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., ~~, the methods are hereby incorporated by reference.~~

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).

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)).

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

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.

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.~~, which is incorporated in its entirety by reference herein.~~

Esters can be prepared from ~~substrates of formula (I)~~ compounds as provided herein 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:

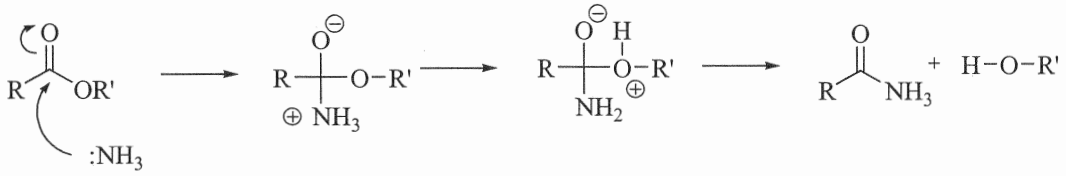
Scheme 1



Acyl Chloride Alkoxide Ester

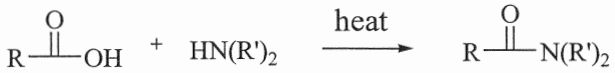
Amides can be prepared from ~~substrates of formula (I)~~ compounds as provided herein containing either an amino group or a carboxy group in similar fashion. Esters can also react with amines or ammonia to form amides.

Scheme 2



Another way to make amides from ~~compounds of formula (I)~~ compounds as provided herein is to heat carboxylic acids and amines together.

Scheme 3



In Schemes 2 and 3 above, R and R' are independently ~~substrates of formula (I)~~ compounds as provided herein, alkyl or hydrogen.

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

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}phenyl)sulfonyl]benzamide;

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;

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.

This inhibitory data demonstrates the utility of ~~compounds having formula (I)~~ compounds as provided herein as inhibitors of anti-apopotic Bcl-2 protein.

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/A1 proteins.

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.

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.

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,

WHAT IS CLAIMED IS:

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

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}phenyl)sulfonyl]benzamide; and

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-(1-methyl-2-oxo-3-azabicyclo[3.1.1]hept-3-yl)phenyl]sulfonyl}benzamide.

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

3. A use of the compound or therapeutically acceptable salt of claim 1 in the preparation of a medicament 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.

4. The compound or therapeutically acceptable salt of claim 1 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 in a patient.

WHAT IS CLAIMED IS:

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

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}phenyl)sulfonyl]benzamide;

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-{6-[adamantan-1-ylmethyl]-2,6-diazabicyclo[3.2.1]oct-2-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(4-{[(2R)-4-(morpholin-4-yl)-1-(phenylthio)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)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-{[(2R)-4-(morpholin-4-yl)-1-(phenylthio)butan-2-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-{(1S,4S)-5-[adamantan-1-ylmethyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

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;

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-(1-methyl-2-oxo-3-azabicyclo[3.1.1]hept-3-yl)phenyl]sulfonyl}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-cyclooctyl-5-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-2-furamide;

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;

4-{4-[adamantan-1-ylcarbonyl]piperazin-1-yl}-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

4-{4-[adamantan-2-ylcarbonyl]piperazin-1-yl}-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

4-{5-[adamantan-1-ylcarbonyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

4-{1S,5S)-3-[adamantan-1-ylcarbonyl]-3,6-diazabicyclo[3.2.0]hept-6-yl}-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}-4-(4-{(3-phenylpropyl)[(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-(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;

6-{3-[adamantan-1-yl]-4-hydroxyphenyl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-naphthamide;

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

4-{[adamantan-2-ylmethyl]amino}-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

4-{2-[adamantan-1-yl]ethoxy}-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

N^3-[adamantan-1-ylacetyl]-N^3-benzyl-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-beta-alaninamide;

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;

[(3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b4',5'-d]pyran-3a-yl]methyl;

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]piperazin-1-yl}-N-({[(1R,4S)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methyl}sulfonyl)benzamide;
4-(4-{2-[adamantan-1-yl]ethyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-{4-[(4'-chlorobiphenyl-2-yl)methyl]piperazin-1-yl}-N-({[(1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methyl}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;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{2-[5-(4-phenyl-1,3-thiazol-2-yl)-2-thienyl]benzyl}piperazin-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;
5-{2-[(4-{4-[({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)carbamoyl]phenyl}piperazin-1-yl)methyl]phenyl}-N-(2-phenyl-1,3-benzoxazol-5-yl)-2-furamide;
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-{4-[2-(triphenylvinyl)benzyl]piperazin-1-yl}benzamide;
4-{4-[2-(5-methyl-5,6-dihydrophenanthridin-6-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-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]piperazin-1-yl}benzamide;
4-(4-{2-[2-(2,6-dimethoxybenzoyl)-3-thienyl]benzylidene}piperidin-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;

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

N-[(4-{[adamantan-1-ylmethyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-oxo-4H-chromen-6-yl)benzamide;

N-[(4-{[adamantan-1-ylmethyl]amino}-3-nitrophenyl)sulfonyl]-4-(1-octyl-1H-pyrazol-4-yl)benzamide;

4-[5-(4-{[(4-{[adamantan-1-ylmethyl]amino}-3-nitrophenyl)sulfonyl]carbamoyl}phenyl)-1,3-benzothiazol-2-yl]butanoic;

N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}-4-[(1R,5S)-1,8,8-trimethyl-3-azabicyclo[3.2.1]oct-3-yl]benzamide;

6-{3-[adamantan-1-yl]-4-methoxyphenyl}-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-naphthamide;

4-{4-[adamantan-1-ylacetyl]piperazin-1-yl}-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

4-{[adamantan-1-ylmethyl]amino}-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

N-{1-[4-({[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}carbamoyl)phenyl]piperidin-4-yl}adamantane-1-carboxamide;

4-[adamantan-2-ylamino]-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

and

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

2. A pharmaceutical composition

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

3. 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.

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

6. The compound or therapeutically acceptable salt of claim 1 or claim 3 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 in a patient.