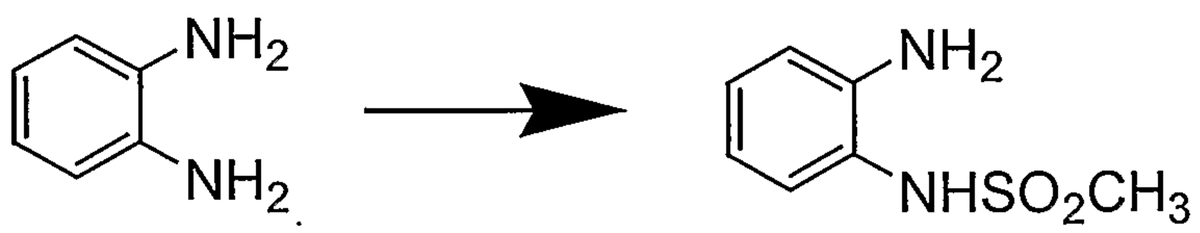
Isomer A (86mg) was reacted following the procedure set forth in Step B above to give the amine salt.

PREPARATIVE EXAMPLE 156.12



The above nitro compound was reduced following the Preparative Example 2, Step B.

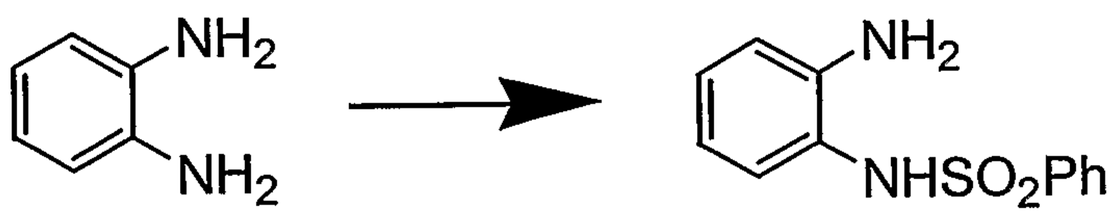
PREPARATIVE EXAMPLE 156.13



To a solution of 1,2-phenylenediame (1.5g) in CH_2Cl_2 (30ml) at 0°C was added TEA (2.91ml), followed by dropwise addition of $MeSO_2Cl$ (1.07ml). The mixture was allowed to warm to room temperature and stir overnight. 1M HCl added and the layers were separated. The aqueous layer was adjusted to pH=11 with solid NaOH, extracted with CH_2Cl_2. The basified aqueous layer was then neutralized using 3N HCl

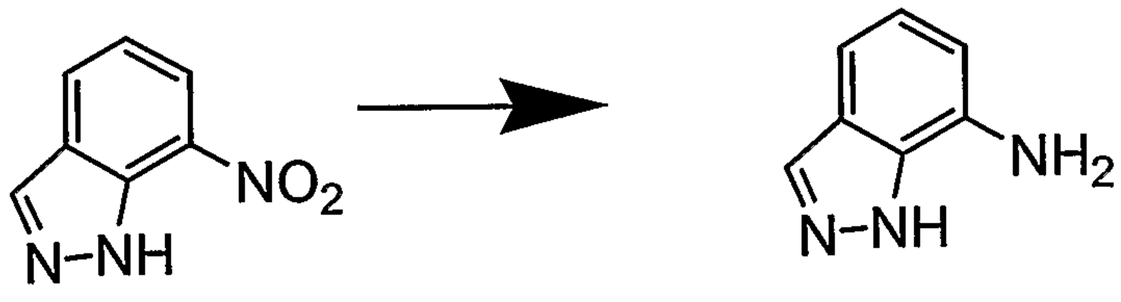
and extracted with CH_2Cl_2, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give 1.8g of product (71%).

PREPARATIVE EXAMPLE 156.14



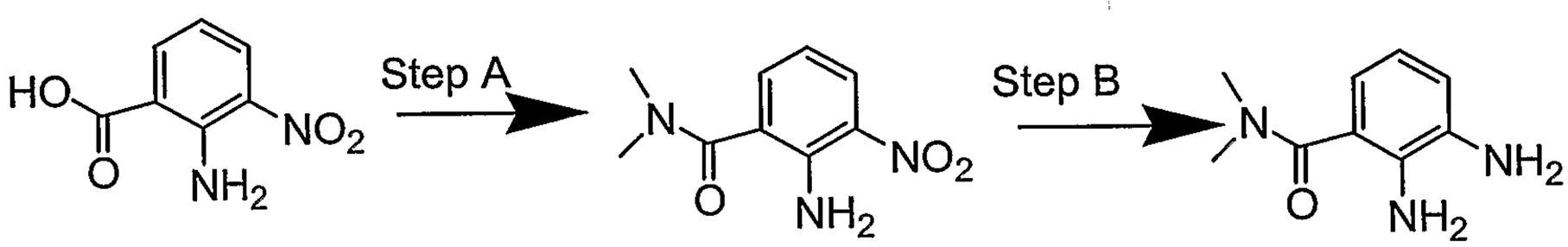
The above compound was prepared using the procedure set forth in Preparative Example 156.13, but using $PhSO_2Cl$.

PREPARATIVE EXAMPLE 156.15



The nitro compound was reduced following a similar procedure as in Preparative Example 2, Step B.

PREPARATIVE EXAMPLE 156.16



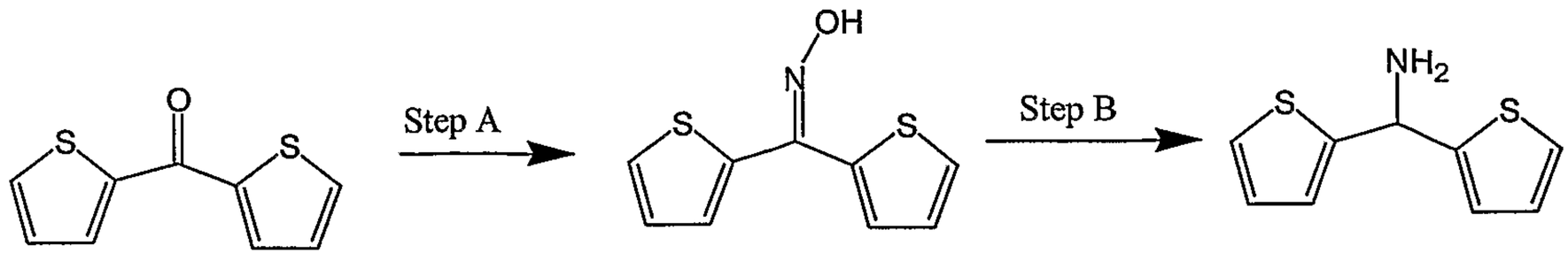
Step A

The known acid (410mg) above (*J.Med.Chem.* **1996**, 34,4654, the disclosure of which is incorporated herein by reference thereto.) was reacted following the procedure set forth in Preparative Example 2, Step A to yield 380mg of an oil (80%).

Step B

The amide (200mg) from above was reacted following the procedure set forth in Preparative Example 2, Step B to yield 170mg of an oil (100%).

PREPARATIVE EXAMPLE 156.17



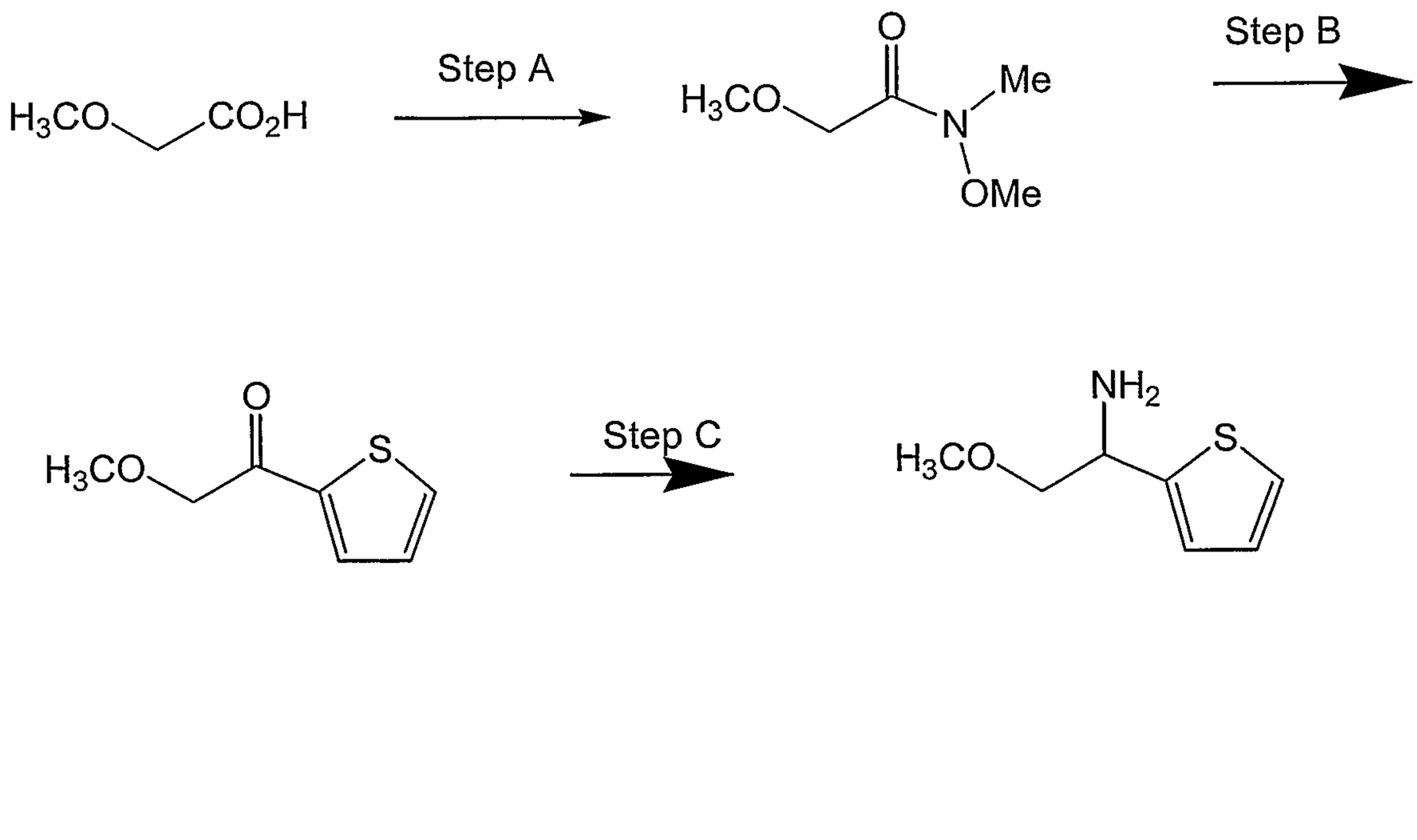
Step A

To a solution of ketone (500mg) in EtOH/water (3:1, 4ml) at room temperature was added hydroxylamine hydrochloride (214mg) followed by NaOH to afford a heterogenous mixture. The reaction was not complete so another equivalent of hydroxylamine hydrochloride was added and refluxed overnight. The reaction was cooled to 0^0C and treated with 3N HCl and extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 500mg of product (92%).

Step B

To a solution of oxime (300mg) in THF (5ml) at 0°C was added $LiAlH_4$ (266mg) portionwise. The heterogenous solution was stirred at room temperature for 14hr and then refluxed for 8hr. The solution was cooled to 0°C and water, 2M NaOH, water and ether were added to the reaction. The mixture was filtered through a celite pad. The filtrate was treated with 3N HCl. The aqueous layer was cooled to 0°C, basified with NaOH pellets and extracted with ether. The ether layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the product (143mg, 69%).

PREPARATIVE EXAMPLE 156.18



Step A

Methoxyacetic acid (14 mL) in CH_2Cl_2 (120 mL) and cooled in an ice-water bath was treated with DMF (0.9 mL) and oxalyl chloride (21 mL). After stirring at RT overnight, the mixture was concentrated *in vacuo* and redissolved in CH_2Cl_2 (120 mL). N-methyl-N-methoxylamine (20 g) was added and the mixture stirred at RT overnight. Filtration and concentration *in vacuo* afforded the desired amide (21 g, 89%).

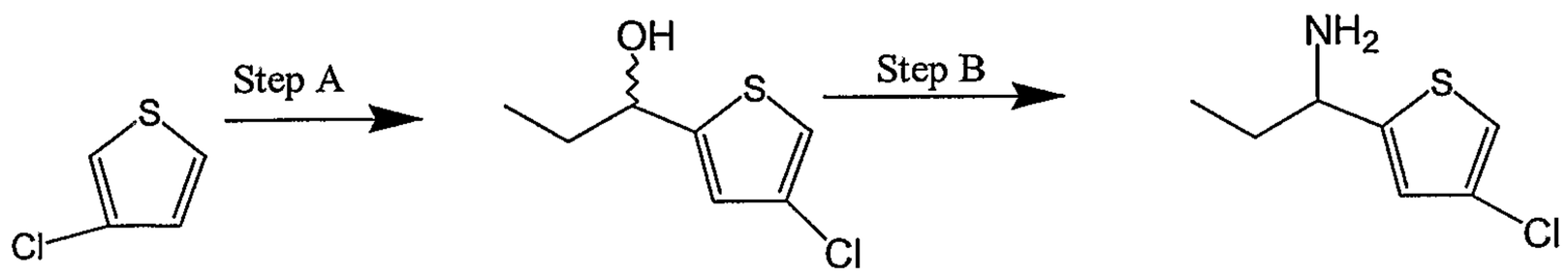
Step B

To a solution of the above amide (260mg) in THF (5ml) at -78 °C was added a solution of 2-thienyllithium (1M in THF, 2.15ml). The solution was stirred for 2hr at -78 °C and warmed to –20 °C for an additional 2hr. The reaction was quenched with saturated ammonium chloride and extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 250mg of product (82%).

Step C

The ketone from above (250mg) was reacted via the procedure set forth in Preparative Example 156.17 Steps A and B to yield 176 mg of the amine (79%).

PREPARATIVE EXAMPLE 156.19



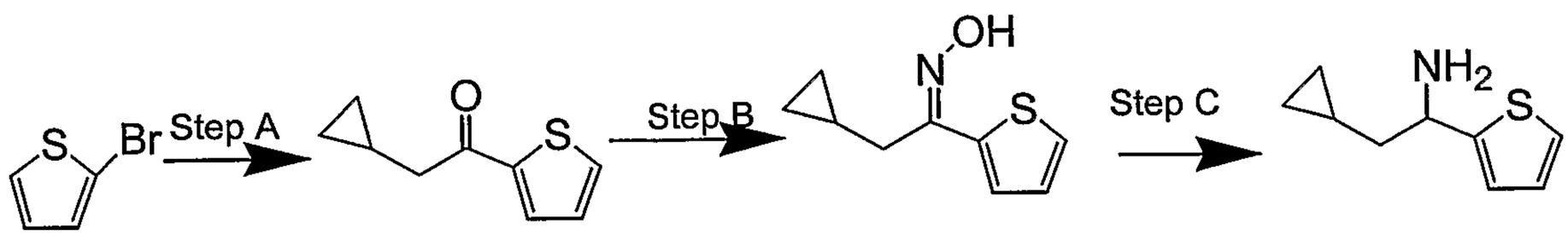
Step A

To a solution of 3-chlorothiophene (1.16ml) in ether (20ml) at –10 °C was added n-BuLi (2.5M in hexane, 5ml). After solution was stirred at –10 °C for 20min, propionaldehyde (0.82ml) in ether (20ml) was added dropwise and let warm to room temperature slowly. The reaction was quenched with saturated ammonium chloride and extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 1.37g of product (62%).

Step B

The alcohol from Step A above was reacted via the procedures set forth in Preparative Example 75.75, Steps B and C to give the amine.

PREPARATIVE EXAMPLE 156.20



Step A

To a solution of magnesium metal (360mg) in THF (15ml) at 0 °C was added 2-bromothiophene (1.45ml) in THF (10ml) dropwise over 20min. The solution was warmed to room temperature for 3hr, recooled to 0 °C whereupon a solution of cyclopropylacetonitrile (1g) in ether (30ml) was added dropwise via a syringe and let warm to room temperature and stir overnight. 3M HCl was added and washed with CH_2Cl_2. The aqueous layer was basified with NaOH pellets and extracted with ether, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give 625mg of product (68%).

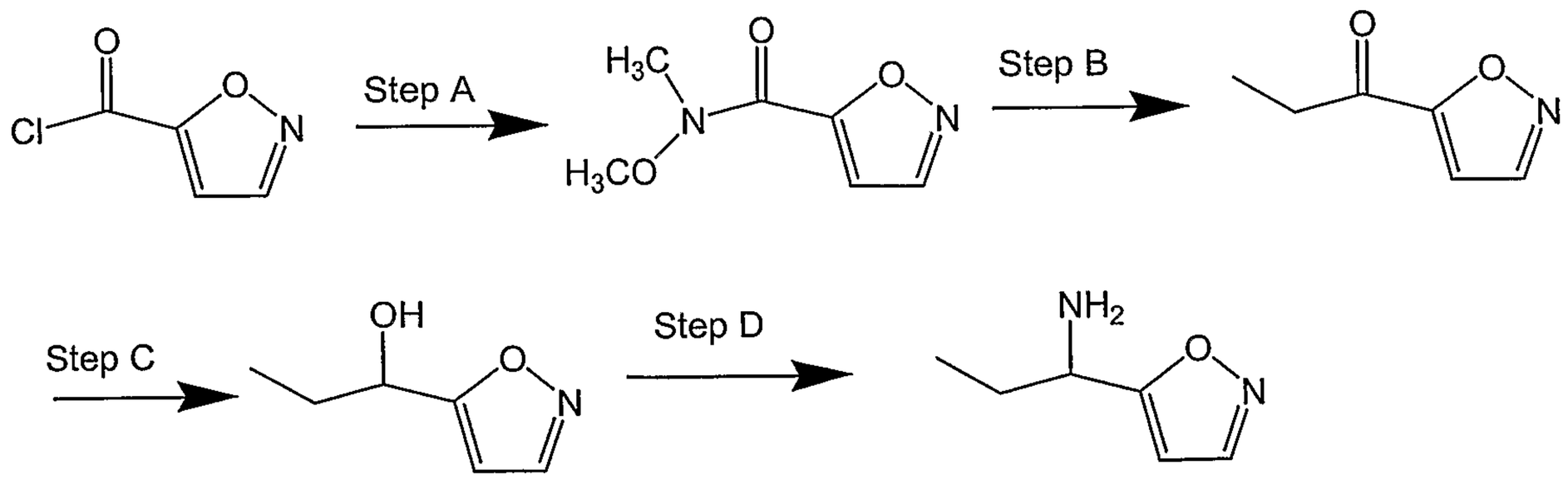
Step B

The ketone was reacted via the procedure set forth in Preparative Example 156.17 Step A to give the oxime.

Step C

The oxime from above was reacted via the procedure set forth in Preparative Example 156.17 Step B to give the amine.

PREPARATIVE EXAMPLE 156.21



Step A

To a solution of $CH_3ONHCH_3.HCl$ (780mg) and acid chloride (1g) in CH_2Cl_2 at 0 °C was added dry pyridine (1.35ml) to afford a heterogenous mixture The solution was warmed to room temperature and stirred overnight. 1M HCl was added to the reaction and the organic layer was separated, washed with brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give 1g of product (85%).

Step B

To a solution of EtI (614ul) in ether (5ml) at –78°C was added t-BuLi (1.7M in pentane, 9ml) dropwise. The mixture was warmed to room temperature for 1hr, cooled to –78°C where the amide (1g) from Step A in THF (4ml) was added and allowed to warm to 0 °C for 2hr. 1M HCl was added to the reaction and extracted with CH_2Cl_2, washed with brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give 500mg of product (63%).

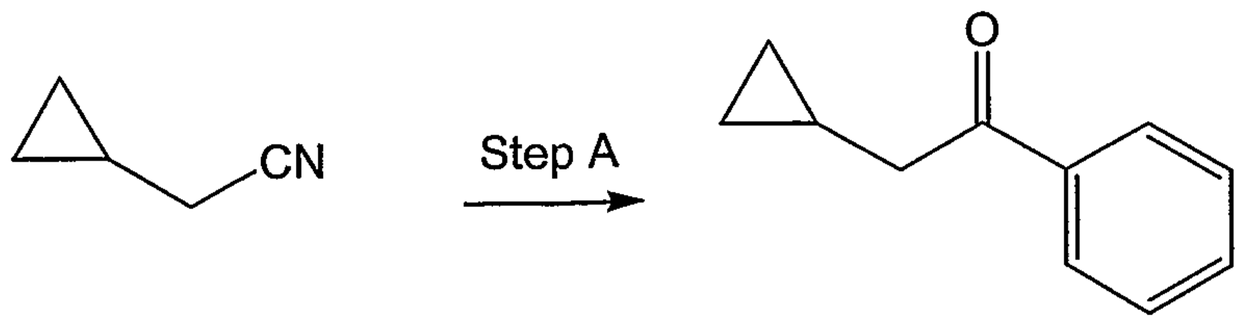
Step C

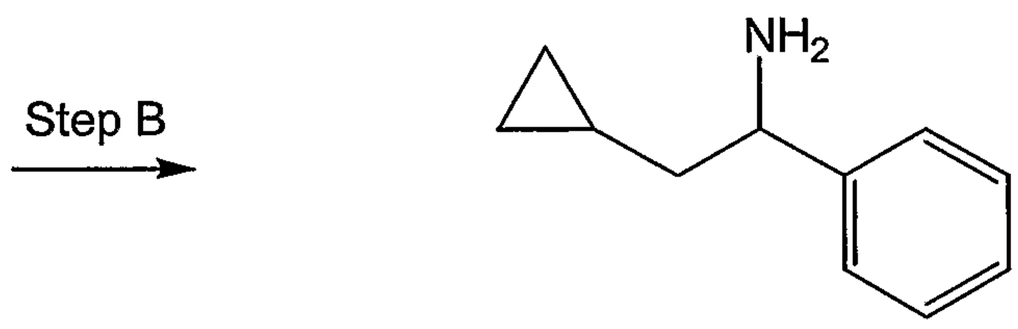
To a solution of ketone (800mg) in THF/water (10:1, 20ml) at 0 °C was added sodium borohydride (363mg) portionwise. The solution was stirred for 2hr at 0 °C. The mixture was concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2, washed with 1N NaOH and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give 560mg of product (69%).

Step D

The alcohol from above was reacted via the procedures set forth in Preparative Example 75.75, Steps B and C to give the amine (176mg, 59%).

PREPARATIVE EXAMPLE 156.22





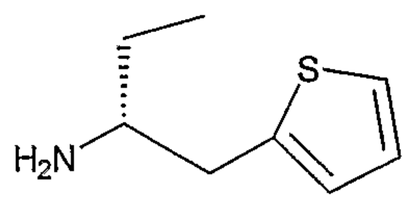
Step A

Cyclopropylacetonitrile (12 mmol) in Et_2O (50 mL) at 0°C was treated with PhMgBr (14 mmol) and the mixture was stirred for 2 hrs at 0°C, then at RT overnight. Hydrochloric acid (3 *M*) was added, and after stirring for an additional 12 hrs, the mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the desired ketone (1.34 g, 70%).

Step B

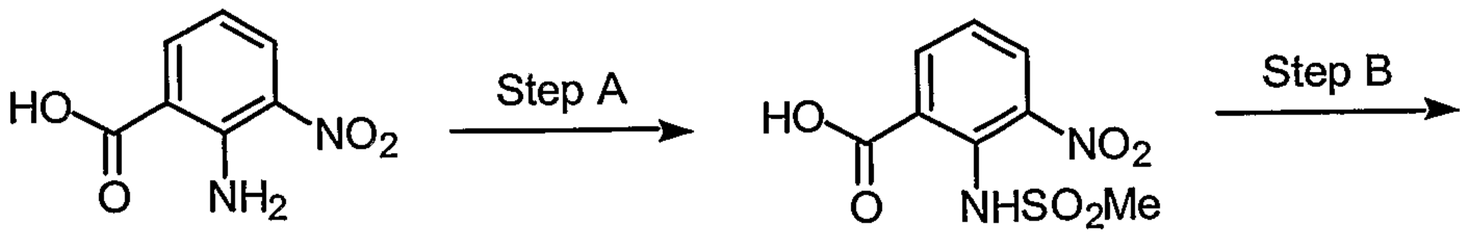
Following the procedures set forth in Preparative Example 156.20 Steps B and C, the amine was prepared.

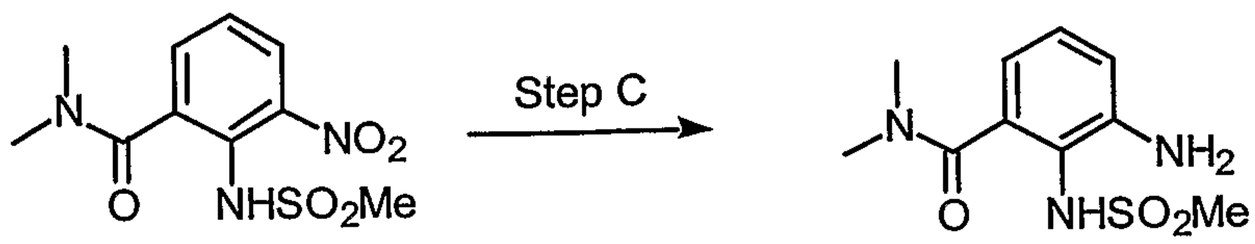
PREPARATIVE EXAMPLE 156.23



The above amine was prepared using the procedures set forth in WO 98/11064 (the disclosure of which is incorporated herein by refernce thereto.

PREPARATIVE EXAMPLE 157





Step A

By taking the known carboxylic acid (*J. Med. Chem.* **1996**, *39*, 4654-4666, the disclosure of wnich is incorporated herein by refernce thereto) and subjecting it to the conditions outlined in Preparative Example 112, the product can be prepared.

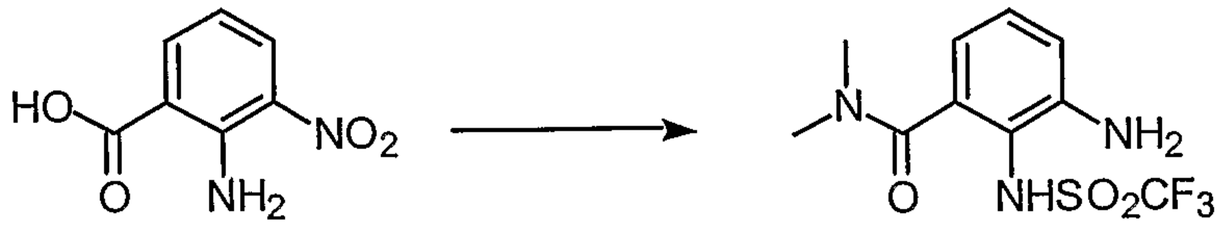
Step B

Following a similar procedure used in Preparative Example 2, Step A, except using dimethylamine and the compound from Step A above, the product can be prepared.

Step C

Following a similar procedure used in Preparative Example 2, Step B, except using the compound from Step B above, the product can be prepared.

PREPARATIVE EXAMPLE 158



Following a similar procedure used in Preparative Example 157, Steps A-C, except using trifluoromethylsulfonylchloride in Step A above, the product can be prepared.

PREPARATIVE EXAMPLES 160-457

Following a similar procedure as that set forth in Preparative Example 22.1 but using the commercially available (or prepared amine) indicated in the Table below and using EtOH as solvent instead of MeOH, the following thiadiazoleoxide intermediates could be obtained.

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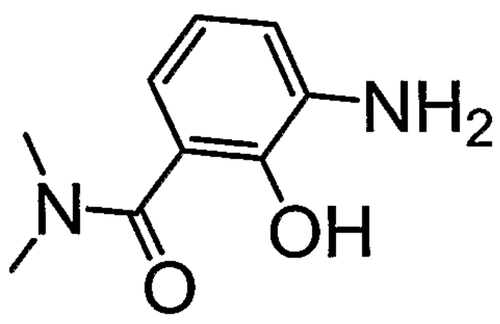
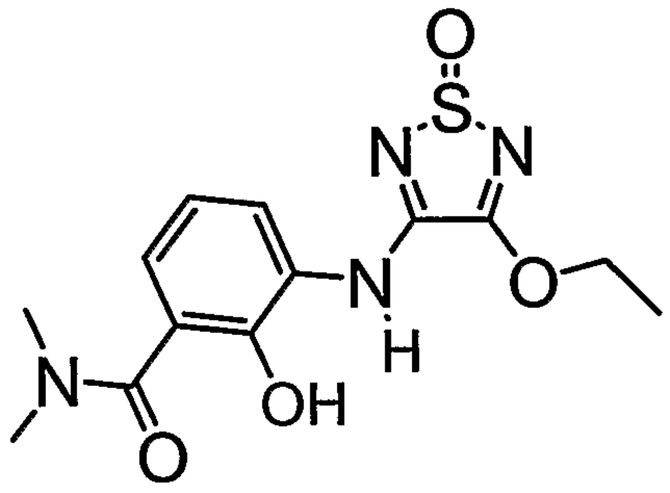
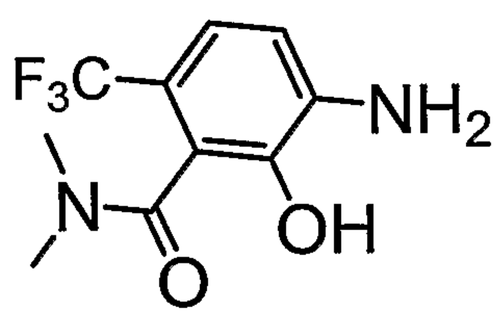
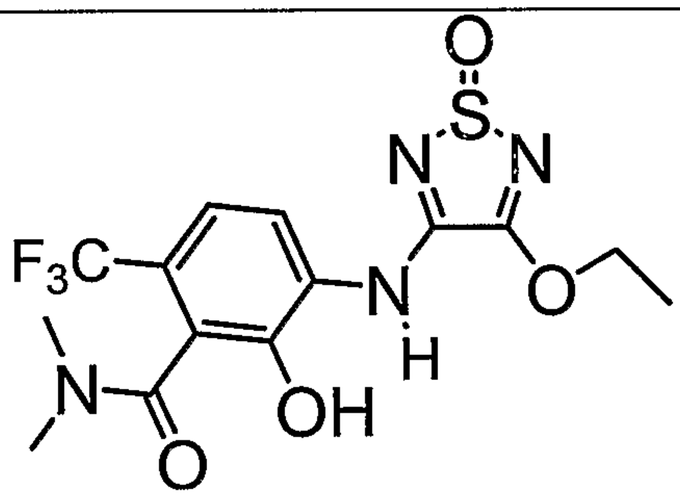
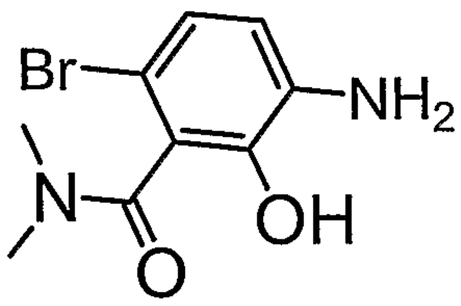
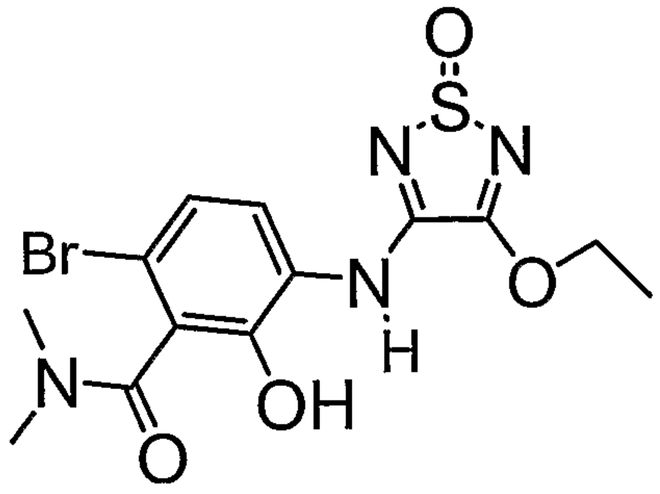
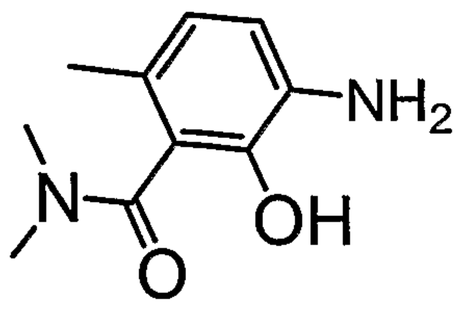
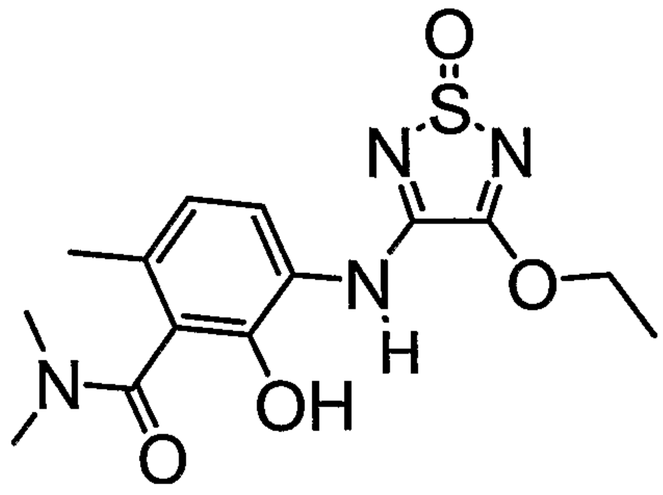
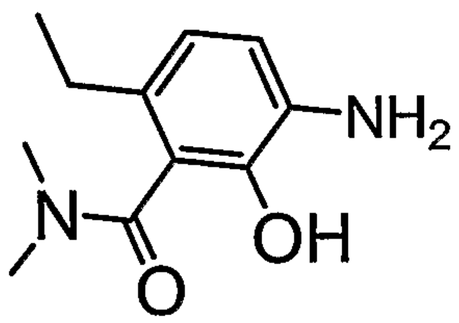
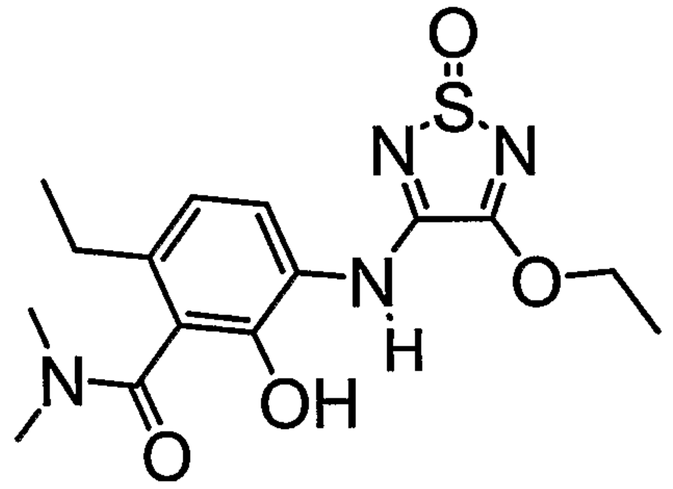
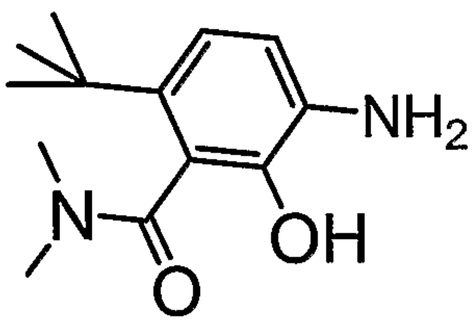
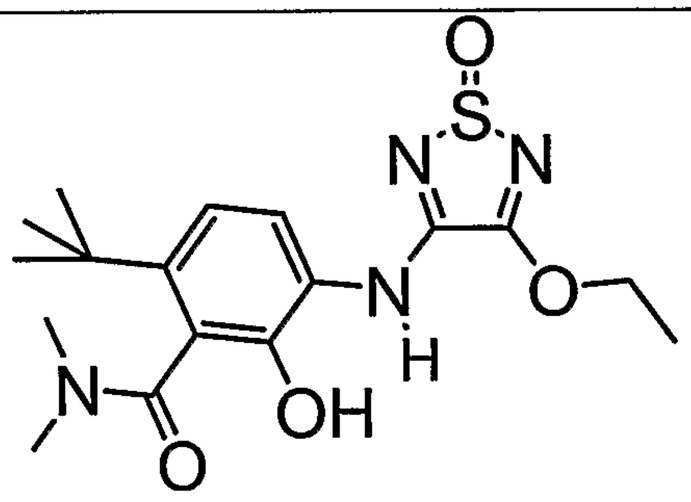
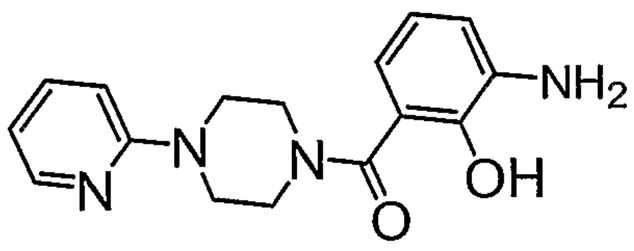
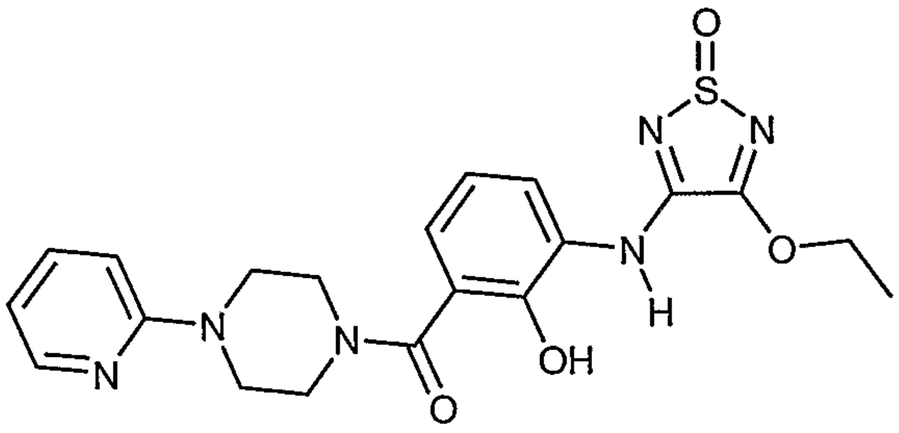
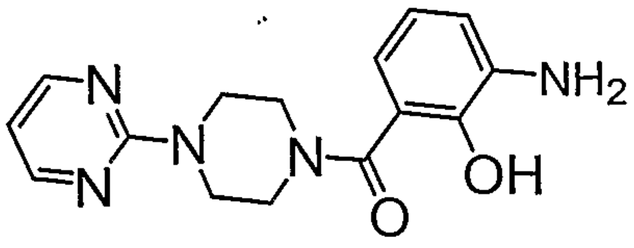
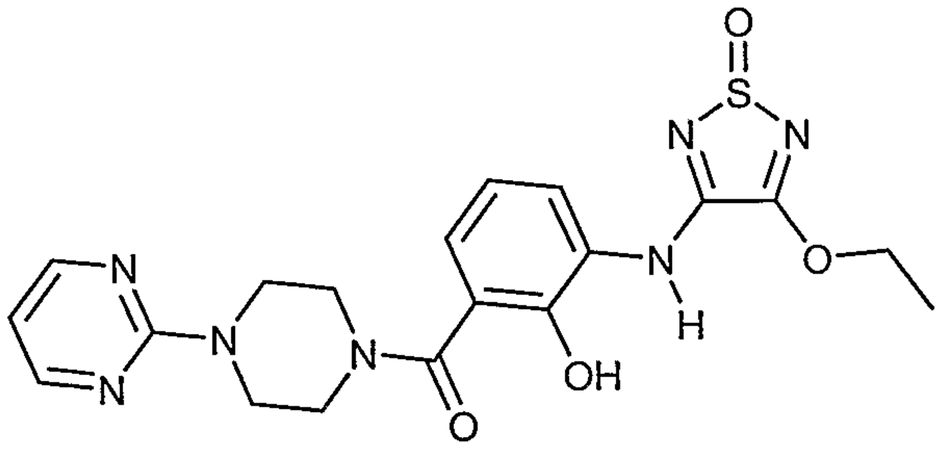
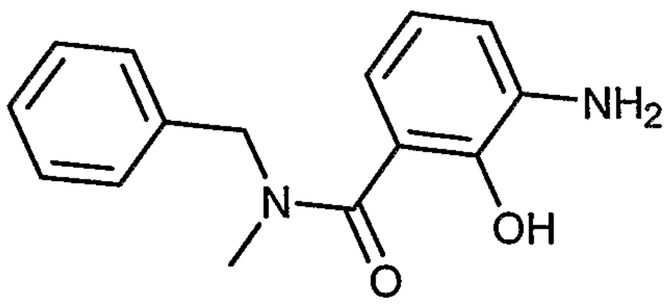
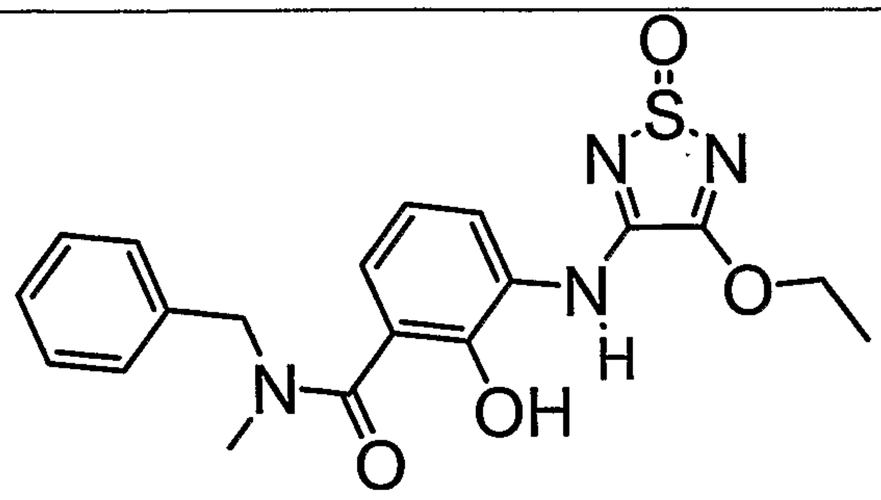
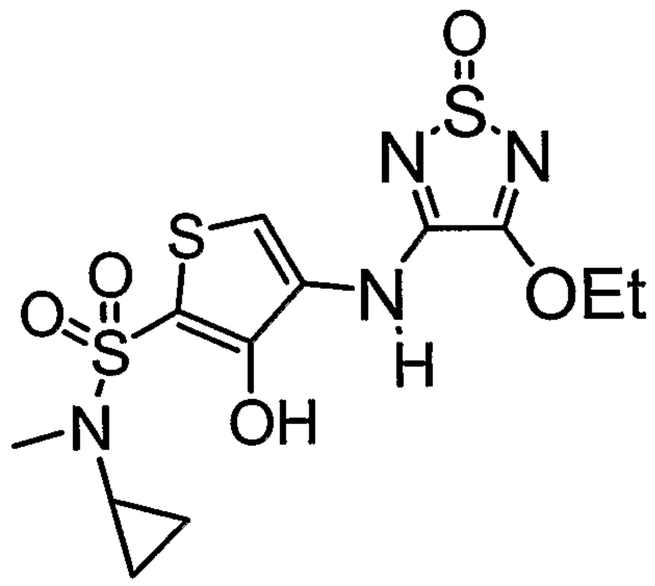
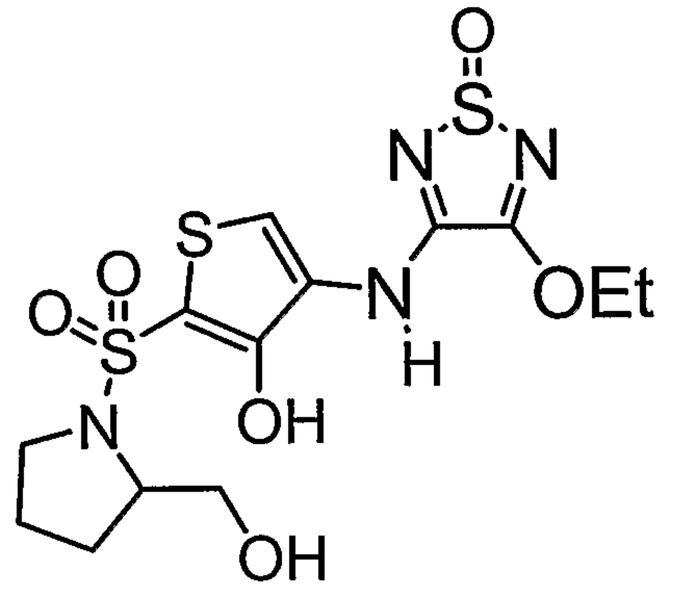
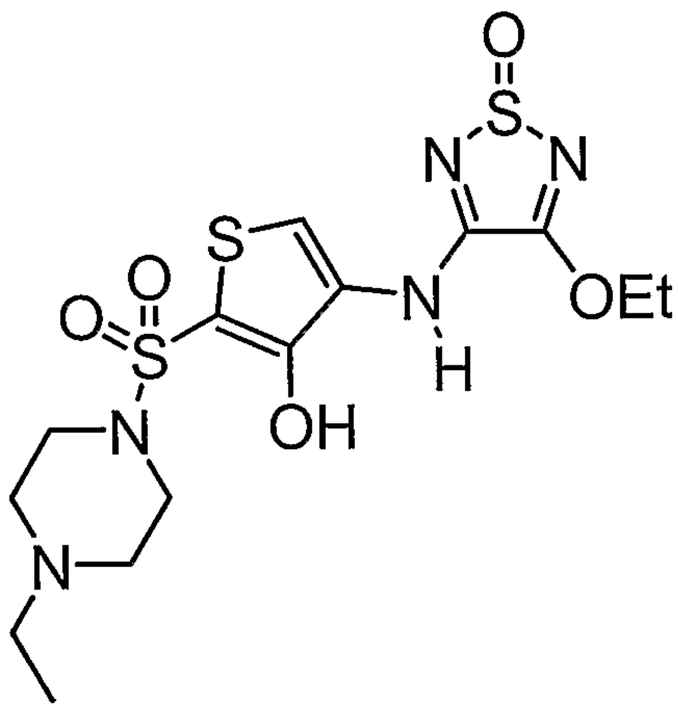
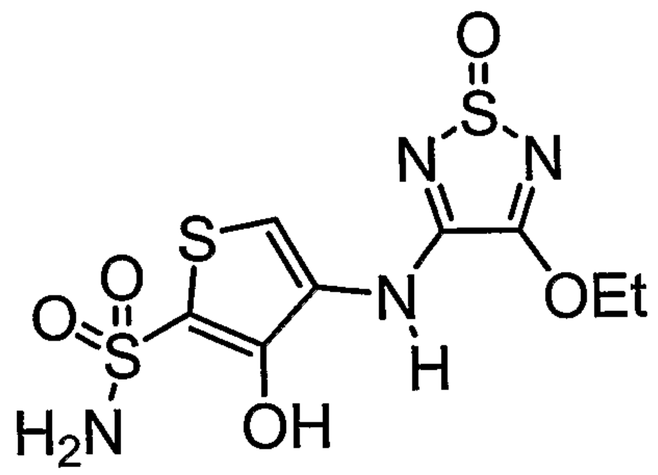
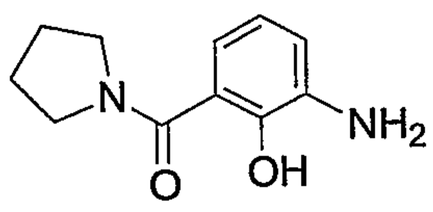
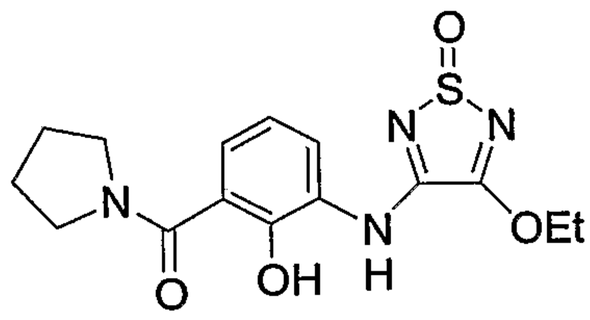
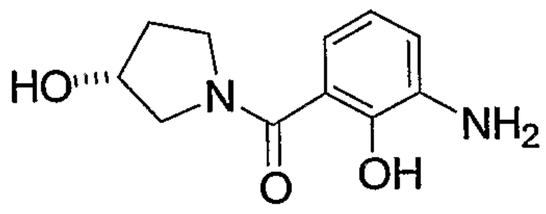
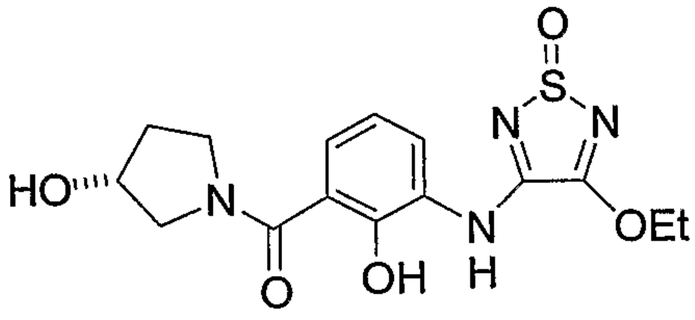
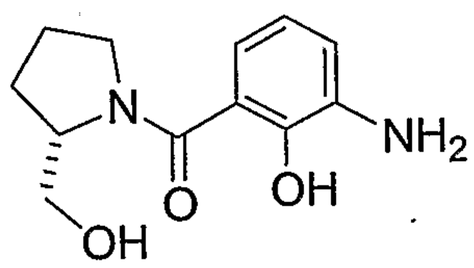
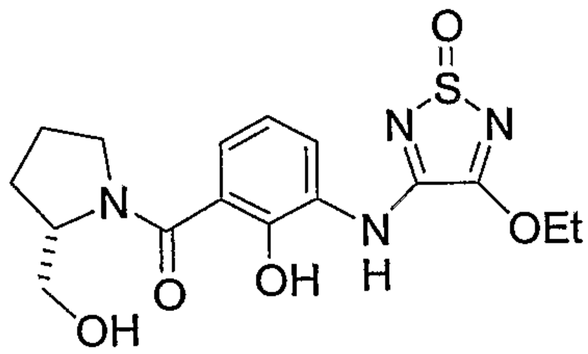
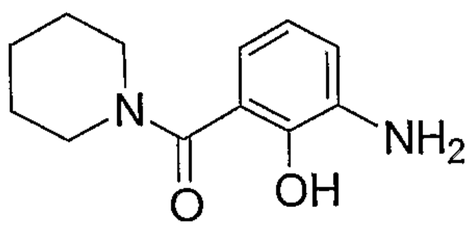
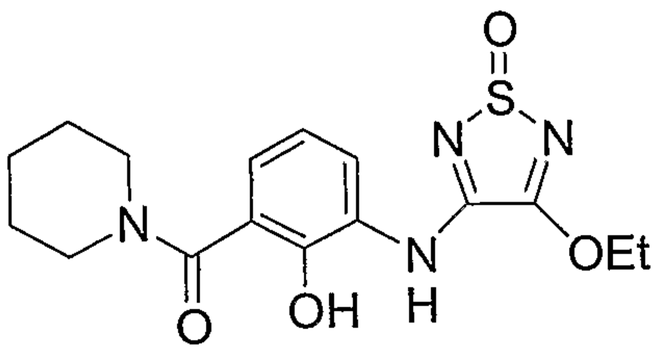
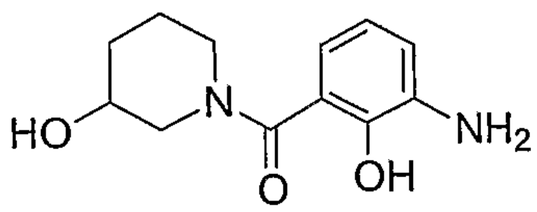
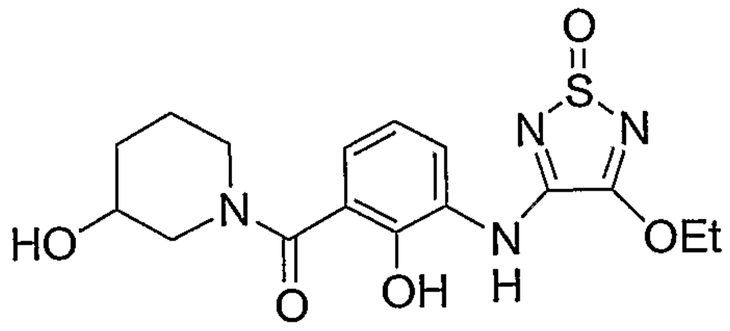
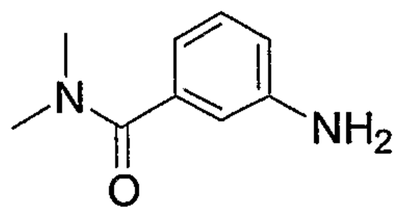
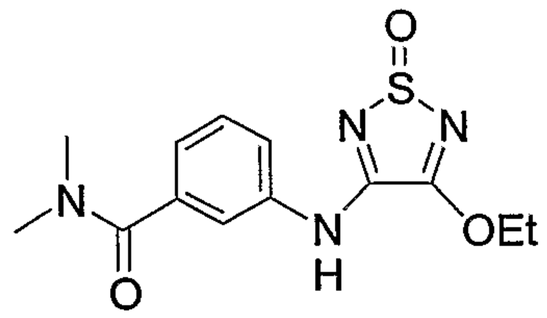
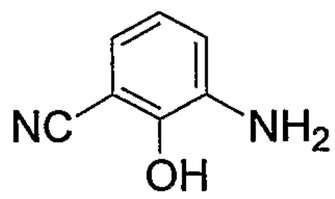
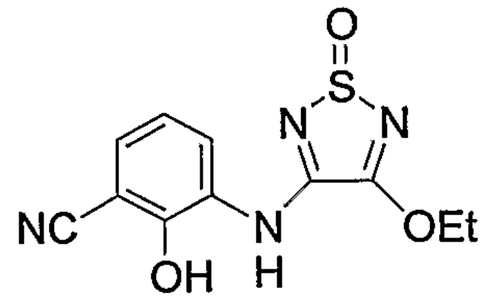
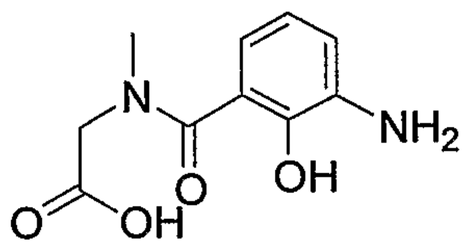
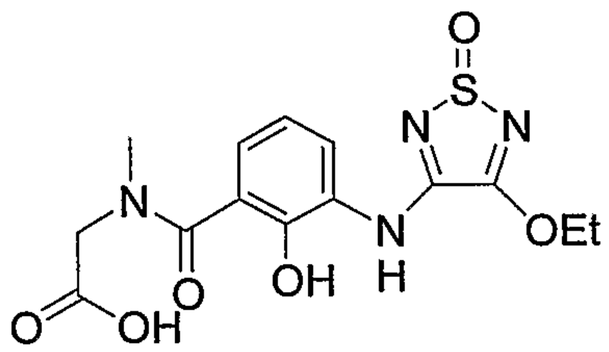
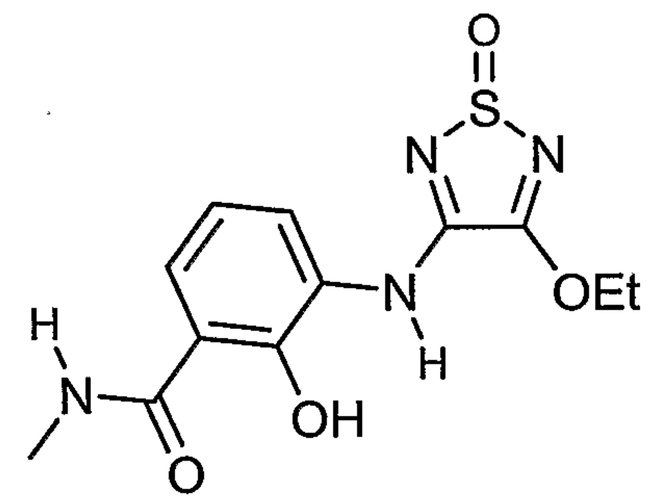
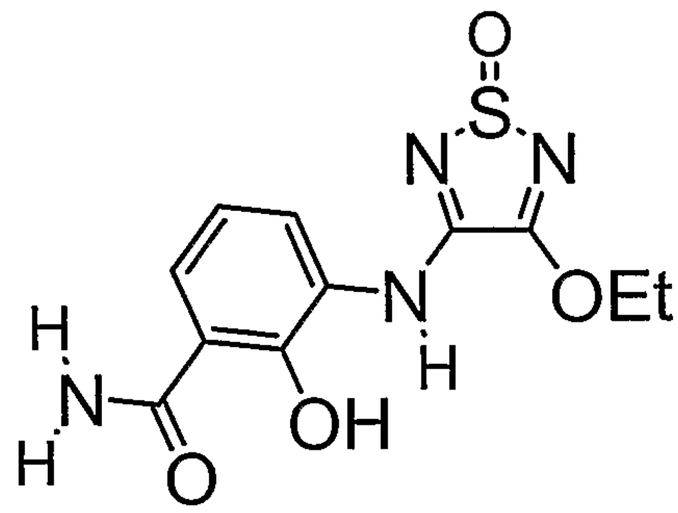
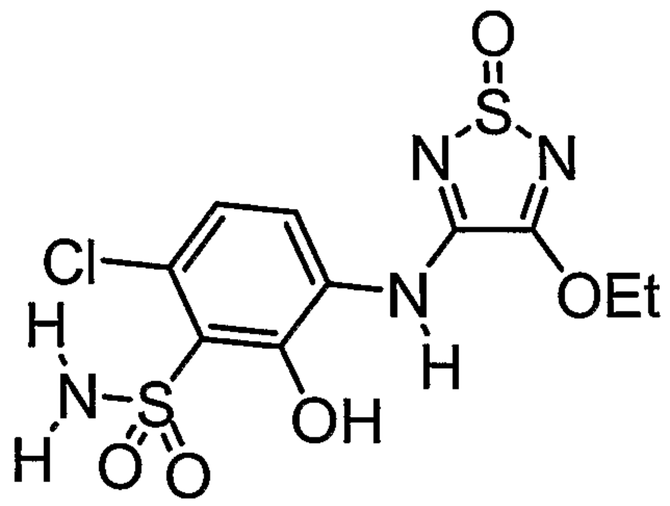
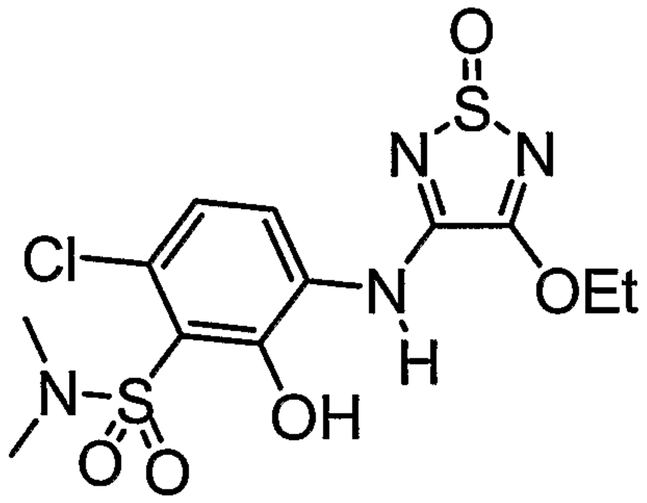
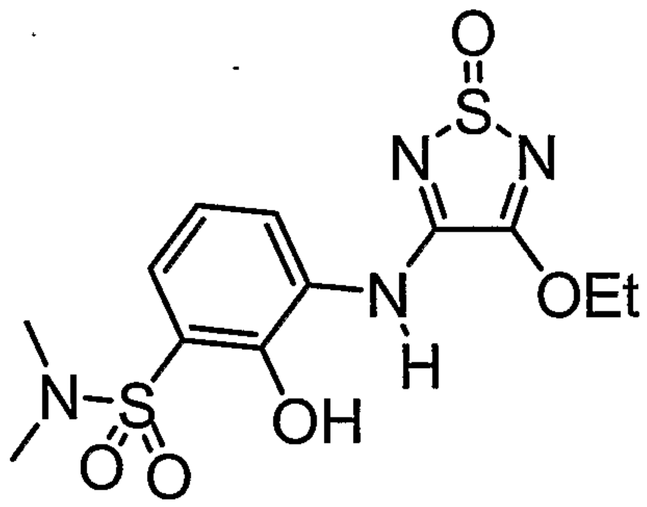
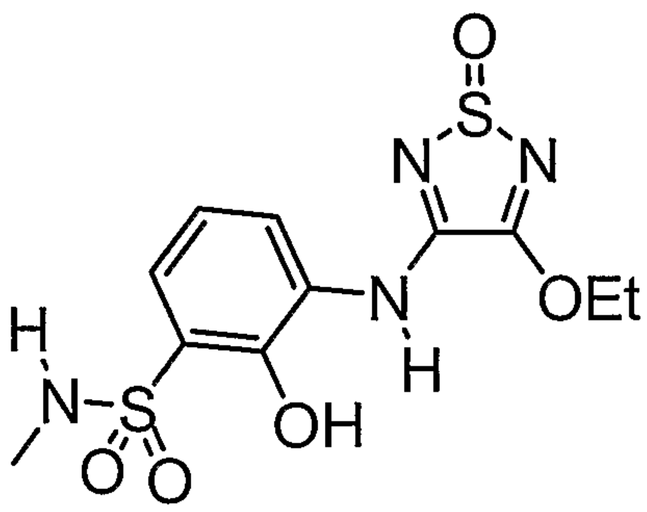
160		
161		
162		

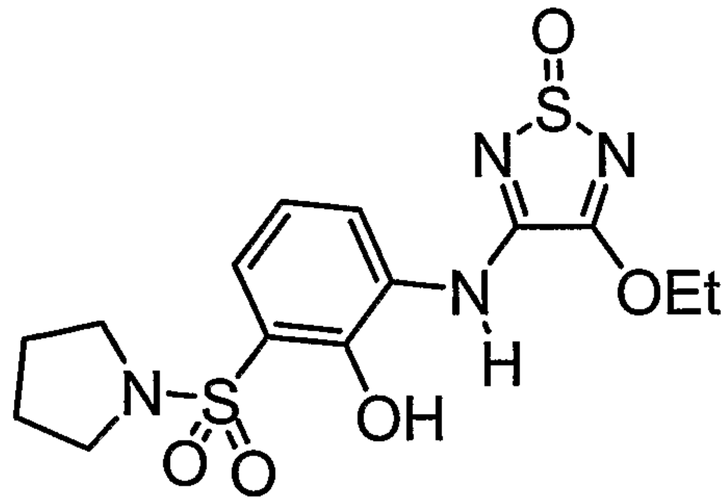
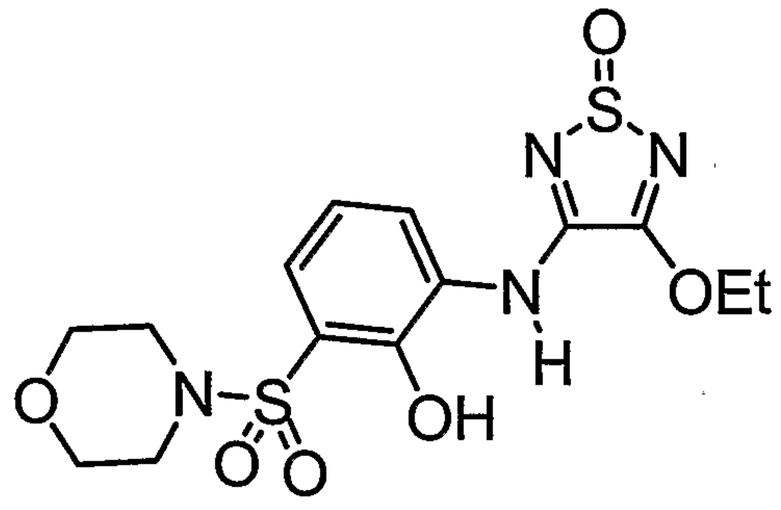
163		
164		
165		
166		
167		

168		
250	1316A	
251	1317	
252	1318	

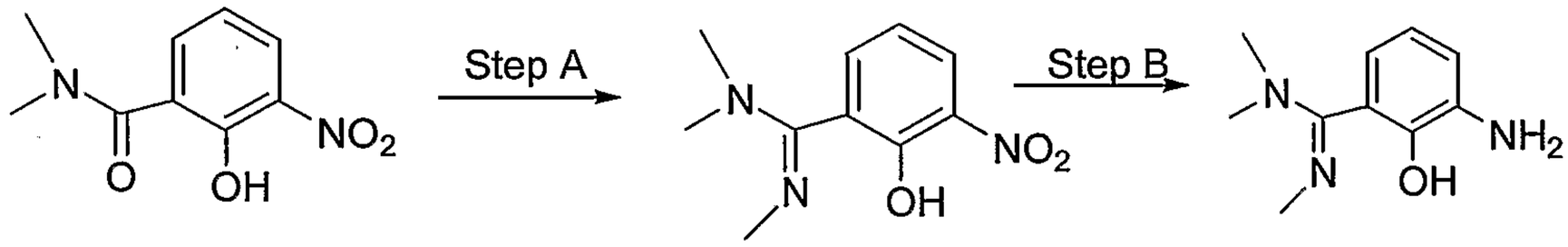
253	1205A	
350		
351		
352		
353		
354		

355		
356		
357		
450	6	
451	5	

452	13.9	
453	19.1	
454	19	
455	1304B	

456	23.10A	
457	1304A	

PREPARATIVE EXAMPLE 500.1



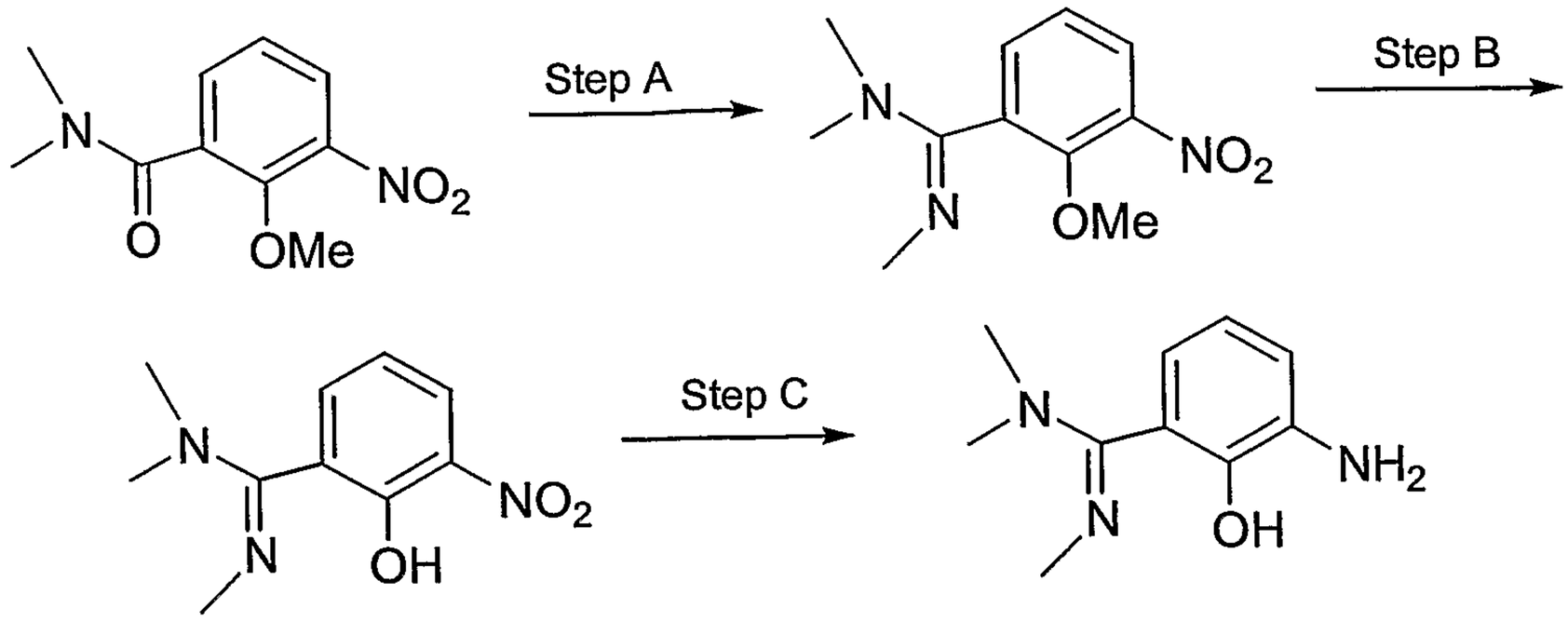
Step A

By using the nitro-amide from Preparative Example 13.3, Step A, the amidine structure can be prepared following a similar procedure to that in *Tetrahedron Lett.,* **2000**, 41 (11), 1677-1680 (the disclosure of which is incorporated herein by refernce thereto).

Step B

By using the product from Step A and the procedure set forth in Preparative Example 2, Step B, one could obtain the desired amine-amidine.

ALTERNATE PREPARATIVE EXAMPLE 500.2



Step A

By treating the nitro-amide from Preparative Example 13.3, Step B with $POCl_3$ and subsequently $MeNH_2$, according to procedures known in the art, one would obtain the desired compound.

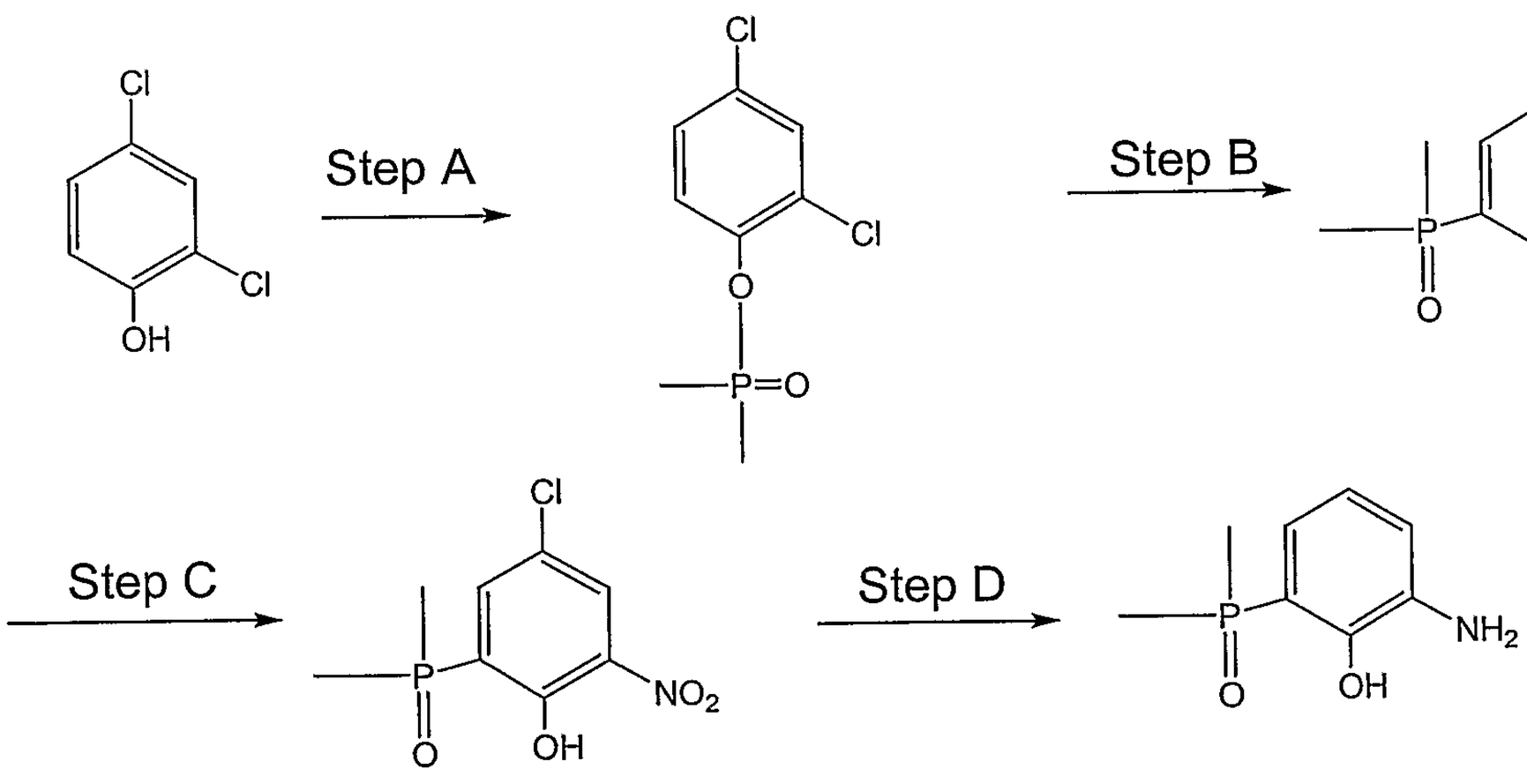
Step B

By treating the product from Step A according to the procedure set forth in Preparative Example 13.3, Step E, one could obtain the desired compound.

Step C

By using the product from Step B and the procedure set forth in Preparative Example 2 Step B, one would obtain the desired compound.

PREPARATIVE EXAMPLE 500.3



Step A

By following a similar procedure as that described in *Zh. Obshch. Khim.*, 27, **1957**, 754, 757 (the disclosure of which is incorporated herein by reference thereto), but instead using 2,4-dichlorophenol and dimethylphosphinic chloride, one would obtain the desired compound.

Step B

By following a similar procedure as that described in *J. Organomet. Chem.*; 317, **1986**, 11-22 (the disclosure of which is incorporated herein by reference thereto), one would obtain the desired compound.

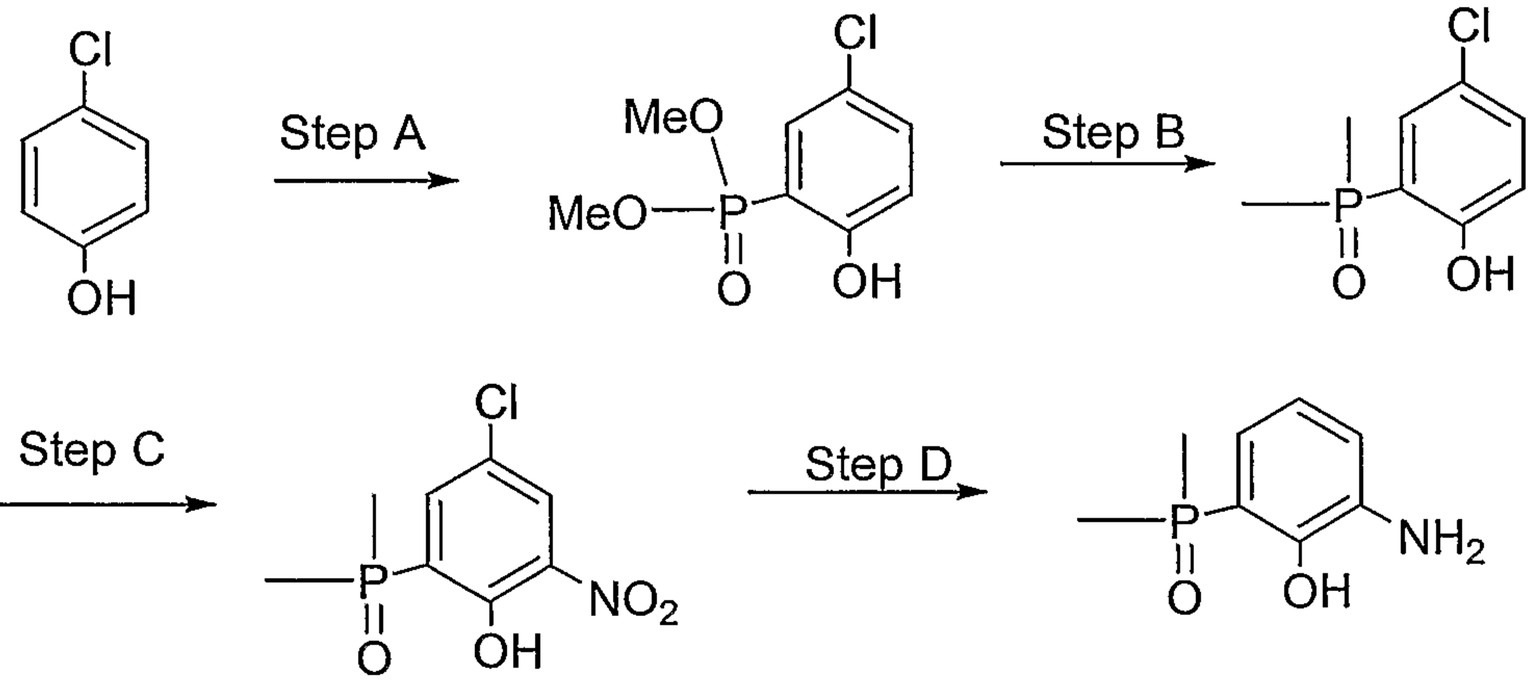
Step C

By following a similar procedure as that described in *J. Amer. Chem. Soc.*, 77, **1955**, 6221 (the disclosure of which is incorporated herein by reference thereto), one would obtain the desired compound.

Step D

By following a similar procedure as that described in *J. Med. Chem.*, 27, **1984**, 654-659 (the disclosure of which is incorporated herein by reference thereto), one would obtain the desired compound.

ALTERNATE PREPARATIVE EXAMPLE 500.4



Step A

By following a similar procedure as that described in *Phosphorous, Sulfur Silicon Relat. Elem.*; EN; 61, 12, **1991**, 119-129 (the disclosure of which is

incorporated herein by reference thereto), but instead using 4-chlorophenol, one would obtain the desired compound.

Step B

By using a similar procedure as that in *Phosphorous, Sulfur Silicon Relat. Elem.*; EN; 61, 12, **1991**, 119-129 (the disclosure of which is incorporated herein by reference thereto), but instead using MeMgBr, the desired compound could be prepared.

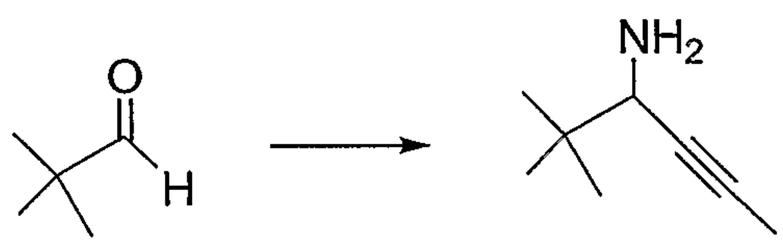
Step C

By following a similar procedure as that described in *J. Amer. Chem. Soc.*, 77, **1955**, 6221 (the disclosure of which is incorporated herein by reference thereto), one would obtain the desired compound.

Step D

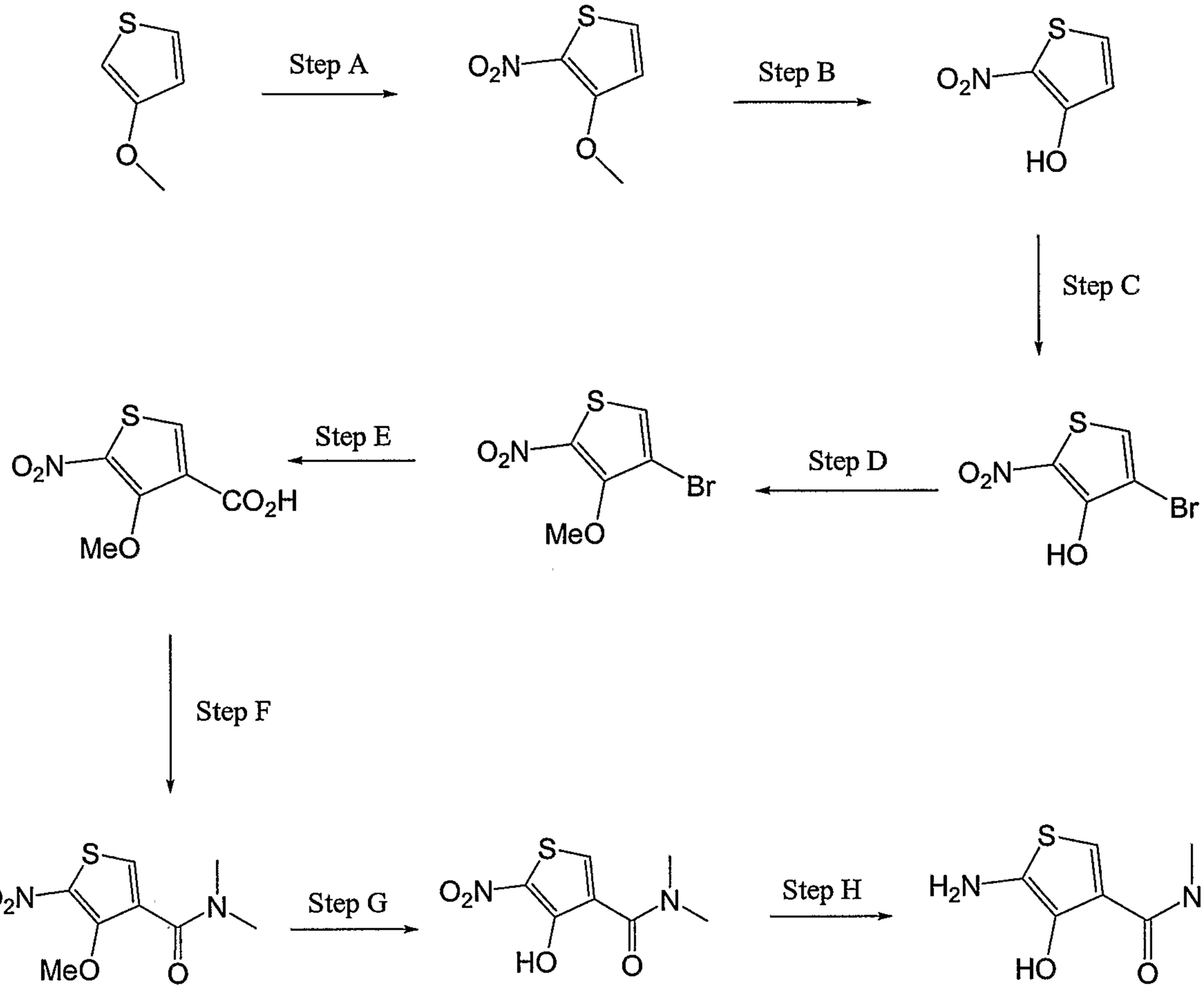
By following a similar procedure as that described in *J.Med. Chem.*, 27, **1984**, 654-659 (the disclosure of which is incorporated herein by reference thereto), one would obtain the desired compound.

PREPARATIVE EXAMPLE 500.5



By following a similar procedure as that set forth in *J. Org. Chem.* **1998**, 63, 2824-2828 (the disclosure of which is incorporated herein by reference thereto), but using $CH_3CCMgBr$, one could obtain the desired compound.

PREPARATIVE EXAMPLE 500.6



Step A

By following the procedure set forth in Preparative Example 13.1, Step B using 3-methoxythiophene, one could obtain the desired product.

Step B

By using the product from step A and following the procedure set forth in Preparative Example 13.19, Step E, the desired compound could be obtained.

Step C

By using the product from Step B and following the procedure set forth in Preparative Example 13.29, Step D, one could obtain the desired compound.

Step D

By using the product from Step C and following the procedure set forth in Preparative Example 13.3, Step B, the desired compound could be obtained.

Step E

By treating the product from Step D with n-BuLi at –78°C in THF and quenching the resulting anion with CO_2 according to standard literature procedure, one could obtain the desired compound following aqueous acid work up.

Step F

By using the product from Step E and the procedure set forth in Prepartive Example 13.19, Step C, one could obtain the desired compound.

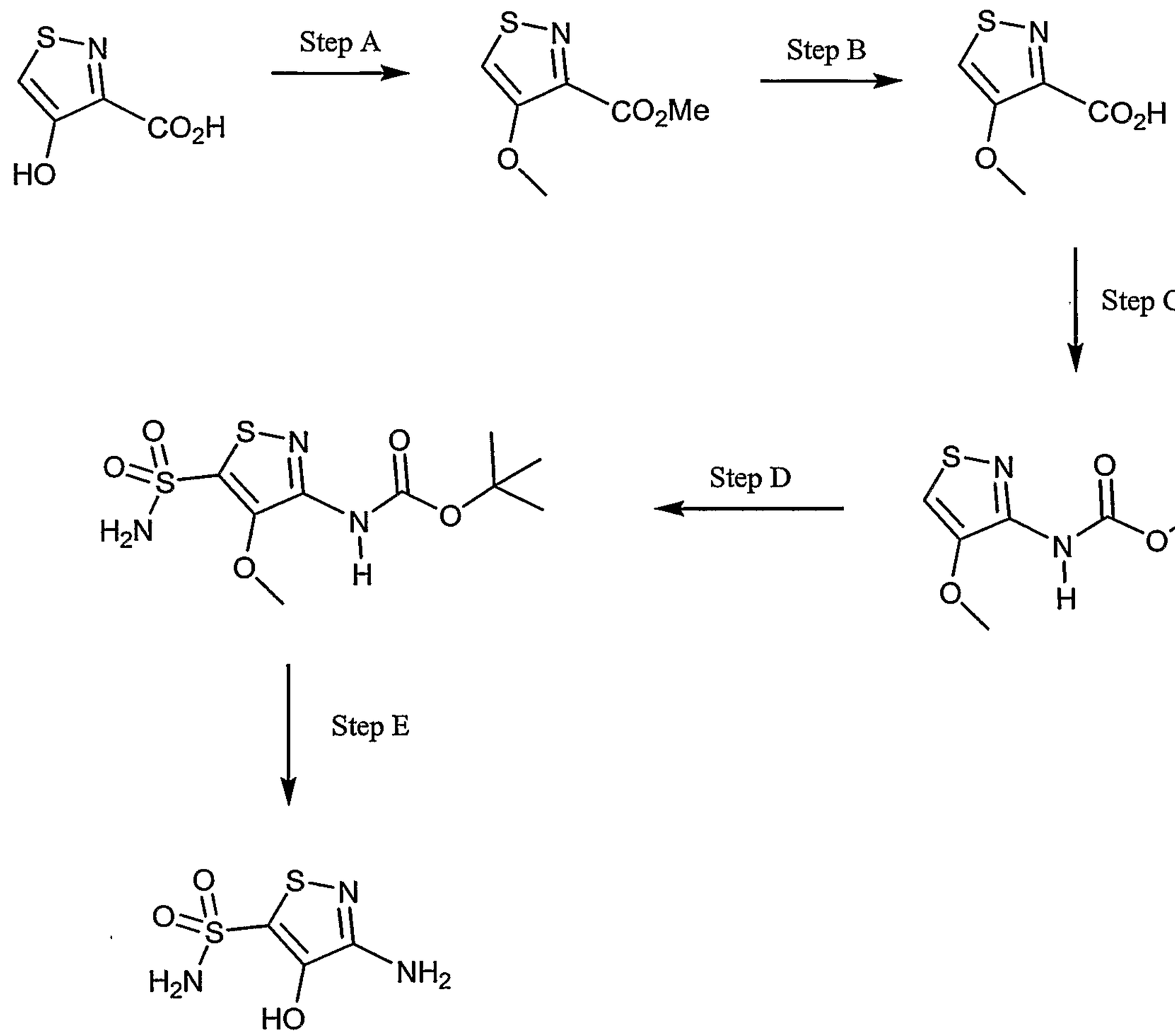
Step G

By using the product from step F and following the procedure set forth in Preparative Example 13.19, Step E, the desired compound could be obtained.

Step H

By using the product from Step G and following the procedure set forth in Preparative Example 2, Step B, the desired compound could be obtained.

PREPARATIVE EXAMPLE 500.7



Step A

If one were to use a similar procedure to that used in Preparative Example 13.3 Step B, except using the hydroxy acid from *Bioorg. Med. Chem. Lett.* 6(9), 1996, 1043 (the disclosure of which is incorporated herein by reference thereto), one would obtain the desired methoxy compound.

Step B

If one were to use a similar procedure to that used in Preparative Example 13.19 Step B, except using the product from Step A above, one would obtain the desired compound.

Step C

If one were to use a similar procedure to that used in *Synth. Commun.* 1980, 10, p. 107 (the disclosure of which is incorporated herein by reference thereto), except

using the product from Step B above and t-butanol, one would obtain the desired compound.

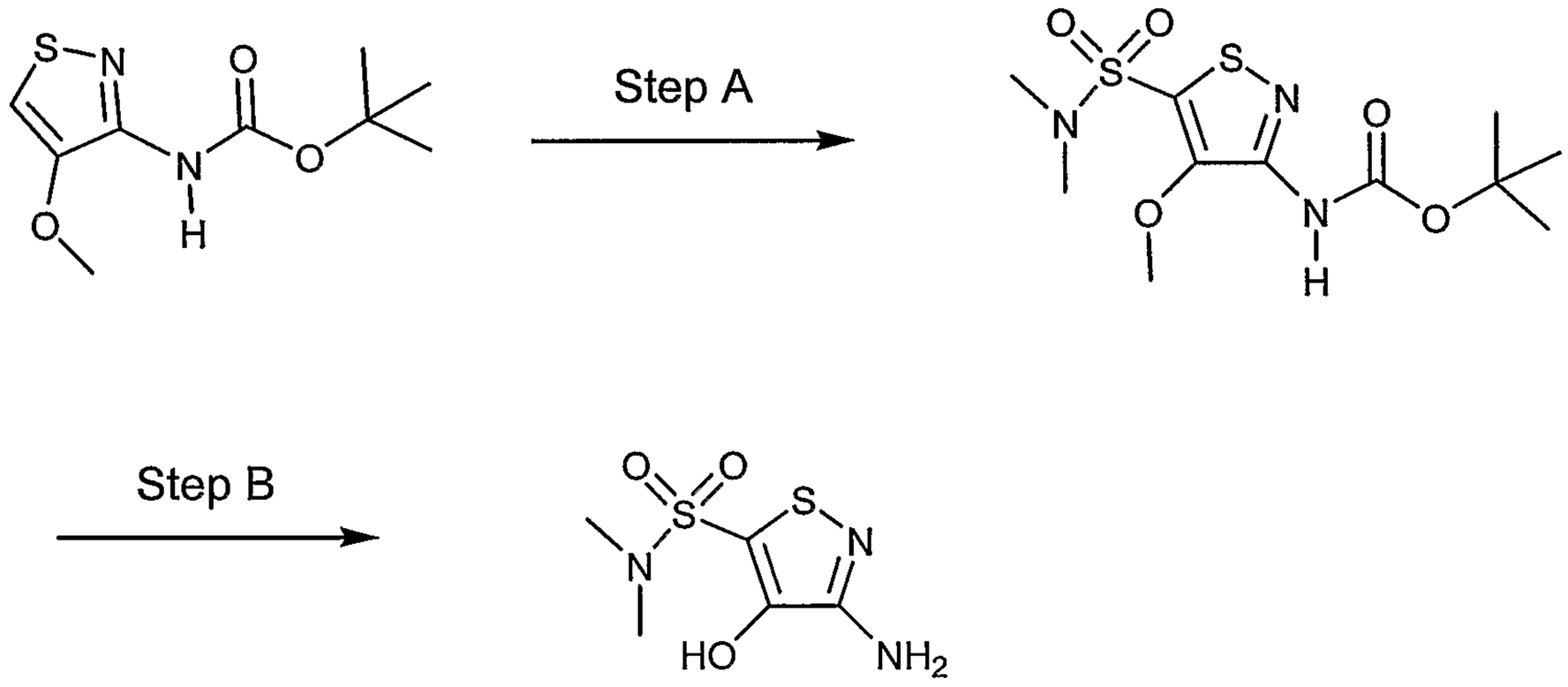
Step D

If one were to use a similar procedure to that used in *Synthesis,* 1986, 1031 (the disclosure of which is incorporated herein by reference thereto), except using the product from Step C above, one would obtain the desired sulfonamide compound.

Step E

If one were to use a similar procedure to that used in Preparative Example 13.19 Step E, except using the product from Step D above, one would obtain the desired compound.

PREPARATIVE EXAMPLE 500.8



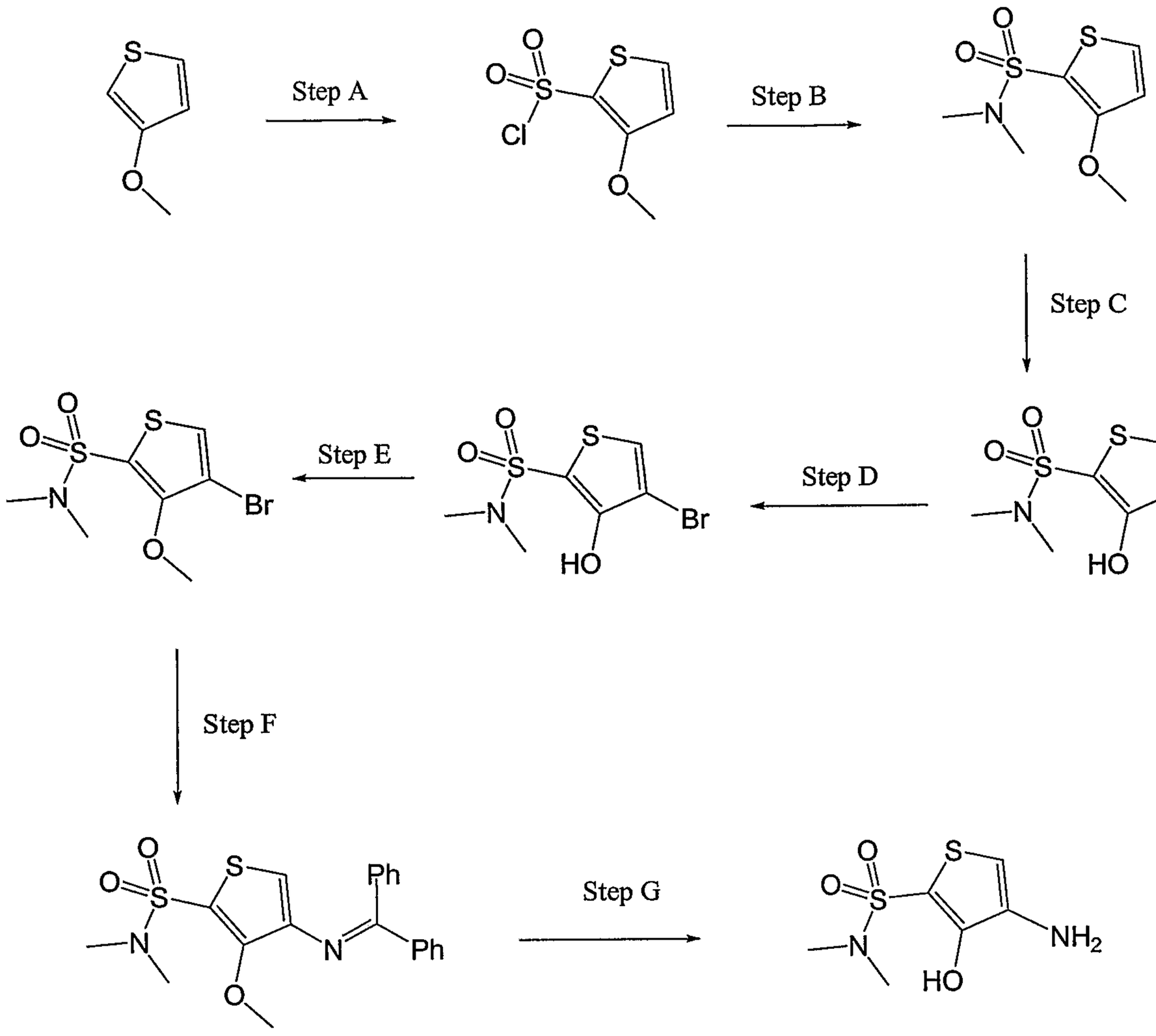
Step A

If one were to treat the product from Step C of Example 1125 with BuLi (2.2 eq.) in THF followed by quenching of the reaction mixture with N,N,-dimethylsulfamoyl chloride (1.1 eq.) then one would obtain

Step B

If one were to use the product of Step A above and follow Step E of Preparative Example 500.7, then one would obtain the title compound.

PREPARATIVE EXAMPLE 500.9



Step A

To a solution of 3-methoxythiophene (3 g) in dichloromethane (175 mL) at –78°C was added chlorosulfonic acid (8.5 mL) dropwise. The mixture was stirred for 15 min at –78°C and 1.5 h at room temp. Afterwards, the mixture was poured carefully into crushed ice, and extracted with dichloromethane. The extracts were washed with brine, dried over magnesium sulfate, filtered through a 1-in silica gel pad. The filtrate was concentrated in vacuo to give the desired compound (4.2 g).

Step B

The product from Step A above (4.5 g) was dissolved in dichloromethane (140 mL) and added with triethylamine (8.8 mL) followed by diethyl amine in THF (2*M*, 21 mL). The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine and saturated bicarbonate (aq) and brine again, dried over

sodium sulfate, filtered through a 1-in silica gel pad. The filtrate was concentrated in vacuo to give the desired compound (4.4 g).

Step C

The product from Step B above (4.3 g) was dissolved in dichloromethane (125 mL) and cooled in a -78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 24.3 mL) was added. The mixture was stirred for 4 h while the temperature was increased slowly from -78°C to 10°C. H_2O was added, the two layers were separated, and the aqueous layer was extracted with dichloro- methane. The combined organic layer and extracts were wahed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 3.96 g of the desired hydroxy-compound.

Step D

The product from step C above (3.96 g) was dissolved in 125 mL of dichloromethane, and added with potassium carbonate (6.6 g) followed by bromine (2 mL). The mixture was stirred for 5 h at room temperature, quenched with 100 mL of H_2O. The aqueous mixture was addjusted to pH ~ 5 using a 0.5N hydrogen chloride aqueous solution, and extracted with dichloromethane. The extracts were washed with brine, dried over sodium sulfate, and filtered through a celite pad. The filtrate was concentrated in vacuo to afford 4.2 g of the desired bromo-compound.

Step E

The product from Step D (4.2 g) was dissolved in 100 mL of acetone and added with potassium carbonate (10 g) followed by iodomethane (9 mL). The mixture was heated to reflux and continued for 3.5 h. After cooled to room temperature, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo to a dark brown residue, which was purified by flash column chromatography eluting with dichloromethane-hexanes (1:1, v/v) to give 2.7 g of the desired product.

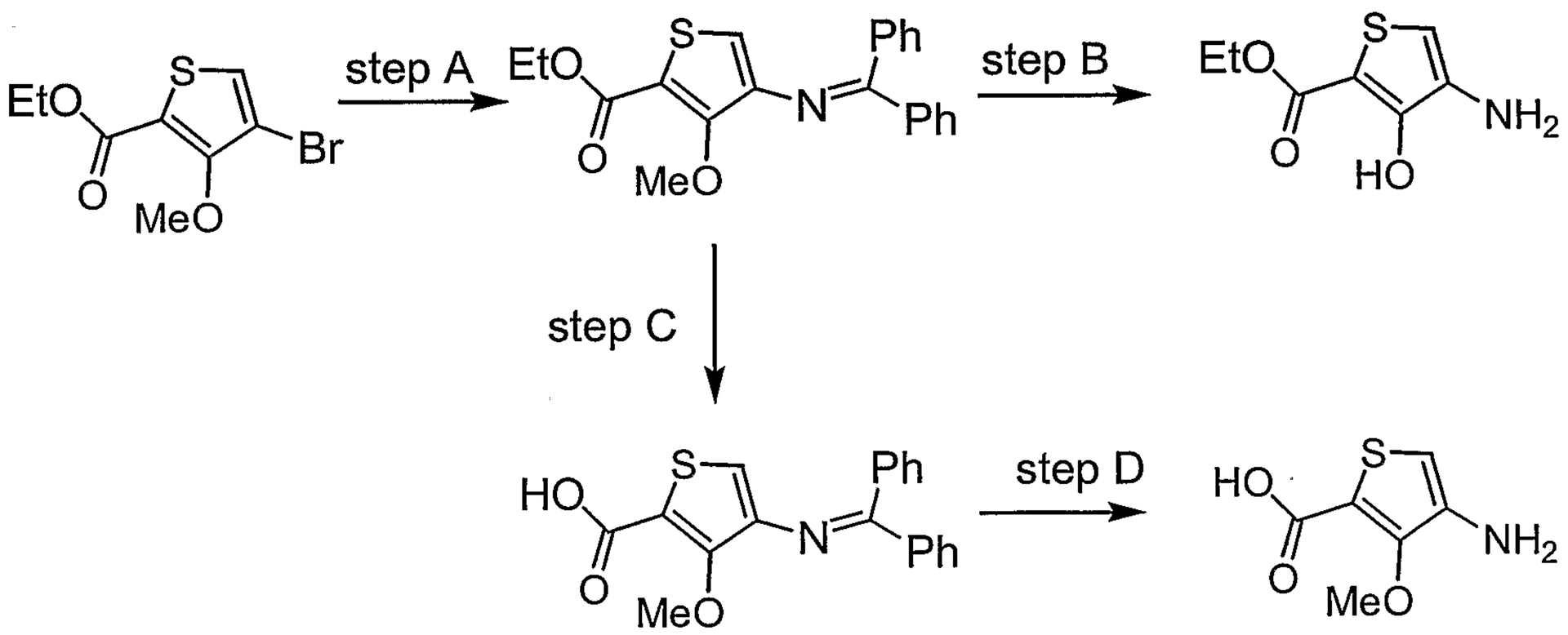
Step F

The product from step E (2.7 g) was converted to the desired imine compound (3 g), following the similar procedure to that of Preparative Example 13.19 step D.

Step G

The imine product from step F (3 g) was dissolved in 80 mL of dichloromethane and cooled in a –78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 9.2 mL) was added dropwise. The mixture was stirred for 4.25 h from -78°C to 5°C. H_2O (50 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane. The organic layer and extracts were combined, washed with brine, and concentrated to an oily residue. The residue was dissolved in 80 mL of methanol, stirred with sodium acetate (1.5 g) and hydroxyamine hydrochloride (0.95 g) at room temperature for 2 h. The mixture was poured into an aqueous mixture of sodium hydroxide (1.0 M aq, 50 mL) and ether (100 mL). The two layers were separated. The aqueous layer was washed with ether three times. The combined ether washings were re-extracted with H_2O once. The aqueous layers were combined, washed once with dichloromethane, adjusted to pH ~ 6 using 3.0 M and 0.5 M hydrogen chloride aqueous solutions, and extracted with dichloromethane. The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 1.2 g of desired amine compound.

PREPARATIVE EXAMPLE 600



Step A

Following the procedure set forth in Preparative Example 13.19 Step D, the imine was prepared from the known bromoester (1.0g) to yield 1.1g (79%) as a yellow solid.

Step B

The product of Step A (0.6g) was reacted following the procedure set forth in Preparative Example 13.19 Step E to give the amine product 0.19g (64%).

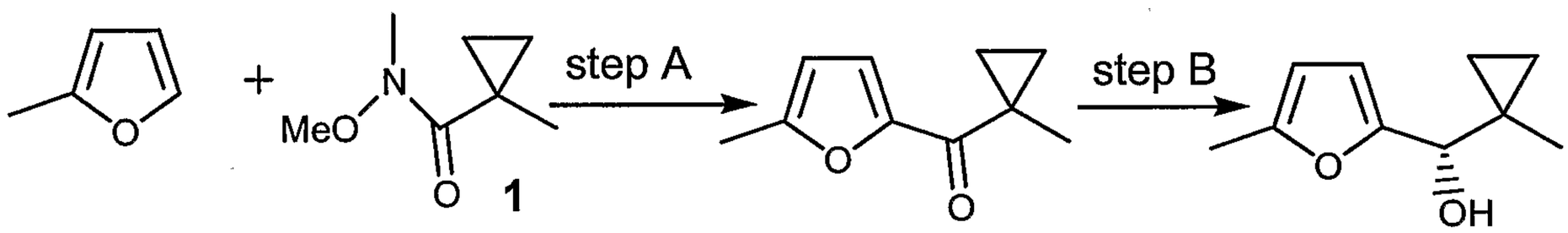
Step C

The product of Step B (1.0g) was reacted following the procedure set forth in Preparative Example 13.19 Step B to give the acid as yellow solid 0.9g (94%).

Step D

The product of Step C (0.35g) was reacted following the procedure set forth in Preparative Example 13.19 Step E to give the amino acid as yellow solid 0.167g (93%).

PREPARATIVE EXAMPLE 601



Step A

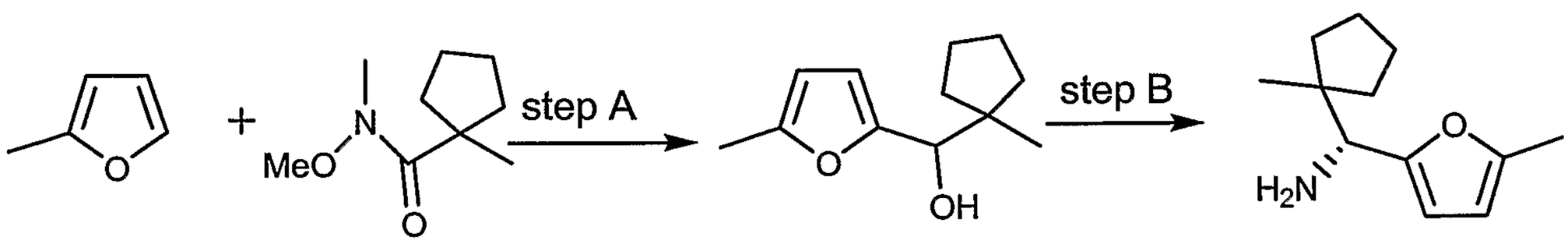
To a solution of 2-methyl furan (1.72g) in ether was added BuLi (8.38mL) at -78^0C and stirred at room temperature for half an hour. The reaction mixture again cooled to -78^0C and quenched with cyclopropyl amide **1** and stirred for two hours at -78^0C and slowly warmed to room temperature. The reaction mixture stirred for three hours at room temperature and quenched with the addition of saturated ammonium chloride solution. The mixture was taken to a separatory funnel, washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was purified by using column chromatography to afford the ketone 3.0g (87%) as a pale yellow oil.

Step B

To a solution of ketone (1.0g) from Step A above in THF (5.0mL) at 0^0C was added *R*-methyl oxazoborolidine (1.2Ml, 1M in toluene) dropwise followed by addition of a solution of borane complexed with dimethyl sulfide (1.85mL, 2M in THF). The reaction mixture was stirred for 30minutes at 0^0C and than at room temperature for

one hour. The reaction mixture was cooled to 0^0C and MeOH was added carefully. The mixture was stirred for 20 minutes and was concentrated under reduced pressure. The residue was extracted with ether, washed with water, 1M HCl (10mL), saturated sodium bicarbonate (10.0mL) water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and removal of solvent afforded the crude alcohol which was purified by silica gel chromatography to afford the pure alcohol 0.91g (91%) as yellow oil.

PREPARATIVE EXAMPLE 601.A



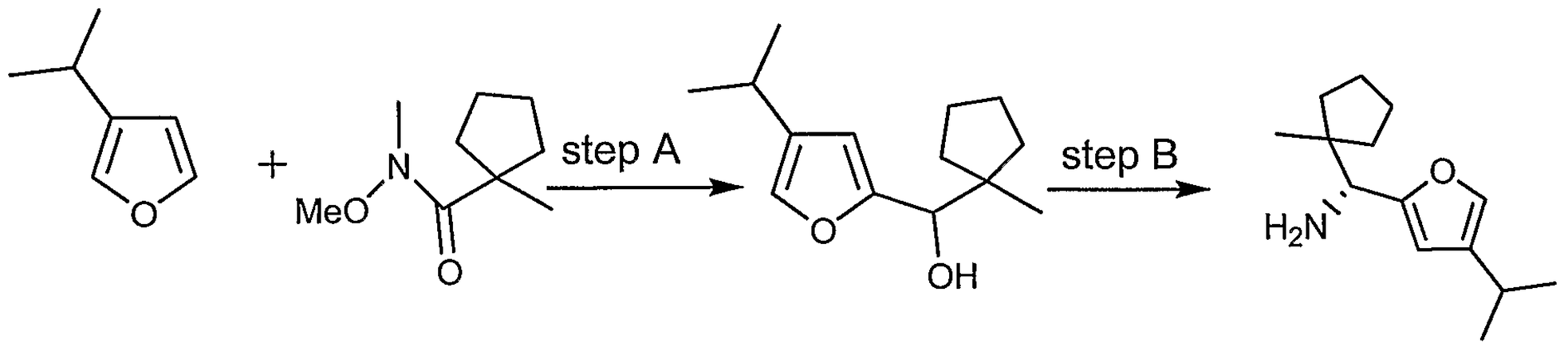
Step A

If one were to follow the procedure set forth in Preparative Example 601, but using the cyclopentylamide instead of the cyclopropylamide (prepared according to standard procedures), then one would obtain the desired alcohol.

Step B

If one were to follow the procedure set forth in Preparative Example 13.25, but instead using the alcohol from Step A above, then one would obtain the title amine.

PREPARATIVE EXAMPLE 601.B



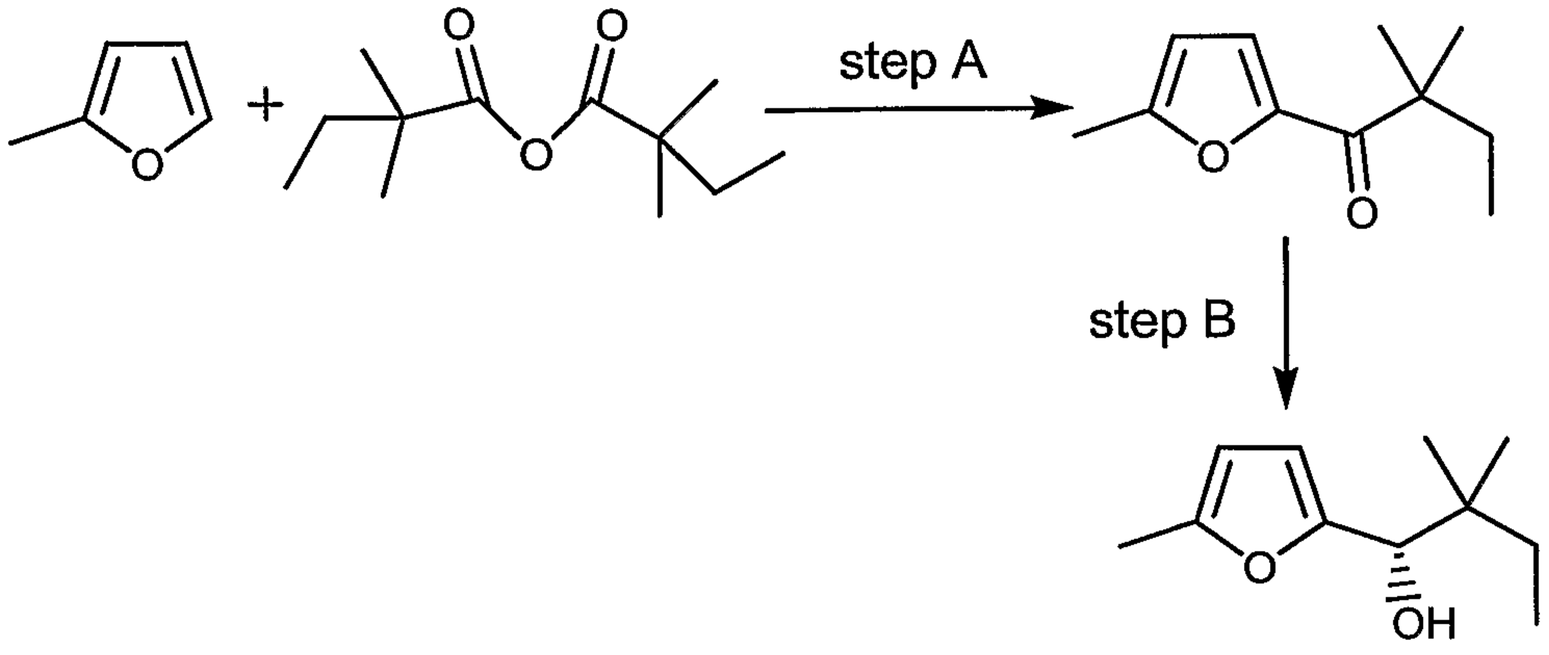
Step A

If one were to follow the procedure set forth in Preparative Example 601.A, but using 4-isopropylfuran instead of 5-methylfuran, then one would obtain the desired alcohol.

Step B

If one were to follow the procedure set forth in Preparative Example 13.25, but instead using the alcohol from Step A above, then one would obtain the title amine.

PREPARATIVE EXAMPLE 602



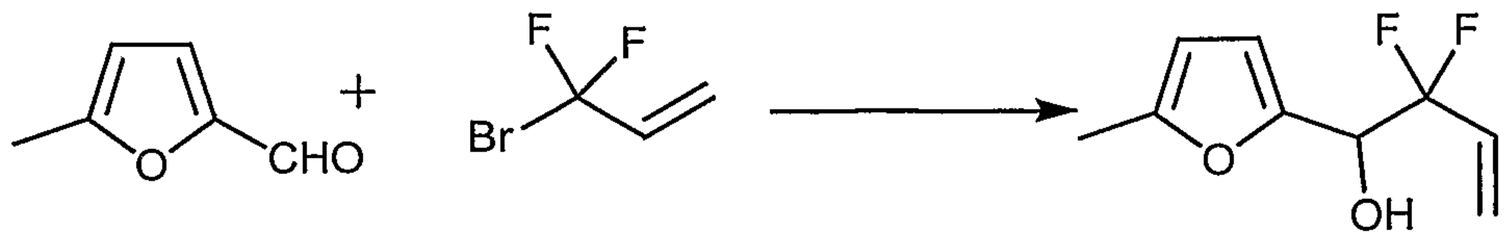
Step A

An equimolar mixture of 2-methylfuran (1.0g) and anhydride (2.6g) was mixed with $SnCl_4$ (0.05mL) and heated at 100^0C for 3 hours. After cooling the reaction mixture, water (10mL) was added, followed by saturated sodium carbonate solution until it becomes alkaline. The reaction mixture was extracted with ether several times and the combined ether layer was washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was purified by using silica gel chromatography to afford the ketone 0.9g (43%) as a yellow oil.

Step B

The title alcohol was obtained following a similar procedure set forth in the Preparative Example 601.

PREPARATIVE EXAMPLE 603

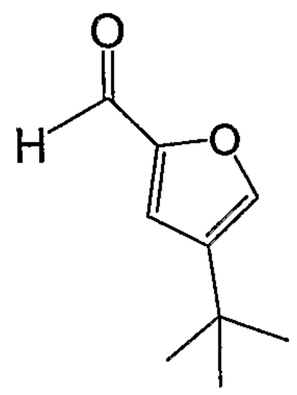
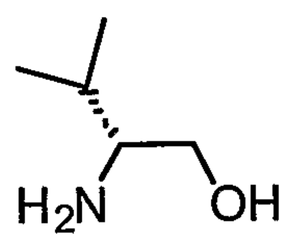
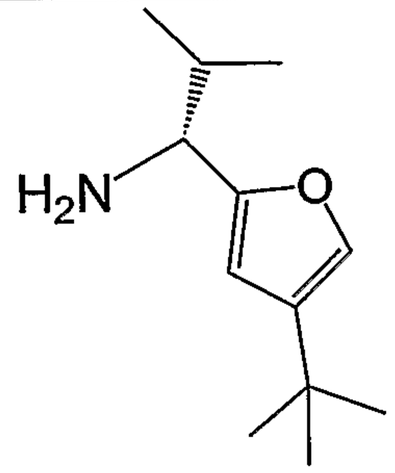
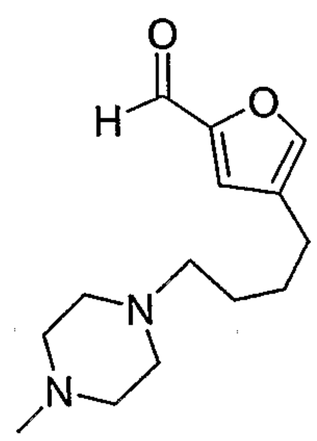
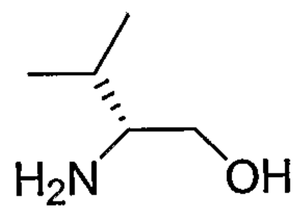
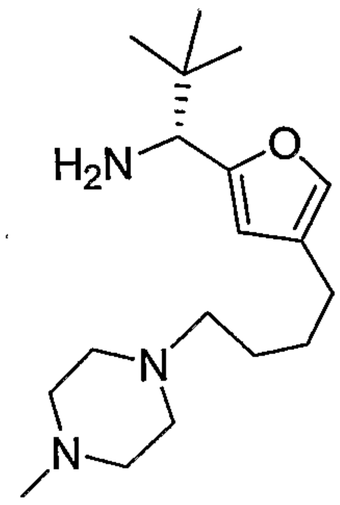
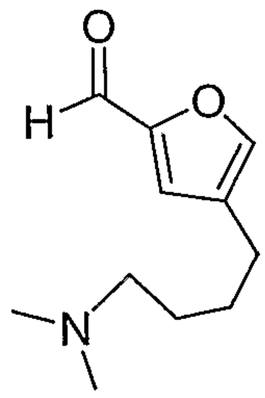
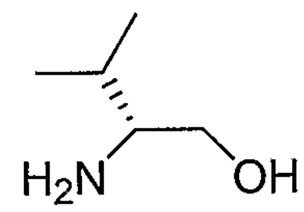
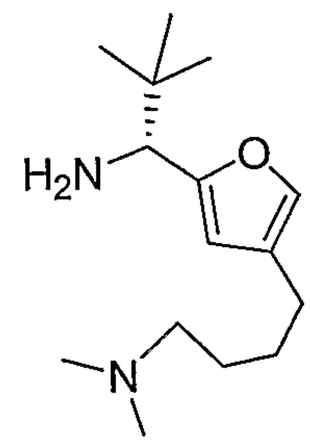


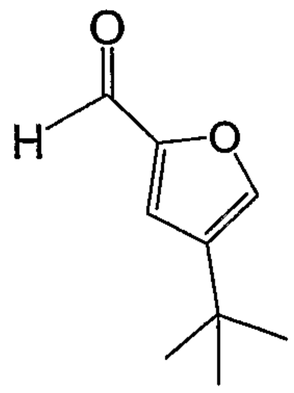
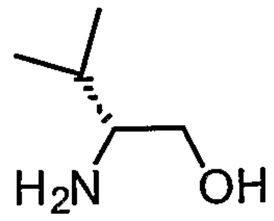
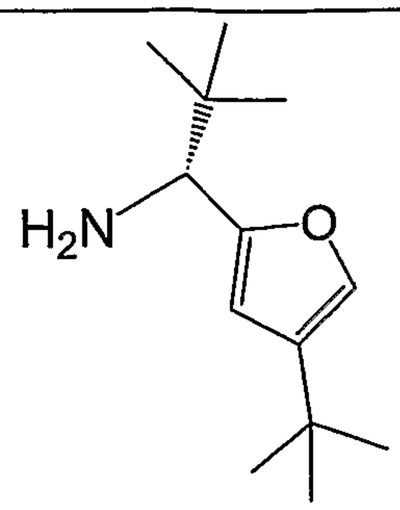
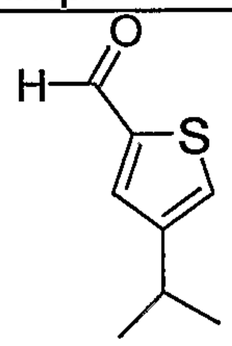
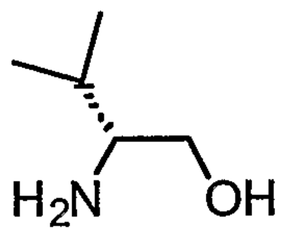
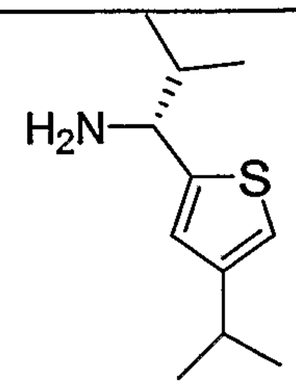
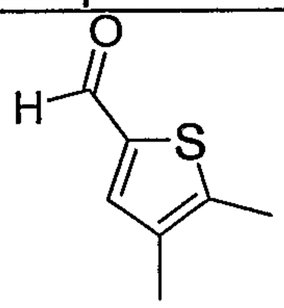
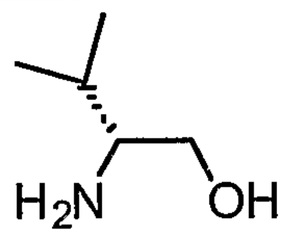
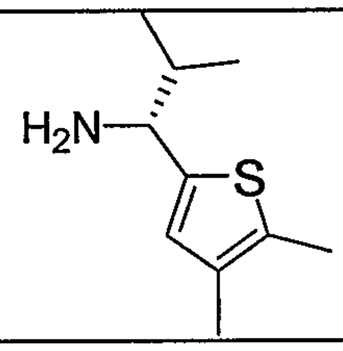
To a solution of 5-methyl furan-2-aldehyde (1.0g) and 3-bromo-3,3-difluoropropene (2.24g) in DMF (30mL) was added indium powder (1.66g) and lithium iodide (50.0mg). The reaction mixture was stirred over night, diluted with water and

extracted with ether. The ether layer was washed with water, brine and purified by silica gel chromatography to afford the pure alcohol 2.8g (92%).

PREPARATIVE EXAMPLES 603A-603F

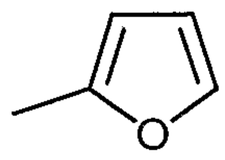
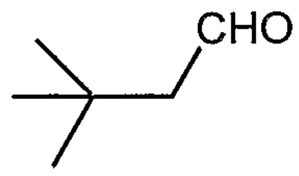
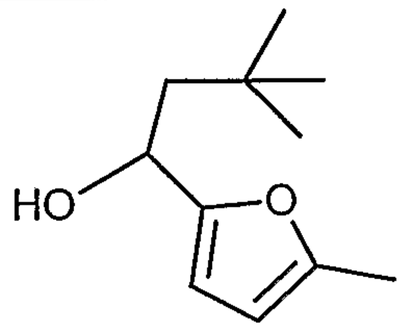
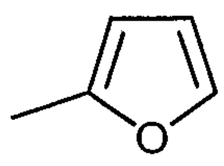
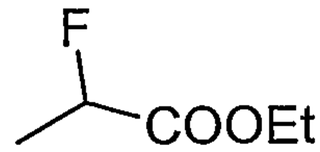
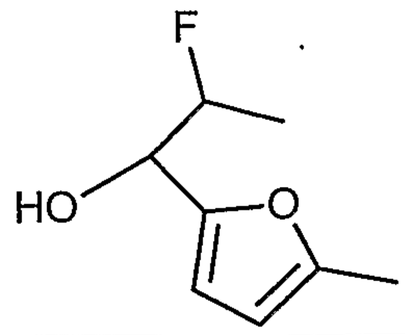
If one were to follow the procedure of Preparative Example 64, using the aldehydes, amino alcohols and organolithiums in the Table below, then the optically pure amine Products in the Table below would be obtained.

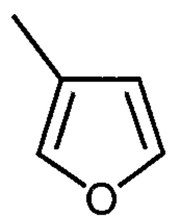
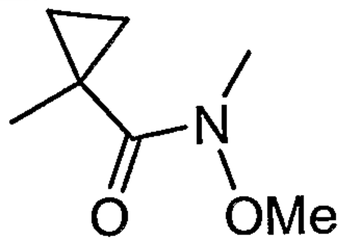
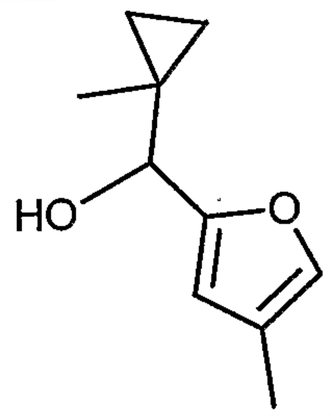
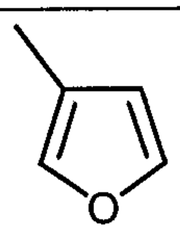
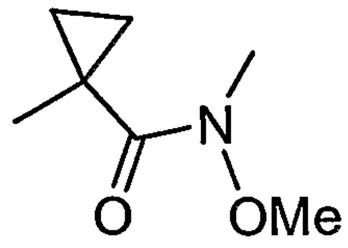
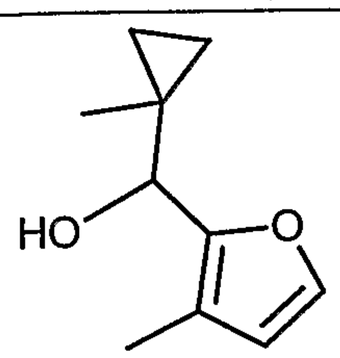
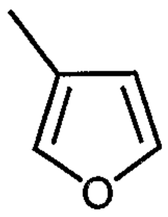
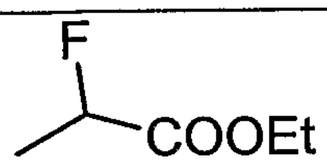
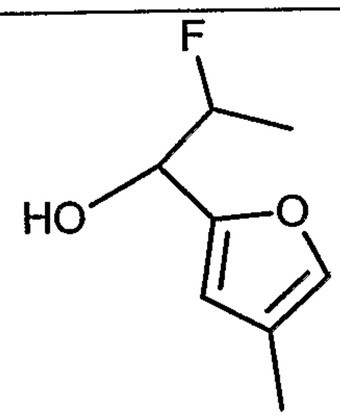
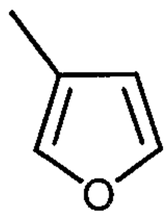
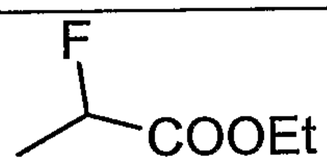
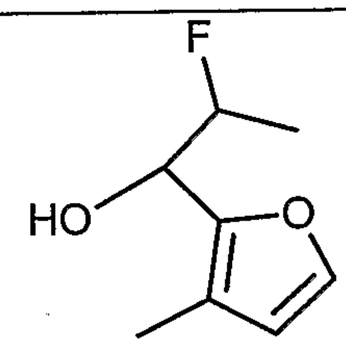
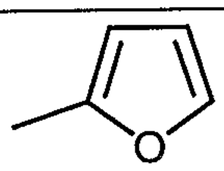
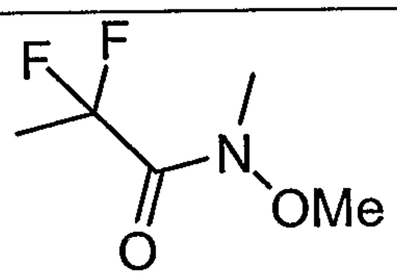
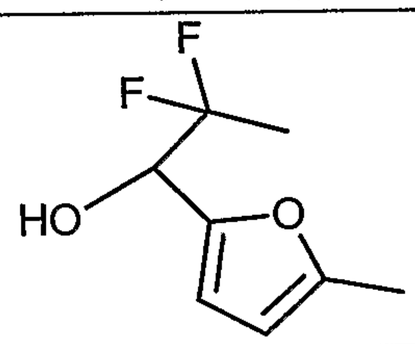
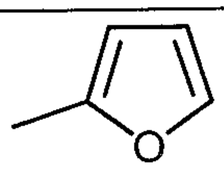
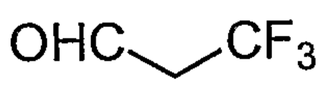
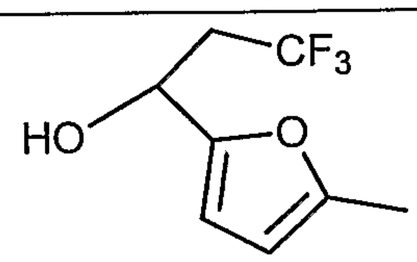
Prep. Ex.	Aldehyde	Amino Alcohol	Organolithium	Product
603A	 (see Preparative Example 1004B)		iPrLi	
603B			tBuLi	
603C			tBuLi	

603D	 (see Preparative Example 1004B)		tBuLi	
603E	 (see preparative example 1002B)		iPrLi	
603F			iPrLi	

PREPARATIVE EXAMPLES 604-611

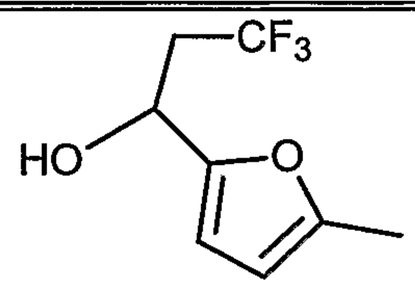
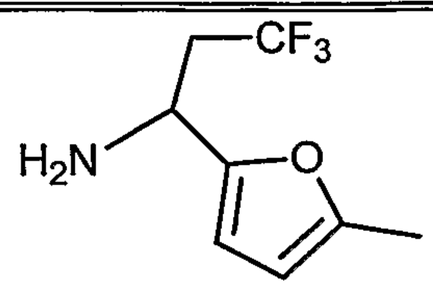
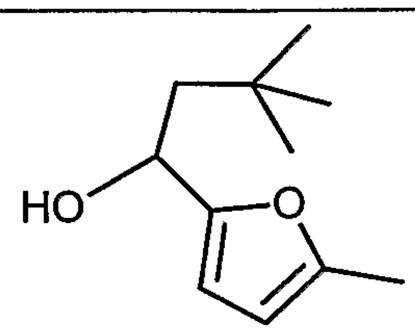
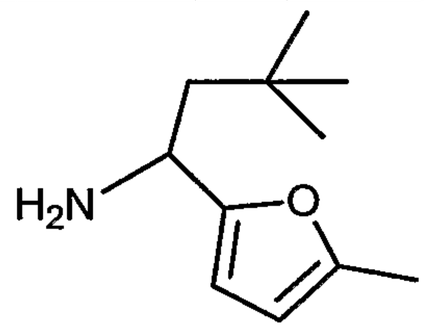
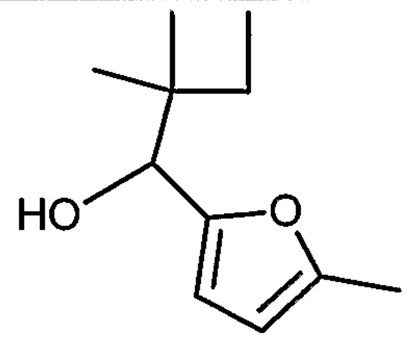
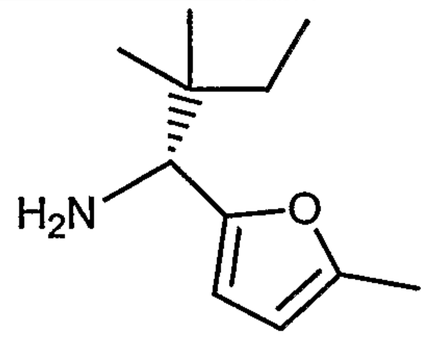
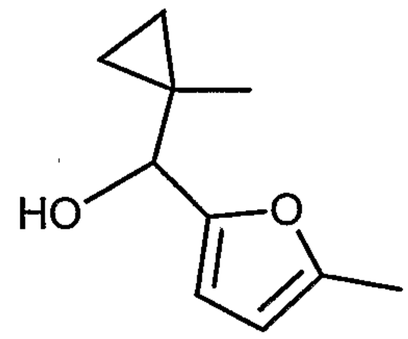
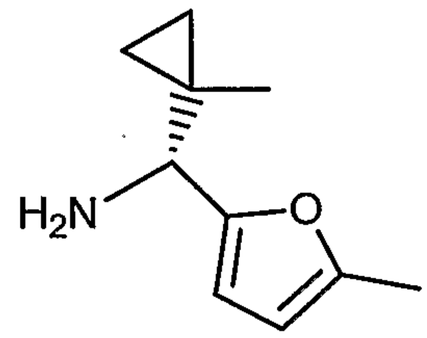
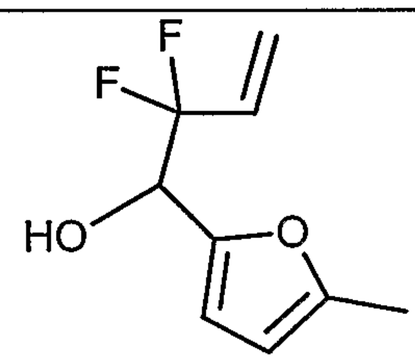
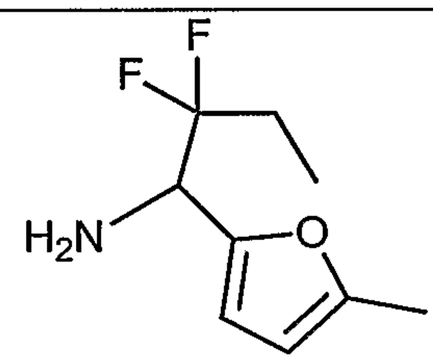
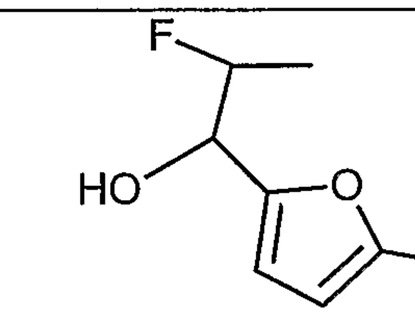
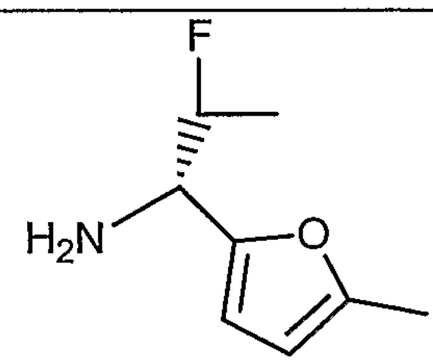
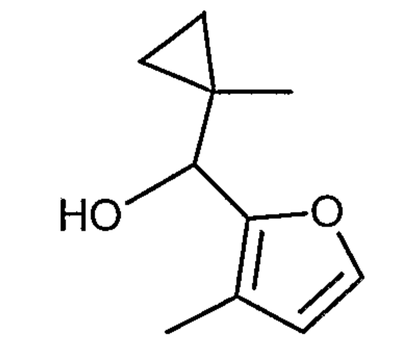
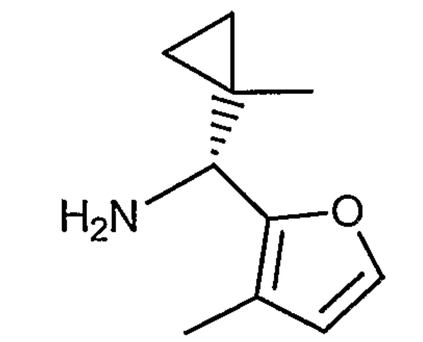
Following a similar procedure set forth in Preparative Examples 13.25 or 601 the following Alcohols were prepared.

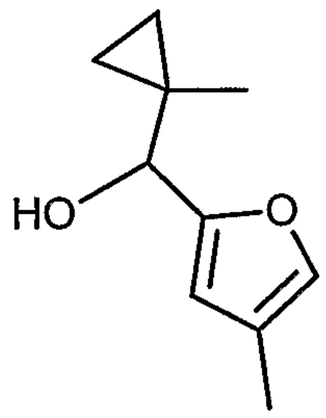
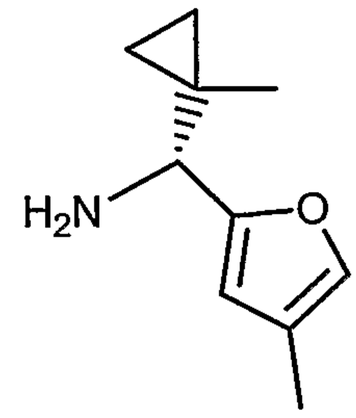
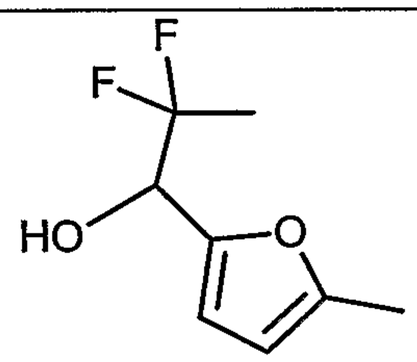
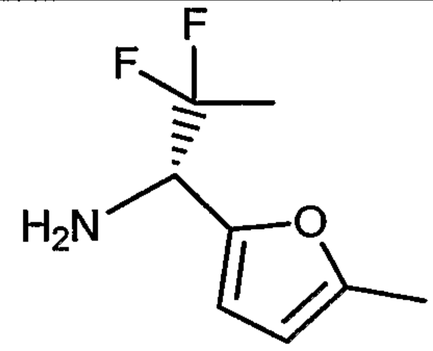
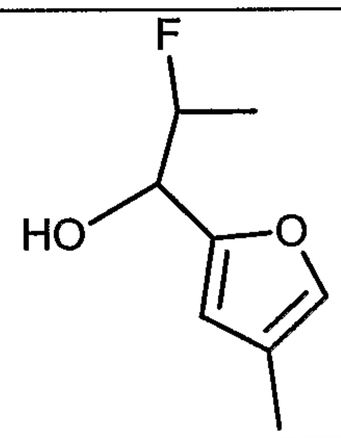
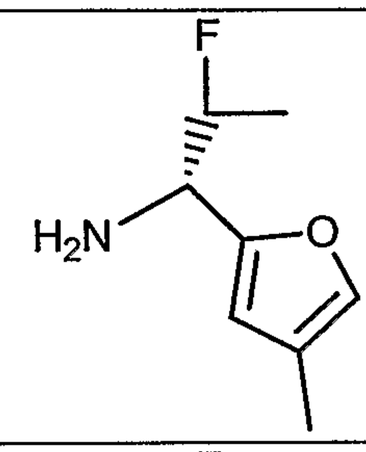
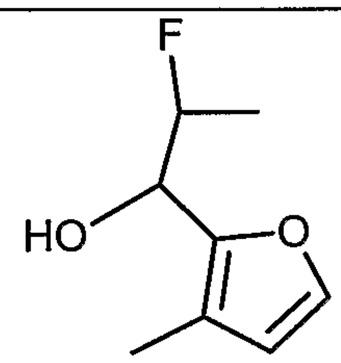
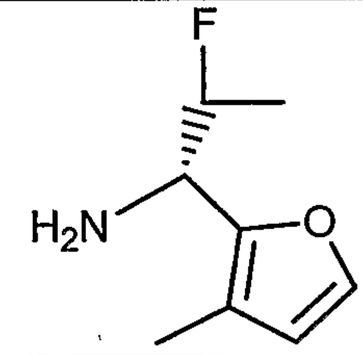
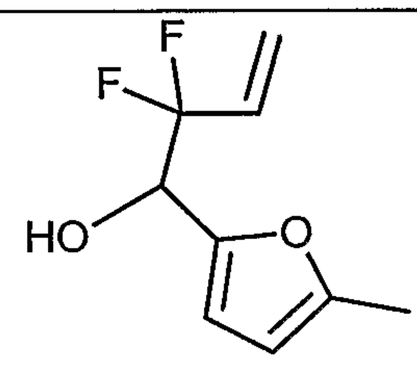
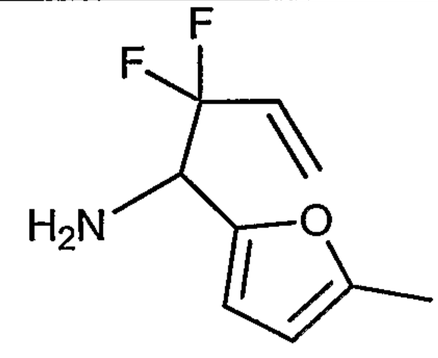
Prep Ex	Furan	Electrophile	Alcohol	Yield
604				86%
605				69%

606				84%
607				82%
608				60%
609				65%
610				82%
611				89%

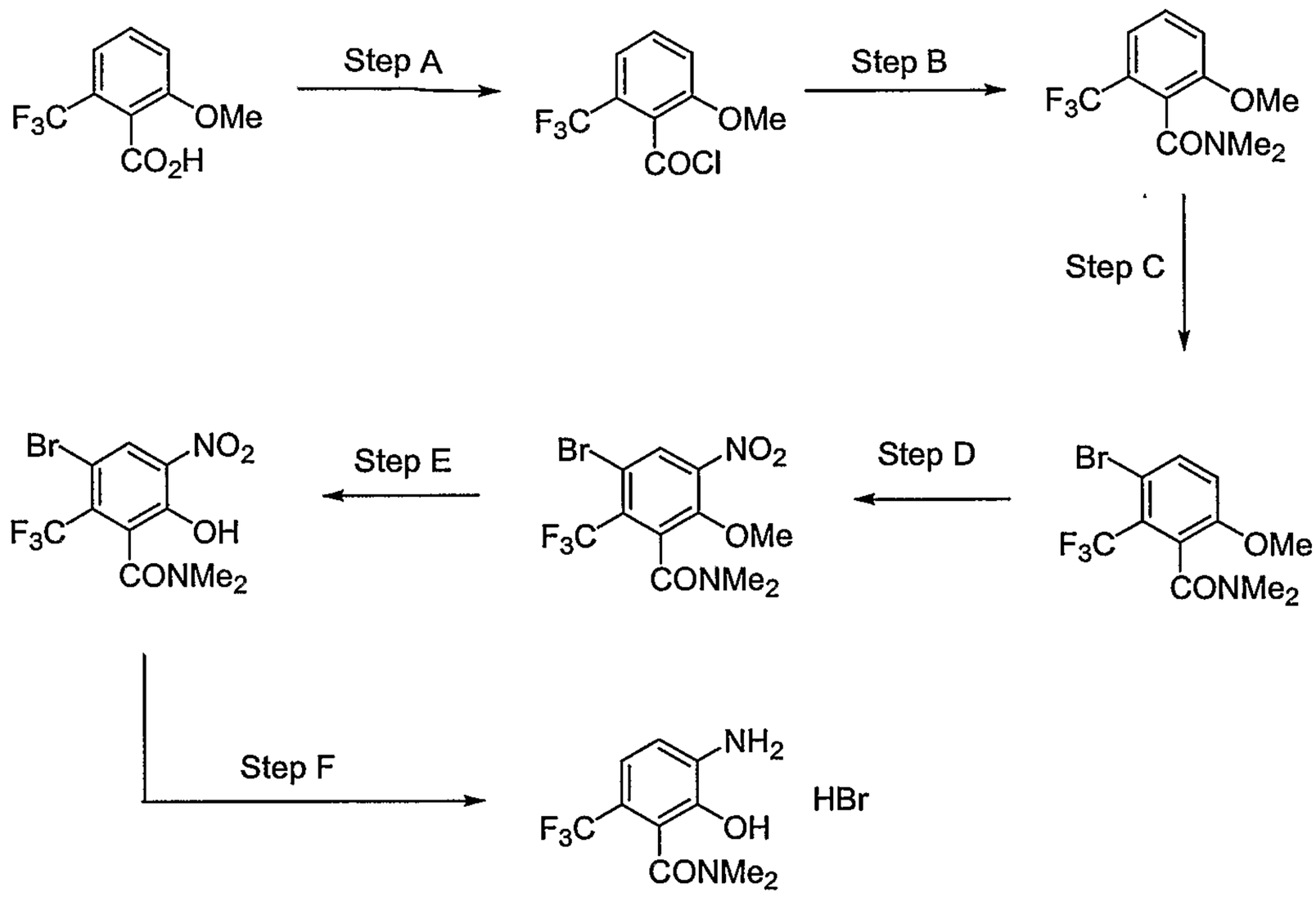
PREPARATIVE EXAMPLES 620-631

Following a similar procedure to that set forth in Preparative Example 13.25 the following Amines were prepared from the corresponding Alcohols.

Prep Ex	ALCOHOL	AMINE	% YIELD
620			28
621			58
622			69
623			81
624			82
625			45
626			57

627			58
628			54
629			53
630			50
631			82%

Preparative Example 1001



Step A

Oxalyl chloride (3 mL, 34.27 mmol) was added dropwise to a mixture of 2-methoxy-6-(trifluoromethyl)benzoic acid (1.5 g, 6.81 mmol) (prepared according to known method, see: EP0897904B1), *N*,*N*-dimethylformamide (0.3 mL), and dichloromethane (40 mL) with stirring at rt. The reaction mixture was stirred overnight. Evaporation of solvent and excess oxalyl chloride and drying under vacuum afforded 2-methoxy-6-(trifluoromethyl)benzoyl chloride as a solid, which was used without purification.

Step B

A solution of 2-methoxy-6-(trifluoromethyl)benzoyl chloride (ca. 6.81 mmol) from Step A above in dichloromethane (20 mL) was added dropwise to a mixture of 4-(dimethylamino)pyridine (42 mg, 0.34 mmol), triethylamine (2.8 mL, 20.09 mmol), and 2 M dimethylamine solution in tetrahydrofuran (7 mL, 14 mmol), and dichloromethane (30 mL) with stirring at rt. The reaction mixture was stirred overnight. A mixture of dichloromethane and water was added. The organic phase was separated, washed with 1N HCl solution, water, and saturated sodium bicarbonate solution and concentrated. The residue was purified by column chromatography (ethyl acetate:hexanes, 3:1 v/v) to give the product as a white solid (1.24 g, 74% over two steps).

Step C

A mixture of the amide from Step B above (1.8 g, 7.28 mmol), carbon tetrachloride (25 mL), and iron powder (305 mg, 5.46 mmol) was cooled to 0 °C. Bromine (0.94 mL, 18.34 mmol) was added dropwise with stirring. After addition, the mixture was stirred at rt for 1 h and at 50 °C for 3 h. The mixture was cooled to rt, diluted with dichloromethane, and slowly poured to a cold 10% $NaHSO_3$ solution. After stirring at rt for 0.5 h, the organic layer was separated and concentrated to give the product as a white solid (2.26 g, 95%).

Step D

Concentrated sulfuric acid (10 mL) was added dropwise to a flask charged with the bromide from Step C above (600 mg, 1.84 mmol) at 0 °C with stirring. A mixture of nitric acid (0.2 mL, 4.76 mmol) and concentrated sulfuric acid (0.3 mL) was then added dropwise. After addition, the mixture was stirred at rt for 3 h. The mixture was added to ice-water, neutralized with 15% NaOH solution to pH 7, and extracted with dichloromethane. The organic layer was concentrated to give the product as a white solid (621 mg, 91%). mp 92 °C, *m/e* 371 (MH^+).

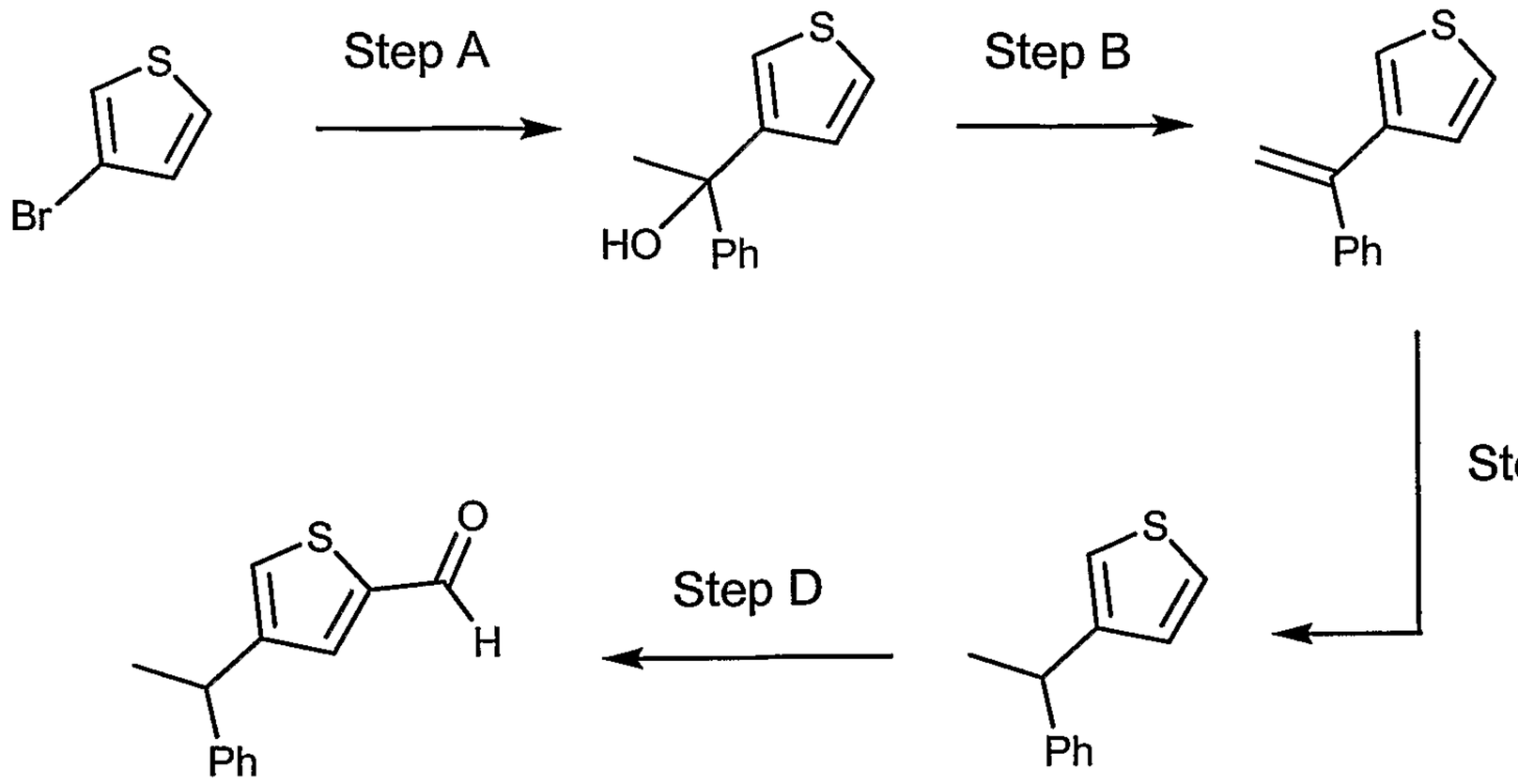
Step E

A solution of the compound from Step D above (1.2 g, 3.23 mmol) in dichloromethane (50 mL) was cooled to –75 °C. 1 M BBr_3 solution in dichloromethane (7.5 mL, 7.5 mmol) was added dropwise with stirring. The mixture was stirred at –75 °C for 2 h. The mixture was added to ice-water. After stirring at rt for 0.5 h, the mixture was extracted with dichloromethane. The organic was concentrated and the residue was purified by column chromatography (dichloromethane-methanol, 9:1 v/v) to give the product as a yellow solid (1.05 g, 91%). *m/e* 357 (MH^+).

Step F

A mixture of the compound from Step E above (1.08 g, 3.02 mmol), methanol (30 mL), and 10% Pd-C (250 mg) was subjected to hydrogenation at 50 psi at rt for 6 h. The mixture was filtered through a layer of Celite. The filtrate was concentrated to give the title compound as a pale yellow solid (930 mg, 96%). mp 132 °C, *m/e* 249.

Preparative Example 1002



Step A

To a cooled (-70°C) etherial (45 mL dry) solution of 3-bromothiophene (3.8 mL) was added BuLi (30 mL of 1.6M in hexane) dropwise, and the mixture was stirred at -70°C for 20 min. Acetophenone (4.6 mL) in ether (6 mL) was added dropwise with stirring at -70°C. After 3 hrs, the mixture was warmed to RT and sat. NH_4Cl (aq) was added and the mixture was extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the title compound which was used in Step B without further purification.

Step B

The crude product from Step A above was stirred with oxalic acid (0.375 g) at 70°C under reduced pressure for 3 hr, then cooled to RT and extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the product as a pale yellow liquid (5.7 g, 78% for Steps A-B).

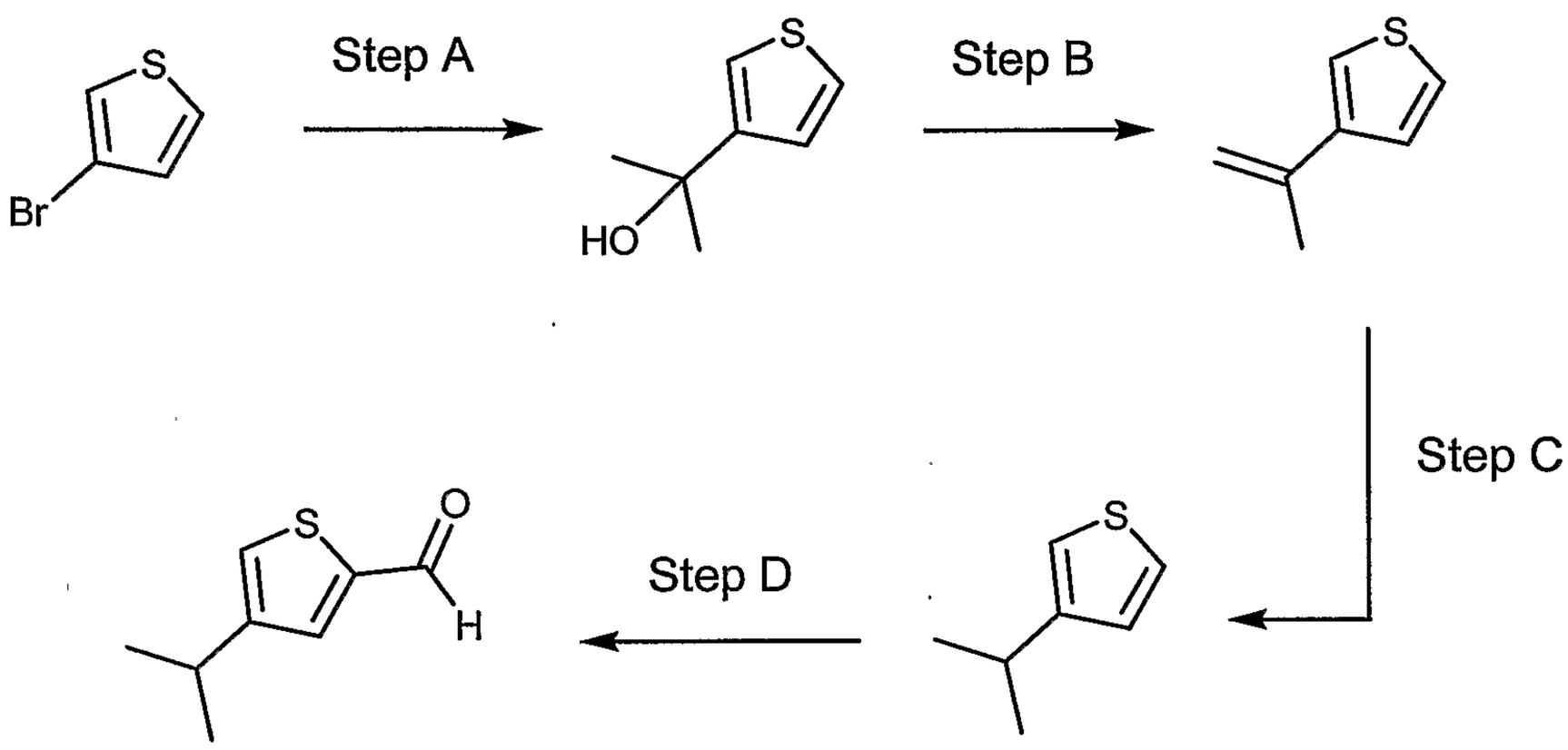
Step C

To the product from Step B above (4.2 g) diluted with dichloromethane (30 mL) and containing triethylsilane (6 mL) was added TFA (3 mL) in dichloromethane (7.5 mL). After stirring at RT for 10 min, the mixture was concentrated in vacuo to give the product as a colorless liquid (4.61 g, 80%).

Step D

To an etherial (3.5 mL dry) solution of the thiophene product (1.5 g) from Step C above was added BuLi (3.2 mL of 2.5M), and the mixture was heated at reflux for 15 min, cooled to RT, and DMF (0.8 mL) in ether (3.5 mL) was added dropwise. After stirring for 30 min, sat. NH_4Cl (aq) was added and the mixture was extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the title compound (1.71 g, 98%).

Preparative Example 1002B



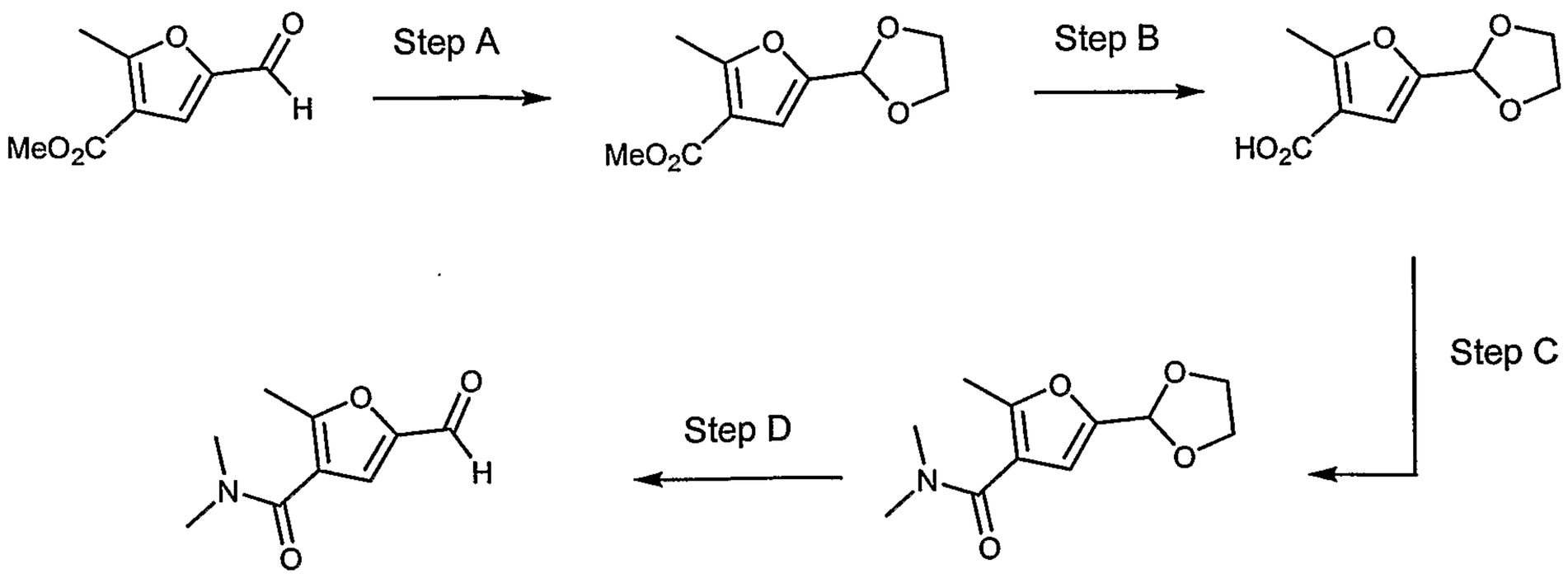
Step A

Following the procedure described in Preparative Example 1002, Step A, but using acetone instead of acetophenone, 2-thiophen-3-yl-2-propanol would be obtained.

Step B, C, D

Following the procedures described in Preparative Example 1002, steps B to D, the product from step A above would be converted to the titled 4-isopropyl-2-thiophen-aldehyde.

Preparative Example 1003



Step A

The aldehyde (0.50 g) was combined with ethylene glycol (1 mL), benzene (40 mL) and pTSA monohydrate (30 mg) and stirred at reflux for 20 hr. Cool to room temperature, add EtOAc and sat. $NaHCO_3$ (aq) solution, separate the organic phase, concentrate in vacuo, and purify by silica gel chromatography (EtOAc-Hex, 1:4) to give a colorless liquid (60 mg)

Step B

The product from Step A above (0.607 g) was stirred at 45°C overnight with 1N NaOH (aq), then cooled to room temperature, acidified with 3N HCl and extracted with EtOAc. Washing with brine and concentration in vacuo gave a solid (5.0 g).

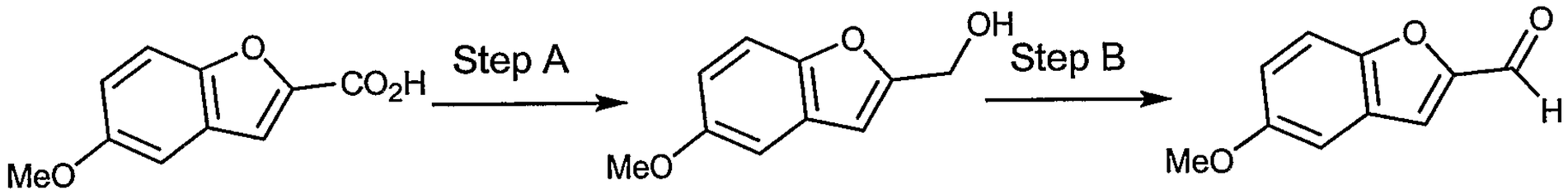
Step C

Following a similar procedure as that used in Preparative Example 1, except using the product from Step B above and dimethylamine in THF (2M), the product was obtained (1.21g crude).

Step D

The product from Step C above was dissolved in THF and stirred with 0.3N HCl (aq) and stirred at RT for 4 hr. Concentration in vacuo gave a pale yellow oil (1.1 g, 67%).

Preparative Example 1004



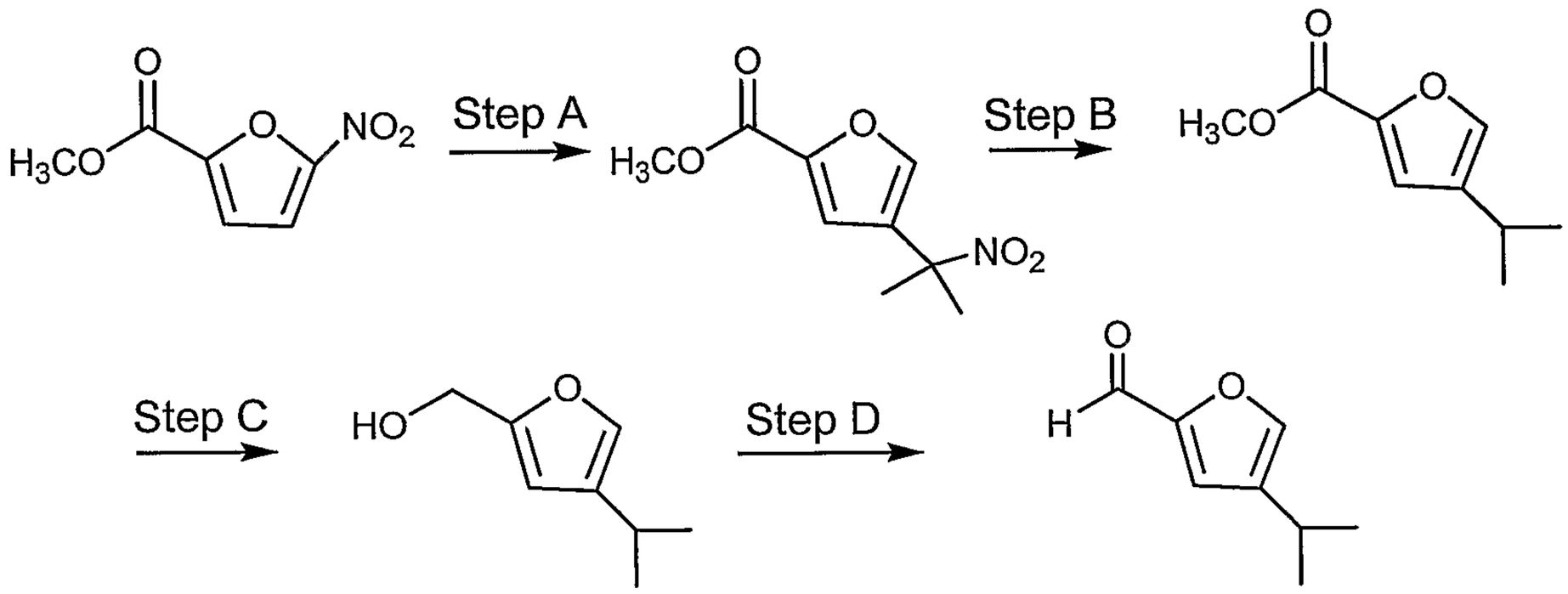
Step A

To a cooled (-78°C) solution of methoxybenzofuran-2-carboxylic acid (1 g) was added DIBAL (30 mL, 1M in THF). After stirring for 20 min, the mixture was warmed to RT and stirred for 4 hr, then poured into sat. NH_4Cl (aq) (35 mL). After stirring at RT for 20 min, 6M HCl (aq) was added and the mixture was extracted with EtOAc, the organic phase dried and then concentrated in vacuo. Purification by silica gel chromatography (EtOAc-hexane, 3:7) afforded the alcohol as a solid (0.4 g, 97%).

Step B

A mixture of the product from Step A above (0.9 g), EtOAc (50 mL) and MnO2 (5.2 g) was stirred at RT for 22 h, then filtered and concentrated in vacuo. The solid was redissolved in EtOAc (50 mL), MnO2 (5.2 g) was added and the mixture was stirred for 4 additional hrs. Filtration, concentration and silica gel purification (EtOAc-Hexane, 1:3) gave the title compound as a solid (0.60 g, 67%).

PREPARATIVE EXAMPLE 1004A



Step A

To a stirred solution of potassium t-butoxide (2.5g) in HMPA (20ml) was added 2-nitropropane (2ml) dropwise. After 5min, a solution of methyl-5-nitro-2-furoate (3.2g) in HMPA (8ml) was added to the mixture and stirred for 16hr. Water was added and the aqueous mixture was extracted with EtOAc. The EtOAc layer was washed with water, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material

was purified by flash column chromatography (Hex/EtOAc, 6:1) to yield 3.6g of product (90%).

Step B

To a solution of product from Step A (3.6g) in toluene (16ml) was added tributyltin hydride (5.4ml) followed by AIBN (555mg). The mixture was heated to 85^0C for 3.5hr. After cooling, the mixture was separated by flash column chromatography (Hex/EtOAc, 7:1) to afford 2.06g of product (73%).

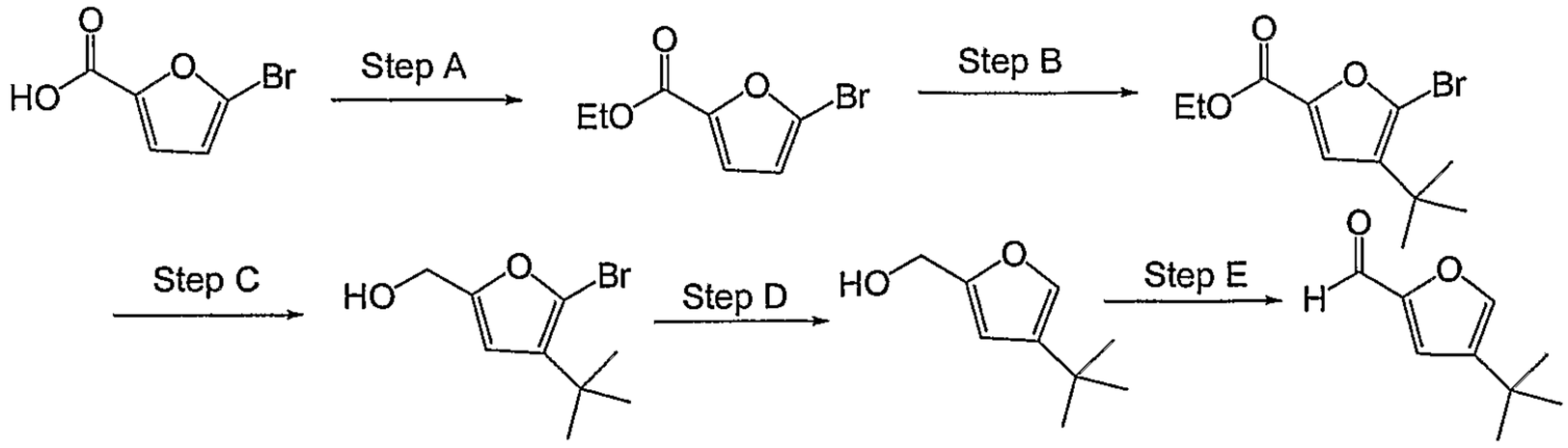
Step C

To a solution of product from Step B (2.05g) in THF (60ml) at 0^0C was added a solution of LAH (1M in ether, 12.8ml). The reaction was stirred at room temperature for 30min. Water and 1M NaOH was added until a precipitate formed, diluted with EtOAc, stirred for 30min and then filtered through a celite pad. The organic filtrate was concentrated *in vacuo* to give 1.56g of product (93%).

Step D

To a solution of product from Step C (2.15g) in CH_2Cl_2 (100ml) was added Dess-Martin oxidant (7.26g) in CH_2Cl_2 (45ml) and stirred for 30min. The mixture was diluted with ether (200ml). The organic layer was washed with 1N NaOH, water and brine, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give oil and solid. The material was extracted with ether and filtered. Some solid crystallized out from the filtrate, filtered again, and the filtrate was concentrated *in vacuo* to give 2.19g of product.

PREPARATIVE EXAMPLE 1004B



Step A

To a suspension of 5-bromo-2-furoic acid (15g) in CH_2Cl_2 (275ml) at room temperature was added oxalyl chloride (6.9ml) followed by a catalytic amount of N,N'-dimethylformamide ((0.3ml). The mixture was stirred for 1hr, whereupon, EtOH (20ml) and TEA (22ml) were added and then let stir overnight. The mixture was concentrated *in vacuo* and extracted with hexanes and hexanes/ CH_2Cl_2. The extracts were concentrated *in vacuo* to give an oil (17.2g, 93%).

Step B

The product from Step A (17.2g), aluminum trichloride (19.52g) and carbon disulfide (150ml) were combined in a flask. A solution of n-octadecyl bromide (24.4g) in carbondisulfide (50ml) was added dropwise over 45min. The reaction was stirred for 2.5hr, whereupon, 300ml of crushed ice and water were added. The layers were separated and the organic layer was washed with saturated sodium bicarbonate, water, and brine. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (hexanes/ CH_2Cl_2, 3:1) to yield 7.91g of product (37%).

Step C

To the product from step B (7.9g) in THF (140ml) at –10°C was added a solution of LAH (1M in THF, 28.5ml). The solution was stirred for 2.5hrs at 15 °C. Water and 1M NaOH were added carefully to the mixture, followed by EtOAc and let stir for 1.5hr. The reaction was filtered through a silica pad and the filtrate was concentrated *in vacuo* to yield 6.48g of crude product (100%).

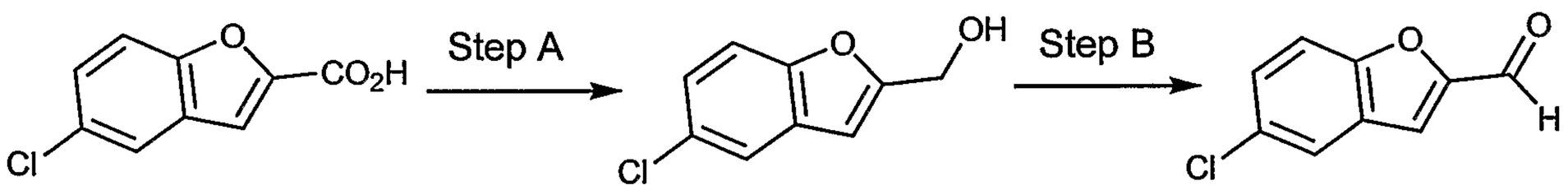
Step D

The product from Step C (6.32g) was dissolved in THF (140ml) and cooled to –78°C. A solution of t-BuLi (2.5M in hexanes, 22ml) was added dropwise and let stir for 15min. An excess of water (70ml) was then added and let the reaction stir another hour. CH_2Cl_2 (300ml) and brine (50ml) were added and the layers were separated. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to give 5.33g of crude product.

Step E

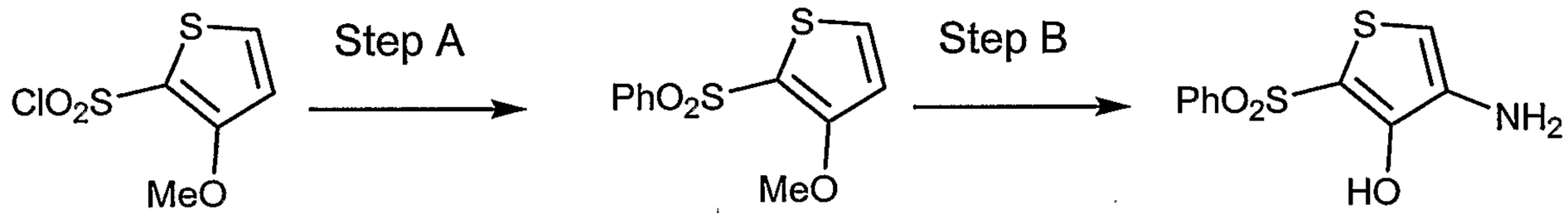
To a solution of the product from Step D (5.33g) in CH_2Cl_2 (100ml) was added a solution of Dess-Martin periodinane in CH_2Cl_2 (15wt%, 12.6g). The mixture was stirred for 1.5hr and then diluted with ether (400ml) and washed with 1N NaOH, water and brine. The organic layer was dried with Na_2SO_4 and filtered through a magnesium sulfate/silica pad. The filtrate was concentrated *in vacuo* and purified via flash column chromatography (hex/EtOAc, 50:1, 25:1) to yield 3.06g of an oil (74%).

Preparative Example 1005



Following a similar procedure as that described in Preparative Example 1004, except using 5-chlorobenzofuran-2-carboxylic acid (1.5 g), the title compound was obtained (solid, 0.31 g, 24%).

Preparative Example 1006



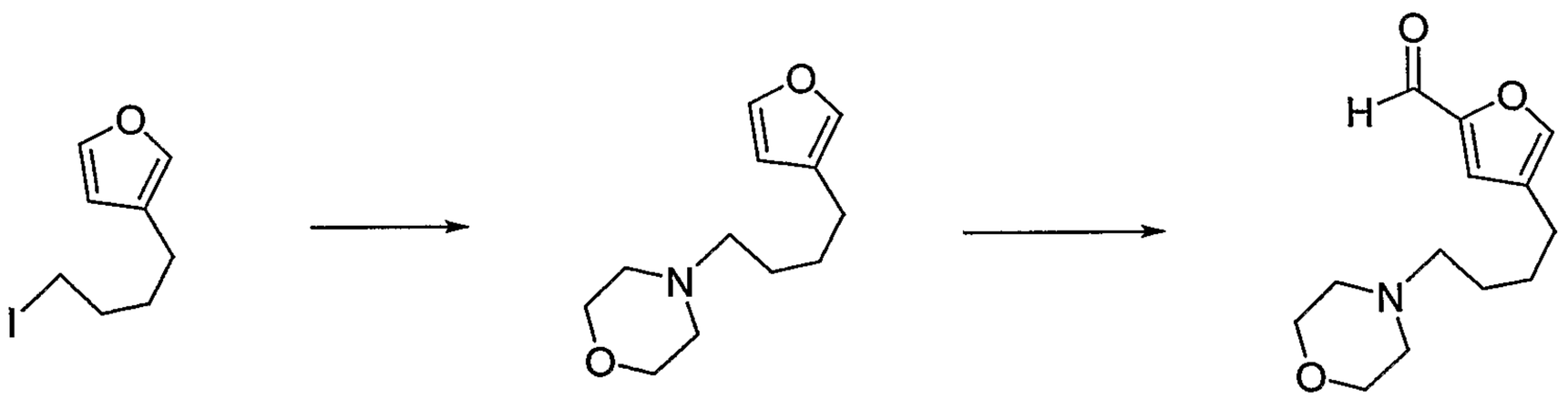
Step A

The sulfonyl chloride from Preparative Example 13.29 Step A (1.5 g) was stirred with AlCl3 and benzene for 15 min at 20 °C. Treatment with NaOH, extraction with Et_2O, concentration in vacuo, and purification by column chromatography (silica, hexane-EtOAc, 5:2) gave the phenylsulfone (1.5g, 84%, MH^+ = 255).

Step B

Following similar procedures as those used in Preparative Example 13.29 Steps C-G, except using the sulfone from Step A above, the title compound was prepared (0.04 g, 27%, MH^+ = 256).

Preparative Example 1030



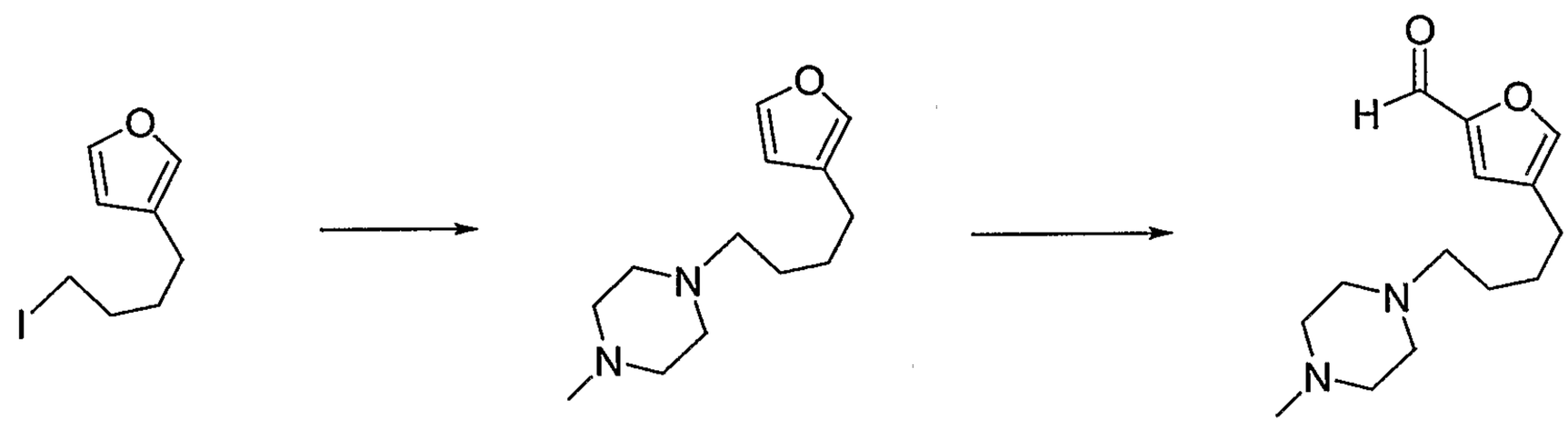
Step A

The product of Preparative Example 34.18 Step B (2 g, 8 mmol) was stirred with morpholine (0.9 mL, 10.29 mmol) and K_2CO_3 (2.2 g, 15.9 mmol) in 50 mL of acetone at RT to obtain the morpholinobutylfuran derivative (1.22 g, 73%).

Step B

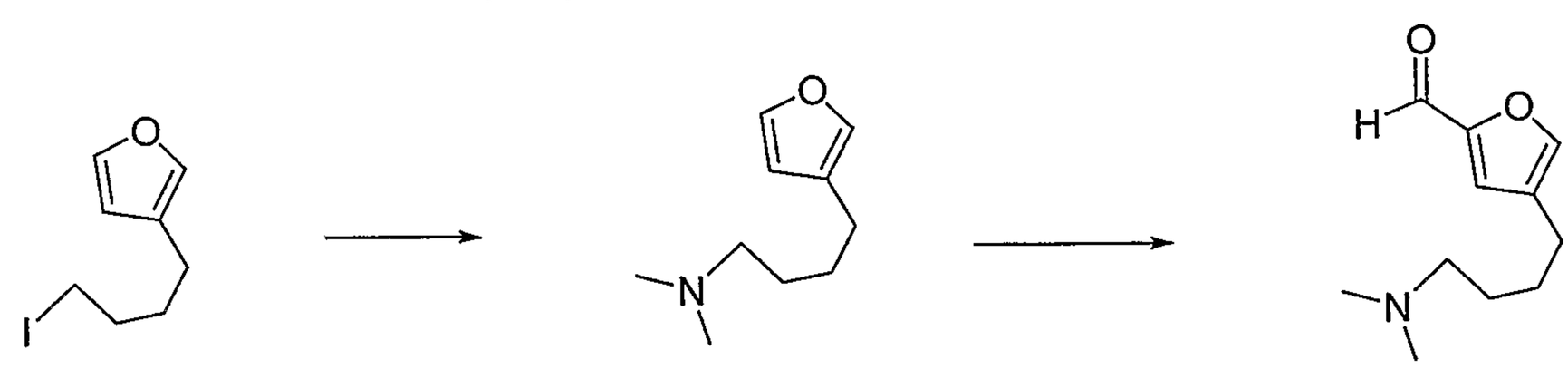
Following a similar procedure as that in Preparative Example 34.18 Step D, but using the product (1.2 g) from Step A above, the title aldehyde was prepared (0.9 g, 66%, 1:0.7 regioisomeric mixture).

Preparative Example 1030-A



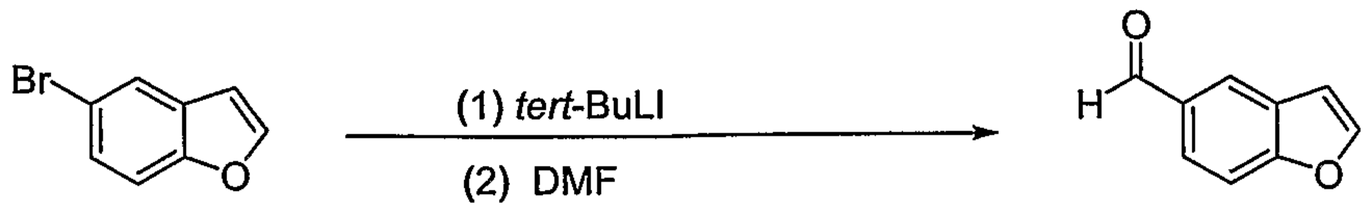
Following a similar procedure as that in Preparative Example 1030 Steps A-B, but using N-methylpiperazine instead of morpholine, the title aldehyde could be prepared.

Preparative Example 1030-B



Following a similar procedure as in Preparative Example 1030 Steps A-B, but using N,N-dimethylamine instead of morpholine, the title aldehyde could be prepared.

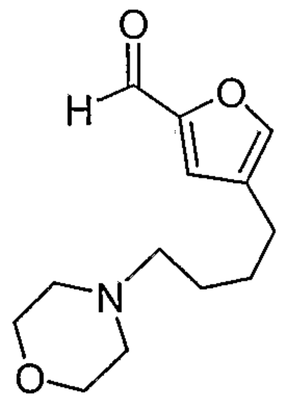
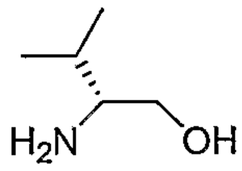
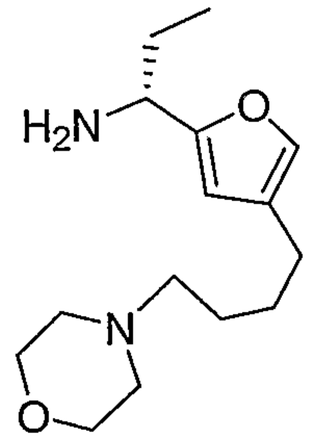
Preparative Example 1031

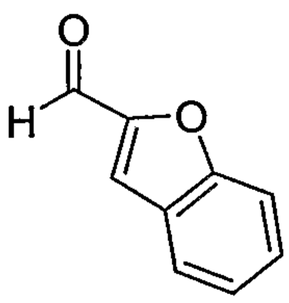
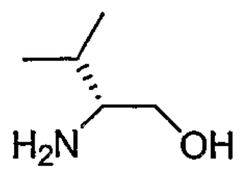
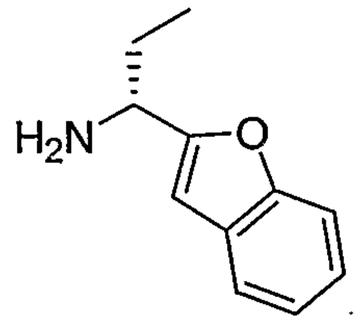
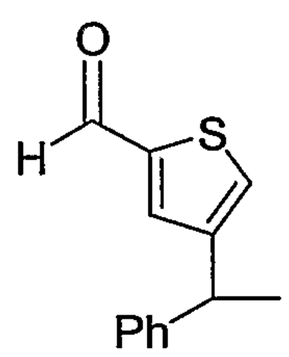
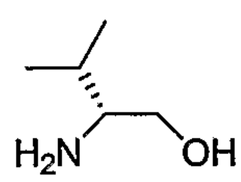
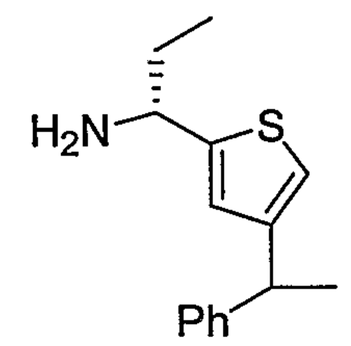
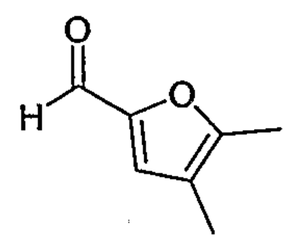
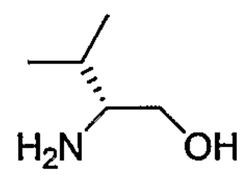
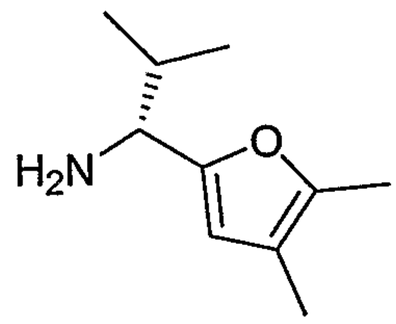
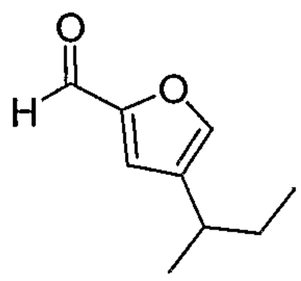
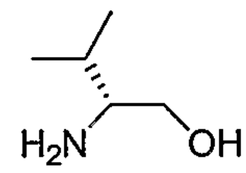
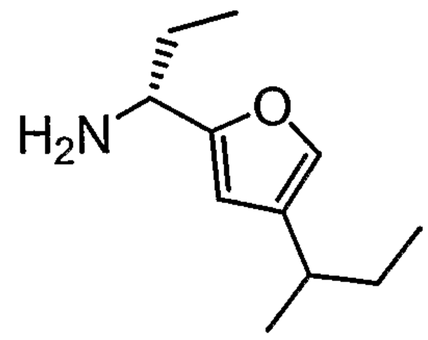
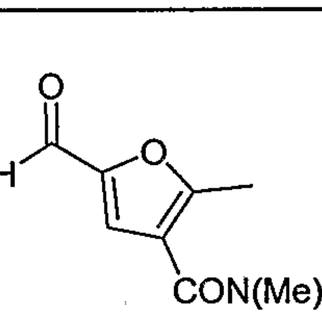
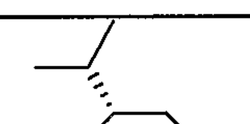
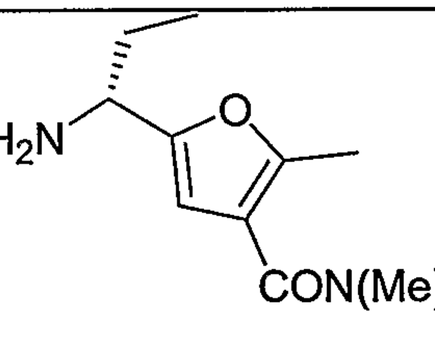
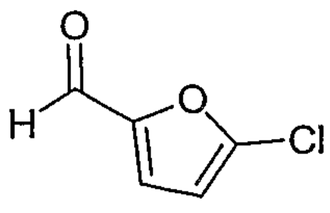
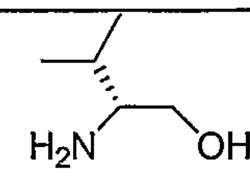
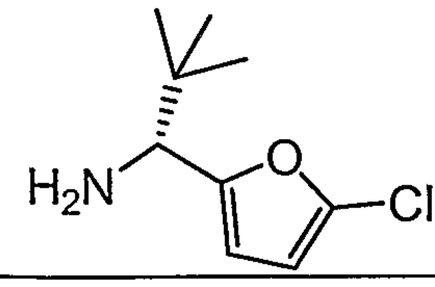


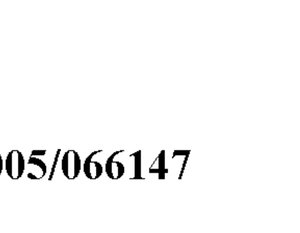
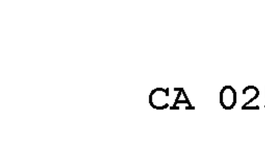
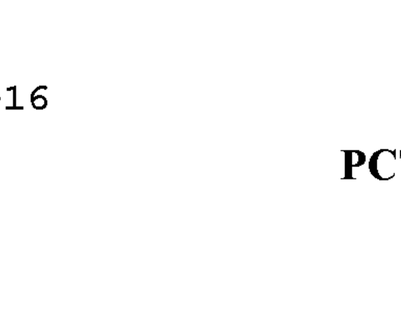
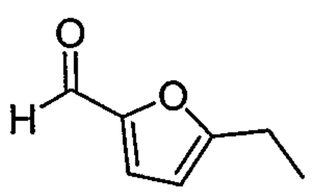
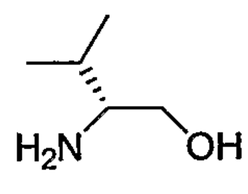
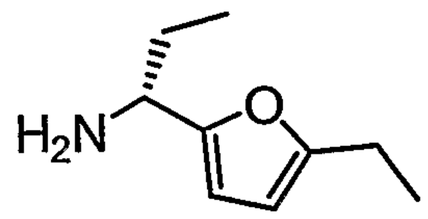
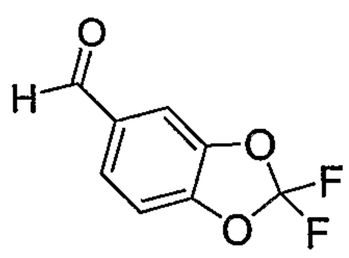
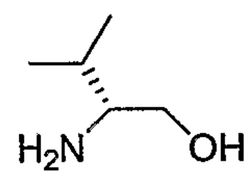
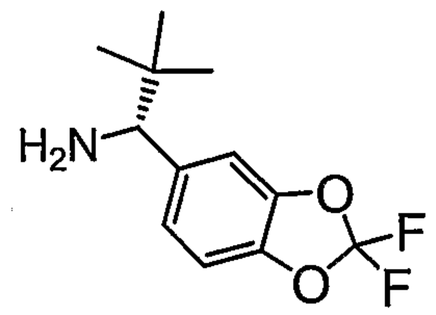
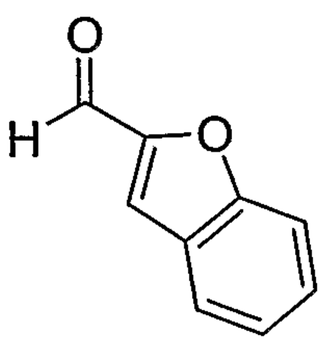
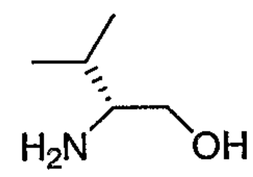
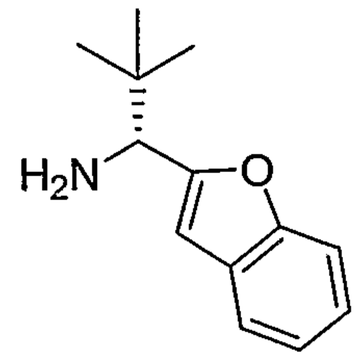
A solution of 5-bromobenzofuran (950 mg, 4.82 mmol) in anhydrous ether (12 mL) was cooled to –78 °C. 1.7 M *tert*-BuLi solution in pentane (6 ml, 10.2 mmol) was added dropwise under argon. After addition, the mixture was stirred at –78 °C for 20 min, followed by addition of a mixture of DMF (0.8 mL) and ether (1 mL). The mixture was allowed to warm to rt and stirred for 0.5 h. Ethyl acetate was added. The mixture was poured to saturated ammonium chloride solution. The organic layer was separated and concentrated. The residue was purified by column chromatography (ethyl acetate-hexanes, 1:5 v/v) to give the title compound as a pale yellow solid (490 mg, 70%).

PREPARATIVE EXAMPLES 1040-1054

Following the procedure set forth in Preparative Example 64 but using the commercially available (or prepared) aldehyde, aminoalcohols, and organolithium reagents in the Table below, the optically pure amine products in the Table below were obtained.

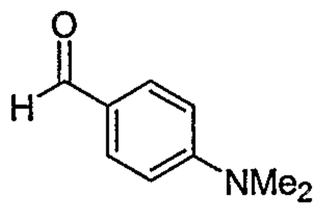
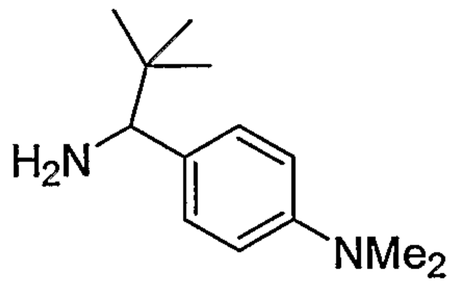
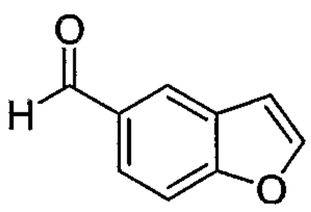
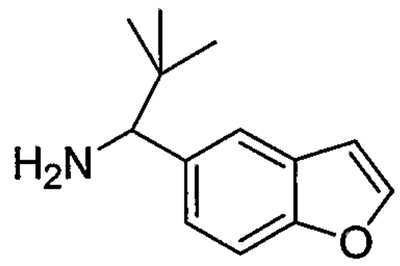
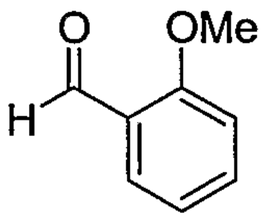
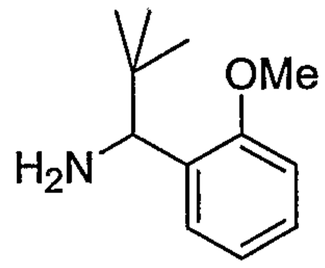
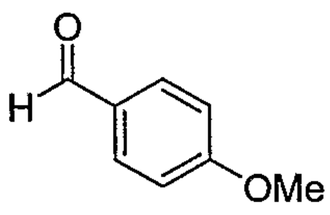
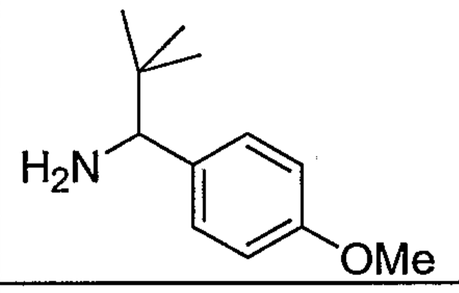
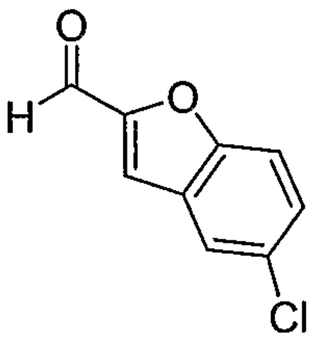
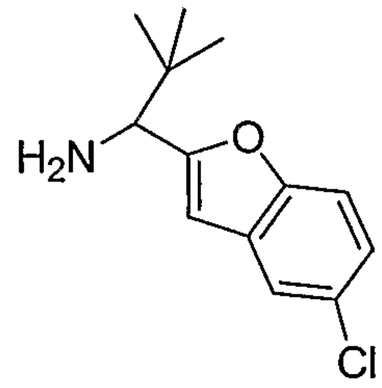
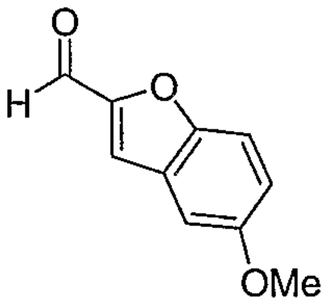
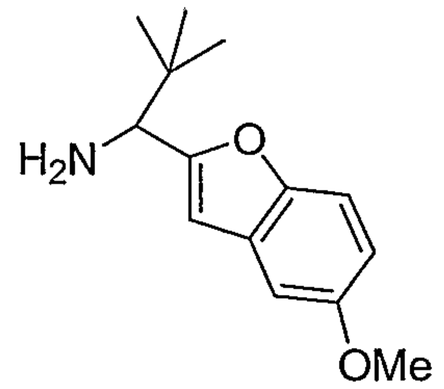
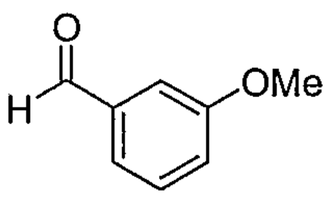
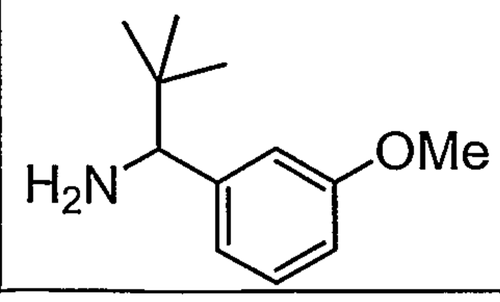
Prep. Ex.	Aldehyde	Amino Alcohol	Organo-lithium	Product	1.Yield (%) 2. $(M+1)^+$
1040			EtLi		1. 24% 2. 267

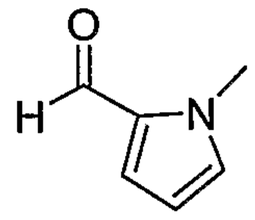
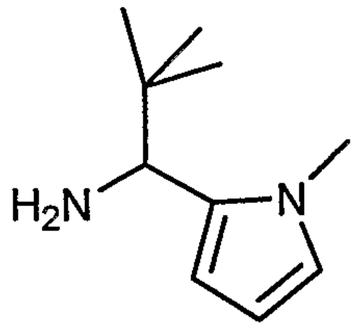
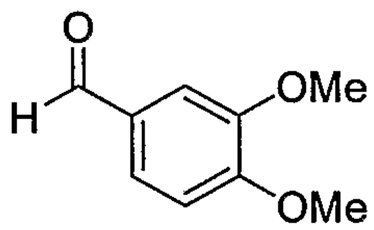
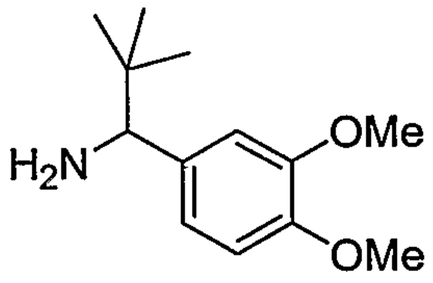
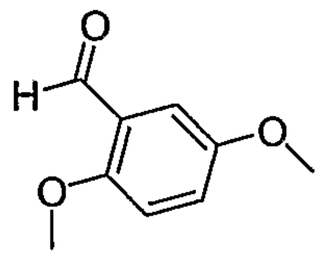
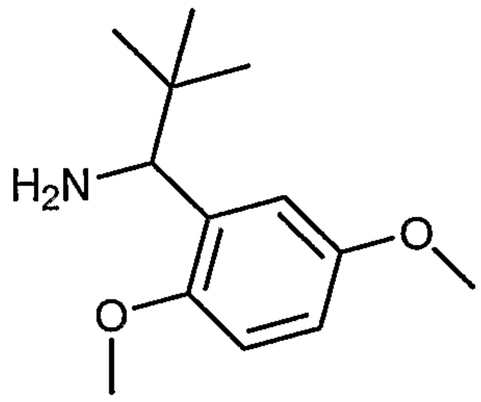
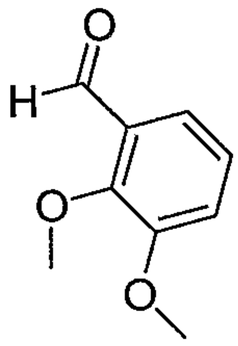
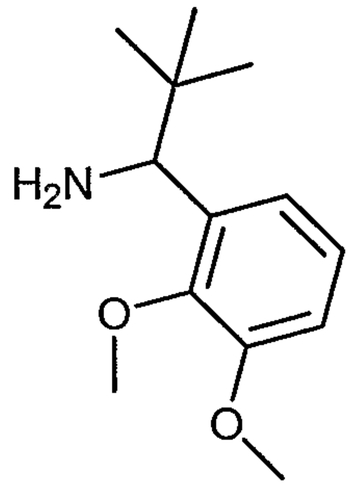
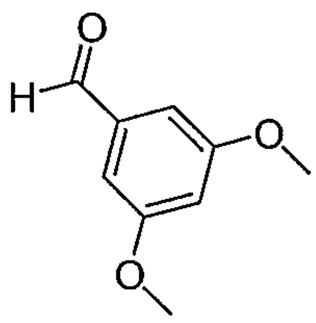
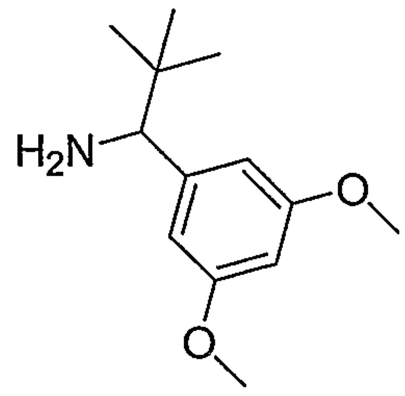
1041			EtLi		1. 94% 2. 176 (m/e)
1042			EtLi		1. 67% 2. 229 (M-16)
1043			i-PrLi		1. 60% 2. 151 [M-16]
1044			EtLi		1. 74% 2. 194 (M-16)
1045			EtLi		1. 33% 2. 165 $[M-NH2]^+$
1046			EtLi		1. 31 2. 179 $[M-NH2]^+$
1047			t-BuLi		1. 31% 2. 188

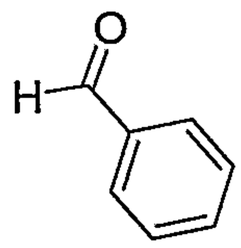
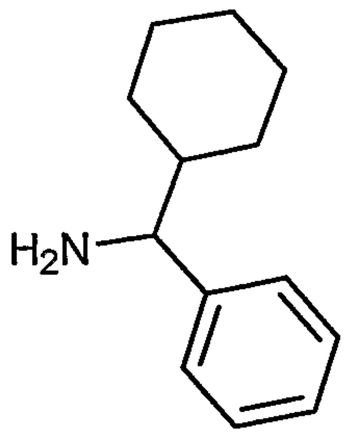
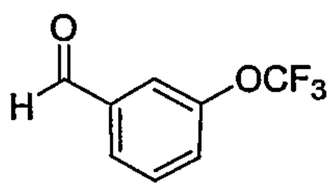
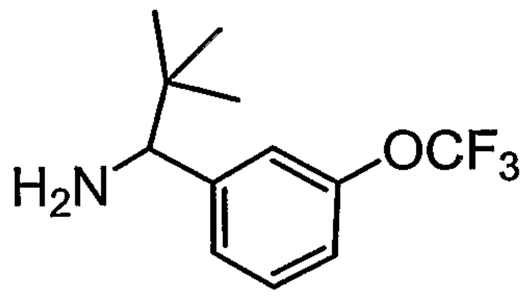
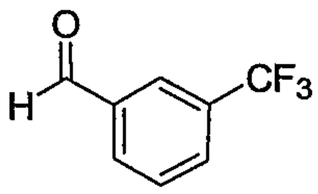
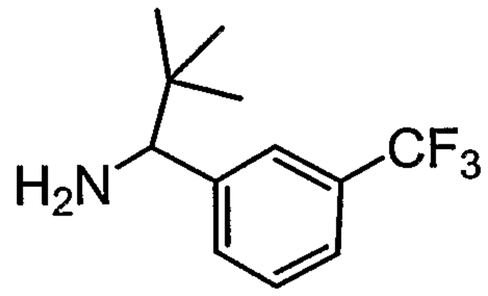
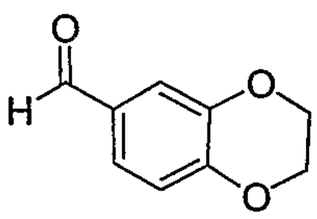
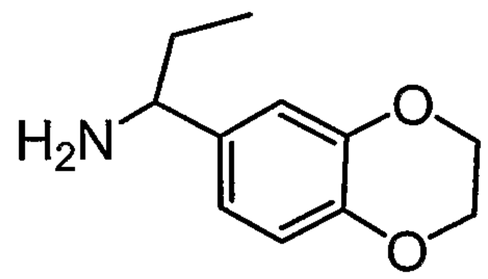
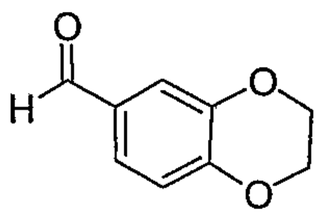
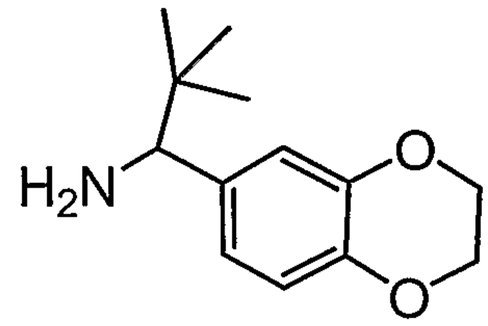
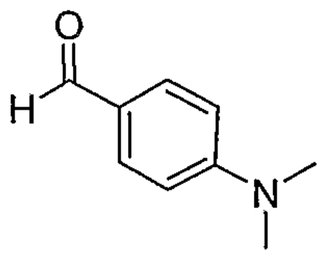
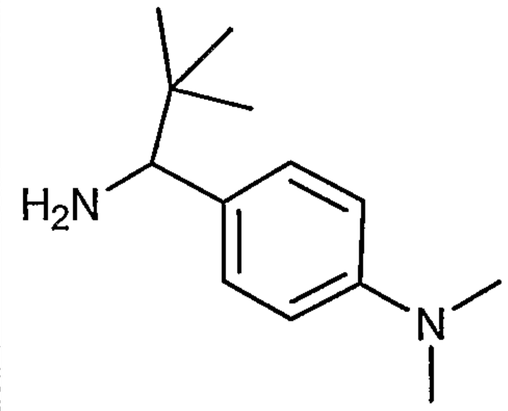
1048			t-BuLi		1. 10% 2. 154
1049			EtLi		1. 73% 2. 137 $[M-NH2]^+$
1051			t-BuLi		1. 17%
1054			t-BuLi		1. 79% 2. 151 (M-16)

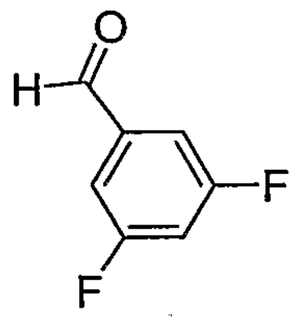
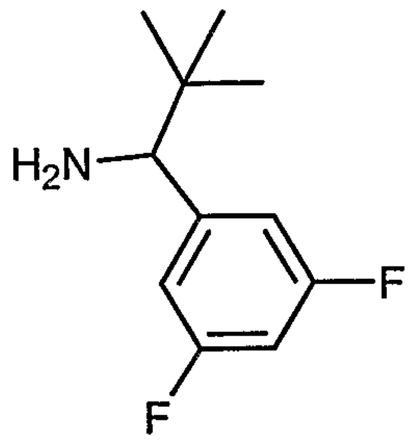
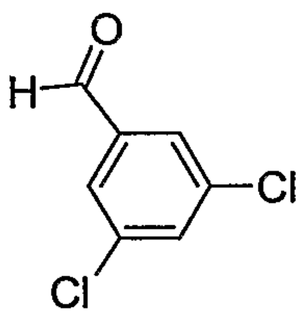
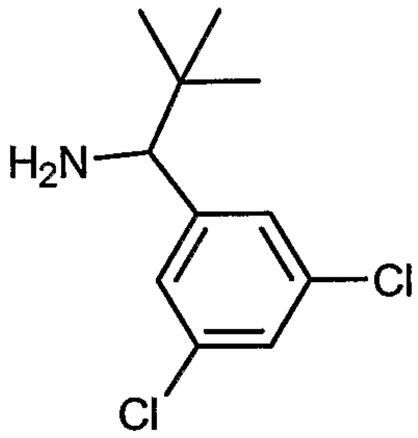
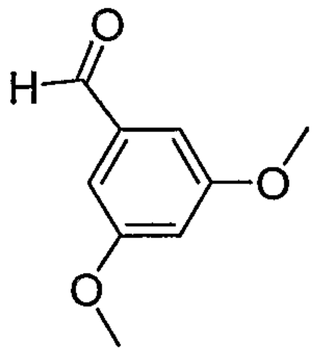
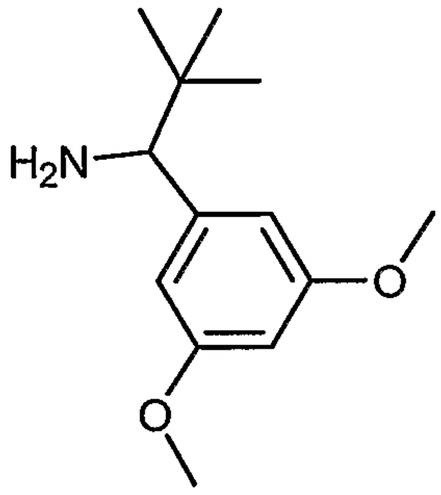
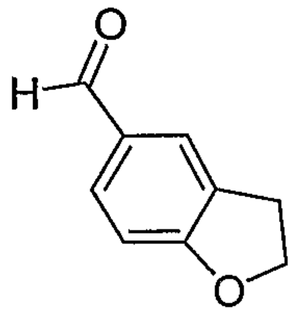
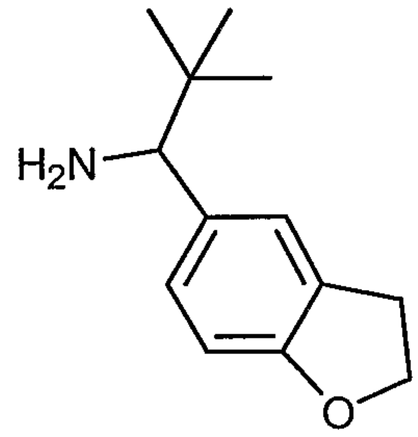
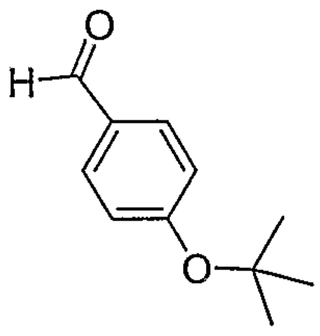
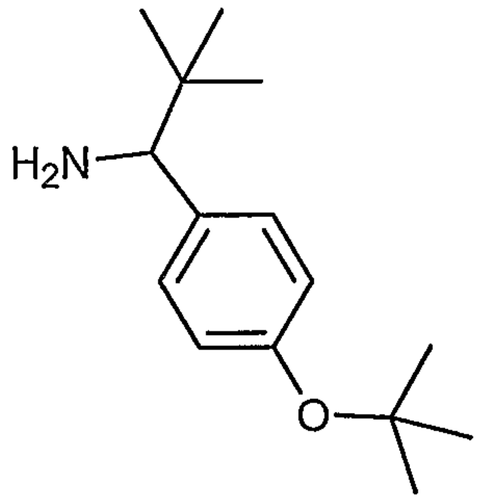
PREPARATIVE EXAMPLES 1100-1126

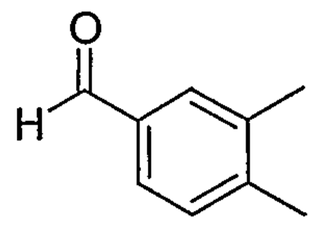
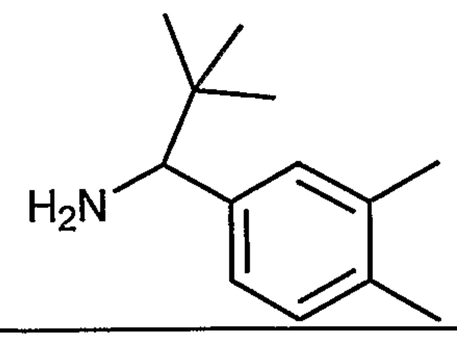
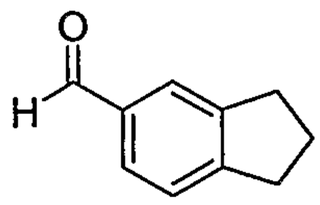
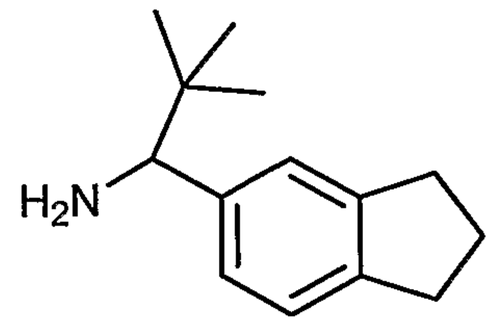
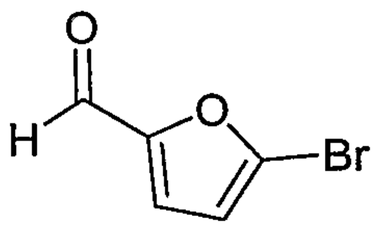
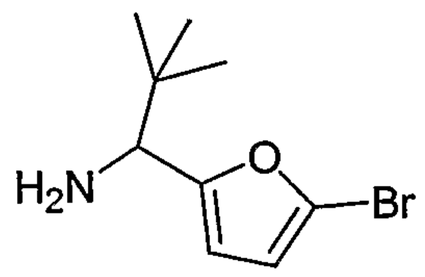
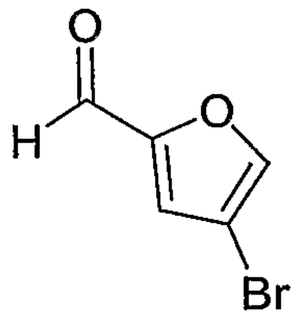
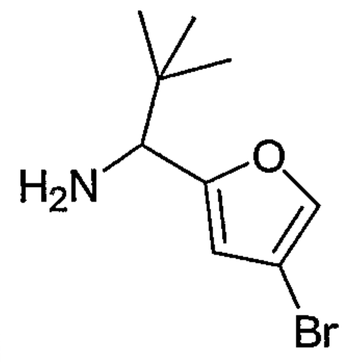
Following the procedure set forth in Preparative Example 34 but using the commercially available aldehydes and Grignard/Organolithium reagents listed in the Table below, the amine products were obtained.

Prep. Ex.	Aldehyde	Organo-metallic Reagent	Product	1.Yield (%) 2. $(M+1)^+$
1100		t-BuLi		1. 83% 2. 190 (M-16)
1101		t-BuLi		1. 46% 2. 204
1102		t-BuLi		1. 48% 2. 194
1103		t-BuLi		1. 51% 2. 194
1104		t-BuLi		1. 12% 2. 238
1105		t-BuLi		1. 39% 2. 234
1106		t-BuLi		1. 44% 2. 194 (m/e)

1107		t-BuLi		1. 57% 2. 150 (M-16)
1108		t-BuLi		1. 31% 2. 224
1109		t-BuLi		1. 11% 2. 224
1110		t-BuLi		1. 57% 2. 224
1111		t-BuLi		1. 21% 2. 224

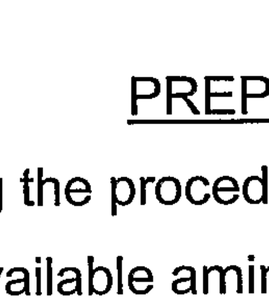
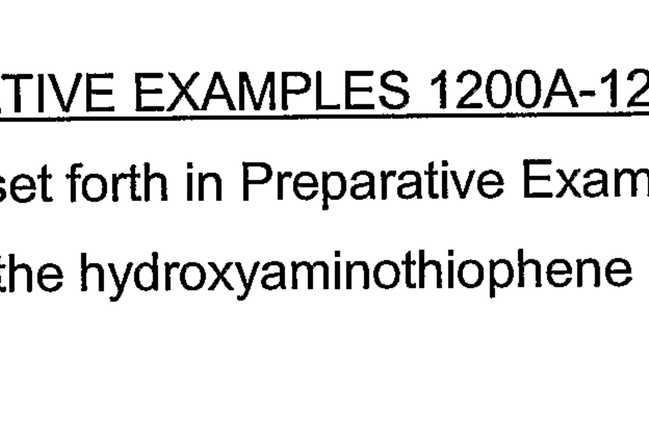
1112		c-Pentyl-Li		1. 58% 2. 190
1113		t-BuLi		1. 20% 2. 248
1114		t-BuLi		1. 24% 2. 232
1115		EtLi		1. 32% 2. 177 (M-NH2)
1116		t-BuLi		1. 26% 2. 205 (M-NH2)
1117		t-BuLi		1. 50% 2. 190 (M-NH2)

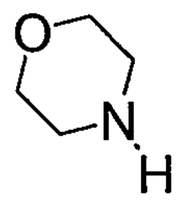
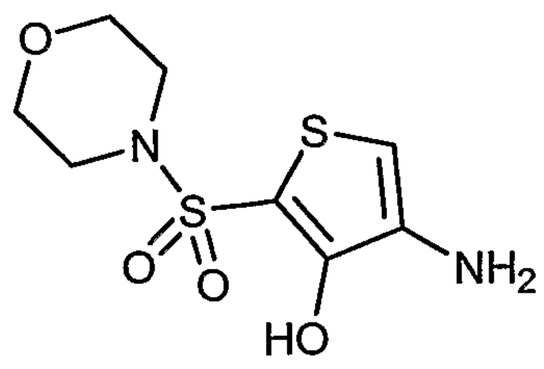
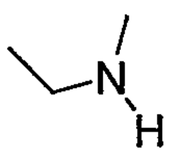
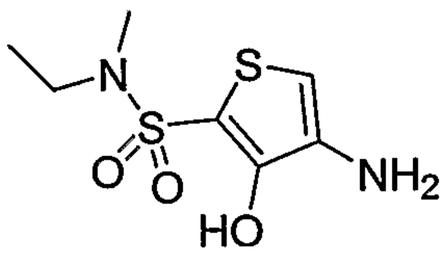
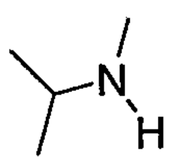
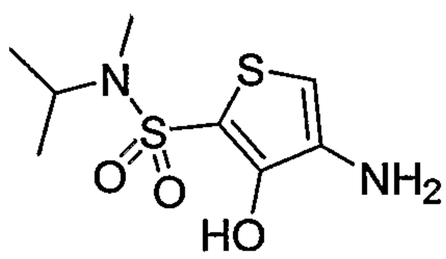
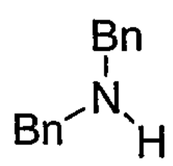
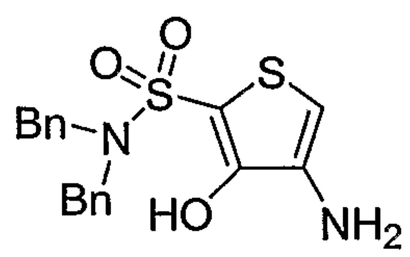
1118		t-BuLi		1. 29% 2. 200
1119		t-BuLi		1. 28% 2. 232
1120		t-BuLi		1. 76% 2. 224
1121		t-BuLi		1. 40% 2. 206
1122		t-BuLi		1. 38% 2. 236

1123		t-BuLi		1. 70% 2. 192
1124		t-BuLi		1. 81% 2. 204
1125		t-BuLi		33%
1126		t-BuLi		50%

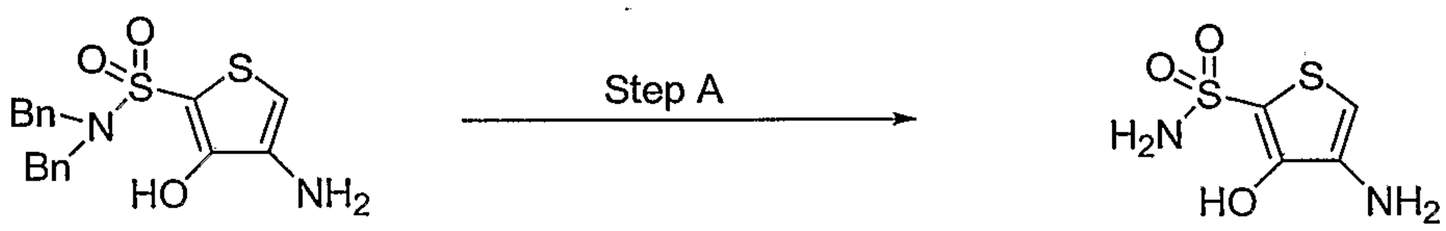
PREPARATIVE EXAMPLES 1200A-1204A

Following the procedure set forth in Preparative Example 13.29 but using the commercially available amines, the hydroxyaminothiophene products listed in the Table below were obtained.

Prep. Ex.	Amine	Product	1.Yield (%) 2. $(M+1)^+$
1200A			1. 3% 2. 342

1201A			1. 41% 2. 265
1202A			1. 17% 2. 237
1203A			1. 1%
1204A			1. 15% 2. 375.1

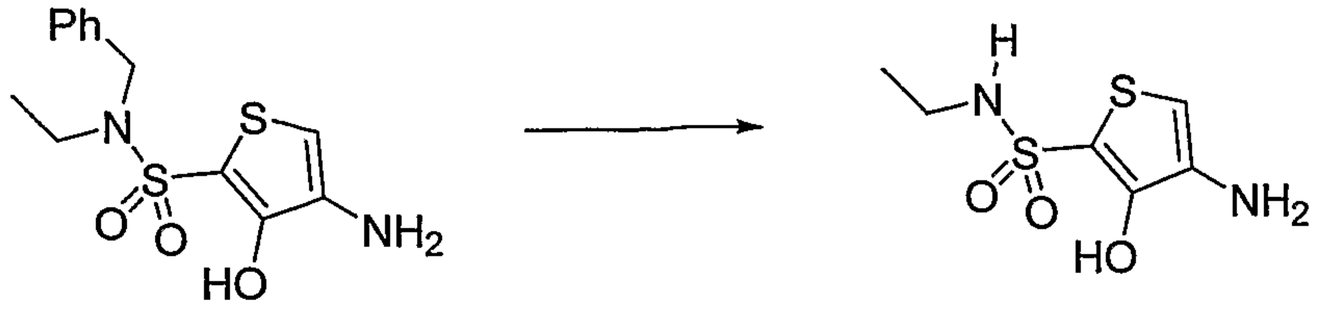
PREPARATIVE EXAMPLE 1205A



Step A

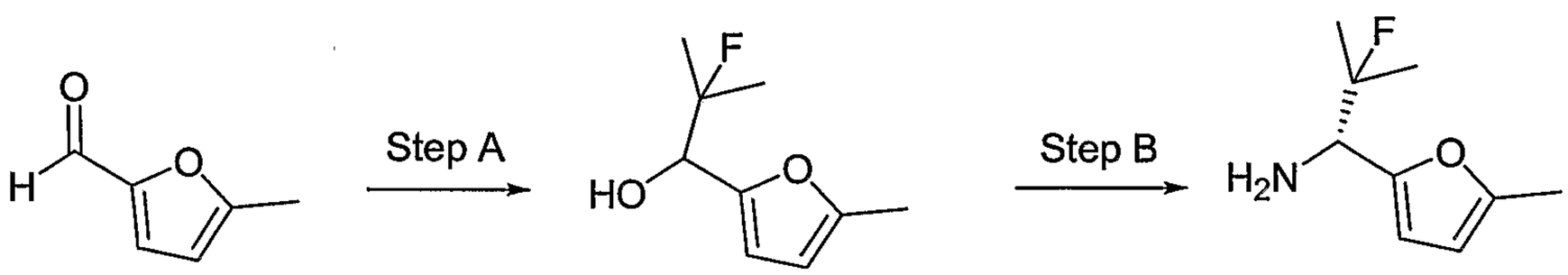
Dibenzylsulfonamide-thiophene-amine (660 mg, 1.76 mmol), available from Preparative Example 1204A, was stirred with 4 mL of concentrated sulfuric acid at room temperature for 5 h. Ice water (50 mL) was added. The aqueous mixture was adjusted to pH ~ 5 using a 1.0 M NaOH aqueous solution, and extracted with ethyl acetate (200 mL x 4). The organic extracts were washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 237 mg of the desired sulfonamide amine (69 %, MH^+ = 194.23, $[M-NH_2]^+$ = 178).

PREPARATIVE EXAMPLES 1300



The title compound from Preparative Example 13.32 (0.35 g) was treated with concentrated sulfuric acid (3 mL) for 6 hrs, then poured on ice, and the pH adjusted to 4 with NaOH. Extraction with EtOAc, and drying of the organic phase over Na_2SO_4 gave the title compound (159 mg, 64%, MH^+ = 223).

PREPARATIVE EXAMPLES 1301



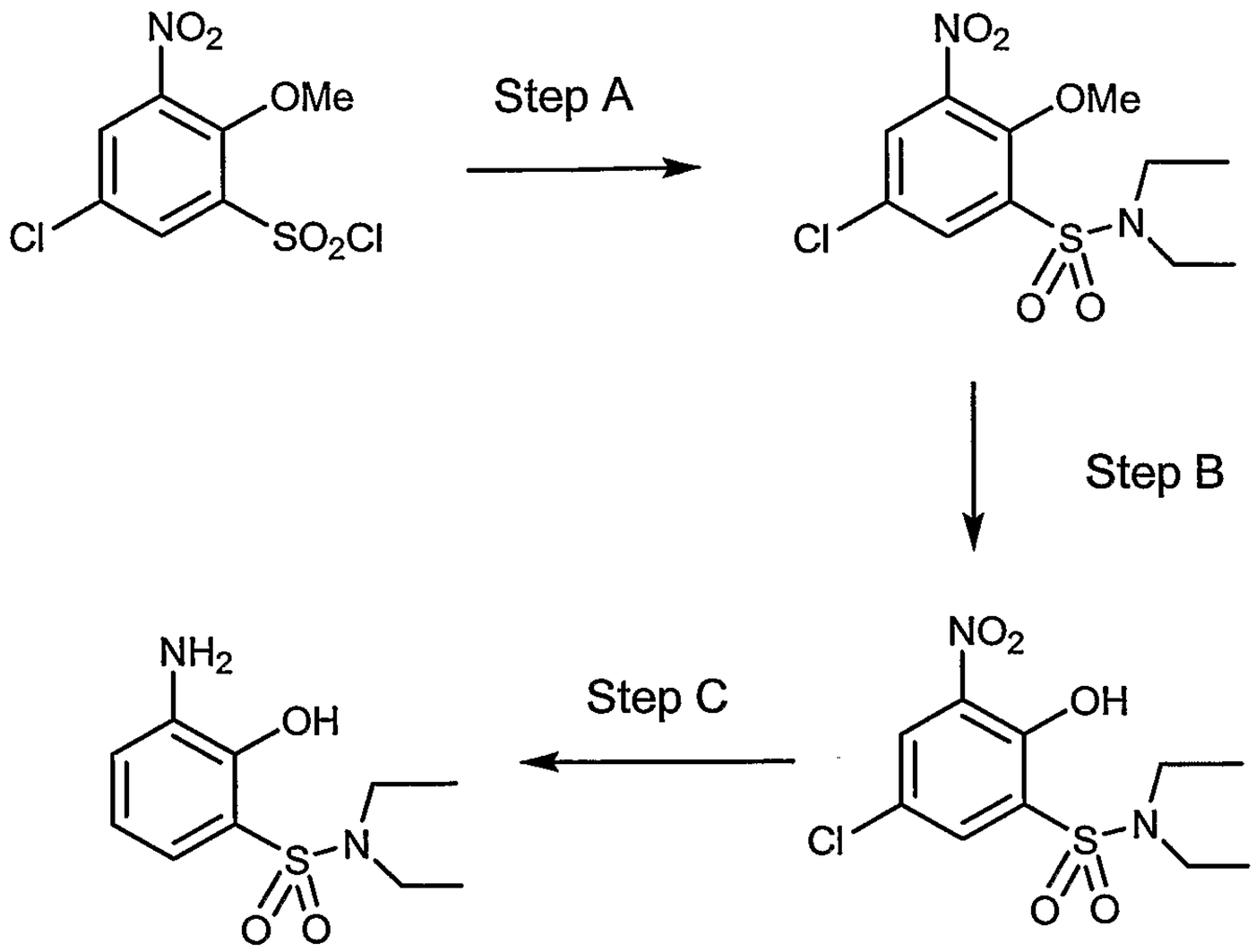
Step A

Following the procedure set forth in Preparative Example 605 but using the commercially available fluoroisopropylester, the alcohol product was obtained (1.2 g, 84%, M-OH = 155).

Step B

Following the procedure set forth in Preparative Example 625 but using the alcohol from Step A above, the amine product was obtained (350 mg, 35%, M-NH2 = 155).

PREPARATIVE EXAMPLES 1302



Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available arylsulfonylchloride (0.15 g) and diethylamine (2.2 eq), the dimethylsulfonamide was obtained (0.12 g, 71%, MH^+ = 323).

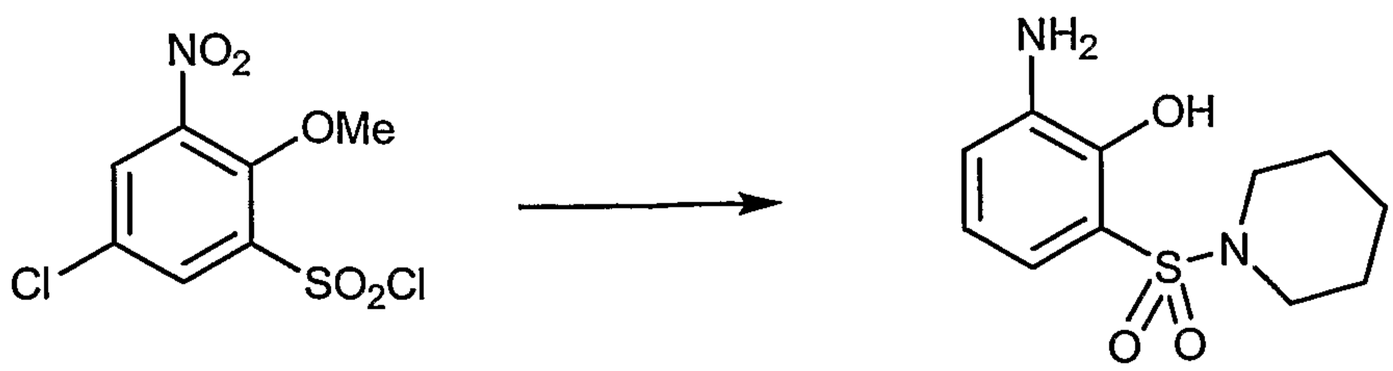
Step B

Following a similar procedure as that used in Preparative Example 13.29 Step C, except using the product from Step A above (0.12 g), the phenol was obtained (0.112 g, 98%).

Step C

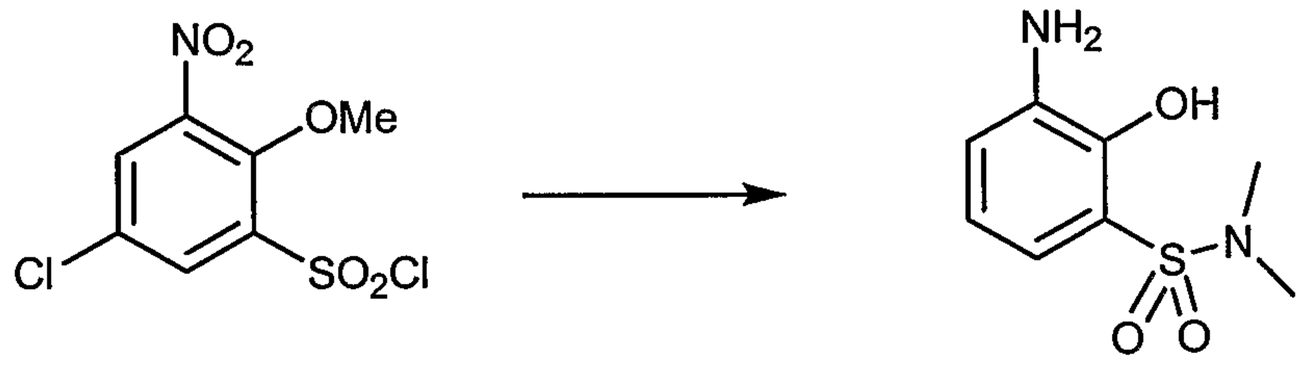
Following a similar procedure as that used in Preparative Example 10.55 Step C, except using the product from Step B above (0.112 g), the title compound was obtained (0.1 g, 99%, MH^+ = 245).

PREPARATIVE EXAMPLES 1303



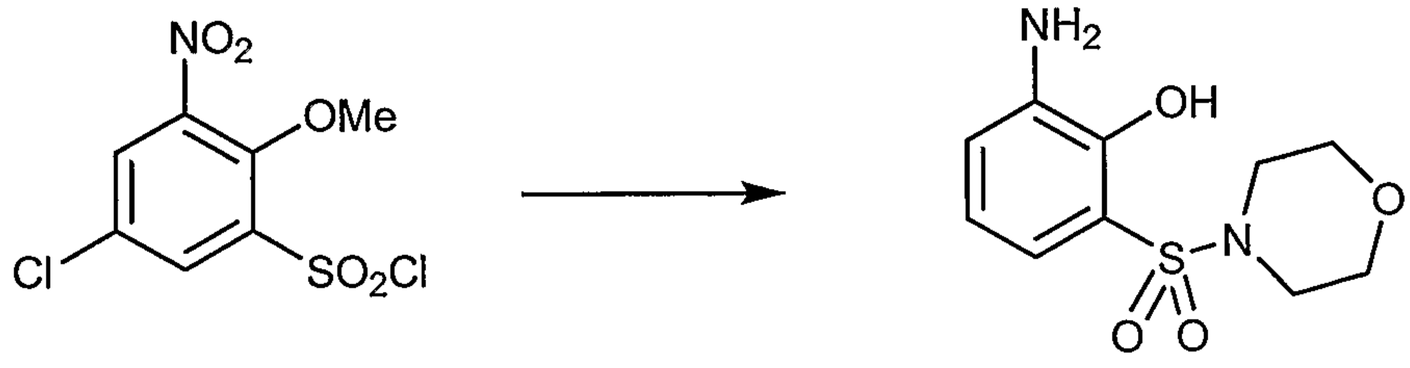
Following a similar procedure as that used in Preparative Example 1302 Steps A-C, except using piperidine in Step A (0.078 g) instead of diethylamine, the title compound was obtained (0.070 g, 35%, MH^+ = 257).

PREPARATIVE EXAMPLES 1304



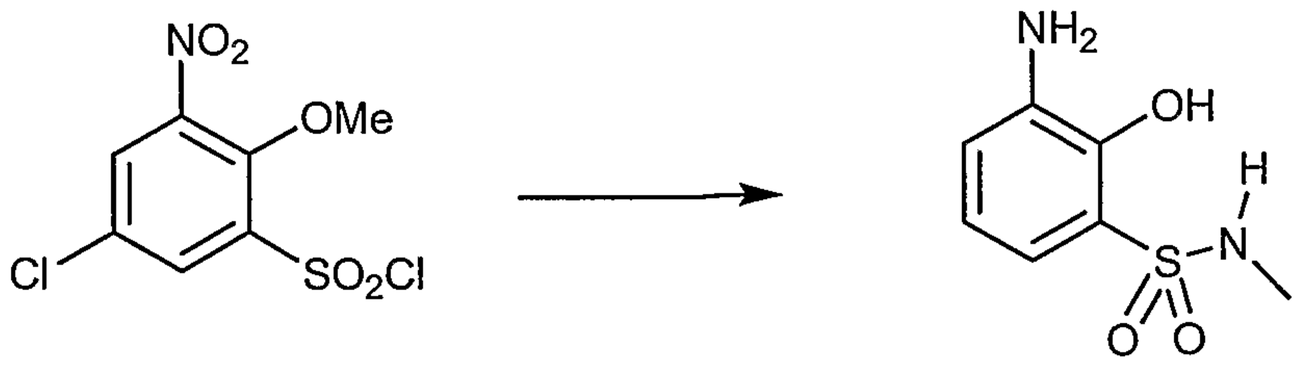
Following a similar procedure as that used in Preparative Example 1302 Steps A-C, except using dimethylamine (2*M* in THF) in Step A instead of diethylamine, the title compound was obtained (1.92g, 72%, MH^+ = 217).

PREPARATIVE EXAMPLES 1304A



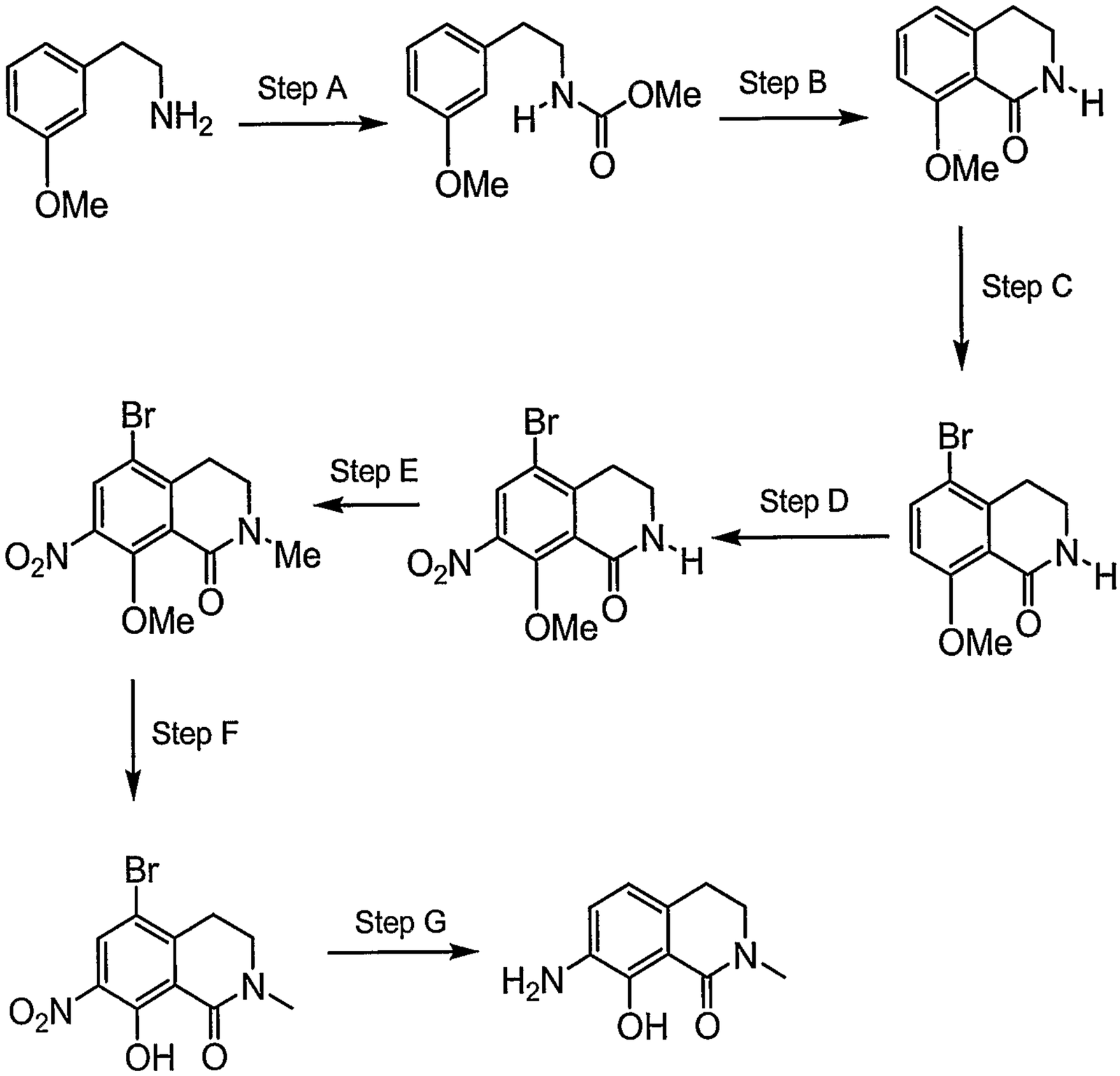
Following a similar procedure as that used in Preparative Example 1302 Steps A-C, except using morpholine in Step A instead of diethylamine, the title compound could be obtained.

PREPARATIVE EXAMPLES 1304B



Following a similar procedure as that used in Preparative Example 1302 Steps A-C, except using N-methylamine in Step A instead of diethylamine, the title compound could be obtained.

PREPARATIVE EXAMPLES 1305



Step A

Following a similar procedure as that used in Preparative Example 1302 Step A, except using the phenethylamine indicated (4.99 g), the product was obtained (5.96 g, 86%, MH^+ = 210).

Step B

The compound from Step A above (5.0 g) was added to 30 g of PPA at 150°C and the resulting mixture stirred for 20 min, before being poured on ice and extracted with dichloromethane. The organic phase was dried over MgSO4, concentrated in

vacuo and purified by silica gel chromatography (EtOAc:MeOH, 95:5) to give the product (0.5 g, 9%).

Step C

Following a similar procedure as that used in Preparative Example 13.3 Step D, except using the compound from Step B above (0.14 g), the product was obtained (0.18 g, 87%, MH^+ = 256).

Step D

Following a similar procedure as that used in Preparative Example 11 Step B, except using the compound from Step C above (0.18 g), the product was obtained (0.17 g).

Step E

Following a similar procedure as that used in Preparative Example 13.3 Step B, except using the compound from Step D above (0.17 g), the product was obtained (0.17 g, 95%, MH^+ = 315).

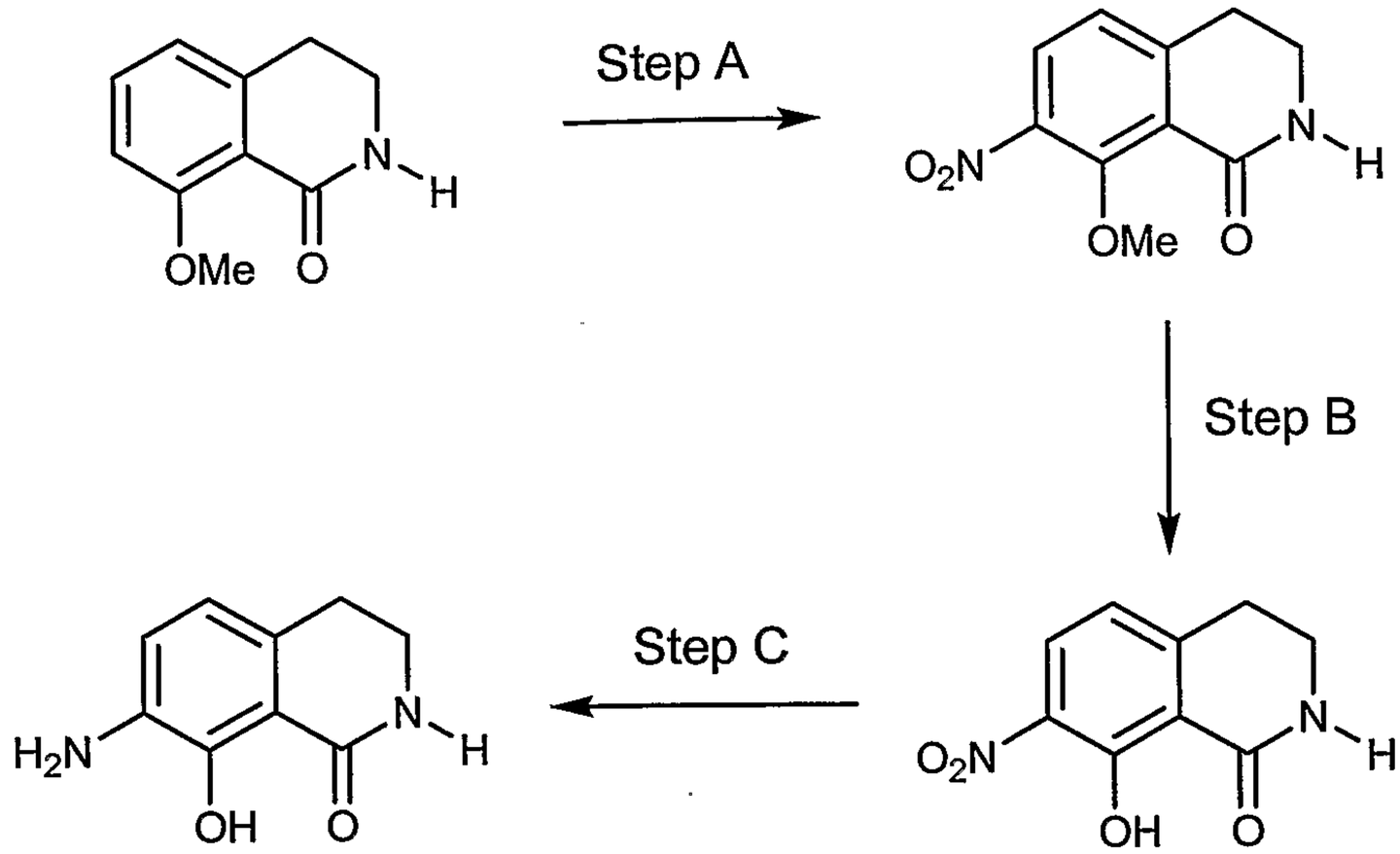
Step F

Following a similar procedure as that used in Preparative Example 13.29 Step C, except using the product from Step E above (0.17 g), the nitrophenol was obtained (0.165 g, 99%, MH^+ = 303).

Step G

Following a similar procedure as that used in Preparative Example 10.55 Step C, except using the product from Step F above (0.165 g), the title compound was obtained (0.128 g, 86%, MH^+ = 193).

PREPARATIVE EXAMPLES 1306



Step A

Following a similar procedure as that used in Preparative Example 11 Step B, except using the lactam (0.179 g), the title compound was obtained (0.25 g, 25%).

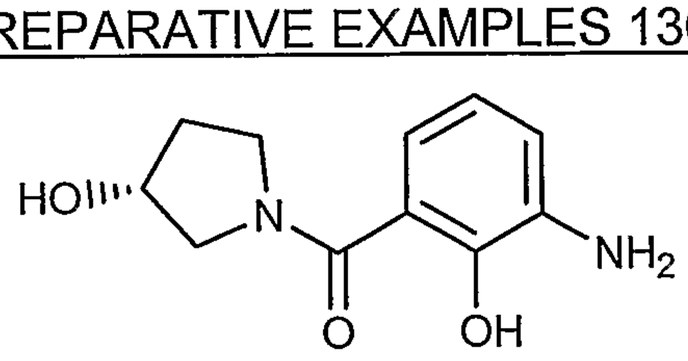
Step B

Following a similar procedure as that used in Preparative Example 13.29 Step C, except using the product from Step A above (0.055 g), the phenol was obtained (0.045 g, 99%).

Step C

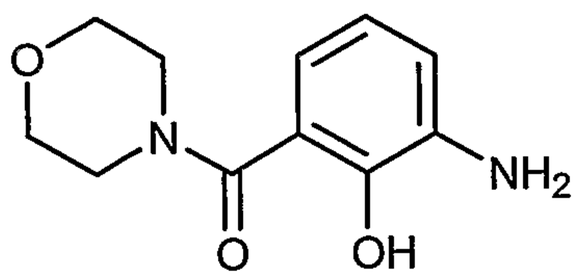
Following a similar procedure as that used in Preparative Example 10.55 Step C, except using the product from Step B above (0.045 g), the title compound was obtained (0.022 g, 57%, MH^+ = 179).

PREPARATIVE EXAMPLES 1307



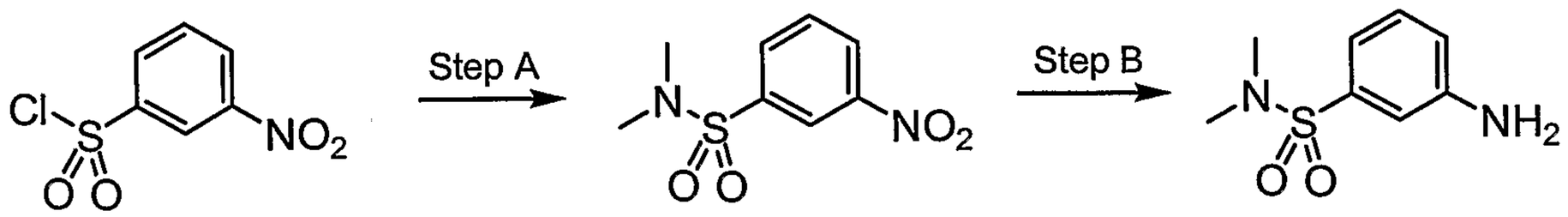
Following a similar procedure as that used in Preparative Example 2, except using 3(*R*)-hydroxypyrrolidine HCl (1.36 g), the title compound was obtained (2.25 g, 89%).

PREPARATIVE EXAMPLES 1308



Following a similar procedure as that used in Preparative Example 2, except using morpholine, the title compound was obtained (3.79 g).

PREPARATIVE EXAMPLES 1309



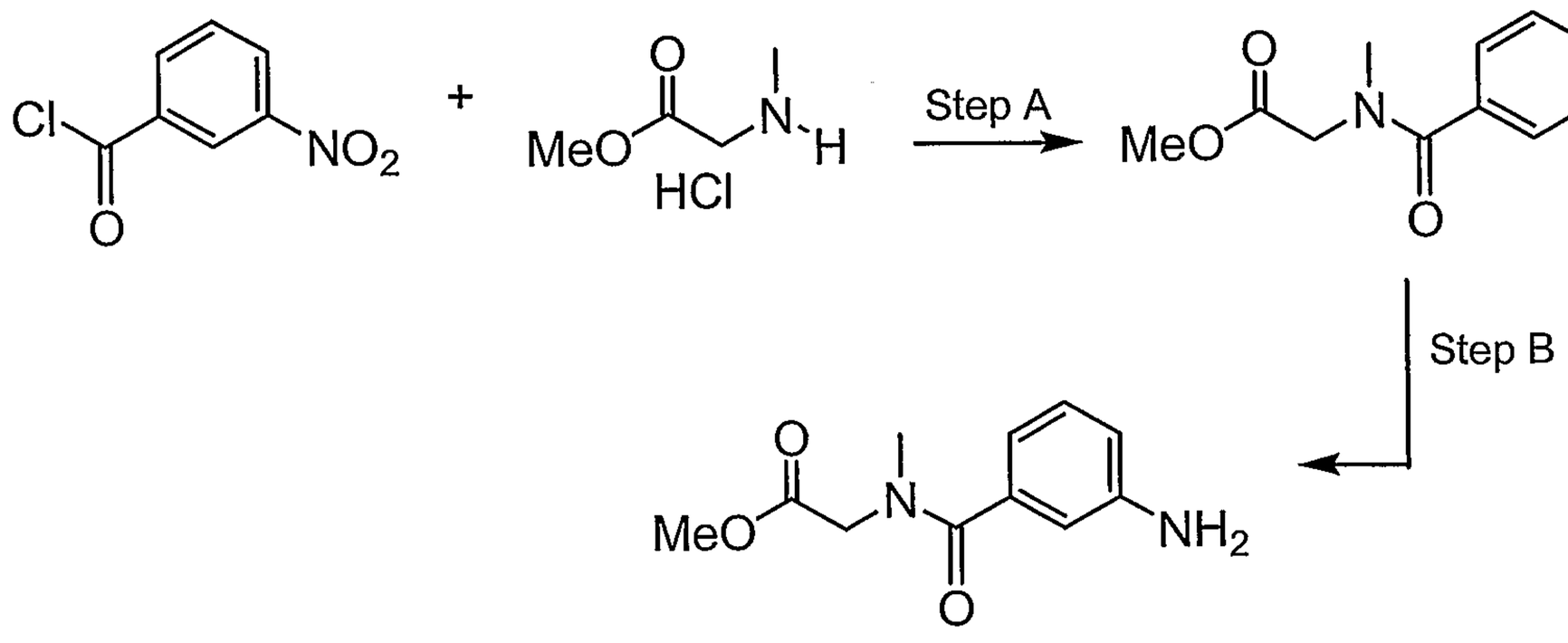
Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available nitrophenylsulfonylchloride and diethylamine (2.2 eq), the dimethylsulfonamide was obtained (90%, MH^+ = 231).

Step B

Following a similar procedure as that used in Preparative Example 10.55 Step C, except using the product from Step B above, the title compound was obtained (45%, MH^+ = 201).

PREPARATIVE EXAMPLES 1310



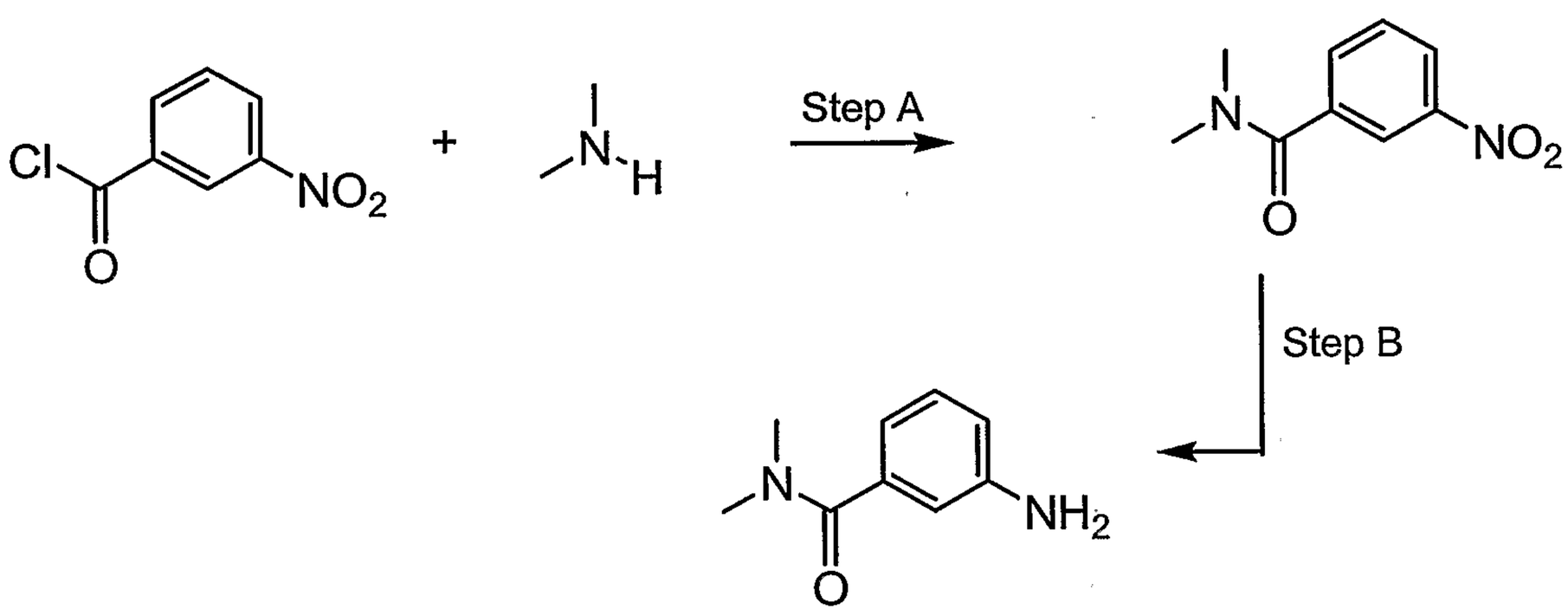
Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available nitrobenzoylchloride and the commercially available amine indicated, the benzamide was obtained (13%, MH^+ = 253).

Step B

Following a similar procedure as that used in Preparative Example 10.55 Step C, except using the product from Step B above, the title compound was obtained (94%, MH^+ = 223).

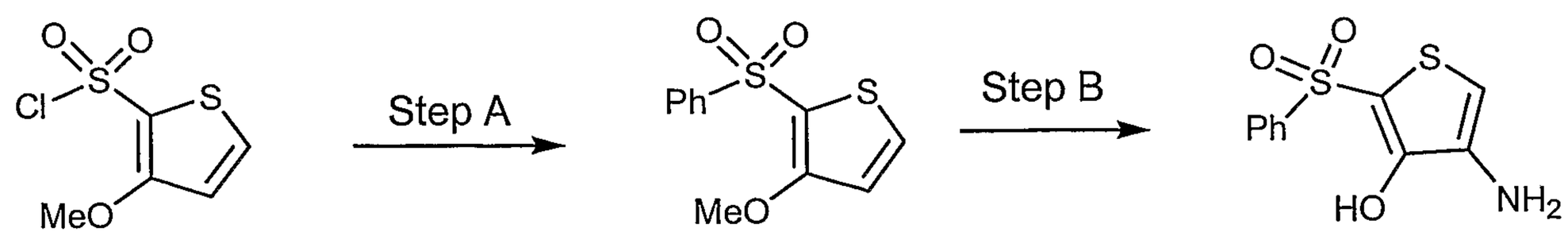
PREPARATIVE EXAMPLES 1310A



Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available nitrobenzoylchloride and dimethylamine, the benzamide could be obtained.

PREPARATIVE EXAMPLES 1311



Step A

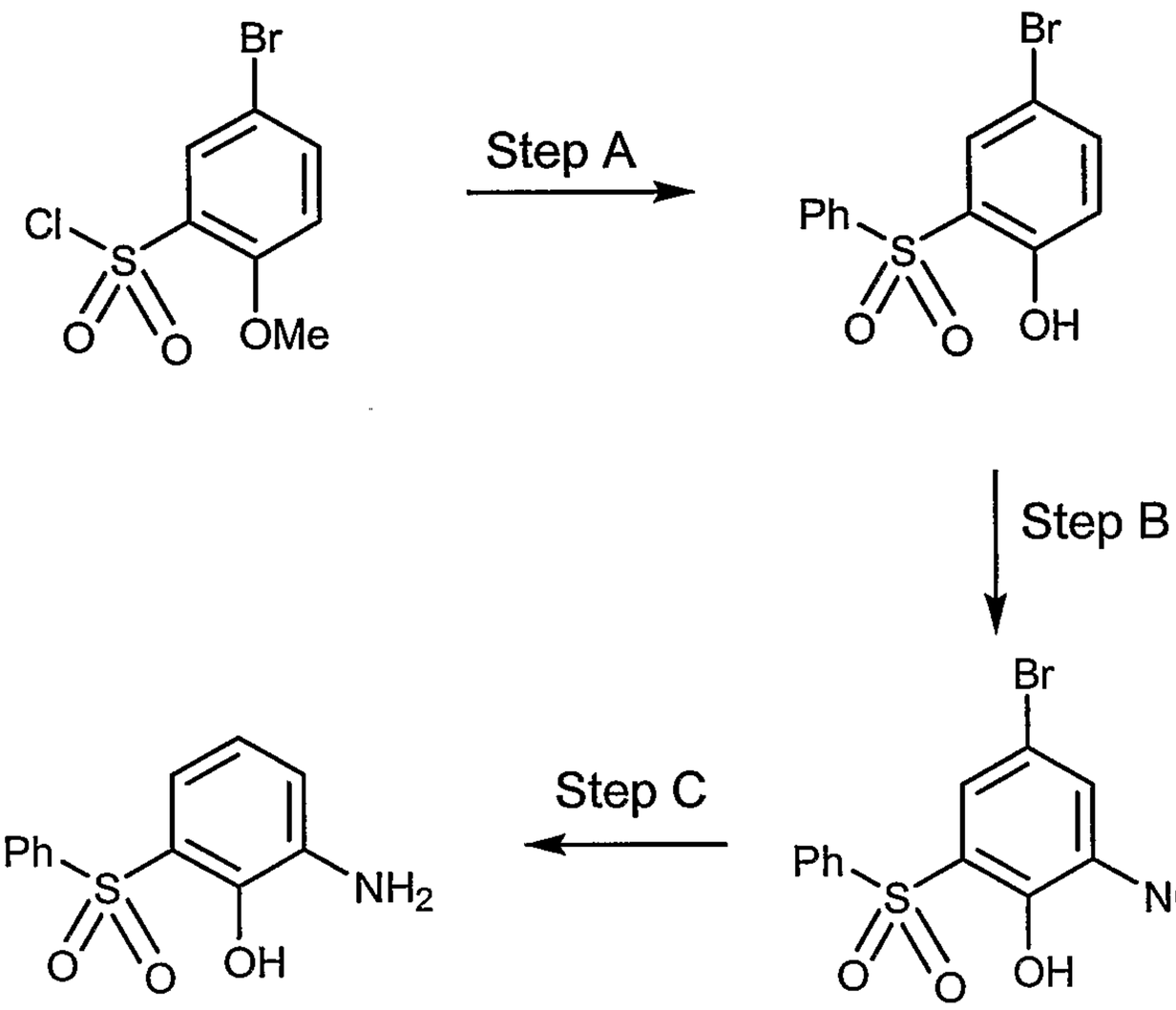
To a benzene (20 mL) solution of methoxythiophenesulfonylchloride (1.5 g) was added $AlCl_3$ (2.0 g) at RT. After 15 min, the mixture was added to 0.1N HCl (aq) with stirring, then extracted with Et_2O. Washing the organic phase with bring, drying

over $MgSO_4$, concentration in vacuo and purification by silica gel chromatography (Hexane:EtOAc, 5:2) gave the title compound (1.5 g, 84%).

Step B

Following a similar procedure as that used in Preparative Example 13.29 Steps C-G, except using the product from Step A above, the title compound was obtained (3%, MH^+ = 380).

PREPARATIVE EXAMPLES 1312



Step A

Following a similar procedure as that used in Preparative Example 1311 Step A, except using the commercially available sulfonylchloride, the diphenylsulfone was obtained (880 mg, 80%).

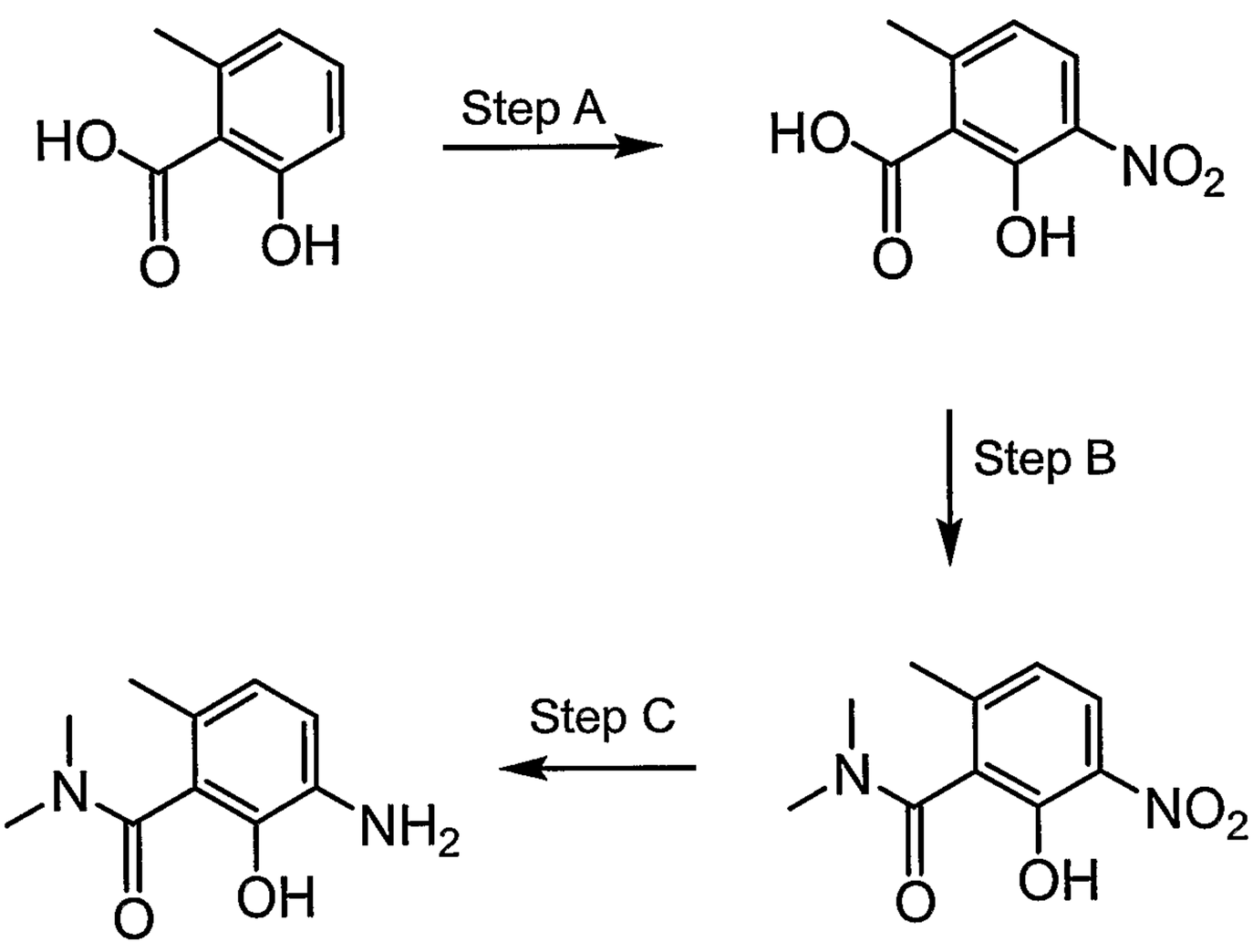
Step B

Following a similar procedure as that used in Preparative Example 11 Step B, except using the product from Step A above, the title compound was obtained (0.90 g, 97%).

Step C

Following a similar procedure as that used in Preparative Example 10.55 Step C, except using the product from Step B above (0.16 g), the title compound was obtained (0.106 g, 95%).

PREPARATIVE EXAMPLES 1313



Step A

Following a similar procedure as that used in Preparative Example 1311 Step A, except using the commercially available phenol (2 g), the nitroacid was obtained (~ 13 mmol).

Step B

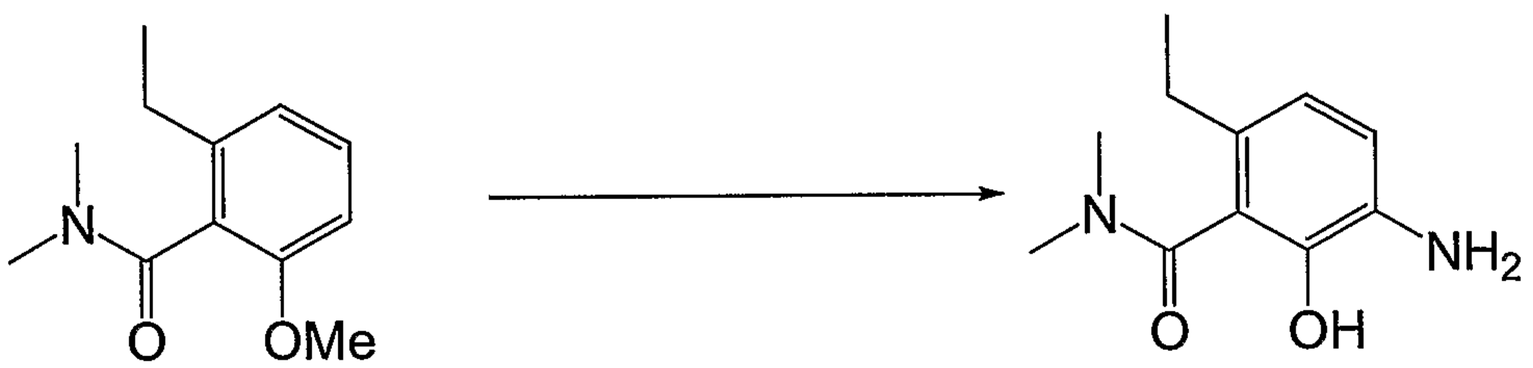
Oxallyl chloride (3.5 mL) and two drops of DMF was added to the product from Step A above (~ 13 mmol) dissolved in dichloromethane (100 mL). After stirring at RT overnight, the mixture was concentrated in vacuo, diluted with dichloromethane (50 mL), cooled to 0°C. Dimethylamine in THF (20 mL of 2N) and TEA (8 mL) were added. After 3 hr of stirring, the mixture was concentrated in vacuo, aq NaOH (1M) was added, and the mixture was extracted with dichloromethane. The pH of the aq layer was adjusted to pH = 2 using 6N HCl (aq), and extracted with dichloromethane.

The combiuned organic extracts were washed with brine, dried, concentrated in vacuo, and the product purified by silica gel chromatography (700 mL dichloromethane/20 mL MeOH/ 1 mL AcOH) to give the title compound (800 mg, 27% for two steps).

Step C

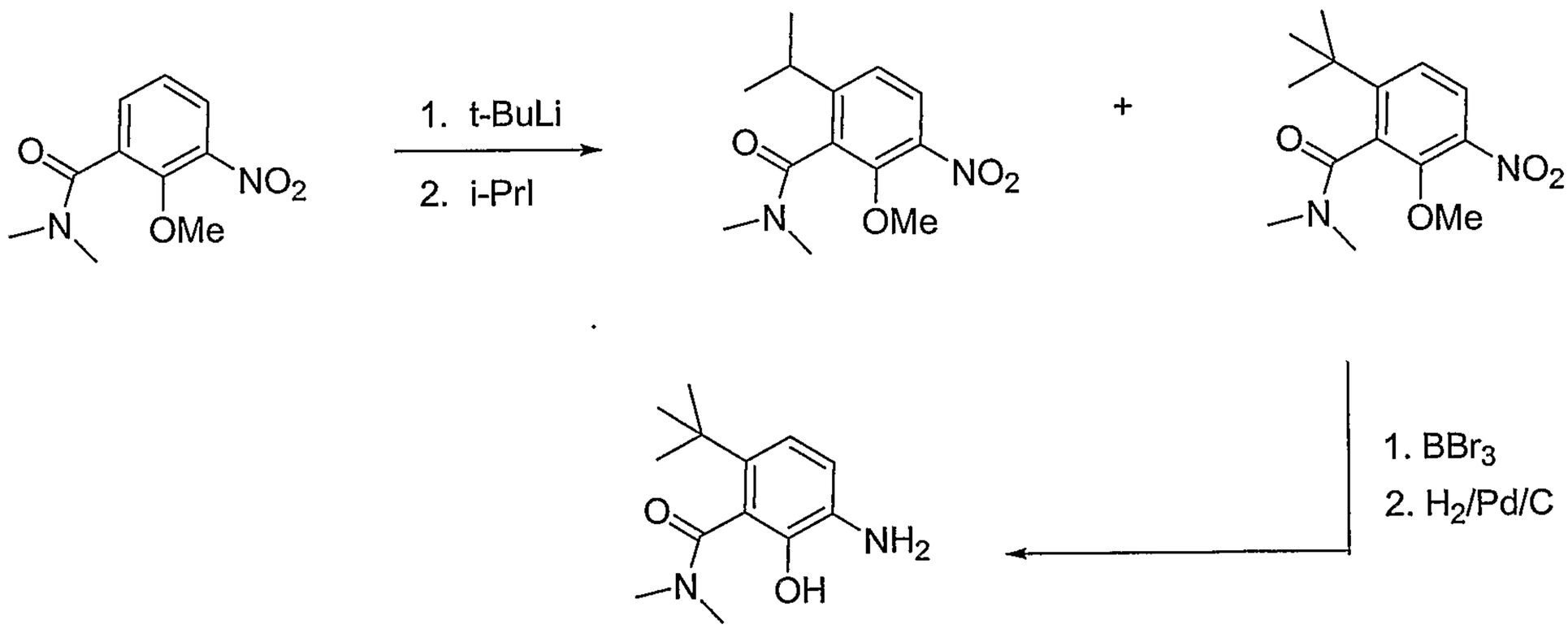
Following a similar procedure as that used in Preparative Example 10.55 Step C, except using the product from Step B above (780 mg), the title compound was obtained (0.46 g, 68%).

PREPARATIVE EXAMPLES 1313A



By following a similar procedure as that used in Preparative Example 1001, steps C, D, E and F, using the known 2-ethyl-6-methoxy-N,N-dimethyl-benzamide (WO 9105781, 2.1g), the amine was obtained (53%,1.1g, MH^+ = 209.1).

PREPARATIVE EXAMPLES 1313B



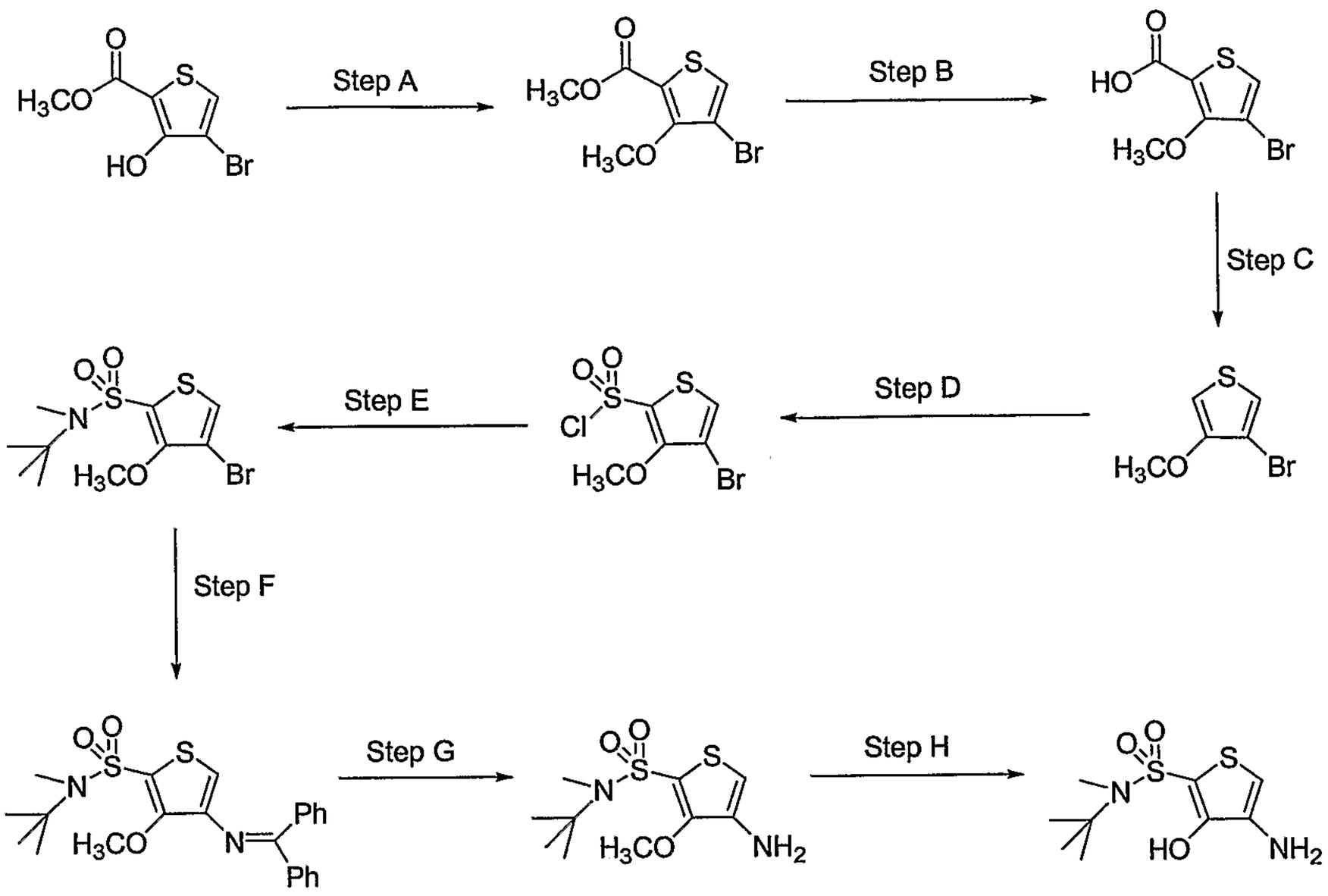
Step A

The benzamide (0.70g, 3.125mmol) was dissolved in dry ether (10ml) under argon and cooled to –78C. t-butyl lithium (4.2mL, as 1.7M solution in pentane) was added. The mixture was stirred at –78C for 1.5hr. 2-Iodopropane (7.8 mmol) was added and the mixture warmed to room temperature and stirred for an additional 16 hrs. Water was added to quench, and the mixture was washed with water, then with 1N HCl. The organic phase was dried (Na2SO4) and concentrated. Flash column chromatography (10:1 Hexane-EtOAC) provided the t-butyl compound (33 mg, 4%, MH+ = 280.9).

Step B

A solution of the compound **1004** (1.2 g, 3.23 mmol) in dichloromethane (50 mL) was cooled to –75 °C. 1 M BBr_3 solution in dichloromethane (7.5 mL, 7.5 mmol) was added dropwise with stirring. The mixture was stirred at –75 °C for 2 h. The mixture was added to ice-water. After stirring at rt for 0.5 h, the mixture was extracted with dichloromethane. The organic was concentrated and the residue was purified by column chromatography (dichloromethane-methanol, 9:1 v/v) to give the product **1005** as a yellow solid (1.05 g, 91%). *m/e* 357 (MH^+), ^1H NMR ($CDCl_3$) δ 8.44(s, 1 H), 3.12 (s, 3 H), 2.87 (s, 3 H).

PREPARATIVE EXAMPLE 1314



Step A

Methyl-4-bromo-3-hydroxy-2-thiophenecarboxylate (20g, 84.36 mmol) was dissolved in 400 mL of acetone. Potassium carbonate (58g, 420.3 mmol) was added followed by iodomethane (45 mL, 424 mmol). The resulting mixture was heated at reflux for 4.5 h. After cooling, the mixture was filtered through a thin Celite pad, rinsing with methylene chloride. The filtrate was concentrated in vacuo to give 22.5 g of methyl-4-bromo-3-methoxy-2-thiophenecarboxylate (crude, 100%, MH^+ = 251.0) as a dark green solid.

Step B

The product from Step A above (22.5g, 84.36 mmol) was dissolved in 60 mL of tetrahydrofuran and added with 125 mL of a 1.0 M NaOH aqueous solution. The mixture was stirred at room temperature for 4 d, then washed with ether (60 mL x 2), acidified to pH ~ 2 using a 1.0 M HCl aqueous solution. Solids were precipitated out after acidification, and collected by filtration. The solid was dissolved in methylene chloride-ethyl acetate (~4:1, v/v). The organic solution was washed with H_2O and brine, dried with Na_2SO_4, and concentrated in vacuo to a light yellow solid, further

dried on hight vacuum, yielding 17.95 g of 4-bromo-3-methoxy-2-thiophene carboxylic acid (90%, MH^+ =237.0).

Step C

The carboxylic acid (3.26 g, 13.75 mmol) available from Step B above was treated with 30 mL of concentrated sulfuric acid. The mixture was sealed in a one-neck round bottom flask, and heated at 65°C for 4.5 h. After cooled to room temperature, the mixture was poured into 200 mL of crushed ice, and extracted with methylene chloride (100 mL x 3). The organic extracts were combined, washed successively with H_2O (50 mL x 2), sat. $NaHCO_3$ (50 mL x 3), and brine (50 mL). The organic solution was dried with Na_2SO_4, and concentrated in vacuo to a dark brown oil, which was purified by flash column chromatography (biotage, SiO_2 column) using hexanes-methylene chloride (3:1, v/v) as eluents. Removal of solvents afforded 1.83 g of 3-bromo-4-methoxy thiophene (69%) as a light yellow oil.

Step D

To a stirred solution of 3-bromo-4-methoxythiophene (550 mg, 2.85 mmol), prepared in Step C above, in 30 mL of methylene chloride at -78°C was added dropwise along the inside wall of the flask chlorosulfonic acid (0.48 mL, 7.21 mmol). The mixture was stirred at -78°C for 10 min, continued at room temperature for 1 h, and filtered through a 1-in silica gel pad, rinsing with methylene chloride. The filtrate was concentrated in vacuuo to give 270 mg of 4-bromo-3-methoxy-2-thiophene sulfonylchloride (33%) as a light yellow oil.

Step E

To a stirred solution of thiophene sulfonylchloride (270 mg, 0.926 mmol) prepared in Step D above in 15 mL of methylene chloride at room temperature was added triethylamine followed by *N*-methyl-tertbutylamine (0.25 mL, 2.094 mmol). After 20 h, the mixture was diluted with 50 mL of methylene chloride, and washed with H_2O and brine. The organic solution was dried over Na_2SO_4, filtered, and concentrated to an oily residue, which was purified by preparative TLC (methylene chloride as eluent) to afford 73 mg of the titled bromo-sulfonamide (23%) as a near colorless oil.

Step F

A one-neck round bottom flask was charged with bromo-sulfonamide (73 mg, 0.2133 mmol, from Step E above), palladium acetate (5 mg, 0.0223 mmol), binap (0.03212 mmol), cesium carbonate (139 mg, 0.4266 mmol), and benzophenonimine (0.06 mL, 0.358 mmol). The mixture was evacuated via house vacuum, and refilled with nitrogen. A 3 mL of anhydrous toluene was added. The mixture was evacuated again, refilled with nitrogen, and heated at reflux for 2.5 d. After cooled to room temperature, methylene chloride (50 mL) was added, the mixture was filtered through a Celite pad, rinsing with methylene chloride. The filtrated was concentrated in vacuo to give 205 mg (crude, MH^+ = 443.1) of the desired imine product as a dark brown oil, used in next step without purification.

Step G

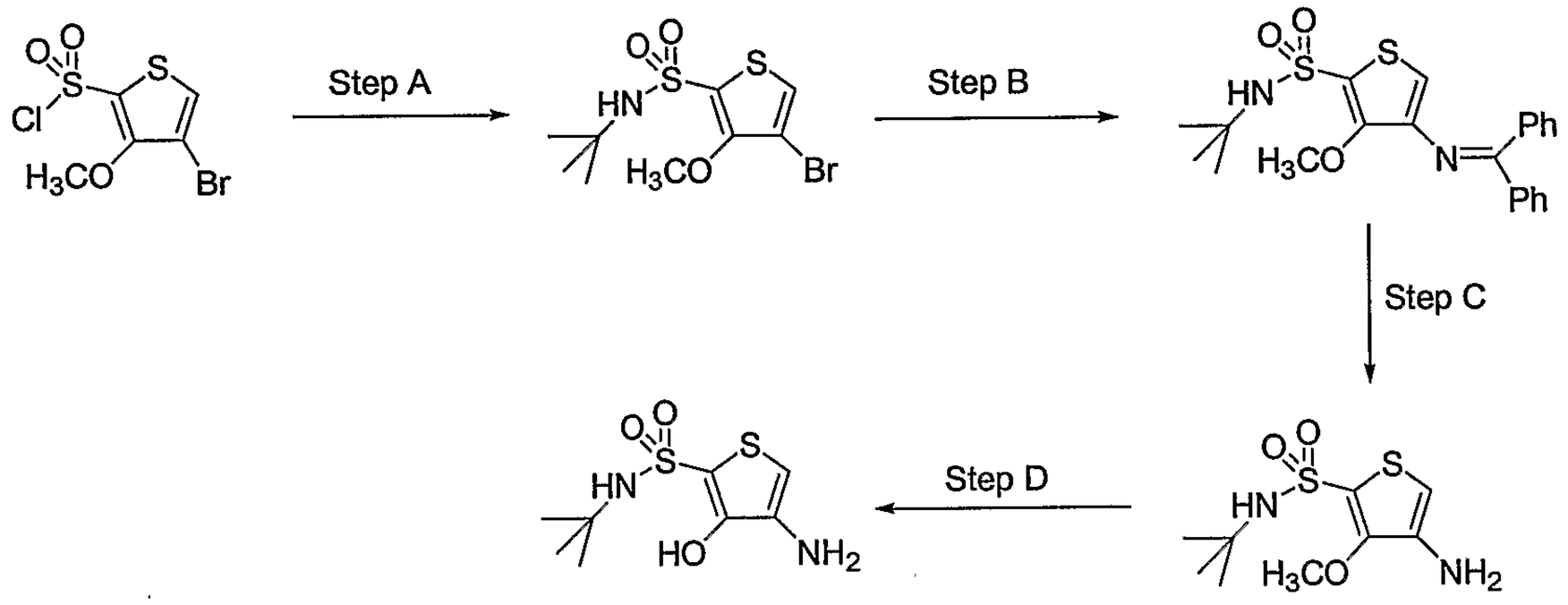
The imine from Step F above (205 mg, crude, 0.2133 mmol) was dissolved in 5 mL of methanol, and added with sodium acetate (81 mg, 0.9873 mmol) followed by hydroxylamine hydrochloride (68 mg, 0.98 mmol). The mixture was stirred at room temperature for 6.5 h, quenched with the addition of 10 mL of a 1.0 M NaOH aqueous solution. The aqueous mixture was extracted with methylene chloride (30 mL x 3). The extracts were combined, washed with brine, dried by Na_2SO_4, and concentrated in vacuo to a dark yellow oil, which was purified by preparative TLC (methylene chloride – methanol = 100:1, v/v) to give 34 mg (57% over two steps, MH^+ = 279.0) of methoxy-thiophenesulfonamide amine as a light yellow oil, solidified on standing.

Step H

To a stirred suspension of sodium hydride (60%, 45 mg, 1.13 mmol) in 3 mL of anhydrous *N,N'*-dimethylformamide (DMF) was added dropwise ethanethiol (0.1 mL, 1.34 mmol). After 10 min, the mixture tured into a clear solution, and 1 mL of this solution was taken up in a syringe and added dropwise to a stirred solution of methoxy-thiophenesulfonamide amine in 1 mL of DMF. The mixture was heated up to 95°C, and continued for 3.5 h. After cooling, the mixture was poured into 20 mL of a 1.0 M NaOH aqueous solution. The aqueous mixture was washed with methylene chloride (30 mL x 3). The organic washings were combined, re-extracted with a 1.0 M NaOH aqueous solution (15 mL) and H_2O (15 mL). The aqueous layer and aqueous

extracts were combined, adjusted to pH~6 using a 1.0 M HCl aqueous solution,and extracted with methylene chloride (75 mL x 3). The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to a dark yellow oil. This oil was dissolved in ethyl acetate (50 mL), washed with H_2O (10 mL x 2) and brine (10 mL). The organic solution was dried (Na_2SO_4), and concentrated in vacuo to afford 36 mg (100%, MH^+ = 265.0) of hydroxyl-thiophene sulfonamide amine as a yellow oil.

PREPARATIVE EXAMPLE 1315



Step A

Following the procedures described in Preparative Example 1314 Step E, 4-bromo-3-methoxy-2-thiophene-sulfonyl chloride (190 mg, 0.65 mmol, available from Step D, Preparative Example 1314) was converted to the titled tert-butyl sulfonamide (56 mg, 26%, MH^+ = 328.1) upon treatment of triethylamine (0.28 mL, 2.0 mmol) and tert-butylamine (0.15 mL, 1.43 mmol) in 10 mL of methylene chloride.

Step B

tert-Butyl sulfonamide (98 mg, 0.3 mmol) available from Step A above was converted to the imine product (296 mg, crude, MH^+ = 429.1) by using the procedure described in Step F of Preparative Example 1314.

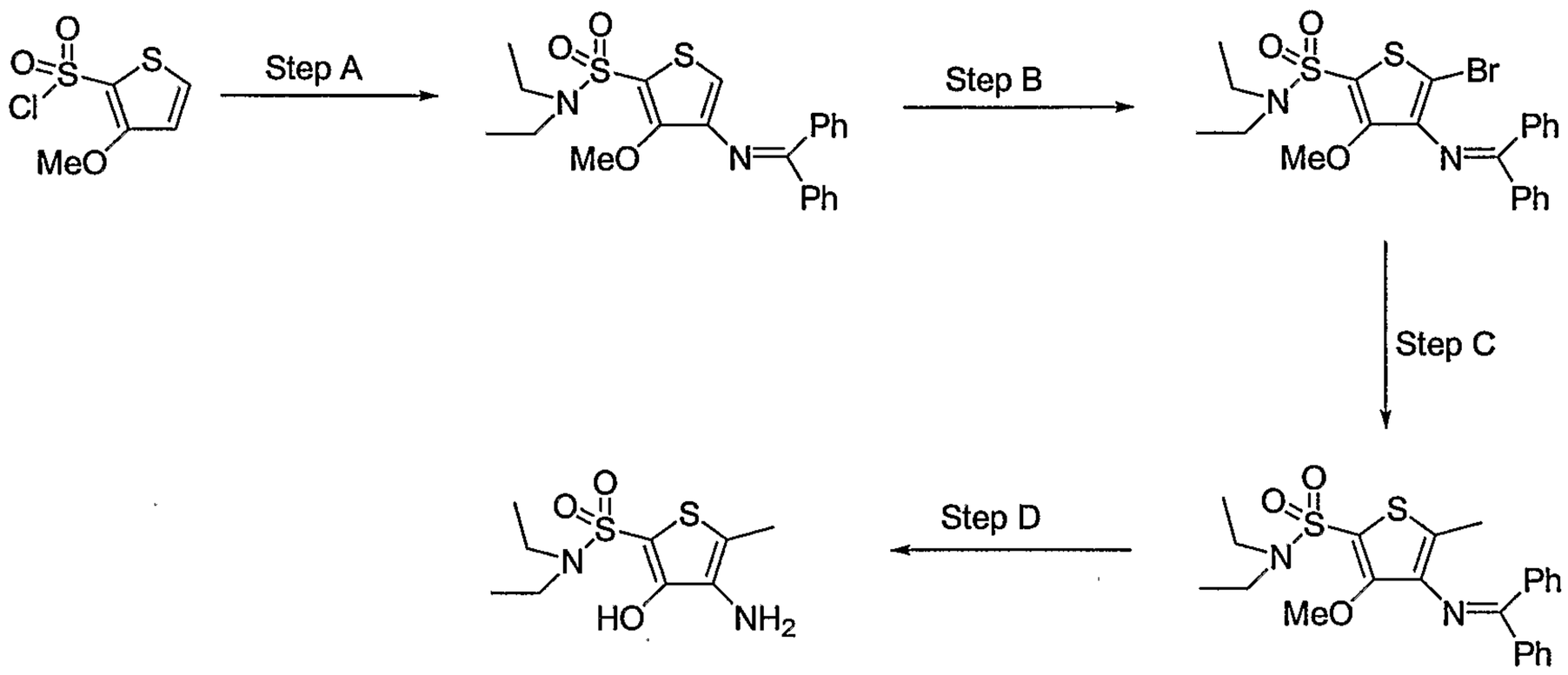
Step C

The imine product (296 mg, crude, ~0.3 mmol) was transformed to the desired thiophene-amine (23 mg, 30% over two steps, MH^+ = 265.0) by using the procedure described in Step G of Preparative Example 1314.

Step D

If one were to apply the procedure set forth in Step H of Preparative Example 1314, but using the thiophene amine available from Step C above, one would obtain the titled hydroxyl thiophene sulfonamide amine.

PREPARATIVE EXPAMPLE 1316



Step A

Following the procedures set forth in Preparative example 13.29 Step B through F, but using diethylamine, 3-methoxy-2-thiophenesulfonyl chloride (available from Step A, Preparative example 13.29) was converted to titled diethylsulfonamido thiophene imine (MH^+ = 429.1)

Step B

Thiophene-imine (1.5 g, 3.5 mmol), available from Step A above, was dissolved in 30 mL of CH_2Cl_2, and added with potassium carbonate (1.2 g, 8.70 mmol) followed by drop wise addition of bromine (0.32 mL, 6.25 mmol). After stirred for 2 d, H_2O was added. The two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL x 2). The organic layers were combined, washed with a 10% $Na_2S_2O_3$ aqueous solution (40 mL x 2) and brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo to a dark brown oil. This oil was separated by preparative TLC (CH_2Cl_2 as eluent), to give 0.96 g (54%) of the desired bromo-imine as a bright yellow oil (M^+ = 507, M + 2 = 509)

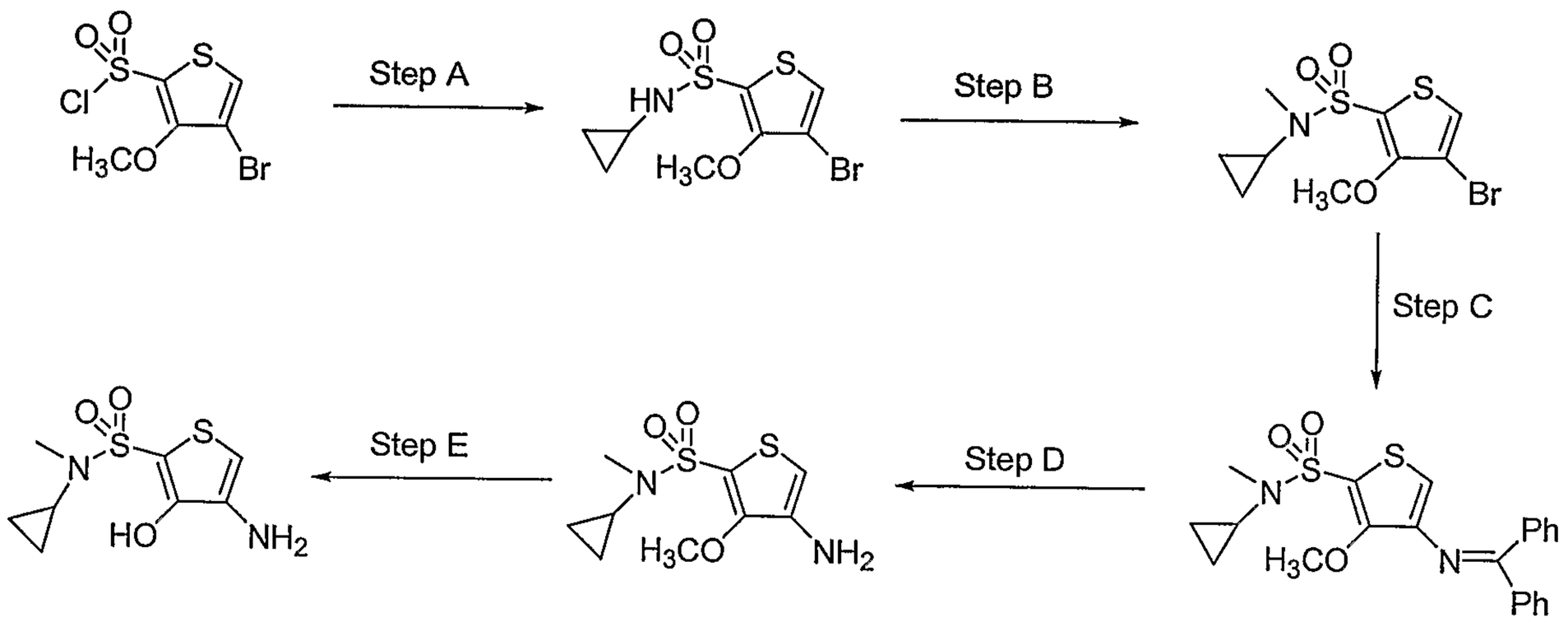
Step C

Bromo-imine (0.95g, 1.87 mmol), available from Step B above, was dissolved in 15 mL of anhydrous THF, cooled in a -78°C bath, and treated with a 2.5 M solution of n-butyl lithium in hexanes (1.2 mL, 3.0 mmol) drop wise along the side wall of the flask. After 30 min, Iodomethane (0.35 mL, 5.62 mmol) was added drop wise. Reaction was continued for 5 h, during which time the cooling bath was allowed to warm slowly to 0°C. The mixture was quenched by H_2O (25 mL), and extracted with CH_2Cl_2 (50 mL x 2). The organic extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo to give 0.93 g (crude, > 100%) of the desired methylated imine as a dark yellow oil (MH^+ = 443.1)

Step D

The crude methyl-imine (0.93 g), prepared in step C above, was converted to the methyl-hydroxyl-amine (0.21 g, 41%, MH^+ = 265.0) by using the procedures described in Step G of Preparative Example 13.29.

PREPARATIVE EXAMPLE 1316A



Step A

Following the procedures described in Preparative Example 1314 Step E, but using cyclopropyl amine, the titled cyclopropyl-sulfonamide was prepared from 4-

bromo-3-methoxy-2-thiophene-sulfonylchloride (available from Step D, Preparative Example 1314).

Step B

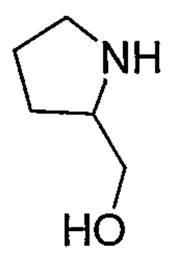
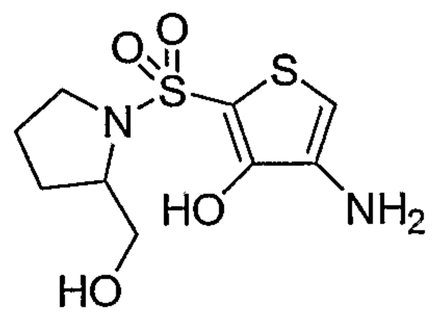
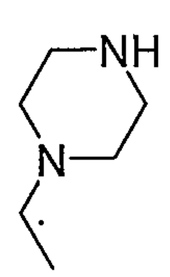
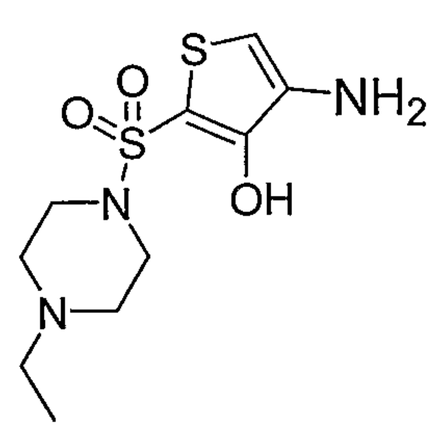
Cyclopropyl-sulfonamide, available from Step A above, was treated with potassium carbonate and iodomethane in reflux acetone to afford *N*-methyl-*N*-cyclopropyl sulfonamide.

Step C, D, E

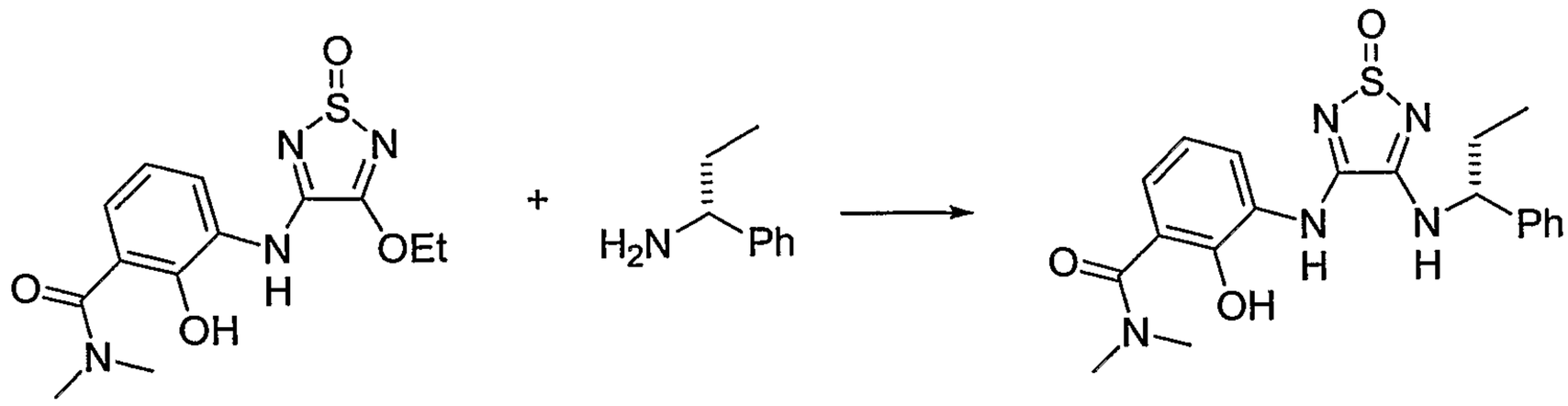
Following the procedures set forth in Preparative Example 1314, steps F to H, *N*-methyl-*N*-cyclopropyl sulfonamide from Step B above was converted to the hydroxyl-amino-thiophene sulfonamide (MH^+ = 249.0)

PREPARATIVE EXAMPLE 1317-1318

Following the procedures set forth in Preparative Example 1314 but using the commercially available amines, the hydroxyaminothiophene products listed in the Table below could be prepared.

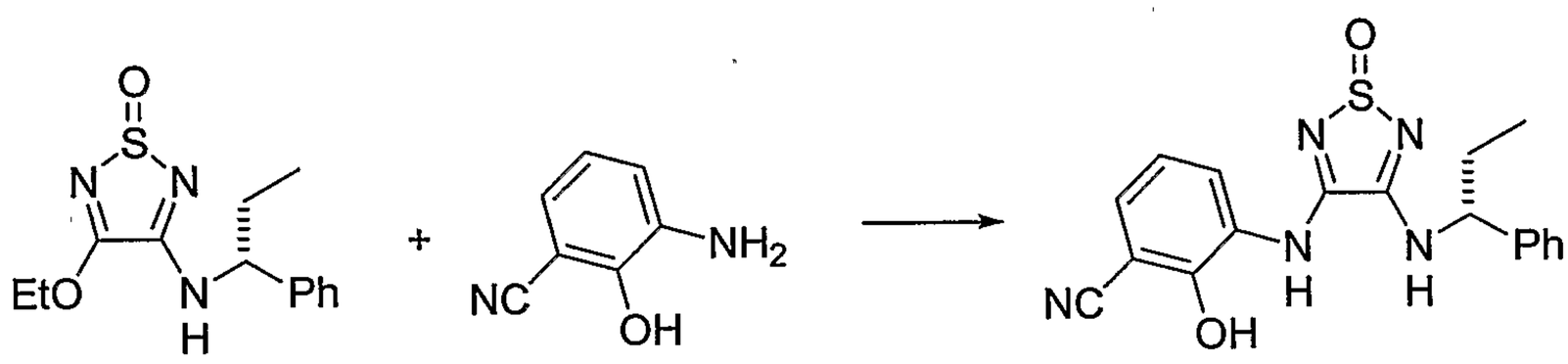
Prep. Ex.	Amine	Product
1317		
1318		

PREPARATIVE EXAMPLE 2000



The thiadiazoleoxide from Preparative Example 22.1 (55mg, 0.17mmol) was added to *R*-2-phenylpropylamine (0.024mL, 0.17mmol) in methanol (2ml) with diiospropylethylamine (100μL). The reaction mixture was microwaved at 100W for 4hr then purified by preparative HPLC. Concentration of desired fractions gave the pure product (12.4mg, 18%). MH^+ = 413.9.

PREPARATIVE EXAMPLE 2001



The thiadiazoleoxide from Preparative Example 22.2 (56mg, 0.2mmol) was added to 2-amino-6-cyanophenol (27mg, 0.2mmol) in methanol (2ml) with diiospropylethylamine (100μL). The reaction mixture was microwaved at 100W for 24hr then purified by preparative HPLC. Concentration of desired fractions gave the pure product (11mg, 15%). MH^+ = 367.9.

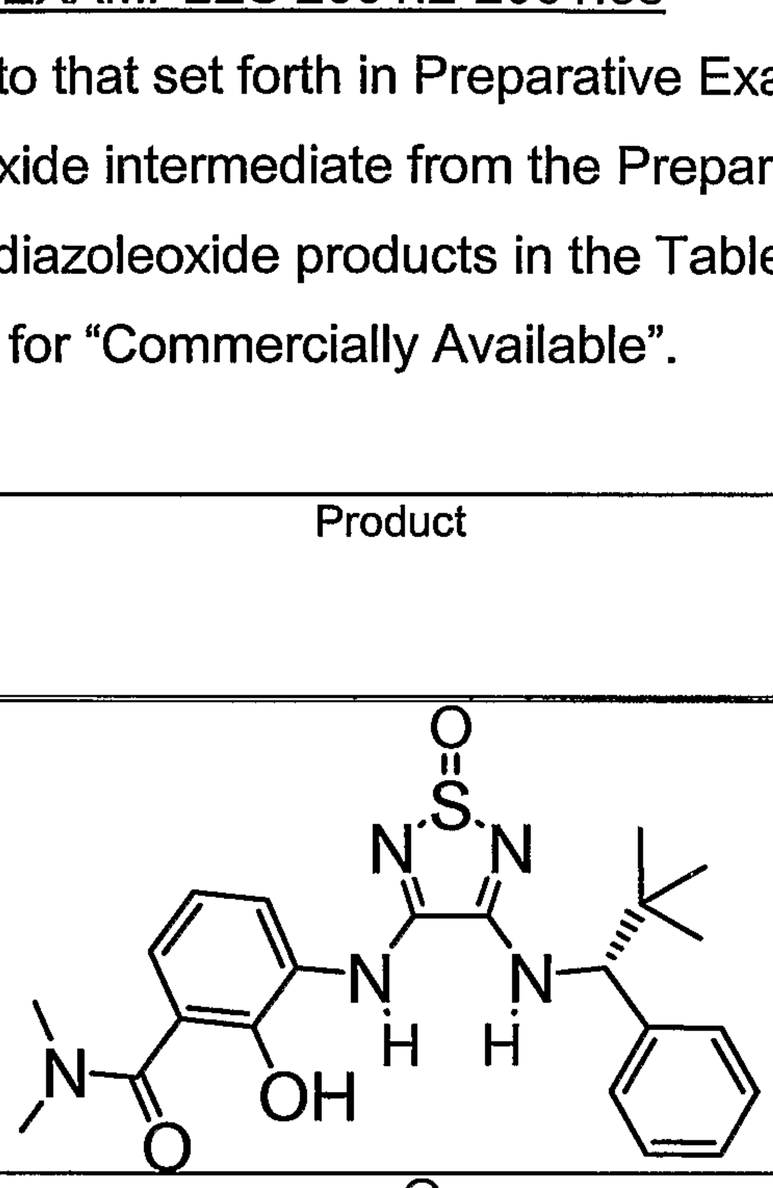
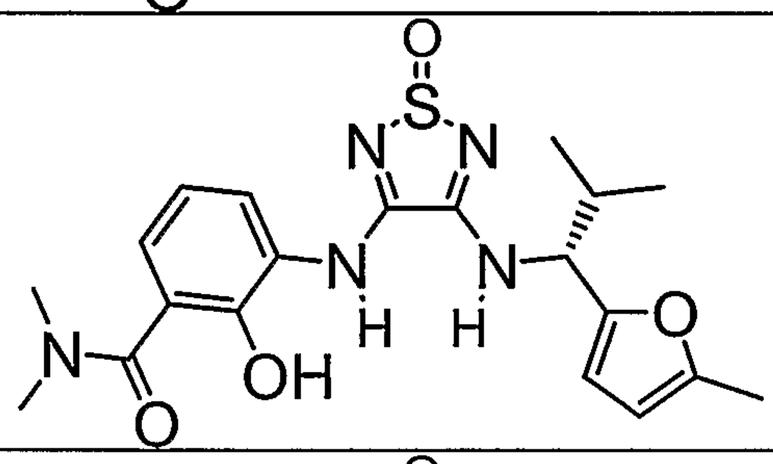
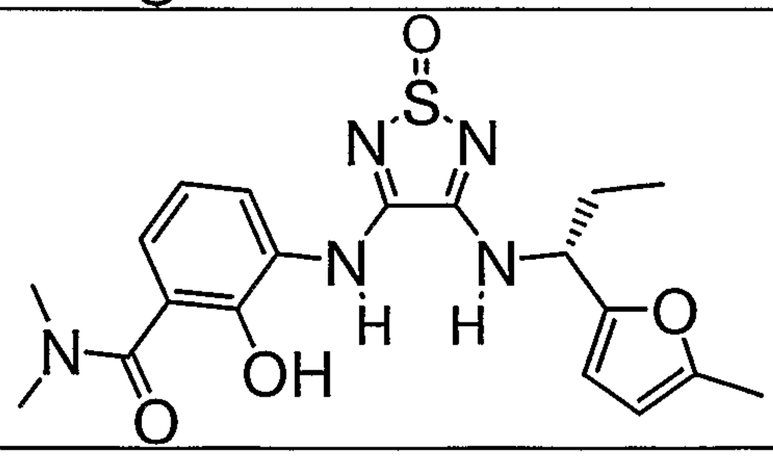
PREPARATIVE EXAMPLE 2001A

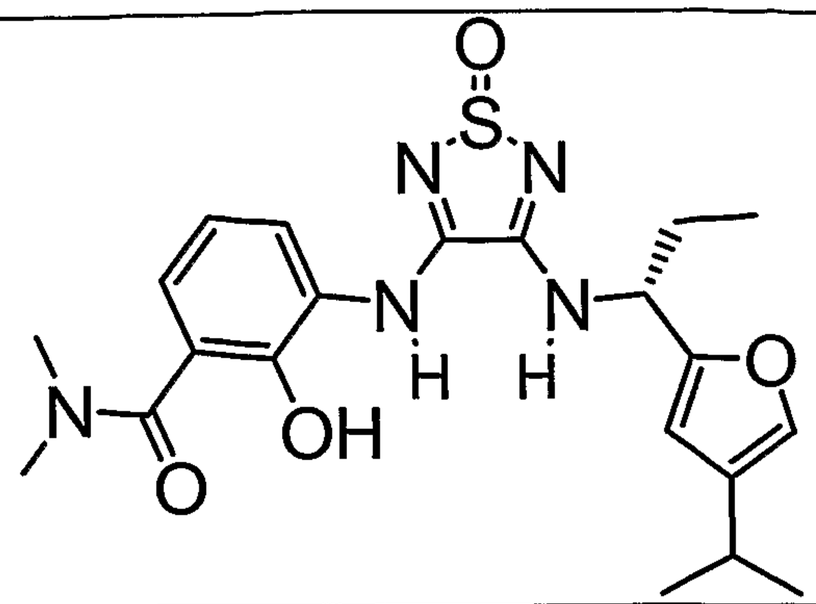
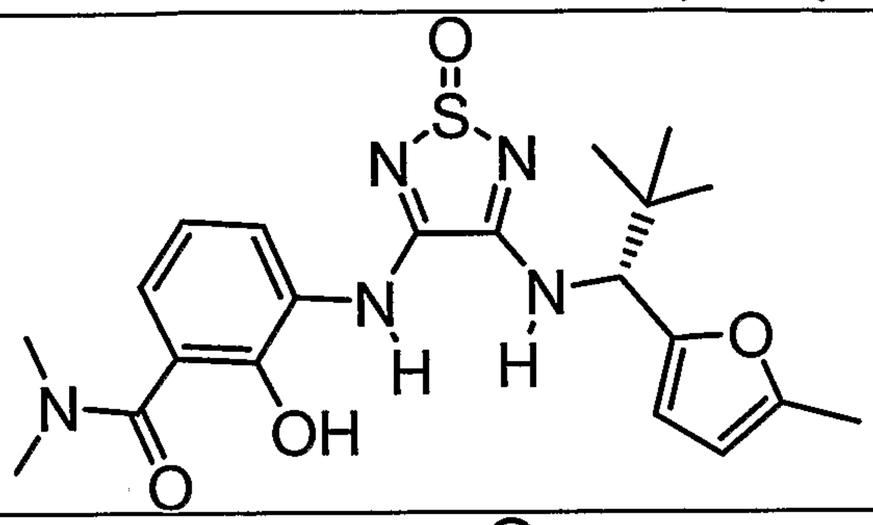
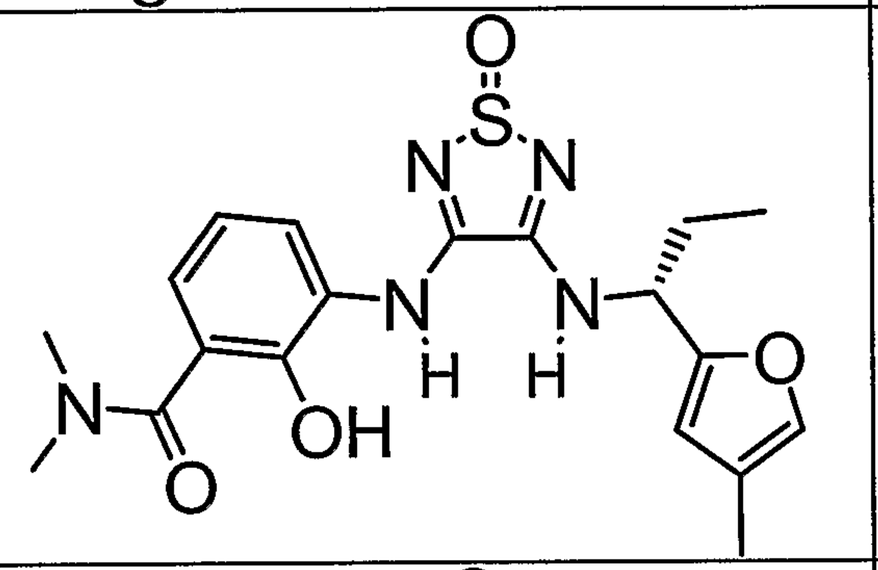
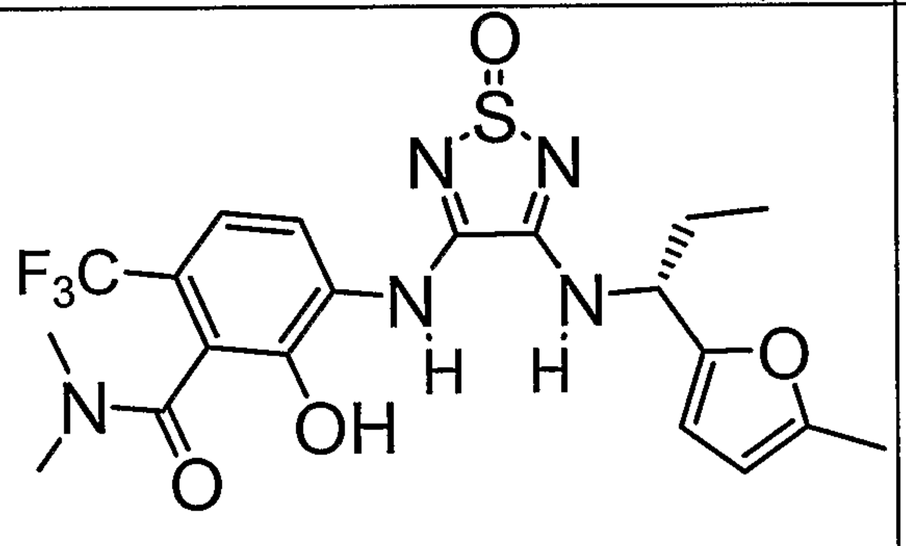
To a solution of the Thiadiazole mono-oxide intermediate from Preparative Example 22.1 (100mg, 0.3086mmol) and the Furyl amine from Preparative Example 75.1 (43mg, 0.3086mmol) in methanol (2mL) was added sodium trifluoro acetate (84mg, 0.6172mmol), followed by drop wise addition of diisopropylethylamine (80mg,

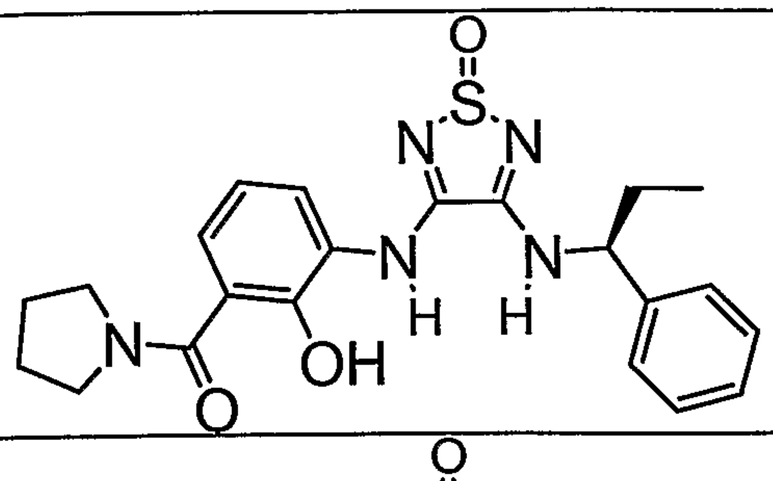
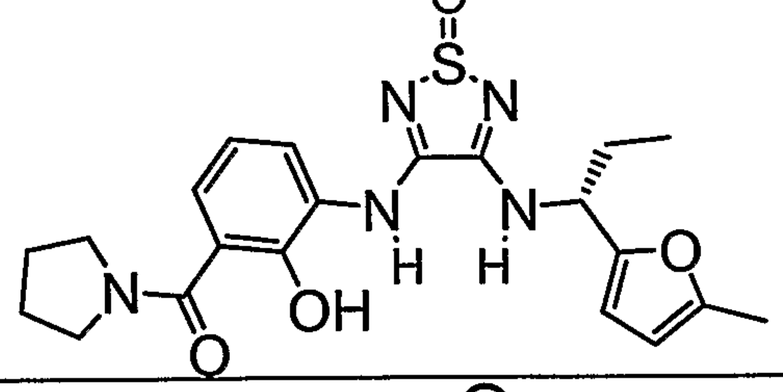
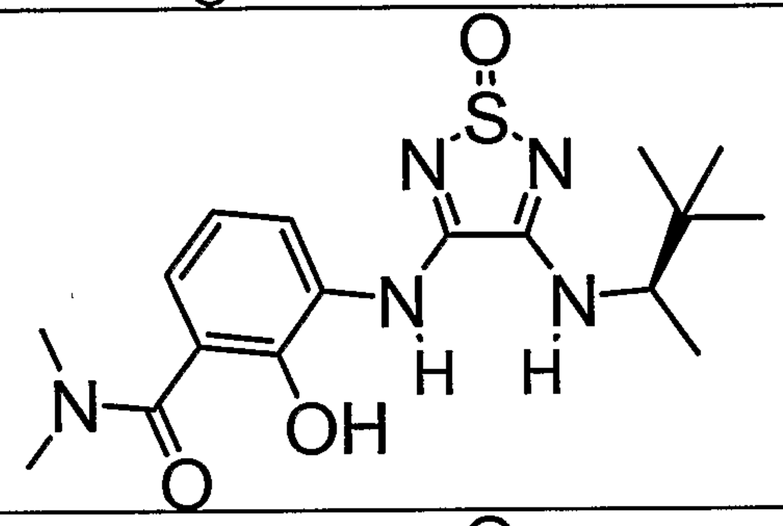
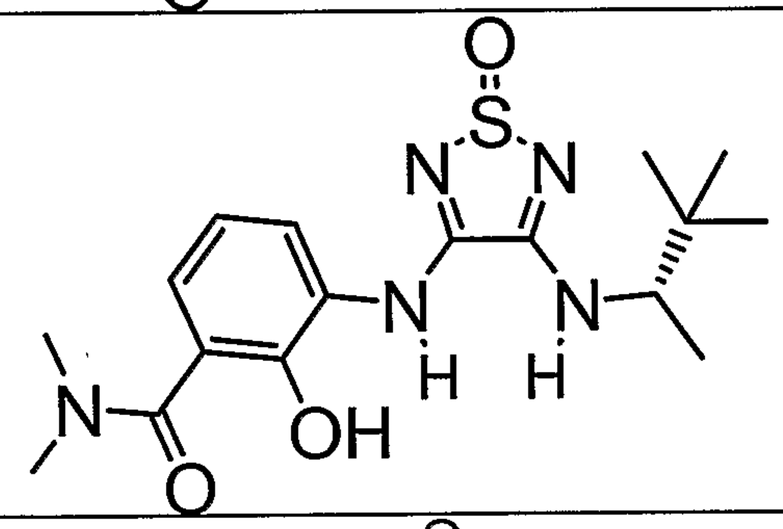
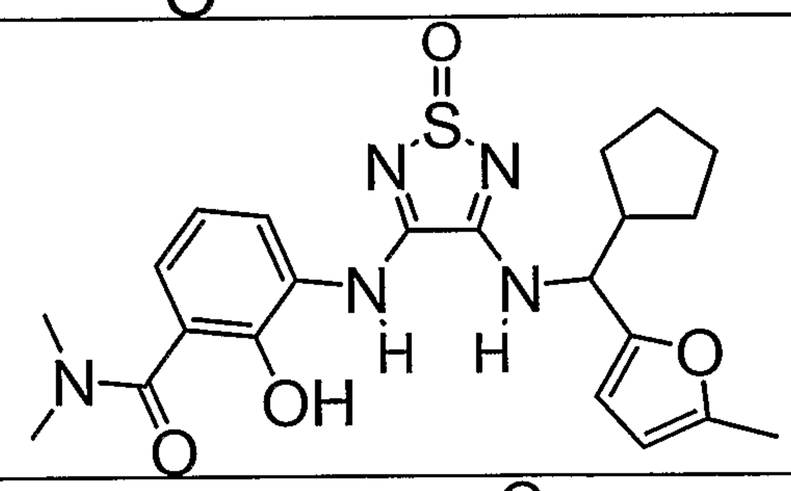
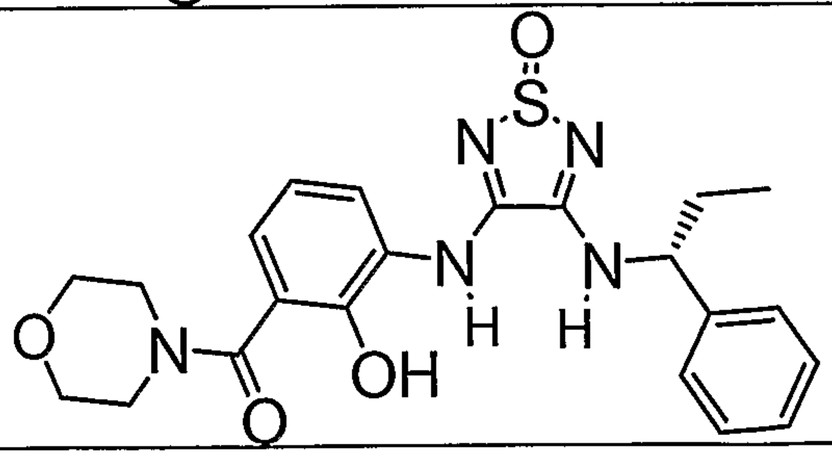
0.6172mmol). The reaction mixture was stirred over night at room temperature, solvents were removed under reduced pressure and the product was purified by preparative thin layer chromatography using Dichloromethane-Methanol (20:1) to afford the compound as a white solid. (Yield: 98mg, 74%, m.p = 140°C)

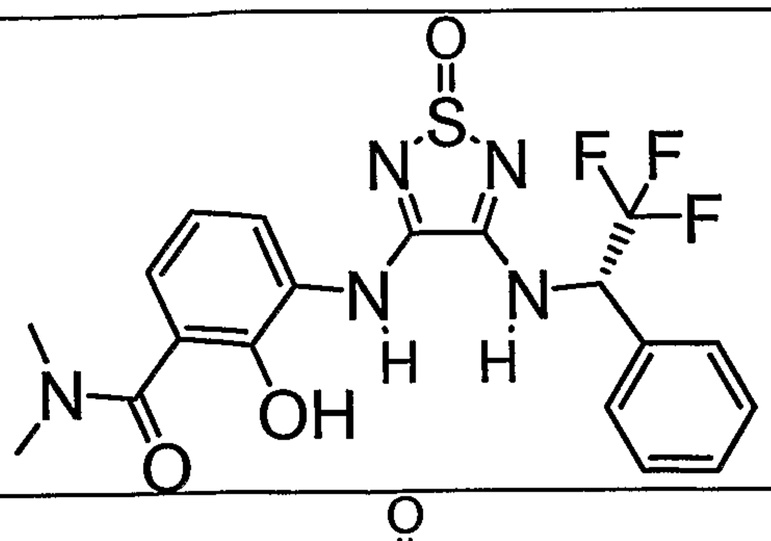
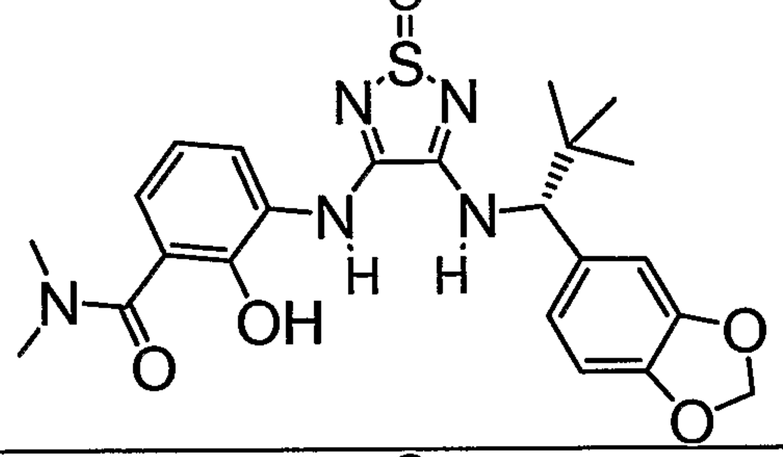
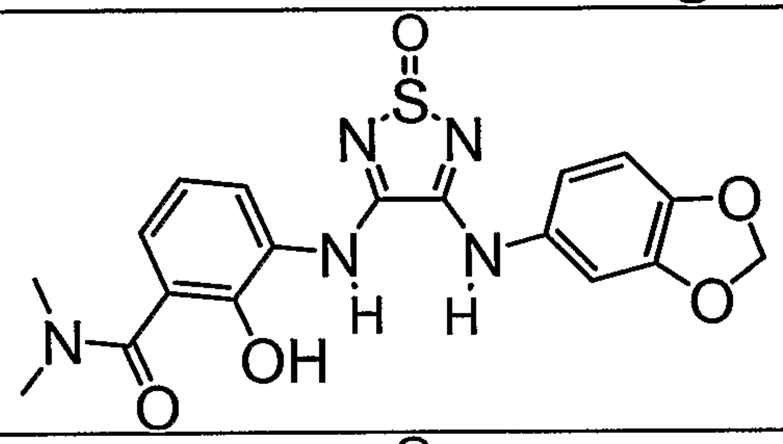
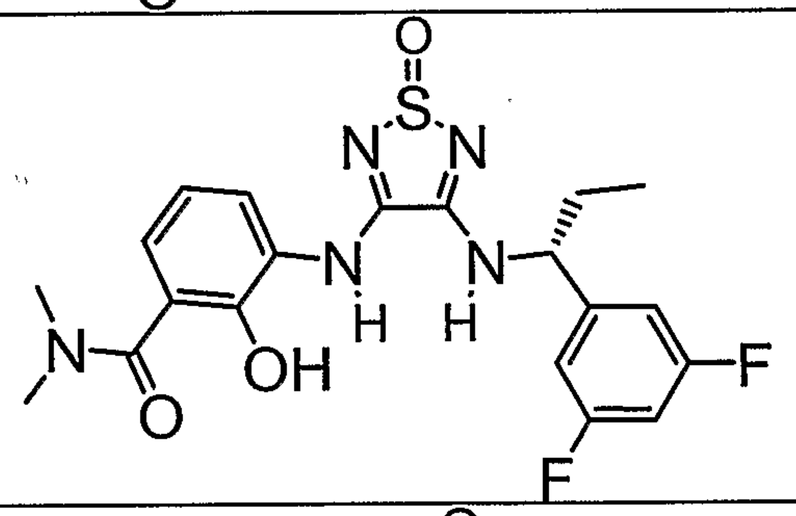
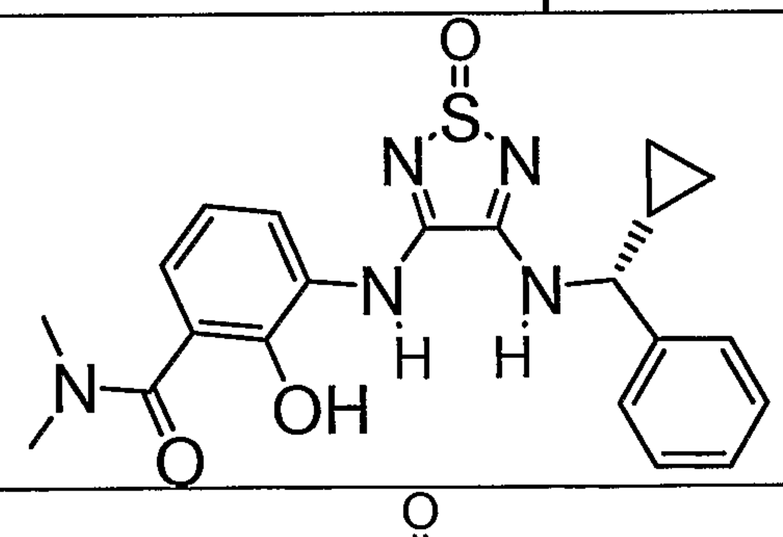
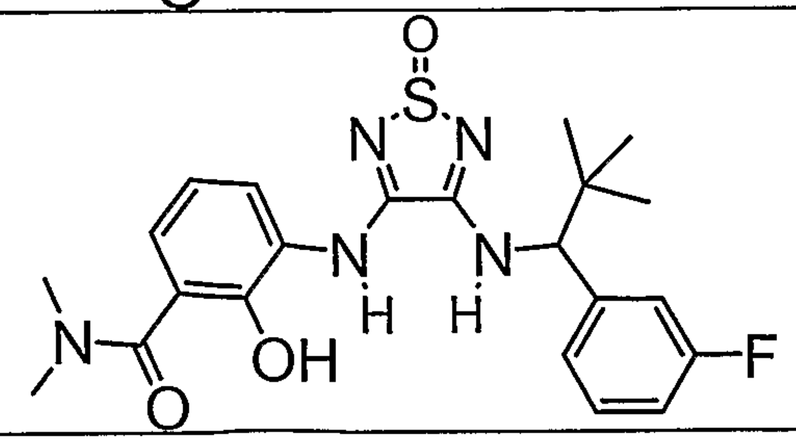
PREPARATIVE EXAMPLES 2001.2-2001.55

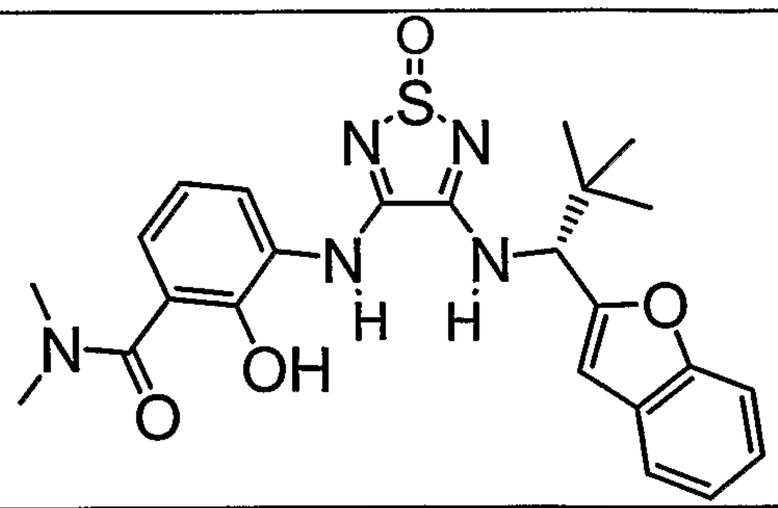
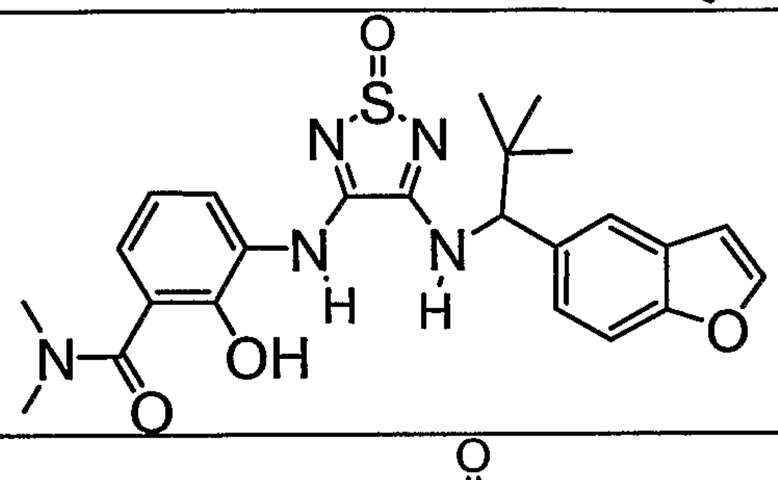
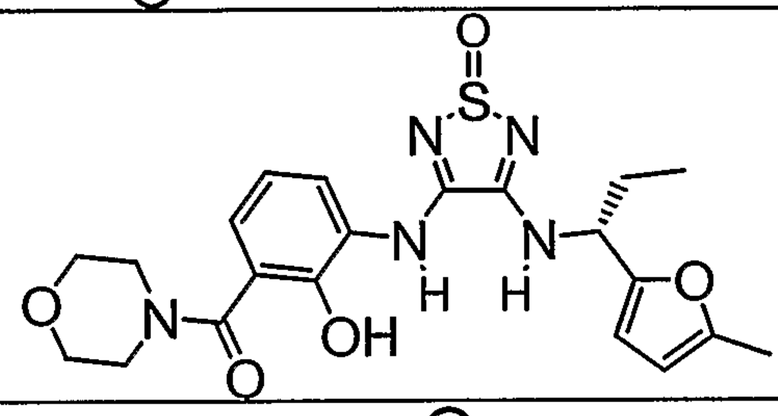
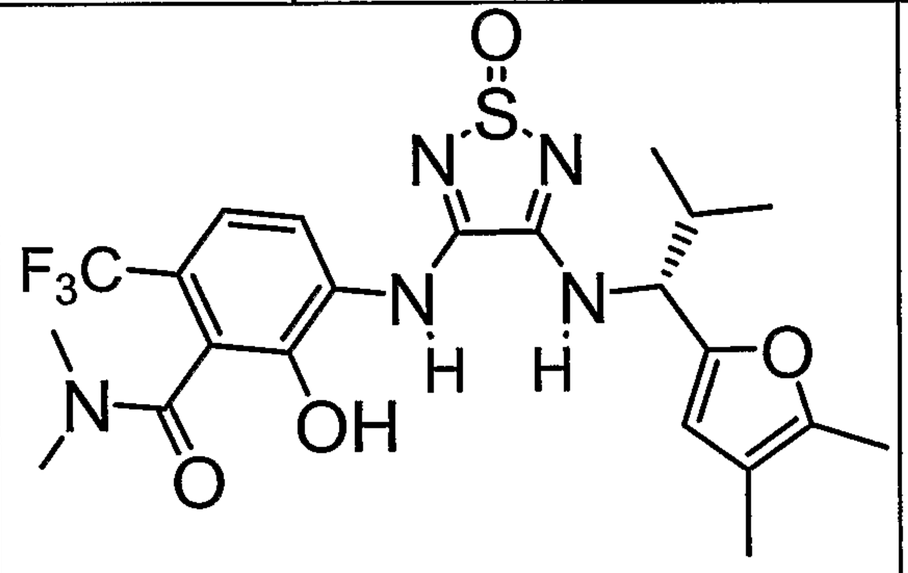
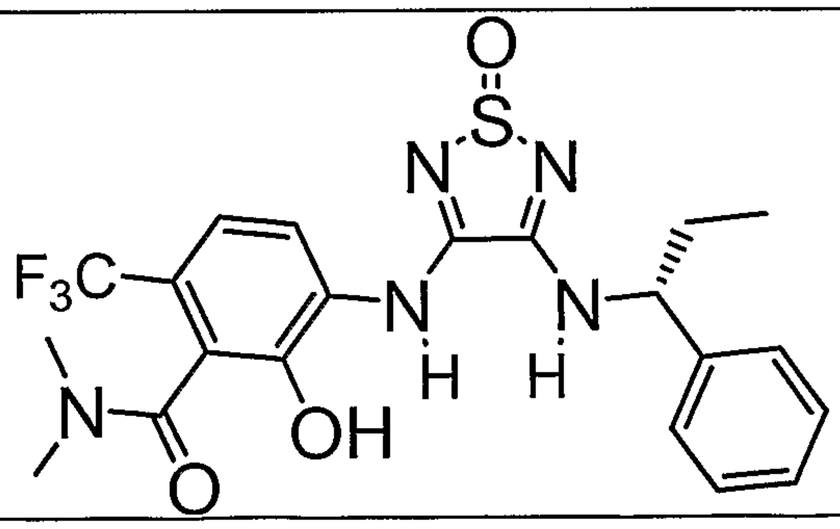
Following a similar procedure to that set forth in Preparative Example 2000, but using the amine and the thiadiazoleoxide intermediate from the Preparative Example indicated in the Table below, the thiadiazoleoxide products in the Table below were prepared. "Comm. Available" stands for "Commercially Available".

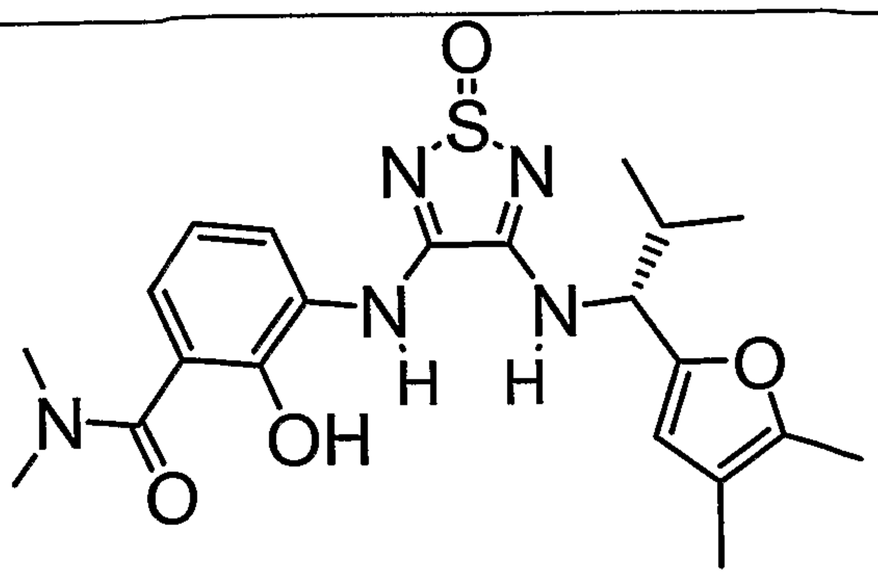
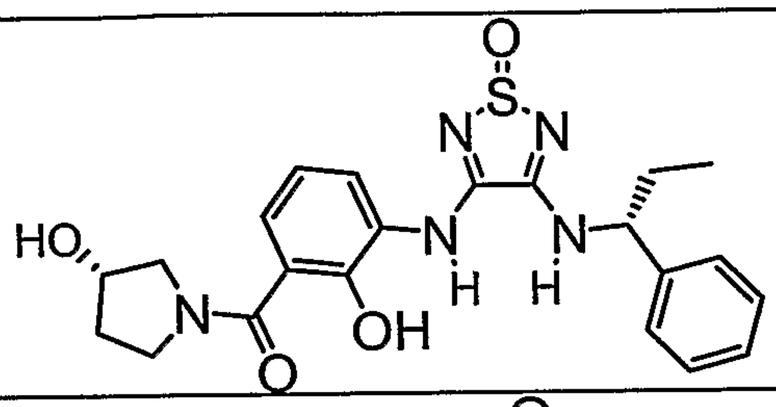
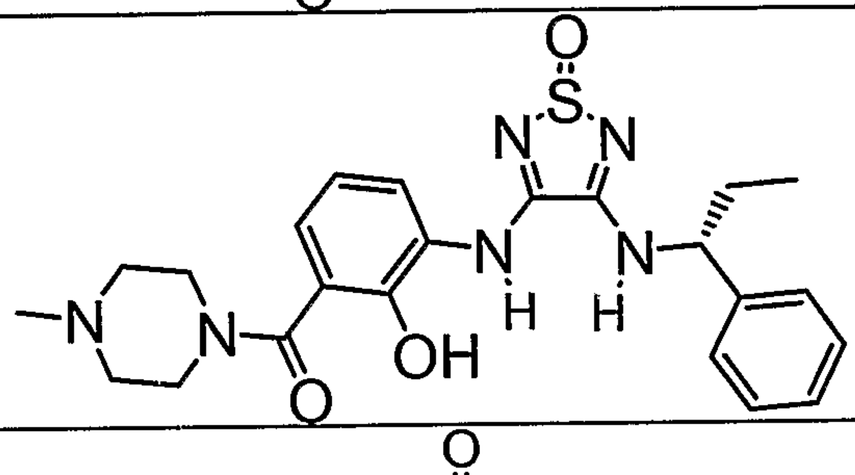
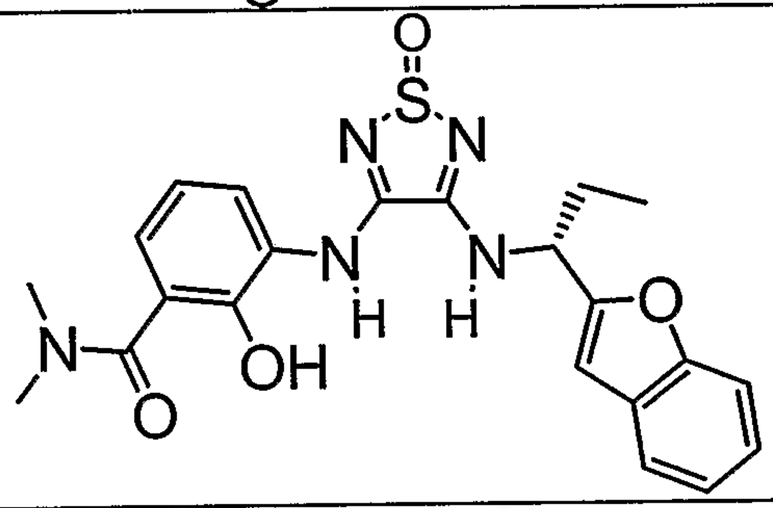
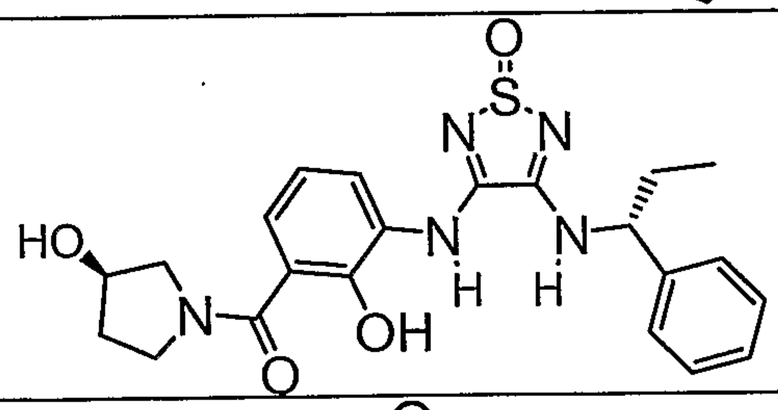
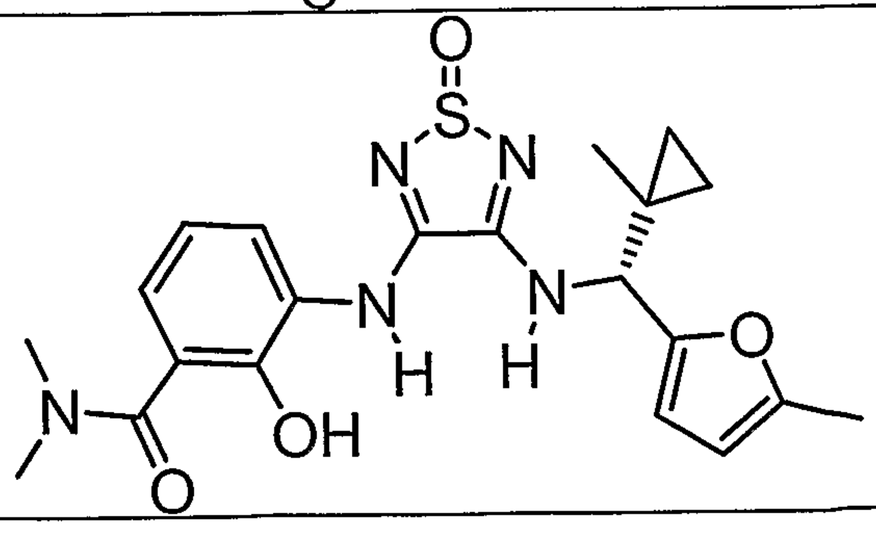
Ex.	Prep Ex of Thiadiazole oxide Intermediate	Prep Ex of Amine	Product	1. Yield 2. mp (°C) 3. MH^+
2001.2	22.1	74		1. 15% 3. 442
2001.3	22.1	75.45		used crude
2001.4	22.1	75.1		1. 62% 3. 417.9

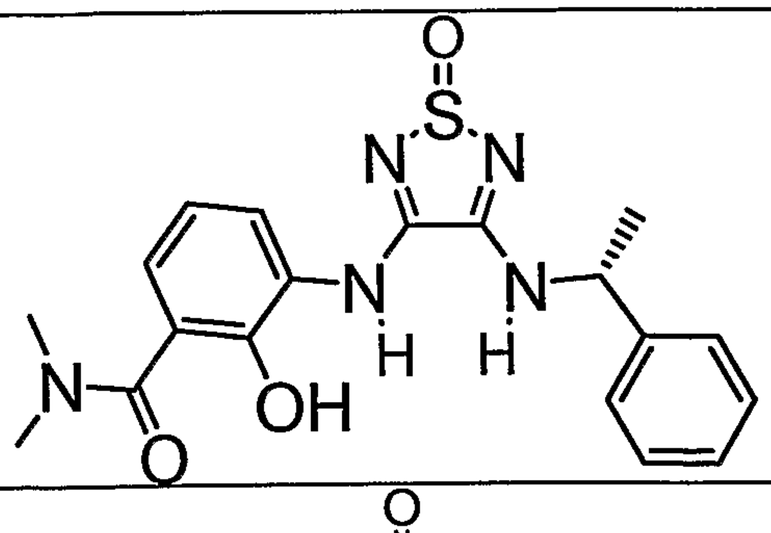
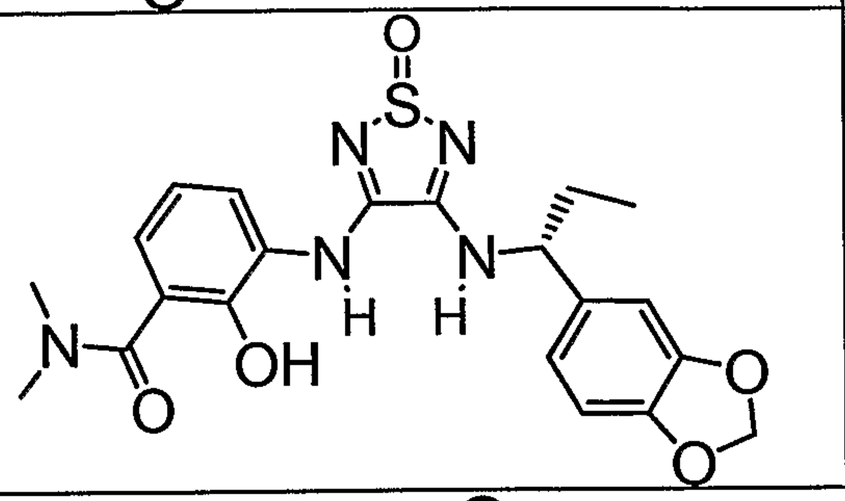
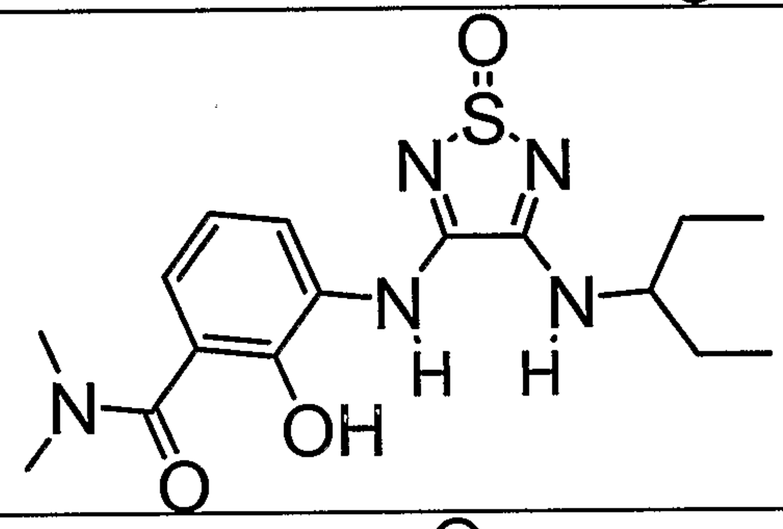
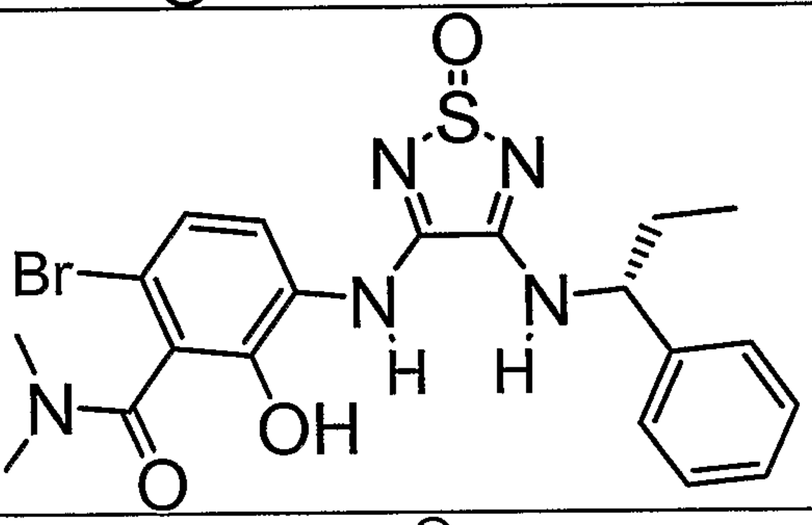
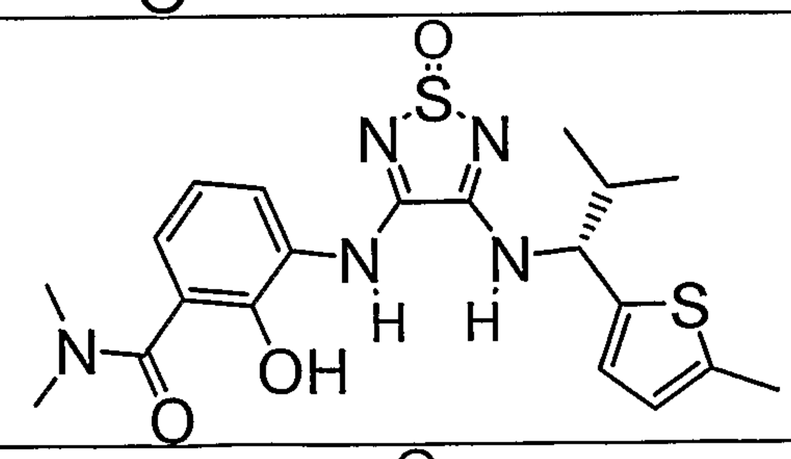
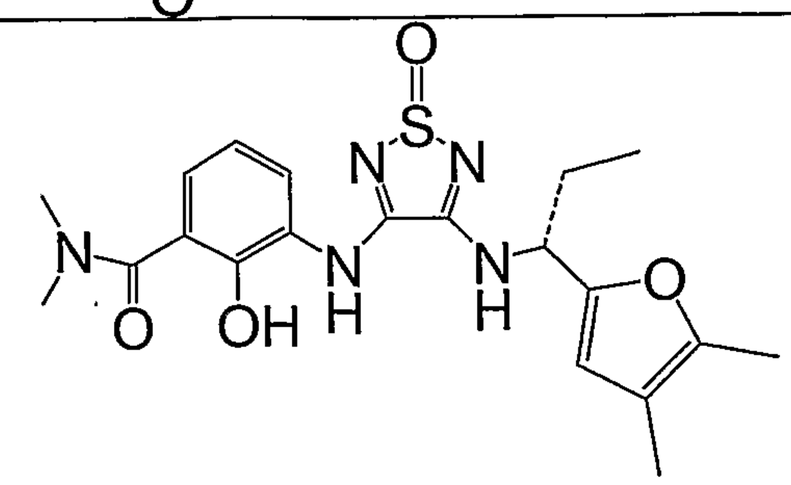
2001.5	22.1	75.9		1. 9% 2. 110 3. 446
2001.6	22.1	75.44		1. 11% 3. 446
2001.7	22.1	75.49		1. 6% 2. 107 3. 418
2001.8	23.1	75.1		1. 32% 3. 486
2001.9	23.9	64.1		1.32% 2. 156 3. 440

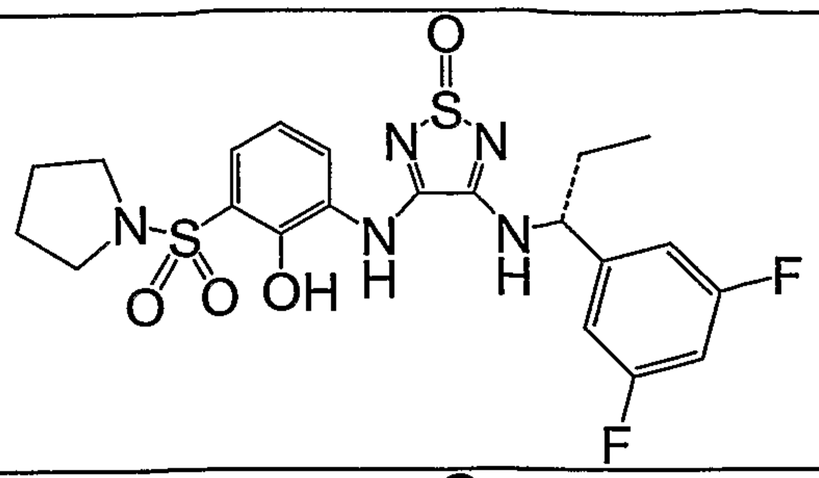
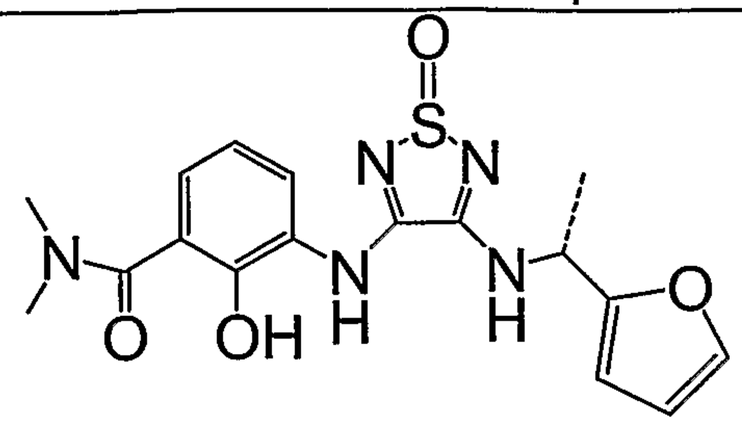
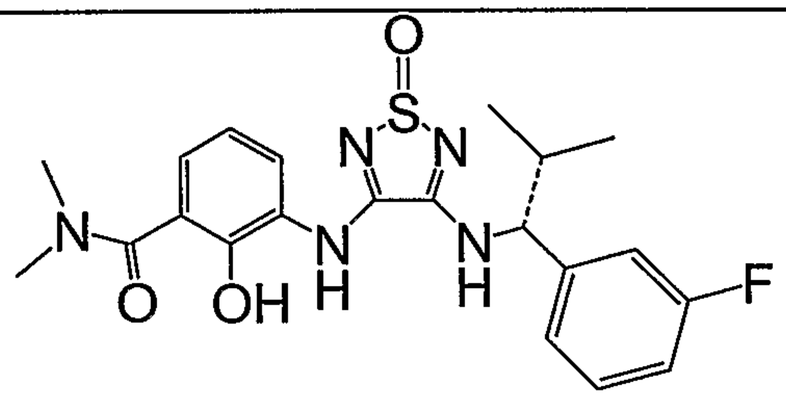
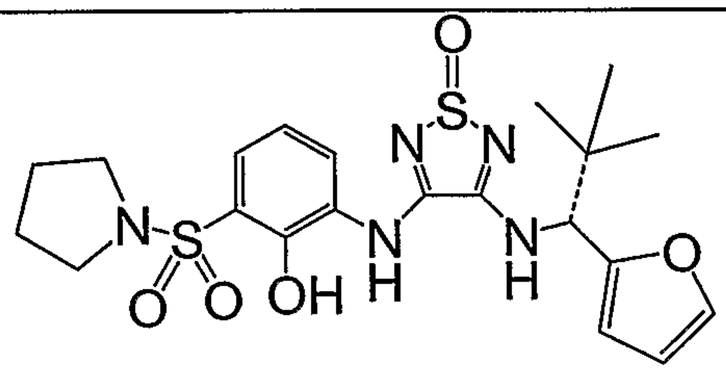
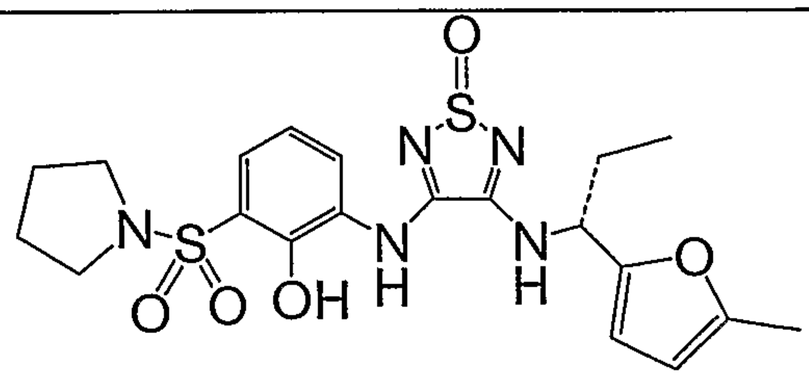
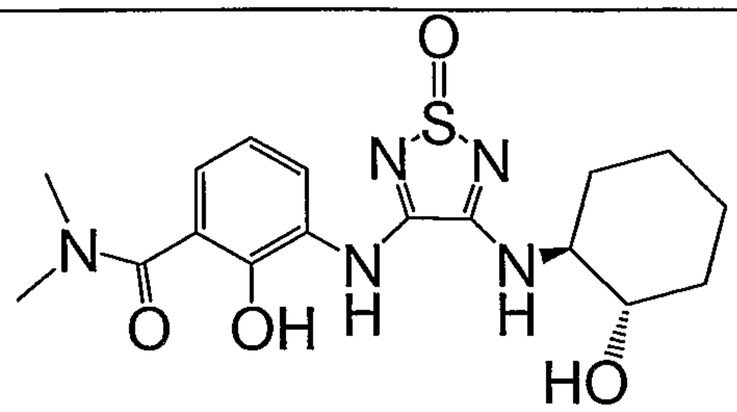
2001.10	23.9	64.2		used crude
2001.11	23.9	75.1		used crude
2001.12	22.1	64.4		1.50% 2. 171 3. 380
2001.13	22.1	64.3		1. 49% 2. 171 3. 380
2001.14	22.1	51.26		used crude
2001.15	22.2	1308		1. 28% 3. 456.1

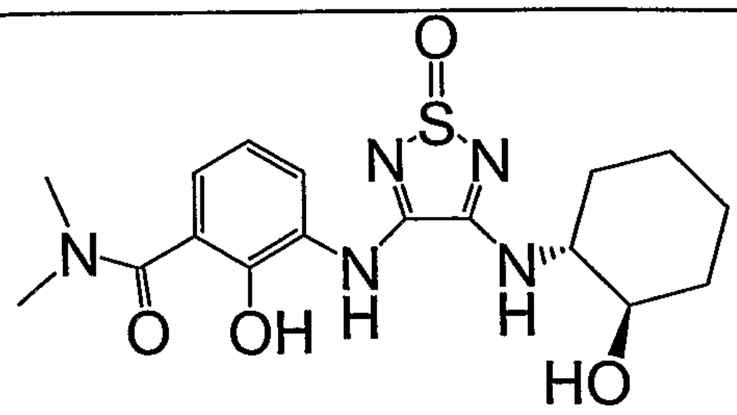
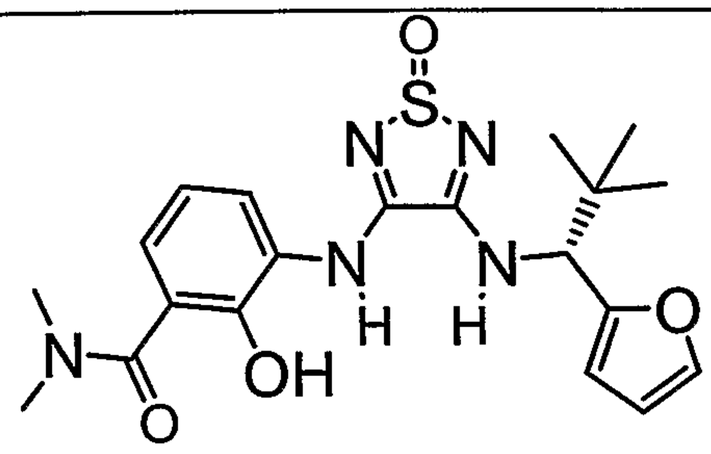
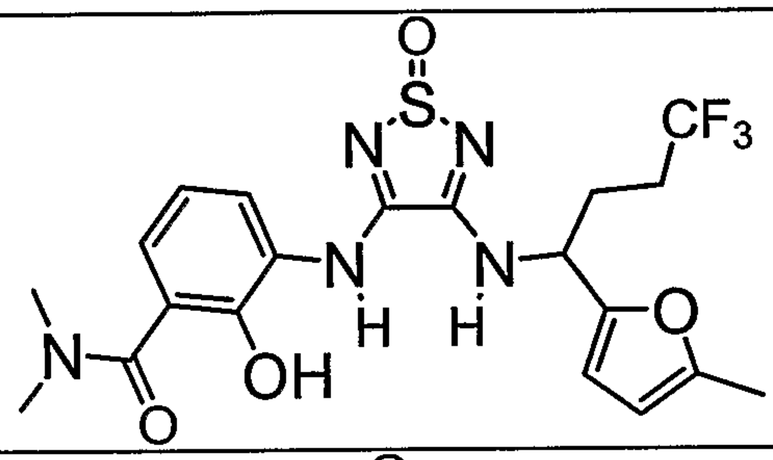
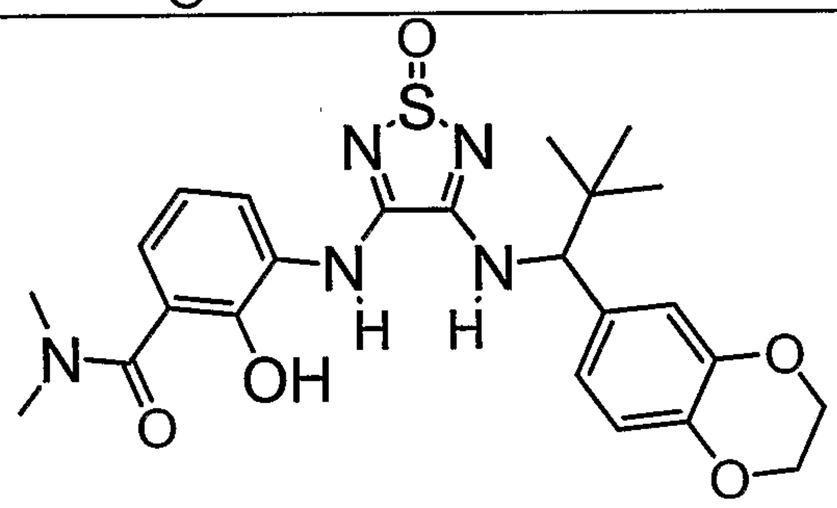
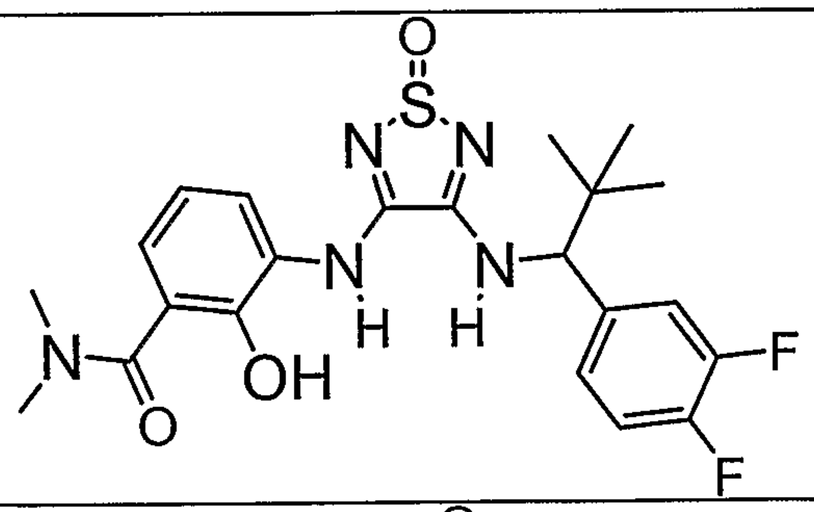
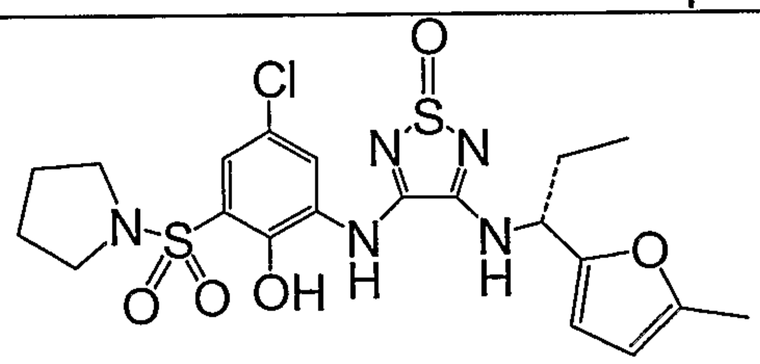
2001.16	22.1	13.18		used crude
2001.17	22.1	75.60		used crude
2001.18	22.1	64.5		used crude
2001.19	22.1	75.29		used crude
2001.20	22.1	72		used crude
2001.21	22.1	75.34		used crude

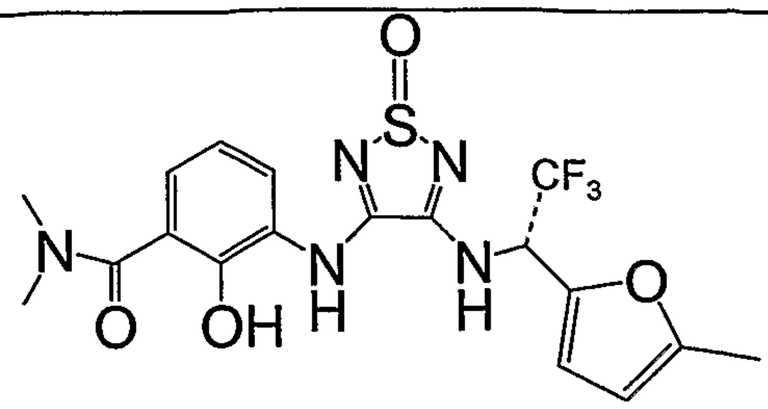
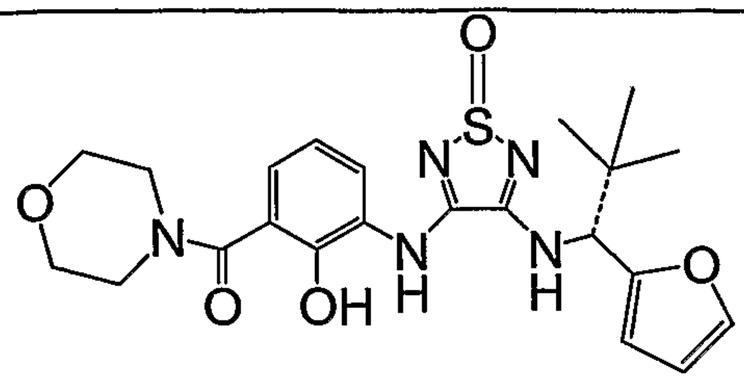
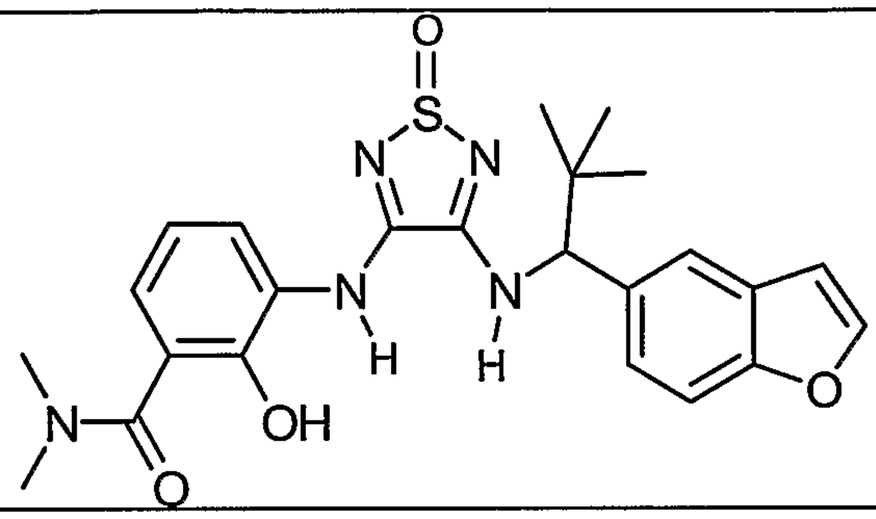
2001.22	22.1	75.62		used crude
2001.23	22.1	75.92		1.25% 2. 102 3. 482
2001.24	23.3	75.1		1. 9% 2. 145 3. 460
2001.25	23.1	75.61		1. 24% 3. 514
2001.26	23.1	64.1		1. 42% 3. 482

2001.27	22.1	75.61		1. 37% 2. 172 3. 446
2001.28	22.2	2		1. 49% 3. 456
2001.29	22.2	145		1. 50% 2. 469
2001.30	22.1	75.63		1. 9% 3. 454
2001.31	22.2	1307		1. 60% 3. 456
2001.32	22.1	623		1.31% 2. 60 3. 444

2001.33	22.1	64.12		1. 6% 3. 400
2001.34	22.1	75.27		1. 11% 3. 457.9
2001.35	22.1	64.6		1. 25% 3. 366
2001.36	23.8	64.1		1. 7% 3. 491.9
2001.39	22.1	75.19		used crude
2001.40	22.1	75.38		1. 37% 2. 149 3.432.1

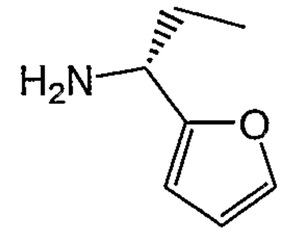
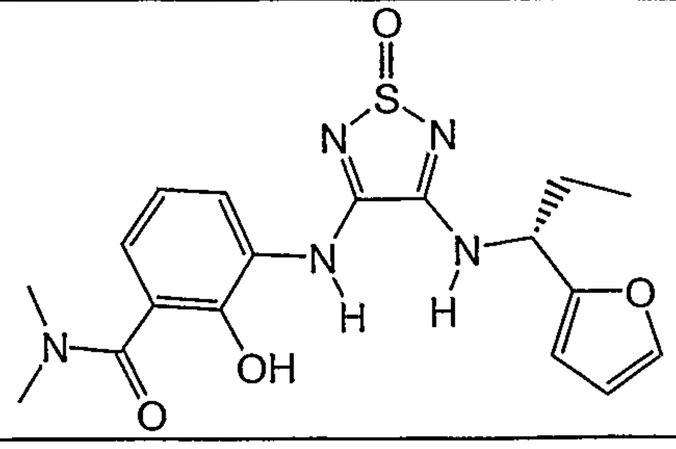
2001.41	23.9	75.29		1. 71% 2. 90 3.512.1
2001.42	22.1	75.68		1. 63 2. 152 3. 390.1
2001.43	22.1	75.31		1. 59% 2. 150 3. 446
2001.44	23.9	75.64		1. 42% 2. 178 3. 494.1
2001.45	23.9	75.1		1. 48% 2. 182 3.480.1
2001.46	22.1	comm. available		1. 82% 2. 80 3.394.1

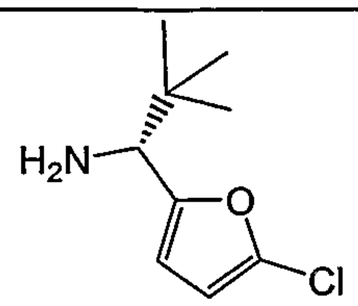
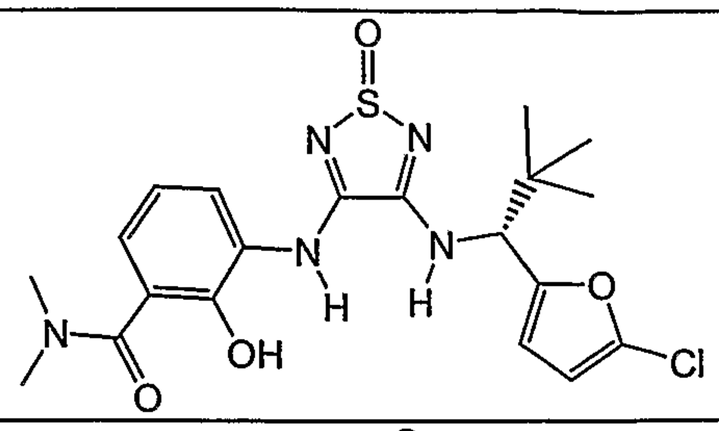
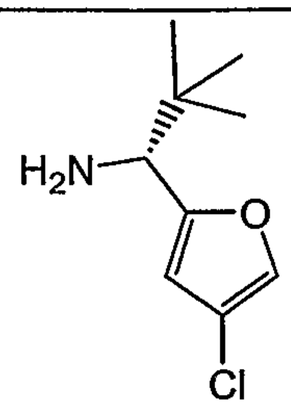
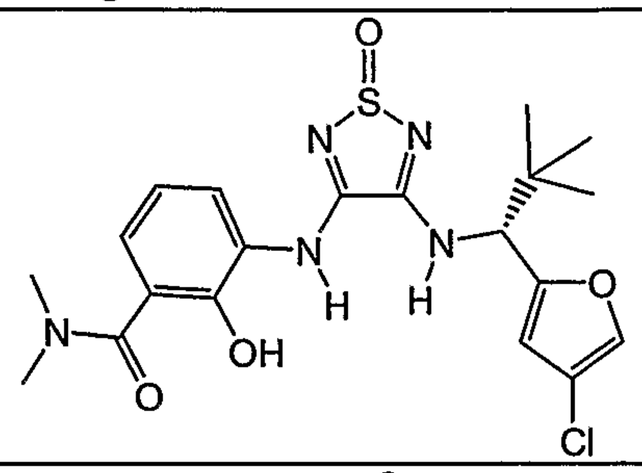
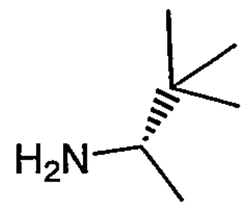
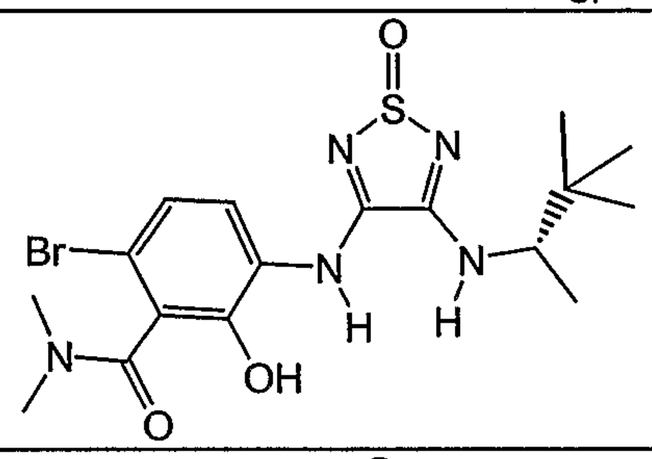
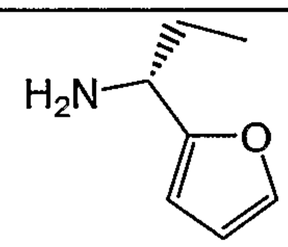
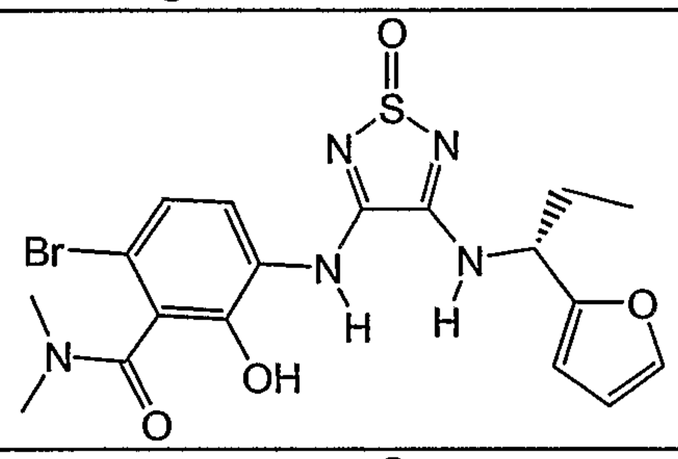
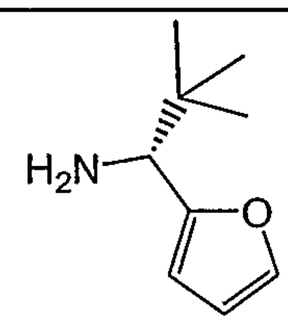
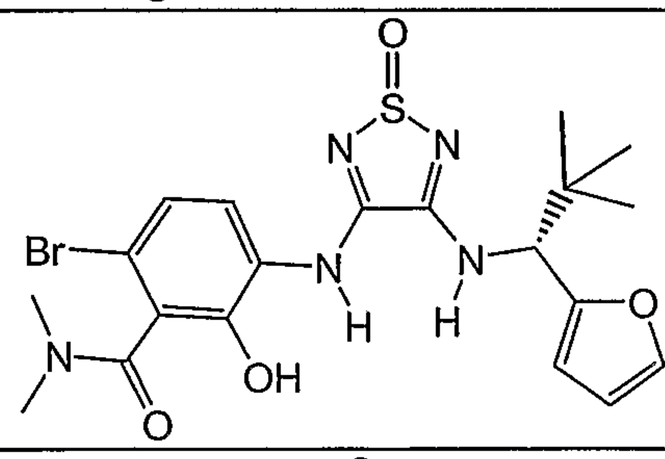
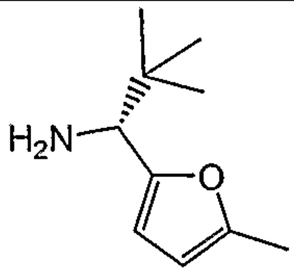
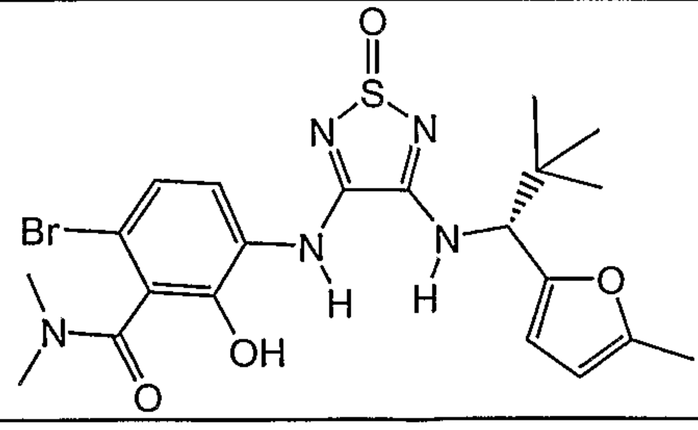
2001.47	22.1	comm. available		1. 87 2. 80 3. 394.1
2001.48	22.1	75.64		1. 32% 2. 149 3. 432.1
2001.49	22.1	13.25		1. 70% 2. 110 3. 486.1
2001.50	22.1	51.22		1. 53% 2. 188 3.500.1
2001.51	22.1	51.21		1. 10% 2. 120 3. 478.1
2001.52	23.10	75.1		used crude

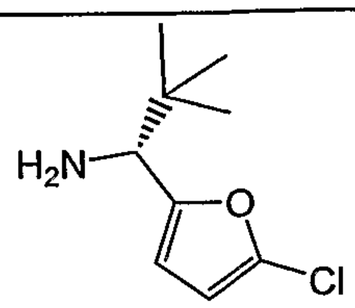
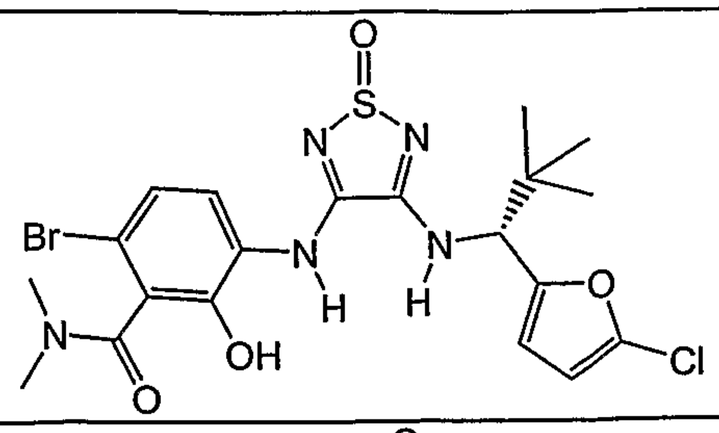
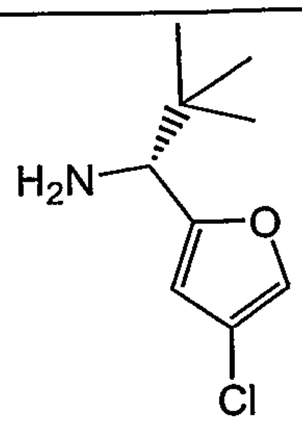
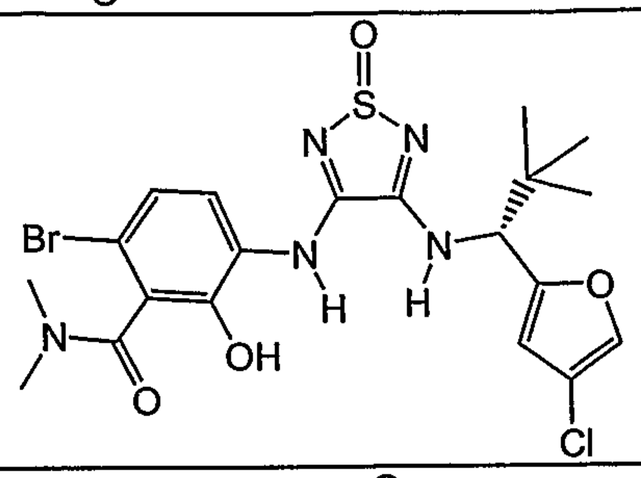
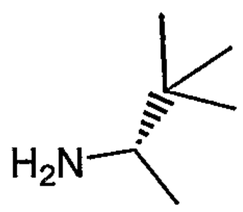
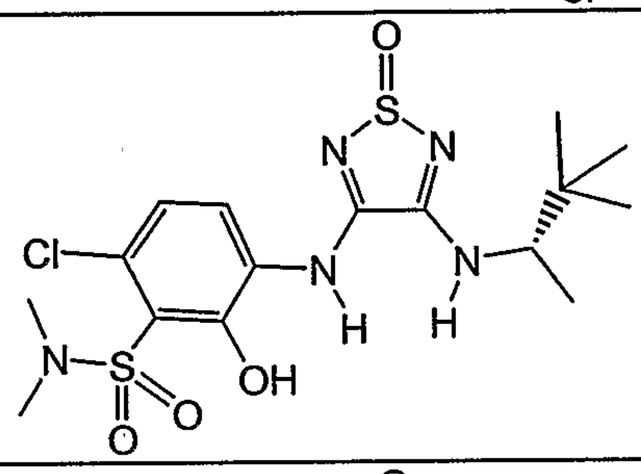
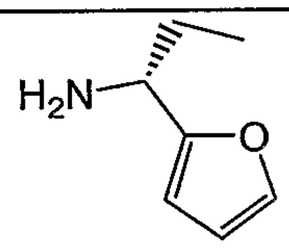
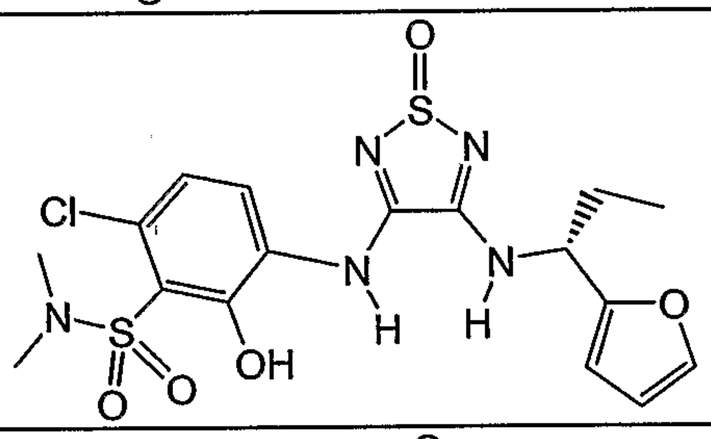
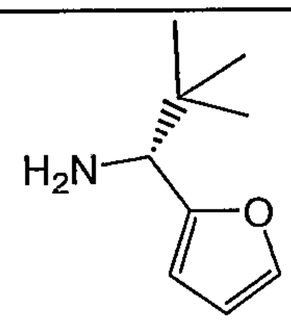
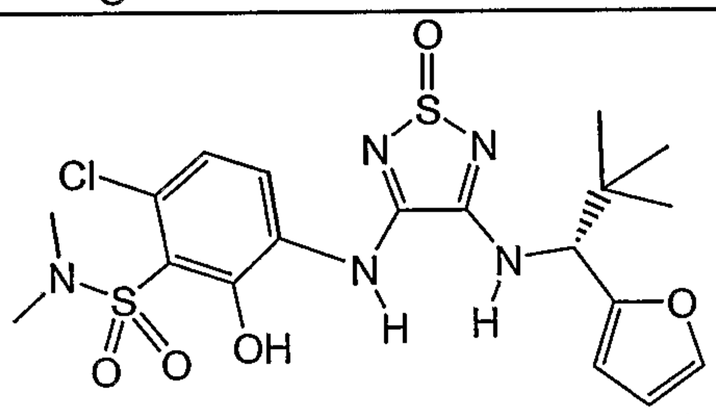
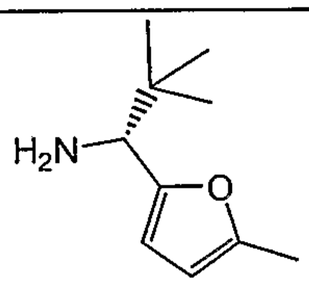
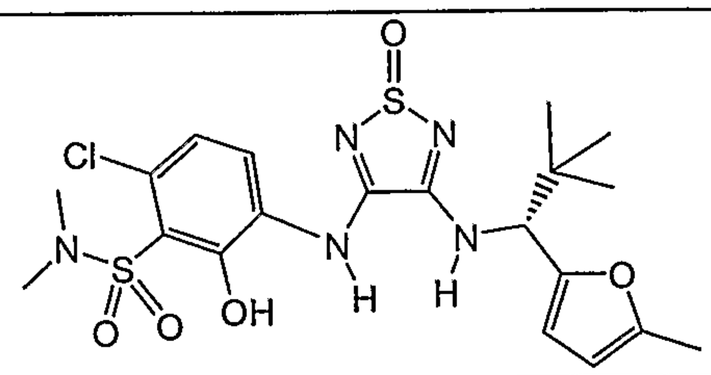
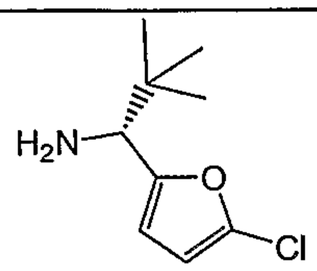
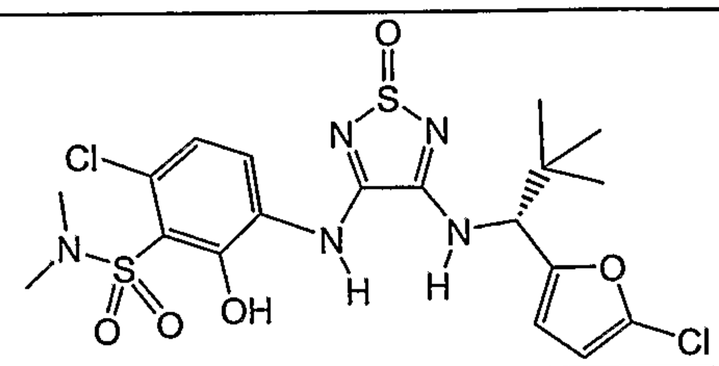
2001.53	22.1	13.11		used crude
2001.54	23.3	75.64		used crude
2001.55	22.1	75.92		1.25% 2. 102 3. 482

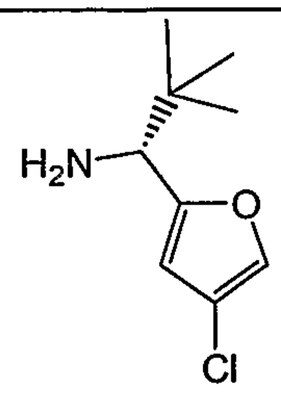
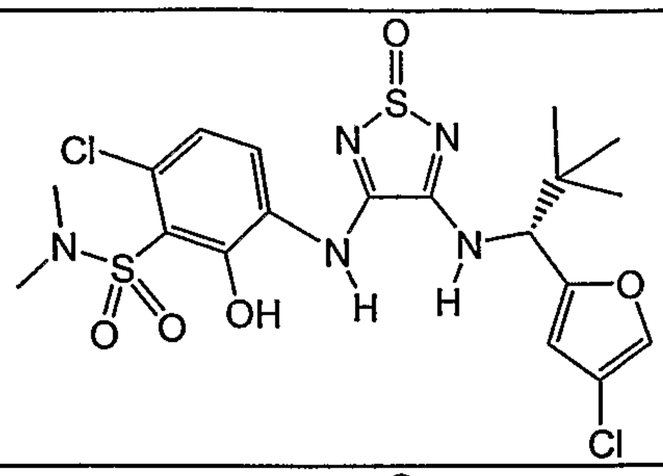
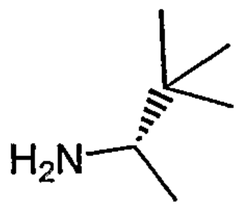
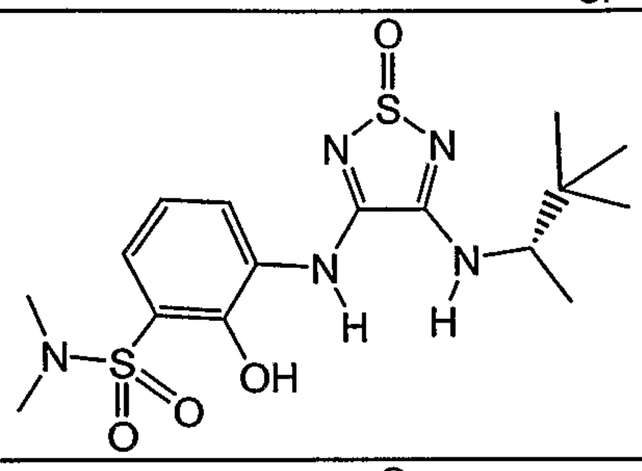
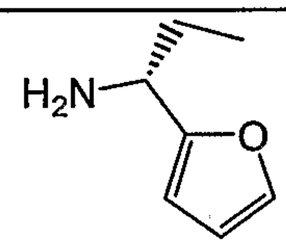
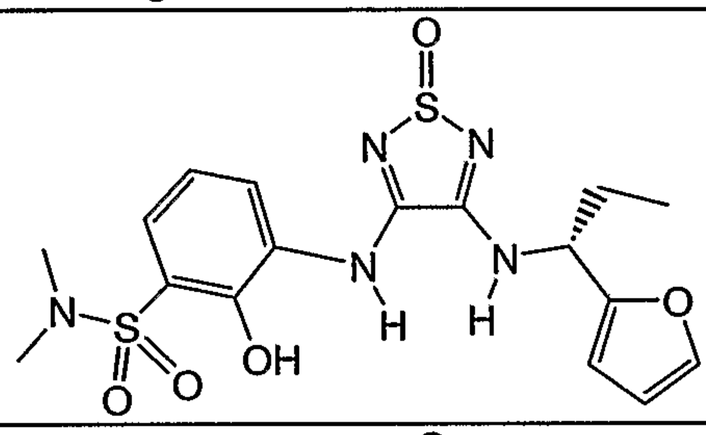
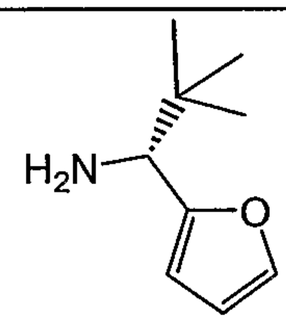
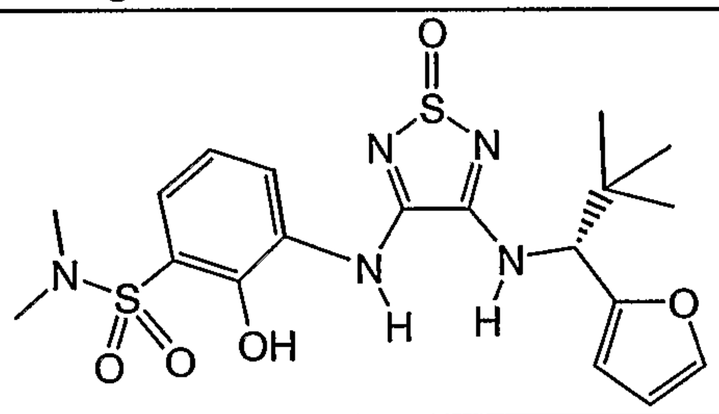
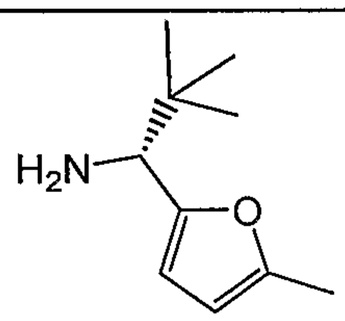
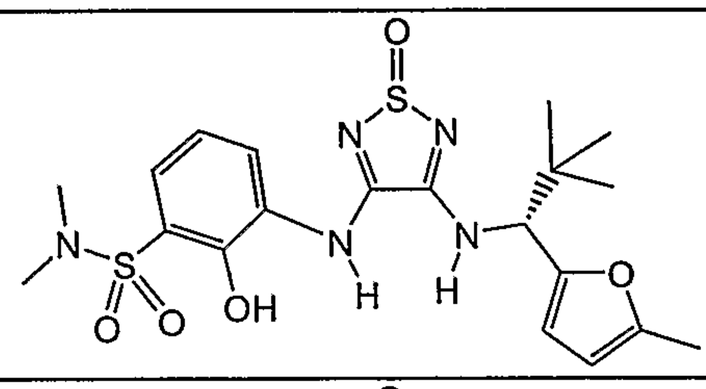
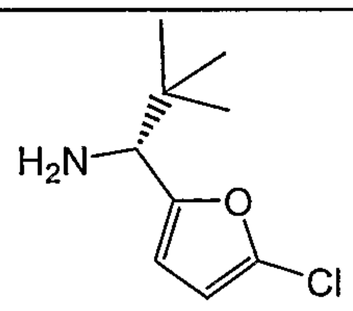
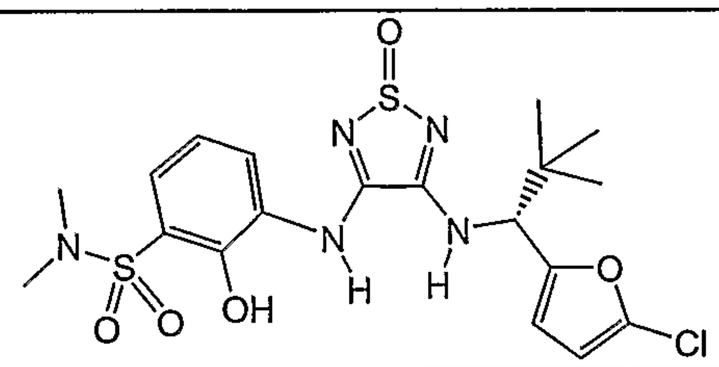
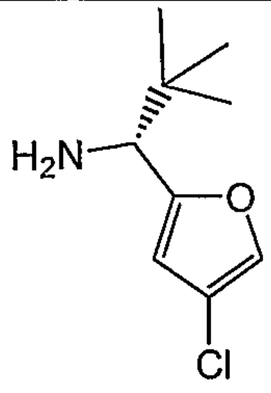
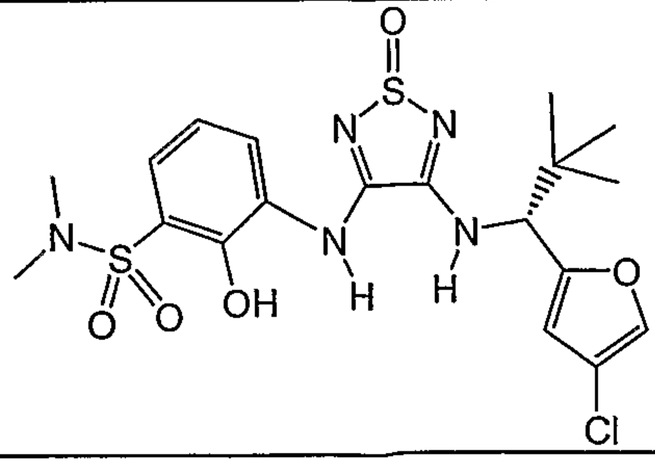
PREPARATIVE EXAMPLES 2203-2245

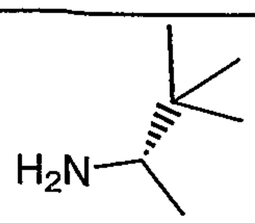
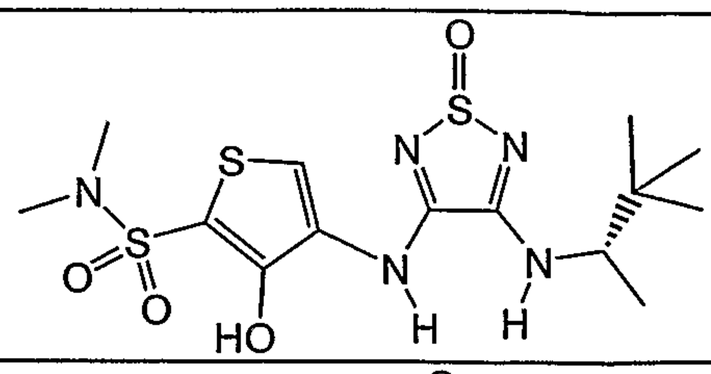
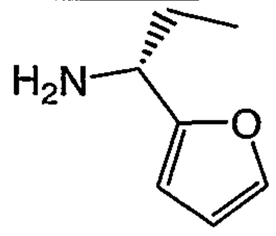
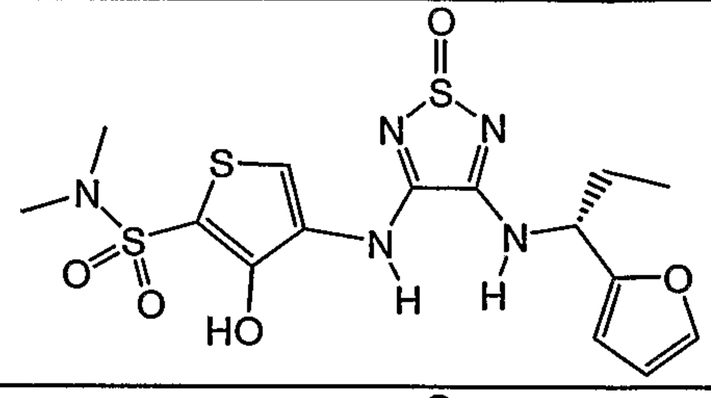
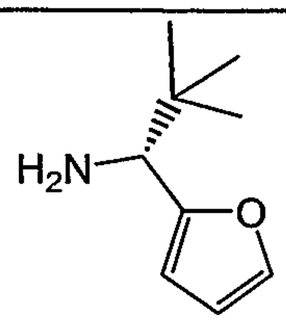
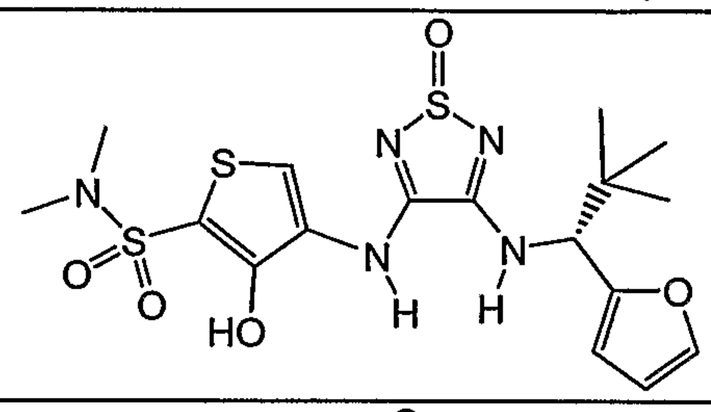
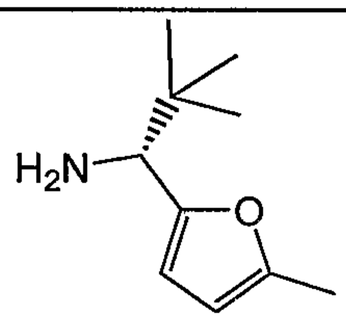
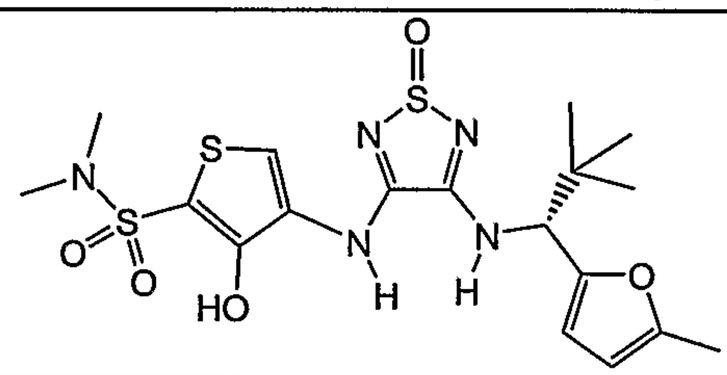
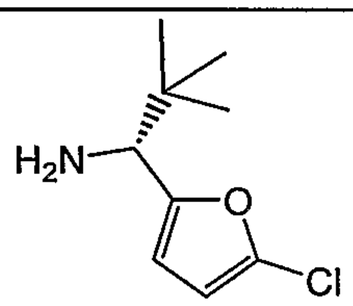
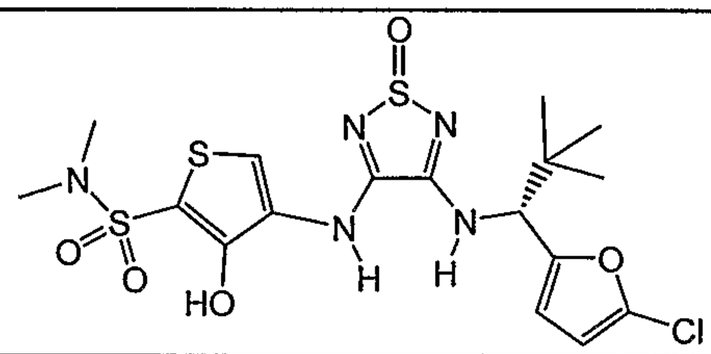
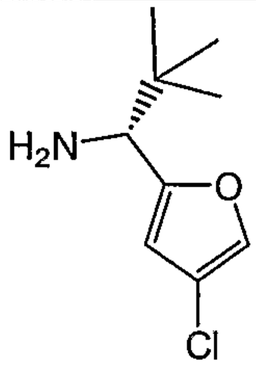
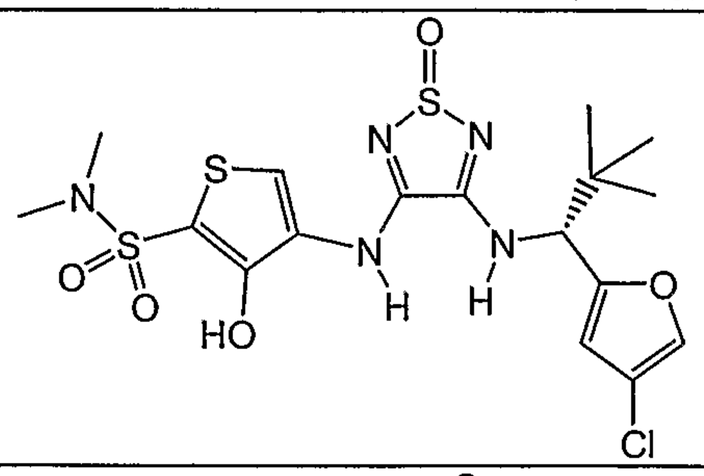
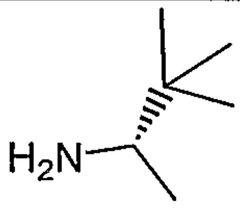
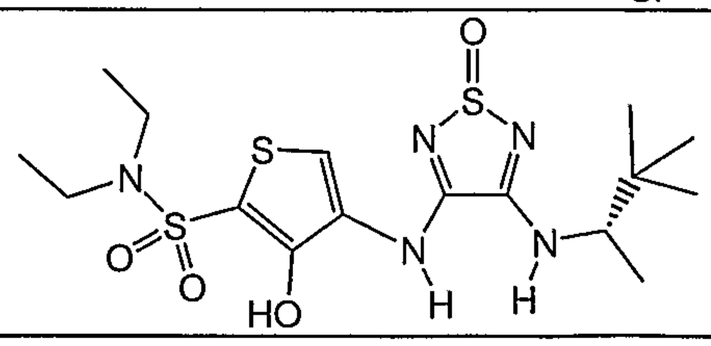
If one were to follow a procedure similar to that set forth in Preparative Example 2001A, but using the commercially available (or prepared amine) and the thiadiazoleoxide intermediate from the Preparative Example(s) indicated in the Table below and stirring the reaction mixtures at room temperature up to reflux, the thiadiazoleoxide products in the Table below could be obtained.

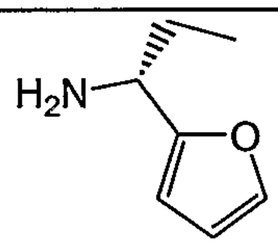
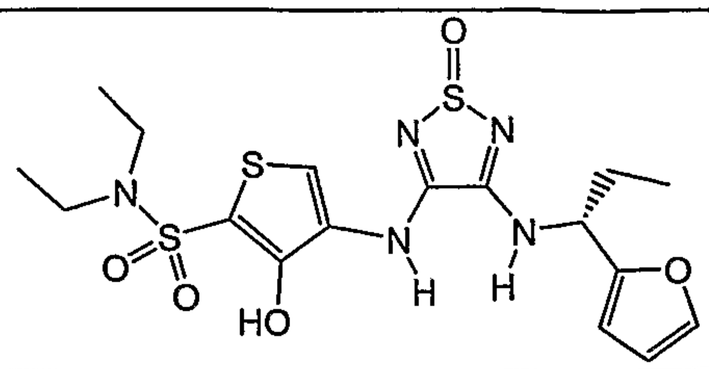
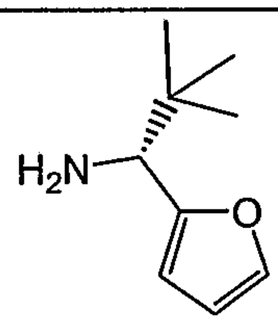
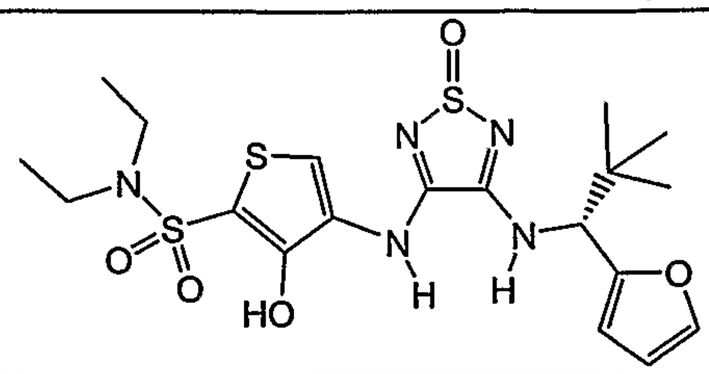
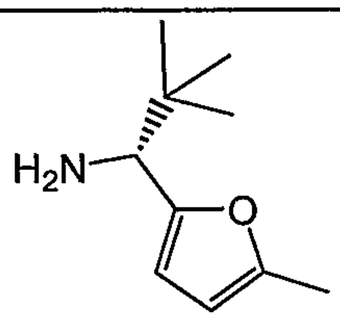
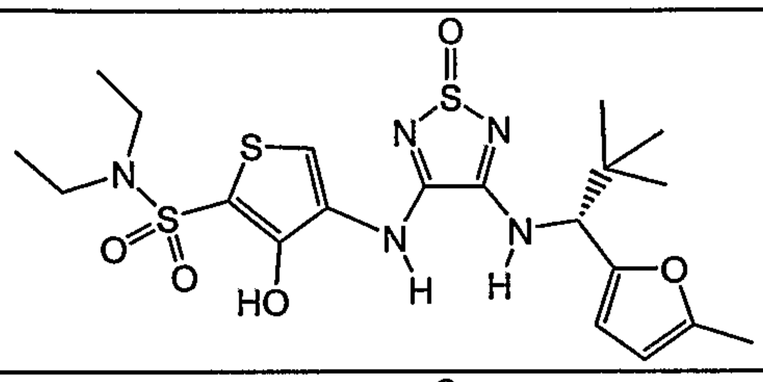
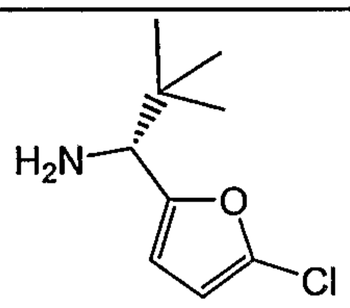
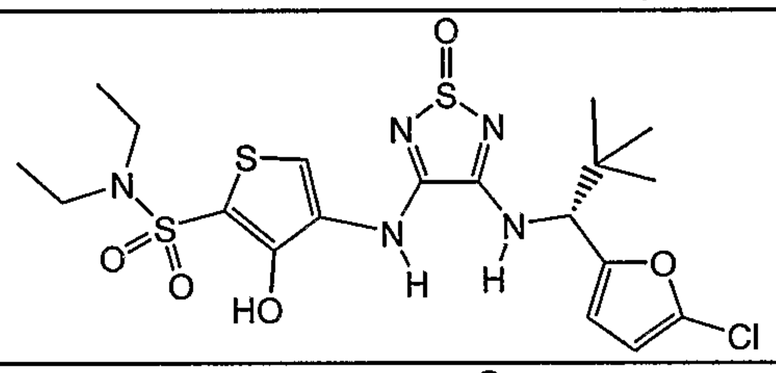
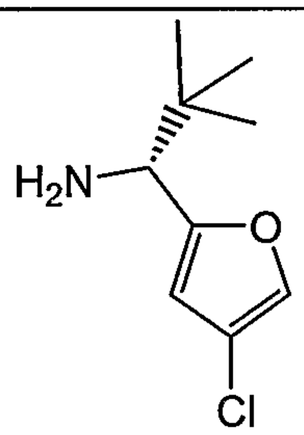
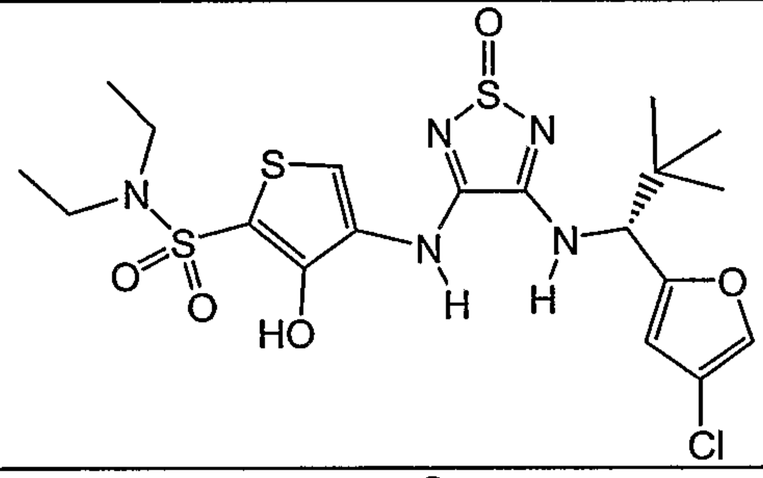
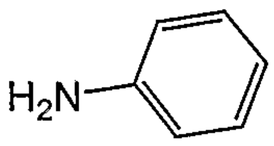
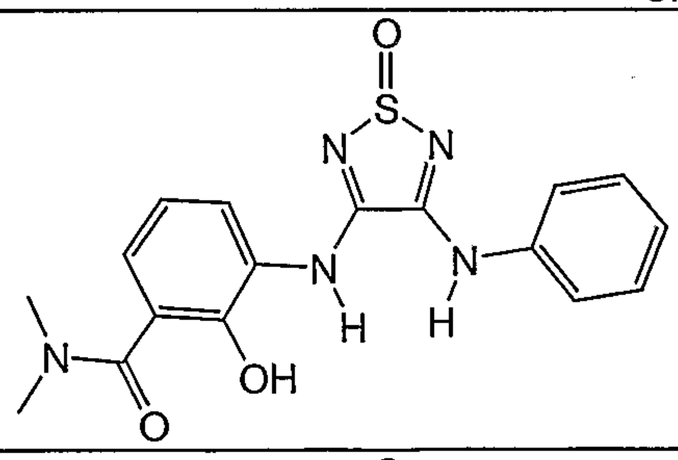
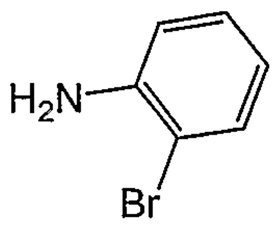
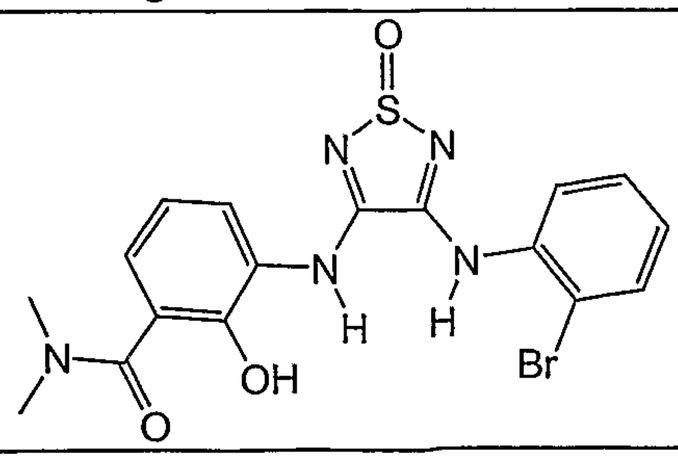
Prep Ex.	Prep Ex of Thiadiazole oxide Intermediate	Amine	Product
2203	22.1		

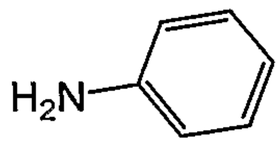
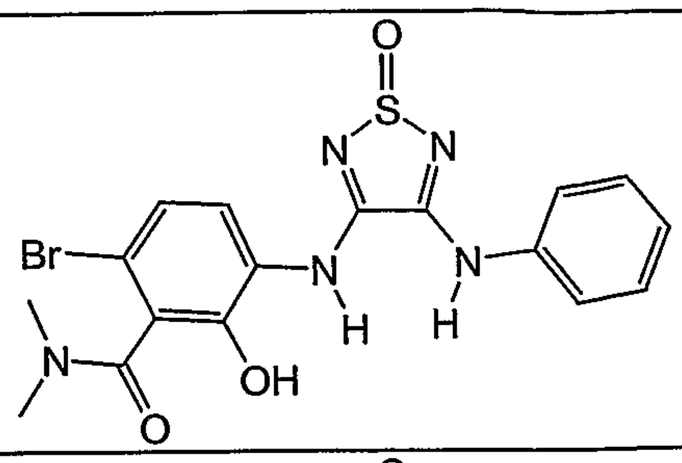
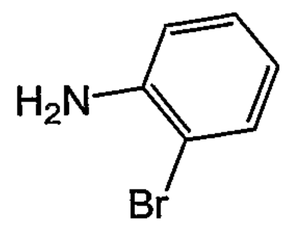
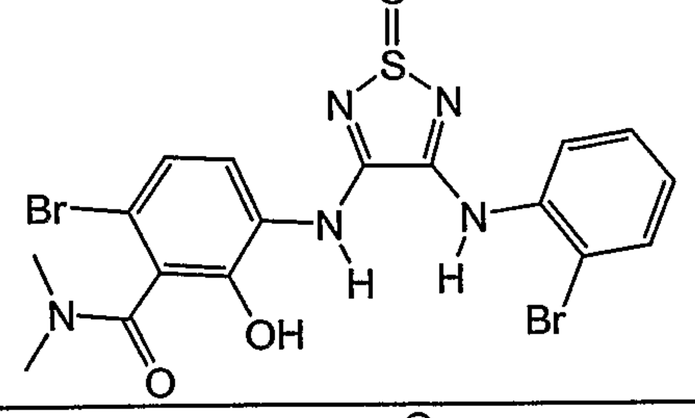
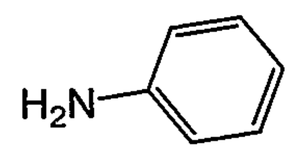
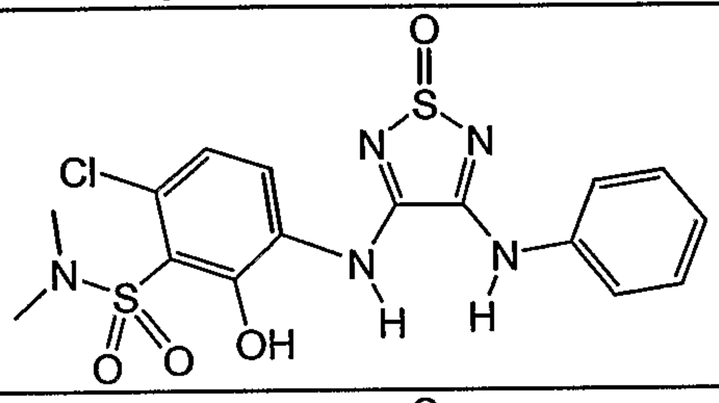
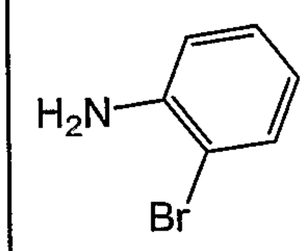
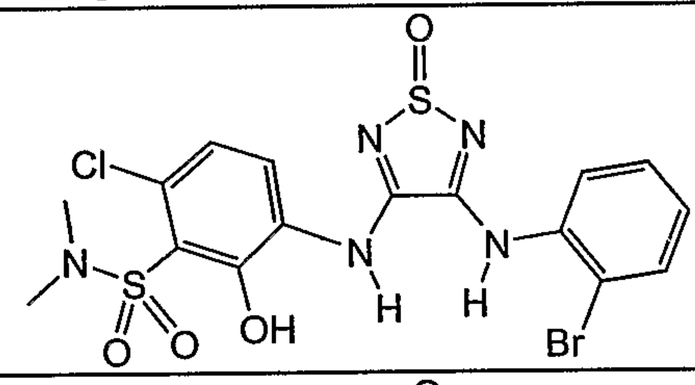
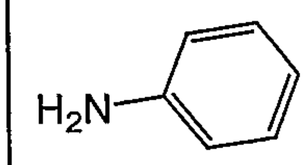
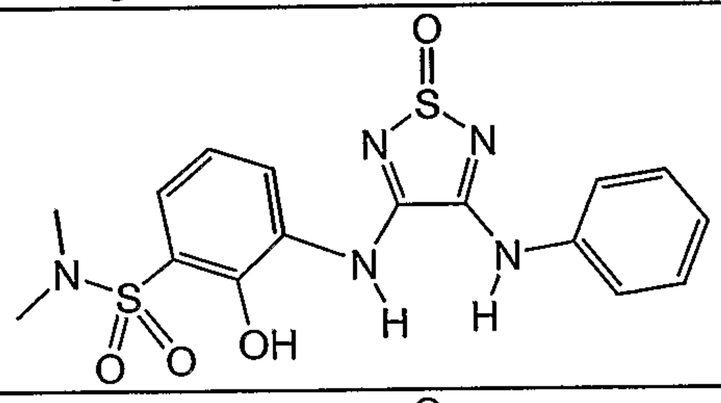
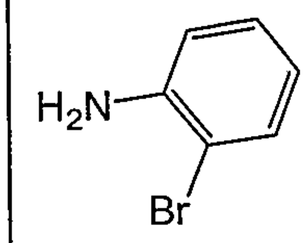
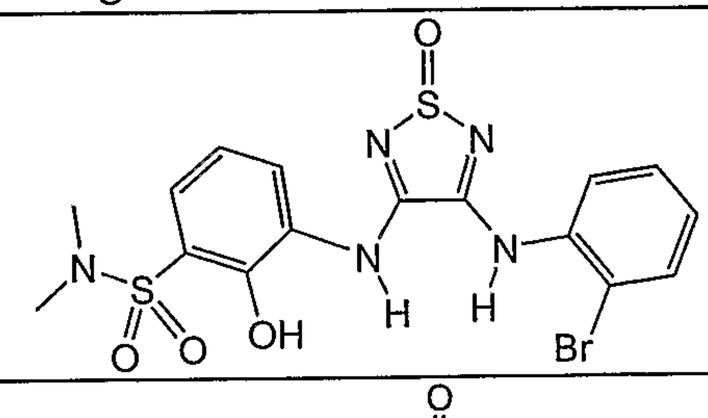
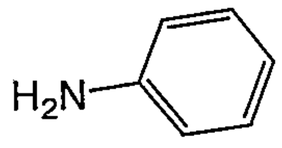
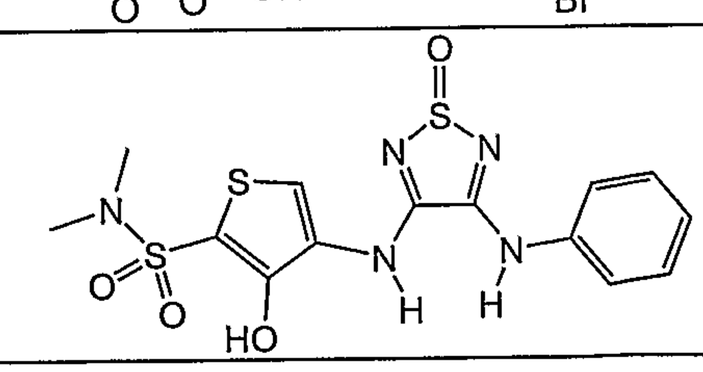
2206	22.1		
2207	22.1		
2208	22.3		
2209	22.3		
2210	22.3		
2211	22.3		

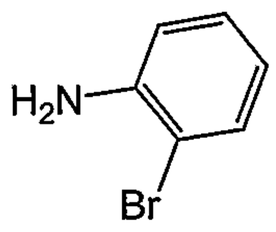
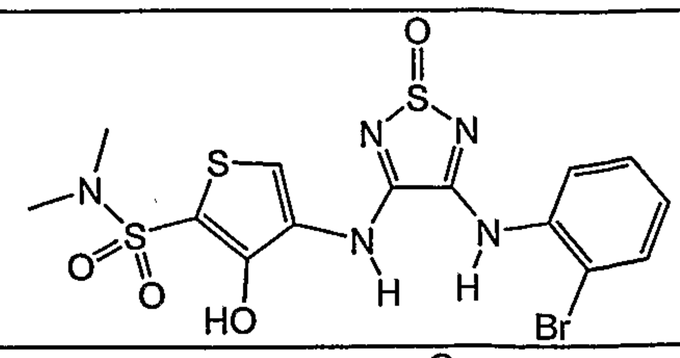
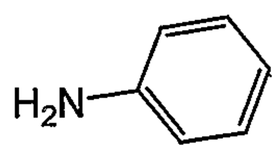
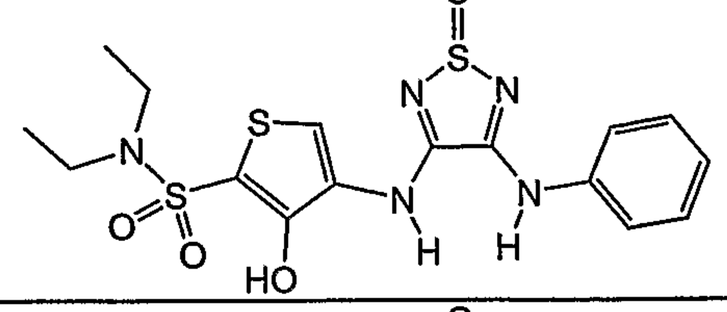
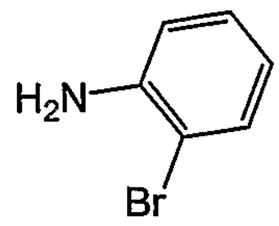
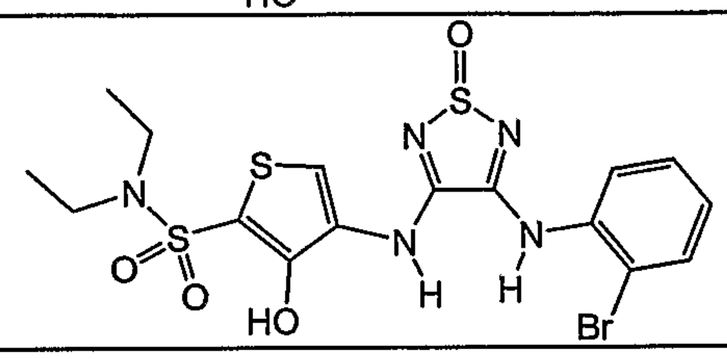
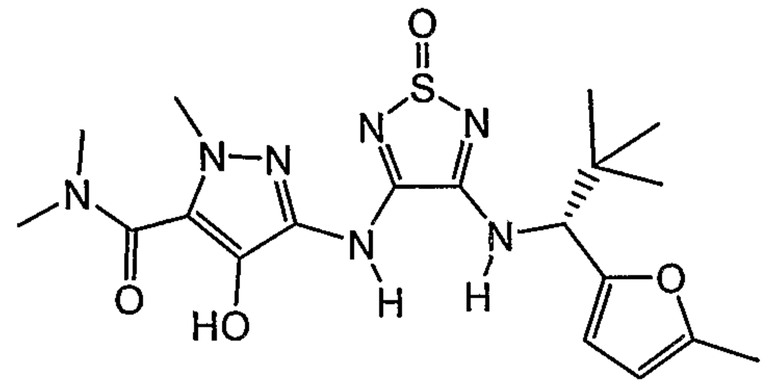
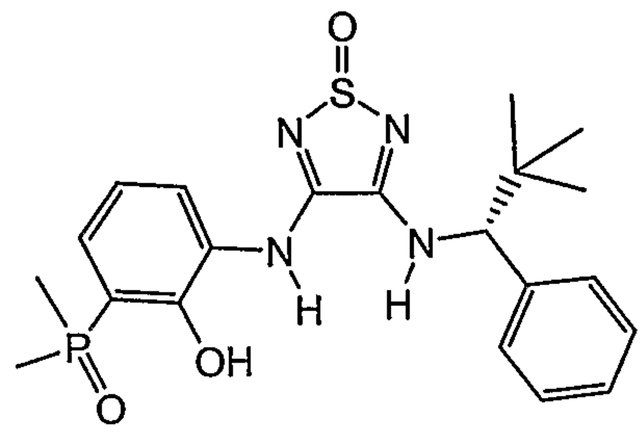
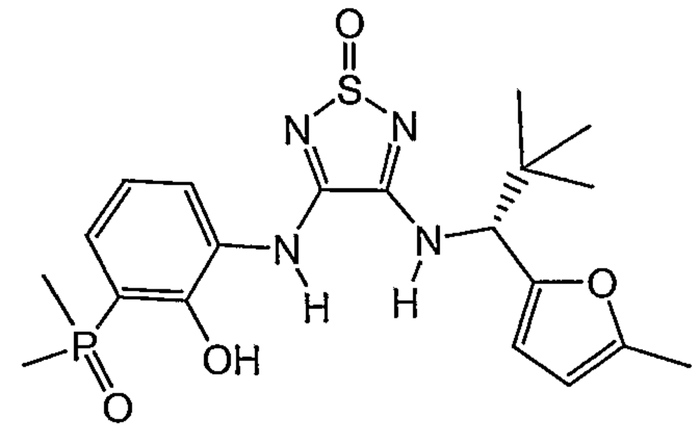
2212	22.3		
2213	22.3		
2214	22.4		
2215	22.4		
2216	22.4		
2217	22.4		
2218	22.4		

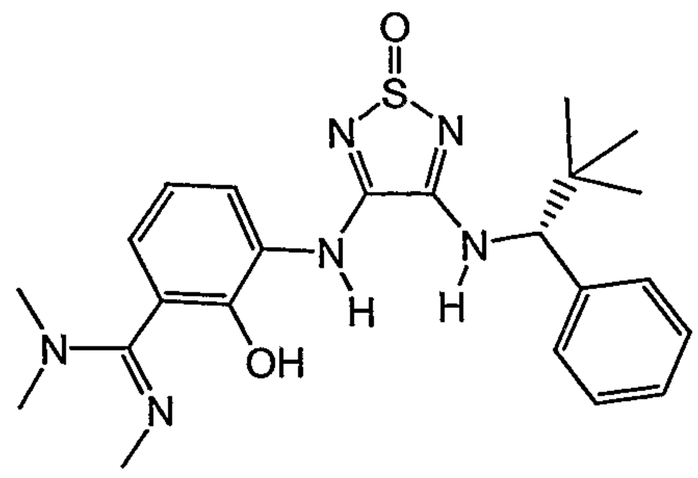
2219	22.4		
2220	22.5		
2221	22.5		
2222	22.5		
2223	22.5		
2224	22.5		
2225	22.5		

2226	22.6		
2227	22.6		
2228	22.6		
2229	22.6		
2230	22.6		
2231	22.6		
2232	22.7		

2233	22.7		
2234	22.7		
2235	22.7		
2236	22.7		
2237	22.7		
2238	22.1		
2239	22.1		

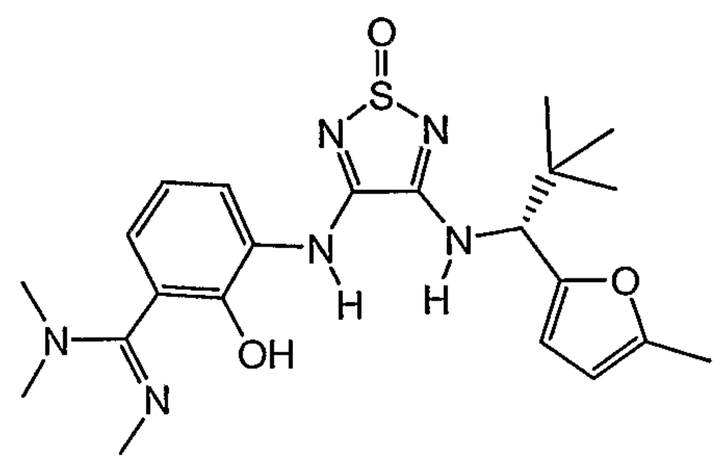
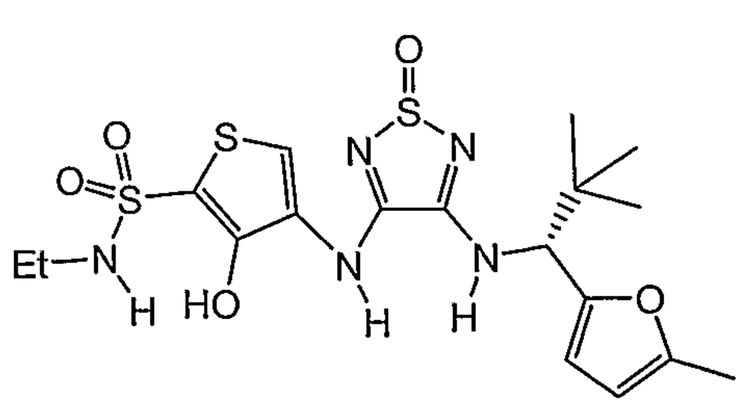
2240	22.3		
2241	22.3		
2242	22.4		
2243	22.4		
2244	22.5		
2245	22.5		
2246	22.6		

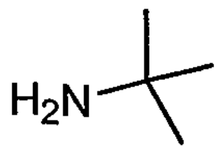
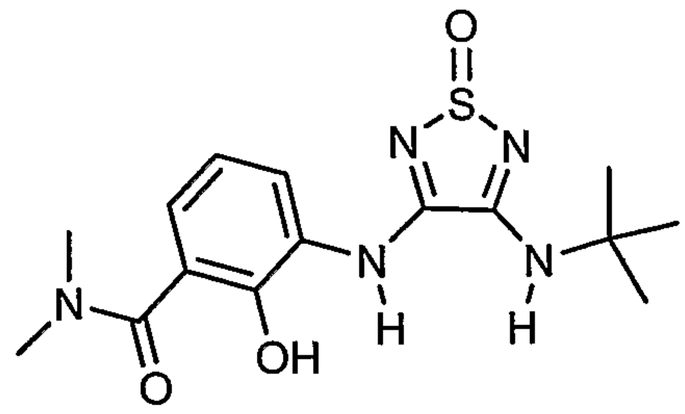
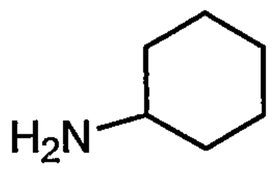
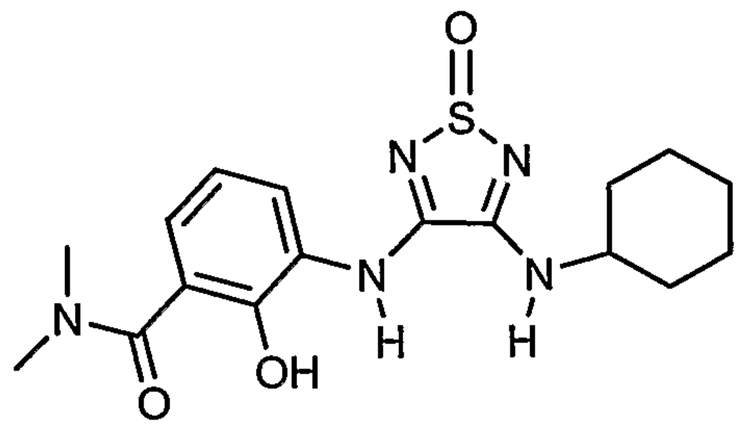
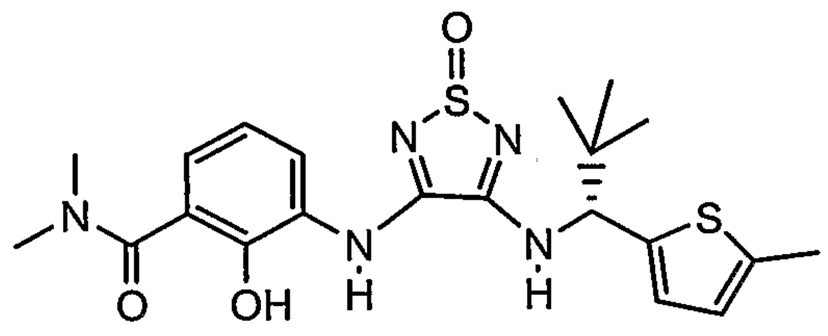
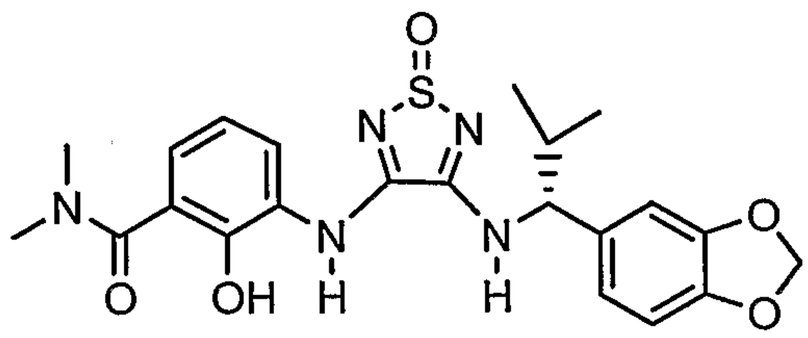
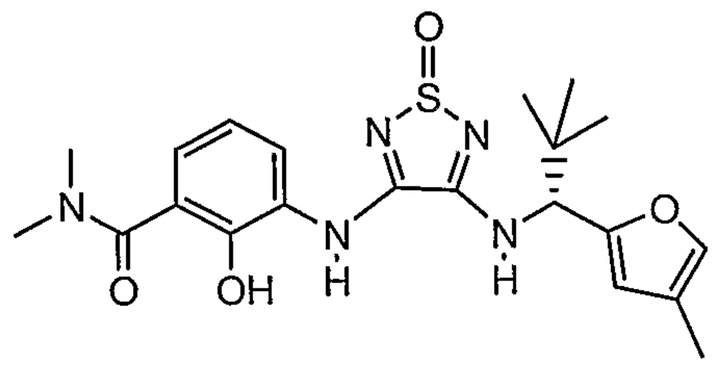
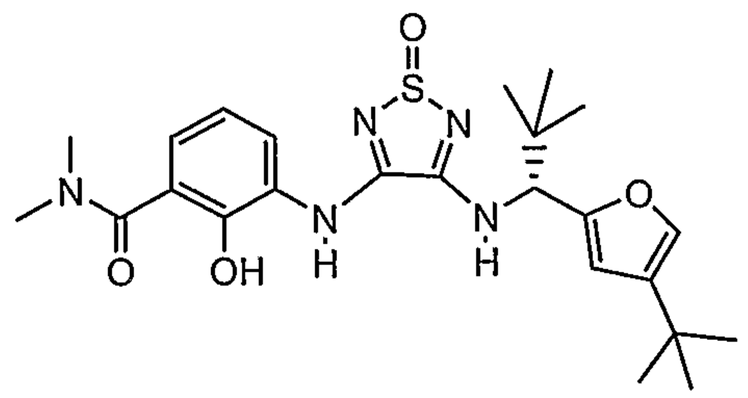
2247	22.6		
2248	22.7		
2249	22.7		
2250	22.25	75.44	
2251A	22.23	74	
2251B	22.23	75.44	

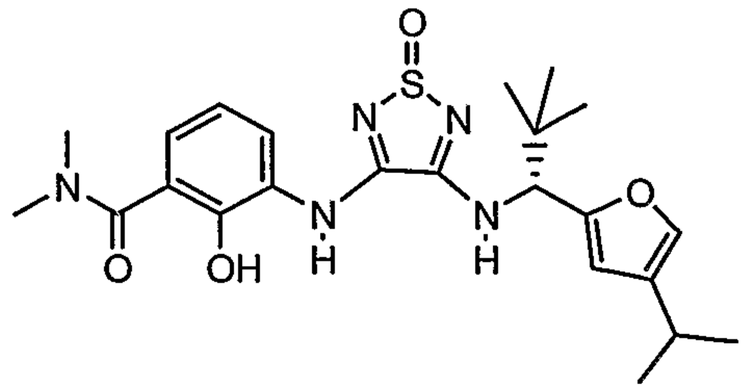
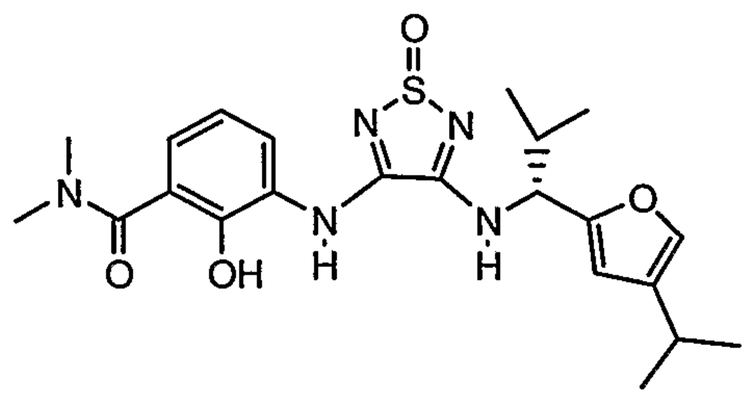
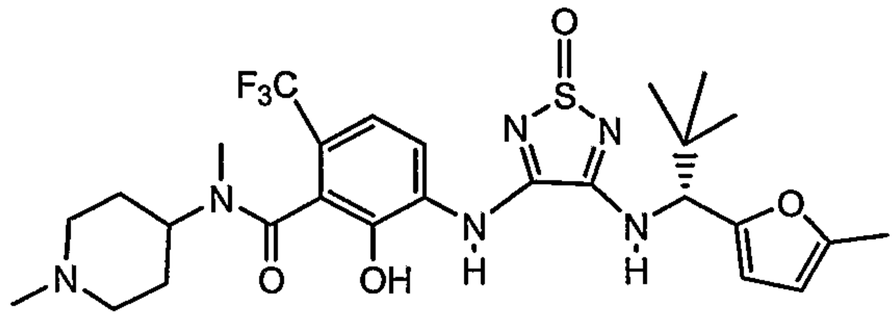
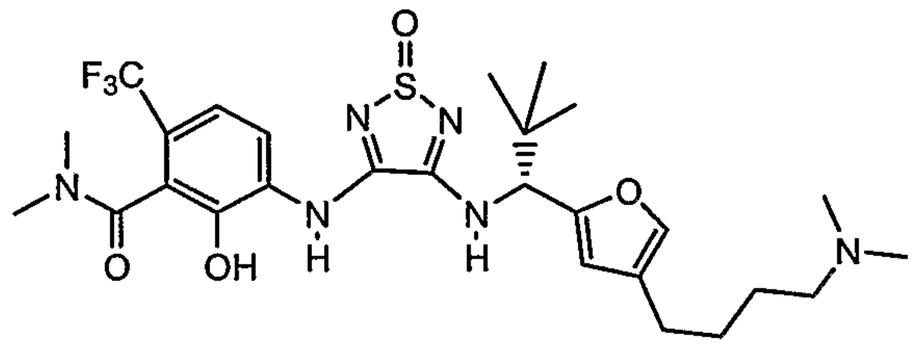
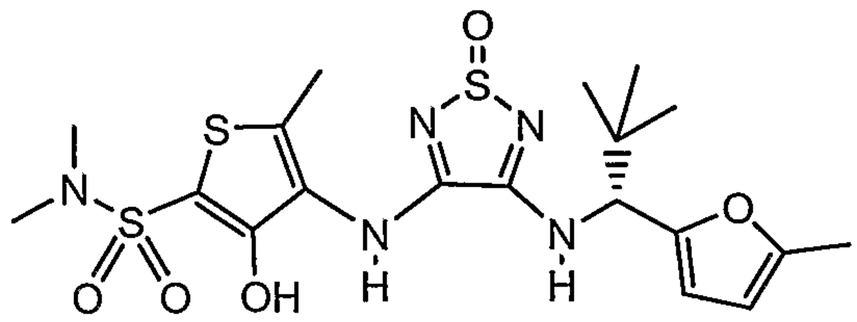
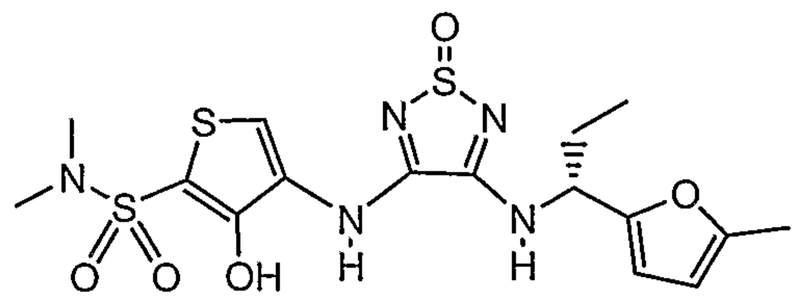
2251C	22.24	74	

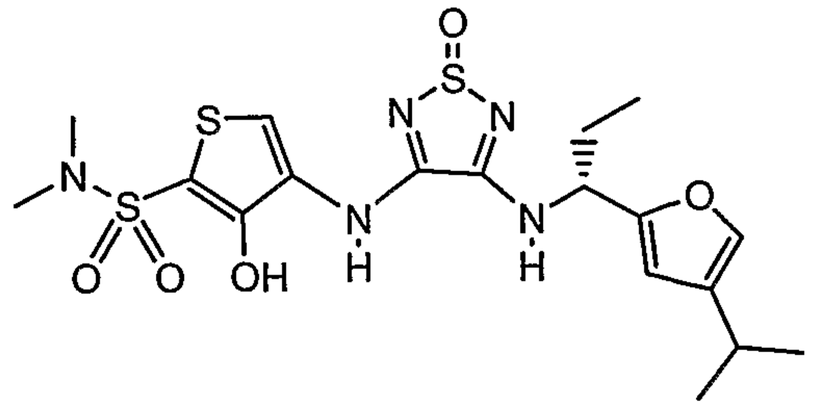
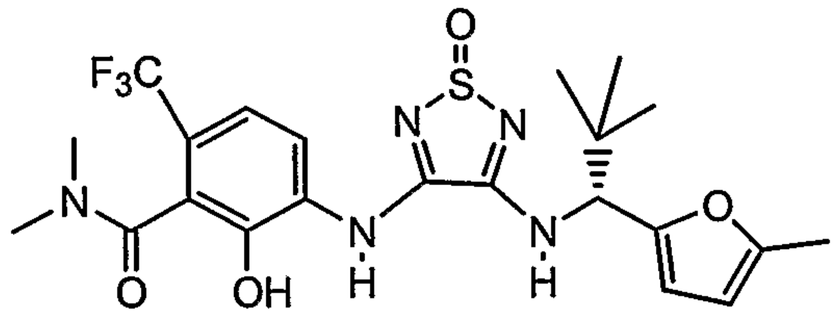
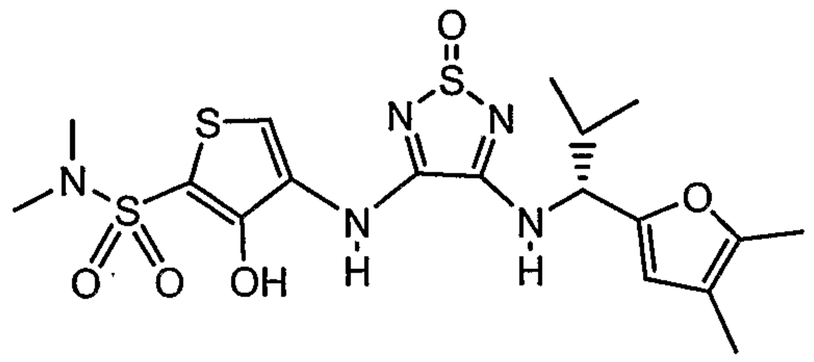
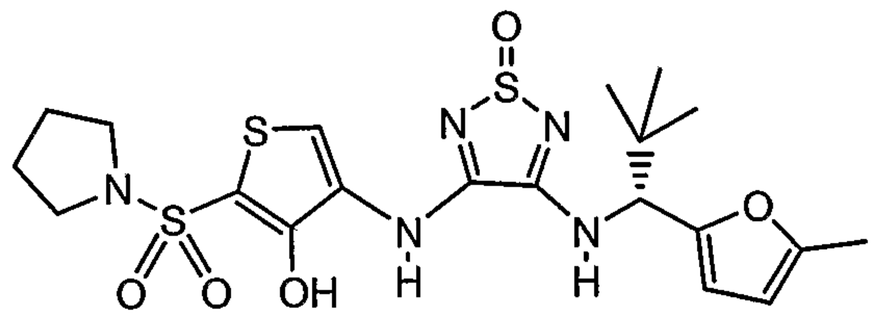
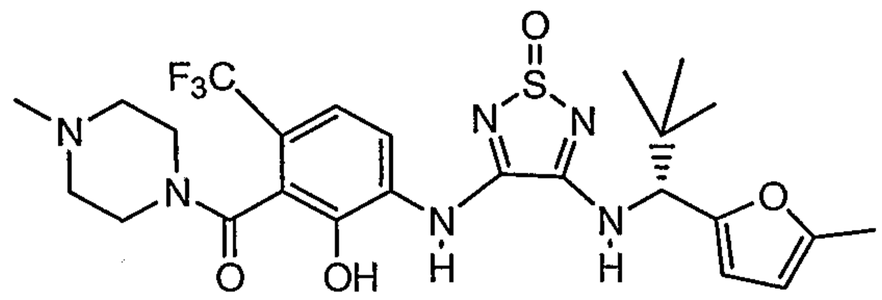
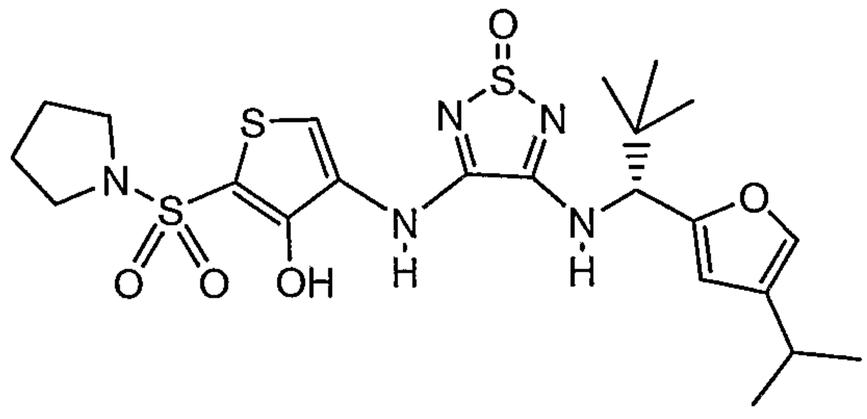
PREPARATIVE EXAMPLES 2252-2373

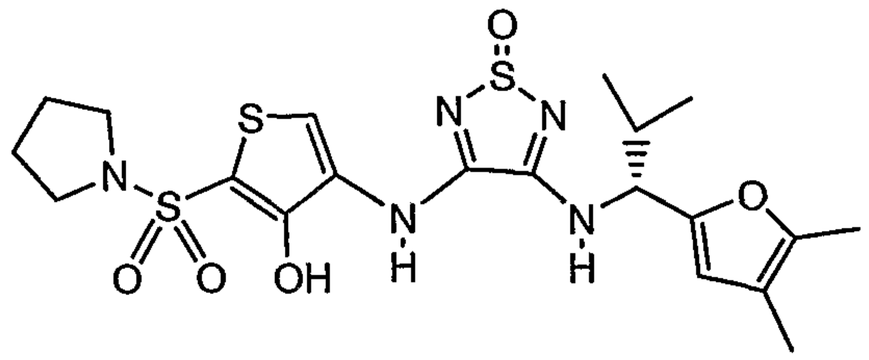
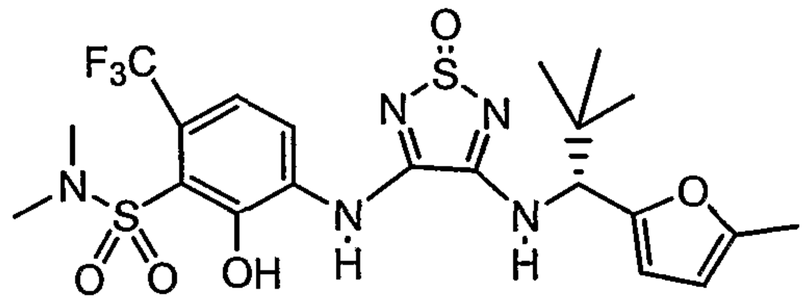
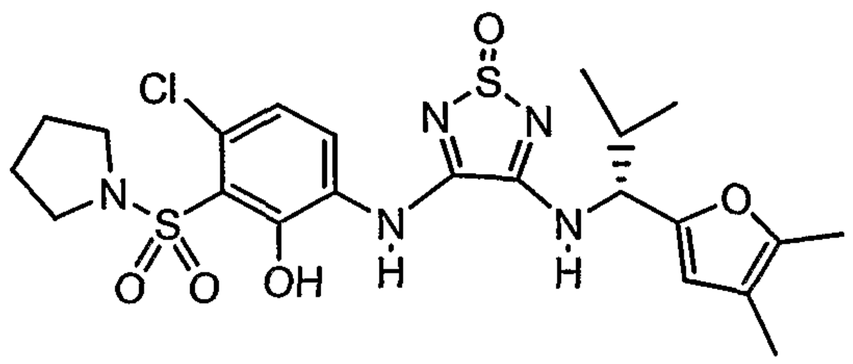
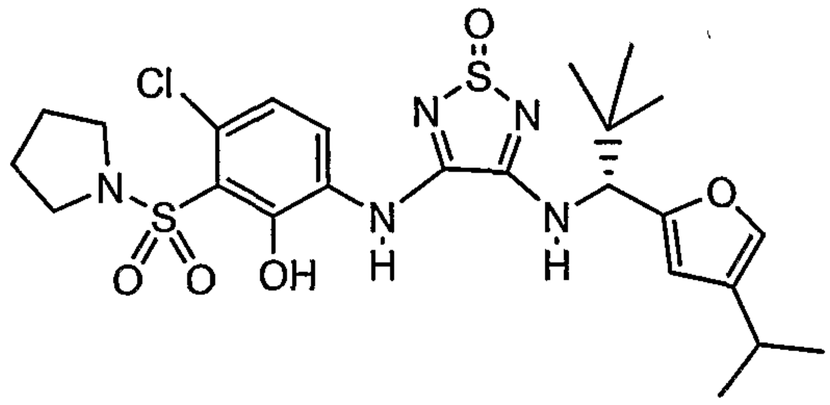
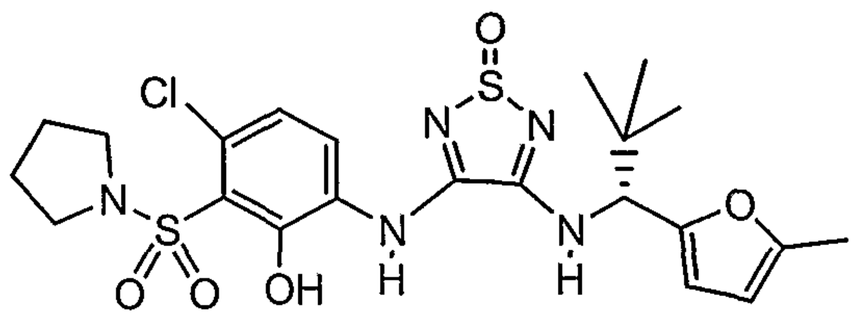
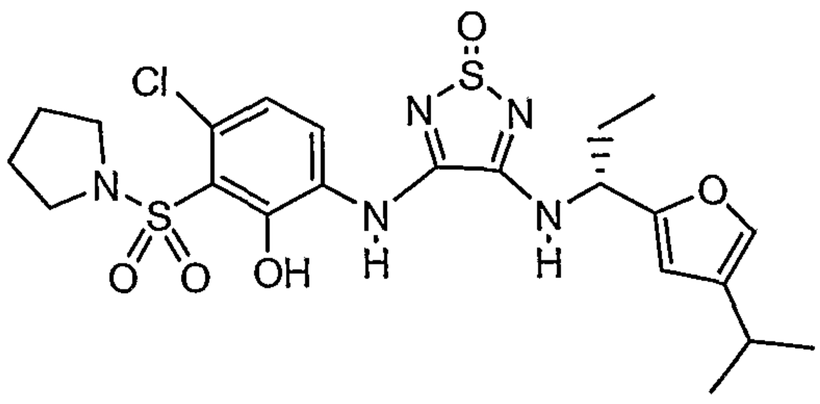
If one were to follow a procedure similar to that set forth in Preparative Example 2201A, but using the amines from the Preparative Examples indicated in the Table below (or the commercially available amines indicated in the Table below), and the thiadiazoleoxide intermediates from the Preparative Examples indicated in the Table below and stirring the reaction mixtures at room temperature up to reflux, the thiadiazoleoxide products in the Table below could be obtained.

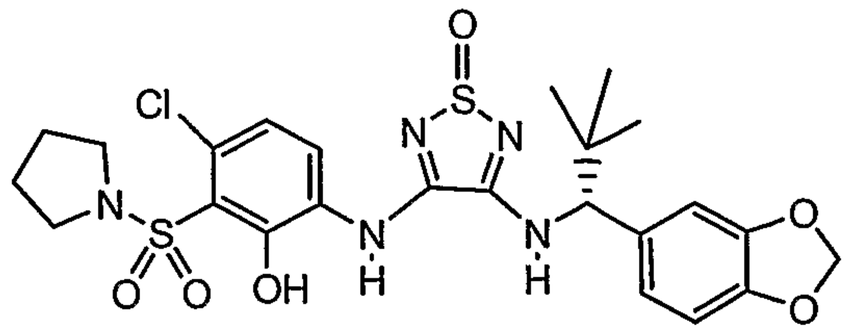
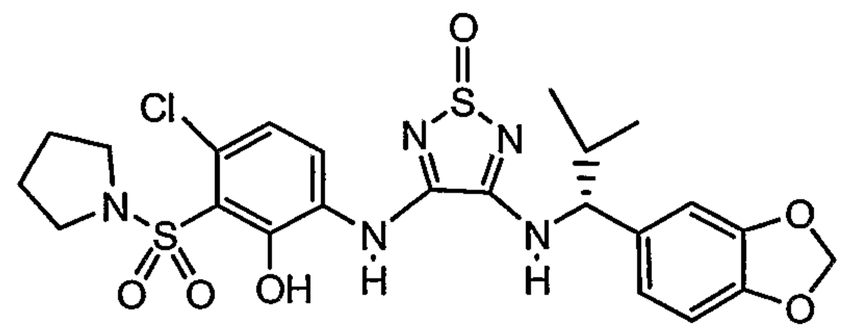
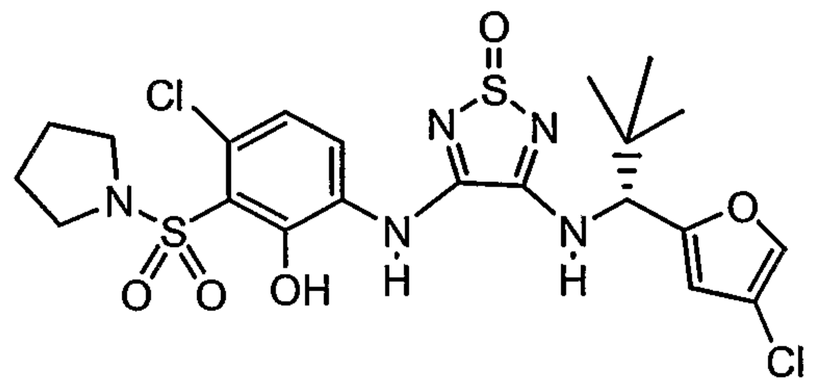
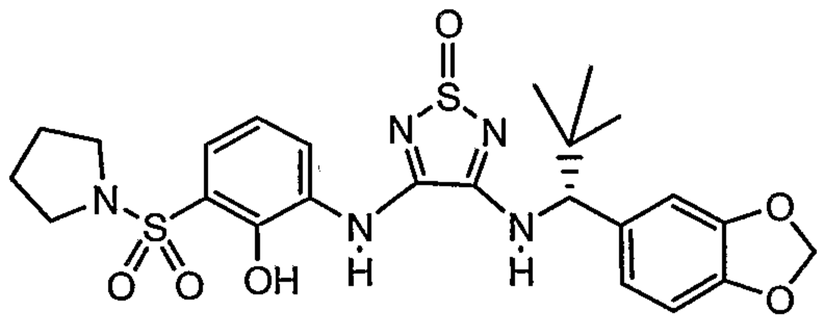
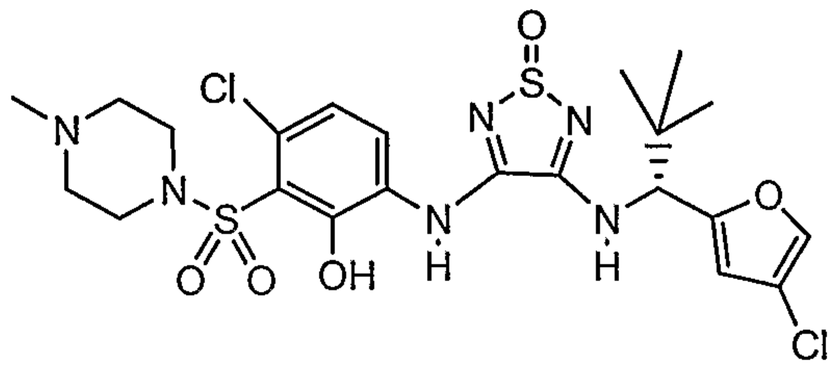
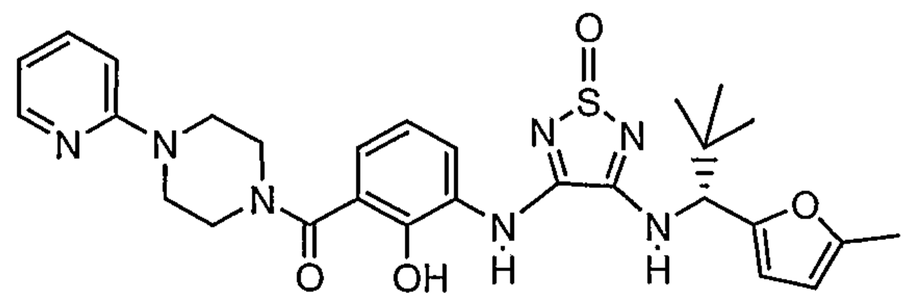
Prep Ex.	Prep. Ex. (Thiadiazole oxide Intermediate)	Prep. Ex. (Amine)	Product
2252	22.24	75.44	
2254	22.26	75.44	

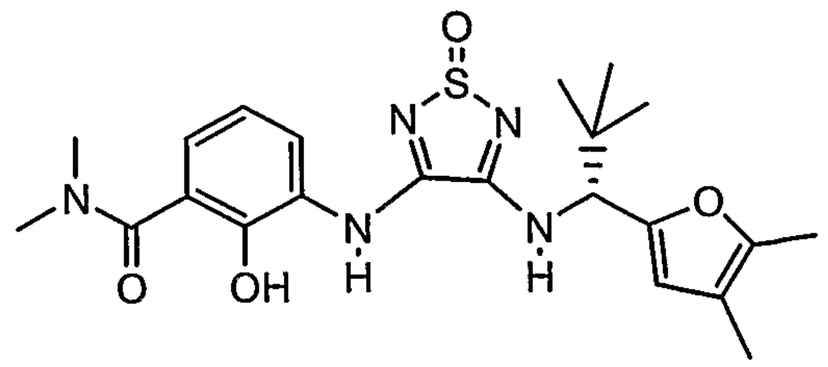
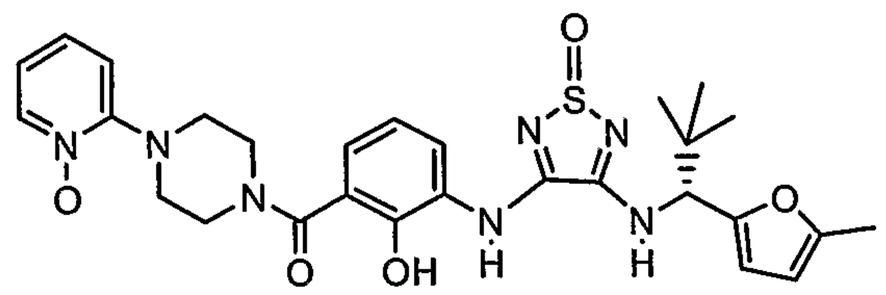
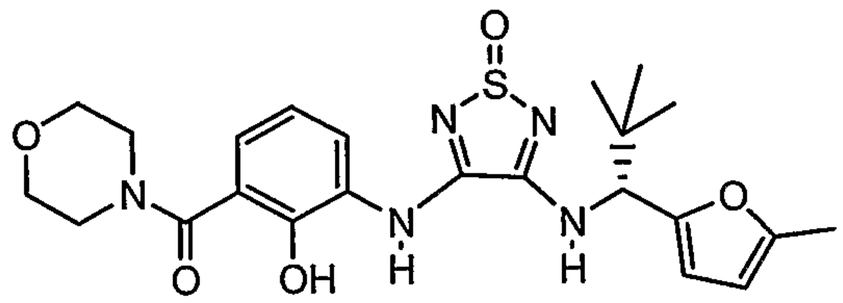
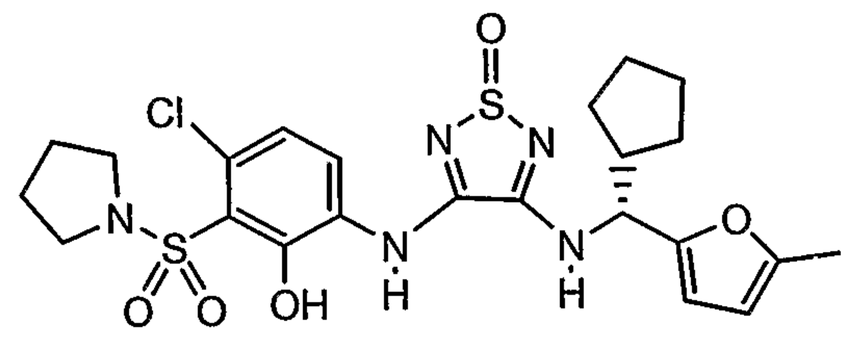
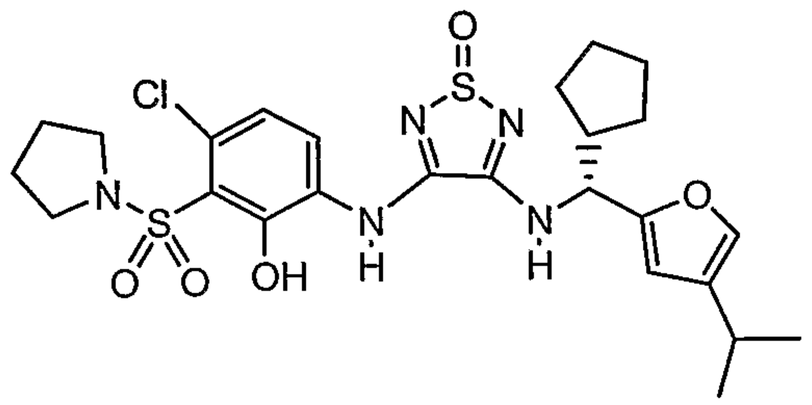
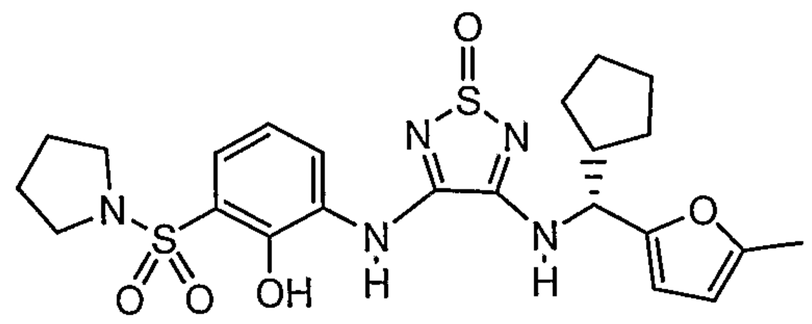
2255	22.1	 (commercially available)	
2256	22.1	 (commercially available)	
2257	22.1	75.66	
2258	22.1	75.30	
2259	22.1	75.50	
2260	22.1	603D	

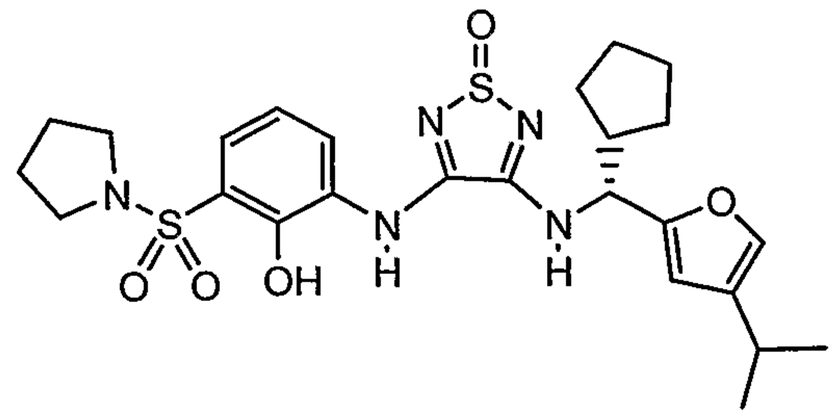
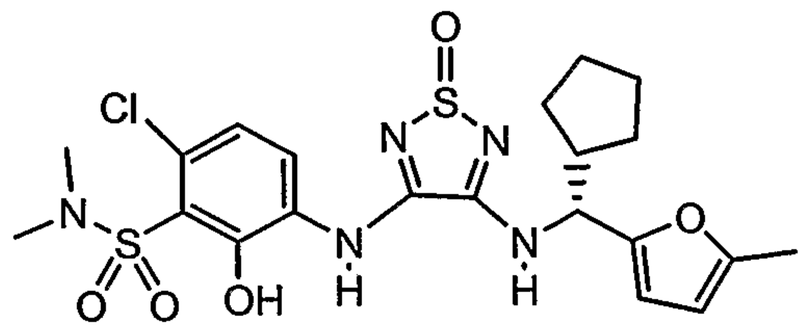
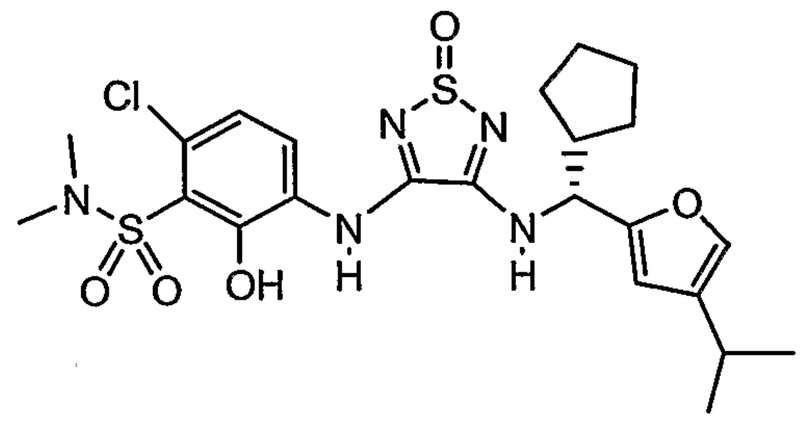
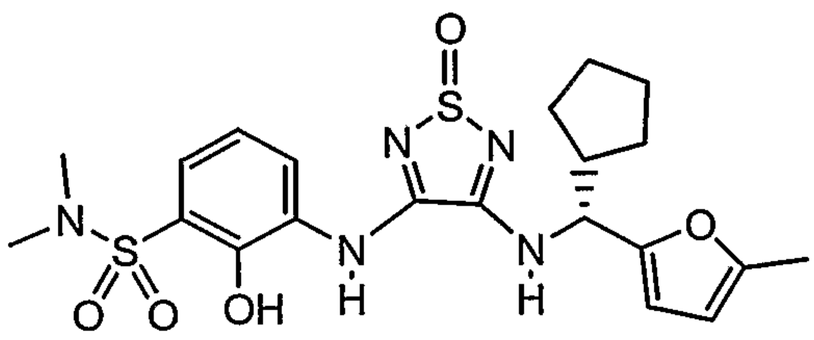
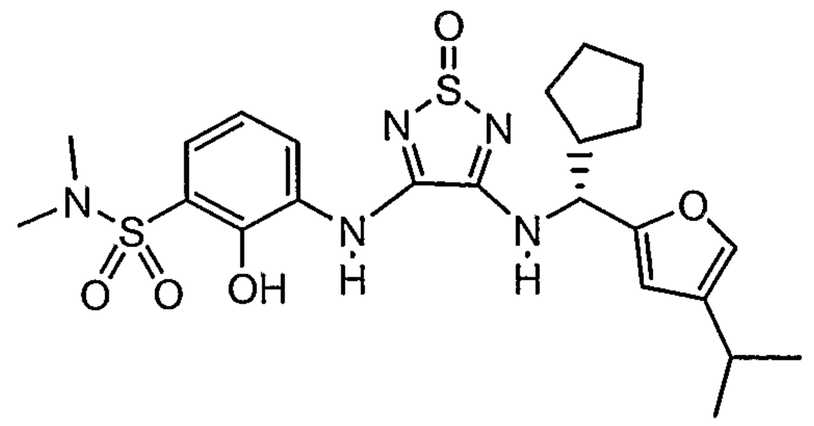
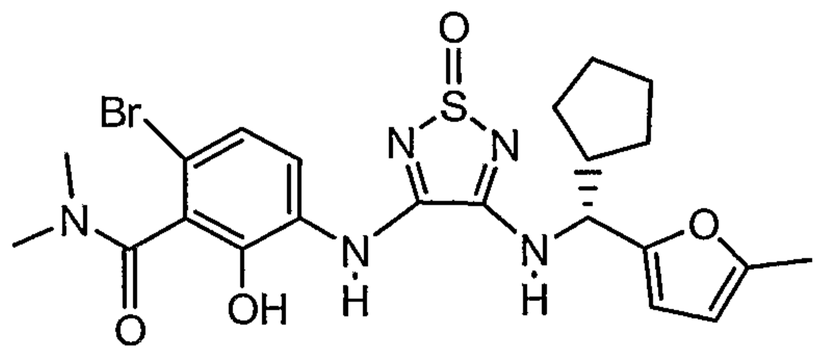
2262	22.1	75.10	
2263	22.1	75.10E	
2264	22.29	75.44	
2265	22.39	603C	
2266	22.30	75.44	
2267	22.6	75.1	

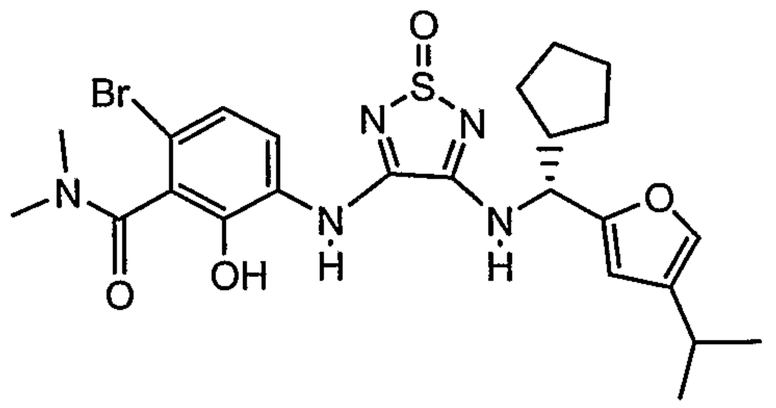
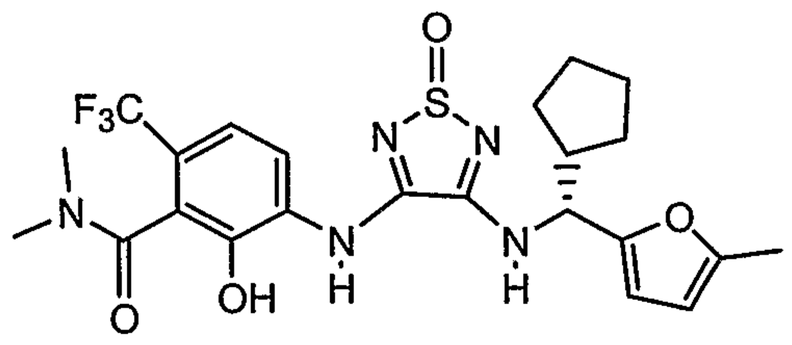
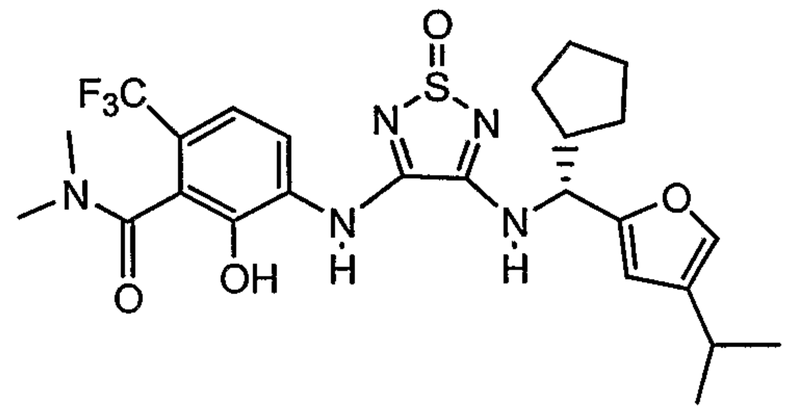
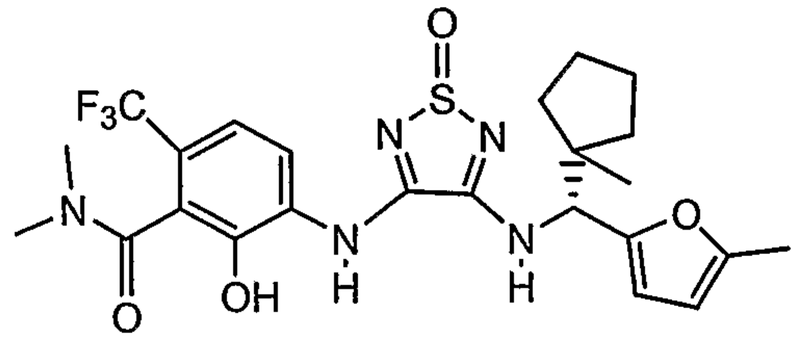
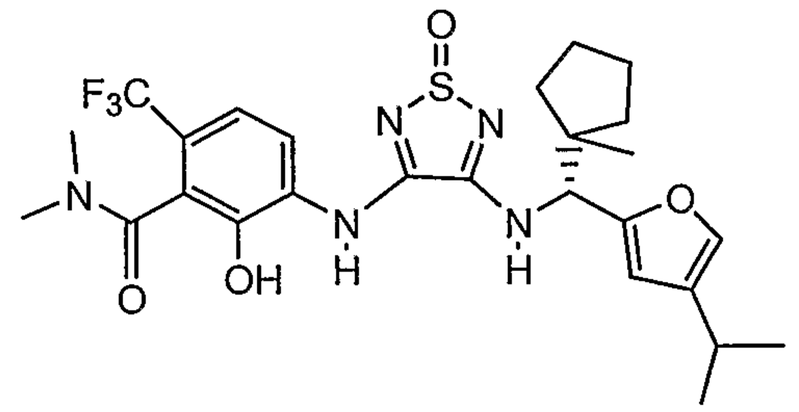
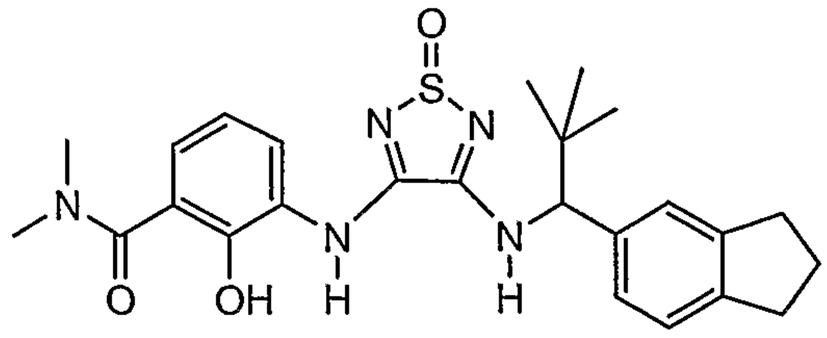
2268	22.6	75.9	
2269	22.39	75.44	
2270	22.6	75.61	
2271	23.9	75.44	
2272	22.27	75.44	
2273	22.28	75.10	

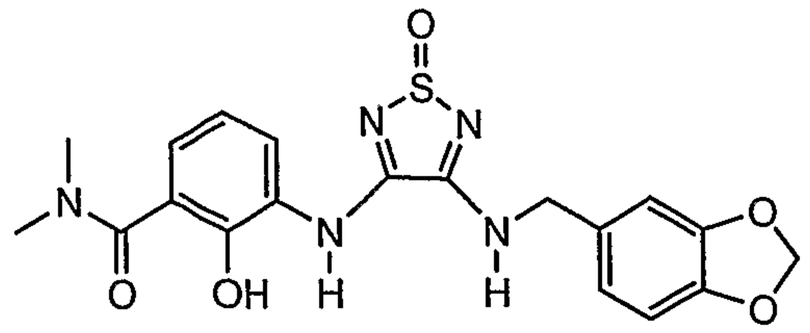
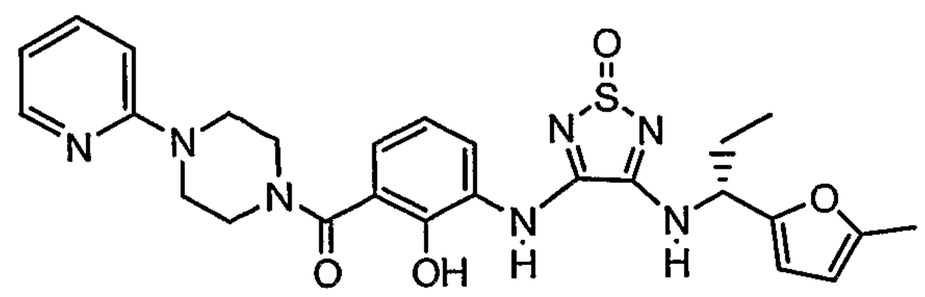
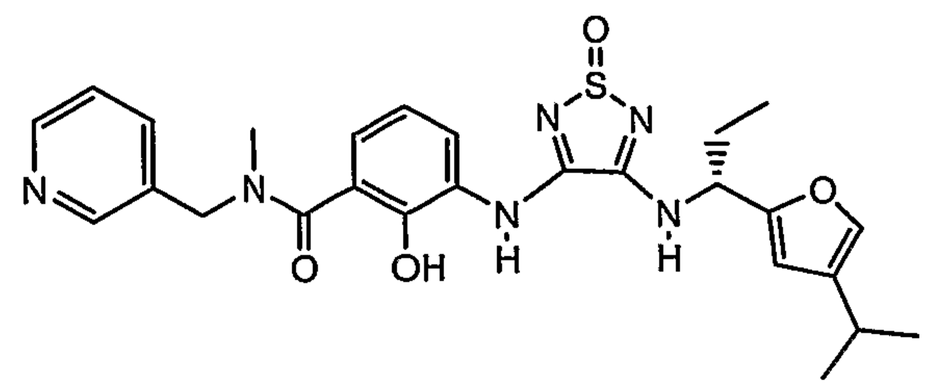
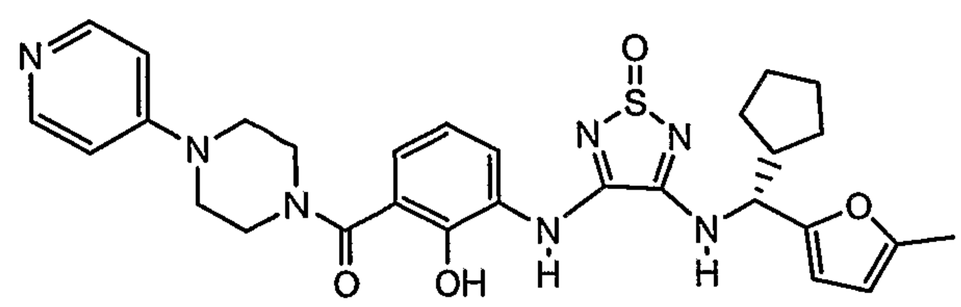
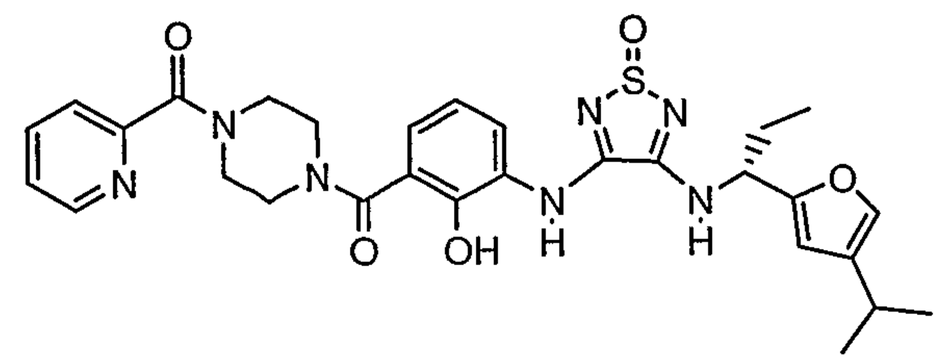
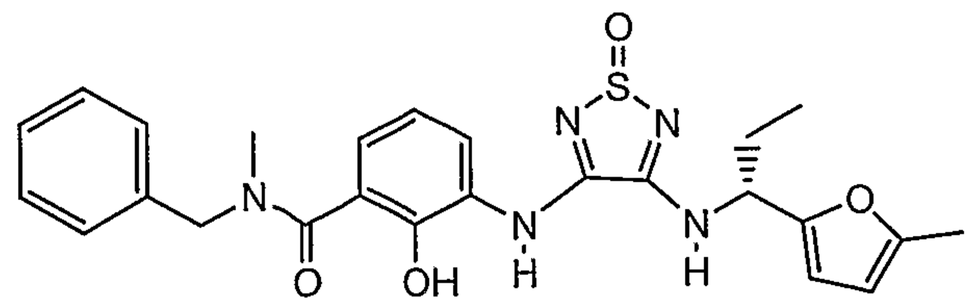
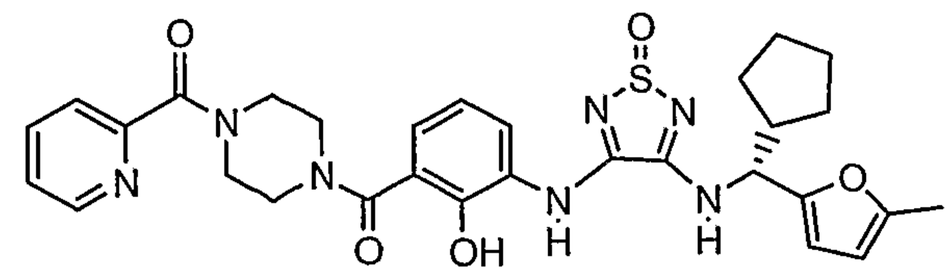
2274	22.28	75.61	
2275	22.31	75.44	
2276	22.32	75.61	
2277	22.32	75.10	
2278	22.32	75.44	
2279	22.32	75.9	

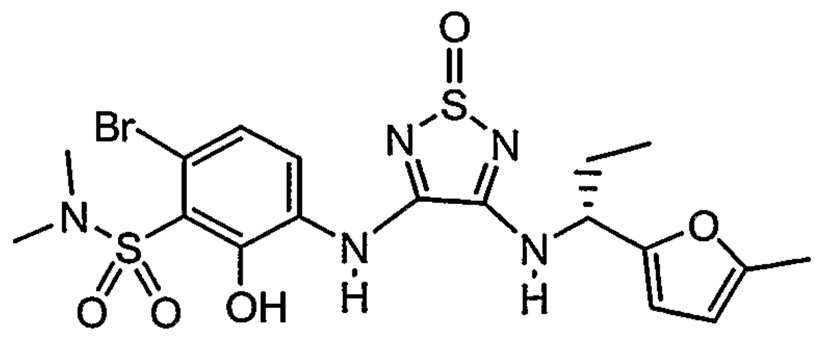
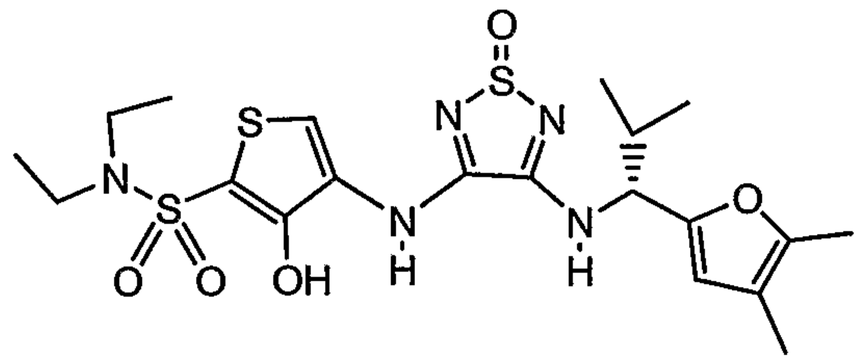
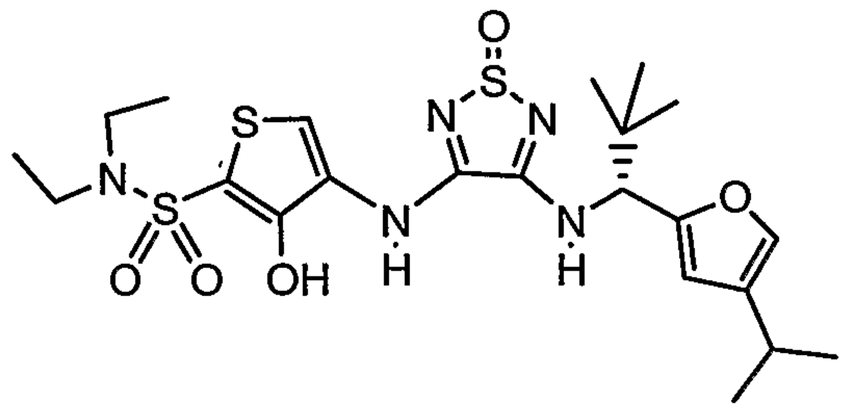
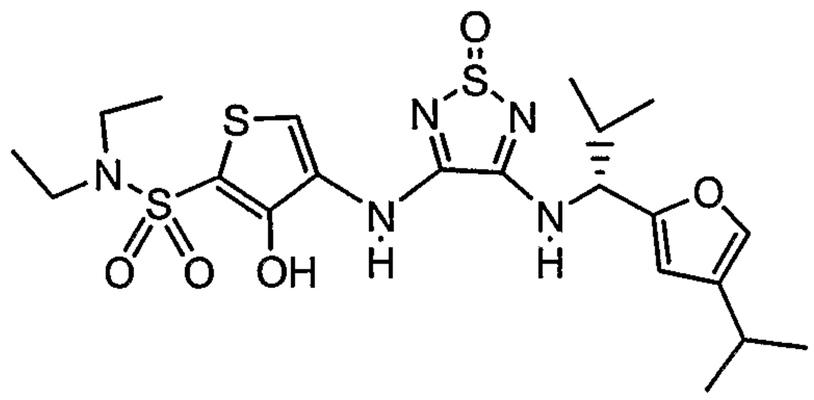
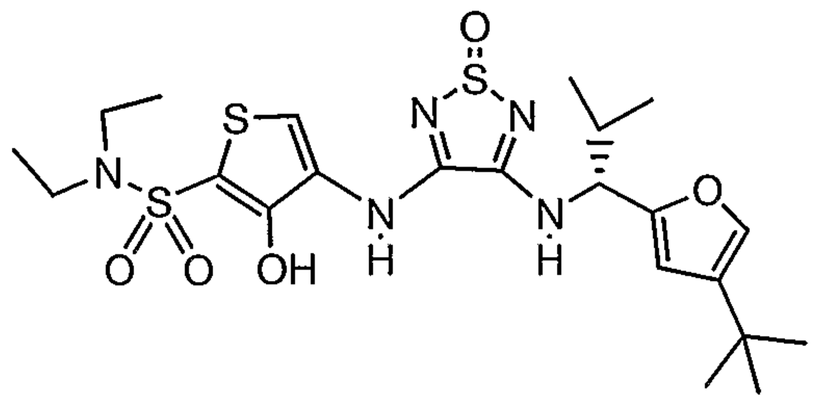
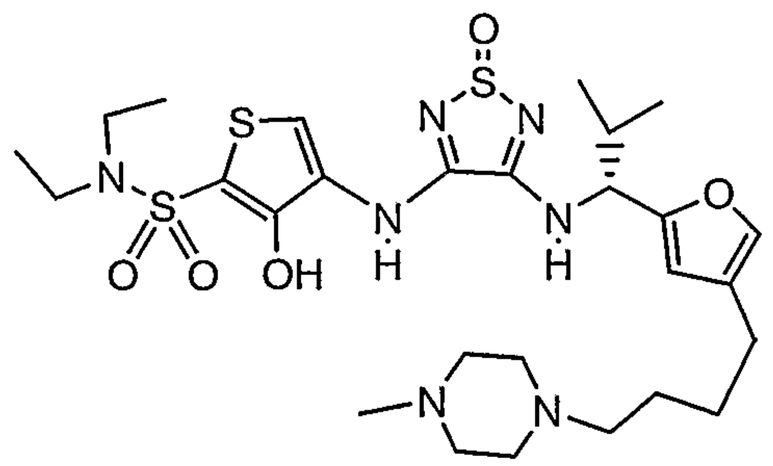
2280	22.32	75.60	
2281	22.32	75.30	
2282	22.32	75.52	
2283	22.47	75.60	
2284	22.34	75.52	
2285	22.48	75.44	

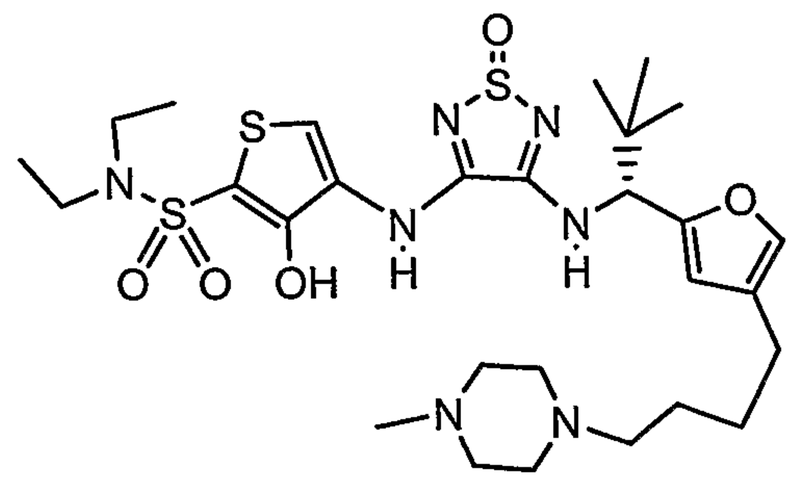
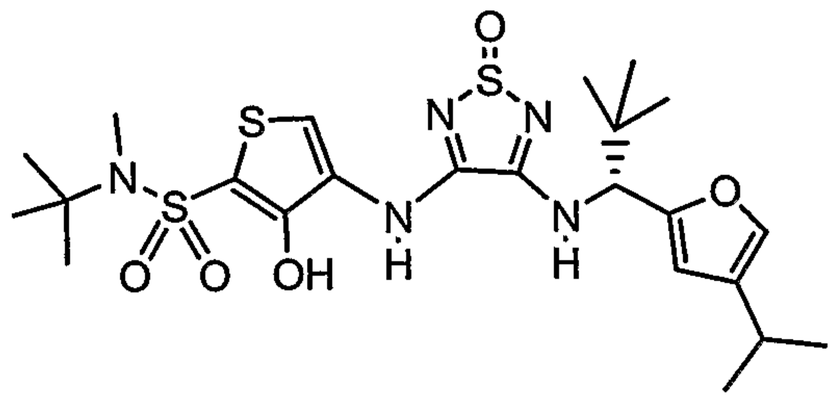
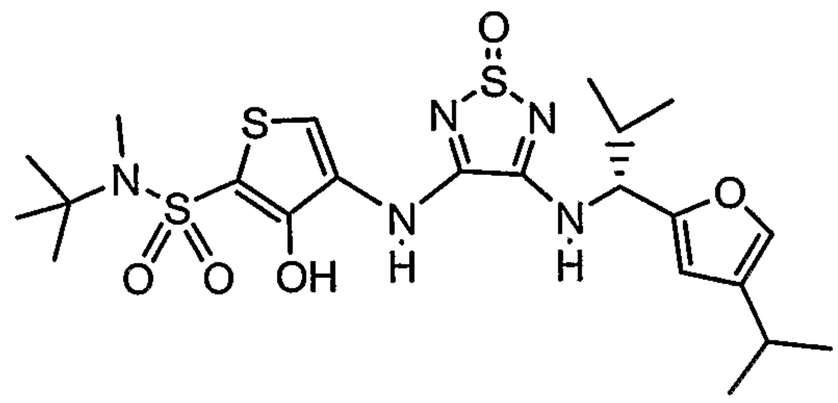
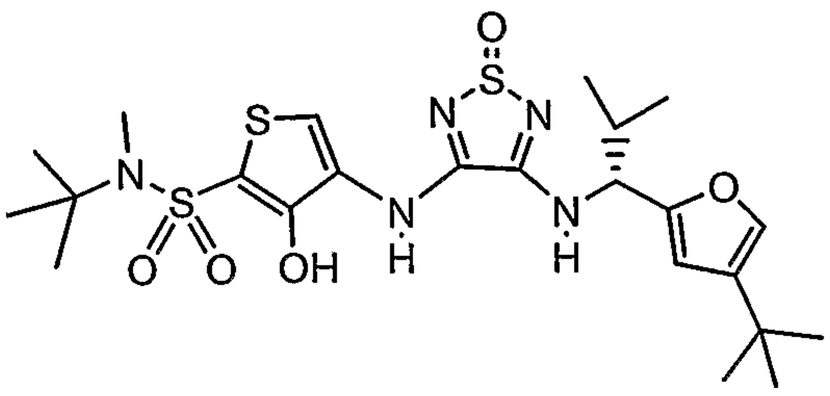
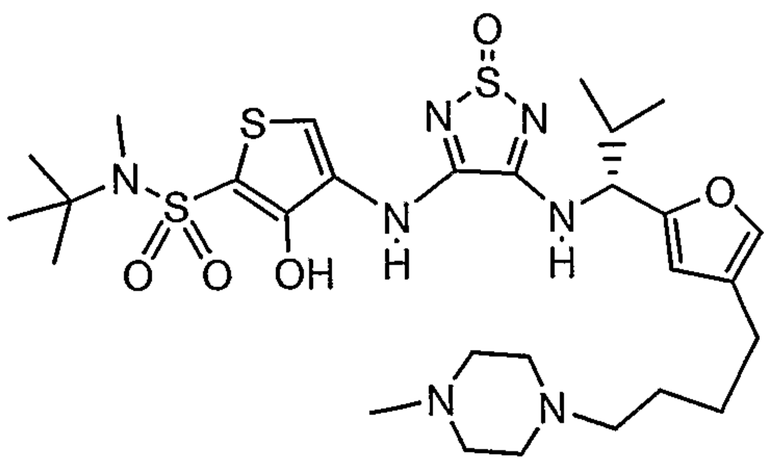
2286	22.1	75.67	
2287	22.36	75.44	
2289	22.41	75.44	
2291	22.32	75.201	
2292	22.32	75.200	
2293	22.47	75.201	

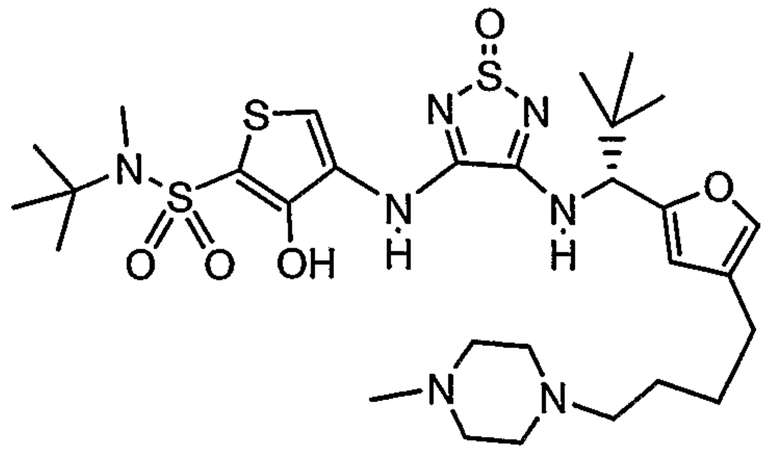
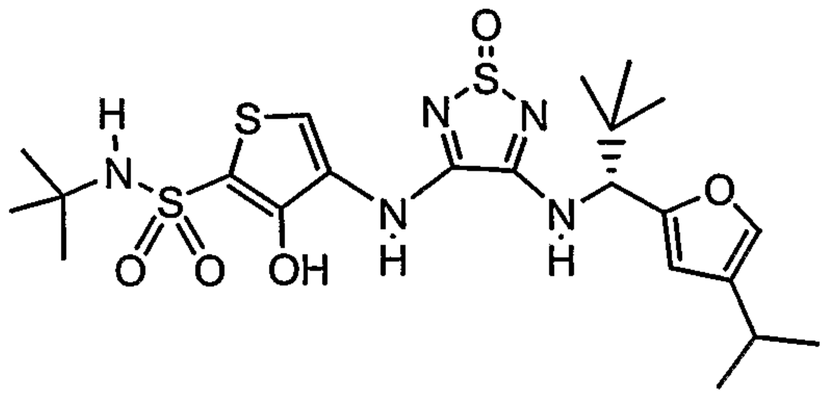
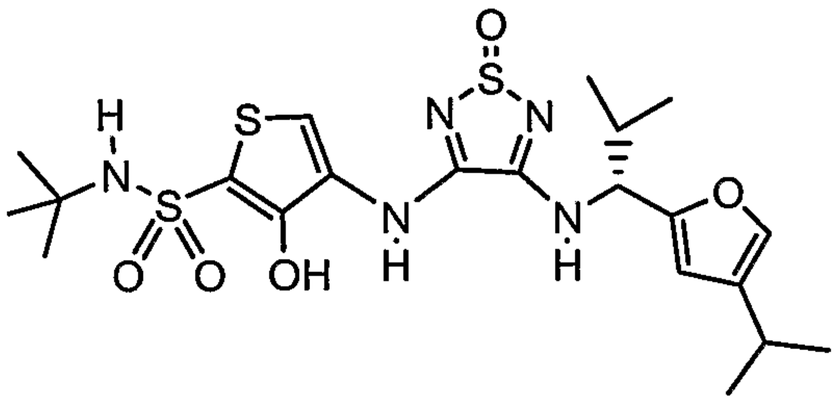
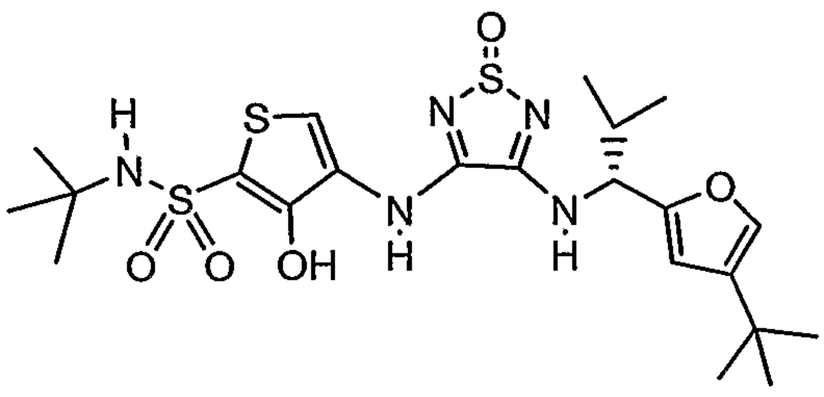
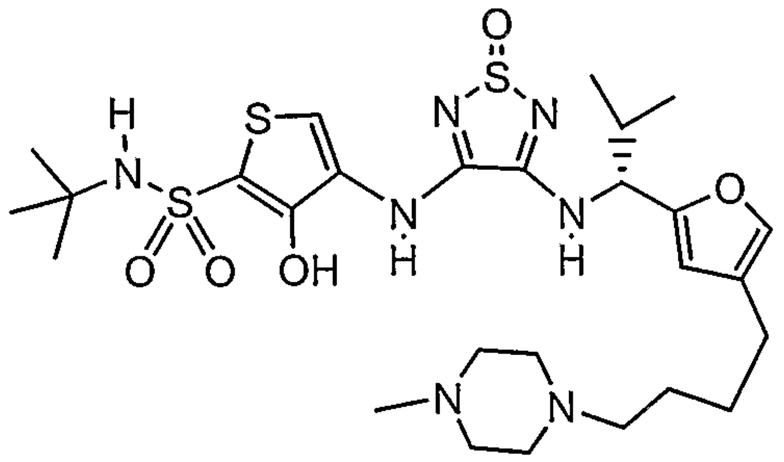
2294	22.47	75.200	
2295	22.4	75.201	
2296	22.4	75.200	
2297	22.45	75.201	
2298	22.45	75.200	
2299	22.46	75.201	

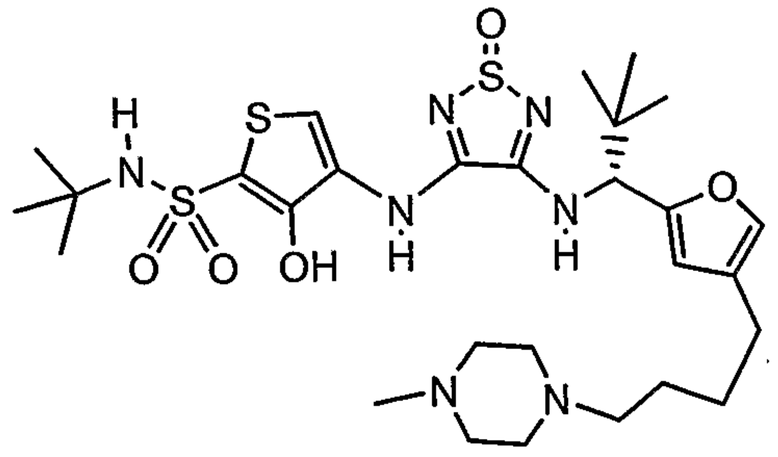
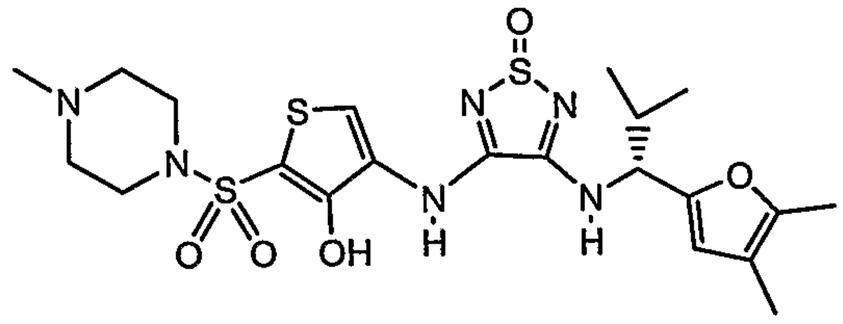
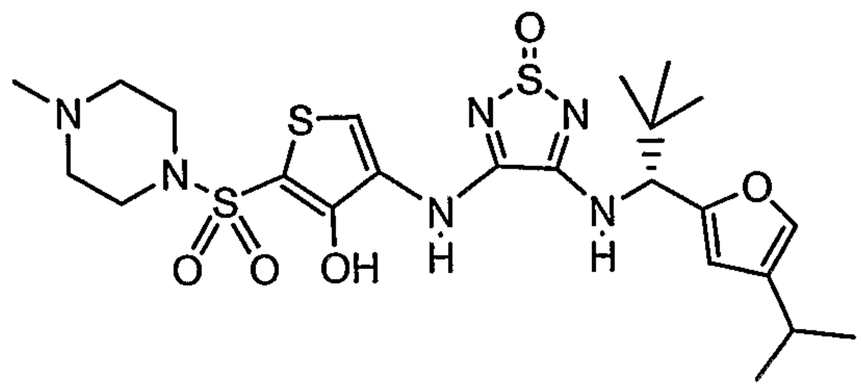
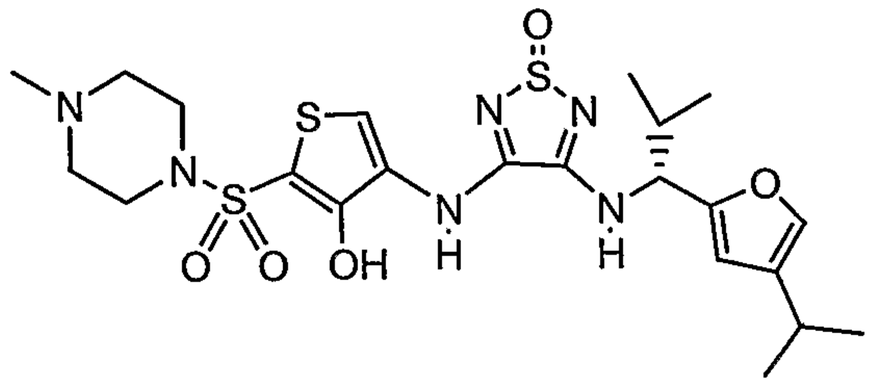
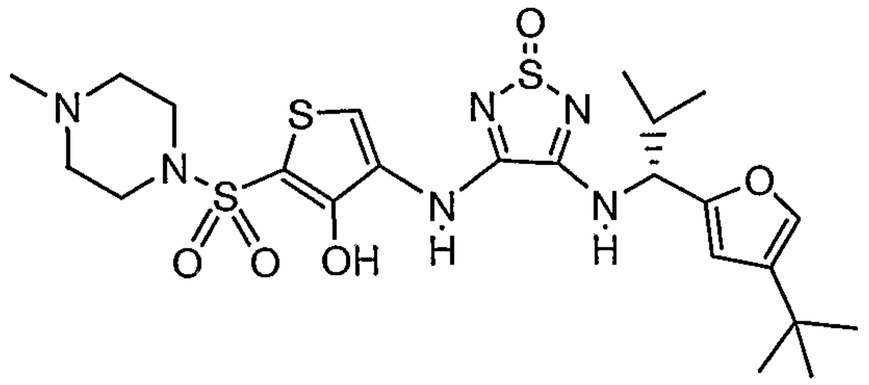
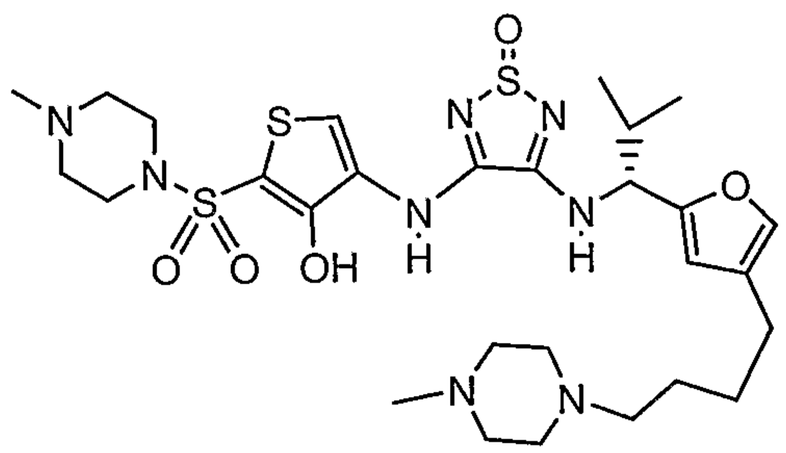
2300	22.46	75.200	
2301	22.39	75.201	
2302	22.39	75.200	
2303	22.39	601.A	
2304	22.39	601.B	
2305	22.1	75.93	

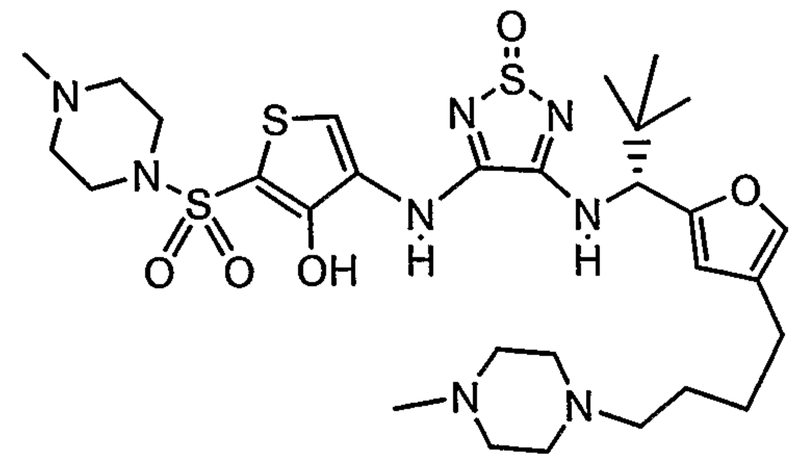
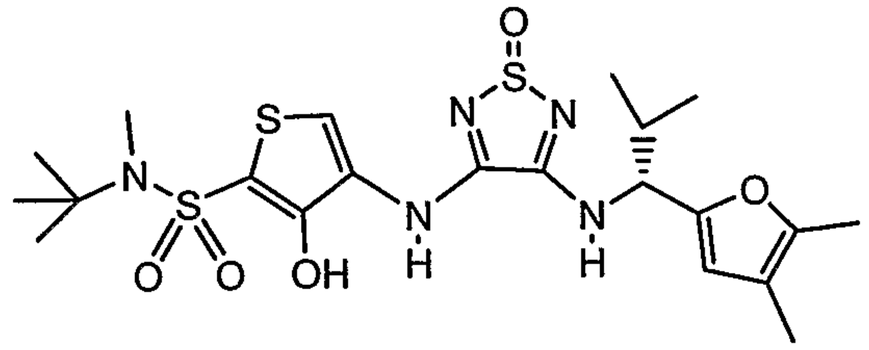
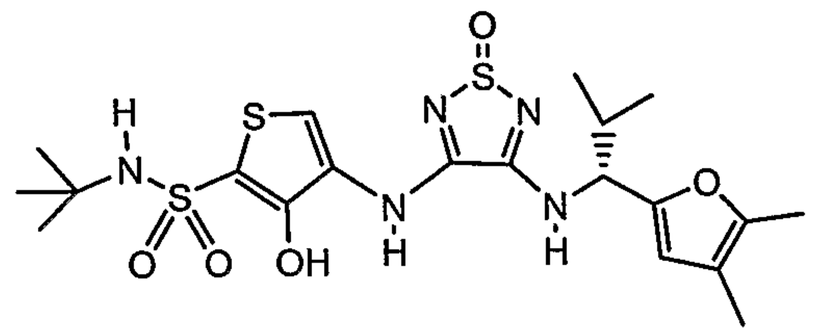
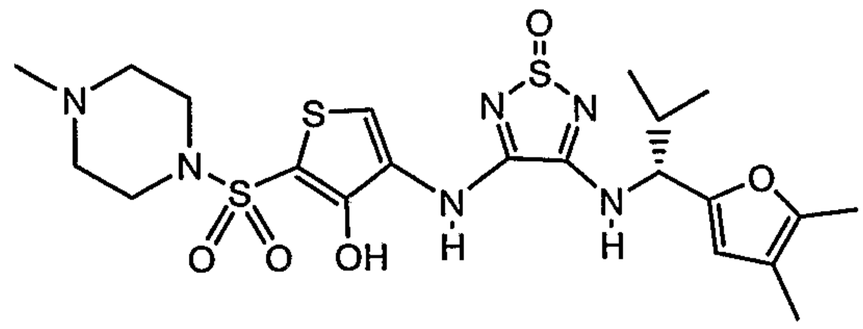
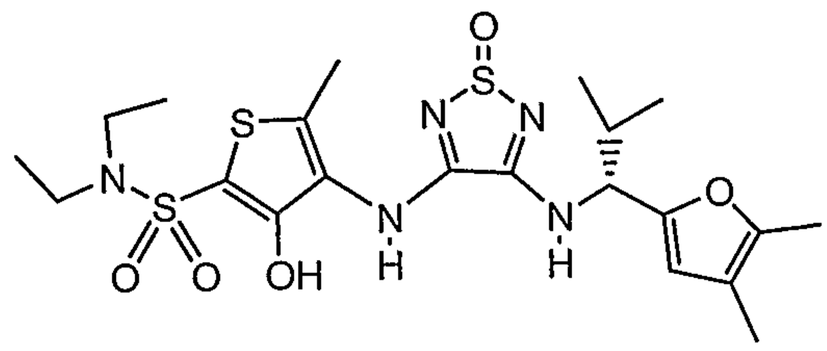
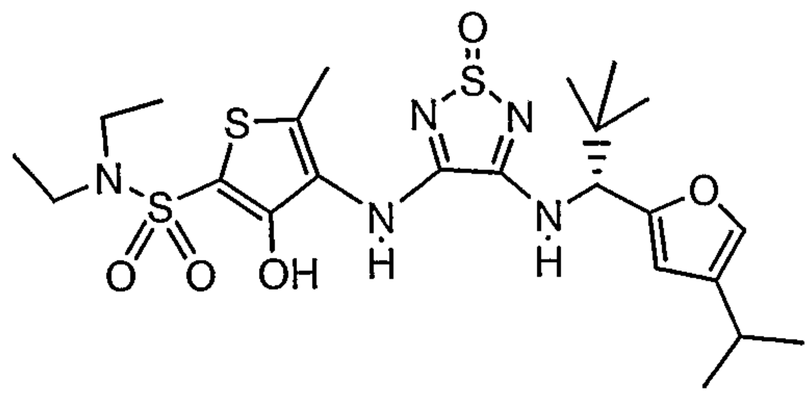
2306	22.1	64.11	
2307	22.48	75.1	
2308	22.37	75.9	
2309	22.50	51.26	
2310	22.51	75.9	
2311	22.16	75.1	
2312	22.51	51.26	

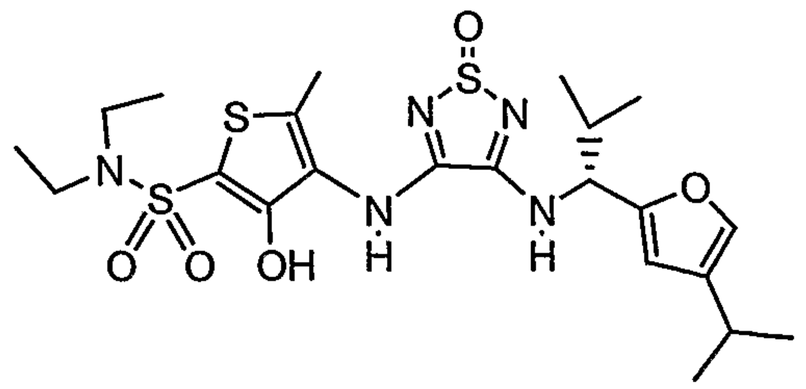
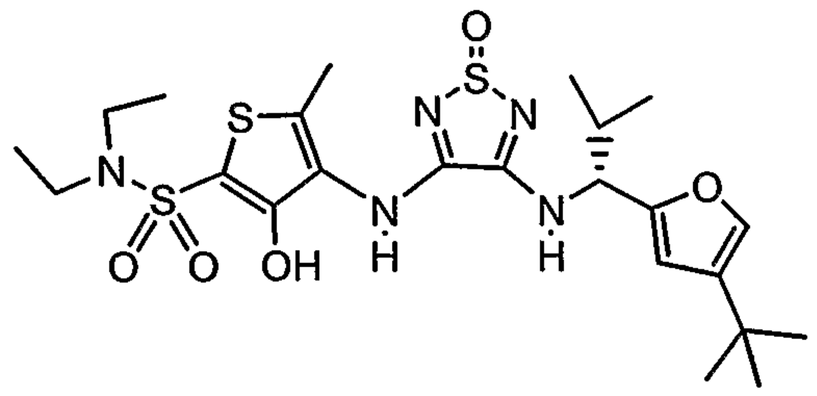
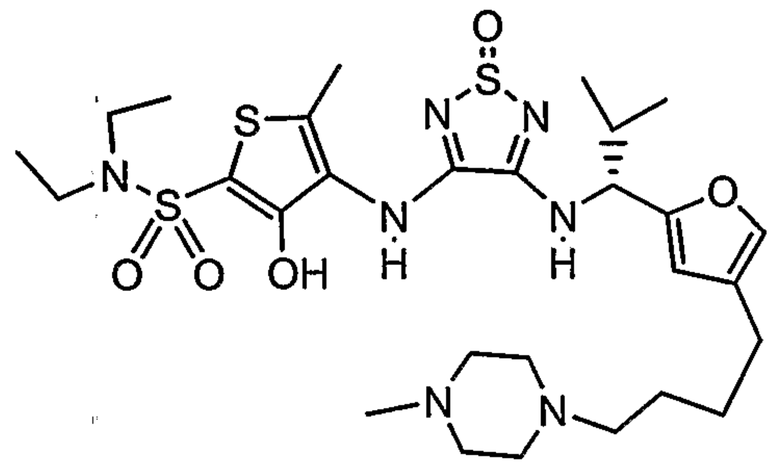
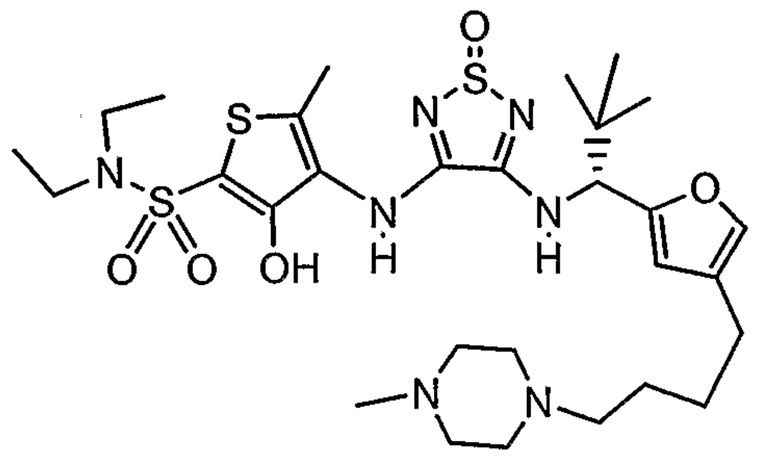
2313	22.38	75.1	
2314	22.7	75.61	
2315	22.7	75.10	
2316	22.7	75.10E	
2317	22.7	603A	
2318	22.7	603B	

2319	22.7	603C	
2320	22.19	75.10	
2321	22.19	75.10E	
2322	22.19	603A	
2323	22.19	603B	

2324	22.19	603C	
2325	22.20	75.10	
2326	22.20	75.10E	
2327	22.20	603A	
2328	22.20	603B	

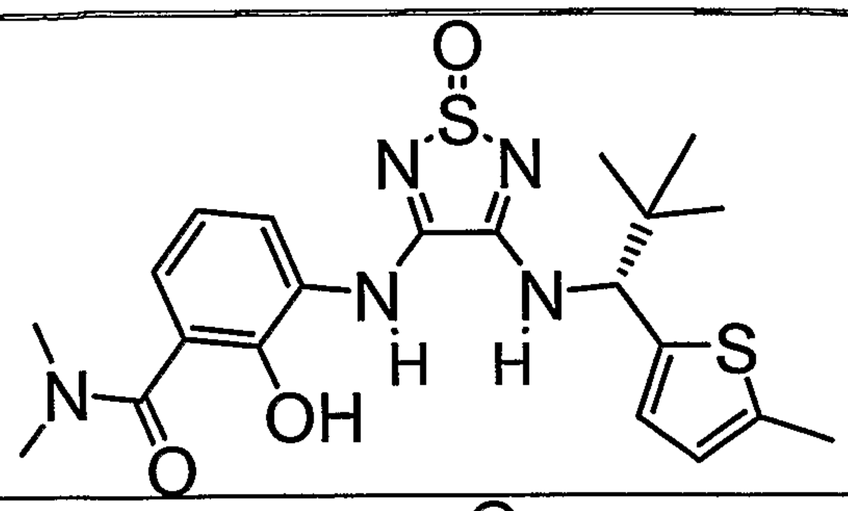
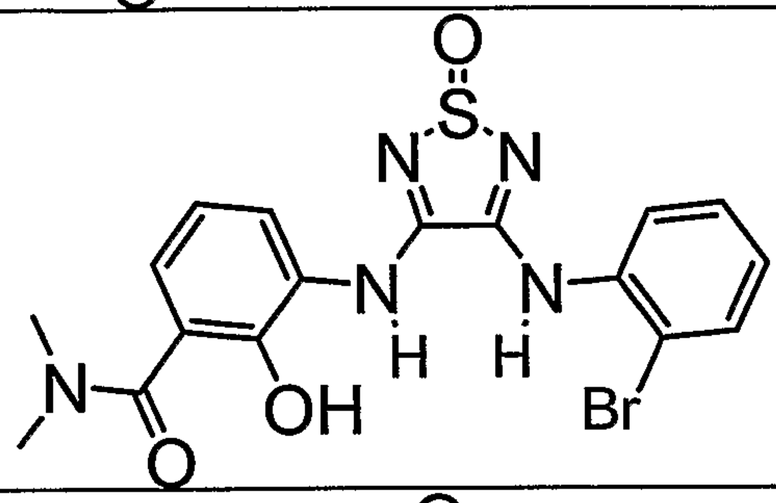
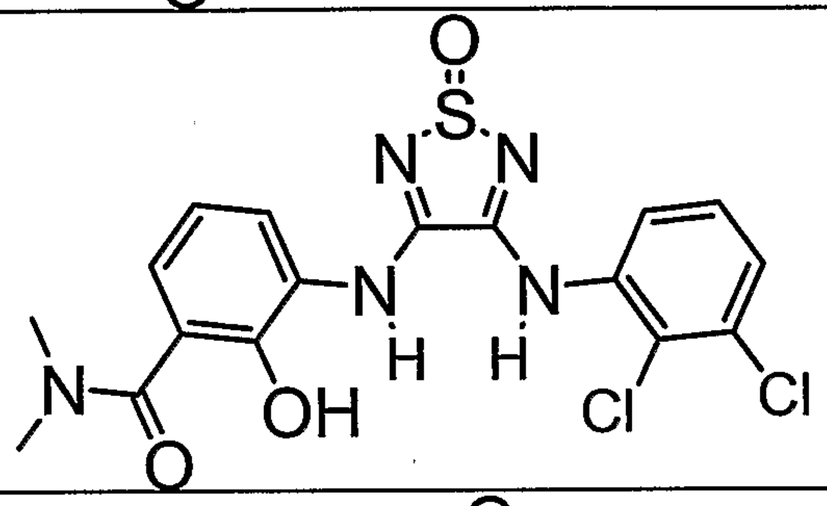
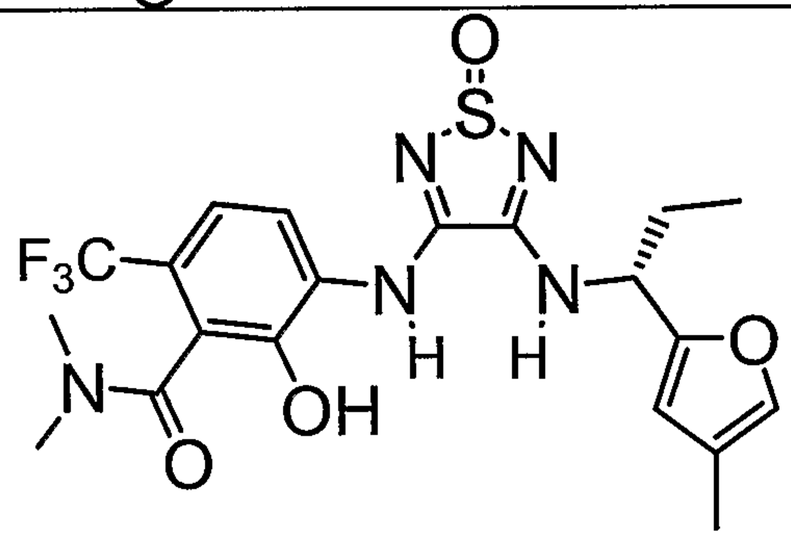
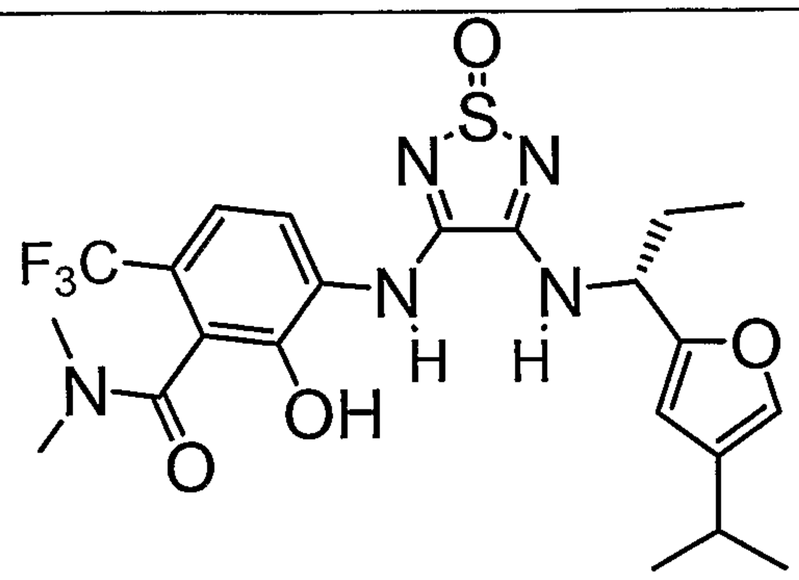
2329	22.20	603C	
2330	22.21	75.10	
2331	22.21	75.10E	
2332	22.21	75.10E	
2333	22.21	603A	
2334	22.21	603B	

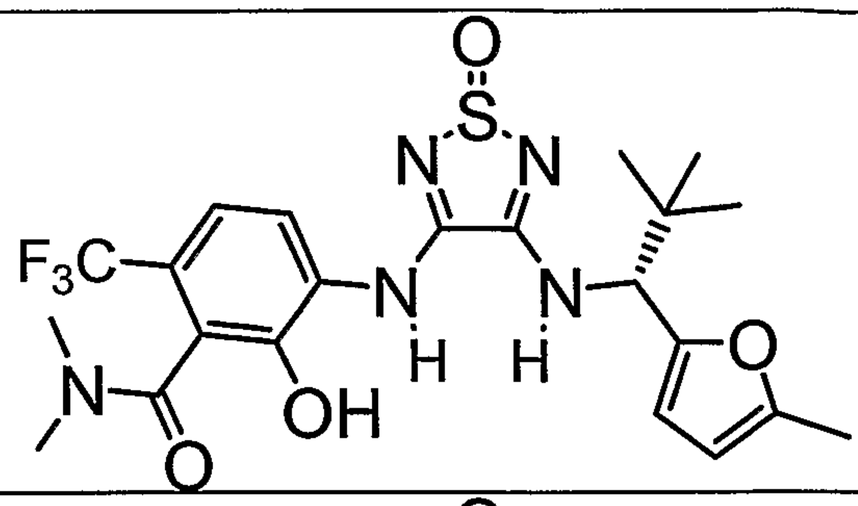
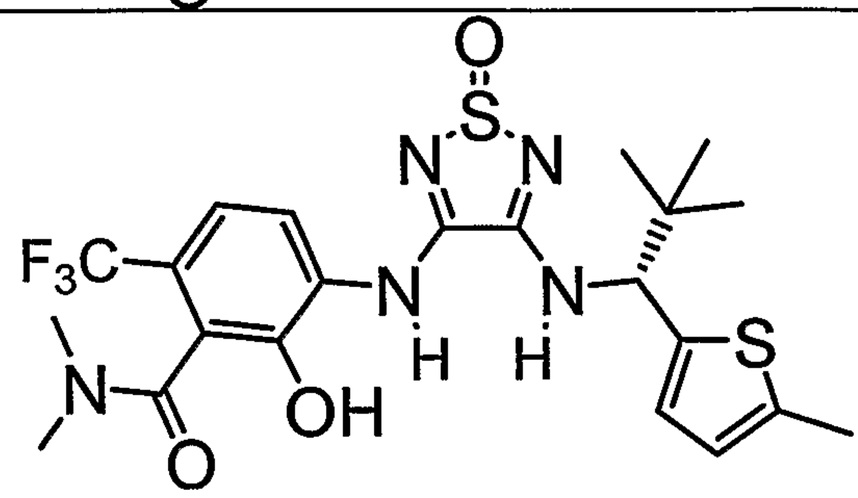
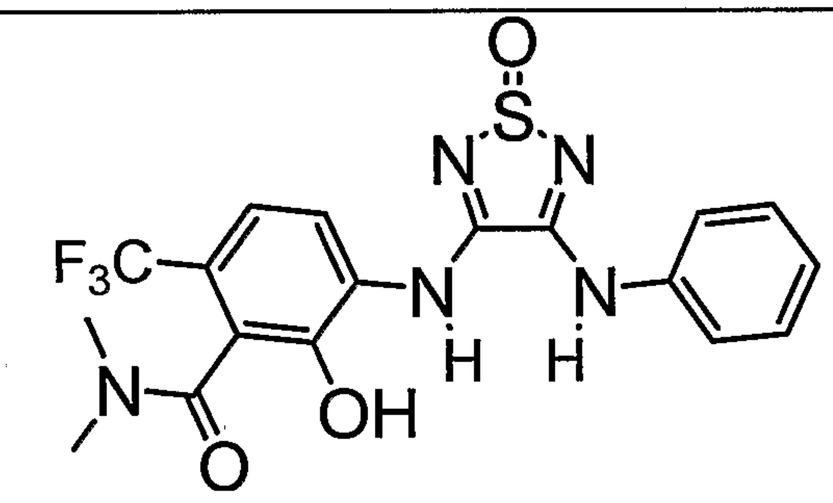
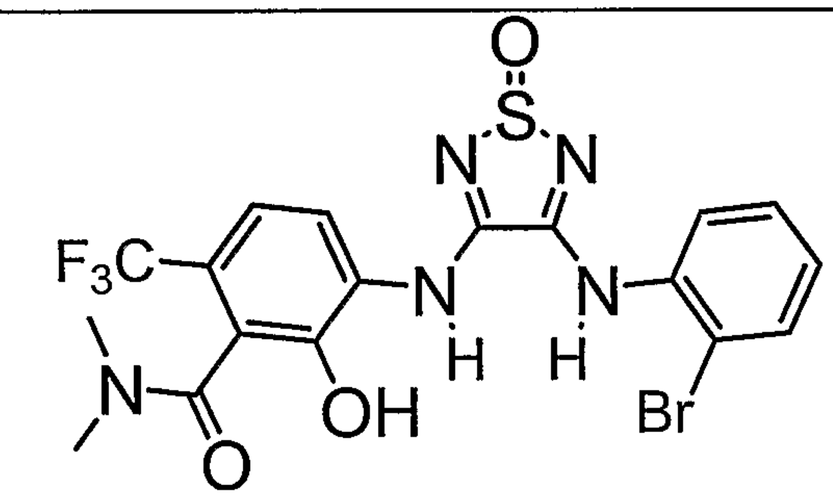
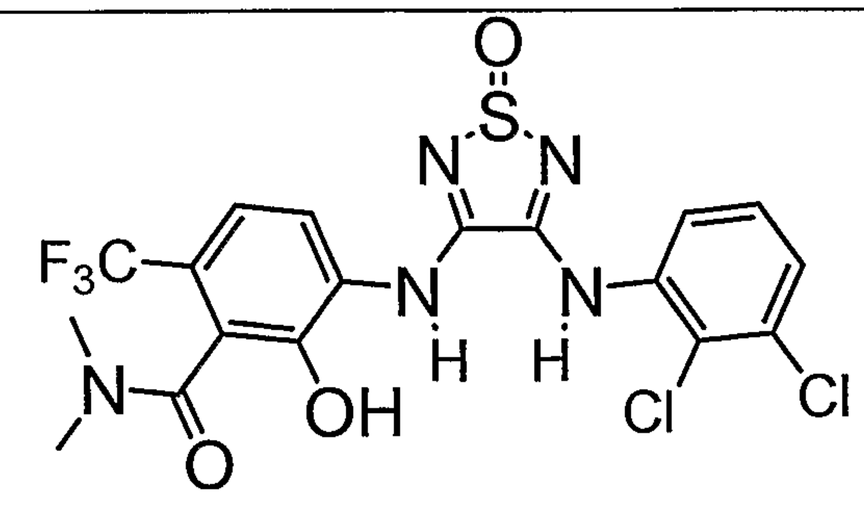
2335	22.21	603C	
2336	22.19	75.61	
2337	22.20	75.61	
2338	22.21	75.61	
2339	22.22	75.61	
2340	22.22	75.10	

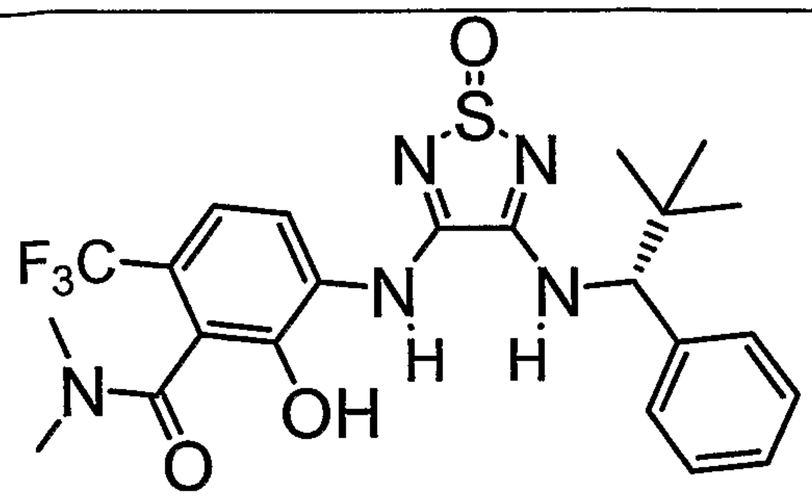
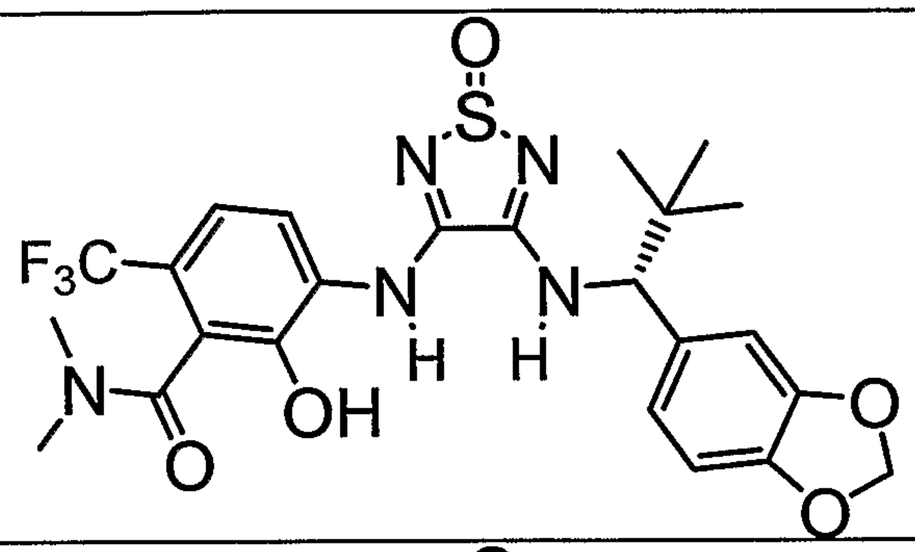
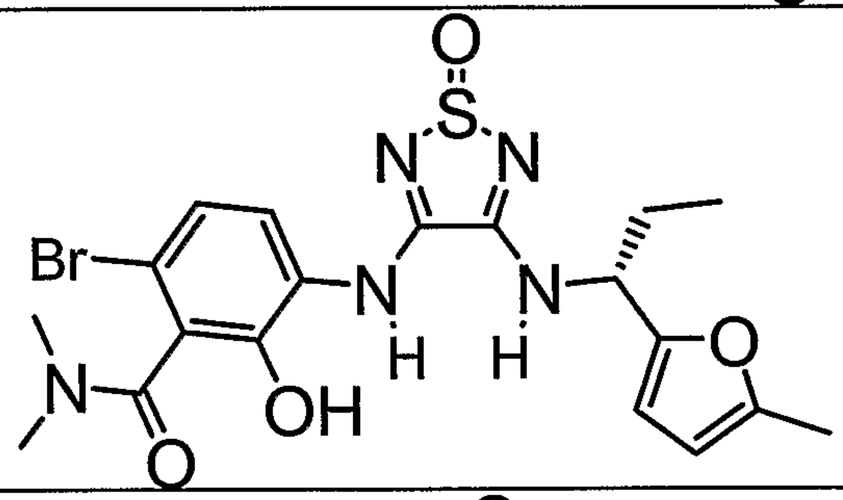
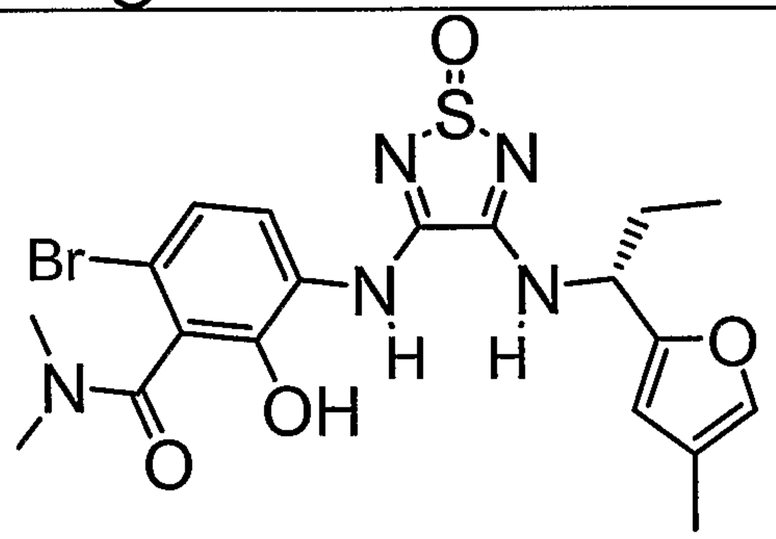
2341	22.22	75.10E	
2342	22.22	603A	
2343	22.22	603B	
2344	22.22	603C	

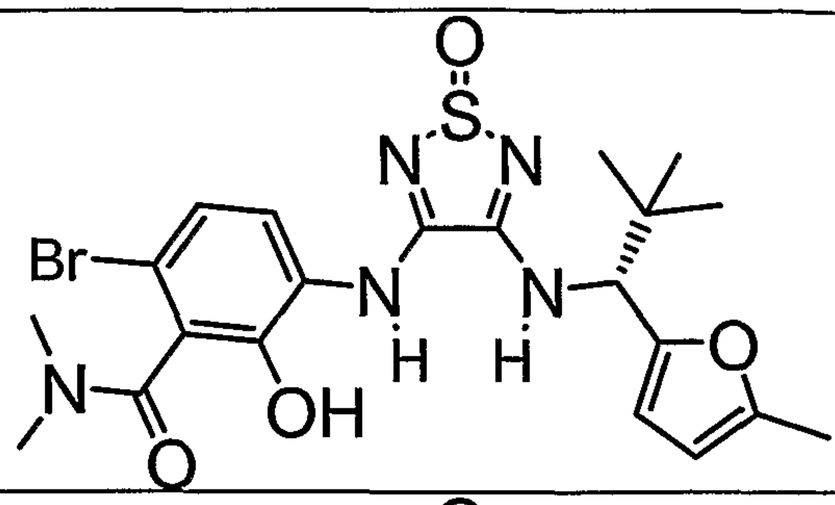
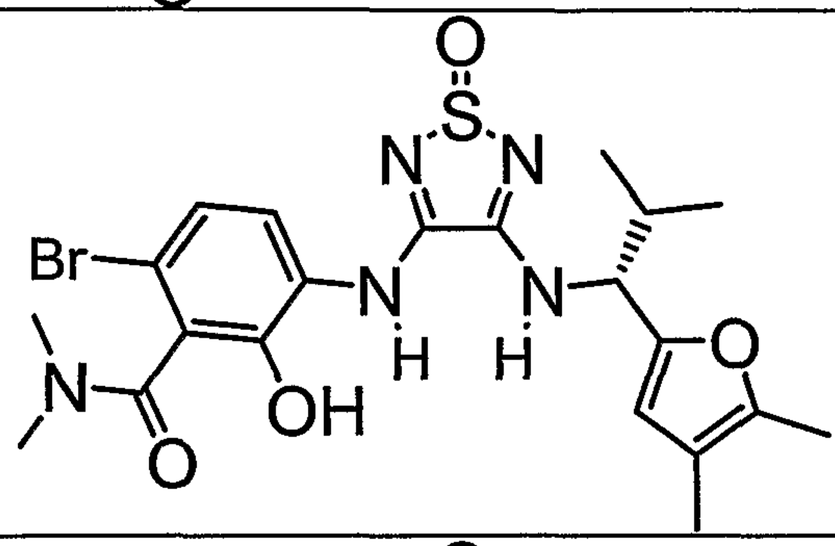
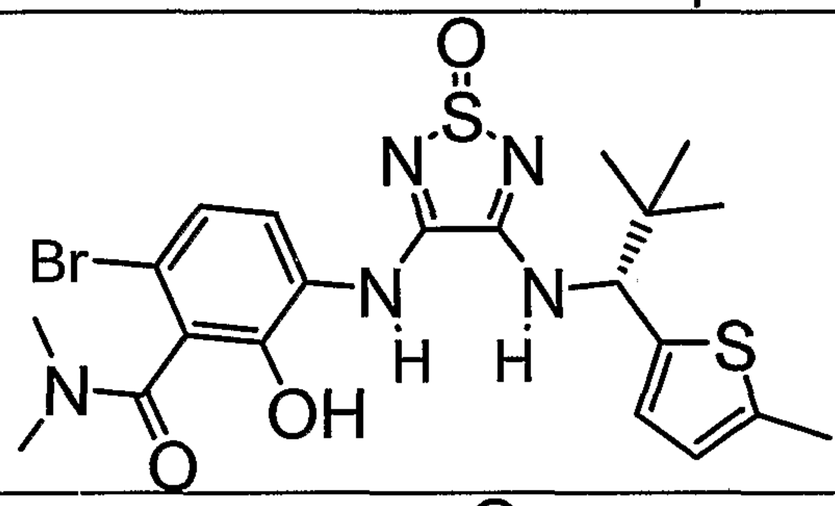
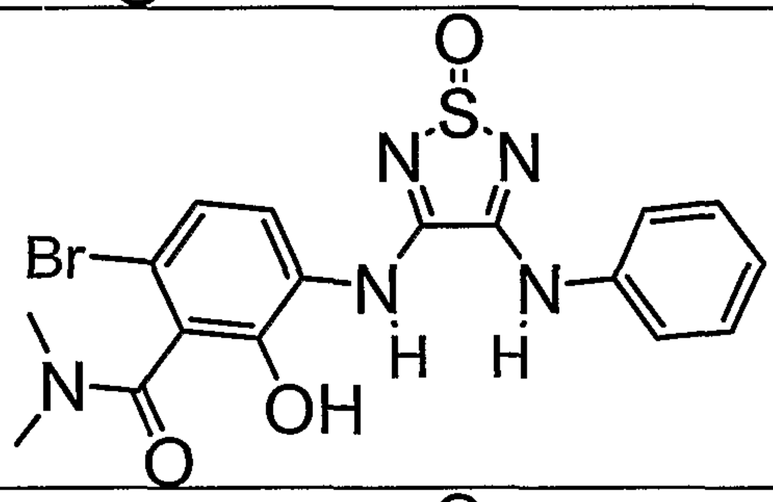
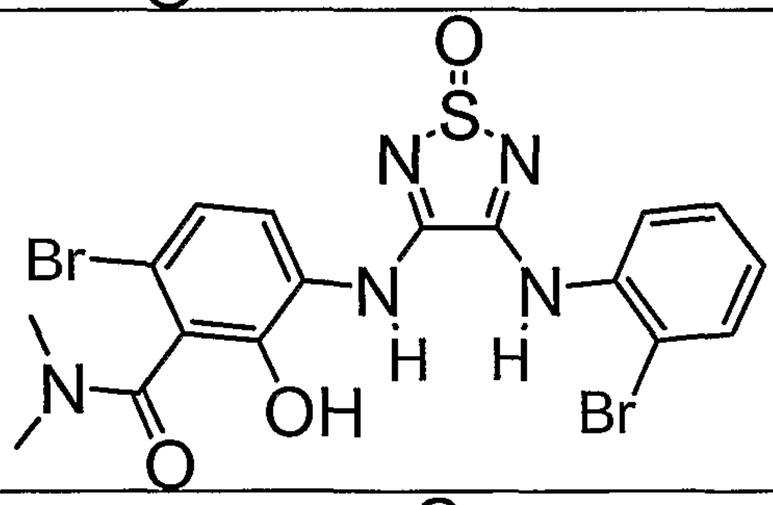
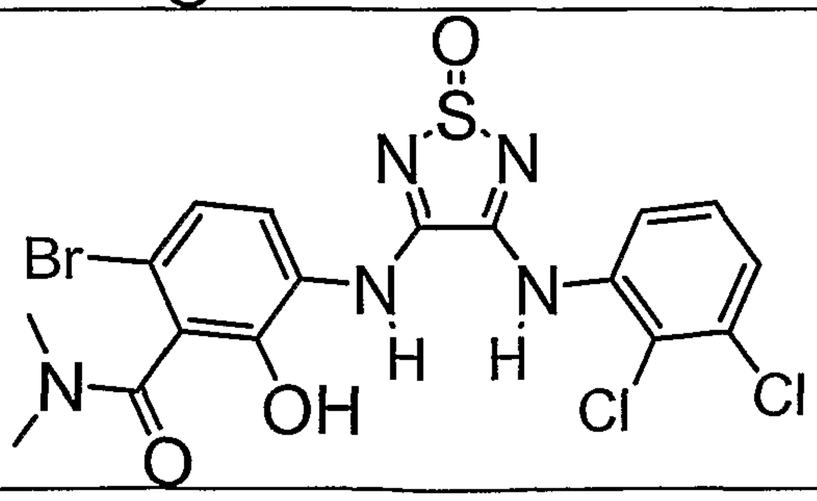
PREPARATIVE EXAMPLES 2400-3087

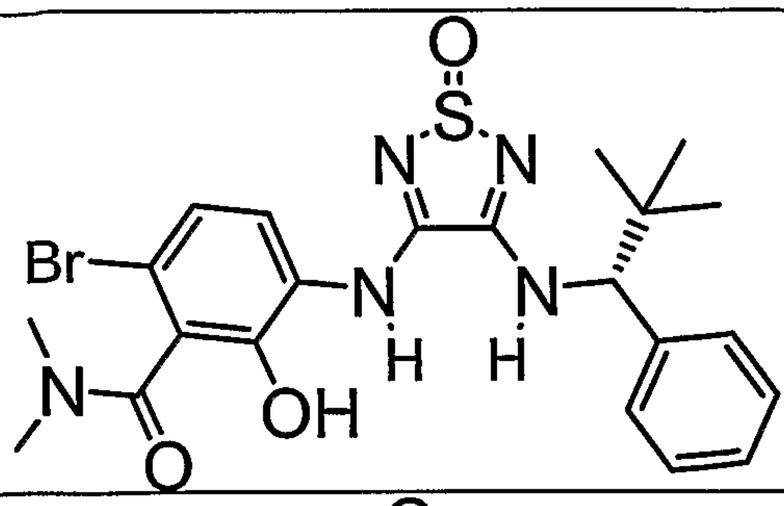
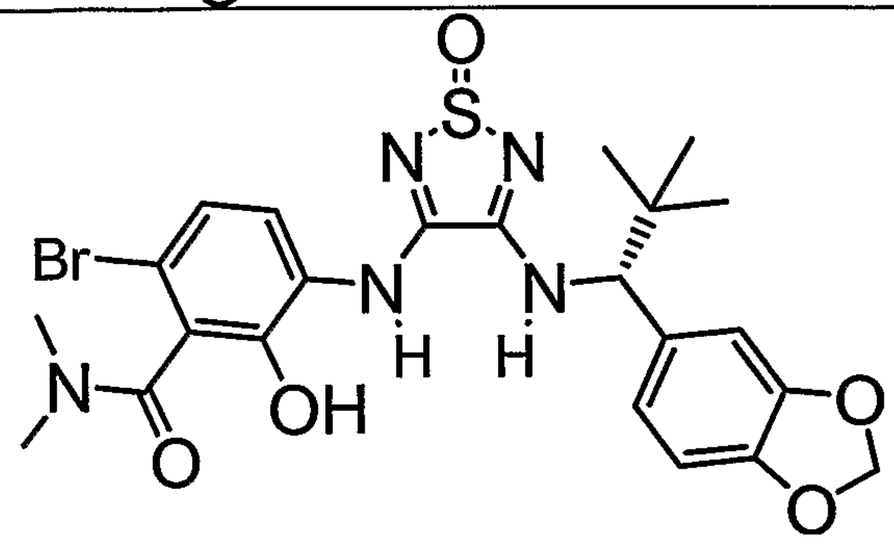
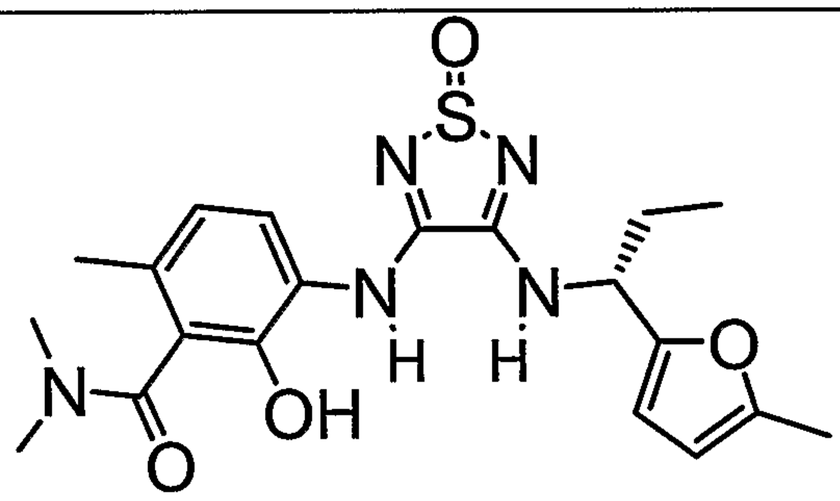
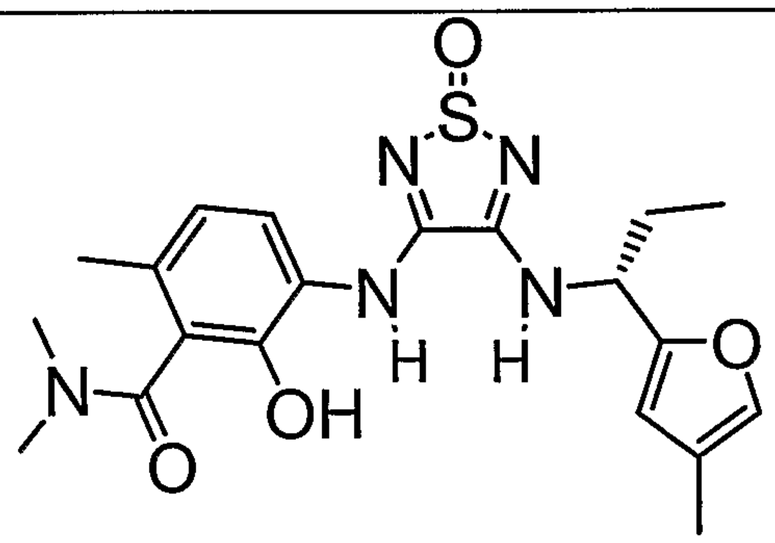
If one were to follow a procedure similar to that set forth in Preparative Example 2201A, but using the amines from the Preparative Examples indicated in the Table below (or the commercially available amines indicated in the Table below), and the thiadiazoleoxide intermediates from the Preparative Examples indicated in the Table below and stirring the reaction mixtures at room temperature up to reflux, the thiadiazoleoxide products in the Table below could be obtained.

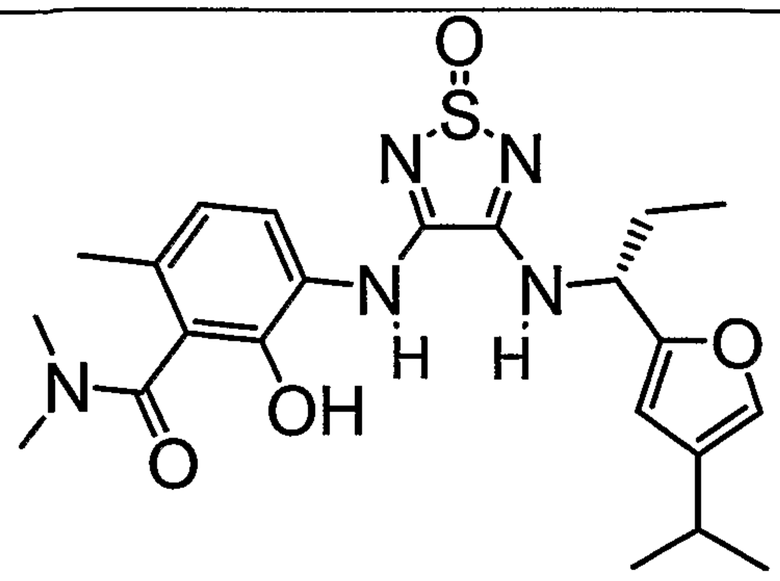
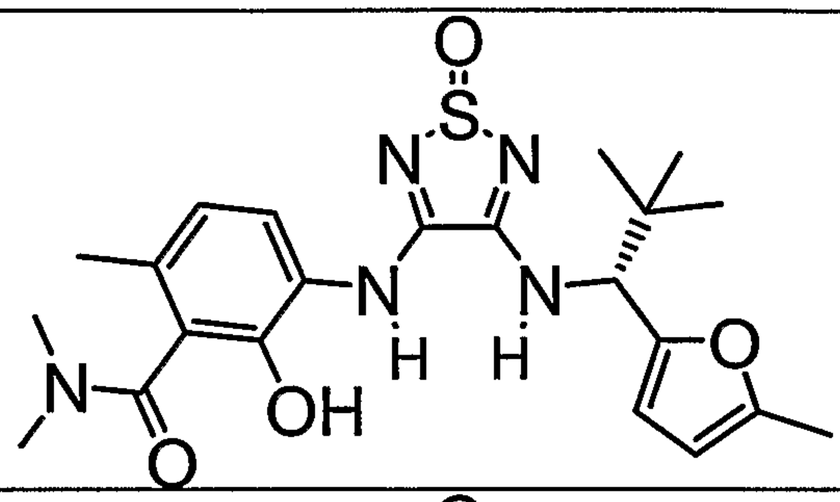
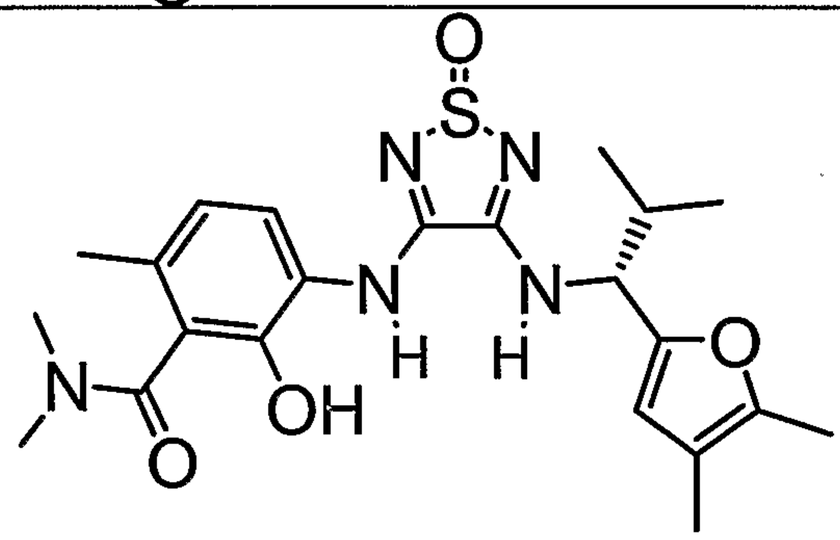
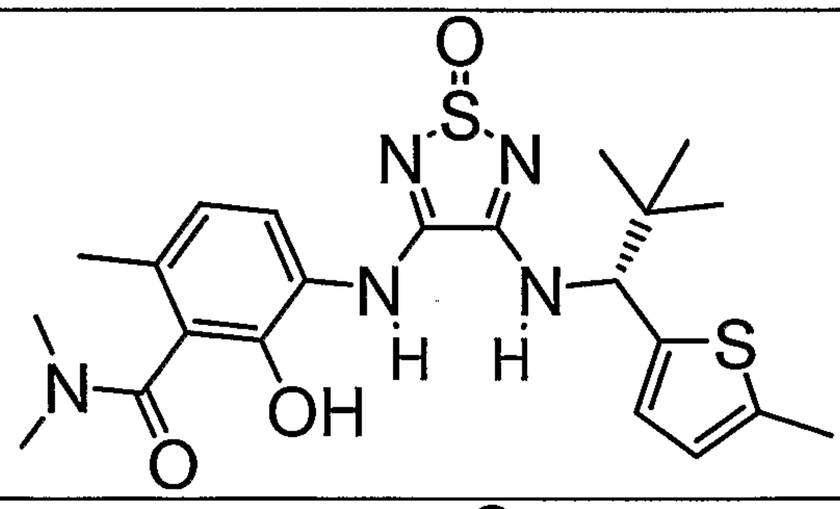
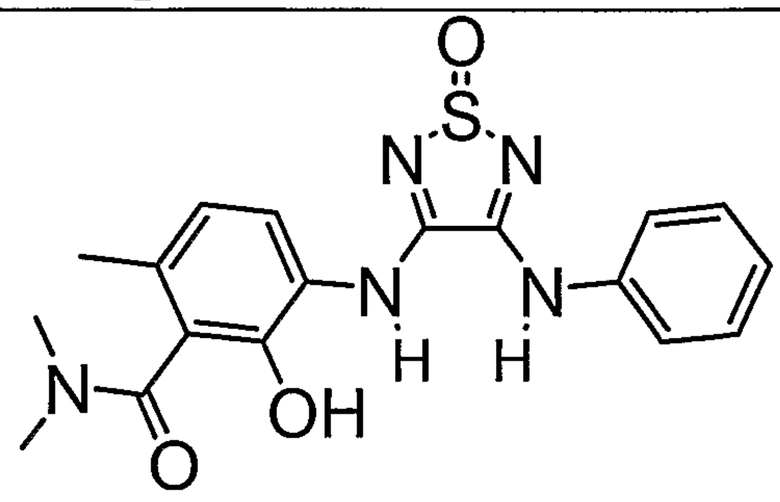
Prep Ex.	Prep Ex	Prep Ex (Amine)	Product
2401	160	75.20	
2402	160	2-Bromo-PhNH2	
2403	160	2,3-Dichloro-PhNH2	
2404	161	75.49	
2405	161	75.9	

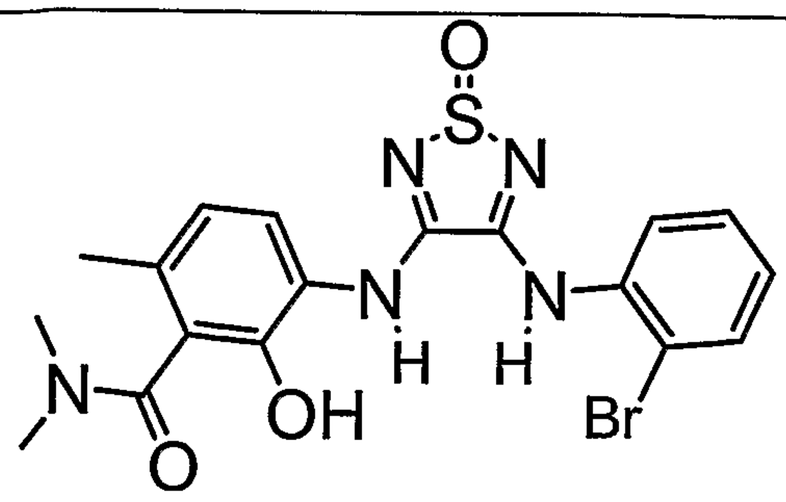
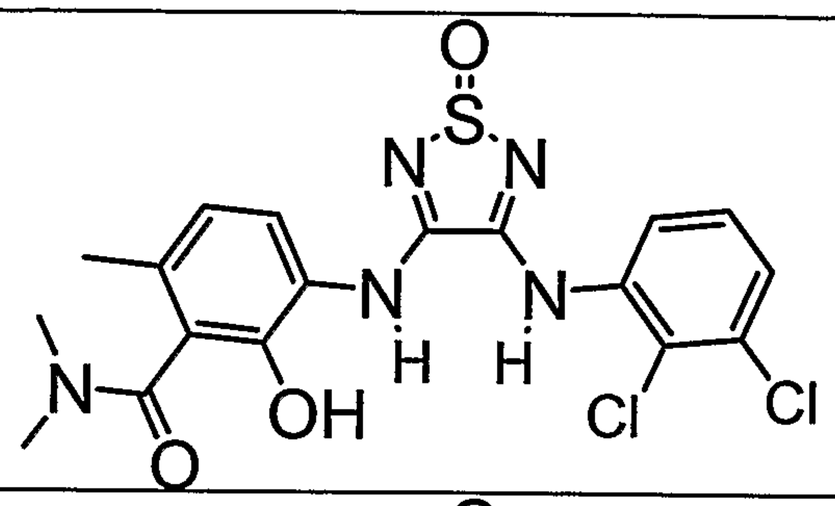
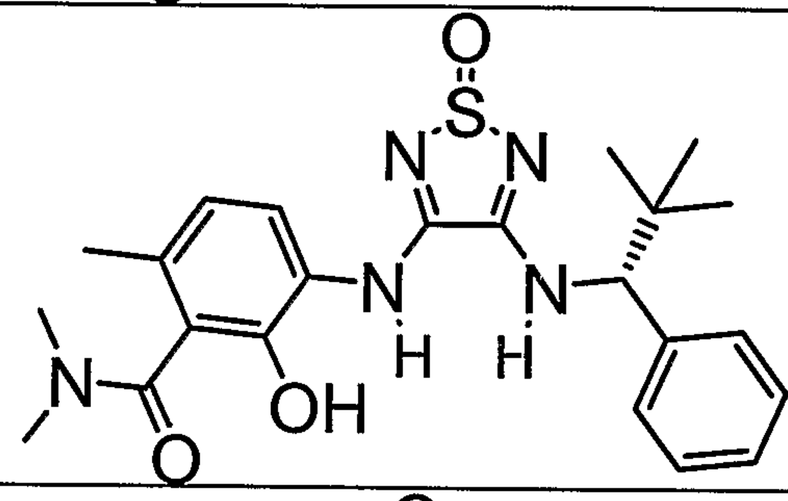
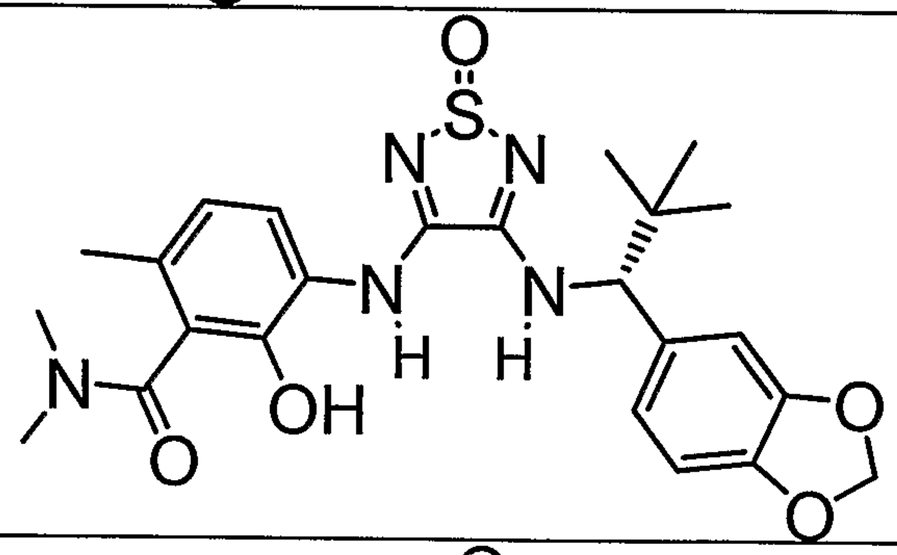
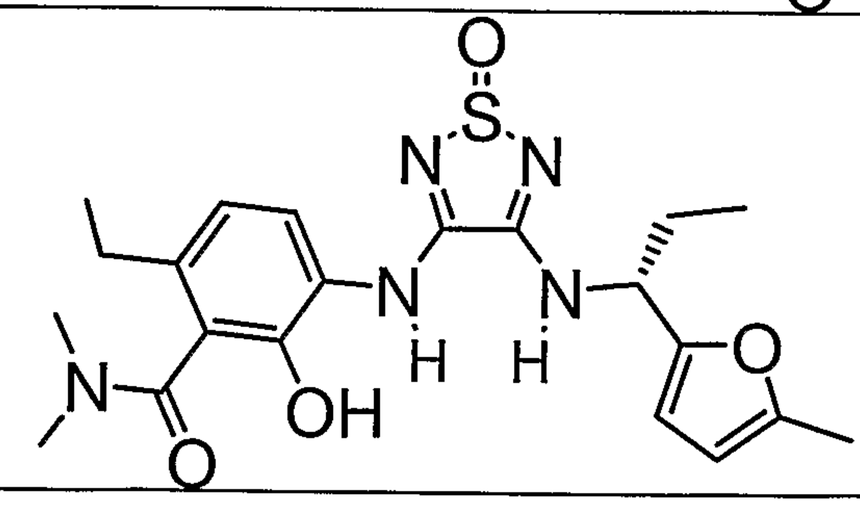
2406	161	75.44	
2408	161	75.20	
2409	161	PhNH2	
2410	161	2-Bromo-PhNH2	
2411	161	2,3-Dichloro-PhNH2	

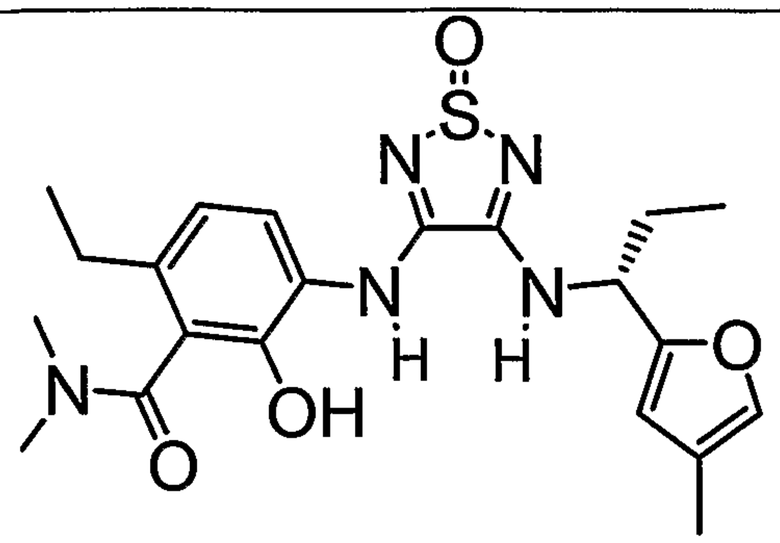
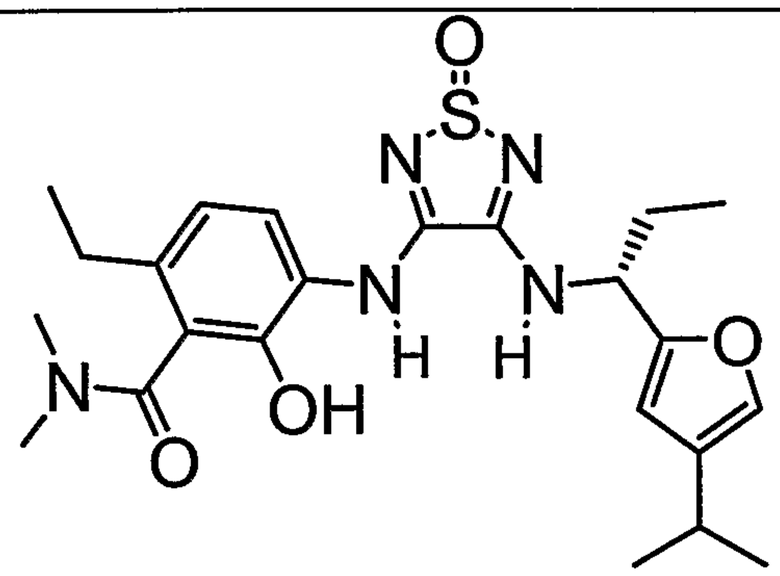
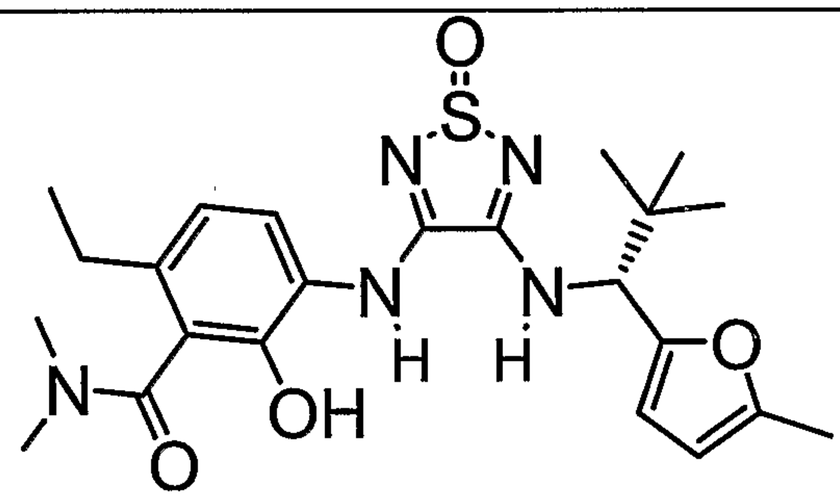
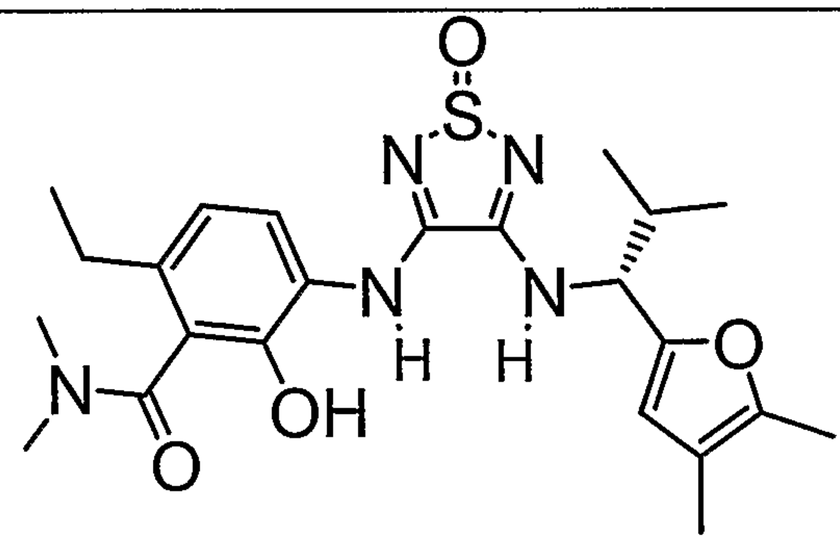
2412	161	74	
2413	161	75.60	
2414	162	75.61	
2415	162	75.49	
2416	162	75.9	

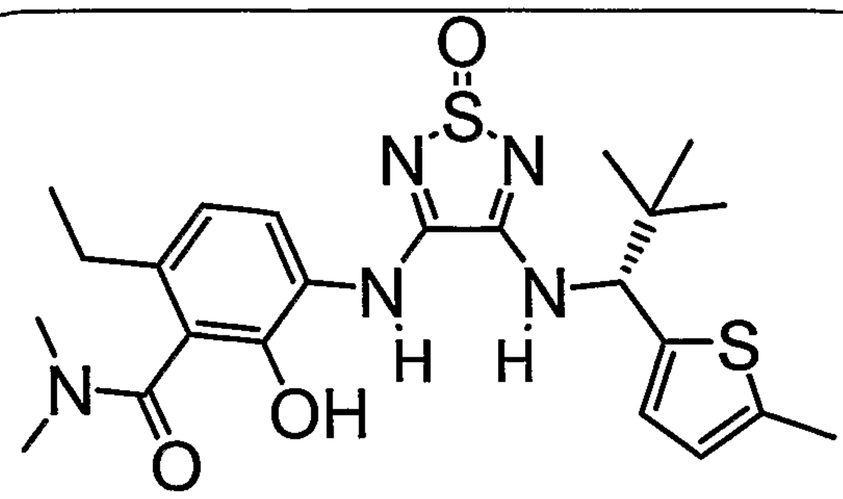
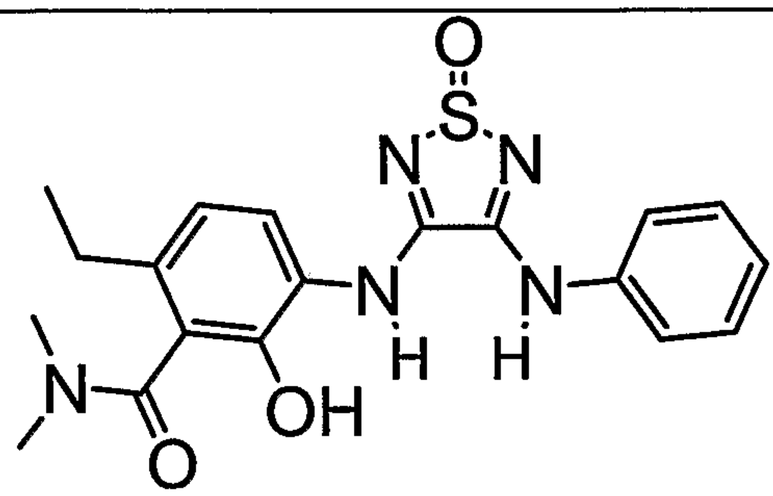
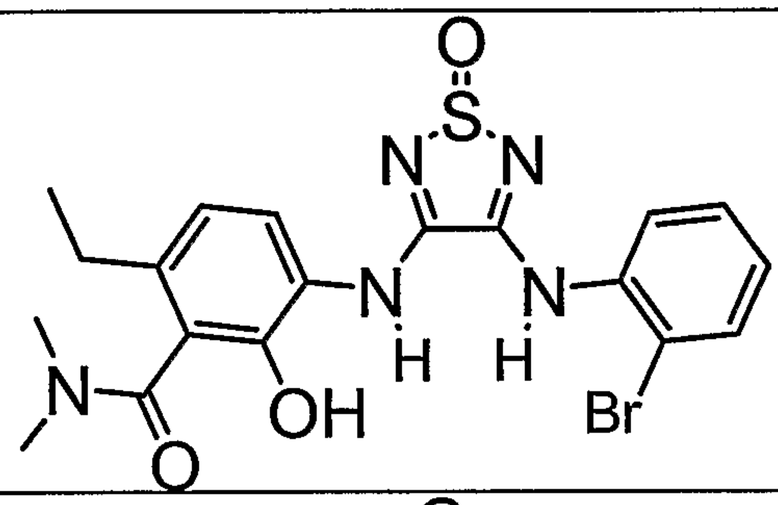
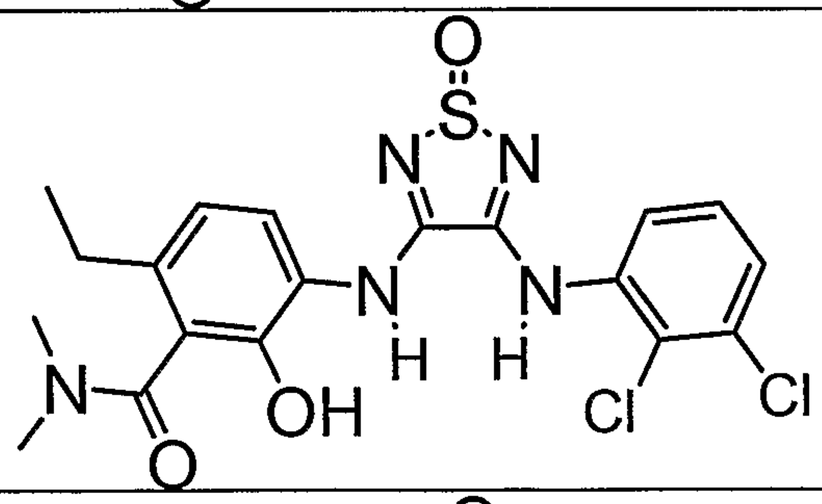
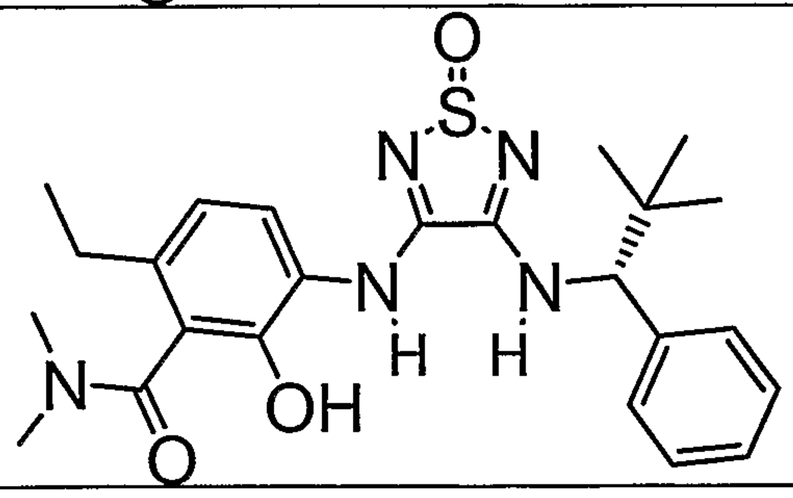
2417	162	75.44	
2418	162	75.61	
2419	162	75.20	
2420	162	PhNH2	
2421	162	2-Bromo-PhNH2	
2422	162	2,3-Dichloro-PhNH2	

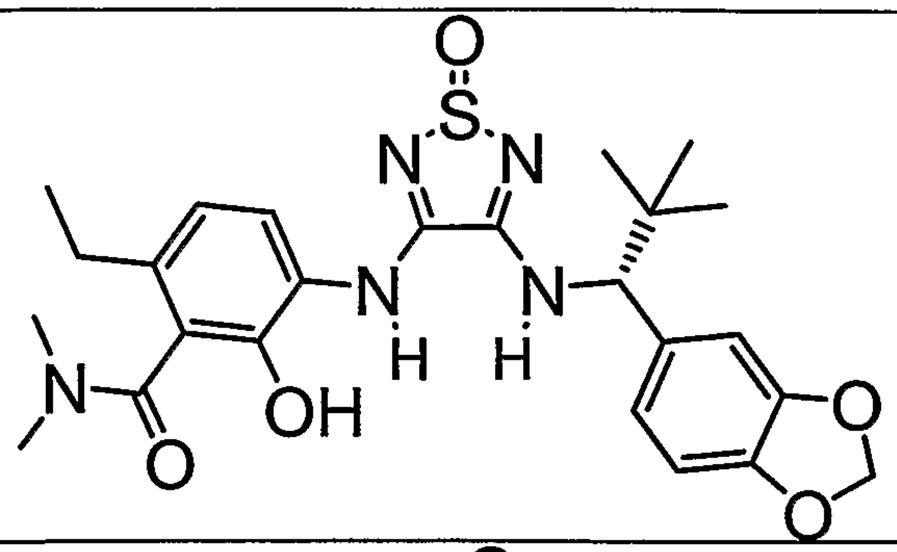
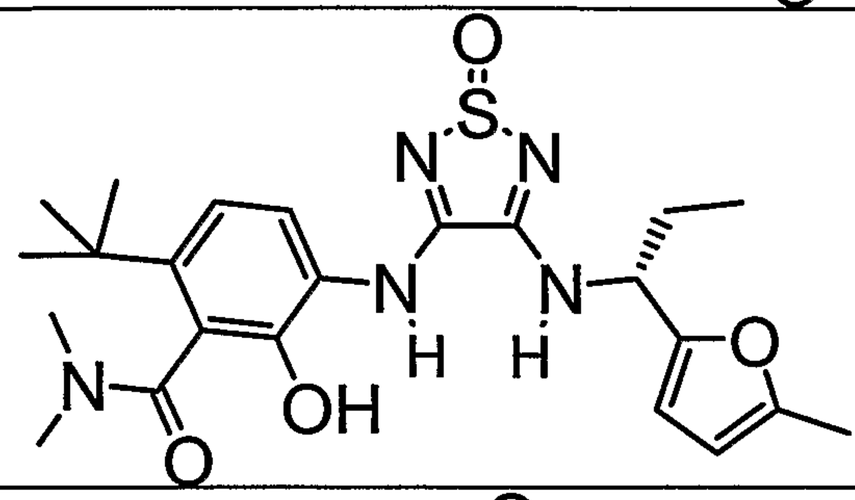
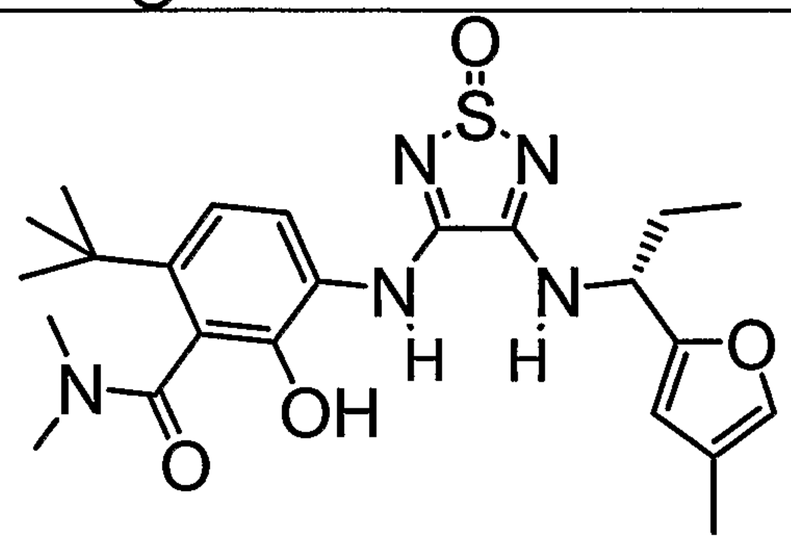
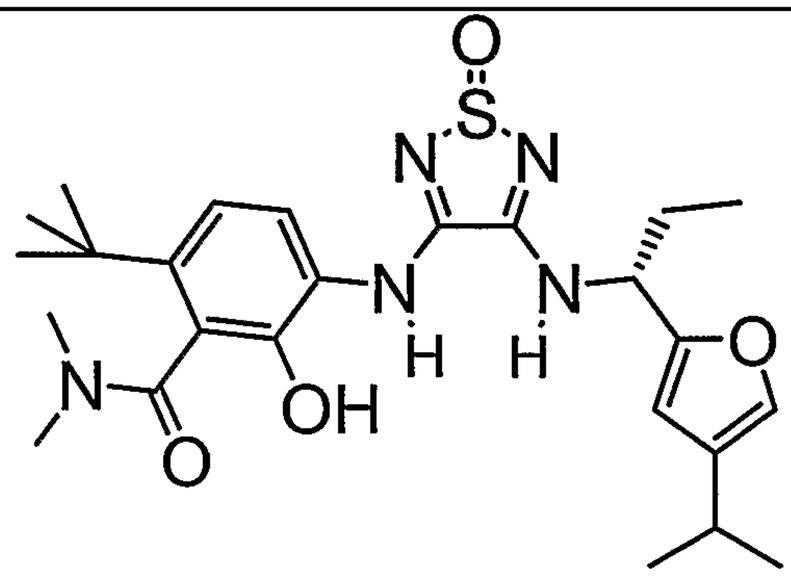
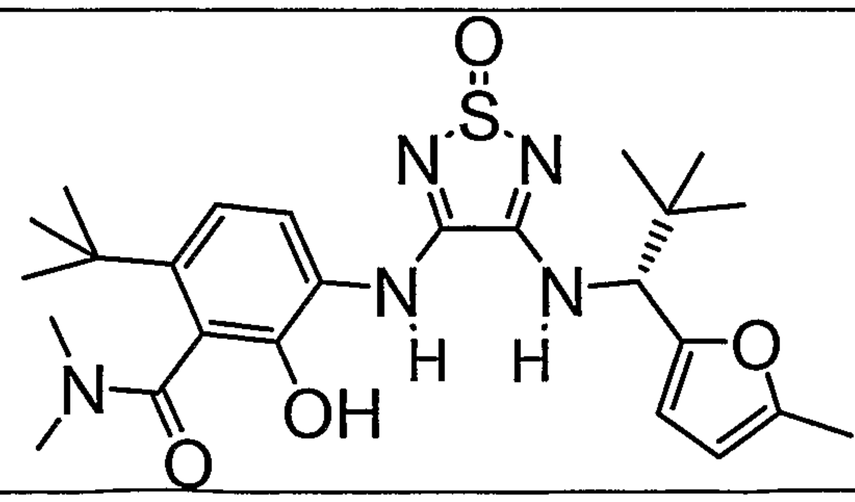
2423	162	74	
2424	162	75.60	
2425	163	75.1	
2426	163	75.49	

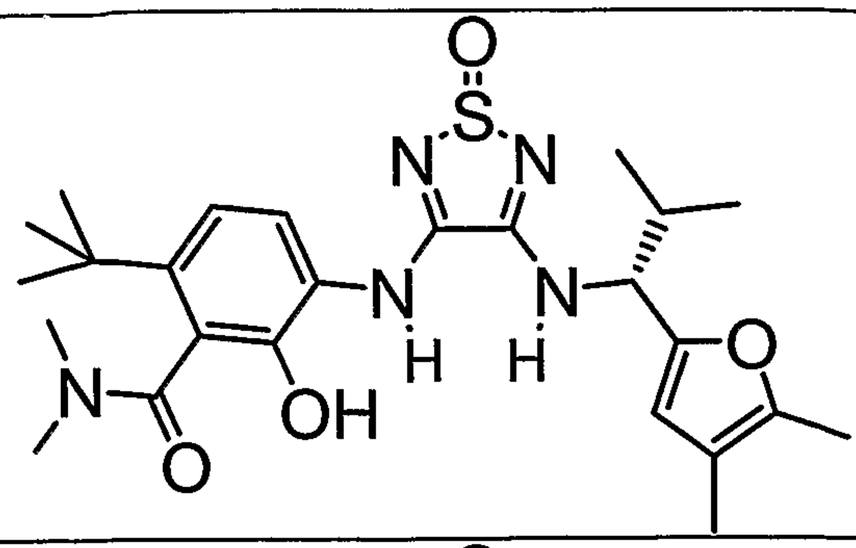
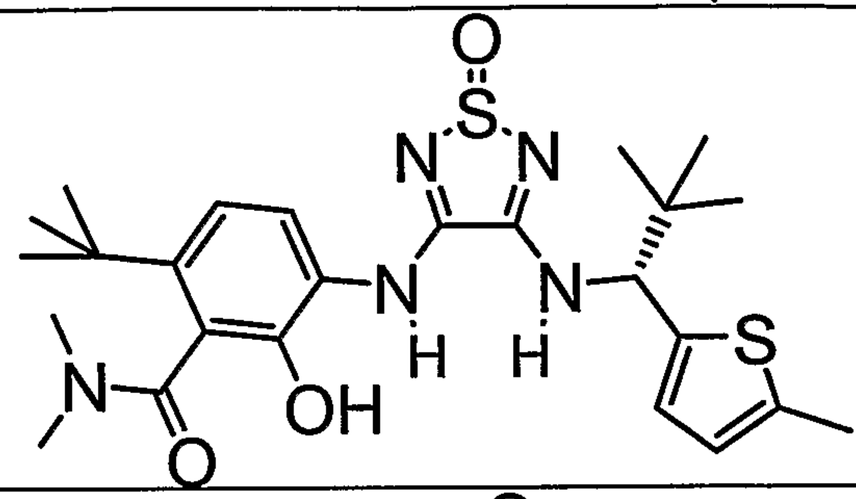
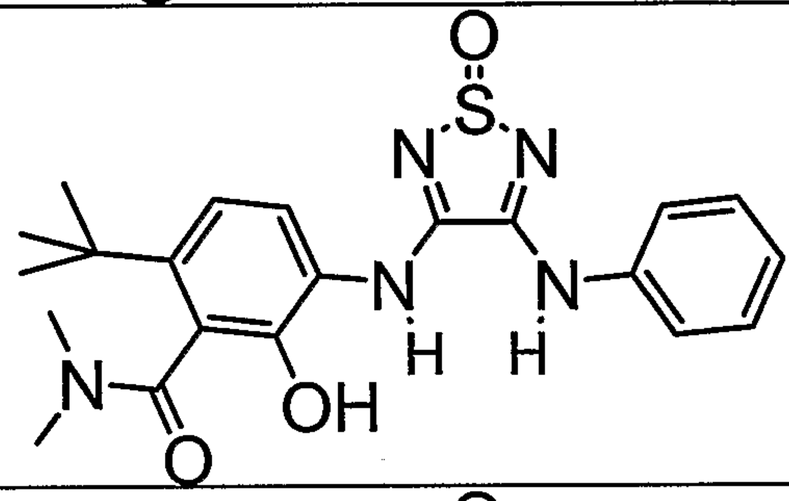
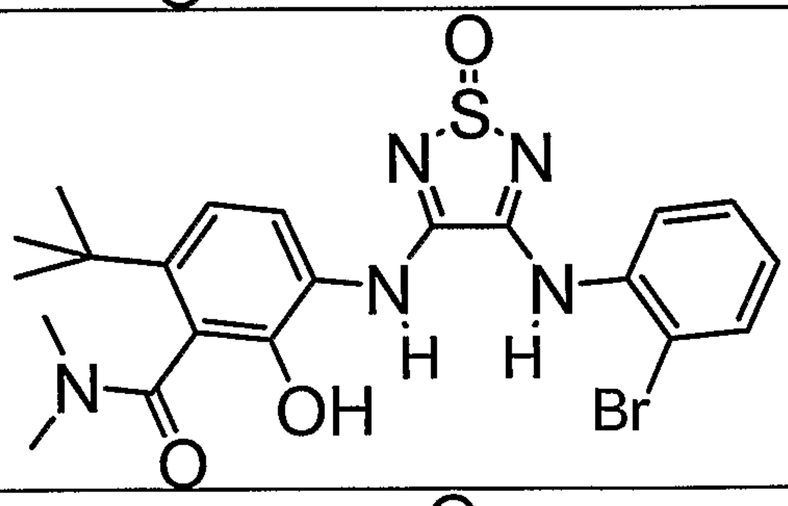
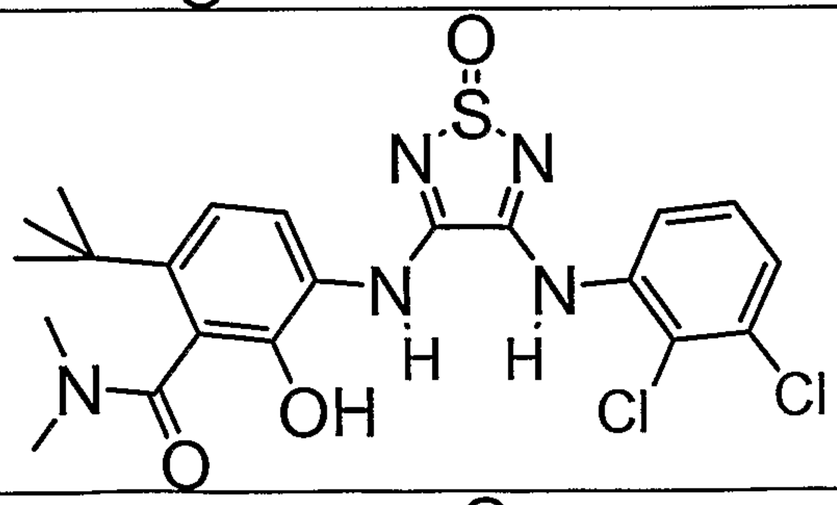
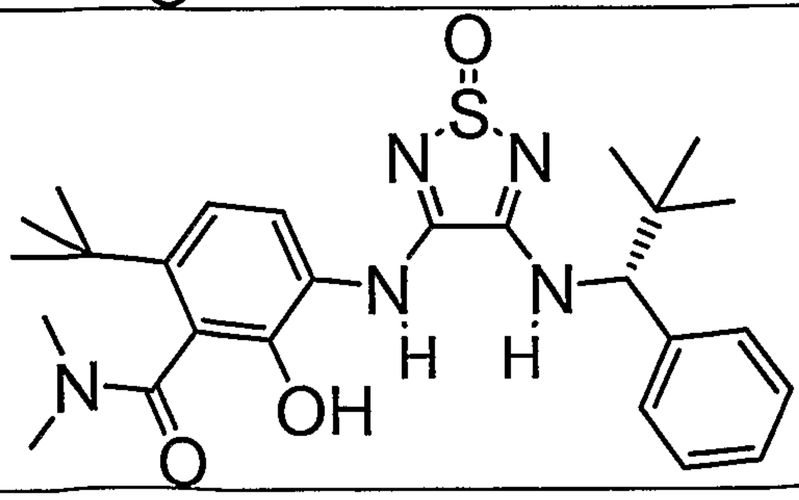
2427	163	75.9	
2428	163	75.44	
2429	163	75.61	
2430	163	75.20	
2431	163	PhNH2	

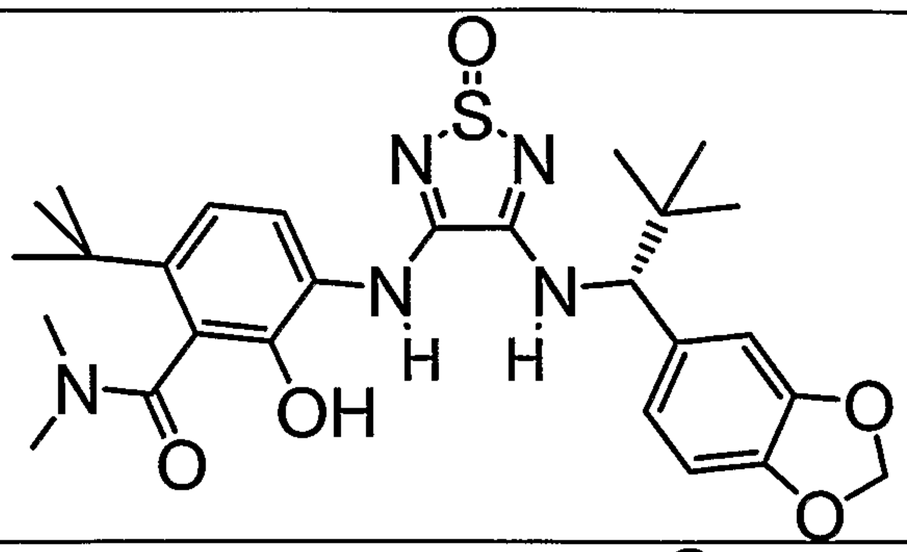
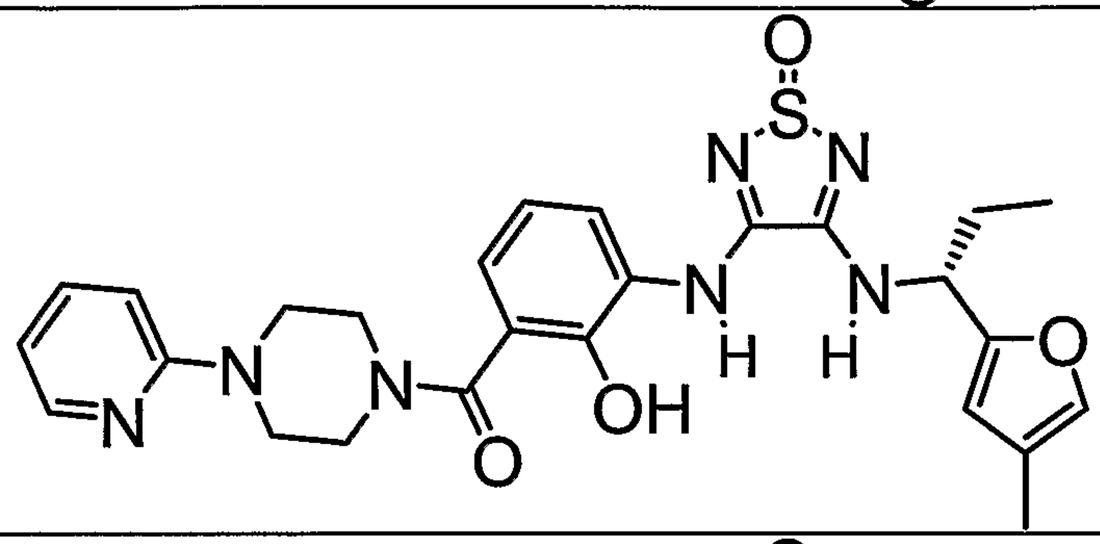
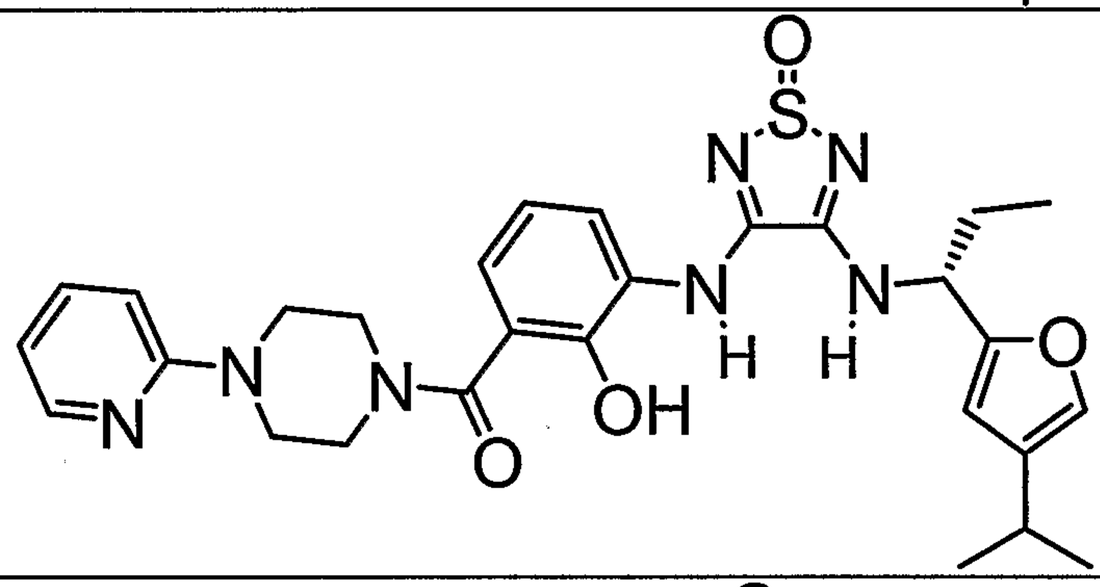
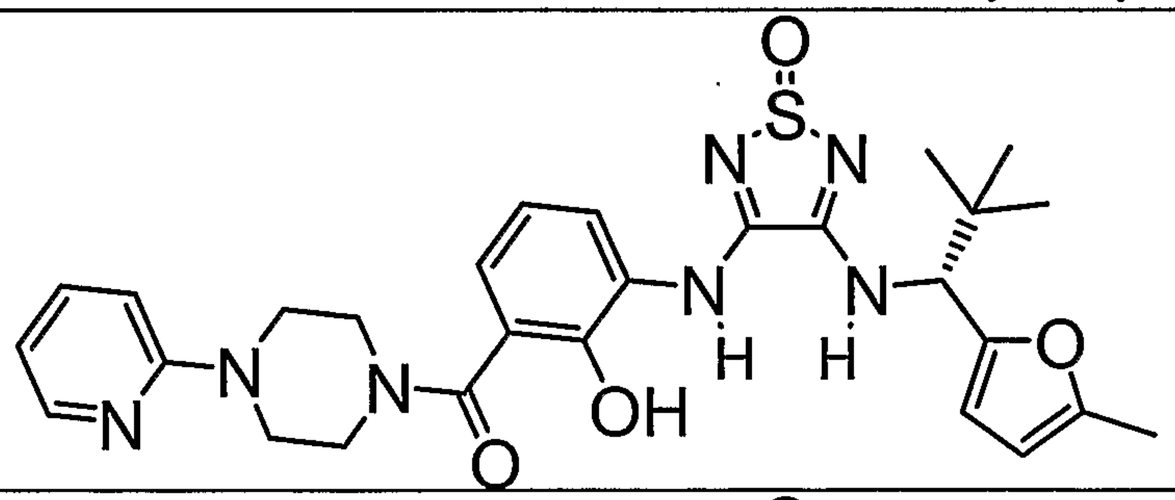
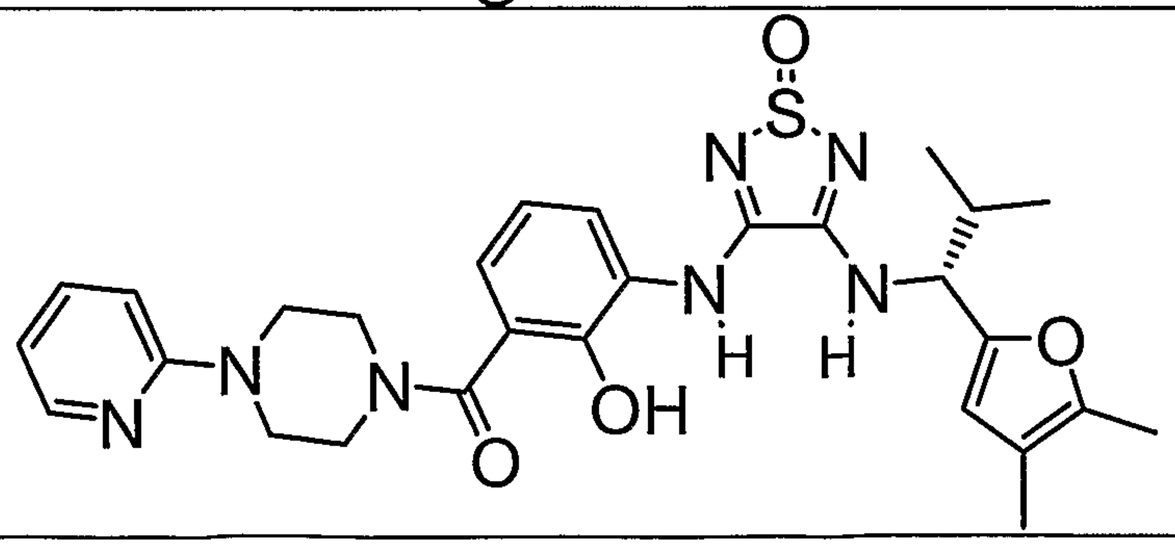
2432	163	2-Bromo-PhNH2	
2433	163	2,3-Dichloro-PhNH2	
2434	163	74	
2435	163	75.60	
2436	164	75.1	

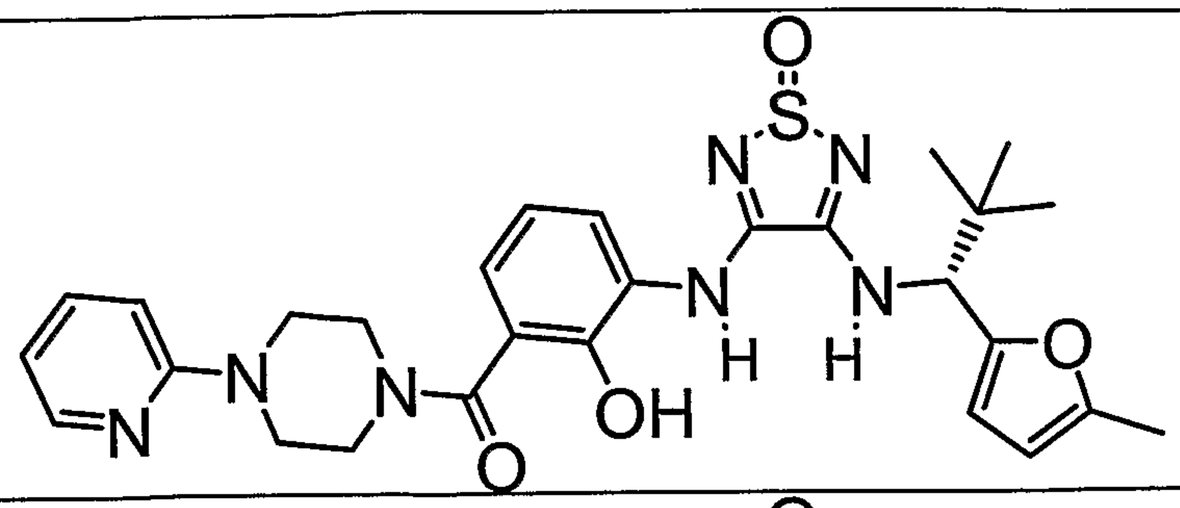
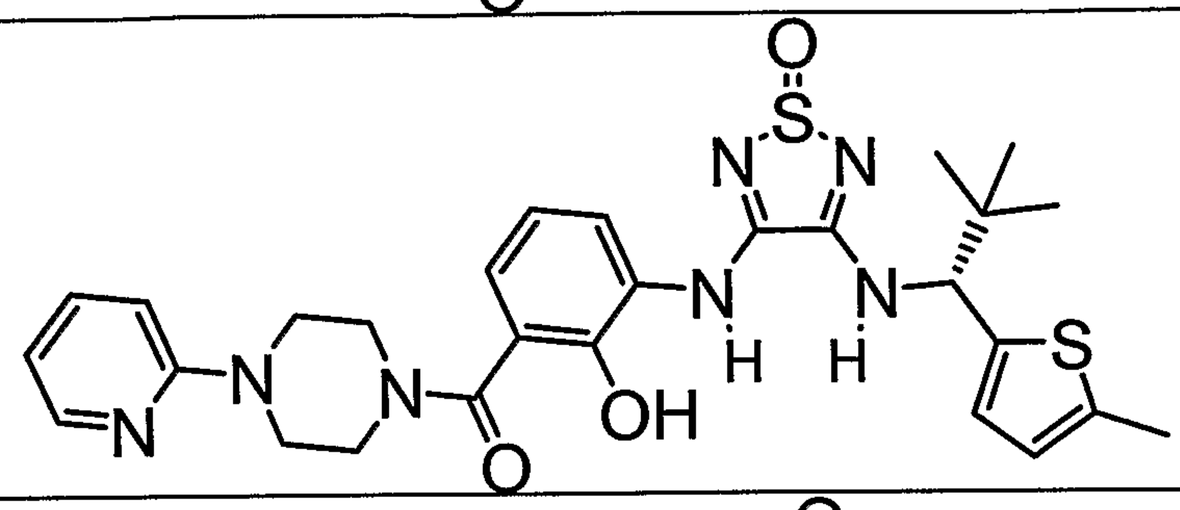
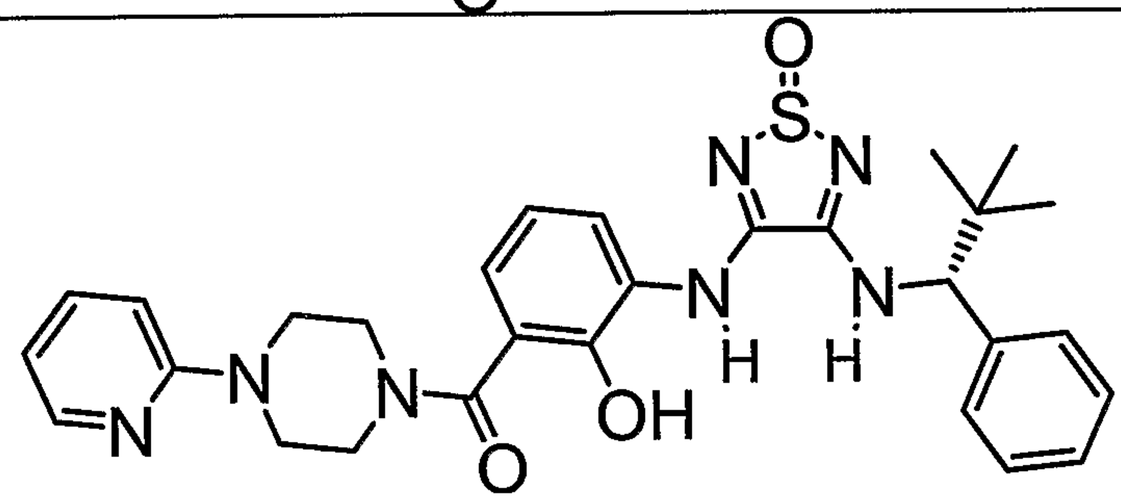
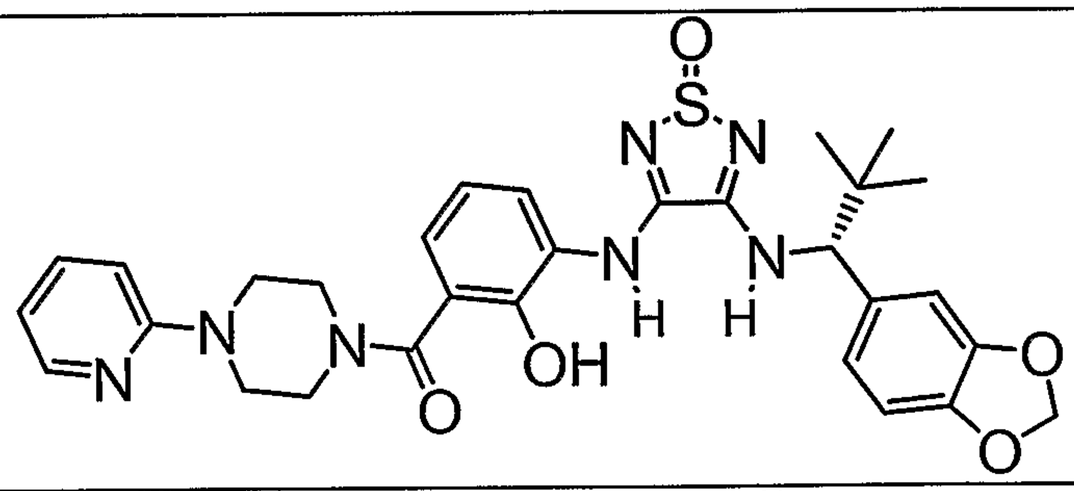
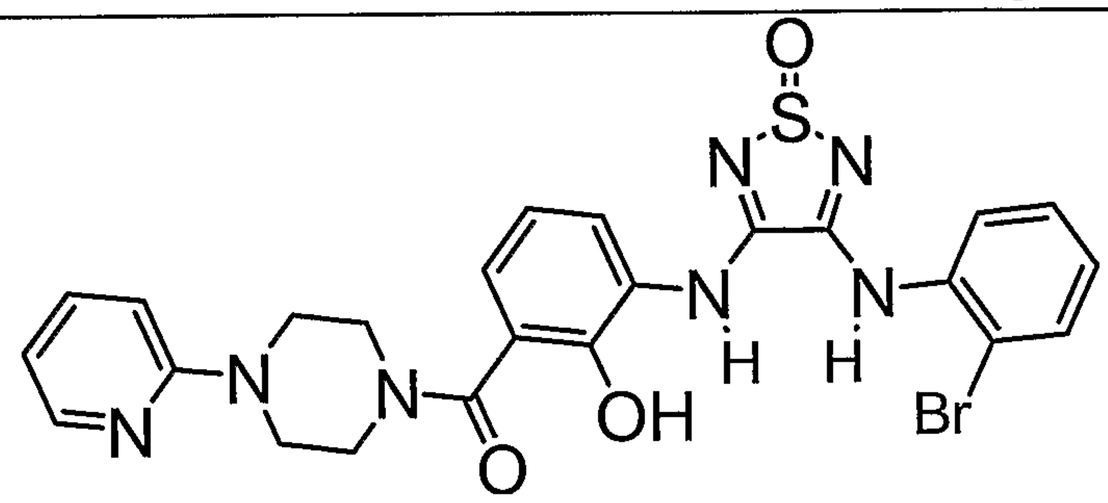
2437	164	75.49	
2438	164	75.9	
2439	164	75.44	
2440	164	75.61	

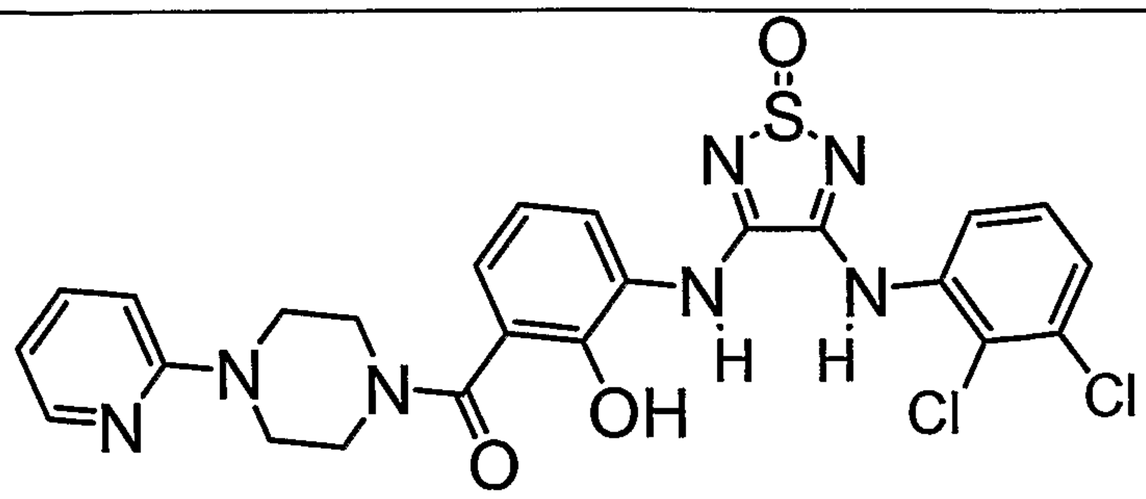
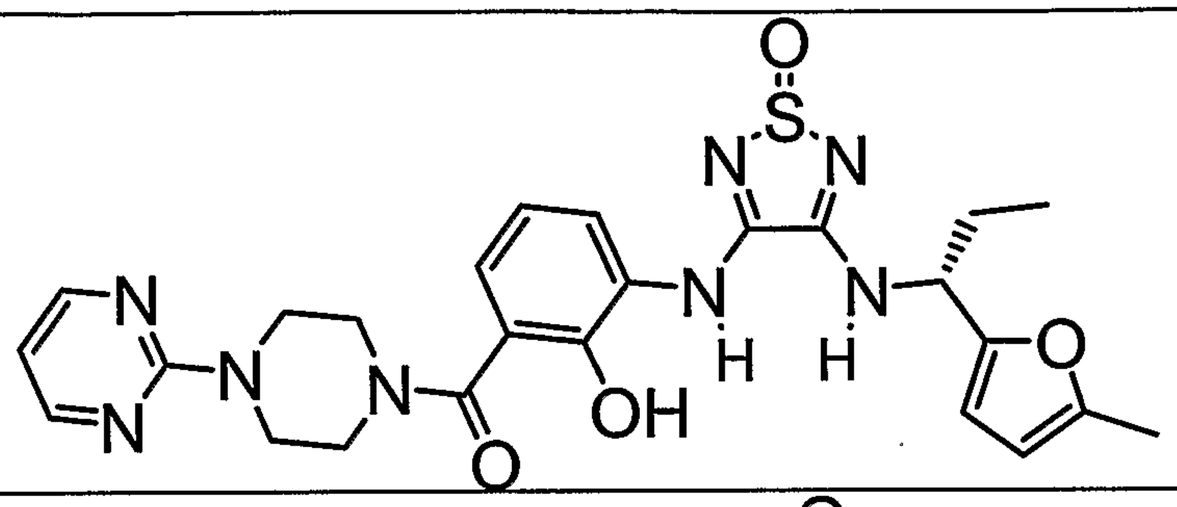
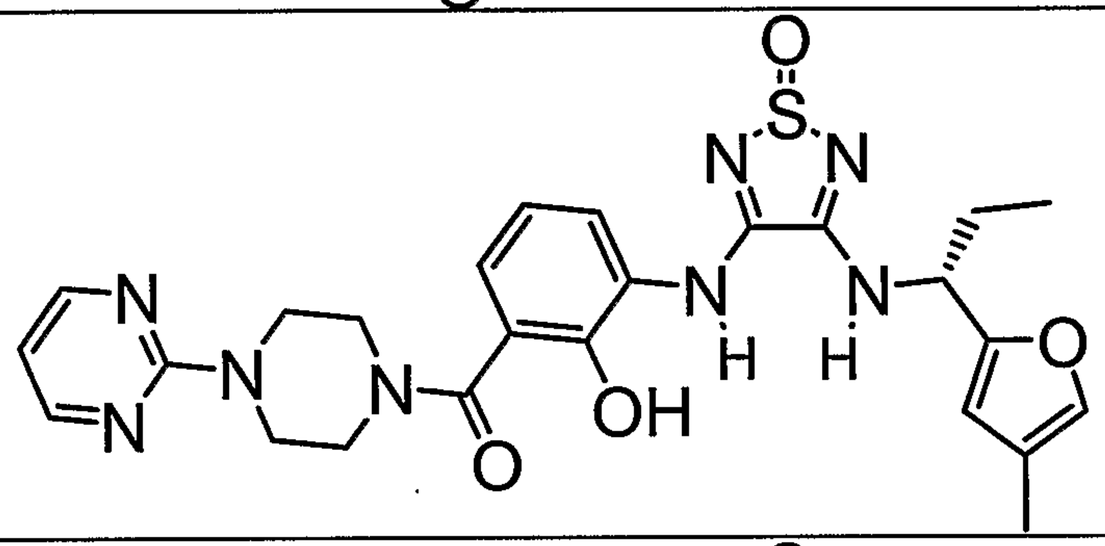
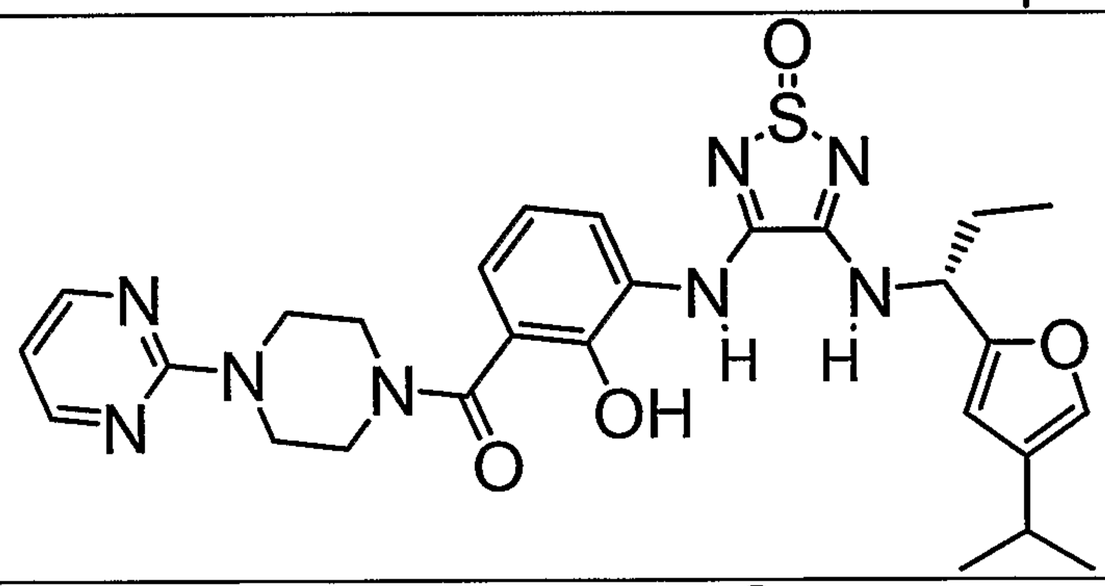
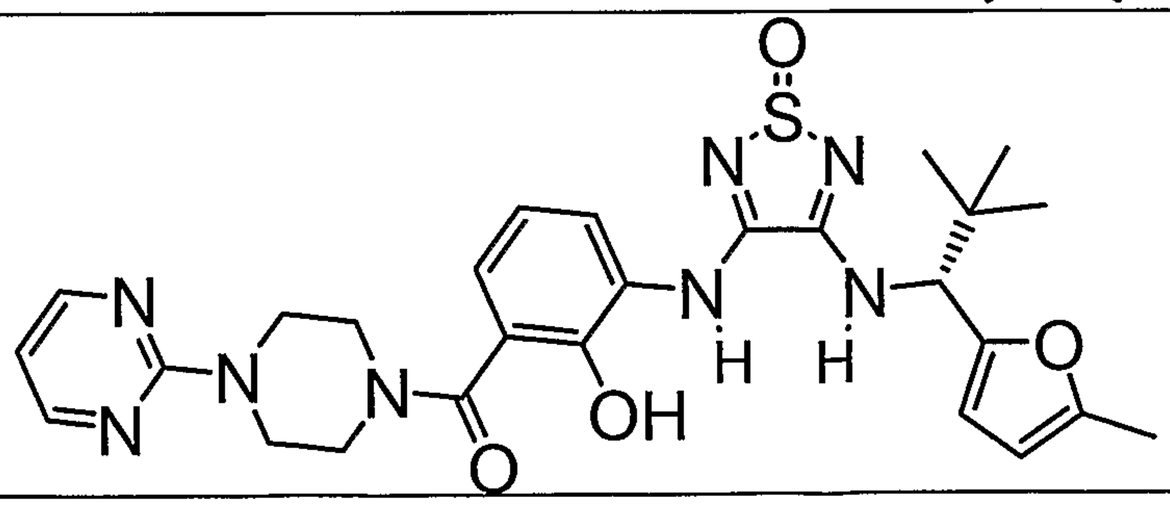
2441	164	75.20	
2442	164	PhNH2	
2443	164	2-Bromo-PhNH2	
2444	164	2,3-Dichloro-PhNH2	
2445	164	74	

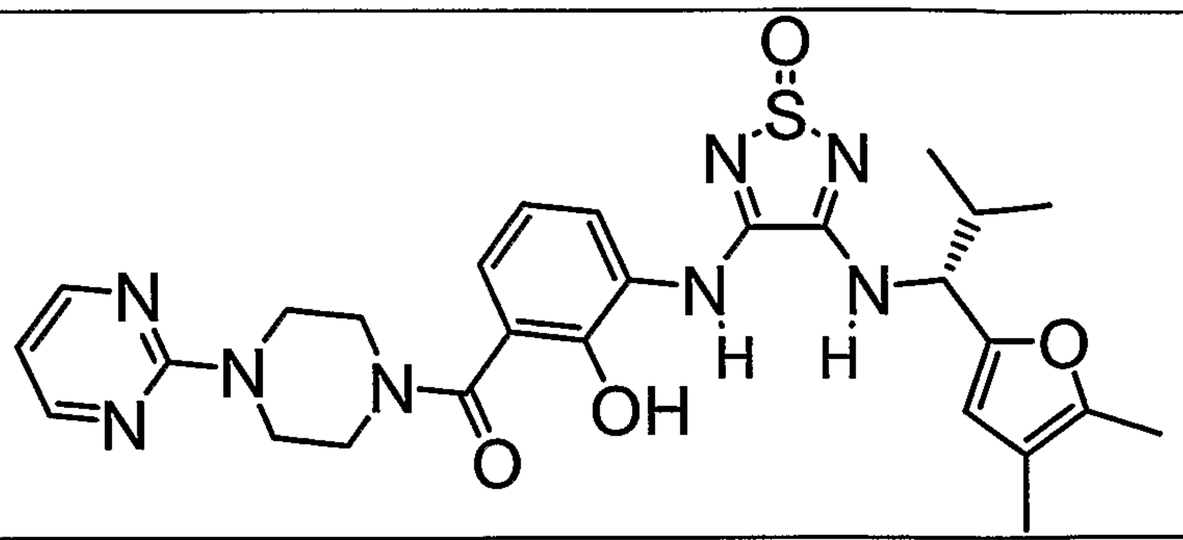
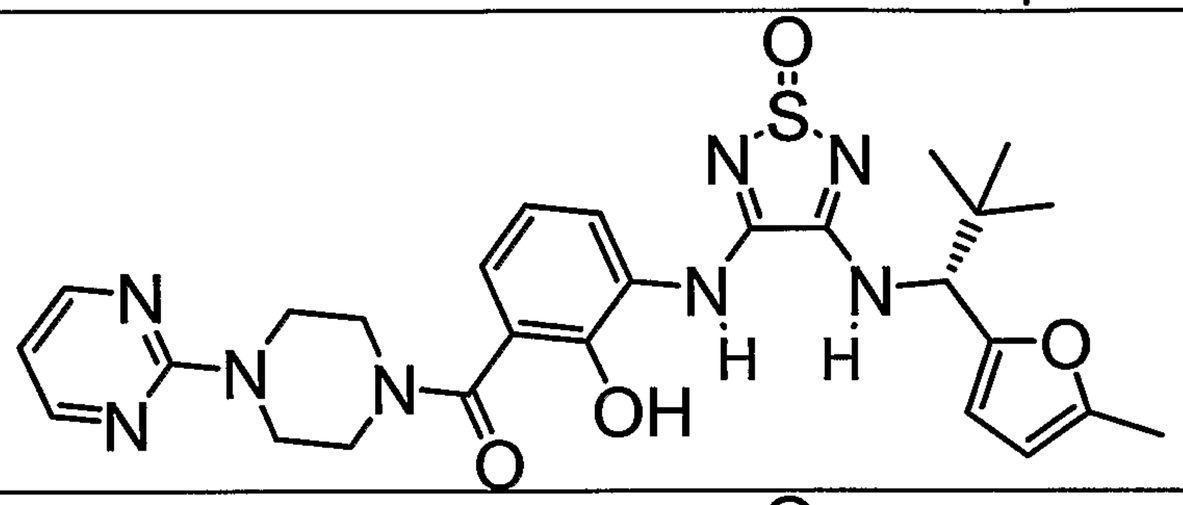
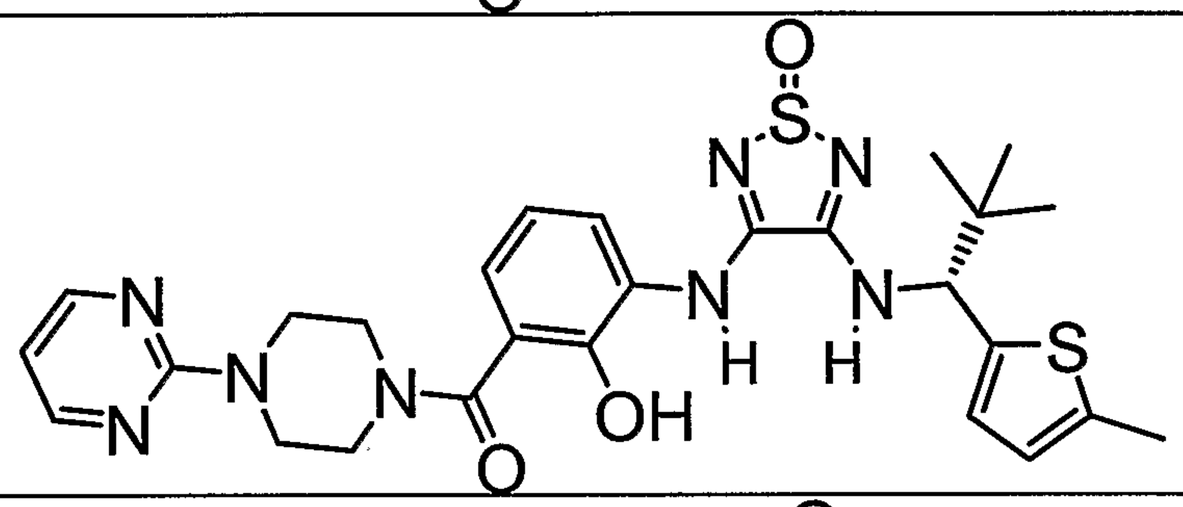
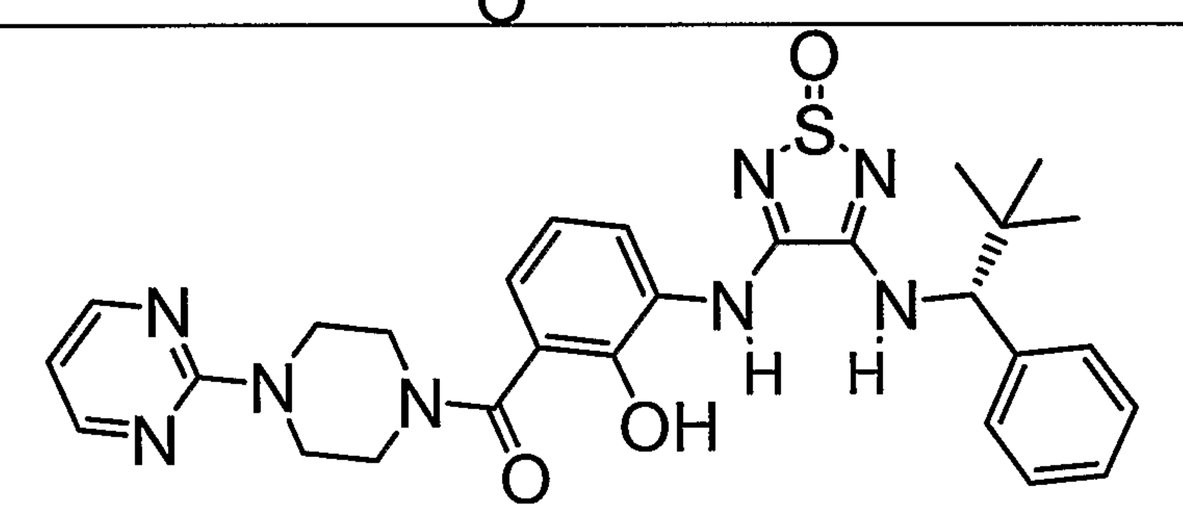
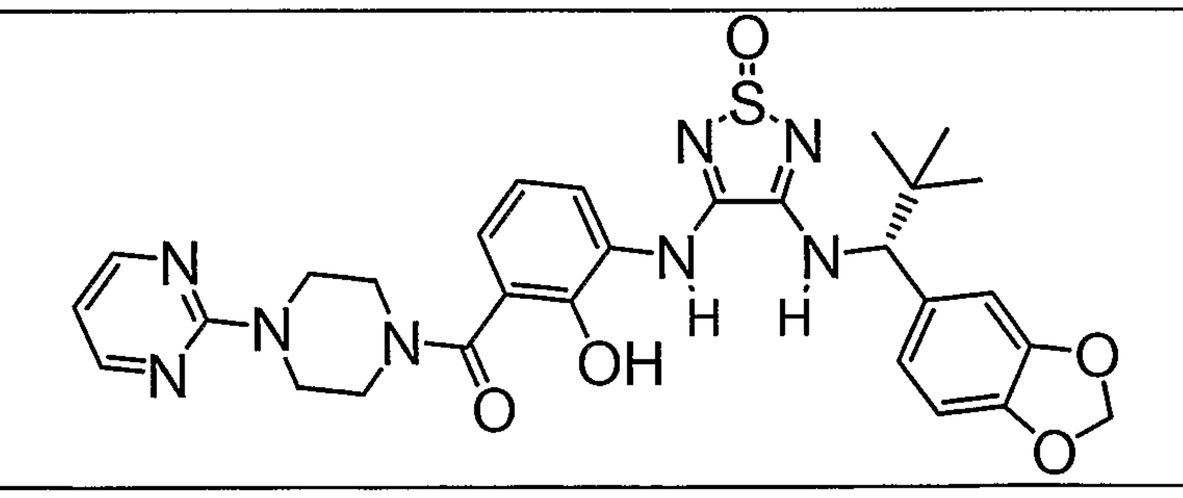
2446	164	75.60	
2447	165	75.1	
2448	165	75.49	
2449	165	75.9	
2450	165	75.44	

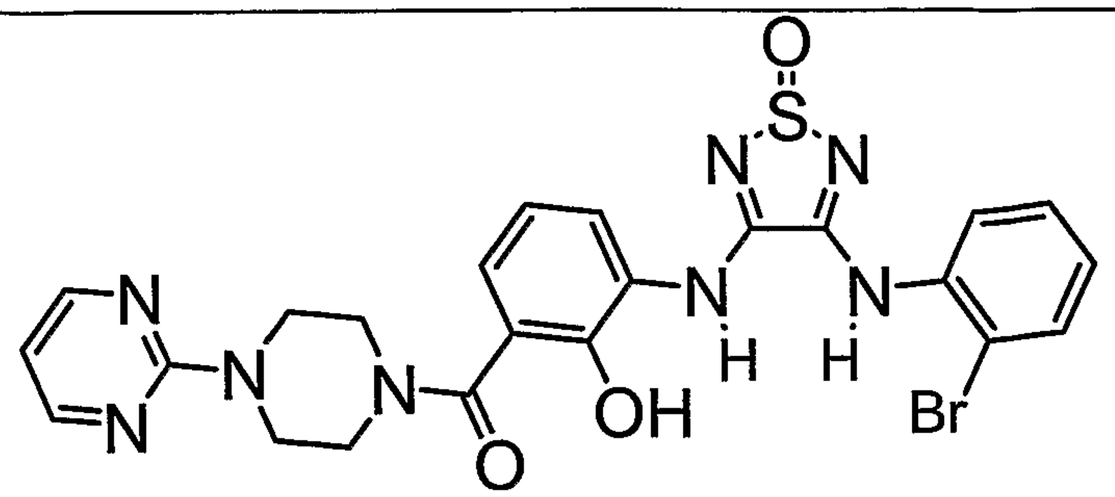
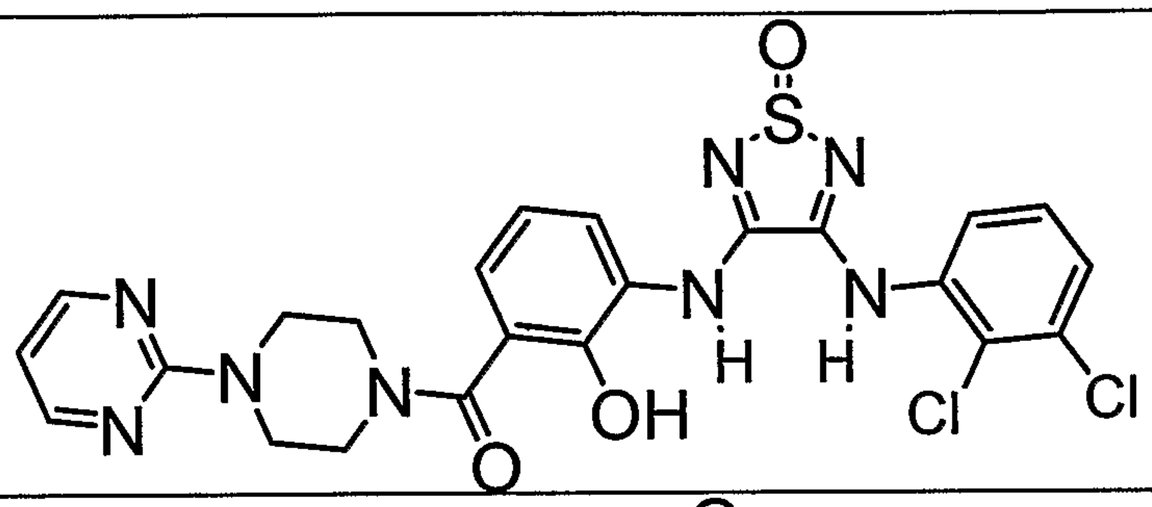
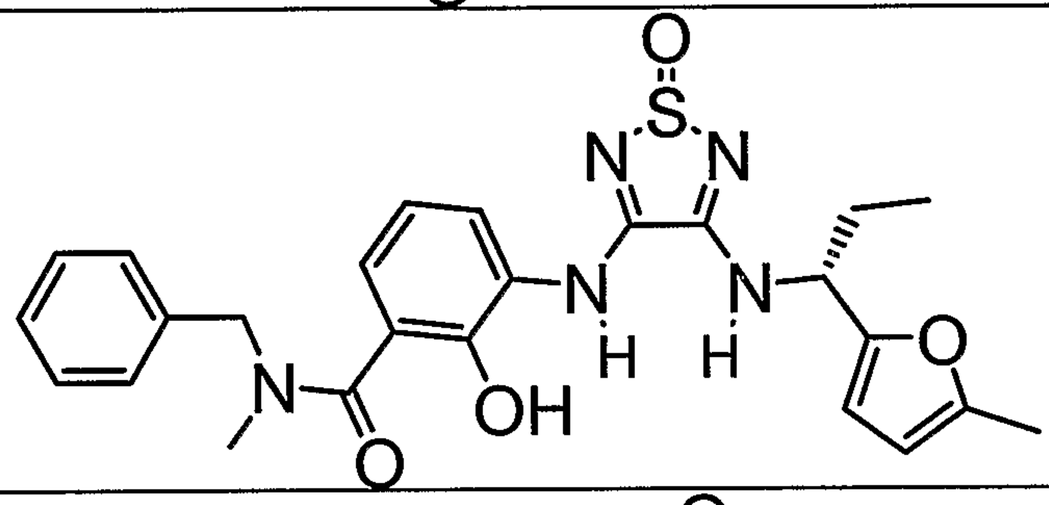
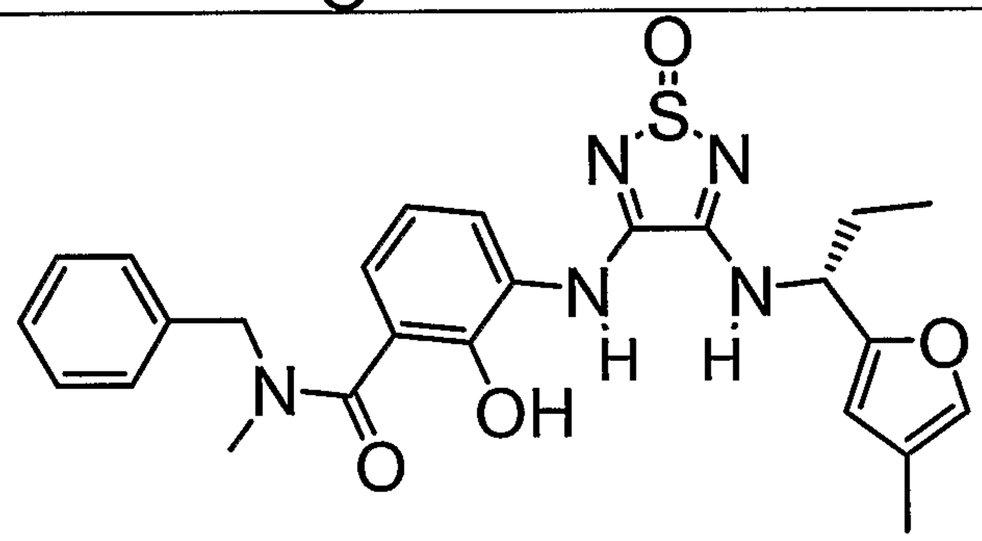
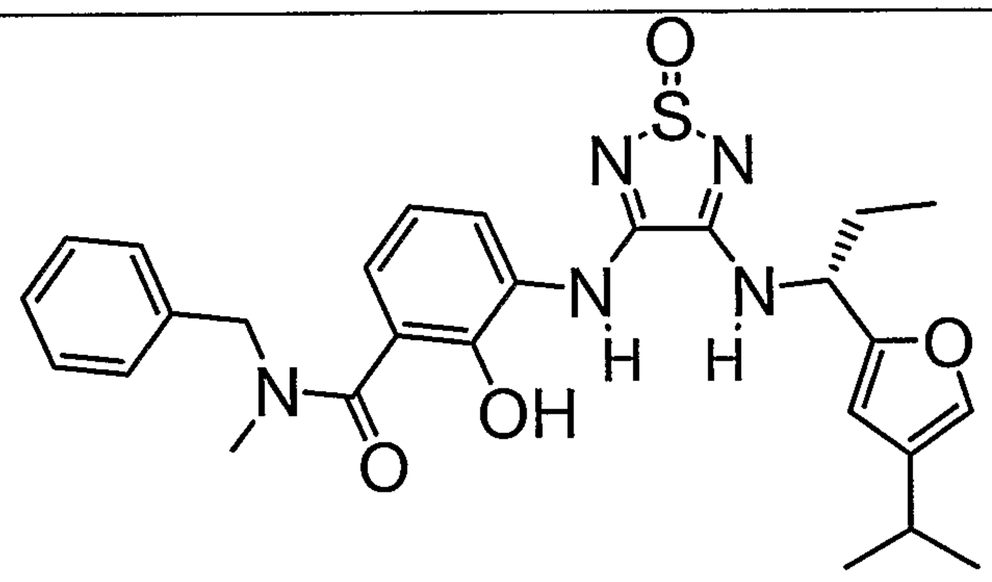
2451	165	75.61	
2452	165	75.20	
2453	165	PhNH2	
2454	165	2-Bromo-PhNH2	
2455	165	2,3-Dichloro-PhNH2	
2456	165	74	

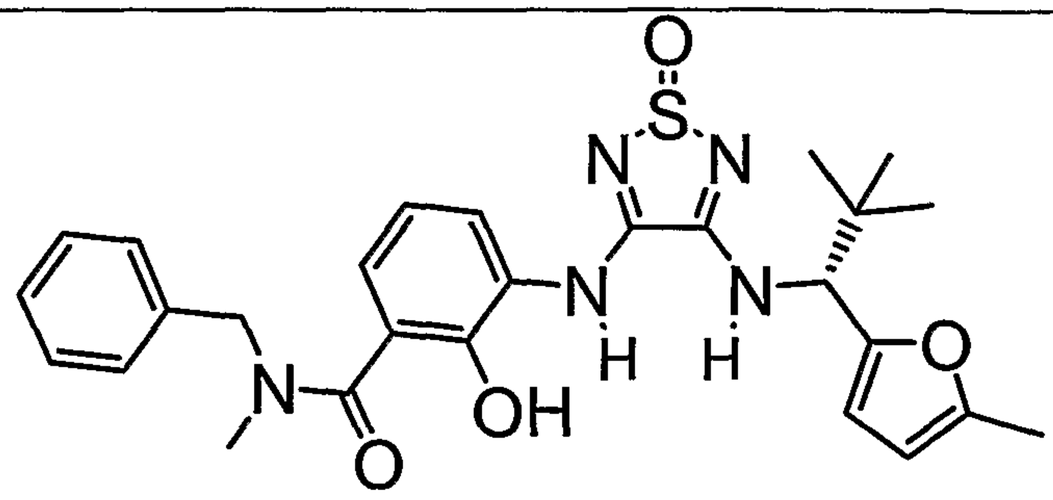
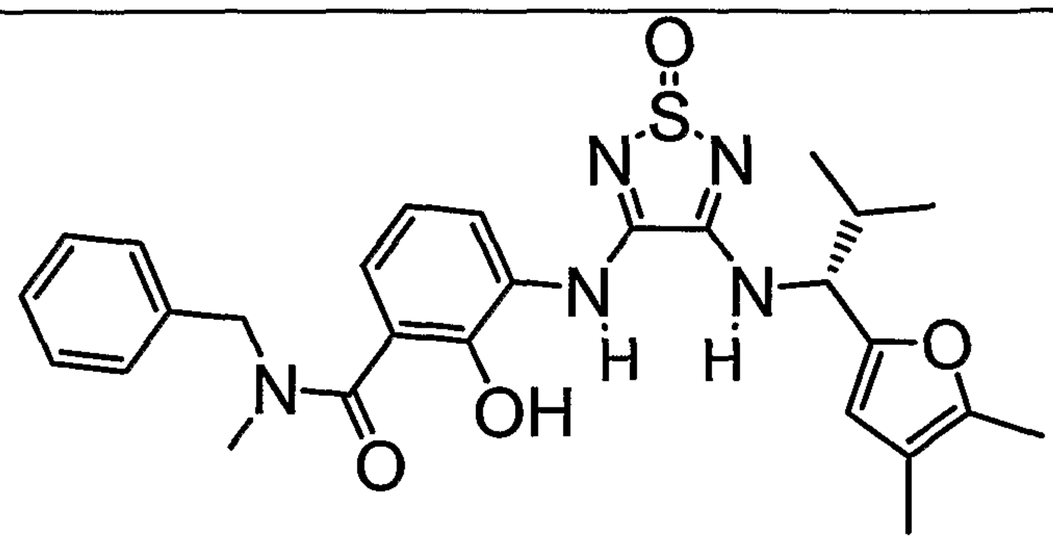
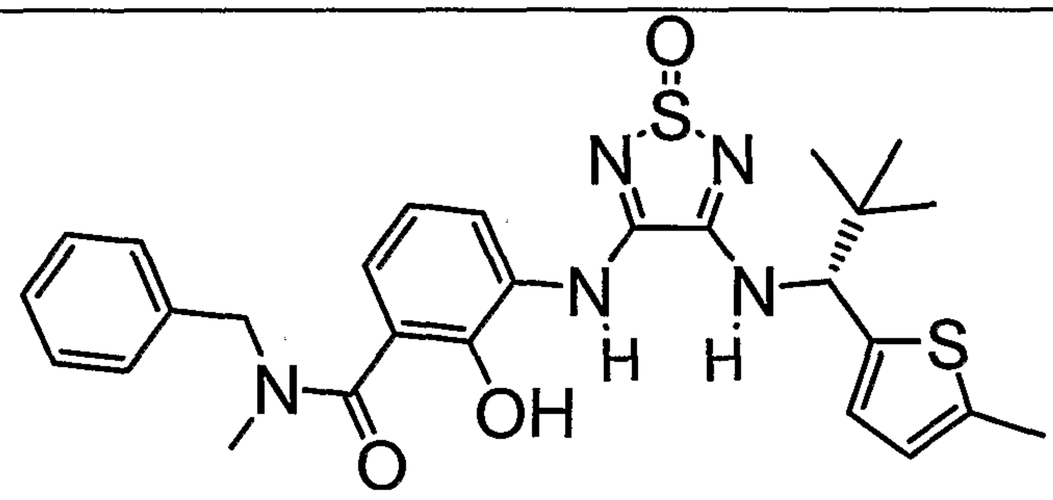
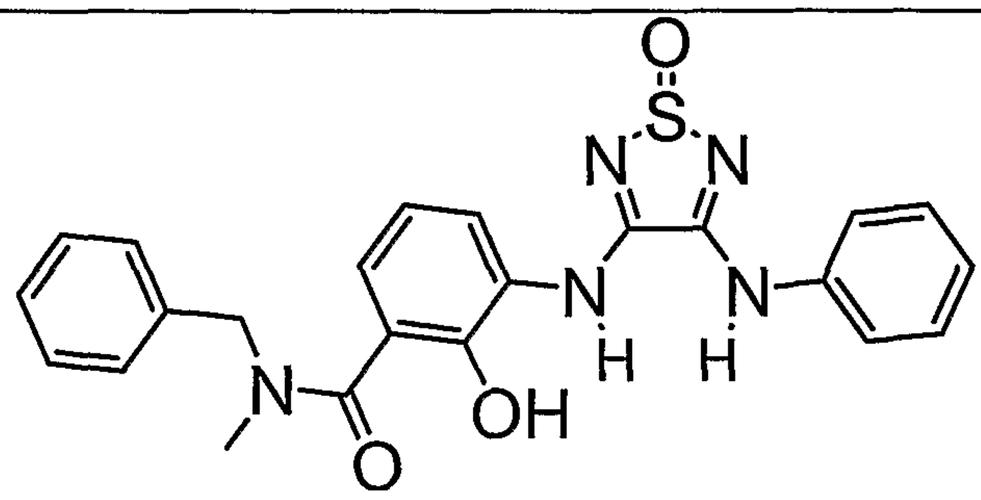
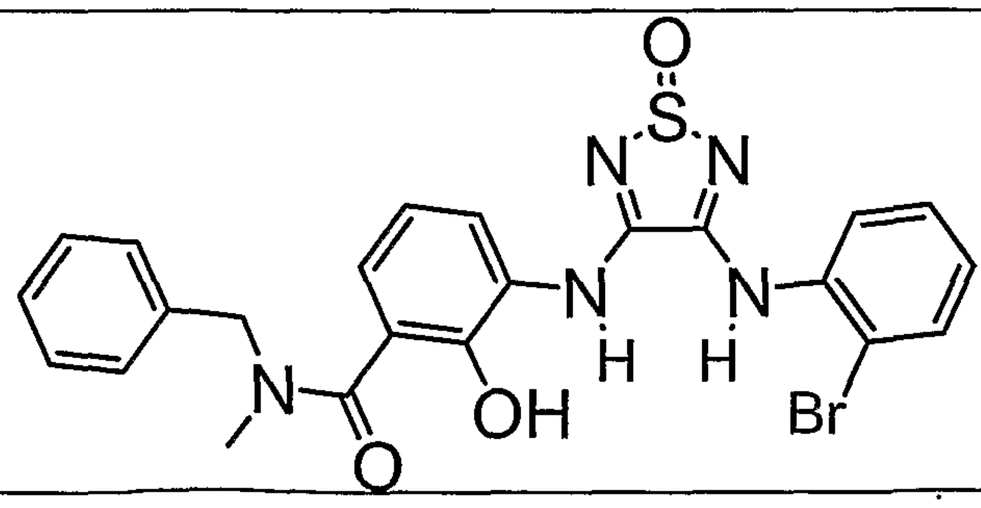
2457	165	75.60	
2458	166	75.49	
2459	166	75.9	
2460	166	75.44	
2461	166	75.61	

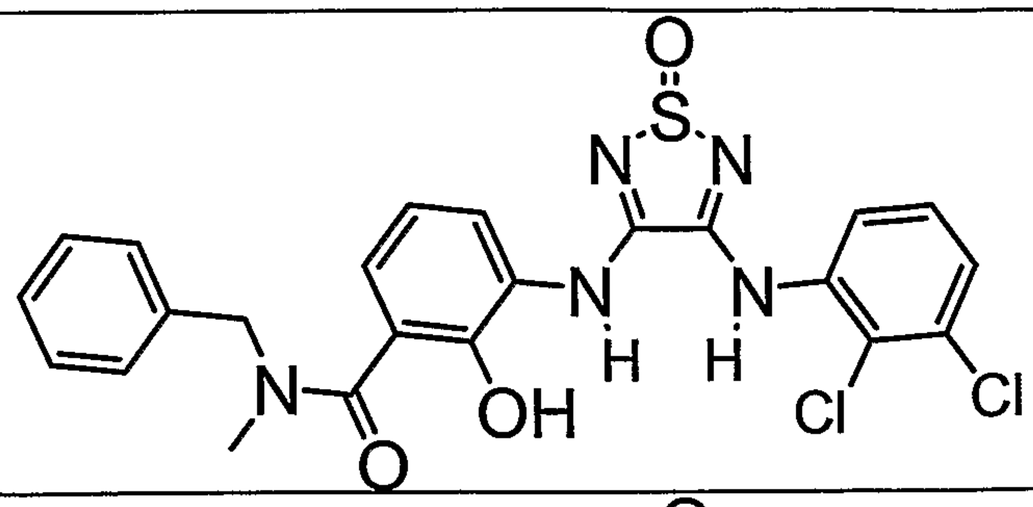
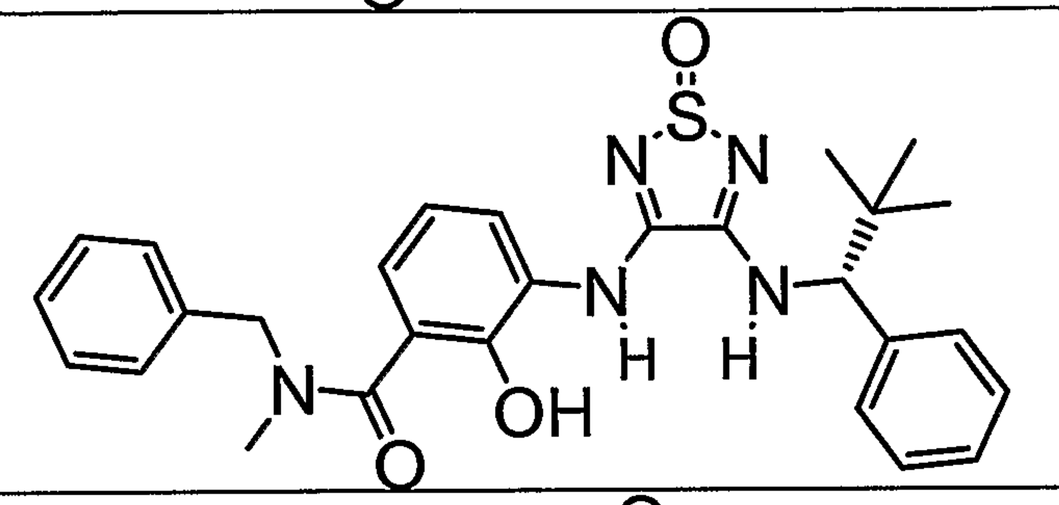
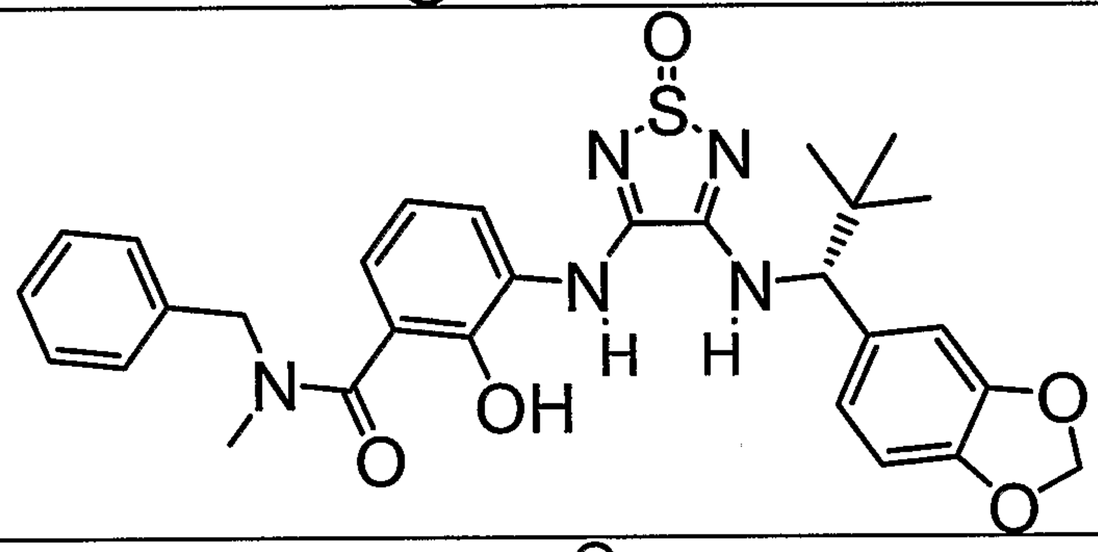
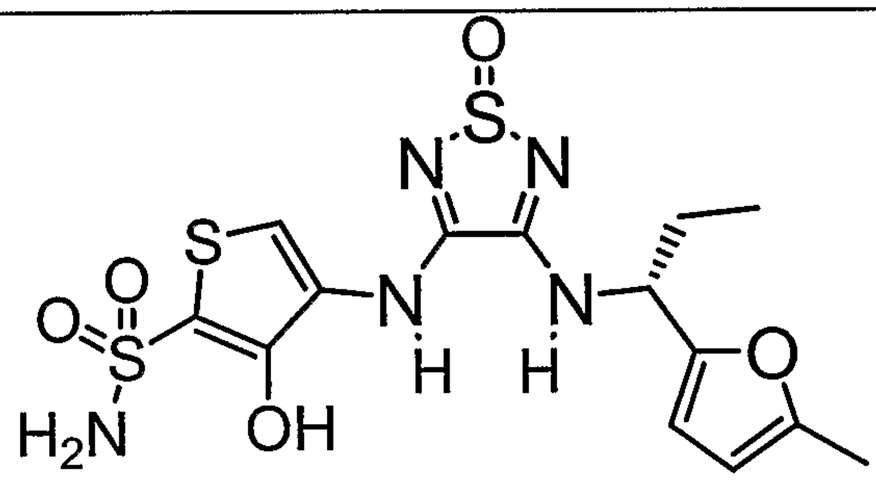
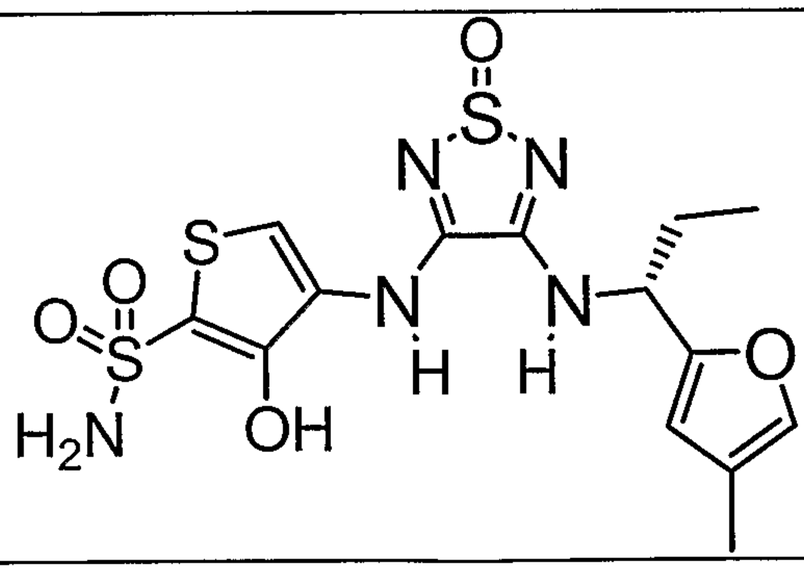
2462	166	75.44	
2463	166	75.20	
2464	166	74	
2465	166	75.60	
2466	166	2-Bromo-PhNH2	

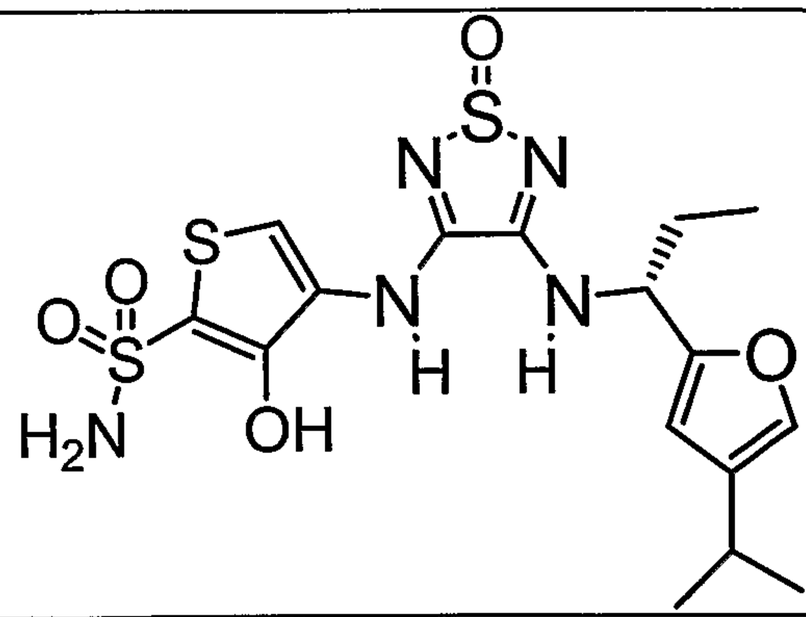
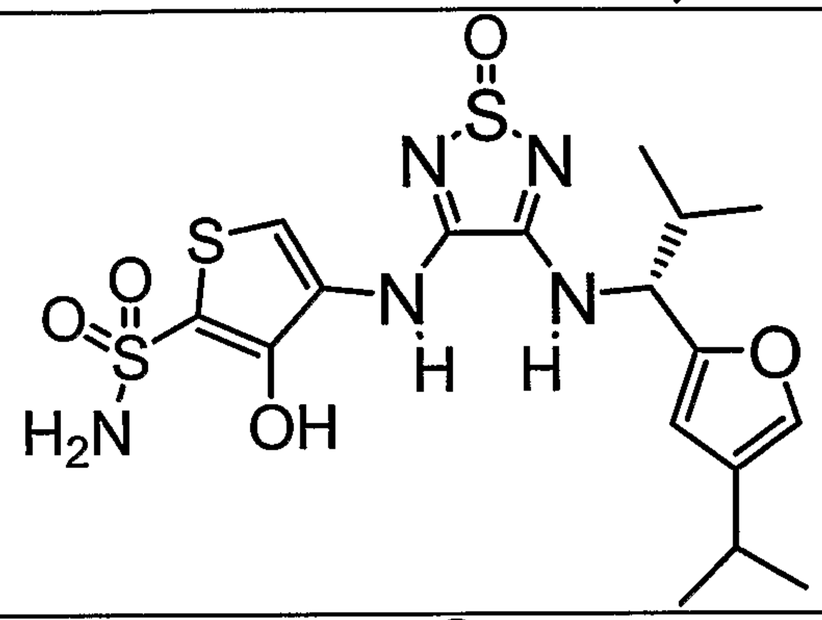
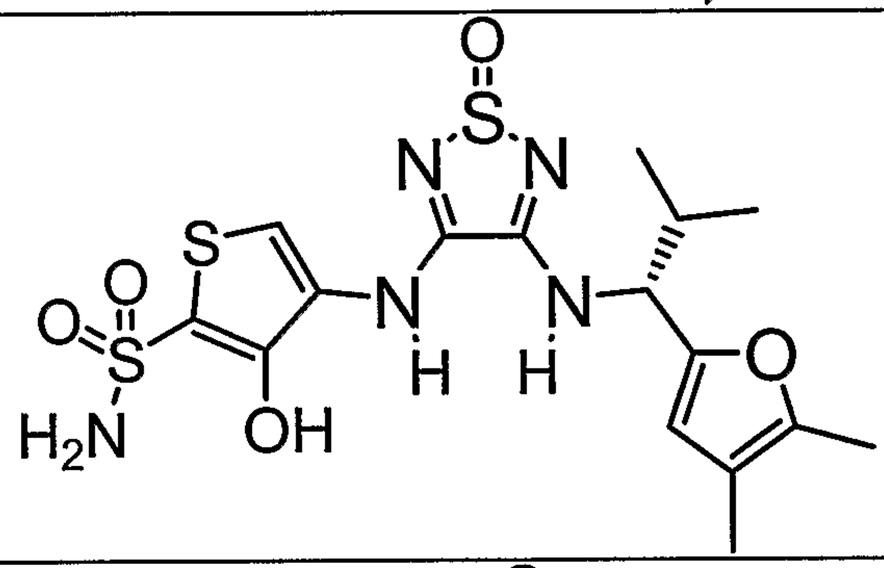
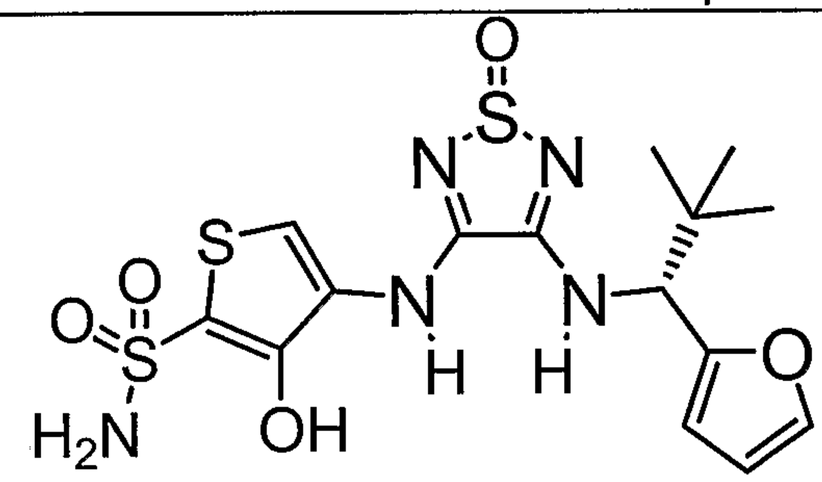
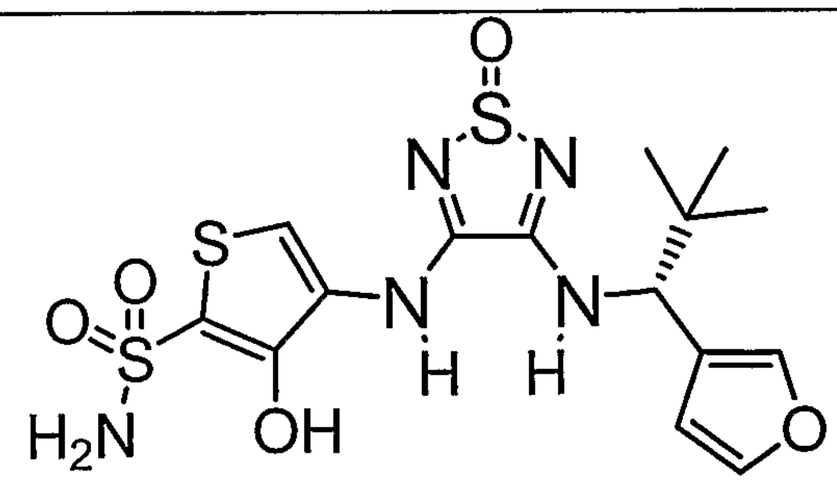
2467	166	2,3-Dichloro-PhNH2	
2468	167	75.1	
2469	167	75.49	
2470	167	75.9	
2471	167	75.44	

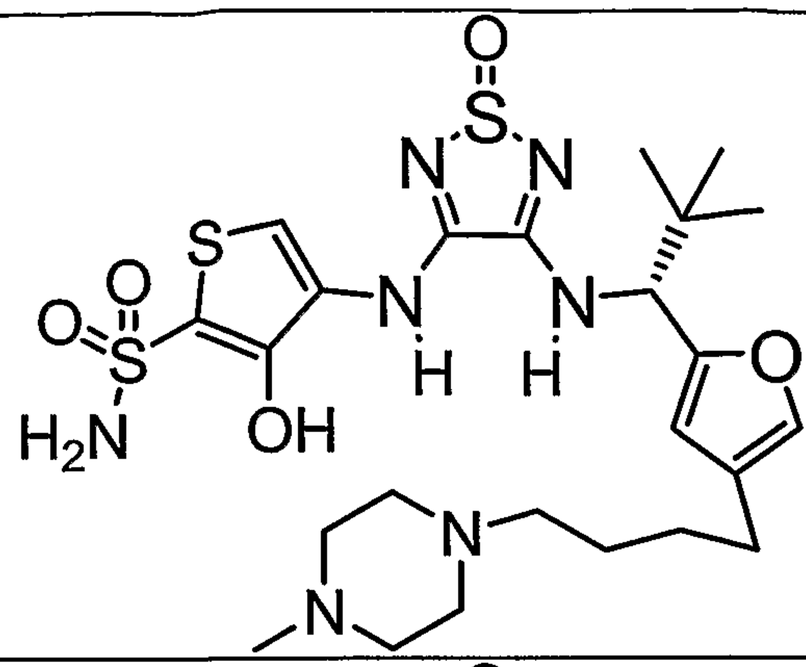
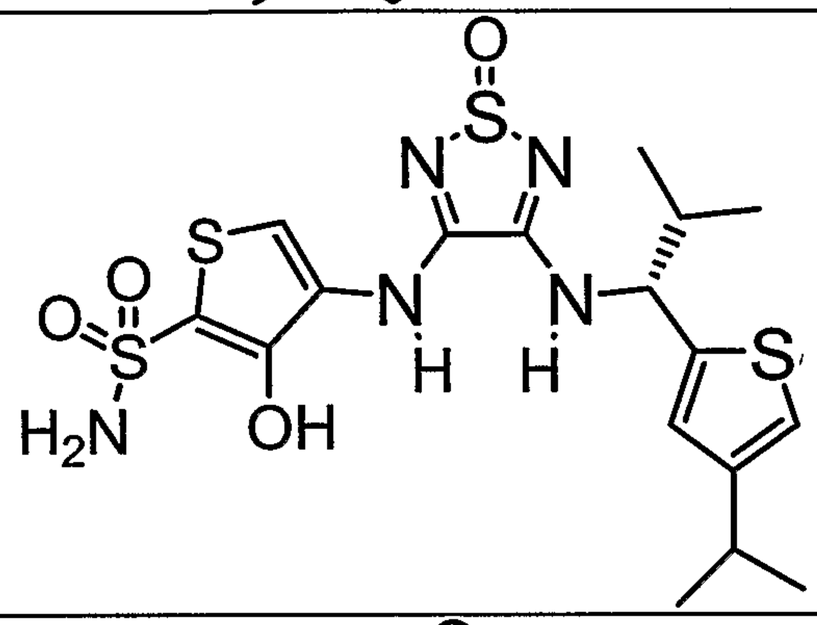
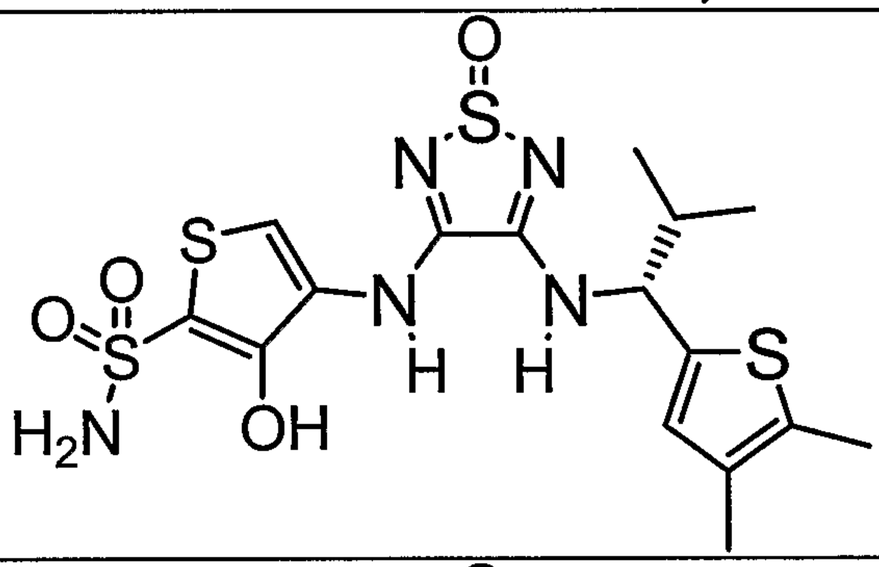
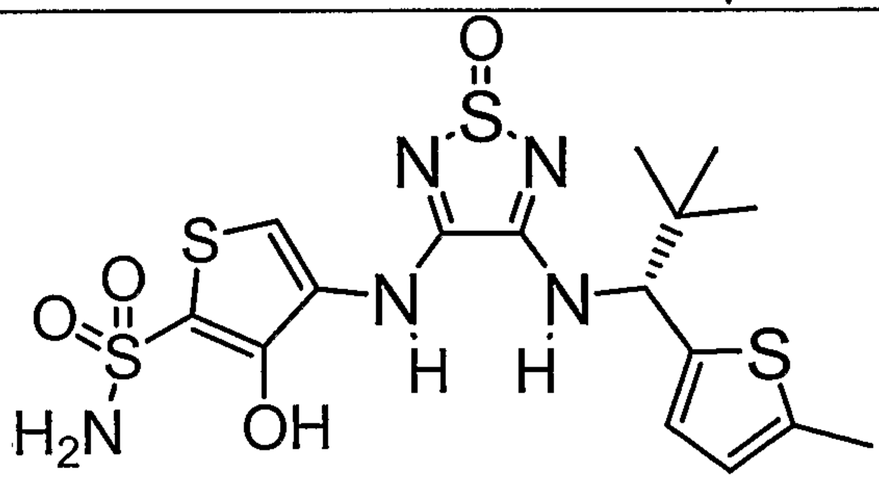
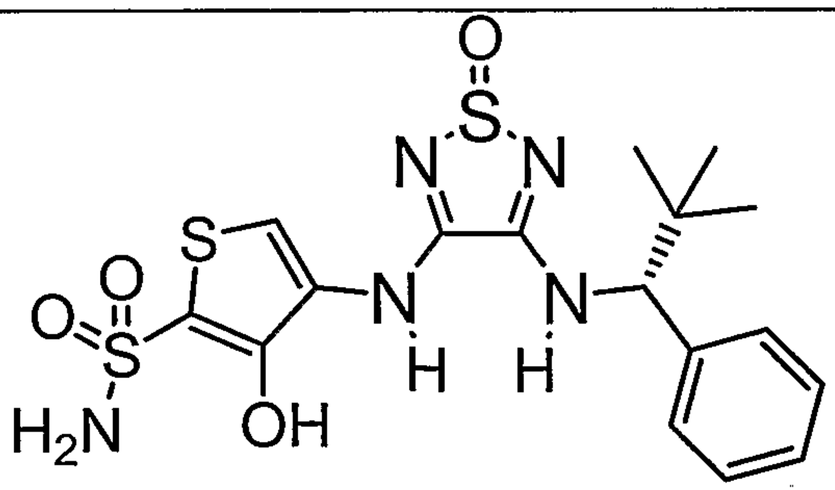
2472	167	75.61	
2473	167	75.44	
2474	167	75.20	
2475	167	74	
2476	167	75.60	

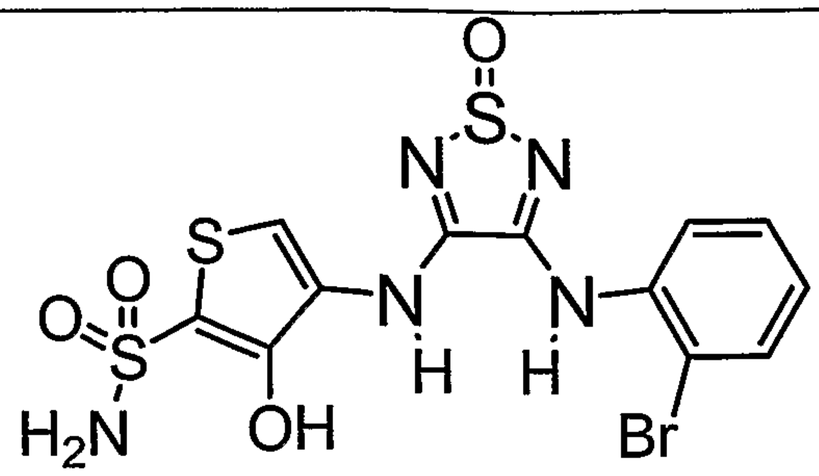
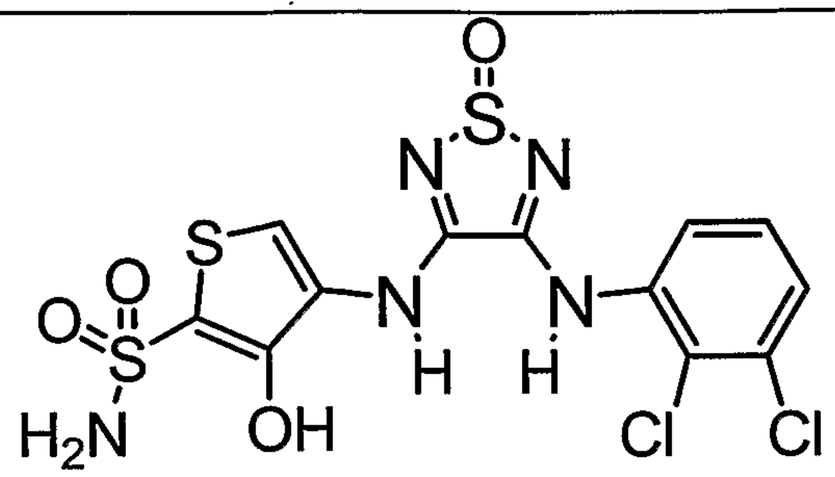
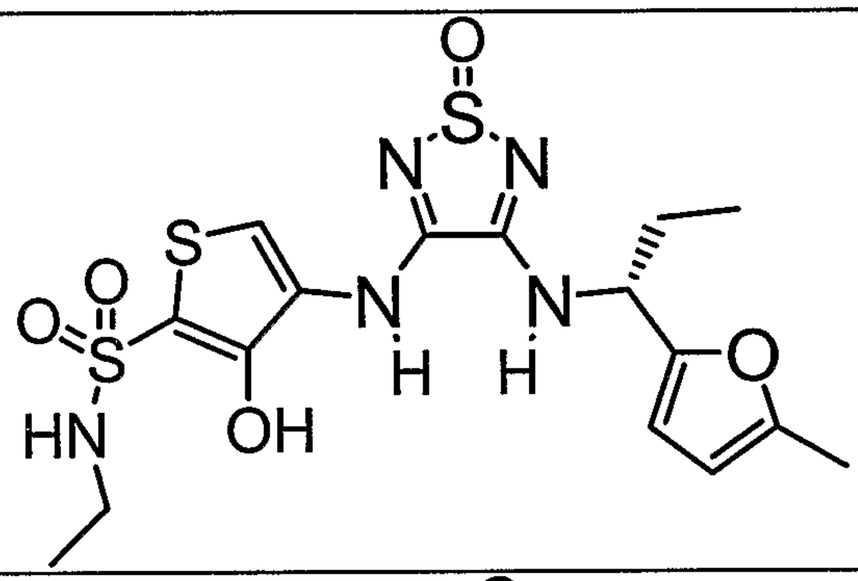
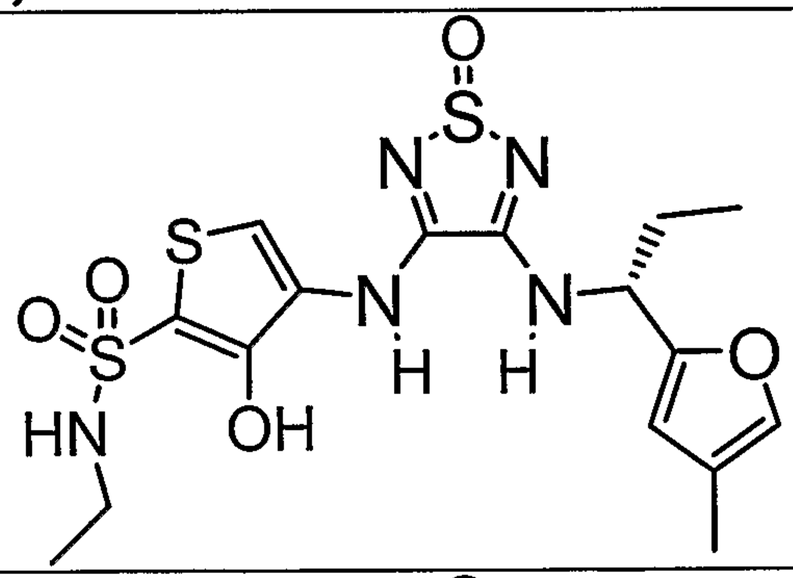
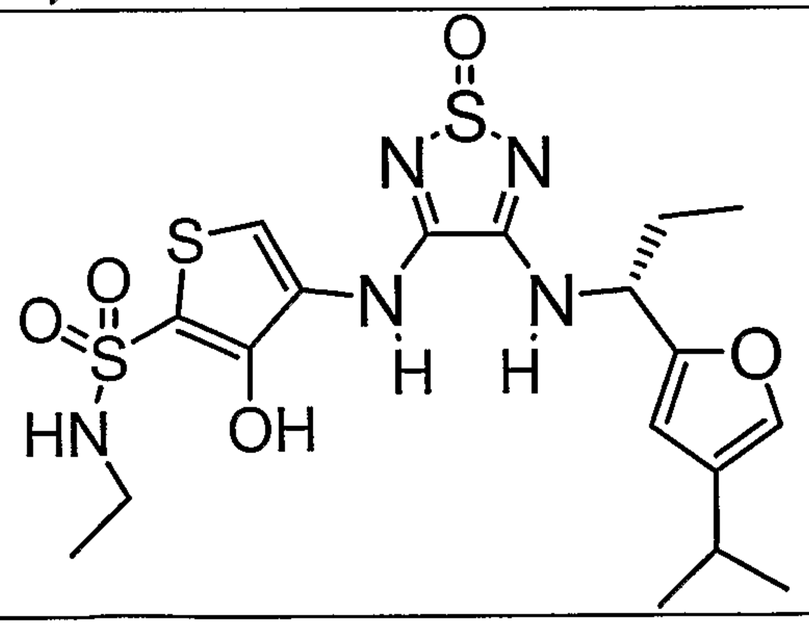
2477	167	2-Bromo-PhNH2	
2478	167	2,3-Dichloro-PhNH2	
2479	168	75.1	
2480	168	75.49	
2481	168	75.9	

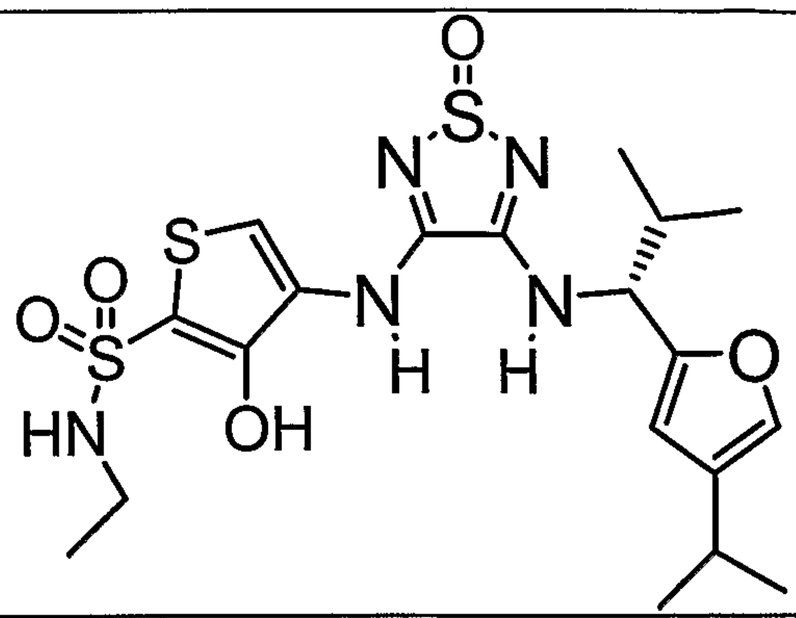
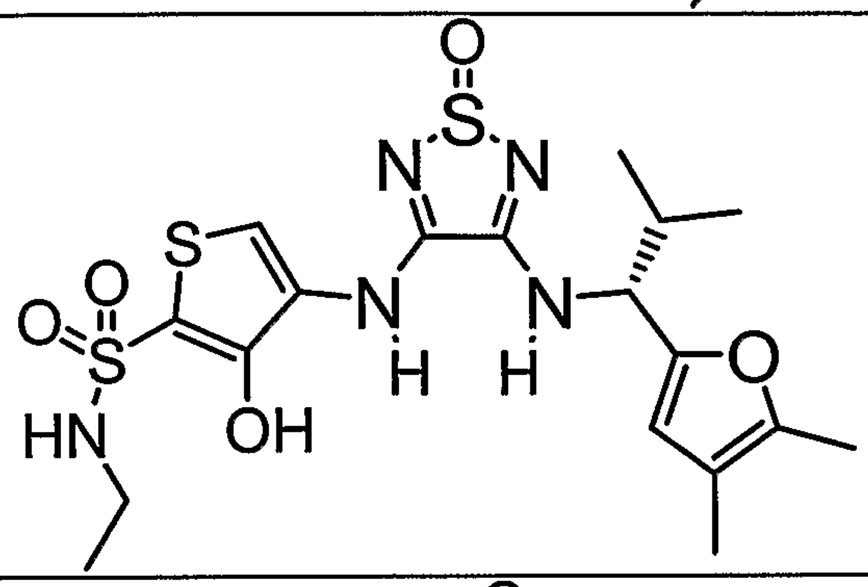
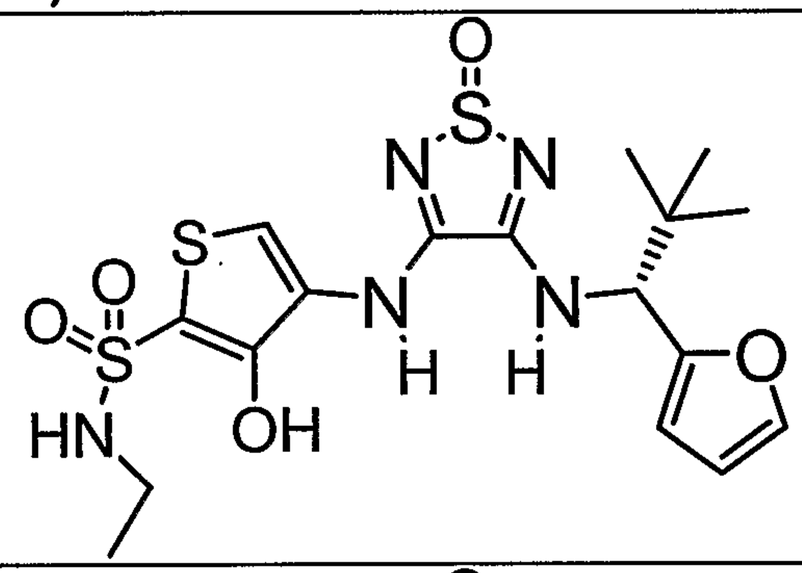
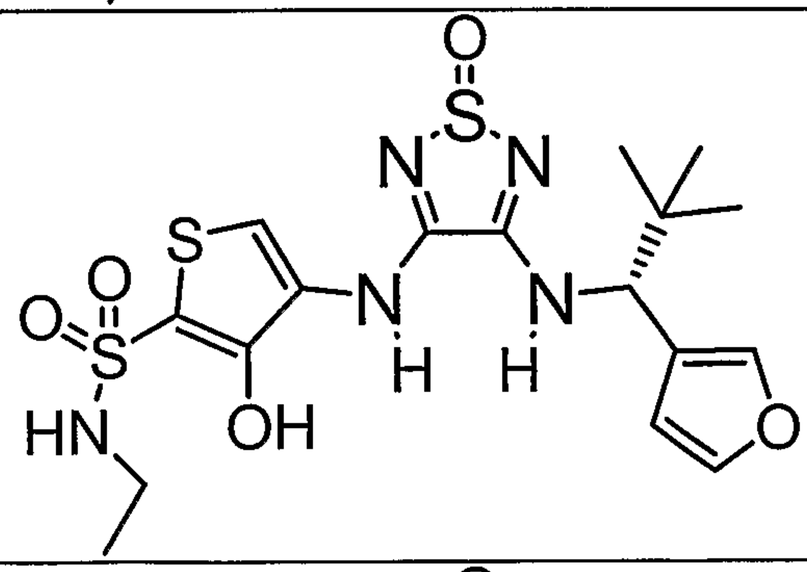
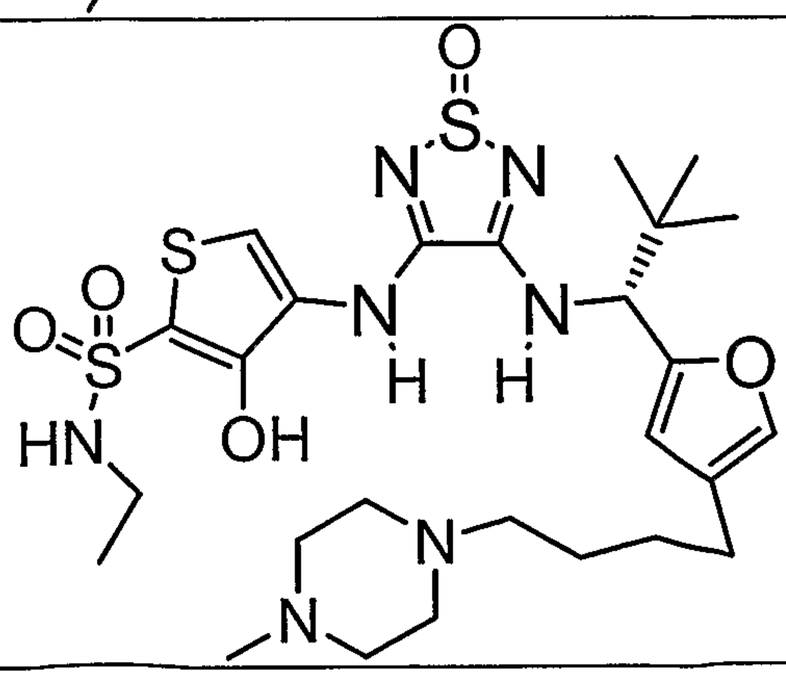
2482	168	75.44	
2483	168	75.61	
2484	168	75.20	
2485	168	PhNH2	
2486	168	2-Bromo-PhNH2	

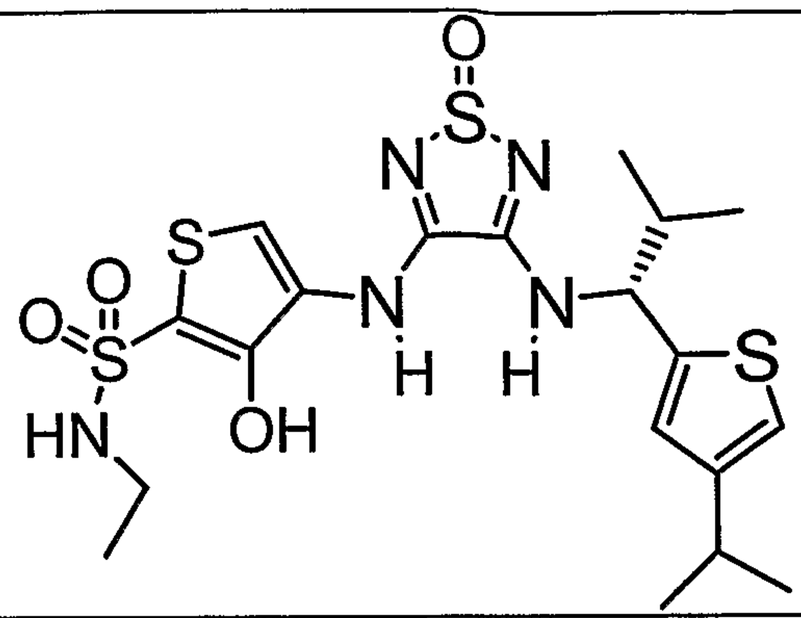
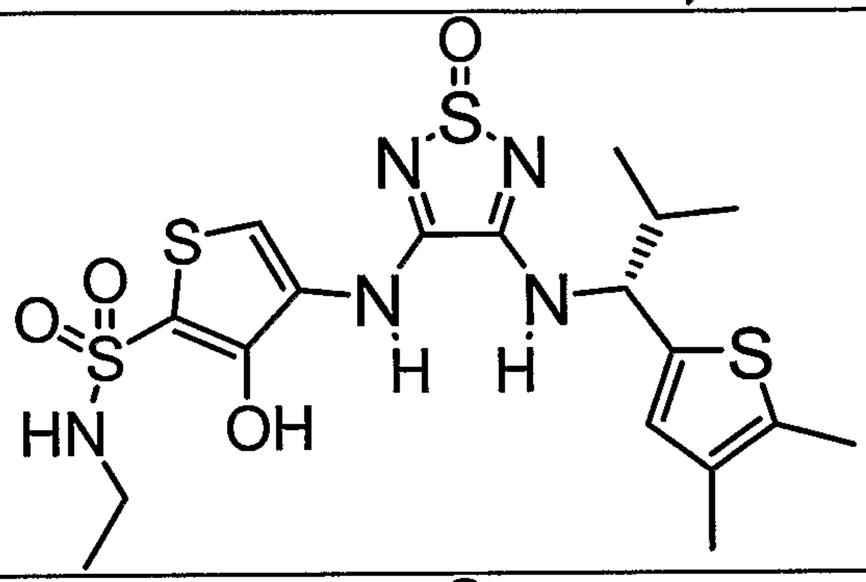
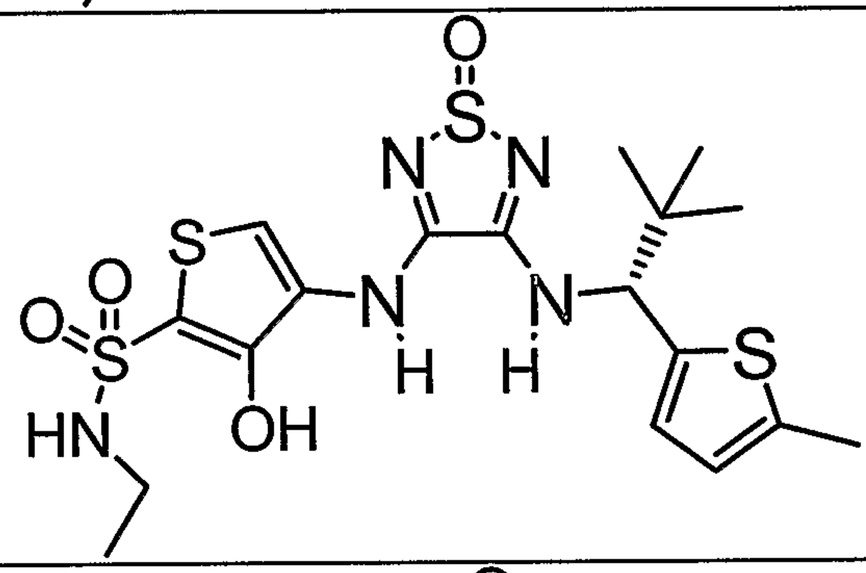
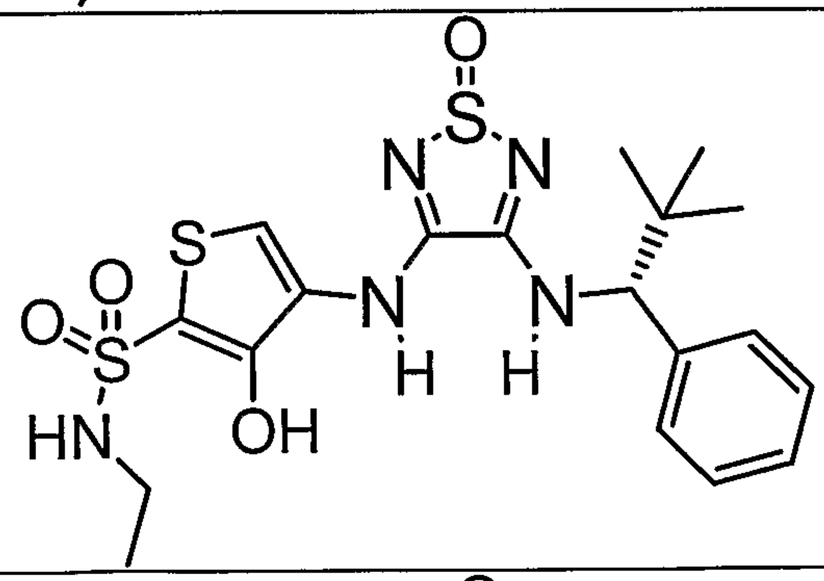
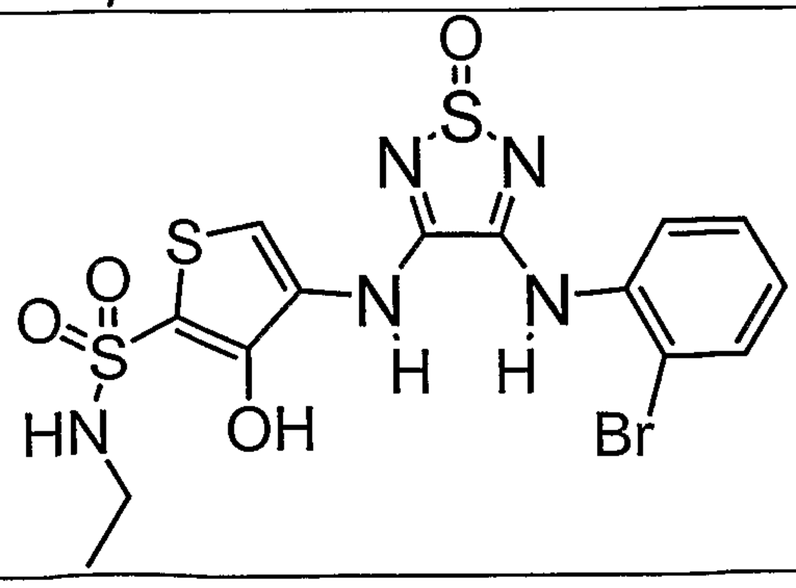
2487	168	2,3-Dichloro-PhNH2	
2488	168	74	
2489	168	75.60	
2600	253	75.1	
2601	253	75.49	

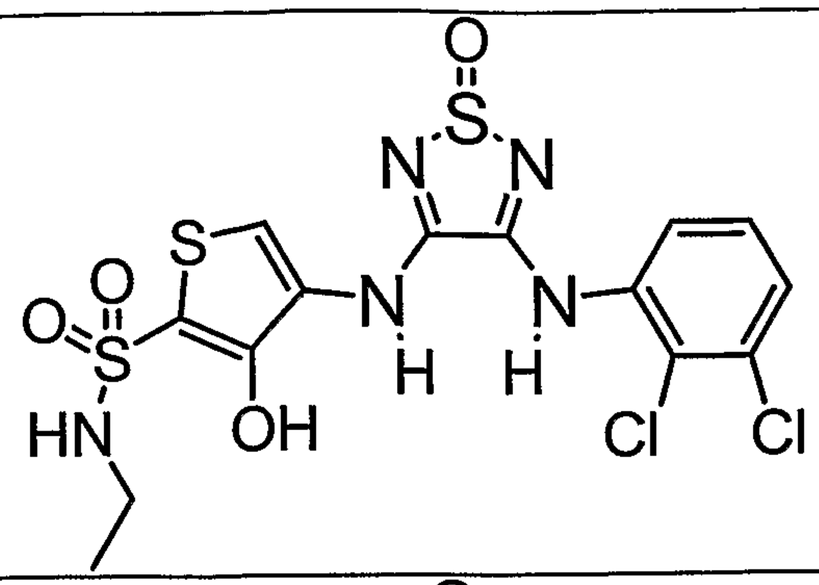
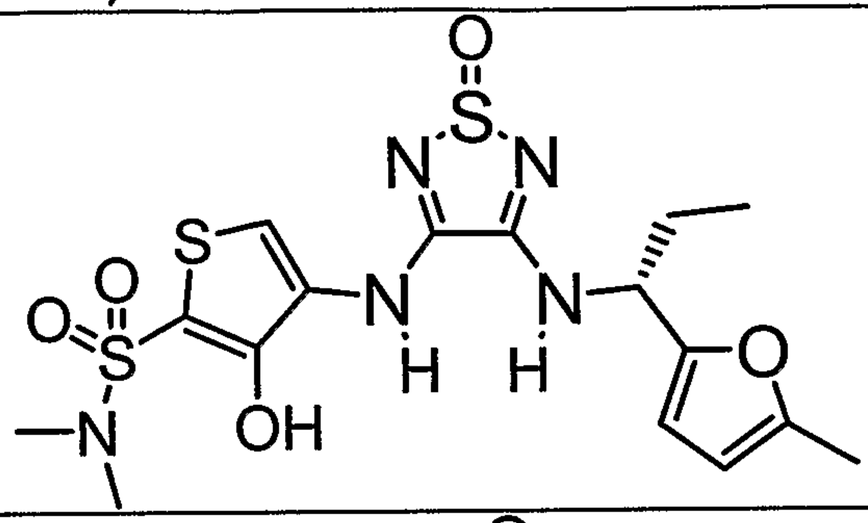
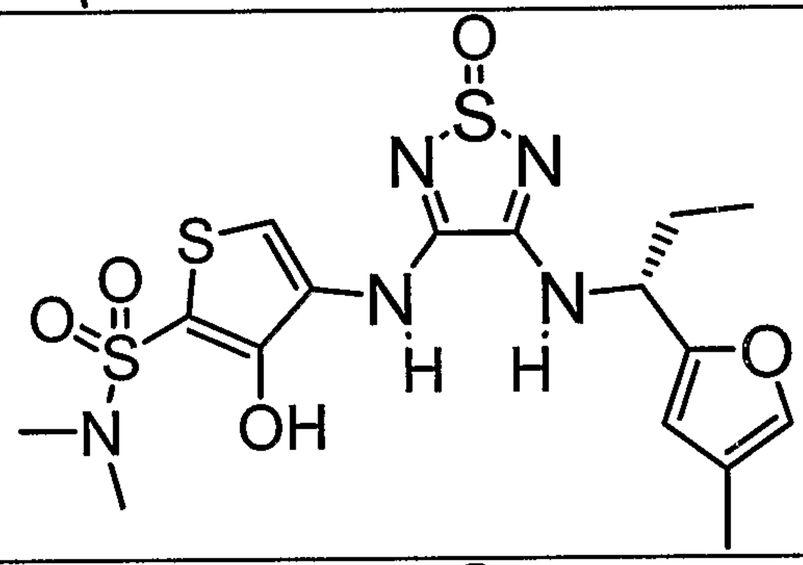
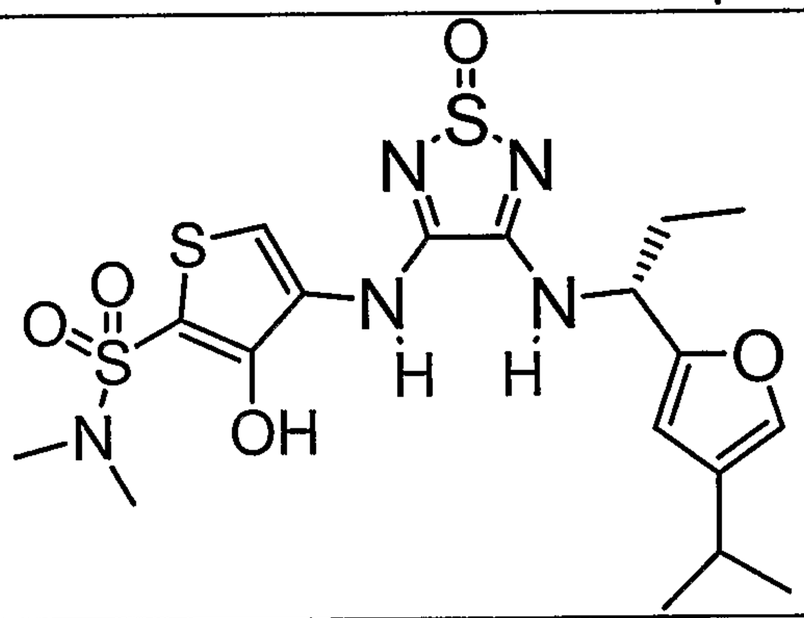
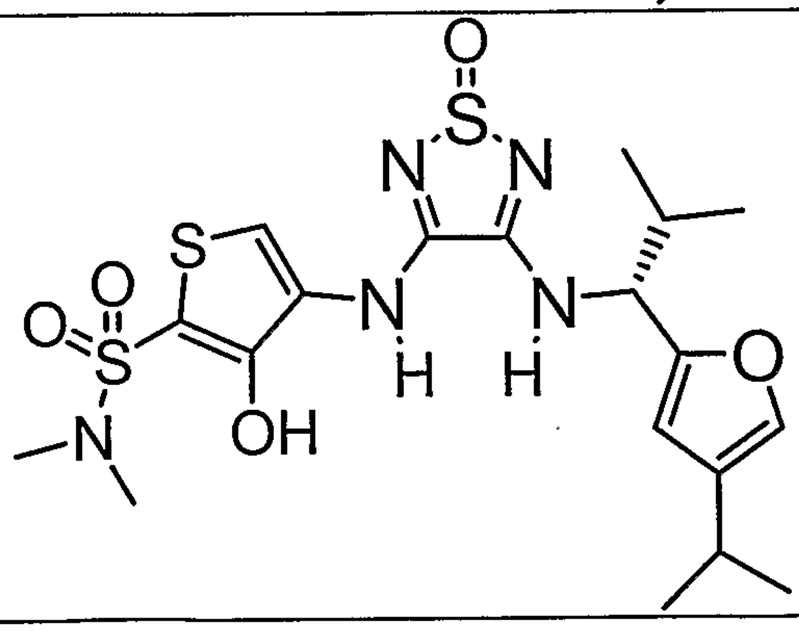
2602	253	75.9	
2603	253	75.10E	
2604	253	75.61	
2605	253	1048	
2606	253	75.69	

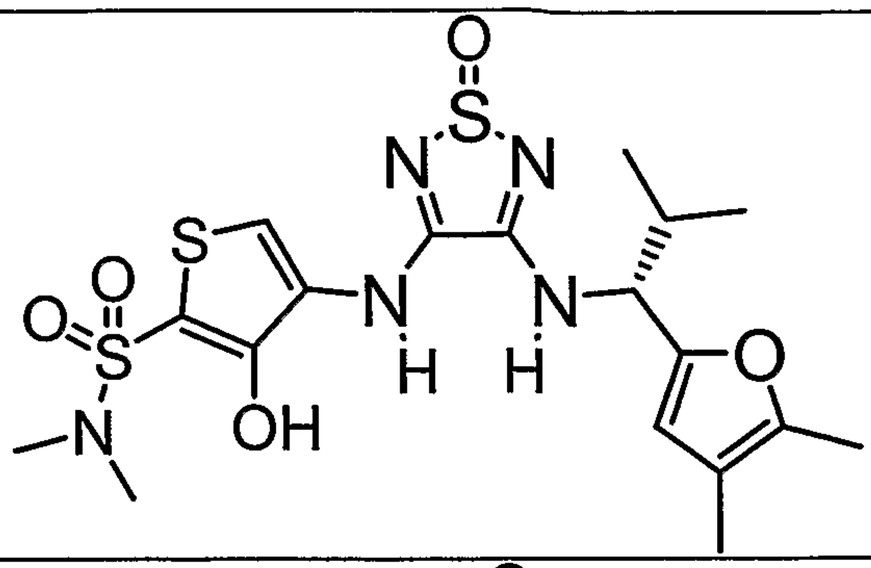
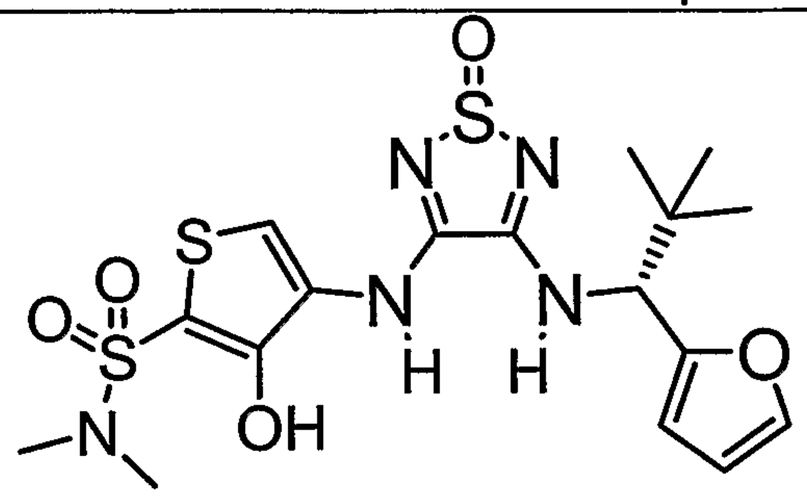
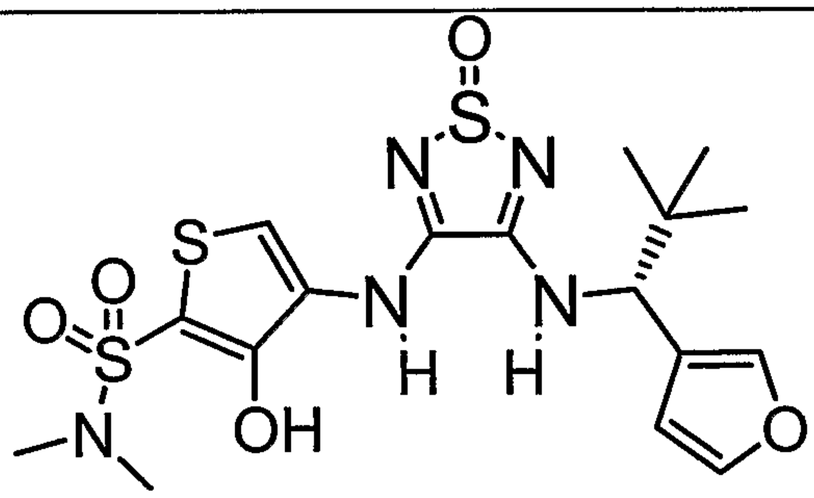
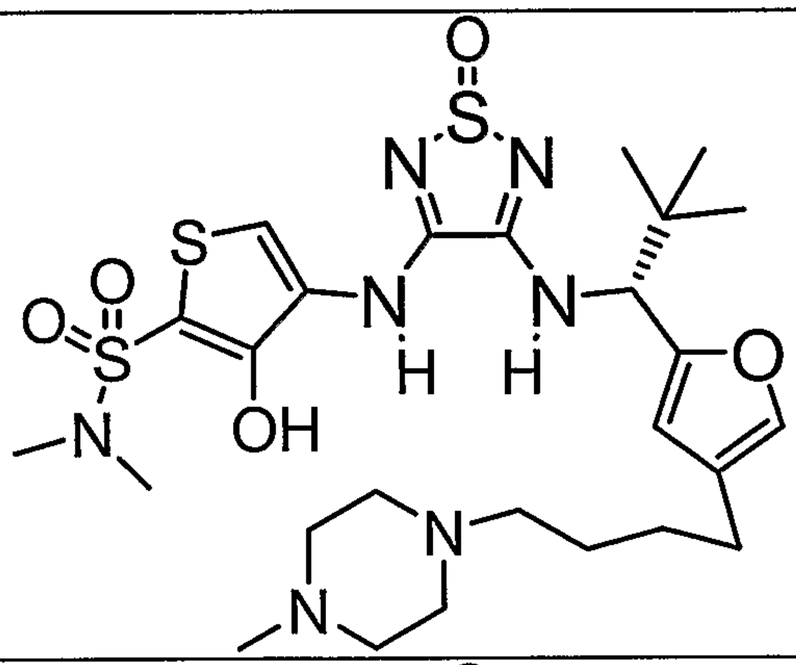
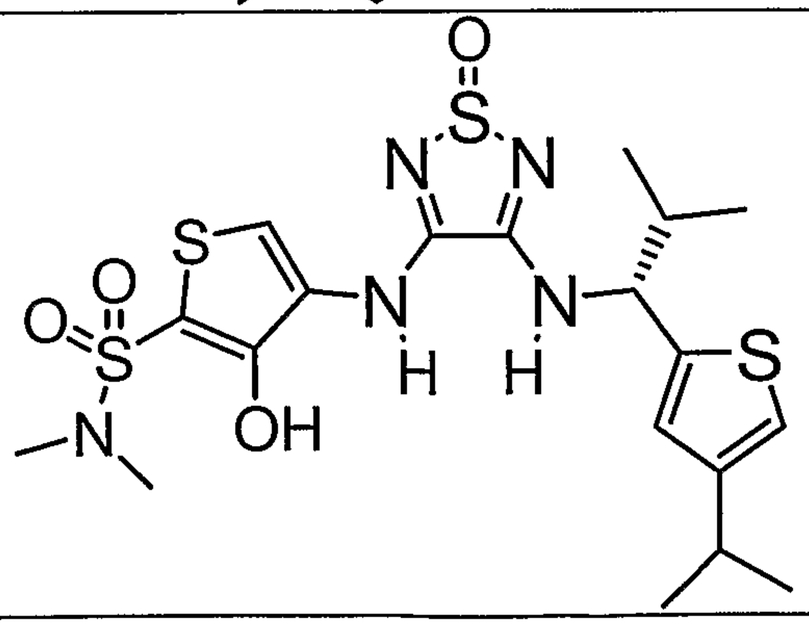
2607	253	603B	
2608	253	603E	
2609	253	603F	
2610	253	75.20	
2611	253	74	

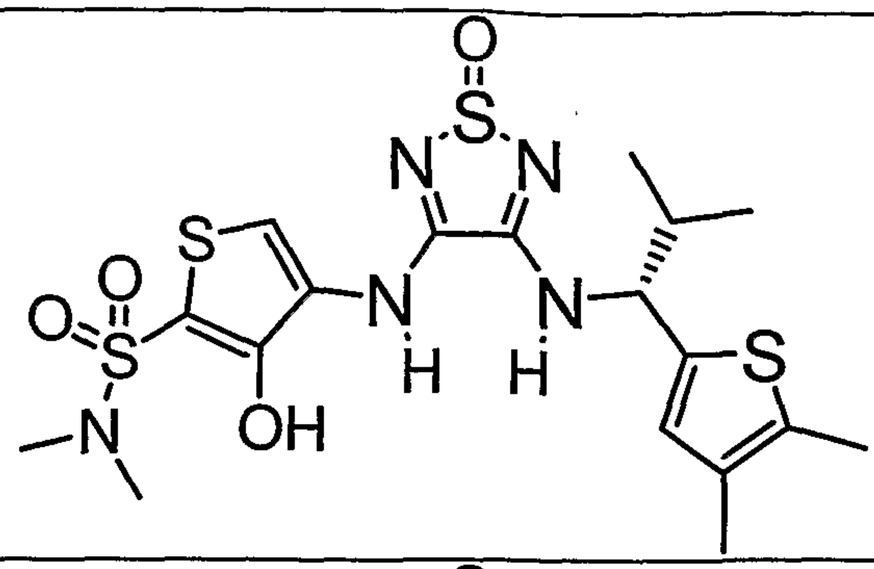
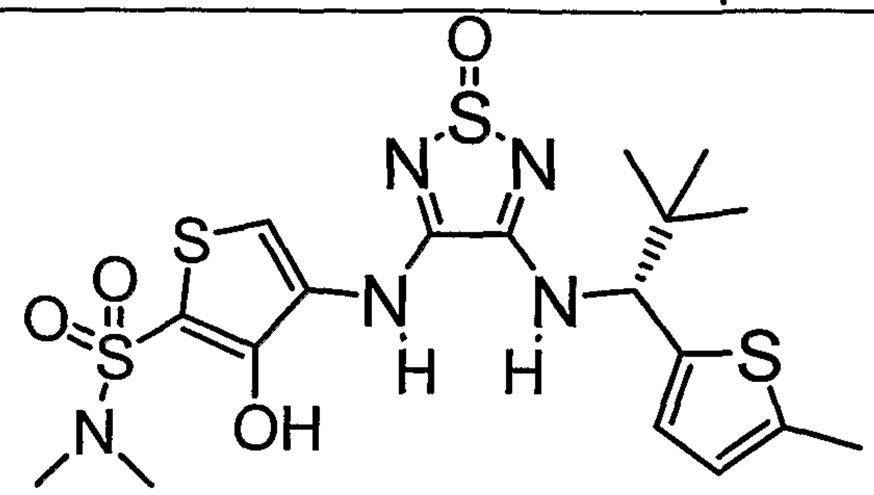
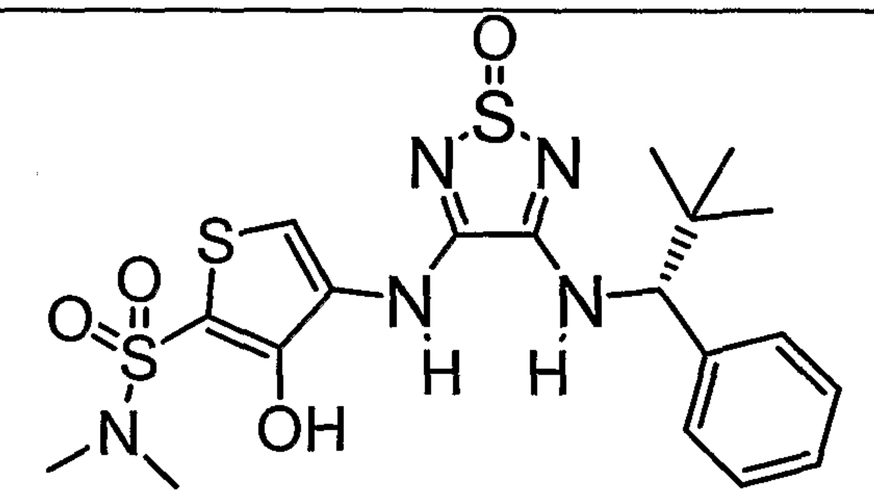
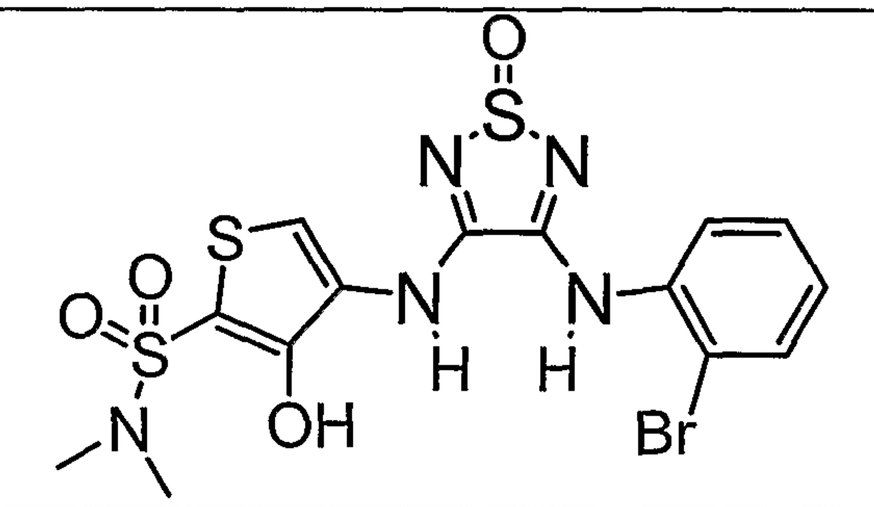
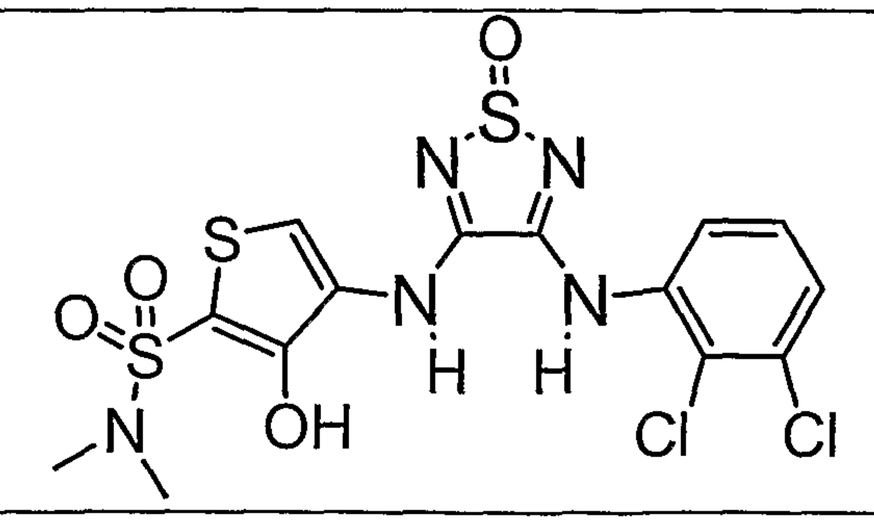
2612	253	2-Bromo-PhNH2	
2613	253	2,3-Dichloro-PhNH2	
2614	22.26	75.1	
2615	22.26	75.49	
2616	22.26	75.9	

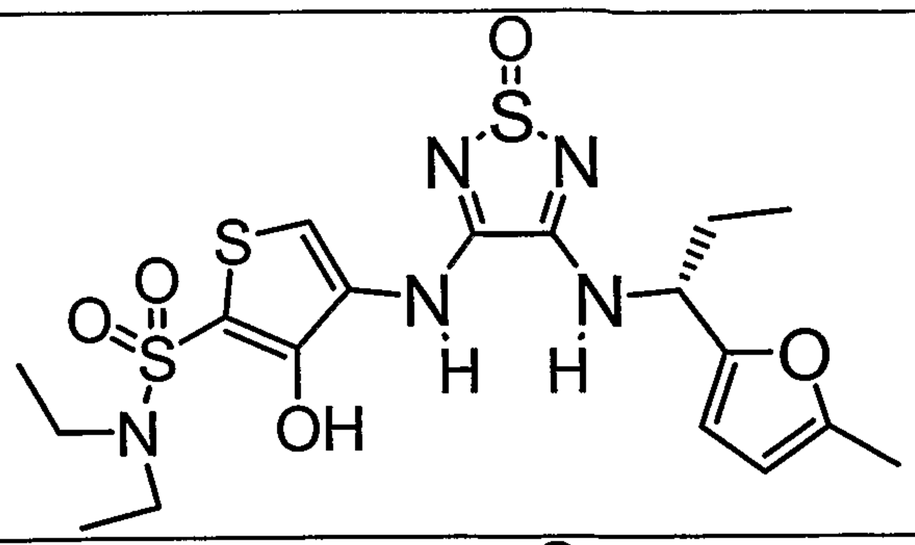
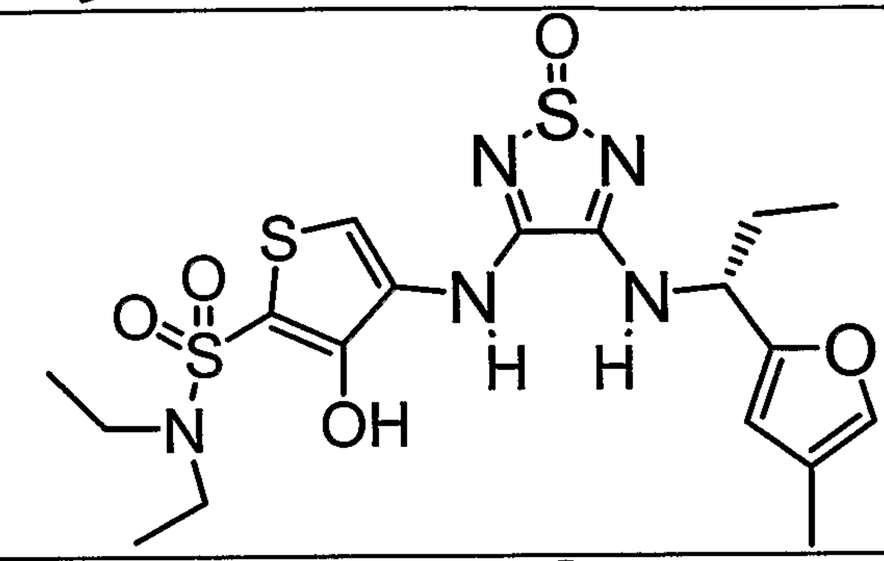
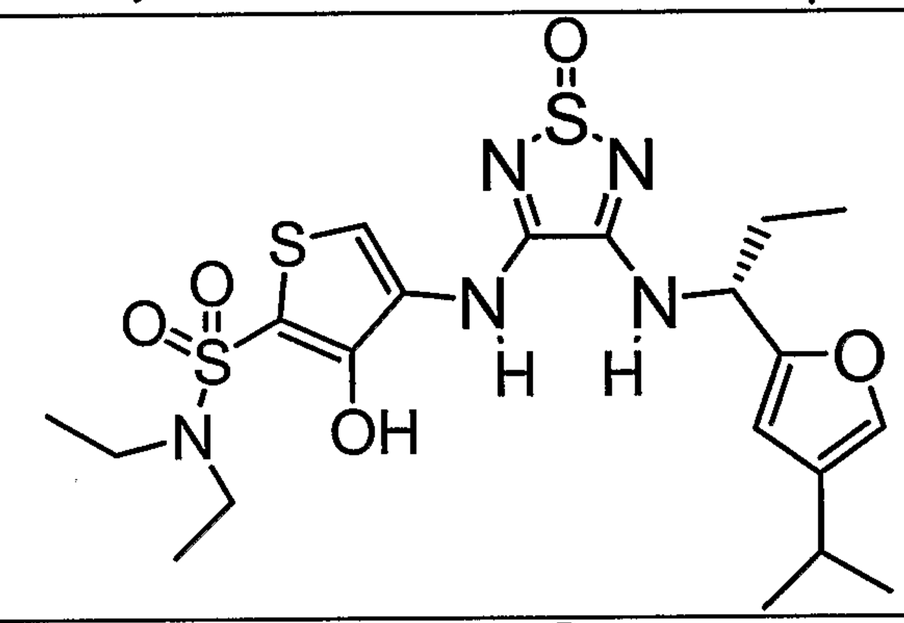
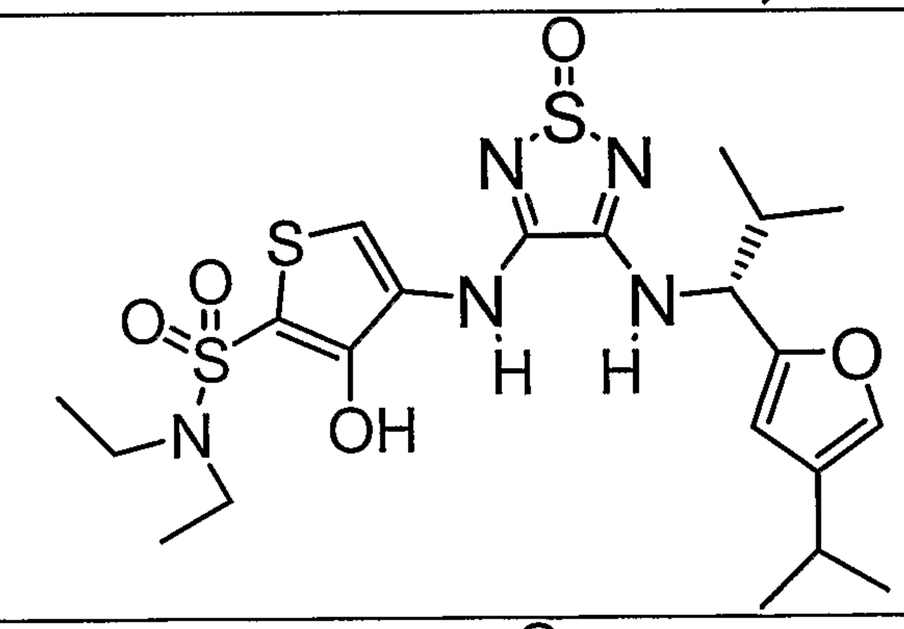
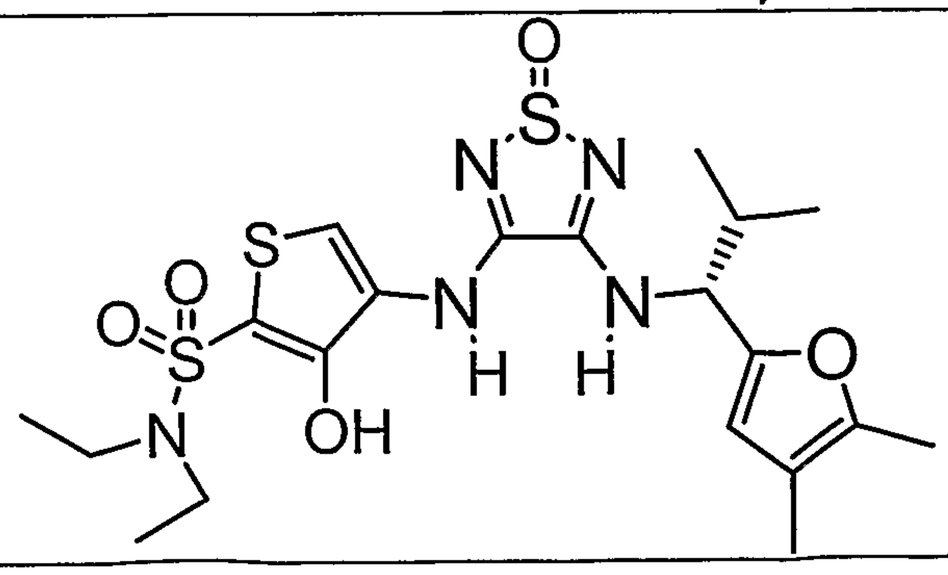
2617	22.26	75.10E	
2618	22.26	75.61	
2619	22.26	1048	
2620	22.26	75.69	
2621	22.26	603B	

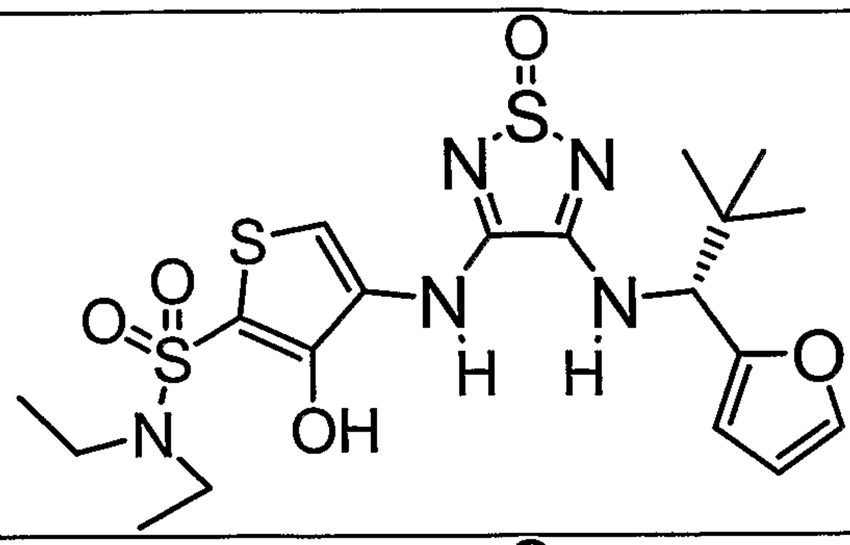
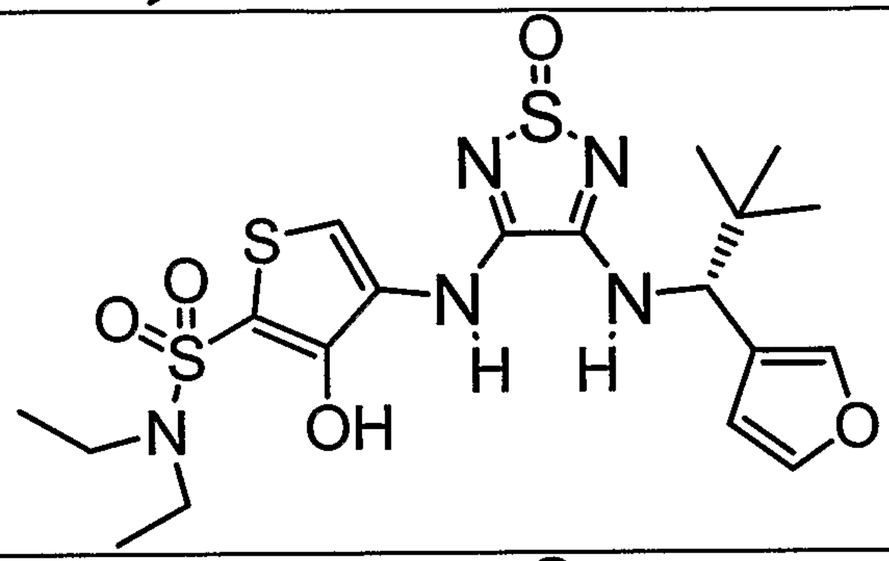
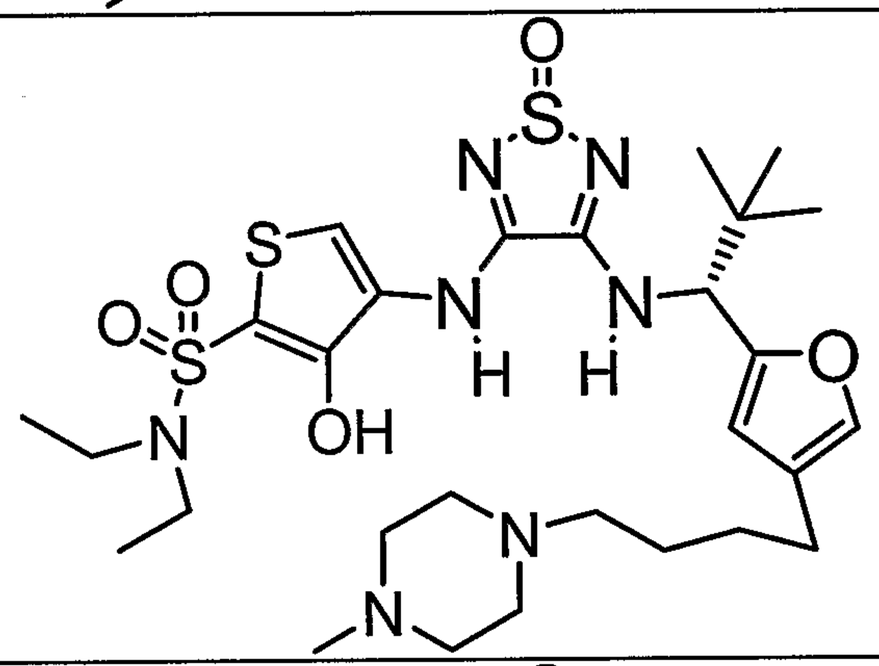
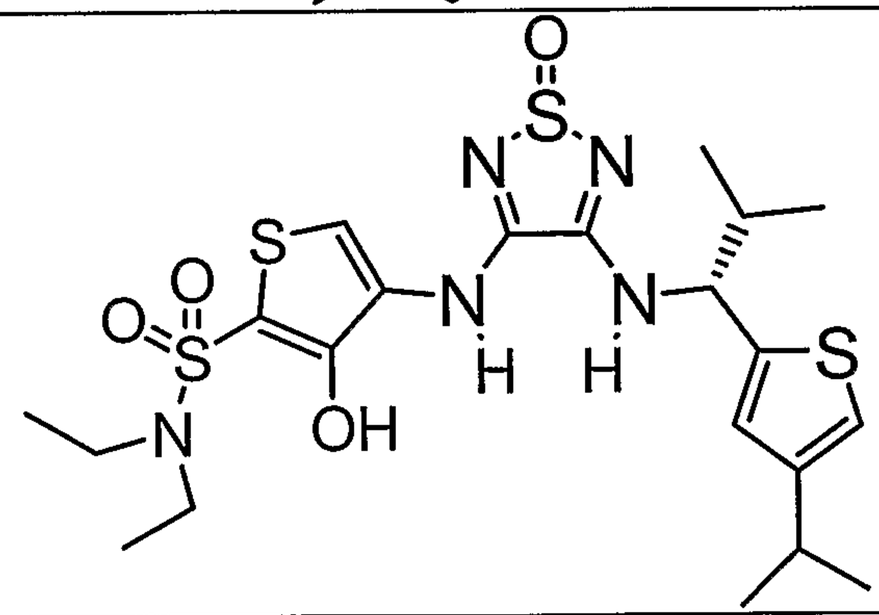
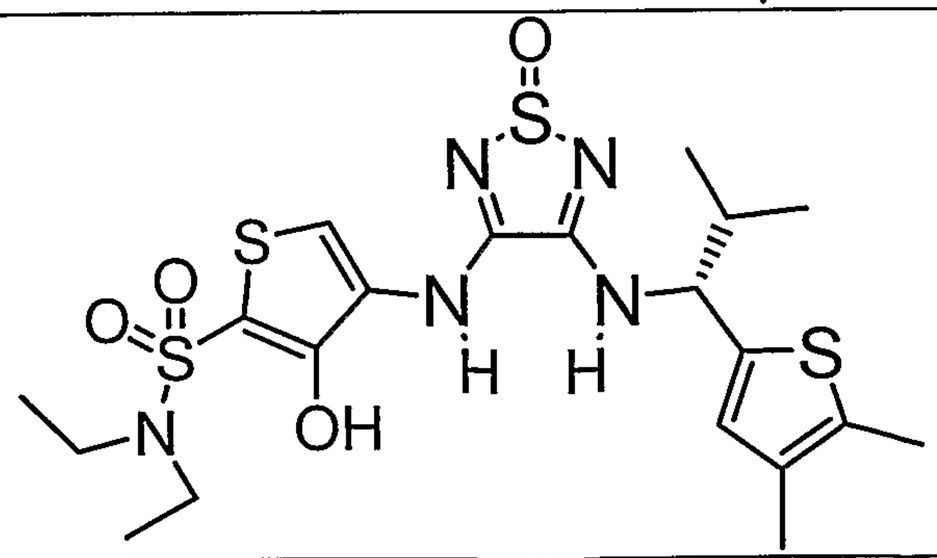
2622	22.26	603E	
2623	22.26	603F	
2624	22.26	75.20	
2625	22.26	74	
2626	22.26	2-Bromo-PhNH2	

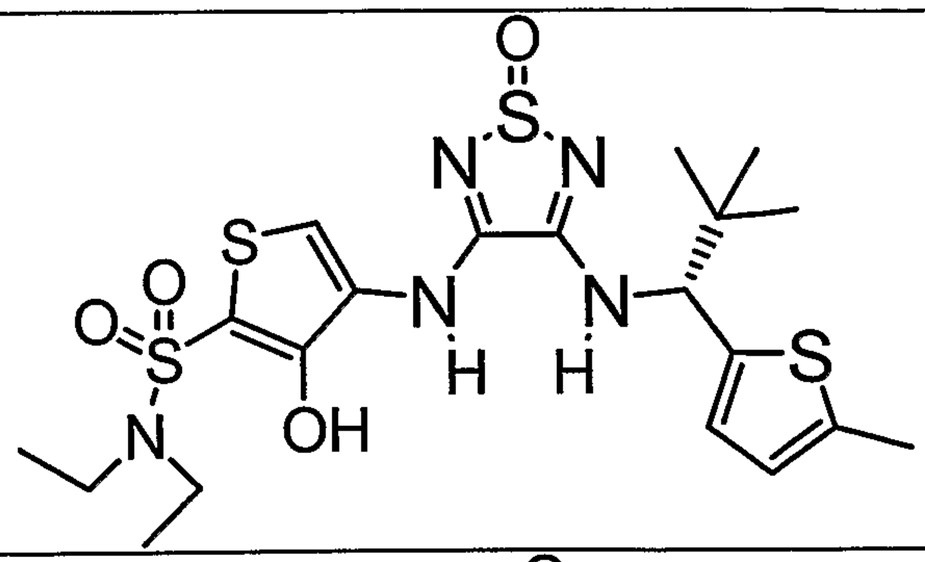
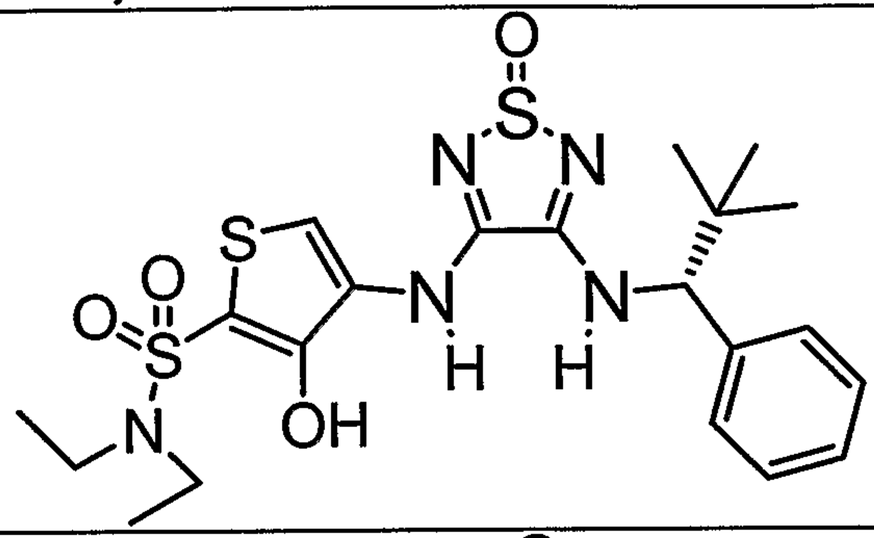
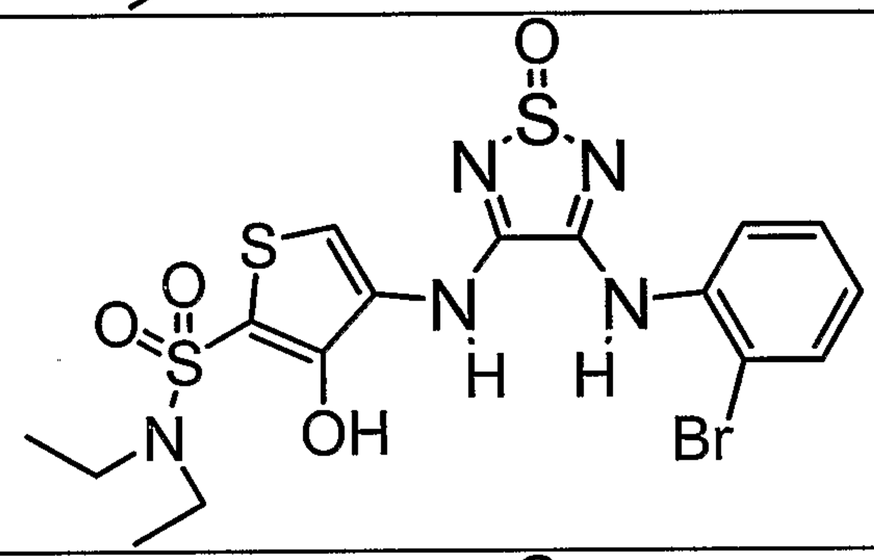
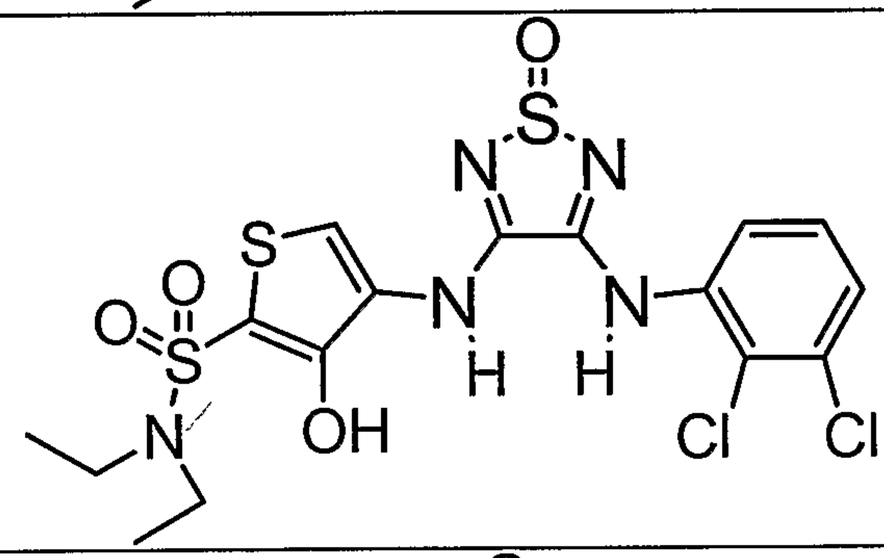
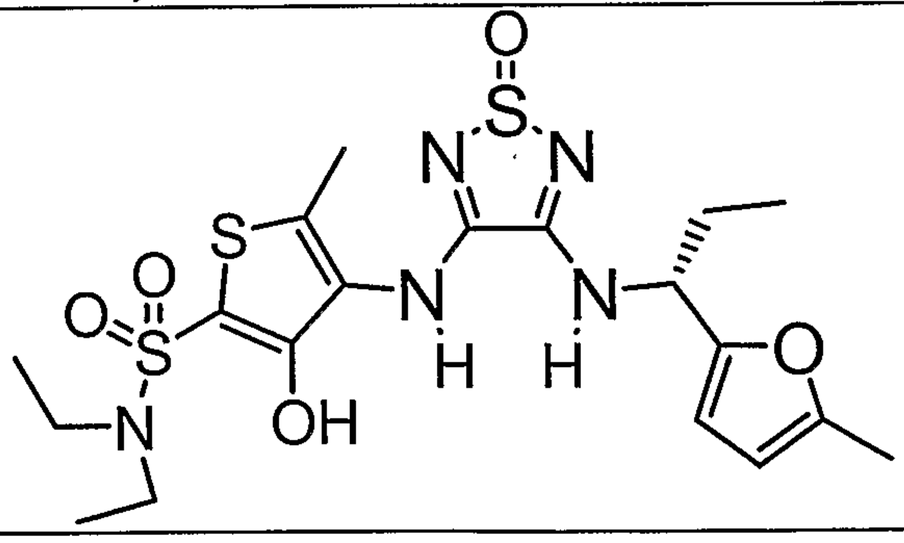
2627	22.26	2,3-Dichloro-PhNH2	
2628	22.6	75.1	
2629	22.6	75.49	
2630	22.6	75.9	
2631	22.6	75.10E	

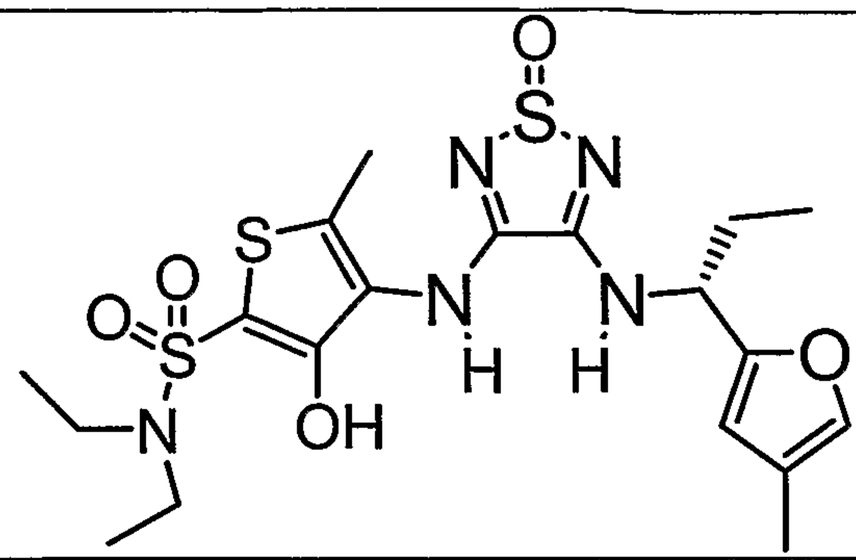
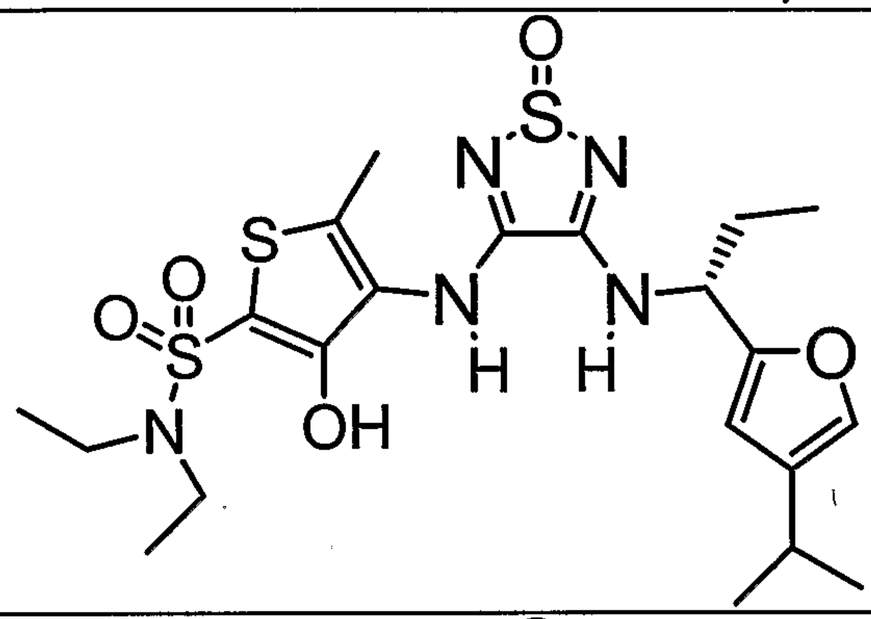
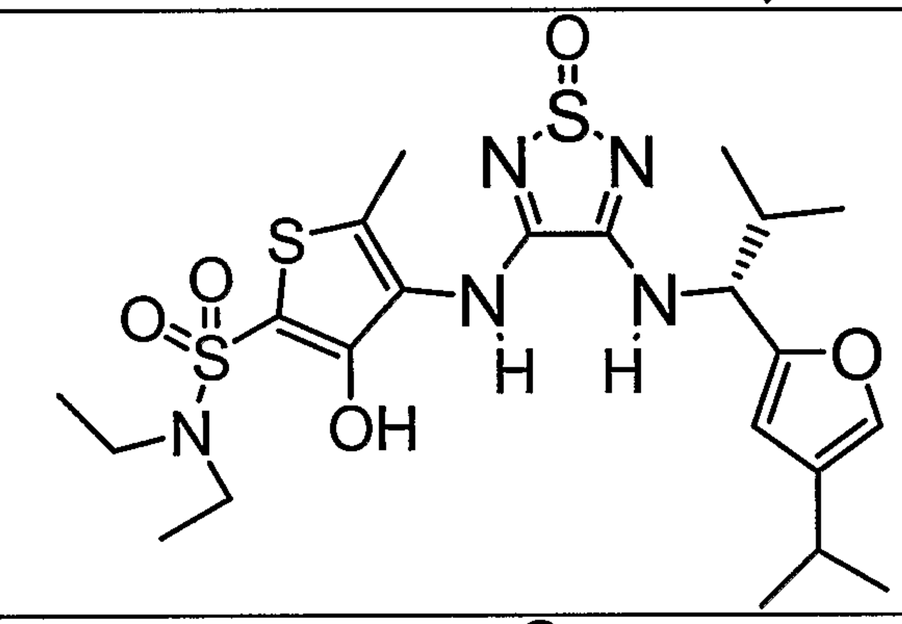
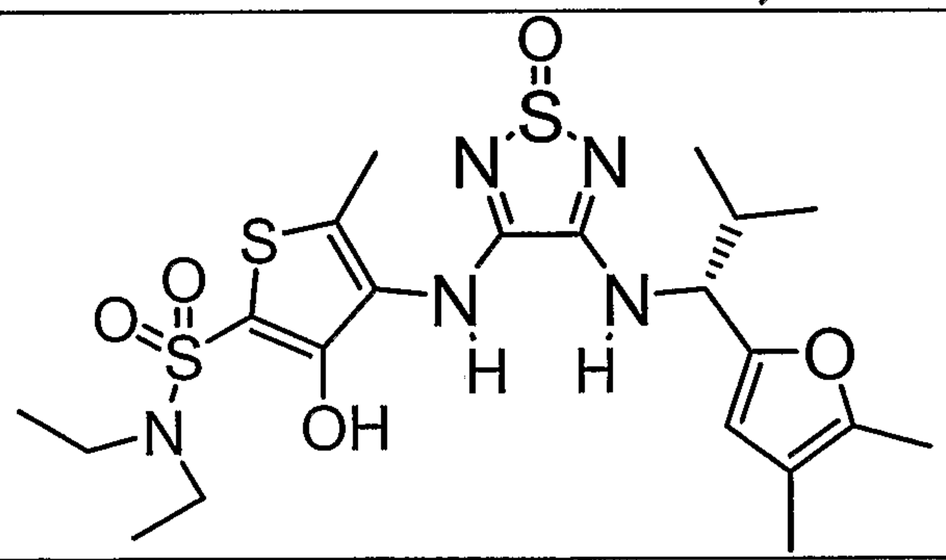
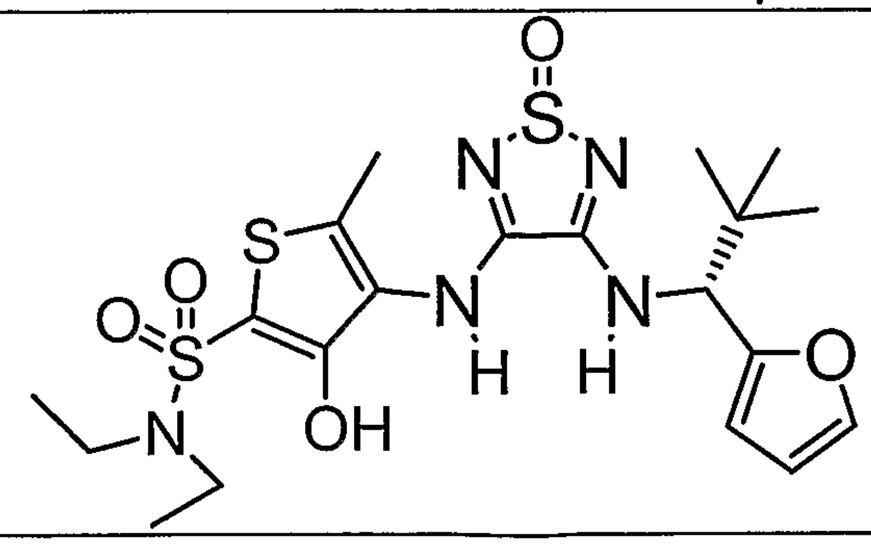
2632	22.6	75.61	
2633	22.6	1048	
2634	22.6	75.69	
2635	22.6	603B	
2636	22.6	603E	

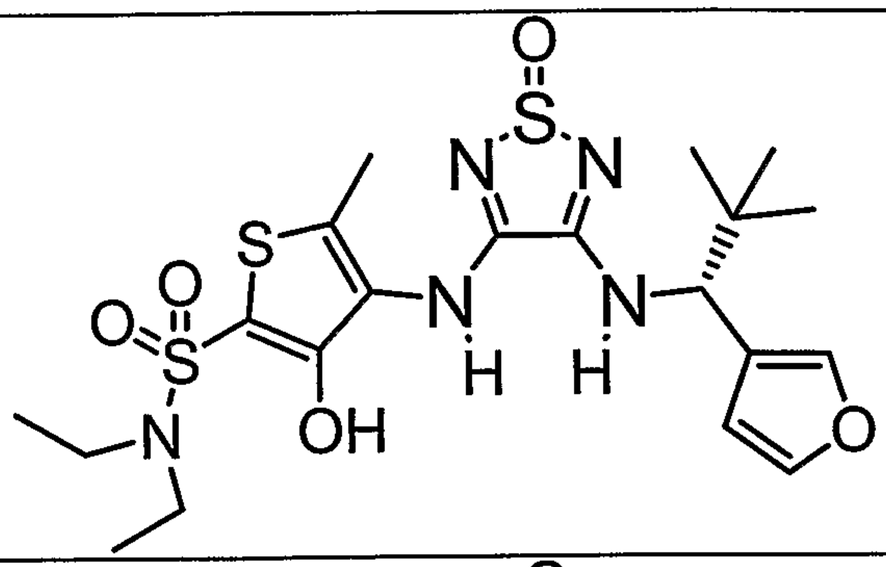
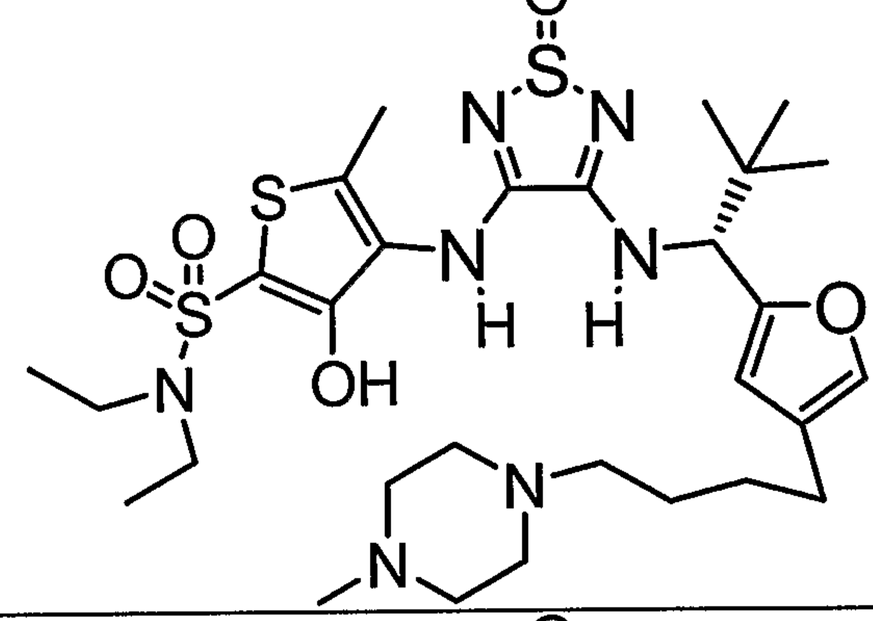
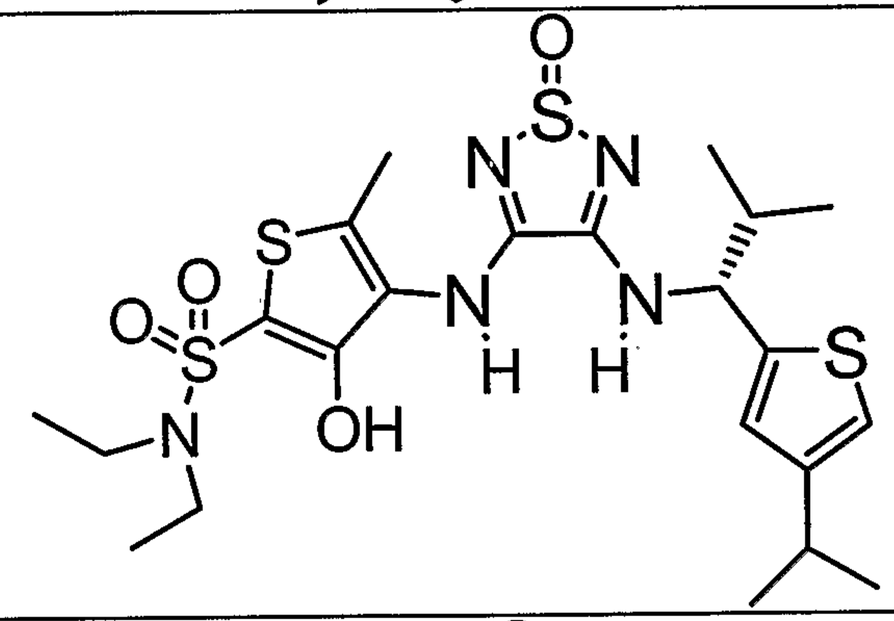
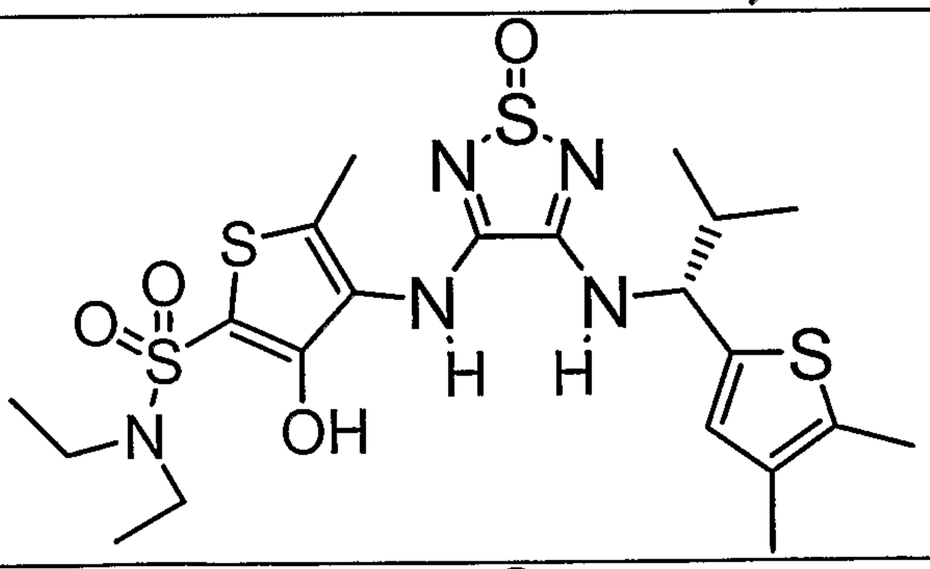
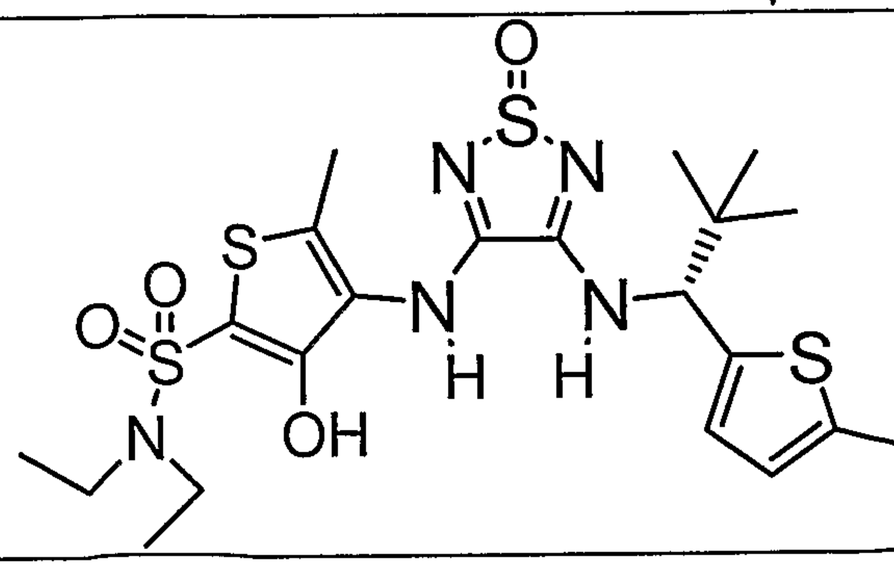
2637	22.6	603F	
2638	22.6	75.20	
2639	22.6	74	
2640	22.6	2-Bromo-PhNH2	
2641	22.6	2,3-Dichloro-PhNH2	

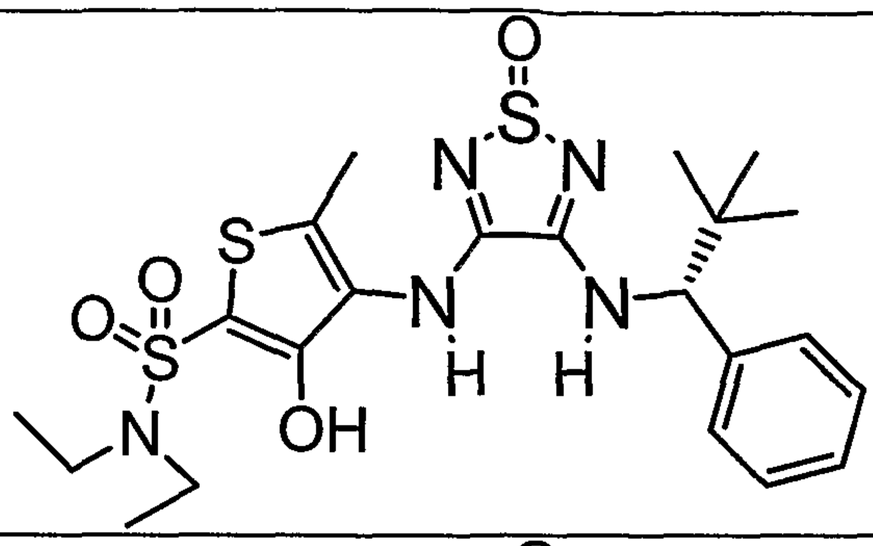
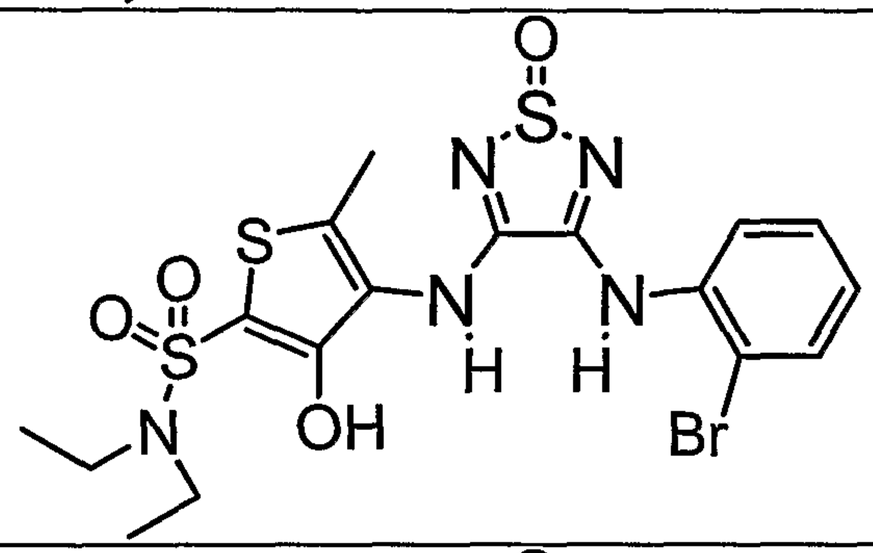
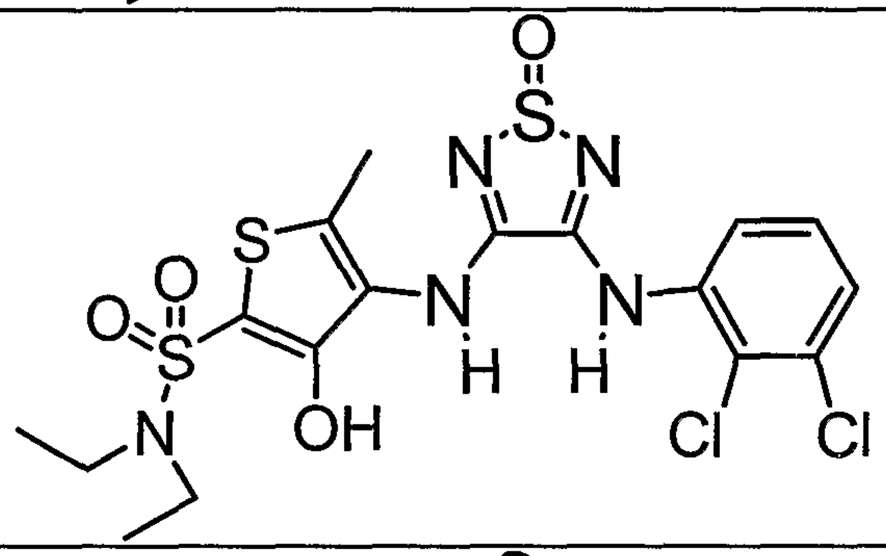
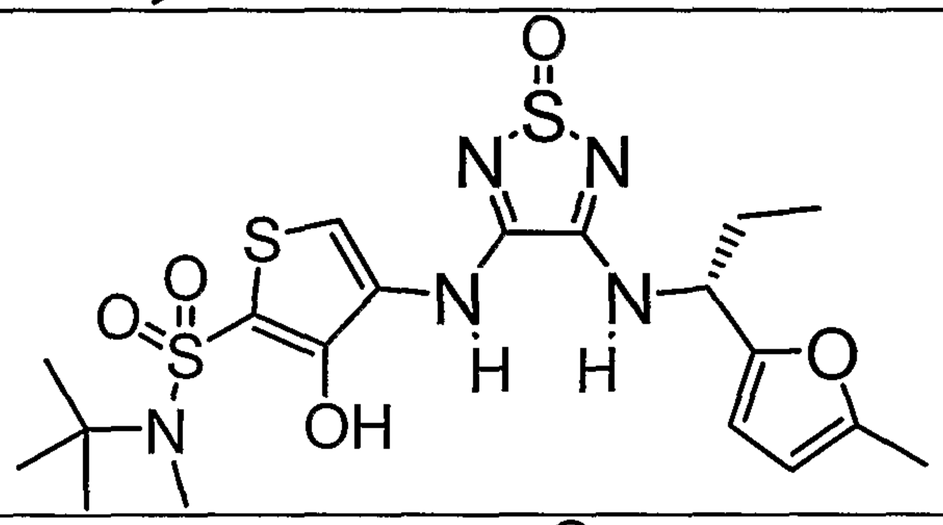
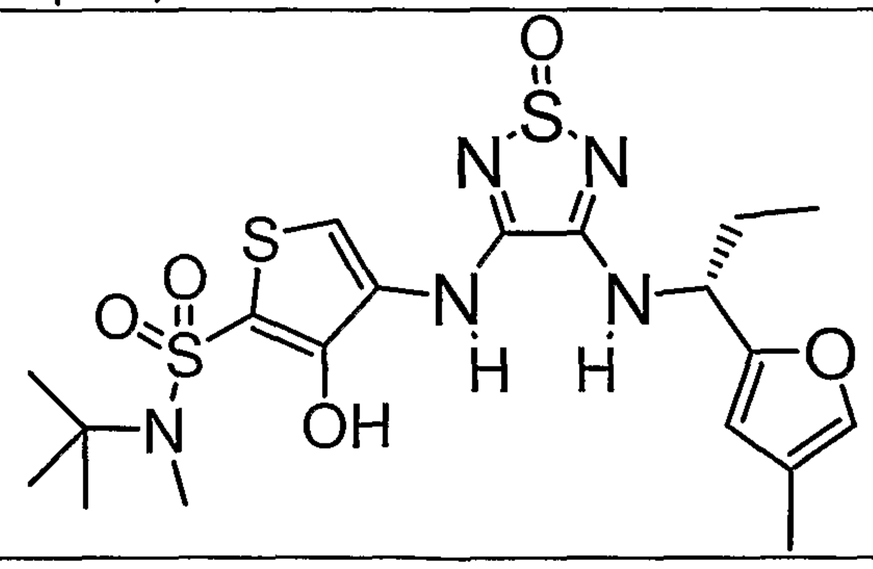
2642	22.7	75.1	
2643	22.7	75.49	
2644	22.7	75.9	
2645	22.7	75.10E	
2646	22.7	75.61	

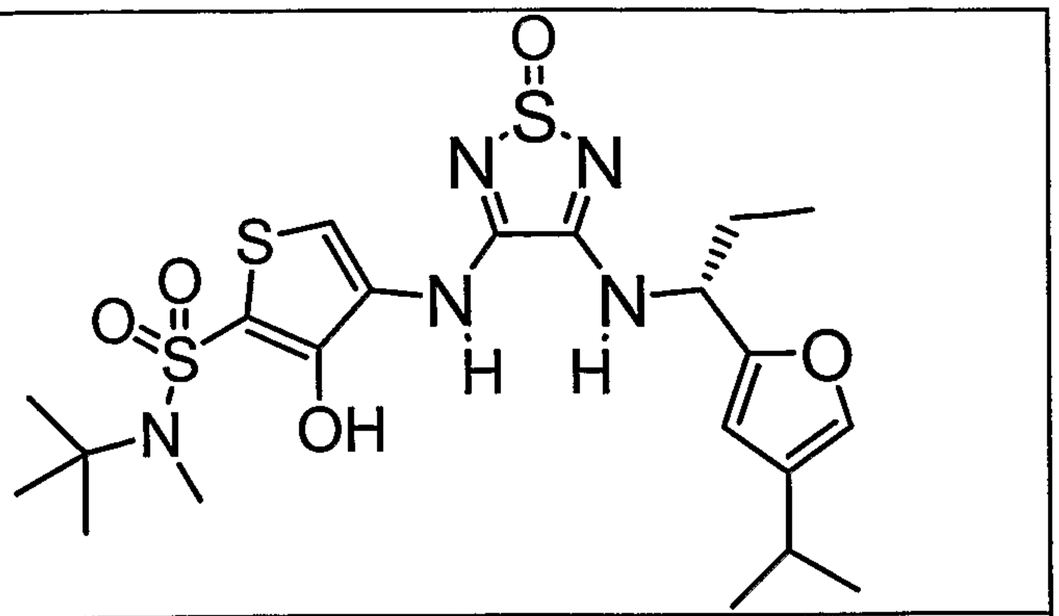
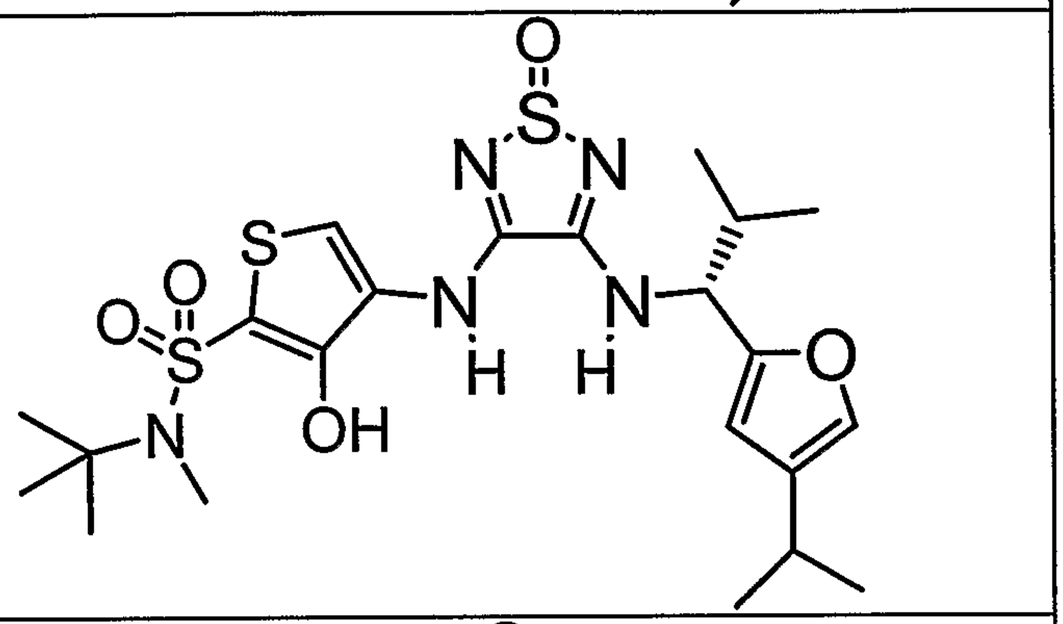
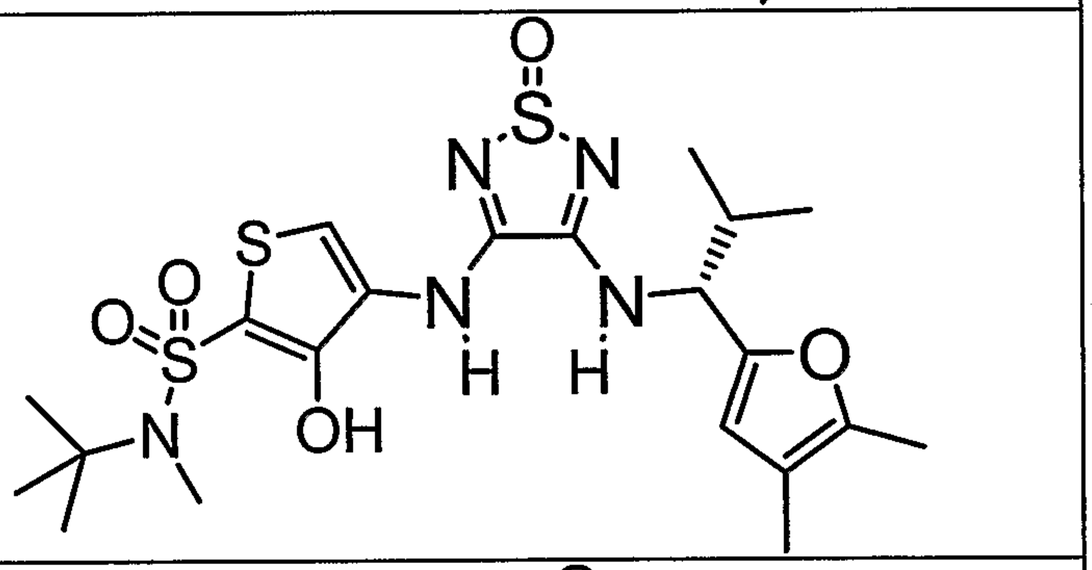
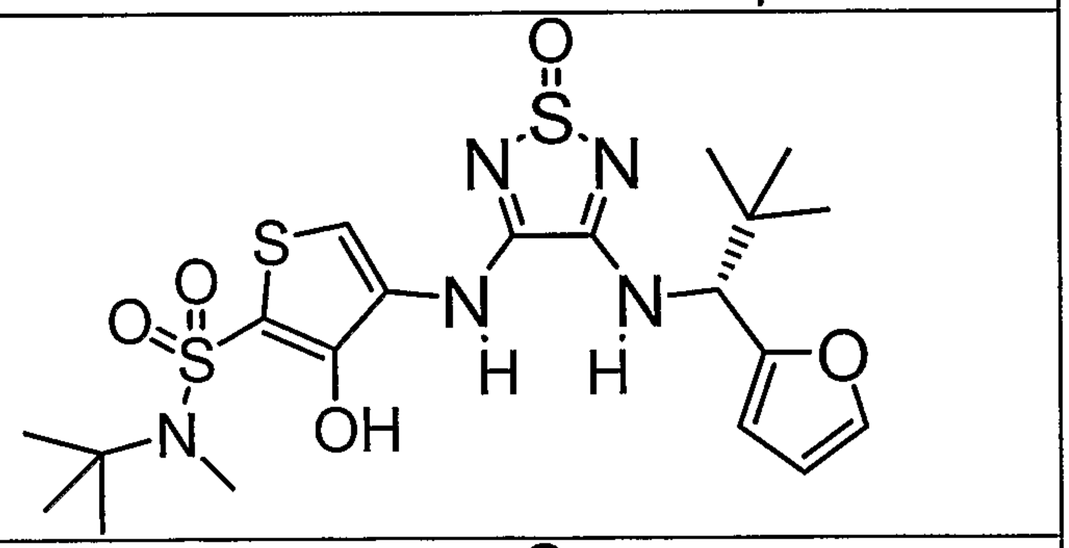
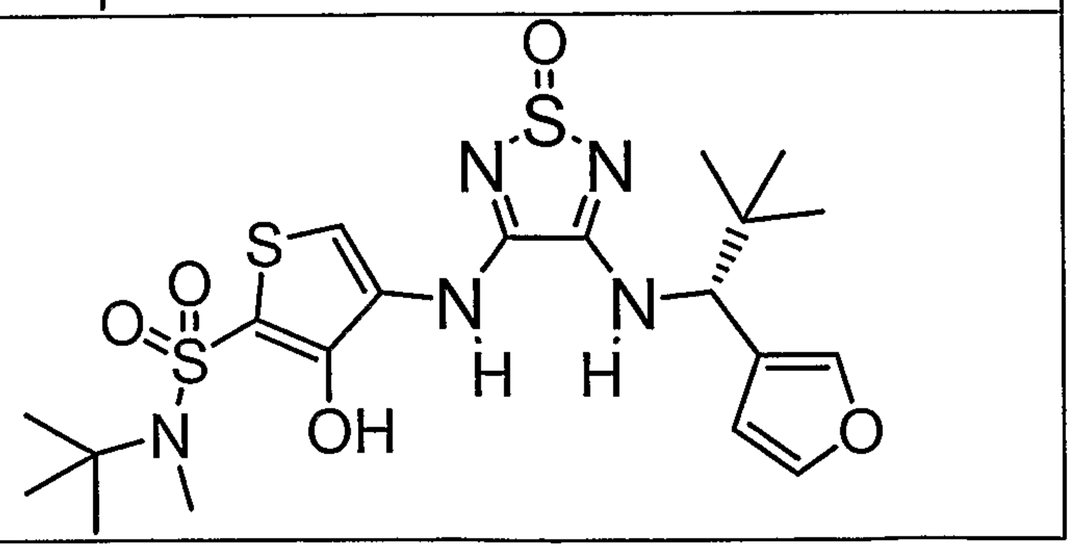
2647	22.7	1048	
2648	22.7	75.69	
2649	22.7	603B	
2650	22.7	603E	
2651	22.7	603F	

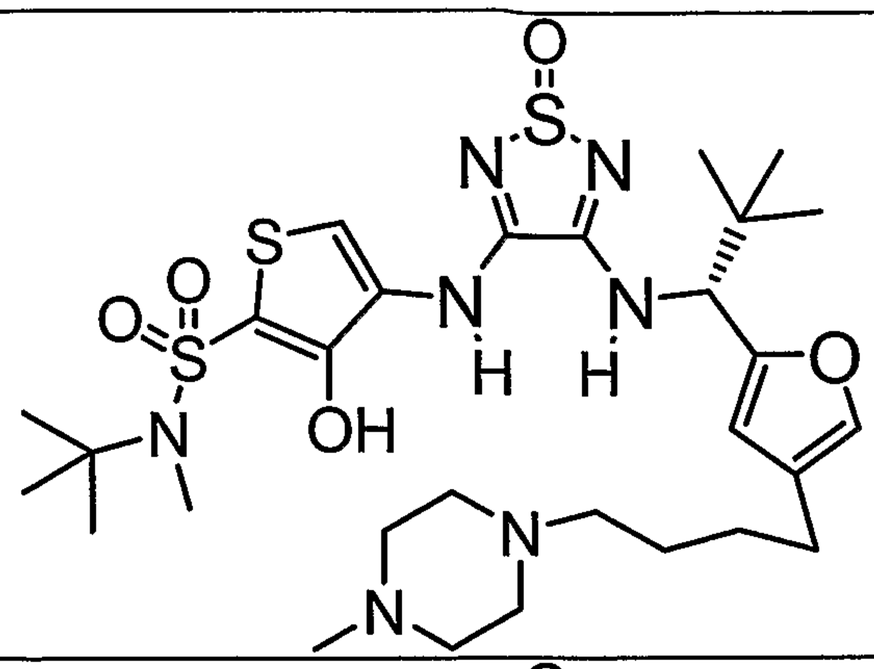
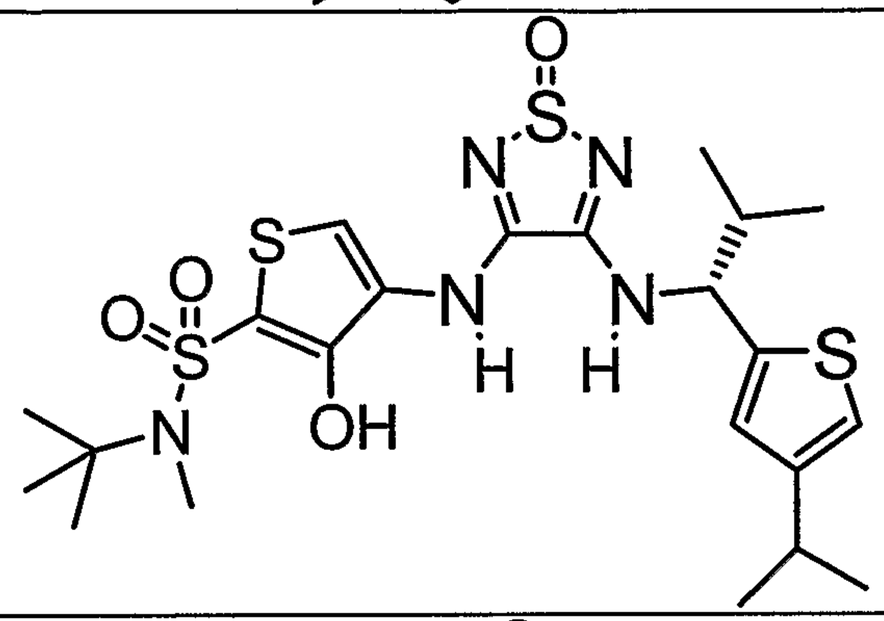
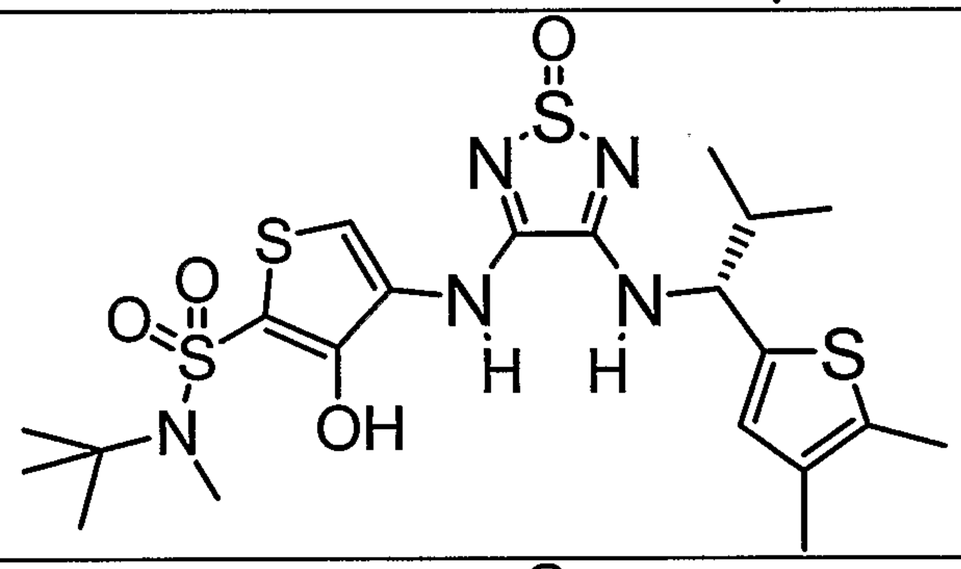
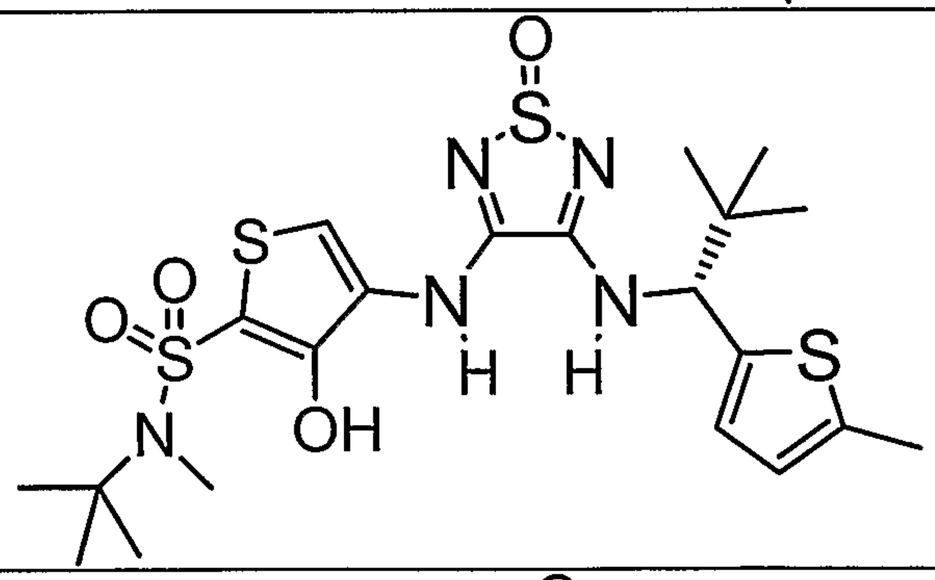
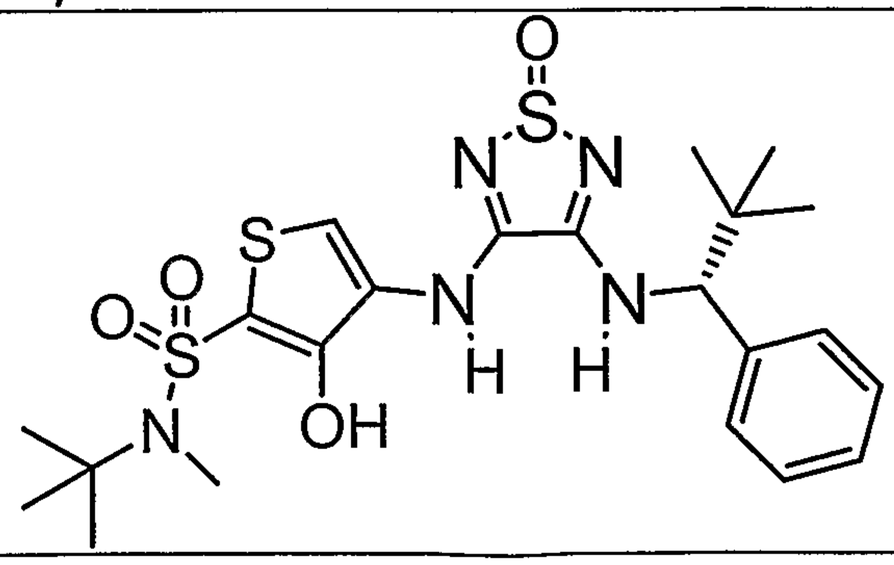
2652	22.7	75.20	
2653	22.7	74	
2654	22.7	2-Bromo-PhNH2	
2655	22.7	2,3-Dichloro-PhNH2	
2656	22.22	75.1	

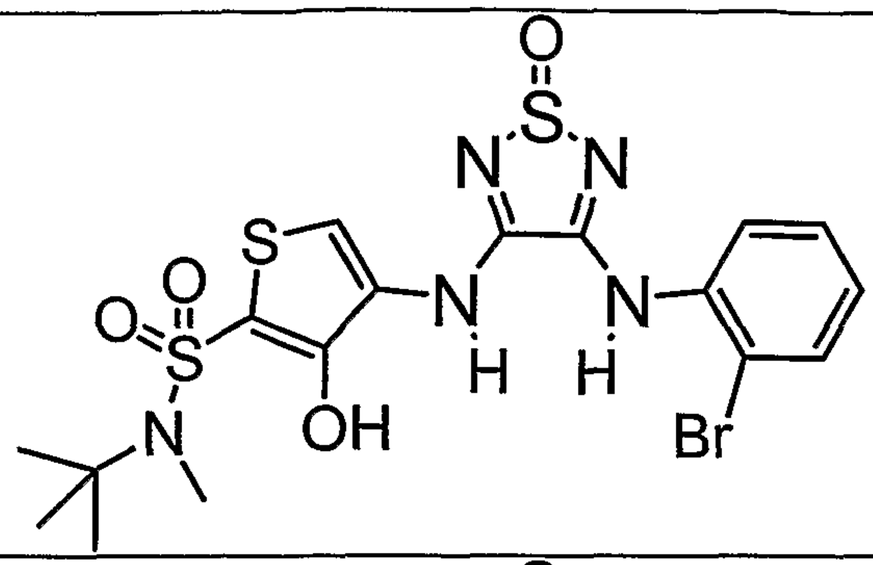
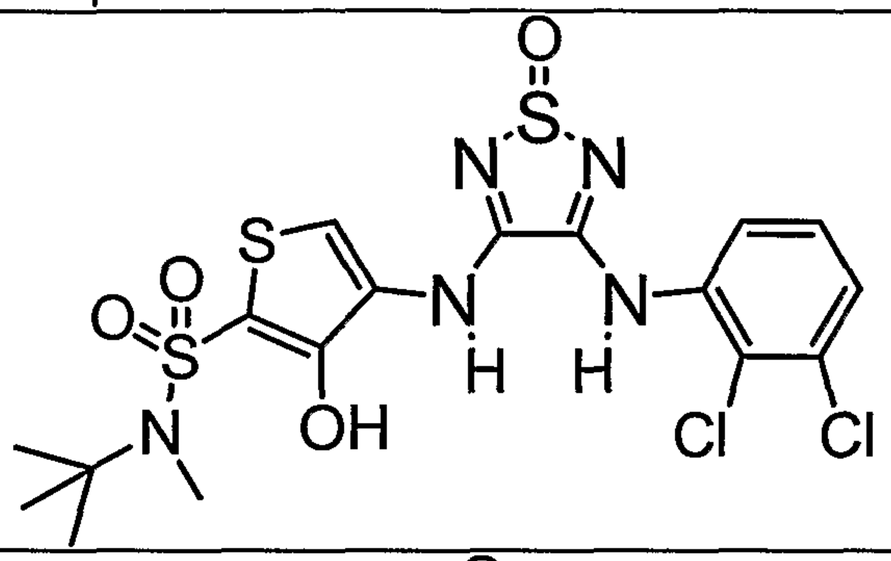
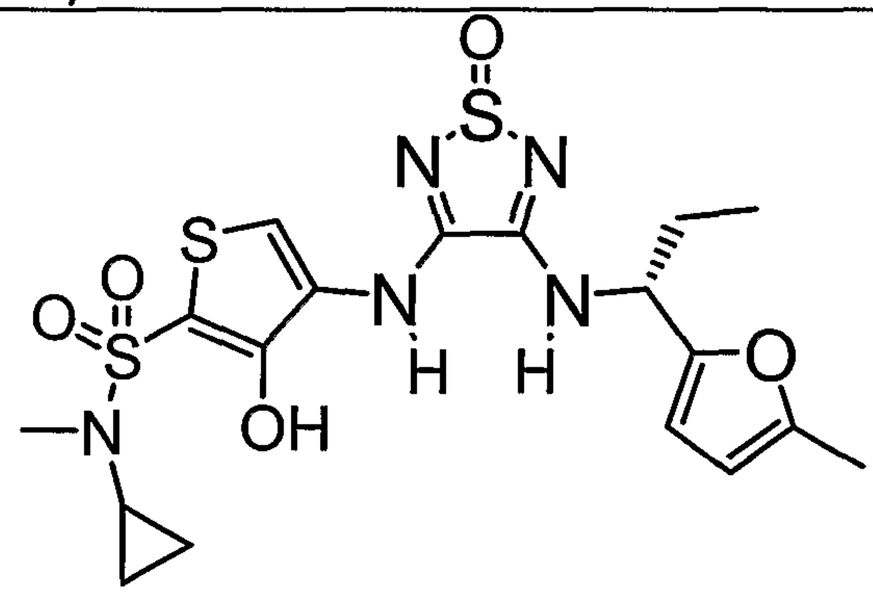
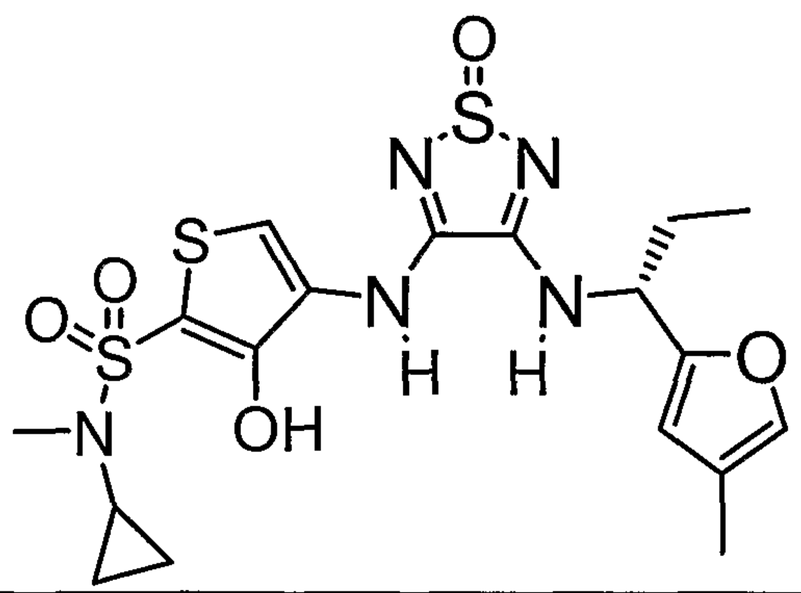
2657	22.22	75.49	
2658	22.22	75.9	
2659	22.22	75.10E	
2660	22.22	75.61	
2661	22.22	1048	

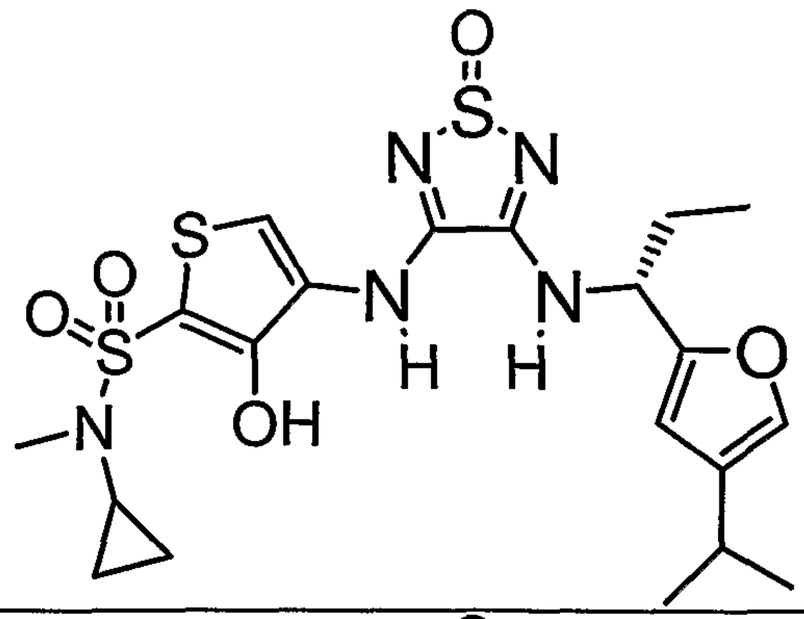
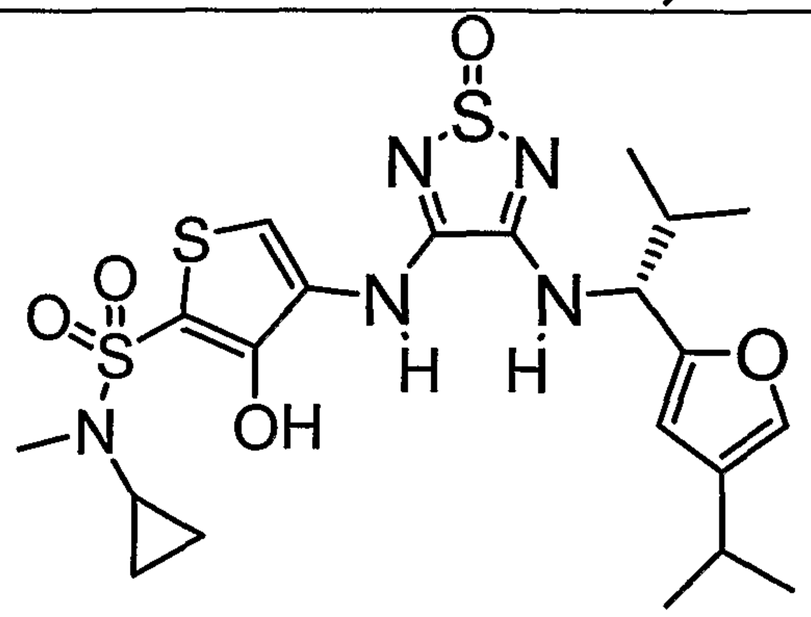
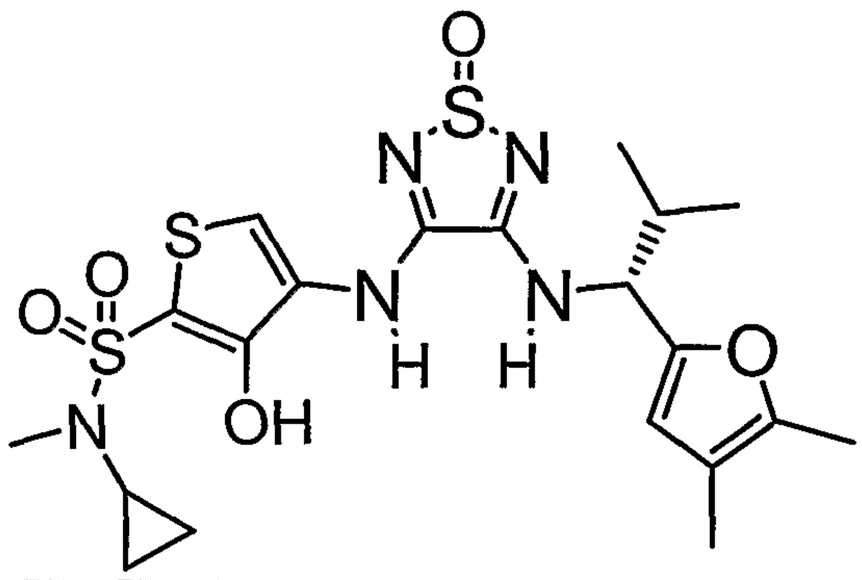
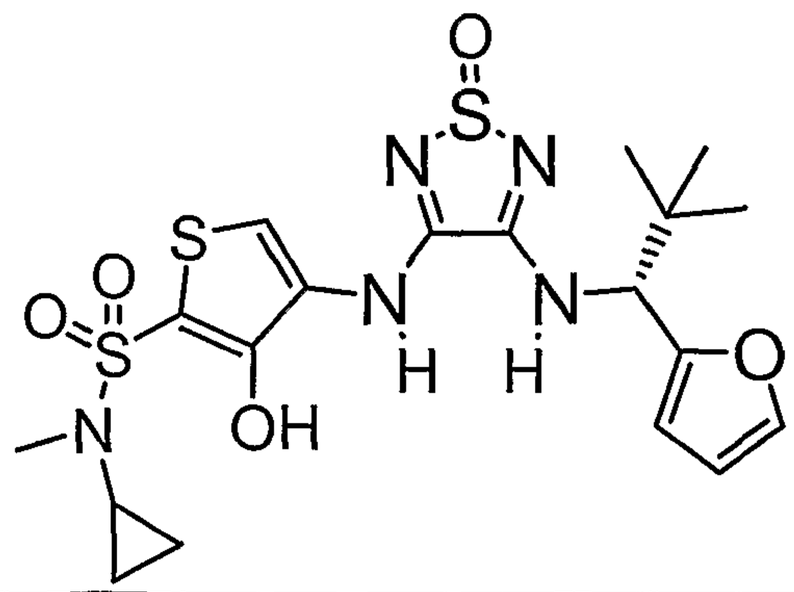
2662	22.22	75.69	
2663	22.22	603B	
2664	22.22	603E	
2665	22.22	603F	
2666	22.22	75.20	

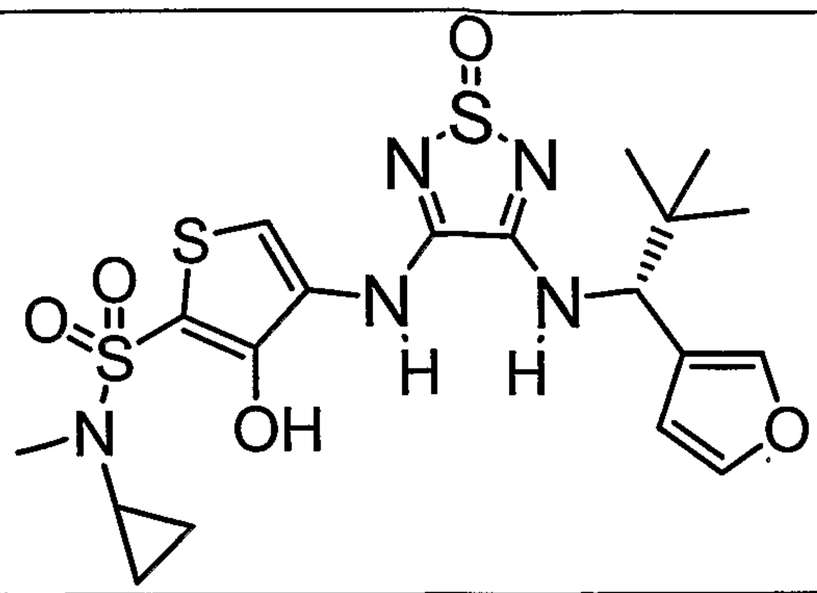
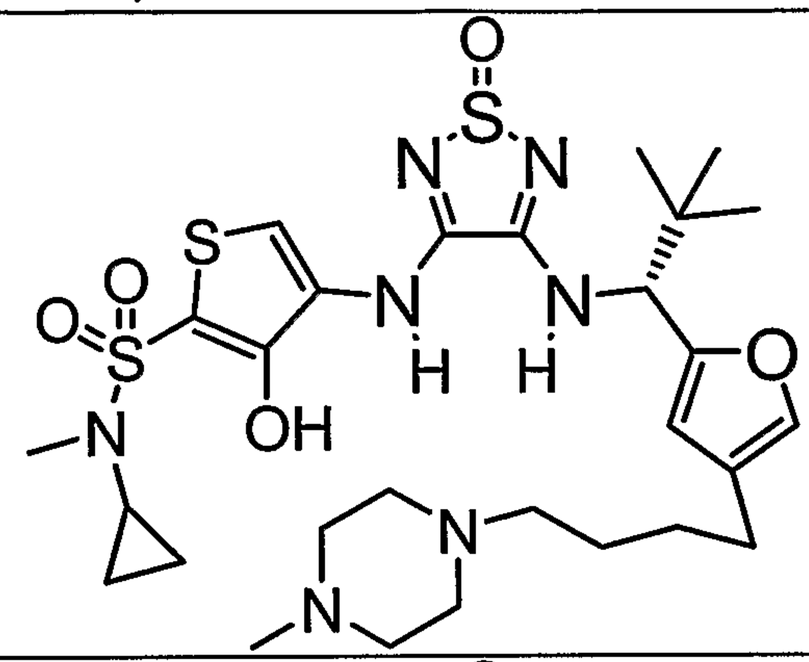
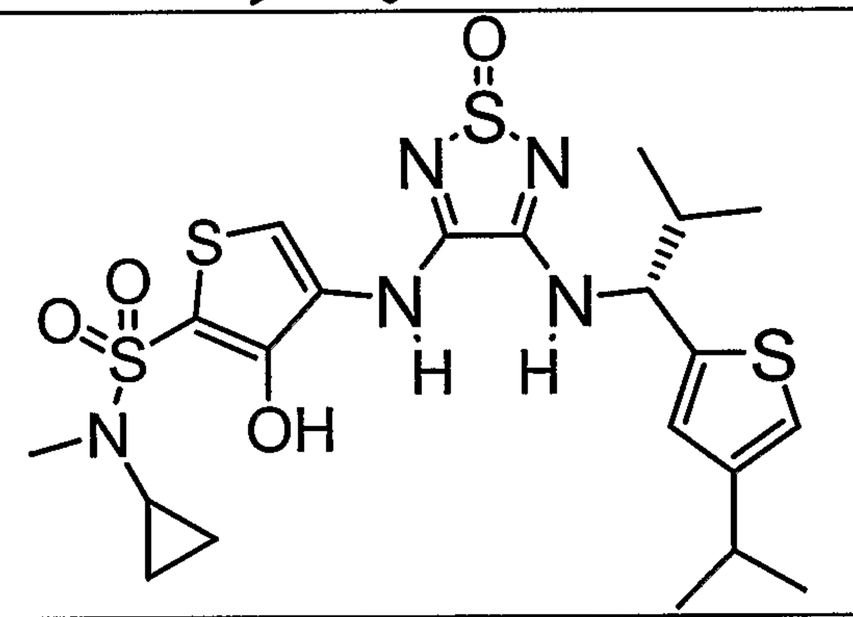
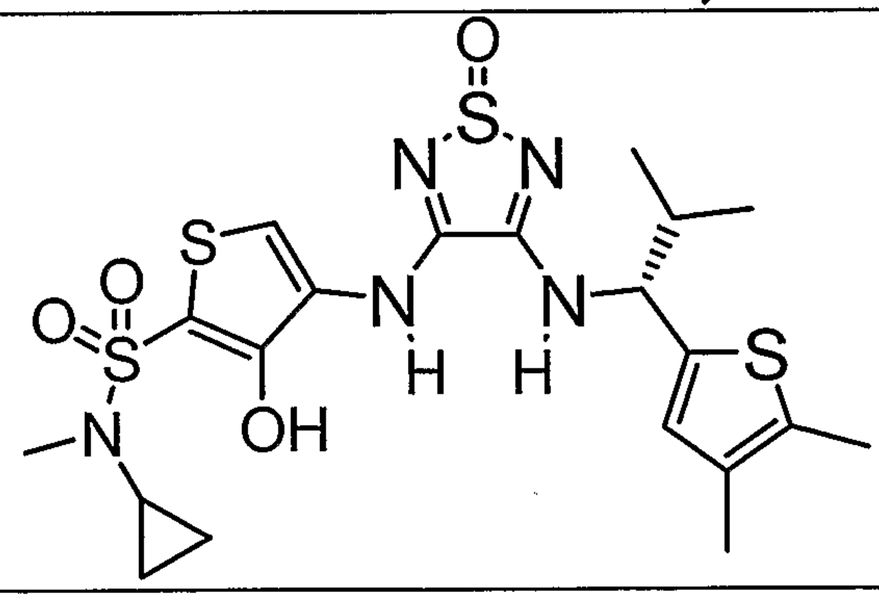
2667	22.22	74	
2668	22.22	2-Bromo-PhNH2	
2669	22.22	2,3-Dichloro-PhNH2	
2670	22.19	75.1	
2671	22.19	75.49	

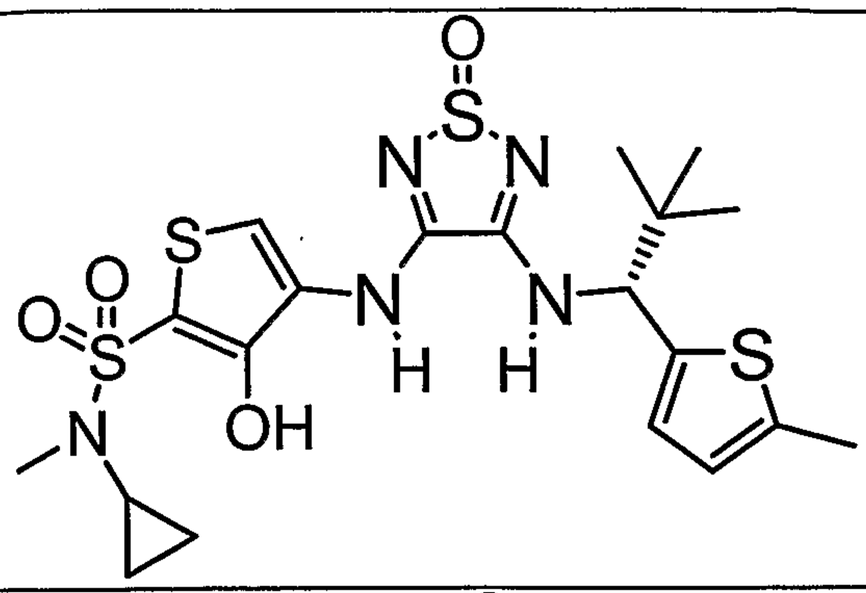
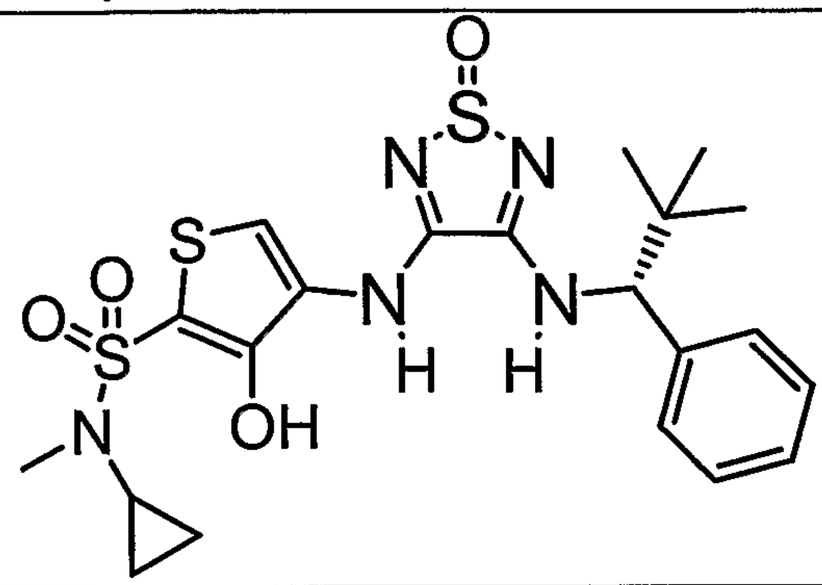
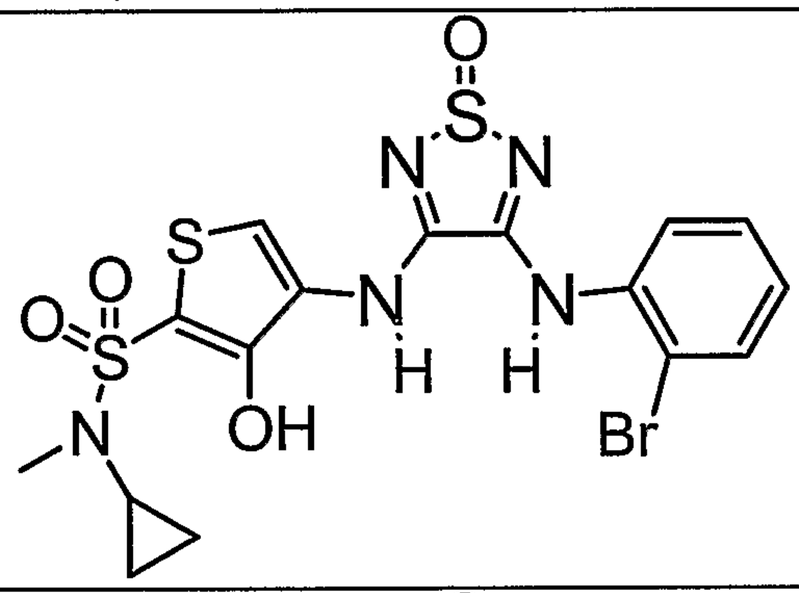
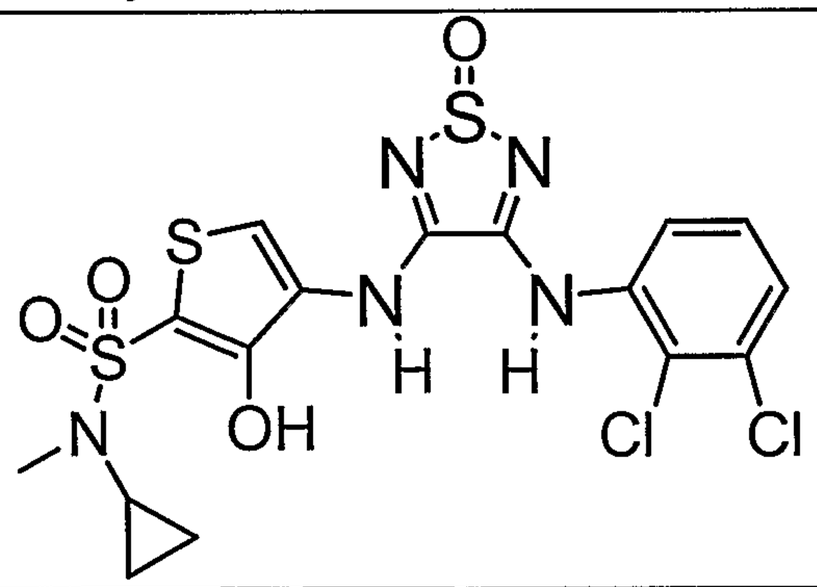
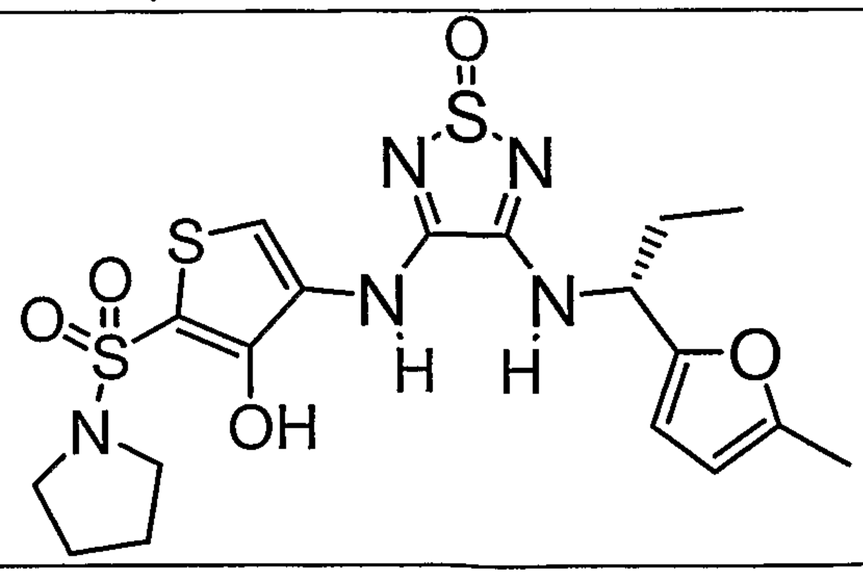
2672	22.19	75.9	
2673	22.19	75.10E	
2674	22.19	75.61	
2675	22.19	1048	
2676	22.19	75.69	

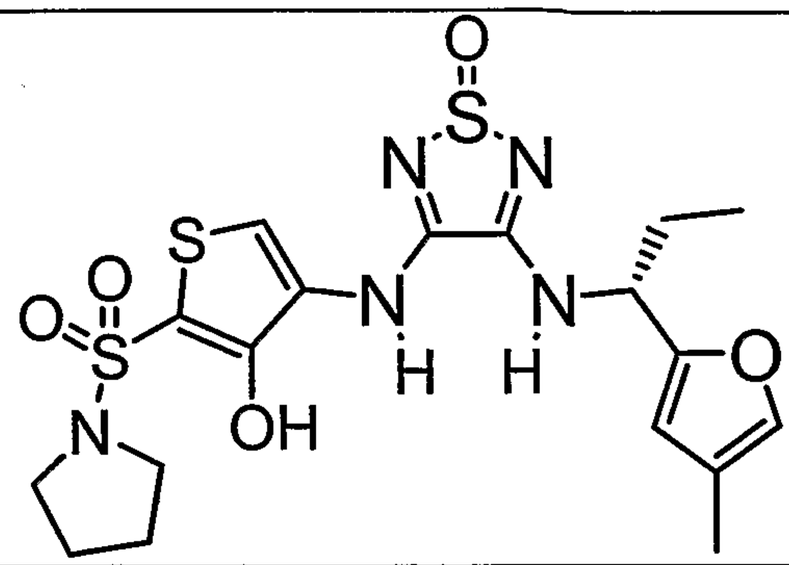
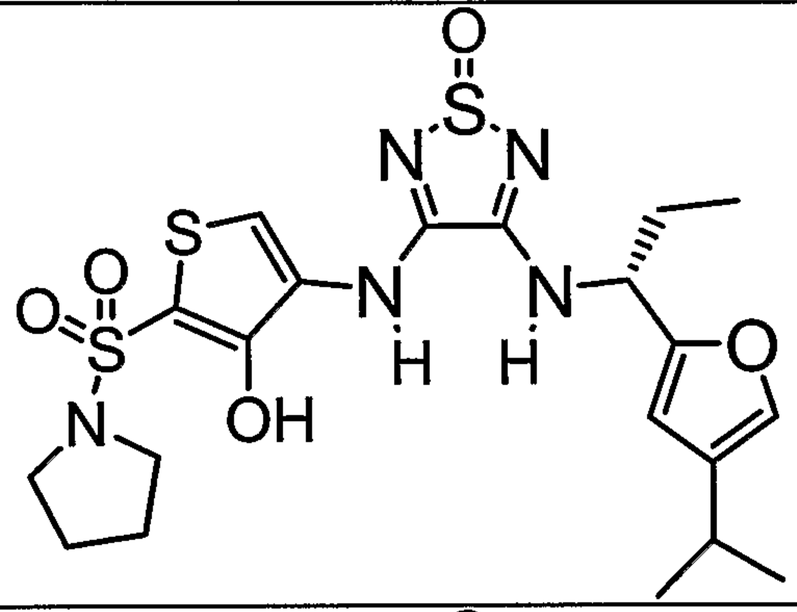
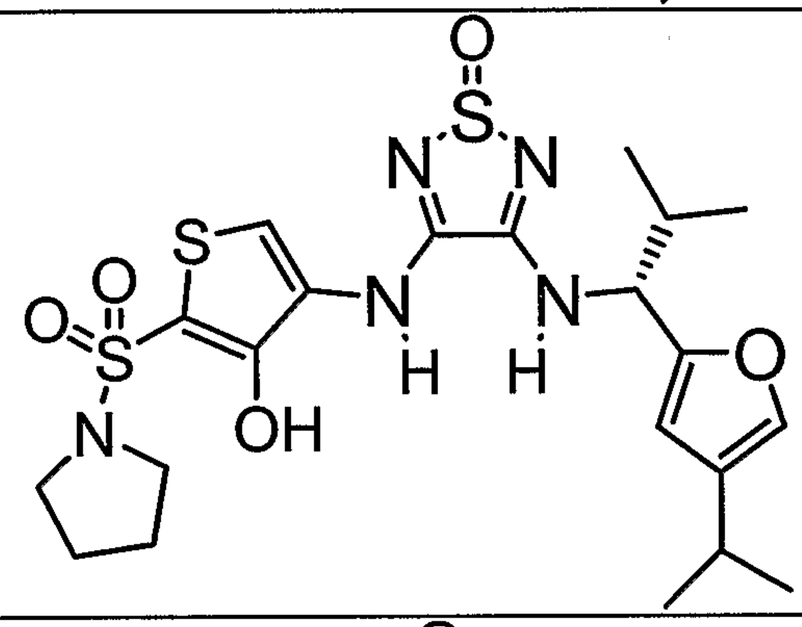
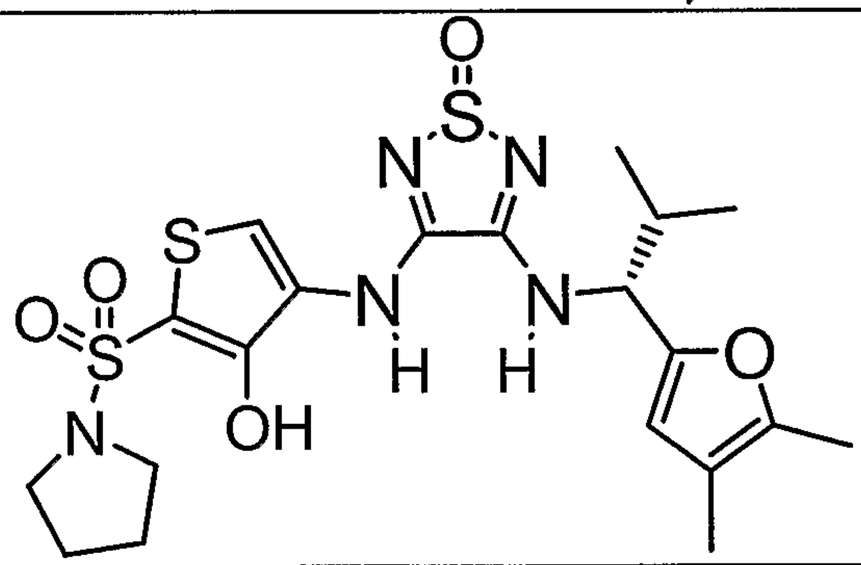
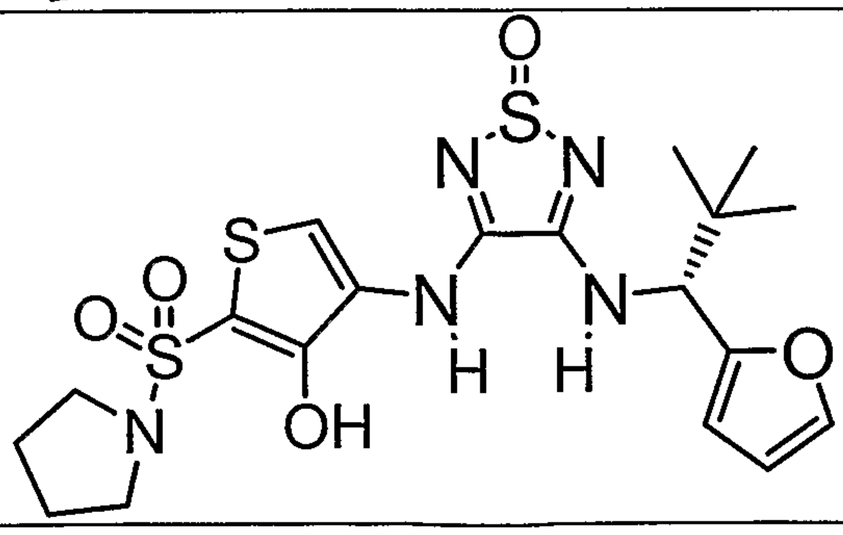
2677	22.19	603B	
2678	22.19	603E	
2679	22.19	603F	
2680	22.19	75.20	
2681	22.19	74	

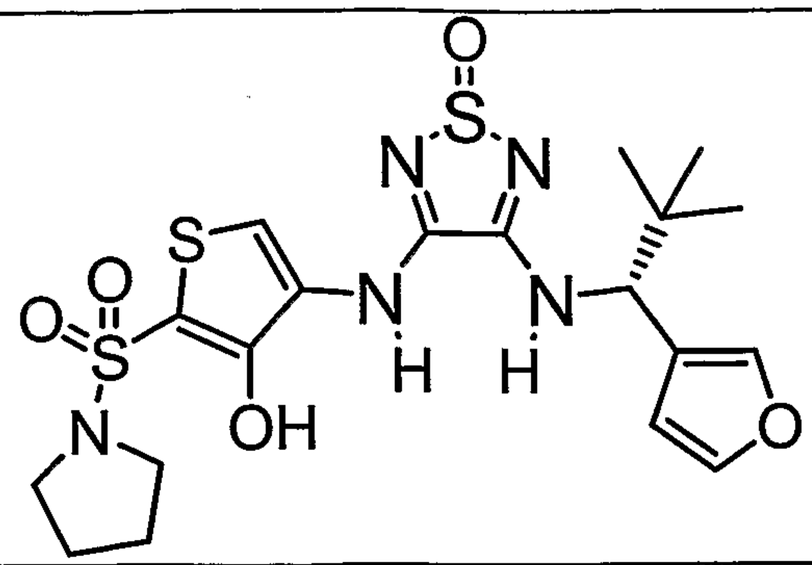
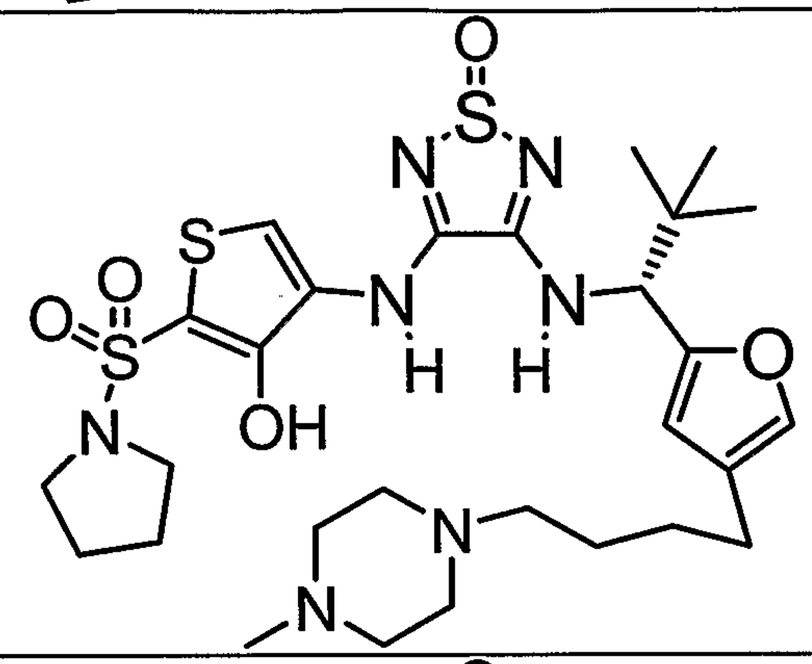
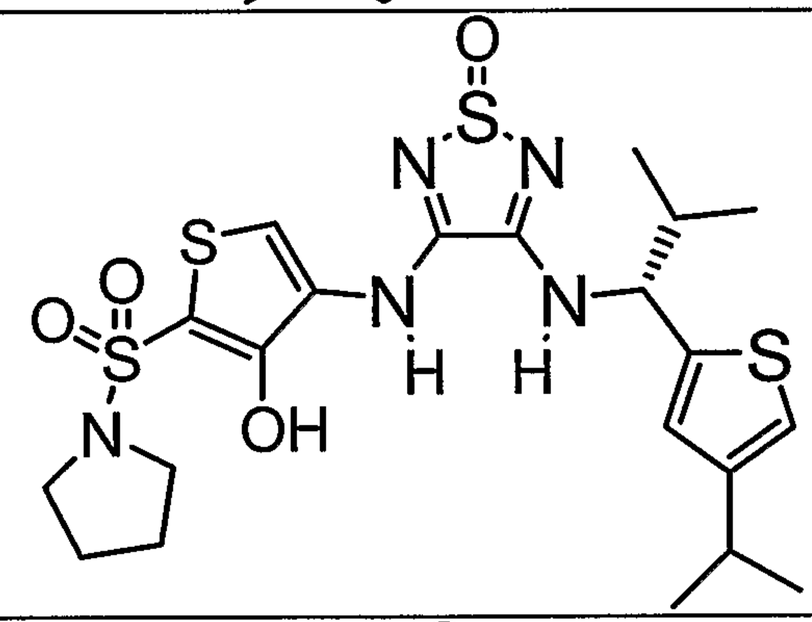
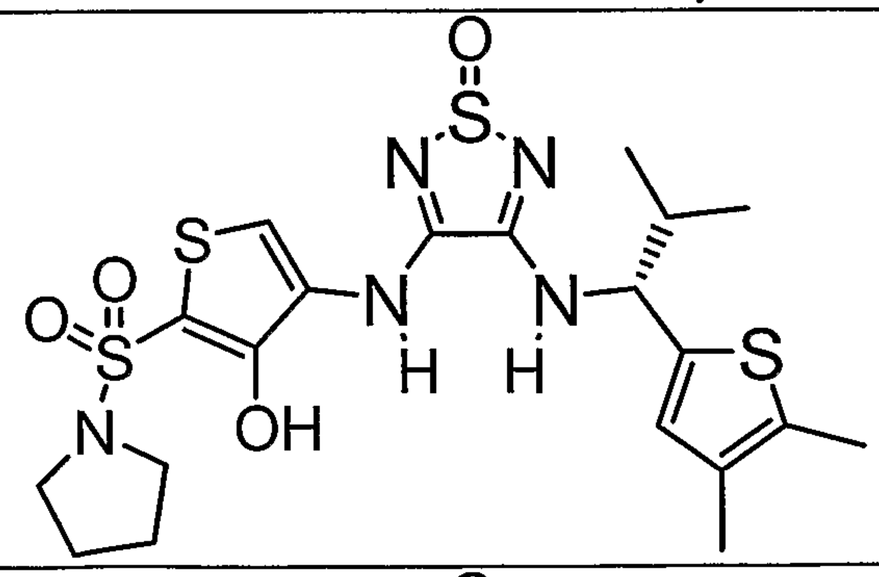
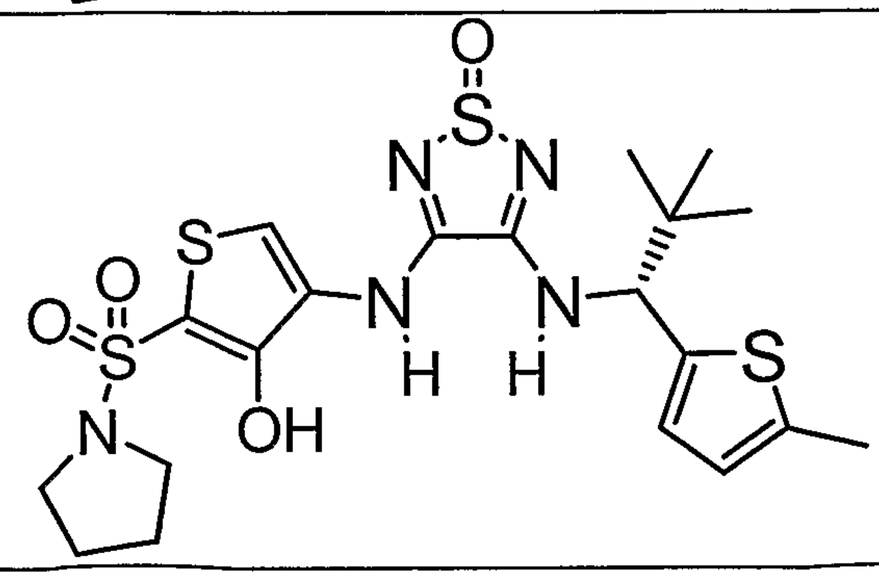
2682	22.19	2-Bromo-PhNH2	
2683	22.19	2,3-Dichloro-PhNH2	
2684	250	75.1	
2685	250	75.49	

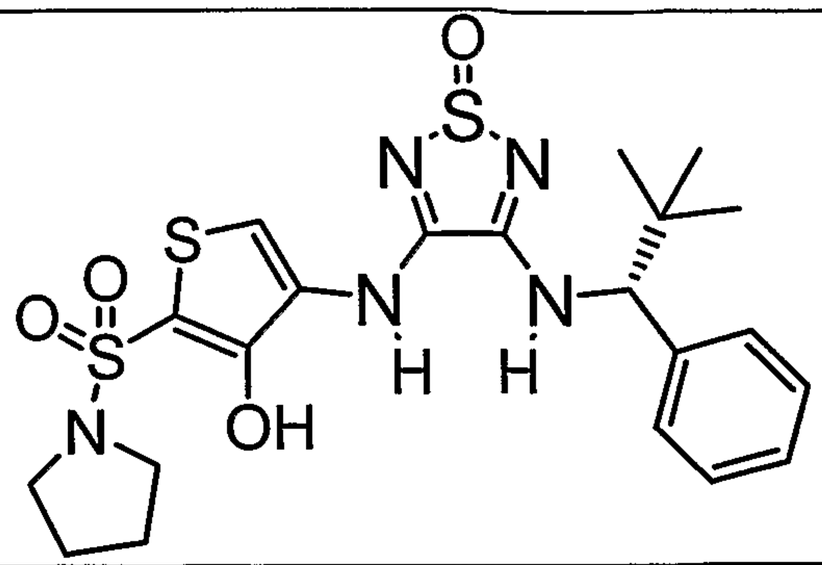
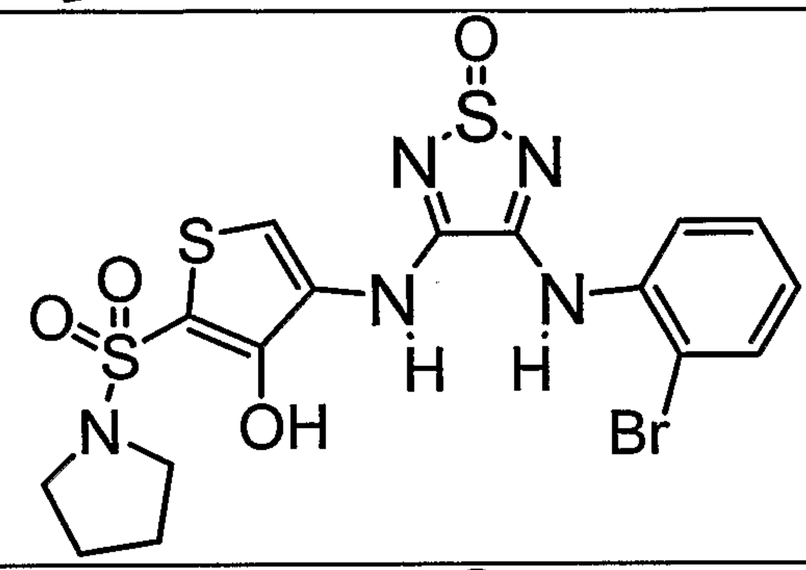
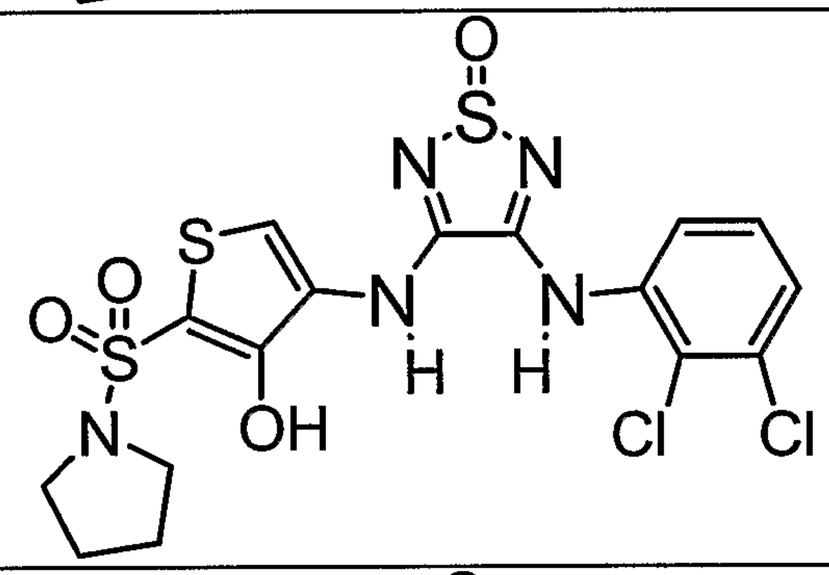
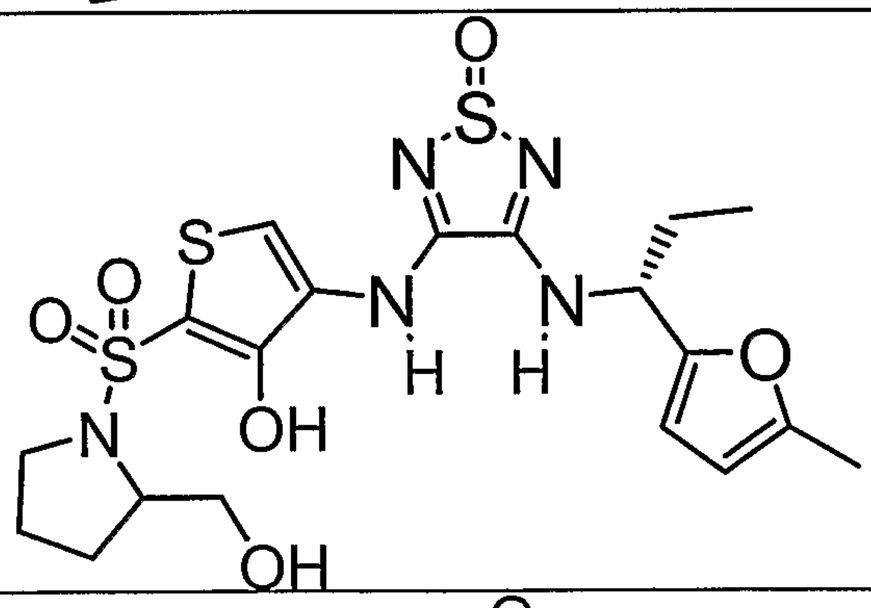
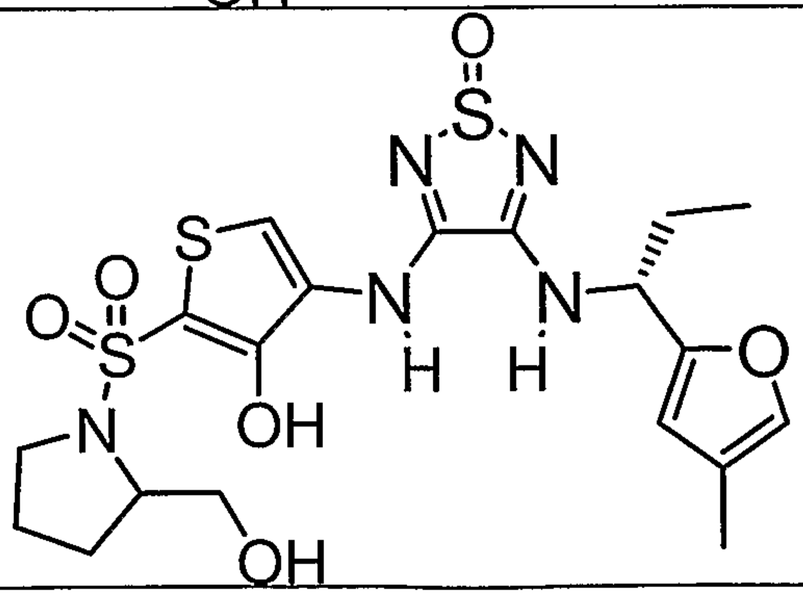
2686	250	75.9	
2687	250	75.10E	
2688	250	75.61	
2689	250	1048	

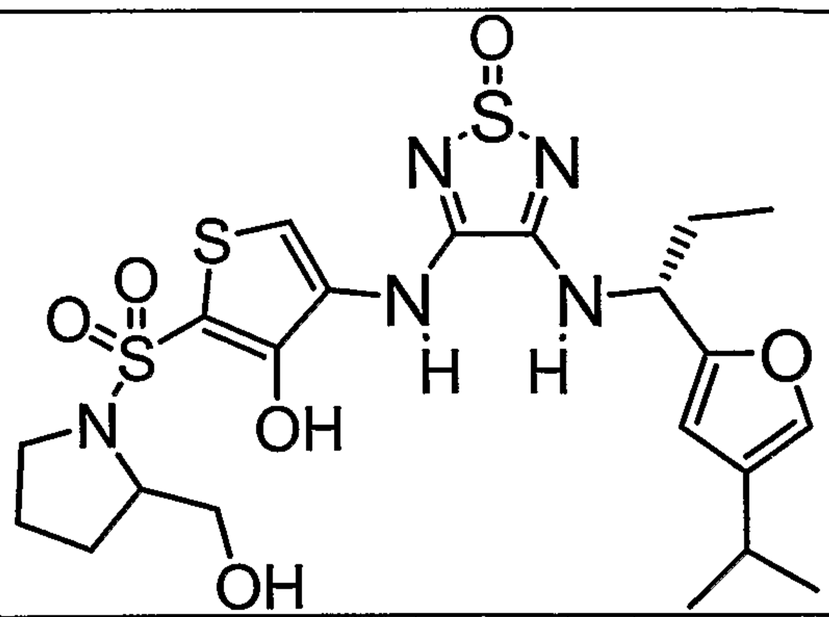
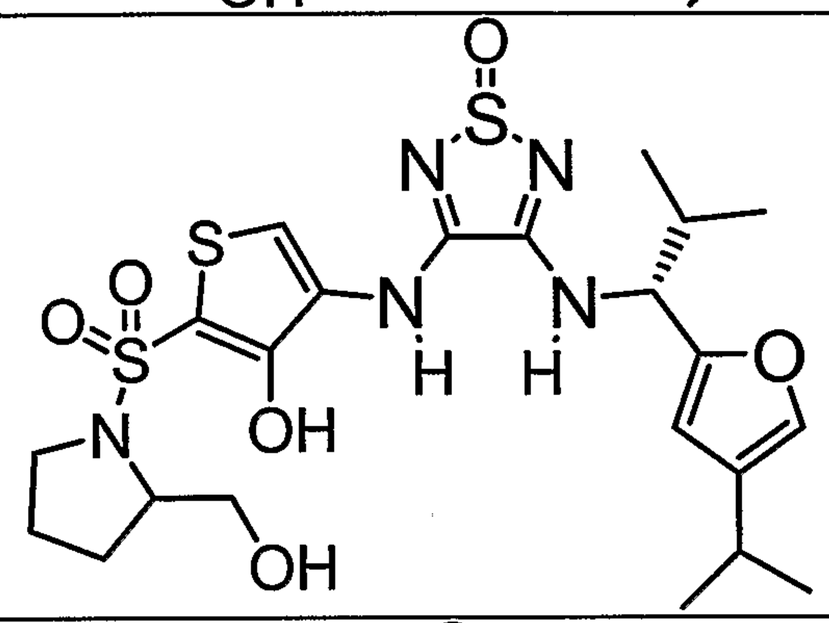
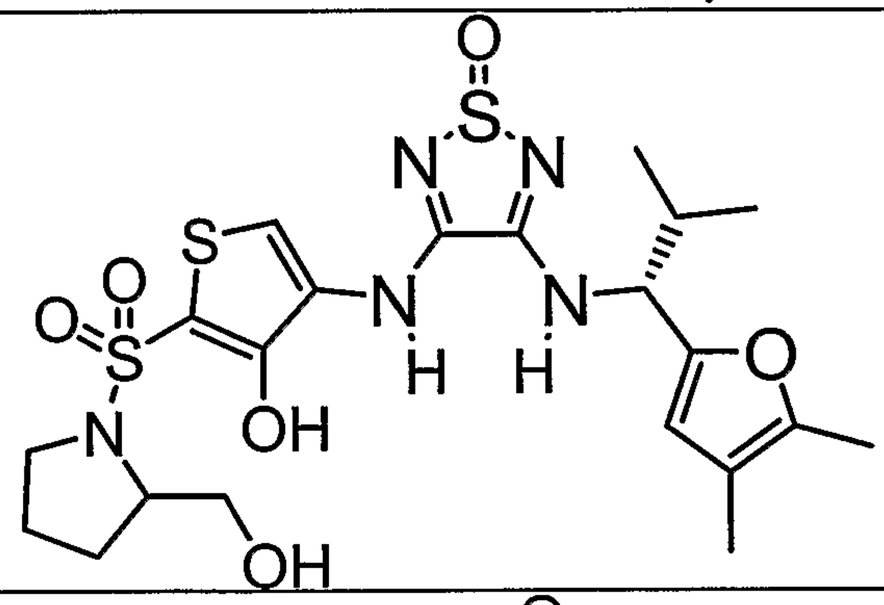
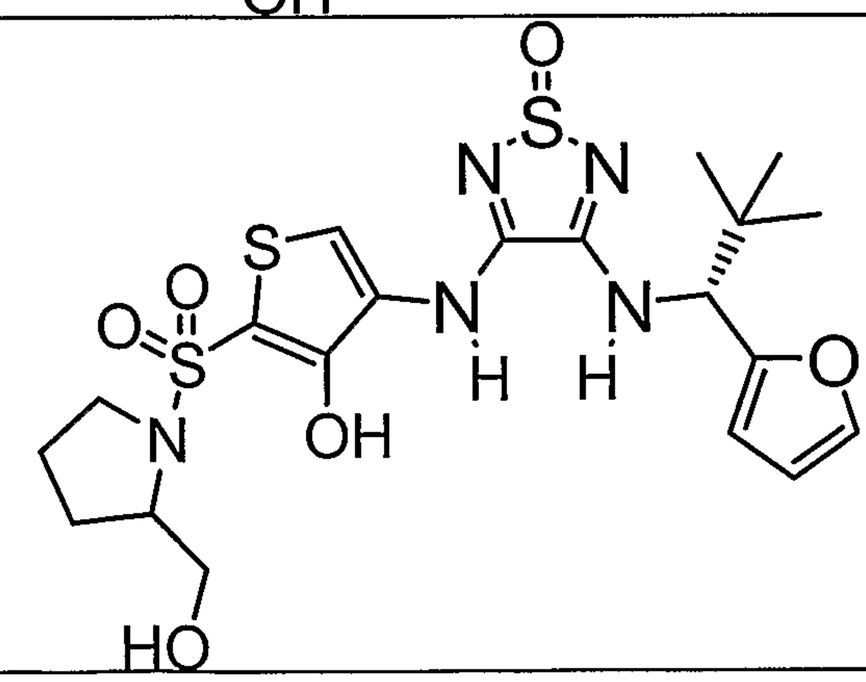
2690	250	75.69	
2691	250	603B	
2692	250	603E	
2693	250	603F	

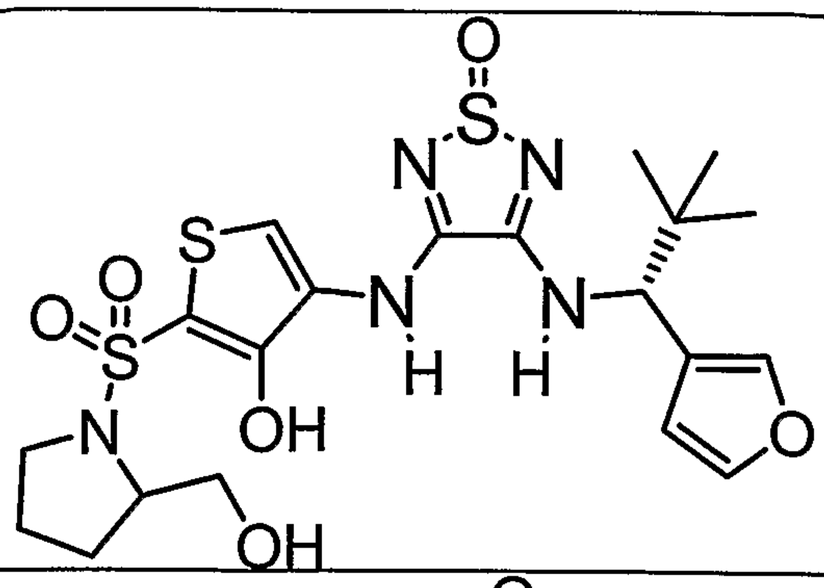
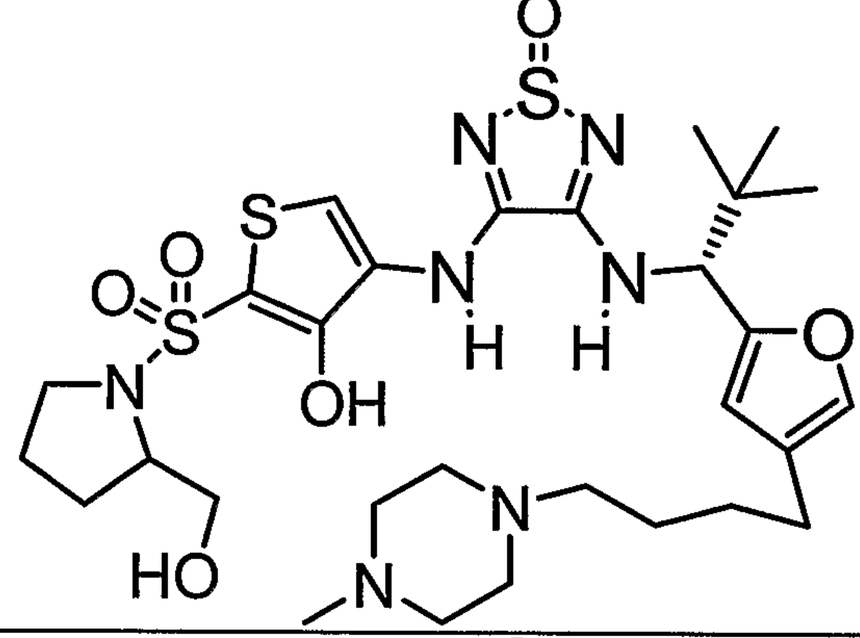
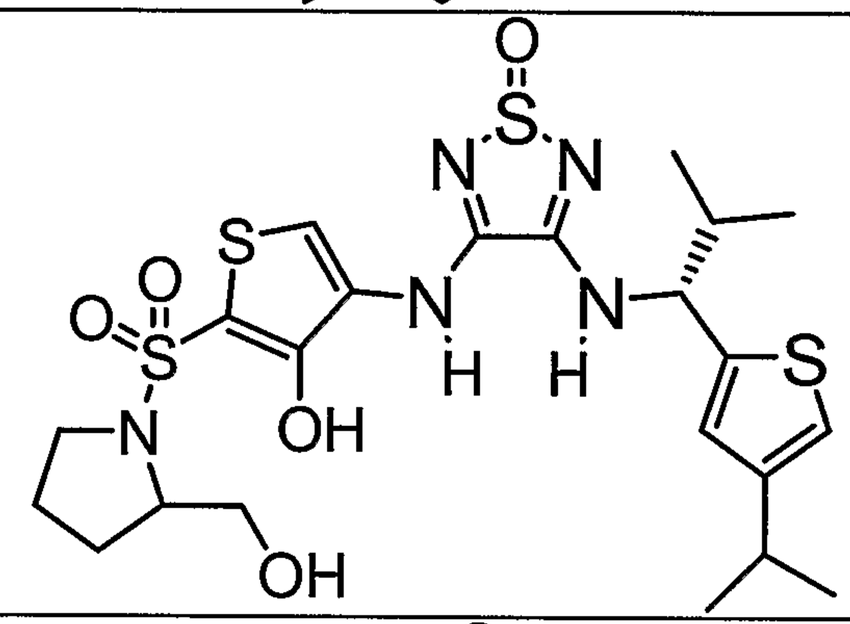
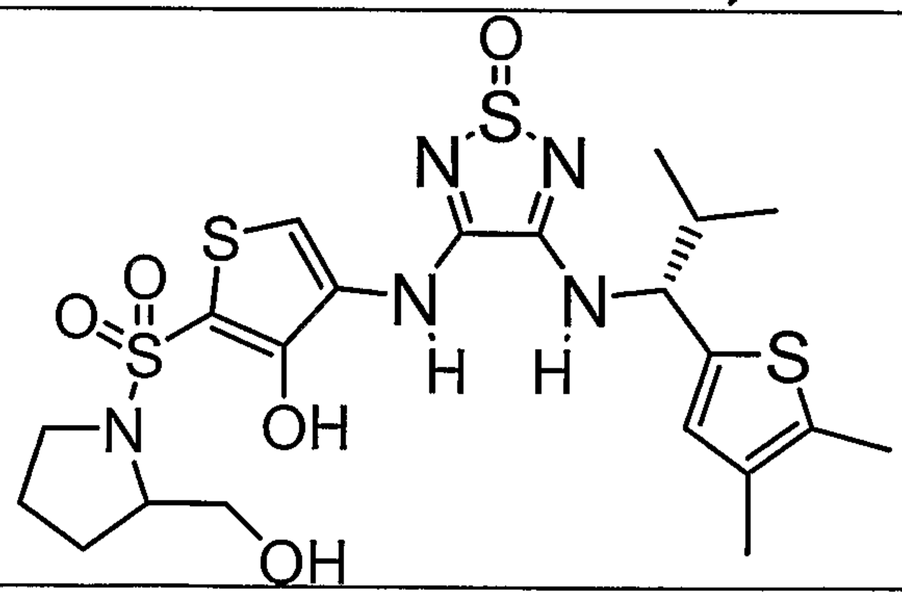
2694	250	75.20	
2695	250	74	
2696	250	2-Bromo-PhNH2	
2697	250	2,3-Dichloro-PhNH2	
2698	22.28	75.1	

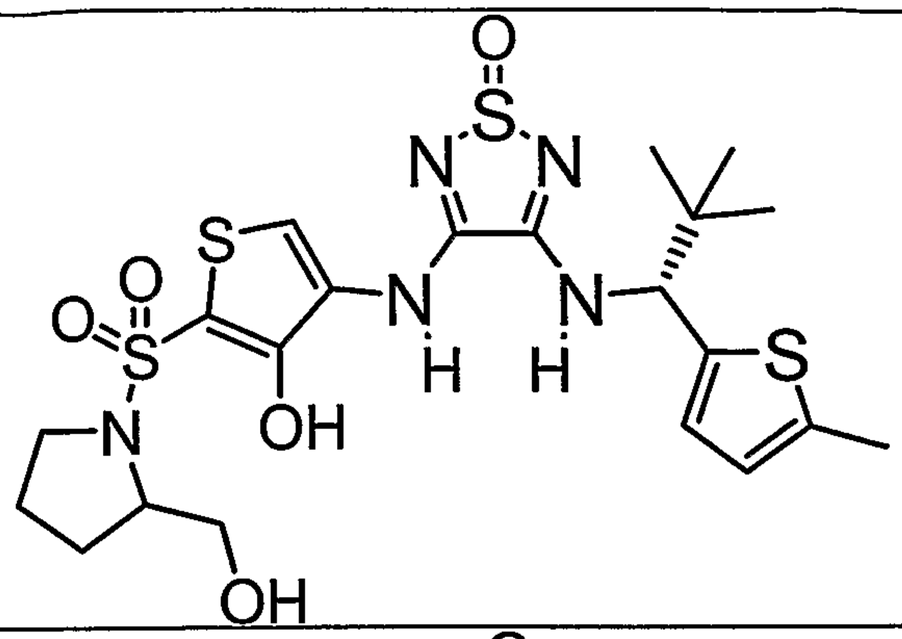
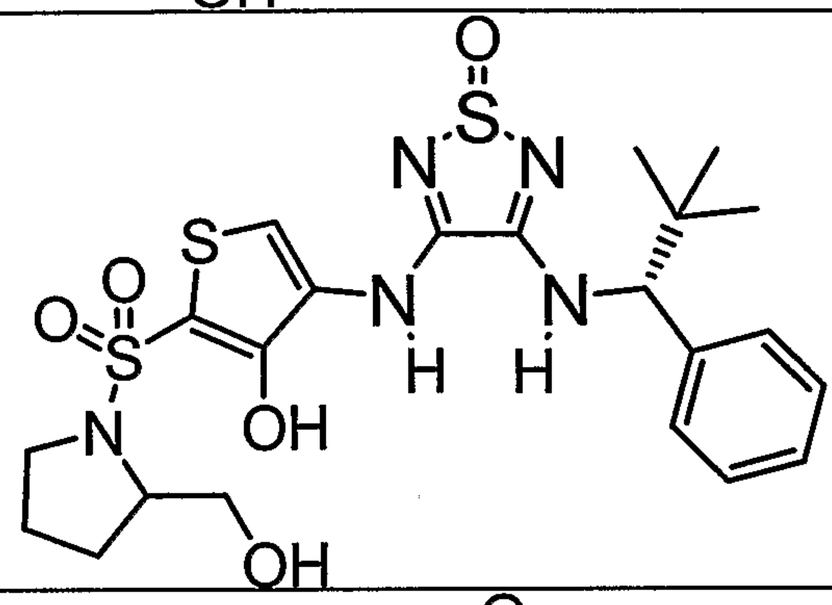
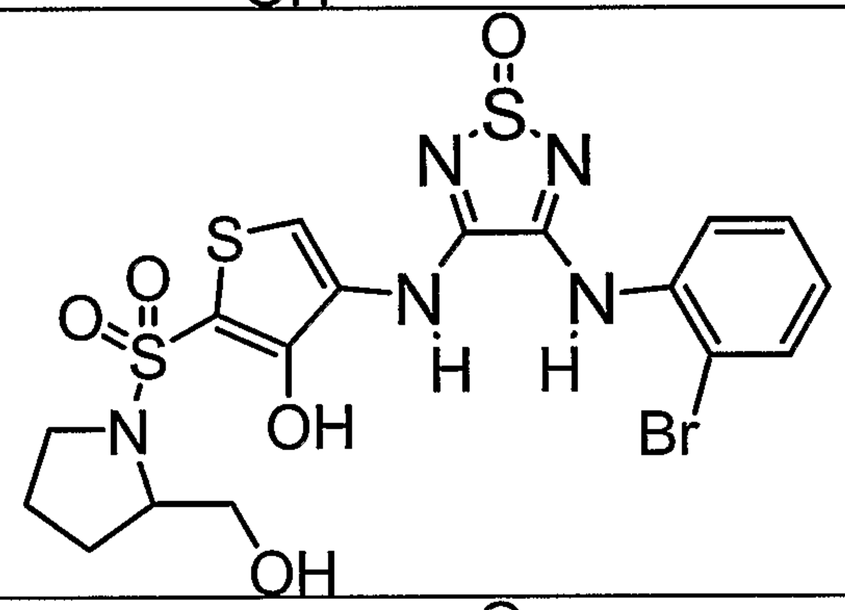
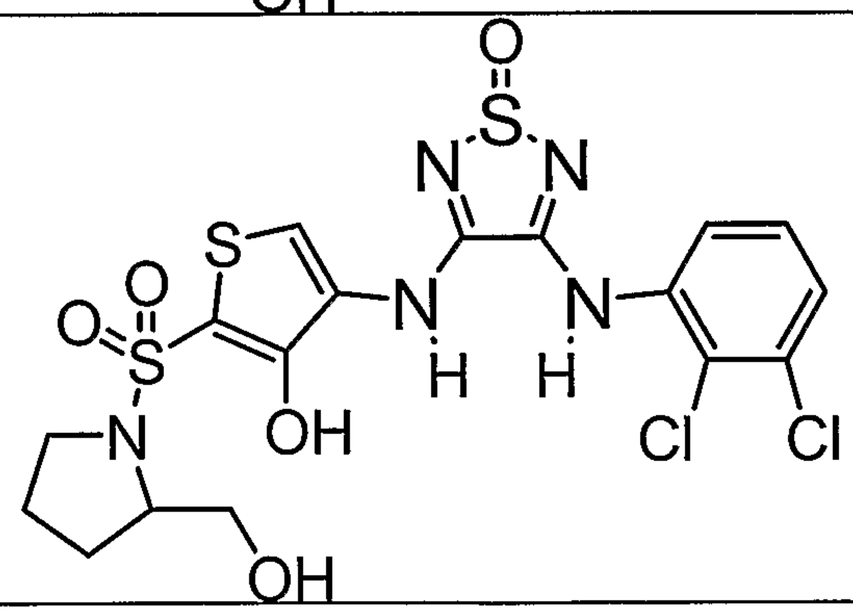
2699	22.28	75.49	
2700	22.28	75.9	
2701	22.28	75.10E	
2702	22.28	75.61	
2703	22.28	1048	

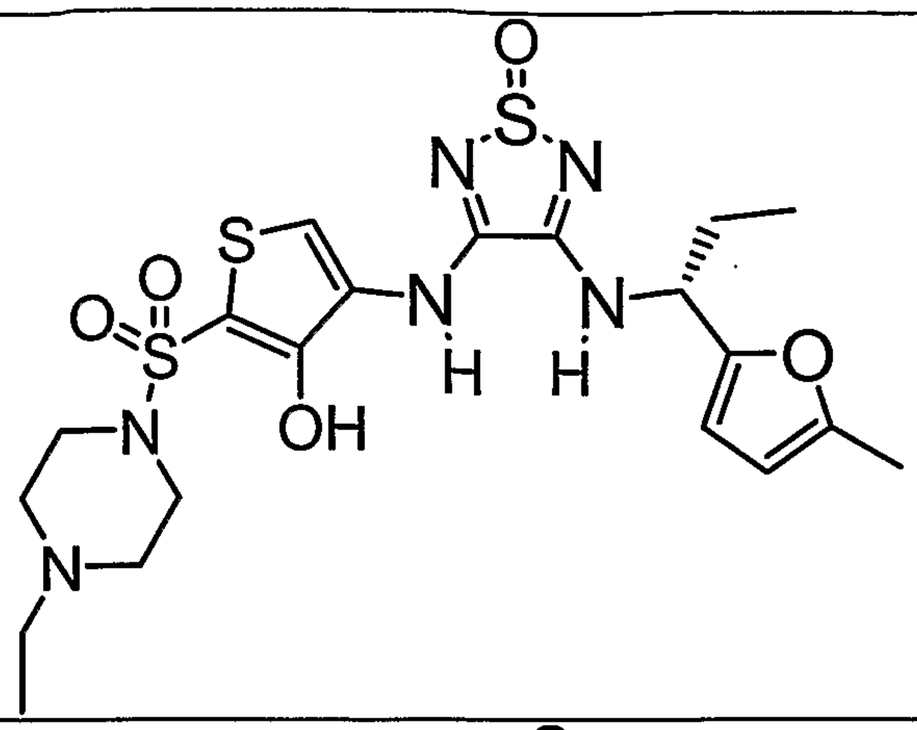
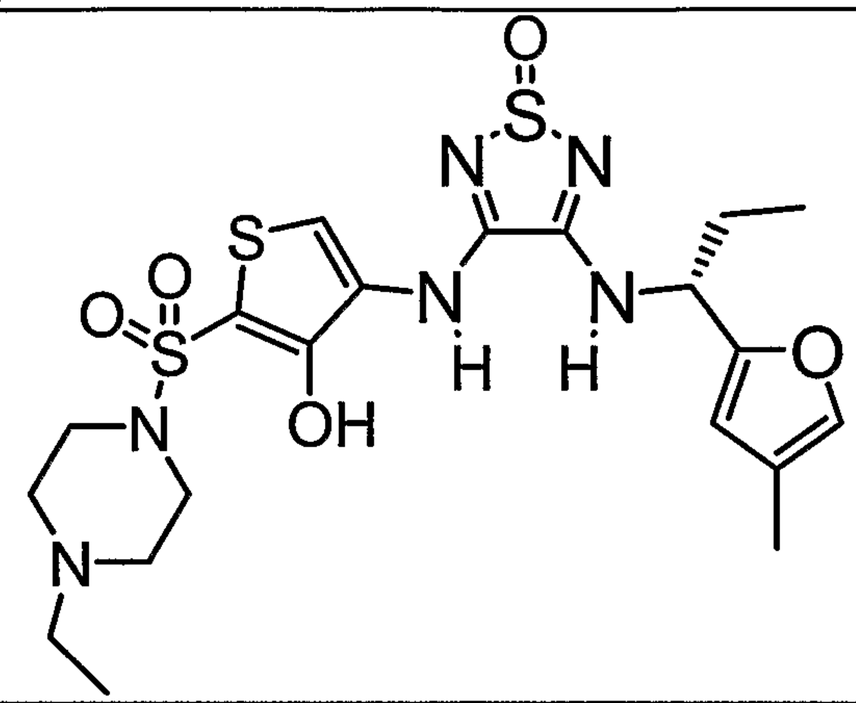
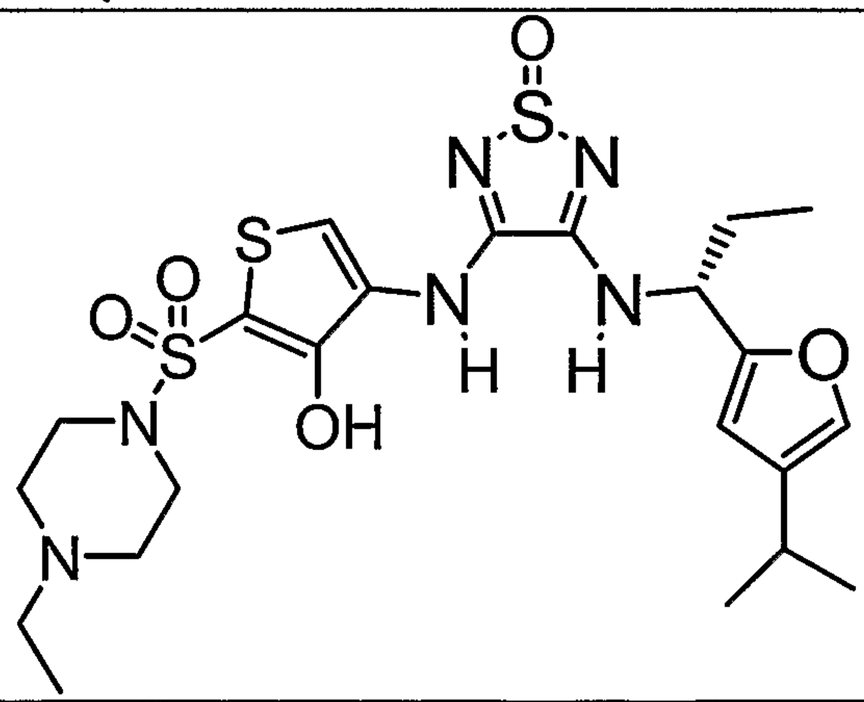
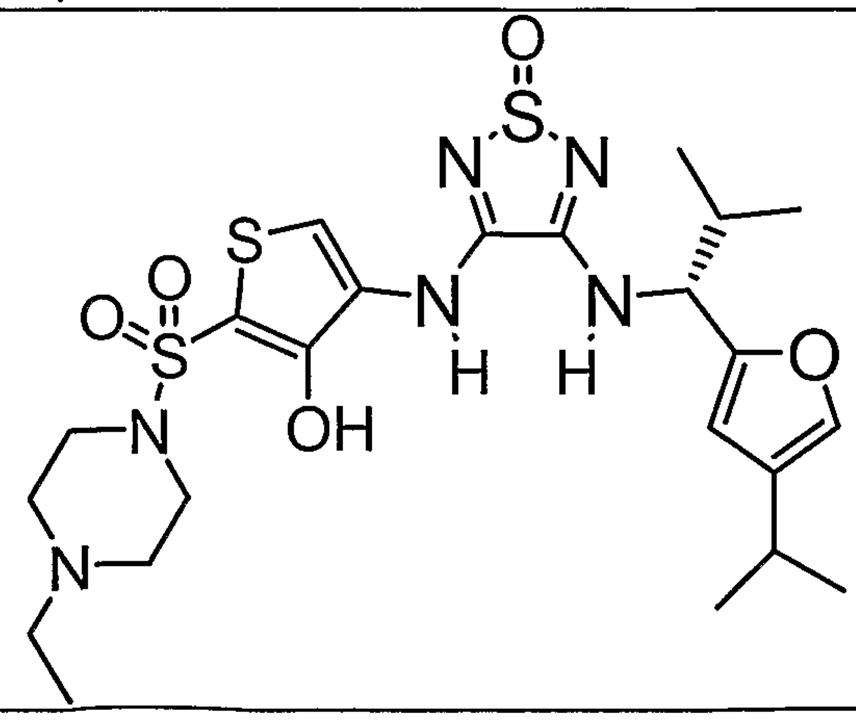
2704	22.28	75.69	
2705	22.28	603B	
2706	22.28	603E	
2707	22.28	603F	
2708	22.28	75.20	

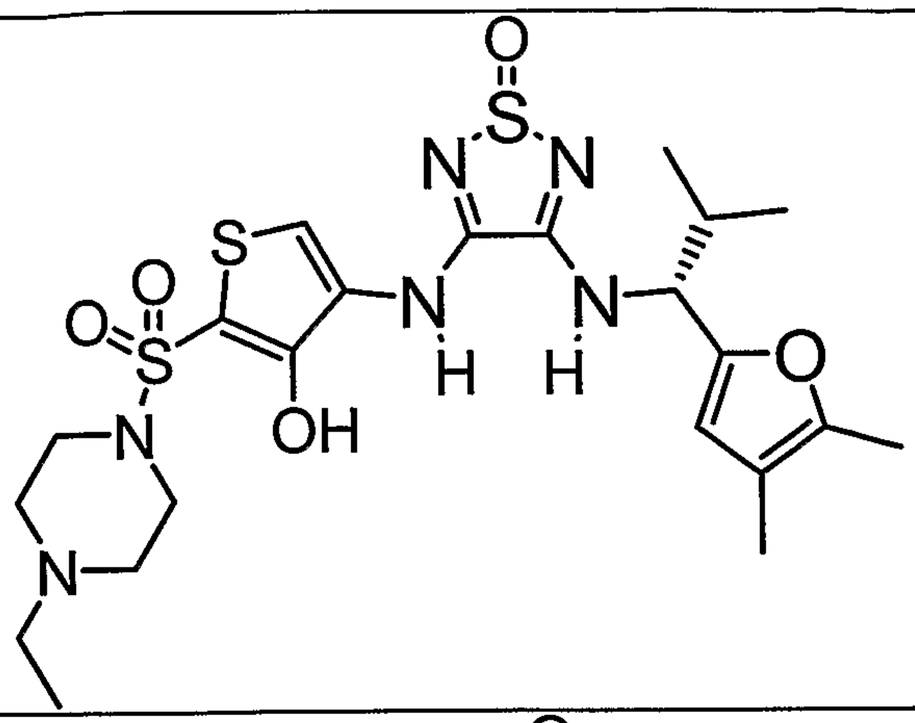
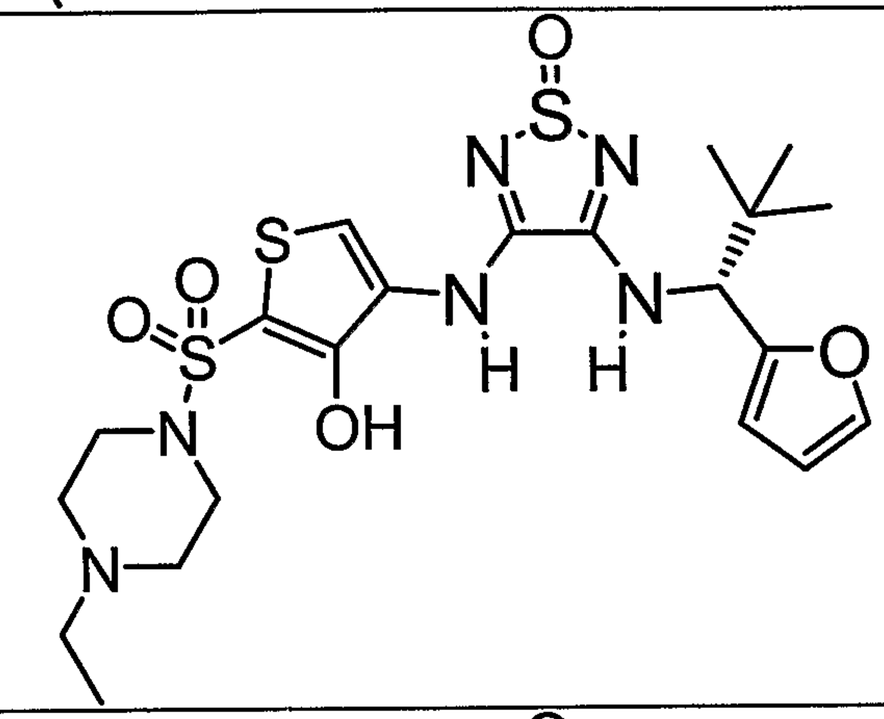
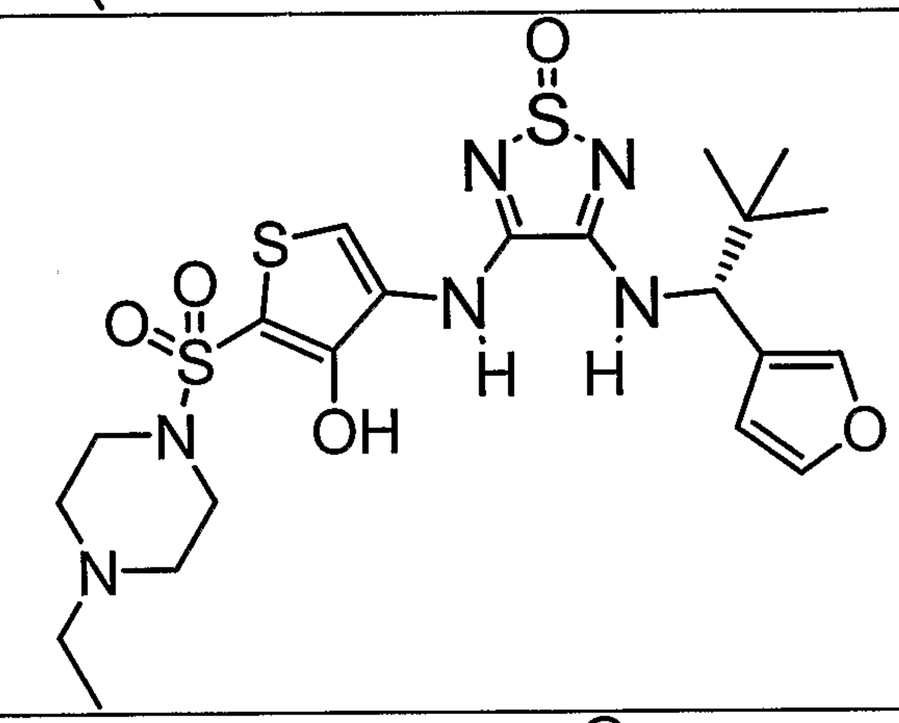
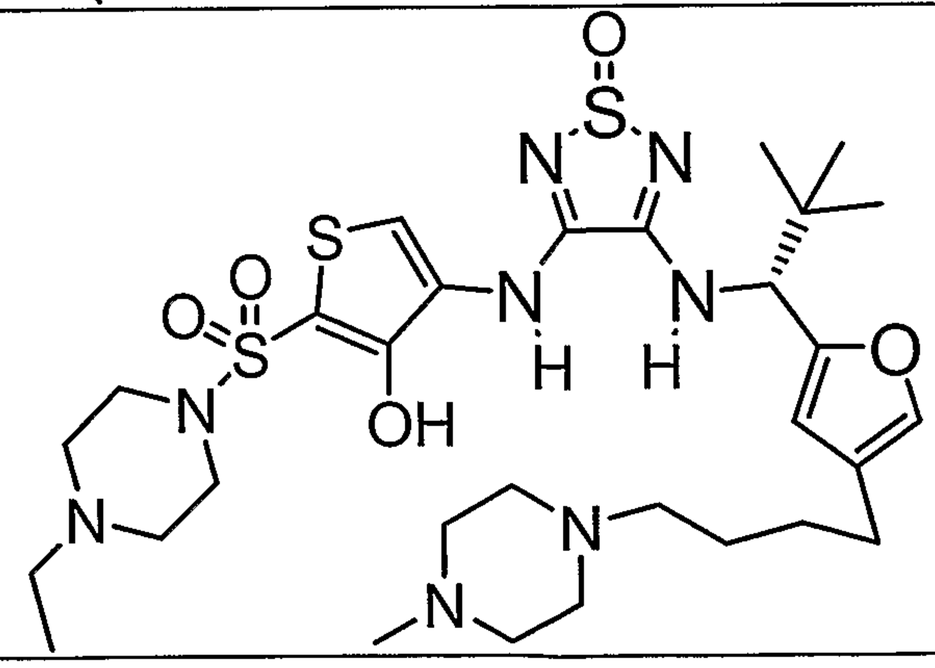
2709	22.28	74	
2710	22.28	2-Bromo-PhNH2	
2711	22.28	2,3-Dichloro-PhNH2	
2712	251	75.1	
2713	251	75.49	

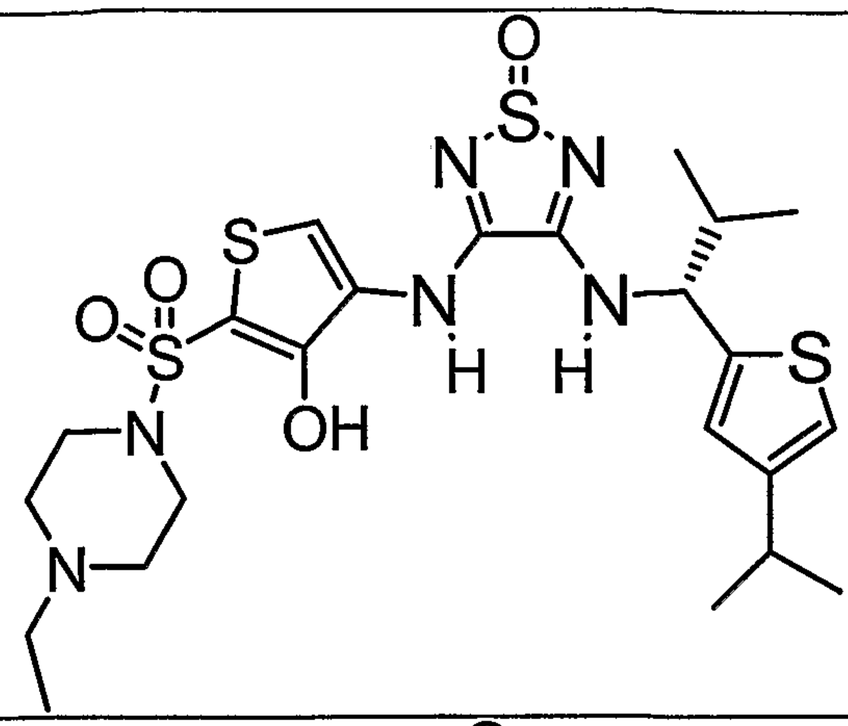
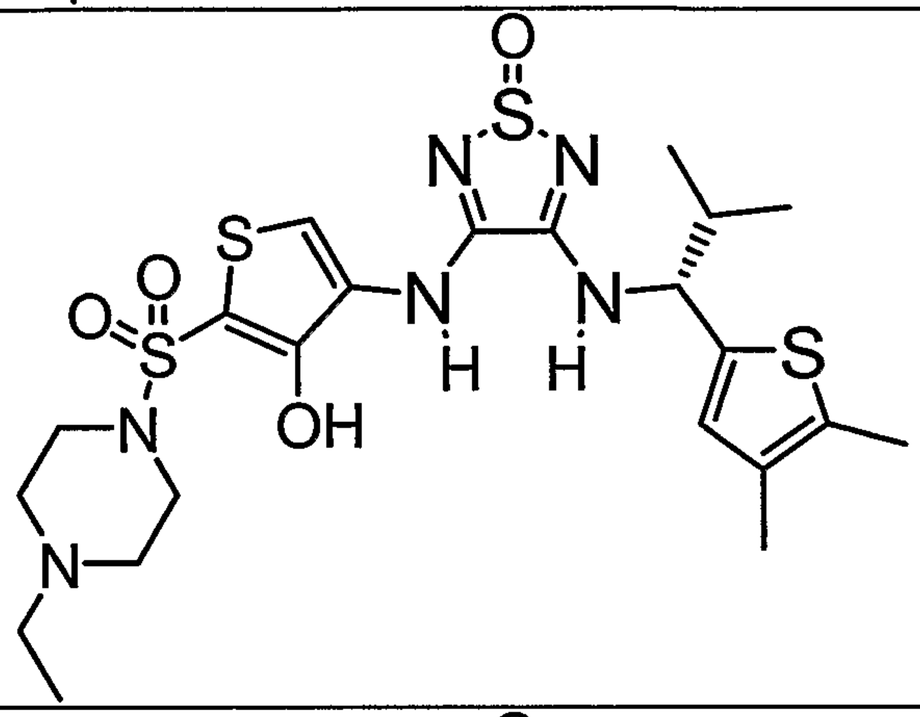
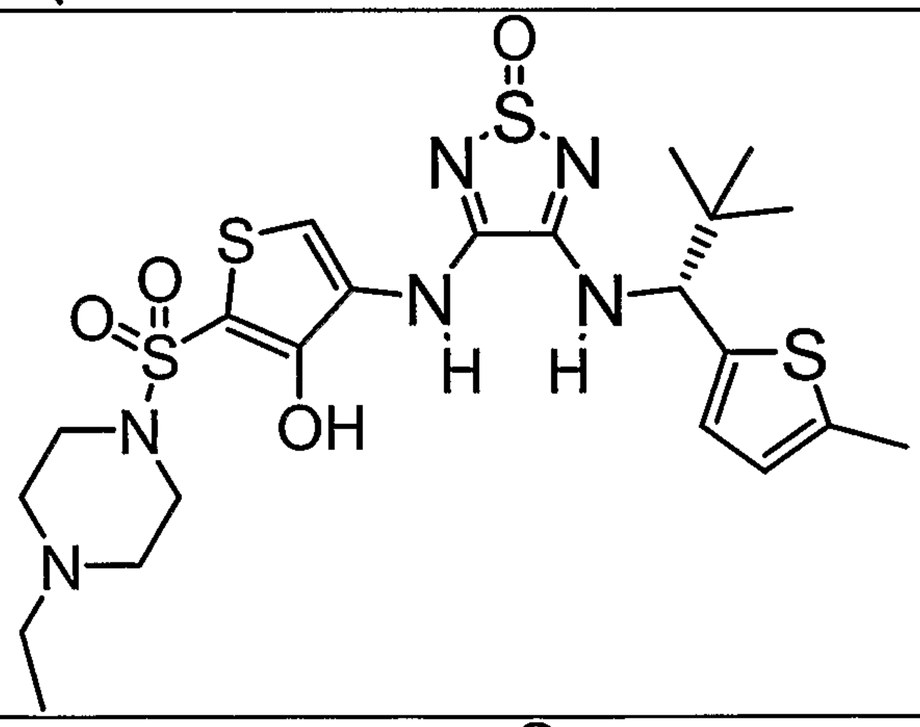
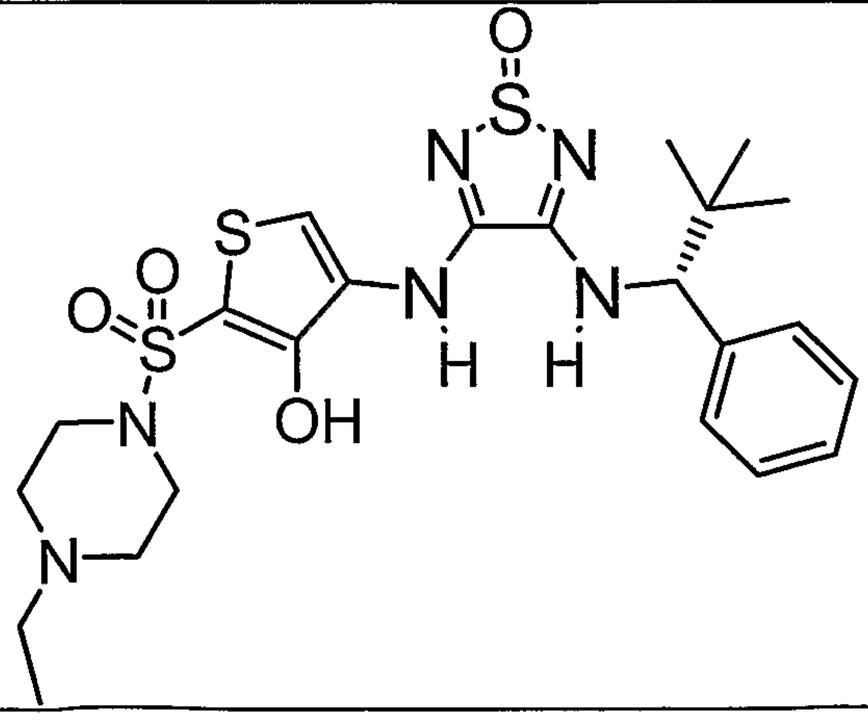
2713	251	75.9	
2715	251	75.10E	
2716	251	75.61	
2717	251	1048	

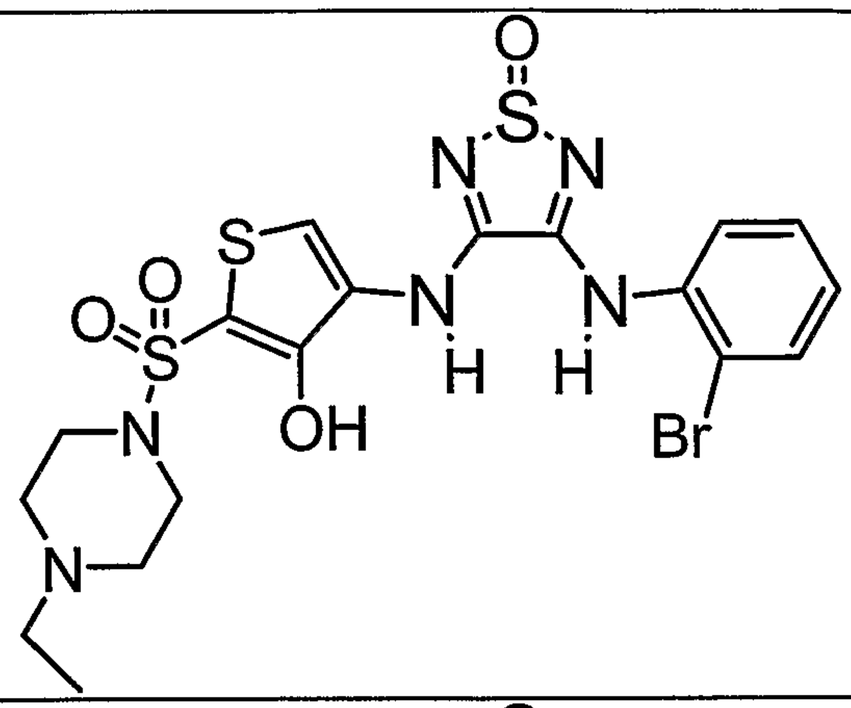
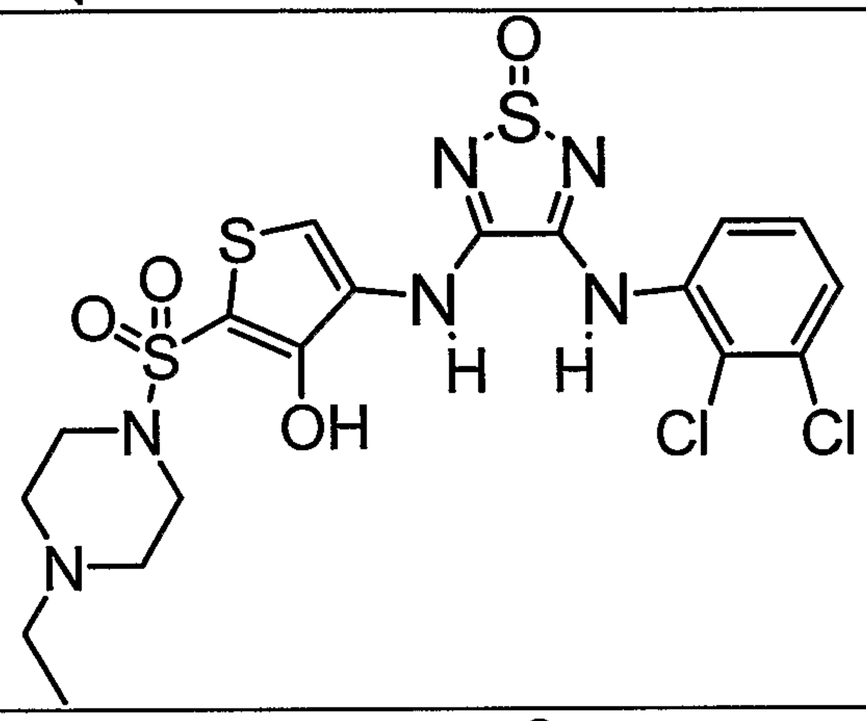
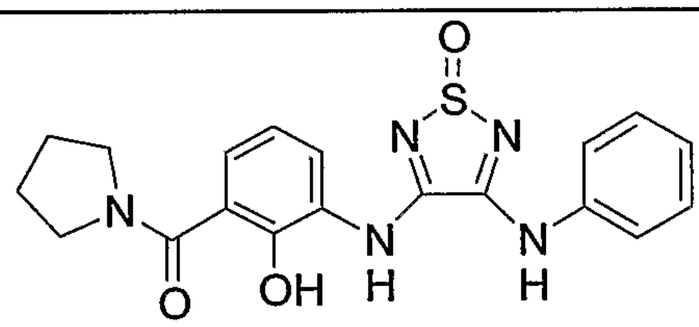
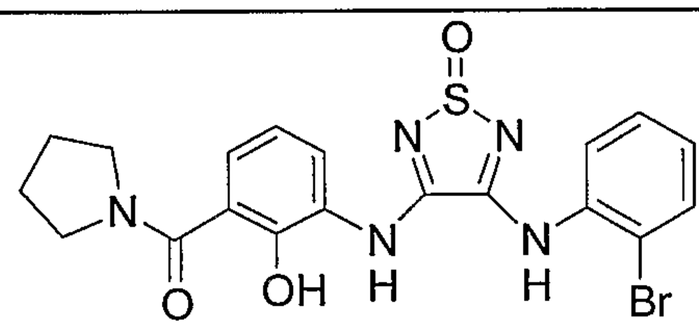
2718	251	75.69	
2719	251	603B	
2720	251	603E	
2721	251	603F	

2722	251	75.20	
2723	251	74	
2724	251	2-Bromo-PhNH2	
2725	251	2,3-Dichloro-PhNH2	

2726	252	75.1	
2727	252	75.49	
2728	252	75.9	
2729	252	75.10E	

2730	252	75.61	
2731	252	1048	
2732	252	75.69	
2733	252	603B	

2734	252	603E	
2735	252	603F	
2736	252	75.20	
2737	252	74	

2738	252	2-Bromo-PhNH2	
2739	252	2,3-Dichloro-PhNH2	
2800	350	PhNH2	
2801	350	2-Bromo-PhNH2	
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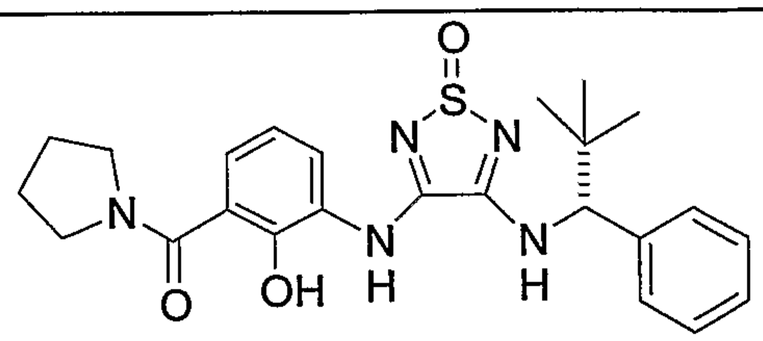
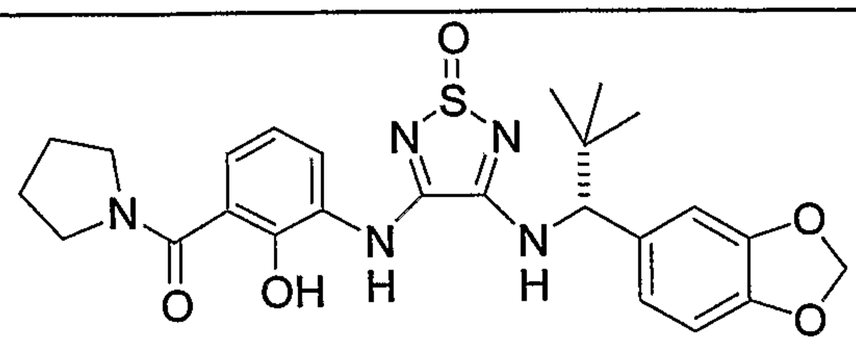
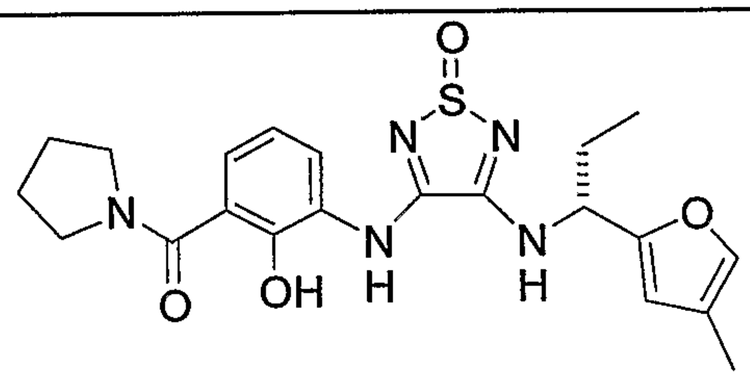
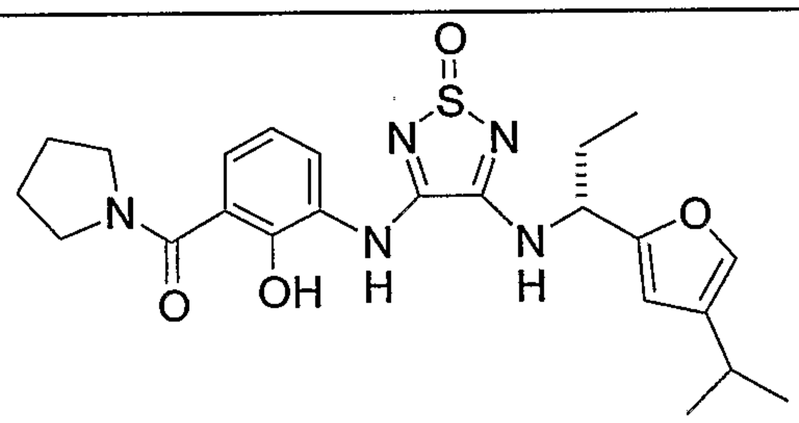
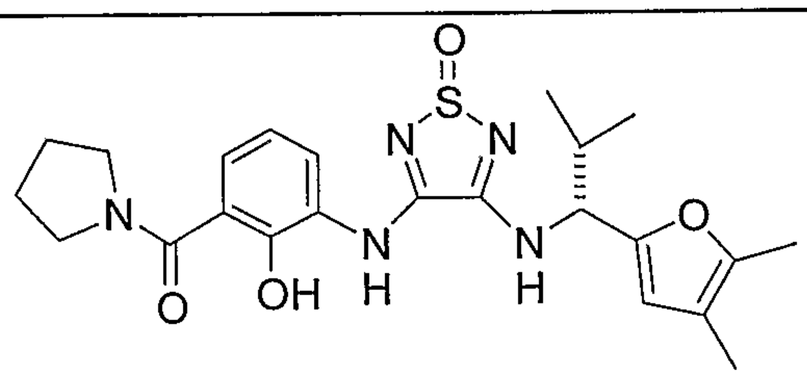
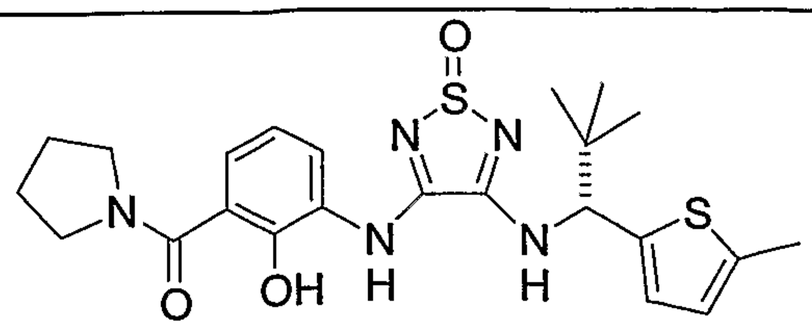
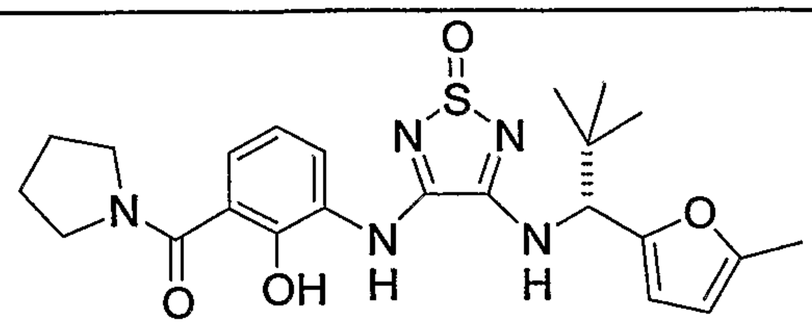
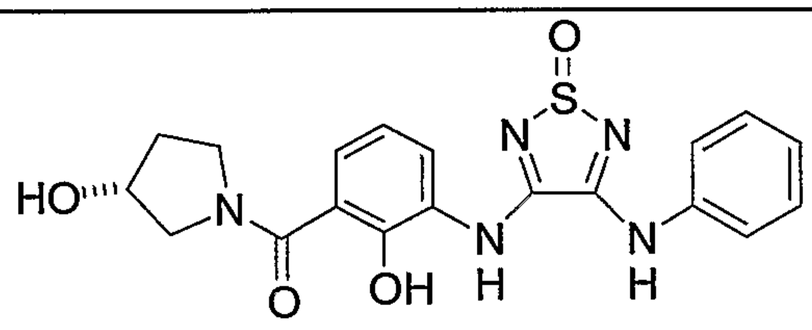
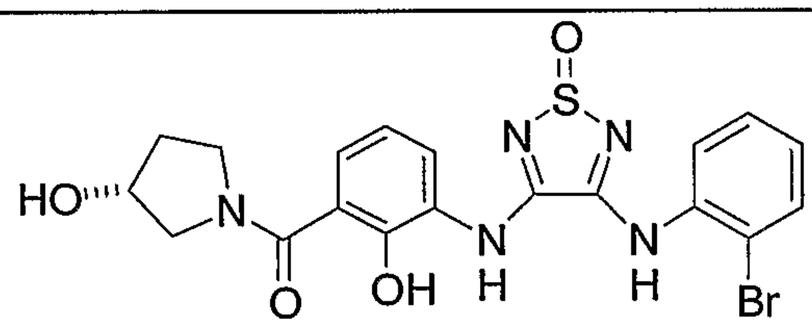
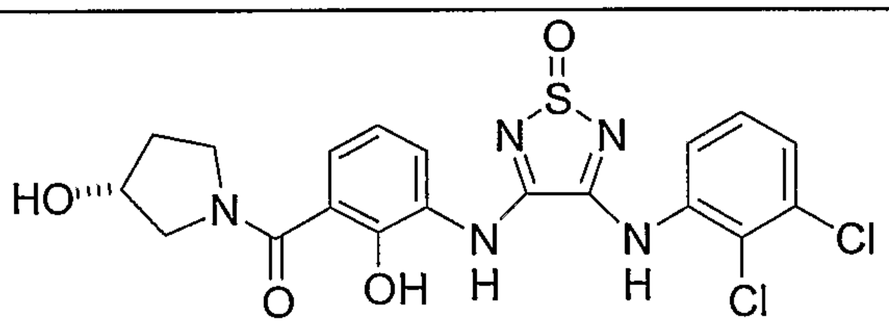
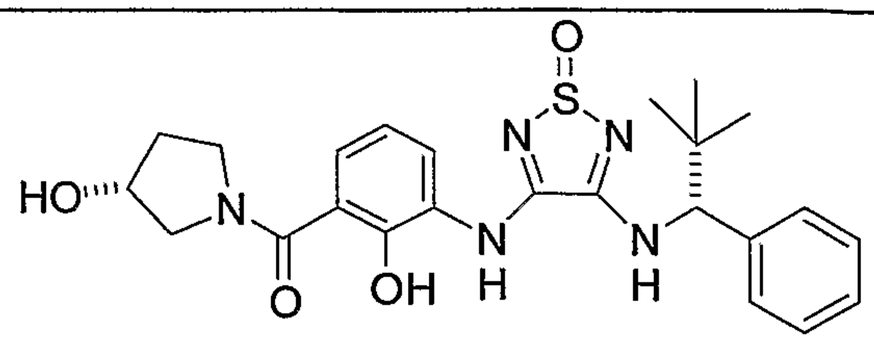
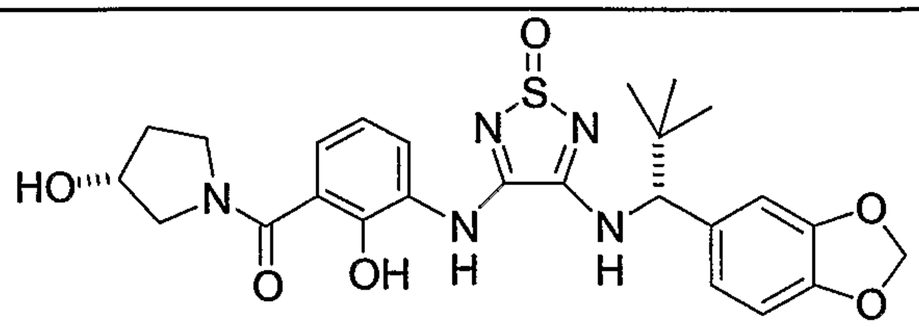
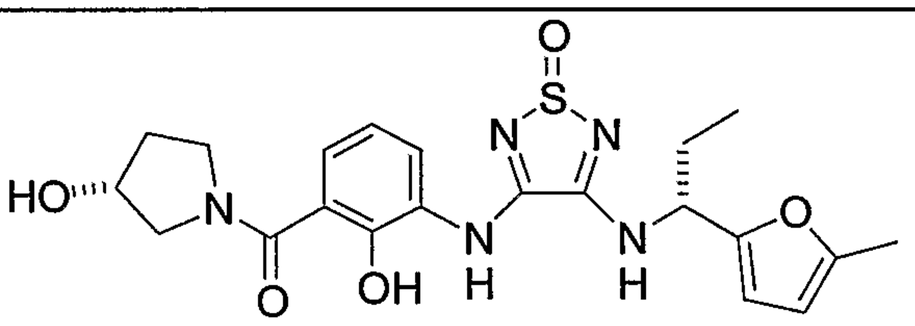
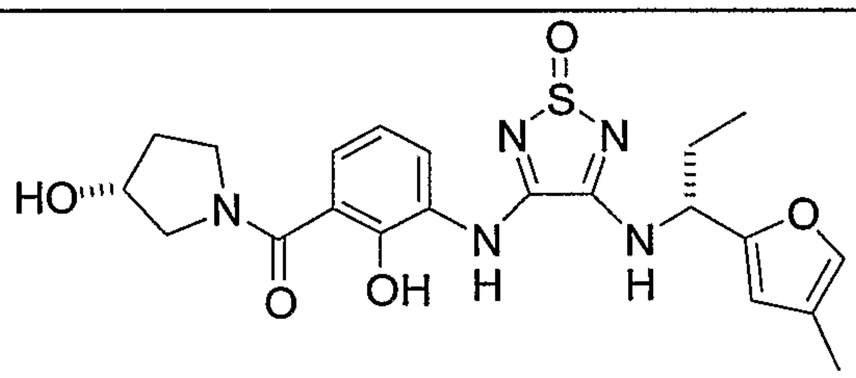
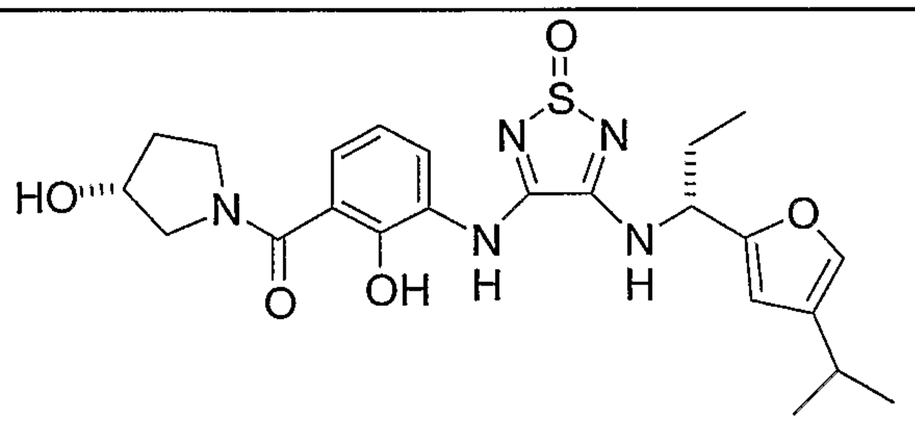
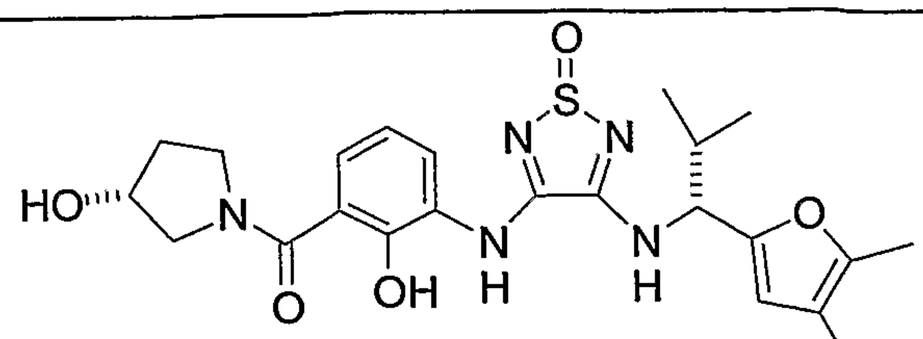
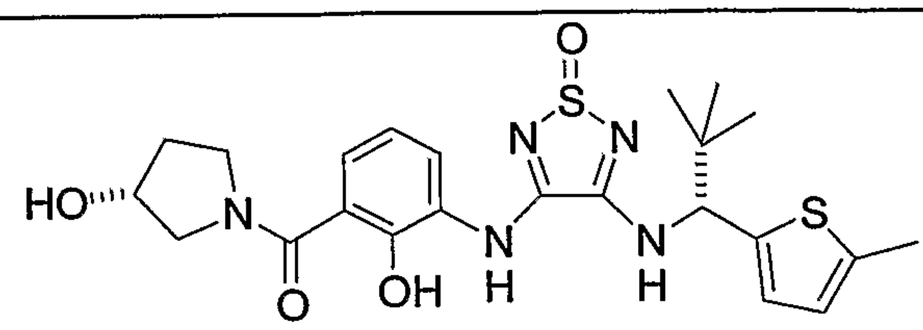
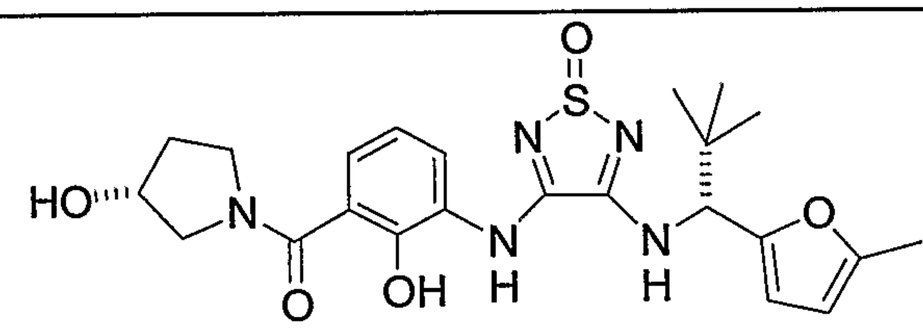
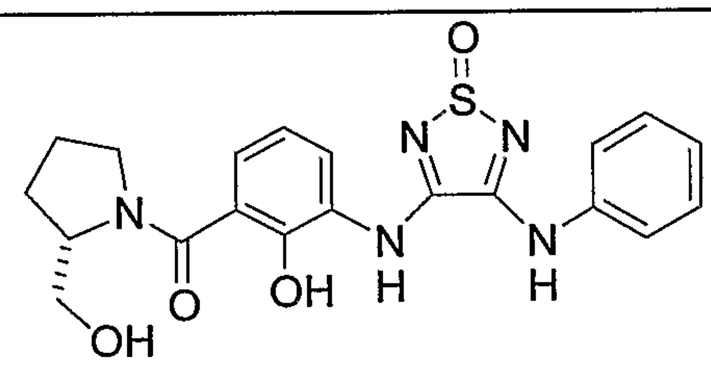
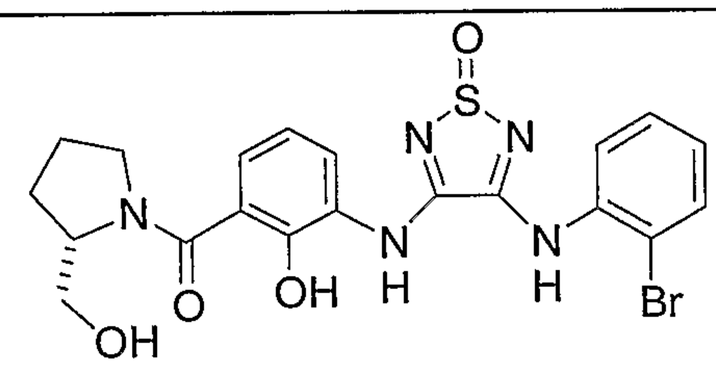
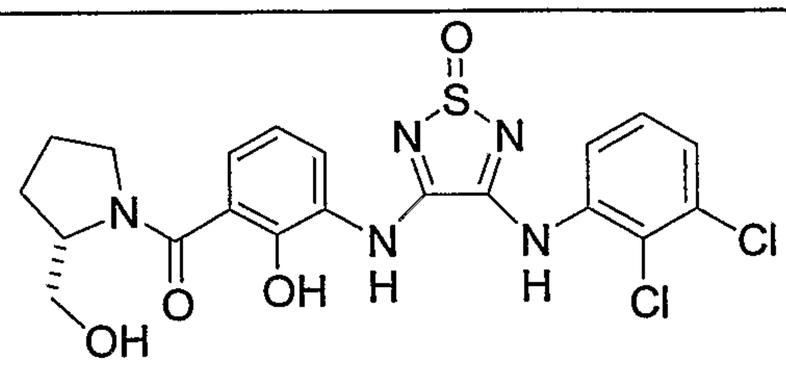
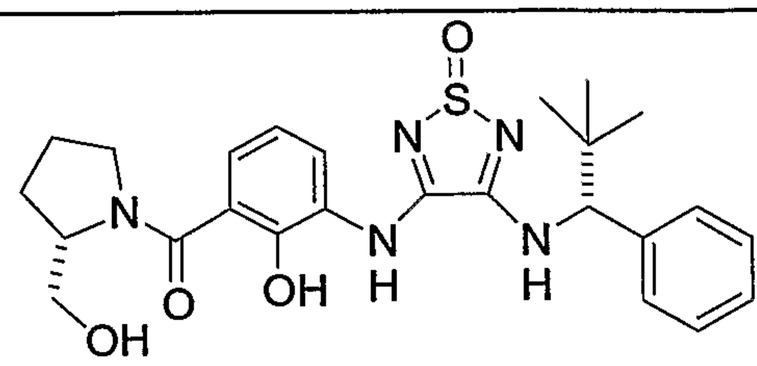
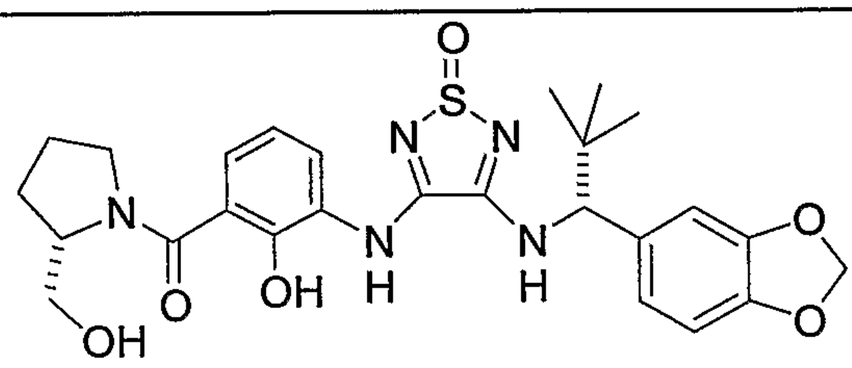
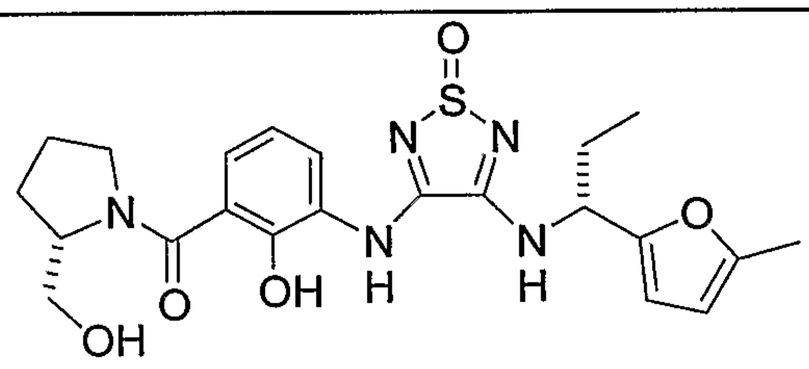
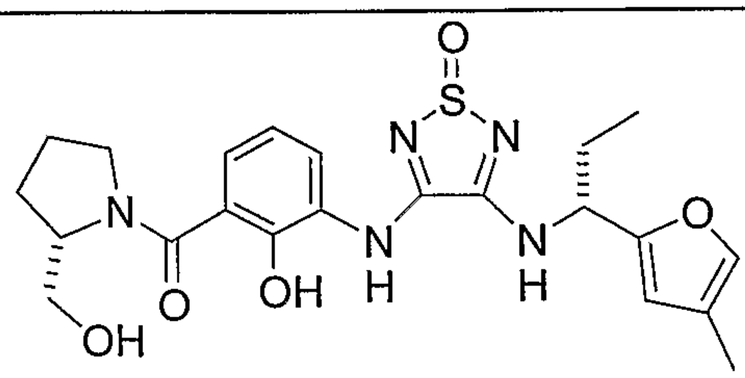
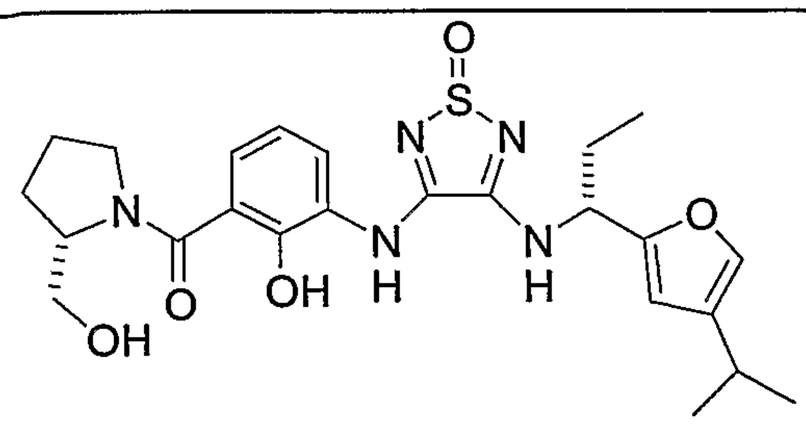
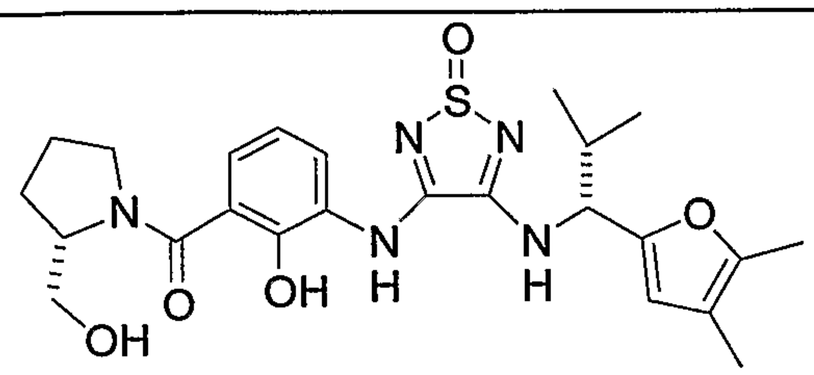
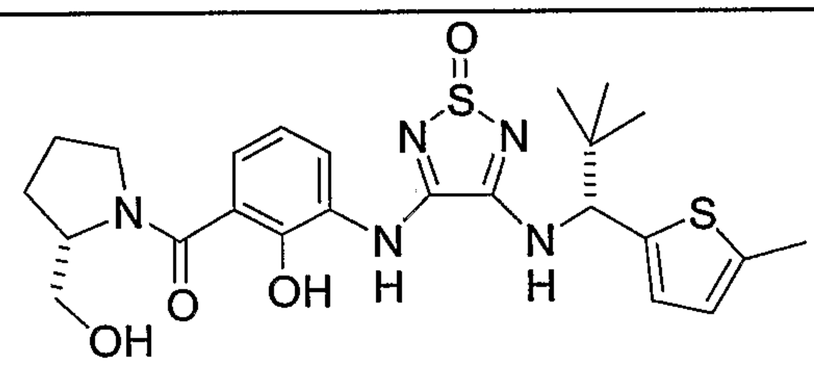
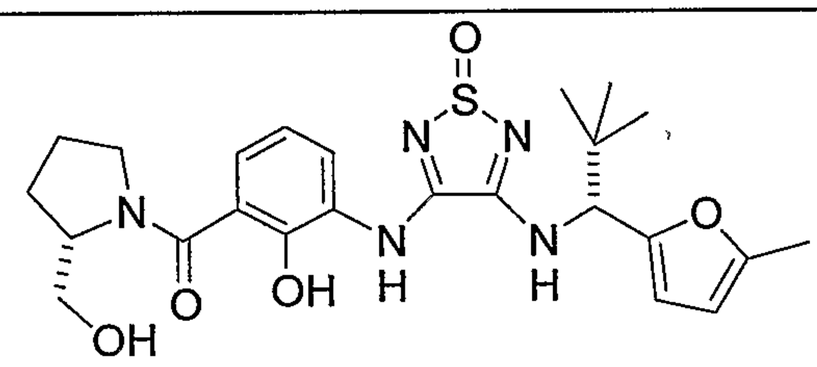
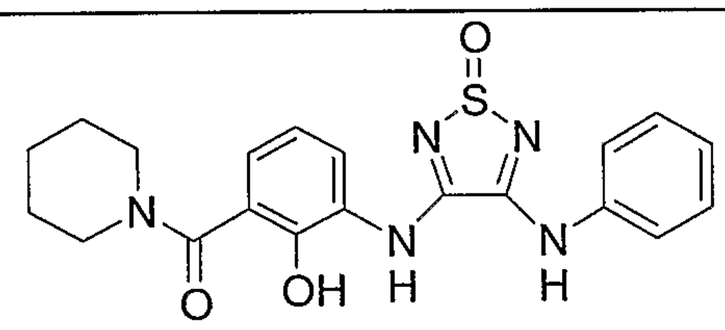
2803	350	74	
2804	350	75.60	
2806	350	75.49	
2807	350	75.9	
2808	350	75.61	

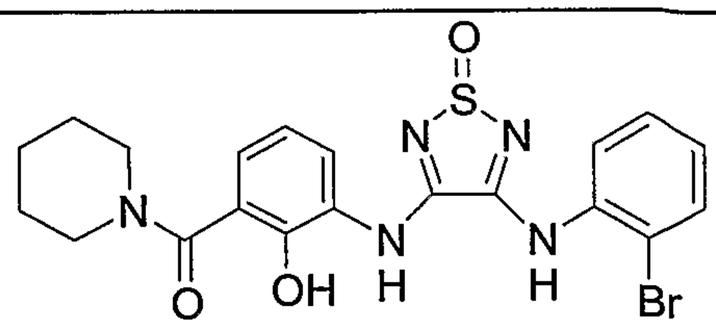
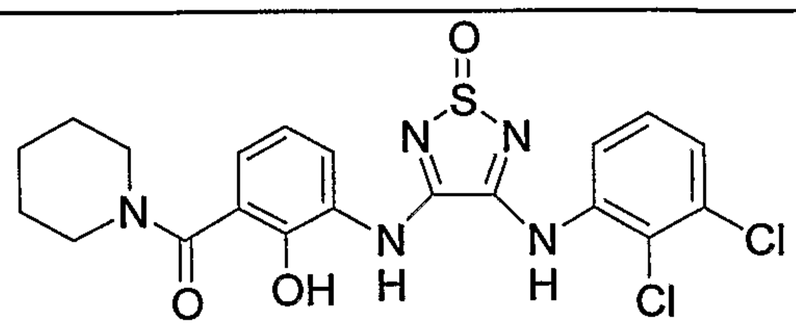
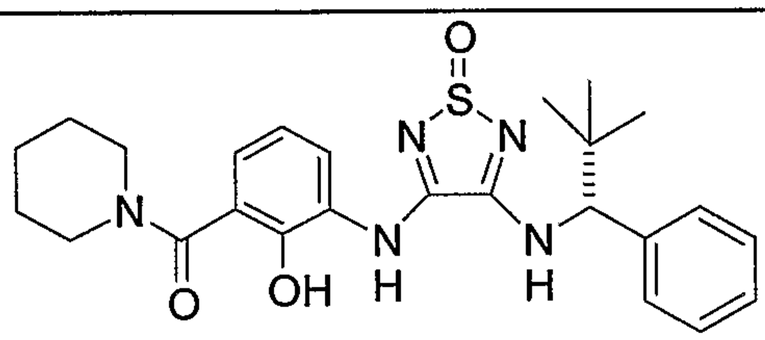
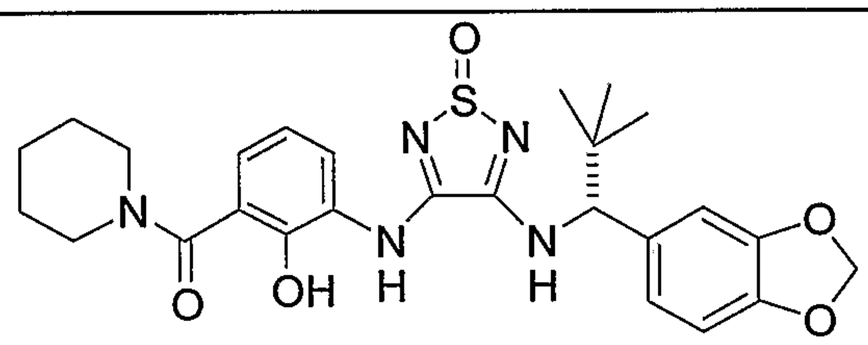
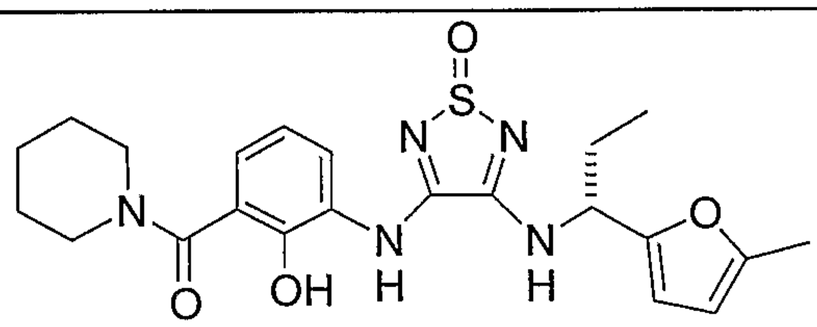
2809	350	75.20	
2810	350	75.44	
2811	351	PhNH2	
2812	351	2-Bromo-PhNH2	
2813	351	2,3-Dichloro-PhNH2	

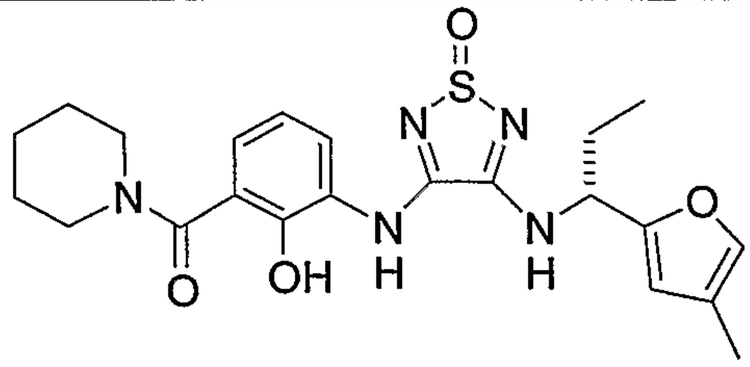
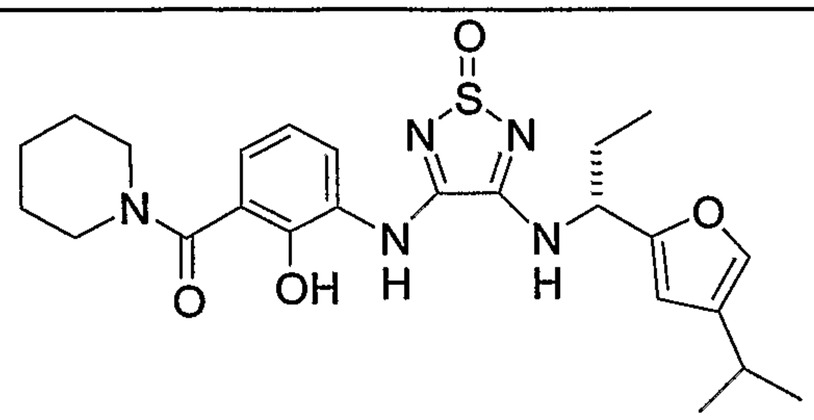
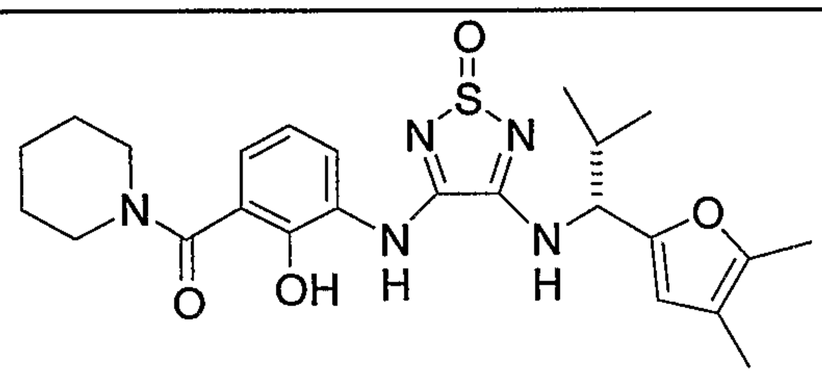
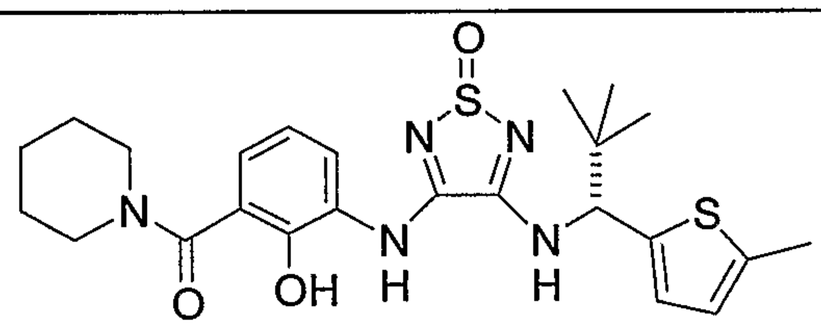
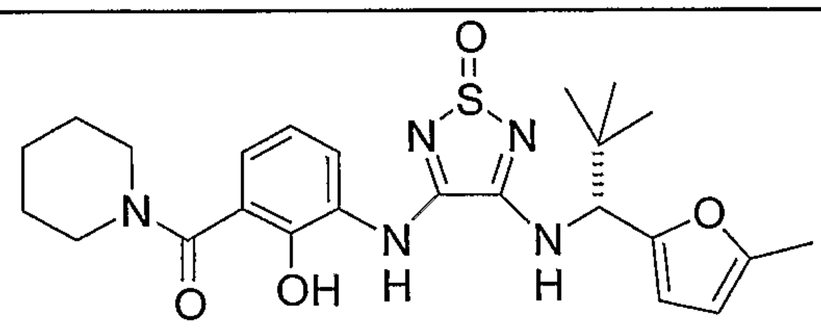
2814	351	74	
2815	351	75.60	
2816	351	75.1	
2817	351	75.49	
2818	351	75.9	

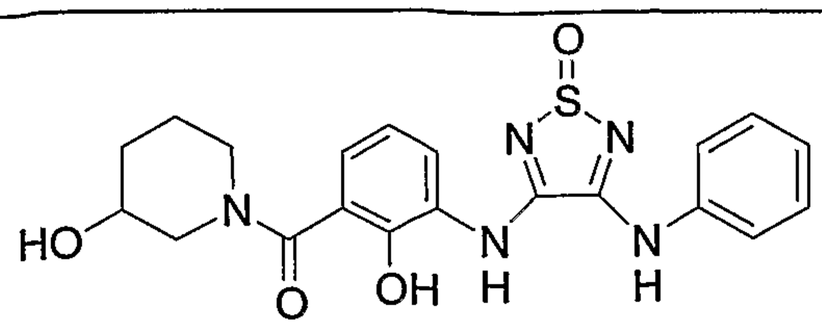
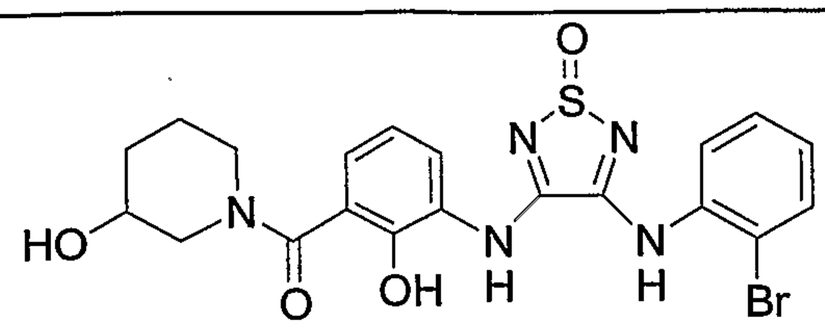
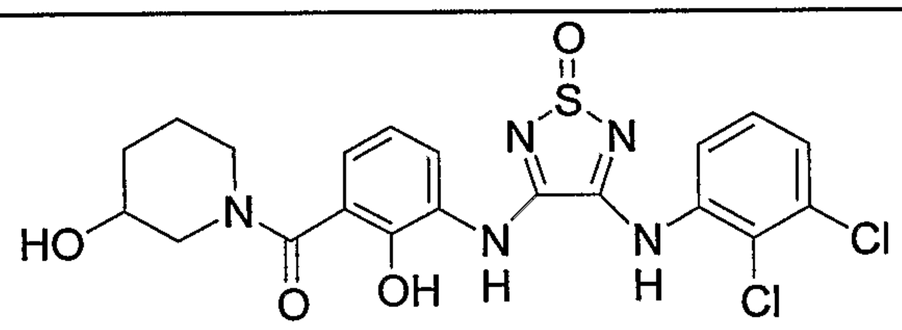
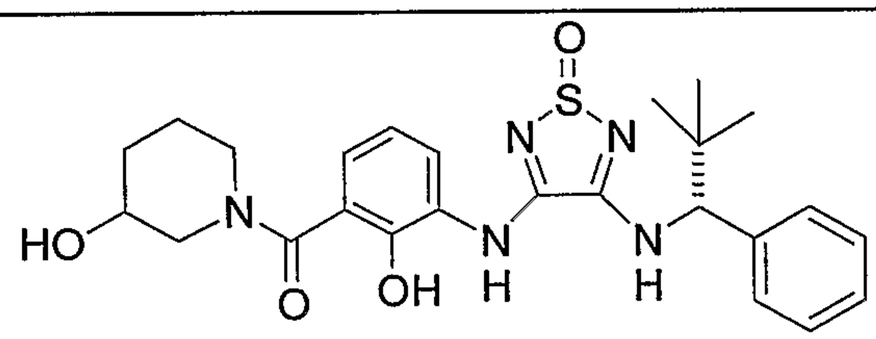
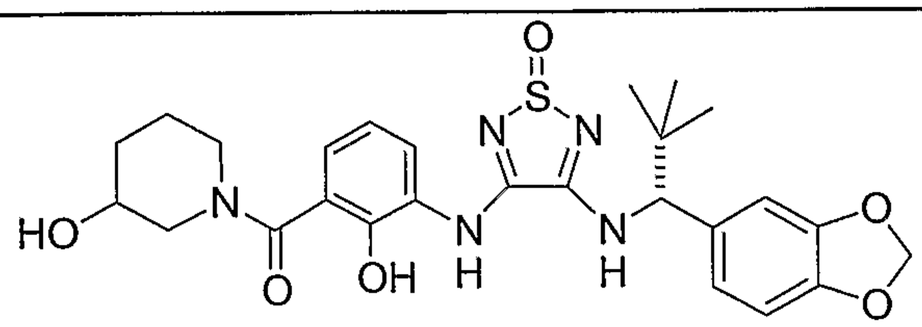
2819	351	75.61	
2820	351	75.20	
2821	351	75.44	
2822	352	PhNH2	
2823	352	2-Bromo-PhNH2	

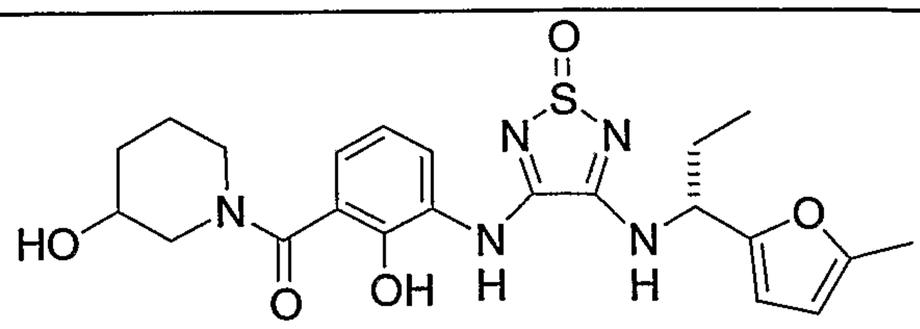
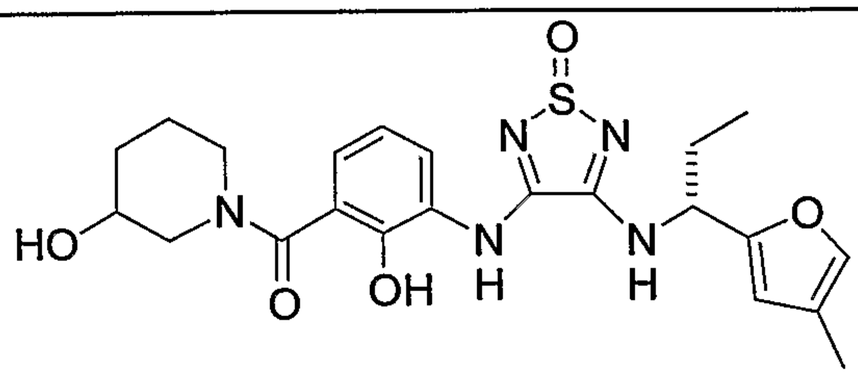
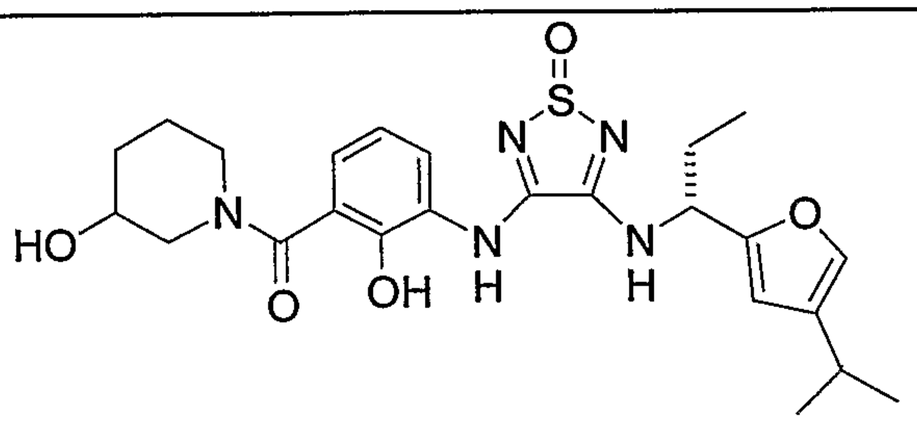
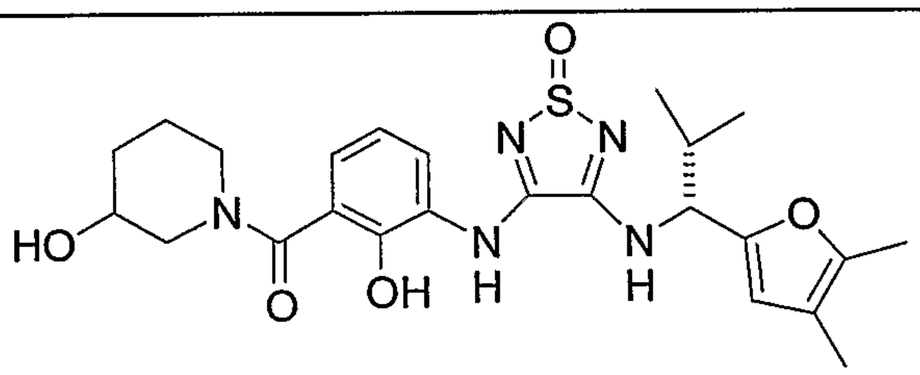
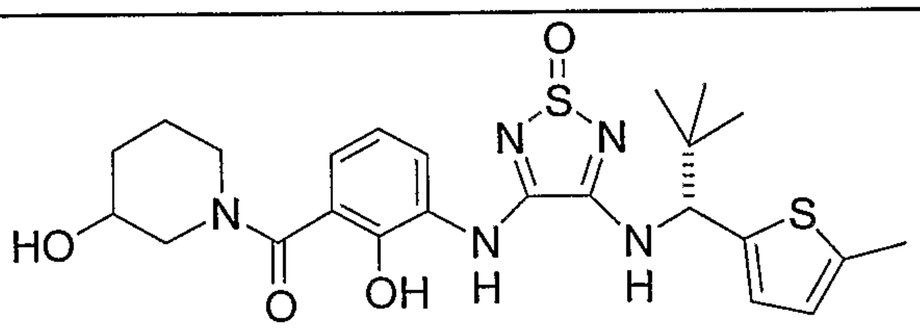
2824	352	2,3-Dichloro-PhNH2	
2825	352	74	
2826	352	75.60	
2827	352	75.1	
2828	352	75.49	

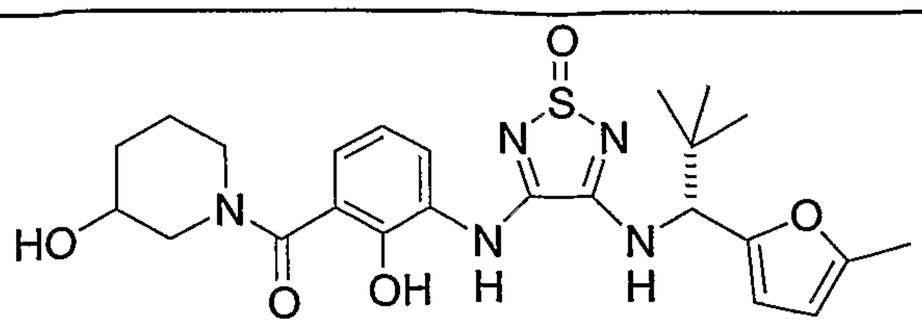
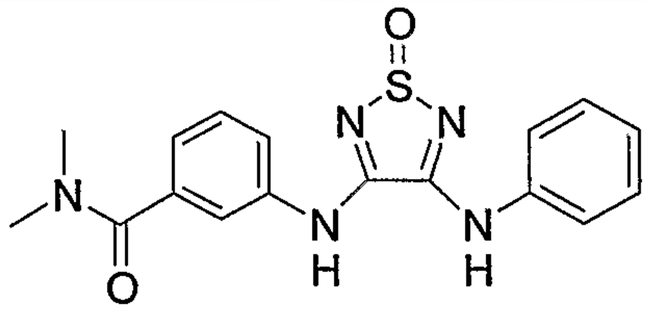
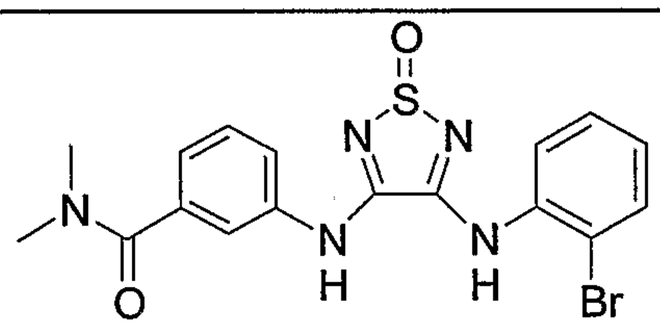
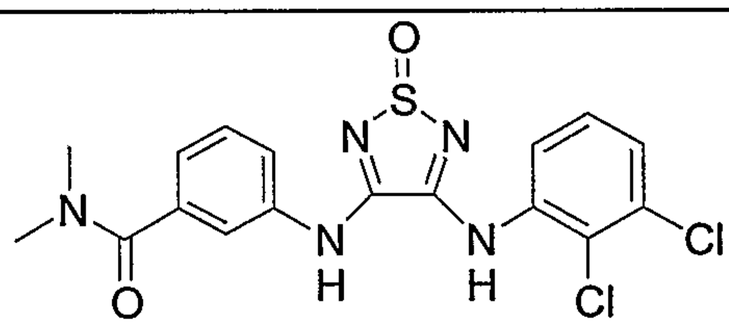
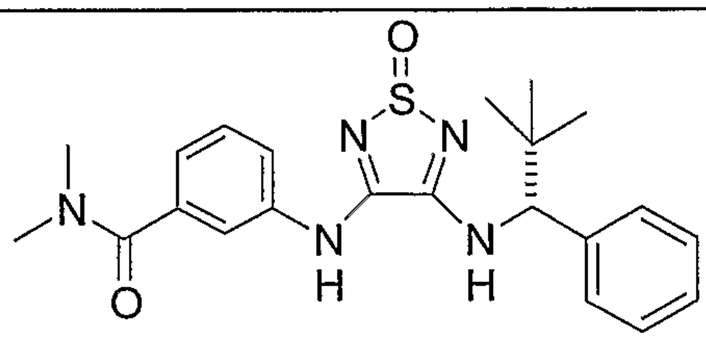
2829	352	75.9	
2830	352	75.61	
2831	352	75.20	
2832	352	75.44	
2833	353	PhNH2	

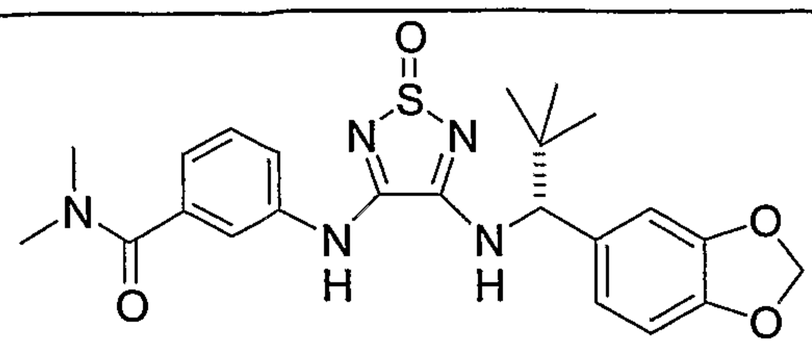
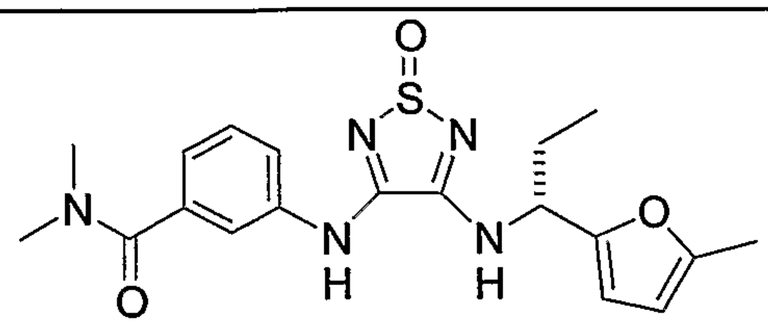
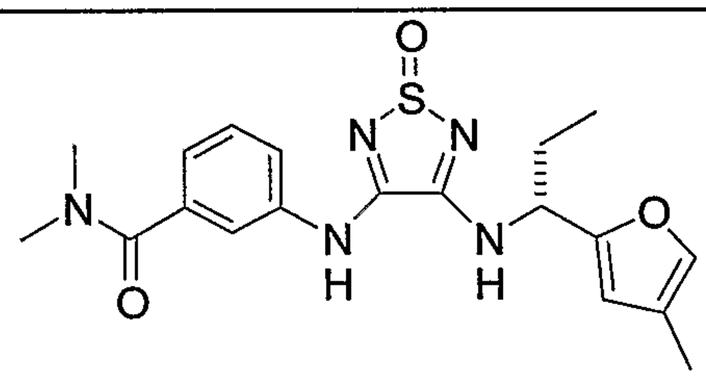
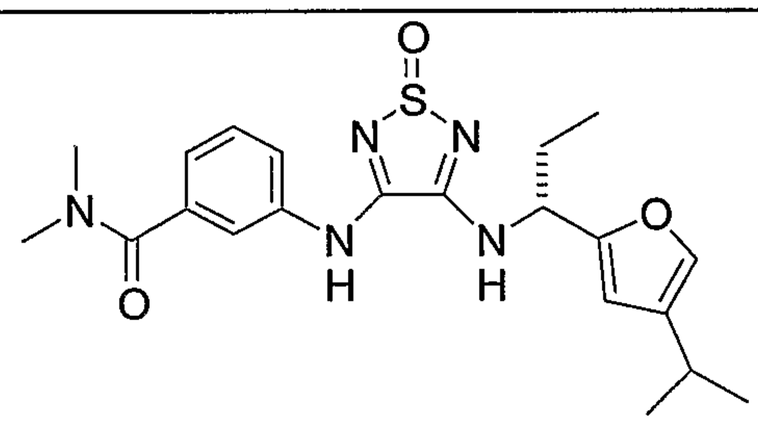
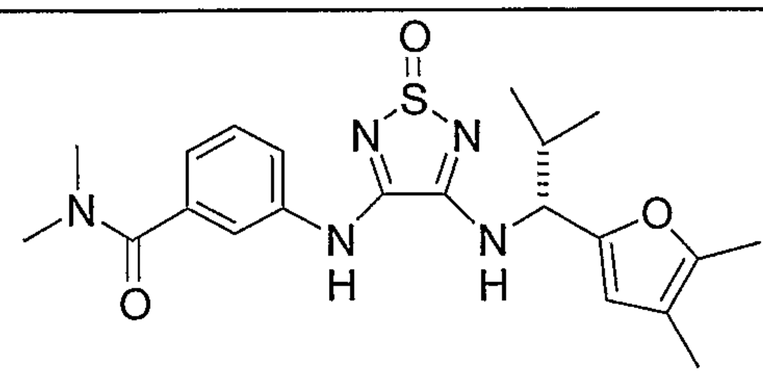
2834	353	2-Bromo-PhNH2	
2835	353	2,3-Dichloro-PhNH2	
2836	353	74	
2837	353	75.60	
2838	353	75.1	

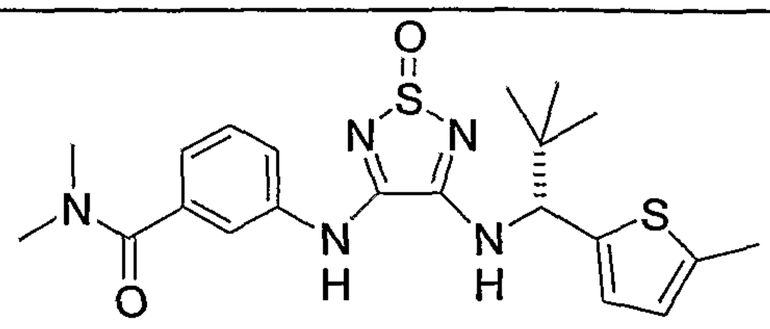
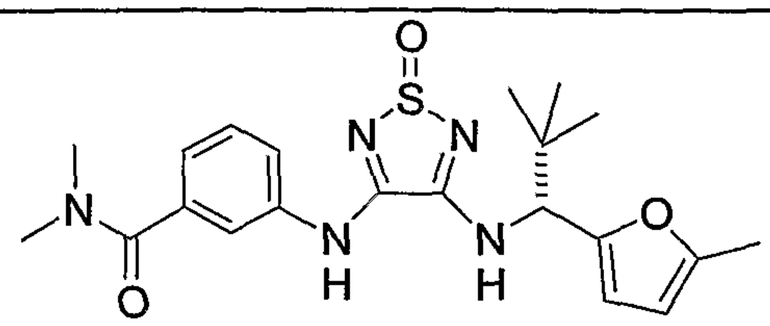
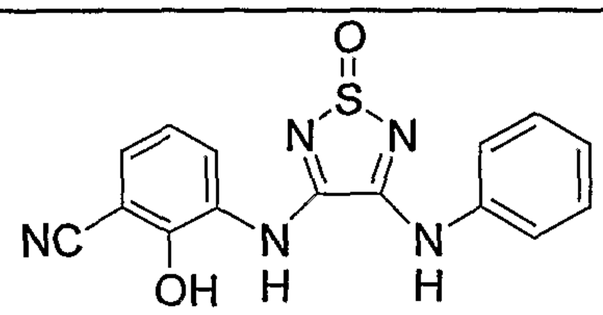
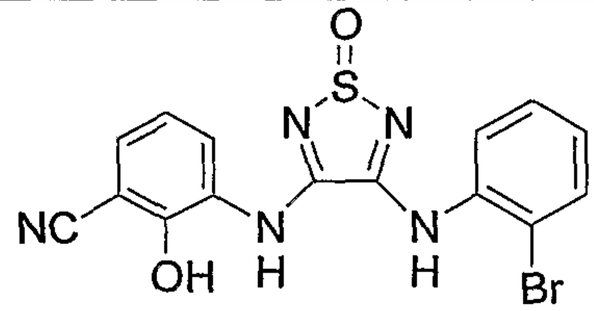
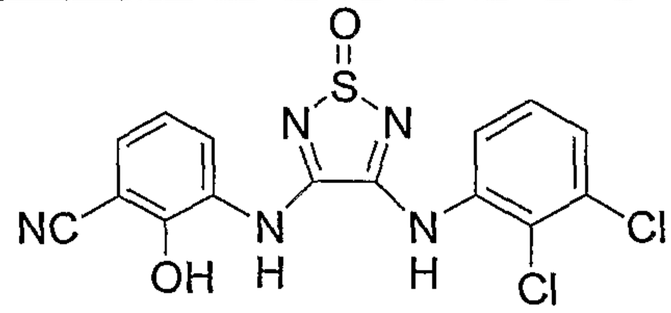
2839	353	75.49	
2840	353	75.9	
2841	353	75.61	
2842	353	75.20	
2843	353	75.44	

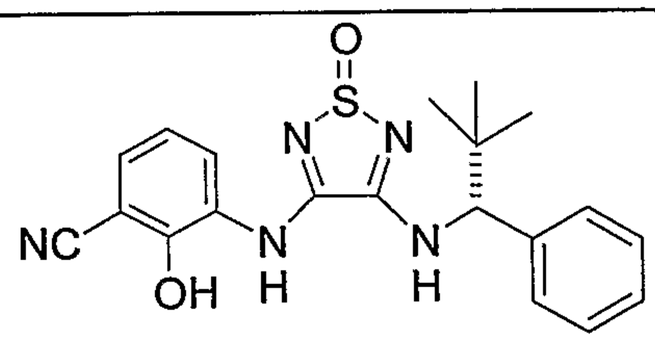
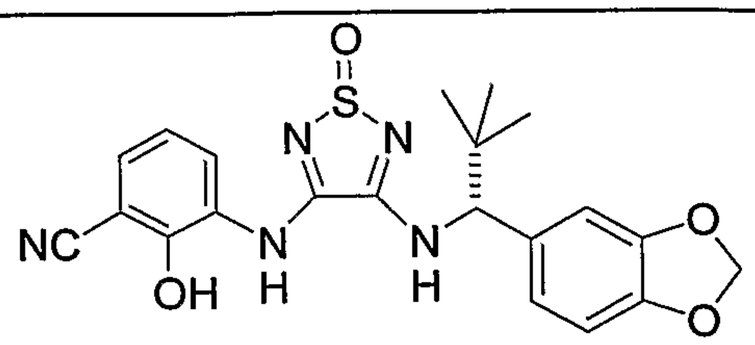
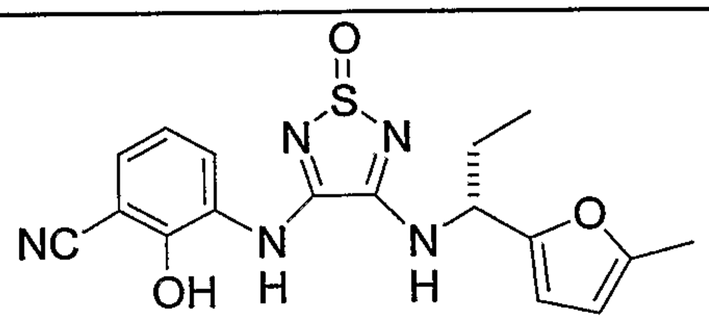
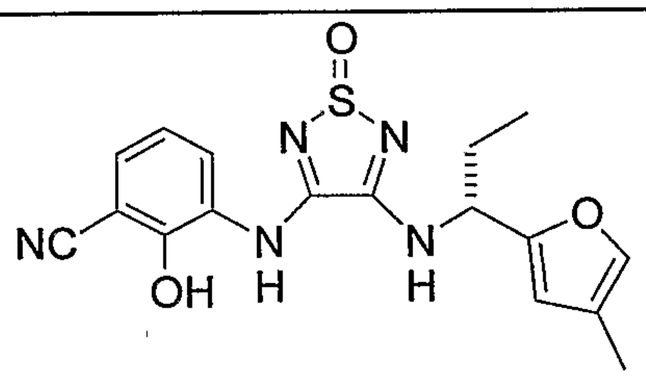
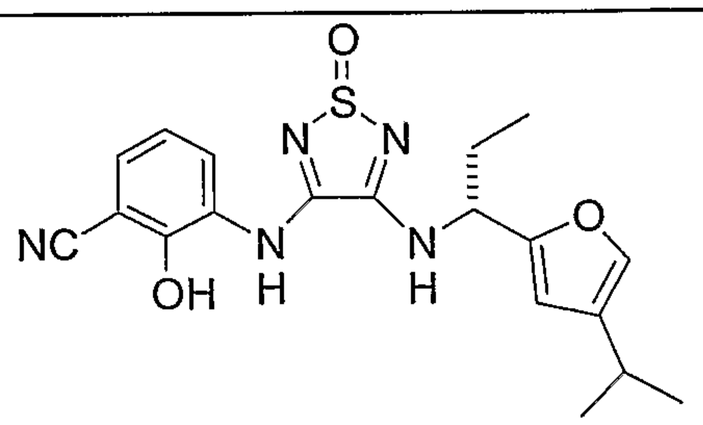
2844	354	PhNH2	
2845	354	2-Bromo-PhNH2	
2846	354	2,3-Dichloro-PhNH2	
2847	354	74	
2848	354	75.60	

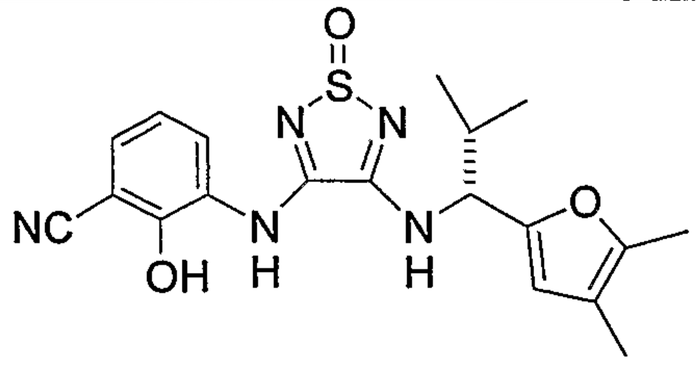
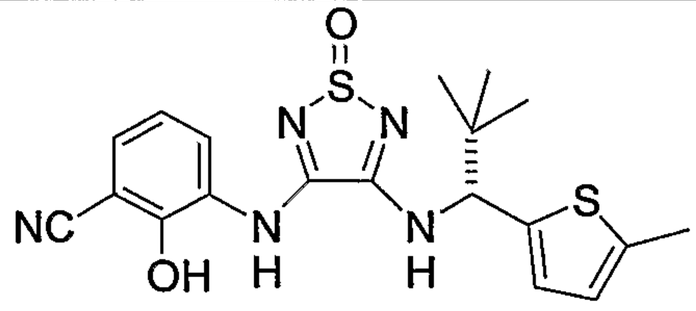
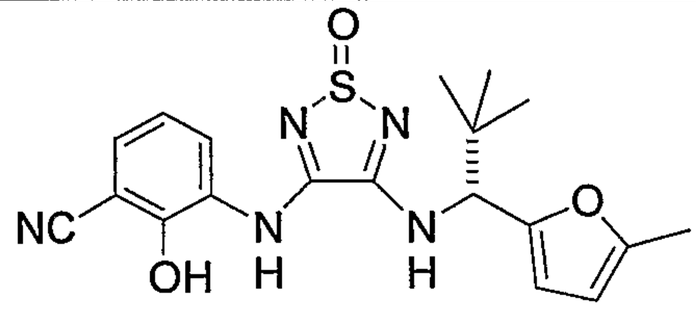
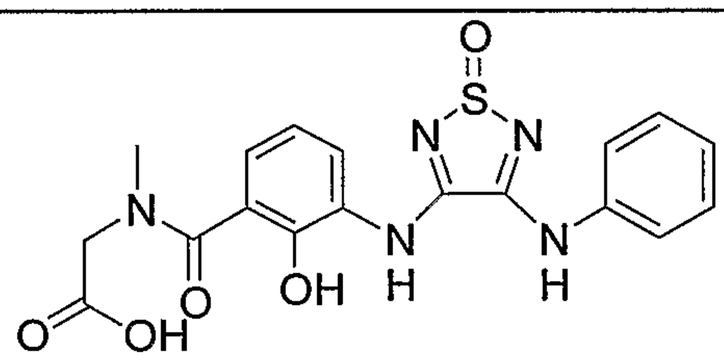
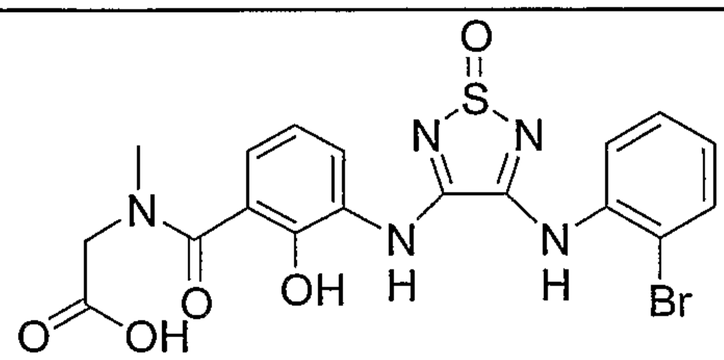
2849	354	75.1	
2850	354	75.49	
2851	354	75.9	
2852	354	75.61	
2853	354	75.20	

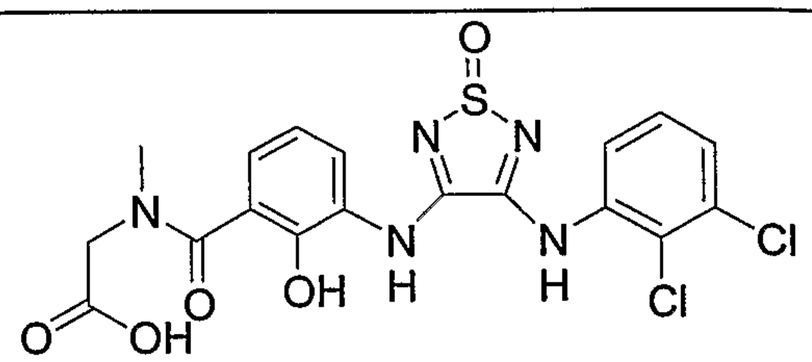
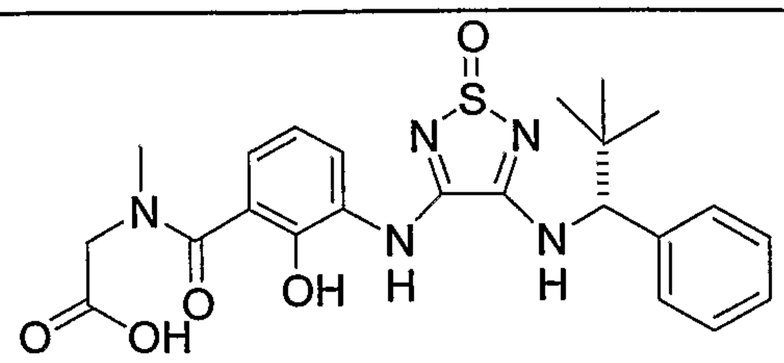
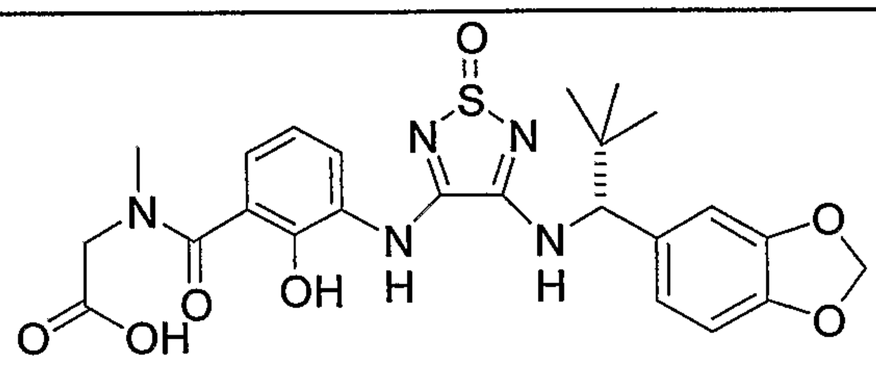
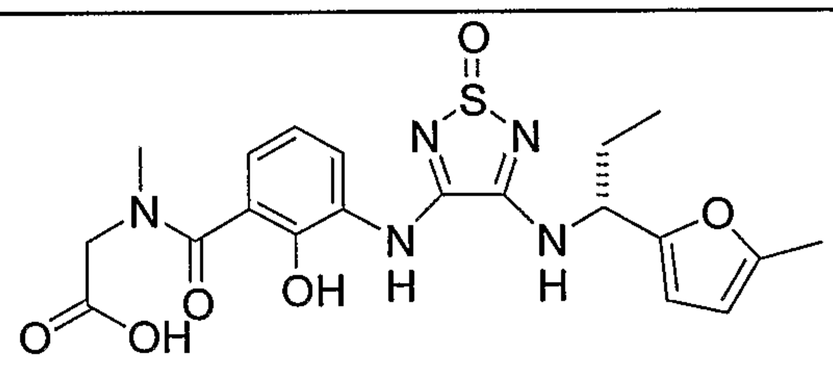
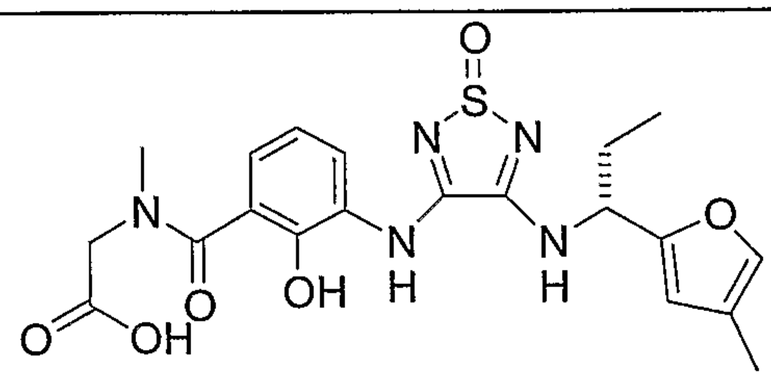
2854	354	75.44	
2855	355	PhNH2	
2856	355	2-Bromo-PhNH2	
2857	355	2,3-Dichloro-PhNH2	
2858	355	75.44	

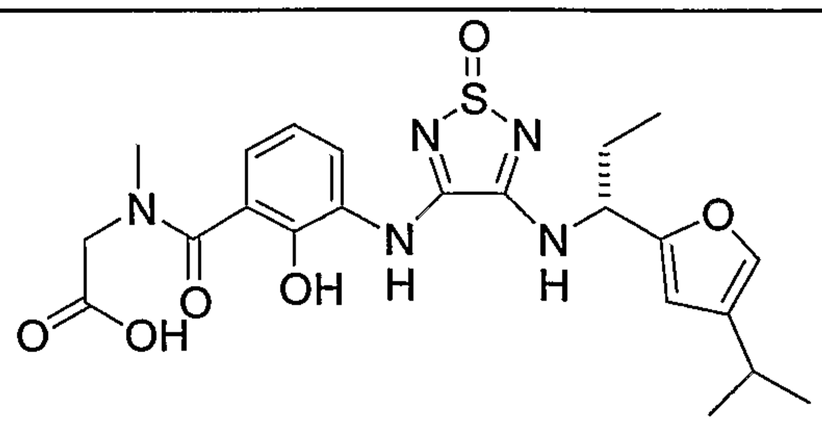
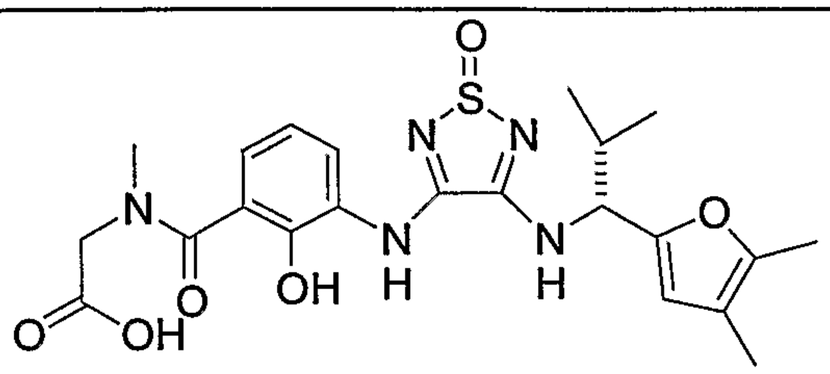
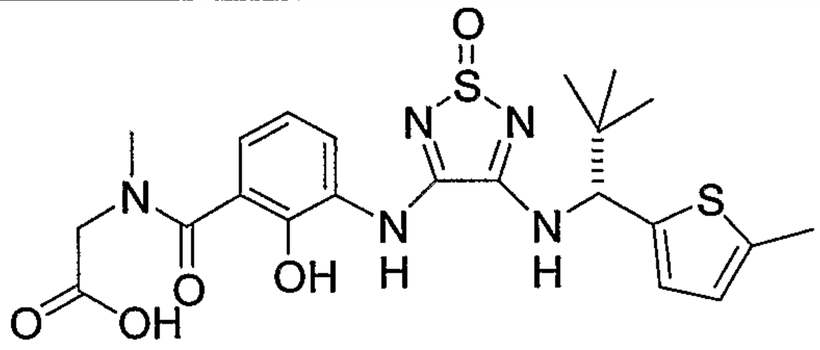
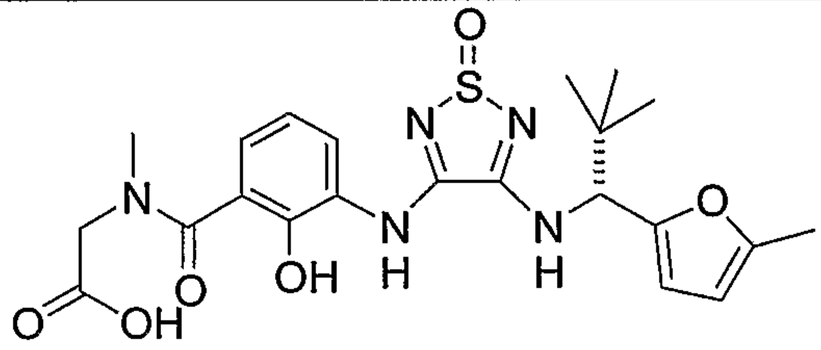
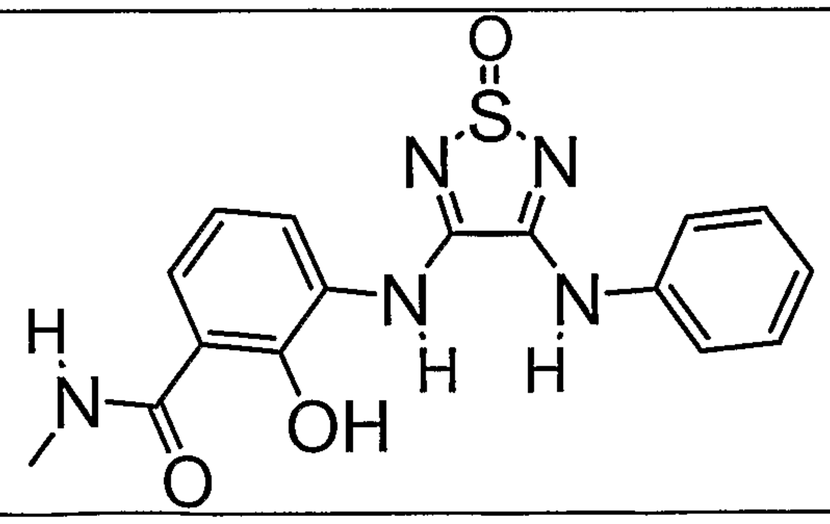
2859	355	75.60	
2860	355	75.1	
2861	355	75.49	
2862	355	75.9	
2863	355	75.61	

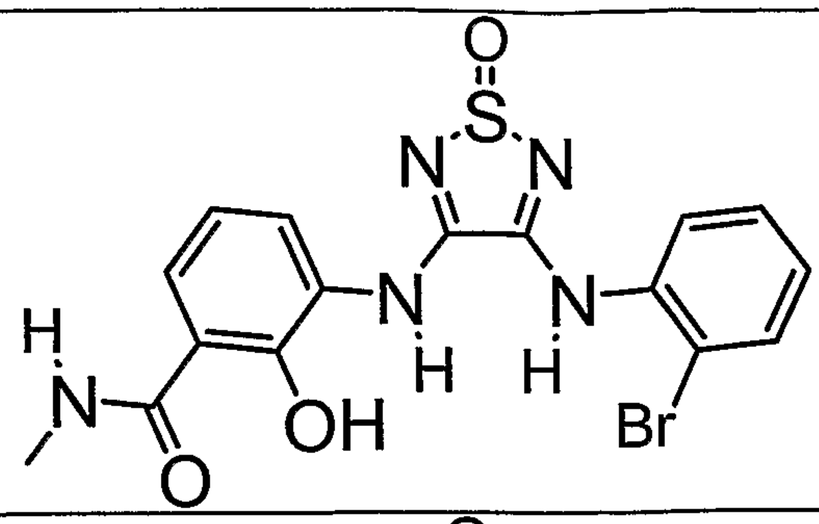
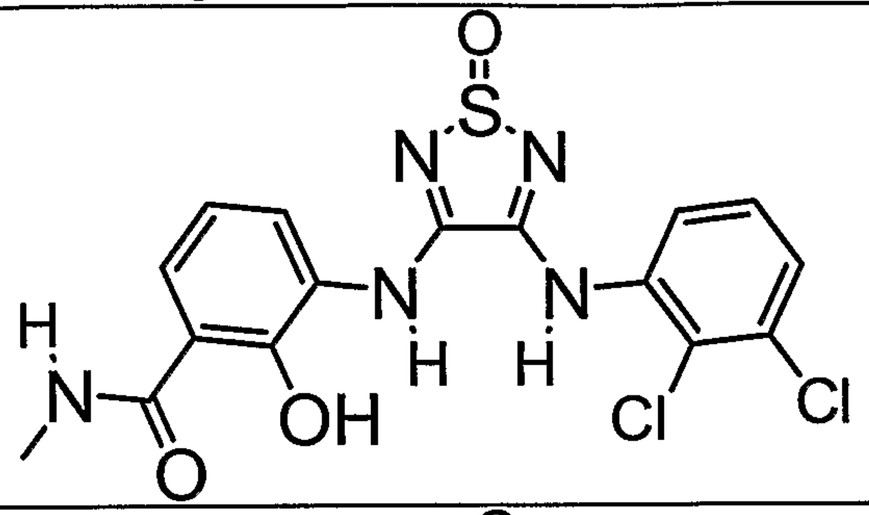
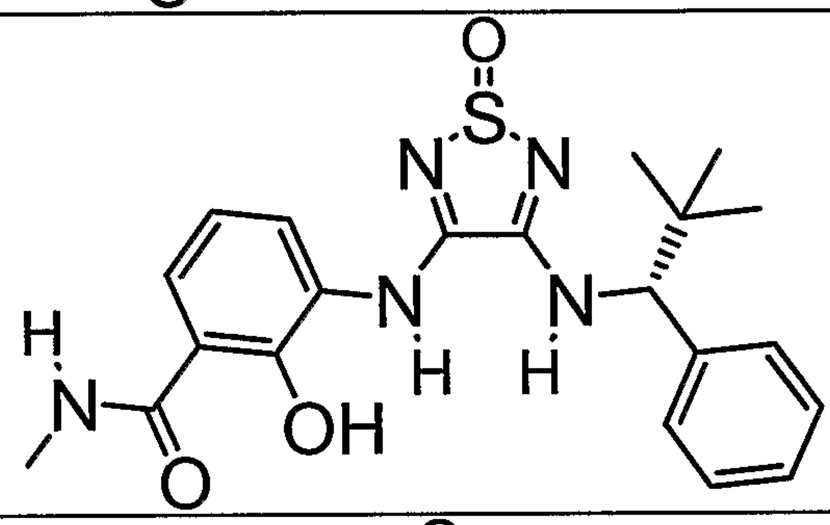
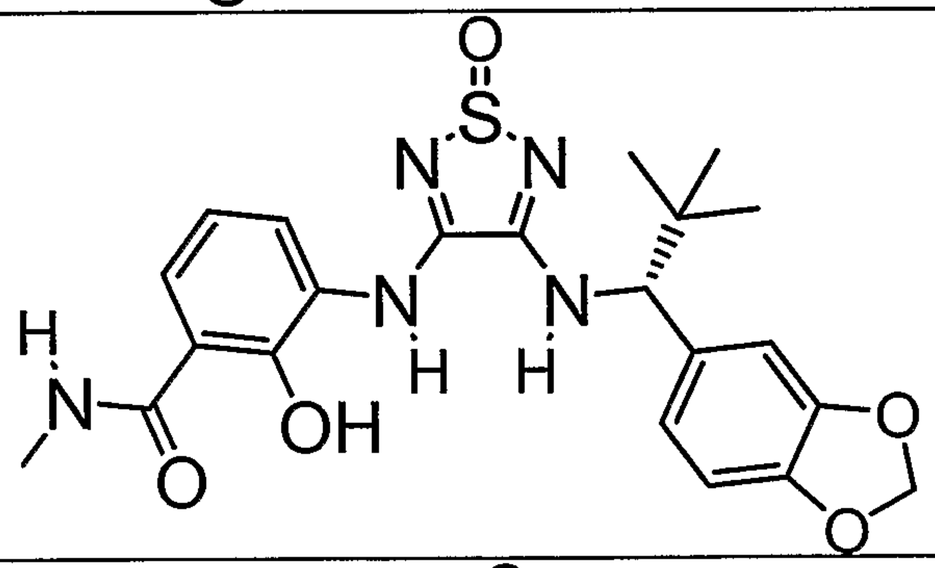
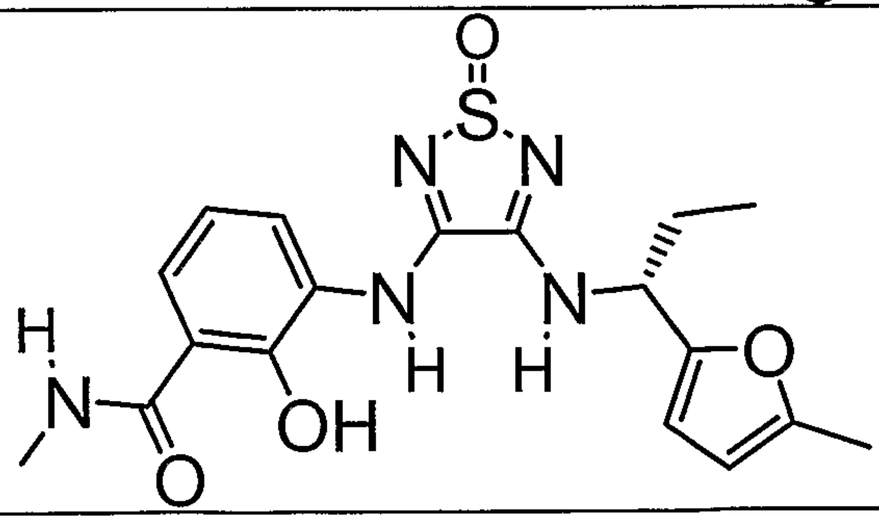
2864	355	75.20	
2865	355	75.44	
2866	356	PhNH2	
2867	356	2-Bromo-PhNH2	
2868	356	2,3-Dichloro-PhNH2	

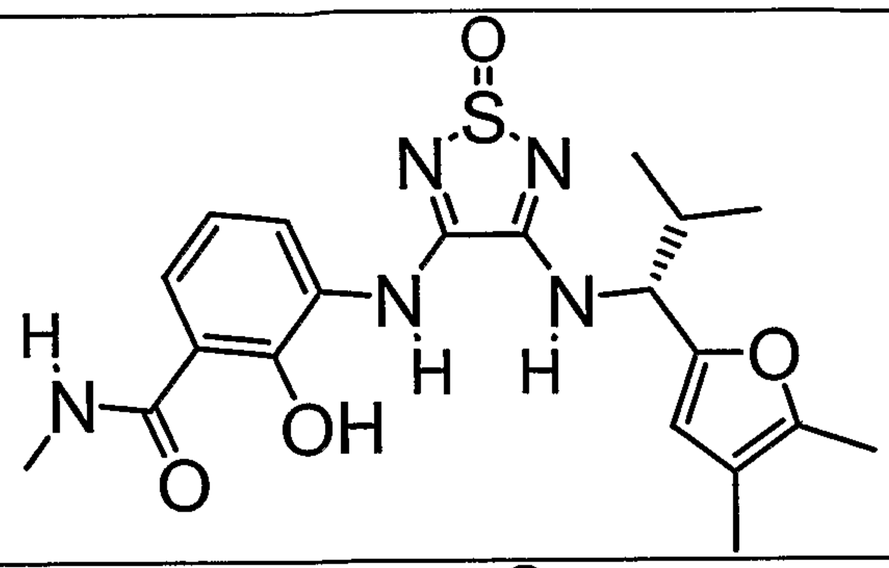
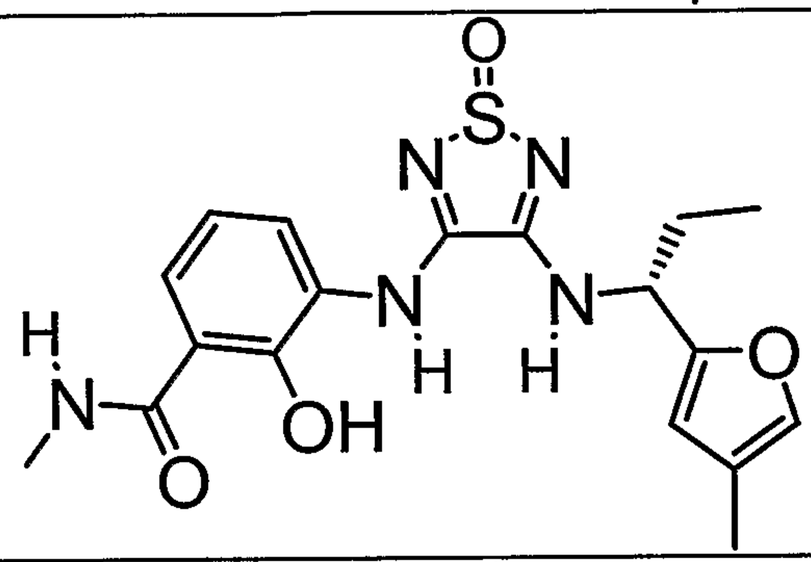
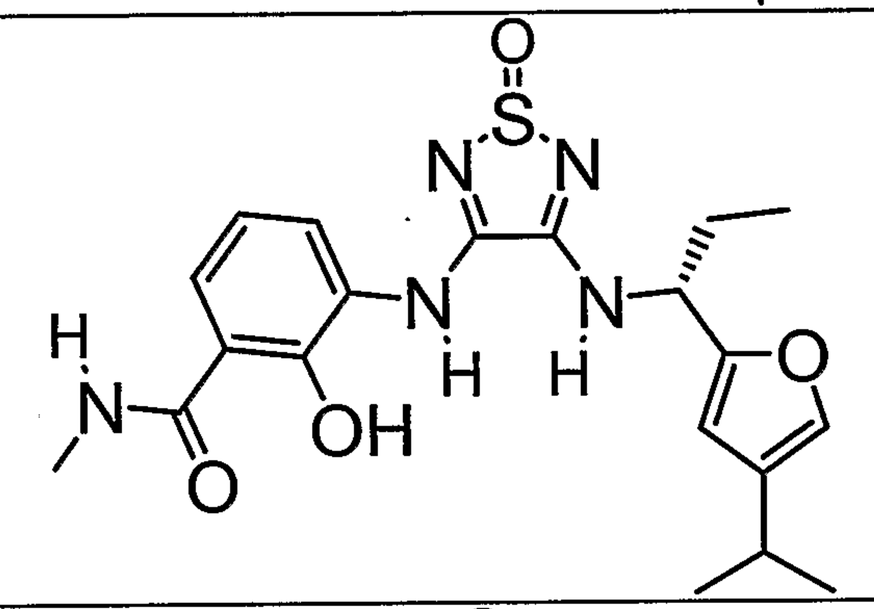
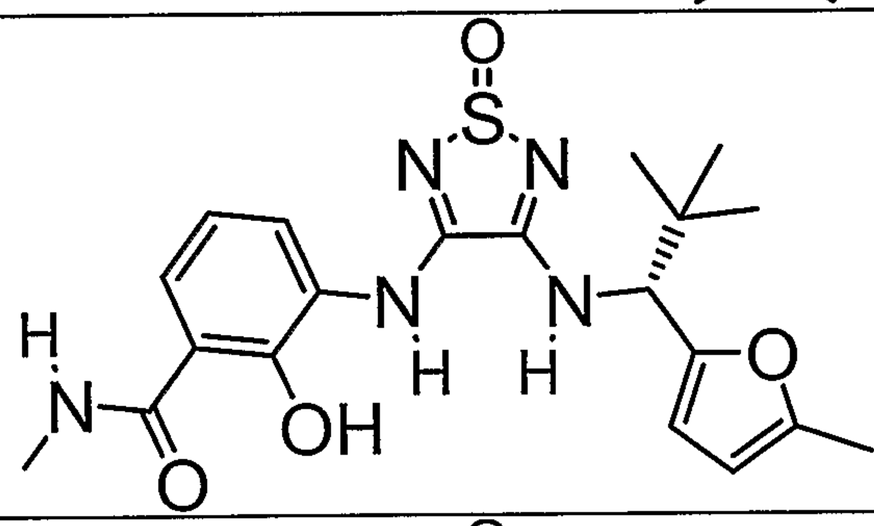
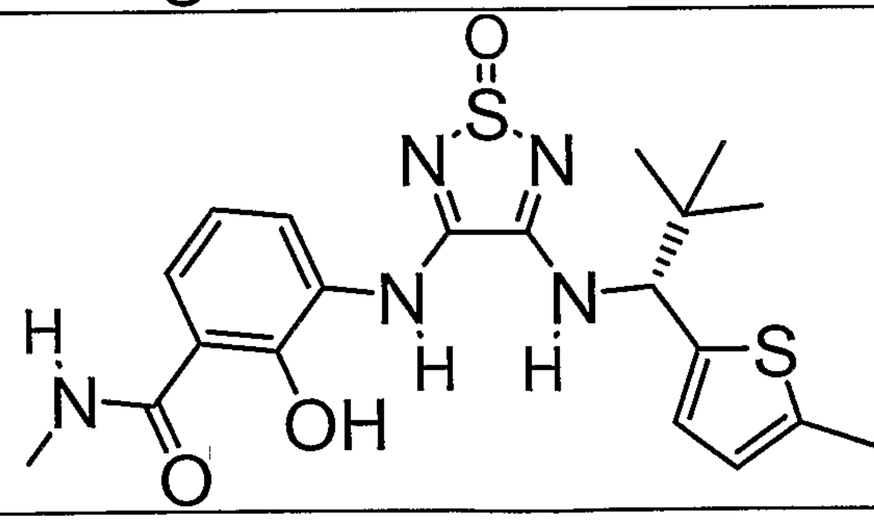
2869	356	74	
2870	356	75.60	
2871	356	75.1	
2872	356	75.49	
2873	356	75.60	

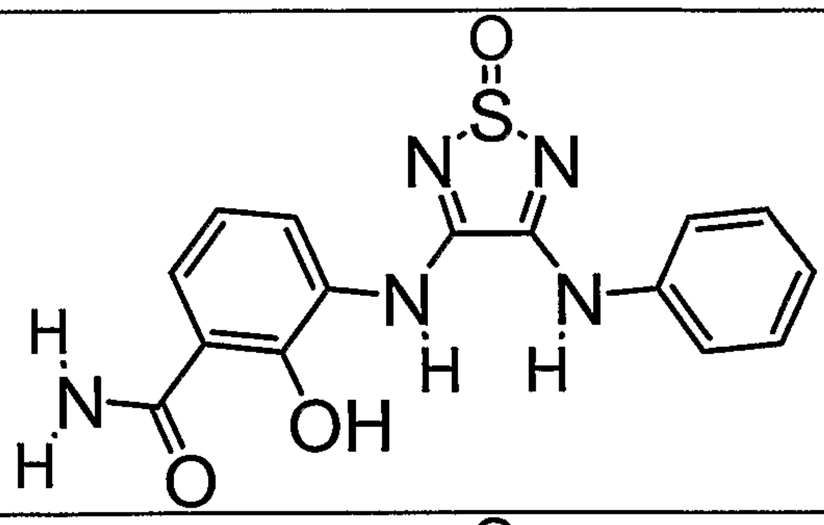
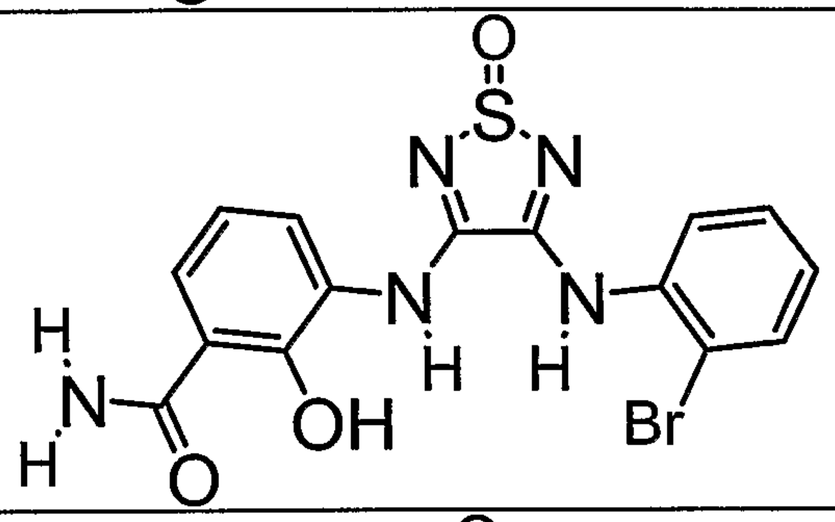
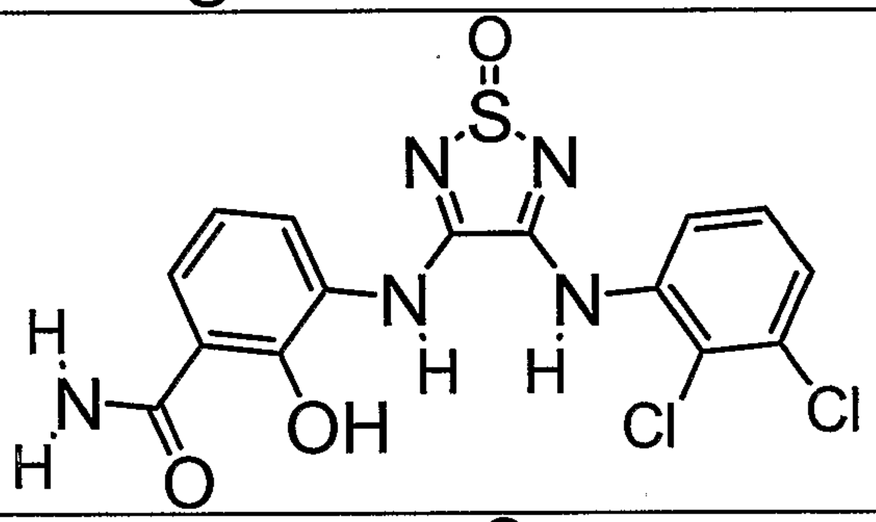
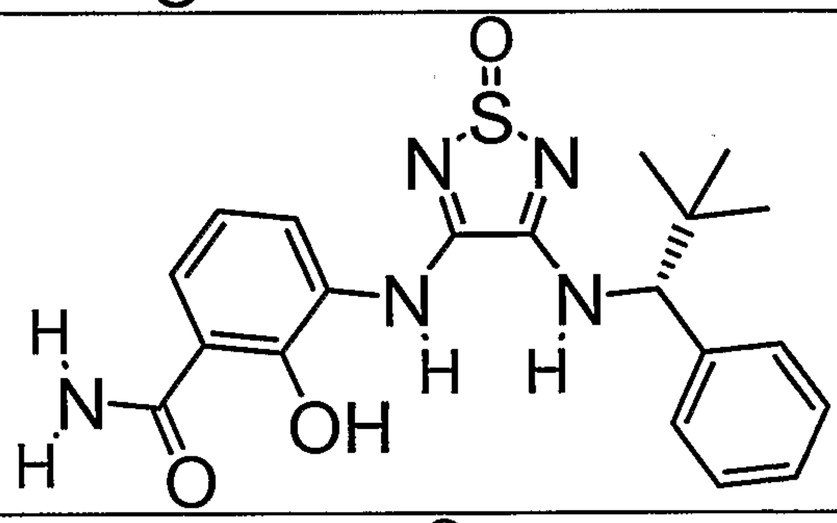
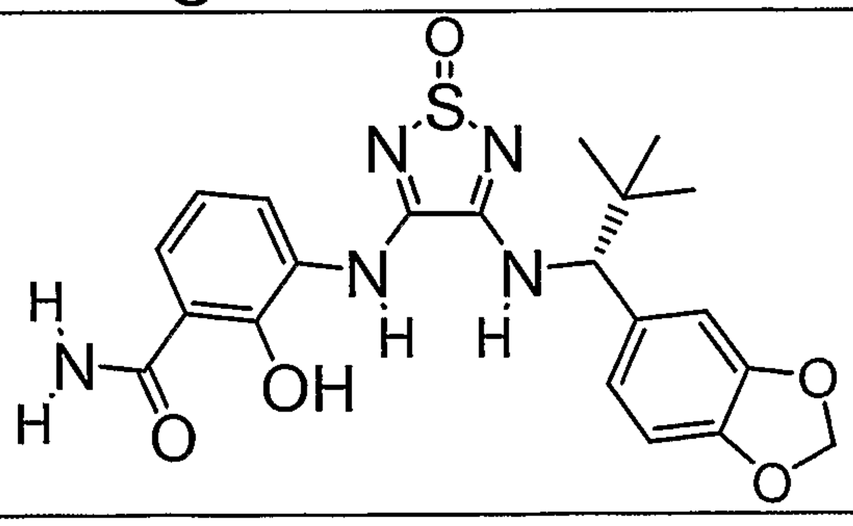
2874	356	75.61	
2875	356	75.20	
2876	356	75.44	
2877	356	PhNH2	
2878	356	2-Bromo-PhNH2	

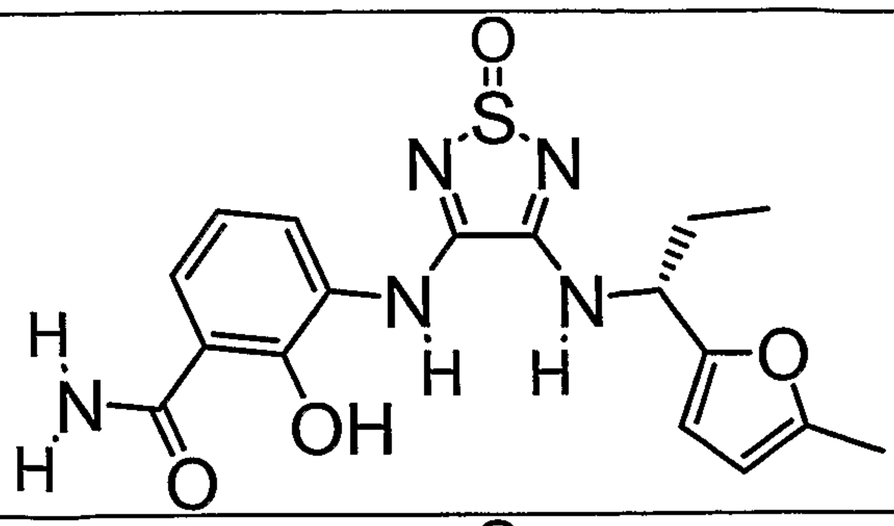
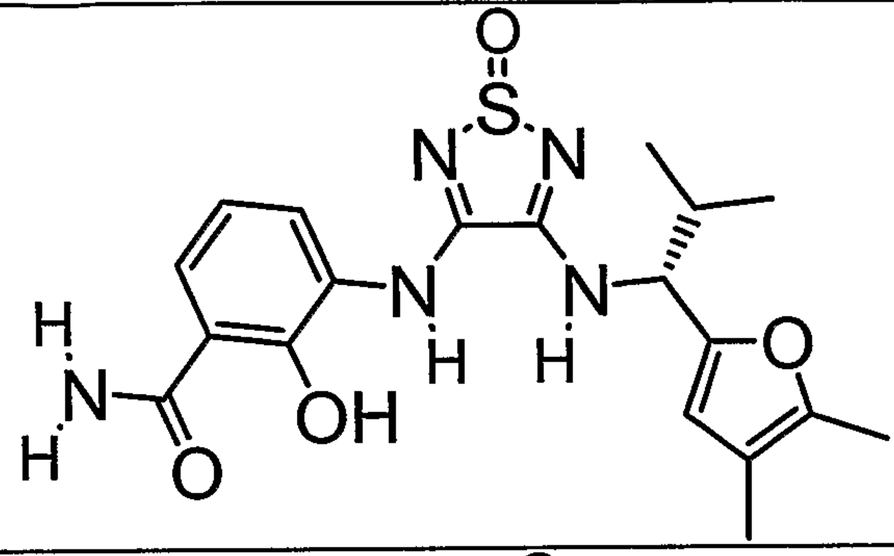
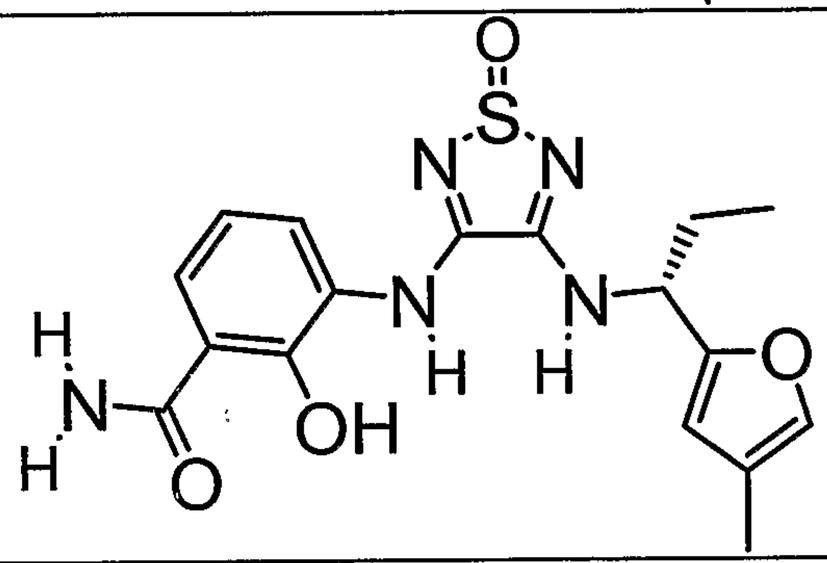
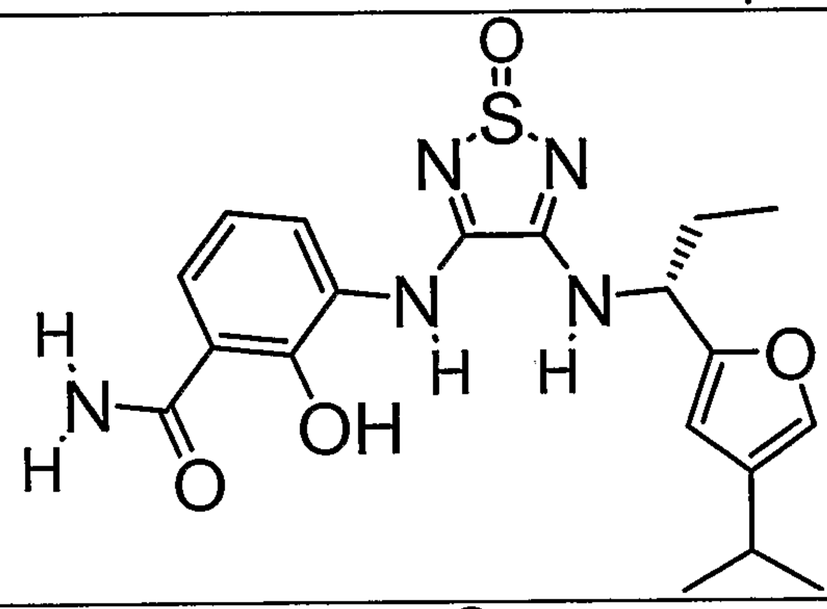
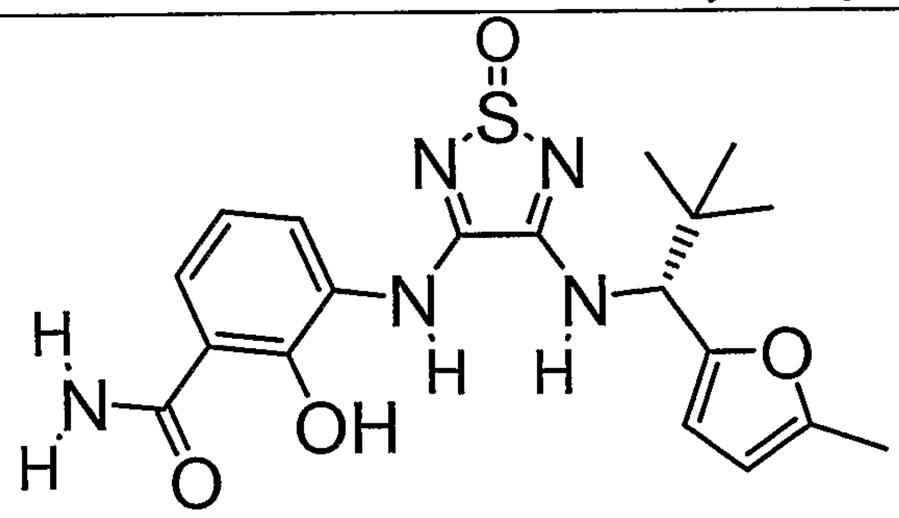
2879	356	2,3-Dichloro-PhNH2	
2880	356	74	
2881	356	75.60	
2882	356	75.1	
2883	356	75.49	

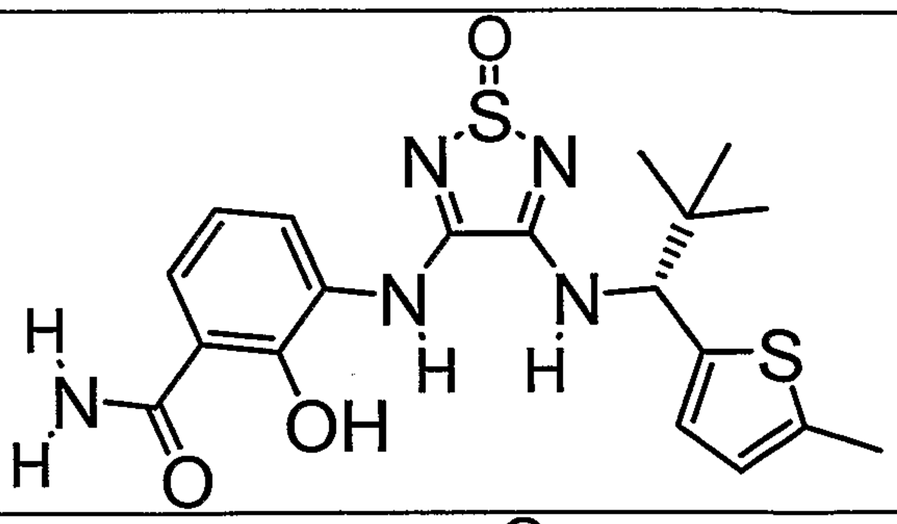
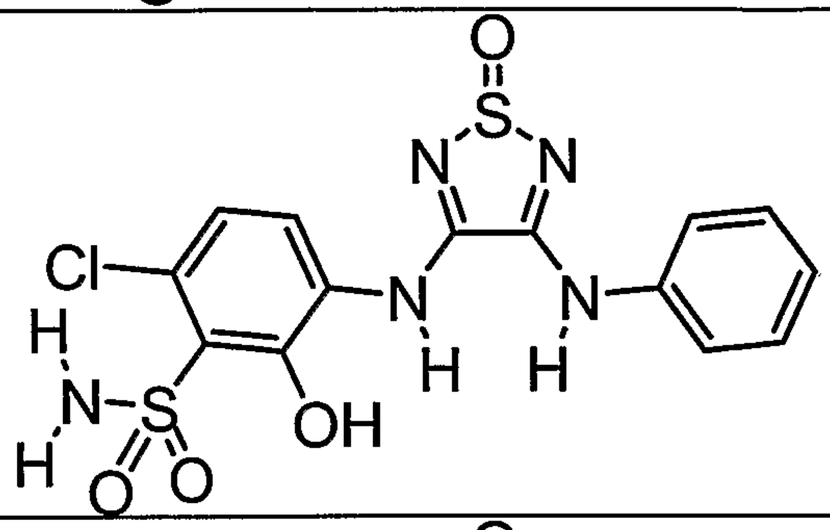
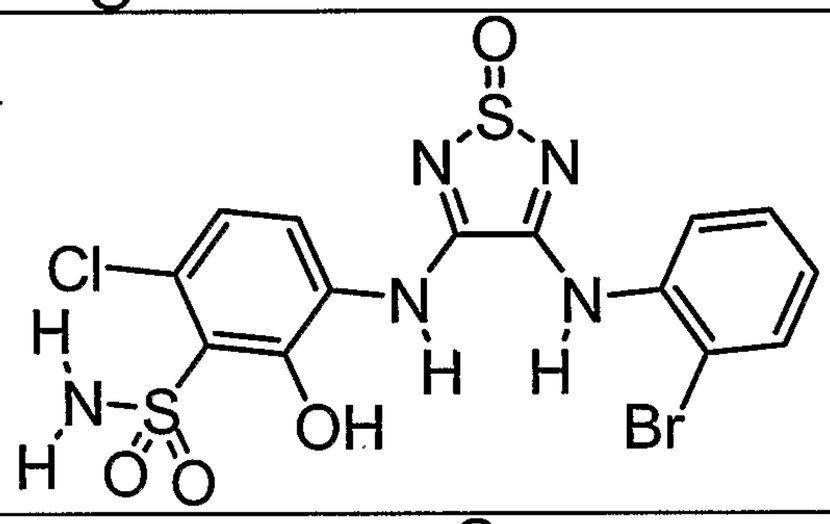
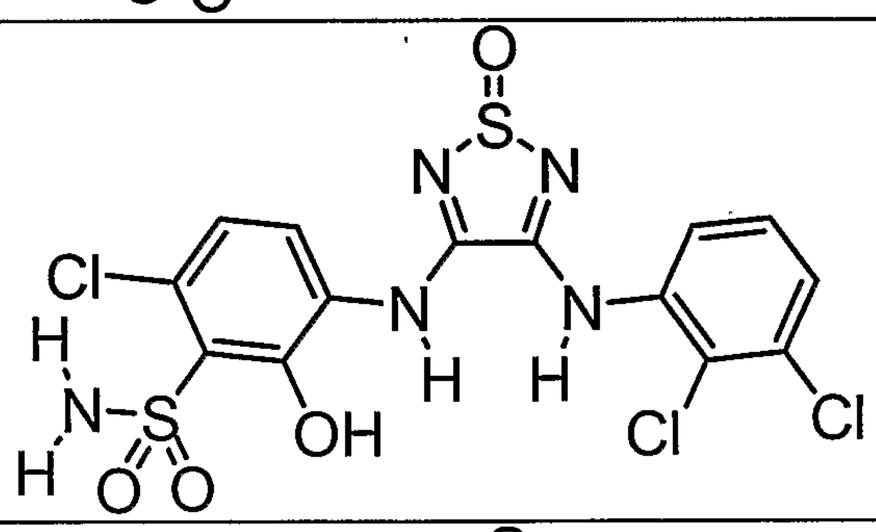
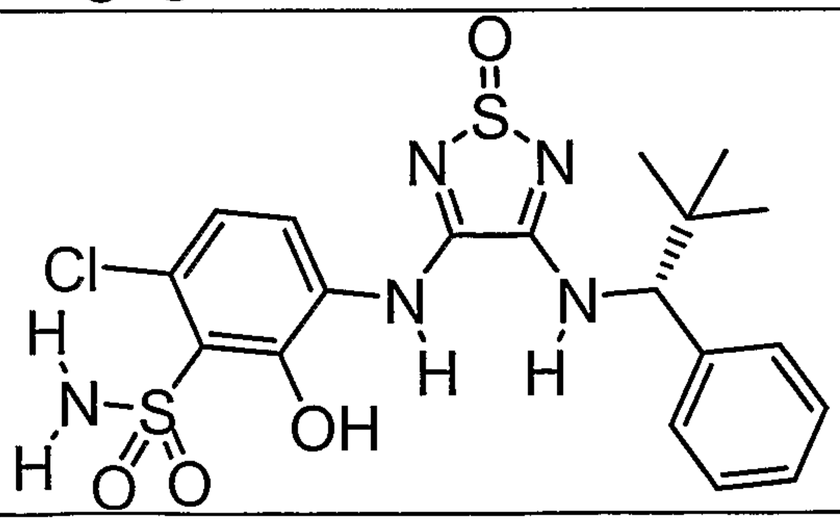
2884	356	75.9	
2885	356	75.61	
2886	356	75.20	
2887	356	75.44	
3000	450	PhNH2	

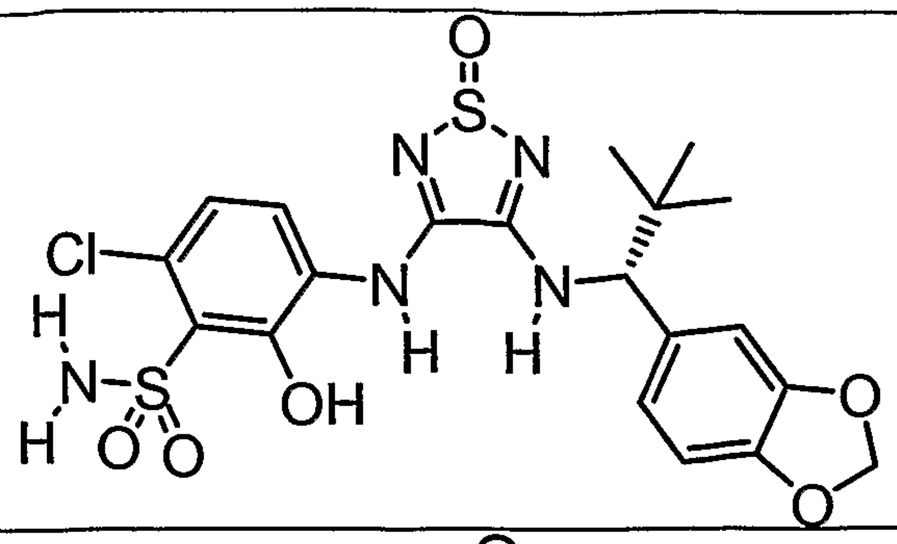
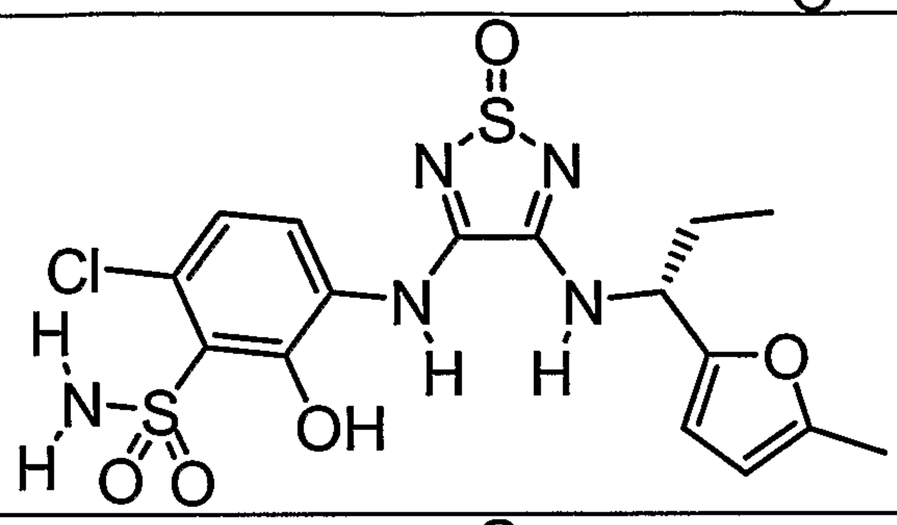
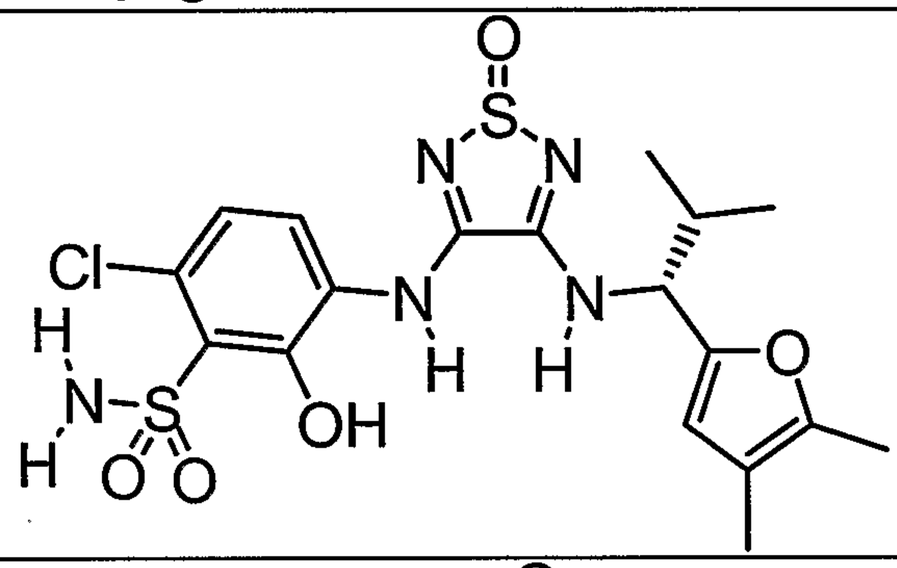
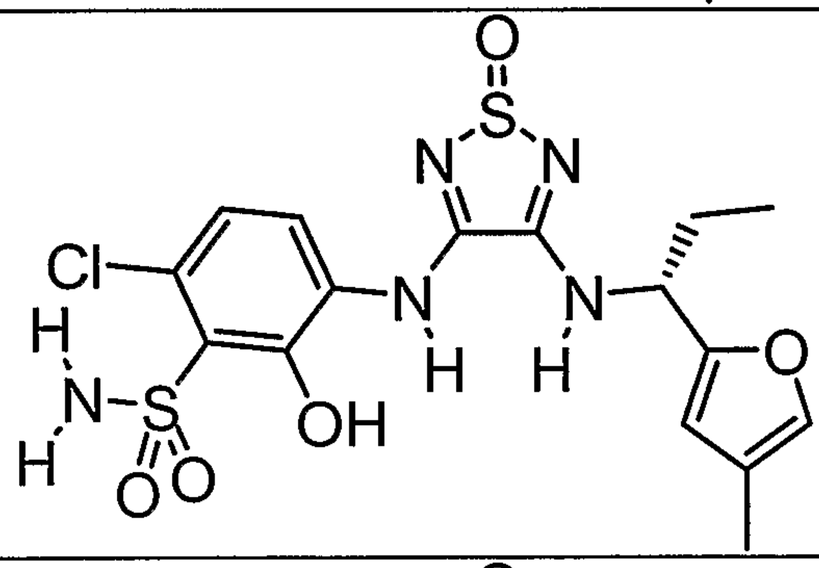
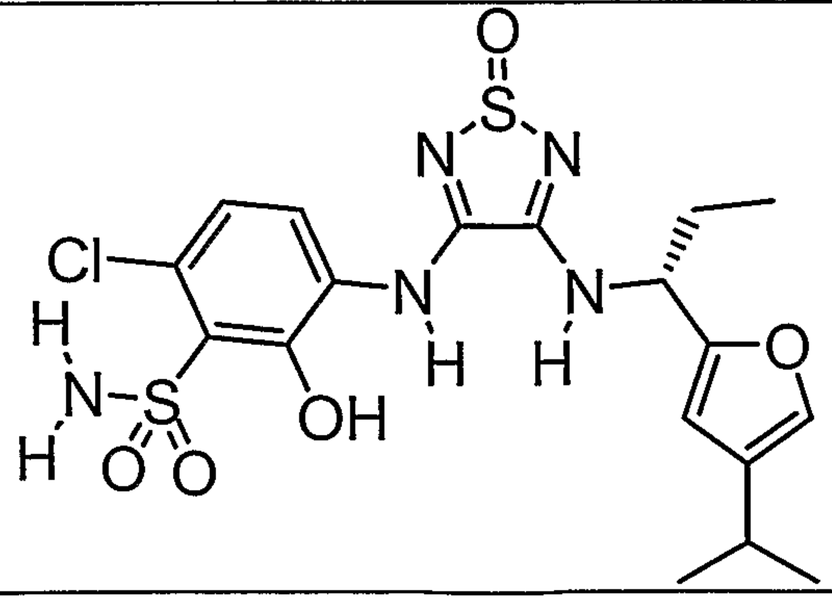
3001	450	2-Bromo-PhNH2	
3002	450	2,3-Dichloro-PhNH2	
3003	450	74	
3004	450	75.60	
3005	450	75.1	

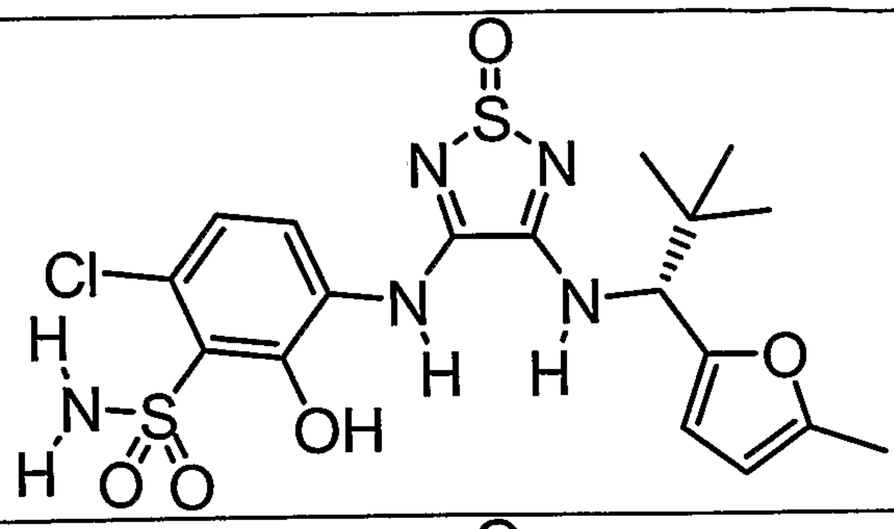
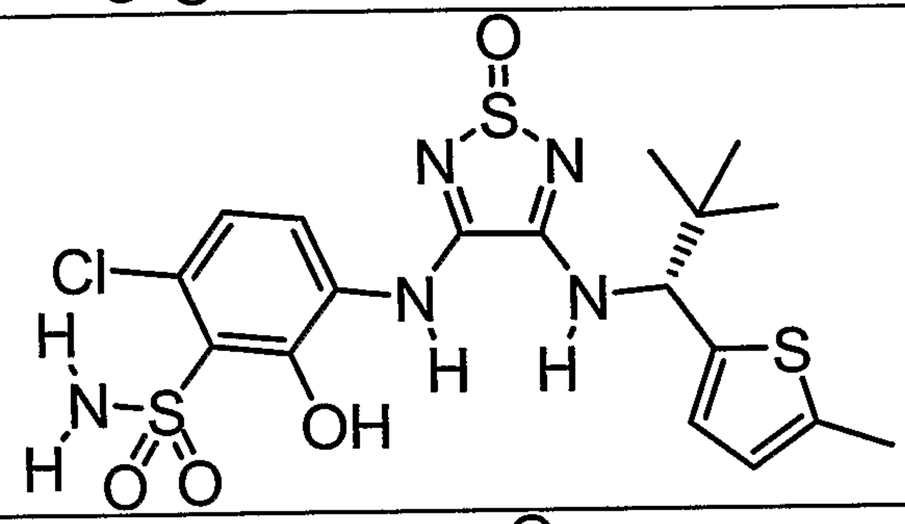
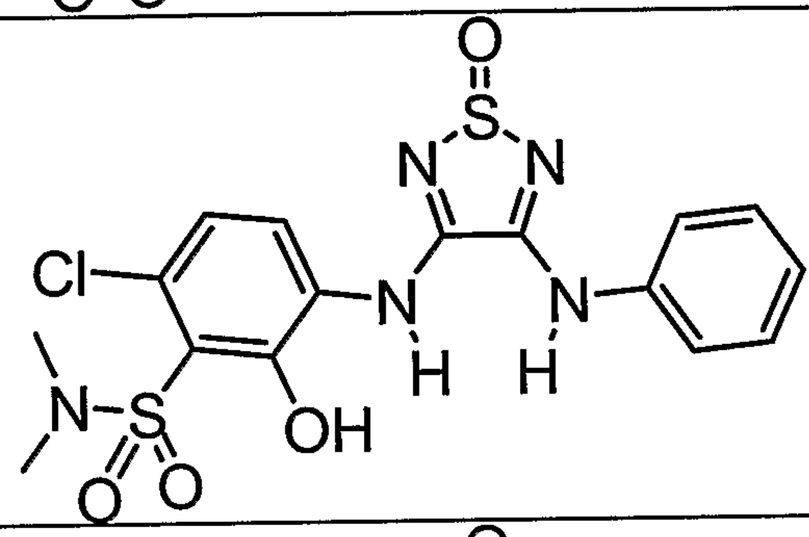
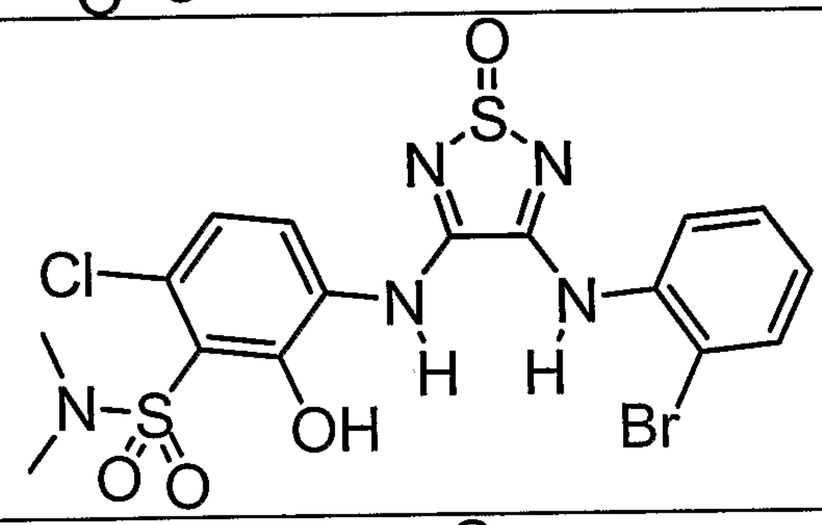
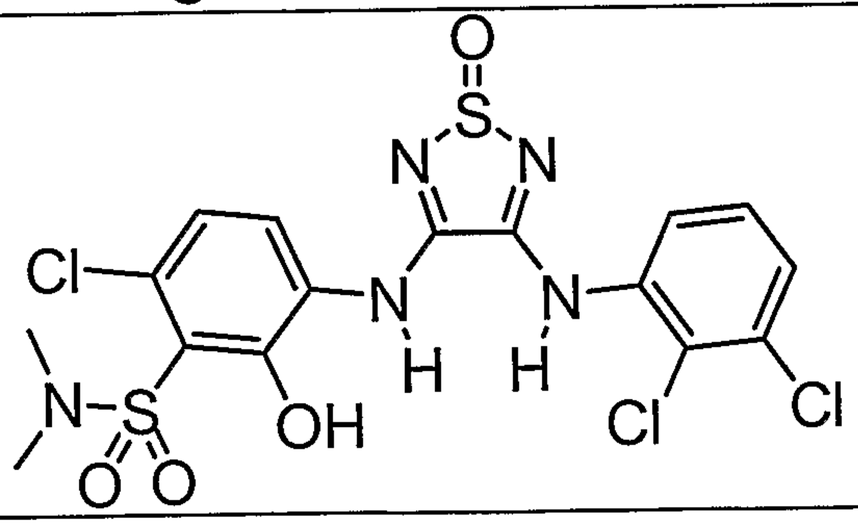
3006	450	75.61	
3007	450	75.49	
3008	450	75.9	
3009	450	75.44	
3010	450	75.20	

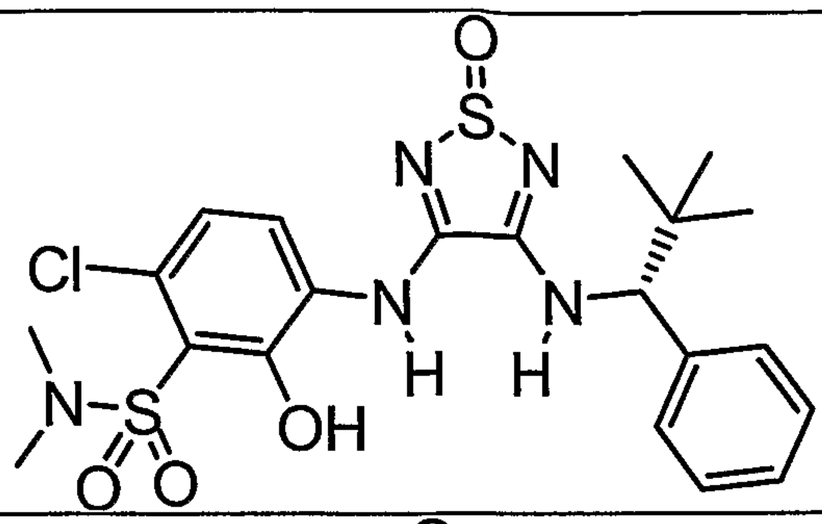
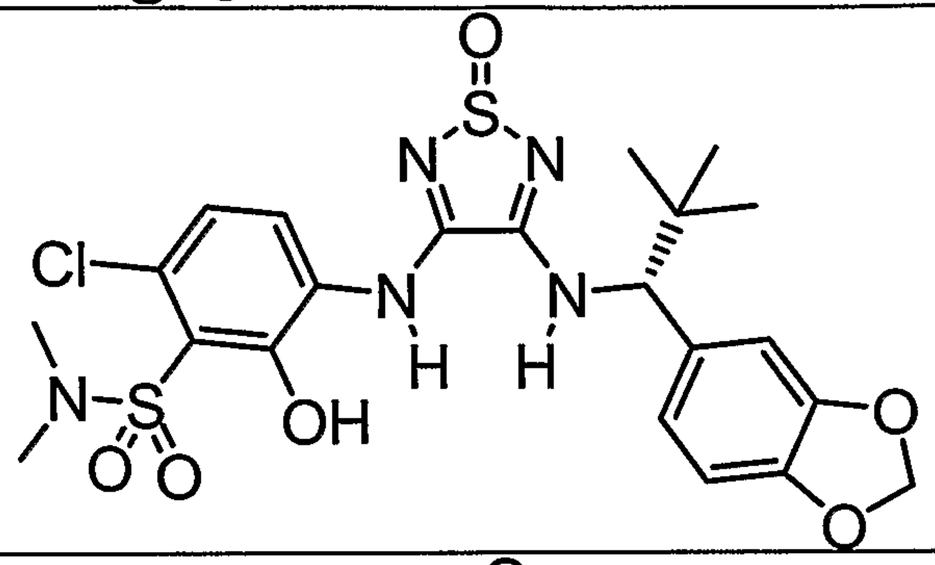
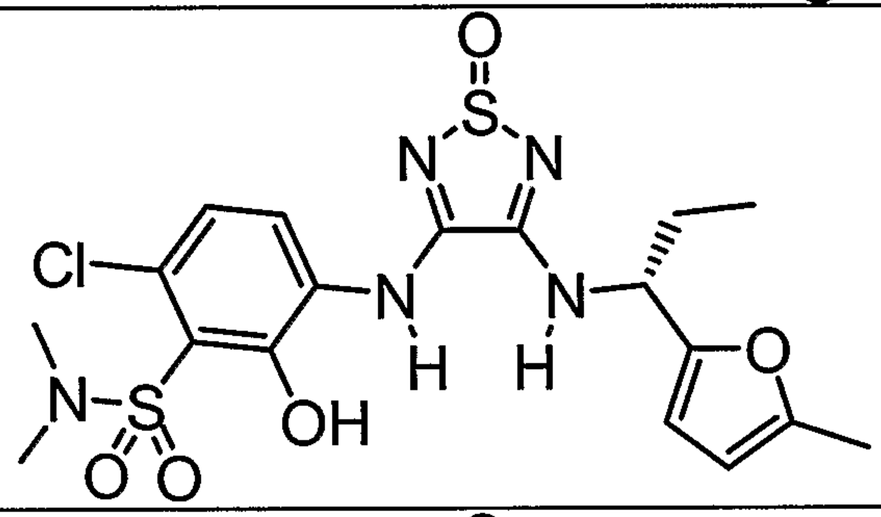
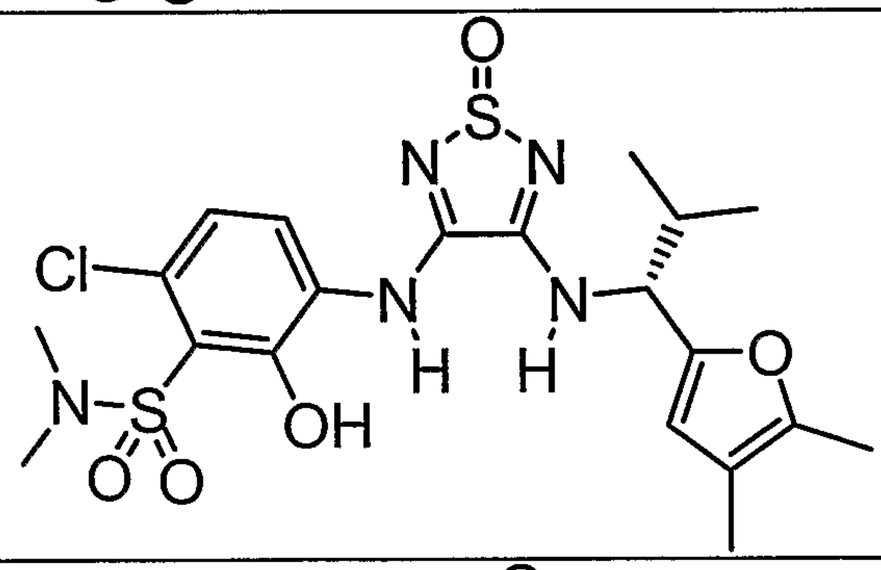
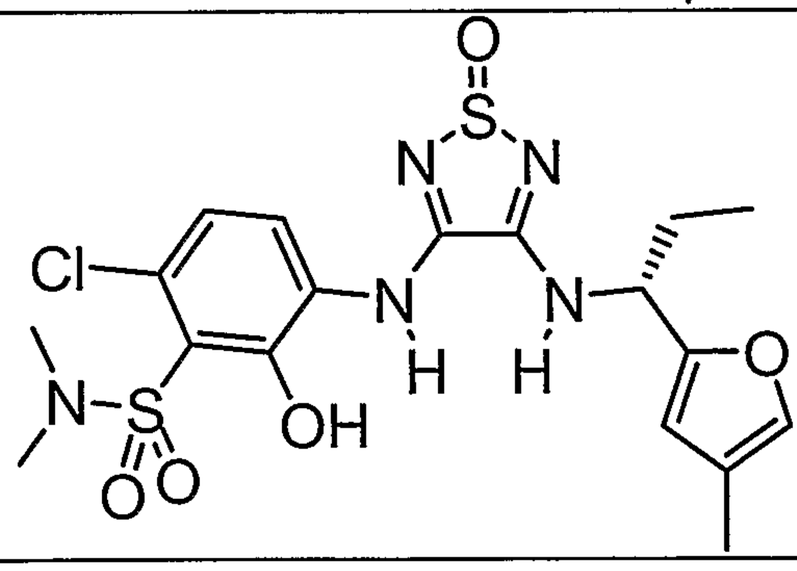
3011	451	PhNH2	
3012	451	2-Bromo-PhNH2	
3013	451	2,3-Dichloro-PhNH2	
3014	451	74	
3015	451	75.60	

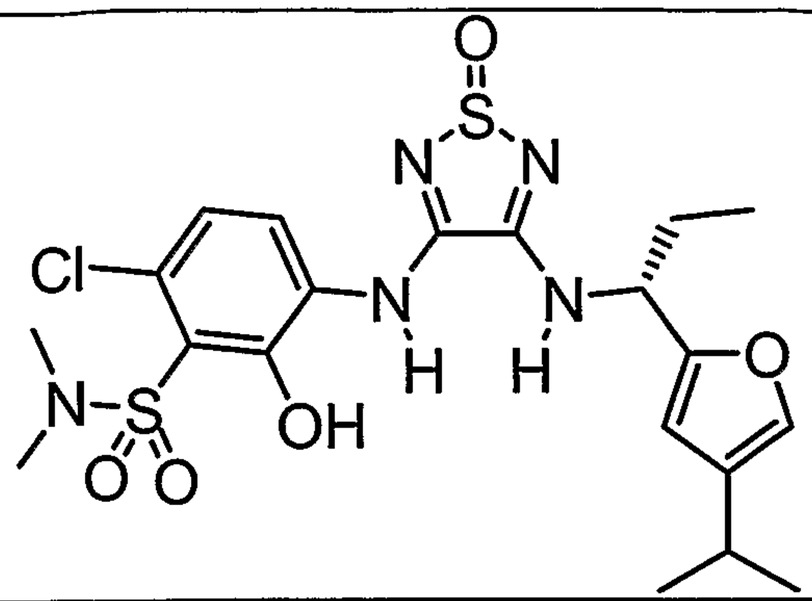
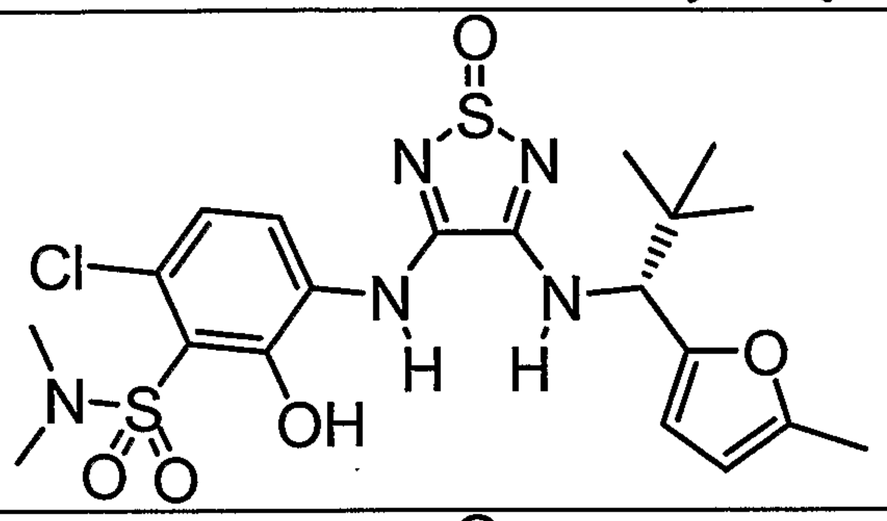
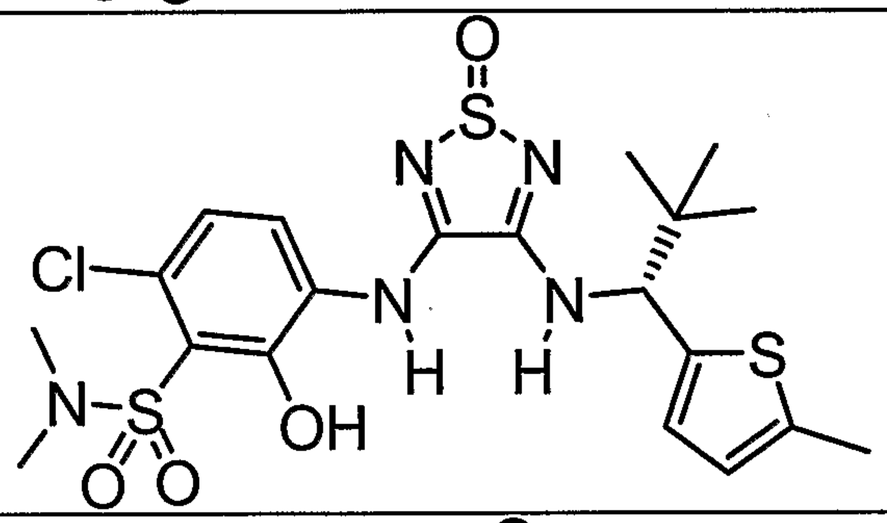
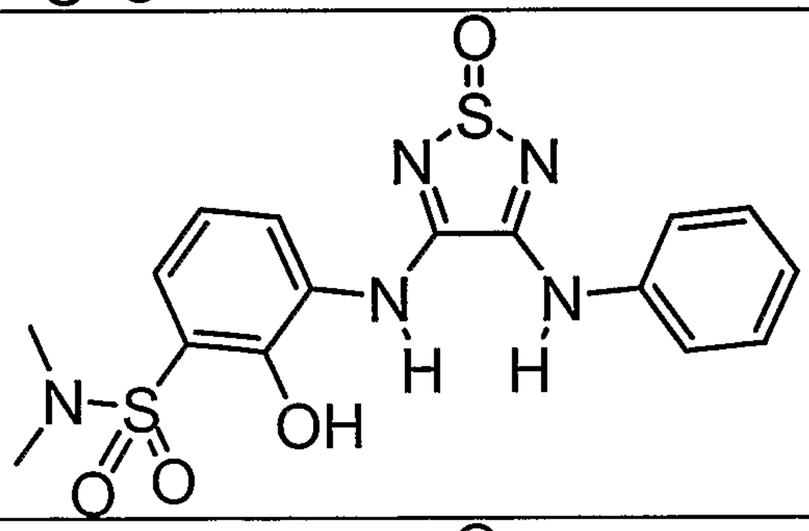
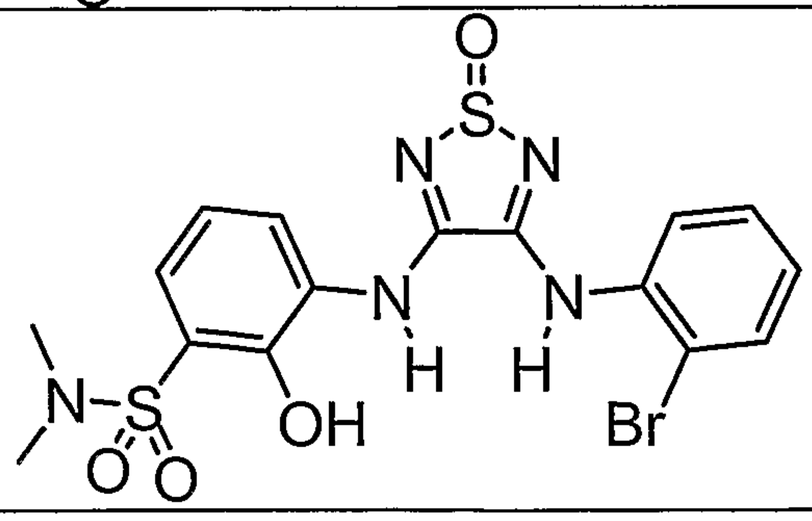
3016	451	75.1	
3017	451	75.61	
3018	451	75.49	
3019	451	75.9	
3020	451	75.44	

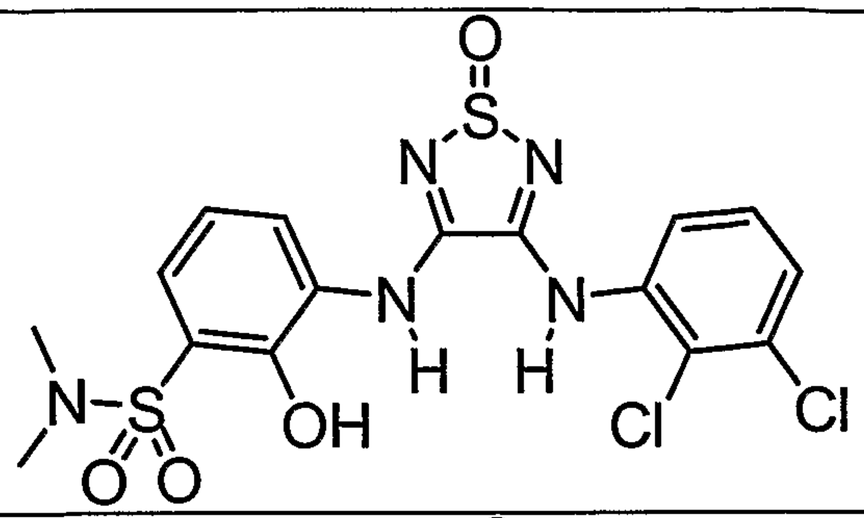
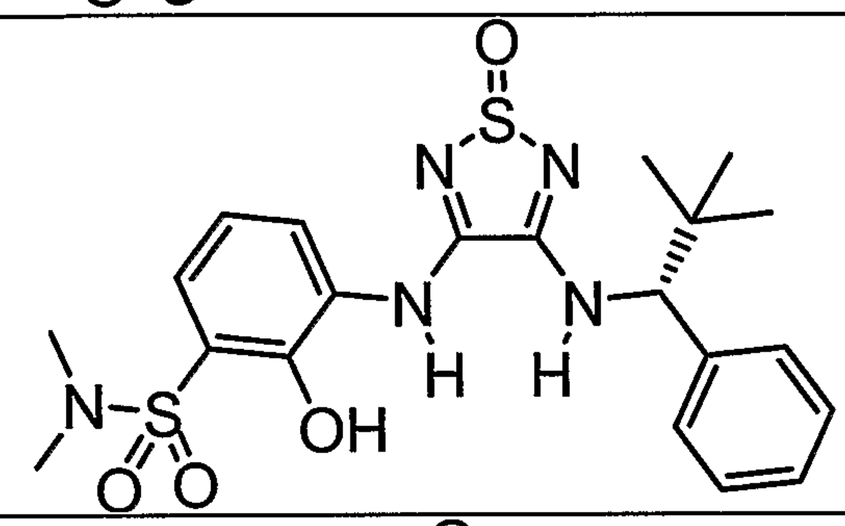
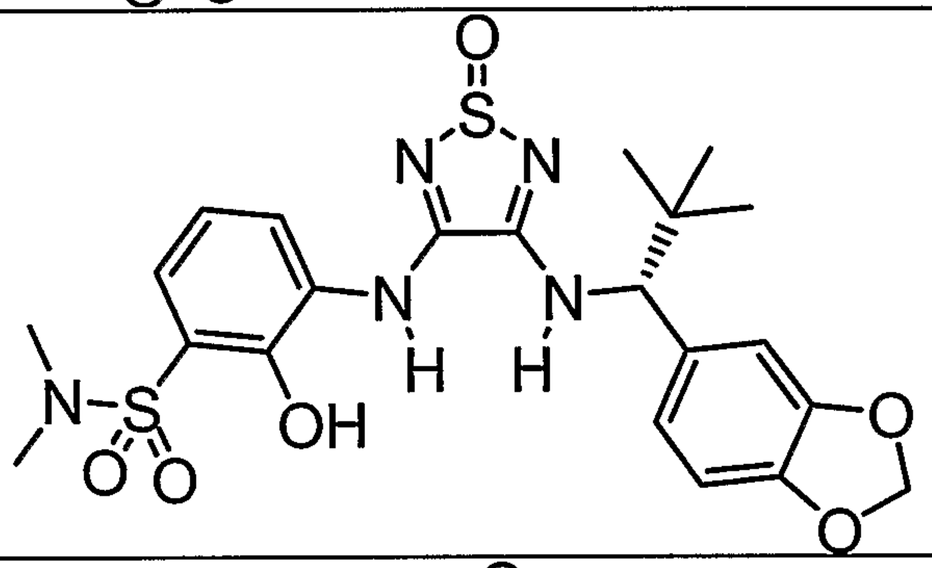
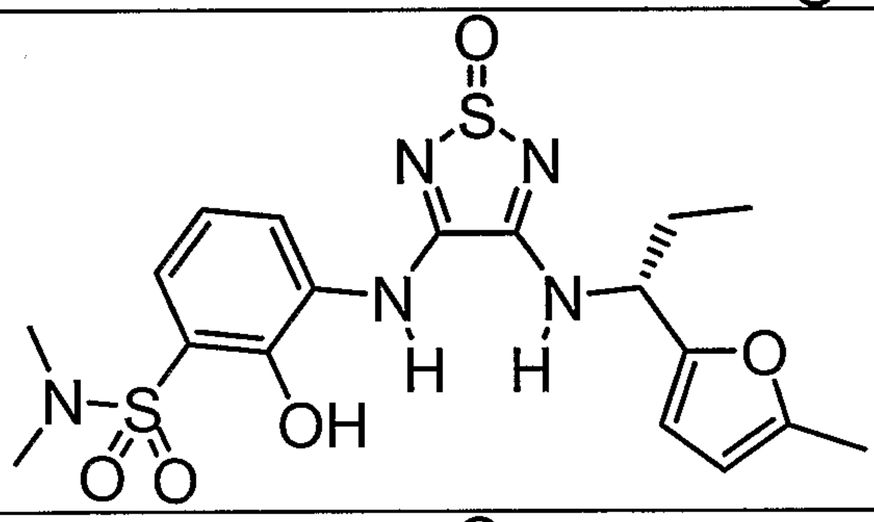
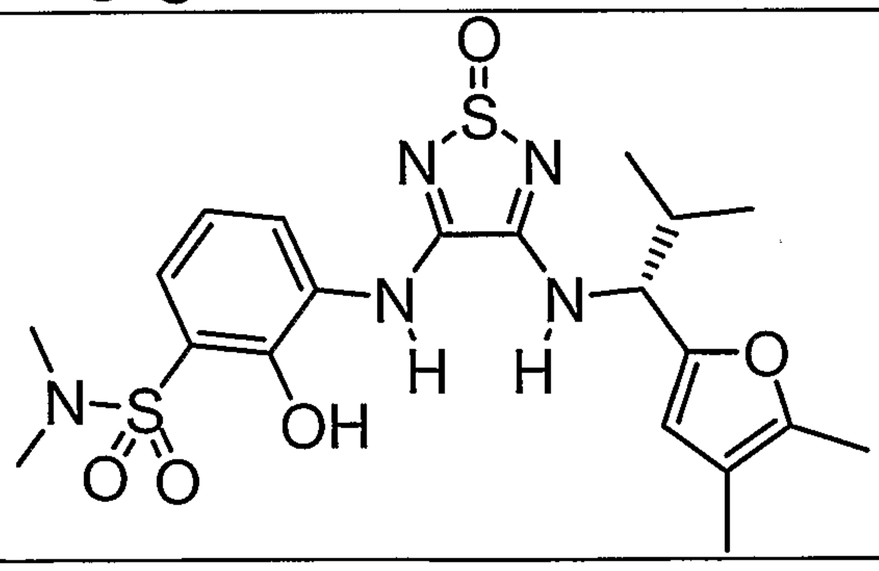
3021	451	75.20	
3022	452	PhNH2	
3023	452	2-Bromo-PhNH2	
3024	452	2,3-Dichloro-PhNH2	
3025	452	74	

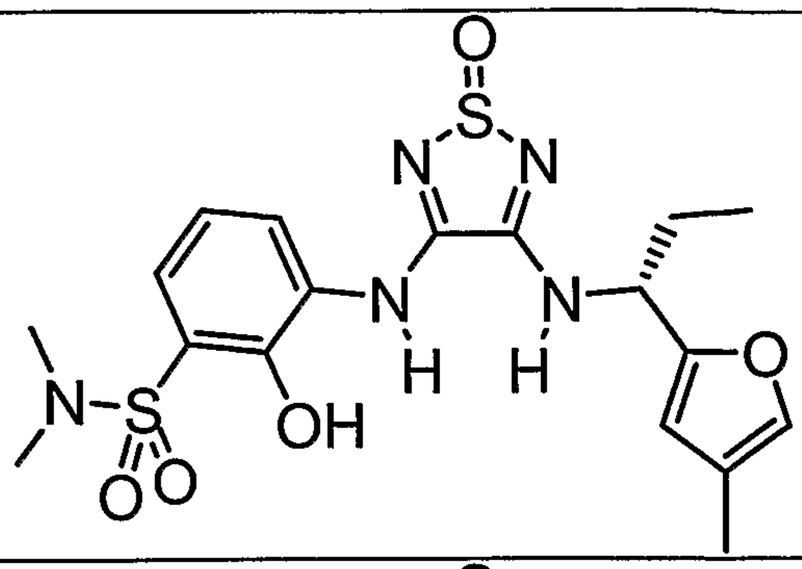
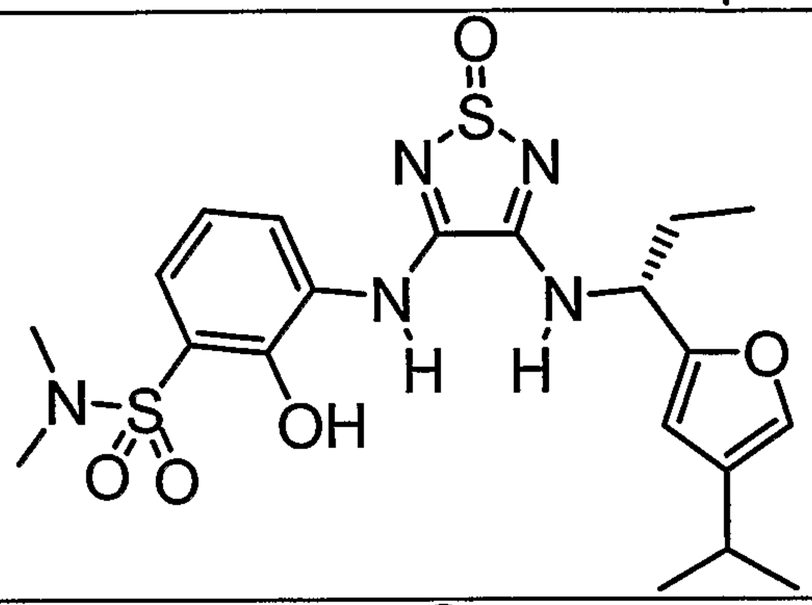
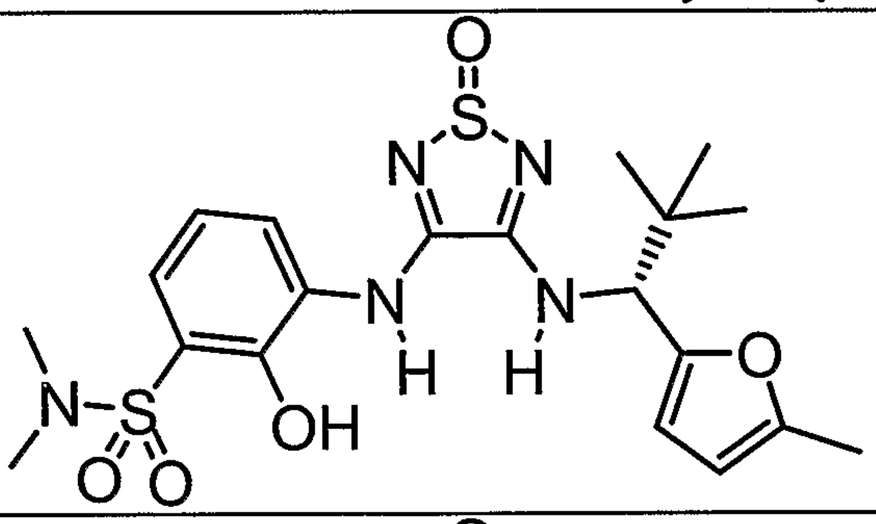
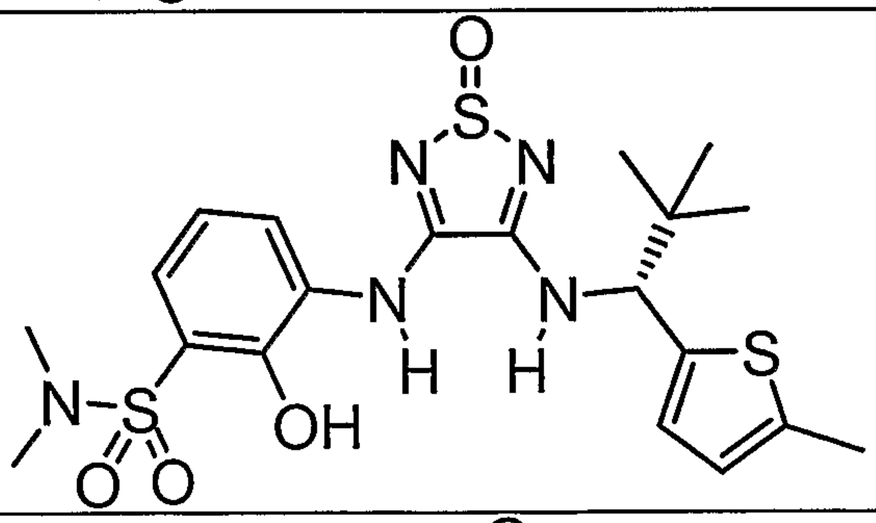
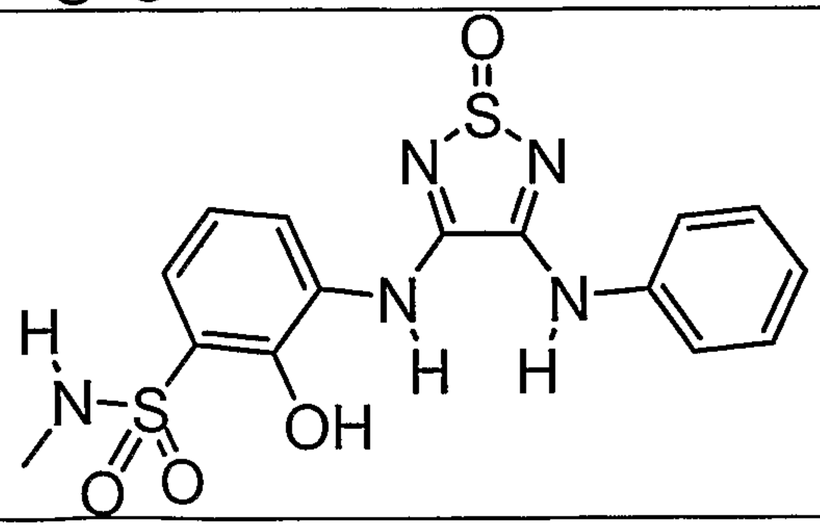
3026	452	75.60	
3027	452	75.1	
3028	452	75.61	
3029	452	75.49	
3030	452	75.9	

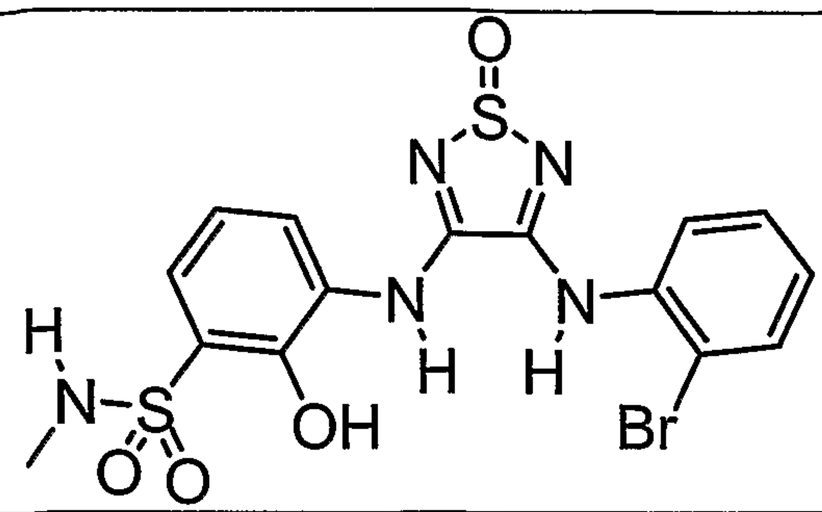
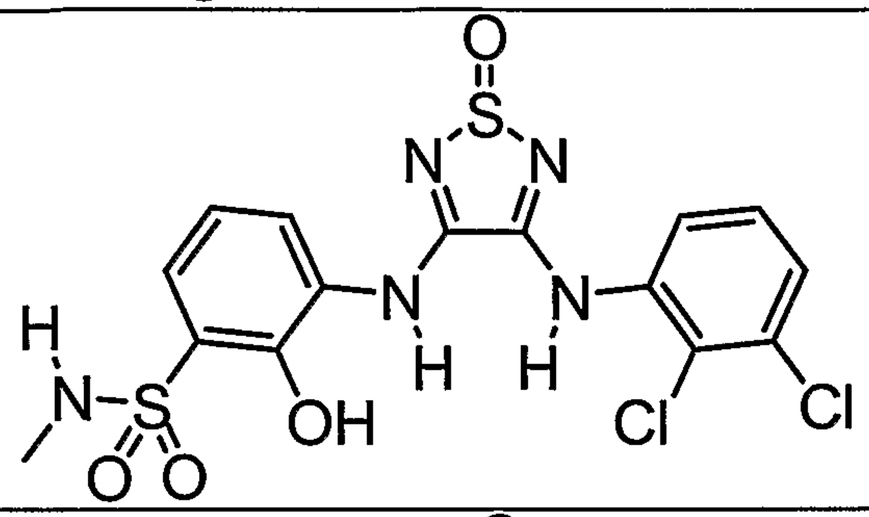
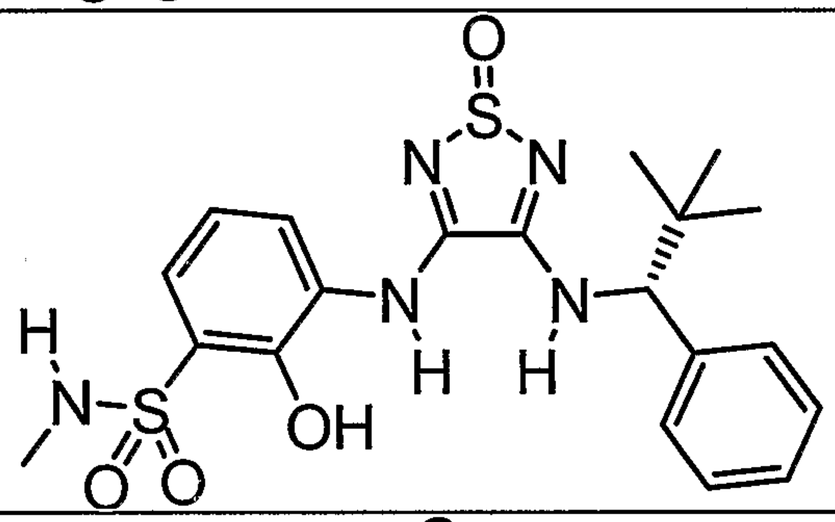
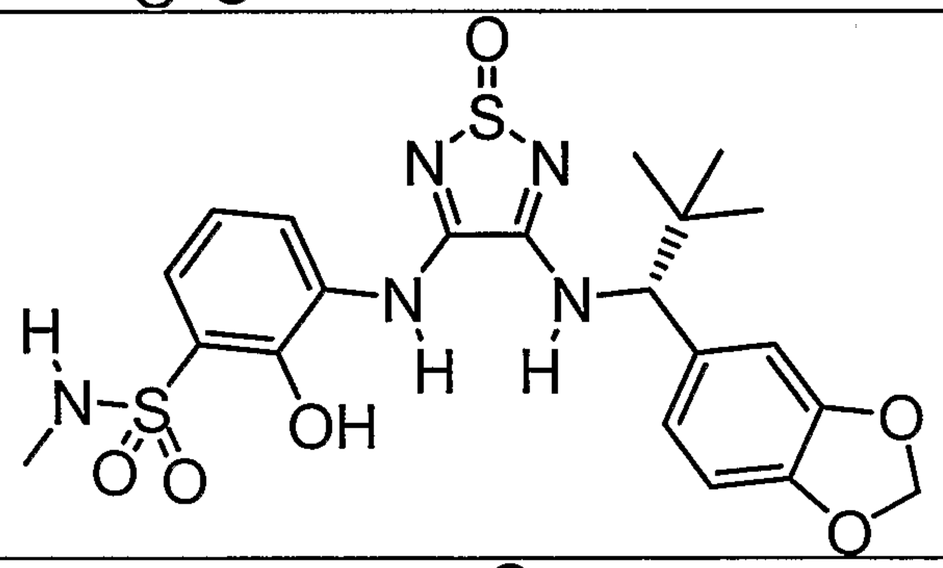
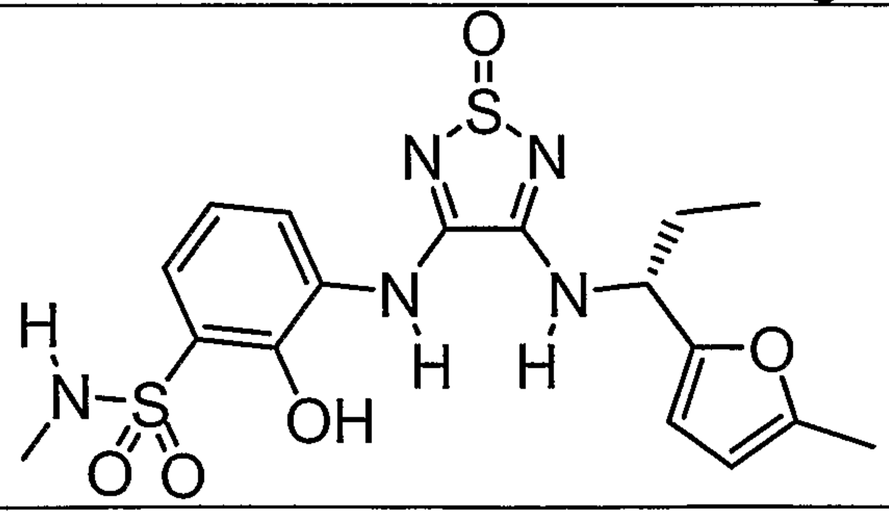
3031	452	75.44	
3032	452	75.20	
3033	453	PhNH2	
3034	453	2-Bromo-PhNH2	
3035	453	2,3-Dichloro-PhNH2	

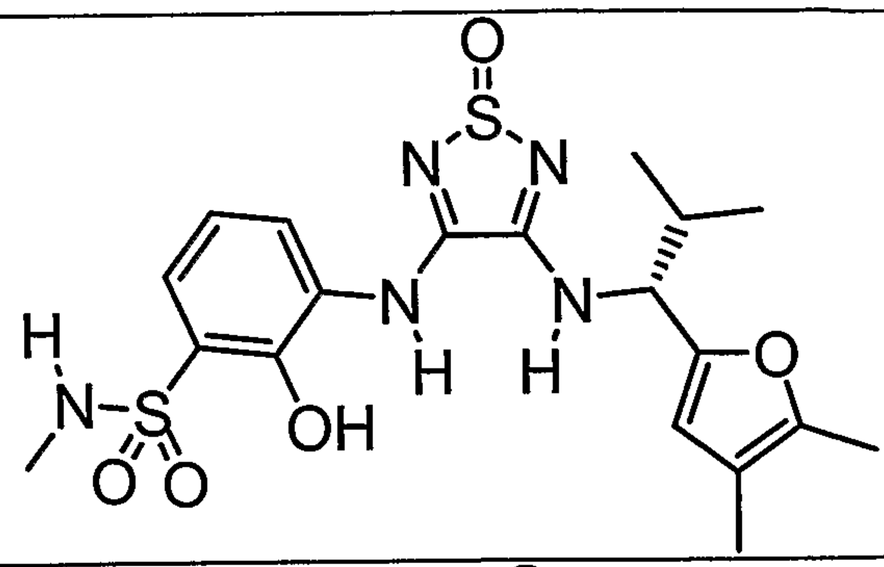
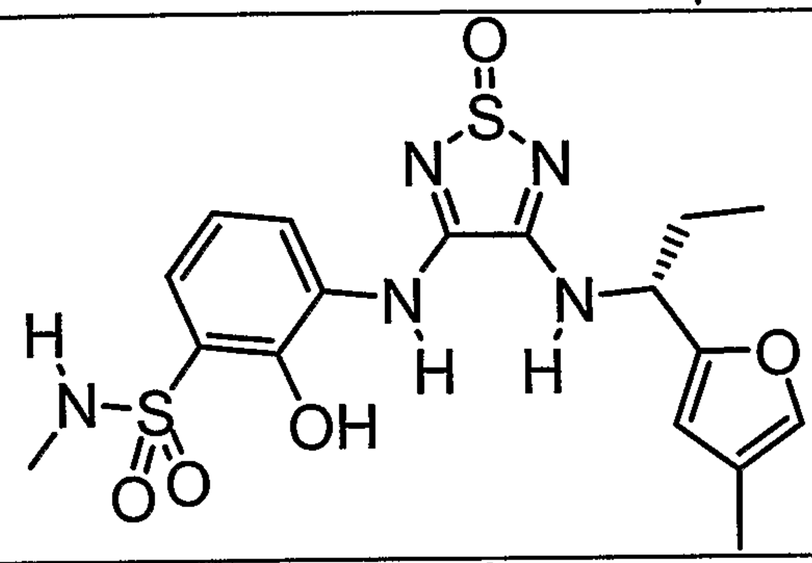
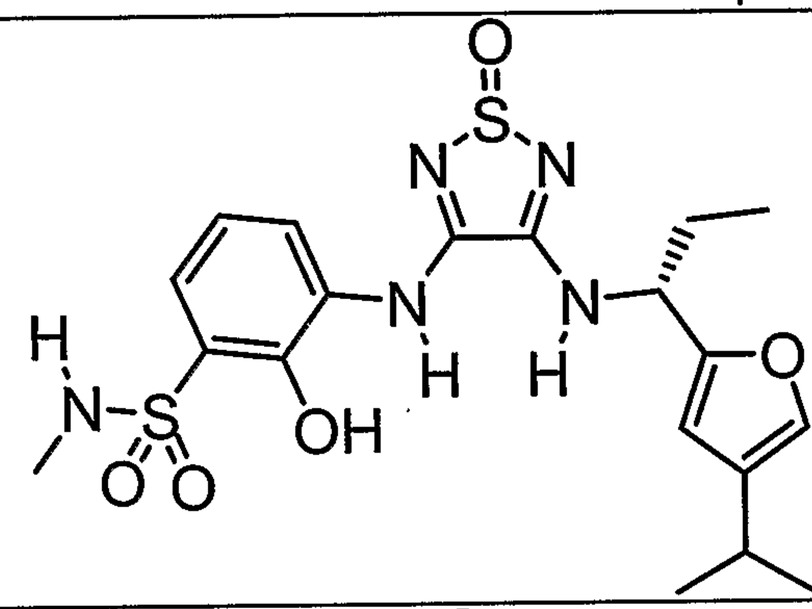
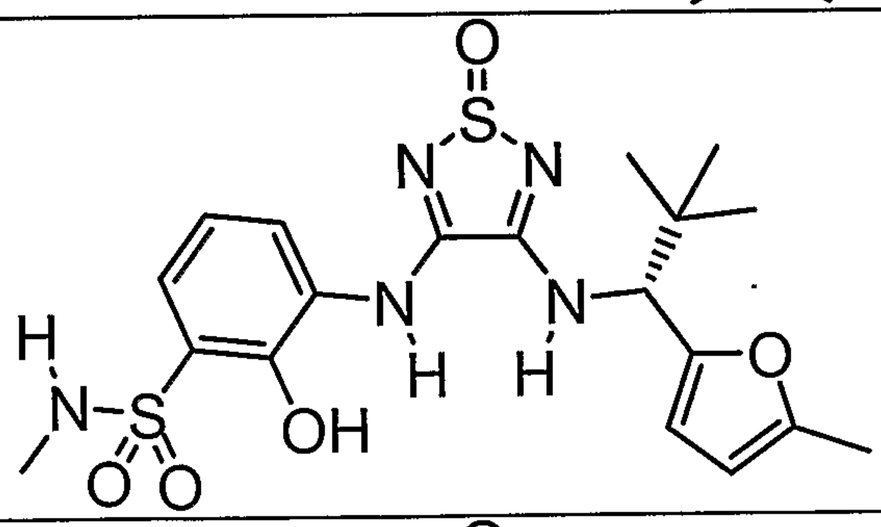
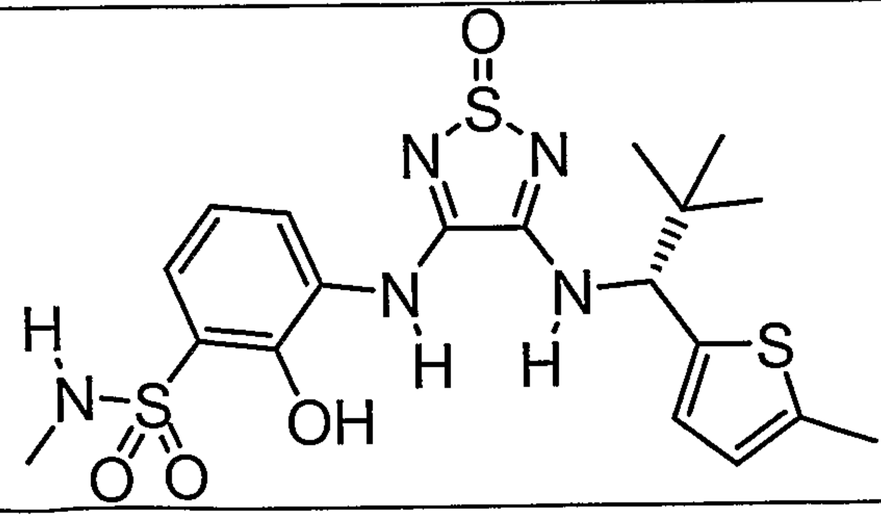
3036	453	74	
3037	453	75.60	
3038	453	75.1	
3039	453	75.61	
3040	453	75.49	

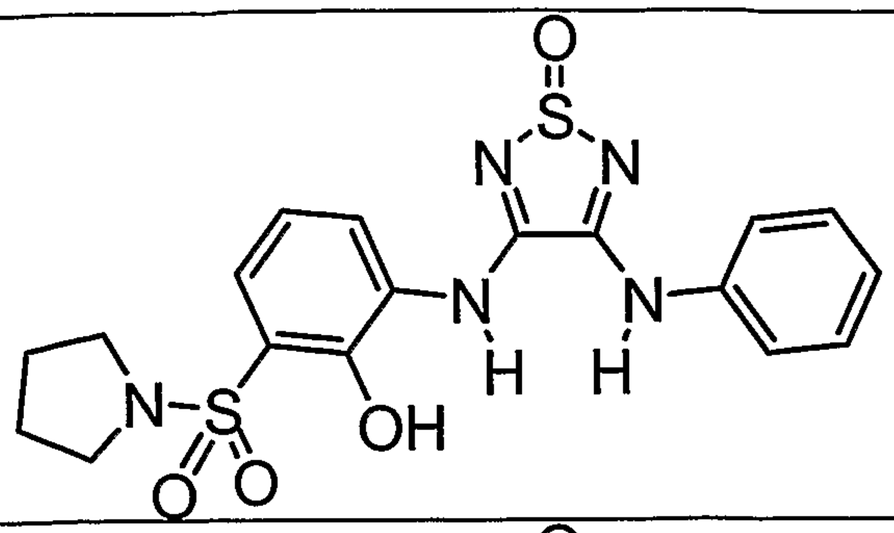
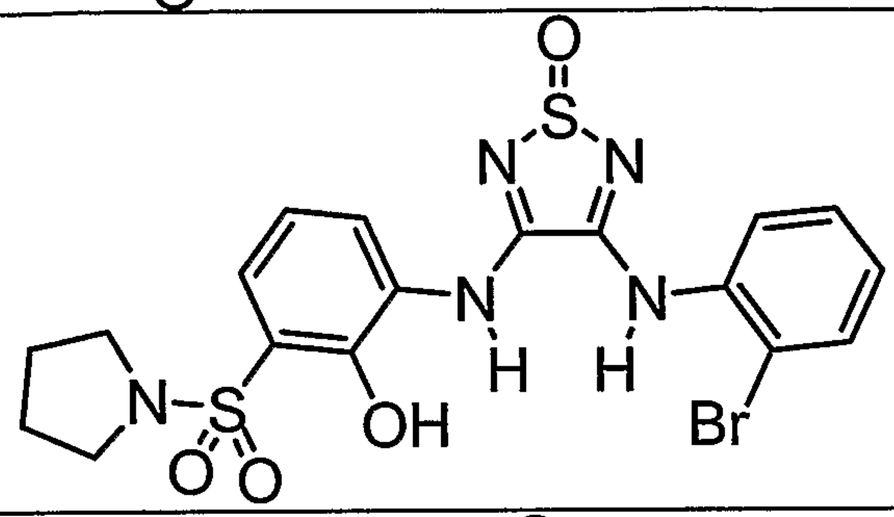
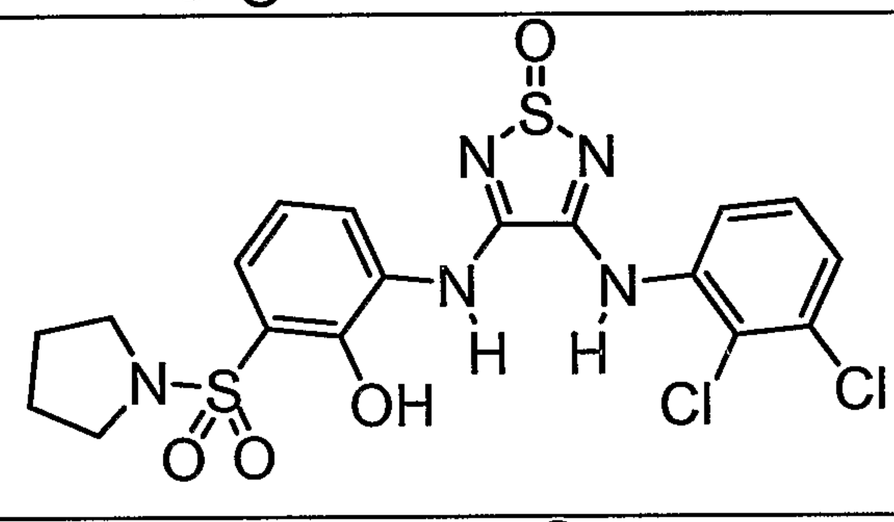
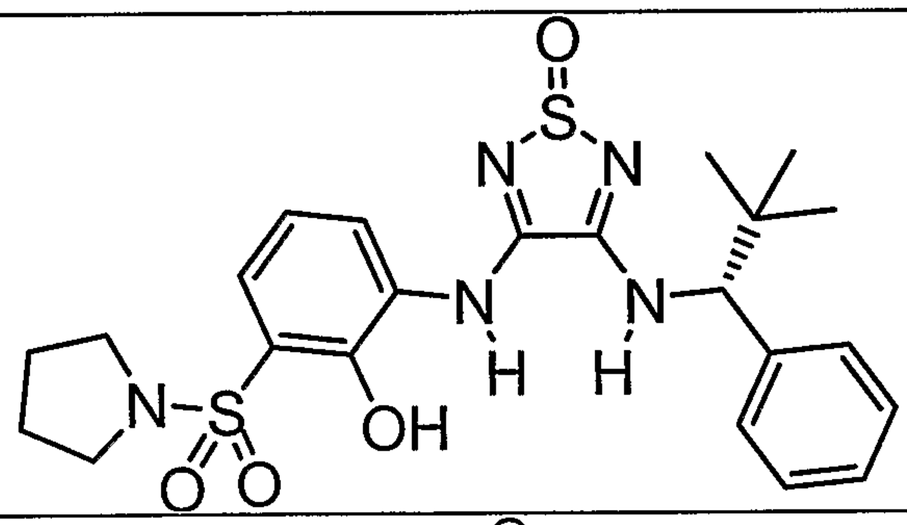
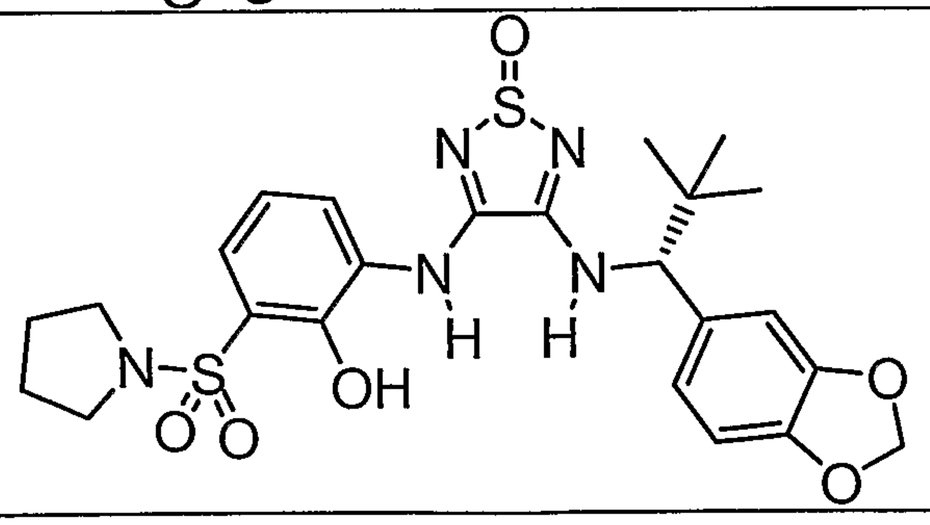
3041	453	75.9	
3042	453	75.44	
3043	453	75.20	
3044	454	PhNH2	
3045	454	2-Bromo-PhNH2	

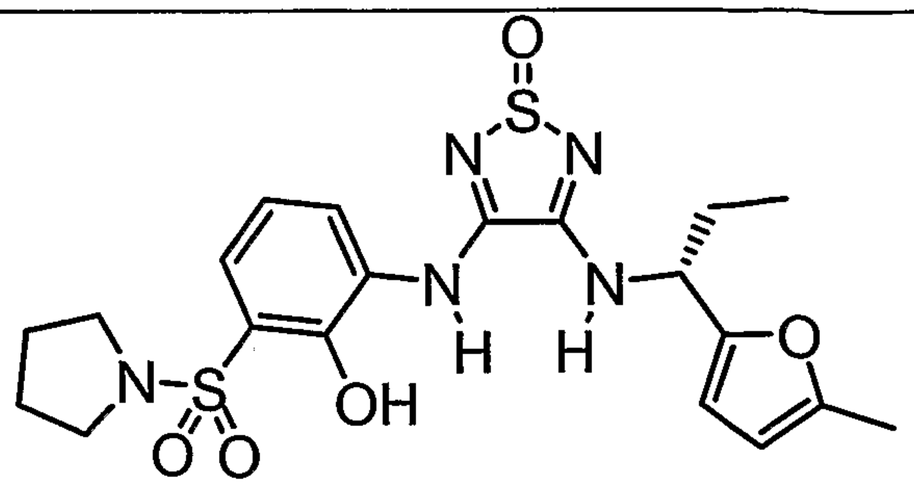
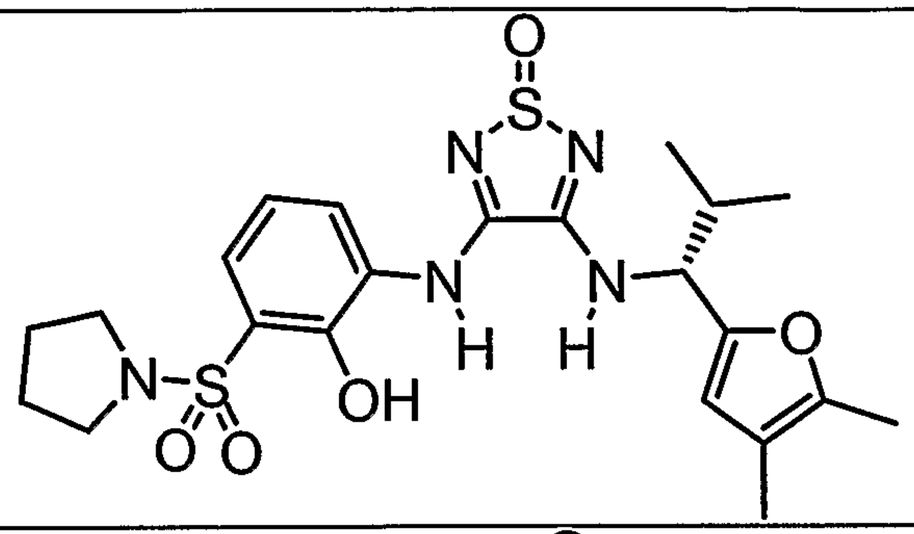
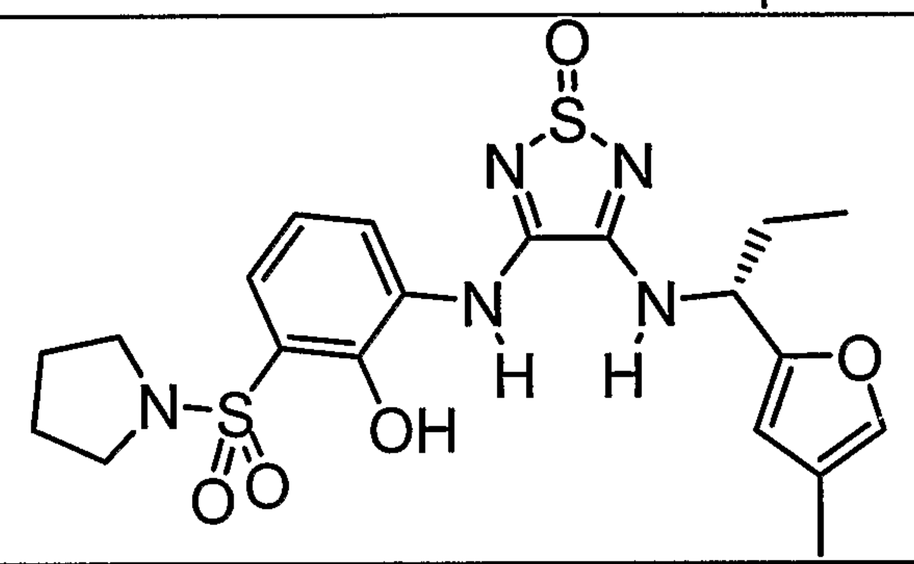
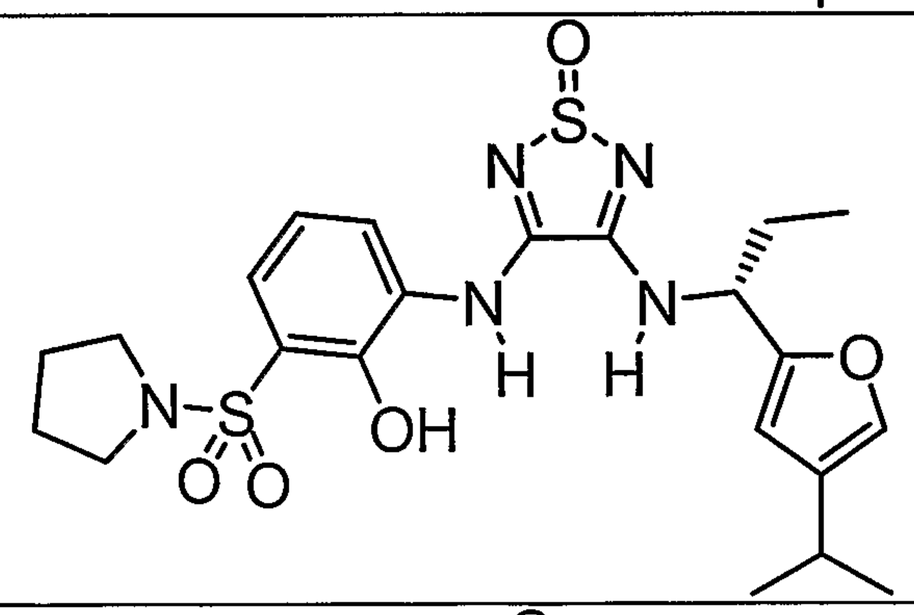
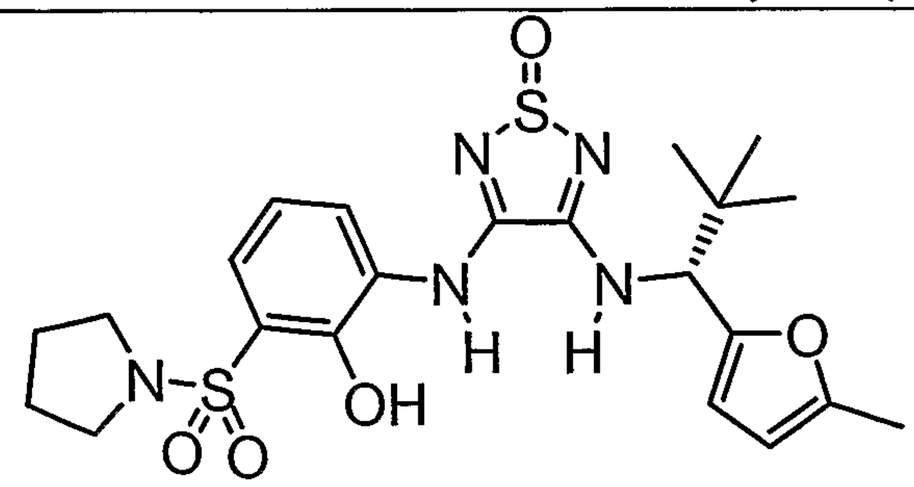
3046	454	2,3-Dichloro-PhNH2	
3047	454	74	
3048	454	75.60	
3049	454	75.1	
3050	454	75.61	

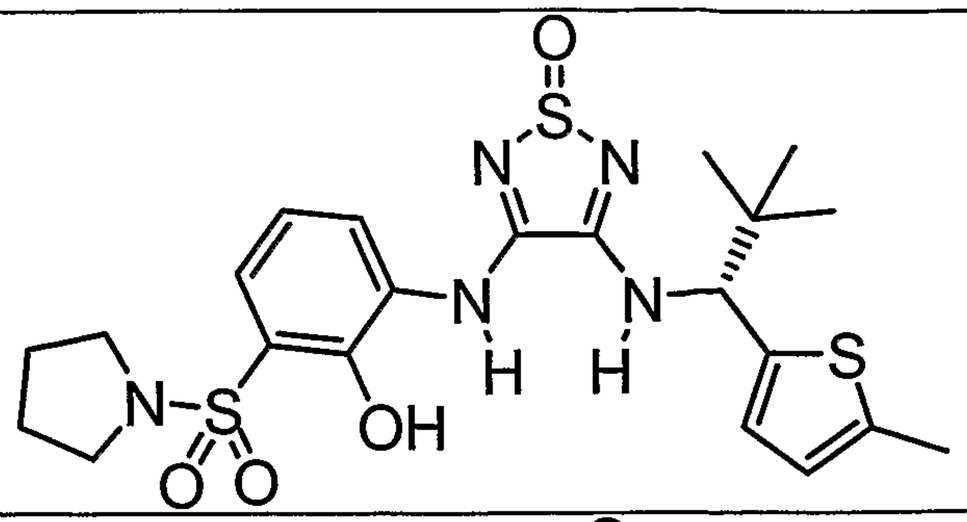
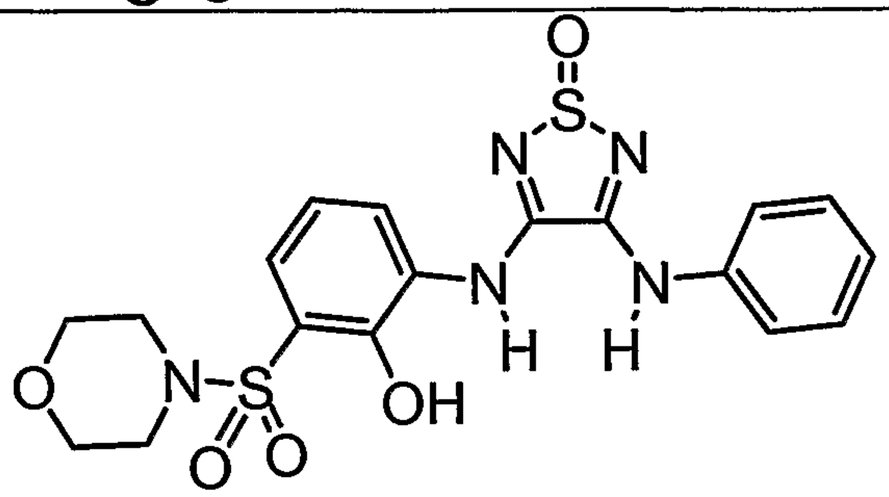
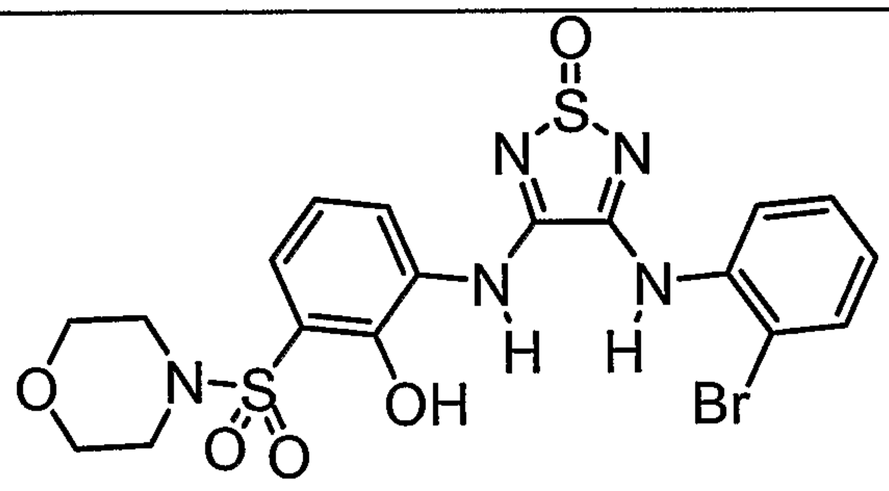
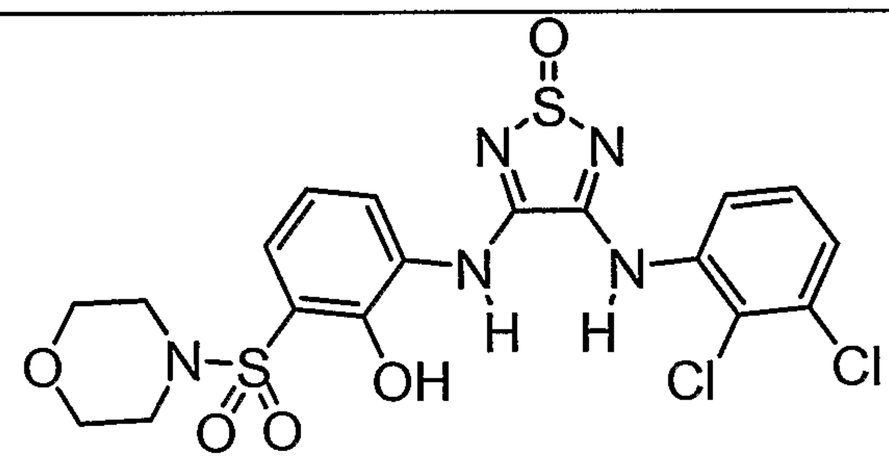
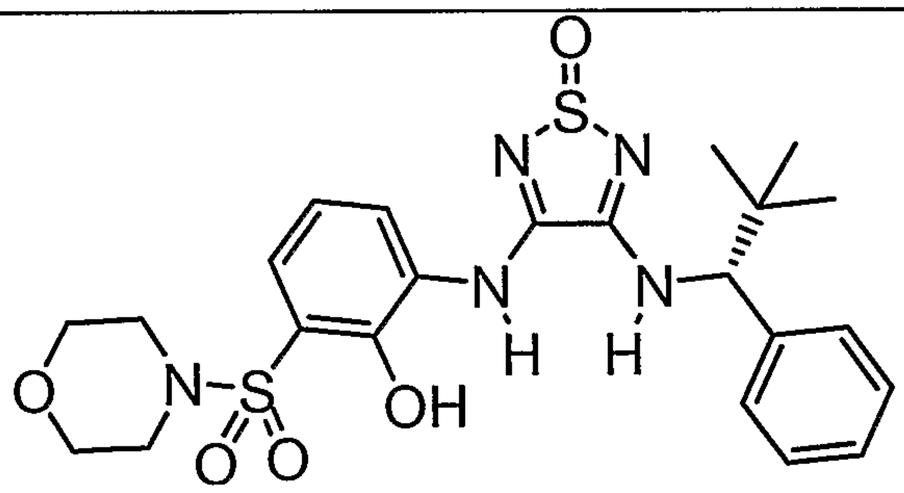
3051	454	75.49	
3052	454	75.9	
3053	454	75.44	
3054	454	75.20	
3055	455	PhNH2	

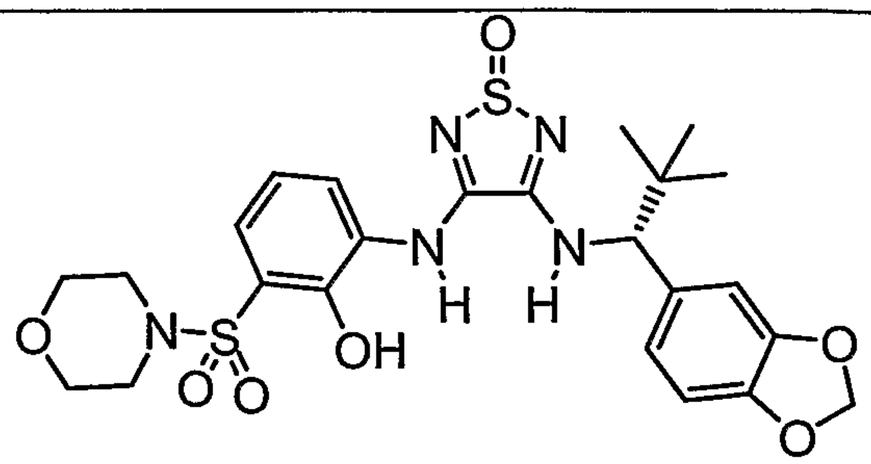
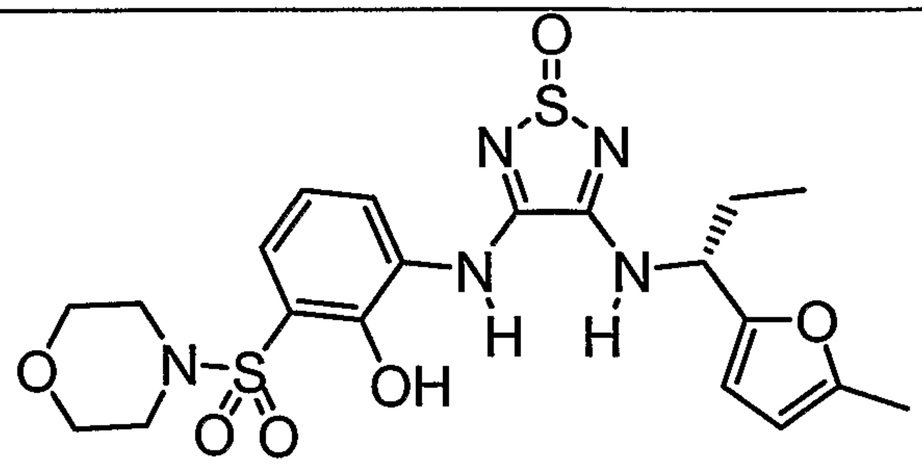
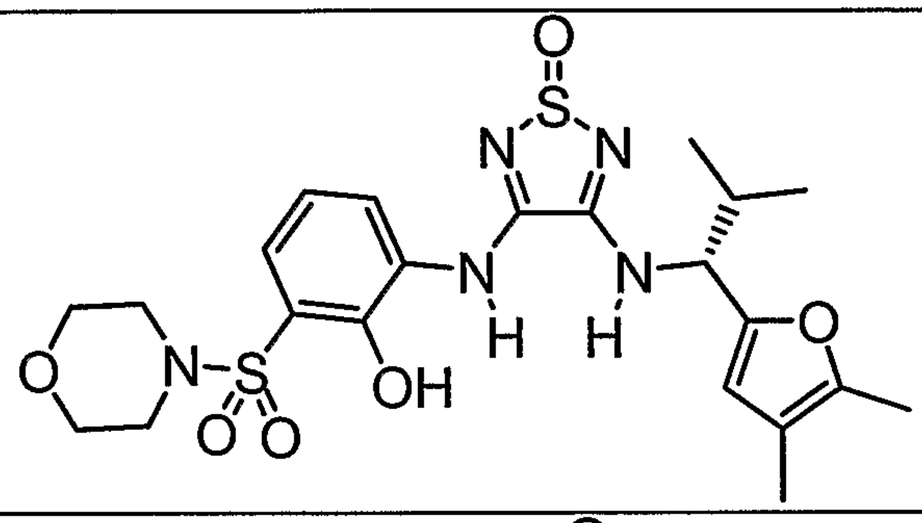
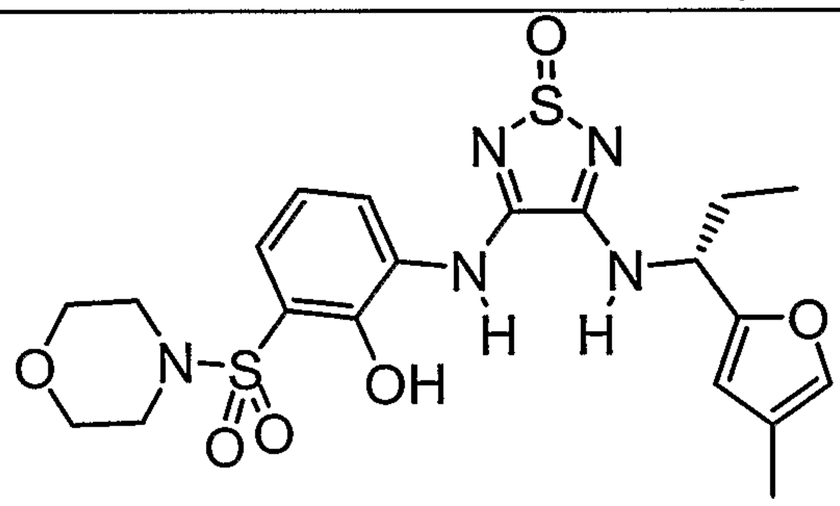
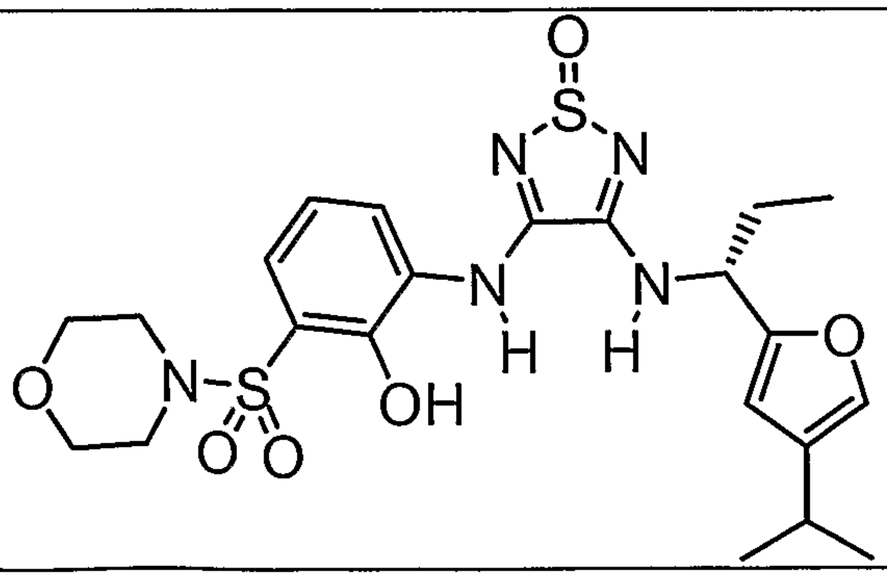
3056	455	2-Bromo-PhNH2	
3057	455	2,3-Dichloro-PhNH2	
3058	455	74	
3059	455	75.60	
3060	455	75.1	

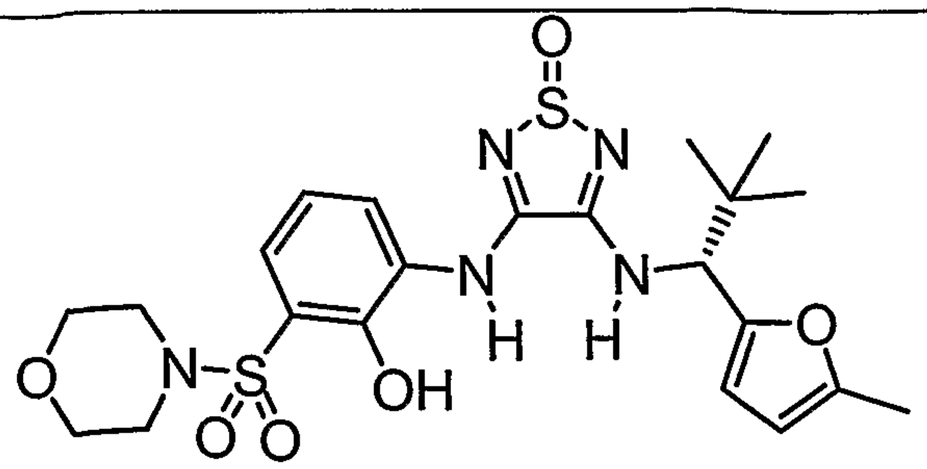
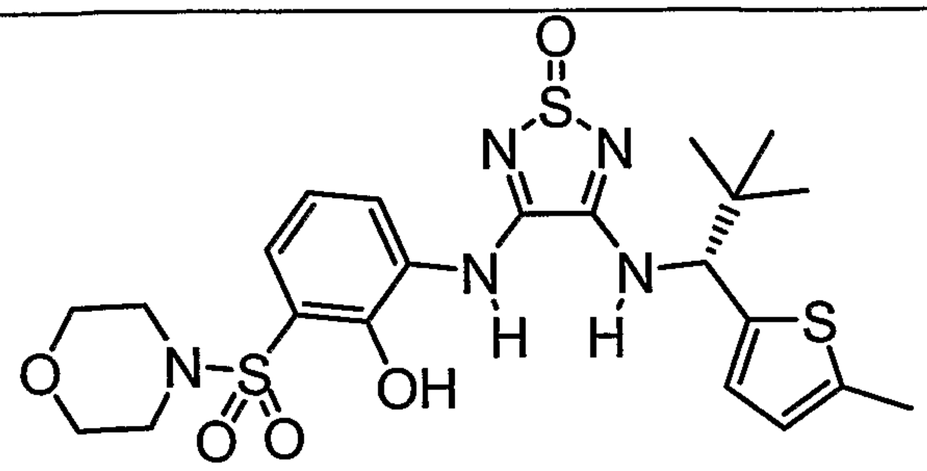
3061	455	75.61	
3062	455	75.49	
3063	455	75.9	
3064	455	75.44	
3065	455	75.20	

3066	456	PhNH2	
3067	456	2-Bromo-PhNH2	
3068	456	2,3-Dichloro-PhNH2	
3069	456	74	
3070	456	75.60	

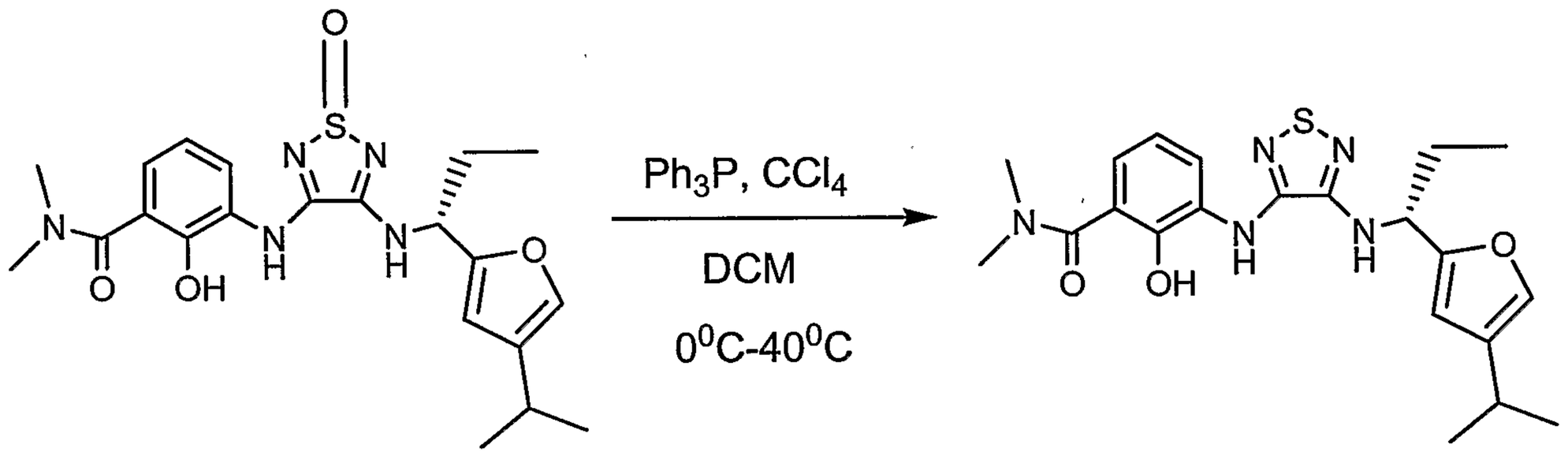
3071	456	75.1	
3072	456	75.61	
3073	456	75.49	
3074	456	75.9	
3075	456	75.44	

3076	456	75.20	
3077	457	PhNH2	
3078	457	2-Bromo-PhNH2	
3079	457	2,3-Dichloro-PhNH2	
3080	457	74	

3081	457	75.60	
3082	457	75.1	
3083	457	75.61	
3084	457	75.49	
3085	457	75.9	

3086	457	75.44	
3087	457	75.20	

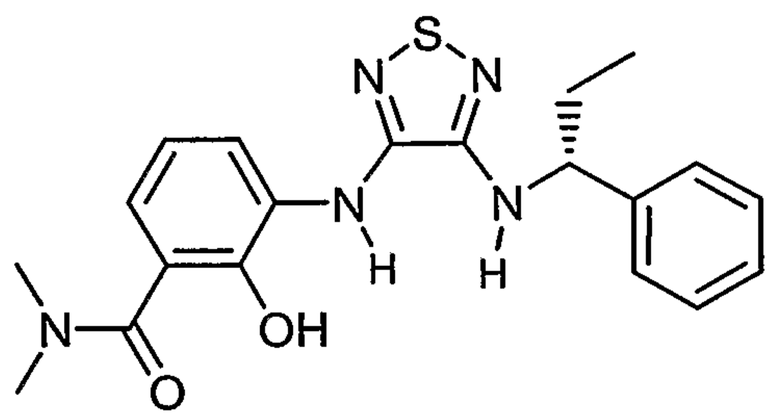
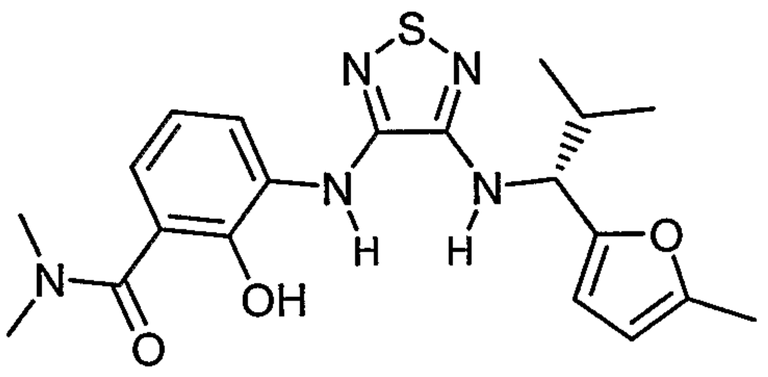
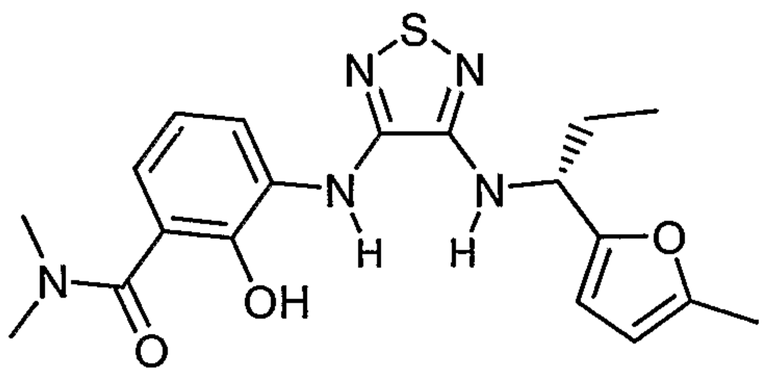
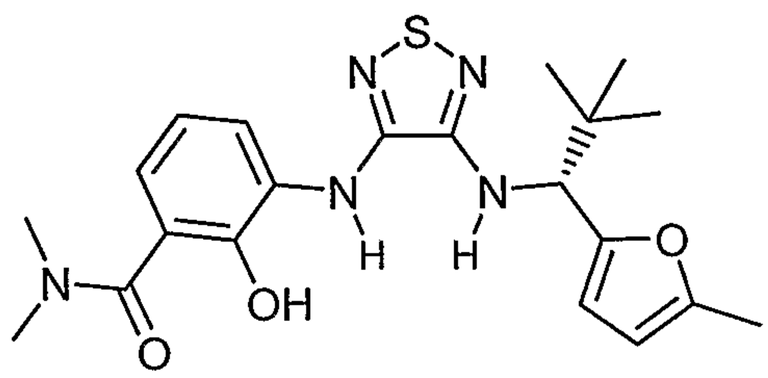
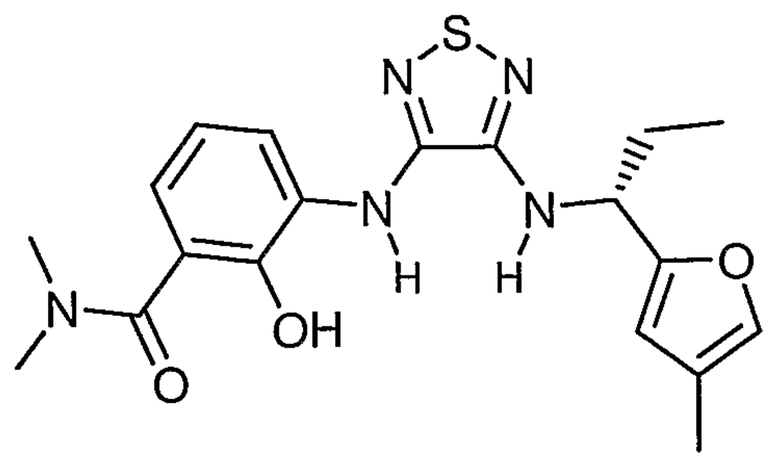
EXAMPLE 1

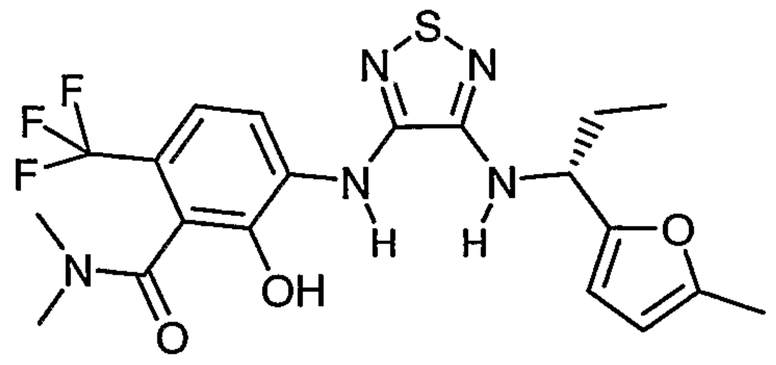
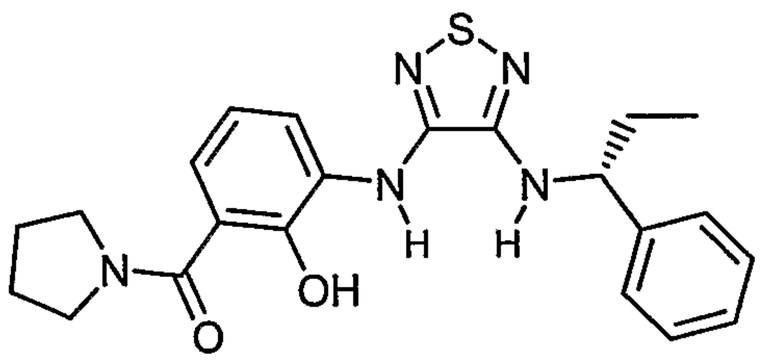
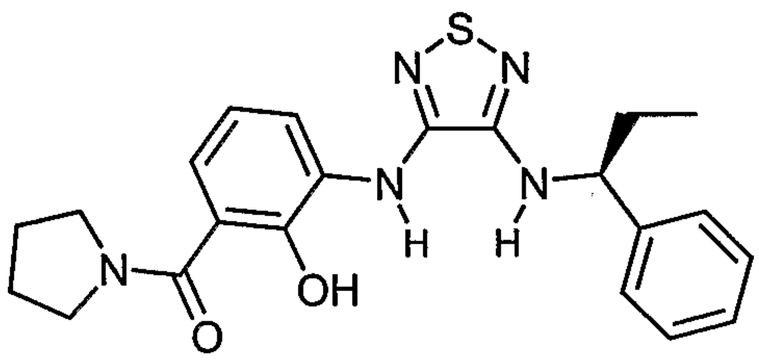
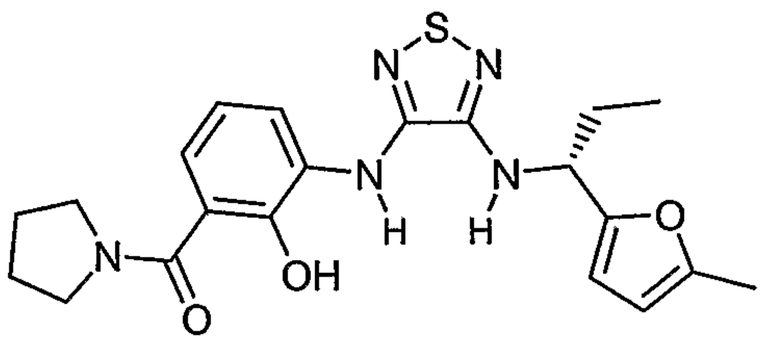
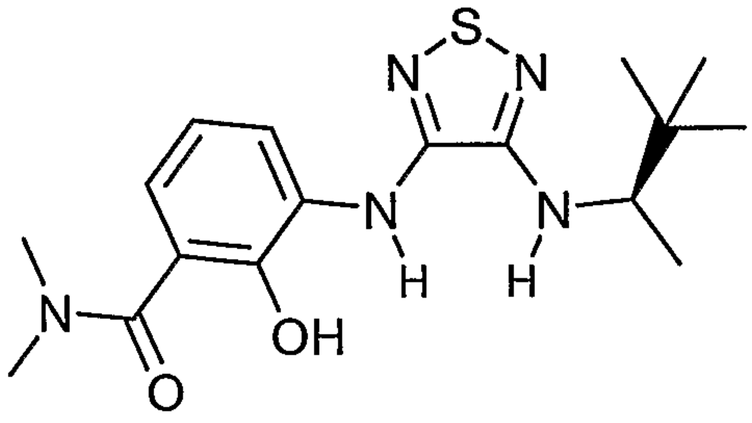
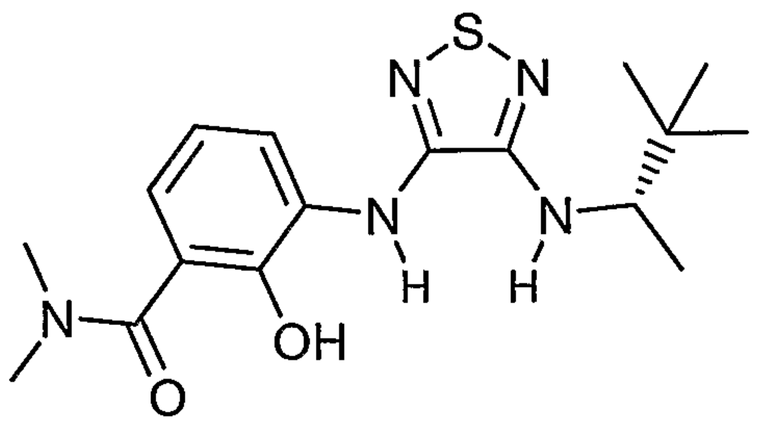


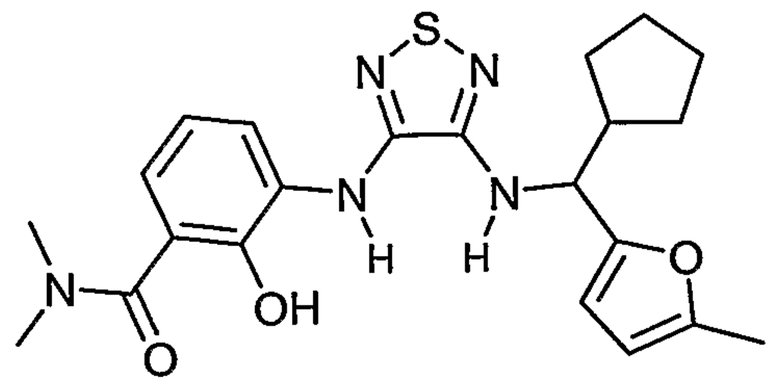
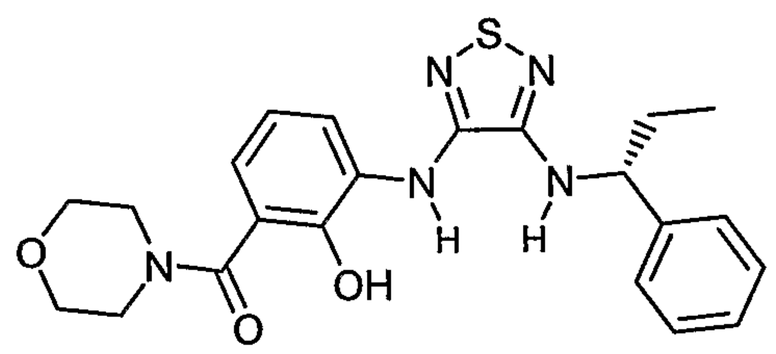
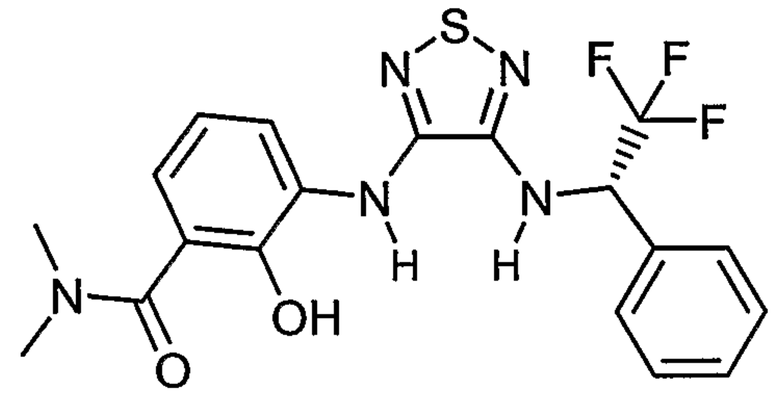
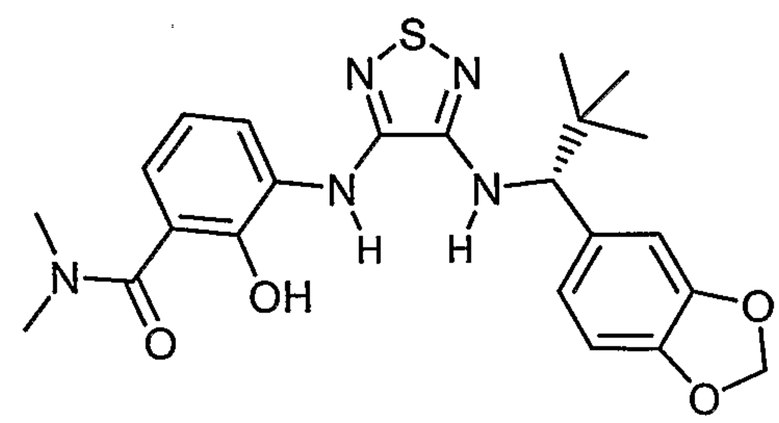
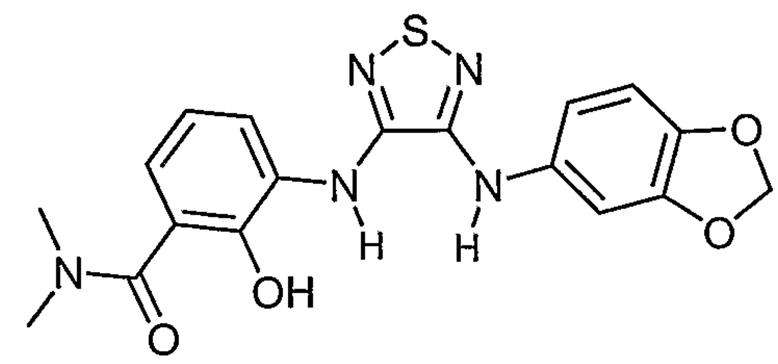
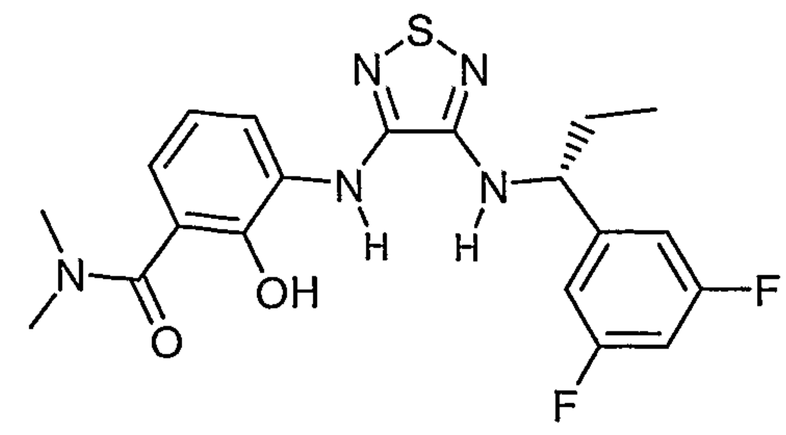
To a stirred solution of the thiadiazole-monoxide from Preparative Example 2001.5 (15.0mg, 0.0336mmol) in anhydrous dichloromethane at 0°C was added triphenylphosphine (44mg, 0.1681mmol) followed by the drop-wise addition of carbon tetrachloride (1.0mL). The reaction mixture was warmed to 40-45°C and stirred for 2-3 hours. The mixture was cooled to room temperature, solvents were removed under reduced pressure and the product was purified by preparative thin layer chromatography using dichloromethane-methanol (20:1) to afford the title compound as a white solid. (6mg, 43%, m.p = 65°C).

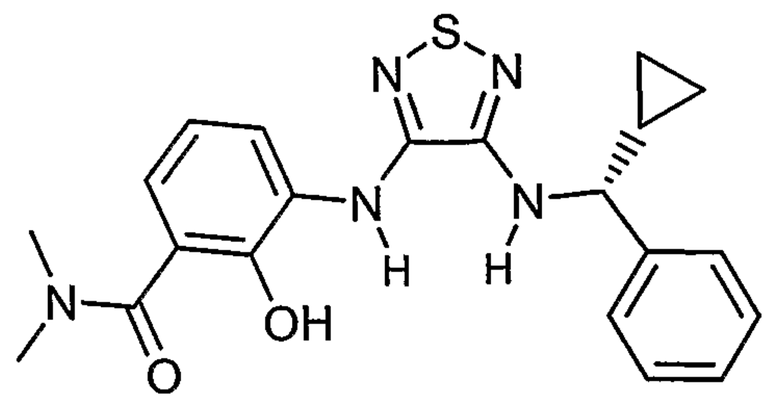
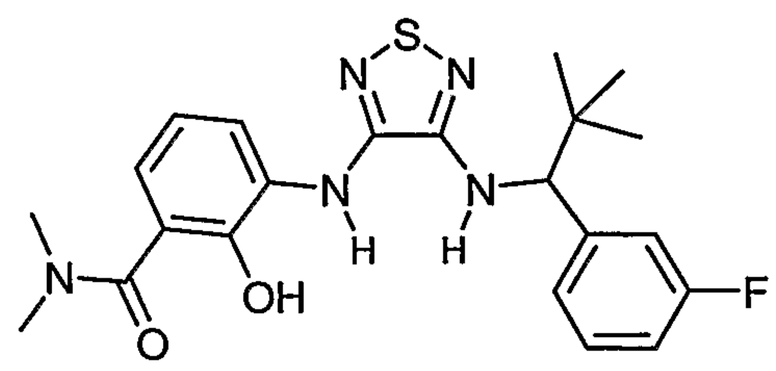
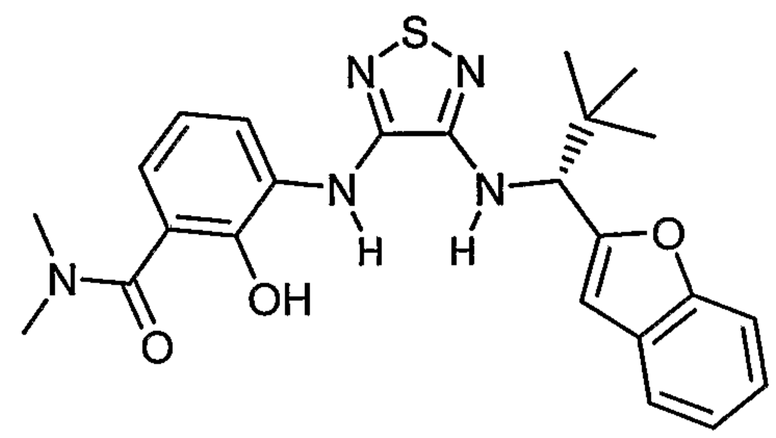
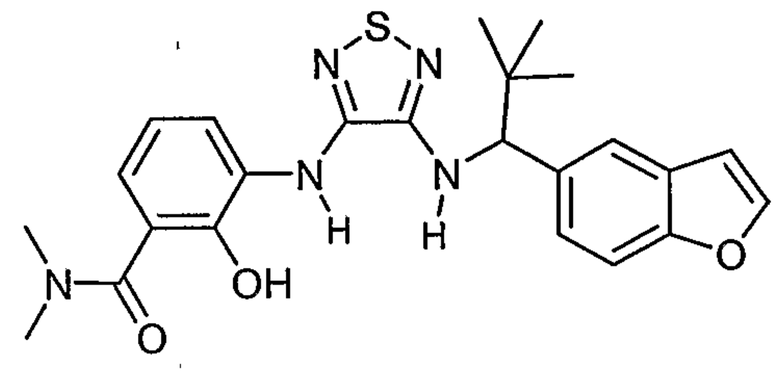
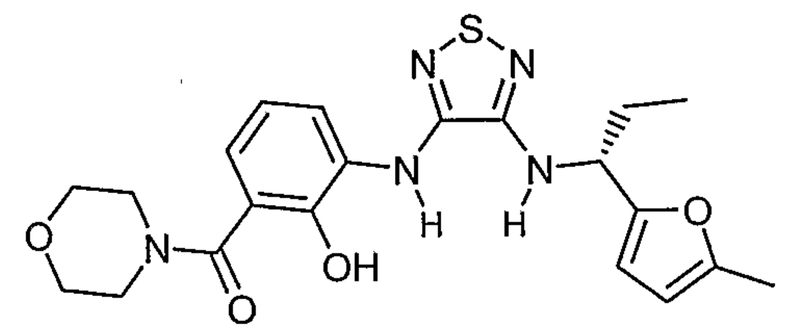
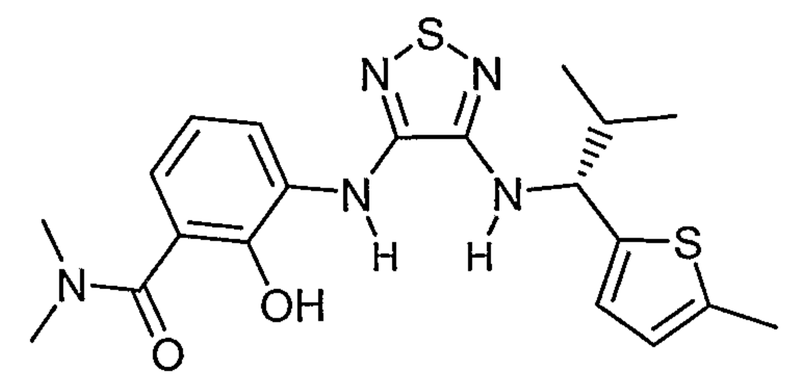
EXAMPLES 2-4 and 6-35

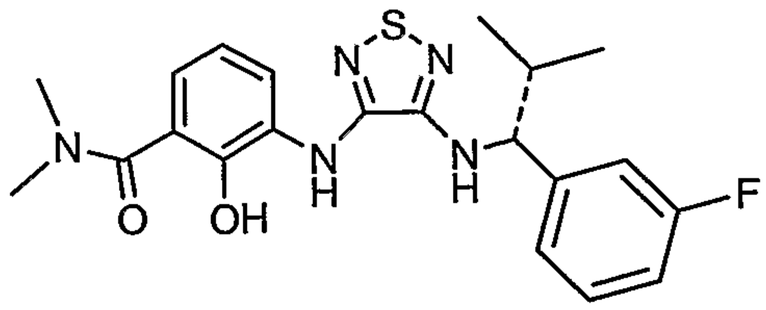
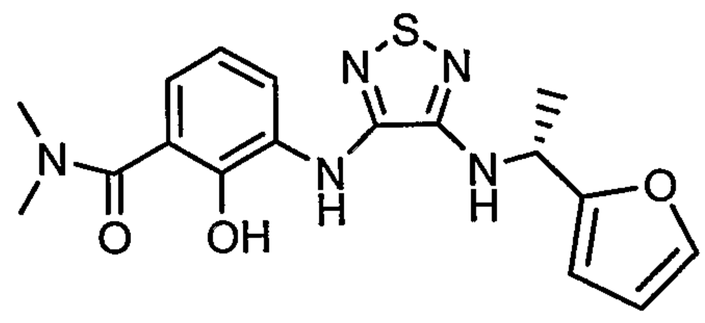
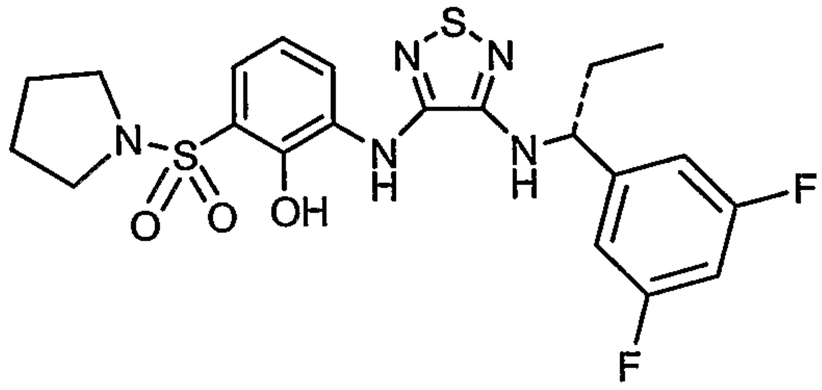
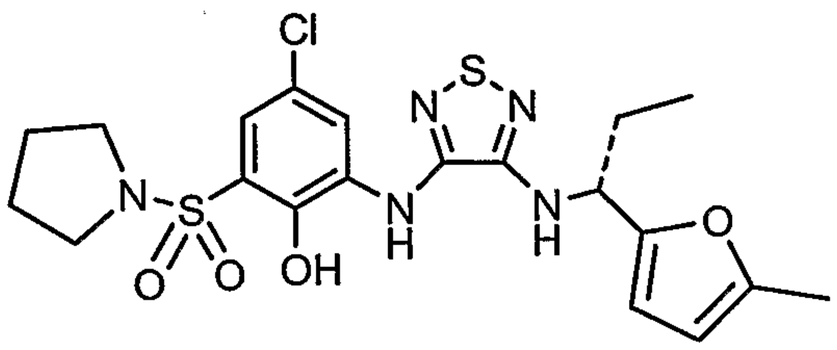
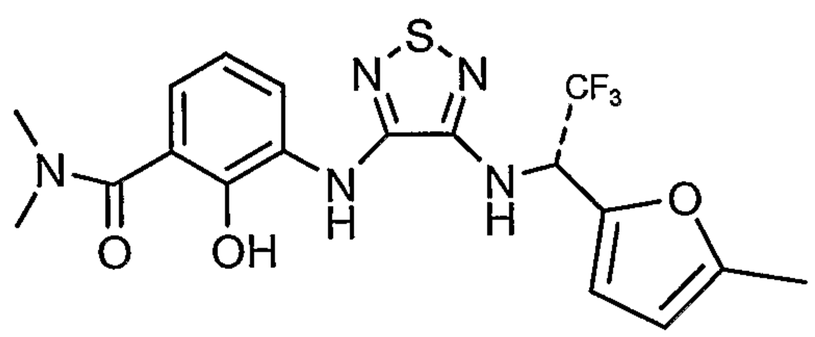
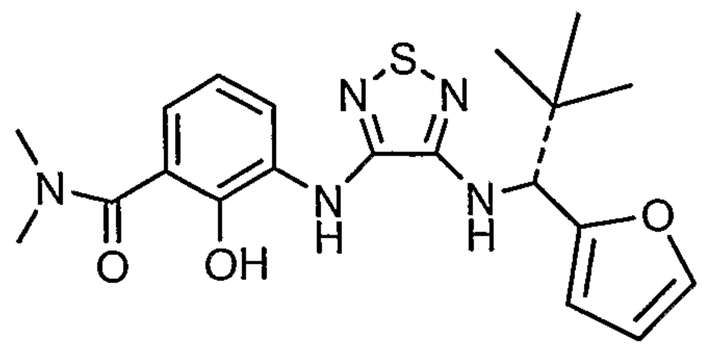
Following a similar procedure to that set forth in Example 1, but using the thiadiazoleoxide intermediate from the Preparative Example indicated in the Table below, the thiadiazole products in the Table below were prepared.

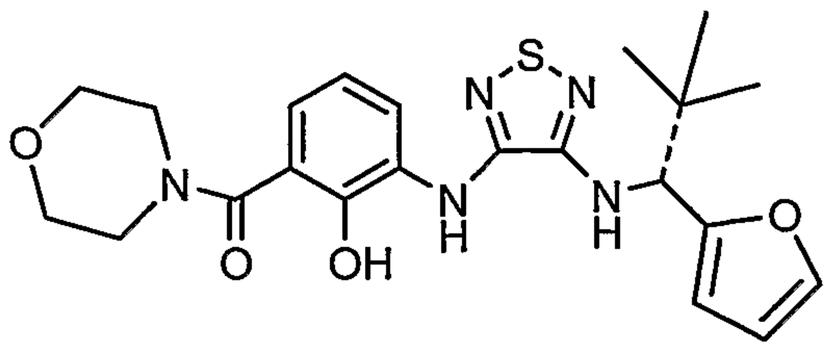
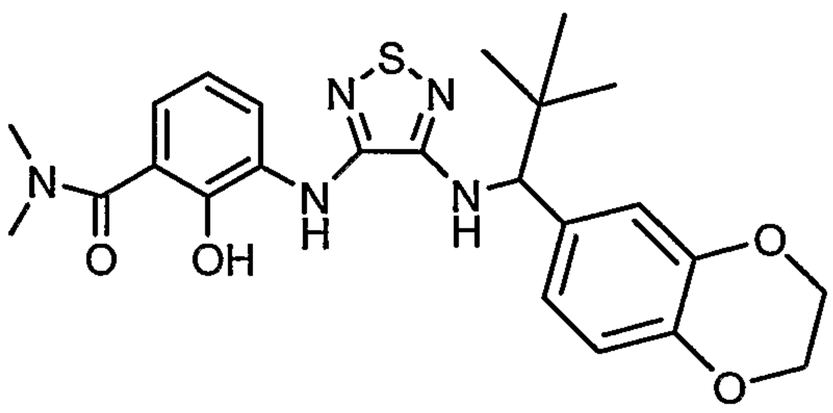
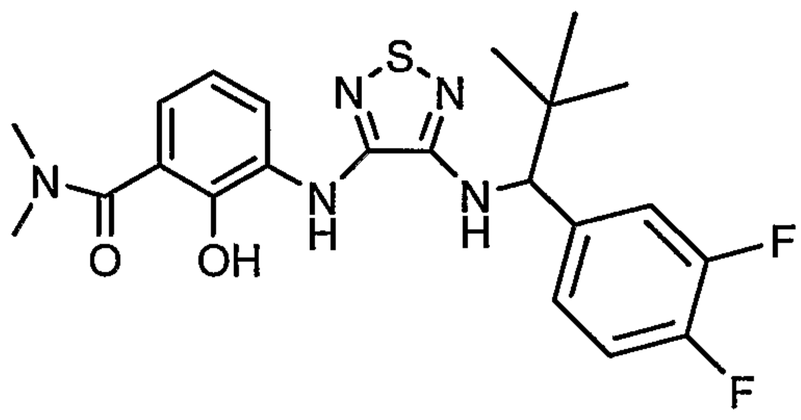
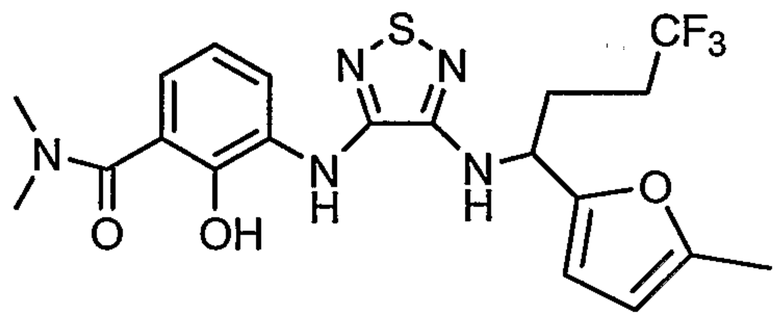
Ex.	Prep Ex of Thiadiazole oxide Intermediate	Product	1. Yield 2. mp (°C) 3. MH^+
2	2000		1. 18% 2. 80 3. 398
3	2001.3		1. 30% 2. 72 3. 416
4	2001.4		1. 21% 2. 62 3. 402
6	2001.6		1. 9% 2. 60 3. 430
7	2001.7		1. 21% 2. 70 3. 402

8	2001.8		1. 13% 2. 3. 279 (M-191)
9	2001.9		1. 60% 2. 69 3. 424
10	2001.10		1. 57% 2. 69 3. 424
11	2001.11		1. 19% 2. 66 3. 428
12	2001.12		1. 59% 2. 86 3. 364
13	2001.13		1. 56% 2. 86 3. 364

14	2001.14		1. 23% 2. 69 3. 442
15	2001.15		1. 40% 2. 100 3. 440
16	2001.16		1. 8% 2. 78 3. 438
17	2001.17		1. 12% 2. 76 3. 470
18	2001.18		1. 8% 2. 92 3. 400
19	2001.19		1. 35% 2. 78 3. 434

20	2001.20		1. 46% 2. 86 3. 410
21	2001.21		1. 11% 2. 96 3. 444
22	2001.22		1. 19% 2. 93 3. 466
23	2001.23		1. 36% 2. 215 3. 466
24	2001.24		1. 42% 2. 73 3. 441
25	2001.39		1. 19% 2. 71 3. 432

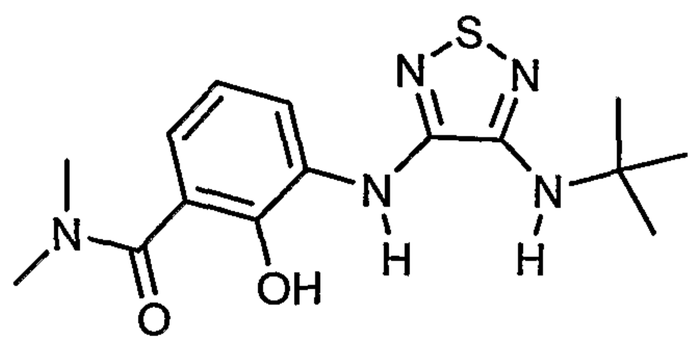
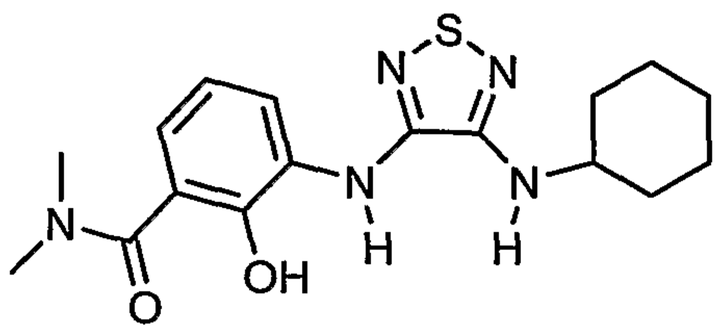
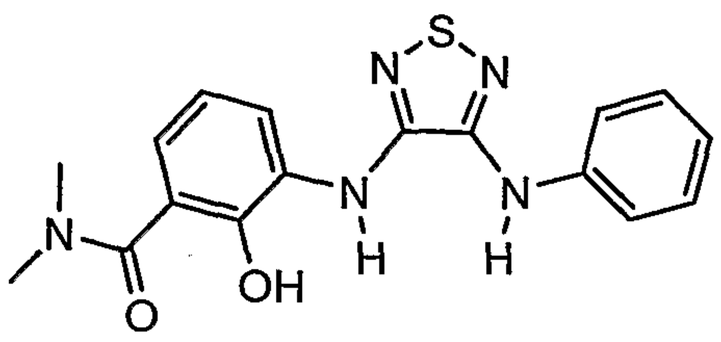
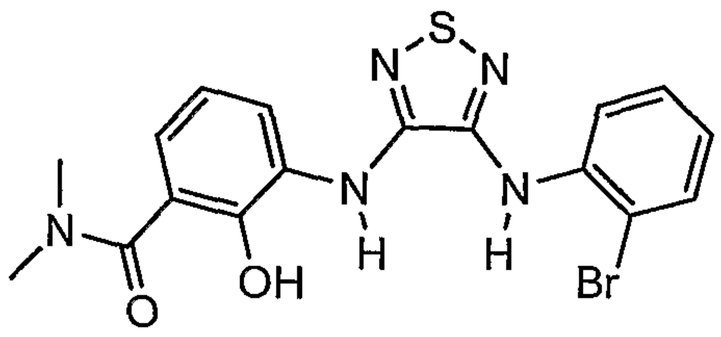
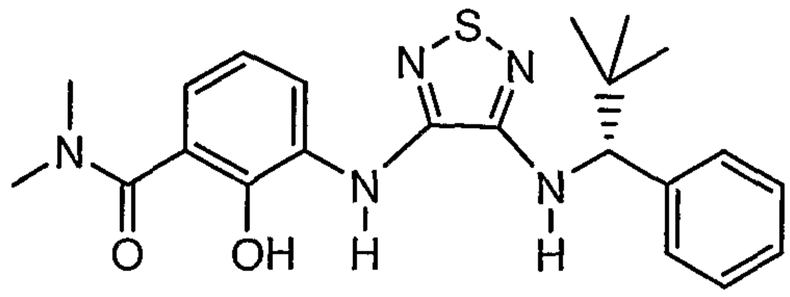
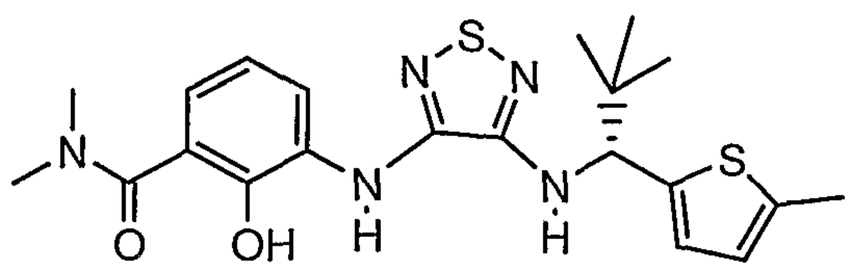
26	2001.43		1. 26% 2. 120 3. 430.1
27	2001.42		1. 27% 2. 66 3. 374.1
28	2001.41		1. 33% 2. 70 3. 496.1
29	2001.52		1. 3% 2. 119 3. 496.1
30	2001.53		1. 8% 2. 70 3. 442.1
31	2001.48		1. 10% 2. 74 3. 416.1

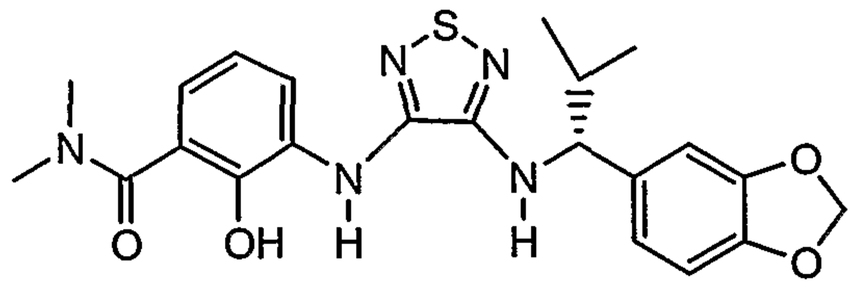
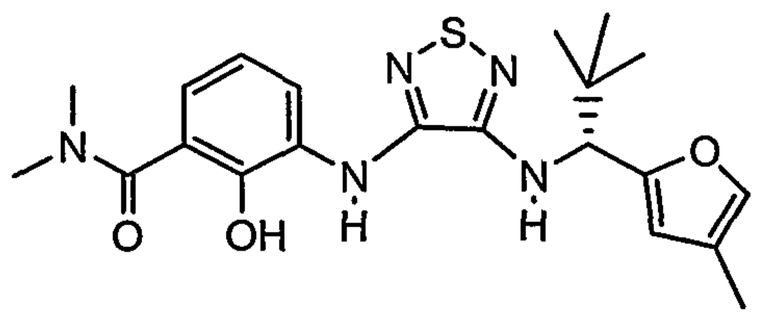
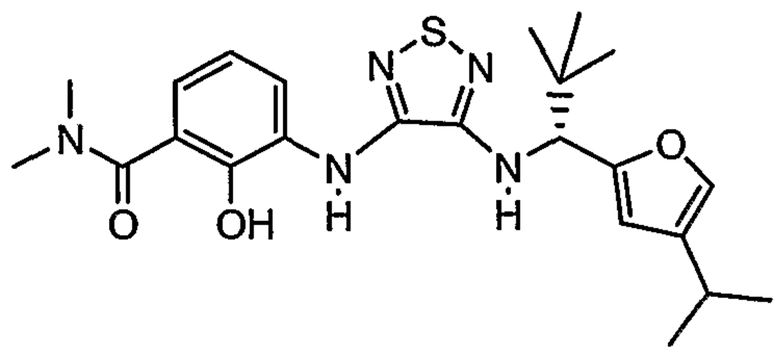
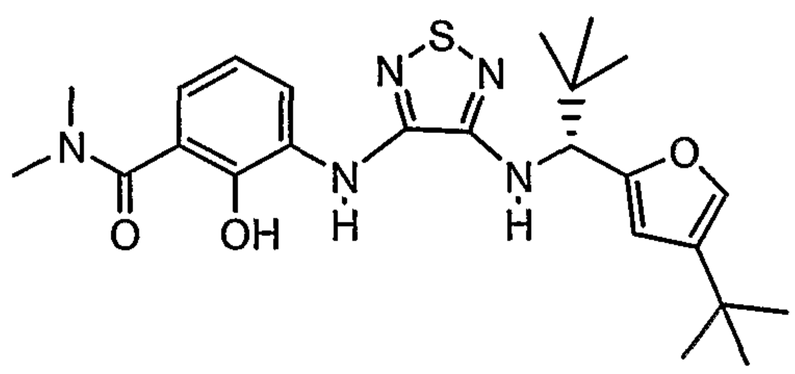
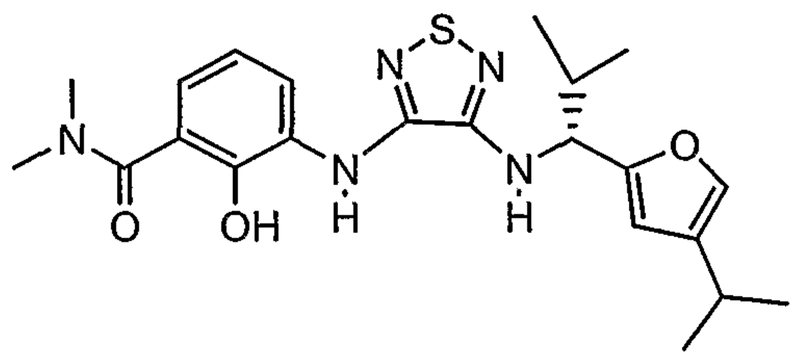
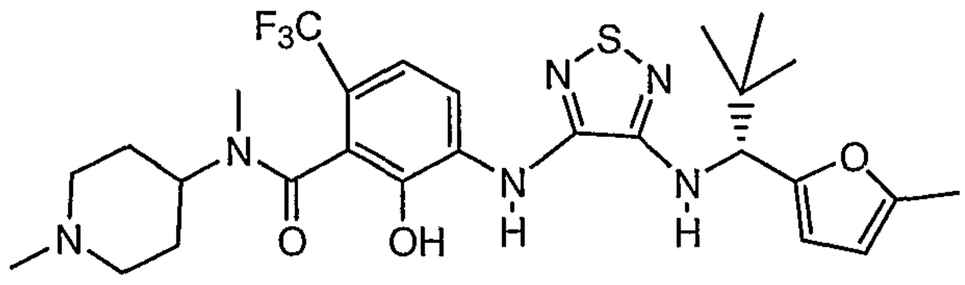
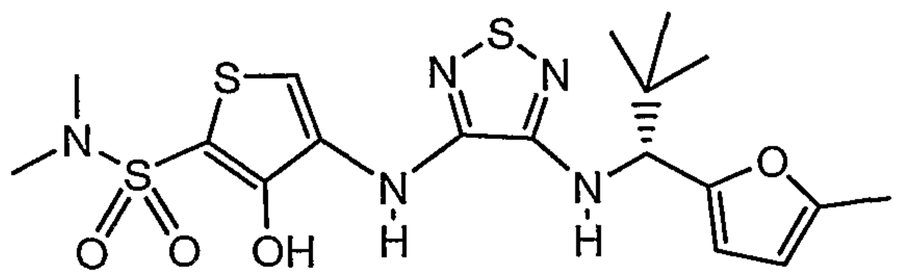
32	2001.54		1. 4% 2. 86 3. 458.1
33	2001.50		1. 52% 2. 123 3. 484.1
34	2001.51		1. 66% 2. 90 3. 462.1
35	2001.49		1. 71% 2. 65 3. 470.1

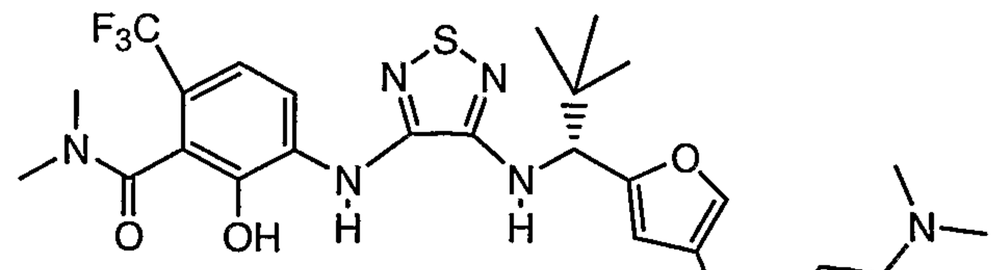
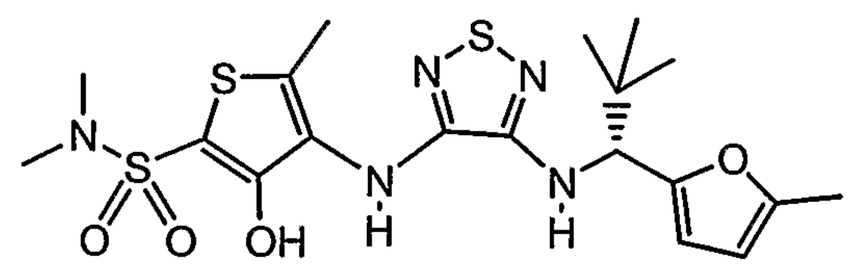
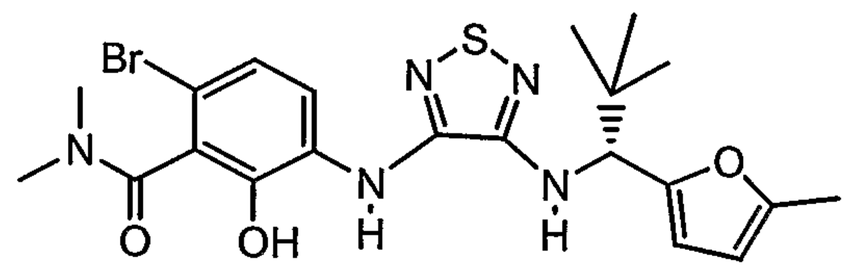
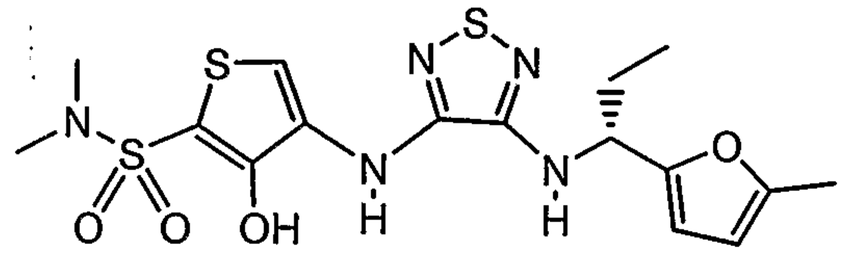
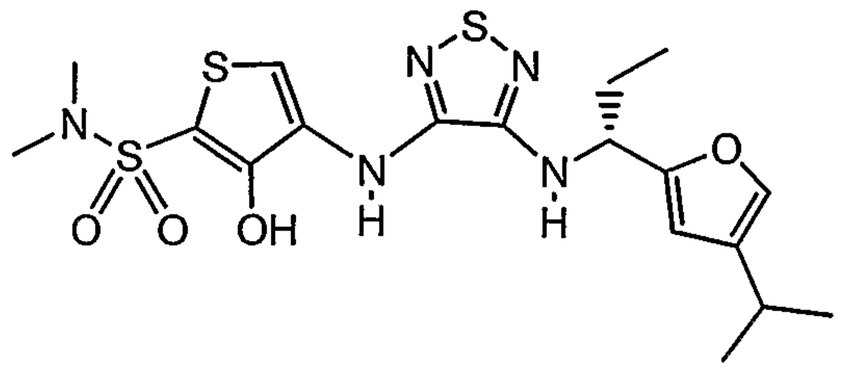
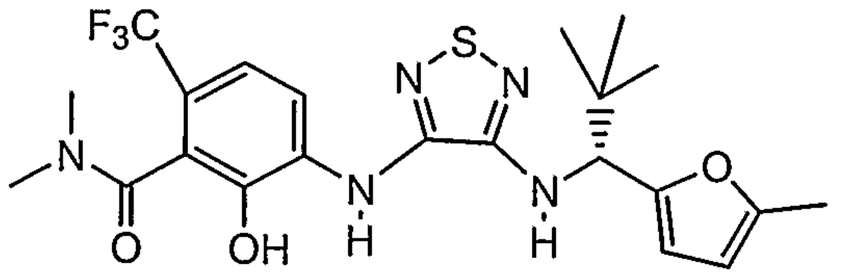
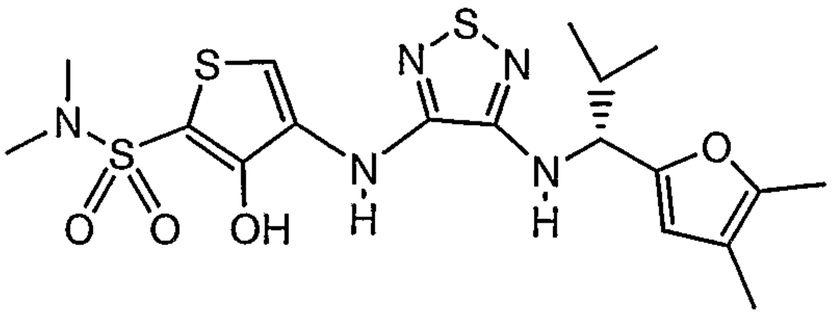
EXAMPLES

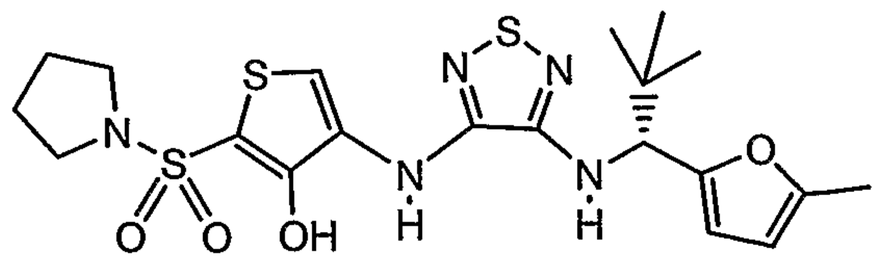
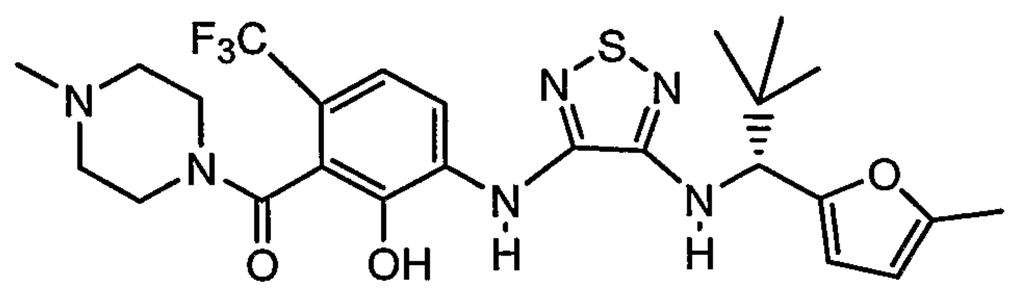
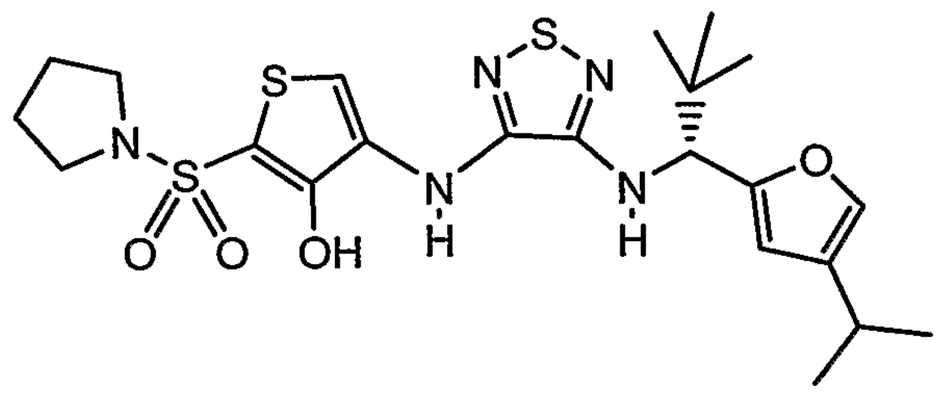
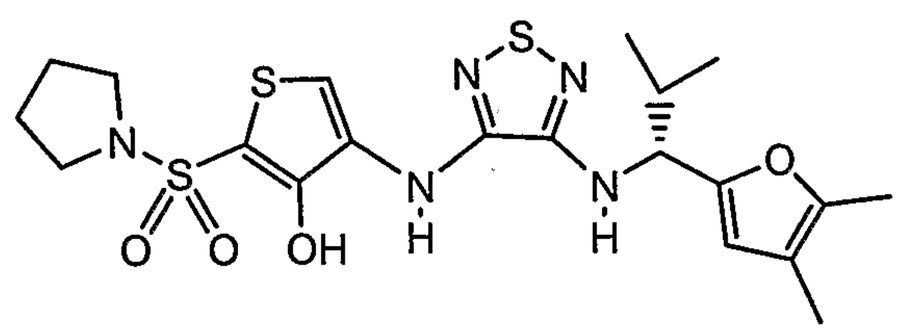
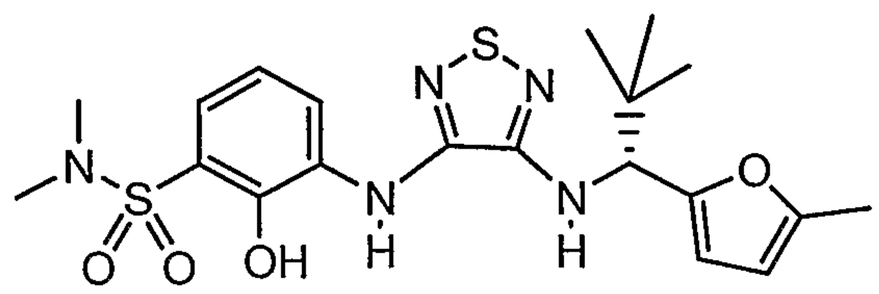
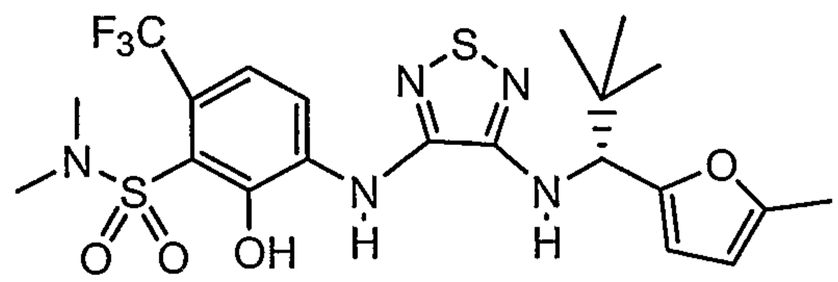
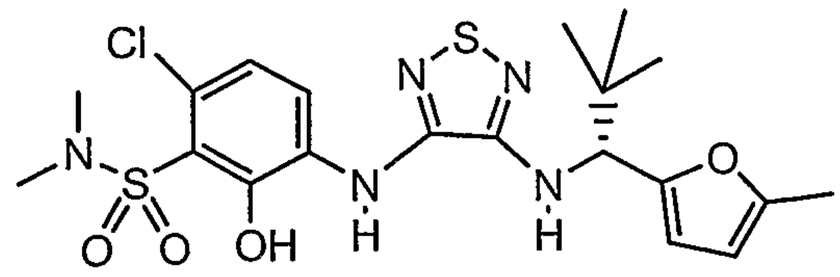
100-105, 107, 108, 110, 111, 112, 114, 115, 116, 118-132, 134-145, 148, 180, 182, 183, 185, 186, and 188

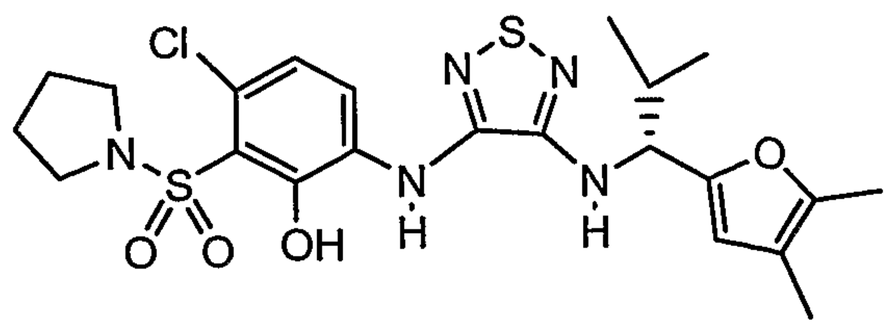
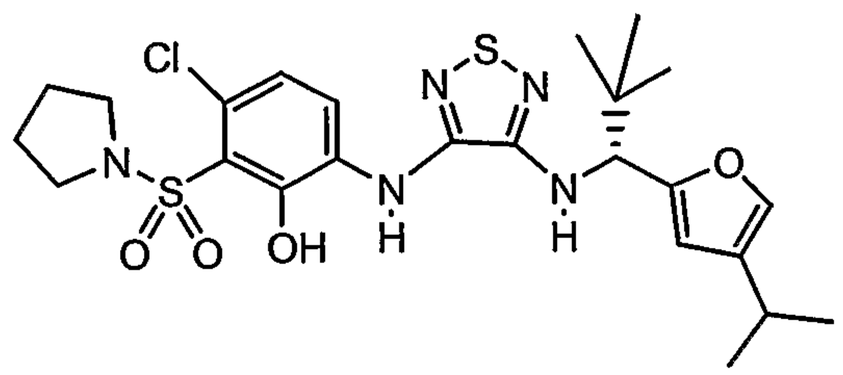
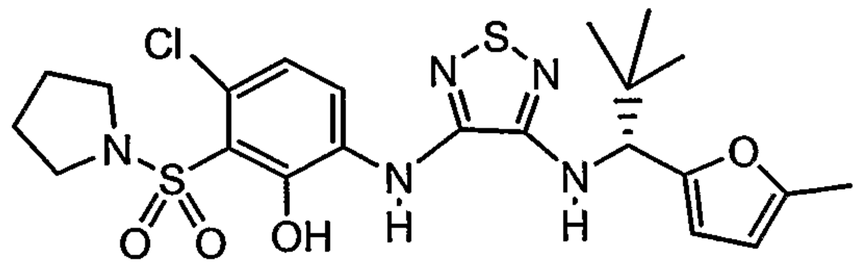
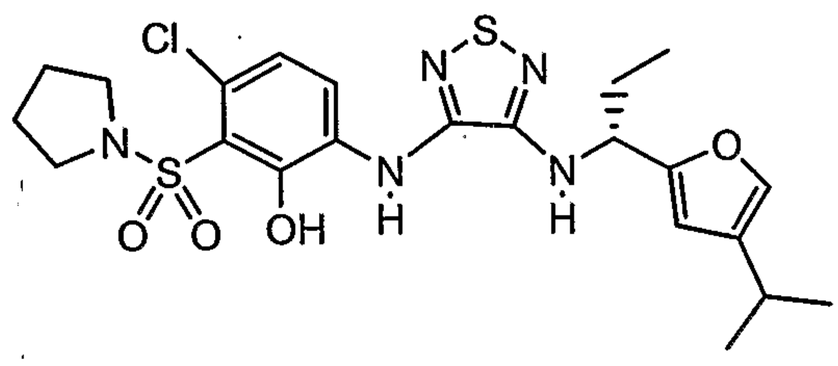
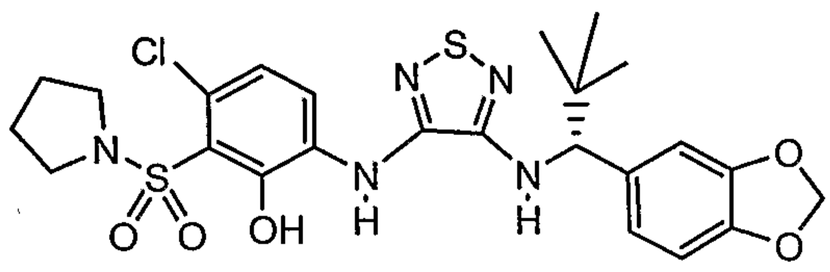
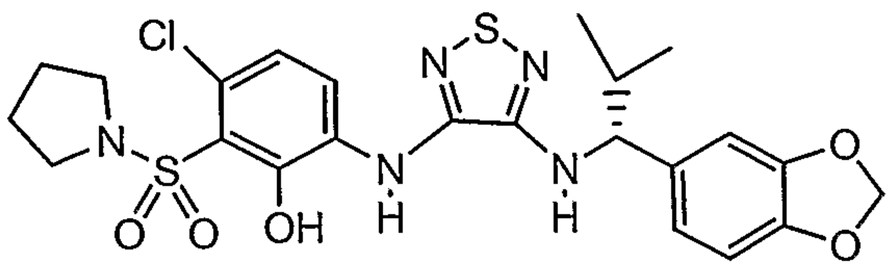
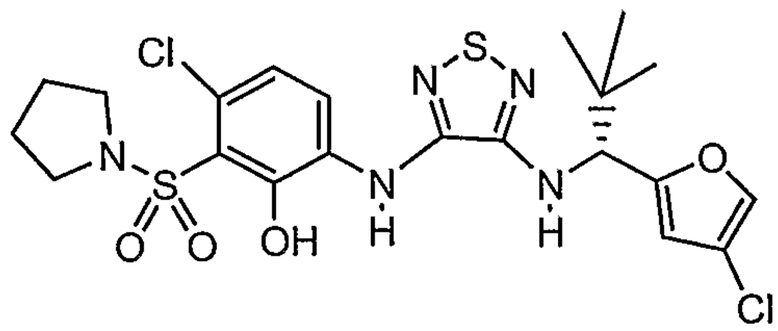
If one were to follow a procedure similar to that set forth in Example 1, but using the thiadiazoleoxide intermediate from the Preparative Example indicated in the Table below, the thiadiazole products in the Table below could be obtained.

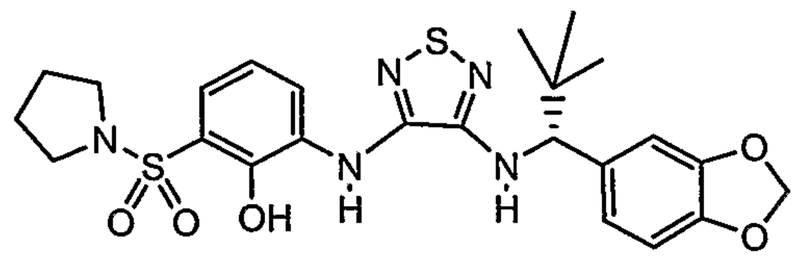
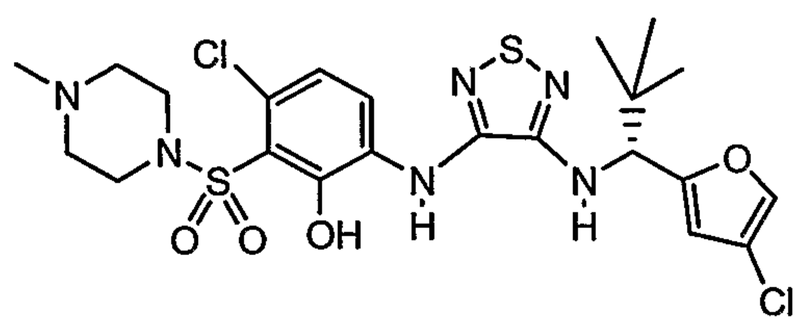
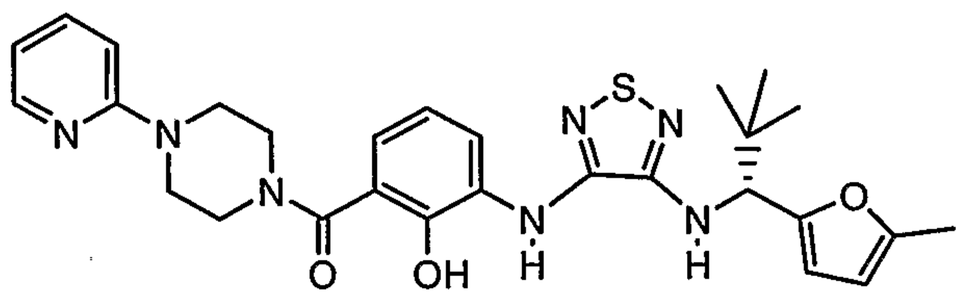
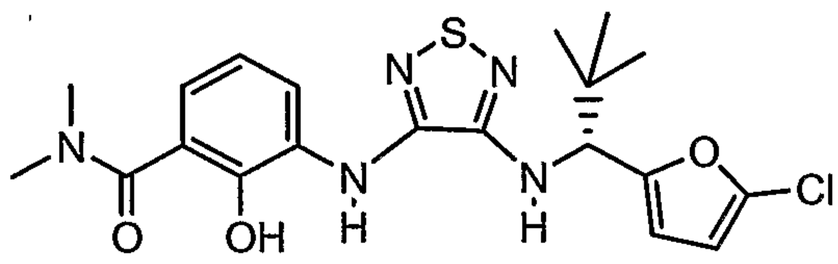
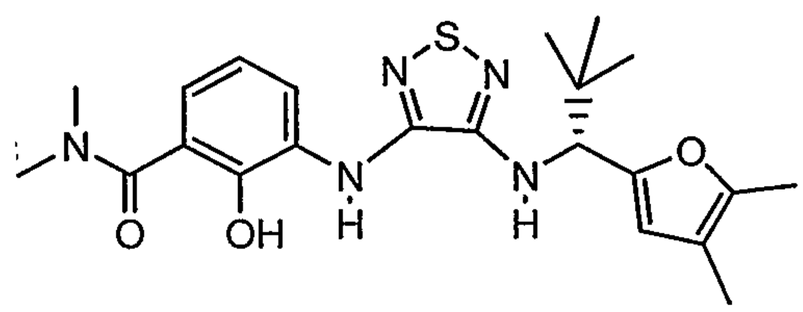
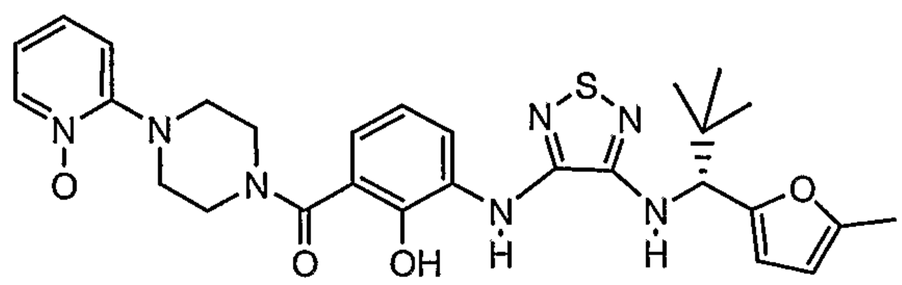
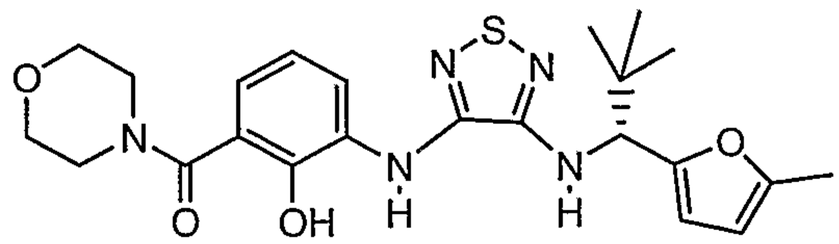
Ex.	Prep Ex of Thiadiazole oxide Intermediate	Product
100	2255	
101	2256	
103	2238	
104	2239	
105	2001.2	
107	2257	

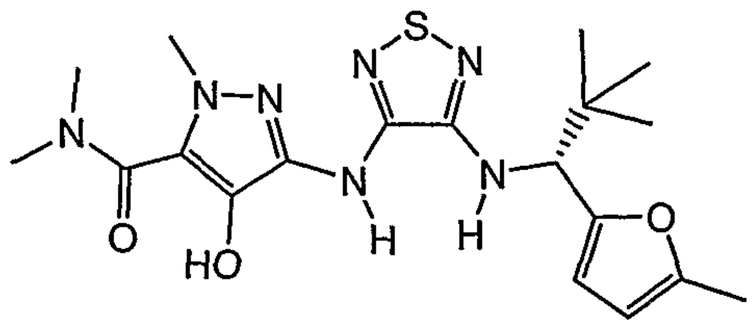
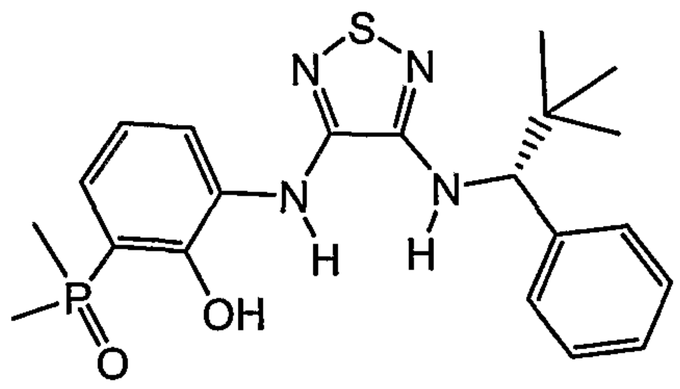
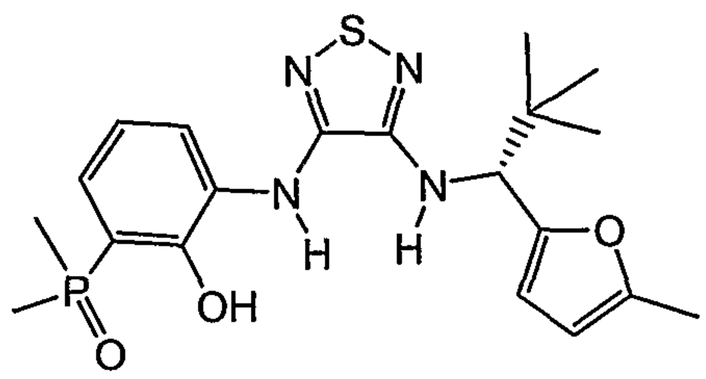
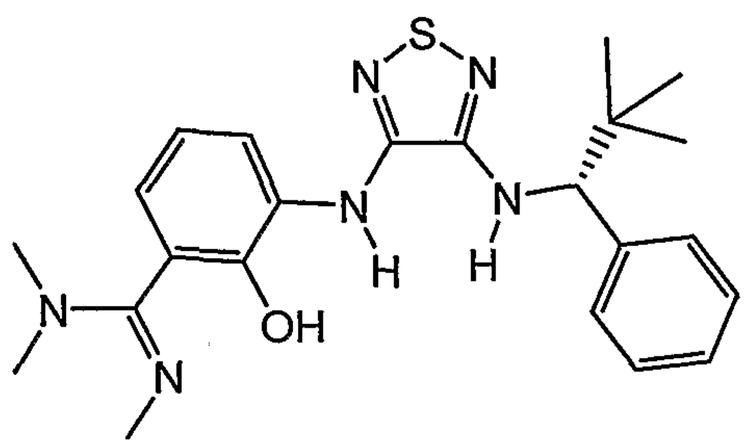
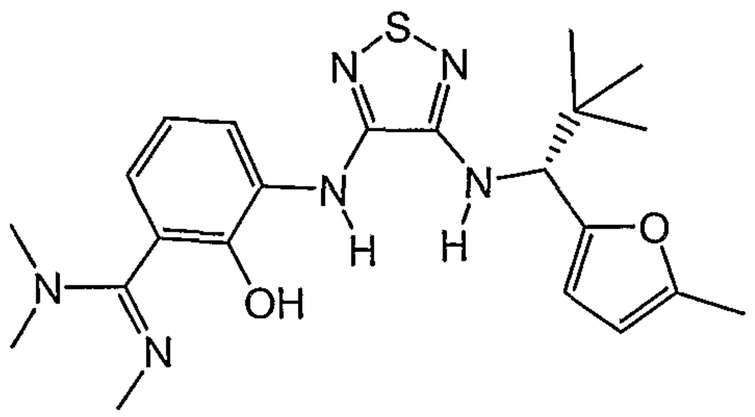
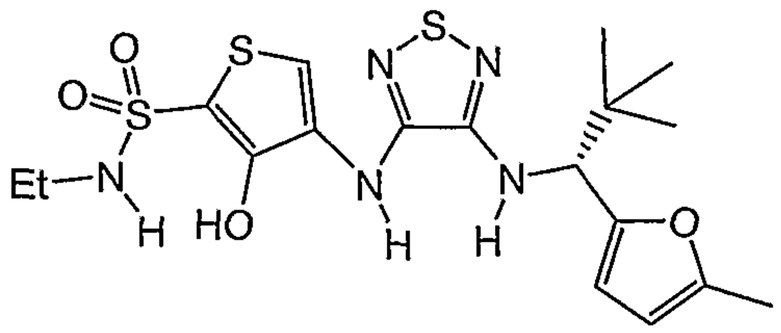
108	2258	
110	2259	
111	2262	
112	2260	
114	2263	
115	2264	
116	2229	

118	2265	
119	2266	
120	2211	
121	2267	
122	2268	
123	2269	
124	2270	

125	2271	
126	2272	
127	2273	
128	2274	
129	2223	
130	2275	
131	2217	

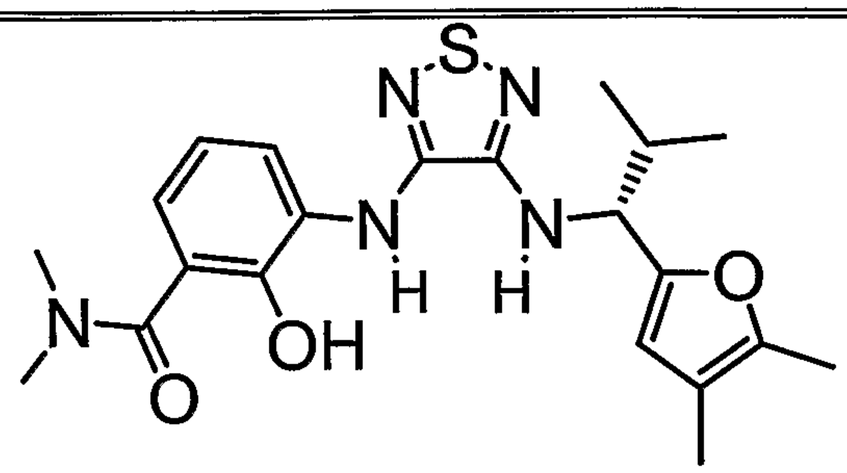
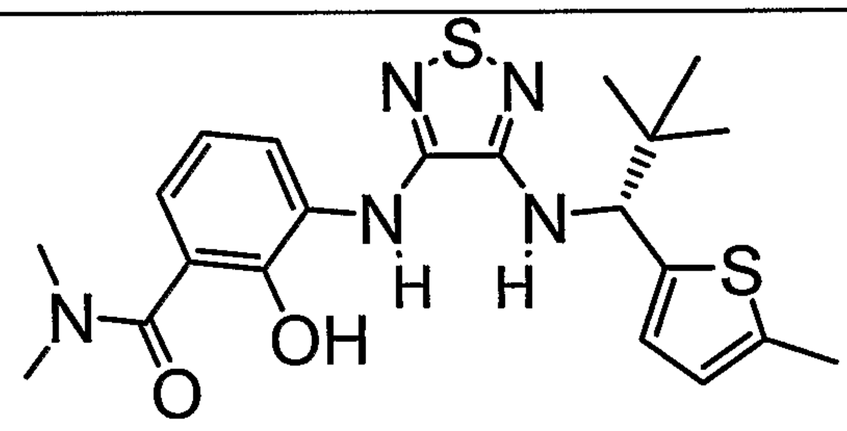
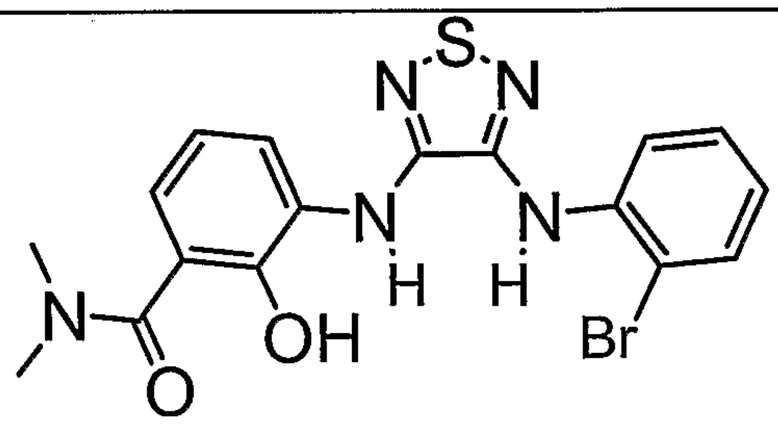
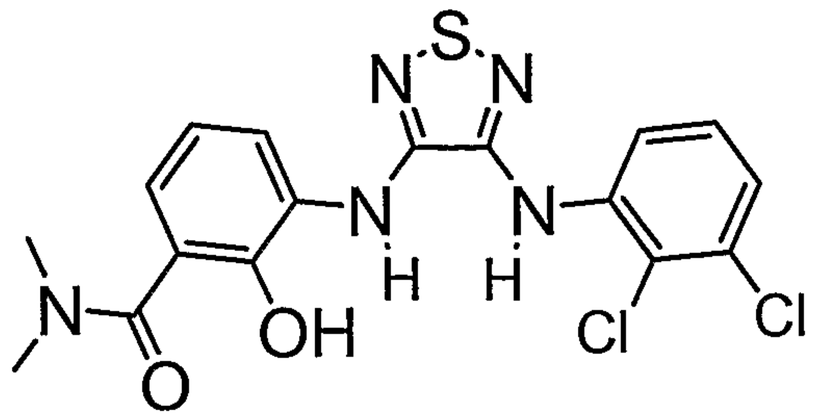
132	2276	
134	2277	
135	2278	
136	2279	
137	2280	
138	2281	
139	2282	

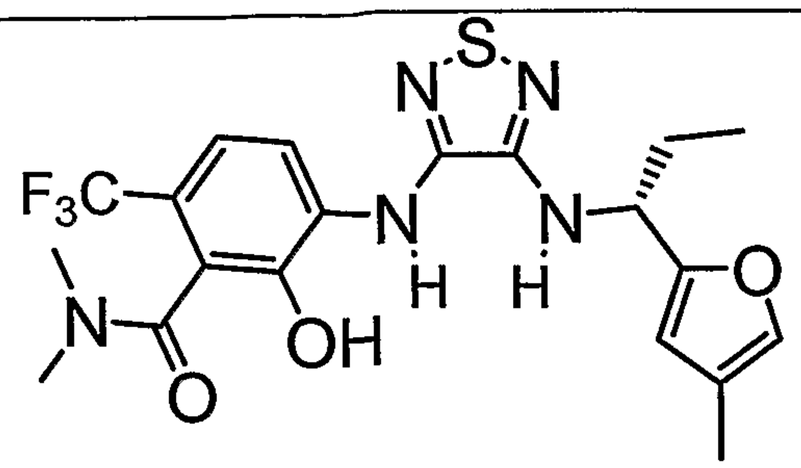
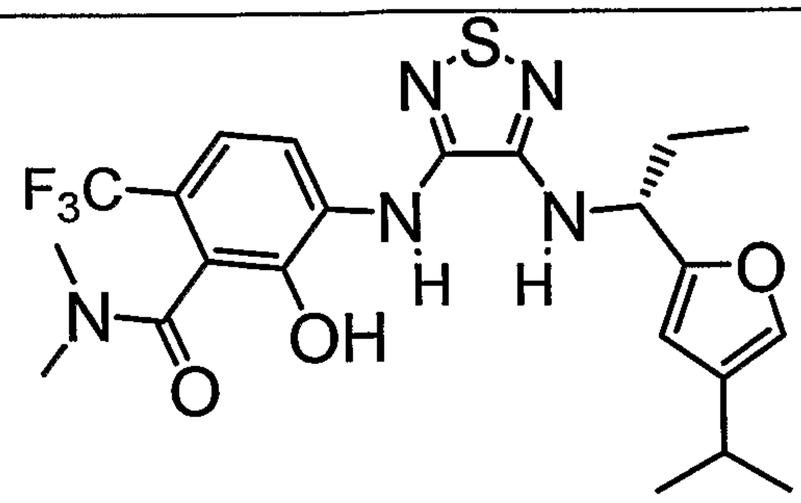
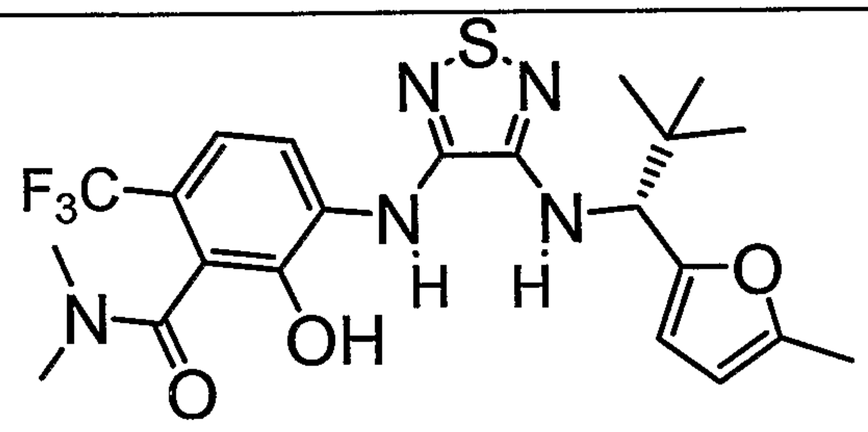
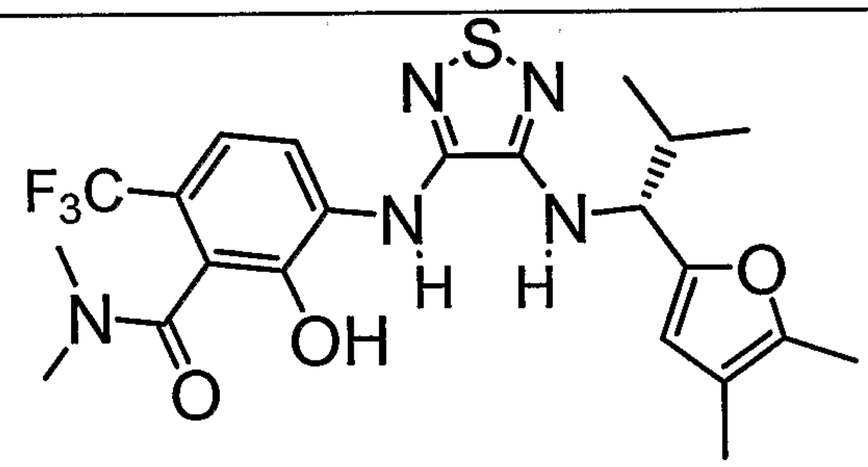
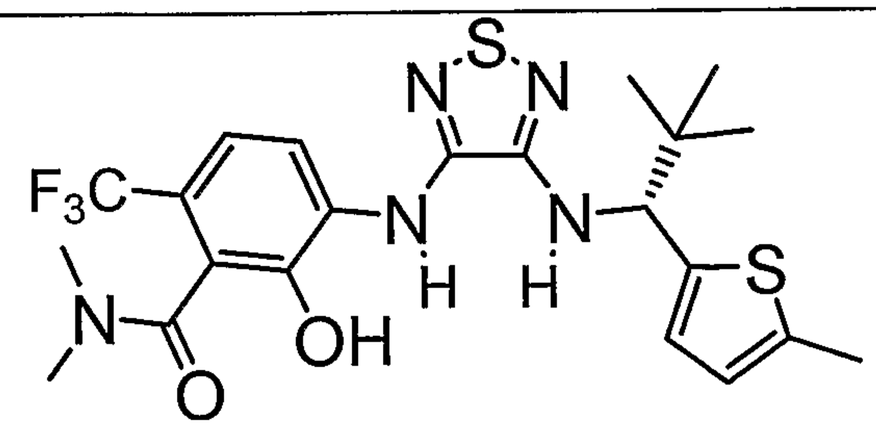
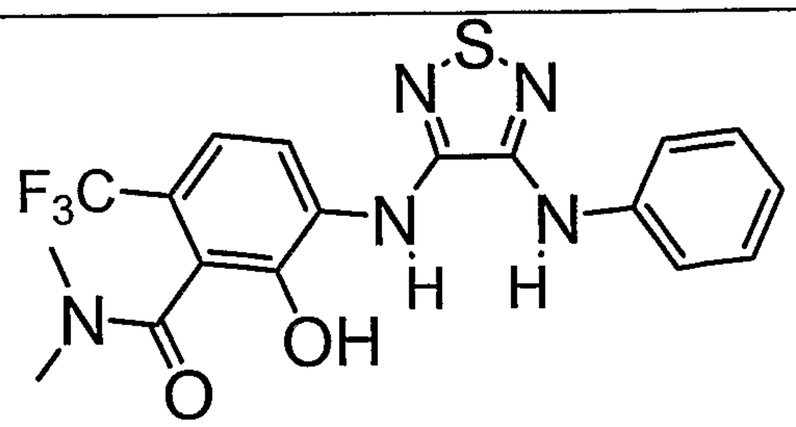
140	2283	
141	2284	
142	2285	
143	2206	
144	2286	
145	2287	
148	2289	

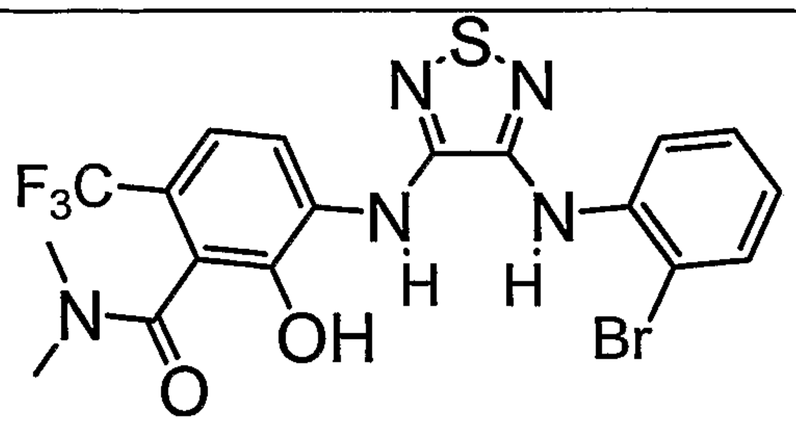
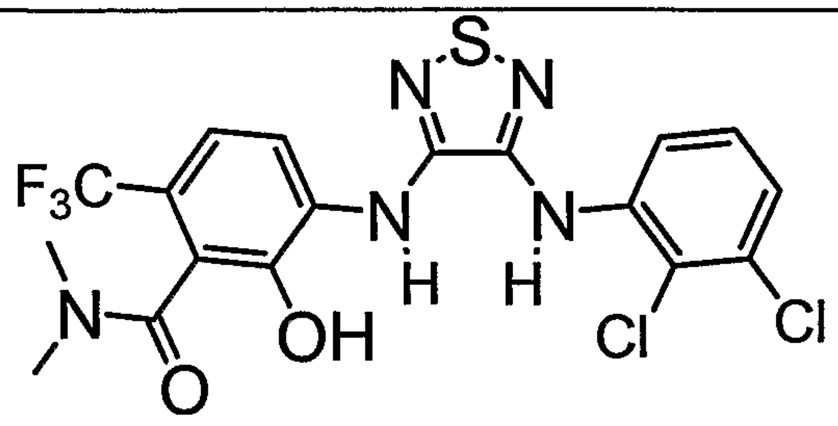
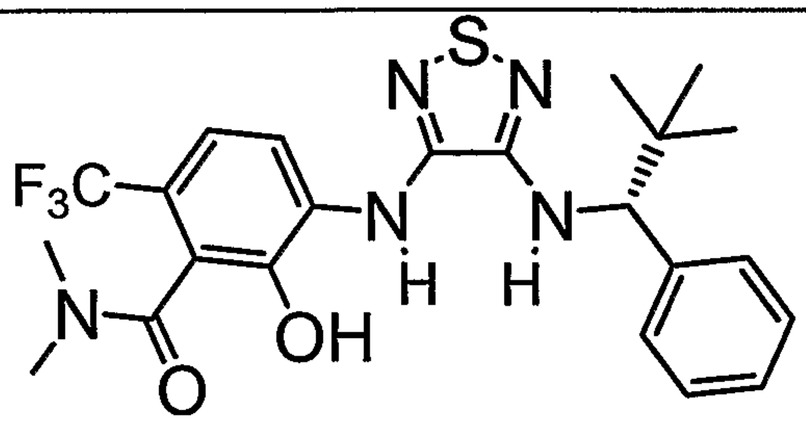
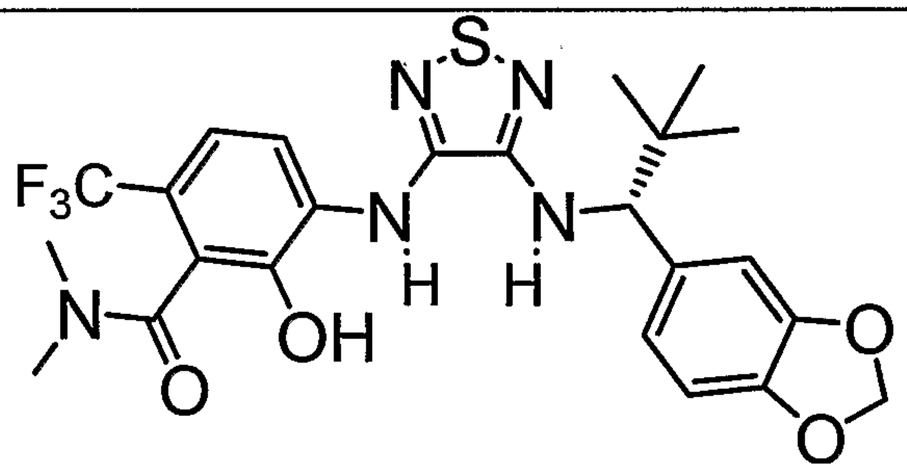
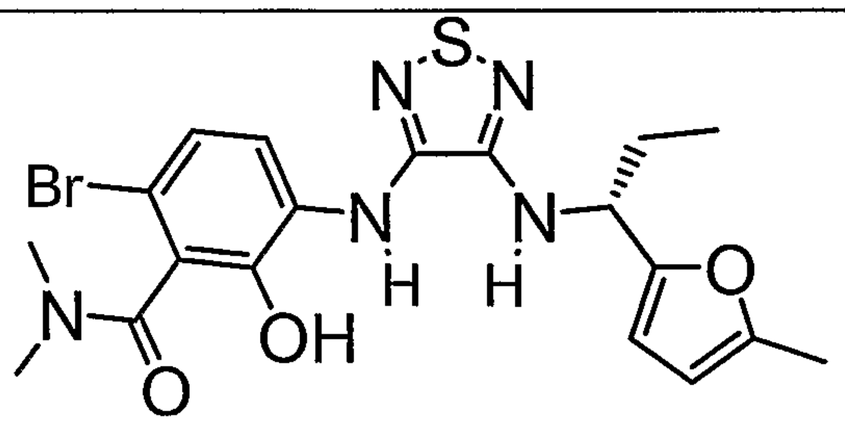
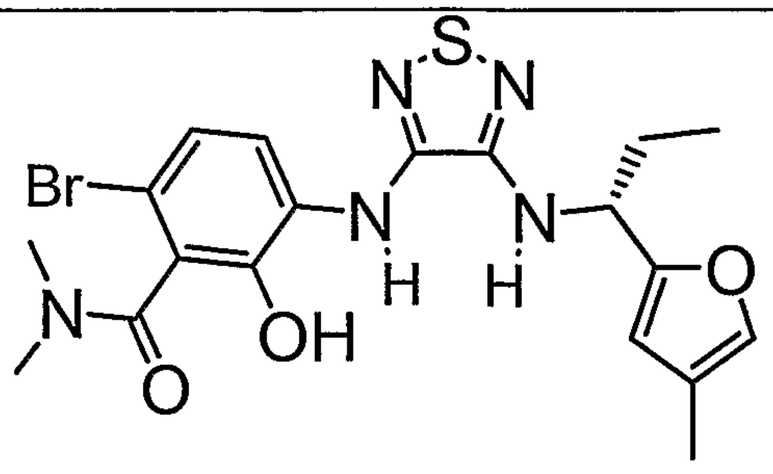
180	2250	
182	2251A	
183	2251B	
185	2251C	
186	2252	
188	2254	

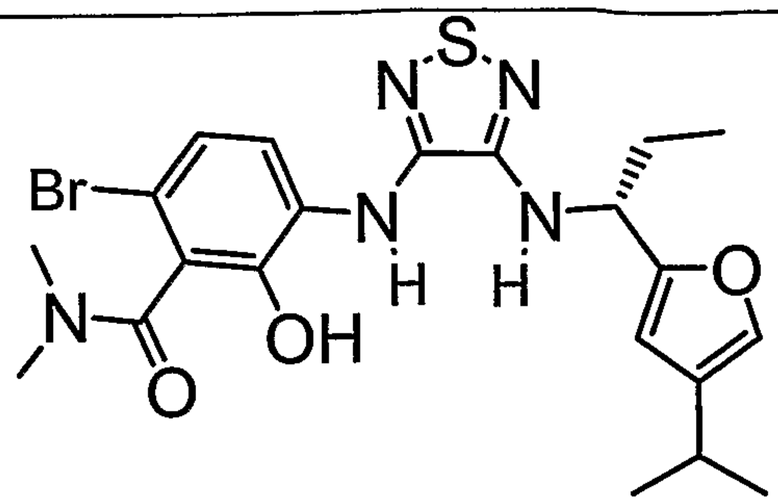
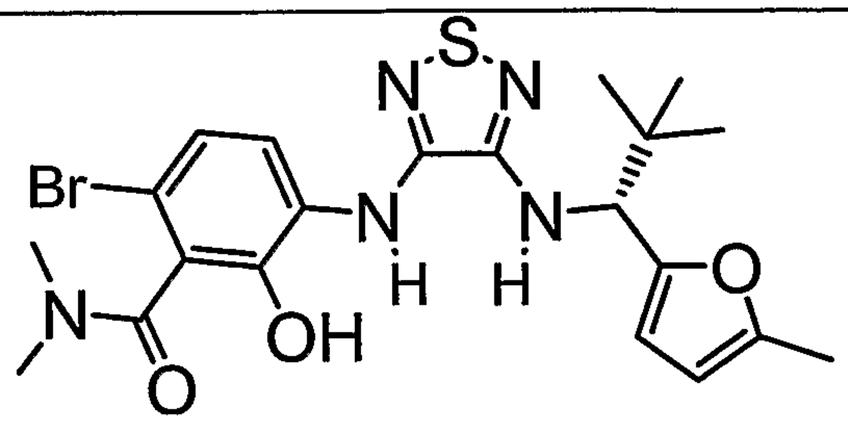
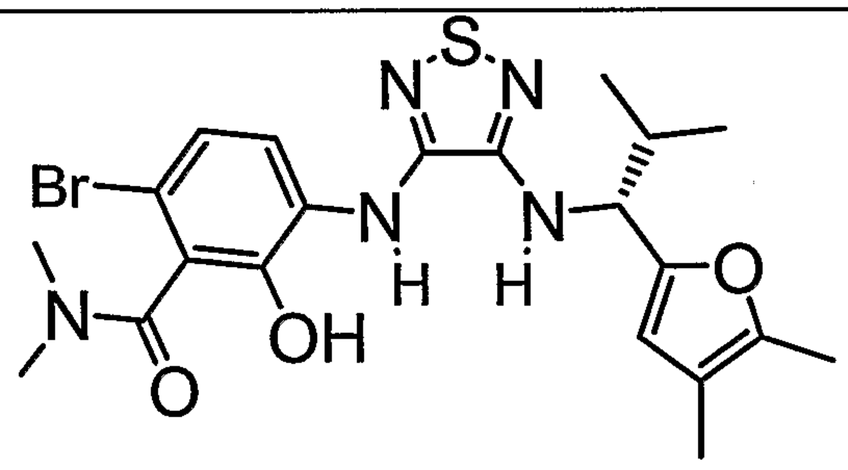
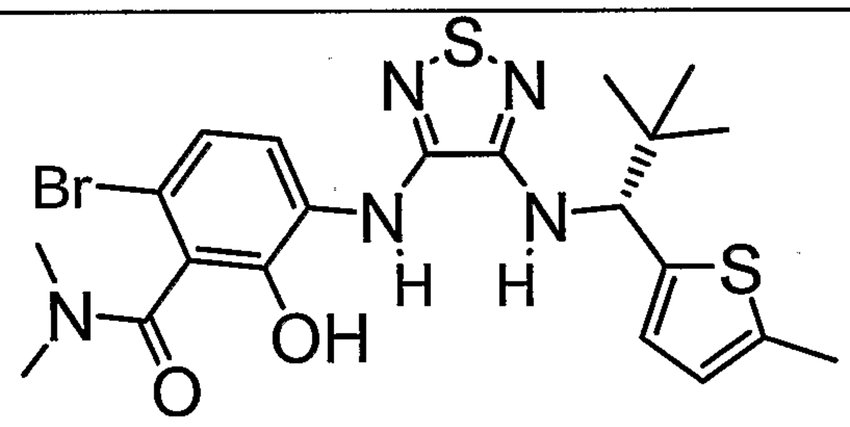
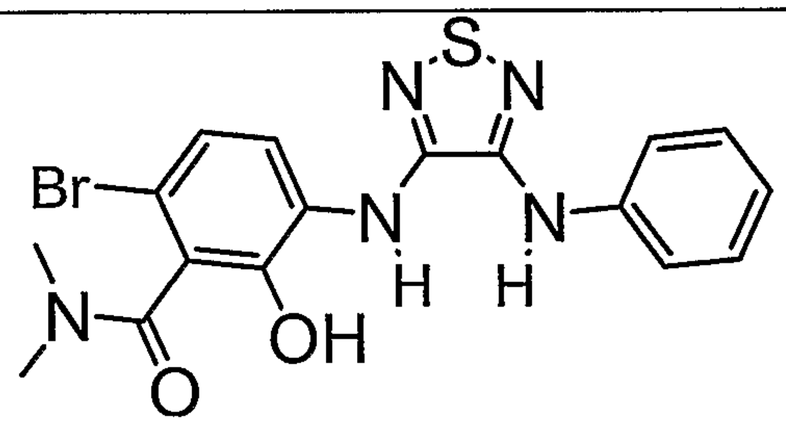
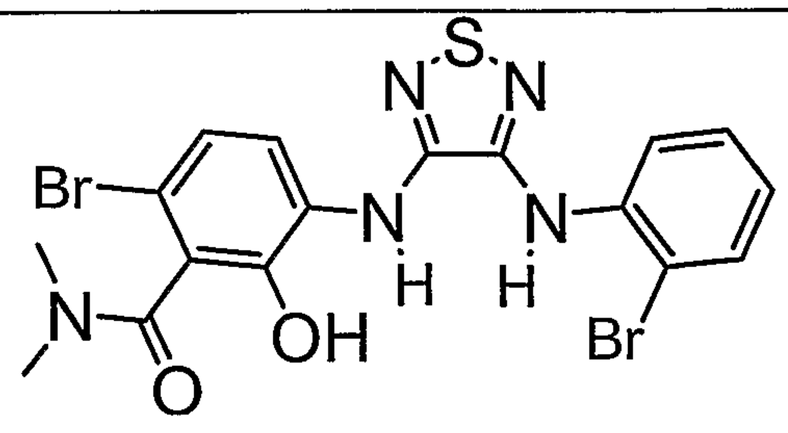
EXAMPLES 300-389, 500-639, 700-787, and 900-987

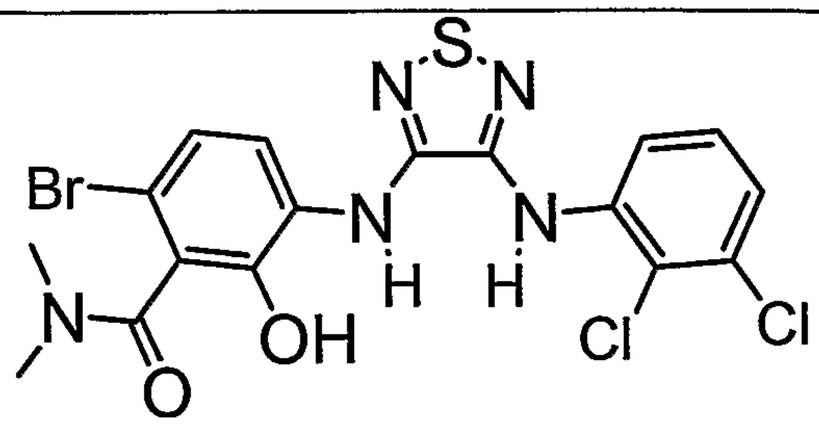
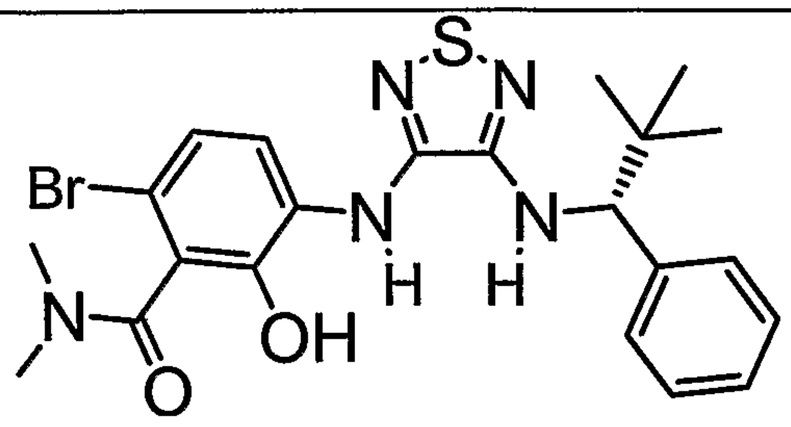
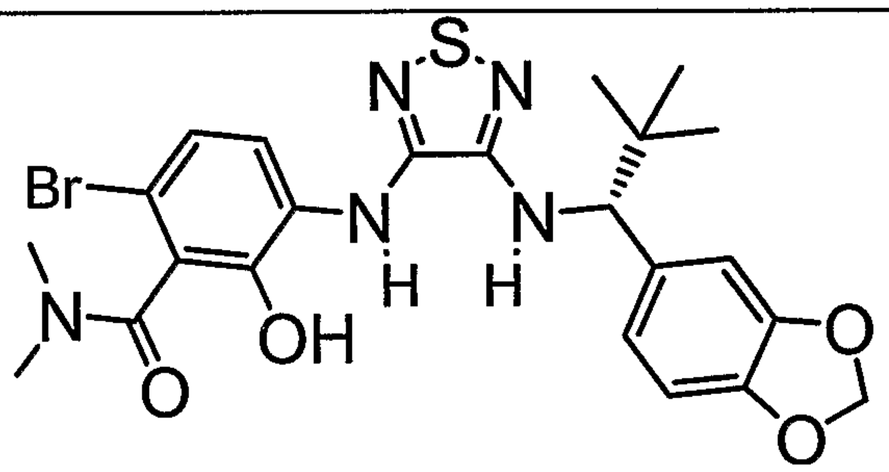
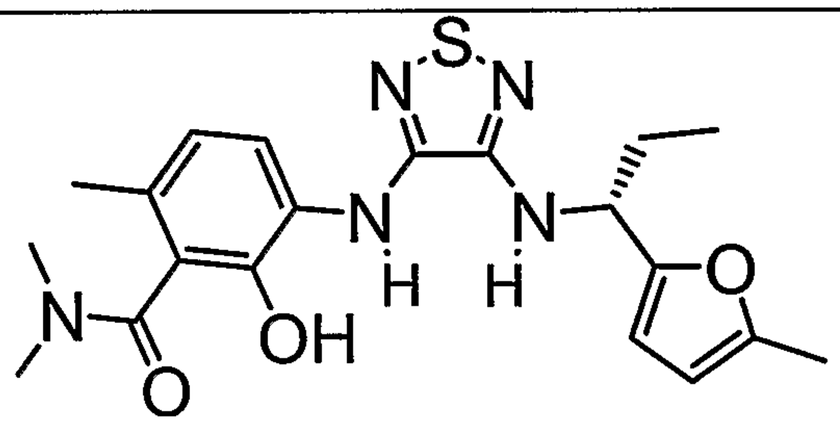
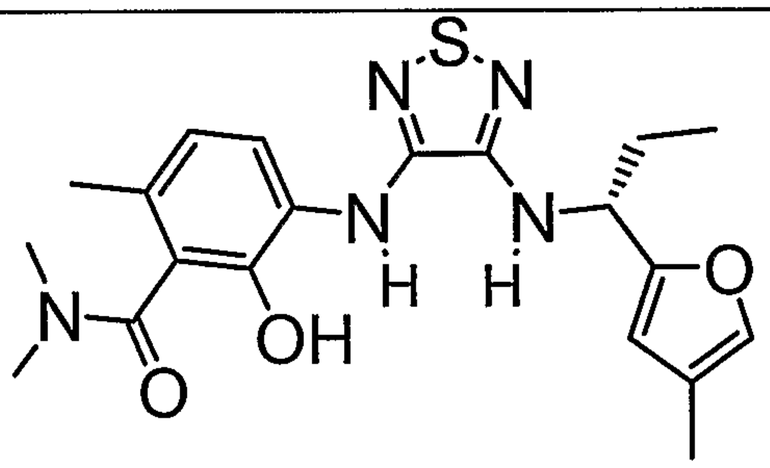
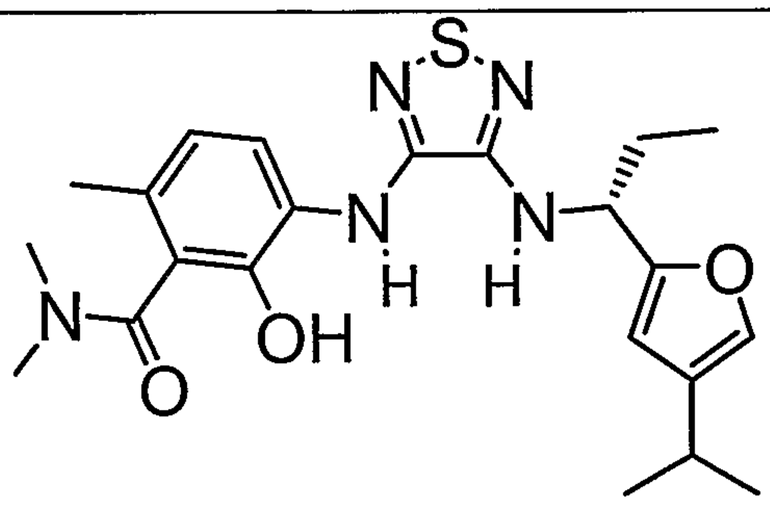
Following a similar procedure to that set forth in Example 1, but using the thiadiazoleoxide intermediate from the Preparative Example indicated in the Table below, the thiadiazole products in the Table below could be prepared.

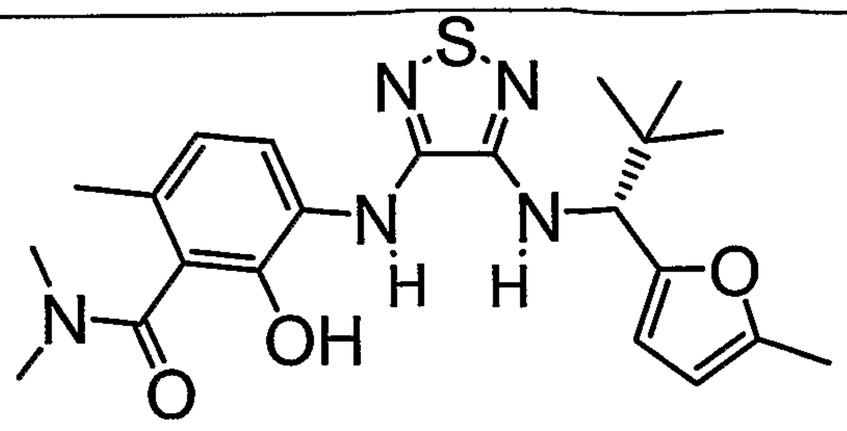
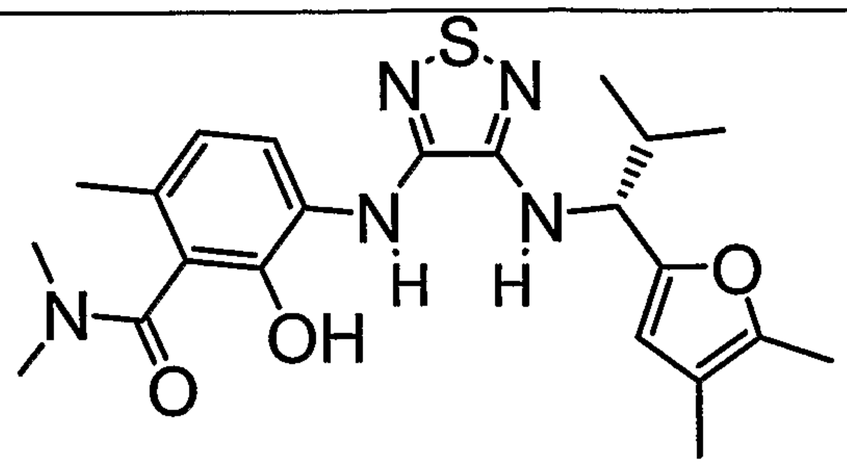
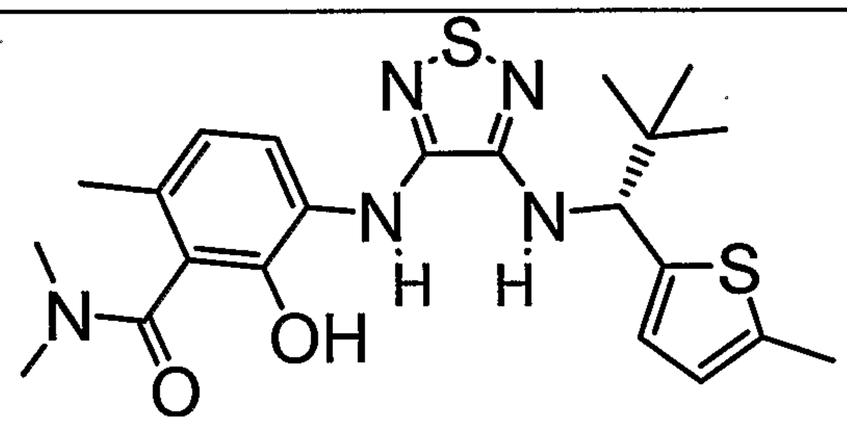
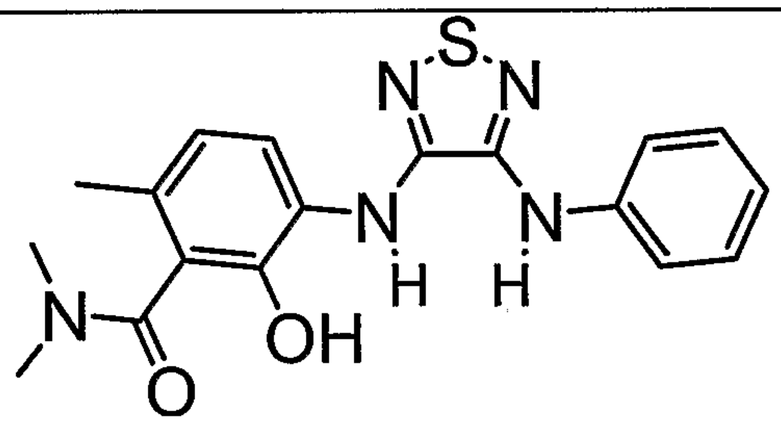
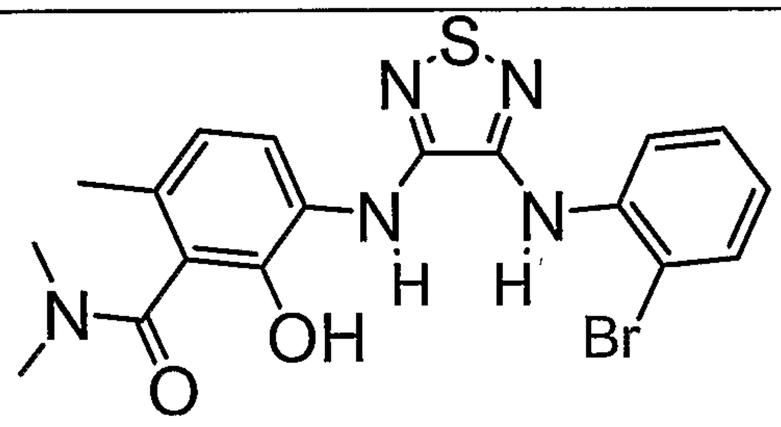
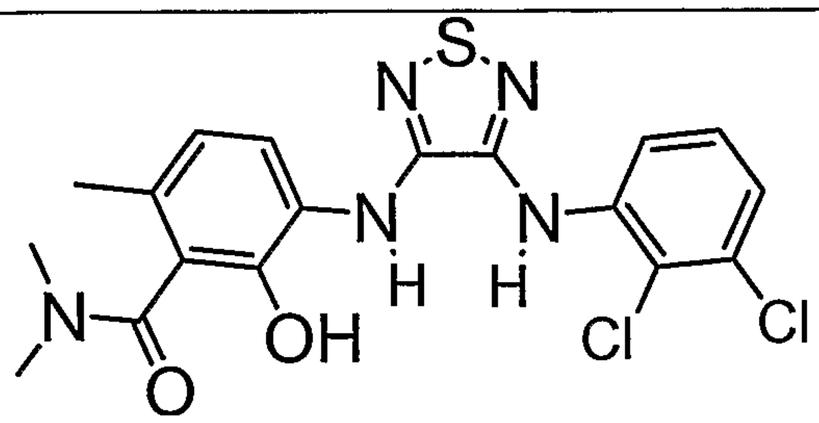
Ex	Prep. of mono-ox compd	Product
300	2400	
301	2402	
302	2402	
303	2403	

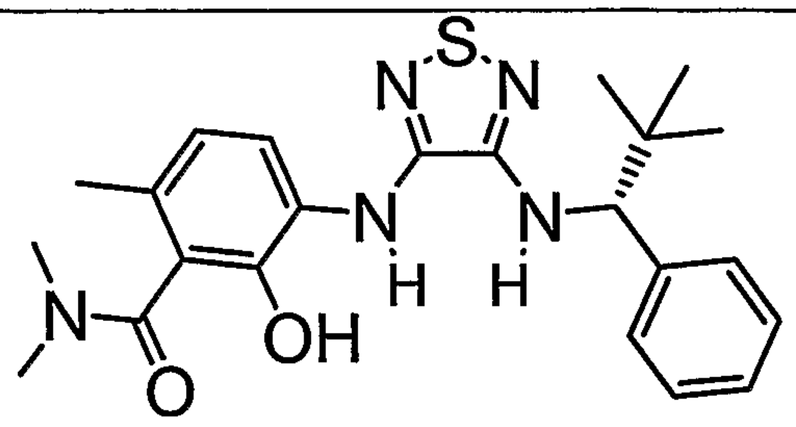
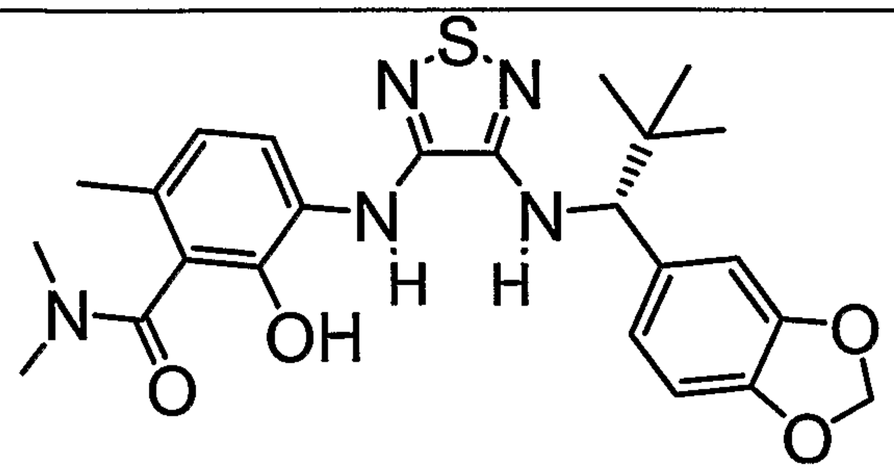
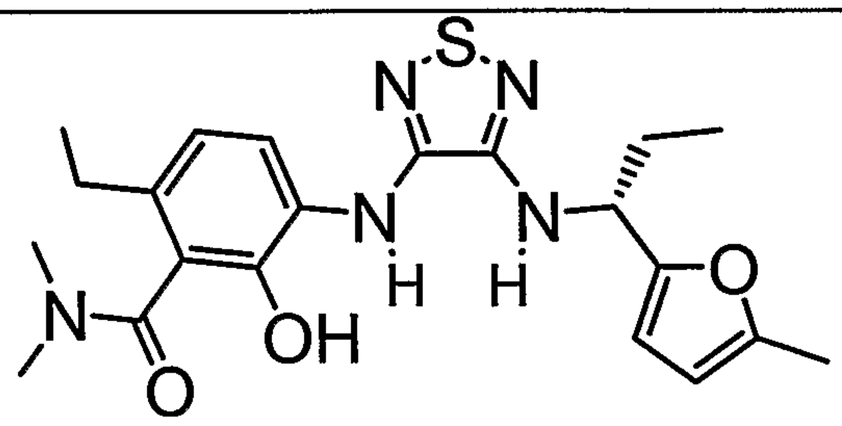
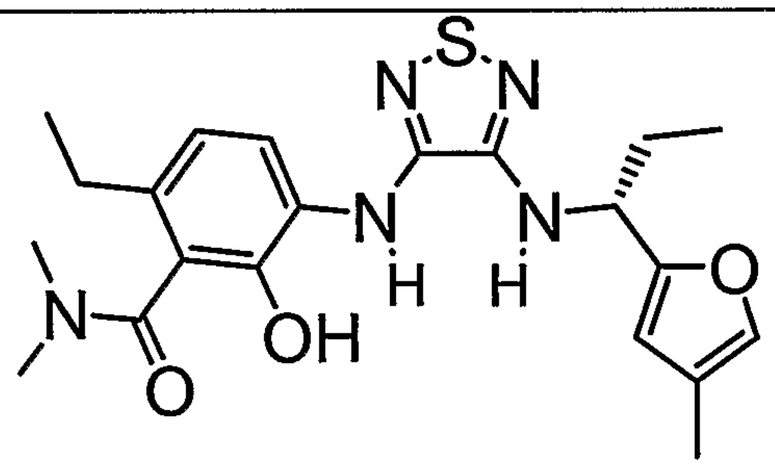
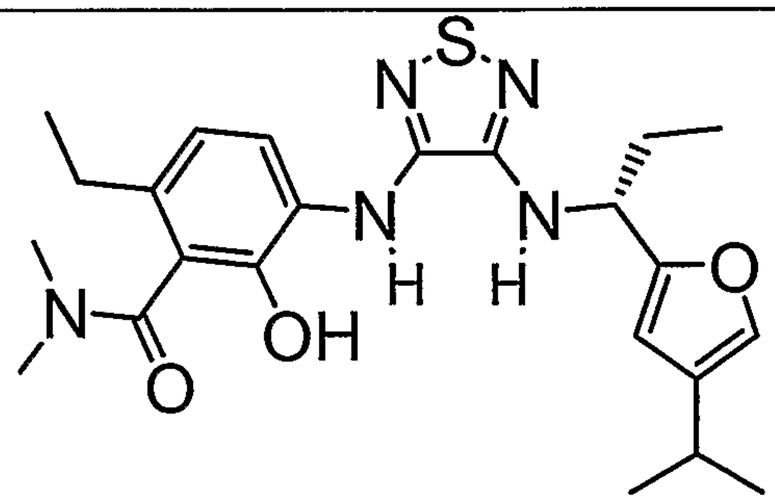
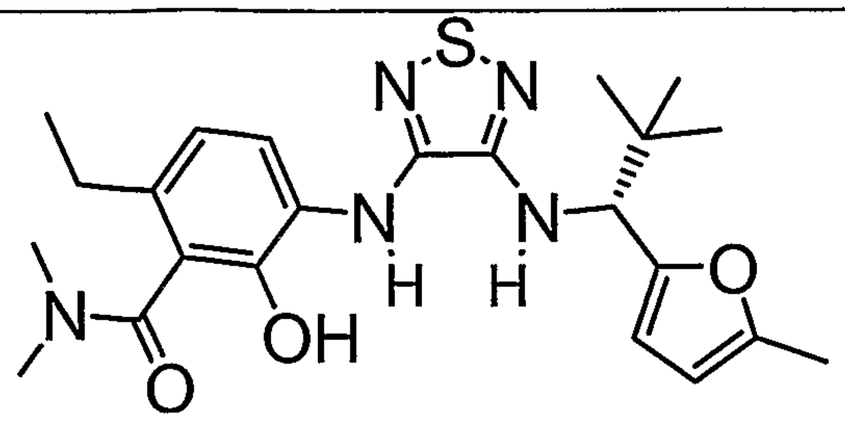
304	2404	
305	2405	
306	2406	
307	2001.25	
308	2408	
309	2409	

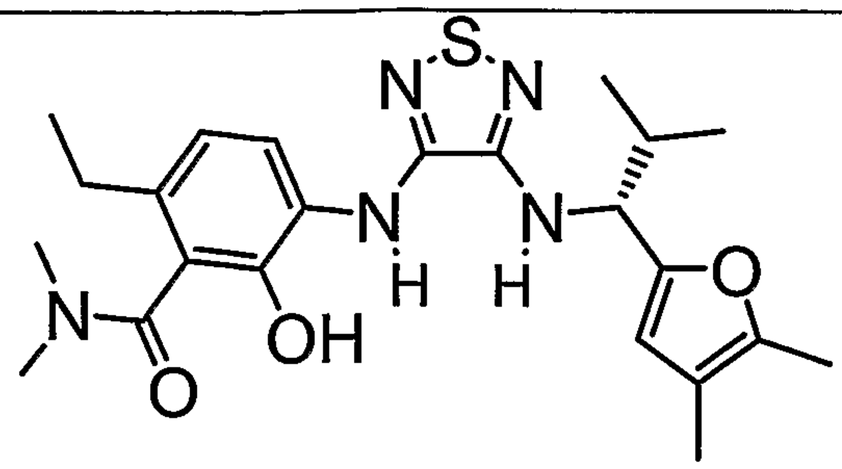
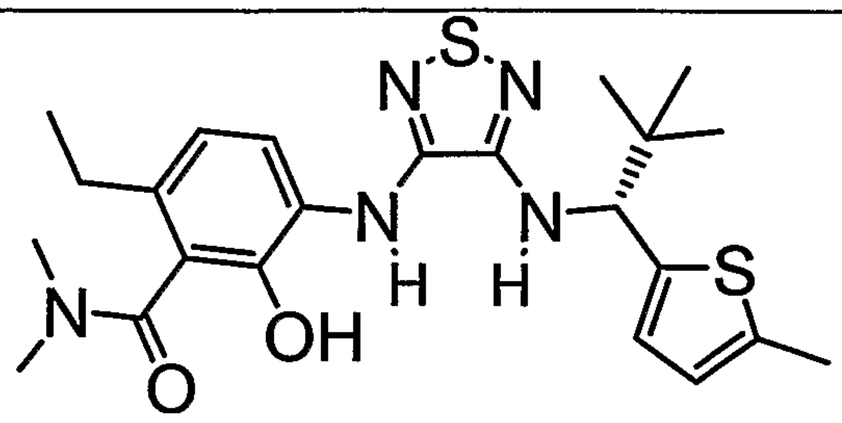
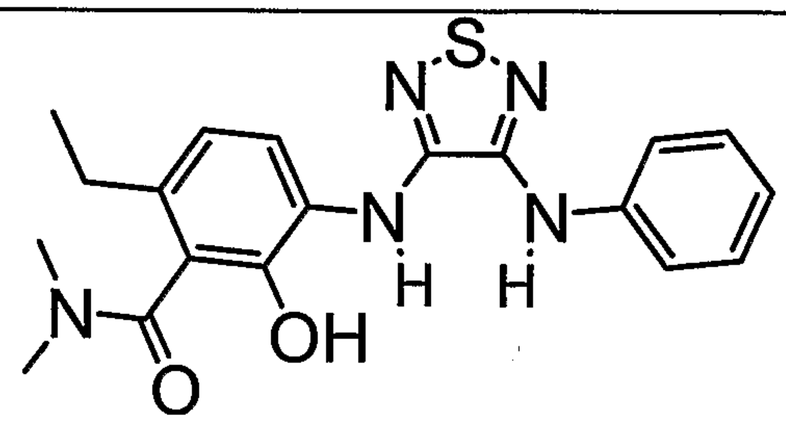
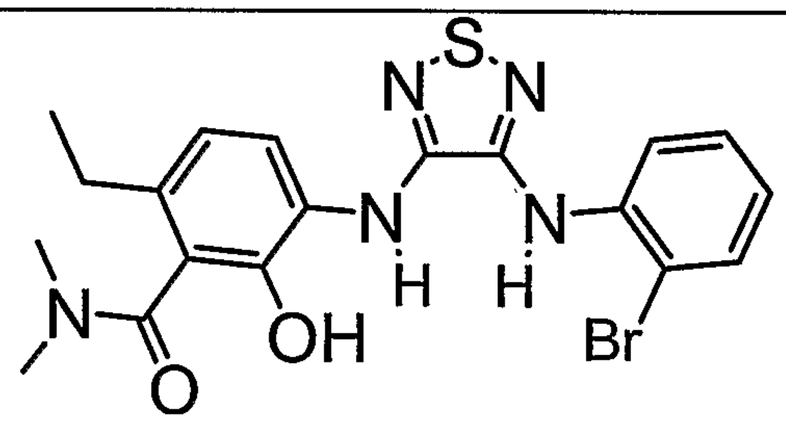
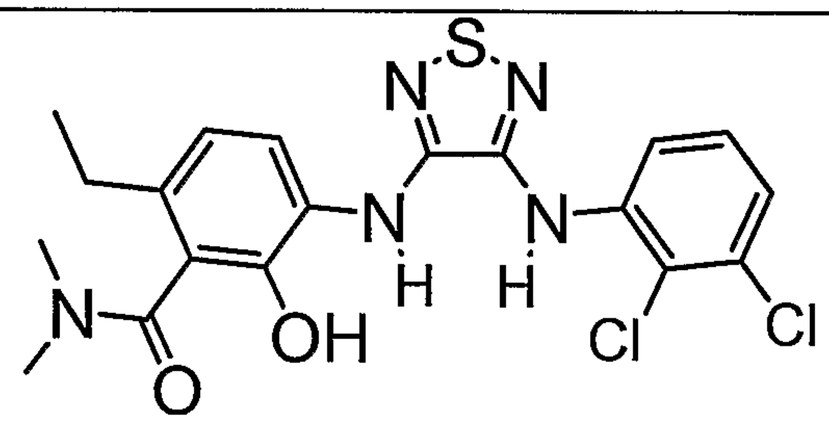
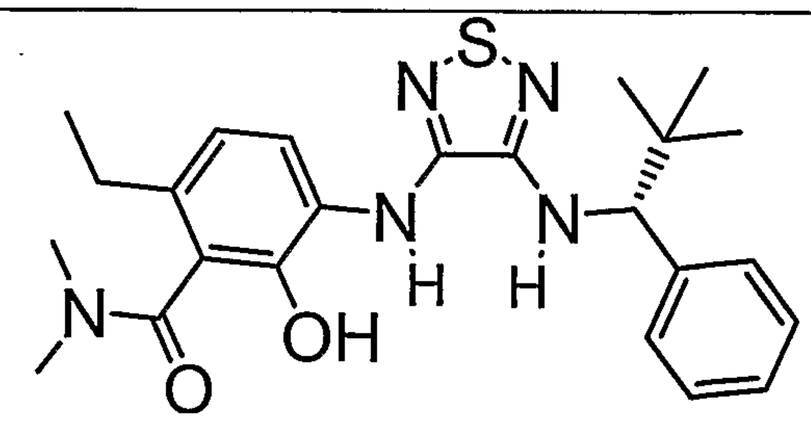
310	2410	
311	2411	
312	2412	
313	2413	
314	2414	
315	2415	

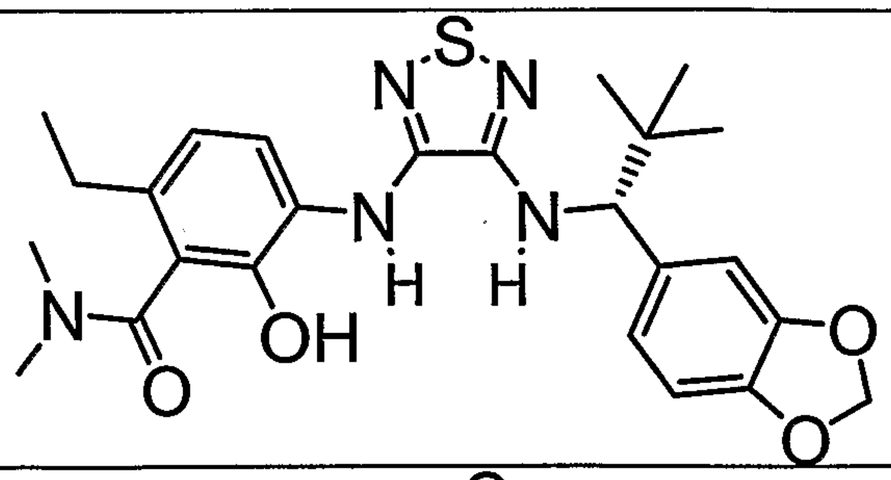
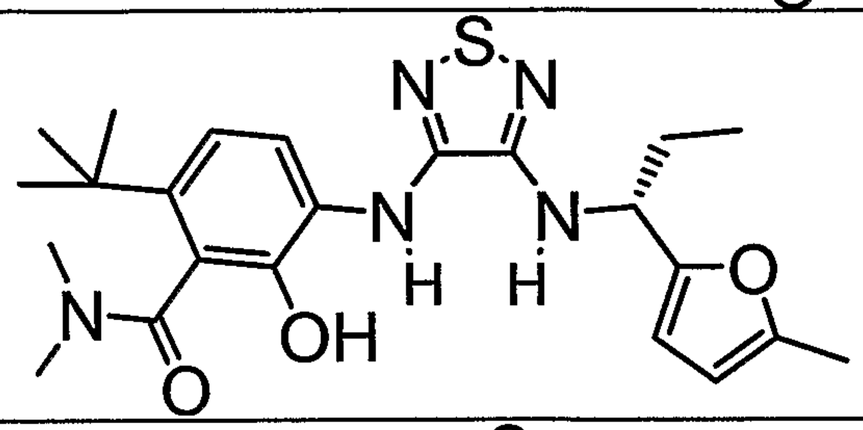
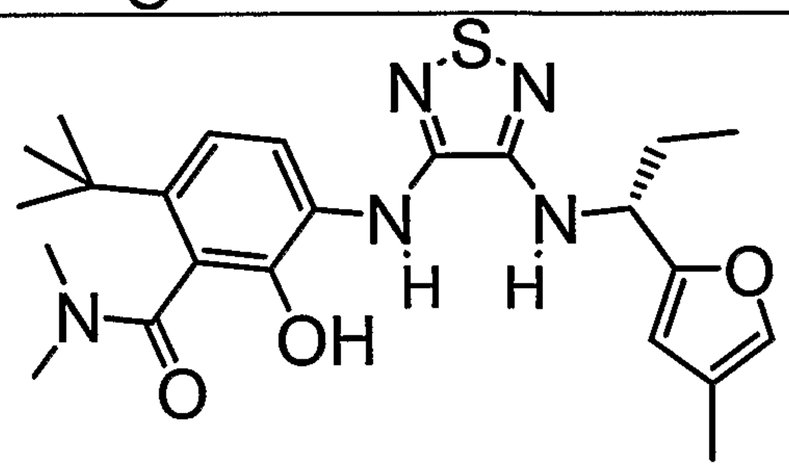
316	2416	
317	2417	
318	2418	
319	2419	
320	2420	
321	2421	

322	2422	
323	2423	
324	2424	
325	2425	
326	2426	
327	2427	

328	2428	
329	2429	
330	2430	
331	2431	
332	2432	
333	2433	

334	2434	
335	2435	
336	2436	
337	2437	
338	2438	
339	2439	

340	2440	
341	2441	
342	2442	
343	2443	
344	2444	
345	2445	

346	2446	
347	2447	
348	2448	
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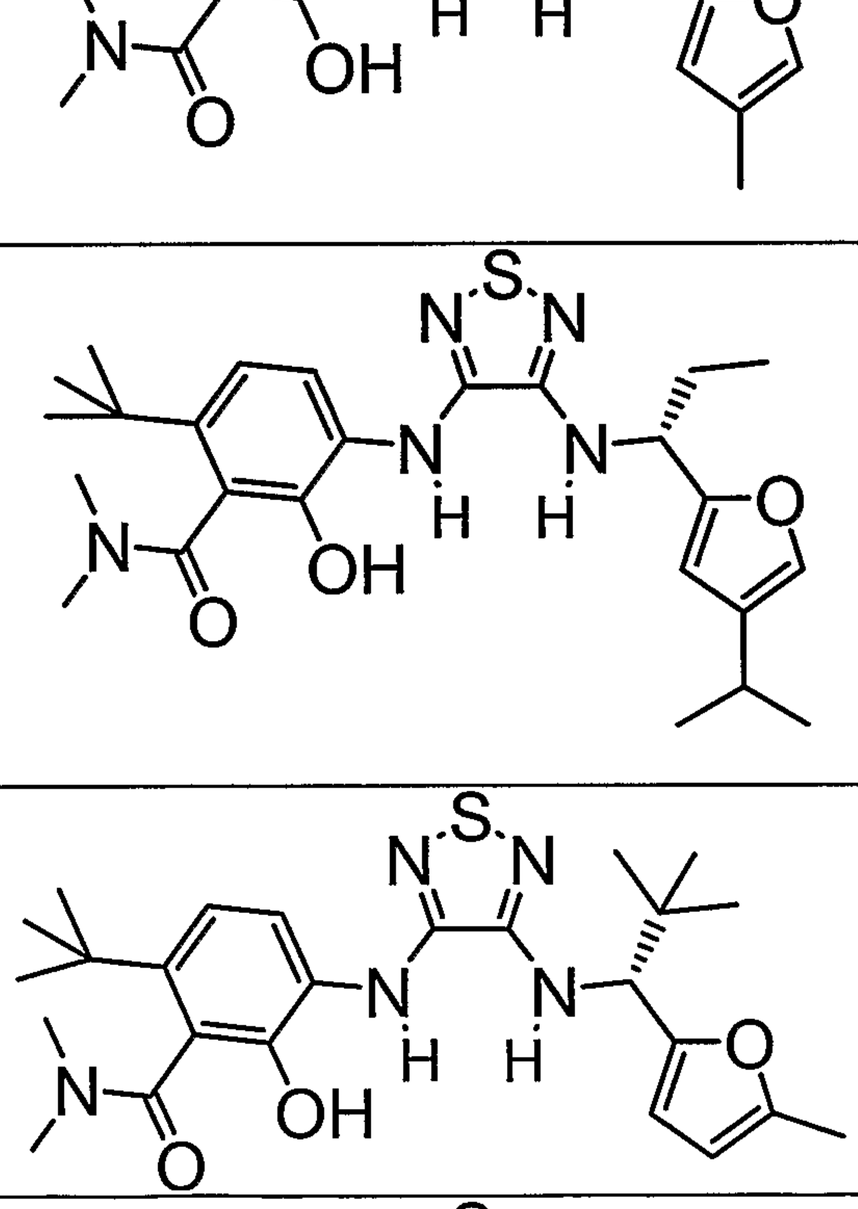
350	2450	
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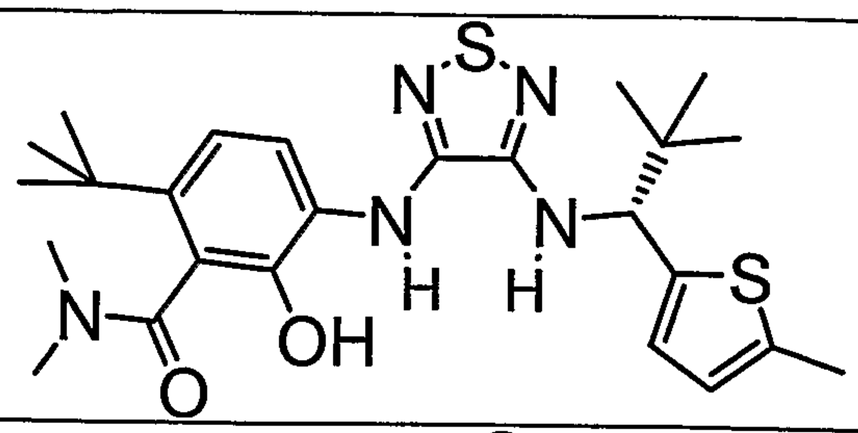
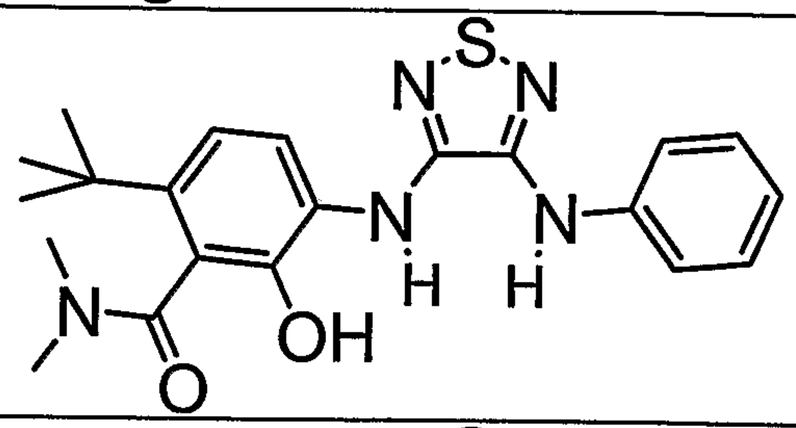
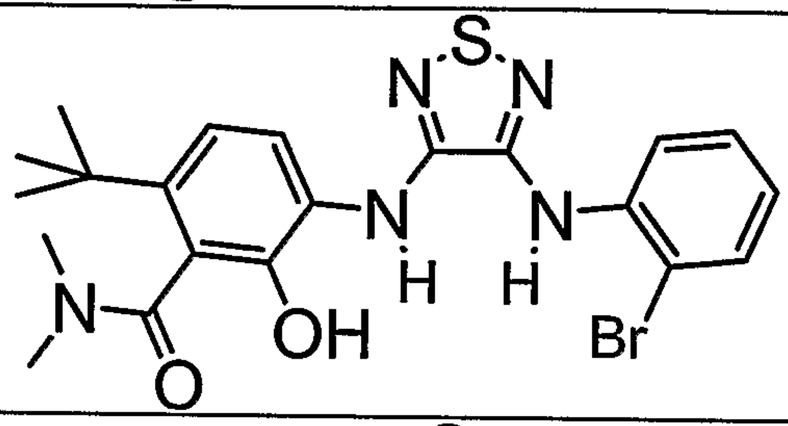
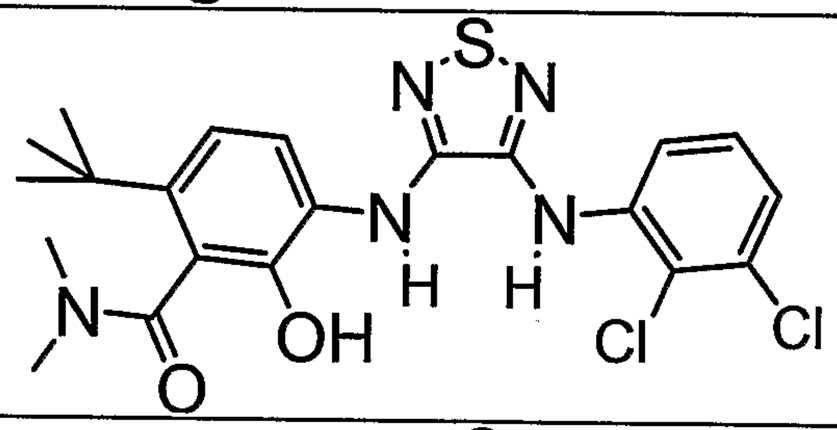
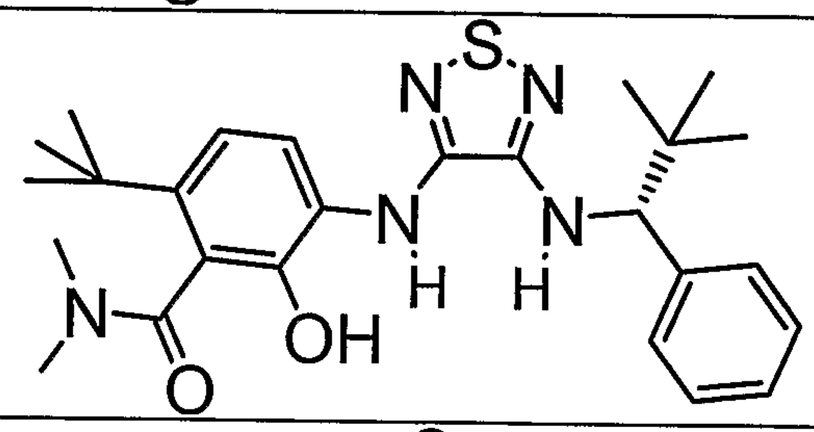
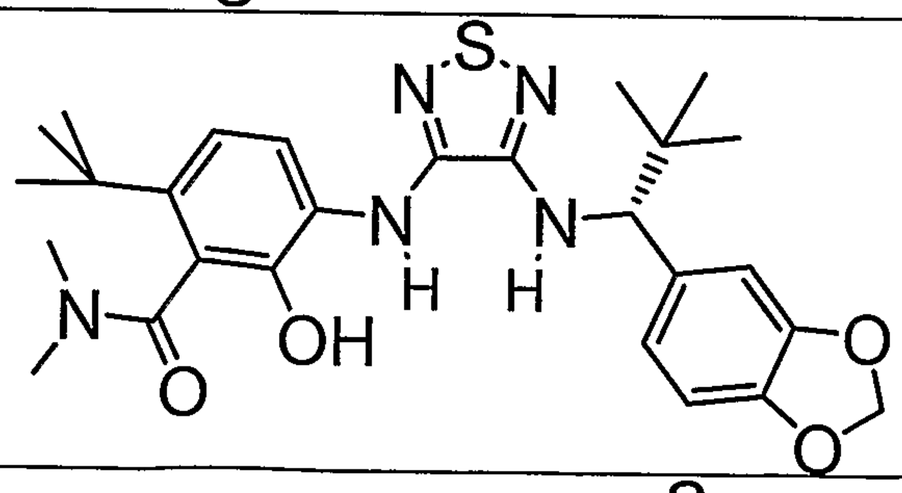
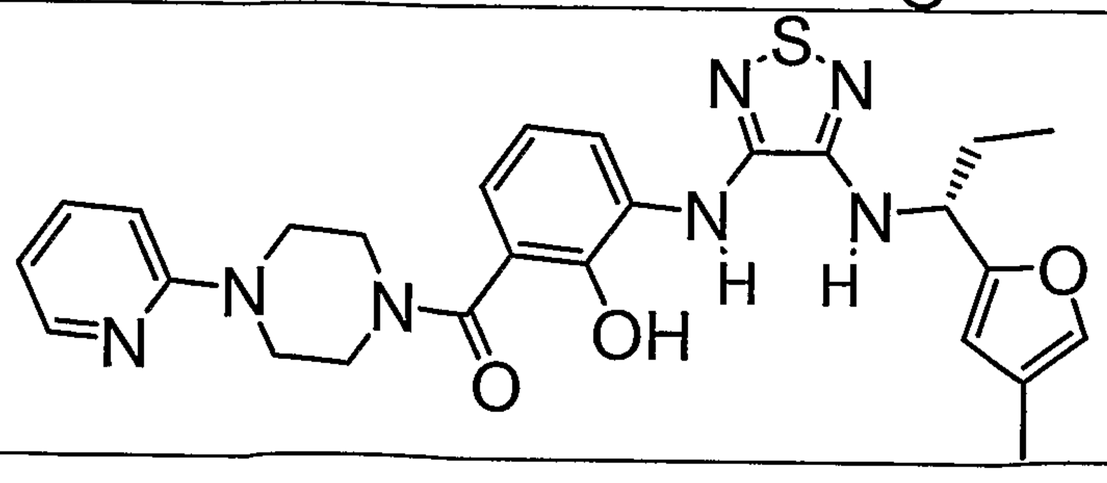
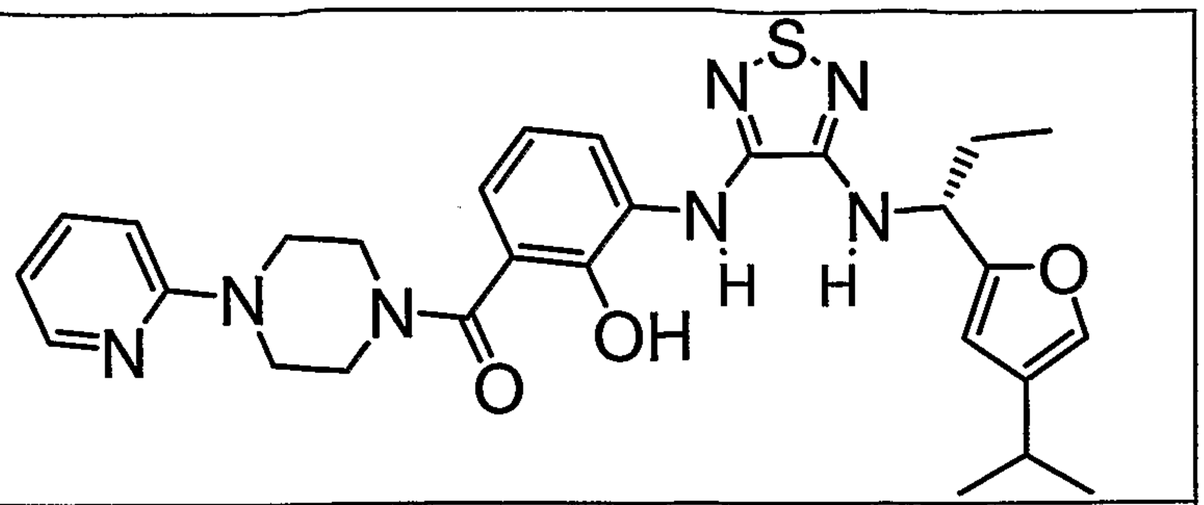
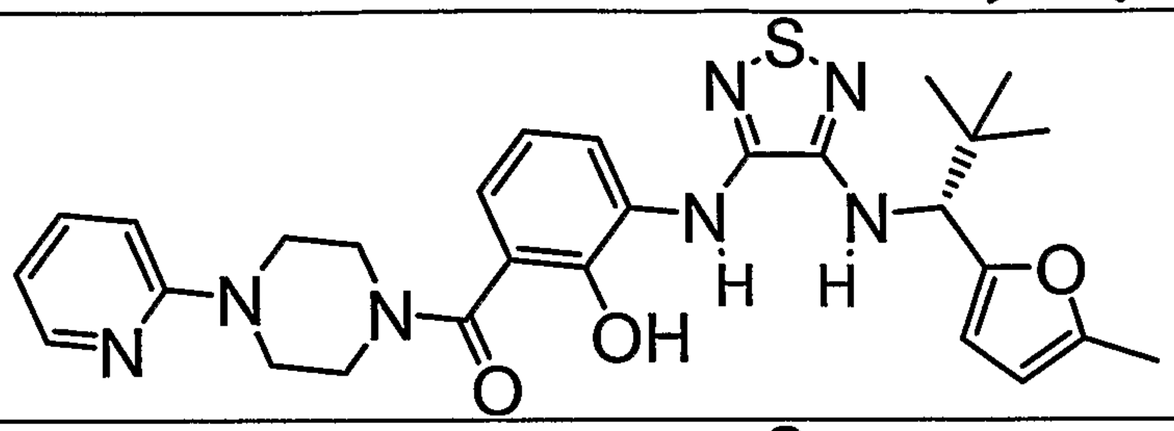
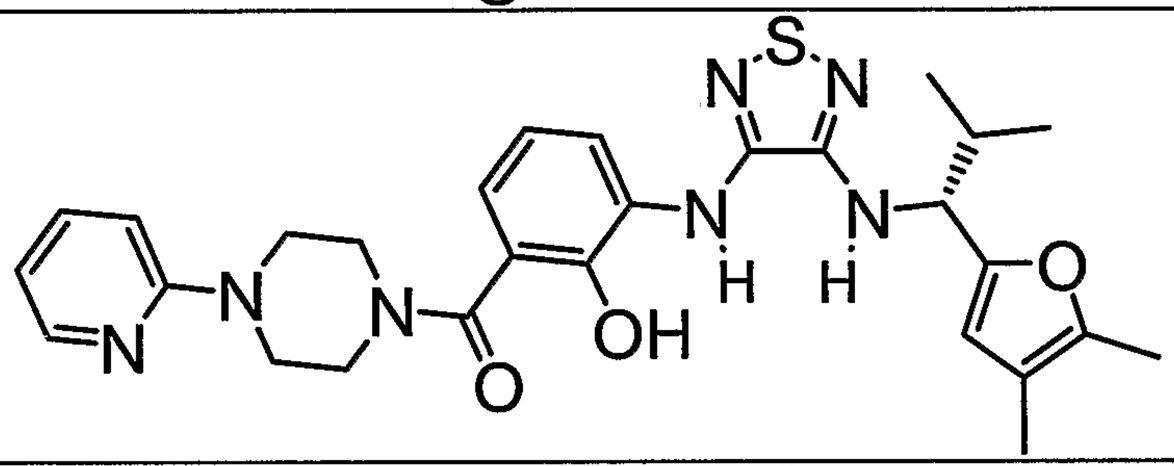
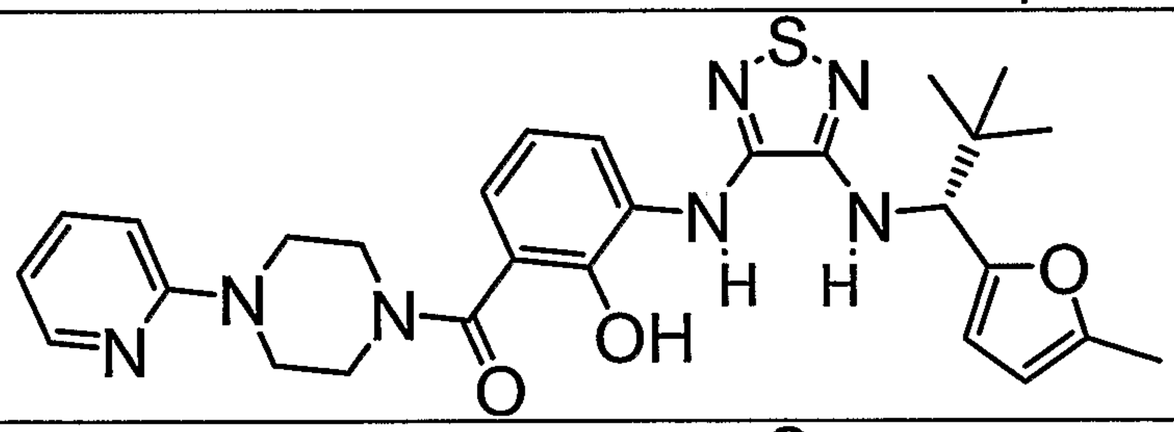
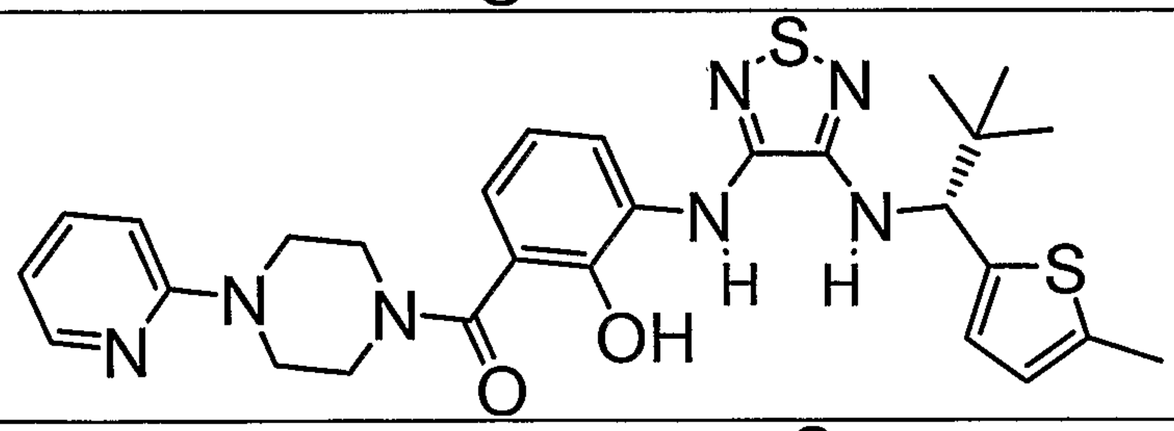
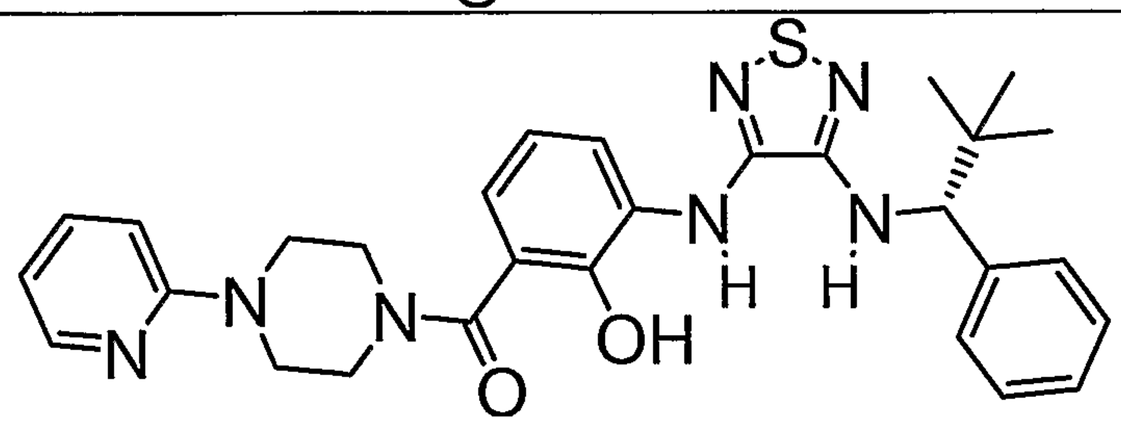
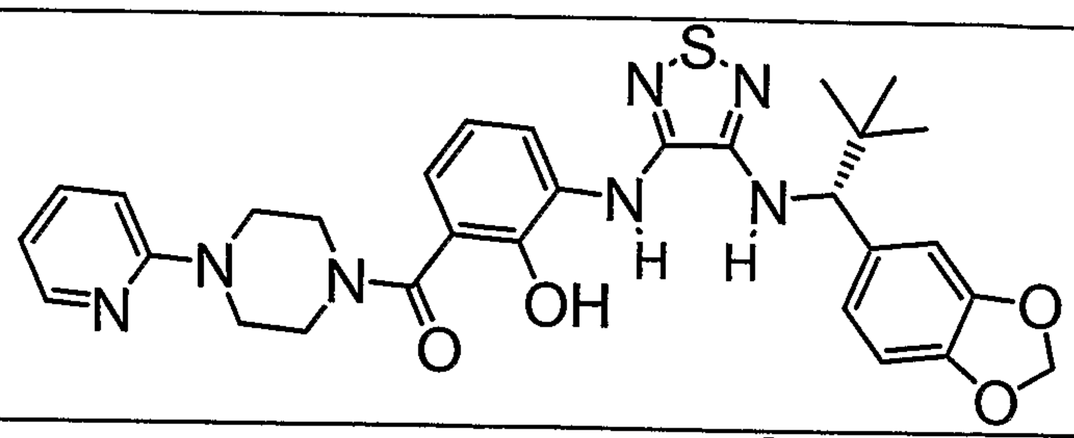
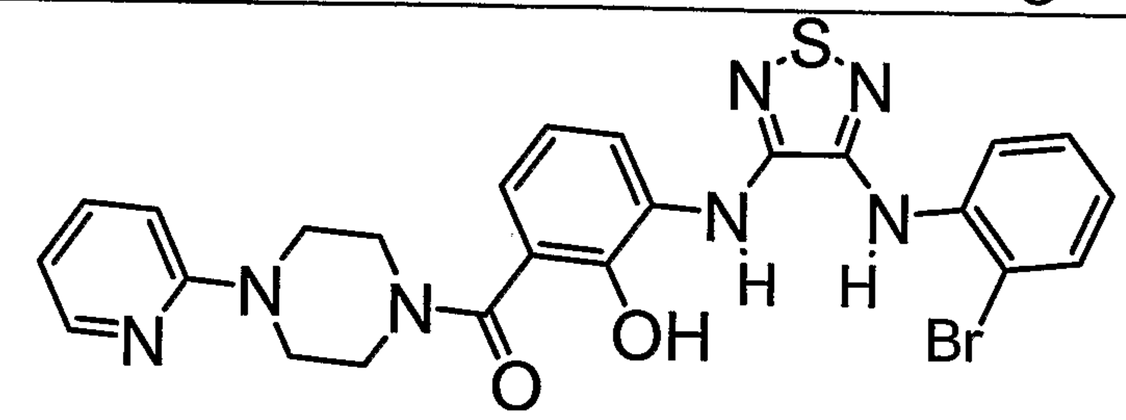
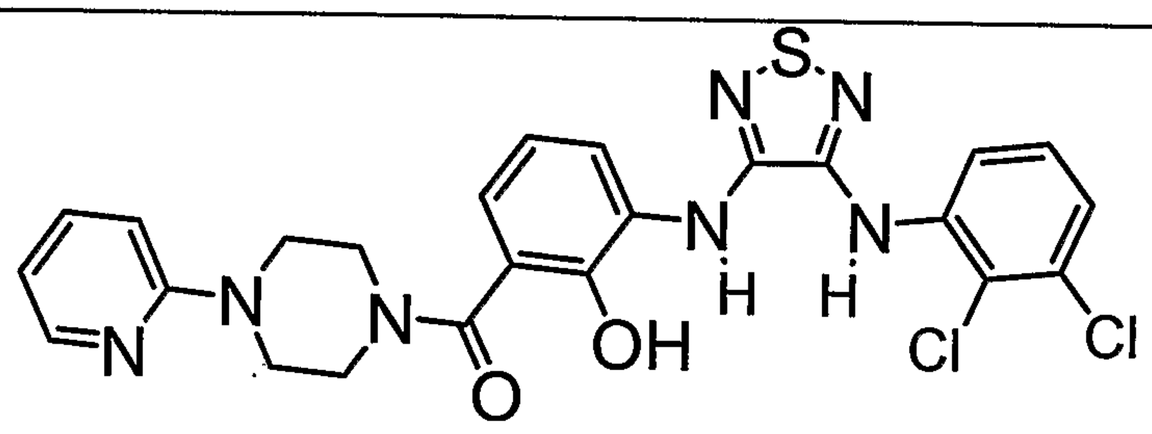
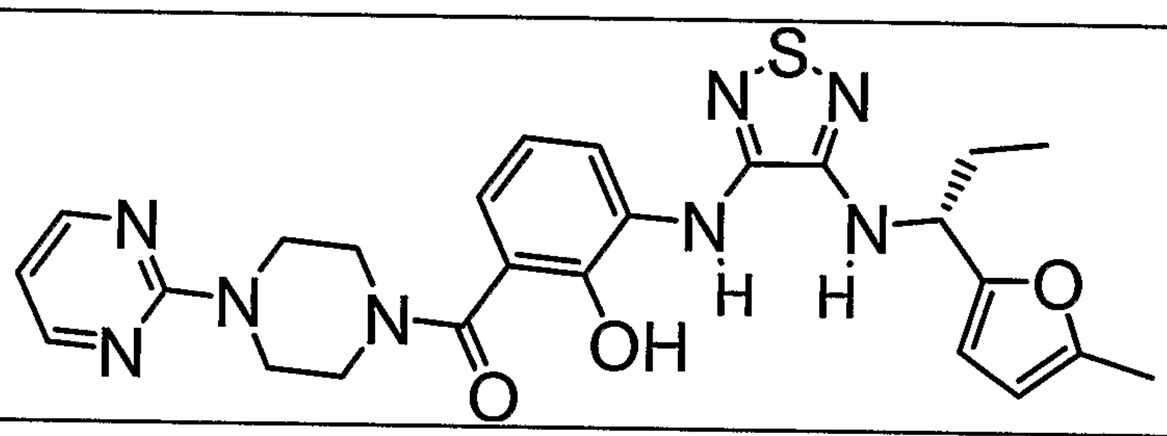
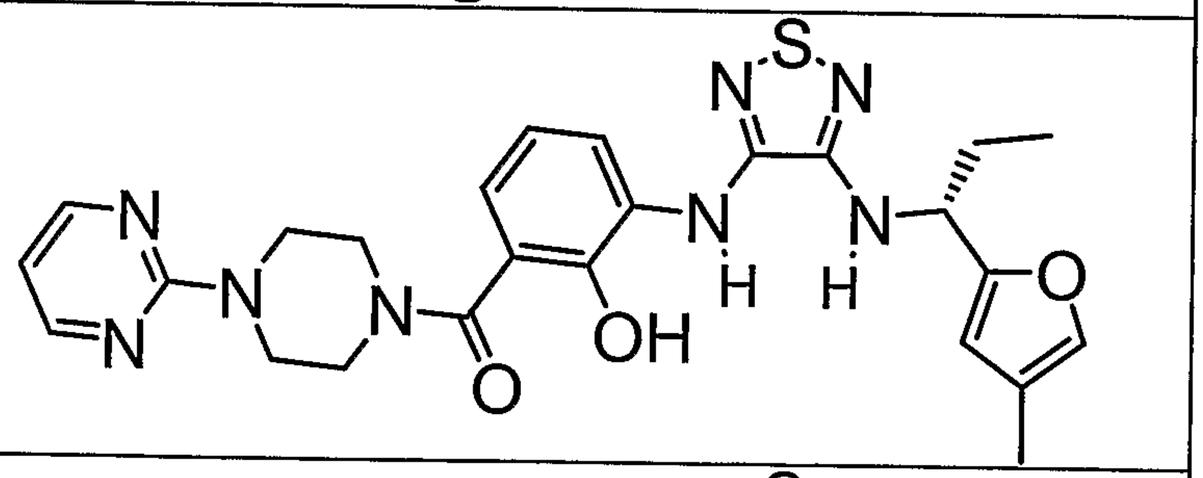
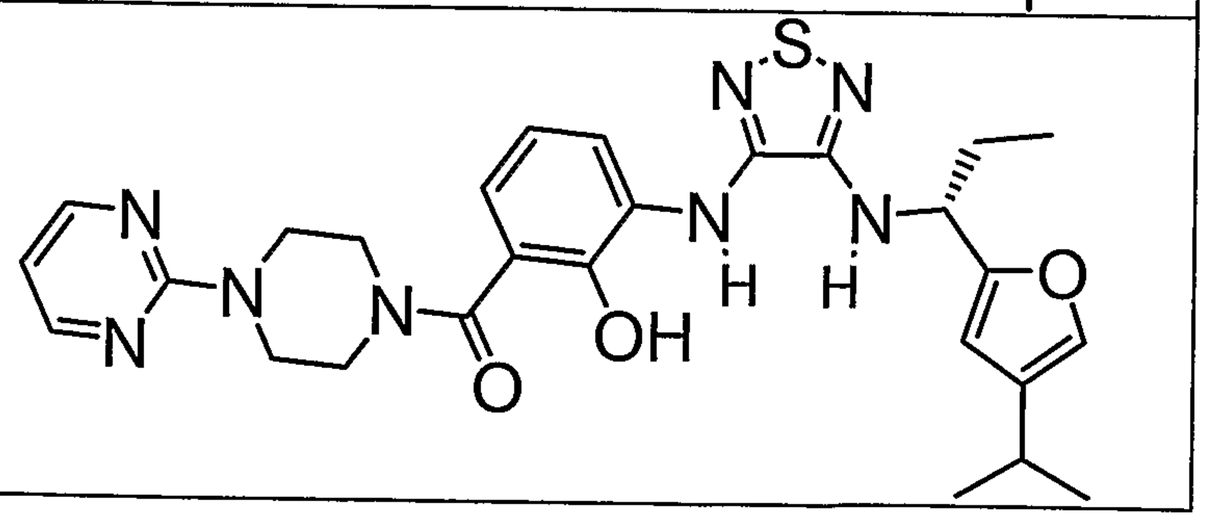
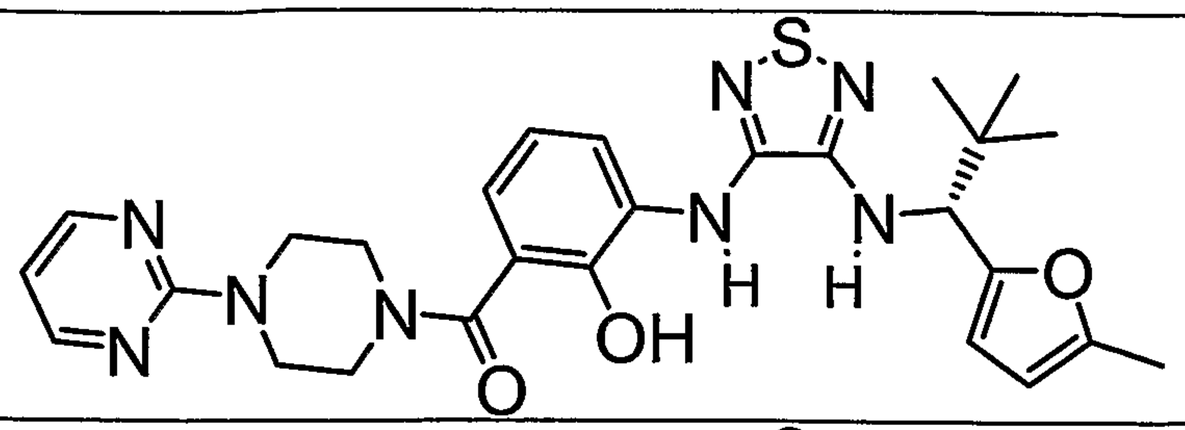
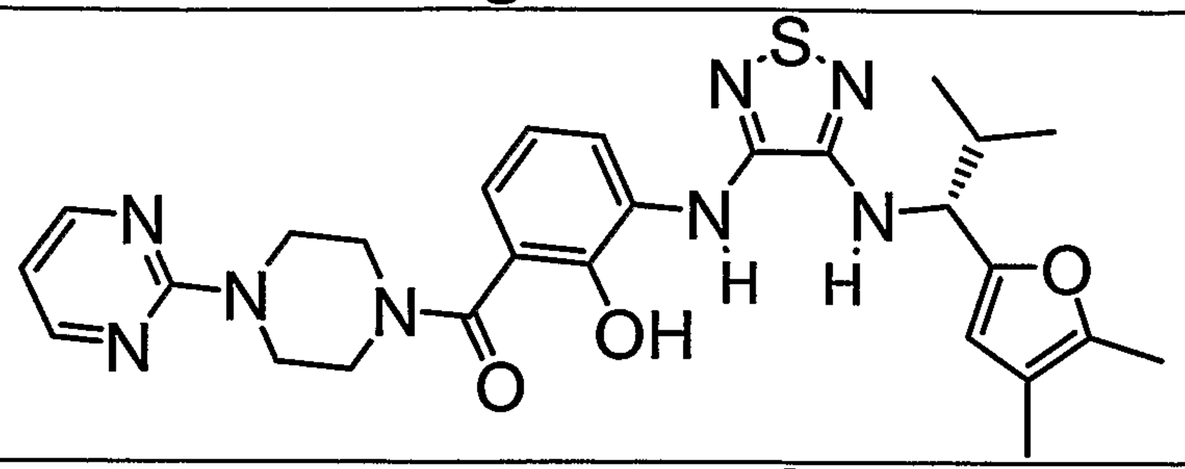
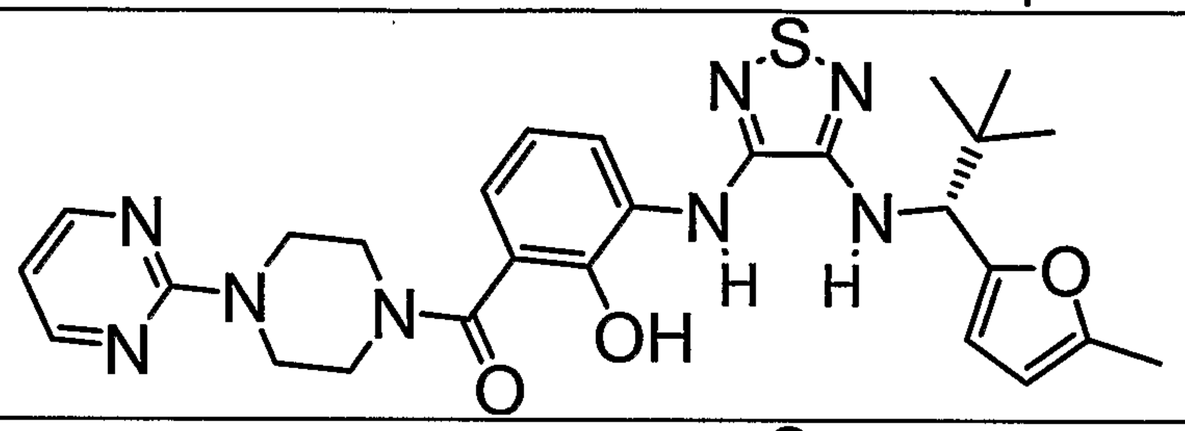
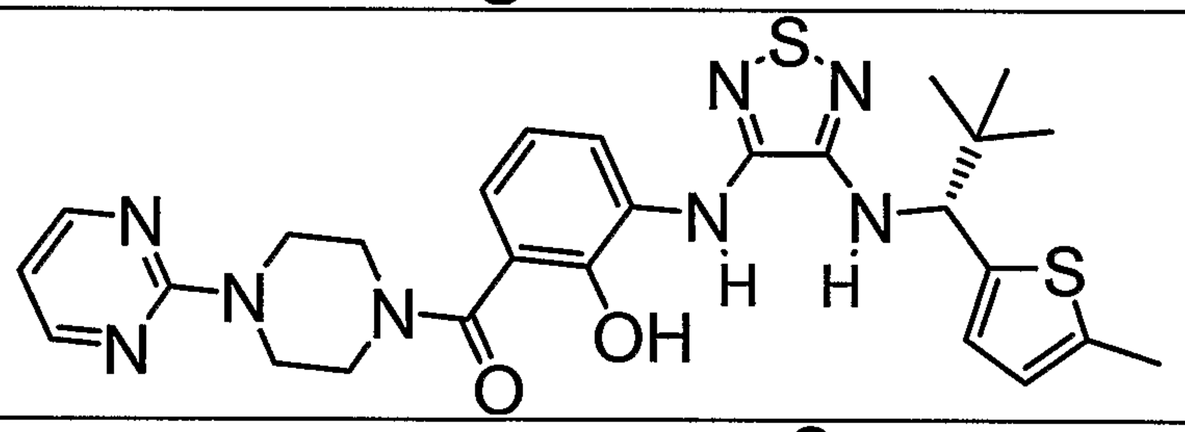
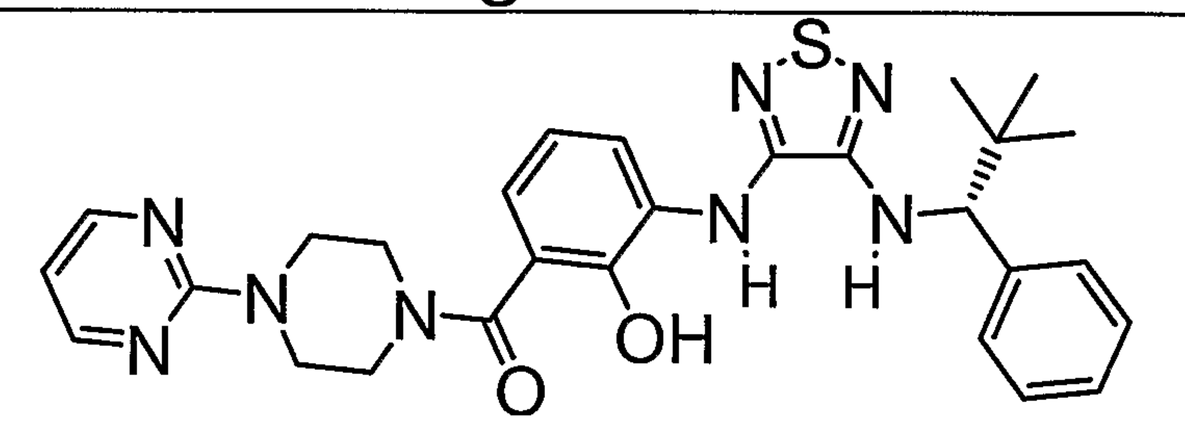
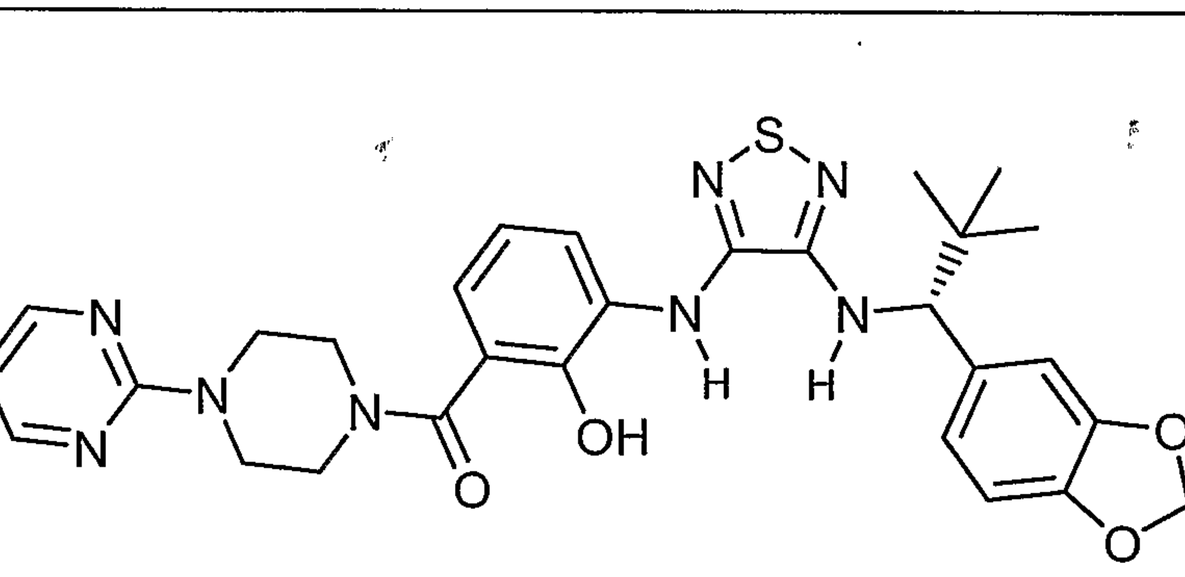
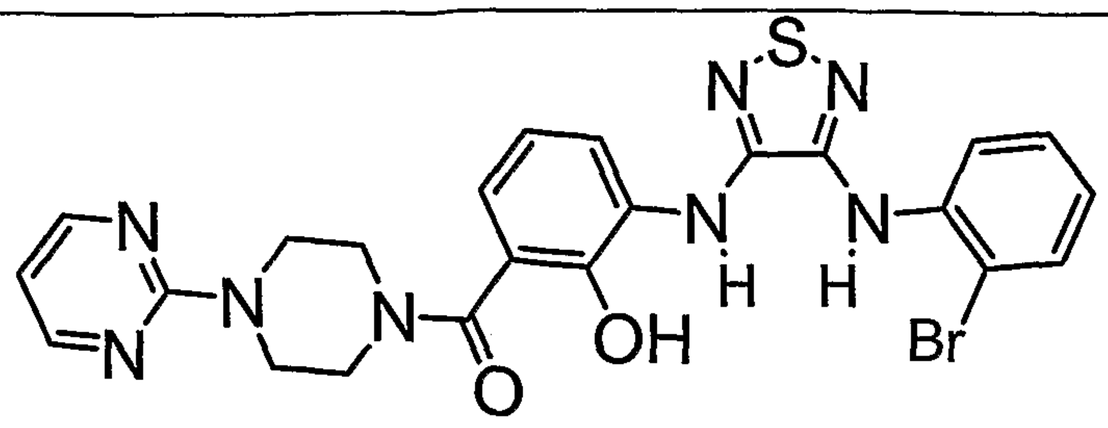
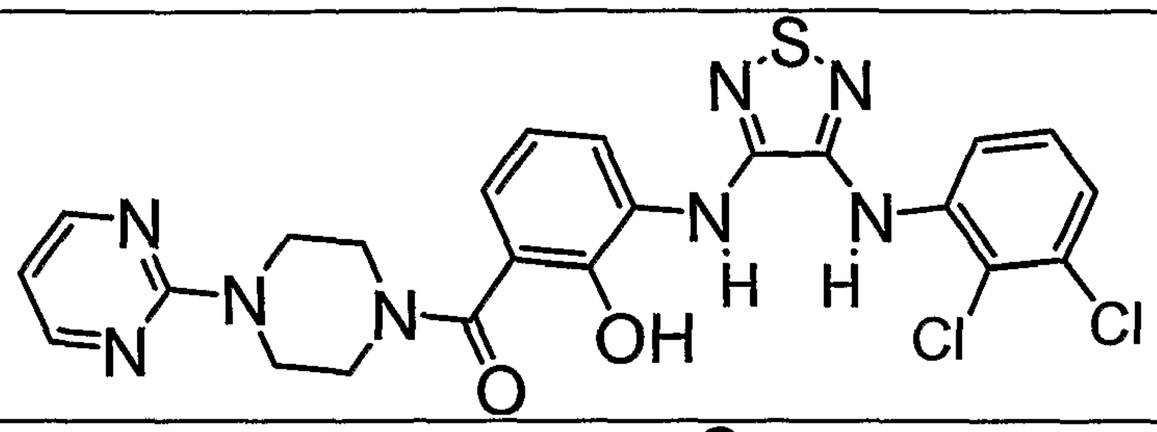
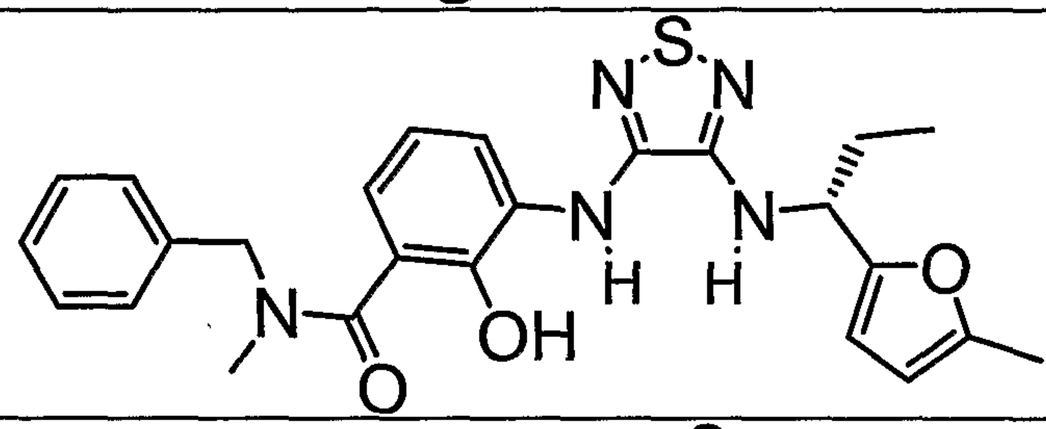
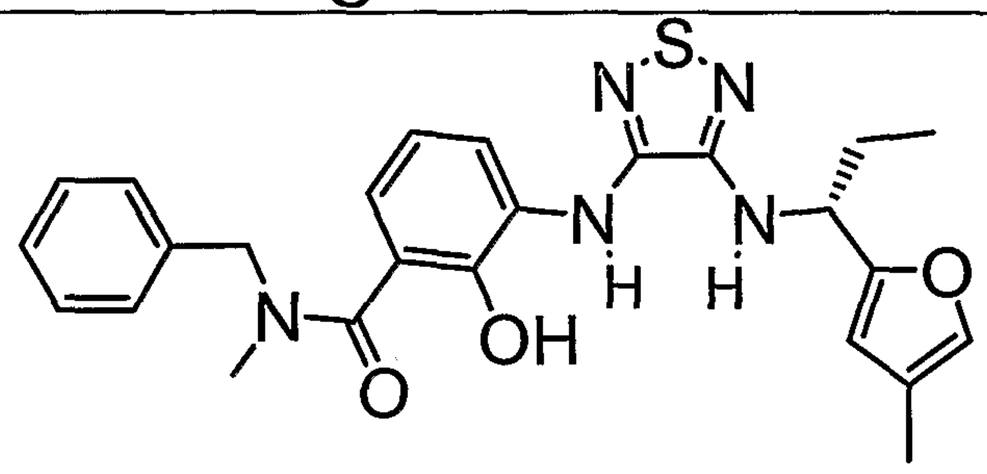
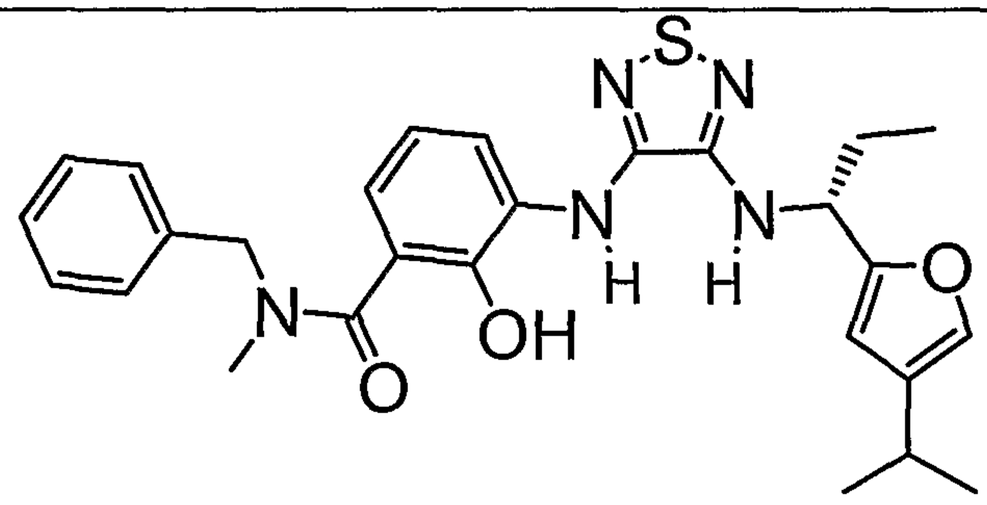
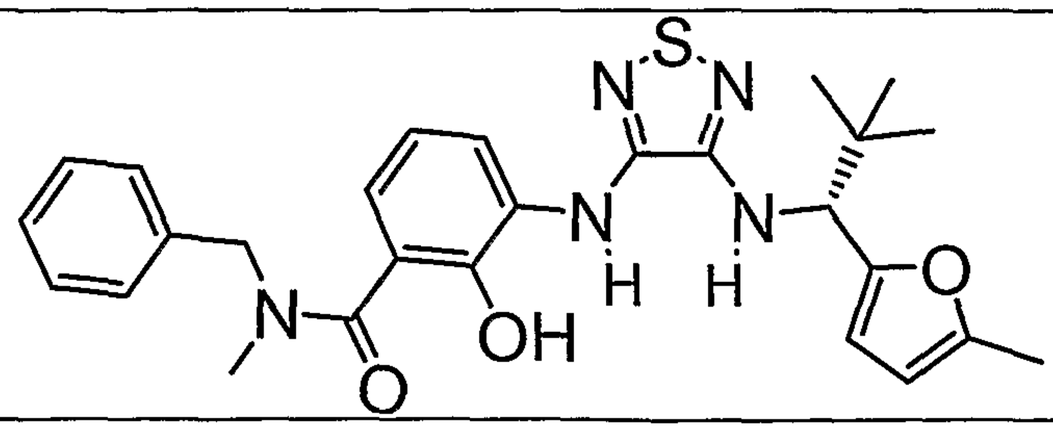
352	2452	
353	2453	
354	2454	
355	2455	
356	2456	
357	2457	
358	2458	

359	2459	
360	2460	
361	2461	
362	2462	
363	2463	
364	2464	

365	2465	
366	2466	
367	2467	
368	2468	
369	2469	
370	2470	

371	2471	
372	2472	
373	2473	
374	2474	
375	2475	
376	2476	

377	2477	
378	2478	
379	2479	
380	2480	
381	2481	
382	2482	

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	2
CONTENANT LES PAGES	1	À	495

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME	1	OF	2
CONTAINING PAGES	1	TO	495

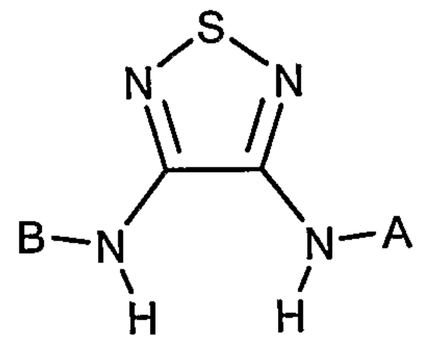
NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

WHAT IS CLAIMED IS:

1. A compound of the formula:

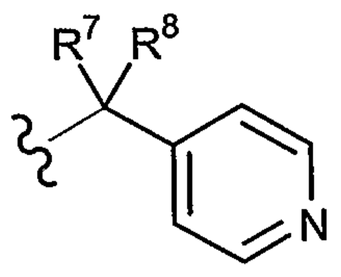


(IA)

and the pharmaceutically acceptable salts thereof, wherein:

A is selected from the group consisting of:

(1)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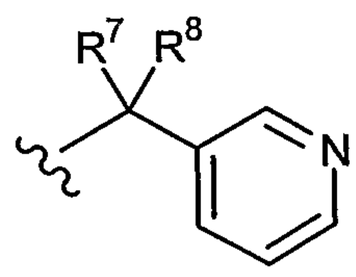
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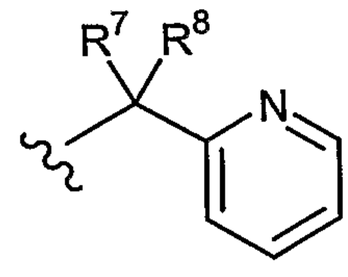
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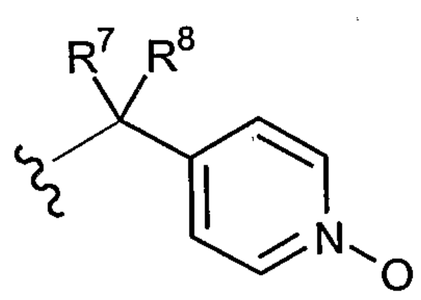
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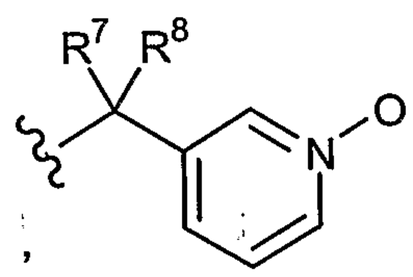
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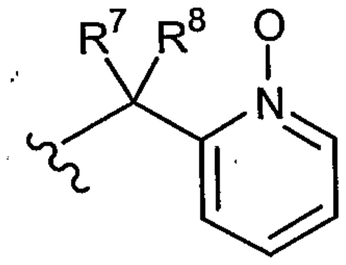
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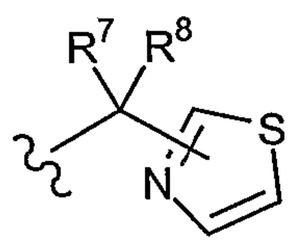
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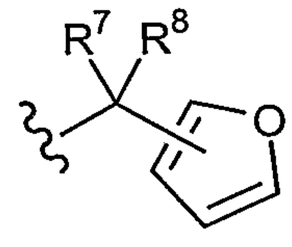
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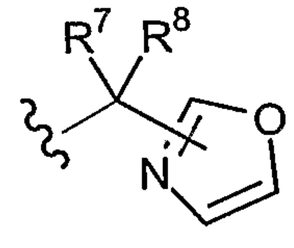
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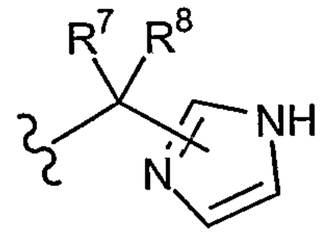
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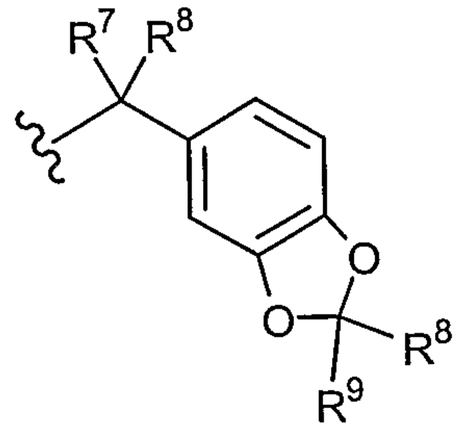
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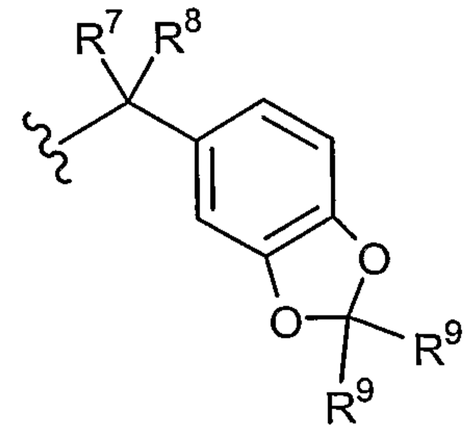
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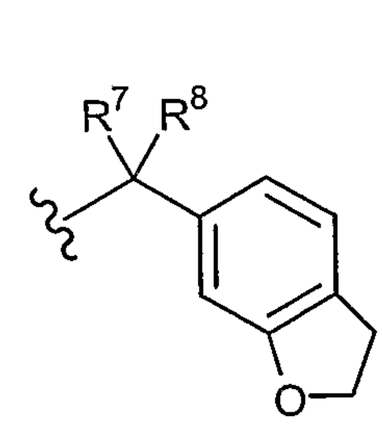
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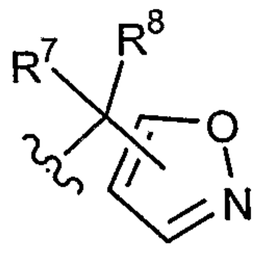
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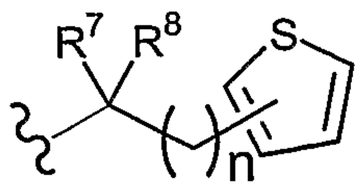
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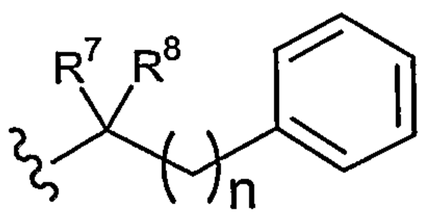
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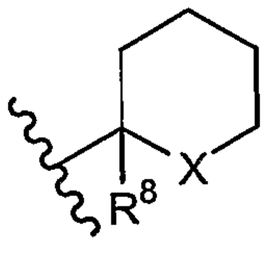
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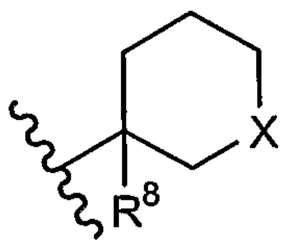
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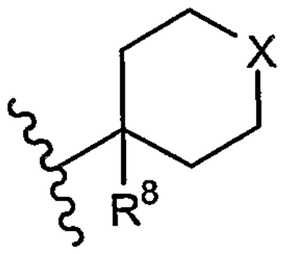
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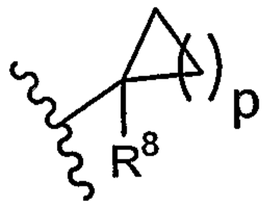
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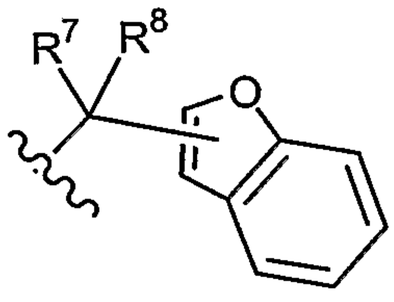
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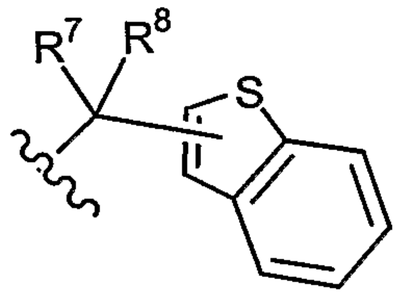
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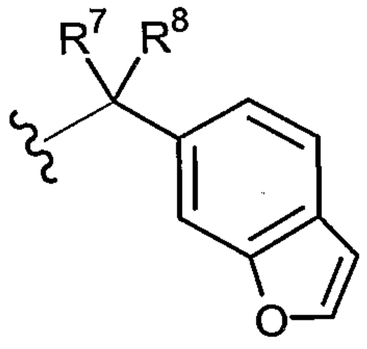
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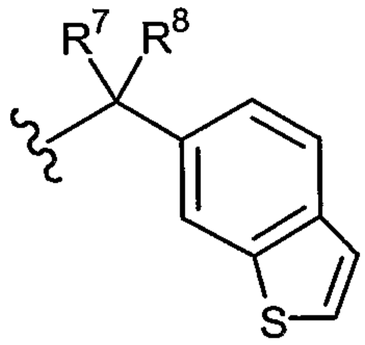
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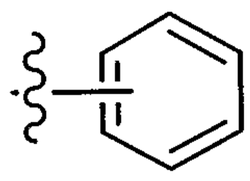
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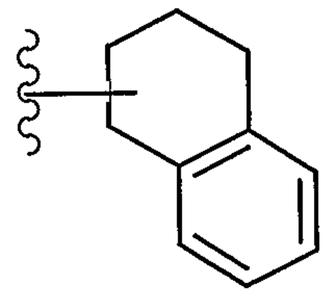
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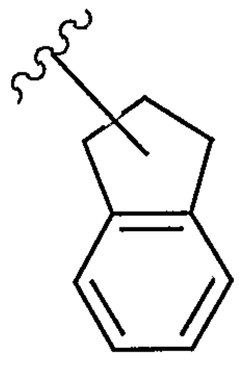
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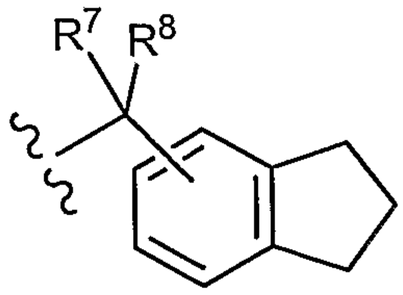
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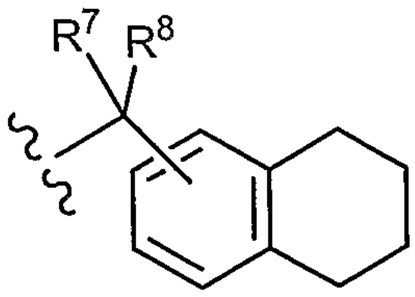
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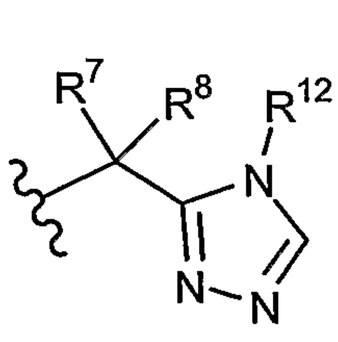
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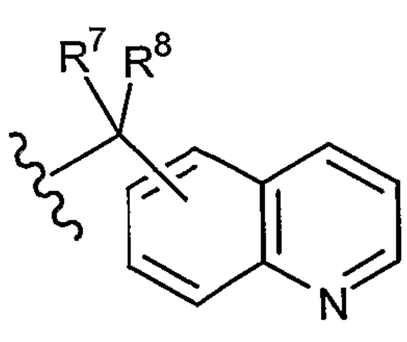
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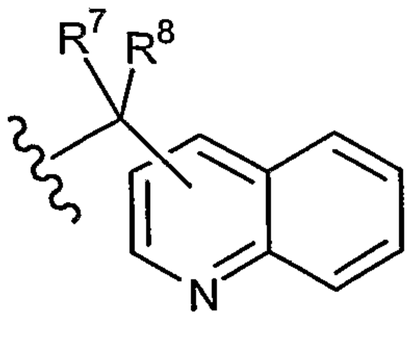
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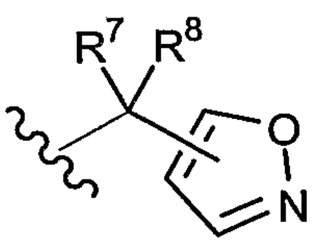
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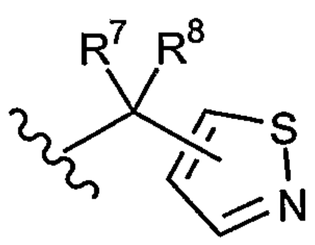
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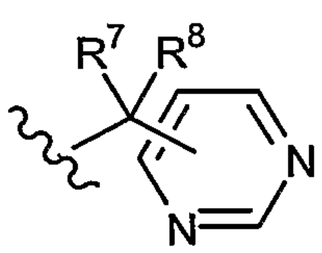
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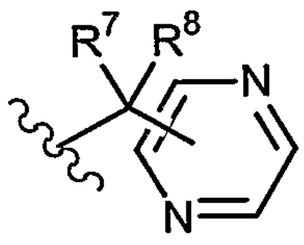
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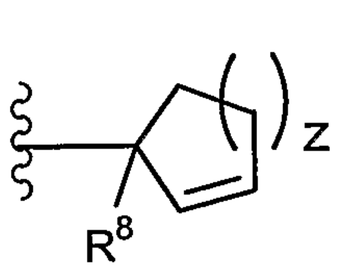
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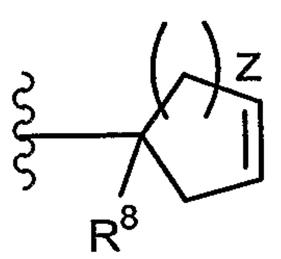
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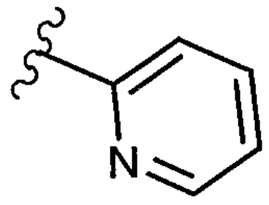
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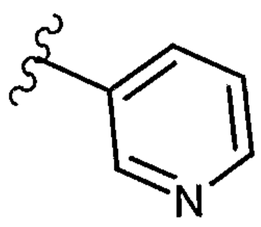
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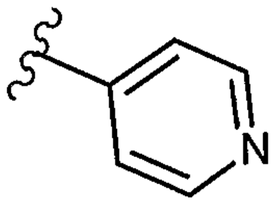
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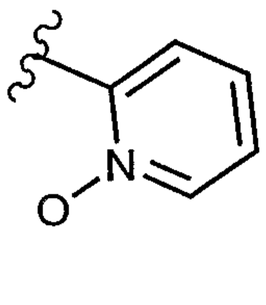
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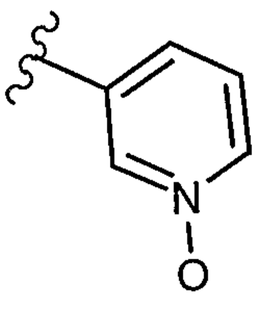
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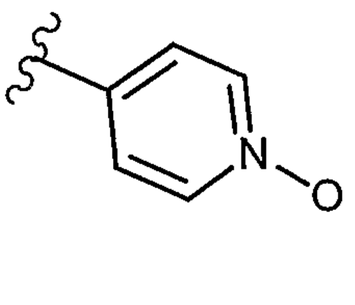
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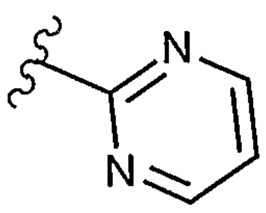
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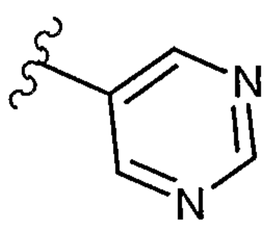
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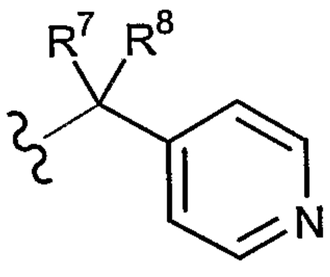
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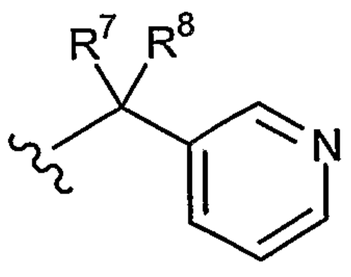
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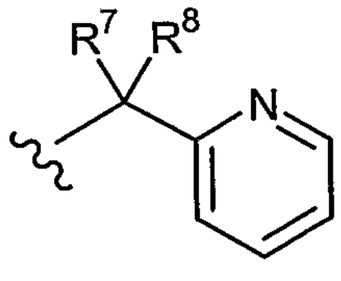
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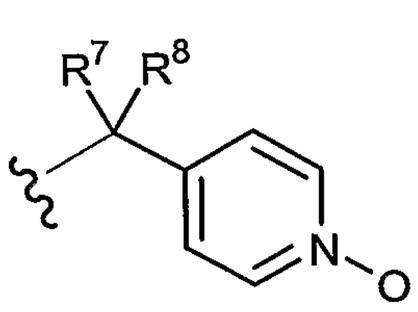
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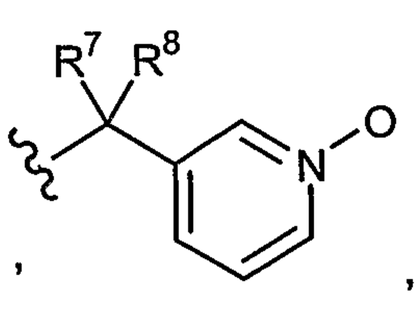
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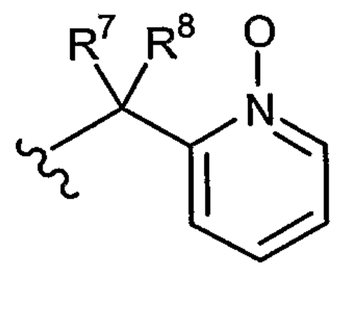
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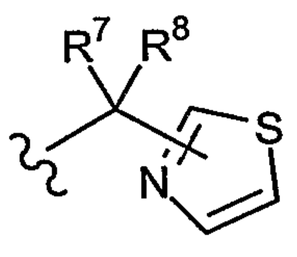
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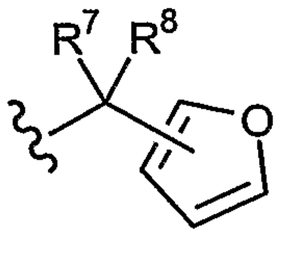
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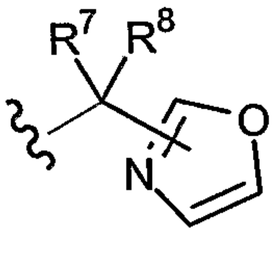
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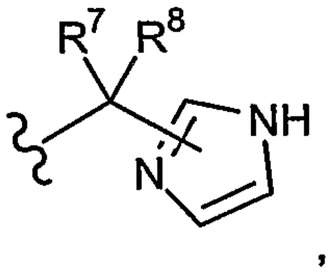
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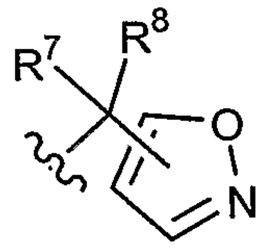
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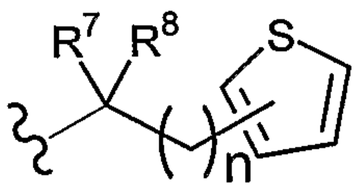
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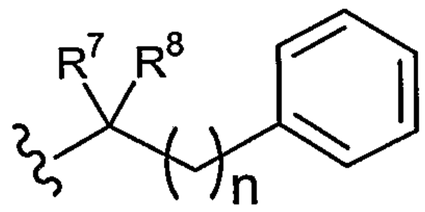
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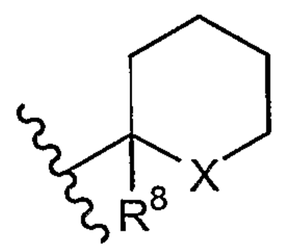
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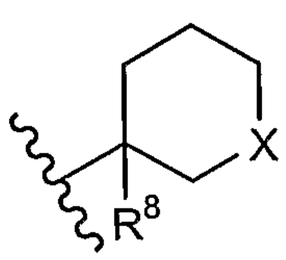
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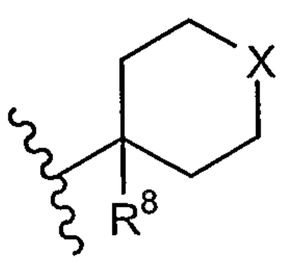
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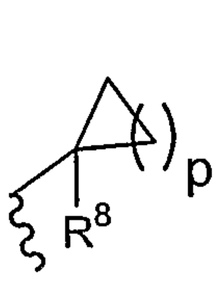
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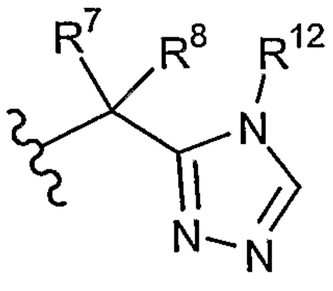
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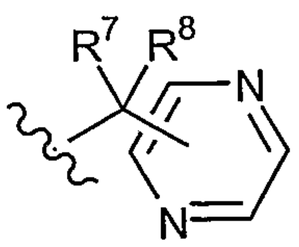
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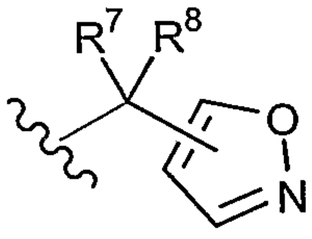
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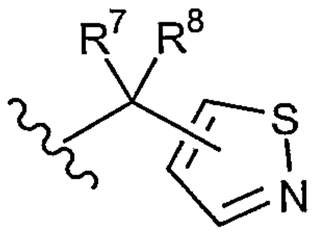
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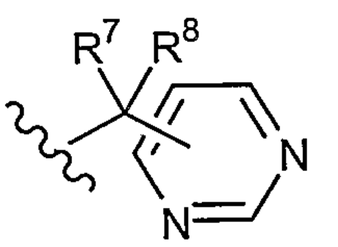
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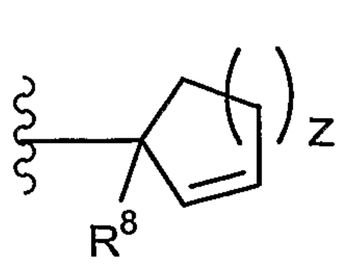
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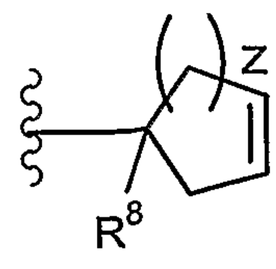
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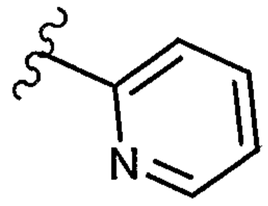
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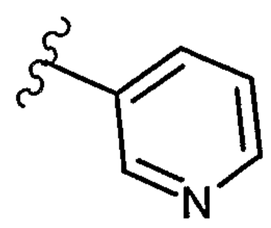
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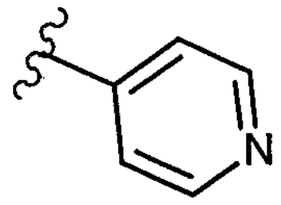
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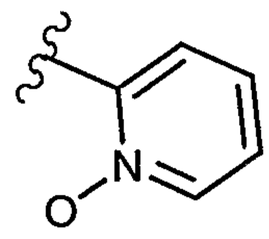
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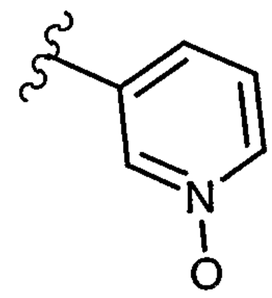
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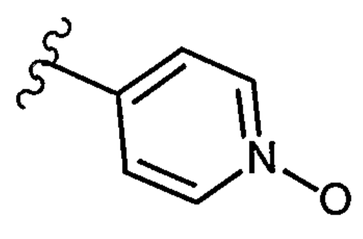
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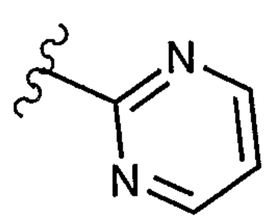
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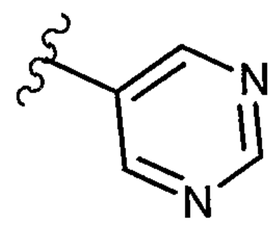
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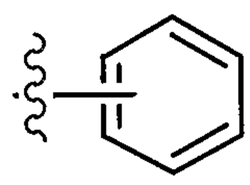
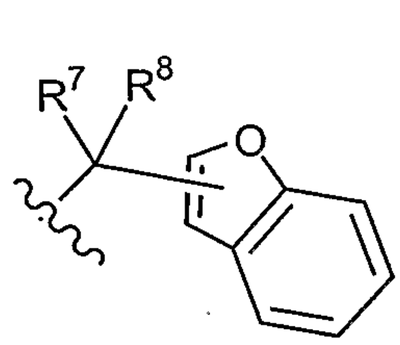

,

wherein the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

(3)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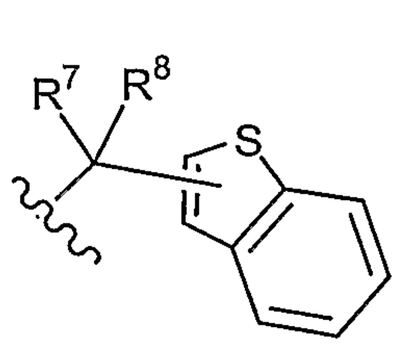
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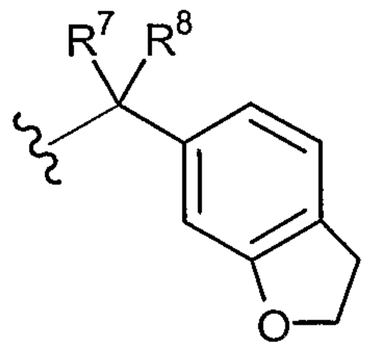
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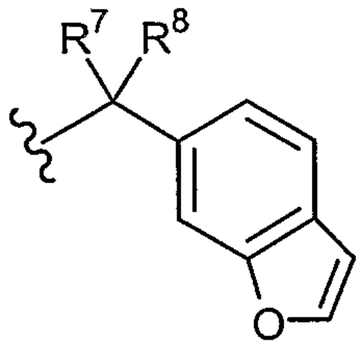
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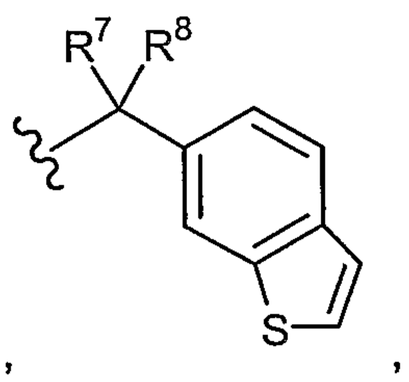
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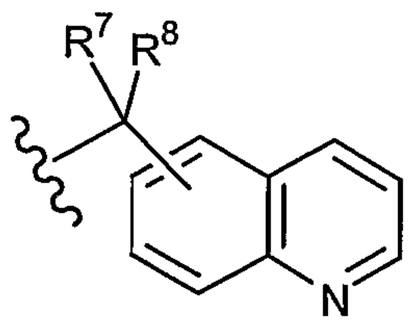
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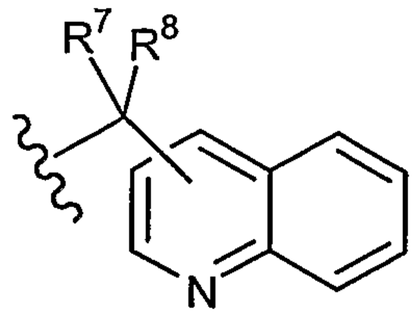
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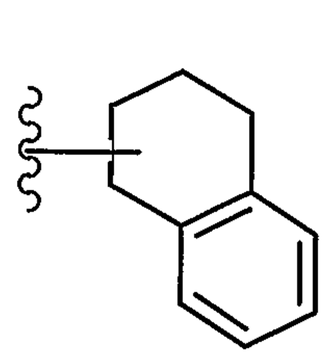
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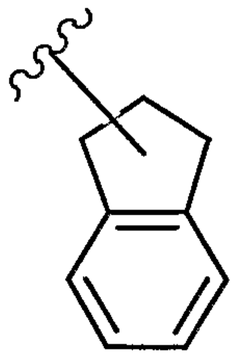

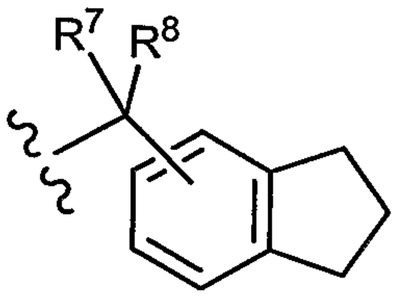
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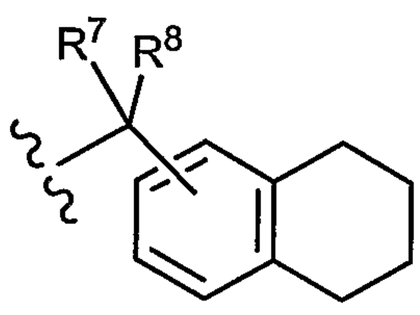
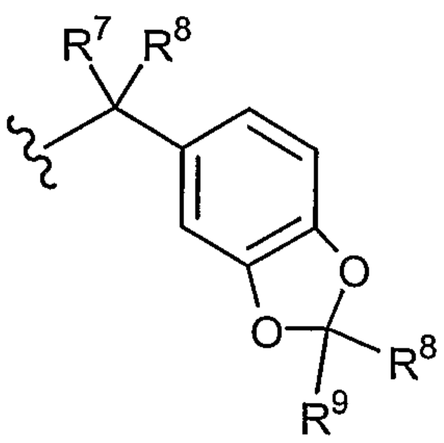

,

wherein one or both of the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

(4)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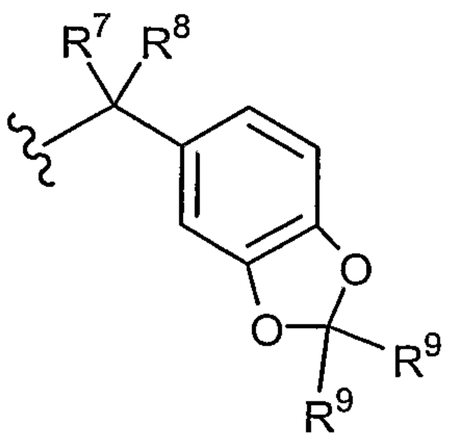
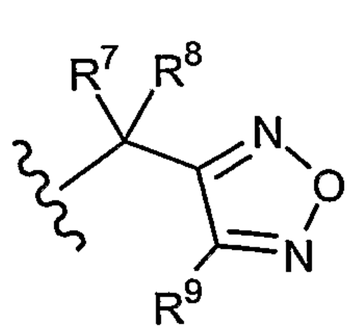


wherein the above phenyl rings of said A groups are substituted with 1 to 3 substituents each independently selected from the group consisting of: R^9 groups; and

(5)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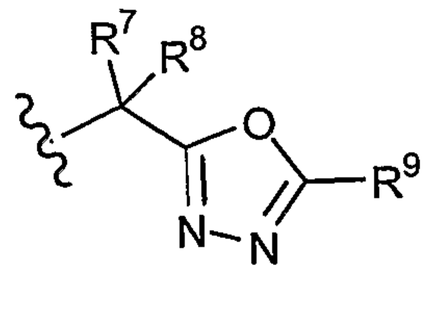
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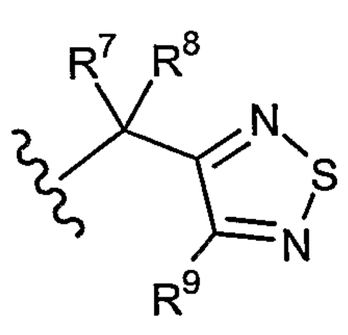
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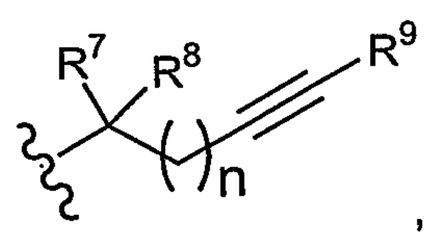
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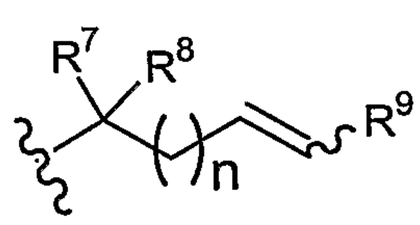
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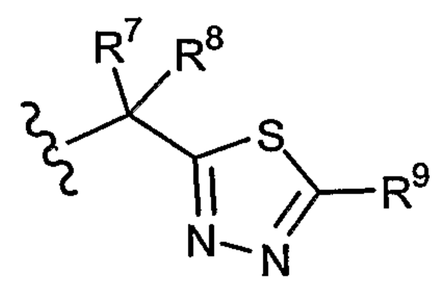
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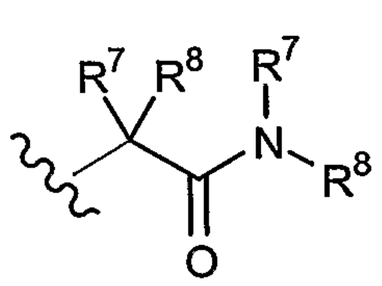
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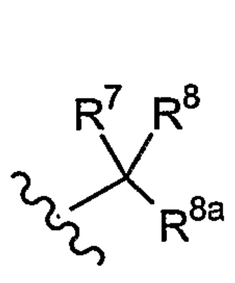
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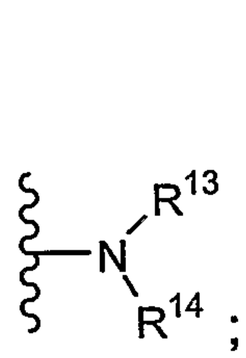
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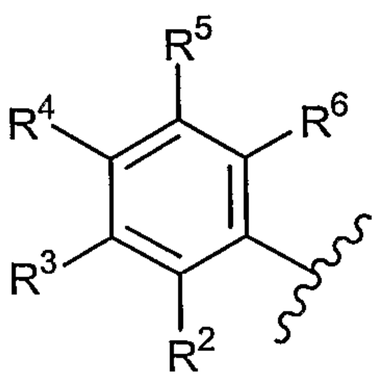
B is selected from the group consisting of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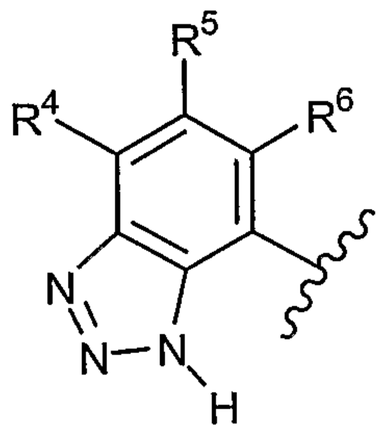
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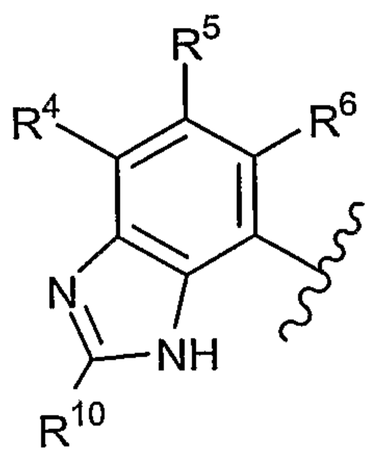
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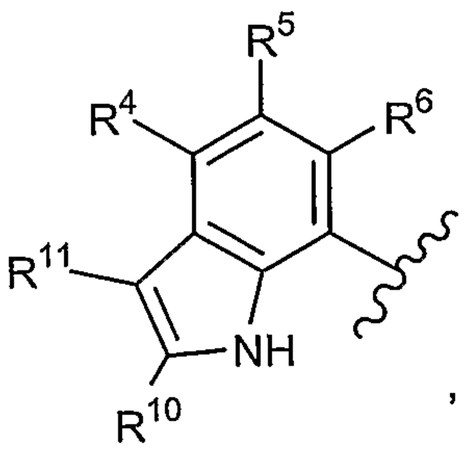
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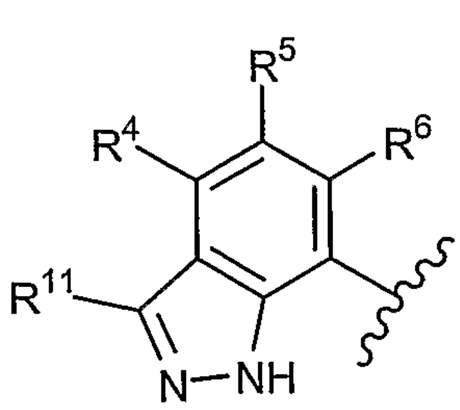
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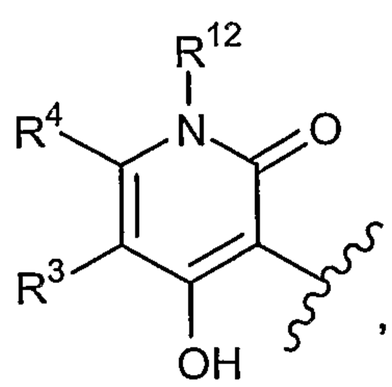
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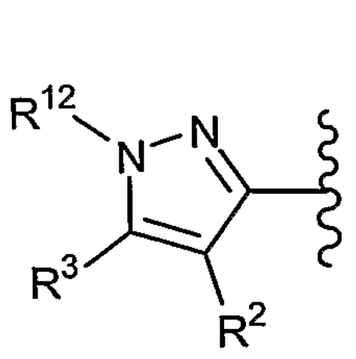
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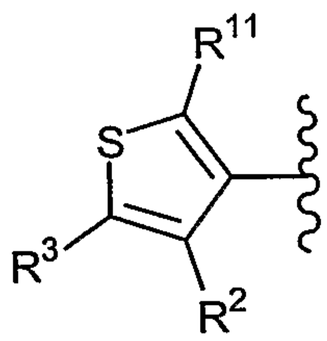
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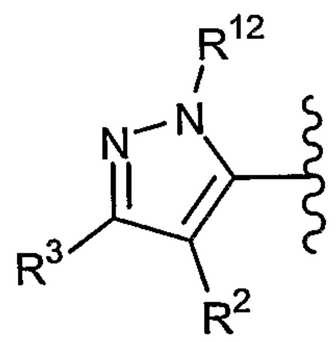
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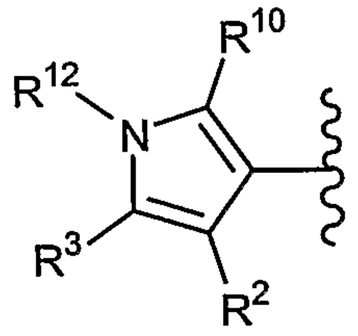
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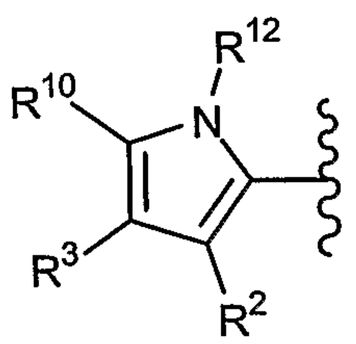
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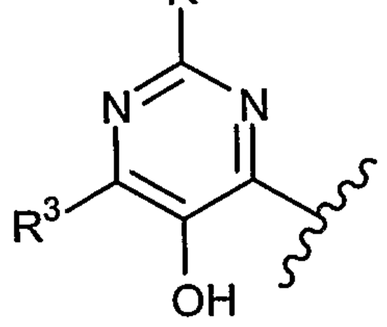
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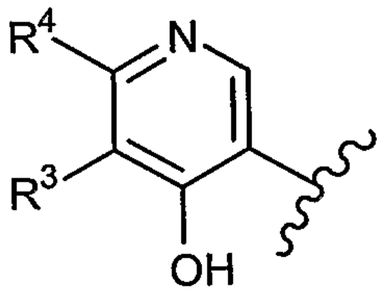
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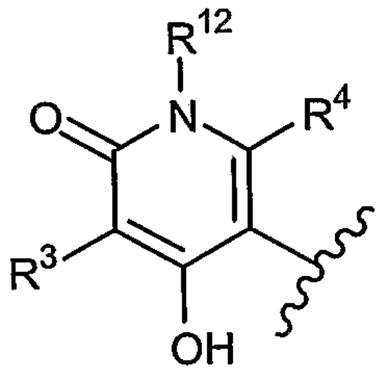
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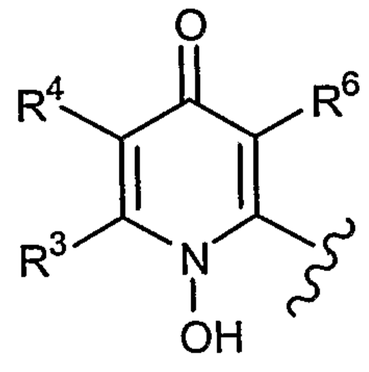
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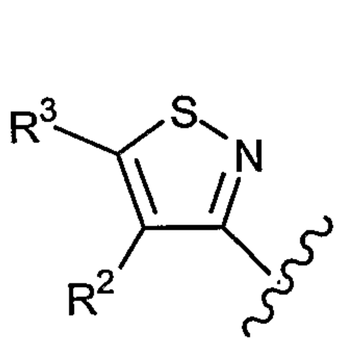
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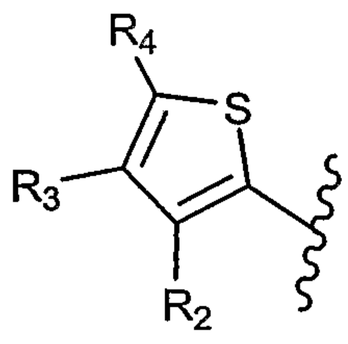
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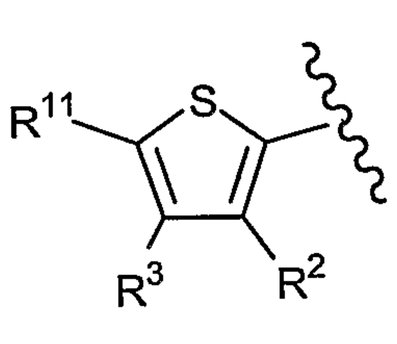

;

n is 0 to 6;

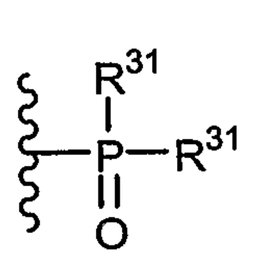
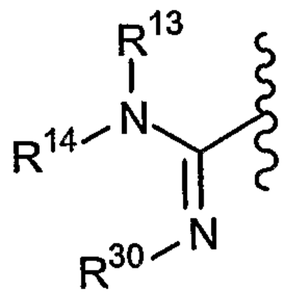
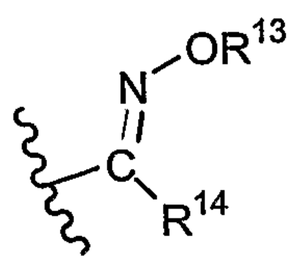
p is 1 to 5;

X is O, NR^{18}, or S;

Z is 1 to 3;

R^2 is selected from the group consisting of: hydrogen, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, - $S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

each R^3 and R^4 is independently selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, cycloalkyl substituted with 1 to 4 alkyl groups wherein each alkyl group is independently selected, unsubstituted cycloalkyl, cycloalkyl substituted with 1 to 4 alkyl groups, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,


, 
and 
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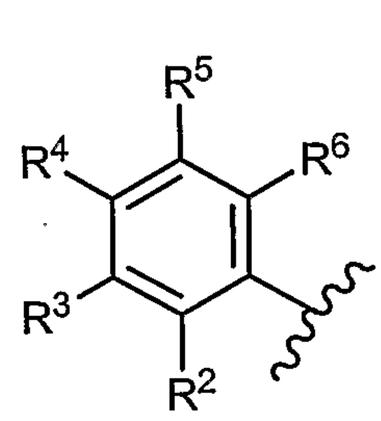
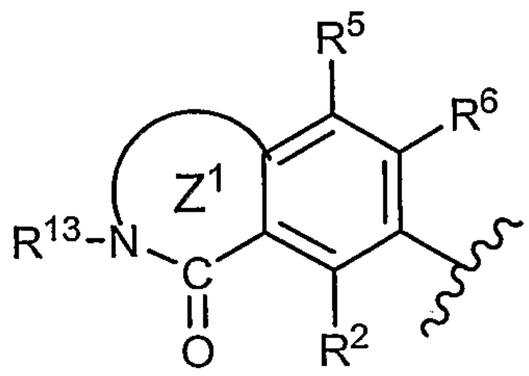
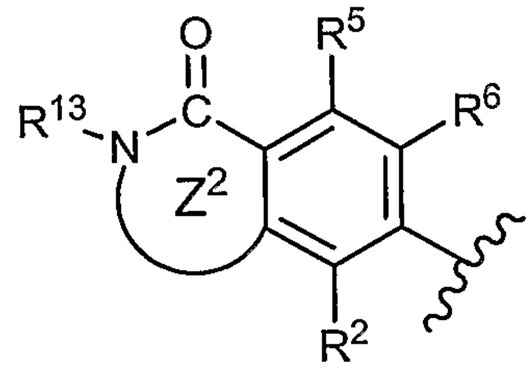
wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups; or

R^3 is and R^4 taken together with the carbons atoms to which they are bonded to in the the phenyl B substituent



form a fused ring of the formula:


or 

wherein Z^1 or Z^2 is an unsubstituted or substituted saturated heterocyclic ring (preferably a 4 to 7 membered heterocyclic ring), said ring Z^1 or Z^2 optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on said ring Z^1 or Z^2, and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$,

$-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$, $-NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group;

each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; and wherein there are one or more substituents on said substituted R^7 and R^8 groups, wherein each substitutent is independently selected from the group consisting of:

a) halogen,
b) $-CF_3$,
c) $-COR^{13}$,
d) $-OR^{13}$,
e) $-NR^{13}R^{14}$,
f) $-NO_2$,
g) $-CN$,
h) $-SO_2OR^{13}$,
i) $-Si(alkyl)_3$, wherein each alkyl is independently selected,
j) $-Si(aryl)_3$, wherein each alkyl is independently selected,
k) $-(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
l) $-CO_2R^{13}$,
m) $-C(O)NR^{13}R^{14}$,
n) $-SO_2NR^{13}R^{14}$,
o) $-SO_2R^{13}$,
p) $-OC(O)R^{13}$,

q) –OC(O)NR^{13}R^{14},

r) –NR^{13}C(O)R^{14} , and

s) –NR^{13}CO$_2$R^{14};

(fluoroalkyl is one non-limiting example of an alkyl group that is substituted with halogen);

R^{8a} is selected from the group consisting of: hydrogen, alkyl, cycloalkyl and cycloalkylalkyl;

each R^9 is independently selected from the group consisting of:

a) -R^{13},

b) halogen,

c) -CF$_3$,

d) –COR^{13},

e) –OR^{13},

f) –NR^{13}R^{14},

g) -NO$_2$,

h) –CN,

i) -SO$_2$R^{13},

j) -SO$_2$NR^{13}R^{14},

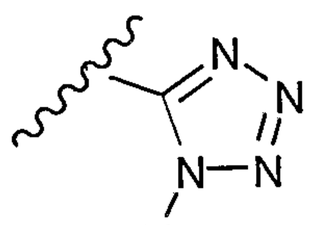
k) –NR^{13}COR^{14},

l) –CONR^{13}R^{14} ,

m) –NR^{13}CO$_2$R^{14},

n) -CO$_2$R^{13},

o)



,

p) alkyl substituted with one or more –OH groups,

q) alkyl substituted with one or more –NR^{13}R^{14} group, and

r) -N(R^{13})SO$_2$R^{14};

each R^{10} and R^{11} is independently selected from the group consisting of R^{13}, halogen, -CF$_3$, -OCF$_3$, -NR^{13}R^{14}, -NR^{13}C(O)NR^{13}R^{14}, -OH, -C(O)OR^{13}, -SH, -SO$_{(t)}$NR^{13}R^{14}, -SO$_2$R^{13}, -NHC(O)R^{13}, -NHSO$_2$NR^{13}R^{14}, -NHSO$_2$R^{13}, -C(O)NR^{13}R^{14}, -C(O)NR^{13}OR^{14}, -OC(O)R^{13} and cyano;

R^{12} is selected from the group consisting of: hydrogen, -C(O)OR^{13}, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6 substituents on the substituted R^{12} groups and each substituent is independently selected from the group consisting of: R^9 groups;

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted cyanoalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cyanocycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl (wherein "heterocyloalkyl" means heterocyclic); wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, -CF_3, -OH, alkoxy, aryl, arylalkyl, fluroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, -N(R^{40})$_2$, -C(O)OR^{15}, -C(O)$NR^{15}R^{16}$, -S(O)$_t$$NR^{15}R^{16}$, -C(O)$R^{15}$, halogen, -NHC(O)$NR^{15}R^{16}$ and -SO_2R^{15} provided that R^{15} is not H; and provided that for the substituted cyanoalkyl and the substituted cyanocycloalkyl moieties the carbon atom to which the cyano group is bound to does not also have bound to said carbon atom a substituent selected from the group consisting of: -OH, alkoxy, -N(R^{40})$_2$, halogen and -NHC(O)$NR^{15}R^{16}$; or

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups -C(O)$NR^{13}R^{14}$ and -$SO_2$$NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring, said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: CN, alkyl, cyanoalkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cyanocycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, -C(O)OR^{15}, -C(O)$NR^{15}R^{16}$, -$SO_t$$NR^{15}R^{16}$, -C(O)$R^{15}$, -$SO_2R^{15}$ (provided that R^{15} is not H), -NHC(O)$NR^{15}R^{16}$, -NHC(O)OR^{15}, halogen, and a heterocycloalkenyl group; and provided that the carbon

atom to which the cyano group is bound to does not also have bound to said carbon atom a substituent selected from the group consisting of: hydroxy, alkoxy, amino, halogen, -NHC(O)$NR^{15}R^{16}$ and -NHC(O)OR^{15};

each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: -SO_2alkyl, -SO_2aryl, -SO_2cycloalkyl, and -SO_2heteroaryl;

R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, -C(O)R^{19}, -SO_2R^{19} and -C(O)$NR^{19}R^{20}$;

each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl;

R^{30} is selected from the group consisting of: alkyl, cycloalkyl, -CN, -NO_2, or -SO_2R^{15} provided that R^{15} is not H;

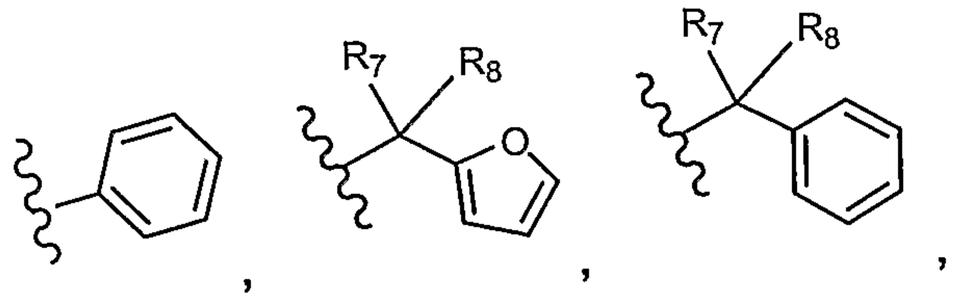
each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6 substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and -CF_3;

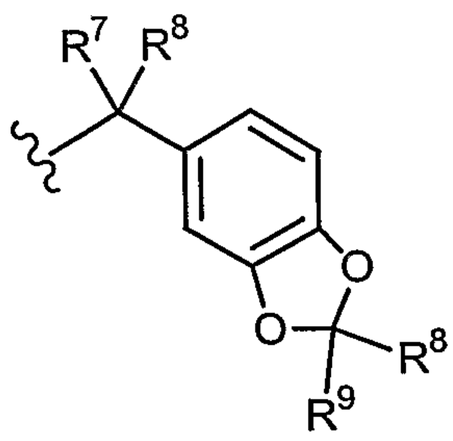
each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

t is 0, 1 or 2.

2. The compound of claim 1 wherein A is selected from the group consisting of:

(1) unsubstituted or substituted:

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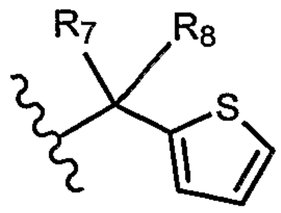
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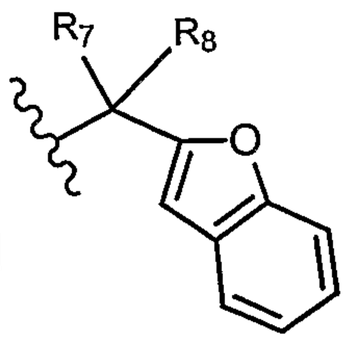
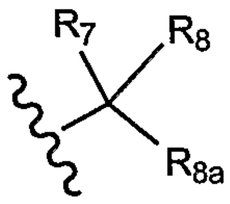

; and

(2)



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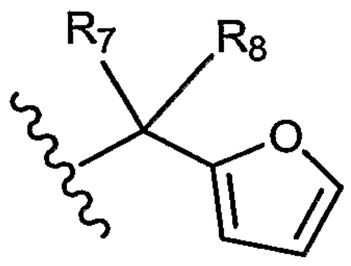
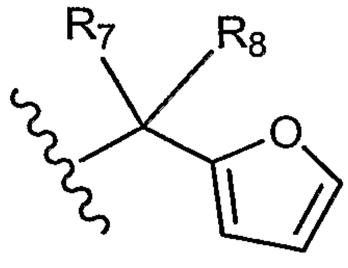
3. The compound of Claim 1 wherein substituent A is:



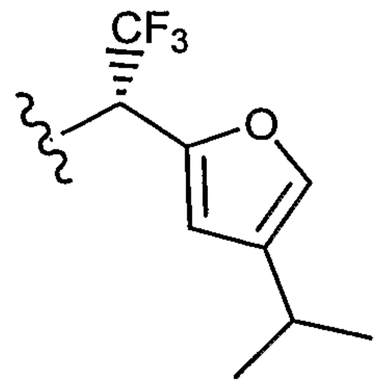
wherein the furan ring is unsubstituted or substituted with 1 or 2 alkyl groups wherein each alkyl group is independently selected, R^7 is selected from the group consisting of: $-CF_3$, alkyl and cycloalkyl, and R^8 is H.

4. The compound of Claim 1 wherein substituent A is:



wherein the furan ring is substituted with 1 or 2 alkyl groups independently selected from the group consisting of methyl, ethyl and isopropyl, R^7 is selected from the group consisting of: ethyl, isopropyl and t-butyl, and R^8 is H.

5. The compound of Claim 1 wherein A is selected from the group consisting of: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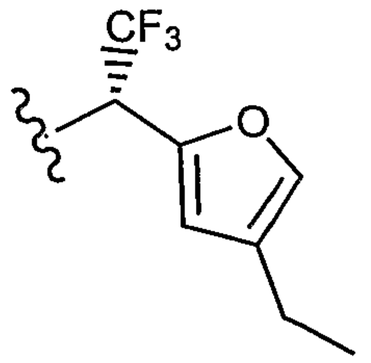
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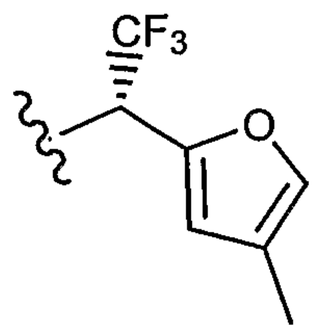
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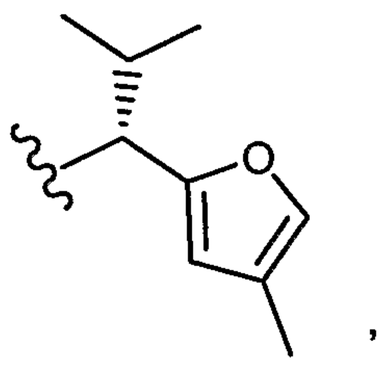
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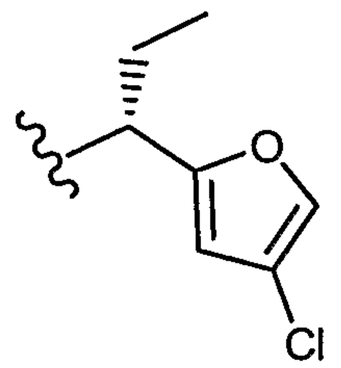
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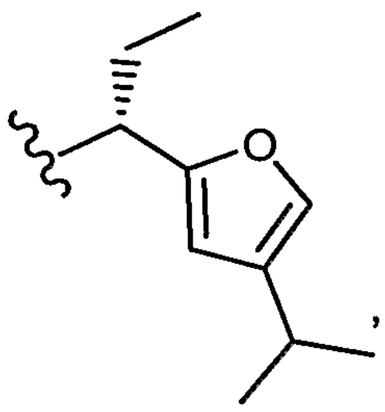
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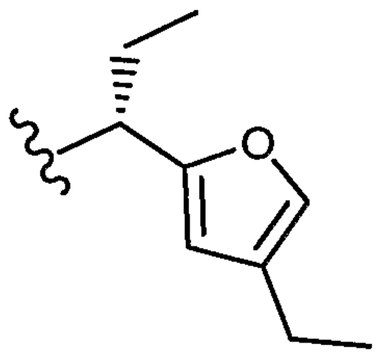
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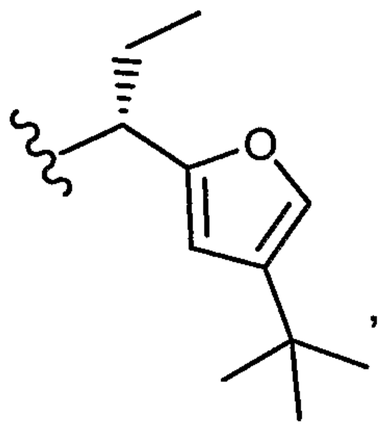
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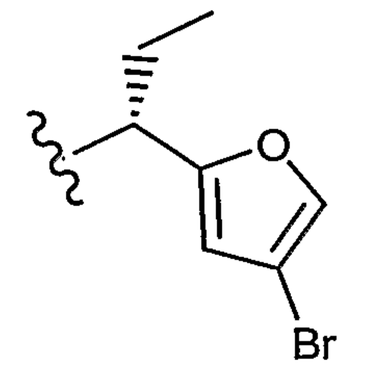
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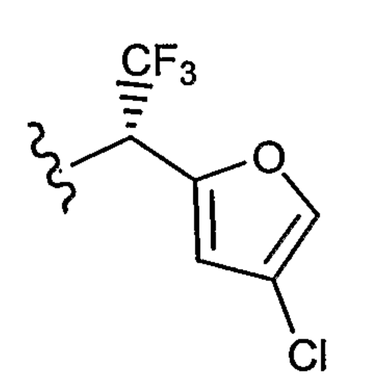
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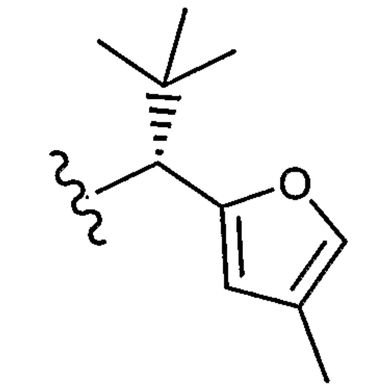
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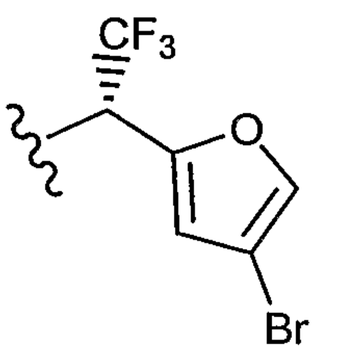
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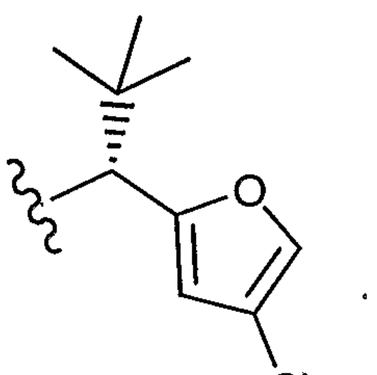
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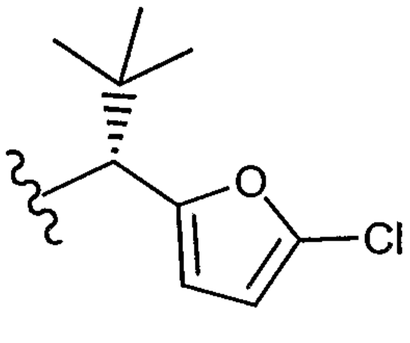
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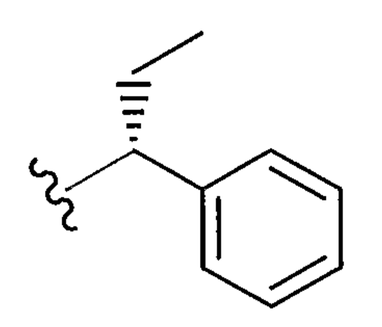
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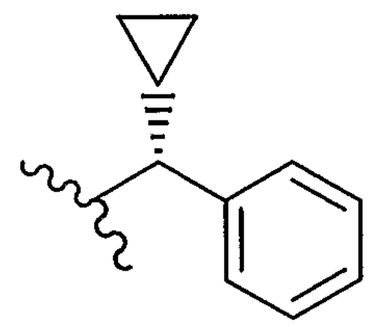
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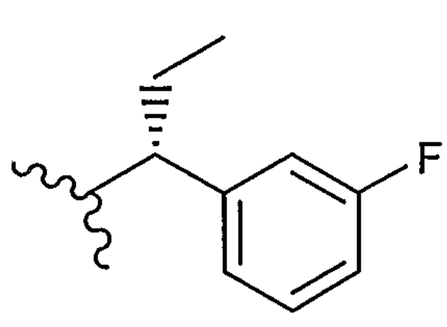
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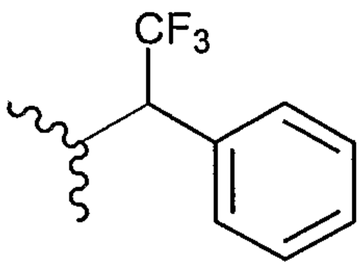
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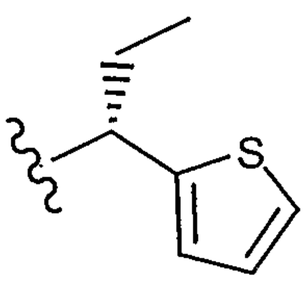
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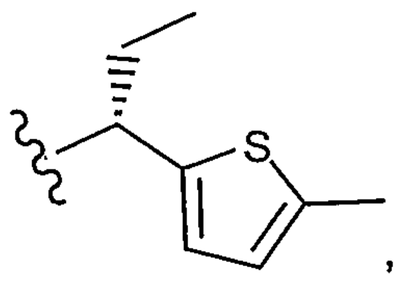
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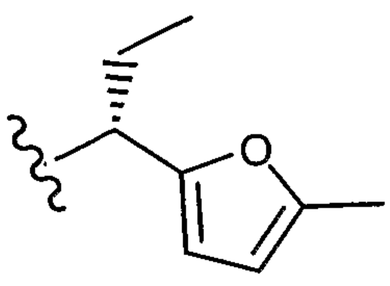
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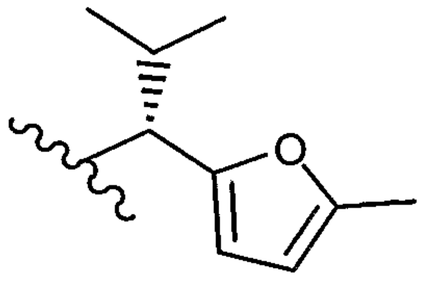
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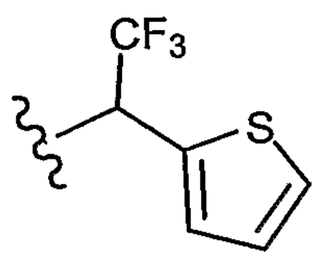
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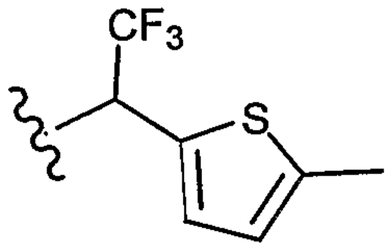
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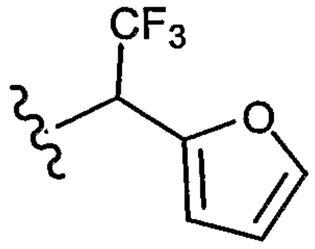
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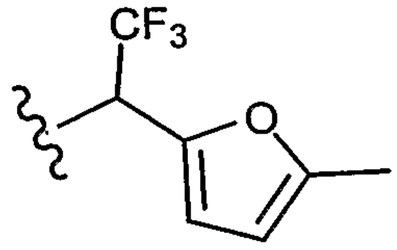
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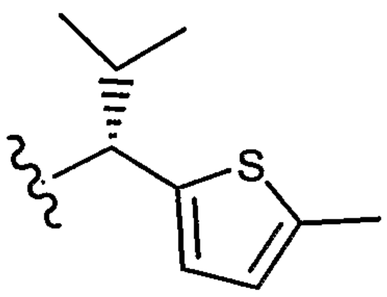
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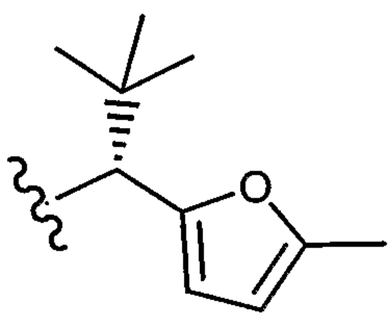
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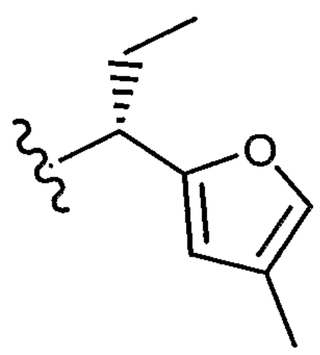
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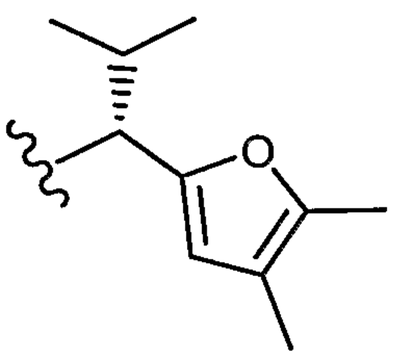
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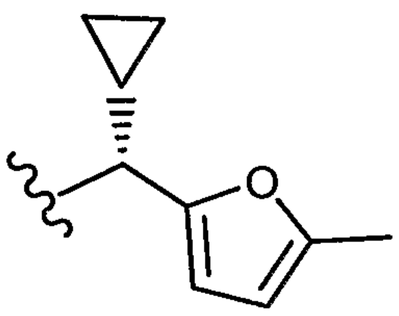
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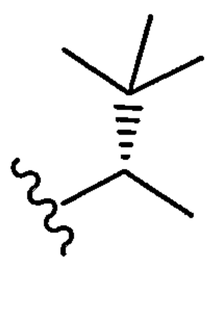
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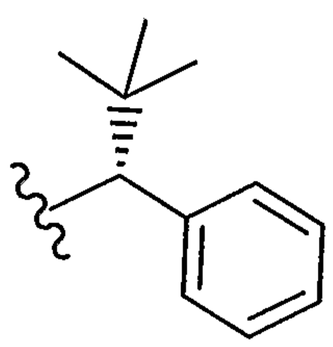
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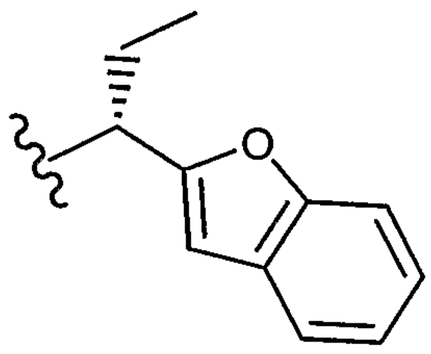
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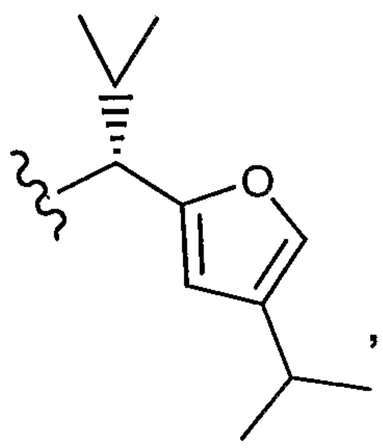
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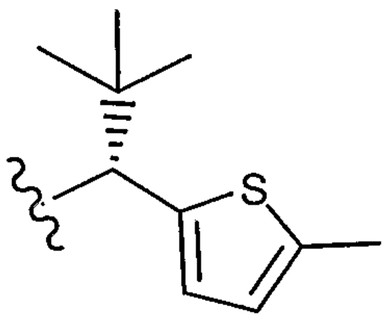
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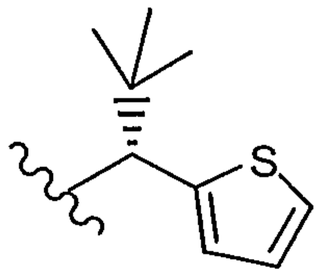
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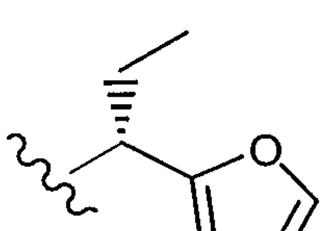
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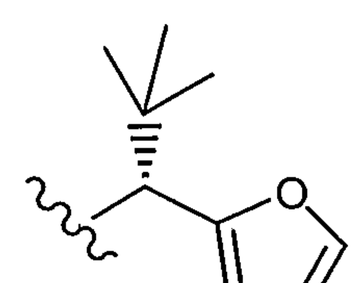
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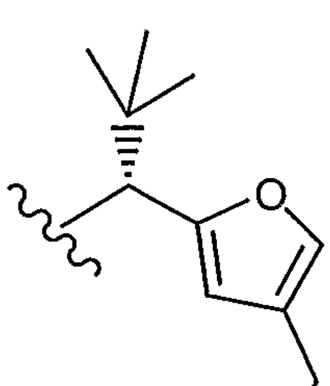
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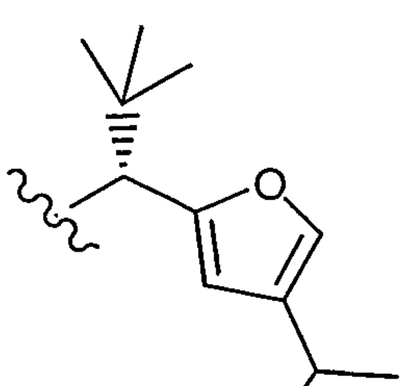
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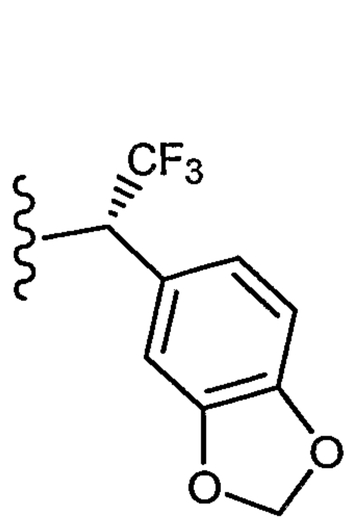
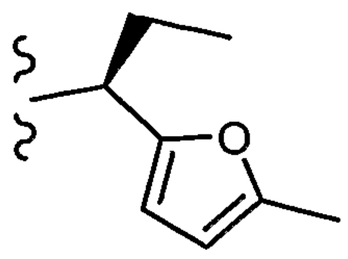
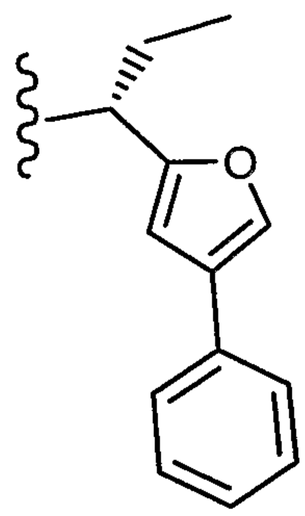
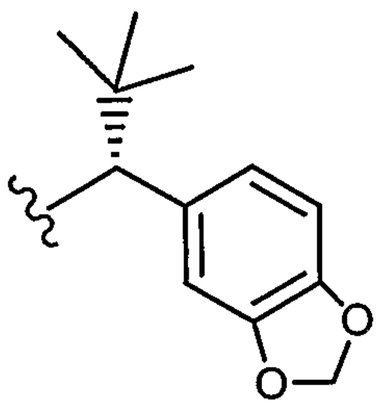
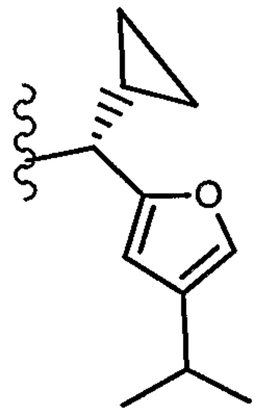
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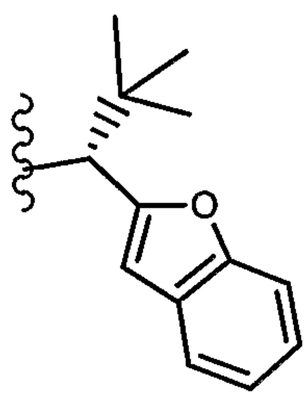
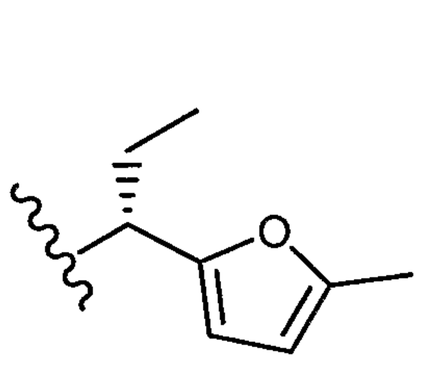
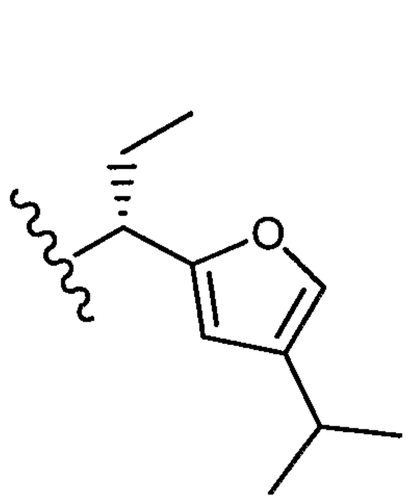
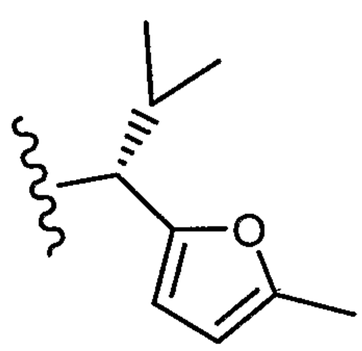
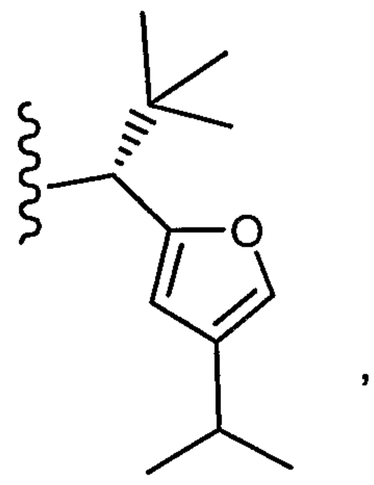
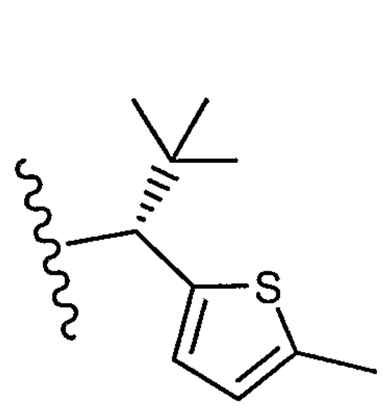
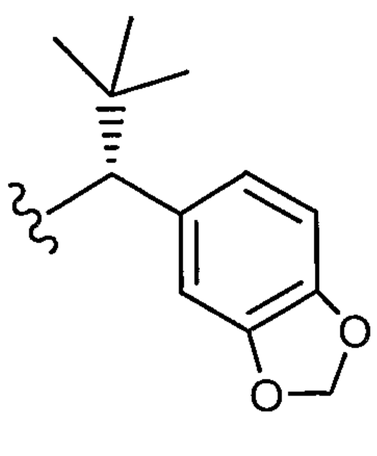
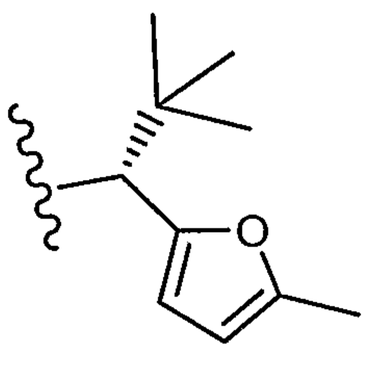
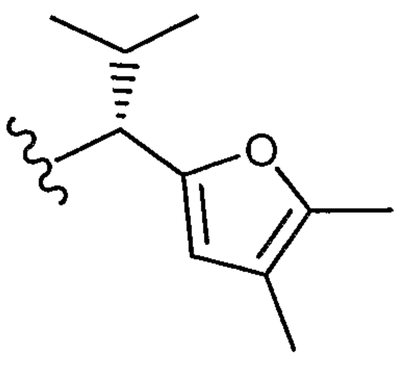
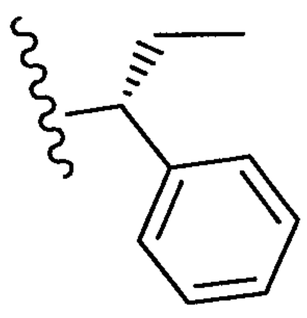


6. The compound of claim 1 wherein A is selected from the group consisting of: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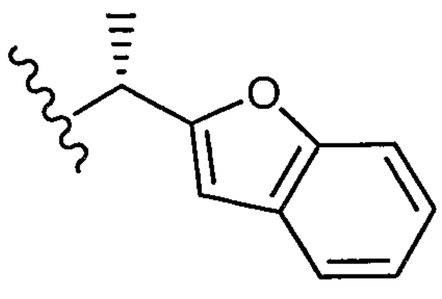
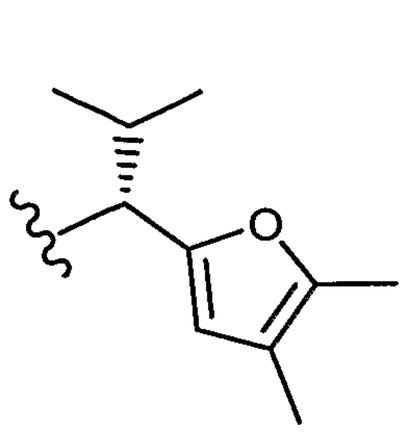


7. The compound of Claim 1 wherein substituent A is selected from the group consisting of: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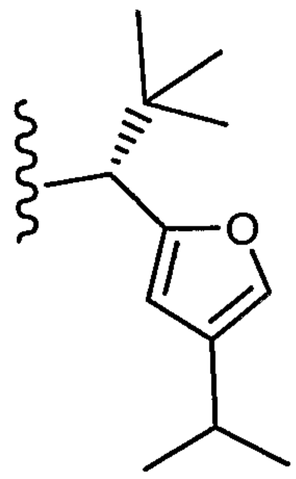
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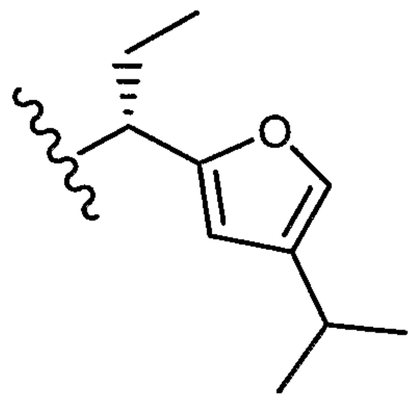
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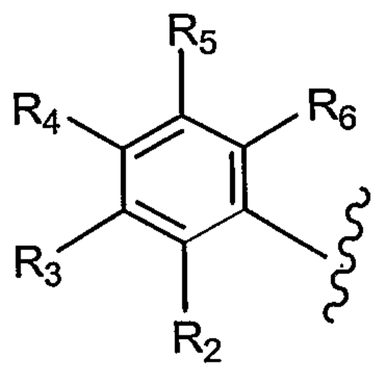
8. The compound of Claim 1 wherein B is selected from the group consisting of: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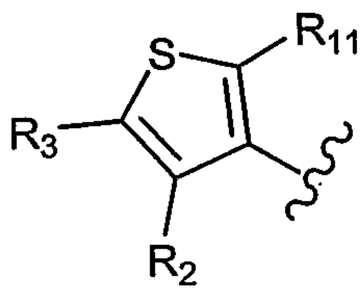
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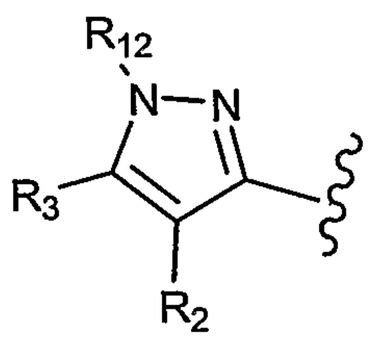
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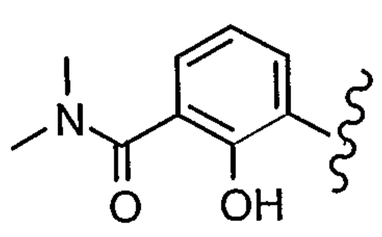
9. The compound of Claim 1 wherein B is selected from the group consisting of: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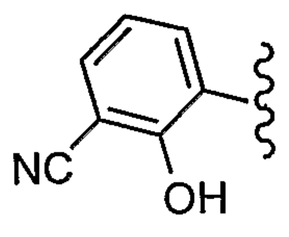
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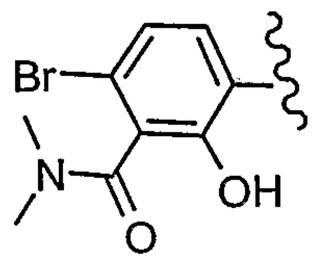
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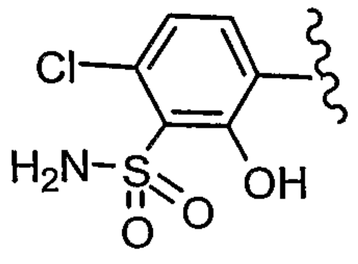
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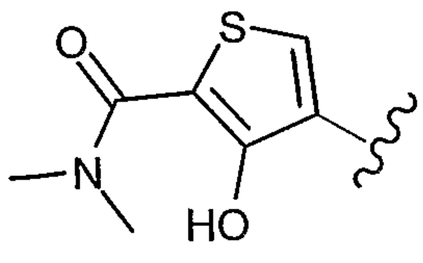
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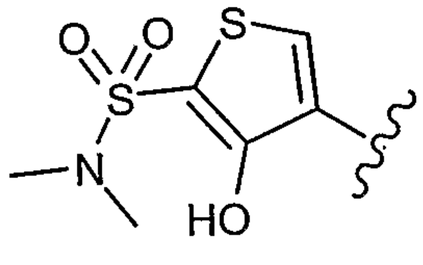
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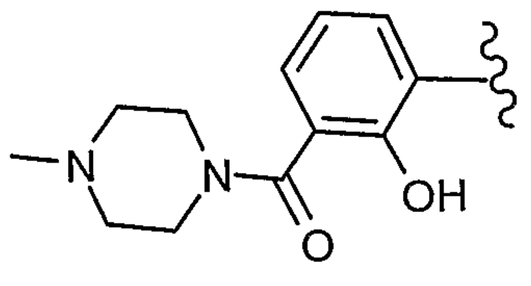
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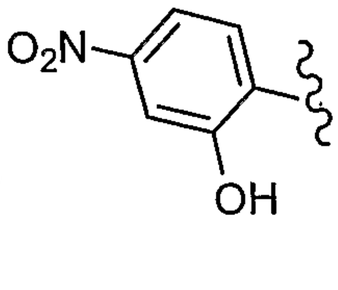
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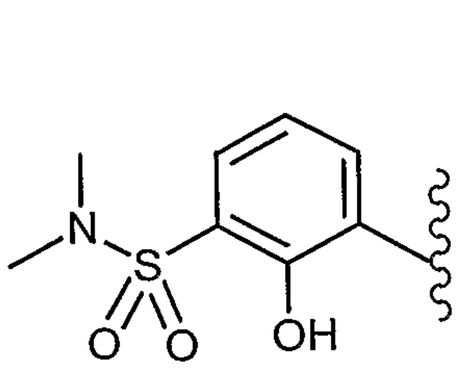
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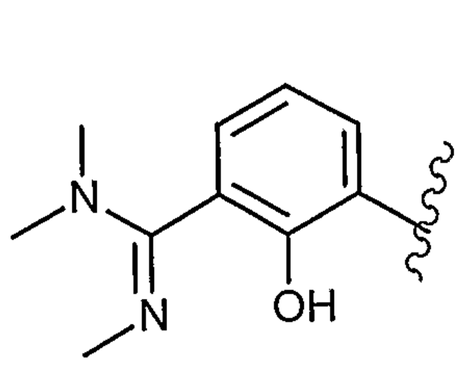
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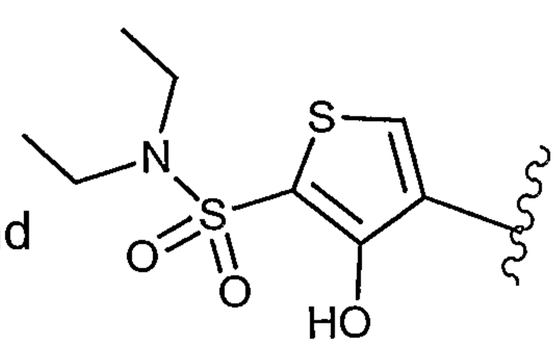
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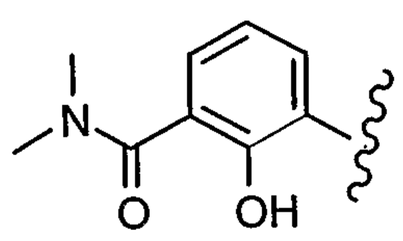
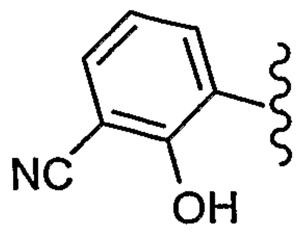
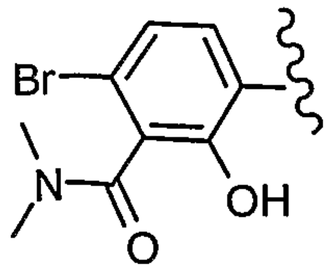
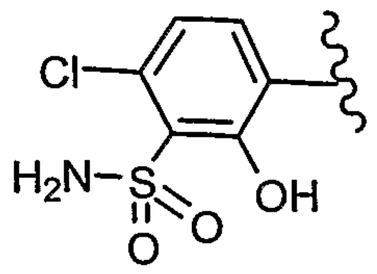
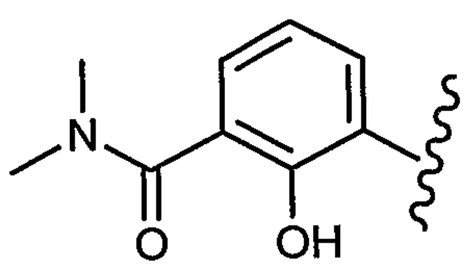
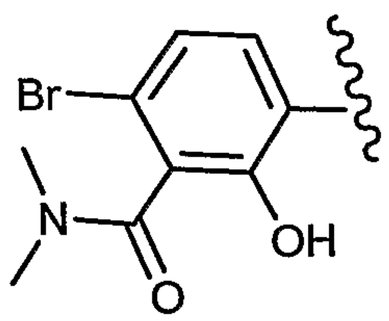
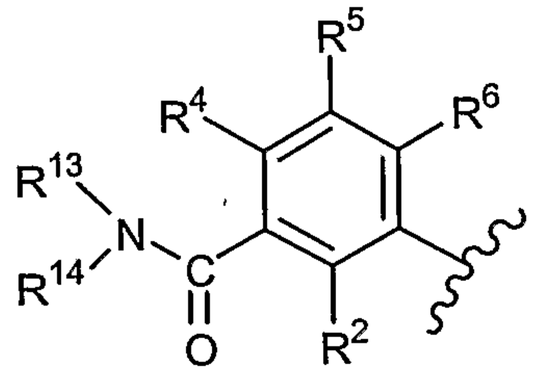
10. The compound of Claim 1 wherein B is selected from the group consisting of:




and


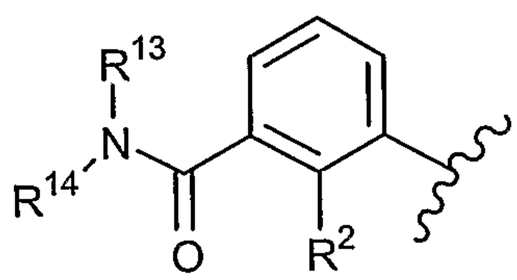
11. The compound of Claim 1 wherein B is selected from the group consisting of:


and


12. The compound of Claim 1 wherein B is

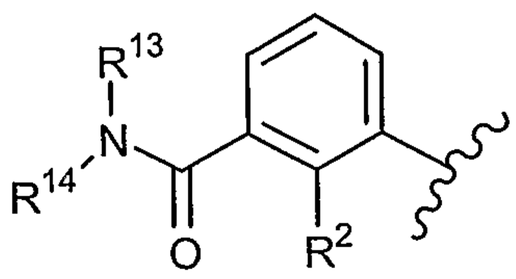


13. The compound of Claim 1 wherein B is:



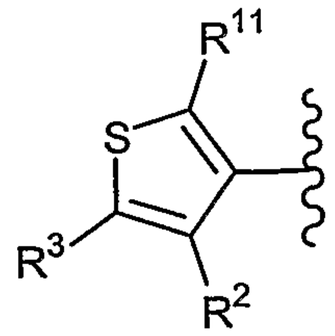
wherein R^2 is –OH.

14. The compound of Claim 1 wherein B is:



wherein R^2 is–OH, and R^{13} and R^{14} are independently selected from the group consisting of H and alkyl.

15. The compound of Claim 1 wherein B is



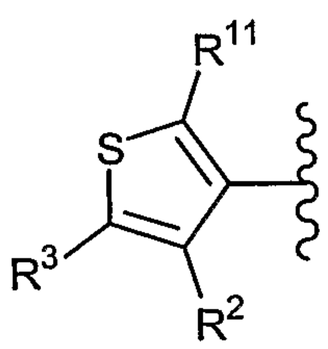
16. The compound of Claim 15 wherein R^{11} is H.

17. The compound of Claim 16 wherein R^2 is –OH.

18. The compound of Claim 17 wherein R^3 is $-C(O)NR^{13}R^{14}$.

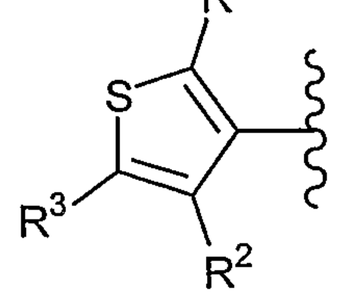
19. The compound of Claim 17 wherein R^3 is $-S(O)_tNR^{13}R^{14}$.

20. The compound of Claim 1 wherein B is:



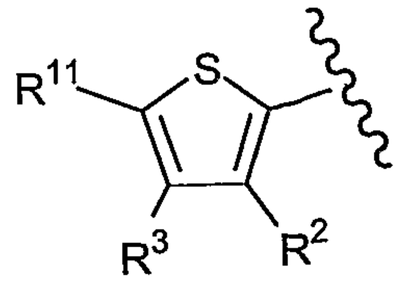
wherein R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H or methyl, and R^{13} and R^{14} are independently selected from the group consisting of: H, alkyl, unsubstituted cycloalkyl, substituted cycloalkyl, unsubstituted heteroaryl and substituted heteroaryl.

21. The compound of Claim 1 wherein B is:



wherein R^2 is –OH, R^3 is $-S(O)_tNR^{13}R^{14}$, R^{11} is H or methyl, and R^{13} and R^{14} are independently selected from the group consisting of H, alkyl, unsubstituted cycloalkyl and substituted cycloalkyl.

22. The compound of Claim 1 wherein B is:



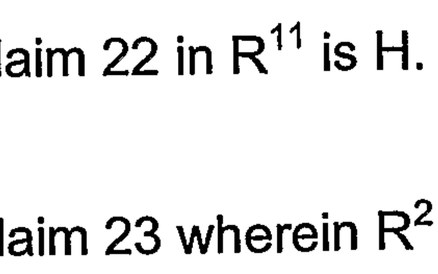
23. The compound of Claim 22 in R^{11} is H.

24. The compound of Claim 23 wherein R^2 is –OH.

25. The compound of Claim 24 wherein R^3 is $-C(O)NR^{13}R^{14}$.

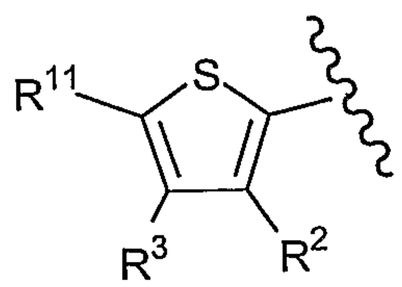
26. The compound of Claim 24 wherein R^3 is $-S(O)_tNR^{13}R^{14}$.

27. The compound of Claim 1 wherein B is:



wherein R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H, and R^{13} and R^{14} are independently selected from the group consisting of: H, alkyl, unsubstituted heteroaryl and substituted heteroaryl.

28. The compound of Claim 1 wherein B is:

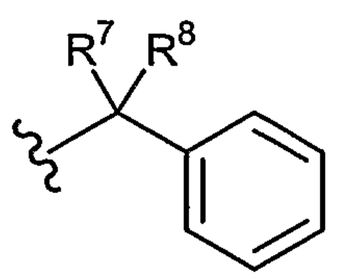
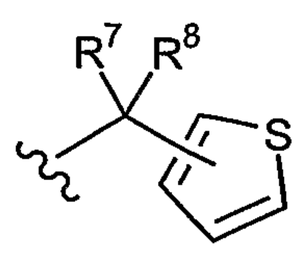
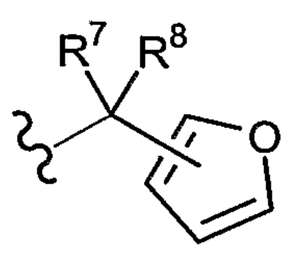


wherein R^2 is –OH, R^3 is $-S(O)_tNR^{13}R^{14}$, R^{11} is H, and R^{13} and R^{14} are independently selected from the group consisting of H and alkyl.

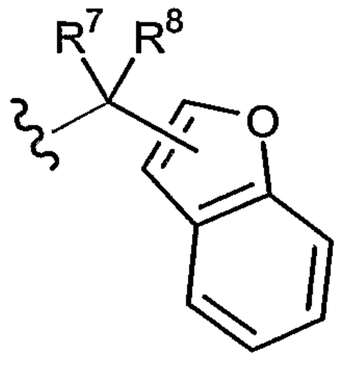
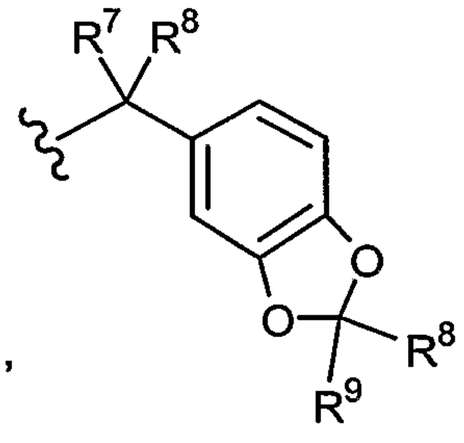
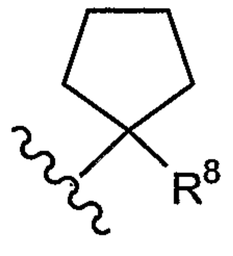
29. The compound of Claim 1 wherein:

(1) substituent A in formula IA is selected from the group consisting of:

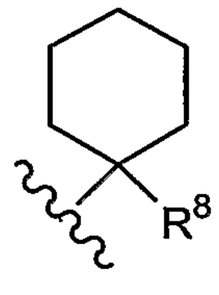
(a)

,

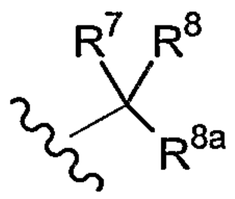




and



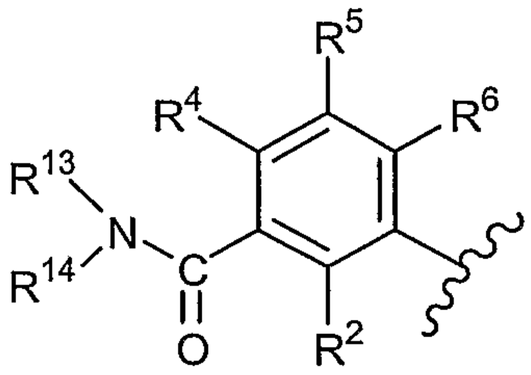
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)

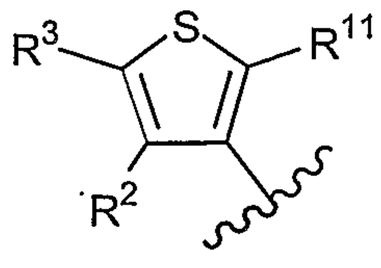


wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined in Claim 1;

(2) substituent B in formula IA is selected from the group consisting of:



and



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$ $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, and $-SO_2R^{13}$;

R^4 is selected from the group consisting of: H, -NO_2, cyano, alkyl, halogen and -CF_3;

R^5 is selected from the group consisting of: H, -CF_3, -NO_2, halogen and cyano;

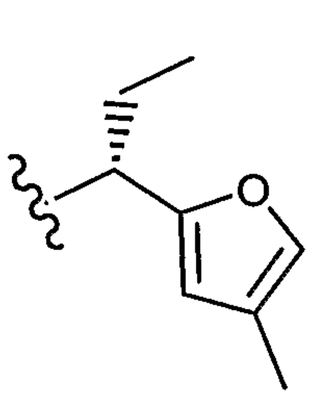
R^6 is selected from the group consisting of: H, alkyl and -CF_3;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted alkyl.

30. The compound of Claim 1 wherein:

(1) substituent A in formula IA is selected from the group consisting of: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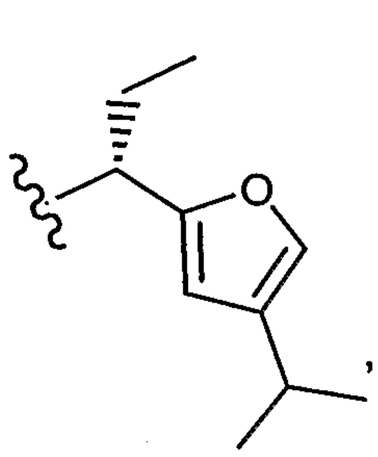
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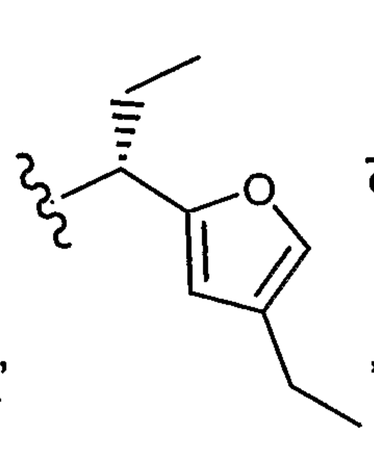
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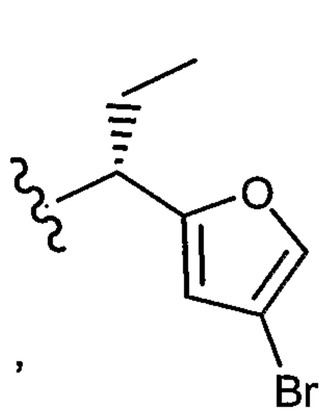
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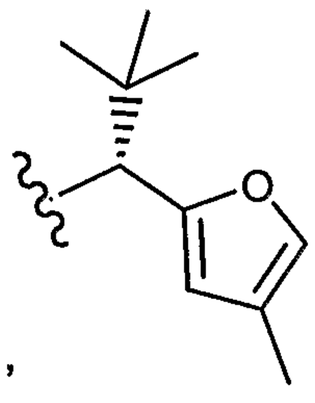
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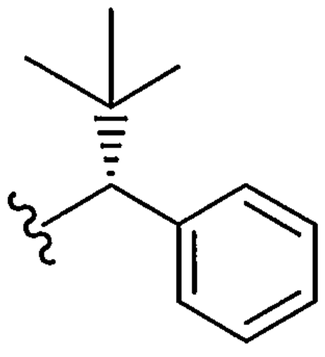
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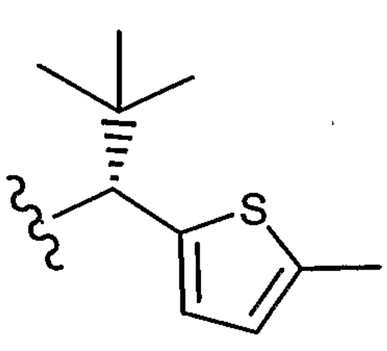
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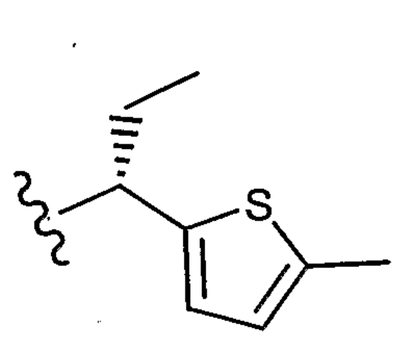
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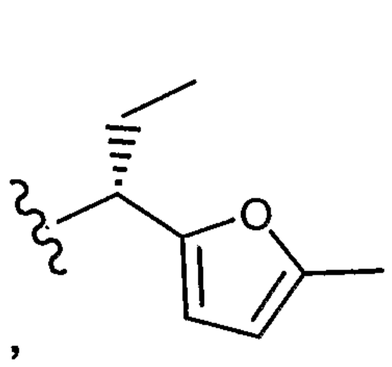
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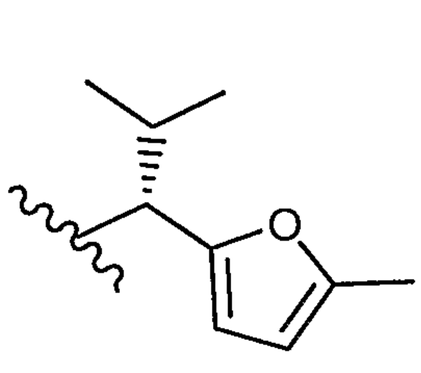
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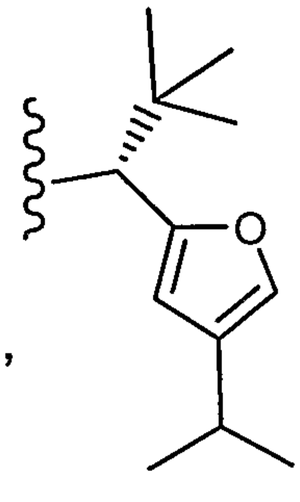
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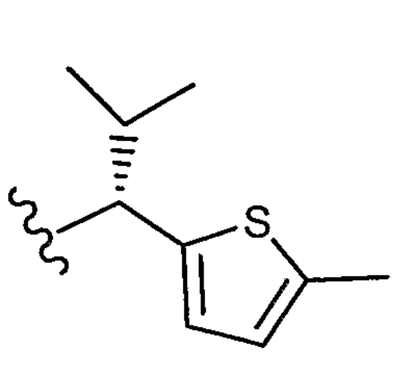
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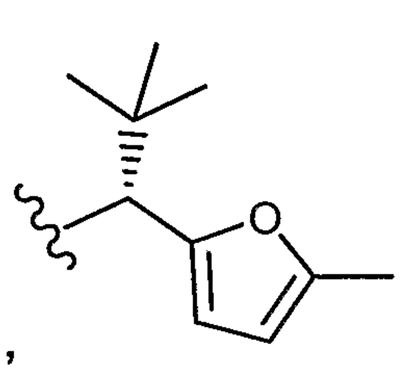
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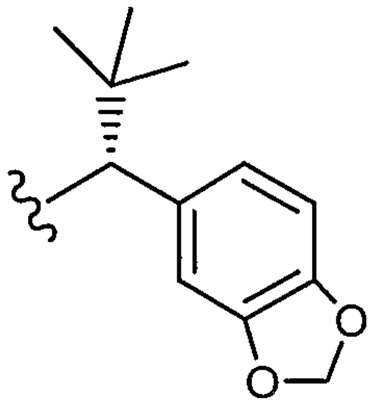
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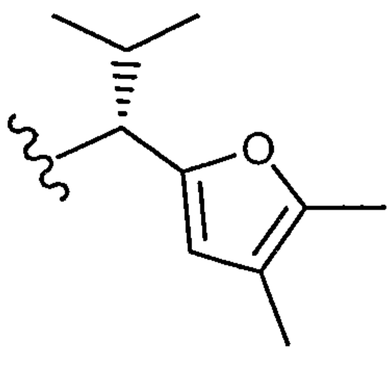
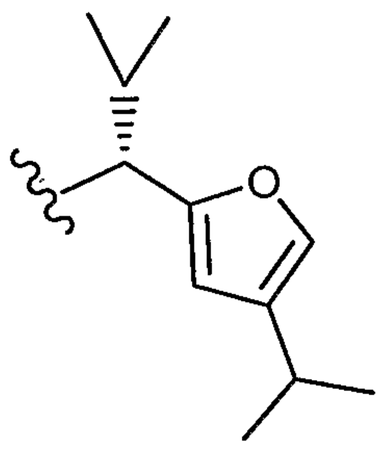
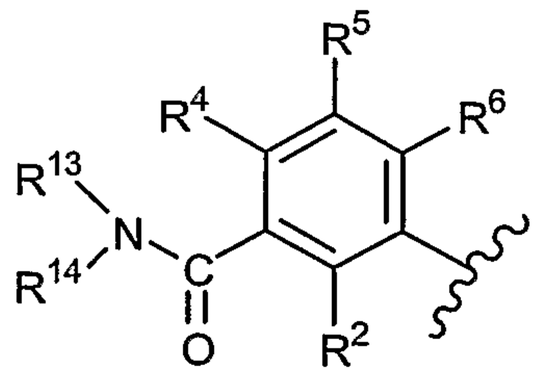
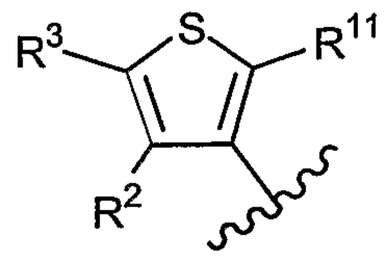

and

; and

15

(2) substituent B in formula IA is selected from the group consisting of:


and


wherein:

R^2 is –OH;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;

R^4 is selected form the group consisting of: H, Br, $-CH_3$, ethyl and $-CF_3$;

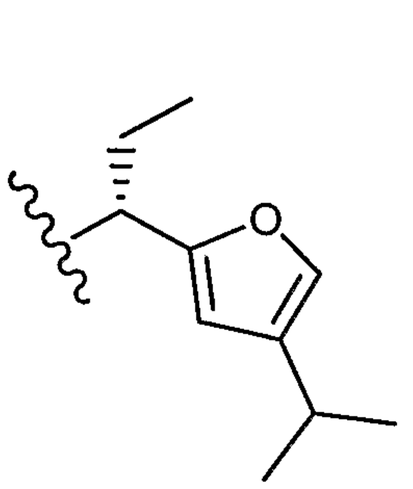
R^5 is selected from the group consisting of: H and cyano;

R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$;

R^{11} is H; and

R^{13} and R^{14} are independently selected from the group consisting of H and methyl.

31. The compound of Claim 1 wherein substituent A is selected from the group consisting of: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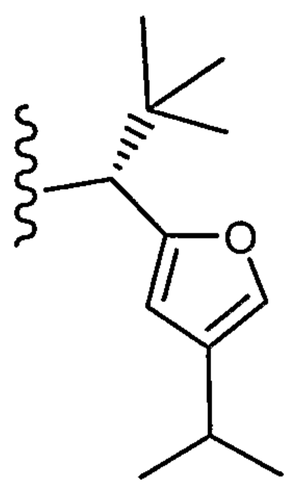
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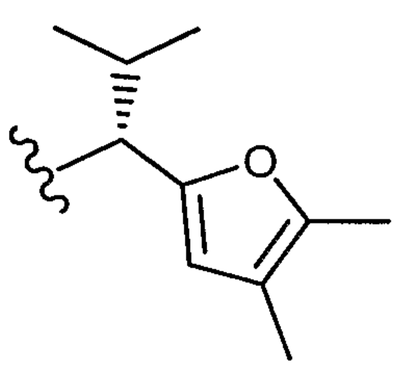
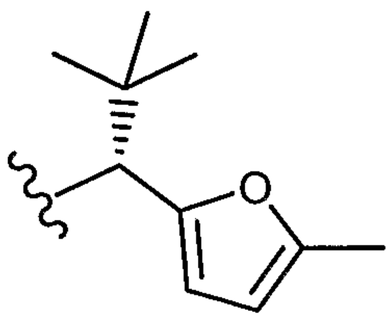
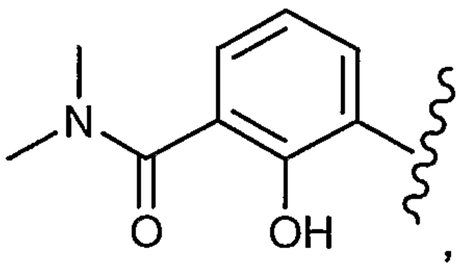
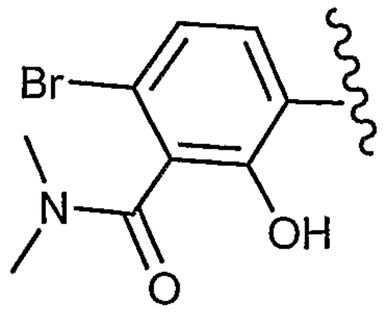
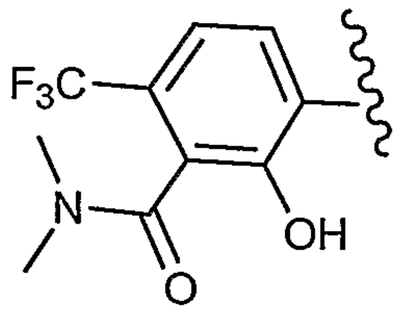
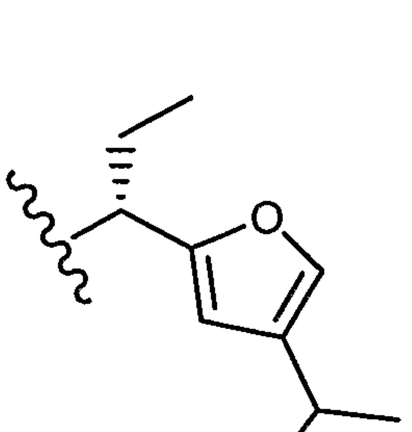
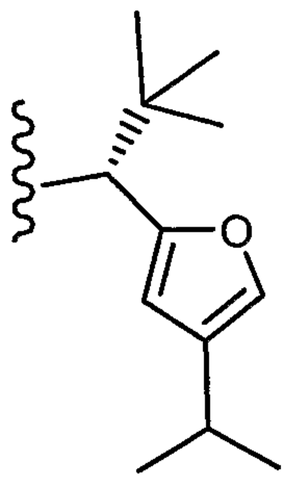
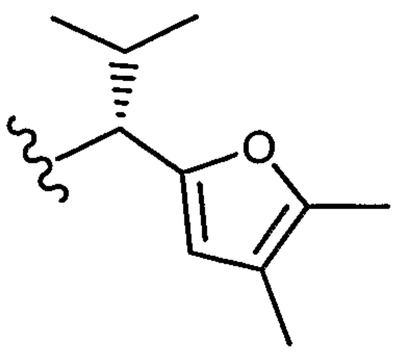
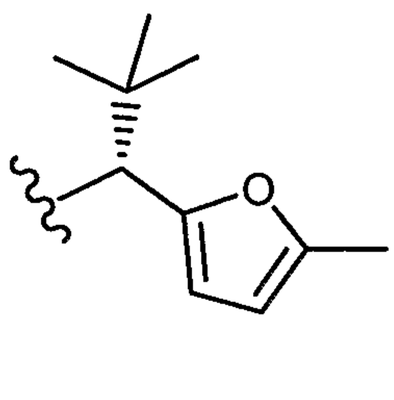

and

,

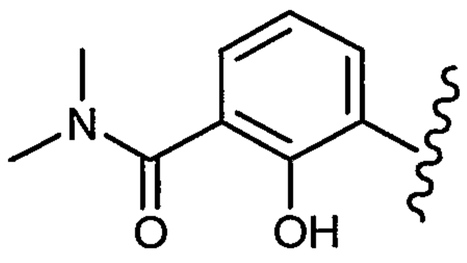
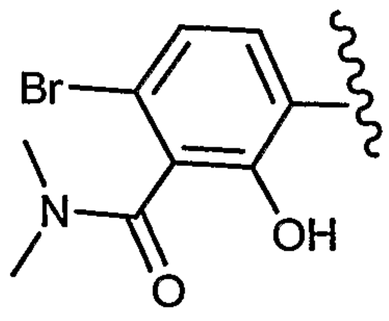
and substituent B is selected from the group consisting of:


,

and

.

32. The compound of Claim 1 wherein substituent A is selected from the group consisting of:


,

,

and

,

and substituent B is selected from the group consisting of:


and

.

33. A pharmaceutically acceptable salt of a compound of any of Claims 1 to 32.

34. A sodium salt of a compound of any of Claims 1 to 32.

35. A calcium salt of a compound of any of Claims 1 to 32.

36. The compound of Claim 1 selected from the group consisting of the final compounds of Examples 1, 2-4, 6-35, 100-105, 107, 108, 110, 111, 112, 114-116, 118-132, 134-145, 148, 180, 182, 183, 185, 186, 188, 300-389, 500-639, 700-787, and 900-987, and the pharmaceutically acceptable salts thereof.

37. The compound of Claim 1 selected from the group consisting of the final compounds of Examples 1, 6, 8, 110, 111, 112, 114, 122, 120, 123, 124, 129, 130, 131, 142, 144, 145, 300, 305, 306, 307, 313, 316, 317, 318, 323, 324, 327, 328, 329, 334, 335, 338, 339, 340, 349, 350, 351, 359, 360, 361, 362, 364, 370, 372, 373, 374, 381, 544, 545, 546, 548, 558, 559, 560, 561, 562, 572, 708,718, 719, 721, 732, 754, 774, 784, 928, 930, 931, 939, 942, 941, 950, 952, and the pharmaceutically acceptable salts thereof.

38. The compound of Claim 1 selected from the group consisting of the final compounds of Examples 1, 6, 8, 114, 120, 123, 129, 131, 300, 305, 306, 307, 316, 317, 318, 323, 327, 328, 329, 334, 359, 360, 361, 370, 372, 373, 374, 544, 545, 546, 548, 558, 559, 560, 561, 562, 928, 930, 931, 939, 942, 941, 950, 952, and the pharmaceutically acceptable salts thereof.

39. The compound of Claim 1 wherein said compound is the final compound of Example 1, or a pharmaceutically acceptable salt thereof.

40. The compound of Claim 1 wherein said compound is the final compound of Example 6, or a pharmaceutically acceptable salt thereof.

41. The compound of Claim 1 wherein said compound is the final compound of Example 8, or a pharmaceutically acceptable salt thereof.

42. The compound of Claim 1 wherein said compound is the final compound of Example 120, or a pharmaceutically acceptable salt thereof.

43. The compound of Claim 1 wherein said compound is the final compound of Example 131, or a pharmaceutically acceptable salt thereof.

44. The compound of Claim 1 wherein said compound is the final compound of Example 545, or a pharmaceutically acceptable salt thereof.

45. The compound of Claim 1 wherein said compound is the final compound of Example 561, or a pharmaceutically acceptable salt thereof.

46. The compound of Claim 1 wherein said compound is the final compound of Example 928, or a pharmaceutically acceptable salt thereof.

47. The compound of Claim 1 wherein said compound is the final compound of Example 930, or a pharmaceutically acceptable salt thereof.

48. The compound of Claim 1 wherein said compound is the final compound of Example 931, or a pharmaceutically acceptable salt or thereof.

49. The compound of any of Claims 1 to 48 in isolated and pure form.

50. A pharmaceutical composition comprising at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

51. A pharmaceutical composition comprising at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, and at least one other agent, medicament, antibody and/or inhibitor for treating a chemokine mediated disease, in combination with a pharmaceutically acceptable carrier.

52. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a chemokine mediated disease.

53. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cancer.

54. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one anticancer agent selected from the group consisting of: (a) microtubule affecting agents, (b) antineoplastic agents, (c) anti-angiogenesis agents, or (d) VEGF receptor kinase inhibitors, (e) antibodies against the VEGF receptor, (f) interferon and g) radiation, for treating cancer

55. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one antineoplastic agent selected from the group consisting of:

gemcitabine, paclitaxel, 5-Fluorourcil, cyclophosphamide, temozolomide and Vincristine, for treating cancer.

56. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use concurrently or sequentially with a microtubule affecting agent, for treating cancer.

57. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use concurrently or sequentially with (b) at least one agent selected from the group consisting of: (1) antineoplastic agents, (2) microtubule affecting agents, and (3) anti-angiogenesis agents, for treating cancer.

58. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting angiogenesis.

59. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating angiogenic ocular disease.

60. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a disease or condition selected from the group consisting of: pain, acute inflammation, chronic inflammation, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, ischemia reperfusion injury, renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral ischemia, cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma

associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute pancreatitis, chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred, corneal neovascularization, polymyositis, vasculitis, acne, gastric ulcers, duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, cancer, transplant reperfusion injury, early transplantation rejection, airway hyperreactivity, allergic contact dermatitis, allergic rhinitis, alopecia areata, antiphospholipid syndromes, aplastic anemia, autoimmune deafness, autoimmune hemolytic syndromes, autoimmune hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, bullous pemphigoid, chronic allograft vasculopathy, chronic inflammatory demyelinating polyneuropathy, cirrhosis, cor pneumoniae, cryoglobulinemia, dermatomyositis, diabetes, drug-induced autoimmunity, epidermolysis bullosa acquisita, endometriosis, fibrotic diseases, gastritis, Goodpasture's syndrome, Graves' disease, Gullain-Barre disease, Hashimoto's thyroiditis, hepatitis-associated autoimmunity, HIV-related autoimmune syndromes and hematologic disorders, hypophytis, idiopathic thrombocytic pupura, interstitial cystitis, juvenile arthritis, Langerhans' cell histiocytitis, lichen planus, metal-induced autoimmunity, myasthenia gravis, myelodysplastic syndromes, myocarditis, myositis, Neuropathies, nephritic syndrome, optic neuritis, pancreatitis, paroxysmal nocturnal hemoglobulinemia, pemphigus, polymyalgia, post-infectious autoimmunity, primary biliary cirrhosis, reactive arthritis, ankylosing spondylitis, Raynaud's phenomenon, Reiter's syndrome,

reperfusion injury, scleritis, scleroderma, secondary hematologic manifestation of autoimmune diseases, silicone implant associated autoimmune disease, Sjogren's syndrome, systemic lupus erythematosus, thrombocytopenia, transverse myelitis, tubulointerstitial nephritis, uveitis, vasculitis syndromes, and Vitiligo.

61. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament, for treating a chemokine mediated disease or condition, for use with at least one other medicament useful for the treatment of chemokine mediated diseases.

62. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one other medicament selected from the group consisting of:

a) disease modifying antirheumatic drugs;
b) nonsteroidal anitinflammatory drugs;
c) COX-2 selective inhibitors;
d) COX-1 inhibitors;
e) immunosuppressives;
f) steroids;
g) biological response modifiers; and
h) other anti-inflammatory agents or therapeutics useful for the treatment of chemokine mediated diseases.

for treating a chemokine mediated disease or condition.

63. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament foruse with at least one compound selected from the group consisting of: glucocorticoids, 5-lipoxygenase inhibitors, β-2 adrenoceptor agonists, muscarinic M1 antagonists, muscarinic M3 antagonists, muscarinic M2 agonists, NK3 antagonists, LTB4 antagonists, cysteinyl leukotriene antagonists, bronchodilators, PDE4 inhibitors, PDE inhibitors, elastase inhibitors, MMP inhibitors, phospholipase A2 inhibitors, phospholipase D inhibitors, histamine H1 antagonists, histamine H3 antagonists, dopamine agonists, adenosine A2 agonists, NK1 and NK2 antagonists, GABA-b

agonists, nociceptin agonists, expectorants, mucolytic agents, decongestants, antioxidants, anti-IL-8 anti-bodies, anti-IL-5 antibodies, anti-IgE antibodies, anti-TNF antibodies, IL-10, adhesion molecule inhibitors and growth hormones, for treating a pulmonary disease.

64. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one compound selected from the group consisting of glatiramer acetate, glucocorticoids, methotrexate, azothioprine, mitoxantrone, chemokine inhibitors and CB2-selective agents, for treating multiple sclerosis.

65. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one compound selected from the group consisting of: methotrexate, cyclosporin, leflunimide, sulfasalazine, β-methasone, β-interferon, glatiramer acetate and prednisone, for treating multiple sclerosis.

66. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating rheumatoid arthritis.

67. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one compound selected from the group consisting of COX-2 inhibitors, COX inhibitors, immunosuppressives, steroids, PDE IV inhibitors, anti-TNF-α compounds, MMP inhibitors, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, and other classes of compounds indicated for the treatment of rheumatoid arthritis, for treating rheumatoid arthritis.

68. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one compound selected from the group consisting of thrombolitics,

antiplatelet agents, antagonists, anticoagulants, and other compounds indicated for the treatment of rheumatoid arthritis, for treating rheumatoid arthritis.

69. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one compound selected from the group consisting of tenecteplase, TPA, alteplase, abciximab, eftiifbatide, and heparin, for treating stroke and cardiac reperfusion injury.

70. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one compound selected from the group consisting of immunosuppressives, steroids, and anti-TNF-α compounds, for treating psoriasis.

71. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating COPD.

72. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating pain.

73. The use of Claim 72 wherein said pain is associated with: allodynia, ankylosing spondylitis, appendicitis, autoimmune disorders, bacterial infections, Behcet's syndrome, broken bones, bronchitis, burns, bursitis, cancer including metastatic cancer, candidiasis, cardiovascular conditions, casualgia, chemical injury, childbirth, chronic regional neuropathies, Crohn's disease, colorectal cancer, connective tissue injuries, conjunctivitis, COPD, decreased intracranial pressure, dental procedures, dermatitis, diabetes, diabetic neuropathy, dysesthesia, dysmenorrhea, eczema, emphysema, fever, fibromyalgia, gastric ulcer, gastritis, giant cell arteritis, gingivitis, gout, gouty arthritis, headache, headache pain resulting from lumbar puncture, headaches including migraine headache, herpes simplex virus infections, HIV, Hodgkin's disease, hyperalgesia, hypersensitivity, inflammatory bowel

disease, increased intracranial pressure, irritable bowel syndrome, ischemia, juvenile arthritis, kidney stones, lumbar spondylanhrosis, lower back, upper back and lumbrosacral conditions, lumbar spondylarthrosis, menstrual cramps, migraines, minor injuries, multiple sclerosis, myasthenia gravis, myocarditis, muscle strains, musculoskeletal conditions, myocardial ischemia, nephritic syndrome, nerve root avulsion, neuritis, nutritional deficiency, ocular and corneal conditions, ocular photophobia, ophthalmic diseases, osteoarthritis, otic surgery, otitis externa, otitis media, periarteritis nodosa, peripheral neuropathies, phantom limb pain, polymyositis, post-herpetic neuralgia, post-operative/surgical recovery, post-thoracotomy, psoriatic arthritis, pulmonary fibrosis, pulmonary edema, radiculopathy, reactive arthritis, reflex sympathetic dystrophy, retinitis, retinopathies, rheumatic fever, rheumatoid arthritis, sarcoidosis, sciatica, scleroderma, sickle cell anemia, sinus headaches, sinusitis, spinal cord injury, spondyloarthropathies, sprains, stroke, swimmer's ear, tendonitis, tension headaches, thalamic syndrome, thrombosis, thyroiditis, toxins, traumatic injury, trigeminal neuralgia, ulcerative colitis, urogenital conditions, uveitis, vaginitis, vascular diseases, vasculitis, viral infections and/or wound healing.

74. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one medicament selected from the group consisting of: NSAIDs, COXIB inhibitors, anti-depressants and anti-convulsants, for treating pain.

75. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one NSAID, for treating pain.

76. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one COXIB inhibitor, for treating pain.

77. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one anti-depressant, for treating pain.

78. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use with at least one anti-convulsant, for treating pain.

79. The use of Claim 75 wherein said NSAID is selected from the group consisting of: piroxicam, ketoprofen, naproxen, indomethacin, and ibuprofen.

80. The use of Claim 76 wherein said COXIB inhibitor is selected from the group consisting of: rofecoxib and celecoxib.

81. The use of Claim 77 wherein said anti-depressant is selected from the group consisting of: amitriptyline and nortriptyline.

82. The method of Claim 78 wherein said ant-convulsant is selected from the group consisting of: gabapentin, carbamazepine, pregabalin, and lamotragine.

83. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating acute pain.

84. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating acute inflammatory pain.

85. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating chronic inflammatory pain.

86. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating neuropathic pain.

87. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating arthritis.

88. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating osteoarthritis.

89. The use of Claim 60 wherein said

(a) Allograft rejections are selected from the group consisting of acute allograft rejections and chronic allograft rejections,

(b) Early transplantation rejection is an acute allograft rejection,

(c) Autoimmune deafness is Meniere's disease,

(d) Myocarditis is viral myocarditis,

(e) Neuropathies are selected from the group consisting of IgA neuropathy, membranous neuropathy and idiopathic neuropathy,

(f) Autoimmune diseases are anemias,

(g) Vasculitis syndromes are selected from the group consisting of giant cell arteritis, Behcet's disease and Wegener's granulomatosis, and

(h) pain is selected from the group consisting of: acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain.

90. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a CXCR1 and/or a CXCR2 mediated disease or condition selected from the group consisting of: pain, acute inflammation, chronic inflammation, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, ischemia reperfusion injury, renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral ischemia, cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis,

angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute pancreatitis, chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred, corneal neovascularization, polymyositis, vasculitis, acne, gastric ulcers, duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, cancer, transplant reperfusion injury, and early transplantation rejection.

91. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a CCR7 mediated disease or condition selected from the group consisting of: pain, acute inflammation, chronic inflammation, acute allograft rejection, acute respiratory distress syndrome, adult respiratory disease, airway hyperreactivity, allergic contact dermatitis, allergic rhinitis, alopecia areata, alzheimer's disease, angiogenic ocular disease, antiphospholipid syndromes, aplastic anemia, asthma, atherosclerosis, atopic dermatitis, autoimmune deafness, autoimmune hemolytic syndromes, autoimmune hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, bronchiolitis, bronchiolitis obliterans syndrome, bullous pemphigoid, burn therapy, cancer, cerebral ischemia, cardiac ischemia, chronic allograft rejection, chronic allograft vasculopathy, chronic bronchitis, chronic inflammatory demyelinating polyneuropathy, chronic sinusitis,

cirrhosis, CNS vasculitis, COPD, Cor pneumoniae, Crohn's disease, cryoglobulinemia, crystal-induced arthritis, delayed-type hypersensitivity reactions, dermatomyositis, diabetes, diabetic retinopathy, drug-induced autoimmunity, dyspnea, emphysema, epidermolysis bullosa acquisita, endometriosis, fibrotic diseases, gastritis, glomerulonephritis, Goodpasture's syndrome, graft vs host disease, Graves' disease, Gullain-Barre disease, Hashimoto's thyroiditis, hepatitis-associated autoimmunity, HIV-related autoimmune syndromes and hematologic disorders, hyperoxia-induced inflammation, hypercapnea, hyperinflation, hypophytis, hypoxia, idiopathic thrombocytic pupura, inflammatory bowel diseases, interstitial cystitis, interstitial pneumonitis, juvenile arthritis, Langerhans' cell histiocytitis, lichen planus, metal-induced autoimmunity, multiple sclerosis, myasthenia gravis, myelodysplastic syndromes, myocarditis including viral myocarditis, myositis, neuropathies, nephritic syndrome, ocular inflammation, optic neuritis, osteoarthritis, pancreatitis, paroxysmal nocturnal hemoglobulinemia, pemphigus, polymyalgia, polymyositis, post-infectious autoimmunity, pulmonary fibrosis, primary biliary cirrhosis, psoriasis, pruritis, rheumatoid arthritis, reactive arthritis, ankylosing spondylitis, psoriatic arthritis, Raynaud's phenomenon, Reiter's syndrome, reperfusion injury, restenosis, sarcoidosis, scleritis, scleroderma, secondary hematologic manifestation of autoimmune diseases, silicone implant associated autoimmune disease, Sjogren's syndrome, systemic lupus erythematosus, thrombocytopenia, thrombosis, transverse myelitis, tubulointerstitial nephritis, ulcerative colitis, uveitis, vasculitis and vasculitis syndromes, and vitiligo.

92. The use of Claim 90 wherein said:

(a) Allograft rejections are selected from the group consisting of acute allograft rejections and chronic allograft rejections,

(b) Early transplantation rejection is an acute allograft rejection,

(c) Autoimmune deafness is Meniere's disease,

(d) Myocarditis is viral myocarditis,

(e) Neuropathies are selected from the group consisting of IgA neuropathy, membranous neuropathy and idiopathic neuropathy,

(f) Autoimmune diseases are anemias,

(g) Vasculitis syndromes are selected from the group consisting of giant cell arteritis, Behcet's disease and Wegener's granulomatosis, and

(h) pain is selected from the group consisting of: acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain.

93. The use of Claim 91 wherein said

(a) Allograft rejections are selected from the group consisting of acute allograft rejections and chronic allograft rejections,

(b) Early transplantation rejection is an acute allograft rejection,

(c) Autoimmune deafness is Meniere's disease,

(d) Myocarditis is viral myocarditis,

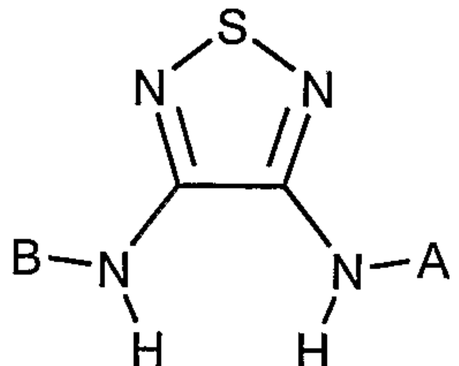
(e) Neuropathies are selected from the group consisting of IgA neuropathy, membranous neuropathy and idiopathic neuropathy,

(f) Autoimmune diseases are anemias,

(g) Vasculitis syndromes are selected from the group consisting of giant cell arteritis, Behcet's disease and Wegener's granulomatosis, and

(h) pain is selected from the group consisting of: acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain.

94. Use of at least one compound of any of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating angina.



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