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(54) **APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE AND AUTOIMMUNE DISEASES**

APOPTOSEINDUKTOREN FÜR DIE BEHANDLUNG VON KREBS SOWIE IMMUN- UND AUTOIMMUNERKRANKUNGEN

AGENTS INDUISANT L'APOPTOSE POUR LE TRAITEMENT DU CANCER ET DE MALADIES IMMUNES ET AUTO-IMMUNES

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WO-A2-2005/049593 **WO-A2-2007/040650**
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- **WENDT M D ET AL: "Discovery and Structure-Activity Relationship of Antagonists of B-Cell Lymphoma 2 Family Proteins with Chemopotentiation Activity in Vitro and in Vivo", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 49, no. 3, 9 February 2006 (2006-02-09), pages 1165-1181, XP002615911, ISSN: 0022-2623, DOI: 10.1021/JM050754U [retrieved on 2006-01-11]**

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- CHEOL-MIN PARK ET AL: "Discovery of an Orally Bioavailable Small Molecule Inhibitor of Prosurvival B-Cell Lymphoma2 Proteins", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 51, no. 21, 13 November 2008 (2008-11-13), pages 6902-6915, XP002610165, ISSN: 0022-2623, DOI: 10.1021/JM800669S [retrieved on 2008-10-08]

Description

FIELD OF THE INVENTION

[0001] This invention pertains to compounds which inhibit the activity of Bcl-2 anti-apoptotic proteins, compositions containing the compounds, and methods of treating diseases during which anti-apoptotic Bcl-2 proteins are expressed.

BACKGROUND OF THE INVENTION

[0002] Anti-apoptotic Bcl-2 proteins are associated with a number of diseases. There is therefore an existing need in the therapeutic arts for compounds which inhibit the activity of anti-apoptotic Bcl-2 proteins.

[0003] Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system.

[0004] Involvement of Bcl-2 proteins in bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, spleen cancer, and the like is described in commonly-owned PCT US 2004/36770, published as WO 2005/049593, and PCT US 2004/37911, published as WO 2005/024636.

[0005] Involvement of Bcl-2 proteins in immune and autoimmune diseases is described in Current Allergy and Asthma Reports 2003, 3, 378-384; British Journal of Haematology 2000, 110(3), 584-90; Blood 2000, 95(4), 1283-92; and New England Journal of Medicine 2004, 351(14), 1409-1418. Involvement of Bcl-2 proteins in arthritis is disclosed in commonly-owned United States Provisional Patent Application Serial No. 60/988,479. Involvement of Bcl-2 proteins in bone marrow transplant rejection is disclosed in commonly-owned United States Patent Application Serial No. 11/941,196.

[0006] WO 02/24636 A2 discloses N-Benzoyl arylsulfonamides which are BCL-XI inhibitors and are useful for promoting apoptosis. Also disclosed therein are BCL-XI inhibiting compositions and methods of promoting apoptosis in a mammal.

[0007] WO 2009/036035 A1 relates to Bcl-2 inhibitors and their use in the treatment of cell proliferative diseases such as cancer.

[0008] WO 2005/049593 A2 discloses N-acylsulfonamide compounds which inhibit the activity of anti-apoptotic protein family members, compositions containing the compounds and uses of the compounds for preparing medicaments for treating diseases during which are expressed one or more than one of an anti-apoptotic protein family member.

[0009] WENDT M D ET AL: "Discovery and Structure-Activity Relationship of Antagonists of B-Cell Lymphoma 2 Family Proteins with Chemopotentiation Activity in Vitro and in Vivo"; JOURNAL OF MEDICAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 49, no. 3, (2006-02-09), pages 1165-1181, XP002615911 describes the development of a rationally designed potentiator of cancer chemotherapy, via inhibition of Bcl-X_L function.

[0010] CHEOL-MIN PARK ET AL: "Discovery of an Orally Bioavailable Small Molecule Inhibitor of Prosurvival B-Cell Lymphoma2 Proteins", JOURNAL OF MEDICAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 51, no. 21, (2008-11-13), pages 6902-6915, XP002610165 reports on a compound 2 (ABT-263), which is orally efficacious in an established xenograft model of human small cell lung cancer, inducing complete tumor regressions in all animals.

[0011] US 2007/015787 A1 discloses compounds which inhibit the activity of anti-apoptotic protein family members, compositions containing the compounds and uses of the compounds for preparing medicaments for treating diseases during which occurs expression one or more than one of an anti-apoptotic protein family member.

[0012] WO 2007/040650 A2 discloses compounds which inhibit the activity of anti-apoptotic family protein members, compositions containing the compounds and methods of treating diseases during which occur expression of one or more than one of an anti-apoptotic family protein member.

SUMMARY OF THE INVENTION

[0013] One embodiment of this invention pertains to compounds or therapeutically acceptable salts, thereof, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds chosen from

4-(4-{acetyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{benzoyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-3'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino} biphenyl-4-carboxamide;

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(phenylacetyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyc-

lo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide;
4-(4-{[3-bromo-5-methyladamantan-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[3,5-dimethyladamantan-1-yl]methyl}piperazin-1-yl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-octahydro-1H-4,7-methanoinden-5-ylamino]benzyl}piperazin-1-yl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,4R,6S)-5,5,6-trimethylbicyclo[2.2.1]hept-2-yl]amino}benzyl)piperazin-1-yl]benzamide;
4-[4-(2-{[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[(1R,5R)-2-(4-chlorophenyl)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-{4-[(2-{[adamantan-2-ylmethyl]amino}-5,5-dimethylcyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[(5,5-dimethyl-2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}cyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)-5-nitrobenzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{2-[2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
1-[adamantan-1-yl]-4-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N,N-diphenyl-1H-pyrazole-3-carboxamide;
4-(4-{2-[2-(adamantan-1-yl)-6-methylimidazo[1,2-a]pyridin-8-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-(adamantan-2-yl)-6-methyl-8-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}imidazo[1,2-a]pyridine-2-carboxamide;
4-(4-{2-[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[5,5,6-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzamide;
N-benzyl-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide;
4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzyl)piperazin-1-yl]benzamide;
4-(4-{2-[3-azabicyclo[3.2.2]non-3-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[tricyclo[4.3.1.1^{3,8}]undec-4-en-4-yl]benzyl}piperazin-1-yl)benzamide;
7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-phenylbicyclo[2.2.1]hept-2-ene-1-carboxamide;
7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]bicyclo[2.2.1]hept-2-ene-1-carboxamide;
N-(adamantan-1-ylmethyl)-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide;
N-cyclopropyl-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide;
7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxylic;

4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;
4-{4-[adamantan-1-ylmethyl]piperazin-1-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{2-[adamantan-1-yl]-2-oxoethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl} sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazin-1-yl}benzamide;
4-{4-[adamantan-1-yl]piperazin-1-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[3,5-dimethyladamantan-1-yl]piperazin-1-yl benzamide;
4-(4-{2-[adamantan-1-yl]ethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-({(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-y]]amino}methyl)biphenyl-4-carboxamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzylidene}piperidin-1-yl)benzamide;
4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
1-[adamantan-1-yl]-4-{2-[(1-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperidin-4-ylidene)methyl]phenyl}-N,N-diphenyl-1H-pyrazole-3-carboxamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[octahydro-1H-4,7-methanoinden-5-yl(3-phenylpropanoyl)amino]benzyl}piperazin-1-yl)benzamide;
4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(4-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(3-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide;
4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

[0014] Another embodiment pertains to a pharmaceutical composition for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of a compound of this invention.

[0015] Another embodiment pertains to the use of a compound of this invention for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, said use comprising administering to the patient a therapeutically effective amount of a compound of this invention.

[0016] Another embodiment pertains to the use of a compound of this invention for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said use comprising administering to the patient therapeutically effective amount of a compound of this invention and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

[0017] Variable moieties herein are represented by identifiers (capital letters with numerical and/or alphabetical superscripts) and may be specifically embodied.

[0018] It is meant to be understood that proper valences are maintained for all moieties and combinations thereof, that monovalent moieties having more than one atom are drawn from left to right and are attached through their left

ends, and that divalent moieties are also drawn from left to right.

[0019] It is also meant to be understood that a specific embodiment of a variable moiety herein may be the same or different as another specific embodiment having the same identifier.

Compounds

[0020] Geometric isomers may exist in the present compounds. Compounds of this invention may contain carbon-carbon double bonds or carbon-nitrogen double bonds in the E or Z configuration, wherein the term "E" represents higher order substituents on opposite sides of the carbon-carbon or carbon-nitrogen double bond and the term "Z" represents higher order substituents on the same side of the carbon-carbon or carbon-nitrogen double bond as determined by the Cahn-Ingold-Prelog Priority Rules. The compounds of this invention may also exist as a mixture of "E" and "Z" isomers. Substituents around a cycloalkyl or heterocycloalkyl are designated as being of cis or trans configuration.

[0021] Compounds of this invention may contain asymmetrically substituted carbon atoms in the R or S configuration, in which the terms "R" and "S" are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those carbon atoms. Atoms with an excess of one configuration over the other are assigned the configuration present in the higher amount, preferably an excess of about 85%-90%, more preferably an excess of about 95%-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

[0022] Compounds of this invention containing NH, C(O)OH, OH or SH moieties may have attached thereto prodrug-forming moieties. The prodrug-forming moieties are removed by metabolic processes and release the compounds having the freed hydroxyl, amino or carboxylic acid in vivo. Prodrugs are useful for adjusting such pharmacokinetic properties of the compounds as solubility and/or hydrophobicity, absorption in the gastrointestinal tract, bioavailability, tissue penetration, and rate of clearance.

Isotope Enriched or Labeled Compounds

[0023] Compounds of the invention can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or nonradioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I. Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

[0024] In another embodiment, the isotope-labeled compounds contain deuterium (^{2}H), tritium (^{3}H) or ^{14}C isotopes. Isotope-labeled compounds of this invention can be prepared by the general methods well known to persons having ordinary skill in the art. Such isotope-labeled compounds can be conveniently prepared by carrying out the procedures disclosed in the Examples disclosed herein and Schemes by substituting a readily available isotope-labeled reagent for a non-labeled reagent. In some instances, compounds may be treated with isotope-labeled reagents to exchange a normal atom with its isotope, for example, hydrogen for deuterium can be exchanged by the action of a deuteric acid such as D_2SO_4/D_2O. In addition to the above, relevant procedures and intermediates are disclosed, for instance, in Lizondo, J et al., Drugs Fut, 21(11), 1116 (1996); Brickner, S J et al., J Med Chem, 39(3), 673 (1996); Mallesham, B et al., Org Lett, 5(7), 963 (2003); PCT publications WO1997010223, WO2005099353, WO1995007271, WO2006008754; US Patent Nos. 7538189; 7534814; 7531685; 7528131; 7521421; 7514068; 7511013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; and 20090082471.

[0025] The isotope-labeled compounds of the invention may be used as standards to determine the effectiveness of Bcl-2 inhibitors in binding assays. Isotope containing compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the nonisotope-labeled parent compound (Blake et al. J. Pharm. Sci. 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the *in vivo* active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., Advances in Drug Research Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al., J. Labelled Comp. Radiopharmaceut., 36(10):927-932 (1995); Kushner et al., Can. J Physiol. Pharmacol., 77, 79-88 (1999).

[0026] In addition, non-radio active isotope containing drugs, such as deuterated drugs called "heavy drugs," can be used for the treatment of diseases and conditions related to Bcl-2 activity. Increasing the amount of an isotope present in a compound above its natural abundance is called enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %. Replacement of up to about 15% of normal atom with a heavy isotope has been effected and maintained

for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, Ann. N.Y. Acad. Sci. 1960 84: 770; Thomson J F, Ann. New York Acad. Sci 1960 84: 736; Czakja D M et al., Am. J. Physiol. 1961 201: 357). Acute replacement of as high as 15%-23% in human fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp. 125-134; Diabetes Metab. 23: 251 (1997)).

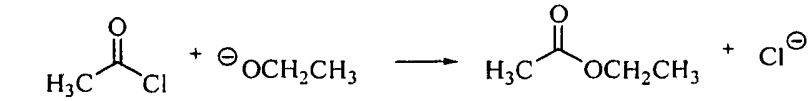
[0027] Stable isotope labeling of a drug can alter its physico-chemical properties such as pKa and lipid solubility. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. Accordingly, the incorporation of an isotope at a site of metabolism or enzymatic transformation will slow said reactions potentially altering the pharmcokinetic profile or efficacy relative to the non-istopic compound.

Amides. Esters and Prodrugs

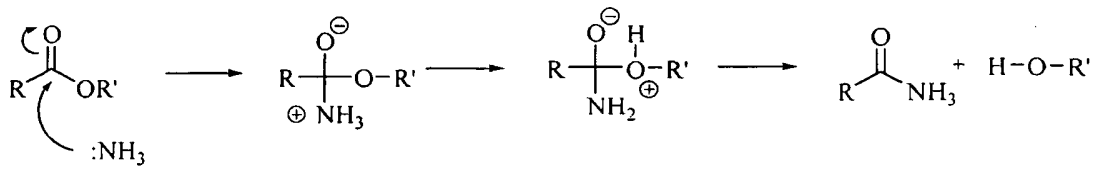
[0028] Prodrugs are derivatives of an active drug designed to ameliorate some identified, undesirable physical or biological property. The physical properties are usually solubility (too much or not enough lipid or aqueous solubility) or stability related, while problematic biological properties include too rapid metabolism or poor bioavailability which itself may be related to a physicochemical property.

[0029] Prodrugs are usually prepared by: a) formation of ester, hemi esters, carbonate esters, nitrate esters, amides, hydroxamic acids, carbamates, imines, Mannich bases, phosphates, phosphate esters, and enamines of the active drug, b) functionalizing the drug with azo, glycoside, peptide, and ether functional groups, c) use of aminals, hemi-aminals, polymers, salts, complexes, phosphoramides, acetals, hemiacetals, and ketal forms of the drug. For example, see Andrejus Korolkovas's, "Essentials of Medicinal Chemistry", John Wiley-Interscience Publications, John Wiley and Sons, New York (1988), pp. 97-118.

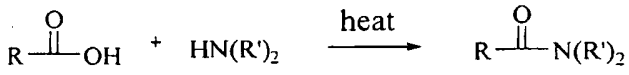
[0030] Esters can be prepared from substrates containing either a hydroxyl group or a carboxy group by general methods known to persons skilled in the art. The typical reactions of these compounds are substitutions replacing one of the heteroatoms by another atom, for example:



[0031] Amides can be prepared from substrates containing either an amino group or a carboxy group in similar fashion. Esters can also react with amines or ammonia to form amides.



[0032] Another way to make amides from compounds is to heat carboxylic acids and amines together.



[0033] One embodiment of this invention pertains to compounds or therapeutically acceptable salts thereof, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds chosen from

4-(4-{acetyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{benzoyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-3'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(phenylacetyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide;
4-(4-{[3-bromo-5-methyladamantan-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[3,5-dimethyladamantan-1-yl]methyl}piperazin-1-yl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-octahydro-1H-4,7-methanoinden-5-ylamino]benzyl}piperazin-1-yl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,4R,6S)-5,5,6-trimethylbicyclo[2.2.1]hept-2-yl]amino}benzyl)piperazin-1-yl]benzamide;
4-[4-(2-{[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[(1R,5R)-2-(4-chlorophenyl)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-{4-[(2-{[adamantan-2-ylmethyl]amino}-5,5-dimethylcyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[(5,5-dimethyl-2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}cyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)-5-nitrobenzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{2-[2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
1-[adamantan-1-yl]-4-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N,N-diphenyl-1H-pyrazole-3-carboxamide;
4-(4-{2-[2-(adamantan-1-yl)-6-methylimidazo[1,2-a]pyridin-8-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-(adamantan-2-yl)-6-methyl-8-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}imidazo[1,2-a]pyridine-2-carboxamide;
4-(4-{2-[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[5,5,6-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzamide;
N-benzyl-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide;
4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzyl)piperazin-1-yl]benzamide;
4-(4-{2-[3-azabicyclo[3.2.2]non-3-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[tricyclo[4.3.1.1^{3,8}]undec-4-en-4-yl]benzyl}piperazin-1-yl)benzamide;
7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-phenylbicyclo[2.2.1]hept-2-ene-1-carboxamide;
7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]bicyclo[2.2.1]hept-2-ene-1-carboxamide;
N-(adamantan-1-ylmethyl)-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phe-

nyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide;
N-cyclopropyl-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenylpiperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide;
7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxylic;
4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;
4-{4-[adamantan-1-ylmethyl]piperazin-1-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{2-[adamantan-1-yl]-2-oxoethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazin-1-yl}benzamide;
4-{4-[adamantan-1-yl]piperazin-1-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[3,5-dimethyladamantan-1-yl]piperazin-1-yl}benzamide;
4-(4-{2-[adamantan-1-yl]ethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-({(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}methyl)biphenyl-4-carboxamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzylidene}piperidin-1-yl)benzamide;
4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
1-[adamantan-1-yl]-4-{2-[(1-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperidin-4-ylidene)methyl]phenyl}-N,N-diphenyl-1H-pyrazole-3-carboxamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[octahydro-1H-4,7-methanoinden-5-yl(3-phenylpropanoyl)amino]benzyl}piperazin-1-yl)benzamide;
4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(4-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(3-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide;
4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Pharmaceutical Compositions, Combination Therapies. Use of compounds, and Administration

[0034] Another embodiment comprises pharmaceutical compositions comprising a compound of this invention and an excipient.

[0035] Still another embodiment comprises the use of a compound of this invention for use in treating cancer in a mammal comprising administering thereto a therapeutically acceptable amount of a compound of this invention.

[0036] Still another embodiment comprises the use of a compound of this invention for use in treating autoimmune disease in a mammal comprising administering thereto a therapeutically acceptable amount of a compound of this invention.

[0037] Still another embodiment pertains to pharmaceutical compositions for use in treating diseases during which anti-apoptotic Bcl-2 proteins are expressed, said compositions comprising an excipient and a therapeutically effective amount of the compound of this invention.

[0038] Still another embodiment pertains to the use of a compound of this invention for use in treating disease in a patient during which anti-apoptotic Bcl-2 proteins are expressed, said methods comprising administering to the patient a therapeutically effective amount of a compound of this invention.

[0039] Still another embodiment pertains to pharmaceutical compositions for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound of this invention.

[0040] Still another embodiment pertains to the use of a compound of this invention for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of a compound of this invention.

[0041] Still another embodiment pertains to pharmaceutical compositions for use in treating diseases during which are expressed anti-apoptotic Bcl-2 proteins, said compositions comprising an excipient and a therapeutically effective amount of the compound of this invention and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

[0042] Still another embodiment pertains to the use of a compound of this invention for use in treating disease in a patient during which are expressed anti-apoptotic Bcl-2 proteins, said methods comprising administering to the patient a therapeutically effective amount of a compound of this invention and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

[0043] Still another embodiment pertains to pharmaceutical compositions for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound of this invention and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

[0044] Still another embodiment pertains to the use of a compound of this invention for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of the compound of this invention and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

[0045] Metabolites of compounds of this invention, produced by in vitro or in vivo metabolic processes, may also have utility for treating diseases associated with anti-apoptotic Bcl-2 proteins.

[0046] Certain precursor compounds which may be metabolized in vitro or in vivo to form compounds of this invention may also have utility for treating diseases associated with expression of anti-apoptotic Bcl-2 proteins.

[0047] Compounds of this invention may exist as acid addition salts, basic addition salts or zwitterions. Salts of the compounds are prepared during isolation or following purification of the compounds. Acid addition salts of the compounds are those derived from the reaction of the compounds with an acid. For example, the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsufonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trichloroacetic, trifluoroacetic, para-toluenesulfonate, and undecanoate salts of the compounds and prodrugs thereof are contemplated as being embraced by this invention. Basic addition salts of the compounds are those derived from the reaction of the compounds with the hydroxide, carbonate or bicarbonate of cations such as lithium, sodium, potassium, calcium, and magnesium.

[0048] The compounds of this invention may be administered, for example, bucally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperitoneally intrastemally, intravenously, subcutaneously), rectally, topically, transdermally or vaginally.

[0049] Therapeutically effective amounts of compounds of this invention depend on the recipient of the treatment, the disorder being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered. The amount of a compound of this invention of this invention used to make a composition to be administered daily to a patient in a single dose or in divided doses is from about 0.03 to about 200 mg/kg body weight. Single dose compositions contain these amounts or a combination of submultiples thereof.

[0050] Compounds of this invention may be administered with or without an excipient. Excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof.

[0051] Excipients for preparation of compositions comprising a compound of this invention to be administered orally

in solid dosage form include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention to be administered ophthalmically or orally in liquid dosage forms include, for example, 1,3-butylene glycol, castor oil, corn oil, cottonseed oil, ethanol, fatty acid esters of sorbitan, germ oil, groundnut oil, glycerol, isopropanol, olive oil, polyethylene glycols, propylene glycol, sesame oil, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention to be administered osmotically include, for example, chlorofluorohydrocarbons, ethanol, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention to be administered parenterally include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention to be administered rectally or vaginally include, for example, cocoa butter, polyethylene glycol, wax and mixtures thereof.

[0052] Compounds are expected to be useful when used with alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, other apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1) inhibitors, activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, cyclindependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNA's, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSALDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteosome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, etinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, and the like, and in combination with one or more of these agents.

[0053] BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by T-cells when targeted to cancer cells (V.R. Sutton, D.L. Vaux and J.A. Trapani, J. of Immunology 1997, 158 (12), 5783).

[0054] SiRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxynucleotide, 2'-OCH_3-containing ribonucleotides, 2'-F-ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (e.g., hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/ or the 3'-ends of a given strand. For example, siRNAs targeting Mcl-1 have been shown to enhance the activity of ABT-263, (i.e., N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide) or ABT-737 (i.e., N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) in multiple tumor cell lines (Tse et. al, Cancer Research 2008, 68(9), 3421 and references therein).

[0055] Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (i.e., capable of binding one antigen) or multispecific (i.e., capable of binding two or more antigens). DVD binding proteins comprising two heavy

chain DVD polypeptides and two light chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site. Multispecific DVDs include DVD binding proteins that bind DLL4 and VEGF, or C-met and EFGR or ErbB3 and EGFR.

[0056] Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, CLORETAZINE® (laromustine, VNP 40101M), cyclophosphamide, decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepa, TREANDA® (bendamustine), treosulfan, rofosfamide and the like.

[0057] Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

[0058] Antimetabolites include ALIMTA® (pemetrexed disodium, LY231514, MTA), 5-azacitidine, XELODA® (capecitabine), carmofur, LEUSTAT® (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethnylcytidine, fludarabine, 5-fluorouracil alone or in combination with leucovorin, GEMZAR® (gemcitabine), hydroxyurea, ALKERAN®(melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-l, tiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

[0059] Antivirals include ritonavir, hydroxychloroquine and the like.

[0060] Aurora kinase inhibitors include ABT-348, AZD-1152, MLN-8054, VX-680, Aurora A-specific kinase inhibitors, Aurora B-specific kinase inhibitors and pan-Aurora kinase inhibitors and the like.

[0061] Bcl-2 protein inhibitors include AT-101 ((-)gossypol), GENASENSE® (G3139 or oblimersen (Bcl-2-targeting antisense oligonucleotide)), IPI-194, IPI-565, N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide)(ABT-737), N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (ABT-263), GX-070 (obatoclax) and the like.

[0062] Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (imatinib) and the like.

[0063] CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

[0064] COX-2 inhibitors include ABT-963, ARCOXIA® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX® (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX® (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl-1H-pyrrole), MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) and the like.

[0065] EGFR inhibitors include ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX® (cetuximab), HR3, IgA antibodies, IRESSA® (gefitinib), TARCEVA® (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB® (lapatinib) and the like.

[0066] ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), HERCEPTIN® (trastuzumab), TYKERB® (lapatinib), OMNITARG® (2C4, petuzumab), TAK-165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER-2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecfic antibodies, mAB AR-209, mAB 2B-1 and the like.

[0067] Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

[0068] HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB® (human recombinant antibody to HSP-90), NCS-683664, PU24FCl, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and the like.

[0069] Inhibitors of inhibitors of apoptosis proteins include HGS1029, GDC-0145, GDC-0152, LCL-161, LBW-242 and the like.

[0070] Antibody drug conjugates include anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am SGN-35, SGN-75 and the like

[0071] Activators of death receptor pathway include TRAIL, antibodies or other agents that target TRAIL or death receptors (e.g., DR4 and DR5) such as Apomab, conatumumab, ETR2-ST01, GDC0145, (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.

[0072] Kinesin inhibitors include Eg5 inhibitors such as AZD4877, ARRY-520; CENPE inhibitors such as GSK923295A and the like.

[0073] JAK-2 inhibitors include CEP-701 (lesaurtinib), XL019 and INCB018424 and the like.

[0074] MEK inhibitors include ARRY-142886, ARRY-438162 PD-325901, PD-98059 and the like.

[0075] mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30, Torin 1 and the like.

[0076] Non-steroidal anti-inflammatory drugs include AMIGESIC® (salsalate), DOLOBID® (diflunisal), MOTRIN® (ibuprofen), ORUDIS® (ketoprofen), RELAFEN® (nabumetone), FELDENE® (piroxicam), ibuprofen cream, ALEVE® (naproxen) and NAPROSYN® (naproxen), VOLTAREN® (diclofenac), INDOCIN® (indomethacin), CLINORIL® (sulindac), TOLECTIN® (tolmetin), LODINE® (etodolac), TORADOL® (ketorolac), DAYPRO® (oxaprozin) and the like.

[0077] PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

[0078] Platinum chemotherapeutics include cisplatin, ELOXATIN® (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN® (carboplatin), satraplatin, picoplatin and the like.

[0079] Polo-like kinase inhibitors include BI-2536 and the like.

[0080] Phosphoinositide-3 kinase (PI3K) inhibitors include wortmannin, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 and the like.

[0081] Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

[0082] VEGFR inhibitors include AVASTIN® (bevacizumab), ABT-869, AEE-788, ANGIOZYME™ (a ribozyme that inhibits angiogenesis (Ribozyme Pharmaceuticals (Boulder, CO.) and Chiron, (Emeryville, CA)), axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, MACUGEN (pegaptamib), NEXAVAR® (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787, ZK-222584), SUTENT® (sunitinib, SU-11248), VEGF trap, ZACTIMA™ (vandetanib, ZD-6474), GA101, ofatumumab, ABT-806 (mAb-806), ErbB3 specific antibodies, BSG2 specific antibodies, DLL4 specific antibodies and C-met specific antibodies, and the like.

[0083] Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE® (bleomycin), daunorubicin, CAELYX® or MYOCET® (liposomal doxorubicin), elsamitrucin, epirbucin, glarbuicin, ZAVEDOS® (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR® (valrubicin), zinostatin and the like.

[0084] Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR® (irinotecan hydrochloride), camptothecin, CARDIOXANE® (dexrazoxine), diflomotecan, edotecarin, ELLENCE® or PHARMORUBICIN® (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarbucin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

[0085] Antibodies include AVASTIN® (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, ERBITUX® (cetuximab), HUMAX-CD4® (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX® (edrecolomab), RENCAREX® (WX G250), RITUXAN® (rituximab), ticilimumab, trastuzimab, CD20 antibodies types I and II and the like.

[0086] Hormonal therapies include ARIMIDEX® (anastrozole), AROMASIN® (exemestane), arzoxifene, CASODEX® (bicalutamide), CETROTIDE® (cetrorelix), degarelix, deslorelin, DESOPAN® (trilostane), dexamethasone, DROGENIL® (flutamide), EVISTA® (raloxifene), AFEMA™ (fadrozole), FARESTON® (toremifene), FASLODEX® (fulvestrant), FEMARA® (letrozole), formestane, glucocorticoids, HECTOROL® (doxercalciferol), RENAGEL® (sevelamer carbonate), lasofoxifene, leuprolide acetate, MEGACE® (megesterol), MIFEPREX® (mifepristone), NILANDRON™ (nilutamide), NOLVADEX® (tamoxifen citrate), PLENAXIS™ (abarelix), prednisone, PROPECIA® (finasteride), rilostane, SUPREFACT® (buserelin), TRELSTAR® (luteinizing hormone releasing hormone (LHRH)), VANTAS® (Histrelin implant), VETORYL® (trilostane or modrastane), ZOLADEX® (fosrelin, goserelin) and the like.

[0087] Deltoids and retinoids include seocalcitol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinide, PANRETIN® (aliretinoin), ATRAGEN® (liposomal tretinoin), TARGRETIN® (bexarotene), LGD-1550 and the like.

[0088] PARP inhibitors include ABT-888 (veliparib), olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

[0089] Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

[0090] Proteasome inhibitors include VELCADE® (bortezomib), MG132, NPI-0052, PR-171 and the like.

[0091] Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE® (interferon gamma-1b) or interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE® ,(IFN-α), BAM-002 (oxidized glutathione), BEROMUN® (tasonermin), BEXXAR® (tositumomab), CAMPATH® (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE® (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010 (anti-CTLA-4), melanoma vaccine, mitumomab, molgramostim, MYLOTARG™ (gemtuzumab ozogamicin), NEUPOGEN® (filgrastim), OncoVAC-CL, OVAREX® (oregovomab), pemtumomab (Y-muHMFG1), PROVENGE® (sipuleucel-T), sargaramostim, sizofilan, teceleukin, THERACYS® (Bacillus Calmette-Guerin), ubenimex, VIRULIZIN® (immunotherapeutic, Lorus Pharmaceuticals), Z-100 (Specific Substance of Maruyama (SSM)), WF-10 (Tetrachlorodecaoxide (TCDO)), PROLEUKIN® (aldesleukin), ZADAXIN® (thymalfasin), ZENAPAX® (daclizumab), ZEVALIN® (90Y-Ibritumomab tiuxetan) and the like.

[0092] Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth or differentiation of tissue cells to direct them to have anti-tumor activity and include krestin, lentinan, sizofiran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

[0093] Pyrimidine analogs include cytarabine (ara C or Arabinoside C), cytosine arabinoside, doxifluridine, FLUDARA® (fludarabine), 5-FU (5-fluorouracil), floxuridine, GEMZAR® (gemcitabine), TOMUDEX® (ratitrexed), TROXATYL™ (triacetyluridine troxacitabine) and the like.

[0094] Purine analogs include LANVIS® (thioguanine) and PURI-NETHOL® (mercaptopurine).

[0095] Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE® (docetaxel), PNU100940 (109881), patupilone, XRP-9881 (larotaxel), vinflunine, ZK-EPO (synthetic epothilone) and the like.

[0096] Ubiquitin ligase inhibitors include MDM2 inhibitors, such as nutlins, NEDD8 inhibitors such as MLN4924 and the like.

[0097] Compounds of this invention can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Examples of radiotherapy include external beam radiotherapy, teletherapy, brachytherapy and sealed, unsealed source radiotherapy and the like.

[0098] Additionally, compounds of this invention may be combined with other chemotherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN® (Ad5CMV-p53 vaccine), ALTOCOR® or MEVACOR® (lovastatin), AMPLIGEN® (poly I:poly C12U, a synthetic RNA), APTOSYN® (exisulind), AREDIA® (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-diene), AVAGE® (tazarotene), AVE-8062 (combreastatin derivative) BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CEAVAC® (cancer vaccine), CELEUK® (celmoleukin), CEPLENE® (histamine dihydrochloride), CERVARIX® (human papillomavirus vaccine), CHOP® (C: CYTOXAN® (cyclophosphamide); H: ADRIAMYCIN® (hydroxydoxorubicin); O: Vincristine (ONCOVIN®); P: prednisone), CYPAT™ (cyproterone acetate), combrestatin A4P, DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor) or TransMID-107R™(diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), eniluracil, EVIZON™ (squalamine lactate), DIMERICINE® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906 (epithilone B), GARDASIL® (quadrivalent human papillomavirus (Types 6, 11,16, 18) recombinant vaccine), GASTRIMMUNE®, GENASENSE®, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon-α, interferon-γ, JUNOVAN™ or MEPACT™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTAT®(AE-941), NEUTREXIN® (trimetrexate glucuronate), NIPENT® (pentostatin), ONCONASE® (a ribonuclease enzyme), ONCOPHAGE® (melanoma vaccine treatment), ONCOVAX® (IL-2 Vaccine), ORATHECINT™ (rubitecan), OSIDEM® (antibody-based cell drug), OVAREX® MAb (murine monoclonal antibody), paclitaxel, PANDIMEX™ (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC®-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB® (catumaxomab), REVLIMID® (lenalidomide), RSR13 (efaproxiral), SOMATULINE® LA (lanreotide), SORIATANE® (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN® (bexarotene), TAXOPREXIN® (DHA-paclitaxel), TELCYTA® (canfosfamide, TLK286), temilifene, TEMODAR® (temozolomide), tesmilifene, thalidomide, THERATOPE® (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFERADE™ (adenovector: DNA carrier containing the gene for tumor necrosis factor-α), TRACLEER® or ZAVESCA® (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX® (arsenic trioxide), VIRULIZIN®, ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti-alphavbeta3 antibody), XCYTRIN® (motexafin gadolinium), XINLAY™ (atrasentan), XYOTAX™ (paclitaxel poliglumex), YONDELIS® (trabectedin), ZD-6126, ZINECARD® (dexrazoxane), ZOMETA® (zolendronic acid), zorubicin and the like.

Determination of Biological Activity

[0099] Assays for the inhibition of Bcl-2 family proteins, using Bcl-xL as a representative example, were performed in 96-well microtiter plates. Compounds of the present invention were diluted in DMSO to concentrations between 10 M and 10 pM and introduced into each cell of the plate. A mixture totaling 125 L per well of assay buffer (20 mM phosphate buffer (pH 7.4), 1 mM EDTA, 50 mM NaCl, 0.05% pluronic F-68), 6 nM of BCL-X_L protein (prepared according to the procedure described in Science 1997, 275, 983-986), 1 nM fluorescein-labeled BAD peptide (purchased from Synpep, CA), and the DMSO solution of the compound of the present invention was shaken for 2 minutes and placed in a LJL Analyst (LJL Bio Systems, CA). A negative control (DMSO, 15 nM BAD peptide, assay buffer) and a positive control (DMSO, 15 nM BAD peptide, 30 nM BCL-X_L, assay buffer) were used to determine the range of the assay. Polarization was measured at room temperature using a continuous Fluorescein lamp (excitation 485 nm, emission 530 nm). The K_i value was calculated directly from the mP value by Microsoft Excel.

[0100] Assays for the inhibition of Bcl-2 were performed in 96-well microtiter plates. Compounds of the instant invention were diluted in DMSO to concentrations between 10 M and 10 pM and introduced into each well of the plate. A mixture totaling 125 L per well of assay buffer (20 mM phosphate buffer (pH 7.4), 1 mM EDTA, 0.05% PF-68), 10 nM of Bcl-2 protein (prepared according to the procedure described in PNAS 2001, 98, 3012 - 3017), 1 nM fluorescein-labeled BAX peptide (prepared in-house), and the DMSO solution of the compound of the instant invention was shaken for 2 minutes and placed in a LJL Analyst (LJL Bio Systems, CA. Polarization was measured at room temperature using a continuous Fluorescein lamp (excitation 485 nm, emission 530 nm). K_i values were calculated using Microsoft Excel.

[0101] Inhibition constants (K_i) for compounds according to the invention are shown in TABLE 1 below. Where the K_i for a compound is represented as ">" (greater than) a certain numerical value, it is intended to mean that the binding affinity value is greater than the limits of detection of the assay used. Where the K_i for a compound is represented as "<" (less than) a certain numerical value, it is intended to mean that the binding affinity value is lower than the limit of detection of the assay used.

TABLE 1. FPA Bcl-2 Binding Ki (μM)

Example No.	Bcl-2 FPA 11pt Ki (uM)	Example No.	Bcl-2 FPA 11pt Ki (uM)
*1	0.174	44	>6.245
2	0.22	45	0.079
3	0.065	46	0.033
4	0.19089	47	0.066928
5	0.059174	48	1.388
6	0.15496	49	0.342
7	1.2644	50	3.556
*8	0.084635	51	1.049
*9	< 0.020	52	1.392
*10	< 0.020	53	0.84492
*11	1.3044	54	>9.7305
12	0.3038	55	0.35156
13	0.60807	56	< 0.020
*14	0.047406	57	0.13387
15	< 0.020	58	> 18.674
16	0.039706	59	0.066678
17	0.030083	60	0.50423
18	< 0.020	61	< 0.020
19	0.6035	62	0.28077
20	>51.897	63	0.27762
21	5.5988	64	1.4727
22	0.031403	65	0.9281
23	< 0.020	66	0.0078655
24	2.2651	67	4.0442
25	0.97859	68	0.092644
26	1.1655	69	0.78864
27	0.027114	70	0.03537
28	0.029579	71	< 0.020
*29	0.35402	72	0.28748

(continued)

Example No.	Bcl-2 FPA 11pt Ki (uM)	Example No.	Bcl-2 FPA 11pt Ki (uM)
30	0.29489	73	0.093189
31	0.031861	74	0.10238
32	0.091893	75	0.25081
33	< 0.020	76	nd
34	0.047684	77	nd
35	0.021652	78	nd
36	0.12146	79	1.42
37	0.16544	80	1.303
38	0.14942	81	4.726
39	2.9135	82	2.18
40	0.054683	83	> 6.245
*41	5.186	84	2.378
*42	2.479	85	2.878
*43	>6.245		
* comparative			

[0102] The inhibition constant (K_i) is the dissociation constant of an enzyme-inhibitor complex or a protein/small molecule complex, wherein the small molecule is inhibiting binding of one protein to another protein. So a large K_i value indicates a low binding affinity and a small K_i value indicates a high binding affinity.

[0103] This inhibitory data demonstrates the utility of compounds having formula (I) as inhibitors of anti-apopotic Bcl-2 protein.

[0104] It is expected that, because compounds of this invention bind to Bcl-2, they would also have utility as binders to anti-apoptotic proteins having close structural homology to Bcl-2, such as, for example, anti-apoptotic Bcl-X_L, Bcl-w, Mcl-1 and Bfl-1/Al proteins.

[0105] Involvement of Bcl-2 proteins in bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer spleen cancer, and the like is described in commonly-owned PCT US 2004/36770, published as WO 2005/049593, and PCT US 2004/37911, published as WO 2005/024636.

[0106] Involvement of Bcl-2 proteins in immune and autoimmune diseases is described in Current Allergy and Asthma Reports 2003, 3, 378-384; Brutish Journal of Haematology 2000, 110(3), 584-90; Blood 2000, 95(4), 1283-92; and New England Journal of Medicine 2004, 351(14), 1409-1418.

[0107] Involvement of Bcl-2 proteins in arthritis is disclosed in commonly-owned United States Provisional Patent Application Serial No. 60/988,479.

[0108] Involvement of Bcl-2 proteins in bone marrow transplant rejection is disclosed in commonly-owned United States Patent Application Serial No. 11/941,196.

[0109] Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system. Cancers include, but are not limited to, hematologic and solid tumor types such as acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer (including estrogen-receptor positive breast cancer), bronchogenic carcinoma, Burkitt's lymphoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, gastric car-

cinoma, germ cell testicular cancer, gestational trophobalstic disease, glioblastoma, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer (including small cell lung cancer and non-small cell lung cancer), lymphangioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (lymphoma, including diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, peripheral T-cell lymphoma, pineaoma, polycythemia vera, prostate cancer (including hormone-insensitive (refractory) prostate cancer), rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, Waldenström's macroglobulinemia, testicular tumors, uterine cancer, Wilms' tumor and the like.

[0110] It is also expected that compounds of this invention would inhibit growth of cells expressing Bcl-2 proteins derived from a pediatric cancer or neoplasm including embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoid/rhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer and the like.

[0111] Autoimmune disorders include acquired immunodeficiency disease syndrome (AIDS), autoimmune lymphoproliferative syndrome, hemolytic anemia, inflammatory diseases, and thrombocytopenia, acute or chronic immune disease associated with organ transplantation, Addison's disease, allergic diseases, alopecia, alopecia areata, atheromatous disease/arteriosclerosis, atherosclerosis, arthritis (including osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis and reactive arthritis), autoimmune bullous disease, abetalipoprotemia, acquired immunodeficiency-related diseases, acute immune disease associated with organ transplantation, acquired acrocyanosis, acute and chronic parasitic or infectious processes, acute pancreatitis, acute renal failure, acute rheumatic fever, acute transverse myelitis, adenocarcinomas, aerial ectopic beats, adult (acute) respiratory distress syndrome, AIDS dementia complex, alcoholic cirrhosis, alcohol-induced liver injury, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allergy and asthma, allograft rejection, alpha-1- antitrypsin deficiency, Alzheimer's disease, amyotrophic lateral sclerosis, anemia, angina pectoris, ankylosing spondylitis associated lung disease, anterior horn cell degeneration, antibody mediated cytotoxicity, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneurysms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, arthropathy, asthenia, asthma, ataxia, atopic allergy, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, atrophic autoimmune hypothyroidism, autoimmune haemolytic anaemia, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), autoimmune mediated hypoglycaemia, autoimmune neutropaenia, autoimmune thrombocytopaenia, autoimmune thyroid disease, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bronchiolitis obliterans, bundle branch block, burns, cachexia, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chlamydia, choleosatatis, chronic alcoholism, chronic active hepatitis, chronic fatigue syndrome, chronic immune disease associated with organ transplantation, chronic eosinophilic pneumonia, chronic inflammatory pathologies, chronic mucocutaneous candidiasis, chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal common varied immunodeficiency (common variable hypogammaglobulinaemia), conjunctivitis, connective tissue disease associated interstitial lung disease, contact dermatitis, Coombs positive haemolytic anaemia, cor pulmonale, Creutzfeldt-Jakob disease, cryptogenic autoimmune hepatitis, cryptogenic fibrosing alveolitis, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, Crohn's disease, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatitis scleroderma, dermatologic conditions, dermatomyositis/polymyositis associated lung disease, diabetes, diabetic arteriosclerotic disease, diabetes mellitus, Diffuse Lewy body disease, dilated cardiomyopathy, dilated congestive cardiomyopathy, discoid lupus erythematosus, disorders of the basal ganglia, disseminated intravascular coagulation, Down's Syndrome in middle age, drug-induced interstitial lung disease, drug-induced hepatitis, drug-induced movement disorders induced by drugs which block CNS dopamine, receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, enteropathic synovitis, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hematophagocytic lym-

phohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, female infertility, fibrosis, fibrotic lung disease, fungal sepsis, gas gangrene, gastric ulcer, giant cell arteritis, glomerular nephritis, glomerulonephritides, Goodpasture's syndrome, goitrous autoimmune hypothyroidism (Hashimoto's disease), gouty arthritis, graft rejection of any organ or tissue, graft versus host disease, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, group B streptococci (GBS) infection, Grave's disease, haemosiderosis associated lung disease, hairy cell leukemia, hairy cell leukemia, Hallerrorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hematopoietic malignancies (leukemia and lymphoma), hemolytic anemia, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, Henoch-Schoenlein purpurea, Hepatitis A, Hepatitis B, Hepatitis C, HIV infection/HIV neuropathy, Hodgkin's disease, hypoparathyroidism, Huntington's chorea, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hyperthyroidism, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic leucopaenia, idiopathic pulmonary fibrosis, idiopathic thrombocytopaenia, idiosyncratic liver disease, infantile spinal muscular atrophy, infectious diseases, inflammation of the aorta, inflammatory bowel disease, insulin dependent diabetes mellitus, interstitial pneumonitis, iridocyclitis/uveitis/optic neuritis, ischemia-reperfusion injury, ischemic stroke, juvenile pernicious anaemia, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, Kawasaki's disease, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, linear IgA disease, lipidema, liver transplant rejection, Lyme disease, lymphederma, lymphocytic infiltrative lung disease, malaria, male infertility idiopathic or NOS, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, microscopic vasculitis of the kidneys, migraine headache, mitochondrial multisystem disorder, mixed connective tissue disease, mixed connective tissue disease associated lung disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel Dejerine-Thomas Shi-Drager and Machado-Joseph), myalgic encephalitis/Royal Free Disease, myasthenia gravis, microscopic vasculitis of the kidneys, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodyplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, nephrotic syndrome, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever, Non-alcoholic Steatohepatitis, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, organ transplant rejection, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoarthrosis, osteoporosis, ovarian failure, pancreas transplant rejection, parasitic diseases, parathyroid transplant rejection, Parkinson's disease, pelvic inflammatory disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, perennial rhinitis, pericardial disease, peripheral atherlosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, phacogenic uveitis, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiotomy syndrome, postinfectious interstitial lung disease, premature ovarian failure, primary biliary cirrhosis, primary sclerosing hepatitis, primary myxoedema, primary pulmonary hypertension, primary sclerosing cholangitis, primary vasculitis, Progressive supranucleo Palsy, psoriasis, psoriasis type 1, psoriasis type 2, psoriatic arthropathy, pulmonary hypertension secondary to connective tissue disease, pulmonary manifestation of polyarteritis nodosa, post-inflammatory interstitial lung disease, radiation fibrosis, radiation therapy, Raynaud's phenomenon and disease, Raynoud's disease, Refsum's disease, regular narrow QRS tachycardia, Reiter's disease, renal disease NOS, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, rheumatoid arthritis associated interstitial lung disease, rheumatoid spondylitis, sarcoidosis, Schmidt's syndrome, scleroderma, senile chorea, Senile Dementia of Lewy body type, sepsis syndrome, septic shock, seronegative arthropathies, shock, sickle cell anemia, Sjögren's disease associated lung disease, Sjörgren's syndrome, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, sperm autoimmunity, multiple sclerosis (all subtypes), spinal ataxia, spinocerebellar degenerations, spondyloarthropathy, spondyloarthopathy, sporadic, polyglandular deficiency type I sporadic, polyglandular deficiency type II, Still's disease, streptococcal myositis, stroke, structural lesions of the cerebellum, Subacute sclerosing panencephalitis, sympathetic ophthalmia, Syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic lupus erythematosus-associated lung disease, systemic sclerosis, systemic sclerosis-associated interstitial lung disease, T-cell or FAB ALL, Takayasu's disease/arteritis, Telangiectasia, Th2 Type and Th1 Type mediated diseases, thromboangitis obliterans, thrombocytopenia, thyroiditis, toxicity, toxic shock syndrome, transplants, trauma/hemorrhage, type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), type B insulin resistance with acanthosis nigricans, type III hypersensitivity reactions, type IV hypersensitivity, ulcerative colitic arthropathy, ulcerative colitis, unstable angina, uremia, urosepsis, urticaria, uveitis, valvular heart diseases, varicose veins, vasculitis, vasculitic diffuse lung disease, venous diseases, venous thrombosis, ventricular fibrillation, vitiligo acute liver disease, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wegener's granulomatosis, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, yersinia and salmonella-associated arthropathy and the like.

Schemes and Experimentals

[0112] The following abbreviations have the meanings indicated. ADDP means 1,1'-(azodicarbonyl)dipiperidine; AD-mix-β means a mixture of $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, and K_2SO_4; 9-BBN means 9-borabicyclo(3.3.1)nonane; Boc means tert-butoxycarbonyl; $(DHQD)_2PHAL$ means hydroquinidine 1,4-phthalazinediyl diethyl ether; DBU means 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL means diisobutylaluminum hydride; DIEA means diisopropylethylamine; DMAP means N,N-dimethylaminopyridine; DMF means N,N-dimethylformamide; dmpe means 1,2-bis(dimethylphosphino)ethane; DMSO means dimethylsulfoxide; dppb means 1,4-bis(diphenylphosphino)-butane; dppe means 1,2-bis(diphenylphosphino)ethane; dppf means 1,1'-bis(diphenylphosphino)ferrocene; dppm means 1,1-bis(diphenylphosphino)methane; EDAC·HCl means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Fmoc means fluorenylmethoxycarbonyl; HATU means O-(7-azabenzotriazol-1-yl)-N,N'N'N'-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; IPA means isopropyl alcohol; MP-BH_3 means macroporous triethylammonium methylpolystyrene cyanoborohydride; TEA means triethylamine; TFA means trifluoroacetic acid; THF means tetrahydrofuran; NCS means N-chlorosuccinimide; NMM means N-methylmorpholine; NMP means N-methylpyrrolidine; PPh_3 means triphenylphosphine.

[0113] Compounds of this invention may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned, and that vulnerable moieties may be protected and deprotected, as necessary.

[0114] The following examples are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. The exemplified compounds and intermediates were named using ACD/ChemSketch Version 12.01 (13 May 2009), Advanced Chemistry Development Inc., Toronto, Ontario), or ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA).

EXAMPLE 2

4-(4-{acetyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 2A

4-{4-[acetyl-((1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amino]-piperidin-1-yl}-benzoic acid ethyl ester

[0115] EXAMPLE 45C (50 mg) was dissolved in dichloromethane (2 mL). Triethylamine (0.022 mL, 16 mg) was added, followed by acetyl chloride (0.010 mL, 11 mg). The solution was mixed at room temperature for 16 hours and then purified by flash column chromatography on silica gel using 30% ethyl acetate in hexanes to afford the title compound.

EXAMPLE 2B

4-{4-[Acetyl-((1S,2S,3S,SR)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amino]-piperidin-1-yl}-benzoic acid

[0116] EXAMPLE 2A (55 mg) was dissolved in tetrahydrofuran (0.6 mL), methanol (0.2 mL), and water (0.2 mL) and treated with lithium hydroxide monohydrate (22 mg). The solution was stirred at room temperature for 16 hours. The solution was acidified with 1 M hydrochloric acid, extracted with ethyl acetate, dried with anhydrous sodium sulfate, filtered, and concentrated to afford the title compound.

EXAMPLE 2C

4-Fluoro-3-nitro-benzenesulfonamide

[0117] 2-Fluoronitrobenzene (141 g, 1.0 mol) and chlorosulfonic acid (300 mL) were heated at 60°C for 10 hours. After the reaction mixture cooled to room temperature, it was carefully poured to ice (about 1 kg) in a four liter Erlenmeyer flask and cooled efficiently by an ice-brine bath. The mixture was extracted with ether (4 L), and brine (2 L). The resulting solution was cooled to -40°C. Concentrated ammonium hydroxide (300 mL) was then added with vigorous stirring, and the addition rate was controlled to allow the reaction mixture to stay below-10°C (internal temperature). Dry ice cubes were added to the reaction mixture to lower the temperature when necessary. Immediately after the addition was complete, the resulting mixture was separated, and the aqueous phase was extracted with ethyl acetate (2 L). The combined organic phases were washed with the aqueous 4 M hydrochloric acid (300 mL) and brine (100 mL), dried on anhydrous

magnesium sulfate, filtered, and concentrated. The resulting solid was recrystallized from ethyl acetate/hexane mixture. The mother liquid from the recrystallization was concentrated and recrystallized in the same manner, and the resulting solids were combined to afford the title compound.

-EXAMPLE 2D

4-(Cyclohexylmethyl-amino)-3-nitro-benzenesulfonamide

[0118] To a solution of EXAMPLE 2C (7.70 g) in tetrahydrofuran (35 mL) was added dropwise a solution of cyclohexylmethylamine (6.0 mL, 5.22 g) and diisopropylethylamine (8.0 mL, 5.92 g) in tetrahydrofuran (15 mL). After the addition, tetrahydrofuran (20 mL) was added, and the reaction was stirred at room temperature for 16 hours. The solution was added to water and extracted with a solution of ethyl acetate and dichloromethane (1:1 by volume). The solution was dried over anhydrous sodium sulfate, filtered, and the filtrate volume was reduced to isolate the title compound by crystallization.

EXAMPLE 2E

4-(4-{acetyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0119] The title compound was prepared by substituting EXAMPLE 2B for EXAMPLE 1A and EXAMPLE 2D for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}HNMR (300MHz, dimethylsulfoxide-d_6) δ 8.50 (br s, 1H), 8.40 (m, 1H), 7.88 (dd, 1H), 7.73 (d, 1H), 7.71 (d, 1H), 7.06 (dd, 1H), 6.86 (d, 1H), 6.81 (d, 1H), 4.16 (m, 1H), 3.96-3.77 (m, 2H), 3.25 (t, 4H), 3.18-3.06 (m, 2H), 2.77 (m, 4H), 2.48-2.23 (m, 2H), 2.14-1.95 (m, 8H), 1.86 (m, 2H), 1.77-1.60 (m, 11H), 1.25-1.14 (m, 8H), 1.07-1.00 (m, 4H), 0.95-0.86 (m, 2H).

EXAMPLE 3

4-(4-{benzoyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 3A

4-{4-[Benzoyl-((1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amino]-piperidin-1-yl}-benzoic acid ethyl ester

[0120] The title compound was prepared by substituting benzoyl chloride for acetyl chloride in EXAMPLE 2A.

EXAMPLE 3B

4-{4-[Benzoyl-((1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amino]-piperidin-1-yl}-benzoic acid

[0121] The title compound was prepared by substituting EXAMPLE 3A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 3C

4-(4-{benzoyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0122] The title compound was prepared by substituting EXAMPLE 3B for EXAMPLE 1A and EXAMPLE 2D for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.98 (br s, 1H), 8.51 (br s, 1H), 8.42 (br s, 1H), 7.89 (dd, 1H), 7.43 (d, 2H), 7.42 (m, 3H), 7.29 (d, 2H), 7.08 (d, 1H), 6.85 (d, 2H), 4.03-3.75 (m, 3H), 3.24 (t, 4H), 2.86 (m, 2H), 2.37 (m, 2H), 2.11 (m, 2H), 1.97-1.82 (m, 2H), 1.78-1.55 (m, 10H), 1.23-0.91 (m, 11H), 0.79 (d, 2H), 0.45 (s, 1H).

EXAMPLE 4

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-3'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide

EXAMPLE 4A

methyl 3'-bromobiphenyl-4-carboxylate

[0123] 4-(Methoxycarbonyl)phenylboronic acid (1.55 g, 8.63 mmol), 1-bromo-3-iodobenzene (2.22 g, 7.84 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.29 g, 0.392 mmol), and CsF (2.38 g, 15.7 mmol) in dioxane (40 mL) were stirred at 80°C for 8 hours. The reaction was cooled, poured into ethyl acetate, washed twice with water and brine, and the combined organic layers were concentrated. The residue was chromatographed on silica gel using 2-20% ethyl acetate in hexanes afford the title compound.

EXAMPLE 4B

methyl 3'-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)biphenyl-4-carboxylate

[0124] EXAMPLE 4A (146 mg, 0.50 mmol), (1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (92 mg, 0.60 mmol), tris(dibenzylideneacetone)dipalladium(0) (23 mg, 0.025 mmol), tri-t-butylphosphonium tetrafluoroborate (11.7 mg, 0.04 mmol), and K_3PO_4 (160 mg, 0.75 mmol) in diglyme (5 mL) were stirred at 100°C for 24 hours. The reaction was cooled and was chromatographed on silica gel using 5% ethyl acetate in hexanes to afford the title compound.

EXAMPLE 4C

3'-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)biphenyl-4-carboxylic acid

[0125] The title compound was prepared as described in EXAMPLE 2B using EXAMPLE 4B in place of EXAMPLE 2A.

EXAMPLE 4D

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-3'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide

[0126] The title compound was prepared as described in EXAMPLE 1B using EXAMPLE 4C in place of EXAMPLE 1A and EXAMPLE 2D in place of 4-chloro-3-nitrobenzenesulfonamide. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.90 (s, 1H), 8.65 (m, 2H), 7.97 (d, 1H), 7.93 (d, 2H), 7.68 (d, 2H), 7.28 (d, 1H), 7.17 (t, 1H), 6.88 (s, 1H), 6.82 (d, 1H), 6.66 (d, 1H), 5.70 (m, 1H), 3.65 (m, 1H), 2.55 (m, 2H), 2.34 (m, 4H), 1.72 (m, 6H), 1.52 (m, 1H), 0.99-1.49 (m, 16H).

EXAMPLE 5

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(phenylacetyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

EXAMPLE 5A

4-{4-[Phenylacetyl-((1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amino]-piperidin-1-yl}-benzoic acid ethyl ester

[0127] The title compound was prepared by substituting phenylacetyl chloride for acetyl chloride in EXAMPLE 2A.

EXAMPLE 5B

4-{4-[Phenylacetyl-((1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amino]-piperidin-1-yl}-benzoic acid

[0128] The title compound was prepared by substituting EXAMPLE 5A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 5C

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(phenylacetyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

[0129] The title compound was prepared by substituting EXAMPLE 5B for EXAMPLE 1A and EXAMPLE 2D for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.98 (br s, 1 H), 8.63 (m, 2H), 7.93 (dt, 1 H), 7.73 (d, 1 H), 7.71 (d, 1H), 7.33-7.19 (m, 6H), 6.91 (d, 2H), 4.10 (m, 1H), 3.95 (m, 2H), 3.78 (d, 1H), 3.29 (t, 4H), 3.00-2.60 (m, 4H), 2.34 (m, 1H), 2.17 (m, 1H), 2.05 (m, 1 H), 1.90 (m, 1 H), 1.80-1.53 (m, 9H), 1.23-1.17 (m, 8H), 0.99 (m, 2H), 0.92-0.86 (m, 6H).

EXAMPLE 6

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{[1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}bipheny)-4-carboxamide

EXAMPLE 6A

methyl 4'-bromobiphenyl-4-carboxylate

[0130] The title compound was prepared as described in EXAMPLE 4A using 1-bromo-4-iodobenzene in place of 1-bromo-3-iodobenzene.

EXAMPLE 6B

methyl 4'-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)biphenyl-4-carboxylate

[0131] The title compound was prepared as described in EXAMPLE 4B using EXAMPLE 6A in place of EXAMPLE 4A.

EXAMPLE 6C

4'-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)biphenyl-4-carboxylic acid

[0132] The title compound was prepared as described in EXAMPLE 2B using EXAMPLE 6B in place of EXAMPLE 2A.

EXAMPLE 6D

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide

[0133] The title compound was prepared as described in EXAMPLE 1B using EXAMPLE 6C in place of EXAMPLE 1A and EXAMPLE 2D in place of 4-chloro-3-nitrobenzenesulfonamide. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.90 (s, 1H), 8.66 (m, 2H), 7.97 (d, 1H), 7.87 (d, 2H), 7.66 (d, 2H), 7.51 (d, 2H), 7.26 (d, 2H), 7.18 (m, 1H), 6.79 (d, 2H), 5.95 (m, 1H), 3.65 (m, 1H), 2.60 (m, 2H), 2.33 (m, 2H), 1.94 (m, 2H), 1.72 (m, 6H), 1.23 (s, 3H), 1.19 (m, 4H), 0.93-1.15 (m, 11H).

EXAMPLE 7

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide

EXAMPLE 7A

4'-((3-phenylpropyl)((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)amino)biphenyl-4-carboxylic acid

[0134] EXAMPLE 6C (100 mg, 0.286 mmol), 3-phenylpropanal (101 mg, 0.715 mmol), and sodium triacetoxyborohydride (182 mg, 0.858 mmol) was stirred in 1,2-dichloroethane (5 mL) for 24 hours. The mixture was triturated with dichloromethane and ether to afford the title compound.

EXAMPLE 7B

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide

[0135] The title compound was prepared as described in EXAMPLE 1B using EXAMPLE 7A in place of EXAMPLE 1A and EXAMPLE 2D in place of 4-chloro-3-nitrobenzenesulfonamide.

EXAMPLE 12

4-(4-{[3-bromo-5-methyladamantan-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 12A

ethyl 4-(4-{[3-bromo-5-methyladamantan-1-yl]carbonyl}piperazin-1-yl)benzoate

[0136] The title compound was prepared by substituting EXAMPLE 10A for EXAMPLE 8B and 3-methyl-5-bromo-adamantane-1-carboxylic acid for adamantane-1-carboxylic acid in EXAMPLE 8C.

EXAMPLE 12B

ethyl 4-(4-{[3-bromo-5-methyladamantan-1-yl]methyl}piperazin-1-yl)benzoate

[0137] The title compound was prepared by substituting EXAMPLE 12A for EXAMPLE 8C in EXAMPLE 8D.

EXAMPLE 12C

4-(4-{[3-bromo-5-methyladamantan-1-yl]methyl}piperazin-1-yl)benzoic acid

[0138] The title compound was prepared by substituting EXAMPLE 12B for EXAMPLE 8D in EXAMPLE 8E.

EXAMPLE 12D

4-(4-{[3-bromo-5-methyladamantan-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0139] The title compound was prepared by substituting EXAMPLE 12C for EXAMPLE 8E in EXAMPLE 8F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.05 (v br s, 1H), 8.97 (v br s, 1H), 8.63 (m,2H), 7.93 (dd, 1H), 7.80 (d, 2H), 7.25 (d, 1H), 7.00 (d, 2H), 3.90 (br m, 1H), 3.60, 3.40, 3.20, 3.00 (all br m, total 10H), 2.21 (s, 5H) 2.02 (m, 2H), 1.70 (m, 7H), 1.40 (m, 5H), 1.20 (m, 4H), 1.00 (m, 2H), 0.86 (s, 3H).

EXAMPLE 13

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[3,5-dimethyladamantan-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 13A

ethyl 4-(4-{[3,5-dimethyladamantan-1-yl]carbonyl}piperazin-1-yl)benzoate

[0140] The title compound was prepared by substituting EXAMPLE 10A for EXAMPLE 8B and 3,5-dimethyl-adamantane-1-carboxylic acid for adamantane-1-carboxylic acid in EXAMPLE 8C.

EXAMPLE 13B

ethyl 4-(4-{[3,5-dimethyladamantan-1-yl]methyl}piperazin-1-yl)benzoate

[0141] The title compound was prepared by substituting EXAMPLE 13A for EXAMPLE 8C in EXAMPLE 8D.

EXAMPLE 13C

4-(4-{[3,5-dimethyladamantan-1-yl]methyl}piperazin-1-yl)benzoic acid

[0142] The title compound was prepared by substituting EXAMPLE 13B for EXAMPLE 8D in EXAMPLE 8E.

EXAMPLE 13D

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[3,5-dimethyladamantan-1-yl]methyl}piperazin-1-yl)benzamide

[0143] The title compound was prepared by substituting EXAMPLE 13C for EXAMPLE 8E in EXAMPLE 8F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.05 (v br s, 1H), 8.97 (v br s, 1H), 8.63 (m,2H), 7.93 (dd, 1H), 7.80 (d, 2H), 7.25 (d, 1H), 7.00 (d, 2H), 3.90 (br m, 1H), 3.55 (br m, 1H), 3.30 (m, 8H), 2.99 (br s, 2H), 2.08 (br m, 1H), 1.70 (m, 7H),1.45 (s, 2H),1.20 (m, 12H), 1.00 (m, 2H), 0.82 (s, 6H).

EXAMPLE 15

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzamide

EXAMPLE 15A

ethyl 4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzoate

[0144] EXAMPLE 62A (100 mg), (1S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-ylboronic acid (44.6 mg), tris(dibenzylideneacetone)dipalladium(0) (11 mg), tri-t-butylphosphonium tetrafluoroborate (4 mg) and CsF (113 mg) were dissolved in anhydrous tetrahydrofuran (2 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated, and the crude material was purified using flash chromotography with 0-15% ethyl acetate/hexane to afford the title compound.

EXAMPLE 15B

4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzoic acid

[0145] The title compound was prepared by substituting EXAMPLE 15A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 15C

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzamide

[0146] The title compound was prepared by substituting EXAMPLE 15B for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.12 (m, 1H), 8.66 (m, 2H), 7.94 (dd, 1H), 7.79 (d, 2H), 7.64 (m, 1H), 7.41 (m, 2H), 7.30 (d, 1H), 7.20 (m, 1H), 6.99 (d, 2H), 6.01 (d, 1H), 4.28 (m, 2H), 3.85 (m, 2H), 3.28 (m, 12H), 1.92 (m, 2H), 1.62 (m, 3H), 1.24 (m, 5H), 0.94 (s, 3H), 0.83 (d, 6H).

EXAMPLE 16

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-octahydro-1H-4,7-methanoinden-5-ylamino]benzyl}piperazin-1-yl)benzamide

EXAMPLE 16A

ethyl 4-(4-(2-nitrobenzyl)piperazin-1-yl)benzoate

[0147] Ethyl 4-(piperazin-1-yl)benzoate (1.5 g), 1-(bromomethyl)-2-nitrobenzene (1.383 g) and sodium carbonate (2.036 g) were suspended in anhydrous N,N-dimethylformamide (20 mL) at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine, and concentrated. The residue was purified by flash column purification with 10-40% ethyl acetate/hexane to afford the title compound.

EXAMPLE 16B

Ethyl 4-(4-(2-aminobenzyl)piperazin-1-yl)benzoate

[0148] EXAMPLE 16A (1.5 g) and 5% Pd/C (0.3 g) were suspended in anhydrous ethanol (75 mL). The reaction mixture was stirred under 1 atmosphere hydrogen for 2 hours. The mixture was filtered, and the filtrate was concentrated to afford the product.

EXAMPLE 16C

ethyl 4-(4-{2-[octahydro-1*H*-4,7-methanoinden-5-ylamino]benzyl}piperazin-1-yl)benzoate

[0149] The title compound was prepared by substituting tricyclo[5.2.1.02,6]decan-8-one for 2-formylphenylboronic acid and EXAMPLE 16B for EXAMPLE 23C in EXAMPLE 40A.

EXAMPLE 16D

4-(4-{2-[octahydro-1*H*-4,7-methanoinden-5-ylamino]benzyl}piperazin-1-yl)benzoic acid

[0150] The title compound was prepared by substituting EXAMPLE 16C for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 16E

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[octahydro-1H-4,7-methanoinden-5-ylamino]benzyl}piperazin-1-yl)benzamide

[0151] The title compound was prepared by substituting EXAMPLE 16D for EXAMPLE 1 A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.09 (bs, 1H), 8.66 (m, 2H), 7.94 (dd, 1H), 7.79 (d, 2H), 7.30 (d, 1H), 7.22 (t, 2H), 7.01 (m, 2H), 6.72 (d, 1H), 6.65 (m, 1H), 4.26 (m, 2H), 3.85 (dd, 2H), 3.66 (m, 2H), 3.28 (m, 10H), 2.26-1.61 (m, 14H), 1.40-0.92 (m, 8H).

EXAMPLE 17

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,4R,6S)-5,5,6-trimethylbicyclo[2.2.1]hept-2-yl]amino}benzyl)piperazin-1-yl]benzamide

EXAMPLE 17A

ethyl 4-(4-(2-((1R,4R,6S)-5,5,6-trimethylbicyclo[2.2.1]heptan-2-ylamino)benzyl)piperazin-1-yl)benzoate

[0152] The title compound was prepared by substituting (1R,4R,6S)-5,5,6-trimethylbicyclo[2.2.1]heptan-2-one for 2-formylphenylboronic acid and EXAMPLE 16B for EXAMPLE 23C in EXAMPLE 40A.

EXAMPLE 17B

Ethyl 4-(4-(2-((1R,4R,6S)-5,5,6-trimethylbicyclo[2.2.1]heptan-2-ylamino)benzyl)piperazin-1-yl)benzoate

[0153] The title compound was prepared by substituting EXAMPLE 17A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 17C

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,4R,6S)-5,5,6-trimethylbicyclo[2.2.1]hept-2-yl]amino}benzyl)piperazin-1-yl]benzamide

[0154] The title compound was prepared by substituting EXAMPLE 17B for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.06 (bs, 1H), 8.64 (m, 2H), 7.94 (m, 1H), 7.79 (d, 2H), 7.30 (d, 1H), 7.20 (m, 2H), 7.00 (d, 2H), 6.65 (m, 2H), 3.83 (m, 2H), 3.61 (m, 2H), 3.30 (m, 14H), 2.05 (s, 1H), 1.86 (m, 3H), 1.61 (m, 4H), 1.45 (m, 1H), 1.28 (m, 3H), 0.99 (s, 3H), 0.86 (s, 3H), 0.77 (d, 3H).

EXAMPLE 18

4-[4-(2-{[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 18A

Ethyl 4-(4-(2-((1R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-ylamino)benzyl)piperazin-1-yl)benzoate

[0155] The title compound was prepared by substituting (1R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-one for 2-formylphenylboronic acid and EXAMPLE 16B for EXAMPLE 23C in EXAMPLE 40A.

EXAMPLE 18B

4-(4-(2-((1R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-ylamino)benzyl)piperazin-1-yl)benzoic acid

[0156] The title compound was prepared by substituting EXAMPLE 18A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 18C

4-[4-(2-{[[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0157] The title compound was prepared by substituting EXAMPLE 18B for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.09 (s, 1H), 8.66 (m, 2H), 7.94 (dd, 1H), 7.79 (d, 2H), 7.30 (d, 1H), 7.19 (m, 2H), 6.99 (d, 2H), 6.59 (m, 2H), 3.85 (m, 4H), 3.29 (m, 14H), 2.33 (m, 2H), 2.17 (m, 1H), 1.82 (m, 7H), 1.27 (dd, 2H), 1.18 (s, 3H), 1.09 (s, 3H), 1.03 (d, 1H).

EXAMPLE 19

4-(4-{[(1R,5R)-2-(4-chlorophenyl)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl} sulfonyl)benzamide

EXAMPLE 19A

(1R,5R)-6,6-Dimethyl-3-methylene-bicyclo[3.1.1]heptan-2-one

[0158] (1R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2-one (0.938 mL, 920 mg) was added to tetrahydrofuran (50 mL) and the mixture was cooled to -78°C using an isopropanol / dry ice bath. Lithium bis(trimethylsilyl)amide (1M in tetrahydrofuran, 7.99 mL) was added, and the solution was stirred at -78°C for 15 minutes. The solution was allowed to warm to 0°C in a water / ice bath and the mixture was stirred for 45 minutes. Paraformaldehyde (2000 mg) was added. The solution was stirred at 0°C for 15 minutes, allowed to warm to room temperature and stir for an additional four hours.

The reaction was quenched with saturated aqueous ammonium chloride, extracted with diethyl ether, washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by flash column chromatography on silica gel using 5% ethyl acetate in hexanes.

EXAMPLE 19B

4-[4-((1R,5R)-6,6-Dimethyl-2-oxo-bicyclo[3.1.1]hept-3-ylmethyl)-piperazin-1-yl]-benzoic acid ethyl ester

[0159] EXAMPLE 19A (417 mg) and ethyl 4-(piperazin-1-yl)benzoate (520 mg) were added to acetonitrile (6 mL). Bismuth (III) trifluoromethanesulfonate (113 mg) was added, and the mixture was heated at 50°C for 5.5 hours. The mixture was cooled and purified by flash column chromatography on silica gel using 5% methanol in dichloromethane.

EXAMPLE 19C

4-{4-[(1R,5R)-2-(4-Chloro-phenyl)-2-hydroxy-6,6-dimethyl-bicyclo[3.1.1]hept-3-ylmethyl]-piperazin-1-yl)-benzoic acid ethyl ester

[0160] EXAMPLE 19B (452 mg) was dissolved in tetrahydrofuran (10 mL) and the mixture was cooled to -60°C using a chloroform / dry ice bath. (4-Chlorophenyl)magnesium bromide (1M in tetrahydrofuran, 2.35 mL) was added dropwise. Upon completion of the addition, the mixture was warmed quickly to -25°C using a carbon tetrachloride / dry ice bath and stirred for four hours. The reaction was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, dried on anhydrous sodium sulfate, and purified by flash column chromatography on silica gel using 20% ethyl acetate in hexanes.

EXAMPLE 19D

4-{4-[(1R,5R)-2-(4-Chloro-phenyl)-6,6-dimethyl-bicyclo[3.1.1]hept-2-en-3-ylmethyl]-piperazin-1-yl}-benzoic acid ethyl ester

[0161] EXAMPLE 19C (363 mg) was dissolved in tetrahydrofuran (6 mL) and Burgess reagent ((methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt, 209 mg) was added. The solution was stirred at room temperature for 16 hours and purified by flash column chromatography on silica gel using 20% ethyl acetate in hexanes.

EXAMPLE 19E

4-{4-[(1R,5R)-2-(4-Chloro-phenyl)-6,6-dimethyl-bicyclo[3.1.1]hept-2-en-3-ylmethyl]-piperazin-1-yl}-benzoic acid

[0162] The title compound was prepared by substituting EXAMPLE 19D for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 19F

4-(4-{[(1R,5R)-2-(4-chlorophenyl)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0163] The title compound was prepared by substituting EXAMPLE 19E for EXAMPLE 1A and EXAMPLE 2D for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.56 (m, 1H), 8.48 (m, 1H), 7.90 (dd, 1H), 7.76 (d, 2H), 7.48 (d, 1H), 7.40 (d, 1H), 7.14 (d, 1H), 6.91 (d, 2H), 6.88 (d, 1H), 6.42 (d, 1H), 4.14 (dd, 1H), 3.26 (m, 8H), 2.71 (br s, 2H), 1.95 (m, 2H), 1.77-1.53 (m, 8H), 1.33-1.11 (m, 6H), 1.07 (s, 3H), 0.97 (s, 3H), 0.86 (m, 2H).

EXAMPLE 20

4-{4-[(2-{[adamantan-2-ylmethyl]amino}-5,5-dimethylcyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 20A

ethyl 4-[4-({2-[(adamantan-2-ylmethyl)amino]-5,5-dimethylcyclohexyl}methyl)piperazin-1-yl]benzoate

[0164] (2-Adamantylmethyl)amine hydrochloride salt (195 mg), ethyl 4-(4-((5,5-dimethyl-2-oxocyclohexyl)methyl)piperazin-1-yl)benzoate (200 mg) and sodium acetate (44 mg) were suspended in anhydrous dichloroethane. The reaction mixture was stirred at room temperature for 20 minutes, followed by the addition of sodium triacetoxyborohydride (228 mg). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ aqueous solution. The reaction mixture was extracted with ethyl acetate, and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column purification with 0-5% methanol/dichloromethane to afford the title compound.

EXAMPLE 20B

4-[4-({2-[(adamantan-2-ylmethyl)amino]-5,5-dimethylcyclohexyl}methyl)piperazin-1-yl]benzoic acid

[0165] The title compound was prepared by substituting EXAMPLE 20A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 20C

4-{4-[(2-{[adamantan-2-ylmethyl]amino}-5,5-dimethylcyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0166] The title compound was prepared by substituting EXAMPLE 20B for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.05 (s, 1H), 8.65 (m, 2H), 7.94 (dd, 1H), 7.78 (d, 2H), 7.30 (d, 1H), 6.99 (d, 2H), 3.83 (m, 2H), 3.26 (m, 8H), 2.98 (m, 4H), 2.72 (m, 4H), 2.27 (m, 2H), 1.64 (m, 22H), 1.25 (m, 5H), 0.93 (d, 6H).

EXAMPLE 21

4-{4-[(5,5-dimethyl-2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}cyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 21 A

Ethyl 4-(4-((5,5-dimethyl-2-((1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)cyclohexyl)methyl)piperazin-1-yl)benzoate

[0167] The title compound was prepared by substituting (1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine for (2-adamantylmethyl)amine hydrochloride salt in EXAMPLE 20B.

EXAMPLE 21B

4-(4-((5,5-dimethyl-2-((1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)cyclohexyl)methyl)piperazin-1-yl)benzoic acid

[0168] The title compound was prepared by substituting EXAMPLE 21A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 21C

4-{4-[(5,5-dimethyl-2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}cyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0169] The title compound was prepared by substituting EXAMPLE 21B for EXAMPLE 1 A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.07 (m, 1H), 8.65 (m, 2H), 7.94 (dd, 1H), 7.77 (m, 2H), 7.30 (d, 1H), 6.98 (d, 2H), 3.84 (dd, 2H), 3.29 (m, 10H), 2.79 (m, 6H), 2.30 (m, 4H), 1.78 (m, 11H), 1.28 (m, 3H), 1.16 (m, 8H), 0.95 (m, 9H).

EXAMPLE 22

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)-5-nitrobenzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 22A

tert-butyl 4-(4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate

[0170] The title compound was prepared as described in EXAMPLE 45A using tert-butyl piperazine-1-carboxylate in place of 1,4-dioxa-8-azaspiro[4.5]decane.

EXAMPLE 22B

4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid

[0171] The title compound was prepared as described in EXAMPLE 2B using EXAMPLE 22A in place of EXAMPLE 2A.

EXAMPLE 22C

tert-butyl 4-(4-(4-(cyclohexylmethylamino)-3-nitrophenylsulfonylcarbamoyl)phenyl)piperazine-1-carboxylate

[0172] The title compound was prepared as described in EXAMPLE 1B using EXAMPLE 22B in place of EXAMPLE 1A and EXAMPLE 2D in place of 4-chloro-3-nitrobenzenesulfonamide.

EXAMPLE 22D

N-(4-(cyclohexylmethylamino)-3-nitrophenylsulfonyl)-4-(piperazin-1-yl)benzamide trifluoroacetic acid salt

[0173] A solution of EXAMPLE 22C (0.85 g, 1.4 mmol) in dichloromethane (10 mL), trifluoroacetic acid (10 mL) and triethylsilane (1 mL) was stirred for 24 hours. The mixture was concentrated to afford the title compound.

EXAMPLE 22E

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)-5-nitrobenzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0174] EXAMPLE 22D (50 mg, 0.081 mmol), 2-((1s,5s)-3-azabicyclo[3.2.2]nonan-3-yl)-5-nitrobenzaldehyde (27 mg, 0.097 mmol), and polymer-supported sodium cyanoborohydride (41 mg, 0.097 mmol) was stirred in tetrahydrofuran (1 mL) and acetic acid (0.33 mL) for 24 hours. The crude mixture was chromatographed on silica gel using 10% methanol in ethyl acetate, without and then with 1% triethylamine, to afford the title compound. MS (ELSD) m/e 762 $(M+H)^+$.

EXAMPLE 23

4-(4-{2-[2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 23A

3-Nitro-4-[(tetrahydro-pyran-4-ylmethyl)-amino]-benzenesulfonamide

[0175] The title compound was prepared by substituting 4-aminomethyltetrahydropyran for cyclohexylmethylamine in EXAMPLE 2D.

EXAMPLE 23B

4-(4-{3-Nitro-4-[(tetrahydro-pyran-4-ylmethyl)-amino]-benzenesulfonylaminocarbonyl}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

[0176] The title compound was prepared by substituting 4-(4-carboxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B.

EXAMPLE 23C

N-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(piperazin-1-yl)benzamide

[0177] EXAMPLE 23B (3.813 g) was added to dichloromethane (50 mL). Triethylsilane (5.5 mL, 4.004 g) was added, followed by trifluoroacetic acid (6 mL, 8.880 g). The solution was stirred at room temperature for five hours. Heptane was added and the solvents were removed under reduced pressure, after which, toluene was added and the solvents again removed under reduced pressure to isolate the title compound as the mono trifluoroacetic acid salt.

Example 23D

2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-5-yl trifluoromethanesulfonate

[0178] Tricyclo[5.2.1.02,6]decan-8-one (300 mg) was added to tetrahydrofuran (10 mL). Sodium bis(trimethylsilyl)amide (1M in tetrahydrofuran, 2.40 mL) was added, and the solution was stirred at room temperature for 10 minutes. The solution was cooled to -78°C using an isopropanol / dry ice bath, and 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (857 mg) was added. The solution was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was concentrated, diluted with hexanes (20 mL), filtered and again concentrated. The residue was purified by flash column chromatography on silica gel using a gradient of 0 to 10 % ethyl acetate in hexanes.

Example 23E

2-(2,3,3a,4,7,7a-Hexahydro-1H-4,7-methano-inden-5-yl)-benzaldehyde

[0179] EXAMPLE 23D (941 mg), 2-formylphenylboronic acid (600 mg), potassium phosphate, tribasic (1416 mg), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (244 mg) were added to tetrahydrofuran (15 mL) which had been degassed and flushed with nitrogen three times. The solution was heated to 60°C and stirred for 16 hours. The solution was concentrated and purified by flash column chromatography on silica gel using 10 % ethyl acetate in hexanes.

EXAMPLE 23F

4-(4-{2-[2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0180] EXAMPLE 23C (60 mg) and EXAMPLE 23E (26 mg) were added to tetrahydrofuran (1 mL) and acetic acid (0.33 mL). Sodium cyanoborohydride (2.38 mmol / g on resin, 45 mg) was added and the solution was stirred at room temperature for 16 hours. The solution was purified by flash column chromatography on silica gel using 5 % methanol in dichloromethane to isolate the title compound as the mono acetic acid salt. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6)

δ 11.94 (br s, 1H), 8.63 (t, 1H), 8.62 (d, 1H), 7.93 (dd, 1H), 7.73 (d, 2H), 7.42 (d, 1H), 7.28-7.20 (m, 4H), 6.92 (d, 2H), 6.25 (d, 1H), 3.85 (dd, 4H), 3.60-3.41 (m, 6H), 3.37-3.26 (m, 8H), 3.22 (br s, 2H), 2.75 (br s, 2H), 2.64 (br s, 2H), 2.13 (m, 4H), 1.95-1.76 (m, 6H), 1.91 (s, 3H), 1.64-1.50 (m, 6H), 1.32-1.19 (m, 3H), 1.03 (m, 2H).

EXAMPLE 24

1-[adamantan-1-yl]-4-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl} sulfonyl)carbamoyl]phenyl }piperazin-1-yl)methyl]phenyl -N,N-diphenyl-1H-pyrazole-3-carboxamide

EXAMPLE 24A

1-[adamantan-1-yl]-4-(2-formylphenyl)-*N,N*-diphenyl-1*H*-pyrazole-3-carboxamide

[0181] 1-Adamantan-1-yl-4-bromo-1H-pyrazole-3-carboxylic acid diphenylamide (47 mg), 2-formylphenylboronic acid (18 mg), sodium carbonate (32 mg), and tetrakis(triphenylphosphine)palladium(0) (7 mg) were combined in dimethoxyethane/ethanol/water 12/3/4 (1 mL) and heated in a CEM Discover microwave reactor at 180° C for 5 minutes. The reaction was cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration and concentration, the crude material was purified by column chromatography on silica gel using hexanes/ethyl acetate 4/1.

EXAMPLE 24B

1-[adamantan-1-yl]-4-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N,N-diphenyl-1H-pyrazole-3-carboxamide

[0182] The title compound was prepared by substituting EXAMPLE 24A for 2-formylphenylboronic acid in EXAMPLE 40A, except here product was purified by preparative HPLC using a C18 column, 250 x 50 mm, 10μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic aicd in water, giving the product as a trifluoroacetate salt. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 9.70 (br s, 1H), 8.70 (t, 1H), 8.66 (d, 1H), 7.96 (dd, 1H), 7.89 (br s, 1H), 7.80 (d, 2H), 7.63 (br s, 1H), 7.50 (br s, 2H), 7.32 (m, 6H), 7.19 (m, 6H), 6.98 (d, 2H), 4.15 (br s, 1H) 3.80 (m, 4H), 3.40, (m, 4H), 3.25 (m, 4H), 2.97 (br s, 1H), 2.00, 1.80, 1.60 (all m, total 18H), 1.24 (m, 4H).

EXAMPLE 25

4-(4-{2-[2-(adamantan-1-yl)-6-methylimidazo[1,2-a]pyridin-8-yl]benzyl}piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0183] ^{1}H NMR (400 MHz, dimethylsutfoxide-d_6) δ ppm 12.05 (s, 1H), 8.55 - 8.74 (m, 3H), 8.07 (s, 1H), 7.93 (dd, 1H), 7.73 (d, 2H), 7.55 - 7.71 (m, 4H), 7.48 (d, 1H), 7.29 (d, 1H), 6.86 (d, 2H), 3.81 - 3.89 (m, 4H), 3.31 - 3.38 (m, 2H), 3.22 - 3.30 (m, 2H), 2.42 (s, 3H), 2.03 (s, 3H), 1.91 (d, 8H), 1.56 - 1.77 (m, 10H), 1.20 - 1.32 (m, 3H). MS (ESI) m/e 856 $(M-H)^-$.

EXAMPLE 26

N-(adamantan-2-yl)-6-methyl-8-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}imidazo[1,2-a]pyridine-2-carboxamide

[0184] ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ ppm 12.10 (s, 1H), 8.75 (s, 1H), 8.62 - 8.69 (m, 2H), 8.57 (s, 1H), 7.88 - 7.98 (m, 2H), 7.81 (d, *J*=8.9 Hz, 2H), 7.67 - 7.73 (m, 1H), 7.60 - 7.67 (m, 2H), 7.46 - 7.52 (m, 1 H), 7.26 - 7.33 (m, 2H), 6.97 (d, *J*=9.2 Hz, 2H), 4.25 (s, 2H), 3.80 - 3.91 (m, 4H), 3.35 (t, *J*=6.4 Hz, 3H), 3.16 - 3.31 (m, 6H), 2.40 (s, 3H), 1.85 - 2.02 (m, 3H), 1.82 (s, 2H), 1.76 (s, 1H), 1.54 - 1.71 (m, 8H), 1.45 (d, *J*=12.6 Hz, 2H), 1.19 - 1.33 (m, 2H). MS (ESI) m/e 856 $(M-H)^-$.

EXAMPLE 27

4-(4-{2-[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 27A

6,6-dimethylbicyclo[3.1. 1] hept-2-en-2-yl trifluoromethanesulfonate

[0185] The title compound was prepared by substituting (1R)-(+)-nopinone for tricyclo[5.2.1.02,6]decan-8-one in EXAMPLE 23D.

EXAMPLE 27B

2-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-benzaldehyde

[0186] The title compound was prepared by substituting EXAMPLE 27A for EXAMPLE 23D in EXAMPLE 23E.

EXAMPLE 27C

4-(4-{2-[6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0187] The title compound was prepared by substituting EXAMPLE 27B for EXAMPLE 23E in EXAMPLE 23F. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.94 (br s, 1H), 8.63 (t, 1H), 8.62 (d, 1H), 7.93 (dd, 1H), 7.74 (d, 2H), 7.47-7.35 (m, 2H), 7.24 (m, 2H), 7.03 (m, 1H), 6.92 (d, 2H), 5.55 (1H), 3.85 (dd, 2H), 3.63-3.41 (m, 2H), 3.37-3.23 (m, 8H), 2.41 (m, 2H), 2.37-2.29 (m, 4H), 2.15 (m, 2H), 1.91 (s, 3H), 1.62 (d, 2H), 1.40 (d, 1H), 1.30 (s, 3H), 1.26 (m, 4H), 0.98 (s, 3H).

EXAMPLE 28

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[5,5,6-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-l-yl)benzamide

EXAMPLE 28A

5,5,6-trimethylbicyclo[2.2.1]hept-2-en-2-yl trifluoromethanesulfonate

[0188] The title compound was prepared by substituting 5,5,6-trimethylbicyclo[2.2.1]heptan-2-one for tricyclo[5.2.1.02,6]decan-8-one in EXAMPLE 23D.

EXAMPLE 28B

[0189] The title compound was prepared by substituting EXAMPLE 28A for EXAMPLE 23D in EXAMPLE 23E.

EXAMPLE 28C

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[5,5,6-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl)piperazin-1-yl)benzamide

[0190] The title compound was prepared by substituting EXAMPLE 28B for EXAMPLE 23E in EXAMPLE 23F. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.93 (br s, 1H), 8.60 (m, 2H), 7.93 (d, 1H), 7.74 (d, 2H), 7.44 (m, 1H), 7.27-7.17 (m, 4H), 6.90 (d, 2H), 6.20 (br s, 1H), 3.85 (dd, 2H), 3.56 (m, 2H), 3.36-3.23 (m, 8H), 2.62 (br s, 2H), 2.42 (br s, 2H), 1.91 (br s, 3H), 1.82 (d, 2H), 1.62 (dd, 2H), 1.52 (d, 1H), 1.28 (m, 5H), 1.04-1.00 (m, 6H), 0.90 (s, 3H).

EXAMPLE 30

N-benzyl-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl} sulfonyl)carbamoyl]phenyl} piperazin-1-yl)methyl]phenyl}bicyclo [2.2.1]hept-2-ene-1-carboxamide

[0191] ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ ppm 12.11 (s, 1H), 10.06 (s, 1H), 8.85 (s, 1H), 8.60 - 8.69 (m, 2H), 7.93 (dd, *J*=9.1, 2.0 Hz, 1H), 7.79 (d, *J*=8.9 Hz, 1H), 7.37 - 7.51 (m, 3H), 7.28 (d, *J*=9.5 Hz, 1H), 7.18 - 7.25 (m, 1H), 7.01 - 7.12 (m, 3H), 6.97 (d, *J*=9.2 Hz, 2H), 6.85 (d, *J*=6.8 Hz, 2H), 6.12 (d, *J*=2.8 Hz, 1H), 4.79 (d, *J*=10.1 Hz, 1H), 4.14 - 4.30 (m, 2H), 4.07 (dd, *J*=14.9, 6.0 Hz, 2H), 3.77 - 3.87 (m, 2H), 3.30 - 3.36 (m, 2H), 3.18 - 3.29 (m, 4H), 3.14 (s, 2H), 2.83 - 2.98 (m, 2H), 2.74 (d, *J*=11.7 Hz, 1H), 2.61 (t, *J*=3.2 Hz, 1H), 2.07-2.19 (m, 1H), 1.82 - 1.97 (m, 1H), 1.70 - 1.80 (m, 1H), 1.54 - 1.69 (m, 2H), 1.18 - 1.37 (m, 4H), 1.10 (s, 3H), 0.92 (s, 3H). MS (ESI) m/e 845 $(M-H)^-$.

EXAMPLE 31

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 31 A

Ethyl 4-(4-(2-((1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-ylamino)benzyl)piperazin-1-yl)benzoate

[0192] The title compound was prepared by substituting (1R, 5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-one for 2-formylphenylboronic acid and EXAMPLE 16B for EXAMPLE 23C in EXAMPLE 40A.

EXAMPLE 31B

4-(4-(2-((1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-ylamino)benzyl)piperazin-1-yl)benzoic acid

[0193] The title compound was prepared by substituting EXAMPLE 31 A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 31C

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0194] The title compound was prepared by substituting EXAMPLE 31B for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 9.42 (s, 1H), 8.64 (m, 2H), 7.93 (dd, 1H), 7.76 (m, 2H), 7.28 (d, 1H), 7.17 (m, 1H), 6.96 (m, 3H), 6.63 (s, 1H), 3.84 (m, 5H), 3.26 (m, 15H), 2.67 (d, 3H), 2.29 (m, 8H), 1.90 (m, 2H), 1.59 (m, 2H), 1.24 (m, 2H).

EXAMPLE 32

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzyl)piperazin-1-yl]benzamide

EXAMPLE 32A

2-((1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)benzonitrile

[0195] 2-Fluorobenzonitrile (100 mg), (1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (380 mg), triethylamine (1.5 mL) were dissolved in anhydrous dimethylsulfoxide (5mL) and heated at 130°C overnight. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column purification with 0-5% methanol/dichloromethane to afford the title compound.

EXAMPLE 32B

2-((1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)benzaldehyde

[0196] EXAMPLE 32A (80 mg) was dissolved in anhydrous dichloromethane (5 mL). The solution was cooled at 0°C, and diisobutylaluminum hydride 1M in dichloromethane solution (0.7 mL) was added. The reaction mixture was stirred at room temperature for 3 hours. The reaction was quenched with methanol and 5% L-tartaric acid aqueous solution. The solution was extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column purification with 0-30% ethyl acetate in hexane to afford the title compound.

EXAMPLE 32C

Ethyl 4-(4-(2-((1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)benzyl)piperazin-1-yl)benzoate

[0197] The title compound was prepared by substituting EXAMPLE 32B for 2-formylphenylboronic acid and ethyl 4-(piperazin-1-yl)benzoate for EXAMPLE 23C in EXAMPLE 40A.

EXAMPLE 32D

4-(4-(2-((1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)benzyl)piperazin-1-yl)benzoic acid

[0198] The title compound was prepared by substituting EXAMPLE 32C for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 32E

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(11R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzyl)piperazin-1-yl]benzamide

[0199] The title compound was prepared by substituting EXAMPLE 32D for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.10 (s, 1H), 8.65 (m, 2H), 7.93 (dd, 1H), 7.78 (d, 2H), 7.26 (m, 3H), 7.00 (d, 2H), 6.73 (d, 1H), 6.64 (t, 1H), 4.26 (m, 1H), 3.83 (dd, 2H), 3.65 (m, 2H), 3.25 (m, 14H), 2.63 (m, 1H), 2.32 (d, 1H), 2.13 (m, 1H), 1.88 (m, 3H), 1.60 (m, 2H), 1.48 (m, 1H), 1.26 (m, 5H), 1.07 (m, 6H).

EXAMPLE 33

4-(4-{2-[3-azabicyclo[3.2.2]non-3-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 33A

2-(3-azabicyclo[3.2.2]nonan-3-yl)benzaldehyde

[0200] The title compound was prepared by substituting 2-fluorobenzaldehyde for 2-fluorobenzonitrile and (1s,5s)-3-azabicyclo[3.2.2]nonane for (1R,2S,3S,5S2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine in EXAMPLE 32A.

EXAMPLE 33B

Ethyl 4-(4-(2-(3-azabicyclo[3.2.2]nonan-3-yl)benzyl)piperazin-1-yl)benzoate

[0201] The title compound was prepared by substituting EXAMPLE 33A for 2-formylphenylboronic acid and ethyl 4-(piperazin-1-yl)benzoate for EXAMPLE 23C in EXAMPLE 40A.

EXAMPLE 33C

4-(4-(2-(3-azabicyclo[3.2.2]nonan-3-yl)benzyl)piperazin-1-yl)benzoic acid

[0202] The title compound was prepared by substituting EXAMPLE 33B for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 33D

4-(4-{2-[3-azabicyclo[3.2.2]non-3-yl]benzyl}piperazin-1yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0203] The title compound was prepared by substituting EXAMPLE 33C for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.07 (m, 1H), 8.65 (m, 2H), 7.93 (dd, 1H), 7.79 (d, 2H), 7.56 (d, 1H), 7.44 (d, 2H), 7.26 (m, 2H), 7.00 (d, 2H), 4.48 (s, 2H), 4.01 (s, 2H), 3.83 (dd, 2H), 3.28 (m, 10H); 2.98 (d, 4H), 1.90 (m, 7H), 1.62 (m, 6H), 1.25 (m, 2H).

EXAMPLE 34

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[tricyclo[4.3.1.1^{3,8}]undec-4-en-4-yl]benzyl}piperazin-1-yl)benzamide

Example 34A

tricyclo[4.3.1.1^{3,8}]undec-4-en-4-yl trifluoromethanesulfonate

[0204] The title compound was prepared by substituting tricyclo[4.3.1.1^{3,8}]undecan-4-one for tricyclo[5.2.1.02,6]decan-8-one in EXAMPLE 23D.

Example 34B

2-Tricyclo[4.3.1.1^{3,8}]undec-4-en-4-yl-benzaldehyde

[0205] The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 23D in EXAMPLE 23E.

EXAMPLE 34C

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[tricyclo[4.3.1.1^{3,8}]undec-4-en-4-yl]benzyl}piperazin-1-yl)benzamide

[0206] The title compound was prepared by substituting EXAMPLE 34B for EXAMPLE 23E in EXAMPLE 23F. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.97 (br s, 1H), 8.65 (t, 1H), 8.62 (d, 1H), 7.93 (dd, 1H), 7.74 (d, 2H), 7.41 (m, 1H), 7.28-7.21 (m, 3H), 7.08 (m, 1H), 6.92 (d, 2H), 5.52 (m, 1H), 3.84 (dd, 2H), 3.54 (m, 2H), 3.37-3.24 (m, 8H), 2.57-2.44 (m, 2H), 2.29-2.09 (m, 4H), 1.94-1.84 (m, 2H), 1.91 (s, 3H), 1.62 (d, 2H), 1.36-1.18 (m, 4H), 0.88 (s, 9H).

EXAMPLE 35

7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-phenylbicyclo[2.2.1]hept-2-ene-1-carboxamide

[0207] ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ ppm 12.14 (s, 1H), 9.63 (s, 1H), 9.35 (s, 1H), 8.68 (t, 1H), 8.65 (d, 1H), 7.94 (dd, 1H), 7.80 (d, 2H), 7.53 - 7.60 (m, 1H), 7.33 - 7.41 (m, 2H), 7.30 (d, 1H), 7.20 - 7.27 (m, 3H), 7.07 (t, 1H), 7.01 (d, 2H), 6.18 (d, 1H), 4.77 (s, 1H), 4.38 (d, 1H), 4.07 (s, 2H), 3.85 (dd, 3H), 3.32 - 3.37 (m, 4H), 3.22 - 3.30 (m, 4H), 3.07 - 3.20 (m, 2H), 2.71 - 2.84 (m, 1H), 2.65 (t, 1H), 2.12 - 2.25 (m, 1H), 1.85 - 1.96 (m, 1H), 1.74 - 1.82 (m, 1H), 1.56 - 1.66 (m, 2H), 1.20 - 1.34 (m, 4H), 1.17 (s, 3H), 1.00 - 1.05 (m, 3H). MS (ESI) m/e 831 $(M-H)^-$.

EXAMPLE 36

7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]bicyclo[2.2.1]hept-2-ene-1-carboxamide

[0208] ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ ppm 12.11 (s, 1H), 10.24 (s, 1H), 8.57 - 8.73 (m, 2H), 8.00 (d, 1H), 7.94 (dd, *J*=9.2, 2.1 Hz, 1H), 7.80 (d, 2H), 7.50 (dd, 1H), 7.33 - 7.43 (m, 2H), 7.30 (d, 1H), 7.20 (dd, 1H), 7.01 (d, 2H), 6.14 (d, 1H), 4.87 (d, 1H), 4.21 - 4.29 (m, 1H), 4.06 - 4.20 (m, 4H), 3.84 (dd, 4H), 3.51 - 3.59 (m, 2H), 3.35 (t, 2H), 3.21

- 3.31 (m, 4H), 3.01 - 3.20 (m, 2H), 2.94 (d, 1H), 2.63 (t, 1H), 2.53 - 2.61 (m, 1 H), 2.20 - 2.29 (m, 1 H), 2.08 - 2.19 (m, 2H), 1.80 (t, 2H), 1.58 - 1.73 (m, 4H), 1.51 - 1.59 (m, 1H), 1.20 - 1.33 (m, 6H), 1.17 (s, 3H), 1.10 - 1.15 (m, 4H), 0.94 (s, 3H), 0.86 (s, 3H), 0.47 (d, 3H). MS (ESI) m/e 891 $(M-H)^-$.

EXAMPLE 37

N-(adamantan-1-ylmethyl)-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl)piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide

[0209] ^{1}NMR (500 MHz, dimethylsulfoxide-d_6) δ ppm 12.14 (s, 1H), 10.53 (s, 1H), 8.68 (t, 1H), 8.64 (d, 1H), 8.17 (s, 1H), 7.94 (dd, 1H), 7.82 (t, 1H), 7.47 (d, 1H), 7.40 (t, 1H), 7.36 (t, 1H), 7.30 (d, 1H), 7.23 (d, 1H), 6.13 (d, 1H), 4.88 (d, 1H), 4.11 - 4.22 (m, 3H), 3.84 (dd, 2H), 3.56 (d, 1H), 3.22 - 3.29 (m, 4H), 3.14 - 3.22 (m, 2H), 2.88 - 3.03 (m, 2H), 2.80 (dd, 1H), 2.62 - 2.68 (m, 1H), 2.53 - 2.63 (m, 1H), 2.08 - 2.18 (m, 1H), 1.84 - 1.96 (m, 1H), 1.68 (s, 4H), 1.62 (d, 2H), 1.48 (d, 3H), 1.34 (d, 3H), 1.20 - 1.30 (m, 4H), 1.10 - 1.19 (m, 6H), 1.00 - 1.07 (m, 3H), 0.97 (s, 3H). MS (ESI) m/e 903 $(M-H)^-$.

EXAMPLE 38

N-cyclopropyl-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide

[0210] ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ ppm 12.15 (s, 1H), 10.14 (s, 1H), 8.68 (t, 1H), 8.64 (d, 1H), 8.04 (s, 1H), 7.94 (dd, 1H), 7.80 (d, 2H), 7.53 (dd, 1H), 7.35 - 7.43 (m, 2H), 7.30 (d, 1H), 7.12 - 7.17 (m, 1H), 6.99 - 7.05 (m, 2H), 6.10 (d, 1H), 4.82 (d, 1H), 4.27 (d, 1H), 4.13 (t, 2H), 3.85 (dd, 2H), 3.35 (t, 2H), 3.16 - 3.30 (m, 6H), 3.09 (s, 2H), 2.60 (t, 1H), 2.52 - 2.58 (m, 1H), 2.43 - 2.49 (m, 1H), 2.03 - 2.14 (m, 1H), 1.85 - 1.97 (m, 1H), 1.62 (d, 3H), 1.17 - 1.32 (m, 3H), 1.14 (s, 3H), 0.91 (s, 3H), 0.45 - 0.58 (m, 2H), 0.37 - 0.45 (m, 1H), 0.11 - 0.19 (m, 1H). MS (ESI) m/e 795 $(M-H)^-$.

EXAMPLE 39

7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxylic acid

[0211] ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ ppm 11.96 (s, 1H), 8.57 - 8.66 (m, 2H), 7.92 (dd, 1H), 7.73 (d, 2H), 7.46 - 7.51 (m, 1H), 7.40 - 7.46 (m, 1H), 7.26 (d, 1H), 7.11 - 7.22 (m, 4H), 7.06 (d, 2H), 7.00 (dd, 1H), 6.91 (d, 2H), 6.26 (d, 1H), 6.16 (d, 1H), 5.10 (s, 1 H), 4.59 (s, 1H), 3.83 (dd, 2H), 3.65 - 3.73 (m, 1H), 3.38 - 3.52 (m, 3H), 3.23 (s, 2H), 2.50 - 2.56 (m, 4H), 2.26 - 2.42 (m, 2H), 1.98 - 2.07 (m, 2H), 1.90 (s, 3H), 1.46 - 1.66 (m, 4H), 1.19-1.31 (m, 4H), 1.14 (s, 3H), 1.11 (s, 3H), 1.01 - 1.10 (m, 2H), 0.93 (s, 6H). MS (ESI) m/e 757 $(M-H)^-$.

EXAMPLE 40

4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 40A

2-((4-(4-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonylcarbamoyl)phenyl)piperazin-1-yl)methyl)phenylboronic acid

[0212] EXAMPLE 23C (151 mg) and 2-formylphenylboronic acid (54 mg) were combined in a mixture of tetrahydrofuran (3.5 mL) and acetic acid (1.1 mL). Sodium cyanoborohydride resin (252 mg of 2.38 mmol/g resin) was added and the reaction was stirred at room temperature overnight. The reaction mixture was quenched with aqueous $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was washed thoroughly with water and with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was then triturated with ether to afford the title compound.

EXAMPLE 40B

4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)-2-phenoxybenzamide

[0213] EXAMPLE 40A (45 mg), 8-((5-bromothiophen-2-yl)methyl)-8-azabicyclo[3.2.1]octane hydrochloride (27 mg), bis(triphenylphosphine)palladium(II) dichloride (5 mg), and lithium hydroxide (7 mg) were combined in a mixture of dimethoxyethane (1.6 mL), methanol (0.5 mL) and water (0.7 mL) in a microwave vial. The reaction mixture was heated in a CEM Discover microwave reactor at 150°C for 15 minutes. The crude material was purified by preparative HPLC using a C18 column, 250 x 21.20 mm, 5μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic acid in water. ^1H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.79 (br s, 1H), 8.51 (d, 1H), 8.41 (t, 1H), 7.90 (dd, 1H), 7.73 (m, 4H), 7.60 (d, 2H), 7.41 (m, 2H), 7.35 (m, 1H), 6.81 (m, 2H), 3.83 (dd, 2H), 3.65 (s, 2H), 3.51 (s, 2H), 3.17 (m, 4H), 3.08 (m, 4H), 2.45 (m, 6H), 1.92 (m, 2H), 1.62 (m, 4H), 1.54 (m, 3H), 1.38 (m, 6H).

EXAMPLE 46

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

EXAMPLE 46A

ethyl 4-(4-(3-phenyl-N-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)propanamido)cyclohexyl)benzoate

[0214] To a solution of EXAMPLE 45C (192 mg, 0.5 mmol), triethylamine (0.077 mL, 0.55 mmol) and 4-dimethylaminopyridine (6 mg, 0.05 mmol) in tetrahydrofuran (5 mL) was added 3-phenylpropanoyl chloride (0.082 mL, 0.55 mmol), and the reaction was stirred for 24 hours. The residue was chromatographed on silica gel using 20-50% ethyl acetate in hexanes to afford the title compound.

EXAMPLE 46B

4-(4-(3-phenyl-N-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)propanamido)cyclohexyl)benzoic acid

[0215] The title compound was prepared as described in EXAMPLE 2B using EXAMPLE 46A in place of EXAMPLE 2A.

EXAMPLE 46C

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

[0216] The title compound was prepared as described in EXAMPLE 1B using EXAMPLE 46B in place of EXAMPLE 1B and EXAMPLE 2D in place of 4-chloro-3-nitrobenzenesulfonamide. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.90 (s, 1H), 8.61 (m, 2H), 7.92 (d, 1H), 7.72 (d, 2H), 7.20 (m, 5H), 6.90 (m, 2H), 4.07 (m, 4H), 3.93 (m, 2H), 3.18 (m, 4H), 2.65-2.95 (m, 6H), 2.08 (m, 2H), 1.91 (m, 2H), 1.78-1.99 (m, 6H), 1.55-1.76 (m, 11H), 1.22 (s, 3H), 1.17 (m, 2H), 1.01 (s, 3H), 0.99 (d, 2H), 0.90 (d, 2H).

EXAMPLE 47

4-{4-[adamantan-1-ylmethyl]piperazin-1-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl} sulfonyl)benzamide

[0217] The title compound was prepared by substituting EXAMPLE 10D for EXAMPLE 8E in EXAMPLE 8F. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.05 (br s, 1H), 8.82 (br s, 1H), 8.62 (m, 2H), 7.96 (dd, 1H), 7.78 (d, 2H), 7.26 (d, 1H), 7.00 (d, 2H), 3.86 (br s, 1H), 3.55 (br s, 2H), 3.30 (m, 8H), 2.96 (br s, 1H), 1.99 (s, 3H), 1.60 (m, 18H), 1.18 (m, 3H), 1.00 (m, 2H).

EXAMPLE 49

4-(4-{2-[adamantan-1-yl]-2-oxoethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 49A

ethyl 4-(4-{2-[adamantan-1-yl]-2-oxoethyl}piperazin-1-yl)benzoate

[0218] Ethyl 4-(piperazin-1-yl)benzoate (100 mg), 1-admantyl bromomethyl ketone (110 mg) and sodium carbonate (46 mg) were suspended in anhydrous acetonitrile (2 mL). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ aqueous solution, and extracted with ethyl acetate. The organic phase was washed with water, brine, dried over Na_2SO_4, filtered and concentrated to afford the title compound

EXAMPLE 49B

4-(4-{2-[adamantan-1-yl]-2-oxoethyl}piperazin-1-yl)benzoic acid

[0219] The title compound was prepared by substituting EXAMPLE 49A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 49C

4-(4-{2-[adamantan-1-yl]-2-oxoethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0220] The title compound was prepared by substituting EXAMPLE 49B for EXAMPLE 1 A and EXAMPLE 2D for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^1H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.16 (m, 1 H), 8.65 (m, 2H), 7.94 (dd, 1H), 7.81 (d, 2H), 7.26 (d, 1 H), 7.02 (d, 2H), 4.58 (s, 2H), 4.01 (s, 2H), 3.29 (m, 10H), 1.71 (m, 18H), 1.17 (m, 3H), 1.00 (m, 2H).

EXAMPLE 53

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazin-1-yl}benzamide

EXAMPLE 53A

ethyl 4-(bis(2-hydroxyethyl)amino)benzoate

[0221] The title compound was prepared by the methods described in Soloway, A. H., Nyilas, E., J. Org. Chem. 26, 1091 (1961).

EXAMPLE 53B

ethyl 4-(bis(2-(methylsulfonyloxy)ethyl)amino)benzoate

[0222] EXAMPLE 53A (506 mg) was dissolved in dichloromethane (10 mL) and the mixture was cooled to -14° C (acetone-ice bath). Triethylamine (0.83 mL) was added, followed by the addition of methanesulfonyl chloride (0.46 mL) dropwise, keeping the temperature below 2° C. The acetone-ice bath was removed and reaction continued at room temperature under nitrogen for 3.5 hours. The reaction was partitioned between saturated aqueous $NaHCO_3$ and ether. The organic layer was washed twice with 1*M* H_3PO_4, and crystals formed in the organic layer. The mixture was filtered and the solid material was washed with ether and dried to give the product.

EXAMPLE 53C

ethyl 4-(4-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)piperazin-1-yl)benzoate

[0223] EXAMPLE 53B (409 mg) was dissolved in acetonitrile (10 mL), then (1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (0.17 mL), potassium carbonate (375 mg), and lithium bromide (183 mg) were added. The reaction was heated under reflux overnight. The reaction was diluted with water and extracted with ethyl acetate. The

organic layer was washed with brine and dried over sodium'sulfate.The mixture was filtered and the crude material was purified by column chromatography on silica gel using 85/15 hexanes/ethyl acetate.

EXAMPLE 53D

4-(4-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)piperazin-1-yl)benzoic acid

[0224] The title compound was prepared by substituting EXAMPLE 53C for EXAMPLE 8D in EXAMPLE 8E.

EXAMPLE 53E

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazin-1-yl}benzamide

[0225] The title compound was prepared by substituting EXAMPLE 53D for EXAMPLE 8E in EXAMPLE 8F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.15 (br s, 1H), 9.40 (br s, 1H), 8.62 (m, 2H), 7.96 (dd, 1H), 7.80 (d, 2H), 7.26 (d, 1H), 7.03 (d, 2H), 4.14 (br s, 2H), 3.72 (br m, 2H), 3.28 (t, 2H), 3.17 (br m, 4H), 2.30 (m, 3H), 2.00 (m, 2H), 1.83 (m, 1H), 1.70 (m, 6H), 1.20 (m, 8H), 1.07 (m, 4H), 0.95 (s, 3H).

EXAMPLE 54

4-{4-[adamantan-1-yl]piperazin-1-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 54A

ethyl 4-[4-(adamantan-1-yl)piperazin-1-yl]benzoate

[0226] The title compound was prepared by substituting adamantane-1-amine hydrochloride for (1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine in EXAMPLE 53C.

EXAMPLE 54B

4-[4-(adamantan-1-yl)piperazin-1-yl]benzoic acid

[0227] The title compound was prepared by substituting EXAMPLE 54A for EXAMPLE 8D in EXAMPLE 8E.

EXAMPLE 54C

4-{4-[adamantan-1-yl]piperazin-1-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0228] The title compound was prepared by substituting EXAMPLE 54B for EXAMPLE 8E in EXAMPLE 8F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.10 (br s, 1H), 9.18 (br s, 1H), 8.62 (m, 2H), 7.96 (dd, 1H), 7.80 (d, 2H), 7.24 (d, 1H), 7.03 (d, 2H), 4.09 (br d, 2H), 3.65 (br m, 2H), 3.28 (t, 2H), 3.10 (br m, 4H), 2.20 (s, 3H), 1.95 (s, 6H), 1.70 (m, 12H), 1.18 (m, 3H), 1.00 (m, 2H).

EXAMPLE 55

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[3,5-dimethyladamantan-1-yl]piperazin-1-yl benzamide

EXAMPLE 55A

ethyl 4-[4-(3,5-dimethyladamantan-1-yl)piperazin-1-yl]benzoate

[0229] The title compound was prepared by substituting 3,5-dimethyladamantane-1-amine hydrochloride for (1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine in EXAMPLE 53C.

EXAMPLE 55B

4-[4-(3,5-dimethyladamantan-1-yl)piperazin-1-yl]benzoic acid

[0230] The title compound was prepared by substituting EXAMPLE 55A for EXAMPLE 8D in EXAMPLE 8E.

EXAMPLE 55C

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[3,5-dimethyladamantan-1-yl]piperazin-1-yl}benzamide

[0231] The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 8E in EXAMPLE 8F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.10 (v br s, 1H), 9.18 (v br s, 1H), 8.62 (m, 2H), 7.96 (dd, 1H), 7.80 (d, 2H), 7.24 (d, 1H), 7.03 (d, 2H), 4.07 (br s, 2H), 3.62 (br s, 2H), 3.28 (t, 2H), 3.10 (br m, 4H), 2.25 (m, 1H), 1,70 (m, 12H), 1.35 (s, 3H), 1.18 (m, 6H), 1.00 (m, 2H), 0.89 (s, 6H).

EXAMPLE 58

4-(4-{2-[adamantan-1-yl]ethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 58A

ethyl 4-[4-(adamantan-1-ylacetyl)piperazin-1-yl]benzoate

[0232] The title compound was prepared by substituting EXAMPLE 10A for EXAMPLE 8B and 1-adamantylacetic acid for adamantane-1-carboxylic acid in EXAMPLE 8C.

EXAMPLE 58B

ethyl 4-{4-[2-(adamantan-1-yl)ethyl]piperazin-1-yl}benzoate

[0233] The title compound was prepared by substituting EXAMPLE 58A for EXAMPLE 8C in EXAMPLE 8D.

EXAMPLE 58C

4-{4-[2-(adamantan-1-yl)ethyl]piperazin-1-yl}benzoic acid

[0234] The title compound was prepared by substituting EXAMPLE 58B for EXAMPLE 8D in EXAMPLE 8E.

EXAMPLE 58D

4-(4-{2-[adamantan-1-yl]ethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

[0235] The title compound was prepared by substituting EXAMPLE 58C for EXAMPLE 8E in EXAMPLE 8F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.10 (v br s, 1H), 9.44 (v br s, 1H), 8.62 (m, 2H), 7.96 (dd, 1H), 7.80 (d, 2H), 7.26 (d, 1H), 7.02 (d, 2H), 4.07 (br s, 2H), 3.60 (br s, 2H), 3.29 (t, 2H), 3.10 (m, 6H), 1.95 (s, 3H), 1.65 (m, 12H), 1.45 (m, 8H), 1.18 (m, 3H), 1.00 (m, 2H).

EXAMPLE 60

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-({(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}methyl)biphenyl-4-carboxamide

EXAMPLE 60A

methyl 4'-formylbiphenyl-4-carboxylate

[0236] The title compound was prepared as described in EXAMPLE 4A using 4-iodobenzaldehyde in place of 1-bromo-3-iodobenzene.

EXAMPLE 60B

methyl 4'-(((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)methyl)biphenyl-4-carboxylate

[0237] The title compound was prepared as described in EXAMPLE 7A using (1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine in place of EXAMPLE 6C and EXAMPLE 60A in place of phenylpropanal.

EXAMPLE 60C

methyl 4'-((3-phenyl-N-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)propanamido)methyl)biphenyl-4-carboxylate

[0238] The title compound was prepared as described in EXAMPLE 46A using EXAMPLE 60B in place of EXAMPLE 45C.

EXAMPLE 60D

4'-((3-phenyl-N-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)propanamido)methyl)biphenyl-4-carboxylic acid

[0239] The title compound was prepared as described in EXAMPLE 2B using EXAMPLE 60C in place of EXAMPLE 2A.

EXAMPLE 60E

N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-({(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}methyl)biphenyl-4-carboxamide

[0240] The title compound was prepared as described in EXAMPLE 1B using EXAMPLE 60D in place of EXAMPLE 1A and EXAMPLE 2D in place of 4-chloro-3-nitrobenzenesulfonamide. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.90 (s, 1H), 8.63 (d, 1H), 8.59 (m, 1H), 7.94 (m, 3H), 7.73 (d, 2H), 7.68 (d, 1H), 7.62 (d, 1H), 7.05-7.26 (m, 7H), 4.61 (m, 1H), 4.36 (m, 1H), 2.88 (m, 3H), 2.30 (m, 3H), 1.66 (m, 10H), 1.20 (m, 2H), 1.19 (s, 3H), 1.17 (s, 3H), 0.87-1.06 (m, 10H).

EXAMPLE 61

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzylidene}piperidin-1-yl)benzamide

EXAMPLE 61 A

methyl 4-(4-oxopiperidin-1-yl)benzoate

[0241] This EXAMPLE was prepared using methods described by Bruncko, et. al., J. Med. Chem. 2007, 50, 641-662.

EXAMPLE 61B

methyl 4-(4-(2-bromobenzylidene)piperidin-1-yl)benzoate

[0242] Dimethylsulfoxide (22.88 mL) with sodium hydride (0.332 g) was heated to 70 °C for 1 hour, the mixture was cooled to room temperature and (2-bromobenzyl)triphenylphosphonium bromide (3.40 g) was added in several portions. The reaction mixture was stirred at room temperature for 1 hour. A solution of EXAMPLE 6 A (1.8 g) in dimethylsulfoxide (5.20 mL) was then added and the reaction was heated at 70 °C over the weekend. The reaction mixture was acidified with 1M aqueous HCl solution and extracted with ether. The organic layer was washed thoroughly with water and with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified by flash chromatography eluting with 100% hexanes to 20% ethyl acetate in hexanes.

EXAMPLE 61C

4-(4-(2-((1R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)benzylidene)piperidin-1-yl)benzoic acid

[0243] The title compound was prepared by substituting (1S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-ylboronic acid for EXAMPLE 40A and EXAMPLE 61B for 8-((5-bromothiophen-2-yl)methyl)-8-azabicyclo[3.2.1]octane hydrochloride in EXAMPLE 40B.

EXAMPLE 61D

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzylidene}piperidin-1-yl)benzamide

[0244] The title compound was prepared by substituting EXAMPLE 61C for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.97 (s, 1H), 8.64 (m, 2H), 7.93 (dd, 1H), 7.74 (d, 2H), 7.30 (d, 1H), 7.21 (m, 2H), 7.14 (m, 1H), 6.95 (d, 2H), 6.36 (s, 1H), 5.87 (d, 1H), 3.84 (m, 2H), 3.48 (m, 2H), 3.40, 3.32, 3.24 (all m, total 6H), 2.40 (t, 1H), 2.34 (m, 4H), 1.90 (m, 2H), 1.61 (m, 3H), 1.27 (m, 3H), 1.06 (m, 1H), 0.94 (s, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

EXAMPLE 63

4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0245] ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ ppm 12.04 (s, 1H), 8.66 (t, 1H), 8.63 (d, 1H), 7.93 (dd, 1H), 7.75 (d, 3H), 7.63 (d, 1H), 7.57 (s, 3H), 7.29 (d, 1H), 7.20 - 7.26 (m, 2H), 6.95 (d, 2H), 4.56 (s, 1H), 3.78 - 3.89 (m, 2H), 3.31 - 3.37 (m, 6H), 3.26 (dd, 4H), 2.97 - 3.18 (m, 2H), 2.04 (s, 3H), 1.93 (s, 3H), 1.93 (s, 3H), 1.57 - 1.80 (m, 10H), 1.21 - 1.40 (m, 5H). MS (ESI) m/e 891 (M-H)-.

EXAMPLE 69

1-[adamantan-1-yl]-4-{2-[(1-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperidin-4-ylidene)methyl]phenyl}-N,N-diphenyl-1H-pyrazole-3-carboxamide

EXAMPLE 69A

4-{4-[2-(1-adamantan-1-yl-3-diphenylcarbamoyl-1H-pyrazol-4-yl)-benzylidene]-piperidin-1-yl}-benzoic acid ethyl ester

[0246] The title compound was prepared by substituting 1-adamantan-1-yl-4-bromo-1H-pyrazole-3-carboxylic acid diphenylamide for (3-bromothiophen-2-yl)(2,6-dimethoxyphenyl)methanone in EXAMPLE 68B.

EXAMPLE 69B

4-{4-[2-(1-adamantan-1-yl-3-diphenylcarbamoyl-1H-pyrazol-4-yl)-benzylidene]-piperidin-1-yl}-benzoic acid

[0247] The title compound was prepared by substituting EXAMPLE 69A for EXAMPLE 50A in EXAMPLE 50B.

EXAMPLE 69C

1-[adamantan-1-yl]-4-{2-[(1-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperidin-4-ylidene)methyl]phenyl}-N,N-diphenyl-1 H-pyrazole-3-carboxamide

[0248] The title compound was prepared by substituting EXAMPLE 69B for EXAMPLE 1 A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.95 (s, 1H), 8.64 (m, 2H), 7.93 (dd, 1H), 7.43 (d, 2H), 7.52 (s, 1H), 7.26 (m, 4H), 7.19 (m, 4H), 7.13 (m, 3H), 6.91 (m, 6H), 5.58 (s, 1H), 3.83 (dd, 2H), 3.47 (t, 2H), 3.25 (m, 6H), 2.23 (m, 4H), 2.07 (m, 3H), 1.89 (m, 6H), 1.62 (m, 8H), 1.26 (m, 3H).

EXAMPLE 70

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[octahydro-1H-4,7-methanoinden-5-yl(3-phenylpropanoyl)amino]benzyl}piperazin-1-yl)benzamide

EXAMPLE 70A

ethyl 4-(4-{2-[octahydro-1*H*-4,7-methanoinden-5-yl(3-phenylpropanoyl)amino]benzyl}piperazin-1-yl)benzoate

[0249] EXAMPLE 16C (60 mg), 3-phenylpropanoyl chloride (22 mg) and diisopropylethylamine (0.05 mL) were dissolved in anhydrous dichloromethane (3 mL). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ aqueous solution, and extracted with ethyl acetate. The organic phase was washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column purification with 0-5% methanol in dichloromethane to afford the title compound.

EXAMPLE 70B

4-(4-{2-[octahydro-1*H*-4,7-methanoinden-5-yl(3-phenylpropanoyl)amino]benzyl}piperazin-1-yl)benzoic acid

[0250] The title compound was prepared by substituting EXAMPLE 70A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 70C

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[octahydro-1*H*-4,7-methanoinden-5-yl(3-phenylpropanoyl)amino]benzyl}piperazin-1-yl)benzamide

[0251] The title compound was prepared by substituting EXAMPLE 70B for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.03 (m, 1H), 8.64 (m, 2H), 7.93 (dd, 1H), 7.76 (d, 2H), 7.58 (s, 1H), 7.39 (m, 2H), 7.28 (d, 1H), 7.18 (m, 3H), 7.00 (m, 5H), 4.32 (m, 1H), 3.83 (m, 2H), 3.26 (m, 8H), 2.81 (m, 6H), 2.19 (m, 2H), 1.90 (m, 4H), 1.67 (m, 7H), 1.22 (m, 11H).

EXAMPLE 71

4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 71 A

ethyl 4-(4-(2-(5-(8-azabicyclo[3.2.1]octan-8-ylmethyl)thiophen-2-yl)benzylidene)piperidin-1-yl)benzoate

[0252] The title compound was prepared by substituting 8-((5-bromothiophen-2-yl)methyl)-8-azabicyclo[3.2.1]octane hydrochloride for (3-bromothiophen-2-yl)(2,6-dimethoxyphenyl)methanone in EXAMPLE 68B.

EXAMPLE 71B

4-(4-(2-(5-(8-azabicyclo[3.2.1]octan-8-ylmethyl)thiophen-2-yl)benzylidene)piperidin-1-yl)benzoic acid

[0253] The title compound was prepared by substituting EXAMPLE 71 A for EXAMPLE 50A in EXAMPLE 50B.

EXAMPLE 71C

4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-lmethyl)amino]phenyl}sulfonyl)benzamide

[0254] The title compound was prepared by substituting EXAMPLE 71B for EXAMPLE 1A and EXAMPLE 23A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1B. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.54 (s, 1H), 9.36 (br s, 1H), 8.48 (d, 1H), 7.76 (dd, 1H), 7.53 (m, 3H), 7.34 (m, 3H), 7.00 (m, 1H), 6.84 (d, 2H), 6.81 (dd, 1H), 6.44 (d, 1H), 6.37 (br s, 1H), 4.36 (d, 2H), 3.82 (m, 3H), 3.36 (m, 2H), 3.26 (m, 4H), 3.18 (m, 2H), 2.36 (m, 3H), 2.23 (m, 4H), 1.90

(m, 3H), 1.81 (m, 2H), 1.62 (m, 5H), 1.40 (m, 3H).

EXAMPLE 72

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(4-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide

EXAMPLE 72A

ethyl 4-(4-(4-bromobenzylidene)piperidin-1-yl)benzoate

[0255] The title compound was prepared by substituting (4-bromobenzyl)triphenylphosphonium bromide for (2-bromobenzyl)triphenylphosphonium bromide in EXAMPLE 61B.

EXAMPLE 72B

ethyl 4-(4-(4-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)benzylidene)piperidin-1-yl)benzoate

[0256] EXAMPLE 72A (40 mg), (1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (100 μl), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (9.2 mg,), palladium(II) acetate (2.4 mg), and sodium tert-butoxide (14 mg) were added to toluene (0.2 mL), the reaction was purged with nitrogen and heated at 100° C overnight. The reaction was cooled, then diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration and concentration, the crude material was purified by column chromatography on silica gel using 94/6 hexanes/ethyl acetate.

EXAMPLE 72C

4-(4-(4-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)benzylidene)piperidin-1-yl)benzoic acid

[0257] The title compound was prepared by substituting EXAMPLE 72B for EXAMPLE 8D in EXAMPLE 8E.

EXAMPLE 72D

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(4-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide

[0258] The title compound was prepared by substituting EXAMPLE 72C for EXAMPLE 8E and EXAMPLE 23A for EXAMPLE 2D in EXAMPLE 8F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.97 (br s, 1H), 8.65 (t, 1H), 8.63 (d, 1H), 7.95 (dd, 1H), 7.76 (d, 2H), 7.28 (d, 1 H), 7.06 (br s, 2H), 6.95 (d, 2H), 6.90 (v br s, 2H), 6.26 (s, 1H), 3.85 (m, 2H), 3.50 (m, 5H), 3.33 (t, 2H), 3.25 (m, 2H), 2.38 (m, 3H), 2.00 (m, 1H), 1.94 (m, 2H), 1.80 (m, 1H), 1.60 (m, 3H), 1.25 (m, 5H), 1.21 (s, 3H), 1.09 (d, 1H), 1.00 (s, 6H).

EXAMPLE 73

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(3-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide

EXAMPLE 73A

ethyl 4-(4-(3-bromobenzylidene)piperidin-1-yl)benzoate

[0259] The title compound was prepared by substituting (3-bromobenzyl)triphenylphosphonium bromide for (2-bromobenzyl)triphenylphosphonium bromide in EXAMPLE 61B.

EXAMPLE 73B

ethyl 4-(4-(3-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)benzylidene)piperidin-1-yl)benzoate

[0260] The title compound was prepared by substituting EXAMPLE 73A for EXAMPLE 72A in EXAMPLE 72B.

EXAMPLE 73C

4-(4-(3-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)benzylidene)piperidin-1-yl)benzoic acid

[0261] The title compound was prepared by substituting EXAMPLE 73B for EXAMPLE 8D in EXAMPLE 8E.

EXAMPLE 73D

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(3-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide

[0262] The title compound was prepared by substituting EXAMPLE 73C for EXAMPLE 8E and EXAMPLE 23A for EXAMPLE 2D in EXAMPLE 8F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.00 (br s, 1H), 8.68 (t, 1H), 8.63 (d, 1H), 7.95 (dd, 1H), 7.76 (d, 2H), 7.30 (d, 1H), 7.18 (v br s, 2H), 6.96 (d, 2H), 6.75 (v br s, 2H), 6.26 (s, 1H), 3.85 (m, 2H), 3.50 (m, 5H), 3.37 (t, 2H), 3.25 (m, 2H), 2.40 (m, 2H), 2.37 (m, 1H), 2.00 (m, 1H), 1.94 (m, 2H), 1.80 (m, 1H), 1.60 (m, 3H), 1.25 (m, 5H), 1.20 (s, 3H), 1.12 (d, 1H), 1.00 (s, 6H).

EXAMPLE 74

4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

[0263] ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ ppm 11.96 (s, 1H), 8.59 - 8.72 (m, 2H), 7.93 (dd, 1H), 7.72 (d, 2H), 7.64 (dd, 1H), 7.54 (d, 1H), 7.22 - 7.40 (m, 4H), 7.16 (s, 1H), 6.94 (d, 2H), 6.43 (s, 1H), 3.83 (dd, 2H), 3.53 - 3.62 (m, 2H), 3.37 - 3.43 (m, 4H), 3.19 - 3.29 (m, 2H), 2.40 - 2.46 (m, 2H), 2.28 - 2.36 (m, 2H), 1.97 (s, 2H), 1.83 - 1.93 (m, 5H), 1.55 - 1.70 (m, 6H), 1.18 - 1.31 (m, 2H). MS (ESI) m/e 888 $(M-H)^-$.

Claims

1. A compound, or a therapeutically acceptable salt thereof, wherein the compound is chosen from the group consisting of:

4-(4-{acetyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{benzyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-3'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(phenylacetyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamide;
4-(4-{[(1R,5R)-3-bromo-5-methyladamantan-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[3,5-dimethyladamantan-1-yl]methyl}piperazin-1-yl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-octahydro-1H-4,7-methanoin-

den-5-ylamino]benzyl}piperazin-1-yl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,4R,6S)-5,5,6-trimethylbicyclo[2.2.1]hept-2-yl]amino}benzyl)piperazin-1-yl]benzamide;
4-[4-(2-{[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[(1R,5R)-2-(4-chlorophenyl)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-{4-[(2-{[adamantan-2-ylmethyl]amino}-5,5-dimethylcyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[(5,5-dimethyl-2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}cyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)-5-nitrobenzyl]piperazin-l-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{2-[2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
1-[adamantan-1-yl]-4-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N,N-diphenyl-1 H-pyrazole-3-carboxamide;
4-(4-12-[2-(adamantan-1-yl)-6-methylimidazo[1,2-a]pyridin-8-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-(adamantan-2-yl)-6-methyl-8-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}imidazo[1,2-a]pyridine-2-carboxamide;
4-(4-{2-[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[5,5,6-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzamide;
N-benzyl-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide;
4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzyl)piperazin-1-yl]benzamide;
4-(4-{2-[3-azabicyclo[3.2.2]non-3-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[tricyclo[4.3.1.1^{3,8}]undec-4-en-4-yl]benzyl}piperazin-1-yl)benzamide;
7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-phenylbicyclo[2.2.1]hept-2-ene-1-carboxamide;
7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]bicyclo[2.2.1]hept-2-ene-1-carboxamide;
N-(adamantan-1-ylmethyl)-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide;
N-cyclopropyl-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxamide;
7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-ene-1-carboxylic acid;
4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethy1]-2-thienyl}benzyl)piperazin-1-y1]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;
4-{4-[adamantan-1-ylmethyl]piperazin-1-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{2-[adamantan-1-yl]-2-oxoethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazin-1-yl}benzamide;
4-{4-[adamantan-l-yl]piperazin-l-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[3,5-dimethyladamantan-1-yl]piperazin-1-yl}ben-

zamide;
4-(4-{2-[adamantan-1-yl]ethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-({(3-phenylpropanoyl)[(1S,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}methyl)biphenyl-4-carboxamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzylidene}piperidin-1-yl)benzamide;
4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
1-[adamantan-1-yl]-4-{2-[(1-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperidin-4-ylidene)methyl]phenyl}-N,N-diphenyl-1H-pyrazole-3-carboxamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[octahydro-1H-4,7-methanoinden-5-yl(3-phenylpropanoyl)amino]benzyl}piperazin-1-yl)benzamide;
4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(4-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(3-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzylidene)piperidin-1-yl]benzamide; and
4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide.

2. The compound of claim 1, wherein said compound is N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzylidene}piperidin-1-yl)benzamide or a therapeutically acceptable salt thereof.

3. A pharmaceutical composition comprising an excipient and a therapeutically effective amount of the compound or therapeutically acceptable salt of claim 1.

4. The pharmaceutical composition of claim 3, wherein said compound is N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzylidene}piperidin-1-yl)benzamide or a therapeutically acceptable salt thereof.

5. The compound or therapeutically acceptable salt of claim 1 or claim 2 for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer.

Patentansprüche

1. Eine Verbindung oder ein therapeutisch verträgliches Salz davon, worin die Verbindung gewählt ist aus der Gruppe bestehend aus:

4-(4-{Acetyl[(1S,2S,3S,5R)-2,6,6-trimethylbieylo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamid;
4-(4-{Benzoyl[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamid;
N-({4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-3'-{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino)biphenyl-4-carboxamid;
N-({4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(phenylacetyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamid;
N-({4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{[(1S,2S,3S,5R)-2,6,6-trimethybicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamid;
N-({4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}biphenyl-4-carboxamid;
4-(4-{[(1R,5R)-3-Brom-5-methyladamantan-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-ni-

trophenyl}sulfonyl)benzamid;
ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2,2.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benaamid;
N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl-4-(4-{2-octahydro-1H-4,7-methanoinden-5-ylamino]benzyl}piperazin-1-yl)benzamid;
N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(2-{[(1R,4R,6S)-5,5,6-trimethylbicyclo[2.2.1]hept-2-yl]amino}benzyl)piperazin-1-yl]benzamid;
4-[4-(2-{[(1R,5S)-6,6-Dimethylbicyclo[3.1.1]hept-2-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
4-(4-{[(1R,5R)-2-(4-Chlorphenyl)-6,6-dimethylbicylo[3.1.1]hept-2-en-3-yl]methyl]piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamid;
4-{4-[(2-{[Adamantan-2-ylmethyl]amino}-5,5-dimethylcyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
4-{4-[(5,5-Dimethyl-2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}cyclohexyl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
4-{4-[2-(3-Azabicyclo[3.2.2]non-3-yl)-5-nitrobenzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
4-(4-{2-[2,3,3a,4,7,7a-Hexahydro-1H-4,1-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
1-[Adamantan-1-yl]-4-{2-[(4-(4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbomoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N,N-diphenyl-1H-pyrazol-3-carboxamid;
4-(4-(2-[2-(Adamantan-1-yl)-6-methylimidazo[1,2-a]pyridin-8-yl]benzyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
N-(Adamantan-2-yl)-6-methyl-8-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}imidazo[1,2-a]pyridin-2-carboxamid;
4-(4-{2-[(1R,5S)-6,6-Dimethylbicyclo[3.1,1]hept-2-en-2-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4ylmethyl)amino]phenyl}sulfonyl)benzamid;
N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[5,5,6-trimethylbicyclo[2.1.1]hept-2-en-2-yl]benzyl}piperazin-1-yl)benzamid;
N-Benzyl-7,7-dimethyl-2-[2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-en-1-carboxamid;
4-[4-(2-{[(1R,5S)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-9-[4-(2-{[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzyl)piperazin-1-yl]benzamid;
4-(4-{2-[3-Azabicyclo[3.2.2]non-3-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[tricyclo[4.3.1.1^{3,8}]undec-4-en-4-yl]benzyl]piperazin-1-yl)benzamid;
7,7-Dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-phenylbicyclo[2.2.1]hept-2-en-1-carboxamid;
7,7-Dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]bicyclo[2.2,1]hept-2-en-1-carboxamid;
N-(Adamantan-1-ylmethyl)-7,7-dimethyl-2--2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl]piperazin-1-yl)methyl]phenyl}bicyclo[2.2,1]hept-2-en-1-carboxamid;
N-Cyclopropyl-7,7-dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyclo[2.2.1]hept-2-en-1-carboxamid;
7,7-Dimethyl-2-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}bicyco[2.2.1]hept-2-en-1-carbonsäure;
4-[4-(2-{5-[8-Azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
N-({4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamid;
4-{4-[Adamantan-1-ylmethyl]piperazin-1-yl)-N-({4-[{cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamid;
4-(4-{2-[Adamantan-1-yl]-2-oxoethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamid;
N-({4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[(1S,2S,3S,5R)-2,6,6-trimethylbicyc-

lo[3.1.1]hept-3-yl]piperazin-1-yl)benzamid;
4-{4-[Adamantan-1-yl]piperazin-1-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamid;
N-({4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4-{4-[3,5-dimethyladamantan-1-yl]pipererazin-1-yl}benzamid;
4-(9-{2-[Adamantan-1-yl]ethyl}piperazin-1-yl)-N-({4 [(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)bensamid; N-({4-[(Cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-4'-({(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}methyl)biphenyl-4-carboxamid;
N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R}-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyliden}piperidin-1-yl)benzamid;
4-[4-(2-{5-[4-(Adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl]amino]phenyl}sulfonyl)benzamid;
1-[Adamantan-1-yl]-4-{2-[(1-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperidin-4-yliden)methyl]phenyl}-N,N-diphenyl-1H-pyrazol-3-carboxamid;
N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[octahydro-1H-4,7-methanoinden-5-yl(3-phenylpropanoyl)amino]benzyl}piperazin-1-yl)benzamid;
4-[4-(2-{5-[8-Azabicyclo[3.2.1]oct-8-ylmethyl]-2-thienyl}benzyliden)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid;
N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(4-[{(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzyliden)piperidin-1-yl)benzamid;
N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-[4-(3-{[(1S,2S,3S,5R)-2,6,5-trimethylbicyclo[3.1.1]hept-3-yl]amino}benzyliden)piperidin-1-yl]benzamid; und
4-[4-(2-{5-[4-(Adamantan-1-yl)-1,3-thiazol-2-yl]-2-thienyl}benzyliden)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamid.

2. Die Verbindung gemäß Anspruch 1, worin die Verbindung N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethybicyclo[2.2.1]hept-2-en-2-yl]benzyliden}piperidin-1-yl)benzamid oder ein therapeutisch verträgliches Salz davon ist.

3. Eine pharmazeutische Zusammensetzung umfassend einen Hiltsstoff und eine therapeutisch wirksame Menge der Verbindung oder ein therapeutisch verträgliches Salz gemäß Anspruch 1.

4. Die pharmazeutische Zusammensetzung gemäß Anspruch 3, worin die Verbindung N-({3-Nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]benzyliden}piperidin-1-yl)benzamid oder ein therapeutisch verträgliches Salz davon ist.

5. Die Verbindung oder das therapeutisch verträgliche Salz gemäß Anspruch 1 oder Anspruch 2 für die Verwendung in der Behandlung von Blasenkrebs, Hirntumor, Brustkrebs, Knochenmarkkrebs, Gebärmutterhalskrebs, chronischer lymphatischer Leukämie, Kolorektalkrebs, Speiseröhrenkrebs, Leberzellkrebs, Lymphoblastenleukämie, follikulärem Lymphom, einer lymphoiden Malignität T-Zell- oder B-Zell-Ursprungs, Melanom, myeloischer Leukämie, Myelom, Mundkrebs, Eierstockkrebs, nicht-kleinzelligem Lungenkarzinom, Prostatakrebs, kleinzelligem Lungenkarzinom oder Milzkrebs.

Revendications

1. Composé, ou l'un de ses sels thérapeutiquement acceptables, le composé étant choisi dans le groupe constitué 5de :

4-(4-{acétyl[(1S,2S,3S,5R)-2,6,6-triméthylbicyclo[3.1.1]-hept-3-yl]amino}pipéridin-1-yl)-N-({4-[(cyclohexylméthyl)-amino]-3-nitrophény}sulfonyl)benzamide ;
4-(4-(benzoyl[(1S,2S,3S,5R)-2,6,6-triméthylbicyclo-10[3.1.1.]hept-3-yl]amino}pipéridin-1-yl)-N-({14-[(cyclohexyl-méthyl)amino]-3-nitrophényl]sulfonyl)benzamide;
N-({4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)-3'-{[(1S,2S,3S,5R)-2,6,6-triméthylbicyclo[3.1.1]hept-3-yl]-amino}biphényl-4-carboxamide;
N-({4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)-4-{4-{(phénylacétyl)[(1S,2S,3S,5R)-2,6,6-triméthylbicyclo-[3.1.1]hept-3-yl]amino}pipéridin-1-yl)benzamide;
N-({4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)-4'-{[(1S,2S,3S,5R)-2,6,6-triméthylbicyclo[3.1.1]hept-3-yl]-amino}biphényl-4-carboxamide;
N-({4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)-4'-{(3-phénylpropyl)[(1S,2S,3S,5R)-2,6,6-triméthylbi-

cyclo-[3.1.1]hept-3-yl]amino}biphényl-4-carboxamide;
4-(4-{[(1R,5R)-3-bromo-5-méthyladamantan-1-yl]méthyl)-25pipérazin-1-yl)-N-({4-[(cyclohexylméthyl)amino]-3-nitro-phényl}sulfonyl)benzamide;
N-({4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)-4-(4-{[3,5-diméthyladamantan-1-yl]méthyl}pipérazin-1-yl)-benzamide ;
N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)-4-(4-(2-[(1R,4R)-1,7,7-triméthylbicyclo-(2.2.1)hept-2-en-2-yl]benzyl}pipérazin-1-yl)benzamide ;
N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)-4-(4-{2-octahydro-1H-4,7-méthanoindén-5-yl-amino]benzyl]pipérazin-1-yl)benzamide;
N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl)sulfonyl)-4-[4-(2-{[(1R,4R,6S)-5,5,6-triméthyl-bicyclo[2,2.1]hept-2-yl]amino}benzyl)pipérazin-1-yl]benzamide
4-[4-(2-{[(1R,5S)-6,6-diméthylbicyclo[3.1.1]hept-2-yl]-amino}benzyl)pipérazin-1-yl]-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)benzamide ;
4-(4-{[(1R,5R)-2-(9-chlorophényl)-6, 6-diméthylbicyclo-[3.1.1]hept-2-en-3-yl]méthyl}pipérazin-1-yl)-N-({4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)benzamide ;
4-{4-[(2-{[adamantan-2-ylméthyl]amino}-5,5-diméthyl-15cyclohexyl)méthyl]piperazin-1-yl}-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)benzamide ;
4-{4-[(5,5-diméthyl-2-{[(1R,2S,3S,5S)-2,6,6-triméthylbicyclo[3.1.1]hept-3-yl]amino}cyclohexyl)méthyl]pipérazin-1-yl}-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)benzamide ;
4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)-5-nitrobenzyl]-pipérazin-1-yl}-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)benzamide ;
4-(4-{2-[2,3,3a,4,7,7a-hexahydro-1H-4,7-méthanoindén-5-yl}benzyl]pipérazin-1-yl)-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl)sulfonyl)benzamide ;
1-[adamantan-1-yl]-4-{2-[{4-{4-[({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)carbamoyl]phényl}-pipérazin-1-yl)méthyl]phényl}-N,N-diphényl-1H-pyrazole-3-carboxamide ;
4-(4-{2-[2-(adamantan-1-yl)-6-méthylimidazo[1,2-a]-pyridin-8-yl]benzyl}pipérazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylméthyl)amino]phény}sulfonyl)-benzamide ;
N-(adamantan-2-yl)-6-méthyl-8-{2-[(4-{4-[{(3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)-carbamoyl]phényl)pipérazin-1-yl)méthyl]phényl}imidazo[1,2-a]-pyridine-2-carboxamide ;
4-(4-(2-[(1R,5S)-6,6-diméthylbicyclo[3,1.1]hept-2-én-2-yl]benzyl}pipérazin-1-yl)-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfony)benzamide ;
N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl]sulfonyl)-4-(4-{2-[5,5,6-triméthylbicyclo[2.2.1]hept-2-én-2-yl]benzyl}pipérazin-1-yl)benzamide ;
N-benzyl-7,7-diméthyl-2-{2-[(4-{4-[({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)-carbamoyl]phényl}pipérazin-1-yl)méthyl]phényl}bicyclo[2.2.1]-hept-2-ène-1-carboxamide ;
4-[4-(2-([(1R,5S)-8-méthyl-8-azabicyclo[3.2.1]oct-3-yl]-amino}benzyl)pipérazin-1-yl]-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)benzamide ;
N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)-4-[4-(2-{[(1R,2R,3R,5S)-2,6,6-triméthyl-bicyclo[3.1.1]hept-3-yl]amino}benzyl)pipérazin-1-yl]benzamide
4-(4-{2-[3-azabicyclo[3.2.2]non-3-yl]benzyl}pipérazin-1-yl)-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)benzamide ;
N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)-4-(4-{2-[tricyclo[4.3.1.1^{3,8}] undéc-4-én-4-yl]benzyl)pipérazin-1-yl)benzamide ;
7,7-diméthyl-2-{2-[(4-{4-[({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)carbamoyl]phényl}-pipérazin-1-yl)méthyl]phényl}-N-phénylbicyclo[2.2.1]hept-2-ène-1-carboxamide ;
7,7-diméthyl-2-{2-[(4-{4-[({3-nitro-4-[(trétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)carbamoyl]phényl}-pipérazin-1-yl)méthyl]phényl}-N-[(1S,2S,3S,5R)-2,6,6-triméthylbicyclo[3.1.1]hept-3-yl]bicyclo[2.2.1]hept-2-ène-1-5carboxamide ;
N-(adamantan-1-ylméthyl)-7,7-diméthyl-2-{2-[(4-{4-[({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}-sulfonyl)carbamoyl]phényl}pipérazin-1-yl)méthyl]phényl}-bicyclo[2.2.1]hept-2-ène-1-carboxamide ;
N-cyclopropyl-7,7-diméthyl-2-{2-[(4-{4-[({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)-carbamoyl]phényl]pipérazin-1-yl)méthyl]phényl}bicyclo[2.2.1]-hept-2-ène-1-carboxamide ;
acide 7,7-diméthyl-2-{2-[(4-{4-[({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)carbamoyl]phényl}-pipérazin-1-yl)méthyl]phényl}bicyclo[2.2.1]hept-2-ène-1-carboxylique ;
4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylméthyl]-2-thiényl}benzyl)pipérazin-1-yl]-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)benzamide ;
N-({4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)-4-(4-{(3-phénylpropanoyl)[(1S,2S,3S,5R)-2,6,6-triméthyl-bicyclo[3.1.1]hept-3-yl]amino}pipéridin-1-yl)benzamide ;

4-{4-[adamantan-1-ylméthyl]pipérazin-1-yl}-N-({4-4-[(cyclohexylméthyl]amino]-3-nitrophényl]sulfonyl)benzamide ;
4-(4-[2-[adamantan-1-yl]-2-oxoéthyl}pipérazin-1-yl)-N-[{4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)-benzamide ;
N-([4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)-4-{4-[(1S,2S,3S,5R)-2,6,6-triméthylbicyclo[3.1.1]hept-3-yl]-pipérazin-1-yl}benzamide ;
4-{4-[adamantan-1-yl]pipérazin-1-yl)-N-({4-[cyclohexyl-méthyl)amino]-3-nitrophényl}sulfonyl)benzamide ;
N-({4-[(cyclohexylméthyl)amino]-3-nitrophényl}sulfonyl)-4-{4-[3,5-diméthyladamantan-1-yl]pipérazin-1-yl}benzamide ;
4-(4-{2-[adamantan-1-yl]éthyl}pipérazin-yl)-N-({4-{(cyclohexylméthyl)amino]-3-nitrophényl]sulfonyl)benzamide ;
N-({4-[(cyclohexylméthyl)amino]-3-nitrophényl)sulfonyl)-4'-({(3-phénylpropanoyl)[(1S,2S,3S,5R)-2,6,6-triméthylbicyclo-[3.1.1]hept-3-yl]amino}méthyl)biphényl-4-carboxamide ;
N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-triméthylbicyclo-[2.2.1]hept-2-én-2-yl]benzylidène}pipéridin-1-yl)benzamide ;
4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thiényl}benzyl)pipérazin-1-yl]-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)benzamide ;
1-[adamantan-1-yl]-4-(2-[(1-{4-[({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)carbamoyl]phényl}-pipéridin-4-ylidène)méthyl]phényl}-N,N-diphényl-1H-pyrazole-3-carboxamide ;
N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)-4-(4-{2-octahydro-1H-4,7-méthanoindén-5-yl(3-phénylpropanoyl)amino]benzyl}pipérazin-1-yl)benzamide ;
4-[4-(2-{5-[8-azabicyclo[3.2.1]oct-8-ylméthyl]-2-thiényl}benzylidène)pipéridin-1-yl]-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl}sulfonyl)-benzamide ;
N-([3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)-4-[4-(4-{[(1S,2S,3S,5R)-2,6,6-triméthyl-bicyclco[3.1.1]hept-3-yl]amino}benzylidène)pipéridin-1-yl]-benzamide ;
N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}sulfonyl)-4-[4-(3-{[(1S,2S,3S,5R)-2,6,6-triméthyl-bicyclo[3.1.1]hept-3-yl]amino}benzylidène)pipéridin-1-yl]-benzamide ; et
4-[4-(2-{5-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-2-thiényl}benzylidène)pipéridin-1-yl]-N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylmétyl)amino]phényl}sulfonyl)-benzamide,

2. Composé selon la revendication 1, où ledit composé est le N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]-phényl}suifonyl)-4-(4-{2-[(1R,4R)-1,7,7-triméthylbicyclo-[2.2.1]hept-2-én-2-yl]benzylidène}pipéridin-1-yl)benzamide ou l'un de ses sels pharmaceutiquement acceptables.

3. Composition pharmaceutique comprenant un excipient et une quantité thérapeutiquement efficace du composé ou du sel thérapeutiquement acceptable selon la revendication 1.

4. Composition pharmaceutique selon la revendication 3, où ledit composé est le N-({3-nitro-4-[(tétrahydro-2H-pyran-4-ylméthyl)amino]phényl)sulfonyl)-4-(4-{2-[(1R,4R)-1,7,7-triméthylbicyclo[2.2.1]hept-2-én-2-yl]benzylidène}pipéridin-1-yl)benzamide ou l'un de ses sels thérapeutiquement acceptables.

5. Composé ou sel thérapeutiquement acceptable selon la revendication 1 ou la revendication 2 pour une utilisation dans le traitement du cancer de la vessie, du cancer du cerveau, du cancer du sein, du cancer de la moelle osseuse, du cancer du col de l'utérus, de la leucémie lymphocytaire chronique, du cancer colorectal, du cancer oesophagien, du cancer hépatacellulaire, de la leucémie lymphoblastique, du lymphome folliculaire, d'une affection maligne lymphoïde ayant pour origine les lymphocytes T ou les lymphocytes B, du mélanome, de la leucémie myélogène, du myélome, du cancer buccal, du cancer ovarien, du cancer du poumon non à petites cellules, du cancer de la prostate, du cancer du poumon à petites cellules ou du cancer de la rate.

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Szabadalmi igénypontok

1. Vegyület vagy egy gyógyászatilag elfogadható sója, ahol a vegyület a következő csoportból van megválasztva:

4-(4-{acetil[(1S,2S,3S,5R)-2,6,6-trimetilbiciklo[3.1.1]hept-3-il]amino}piperidin-1-il)-N-({4-[(ciklohexilmetil)-amino]-3-nitrofenil}szulfonil)benzamid;

4-(4-{benzoil[(1S,2S,3S,5R)-2,6,6-trimetilbiciklo[3.1.1]hept-3-il]amino}piperidin-1-il)-N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)benzamid;

N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-3'-{[(1S,2S,3S,5R)-2,6,6-trimetilbiciklo[3.1.1]hept-3-il]-amino}bifenil-4-karboxamid;

N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-4-(4-{(fenilacetil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciklo-[3.1.1]hept-3-il]amino}piperidin-1-il)benzamid;

N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-4'-{[(1S,2S,3S,5R)-2,6,6-trimetilbiciklo[3.1.1]hept-3-il]-amino}bifenil-4-karboxamid;

N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-4'-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetil-biciklo[3.1.1]hept-3-il]amino}bifenil-4-karboxamid;

4-(4-{[(1R,5R)-3-bróm-5-metiladamantán-1-il]metil}piperazin-1-il)-N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)benzamid;

N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-4-(4-{[3,5-dimetiladamantán-1-il]metil}piperazin-1-il)benzamid;

N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-(4-{2-[(1R,4R)-1,7,7-trimetilbiciklo-[2.2.1]hept-2-én-2-il]benzil}piperazin-1-il)benzamid;

N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-(4-{2-oktahidro-1H-4,7-metanoindén-5-ilamino]benzil}piperazin-1-il)benzamid;

N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-[4-(2-{[(1R,4R,6S)-5,5,6-trimetilbiciklo-[2.2.1]hept-2-il]amino}benzil)piperazin-1-il]benzamid;

4-[4-(2-{[(1R,5S)-6,6-dimetilbiciklo[3.1.1]hept-2-il]amino}benzil)piperazin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;

4-(4-{[(1R,5R)-2-(4-klórfenil)-6,6-dimetilbiciklo[3.1.1]hept-2-én-3-il]metil}piperazin-1-il)-N-({4-[(ciklohexil-metil)amino]-3-nitrofenil}szulfonil)benzamid;

4-{4-[(2-{[adamantán-2-ilmetil]amino}-5,5-dimetilciklohexil)metil]piperazin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;

4-{4-[(5,5-dimetil-2-{[(1R,2S,3S,5S)-2,6,6-trimetilbiciklo[3.1.1]hept-3-il]amino}ciklohexil)metil]piperazin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;

4-{4-[2-(3-azabiciklo[3.2.2]non-3-il)-5-nitrobenzil]piperazin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;

4-(4-{2-[2,3,3a,4,7,7a-hexahidro-1H-4,7-metanoindén-5-il]benzil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;

1-[adamantán-1-il]-4-{2-[(4-{4-[({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)karbamoil]-fenil}piperazin-1-il)metil]fenil}-N,N-difenil-1H-pirazol-3-karboxamid;

4-(4-12-[2-(adamantán-1-il)-6-metilimidazo[1,2-a]piridin-8-il]benzil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil]amino]fenil}szulfonil)benzamid;

N-(adamantán-2-il)-6-metil-8-{2-[(4-{4-[({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil]amino}fenil}szulfonil)-karbamoil]fenil}piperazin-1-il)metil]fenil}imidazo[1,2-a]piridin-2-karboxamid;

4-(4-{2-[(1R,5S)-6,6-dimetilbiciklo[3.1.1]hept-2-én-2-il]benzil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;

N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-(4-{2-[5,5,6-trimetilbiciklo[2.2.1]hept-2-en-2-il]benzil}piperazin-1-il)benzamid;

N-benzil-7,7-dimetil-2-{2-[(4-{4-[({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)karbamoil]-fenil}piperazin-1-il)metil]fenil}biciklo[2.2.1]hept-2-én-1-karboxamid;

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciklo[3.2.1]okt-3-il]amino}benzil)piperazin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;

N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-[4-(2-{[(1R,2S,3S,5S)-2,6,6-trimetil-biciklo[3.1.1]hept-3-il]amino}benzil)piperazin-1-il]benzamid;

4-(4-{2-[3-azabiciklo[3.2.2]non-3-il]benzil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)-amino]fenil}szulfonil)benzamid;

N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-(4-{2-[triciklo[4.3.1.1^{3,8}]undec-4-én-4-il]benzil}piperazin-1-il)benzamid;

7,7-dimetil-2-{2-[(4-{4-[({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)karbamoil]fenil}-piperazin-1-il)metil]fenil}-N-fenilbiciklo[2.2.1]hept-2-én-1-karboxamid;

7,7-dimetil-2-{2-[(4-{4-[({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)karbamoil]-fenil}piperazin-1-il)metil]fenil}-N-[(1S,2S,3S,5R)-2,6,6-trimetilbiciklo[3.1.1]hept-3-il]biciklo[2.2.1]hept-2-én-1-karboxamid;

N-(adamantán-1-ilmetil)-7,7-dimetil-2-{2-[(4-{4-[({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}-szulfonil)karbamoil]fenil}piperazin-1-il)metil]fenil}biciklo[2.2.1]hept-2-én-1-karboxamid;

N-ciklopropil-7,7-dimetil-2-{2-[(4-{4-[({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-karbamoil]fenil}piperazin-1-il)metil]fenil}biciklo[2.2.1]hept-2-én-1-karboxamid;

7,7-dimetil-2-{2-[(4-{4-[({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)karbamoil]-fenil}piperazin-1-il)metil]fenil}biciklo[2.2.1]hept-2-én-1-karbonsav;

4-[4-(2-{5-[8-azabiciklo[3.2.1]okt-8-ilmetil]-2-tienil}benzil)piperazin-1-yl]-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;

N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetil-biciklo[3.1.1]hept-3-il]amino}piperidin-1-il)benzamid;

4-{4-[adamantán-1-ilmetil]piperazin-1-il}-N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)benzamid;

4-(4-{2-[adamantán-1-il]-2-oxoetil}piperazin-1-il)-N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-benzamid;

N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-4-{4-[(1S,2S,3S,5R)-2,6,6-trimetilbiciklo[3.1.1]hept-3-il]piperazin-1-il}benzamid;

4-{4-[adamantán-1-il]piperazin-1-il}-N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)benzamid;
N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-4-{4-[3,5-dimetiladamantán-1-il]piperazin-1-il}-benzamid;
4-(4-{2-[adamantán-1-il]etil}piperazin-1-il)-N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)benzamid;
N-({4-[(ciklohexilmetil)amino]-3-nitrofenil}szulfonil)-4'-{[(3-fenilpropanoil)[(1S,2S,3S,5S)-2,6,6-trimetil-biciklo[3.1.1]hept-3-il]amino]metil}bifenil-4-karboxamid;
N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-(4-{2-[(R,4R)-1,7,7-trimetilbiciklo-[2.2.1]hept-2-en-2-il]benzilidén}piperidin-1-il)benzamid;
4-[4-(2-{5-[4-(adamantán-1-il)-1,3-tiazol-2-il]-2-tienil}benzil)piperazin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;
1-[adamantán-1-il]-4-{2-[(1-{4-[({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)karbamoil]-fenil}piperidin-4-ilidén)metil]fenil}-N,N-difenil-1H-pirazol-3-karboxamid;
N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-(4-{2-[oktahidro-1H-4,7-metanoindén-5-il(3-fenilpropanoil)amino]benzil}piperazin-1-il)benzamid;
4-[4-(2-{5-[8-azabiciklo[3.2.1]okt-8-ilmetil]-2-tienil}benzilidén)piperidin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid;
N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-[4-(4-{[(1S,2S,3S,5R)-2,6,6-trimetil-biciklo[3.1.1]hept-3-il]amino}benzilidén)piperidin-1-il]benzamid;
N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-[4-(3-{[(1S,2S,3S,5R)-2,6,6-trimetil-biciklo[3.1.1]hept-3-il]amino}benzilidén)piperidin-1-il]benzamid; és
4-[4-(2-{5-[4-(adamantán-1-il)-1,3-tiazol-2-il]-2-tienil}benzilidén)piperidin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)benzamid.

2. Az 1. igénypont szerinti vegyület, ahol a vegyület N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)-amino]fenil}szulfonil)-4-(4-{2-[(1R,4R)-1,7,7-trimetilbiciklo[2.2.1]hept-2-én-2-il]benzilidén}piperidin-1-il)-benzamid vagy egy gyógyászatilag elfogadható sója.

3. Gyógyászati készítmény, amely magába foglal egy segédanyagot és terápiásan hatásos mennyiségben egy, az 1. igénypont szerinti vegyületet vagy egy gyógyászatilag elfogadható sóját.

4. A 3. igénypont szerinti gyógyászati készítmény, ahol a vegyület N-({3-nitro-4-[(tetrahidro-2H-pirán-4-ilmetil)amino]fenil}szulfonil)-4-(4-{2-[(1R,4R)-1,7,7-trimetilbiciklo[2.2.1]hept-2-én-2-il]benzilidén}-piperidin-1-il)benzamid vagy egy gyógyászatilag elfogadható sója.

5. Az 1. vagy 2. igénypont szerinti vegyület vagy egy gyógyászatilag elfogadható sója hólyagrák, agyrák, mellrák, csontvelőrák, nyakrák, krónikus limfocitás fehérvérűség, vastag- és végbélrák, nyelőcsörák, májsejtes rák, akut limfocitás fehérvérűség, tüszös nyirokszövet-daganat, nyiroki rosszindulatú megbetegedés, melanóma, csontvelőből kiinduló fehérvérűség, csontvelődaganat, szájrák, petefészekrák, nem kissejtes tüdőrák, prosztatarák, kissejtes tüdőrák vagy léprák kezelésére való alkalmazásra.