(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 December 2009 (17.12.2009)

PCT

(10) International Publication Number
WO 2009/151569 A2

(51) International Patent Classification:
A61K 31/00 (2006.01) *A61K 31/192* (2006.01)
A61K 31/05 (2006.01) *A61K 31/335* (2006.01)
A61K 31/16 (2006.01) *A61P 35/02* (2006.01)

(21) International Application Number:
PCT/US2009/003449

(22) International Filing Date:
8 June 2009 (08.06.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/060,064 9 June 2008 (09.06.2008) US

(71) Applicant *(for all designated States except US)*: **COMBINATORX, INCORPORATED** [US/US]; 245 First Street, Sixteenth Floor, Cambridge, MA 02142 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **RICKLES, Richard** [US/US]; 10 Knowles Farm Road, Arlington, MA 02474 (US). **LEE, Margaret, S.** [US/US]; 20 Pleasant Street, Middleton, MA 01949 (US).

(74) Agents: **BELLIVEAU, Michael, J.** et al.; Clark & Elbing LLP, 101 Federal Street, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2009/151569 A2

(54) **Title**: BETA ADRENERGIC RECEPTOR AGONISTS FOR THE TREATMENT OF B-CELL PROLIFERATIVE DISORDERS

(57) **Abstract**: The invention features a method of treating a B-cell proliferative disorder by administering to a patient a BAR agonist, e.g., formulated for administration by a route other than inhalation (such as for oral or intravenous administration), in an amount effective to treat the B-cell proliferative disorder. The BAR agonist may be administered as a monotherapy or in combination with one or more other agents, e.g., a PDE inhibitor, an A2A receptor agonist, or an antiproliferative compound, in amounts that together are effective to treat the B-cell proliferative disorder. The invention further features pharmaceutical compositions and kits including a BAR agonist, alone or in combination with additional agents, for the treatment of a B-cell proliferative disorder.

BETA ADRENERGIC RECEPTOR AGONISTS FOR THE TREATMENT OF B-CELL PROLIFERATIVE DISORDERS

BACKGROUND OF THE INVENTION

The invention relates to the field of treatments for proliferative disorders.

Multiple Myeloma (MM) is a malignant disorder of antibody producing B-cells. MM cells flourish in the bone marrow microenvironment, generating tumors called plasmacytomas that disrupt haematopoesis and cause severe destruction of bone. Disease complications include anemia, infections, hypercalcemia, organ dysfunction, and bone pain.

For many years, the combination of glucocorticoids (e.g., dexamethasone or prednisolone) and alkylating agents (e.g., melphalan) was standard treatment for MM, with glucocorticoids providing most of the clinical benefit. In recent years, treatment options have advanced with three drugs approved by the FDA—Velcade™ (bortezomib), thalidomide, and lenalidomide. Glucocorticoids remain the mainstay of treatment and are usually deployed in combination with FDA-approved or emerging drugs. Unfortunately, despite advances in the treatment, MM remains an incurable disease with most patients eventually succumbing to the cancer.

SUMMARY OF THE INVENTION

In general, the invention features methods and composition employing a beta adrenergic receptor agonist ("BAR agonist") for the treatment of a B-cell proliferative disorder.

Accordingly, in one aspect, the invention features a method of treating a B-cell proliferative disorder by administering to a patient a BAR agonist, e.g., formulated for administration by a route other than inhalation (such as for oral or intravenous administration), in an amount effective to treat the B-cell proliferative disorder.

The BAR agonist may be administered as a monotherapy or in combination with one or more other agents, e.g., a PDE inhibitor, an A2A receptor agonist, or an antiproliferative compound, in amounts that together are effective to treat the B-cell proliferative disorder.

The BAR agonist may also be administered with IL-6 to the patient. If not by direct administration of IL-6, patients may be treated with agent(s) to increase the expression or activity of IL-6. Such agents may include other cytokines (e.g., IL-1 or TNF), soluble IL-6 receptor α (sIL-6R α), platelet-derived growth factor, prostaglandin E1, forskolin, cholera toxin, dibutyryl cAMP, or IL-6 receptor agonists, e.g., the agonist antibody MT-18, K-7/D-6, and compounds disclosed in U.S. Patent Nos. 5,914,106, 5,506,107, and 5,891,998.

The individual components of a combination may be administered simultaneously or within a specified period of time, e.g., 28 days.

The invention further features a pharmaceutical composition including a BAR agonist in an amount effective to treat a B-cell proliferative disorder, e.g., wherein the BAR agonist is formulated for administration by a route other than inhalation (such as for oral or intravenous administration). The composition may further include an A2A agonist, PDE inhibitor, IL-6 agonist, or antiproliferative compound in an amount in combination with the BAR agonist that is effective to treat a B-cell proliferative disorder. The pharmaceutical composition may further include a pharmaceutically acceptable excipient.

The invention also features a kit comprising a BAR agonist and an A2A agonist, PDE inhibitor, IL-6 agonist, or antiproliferative compound in amounts that together are effective to treat a B-cell proliferative disorder. In the kits of the invention, the BAR agonist may be formulated for administration by a route other than inhalation, e.g., oral or intravenous administration. Kits of the invention may further include instructions for administering the BAR agonist or combination of agents for treatment of the B-cell proliferative disorder.

Exemplary BAR agonists are beta 2 agonists. Examples of BAR agonists include arbutaline, arfomoterol, bambuterol, bitolterol, broxaterol, clenbuterol, fenoterol, formoterol, hexoprenaline, indacaterol, isoetharine, isoproterenol, levalbuterol, meluadrine, metaproterenol, nylidrin, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salbutamol, salmeterol, tulobuterol, terbutaline, and

xamoterol. Additional BAR agonists are provided in Tables 1 and 2 herein. Exemplary A2A agonists, PDE inhibitors, and antiproliferative compounds are provided herein, e.g., in Tables 3-8. Exemplary combinations of BAR agonists and antiproliferative compounds are provided in Table 9.

In certain embodiments, when the B-cell proliferative disorder is B-CLL, the BAR agonist is not formoterol, isoproterenol, or salmeterol, and when the B-cell proliferative disorder is doxorubicin resistant multiple myeloma, the BAR agonist is not salbutamol. In other embodiments, the BAR agonist is not isoproterenol. In further embodiments, when the B-cell proliferative disorder is mantle cell lymphoma, the BAR agonist is not salmeterol administered with CHOP or bortezomib; when the B-cell proliferative disorder is multiple myeloma, the BAR agonist is not salbutamol administered with VAD; when the B-cell proliferative disorder is multiple myeloma, the BAR agonist is not salmeterol administered with prednisone and melphalan; when the B-cell proliferative disorder is multiple myeloma, the BAR agonist is not salbutamol administered with clodronate; or when the B-cell proliferative disorder is multiple myeloma, the BAR agonist is not salbutamol administered with melphalan, prednisone, and pamidronate for multiple myeloma.

In other embodiments, the patient is not suffering from asthma, bronchiolitis obliterans, COPD, shortness of breath, or an immunoinflammatory disorder (e.g., of the lungs). The patient may also be one not preparing to undergo, not undergoing, or not recovering from allogenic or autologous stem cell replacement. In other embodiments, the patient is not concomitantly treated with a stem cell mobilizer or an mTOR inhibitor and capecitabine. Compositions and kits of the invention may explicitly exclude a stem cell mobilizer or an mTOR inhibitor and capecitabine.

By "beta adrenergic receptor agonist" or "BAR agonist" is meant any member of the class of compounds that agonize a beta adrenergic receptor, as can be determined by assays well known in the art, see, e.g., *Beta2-Agonists in Asthma Treatment*, Pauwels and O'Byrne, Eds., Marcel Dekker 1997. Exemplary BAR agonists for use in the invention are described herein. A BAR agonist may be a beta 1 agonist, a beta 2 agonist, or a beta 3 agonist. In certain embodiments, a BAR agonist of the invention is specific to the beta 2 adrenergic receptor, e.g., has activity at the beta 2 adrenergic receptor that is at least 2, 5, 10, 20, 50, or 100 times greater than at the beta 1 and/or beta 3 adrenergic receptor. In other embodiments, the BAR agonist

has activity at a beta adrenergic receptor that is at least 2, 5, 10, 20, 50, 100, 500, or 1000 times greater than at any alpha adrenergic receptor.

By "beta 2 agonist" is meant a BAR agonist whose antiproliferative effect on MM.1S cells is reduced in the presence of a selective beta 2 adrenergic receptor antagonist (for example, ICI 118,551 or butaxomine). In certain embodiments, the antiproliferative effect of a beta 2 agonist in MM.1S cells (used at a concentration equivalent to the K_i) is reduced by at least 10, 20, 30, 40, 50, 60, 70, 80, or 90 % by a selective beta 2 adrenergic receptor antagonist used at a concentration of at least 10-fold higher than its K_i.

By "A2A receptor agonist" is meant any member of the class of compounds whose antiproliferative effect on MM.1S cells is reduced in the presence of an A2A-selective antagonist, e.g., SCH 58261. In certain embodiments, the antiproliferative effect of an A2A receptor agonist in MM.1S cells (used at a concentration equivalent to the K_i) is reduced by at least 10, 20, 30, 40, 50, 60, 70, 80, or 90 % by an A2A antagonist used at a concentration of at least 10-fold higher than its K_i (for example, SCH 58261 (K_i=5nM) used at 78nM)). An A2A receptor agonist may also retain at least 10, 20, 30, 40, 50, 60, 70, 80, 90, or 95% of its antiproliferative activity in MM.1S cells in the presence of an A1 receptor antagonist (e.g., DPCPX (89nM)), an A2B receptor antagonist (e.g., MRS 1574 (89nM)), an A3 receptor antagonist (e.g., MRS 1523 (87nM)), or a combination thereof. In certain embodiments, the reduction of agonist-induced antiproliferative effect by an A2A antagonist will exceed that of an A1, A2B, or A3 antagonist. Exemplary A2A Receptor Agonists for use in the invention are described herein.

By "PDE inhibitor" is meant any member of the class of compounds having an IC_{50} of 100 μM or lower concentration for a phosphodiesterase. In preferred embodiments, the IC_{50} of a PDE inhibitor is 40, 20, 10 μM or lower concentration. In particular embodiments, a PDE inhibitor of the invention will have activity against PDE 2, 3, 4, or 7 or combinations thereof in cells of the B-type lineage. In preferred embodiments, a PDE inhibitor has activity against a particular type of PDE when it has an IC_{50} of 40 μM, 20 μM, 10 μM, 5 μM, 1 μM, 100 nM, 10 nM, or lower concentration. When a PDE inhibitor is described herein as having activity against a particular type of PDE, the inhibitor may also have activity against other types, unless

otherwise stated. Exemplary PDE inhibitors for use in the invention are described herein.

By "B-cell proliferative disorder" is meant any disease where there is a disruption of B-cell homeostasis leading to a pathologic increase in the number of B cells. A B-cell cancer is an example of a B-cell proliferative disorder. A B-cell cancer is a malignancy of cells derived from lymphoid stem cells and may represent any stage along the B-cell differentiation pathway. B-cell proliferative disorders include autoimmune lymphoproliferative disease, B-cell chronic lymphocytic leukemia (CLL), B-cell prolymphocyte leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma, follicular lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT type), nodal marginal zone lymphoma, splenic marginal zone lymphoma, hairy cell leukemia, plasmacytoma, diffuse large B-cell lymphoma, Burkitt lymphoma, multiple myeloma, indolent myeloma, smoldering myeloma, monoclonal gammopathy of unknown significance (MGUS), B-cell non-Hodgkin's lymphoma, small lymphocytic lymphoma, monoclonal immunoglobin deposition diseases, heavy chain diseases, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, precursor B-lymphoblastic leukemia/lymphoma, Hodgkin's lymphoma (e.g., nodular lymphocyte predominant Hodgkin's lymphoma, classical Hodgkin's lymphoma, nodular sclerosis Hodgkin's lymphoma, mixed cellularity Hodgkin's lymphoma, lymphocyte-rich classical Hodgkin's lymphoma, and lymphocyte depleted Hodgkin's lymphoma), post-transplant lymphoproliferative disorder, and Waldenstrom's macroglobulinemia.

By "effective" is meant the amount or amounts of one or more compounds sufficient to treat a B-cell proliferative disorder in a clinically relevant manner. An effective amount of an active varies depending upon the manner of administration, the age, body weight, and general health of the patient. Ultimately, the prescribers will decide the appropriate amount and dosage regimen. Additionally, an effective amount can be that amount of compound in a combination of the invention that is safe and efficacious in the treatment of a patient having the B-cell proliferative disorder as determined and approved by a regulatory authority (such as the U.S. Food and Drug Administration).

By "treating" is meant administering or prescribing a pharmaceutical composition for the treatment or prevention of a B-cell proliferative disorder.

By "patient" is meant any animal (e.g., a human). Other animals that can be treated using the methods, compositions, and kits of the invention include horses, dogs, cats, pigs, goats, rabbits, hamsters, monkeys, guinea pigs, rats, mice, lizards, snakes, sheep, cattle, fish, and birds.

The term "immunoinflammatory disorder" encompasses a variety of conditions, including autoimmune diseases, proliferative skin diseases, and inflammatory dermatoses. Immunoinflammatory disorders result in the destruction of healthy tissue by an inflammatory process, disregulation of the immune system, and unwanted proliferation of cells. Examples of immunoinflammatory disorders are acne vulgaris; acute respiratory distress syndrome; Addison's disease; adrenocortical insufficiency; adrenogenital ayndrome; allergic conjunctivitis; allergic rhinitis; allergic intraocular inflammatory diseases, ANCA-associated small-vessel vasculitis; angioedema; ankylosing spondylitis; aphthous stomatitis; arthritis, asthma; atherosclerosis; atopic dermatitis; autoimmune disease; autoimmune hemolytic anemia; autoimmune hepatitis; Behcet's disease; Bell's palsy; berylliosis; bronchial asthma; bullous herpetiformis dermatitis; bullous pemphigoid; carditis; celiac disease; cerebral ischaemia; chronic obstructive pulmonary disease; cirrhosis; Cogan's syndrome; contact dermatitis; COPD; Crohn's disease; Cushing's syndrome; dermatomyositis; diabetes mellitus; discoid lupus erythematosus; eosinophilic fasciitis; epicondylitis; erythema nodosum; exfoliative dermatitis; fibromyalgia; focal glomerulosclerosis; giant cell arteritis; gout; gouty arthritis; graft-versus-host disease; hand eczema; Henoch-Schonlein purpura; herpes gestationis; hirsutism; hypersensitivity drug reactions; idiopathic cerato-scleritis; idiopathic pulmonary fibrosis; idiopathic thrombocytopenic purpura; inflammatory bowel or gastrointestinal disorders, inflammatory dermatoses; juvenile rheumatoid arthritis; laryngeal edema; lichen planus; Loeffler's syndrome; lupus nephritis; lupus vulgaris; lymphomatous tracheobronchitis; macular edema; multiple sclerosis; musculoskeletal and connective tissue disorder; myasthenia gravis; myositis; obstructive pulmonary disease; ocular inflammation; organ transplant rejection; osteoarthritis; pancreatitis; pemphigoid gestationis; pemphigus vulgaris; polyarteritis nodosa; polymyalgia rheumatica; primary adrenocortical insufficiency; primary billiary cirrhosis; pruritus scroti;

pruritis/inflammation, psoriasis; psoriatic arthritis; Reiter's disease; relapsing polychondritis; rheumatic carditis; rheumatic fever; rheumatoid arthritis; rosacea caused by sarcoidosis; rosacea caused by scleroderma; rosacea caused by Sweet's syndrome; rosacea caused by systemic lupus erythematosus; rosacea caused by urticaria; rosacea caused by zoster-associated pain; sarcoidosis; scleroderma; segmental glomerulosclerosis; septic shock syndrome; serum sickness; shoulder tendinitis or bursitis; Sjogren's syndrome; Still's disease; stroke-induced brain cell death; Sweet's disease; systemic dermatomyositis; systemic lupus erythematosus; systemic sclerosis; Takayasu's arteritis; temporal arteritis; thyroiditis; toxic epidermal necrolysis; tuberculosis; type-1 diabetes; ulcerative colitis; uveitis; vasculitis; and Wegener's granulomatosis. "Non-dermal inflammatory disorders" include, for example, rheumatoid arthritis, inflammatory bowel disease, asthma, and chronic obstructive pulmonary disease. "Dermal inflammatory disorders" or "inflammatory dermatoses" include, for example, psoriasis, acute febrile neutrophilic dermatosis, eczema (e.g., asteatotic eczema, dyshidrotic eczema, vesicular palmoplantar eczema), balanitis circumscripta plasmacellularis, balanoposthitis, Behcet's disease, erythema annulare centrifugum, erythema dyschromicum perstans, erythema multiforme, granuloma annulare, lichen nitidus, lichen planus, lichen sclerosus et atrophicus, lichen simplex chronicus, lichen spinulosus, nummular dermatitis, pyoderma gangrenosum, sarcoidosis, subcorneal pustular dermatosis, urticaria, and transient acantholytic dermatosis. By "proliferative skin disease" is meant a benign or malignant disease that is characterized by accelerated cell division in the epidermis or dermis. Examples of proliferative skin diseases are psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant keratosis, acne, and seborrheic dermatitis. As will be appreciated by one skilled in the art, a particular disease, disorder, or condition may be characterized as being both a proliferative skin disease and an inflammatory dermatosis. An example of such a disease is psoriasis.

By a "low dosage" is meant at least 5% less (e.g., at least 10%, 20%, 50%, 80%, 90%, or even 95%) than the lowest standard recommended dosage of a particular compound formulated for a given route of administration for treatment of any human disease or condition.

By a "high dosage" is meant at least 5% (e.g., at least 10%, 20%, 50%, 100%, 200%, or even 300%) more than the highest standard recommended dosage of a particular compound for treatment of any human disease or condition.

Compounds useful in the invention may also be isotopically labeled compounds. Useful isotopes include hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, (e.g., ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl). Isotopically-labeled compounds can be prepared by synthesizing a compound using a readily available isotopically-labeled reagent in place of a non-isotopically-labeled reagent.

Compounds useful in the invention include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, esters, amides, thioesters, solvates, and polymorphs thereof, as well as racemic mixtures and pure isomers of the compounds described herein.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the induction of apoptosis after human multiple myeloma cells (MM.1S) were exposed to salmeterol and dexamethasone as single agents and in combination (48 hour timepoint).

Figure 2 is a graph showing the induction of apoptosis after human multiple myeloma cells (MM.1S) were exposed to salmeterol and lenalidomide or trequinsin as single agents and in combination (72 hour timepoint).

Figure 3 is a graph showing the induction of apoptosis after human multiple myeloma cells (MM.1S) were exposed to salmeterol and bortezomib as single agents and in combination (72 hour timepoint).

Figure 4 is a graph of the antiproliferative activity of beta 2 agonist salbutamol against human multiple myeloma cells (MM.1R) after transfection of siRNA.

Figure 5 is a graph of an annexin V/PI assay of control MM.1S cells and cells cultured in the presence of salmeterol or salbutamol for one month after exposure to dexamethasone and salmeterol.

Figure 6 is a graph of the viability of patient multiple myeloma tumor cells treated with dexamethasone (DEX) and salmeterol.

Figure 7 is a graph of the viability of patient multiple myeloma tumor cells treated with bortezomib (Bort) and salmeterol.

Figure 8 is a graph of tumor volume in control and drug treated animals (salmeterol, dexamethasone, and salmeterol/dexamethasone) using the MM.1S tumor model.

Figure 9 is a graph of tumor volume in control and drug treated animals (salmeterol, bortezomib and salmeterol/bortezomib) using the RPMI-8226 tumor model.

Figure 10 is a graph of regression of tumor growth analysis of the activities of salmeterol, dexamethasone, and bortezomib as single agents and in combination using the RPMI-8226 tumor model.

Figure 11 is a graph of analysis of the effects of salmeterol, dexamethasone, and bortezomib on mouse body weight when deployed as single agents and in combination using the RPMI-8226 tumor model.

DETAILED DESCRIPTION OF THE INVENTION

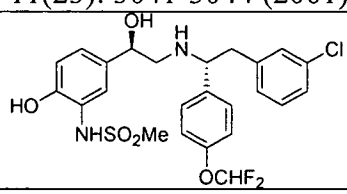
We have identified compounds that display synergistic anti-proliferative activity when used in combination with drugs deployed in the clinic for the treatment of multiple myeloma. BAR agonists are highly synergistic with multiple myeloma standard of care (dexamethasone, lenalidomide, melphalan, doxorubicin, and bortezomib). BAR agonists also synergize with adenosine A2A receptors agonists and PDE inhibitors. The synergistic activities observed with BAR agonists are observed when tested on various multiple myeloma cell lines, as well as OCI-ly10, a diffuse large B-cell lymphoma (DLBCL) cell line, and GA-10, a Burkitt's lymphoma cell line.

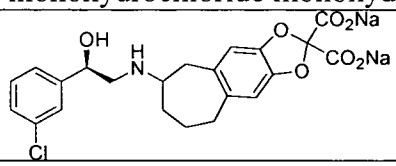
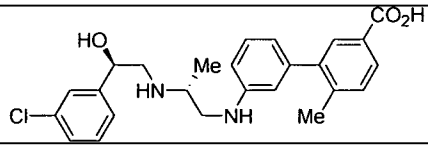
Accordingly, the invention features methods, compositions, and kits for the administration of an effective amount of a BAR agonist, alone or in combination with one or more additional agents, to treat a B-cell proliferative disorder. The invention is described in greater detail below.

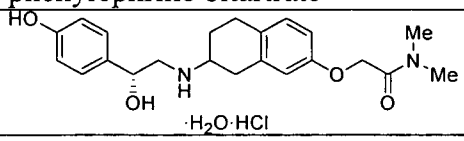
Beta Adrenergic Receptor Agonists

Exemplary BAR agonists for use in the invention are shown in Table 1.

Table 1.

BAR Agonist	Synonym
(-)-pindolol	1-(Indol-4-yloxy)-3-(isopropylamino)-2-propanol
3H-SB-206606	tritiated (4-(2-((2-(3-chlorophenyl)-2-hydroxyethyl)amino)propyl)phenoxy)acetic acid
Amibegron	Ethyl {[(7S)-7-{[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}acetate hydrochloride
Arbutamine	4-(1-hydroxy-2-((4-(4-hydroxyphenyl)butyl)amino)ethyl)- 1,2-Benzenediol
Arformoterol	(-)-Formoterol; (R,R)-Formoterol; arformoterol tartrate; N-(2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)phenyl)- formamide
ASF-1020	WO 2006/108424
AZ-40140	SB-418790
AZD-3199	
Bambuterol	5-(2-(tert-butylamino)-1-hydroxyethyl)-3-phenylene bis(dimethylcarbamate); bambuterol hydrochloride
Bedoradrine	bedoradrine sulfate; Bis(2-(((7S)-7-(((2R)-2-hydroxy-2-(4-hydroxy-3-(2-hydroxyethyl)phenyl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-2-yl)oxy)-N,N-dimethylacetamide) sulfate
BI-1744-CL	
Bitolterol	bitolterol mesylate; 4-(2-(tert-Butylamino)-1-hydroxyethyl)-o-phenylene di-p-toluate methanesulfonate
BMS-187257	U.S. Pat. No. 5,321,036; Bioorganic & Medicinal Chemistry Letters 6(19): 2253-2258 (1996)
BMS-196085	Bioorganic & Medicinal Chemistry Letters 11(23): 3041-3044 (2001).
BMS-210285	
BRL-26830A	methyl 4-(2-((2-hydroxy-2-phenethyl)amino)propyl)benzoate-2-butanedioate
BRL-35135	EP 23385
BRL-37344	(4-(2-((2-(3-chlorophenyl)-2-hydroxyethyl)amino)propyl) phenoxy)acetic acid
Broxaterol	(+/-)-3-Bromo-alpha-((tert-butylamino)methyl)-5-isoxazolemethanol
Carmoterol	
Carvedilol	

BAR Agonist	Synonym
CL-316243	disodium (R,R)-5-(2-[{2-(3-chlorophenyl)-2-hydroxyethyl}-amino]propyl)-1,3-benzodioxole-2,2,Dicarboxylate U.S. Pat. No. 5,061,727
Clenbuterol	4-amino-3,5-dichloro-alpha-(((1,1dimethylethyl)amino)methyl)-Benzenemethanol
CP-114271	UL-TG-307
Ephedrine	ephedrine hydrochloride; ephedrine sulfate; L(-)-Ephedrine
Fenoterol	Fenoterol Hydrobromide; Fenoterol Hydrochloride; Fenoterol + Ipratropium (Duovent or Berodual N)
Formoterol	Eformoterol, budesonide + formoterol; formoterol fumarate; fluticasone + formoterol; beclomethasone dipropionate + formoterol; ciclesonide + formoterol; mometasone + formoterol; Eformoterol fumarate dehydrate
FR-149175	ethyl ((S)-8-((R)-2-(3-chlorophenyl)-2-hydroxy-ethylamino)-6,7,8,9-tetrahydro-5H-benzocyclohepton-2-yloxy)-acetate monohydrochloride monohydrate
FR-165914	
GP-2-128	1-(3,4-dihydroxyphenyl)-2-(3-(4-carbamylphenyl)-1-methylpropylamino)ethanol; GP 2-128 (*R*-(*R*, *R*))-2,3-dihydroxybutanedioate (1:1); GP 2-128 monoacetate
GS-332	sodium(2R)-(3-(3-(2-(3-chlorophenyl)-2-hydroxyethylamino)cyclohexyl)phenoxy)acetate
GSK 678007	WO 03/066033 and WO 03/066036
GSK-642444	fluticasone furoate + GSK-642444
GW-2696X	
Hexoprenaline	Hexoprenaline Sulfate
ICI-198157	methyl (4-(2-((2-hydroxy-3-phenoxypropyl)amino)ethoxy)phenoxy) acetate
Indacaterol	glycopyrronium bromide + indacaterol; mometasone + indacaterol
Ipratropium	Ipratropium Bromide; Ipratropium Bromide, (endo,anti)-Isomer; Ipratropium Bromide, (exo,syn)-Isomer; (endo,syn)-(+-)-3-(3-Hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo(3.2.1)octane;

BAR Agonist	Synonym
Isoetharine	Isoetharine Mesylate; 4-(1-hydroxy-2-((1-methylethyl)amino)butyl)- 1,2-Benzenediol
Isoproterenol	DL-Isoprenaline hydrochloride; DL-Isoproterenol hydrochloride; Isoproterenol Sulfate; 4-(1-Hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol; isoproterenol hydrochloride + phenylephrine bitartrate
KUL-1248	
KUL-7211	2-(4-(2-((2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl)amin) ethyl)phenyloxy) acetic acid
L-742791	(S)-N-(4-[2-{(3-[4-hydroxyphenoxy]-2-hydroxypropyl)amino}ethyl]phenyl)-4-iodobenzenesulfonamide
LAS-10097	
Levalbuterol	controlled-release oral levalbuterol; R-salbutamol sulfate
LM-2616	4-(4-Methyl-1-piperazinyl)-2,7,9-trimethylpyrido(3',2':4,5) thieno(3,2-d)pyrimidine
MAP-0005	Budesonide + formoterol
meluadrine	(-)-(R)-alpha-((tert-Butylamino)methyl)-2-chloro-4-hydroxybenzyl alcohol; meluadrine tartrate
Metaproterenol	(RS)-1-(3,5-Dihydroxyphenyl)-2-isopropylaminoethanol; metaproterenol-3-O-sulfate
Milveterol	fluticasone furoate + milveterol
Mirabegron	2-(2-amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl] acetamide
N-5984	6-(2-(R)-((2-(R)-(3-chlorophenyl)-2-hydroxyethyl)amino) propyl)-2,3-dihydro-1,4-benzodioxine-2-(R)-carboxylic acid
NCX-950	α'-[[(1,1-dimethylethy)amino]methyl]-4-hydroxy-1,3-benzenedimethanol nitrate
Nylidrin	Buphenine Hydrochloride; p-Hydroxy-N-(1-methyl-3-phenylpropyl)norephedrine
PF-610355	PF-610355 + Salmeterol
Picumeterol	picumeterol fumarate; (R)-4-Amino-3,5-dichloro-alpha-(((6-(2-(2-pyridinyl)ethoxy) hexyl)amino)methyl)benzenemethanol
Pirbuterol	pirbuterol acetate; pirbuterol dihydrochloride; pirbuterol sulfate; 2-hydroxymethyl-3-hydroxy-6-(1-hydroxy-2-tert-butylamino ethyl)pyridine, dihydrochloride;

BAR Agonist	Synonym
Procaterol	(*R*, *S*)-(+-)-8-Hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolinone; Procaterol Monohydrochloride; Procaterol Monohydrochloride, (*R*, *R*)-(+)-Isomer; Procaterol Monohydrochloride, (*R*, *R*)-(+-)-Isomer; Procaterol Monohydrochloride, (*R*, *R*)-(-)-Isomer; Procaterol Monohydrochloride, (*R*, *S*)-(+)-Isomer; Procaterol Monohydrochloride, (*R*, *S*)-(-)-Isomer; Procaterol, (*R*, *R*)-(+-)-Isomer; Procaterol, (*R*, *S*)-(-)-Isomer
Rafabegron	(3-{(2R)-2-((2R)-2-(3-Chlorophenyl)-2-hydroxyethyl amino)propyl}-1H-indol-7-yloxy)acetic acid
Reproterol	reproterol monohydrochloride; reproterol, (-)-isomer; Reproterol + cromoglycate
Rimiterol	alpha-(3,4-Dihydroxyphenyl)-2-piperidinemethanol
Ritodrine	Ritodrine Hydrochloride
RP-58802B	2-(3-(1-Benzimidazolyl)-1-methylpropylamino)-1-(4-hydroxy-3-methoxyphenyl)ethanol; alpha-(((3-(1-Benzimidazolyl)-1-methylpropyl)amino)methyl)vanillyl Alcohol; RP 58802B dihydrochloride; RP 58802B, (*R,R*)-(+-)-isomer; RP 58802B, (*R,S*)-(+-)-isomer; RP 58802B, (*R*-(*R,R*))-isomer; RP 58802B, (*R*-(*R,S*))-isomer; RP 58802B, (*S*-(*R,R*))-isomer; RP 58802B, (*S*-(*R,S*))-isomer;
S-1319	4-hydroxy-7-(1-(1-hydroxy-2-methylamino)ethyl)-1,3-benzothiazole-2(3H)-one
Salbutamol	albuterol; albuterol sulfate; ipratropium + salbutamol (Combivent and Duoneb), Merck KGaA; ipratropium bromide + salbutamol sulfate
Salmeterol	fluticasone propionate + salmeterol; R-salmeterol
SAR-150640	ethyl 4-(4-((2-hydroxy-3-(4-hydroxy-3-((methylsulfonyl)amino) phenoxy)propyl) amino) cyclohexyl)benzoate; ethyl-4-{trans-4-[((2S)-2-hydroxy-3-{4-hydroxy-3[(methylsulfonyl)amino] phenoxy}propyl)amino]cyclohexyl} benzoate hydrochloride
SB-220646	Journal of Pharmacology and Experimental Therapeutics, 285: 1084-1095 (1998)
SB-226552	Journal of Pharmacology and Experimental Therapeutics, 285: 1084-1095 (1998)
SB-236923	Journal of Pharmacology and Experimental Therapeutics, 285: 1084-1095 (1998)
SB-251023	(4-[1-{2-(S)-hydroxy-3-(4-hydroxyphenoxy)-propylamino}cyclopentylmethyl]phenoxymethyl) phenylphosphonic acid lithium salt

BAR Agonist	Synonym
Sibenadet	sibenadet hydrochloride
SM-11044	3-(3,4-dihydroxyphenyl)-N-(3-(4-fluorophenyl)propyl)serine pyrrolidine amide hydrobromide; (*R*-(*R*,*S*))-1-(3-(3,4-dihydroxyphenyl)-2-((3-(4-fluorophenyl)propyl)amino)-3-hydroxy-1-oxopropyl)-, monohydrobromidepyrrolidine,
Solabegron	3'-((2-((2-(3-chlorophenyl)-2-hydroxyethyl)amino)ethyl) amino)-(1,1'-biphenyl)-3-carboxylic acid
Sotalol hydrochloride	beta-Cardone; Betapace; Betapace AF; Hydrochloride, Sotalol; MJ 1999; MJ-1999; MJ1999; Monohydrochloride, Sotalol; Sotalol Hydrochloride; Sotalol Monohydrochloride; Sotalex; Sotacor
SR-59062A	Bioorganic & Medicinal Chemistry Letters Volume 4, Issue 16, 25 August 1994, Pages 1921-1924
SR-59104A	N-[(2R)-(6-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)methyl]-(2R)-2-hydroxy-2- (3-chlorophenyl)ethanamine
SR-59119A	N-[(2R)-(7-methoxy-1,2,3,4-tetrahydronaphth-2-yl)methyl]-(2R)-2-hydroxy-2- (3-chlorophenyl)ethanamine
SWR-0342-SA	(S)-(Z)-[4-[[1-[2-[(2-hydroxy-3-phenoxypropyl)]amino]ethyl]-1-propenyl]phenoxy] acetic acid ethanedioic acid
T-0509	4-(2-((2-(3,4-dimethoxyphenyl)ethyl)amino)-1-hydroxyethyl)-1,2-benzenediol; 1-(3,4-dimethoxyphenethyl amino)-2-(3,4-dihydroxyphenyl)ethanol; RP333, (R)-isomer; RP333, dihydrochloride, (+)-isomer; RP333, hydrochloride
Talibegron	4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethoxy]- benzeneacetic acid, hydrochloride
Terbutaline	Terbutaline Sulfate
Tulobuterol	1-(o-chlorophenyl)-2-tert-butylaminoethanol; tulobuterol hydrochloride; alpha-((tert-butylamino)methyl)-o-chlorobenzyl alcohol
UD-CG-212	3(2H)-Pyridazinone, 4,5-dihydro-6-(2-(4-hydroxyphenyl)-1H-benzimidazol-5-yl)-5-methyl-, monohydrochloride;
UK-503590	
UL-TG-307	4-(2-((2-hydroxy-2-(2-(trifluoromethyl)-4-thiazolyl)ethyl)-amino)propyl)phenoxy-acetic acid

BAR Agonist	Synonym
Xamoterol	Xamoterol Fumarate; Xamoterol Hemifumarate; Xamoterol Maleate (2:1); Xamoterol Monohydrobromide; Xamoterol Monohydrochloride; Xamoterol, (S)-Isomer;
ZD-7114	EP 473 285

Preferred BAR agonists include arbutaline, arfomoterol, bambuterol, bitolterol, broxaterol, clenbuterol, fenoterol, formoterol, hexoprenaline, indacaterol, isoetharine, isoproterenol, levalbuterol, meluadrine, metaproterenol, nylidrin, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salbutamol, salmeterol, tulobuterol, terbutaline, and xamoterol.

Additional BAR agonists for use in the invention are shown in Table 2.

Table 2.

159802 (GSK-159802)
ZD-9989
SWR-0335
MN-246
LY-362884
L-751250
KUR-1247
KI-03219
KTO-7924
GSK-597901
GRC-1087
CL-314698
AZD-3199
799943 (GSK-799943)
961081 (GSK-961081)
AR-C-89855
anti-obesity therapy, Nisshin Flour
asthma therapy, Cue Biotech
asthma therapy, Selectus
beta 2 adrenoceptor agonists (asthma/COPD), Novartis
beta 3 adrenoceptor agonists (obesity/diabetes), Wyeth
beta 3 adrenoceptor agonists, University of Tennessee
beta2-agonist, Byk Nederland
beta-3 adrenergic (human) receptor, OncoPharm
beta-3 adrenoceptor agonist, MDI

beta-3 adrenoceptor agonist, Pfizer
beta-3 adrenoceptor agonists (obesity), Merck & Co
beta-3 adrenoceptor agonists, Lilly
beta-3 agonist, Bayer
beta-3 agonists, Fourier de Grenoble
EPI-12323 combination therapy (asthma/ COPD), EpiGenesis
long acting beta agonists (asthma/COPD), Sepracor
short acting beta agonists (solution, asthma), AstraZeneca
salbutamol esters, Cardiff University
SR-58878

In certain embodiments, isoproterenol is not employed.

A2A Receptor Agonists

Exemplary A2A receptor agonists for use in the invention are shown in Table 3.

Table 3.

Compound	Synonym
FK 453	(+)-(R)-[(E)-3-(2-phenylpyrazolo[1,5-a]pyridin-3-yl) acryloyl]-2-piperidine ethanol
N 0861	(+-)-N6-endonorbornan-2-yl-9-methyladenine
CVT 3619	(2-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2-fluorophenylthio) methyl] oxolane-3,4-diol)
T 62	(2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)-(4-chlorophenyl)-methanone
PD 81723	(2-Amino-4,5-dimethyl-3-thienyl)-[3-(trifluoromethyl)phenyl]methanone
CP 608039	(2S, 3S, 4R, 5R)-3-amino-5-{6-[5-chloro-2-(3-methyl-isoxazol-5-ylmethoxy)-benzylamino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide
CVT 3033	(4S,2R,3R,5R)-2-[6-amino-2-(1-pentylpyrazol-4-yl)purin-9-yl]-5-(- hydroxymethyl)oxolane-3,4-diol
FK 352	(E)-(R)-1-[3-(2-phenylpyrazolo[1, 5-a]pyridin-3-yl)acryloyl]pyperidin-2-ylacetic acid
KF 21213	(E)-8-(2,3-dimethyl-4-methoxystyryl)-1, 3,7-trimethylxanthine

Compound	Synonym
KF 17837	(E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine
MDL 102503	(R)-3,7-dihydro-8-(1-methyl-2-phenylethyl)-1,3-dipropyl-1H-purine-2,6-dione
Apaxifylline	(S)-3, 7-dihydro-8-(3-oxocyclopentyl)-1, 3-dipropyl-1H-purine-2, 6-dione
CVT 2759	[(5-{6-[((3*R*)oxolan-3-yl)amino]purin-9-yl}(3*S*,2*R*,4*R*,5*R*)-3,4-dihydroxyoxolan-2-yl)methoxy]-*N*-methylcarboxamide
DAX	1,3-diallyl-8-cyclohexylxanthine
BG 9928	1,3-dipropyl-8-[1-(4-propionate)-bicyclo-[2,2,2]octyl]xanthine
CPX	1,3-dipropyl-8-cyclopentylxanthine
BN 063	1-cyclopropylisoguanosine
AMP 579	1S-[1a,2b,3b,4a(S*)]-4-[7-[[1-[(3-chloro-2-thienyl)methylpropyl]propyl-amino]-3H-imidazo[4,5-b] pyridyl-3-yl]-N-ethyl-2,3-dihydroxycyclopentane carboxamide
Binodenoson (MRE-0470)	2-((cyclohexylmethylene)hydrazino)-Adenosine
HEMADO	2-(1-hexynyl)-N-methyladenosine
YT 146	2-(1-octynyl) adenosine
Regadenoson (CVT 3146)	2-(4-((methylamino)carbonyl)-1H-pyrazol-1-yl)-Adenosine
CGS 21680	2-(4-(2-carboxyethyl)phenethylamino)-5'-N-ethylcarboxamidoadenosine
APEC	2-[(2-aminoethyl-aminocarbonylethyl) phenylethylamino]-5'-N-ethyl-carboxamidoadenosine
MRE 0094	2-[2-(4-chlorophenyl)ethoxy]adenosine
2-Cl-IB-MECA	2-chloro-N^6-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine
CCPA	2-chloro-N^6-cyclopentyladenosine
CV 1808	2-phenylaminoadenosine
MDL 102234	3,7-dihydro-8-(1-phenylpropyl)-1,3-dipropyl-1H-purine-2,6-dione
SF 349	3-acetyl-7-methyl-7,8-dihydro-2,5(1H, 6H) quinolinone
CVT 6883	3-ethyl-1-propyl-8-[1-(3-trifluoromethylbenzyl)-1*H*-pyrazol-4-yl]-3,7-dihydropurine-2,6-dione
UR 7247	3-iso-propyl-5-([2'- { 1 *H* } -tetrazol-5-yl- 1,1 '-biphenyl-4-yl]methyl)- 1 *H*pyrazole-4-carboxylic acid
ZM 241385	4-(2-[7-amino-2-(2-furyl)[1,2,4]-triazolo[2,3-a][1,3,5]triazin-5-yl amino]ethyl)phenol
IRFI 165	4-Cyclopentylamino-1.-methylimidazo[1,2-alquinoxaline
FK 838	6-oxo-3-(2-phenylpyrazolo [1,5-a] pyridin-3-yl)-1(6H)-pyridazinebutanoic acid

Compound	Synonym
KF 20274	7,8-dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1H-imidazo(2,1-j)purin-5(4H)-one
Midaxifylline	8-(1-Aminocyclopentyl)-3,7-dihydro-1,3-dipropyl-(1*H*)-purine-2,6-dione hydrochloride
KFM 19	8-(3oxocyclopentyl)-1,3 -dipropyl-7H-purine-2,6-dione
KW 3902	8-(noradamantan-3-yl)-1,3-dipropylxanthine
Naxifylline	8-[(1*S*,2*R*,4*S*,5*S*,6*S*)-3-oxatricyclo[3.2.1.02,4]oct-6-yl]-1,3-dipropyl-3,7-dihydro-1*H*-purine-2,6-dione
DPCPX	8-cyclopentyl-1,3-dipropylxanthine
MDL 201449	9-[(1R,3R)-trans- cyclopentan-3-ol]adenine
CPC 405	9'-chloro-EHNA
CPC 402	9'-hydroxy-EHNA
CPC 406	9'-phthalimido-EHNA
WRC 0571	C^8-(*N*-methylisopropyl)-amino-N^6(5'-endohydroxy)-endonorbornan-2-yl-9-methyladenine
HE-NECA	hexynyladenosine-5'-N-ethylcarboxamide
GR 79236	N-((1S,trans)-2-hydroxycyclopentyl)adenosine
Metrifudil	N-((2-methylphenyl)methyl)adenosine
R-PIA	N-(1-methyl-2-phenylethyl)adenosine
ADAC	N-(4-(2-((4-(2-((2-aminoethyl)amino)-2-oxoethyl)phenyl)amino)-2-oxoethyl)phenyl)-Adenosine
DPMA	N^6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine
IB-MECA	N^6-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine
I-AB-MECA	N^6-(4-amino-3-iodophenyl)methyl-5'-N-methylcarboxamidoadenosine
WRC 0342	N^6-(5'-endohydroxy)-endonorbornan-2-yl-9-methyladenine
HPIA	N^6-(R-4-hydroxyphenylisopropyl) adenosine
CGS 24012	N6-2-(3,5-dimethoxyphenyl)- 2-(2-methylphenyl)-ethyl adenosine
SDZ WAG 994	*N*^{6}-cyclohexyl-2'-*O*-methyladenosine
CHA	N^6-cyclohexyladenosine
TCPA	N^6-cyclopentyl-2-(3-phenylaminocarbonyltriazene-1-yl)adenosine
N 0840	N6-cyclopentyl-9- methyladenine
CPA	N^6-cyclopentyladenosine
NECA	N-ethylcarboxamidoadenosine
(S)-ENBA	*S*-*N*^{6}-(2-endo-norbornyl)adenosine
Apadenoson	trans-4-(3-(6-amino-9-(N-ethyl-.beta.-D-ribofuranuronamidosyl)-9H-purin-2-yl)-2-propynyl)-Cyclohexanecarboxylic acid methyl ester

Compound	Synonym
CDS 096370	U.S. Patent No. 6,800,633
ATL-313	4-{3-[6-amino-9-(5-cyclopropylcarbamoyl-3,4-dihydroxytetrahydrofuran-2-yl)-9H-purin-2-yl]prop-2-ynyl}piperidine-1-carboxylic acid methyl ester
ATL-193	acetic acid 4-{3-[6-amino-9-(5-ethylcarbamoyl-3, 4-dihydroxy-tetrahydro-furan -2-yl)-9H-purin-2-yl] -prop-2-ynyl}-cyclohexylmethyl ester
ATL2037	5-{6-amino-2-[3-(4-hydroxymethyl-cyclohexyl)-prop-1-ynyl]-purin-9-yl}-3,4-dihydroxy-tetrahydro-furan-2-carboxylic acid ethylamide; BW-1433, 8-(4-carboxyethenylphenyl)-1,3-dipropylxanthine

Additional A2A receptor agonists are described or claimed in US Patent Application Publication Nos. 20020082240, 20030186926, 20050261236, 2006040888, 20060040889, 20060217343, 20070232559, 20080262001, 20080064653, and 20080312160 and U.S. Patent Nos. 5,877,180, 6,448,235, 7,214,665, 7,217,702, 7,226,913, 7,396,825, and 7,442,687.

Additional adenosine receptor agonists are shown in Table 4.

Table 4

3'-Aminoadenosine-5'-uronamides	A15PROH	Adenosine
Adenosine amine congener solid	Adenosine hemisulfate salt	BAY 68-4986
BIIB014	BVT 115959	CF 402
CVT 2501	DTI 0017	GP 3367
GP 3449	GP 4012	GR 190178
GW 328267	GW 493838	Istradefylline
KF 17838	M 216765	MDL 101483
NipentExtra	NNC 210113	NNC 210136
NNC 210147	NNC 901515	OSIC 113760
SCH 420814	SCH 442416	SCH 59761
Selodenoson (DTI-0009)	SLV 320	SSR 161421
SYN 115	Tecadenoson (CVT-510)	UK 432097
UP 20256	WRC 0542	Y 341

Other adenosine receptor agonists are those described or claimed in Gao et al., JPET, 298: 209-218 (2001); U.S. Patent Nos. 5,278,150, 5,424,297, 5,877,180, 6,232,297, 6,448,235, 6,514,949, 6,670,334, and 7,214,665; U.S. Patent Application Publication No. 20050261236, and International Publication Nos. WO98/08855, WO99/34804, WO2006/015357, WO2005/107463, WO03/029264, WO2006/023272,

WO00/78774, WO2006/028618, WO03/086408, and WO2005/097140, incorporated herein by reference.

Preferred A2A agonists include adenosine, regadenoson, apadenoson, sonedenoson, MRE-0094, BVT-115959, UK-432097, acadesine, tocladesine, CGS-21680C and CGS-21680, spongosine, binodenoson, HE-NECA, IB-MECA, CI-IB-MECA, NECA, ATL-313, ATL-1222, and DPMA.

PDE Inhibitors

Exemplary PDE inhibitors for use in the invention are shown in Table 5.

Table 5. PDE Inhibitors

Compound	**Synonym**	**PDE Activity**
349U85	6-piperidino-2(1H)-quinolinone	3
Adibendan	5,7-dihydro-7,7-dimethyl-2-(4-pyridinyl)-pyrrolo(2,3-f)benzimidazol-6(1H)-one	3
Amlexanox	2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carboxylic acid (U.S. Patent No. 4,143,042)	3, 4
Amrinone	5-amino-(3,4'-bipyridin)-6(1H)-one	3, 4
Anagrelide	U.S. Patent No. 3,932,407	3, 4
AP 155	2-(1-piperazinyl)-4H-pyrido[1,2-a]pyrimidin-4-one	4
AR 12456	CAS Reg. No. 100557-06-0	4
Arofylline	3-(4-chlorophenyl)-3,7-dihydro-1-propyl-1H-purine-2,6-dione	4
Ataquimast	1-ethyl-3-(methylamino)-2(1H)-quinoxalinone	3
Atizoram	tetrahydro-5-[4-methoxy-3-[(1S,2S,4R)-2-norbornyloxy]phenyl]-2(1*H*)-pyrimidinone	4
ATZ 1993	3-carboxy-4,5-dihydro-1-[1-(3-ethoxyphenyl)propyl]-7-(5-pyrimidinyl)methoxy-[1H]-benz[g]indazole (Teikoku Hormone)	
Avanafil	4-{[(3-chloro-4-methoxyphenyl)methyl]amino}-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide	5
AVE 8112		4
AWD 12171		5
AWD 12187		7

Compound	Synonym	PDE Activity
AWD 12250		5
AWD12343		4
BAY 38-3045		1
BAY 60-7550 (Alexis Biochemicals)	2-(3,4-dimethoxybenzyl)-7-[(1R)-1-[(1R)-1-hydroxyethyl]-4-phenylbutyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one	2
BBB 022		4
Bemarinone	5,6-dimethoxy-4-methyl-2(1H)-quinazolinone	3
Bemoradan	6-(3,4-dihydo-3-oxo-1,4(2H)-benzoxazin-7-yl)-2,3,4,5-tetrahydro-5-methylpyridazin-3-one	3
Benafentrine	(6-(p-acetamidophenyl)-1,2,3,4,4a,10b-hexahydro-8,9-dimethoxy-2-methyl-benzo[c][1,6]naphthyridine	3, 4
BMY 20844	1,3-dihydro-7,8-dimethyl-2H-imidazo[4,5-b]quinolin-2-one	4
BMY 21190		4
BMY 43351	1-(cyclohexylmethyl)-4-(4-((2,3-dihydro-2-oxo-1H-imidazo(4,5-b)quinolin-7-yl)oxy)-1-oxobutyl)-Piperazine	4
BRL 50481	3-(N,N-dimethylsulfonamido)-4-methyl-nitrobenzene	7
C 3885		4
Caffeine citrate	2-hydroxypropane-1,2,3-tricarboxylic acid	4
CC 10004	N-(2-((1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl)-acetamide	4
CC 1088		4
CC 3052	*The Journal of Immunology,* 1998, 161: 4236–4243	4
CC 7085		4
CCT 62	6-[(3-methylene-2-oxo-5-phenyl-5-tetrahydrofuranyl)methoxy]quinolinone	3
CDC 998		4
CDP 840	4-((2R)-2-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-phenylethyl)-pyridine	4
CGH 2466	2-amino-4-(3,4-dichlorophenyl)-5-pyridin-4-yl-thiazol	4
CI 1018	N-(3,4,6,7-tetrahydro-9-methyl-4-oxo-1-phenylpyrrolo(3,2,1-jk)(1,4)benzodiazepin-3-yl)-4-pyridinecarboxamide	4

Compound	Synonym	PDE Activity
CI 1044	N-[9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]b-enzodiazepin-3(R)-yl]pyridine-3-carboxamide	4
CI 930	4,5-dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-5-methyl-3(2H)-pyridazinone	3
Cilomilast (Ariflo®)	4-cyano-4-(3-cyclopentyloxy-4-methoxy-phenyl)cyclohexane-1-carboxylic acid (U.S. Patent No. 5, 552, 438)	4
Cilostamide	N-cyclohexyl-4-((1, 2-dihydro-2-oxo-6-quinolinyl)oxy)-N-methyl-butanamide	3
Cilostazol	6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone (U.S. Patent No. 4,277,479)	3, 4
Cipamfylline	8-amino-1,3-bis(cyclopropylmethyl)-3,7-dihydro-1H-purine-2,6-dione	4
CK 3197	2H-imidazol-2-one, 1-benzoyl-5-(4-(4,5-dihydro-2-methyl-1H-imidazol-1-yl)benzoyl)-4-ethyl-1,3-dihydro	
CP 146523	4'-methoxy-3-methyl-3'- (5-phenyl-pentyloxy)- biphenyl-4-carboxylic acid	4
CP 220629	1-cyclopentyl-3-ethyl-6-(2-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine	4
CP 248	(Z)-5-fluoro-2-methyl-1-[p-(methylsulfonyl)benzylidene]indene-3-acetic acid	2
CP 293121	(S)-3-(3-cyclopentyloxy-4-methoxy)phenyl-2-isoxazoline-5-hydroxamic acid	4
CP 353164	5-(3-cyclopentyloxy-4-methoxy-phenyl)-pyridine-2-carboxylic acid amide	4
CT 2820		
D 22888	8-methoxy-5-N-propyl-3-methyl-1-ethyl-imidazo [1,5-a]-pyrido [3, 2-e]-pyrazinone	4
D 4418	N-(2,5-dichloro-3-pyridinyl)-8-methoxy-5-quinolinecarboxamide	4
Dasantafil	7-(3-bromo-4-methoxyphenylmethyl)-1-ethyl-8-{[(1R, 2R)-2-hydroxycyclopentyl] = amino}-3-(2-hydroxyethyl)-3,7-dihydro-1H-purine-2,6-dione	5
Dipyridamole	2-{[9-(bis(2-hydroxyethyl)amino)-2,7-bis(1-piperidyl)-3,5,8,10-tetrazabicyclo[4.4.0]deca-2,4,7,9,11-pentaen-4-yl]-(2-hydroxyethyl)amino}ethanol	5, 6, 7, 8, 10, 11

Compound	Synonym	PDE Activity
DN 9693	1,5-dihydro-7-(1-piperidinyl)-imidazo[2,1-b]quinazolin-2(3H)-one dihydrochloride hydrate	4
Doxofylline	7-(1,3-dioxolan-2-ylmethyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (U.S. Patent No. 4,187,308)	4
E 4010	4-(3-chloro-4-metoxybenzyl)amino-1-(4-hydroxypiperidino)-6-phthalazinecarbonitrile monohydrochloride	5
E 4021	sodium 1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl]piperidine-4-carboxylate sesquihydrate	4, 5
EHNA	erythro-9-(2-hydroxy-3-nonyl)adenine	2, 3, 4
EHT 0202	3,7-dimethyl-1-(5-oxohexyl)purine-2,6-dione	4
ELB 353		4
EMD 53998	5-(1-(3,4-dimethoxybenzoyl)-1,2,3,4-tetrahydro-6-quinolyl)-6-methyl-3,6-dihydro-2H-1,3,4-thiadiazin-2-one	3
EMD 57033	(+)-5-[1-(3,4-dimethoxybenzoyl)-3,4-dihydro-2H-quinolin-6-yl]-6-methyl-3,6-dihydro-1,3,4-thiadiazin-2-one	3
EMD 57439	(-)-5-[1-(3,4-dimethoxybenzoyl)-3,4-dihydro-2H-quinolin-6-yl]-6-methyl-3,6-dihydro-1,3,4-thiadiazin-2-one	3
EMD 82639		5
EMR 62203		5
Enoximone	U.S. Patent No. 4,405,635	3
Enprofylline	3-propyl xanthine	4
ER 017996	4-((3,4-(methylenedioxy)benzyl)amino)-6,7,8-trimethoxyquinazoline	
Etazolate	1-ethyl-4-((1-methylethylidene)hydrazino)-1h-pyrazolo(3,4-b) pyridine-5-carboxylic acid	4
Exisulind	(1Z)-5-fluoro-2-methyl-1-[[4-(methylsulfonyl)phenyl]methylene]-1H-indene-3-acetic acid	2, 5
Filaminast	(1E)-1-(3-(cyclopentyloxy)-4-methoxyphenyl)-ethanone O-(aminocarbonyl)oxime	4, 7
FR 226807	N-(3,4-dimethoxybenzyl)-2-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-nitrobenzamide	5
FR 229934		5

Compound	Synonym	PDE Activity
GI 104313	6-{4-[N-[-2-[3-(2-cyanophenoxy)-2-hydroxypropylamino]-2-methylpropyl]carbamoylmethoxy-3-chlorophenyl]} -4,5-dihydro-3(2H) pyridazinone	3
GRC 3015		4
GSK 256066		4
GW 3600	(7aS,7R) -7-(3-cyclopentyloxy-4-methoxyphenyl)-7a-methyl-2,5,6,7,7a-penta-hydro-2-azapyrrolizin-3-one	4
GW 842470	N-(3,5-dichloro-4-pyridinyl)-1-((4-fluorophenyl)methyl)-5-hydroxy-α-oxo-1H-indole-3-acetamide	4
Helenalin	CAS Reg. No. 6754-13-8	5
Hydroxypumafentrine		4
IBMX	3-isobutyl-1-methylxanthine	3, 4, 5
Ibudilast	1-(2-isopropyl-pyrazolo[1,5-a]pyridine-3-yl)-2-methylpropan-1-one (U.S. Patent No. 3,850,941)	Not selective
IC 485		4
IPL 455903	(3S, 5S)-5-(3-cyclopentyloxy-4-methoxy-phenyl)-3-(3- methyl-benzyl)-piperidin-2-one	4
Isbufylline	1,3-dimethyl-7-isobutylxanthine	4
KF 17625	5-phenyl-1H-imidazo(4,5-c)(1,8)naphthyridin-4(5H)-one	4
KF 19514	5-phenyl-3-(3-pyridil) methyl-3H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one	1, 4
KF 31327	3-ethyl-8-[2-[4-(hydroxymethyl)piperidin-1-yl]benzylamino]-2,3-dihydro-1H-imidazo[4,5-g]quinazoline-2-thione	5
Ks-505a	1-carboxy-2,3,4,4a,4b,5,6,6a,6b,7,8,8a,8b,9,10,10a, 14,16,17,17a,17b,18,19,19a,19b, 20,21,21a,21b,22,23,23a-dotriacontahydro-14-hydroxy-8a,10a-bis(hydroxymethyl)-14-(3-methoxy-3-oxopropyl)-1,4,4a, 6,6a,17b,19b,21b-octamethyl beta-D-glucopyranosiduronic acid	1
KT 734		5
KW 4490		4
L 686398	9-[1,S,2R)-2-fluoro-1-methylpropyl]-2-methoxy-6-(1-piperazinyl]-purine hydrochloride	3, 4

Compound	Synonym	PDE Activity
L 826141	4-{2-(3,4-bis-difluromethoxyphenyl)-2-{4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropa n-2-yl)-phenyl]-ethyl}-3-methylpyridine-1-oxide	4
L 869298	(+)-1 | (S)-(+)-3-{2-[(3-cyclopropyloxy-4-difluromethoxy)-phenyl]-2-[5-(2-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoro)ethyl)-thiazolyl]ethyl}pyridine N-oxide	4
L-869299	(-)-1 | (R)-(-)-3-{2-[(3-cyclopropyloxy-4-difluromethoxy)phenyl]-2-[5-(2-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoro)ethyl)thiazolyl]ethyl}pyridine N-Oxide	4
Laprafylline	8-[2-[4-(dicyclohexylmethyl)piperazin-1-yl]ethyl]-1-methyl-3-(2-methylpropyl)-7H-purine-2,6-dione	4
LAS 34179		5
LAS 37779		4
Levosimendan	U.S. Patent No. 5,569,657	3
Lirimilast	methanesulfonic acid 2-(2,4-dichlorophenylcarbonyl)-3-ureidobenzo-furan-6-yl ester	4
Lixazinone	N-cyclohexyl-N-methyl-4-((1,2,3,5-tetrahydro-2-oxoimidazo(2,1-b)quinazolin-7-yl)oxy)-butanamide	3, 4
LPDE4 inhibitor	Bayer	4
Macquarimicin A	J Antibiot (Tokyo). 1995 Jun;48(6):462-6	
MEM 1414		4
MERCK1	(5R)-6-(4-{[2-(3-iodobenzyl)-3-oxocyclohex-1-en-1-yl]amino}phenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one; dihydropyridazinone	3
Mesopram	(5R)-5-(4-methoxy-3-propoxyphenyl)-5-methyl-2-oxazolidinone	4
Milrinone	6-dihydro-2-methyl-6-oxo-3,4'-bipyridine)-5-carbonitrile (U.S. Patent No. 4,478,836)	3, 4
MIMX	1 8-methoxymethyl-3-isobutyl-1-methylxantine	1
MN 001	4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid	4
Mopidamol	U.S. Patent No. 3,322,755	4
MS 857	4-acetyl-1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2H)-isoquinolinone	3
Nanterinone	6-(2,4-dimethyl-1H-imidazol-1-yl)-8-methyl-2(1H)-quinolinone	3

Compound	Synonym	PDE Activity
NCS 613	*J Pharmacol Exp Ther* Boichot et al. 292 (2): 647	4
ND 1251		4
ND7001	Neuro3D Pharmaceuticals	2
Nestifylline	7-(1,3-dithiolan-2-ylmethyl)-1,3-dimethylpurine-2,6-dione	
NIK 616		4
NIP 520		3
NM 702		5
NSP 306		3
NSP 513		3
NSP 804	4,5-dihydro-6-[4-[(2-methyl-3-oxo-1-cyclopentenyl)-amino] phenyl]-3(2H)-pyridazinone	3
NSP 805	4,5-dihydro-5-methyl-6-[4-[(2-methyl-3-oxo-1-cyclopentenyl) amino]phenyl]-3(2H)-pyridazinone	3
NVP ABE 171		4
Oglemilast	N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-8-((methylsulfonyl)amino)dibenzo(b,d)furan-1-carboxamide	4
Olprinone	5-imidazo[2,1-f]pyridin-6-yl-6-methyl-2-oxo-1H-pyridine-3-carbonitrile	3, 4
ONO 1505	4-[2-(2-hydroxyethoxy)ethylamino]-2-(1H-imidazol-1-yl)-6-methoxy-quinazoline methanesulphonate	5
ONO 6126		4
OPC 33509	(-)-6-[3-[3-cyclopropyl-3-[(1R,2R)-2-hydroxyclohexyl]ureido]-propoxy]-2(1H)-quinolinone	3
OPC 33540	6-[3-[3-cyclooctyl-3-[(1R[*],2R[*])-2-hydroxycyclohexyl]ureido]-propoxy]-2(1H)-quinolinone	3
ORG 20241	N-hydroxy-4-(3,4-dimethoxyphenyl)-thiazole-2-carboximidamide	3, 4
ORG 30029	N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximide hydrochloride	3, 4
ORG 9731	4-fluoro-N-hydroxy-5, 6-dimethoxy-benzo[b]thiophene-2-carboximidamide methanesulphonate	3, 4
ORG 9935	4,5-dihydro-6-(5,6-dimethoxy-benzo[b]-thien-2-yl)-methyl-1-(2H)-pyridazinone	3

Compound	Synonym	PDE Activity
OSI 461	N-benzyl-2-[(3Z)-6-fluoro-2-methyl-3-(pyridin-4-ylmethylidene)inden-1-yl]acetamide hydrochloride	5
Osthole	7-methoxy-8-(3-methyl-2-butenyl)-2H-1-benzopyran-2-one	5
Ouazinone	(R)-6-chloro-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazolin-2-one	3
PAB 13	6-bromo-8-(methylamino)imidazo[1,2-a]pyrazine	
PAB 15	6-bromo-8-(ethylamino)imidazo[1,2-a]pyrazine	
PAB 23	3-bromo-8-(methylamino)imidazo[1,2-a]pyrazine	
Papaverine	1-[(3.4-dimethoxyphenyl)-methyl]-6,7-dimethoxyisoquinolone	5, 6, 7, 10
PDB 093		4
Pentoxifylline	3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydropurine-2,6-dione (U.S. Patent No. 3,422,107)	
Piclamilast	3-cyclopentyloxy-N-(3,5-dichloropyridin-4-yl)-4-methoxy-benzamide	4, 7
Pimobendan	U.S. Patent No. 4,361,563	3, 4
Piroximone	4-ethyl-1,3-dihydro-5-(4-pyridinylcarbonyl)-2H-imidazol-2-one	3
Prinoxodan	6-(3,4-dihydro-3-methyl-2-oxoquinazolinyl)-4,5-dihydro-3-pyridazinone	
Propentofylline	U.S. Patent No. 4,289,776	5
Pumafentrine	rel-(M)-4-((4aR,10bS)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo(c)(1,6)naphthyridin-6-yl)-N,N-bis(1-methylethyl)-benzamide	4
R 79595	N-cyclohexyl-N-methyl-2-[[[phenyl (1,2,3,5-tetrahydro-2 oxoimidazo [2,1-b]-quinazolin-7-yl) methylene] amin] oxy] acetamide	3
Revizinone	(E)-N-cyclohexyl-N-methyl-2-(((phenyl(1,2,3,5-tetrahydro-2-oxoimidazo(2,1-b)quinazolin-7-yl)methylene)amino)oxy)-acetamide	3
Ro20-1724	4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone	4
Roflumilast	3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-benzamide	4, 5
Rolipram	4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone (U.S. Patent No. 4,193,926)	4

Compound	Synonym	PDE Activity
RPL554	9,10-dimethoxy-2(2,4,6-trimethylphenylimino)-3-(N-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one	3, 4
RPL565	6,7-dihydro-2-(2,6-diisopropylphenoxy)-9,10-dimethoxy-4H-pyrimido[6,1-a]isoquinolin-4-one	3, 4
RPR 132294		4
RPR 132703		4
Saterinone	1,2-dihydro-5-(4-(2-hydroxy-3-(4-(2-methoxyphenyl)-1-piperazinyl)propoxy)phenyl)-6-methyl-2-oxo-3-pyridinecarbonitrile	3
Satigrel	4-cyano-5,5-bis(4-methoxyphenyl)-4-pentenoic acid (U.S. Patent No. 4,978,767)	2, 3, 5
SCA 40	6-bromo-8-methylaminoimidazol[1,2-a]pyrazine-2carbonitrile	3
SCH 351591	N-(3,5-dichloro-1-oxido-4-pyridinyl)-8-methoxy-2-(trifluoromethyl)-5-quinoline carboxamide	4
SCH 45752	J Antibiot (Tokyo). 1993 Feb;46(2):207-13	
SCH 46642		5
SCH 51866	cis-5,6a,7,8,9,9a-hexahydro-2-(4-(trifluoromethyl)phenylmethyl)-5-methyl-cyclopent (4,5)imidazo(2,1-b)purin-4(3H)-one	1, 5
SCH 59498	cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo-[2,- 1-b]purin-4-one	5
SDZ ISQ 844	6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-3-hydroxymethyl-3,4-dihydroisoquinoline	3, 4
SDZ MKS 492	R(+)-(8-[(1-(3,4-dimethoxyphenyl)-2-hydroxyethyl)amino]-3,7-dihydro-7-(2-methoxyethyl)-1,3-dimethyl-1H-purine-2,6-dione	3
Senazodan		3
Siguazodan	N-cyano-N'-methyl-N''-[4-(1,4,5,6 -tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]guanidine	3, 4
Sildenafil	5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (U.S. Patent No. 5,250,534)	5
SK 3530		5
SKF 94120	5-(4-acetamidophenyl)pyrazin-2(1H)-one	3

Compound	Synonym	PDE Activity
SKF 95654	±-5-methyl-6-[4-(4-oxo-1,4-dihydropyridin-1-yl)phenyl]-4,5-dihydro-3(2H)-pyridazinone	3
SKF 96231	2-(2-propoxyphenyl)-6-purinone	3, 4, 5
SLX 2101		5
Sulmazole	U.S. Patent No. 3,985,891	3
T 0156	2-(2-methylpyridin-4-yl)methyl-4-(3,4,5-trimethoxyphenyl)-8-(pyrimidin-2-yl)methoxy-1,2-dihydro-1-oxo-2,7-naphthyridine-3-carboxylic acid methyl ester hydrochloride	5
T 1032	methyl-2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridylmethoxy)-4-(3,4,5-trimethoxyphenyl)-3-isoquinoline carboxylate sulfate	5
T 440	6,7-diethoxy-1-[1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin- 4-yl]naphthalene-2,3-dimethanol	4
Tadalafil	(6R,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1,2,1,6]pyrido[3,4-b]indole-1,4-dione	4, 5
Tetomilast	6-(2-(3,4-diethoxyphenyl)-4-thiazolyl)-2-pyridinecarboxylic acid	4
Theophylline	3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione	Not selective
Tibenelast	5,6-diethoxybenzo(B)thiophene-2-carboxylic acid	4
Toborinone	(+/-)-6-[3-(3,4-dimethoxybenzylamino)-2-hydroxypropoxy]-2(1H)-quinolinone	3
Tofimilast	9-cyclopentyl-7-ethyl-6,9-dihydro-3-(2-thienyl)-5H-pyrazolo(3,4-c)-1,2,4-triazolo(4,3-a)pyridine	4
Tolafentrine	N-[4-[(4aS,10bR)-8,9-dimethoxy-2-methyl-3,4,4a,10b-tetrahydro-1H-pyrido[4,3-c]isoquinolin-6-yl]phenyl]-4-methylbenzenesulfonamide	3, 4
Torbafylline	7-(ethoxymethyl)-3,7-dihydro-1-(5-hydroxy-5-methylhexyl)-3-methyl-1-H-purine-2,6-dione	4
Trequinsin	2,3,6, 7-tetrahydro-9, 10-dimethoxy-3-methyl-2-((2,4, 6-trimethylphenyl)imino)-4H-pyrimido(6, 1-a)isoquinolin-4-one	2, 3, 4
UCB 29936		4

Compound	Synonym	PDE Activity
UDCG 212	5-methyl-6-[2-(4-oxo-1-cyclohexa-2,5-dienylidene)-1,3-dihydrobenzimidazol-5-yl]-4,5-dihydro-2H-pyridazin-3-one	3
Udenafil	3-(1-methyl-7-oxo-3-propyl-4H-pyrazolo[5,4-e]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide	5
UK 114542	5-[2-ethoxy-5-(morpholinylacetyl) phenyl]-1,6-dihydro-1-methyl-3-propyl-7H-pyrazolo [4,3-d]-pyrimidin-7-one	5
UK 343664	3-ethyl-5-(5-((4-ethylpiperazino)sulphonyl)-2-propoxyphenyl)-2-(2-pyridylmethyl)-6,7-dihydro-2H-pyrazolo(4,3-d)pyrimidin-7-one	5
UK 357903	1-ethyl-4-{3-[3-ethyl-6,7-dihydro-7-oxo-2-(2-pyridylmethyl)-2H-pyrazolo[4,3-d] pyrimidin-5-yl]-2-(2-methoxyethoxy)5-pyridylsulphonyl} piperazine	5
UK 369003		5
V 11294A	3-((3-(cyclopentyloxy)-4-methoxyphenyl)methyl)-N-ethyl-8-(1-methylethyl)-3H-purin-6-amine monohydrochloride	4
Vardenafil	2-(2-ethoxy-5-(4-ethylpiperazin-1-yl-1-sulfonyl)phenyl)-5-methyl- 7-propyl-3H-imidazo(5,1-f)(1,2,4)triazin-4-one	5
Vesnarinone	U.S. Patent No. 4,415,572	3, 5
Vinpocetine	(3-alpha,16-alpha)-eburnamenine-14-carboxylic acid ethyl ester	1, 3, 4
WAY 122331	1-aza-10-(3-cyclopentyloxy-4-methoxyphenyl)-7,8-dimethyl-3-oxaspiro[4.5]dec-7-en-2-one	4
WAY 127093B	[(3S)-3-(3-cyclopentyloxy-4-methoxyphenyl)-2-methyl-5-oxopyrazolidinyl]-N-(3-pyridylmethyl)carboxamide	4
WIN 58237	1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo (3,4-d)pyrimidin-4(5H)-one	5
WIN 58993	5-methyl-6-pyridin-4-yl-3H-[1,3]thiazolo[5,4-e]pyridin-2-one	3
WIN 62005	5-methyl-6-pyridin-4-yl-1,3-dihydroimidazo[4,5-e]pyridin-2-one	3
WIN 62582	6-pyridin-4-yl-5-(trifluoromethyl)-1,3-dihydroimidazo[4,5-b]pyridin-2-one	3
WIN 63291	6-methyl-2-oxo-5-quinolin-6-yl-1H-pyridine-3-carbonitrile	3

Compound	Synonym	PDE Activity
WIN 65579	1-cyclopentyl-6-(3-ethoxy-4-pyridinyl)-3-ethyl-1,7-dihydro-4H-pyrazolo[3,- 4-d]pyrimidin-4-one	5
Y 20487	6-(3,6-dihydro-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3,4-dihydro-2(1H)-quinolinone	3
YM 58997	4-(3-bromophenyl)-1,7-diethylpyrido[2,3-d]pyrimidin-2(1H)-one	4
YM 976	4-(3-chlorophenyl)-1,7-diethylpyrido(2,3-d)pyrimidin-2(1H)-one	4
Z 15370A		4
Zaprinast	1,4-dihydro-5-(2-propoxyphenyl)-7H-1,2,3-triazolo[4,5-d]pyrimidine-7-one	5
Zaprinast	2-o-propoxyphenyl-8-azapurine-6-one	1, 5
Zardaverine	6-(4-(difluoromethoxy)-3-methoxyphenyl)-3(2H)-Pyridazinone	3, 4
Zindotrine	8-methyl-6-(1-piperidinyl)-1,2,4-triazolo(4,3-b)pyridazine	

Additional PDE inhibitors are shown in Table 6.

Table 6.

5E3623	A 021311	A 906119
BFGP 385	BY 244	CC 11050
CP 166907	CP 77059	CT 1579
CT 1786	HFV 1017	IPL 423088
IWF 12214	K 123	KF 31334
MKS 213492	MX 2120	N 3601
ORG 20494	REN 1053	RP 116474
Trombodipine	UK 66838	Vasotrope

Other PDE 1 inhibitors are described in U.S. Patent Application Nos. 20040259792 and 20050075795, incorporated herein by reference. Other PDE 2 inhibitors are described in U.S. Patent Application No. 20030176316, incorporated herein by reference. Other PDE 3 inhibitors are described in the following patents and patent applications: EP 0 653 426, EP 0 294 647, EP 0 357 788, EP 0 220 044, EP 0 326 307, EP 0 207 500, EP 0 406 958, EP 0 150 937, EP 0 075 463, EP 0 272 914, and EP 0 112 987, U.S. Pat. Nos. 4,963,561; 5,141,931, 6,897,229, and 6,156,753; U.S. Patent Application Nos. 20030158133, 20040097593, 20060030611, and

20060025463; WO 96/15117; DE 2825048; DE 2727481; DE 2847621; DE 3044568; DE 2837161; and DE 3021792, each of which is incorporated herein by reference. Other PDE 4 inhibitors are described in the following patents, patent applications, and references: U.S. Patent Nos. 3,892,777, 4,193,926, 4,655,074, 4,965,271, 5,096,906, 5,124,455, 5,272,153, 6,569,890, 6,953,853, 6,933,296, 6,919,353, 6,953,810, 6,949,573, 6,909,002, and 6,740,655; U.S. Patent Application Nos. 20030187052, 20030187257, 20030144300, 20030130254, 20030186974, 20030220352, 20030134876, 20040048903, 20040023945, 20040044036, 20040106641, 20040097593, 20040242643, 20040192701, 20040224971, 20040220183, 20040180900, 20040171798, 20040167199, 20040146561, 20040152754, 20040229918, 20050192336, 20050267196, 20050049258, 20060014782, 20060004003, 20060019932, 20050267196, 20050222207, 20050222207, 20060009481; International Publication No. WO 92/079778; and Molnar-Kimber, K.L. et al. J. Immunol., 150:295A (1993), each of which is incorporated herein by reference. Other PDE 5 inhibitors that can be used in the methods, compositions, and kits of the invention include those described in U.S. Patent Nos. 6,992,192, 6,984,641, 6,960,587, 6,943,166, 6,878,711, and 6,869,950, and U.S. Patent Application Nos. 20030144296, 20030171384, 20040029891, 20040038996, 20040186046, 20040259792, 20040087561, 20050054660, 20050042177, 20050245544, 20060009481, each of which is incorporated herein by reference. Other PDE 6 inhibitors that can be used in the methods, compositions, and kits of the invention include those described in U.S. Patent Application Nos. 20040259792, 20040248957, 20040242673, and 20040259880, each of which is incorporated herein by reference. Other PDE 7 inhibitors that can be used in the methods, compositions, and kits of the invention include those described in the following patents, patent application, and references: U.S. Patent Nos. 6,838,559, 6,753,340, 6,617,357, and 6,852,720; U.S. Patent Application Nos. 20030186988, 20030162802, 20030191167, 20040214843, and 20060009481; International Publication WO 00/68230; and Martinez et al., J. Med. Chem. 43:683-689 (2000), each of which is incorporated herein by reference. Other PDE inhibitors that can be used in the methods, compositions, and kits of the invention are described in U.S. Patent No. 6,953,774.

In certain embodiments, more than one PDE inhibitor may be employed in the invention so that the combination has activity against at least two of PDE 2, 3, 4, and

7. In other embodiments, a single PDE inhibitor having activity against at least two of PDE 2, 3, 4, and 7 is employed.

Additional Compounds

A BAR agonist may also be employed with an antiproliferative compound for the treatment of a B-cell proliferative disorder. Additional compounds that are useful in such methods include alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors (for example, NPI-0052), CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors, cyclin D inhibitors (e.g., cyclin D1), NF-kB inhibitors and pathway modulators, anthracyclines, histone deacetylase inhibitors, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, AKT inhibitors, PI3K inhibitors, TRAF inhibitors, statins, mitotic kinase inhibitors, KSP inhibitors, cyclin dependent kinase inhibitors (e.g., flavopiridol), inhibitors of anti-apoptotic proteins, e.g., BCL-2 (e.g., oblimereson), immune therapies (e.g., anti-CD20 or anti-CD22), calcineurin antagonists, IMiDs, or other agents used to treat proliferative diseases. Specific examples are shown in Tables 7 and 8.

Table 7.

17-AAG (KOS-953)	1D09C3	Activated T cells
AE 941	Aflibercept	AG 490
Alemtuzumab	Alitretinoin oral - Ligand Pharmaceuticals	Alvocidib
AMG162 (denosumab, osteoprotegerin, OPG)	Anti-CD38 antibodies	Anti-CD38 monoclonal antibody AT13/5
Anti-CD46 human monoclonal antibodies	Anti-CD5 monoclonal antibodies	Anti-HM1-24 monoclonal antibody
Anti-MUC1 monoclonal antibody - United Therapeutics/ViRexx Medical Corp	Antineoplaston A10 - injection	Antineoplaston AS2 1 – injection
AP23573	APC 8020	Aplidin®

Apo2L/TRAIL	Apomine™ (SR-45023A)	AR20.5
Arsenic trioxide	AT 101	Atacicept (TACI-Ig)
Atiprimod	Atiprimod	ATN 224
Avastin™ (bevacizumab, rhuMAb-VEGF)	AVN944	Azathioprine
B-B4-DMI	BCX-1777 (forodesine)	Belinostat
Bendamustine (SDX-105)	Benzylguanine	Beta alethine
Bexxar (Iodine I 131 tositumomab)	BIBF-1120	Bortezomib (VELCADE®)
Breva-Rex®	Brostallicin	Bufexamac
BX 471	Cadi-05	Cancer immunotherapies - Cell Genesys
Carmustine	CC 4047	CC007
CC11006	CCI-779	CD74-targeted therapeutics
Celebrex (celecoxib)	CERA (Continuous Erythropoiesis Receptor Activator)	CHIR-12.12
cKap	Clodronic acid	CNTO 328
CP 751871	CRB 15	Curcumin
Cyclophosphamide	Danton	Darinaparsin
Dasatinib	Daunorubicin liposomal	Defibrotide
Dexamethasone	Dexniguldipine	DHMEQ
Dimethylcelecoxib	DOM1112	Doxorubicin
Doxorubicin liposomal (PNU-108112) - ALZA	Doxycycline	Elsilimomab
EM164	ENMD 0995	Erbitux, cetuximab
Ethyol® (amifostine)	Etoposide	Fibroblast growth factor receptor inhibitors
Fludarabine	Fluphenazine	FR901228 (depsipeptide)
G3139	Gallium Maltolate	GCS 100
GCS-100	GCS-100LE	GRN 163L
GVAX® Myeloma Vaccine	GW654652	GX15-070
HGS-ETR1 (TRM-1, mapatumumab)	Highly purified hematopoietic stem cells	Histamine dihydrochloride injection - EpiCept Corporation
hLL1	Holmium-166 DOTMP	HSV thymidine kinase gene therapy
HuLuc63	HuMax-CD38	huN901-DM1
Idarubicin	Imexon - Heidelberg Pharma	Imexon (plimexon) – AmpliMed
IMMU 110	Incadronic acid	Interferon-alpha-2b
IPI 504	Irinotecan	ISIS 345794
Isotretinoin	ITF 2357	Kineret™ (anakinra)
KOS-1022 (alvespimycin HCl; 17-DMAG; NSC707545)	KRX-0401, perifosine	LAF 389

LBH589	Lenalidomide (Revlimid®)	Lestaurtinib
LPAAT-β inhibitors	Lucatumumab	LY2181308
Melphalan	Menogaril	Midostaurin
Minodronic acid	MK 0646	MOR202
MS-275	Multiple myeloma vaccine - GTC	MV-NIS
Myeloma vaccine - Onyvax	MyelomaCide	Mylovenge
Nexavar® (BAY 43-9006, sorafenib, sorafenib tosylate)	Noscapine	NPI 0052
O-6-benzyl-guanine	Obatoclax	Oblimersen
OGX-427	Paclitaxel	Pamidronic acid
Panzem™ (2-meth-oxyestradiol, 2ME2)	Parthenolide	PD173074
Phosphostim	PI 88	Plitidepsin
PR-171	Prednisone	Proleukin® (IL-2, Interleukin-2)
PX-12	PXD101	Pyroxamide
Quadramet® (EDTMP, samarium-153 ethylene diamine tetramethylene phosphonate Samarium)	RAD001 (everolimus)	Radiolabelled BLyS
RANK-Fc	Rituximab	Romidepsin
RTA402	Samarium 153 SM lexidronam	Sant 7
SCIO-469	Scriptaid	SD-208
SDX-101	Seleciclib	SF1126
SGN 40	SGN-70	Sirolimus
Sodium Stibogluconate (VQD-001)	Spironolactone	SR 31747
SU5416	SU6668	Tanespimycin
Temodar® (temozolomide)	Thalidomide	Thrombospondin-1
Tiazofurine	Tipifarnib	TKI 258
Tocilizumab (atlizumab)	Topotecan	Tretinoin
Valspodar	Vandetanib (Zactima™)	Vatalanib
VEGF Trap (NSC 724770)	Vincristine	Vinorelbine
VNP 4010M	Vorinostat	Xcytrin (motexafin gadolinium)
XL999	ZIO-101	Zoledronic acid
ZRx 101	Trichostatin A	Suberoylanilide hydroxamic acid (SAHA)

BAR agonists may also be employed with combinations of antiproliferative compounds. Such additional combinations include CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone), VAD (vincristine, doxorubicin, and dexamethasone), MP (melphalan and prednisone), DT (dexamethasone and

thalidomide), DM (dexamethasone and melphalan), DR (dexamethasone and Revlimid (lenalidomide)), DV (dexamethasone and Velcade), RV (Revlimid and Velcade), and cyclophosphamide and etoposide.

Additional compounds related to bortezomib that may be used in the invention are described in U.S. Patent Nos. 5,780,454, 6,083,903, 6,297,217, 6,617,317, 6,713,446, 6,958,319, and 7,119,080. Other analogs and formulations of bortezomib are described in U.S. Patent Nos. 6,221,888, 6,462,019, 6,472,158, 6,492,333, 6,649,593, 6,656,904, 6,699,835, 6,740,674, 6,747,150, 6,831,057, 6,838,252, 6,838,436, 6,884,769, 6,902,721, 6,919,382, 6,919,382, 6,933,290, 6,958,220, 7,026,296, 7,109,323, 7,112,572, 7,112,588, 7,175,994, 7,223,554, 7,223,745, 7,259,138, 7,265,118, 7,276,371, 7,282,484, and 7,371,729.

Additional compounds related to lenalidomide that may be used in the invention are described in U.S. Patent Nos. 5,635,517, 6,045,501, 6,281,230, 6,315,720, 6,555,554, 6,561,976, 6,561,977, 6,755,784, 6,908,432, 7,119,106, and 7,189,740. Other analogs and formulations of lenalidomide are described in U.S. Patent Nos. RE40,360, 5,712,291, 5,874,448, 6,235,756, 6,281,230, 6,315,720, 6,316,471, 6,335,349, 6,380,239, 6,395,754, 6,458,810, 6,476,052, 6,555,554, 6,561,976, 6,561,977, 6,588,548, 6,755,784, 6,767,326, 6,869,399, 6,871,783, 6,908,432, 6,977,268, 7,041,680, 7,081,464, 7,091,353, 7,115,277, 7,117,158, 7,119,106, 7,141,018, 7,153,867, 7,182,953, 7,189,740, 7,320,991, 7,323,479, and 7,329,761.

Further antiproliferative compounds that may be employed with the combinations of the invention are shown in Table 8.

Table 8.

6-Mercaptopurine	Gallium (III) Nitrate Hydrate	Altretamine
Anastrozole	Bicalutamide	Bleomycin
Busulfan	Camptothecin	Capecitabine
Carboplatin	Chlorambucil	Cisplatin
Cladribine	Cytarabine	Dacarbazine
Dactinomycin	Docetaxel	Epirubicin, e.g., Hydrochloride
Estramustine	Exemestane	Floxuridine
Fluorouracil	Flutamide	Fulvestrant
Gemcitabine, e.g., Hydrochloride	Hydroxyurea	Ifosfamide
Imatinib	Iressa	Ketoconazole

Letrozole	Leuprolide	Levamisole
Lomustine	Mechlorethamine, e.g., Hydrochloride	Megestrol, e.g., Acetate
Methotrexate	Mitomycin	Mitoxantrone, e.g., Hydrochloride
Nilutamide	Oxaliplatin	Pemetrexed
Plicamycin	Prednisolone	Procarbazine
Raltitrexed	Rofecoxib	Streptozocin
Suramin	Tamoxifen Citrate	Teniposide
Testolactone	Thioguanine	Thiotepa
Toremifene	Vinblastine, e.g., Sulfate	Vindesine

Preferred antiproliferative compounds include vincristine, lenalidomide , bortezomib, prednisolone, doxorubicin, cyclophosphamide, dexamethasone, melphalan, cyclophosphamide, etoposide, cytarabine, cisplatin, fludarabine, rituxan, thalidomide, methlyprednisolone, doxil (pegylated doxorubicin), panobinostat, tanespimycin, oblimersen, valspodar, and vorinostat. Other preferred compounds include HDAC inhibitors and HSP90 inhibitors.

Additional preferred antiproliferative compounds include pentostatin, chlorambucil, alemtuzumab, mitoxantrone, carmustine, gemcitabine, procarbazine, ifosfamide, mesma, oxaliplatin, and cladribine.

A BAR agonist may also be employed with IL-6 for the treatment of a B-cell proliferative disorder. If not by direct administration of IL-6, patients may be treated with agent(s) to increase the expression or activity of IL-6. Such agents may include other cytokines (e.g., IL-1 or TNF), soluble IL-6 receptor α (sIL-6R α), platelet-derived growth factor, prostaglandin E1, forskolin, cholera toxin, dibutyryl cAMP, or IL-6 receptor agonists, e.g., the agonist antibody MT-18, K-7/D-6, and compounds disclosed in U.S. Patent Nos. 5,914,106, 5,506,107, and 5,891,998.

Combinations

The invention includes the individual combination of each BAR agonist with each A2A receptor agonist, each PDE inhibitor, and each antiproliferative compound provided herein, as if each combination were explicitly stated. In a particular example, the BAR agonist is arbutaline, arfomoterol, bambuterol, bitolterol, broxaterol, clenbuterol, fenoterol, formoterol, hexoprenaline, indacaterol, isoetharine, isoproterenol, levalbuterol, meluadrine, metaproterenol, nylidrin, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salbutamol, salmeterol,

tulobuterol, terbutaline, or xamoterol, and the A2A agonist, PDE inhibitor, or antiproliferative compounds is any one or more of those described herein. For example, preferred A2A agonists include adenosine, regadenoson, apadenoson, sonedenoson, MRE-0094, BVT-115959, UK-432097, acadesine, tocladesine, CGS-21680C and CGS-21680, spongosine, binodenoson, HE-NECA, IB-MECA, CI-IB-MECA, NECA, ATL-313, ATL-1222, and DPMA. Preferred PDE inhibitors include trequinsin, zardaverine, roflumilast, rolipram, cilostazol, milrinone, papaverine, BAY 60-7550, and BRL-50481. Preferred antiproliferative compounds include vincristine, lenalidomide , bortezomib, prednisolone, doxorubicin, cyclophosphamide, dexamethasone, melphalan, cyclophosphamide, etoposide, cytarabine, cisplatin, fludarabine, rituxan, thalidomide, methlyprednisolone, doxil (pegylated doxorubicin), panobinostat, tanespimycin, oblimersen, valspodar, and vorinostat or pentostatin, chlorambucil, alemtuzumab, mitoxantrone, carmustine, gemcitabine, procarbazine, ifosfamide, mesma, oxaliplatin, and cladribine. Other preferred antiproliferative compounds include HDAC inhibitors and HSP90 inhibitors, as described herein.

Exemplary combinations are shown in Table 9.

Table 9.

BAR agonist	**Additional Compound**
salmeterol	dexamethasone
formoterol	dexamethasone
procaterol	dexamethasone
salbutamol	dexamethasone
levalbuterol	dexamethasone
salmeterol	melphalan
formoterol	melphalan
procaterol	melphalan
salbutamol	melphalan
levalbuterol	melphalan
salmeterol	lenalidomide
formoterol	lenalidomide
procaterol	lenalidomide
salbutamol	lenalidomide
levalbuterol	lenalidomide

BAR agonist	Additional Compound
salmeterol	doxorubicin
formoterol	doxorubicin
procaterol	doxorubicin
salbutamol	doxorubicin
levalbuterol	doxorubicin
salmeterol	bortezomib
formoterol	bortezomib
procaterol	bortezomib
salbutamol	bortezomib
levalbuterol	bortezomib

In certain embodiments, a BAR agonist, e.g., bambuterol, bitolterol, clenbuterol, formoterol, isoproterenol, metaproterenol, pirbuterol, salbutamol, or salmeterol, terbutaline, is not administered with a stem cell mobilizer, e.g., AMD3100, cyclophosphamide, stem cell factor (SCF), filgrastim, or ancestim. In other embodiments, a BAR agonist, e.g., bambuterol, bitolterol, isoetharine, isoproterenol, metaproterenol, salbutamol, or terbutaline, is not administered with an mTOR inhibitor and capecitabine. In further embodiments, a BAR agonist, e.g., bambuterol, terbutaline, pirbuterol, bitolterol, formoterol, salmeterol, or salbutamol, is not administered with a PDE4 inhibitor.

The following combinations may be excluded from treatment of a B-cell proliferative disorder in certain embodiments: salmeterol, fluticasone, and CHOP or bortezomib for treatment of mantle cell lymphoma; salbutamol and VAD for multiple myeloma; salmeterol, beclomethasone, prednisone, and melphalan for multiple myeloma; salmeterol, beclomethasone, prednisone, clodronate, salbutamol, and melphalan for multiple myeloma; and salbutamol, beclomethasone, melphalan, prednisone, and pamidronate for multiple myeloma.

B-cell Proliferative Disorders

B-cell proliferative disorders include B-cell cancers and autoimmune lymphoproliferative disease. B-cell cancers that can be treated according to the methods of the invention include B-cell CLL, B-cell prolymphocyte leukemia,

lymphoplasmacytic lymphoma, mantle cell lymphoma, follicular lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT type), nodal marginal zone lymphoma, splenic marginal zone lymphoma, hairy cell leukemia, plasmacytoma, diffuse large B-cell lymphoma, Burkitt lymphoma, multiple myeloma, indolent myeloma, smoldering myeloma, monoclonal gammopathy of unknown significance (MGUS), B-cell non-Hodgkin's lymphoma, small lymphocytic lymphoma, monoclonal immunoglobin deposition diseases, heavy chain diseases, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, precursor B-lymphoblastic leukemia/lymphoma, Hodgkin's lymphoma (e.g., nodular lymphocyte predominant Hodgkin's lymphoma, classical Hodgkin's lymphoma, nodular sclerosis Hodgkin's lymphoma, mixed cellularity Hodgkin's lymphoma, lymphocyte-rich classical Hodgkin's lymphoma, and lymphocyte depleted Hodgkin's lymphoma), post-transplant lymphoproliferative disorder, and Waldenstrom's macroglobulinemia. A preferred B-cell cancer is multiple myeloma. Other preferred B-cell cancers include mantle cell lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia, and follicular lymphoma. Other such disorders are known in the art.

In certain embodiments, when the B-cell proliferative disorder is B-CLL, the BAR agonist is not formoterol, isoproterenol (e.g., in combination with a PDE inhibitor), or salmeterol.

In other embodiments, when the B-cell proliferative disorder is doxorubicin resistant multiple myeloma, the BAR agonist is not salbutamol. In further embodiments, when the B-cell proliferative disorder is mantle cell lymphoma, the BAR agonist is not salmeterol.

Administration

Therapy according to the invention may be performed alone or in conjunction with another therapy and may be provided at home, the doctor's office, a clinic, a hospital's outpatient department, or a hospital. Treatment optionally begins at a hospital so that the doctor can observe the therapy's effects closely and make any adjustments that are needed, or it may begin on an outpatient basis. The duration of the therapy depends on the type of disease or disorder being treated, the age and

condition of the patient, the stage and type of the patient's disease, and how the patient responds to the treatment.

When combinations are employed, the compounds may be administered within 28 days of each other, within 14 days of each other, within 10 days of each other, within five days of each other, within twenty-four hours of each other, or simultaneously. The compounds may be formulated together as a single composition, or may be formulated and administered separately. Each compound may be administered in a low dosage or in a high dosage, each of which is defined herein.

Routes of administration for the various embodiments include, but are not limited to, topical, transdermal, and systemic administration (such as, intravenous, intramuscular, subcutaneous, inhalation, rectal, buccal, vaginal, intraperitoneal, intraarticular, ophthalmic or oral administration). As used herein, "systemic administration" refers to all nondermal routes of administration, and specifically excludes topical and transdermal routes of administration. In one example, RPL554 is administered intranasally.

In certain embodiments, administration of a BAR agonist occurs by a route other than topical, transdermal, or inhalation. Preferred routes for BAR agonists are oral and intravenous.

In combination therapy, the dosage and frequency of administration of each component of the combination can be controlled independently. For example, one compound may be administered three times per day, while a second compound may be administered once per day. Combination therapy may be given in on-and-off cycles that include rest periods so that the patient's body has a chance to recover from any as yet unforeseen side effects. The compounds may also be formulated together such that one administration delivers both compounds.

Formulation of Pharmaceutical Compositions

The administration of a combination of the invention may be by any suitable means that results in suppression of proliferation at the target region. The compound may be contained in any appropriate amount in any suitable carrier substance, and is generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for the oral, parenteral (e.g., intravenously, intramuscularly), rectal, cutaneous, nasal,

vaginal, inhalant, skin (patch), or ocular administration route. Thus, the composition may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, or aerosols. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. A.R. Gennaro, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

Preferred formulations for BAR agonists include those suitable for oral or intravenous administration.

Each compound of the combination may be formulated in a variety of ways that are known in the art. For example, all agents may be formulated together or separately. Desirably, all agents are formulated together for the simultaneous or near simultaneous administration of the agents. Such co-formulated compositions can include a BAR agonist and any additional compound, e.g., A2A receptor agonist, PDE inhibitor, or antiproliferative compound, formulated together in the same pill, capsule, liquid, etc. It is to be understood that, when referring to the formulation of combinations, the formulation technology employed is also useful for the formulation of the individual agents of the combination, as well as other combinations of the invention. By using different formulation strategies for different agents, the pharmacokinetic profiles for each agent can be suitably matched.

The individually or separately formulated agents can be packaged together as a kit. Non-limiting examples include kits that contain, e.g., two pills, a pill and a powder, a suppository and a liquid in a vial, two topical creams, etc. The kit can include optional components that aid in the administration of the unit dose to patients, such as vials for reconstituting powder forms, syringes for injection, customized IV delivery systems, inhalers, etc. Additionally, the unit dose kit can contain instructions for preparation and administration of the compositions. The kit may be manufactured as a single use unit dose for one patient, multiple uses for a particular patient (at a constant dose or in which the individual compounds may vary in potency as therapy progresses); or the kit may contain multiple doses suitable for administration to multiple patients ("bulk packaging"). The kit components may be assembled in

cartons, blister packs, bottles, tubes, and the like. Any kit of the invention may also include instructions on the administration of the included compounds for the treatment of a B-cell proliferative disorder.

Dosages

Generally, the dosage of the BAR agonist is 0.1 μg to 50 mg per day, preferably 1 μg to 0.1 mg. The dosage of the A2A receptor agonist is 0.1 mg to 500 mg per day, e.g., about 50 mg per day, about 5 mg per day, or desirably about 1 mg per day. The dosage of the PDE inhibitor is, for example, 0.1 to 2000 mg, e.g., about 200 mg per day, about 20 mg per day, or desirably about 4 mg per day.

Dosages of antiproliferative compounds are known in the art and can be determined using standard medical techniques.

Administration of each drug in the combination can, independently, be one to four times daily for one day to one year.

The following examples are to illustrate the invention. They are not meant to limit the invention in any way.

Examples

Example 1.

Materials and Methods

Tumor Cell Culture

MM.1S, MM.1R, EJM, RPMI-8226, INA-6, and ANBL-6 multiple myeloma cell lines were cultured at 37°C and 5% CO_2 in RPMI-1640 media supplemented with 10% FBS. INA-6 and ANBL-6 culture media was supplemented with 10 ng/ml IL-6. The diffuse large B-cell lymphoma line OCI-ly10 was cultured at 37°C and 5% CO_2 in Iscoves media supplemented with 20% human serum. MM.1R and OCI-ly10 cells were provided by the Dana Farber Cancer Institute. MM.1S cells were provided by Steven Rosen, Northwestern University. INA-6 and ANBL-6 cells were from Robert Orlowski, M.D. Anderson Cancer Center. RPMI-8226 and EJM cells were from DSMZ (Cat #'s ACC 402 and ACC 560). GA-10 cells were obtained from ATCC (CRL-2392). Human coronary artery endothelial cells (HCAEC) were obtained from Lonza and cultured as recommended by the supplier.

Compounds

Compounds were prepared in DMSO at 1000× the highest desired concentration. Master plates were generated consisting of serially diluted compounds in 2- or 3-fold dilutions in 384-well format. For single agent dose response curves, the master plates consisted of 9 individual compounds at 12 concentrations in 2- or 3-fold dilutions. For combination matrices, master plates consisted of individual compounds at 6 or 9 concentrations at 2- or 3-fold dilutions.

Anti-Proliferation Assay

Cells were added to 384-well plates 24 hours prior to compound addition, and each well contained 2000 cells in 35 μL of media. Master plates were diluted 100× (1 μL into 100 μL) into 384-well dilution plates containing only cell culture media. 4.5 μL from each dilution plate was added to each assay plate for a final dilution of 1000×. To obtain combination data, two master plates were diluted into the assay plates. Following compound addition, assay plates were kept at 37°C and 5% CO_2 for 72 hours. 30 μL of ATPLite (Perkin Elmer) at room temperature was then added to each well. Final amount of ATP was quantified within 30 minutes using ATPLite luminescent read-out on an Envision 2103 Multilabel Reader (Perkin Elmer). Measurements were taken at the top of the well using a luminescence aperture and a read time of 0.1 seconds per well.

The percent inhibition (%I) for each well was calculated using the following formula:

%I = [(avg. untreated wells – treated well)/(avg. untreated wells)] × 100.

The average untreated well value (avg. untreated wells) is the arithmetic mean of 40 wells from the same assay plate treated with vehicle alone. Negative inhibition values result from local variations in treated wells as compared to untreated wells.

Single agent activity was characterized by fitting a sigmoidal function of the form $I = I_{max}C^{\alpha}/[C^{\alpha}+EC_{50}{}^{\alpha}]$, with least squares minimization using a downhill simplex algorithm (C is the concentration, EC_{50} is the agent concentration required to obtain 50% of the maximum effect, and α is the sigmoidicity). The uncertainty of each fitted parameter was estimated from the range over which the change in reduced chi-squared was less than one, or less than minimum reduced chi-squared if that minimum exceeded one, to allow for underestimated σ_I errors.

Single agent curve data were used to define a dilution series for each compound to be used for combination screening in a 6×6 or 9×9 matrix format. Using a dilution factor f of 2, 3, or 4, depending on the sigmoidicity of the single agent curve, five dose levels were chosen with the central concentration close to the fitted EC_{50}. For compounds with no detectable single agent activity, a dilution factor of 4 was used, starting from the highest achievable concentration.

The Loewe additivity model was used to quantify combination effects. Combinations were ranked initially by Additivity Excess Volume, which is defined as ADD Volume = $\sum C_X,C_Y (I_{data} - I_{Loewe})$, where $I_{Loewe}(C_X,C_Y)$ is the inhibition that satisfies $(C_X/EC_X) + (C_Y/EC_Y) = 1$, and $EC_{X,Y}$ are the effective concentrations at I_{Loewe} for the single agent curves. A "Synergy Score" was also used, where the Synergy Score S = log f_X log $f_Y \sum I_{data} (I_{data}–I_{Loewe})$, summed over all non-single-agent concentration pairs, and where log $f_{X,Y}$ is the natural logarithm of the dilution factors used for each single agent. This effectively calculates a volume between the measured and Loewe additive response surfaces, weighted towards high inhibition and corrected for varying dilution factors. An uncertainty σ_S was calculated for each synergy score, based on the measured errors for the I_{data} values and standard error propagation.

Example 2.

The MM.1S, EJM, RPMI-8226, INA-6, ANBL-6 and OCI-ly10 cell lines were used to examine the activity of various BAR agonists in combination with antiproliferative compounds that have been deployed to treat B-cell malignancies. Synergy scores are provided followed by representative data from some of the combination matrix analysis.

Potent combination synergistic anti-proliferative activities are observed for multiple myeloma, DLBCL and Burkitt's lymphoma cells when the beta 2 adrenergic agonists salmeterol, formoterol, terbutaline, isoetharine, ritodrine, salbutamol, clenbuterol, fenoterol, metaproterenol, levalbuterol, isoproterenol, pirbuterol, broxaterol, picumeterol, or procaterol are used in combination with the glucocorticoid dexamethasone (Table 10).

Table 10: Summary of Synergy Scores for BAR Agonists that Synergize with Dexamethasone in One or More B-cell Malignancy Cell Lines (MM.1S, EJM, RPMI-8226, ANBL-6, and OCI-ly10)

Combination	MM.1S	EJM	RPMI-8226	ANBL-6	OCI-ly10	GA-10
formoterol × dexamethasone	6.74	n.d.	2.83	6.26	n.d.	n.d.
salmeterol × dexamethasone	18.81	9.01	1.65	11.34	9.80	1.87
terbutaline × dexamethasone	6.02	3.19	n.d.	n.d.	n.d.	n.d.
isoetharine × dexamethasone	5.38	5.14	n.d.	n.d.	n.d.	n.d.
ritodrine × dexamethasone	5.71	5.13	n.d.	n.d.	n.d.	n.d.
salbutamol × dexamethasone	6.19	4.27	n.d.	n.d.	n.d.	n.d.
clenbuterol × dexamethasone	9.54	5.08	6.61	6.67	n.d.	n.d.
fenoterol × dexamethasone	4.73	2.09	2.52	n.d.	n.d.	n.d.
metaproterenol × dexamethasone	6.10	3.81	n.d.	n.d.	n.d.	n.d.
levalbuterol × dexamethasone	11.49	5.40	n.d.	n.d.	n.d.	n.d.
isoproterenol × dexamethasone	10.81	n.d.	n.d.	n.d.	n.d.	n.d.
pirbuterol × dexamethasone	9.09	n.d.	n.d.	n.d.	n.d.	n.d.
broxaterol × dexamethasone	10.67	n.d.	n.d.	n.d.	n.d.	n.d.
picumeterol × dexamethasone	5.61	n.d.	n.d.	n.d.	n.d.	n.d.
procaterol × dexamethasone	10.61	n.d.	n.d.	n.d.	n.d.	n.d.

Below are representative high resolution 9 × 9 data where BAR agonists were used in combination with dexamethasone. (Tables 11-20).

Table 11: Antiproliferative Activity of Dexamethasone (DEX) and Formoterol against Human Multiple Myeloma Cells (MM.1S)

Formoterol (μM) / DEX (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
2.03	94	93.7	93	93.8	93	93.7	93.2	92	85.5
0.675	93.6	93.2	92.7	93.6	93.8	93.1	93.4	92.4	84.5
0.225	93.4	93.9	93.3	93.7	93.6	92.4	93.4	89.5	81.8
0.075	93.1	94.1	93.3	93.7	93.4	93.3	92.2	89	78.3
0.025	93.1	93.2	93.3	92.5	92.1	92.5	90.2	87.2	65.7
0.00834	93	92.2	92.8	92.5	90.7	82.5	69.2	56.9	39
0.00278	91.8	90.7	89.3	93.6	81.5	71.7	60.5	49.5	25
0.00093	86.7	82.5	78.6	77.2	71.7	55.6	43.4	27.5	9.24
0	72.5	68.7	65.9	54.7	52.7	40.8	23.8	18.9	8.95

Table 12: Antiproliferative Activity of Dexamethasone (DEX) and Formoterol against Human Multiple Myeloma Cells (ANBL-6)

Formoterol (μM) / DEX (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
2.03	90.5	87.8	93.2	81.2	73	64.2	49.8	37.7	23.4
0.675	90.2	87.9	85.6	79.1	71.8	61.7	47.3	38.9	22.5
0.225	90.6	86	86.1	81.7	71.1	53.1	40.6	28.4	12
0.075	87.8	86.6	83.6	76.2	66.8	51.8	44.2	32.6	14.7
0.025	87.7	80.7	78.6	72.3	64.9	53	41.1	38.2	6.97
0.00834	79.5	78.1	73.6	63.5	54.3	34.7	26	13.7	6.13
0.00278	73.2	66.3	64.7	57.9	45.8	40.2	32	18.7	-3.92
0.00093	68.9	60.1	56.7	51.6	43.7	30.9	26.5	17.6	5.06
0	61.9	61	55.4	48.8	39.9	30	26.7	23.3	6.3

Table 13: Antiproliferative Activity of Dexamethasone (DEX) and Formoterol against Human Multiple Myeloma Cells (RPMI-8226)

Formoterol (μM) / DEX (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
2.03	53.8	55	51.9	50.2	54.7	47.7	41.7	36.9	39.5
0.675	54.4	53	52.1	47.5	47.8	46.9	43.6	41.3	27.8
0.225	55.7	53.3	50.3	52.6	49.4	46.6	39.1	36.4	28
0.075	43.1	54	51.3	45	47.1	45.8	38.8	37.3	27.7
0.025	43.9	45.3	42.2	41.2	40.7	39.2	32.5	29	18.4
0.00834	32.8	31.9	31.1	33.1	28.2	27.8	19	16.4	9.55
0.00278	26.3	23.9	26.7	25.1	23.2	16.4	14.1	14.8	12.3
0.00093	14.2	11.3	15.7	14.5	15.9	10.1	16.3	11	10.9
0	15.4	11.6	10.5	4.33	5.4	11.4	10.2	11.9	5.75

Table 14: Antiproliferative Activity of Dexamethasone (DEX) and Isoetharine against Human Multiple Myeloma Cells (EJM)

Isoetharine (μM) / DEX (μM)	0.0203	0.0101	0.00506	0.00253	0.00127	0.000633	0.000316	0.000158	0
2.03	73.4	57.4	53.2	46.8	33.1	32	29	11.8	5.97
0.675	75.2	56.7	44.3	47.6	39.4	36	22	9.68	-0.146
0.225	71.5	51.5	55.6	47.1	40.1	25.1	23.5	8.15	2.33
0.075	72.9	55.7	51.6	42.4	34.7	30.7	14.6	12.7	-5.53
0.025	66.3	50.9	45.4	44.5	30.4	16.4	21	4.59	5.46
0.00834	58.8	48.2	33.8	35.3	27.1	24.6	-12.4	-2.33	-10.8
0.00278	53.5	24.5	33.6	27.1	20	0.291	17.5	4.95	-3.42
0.00093	46.8	37	27.7	28.6	16.4	16.7	5.17	5.6	-5.82
0	41.4	21.8	29	23.6	19.5	-0.146	7.35	7.35	-1.24

Table 15: Antiproliferative Activity of Dexamethasone (DEX) and Isoetharine against Human Multiple Myeloma Cells (MM.1S)

Isoetharine (μM) / DEX (μM)	0.0203	0.0101	0.00506	0.00253	0.00127	0.000633	0.000316	0.000158	0
2.03	95.4	93.8	93.1	92.6	89.6	80	81.1	69	72.5
0.675	95.2	94.6	91.5	92	88.1	86.9	78.7	78	64.8
0.225	95.6	93.2	94	91.6	90.8	77.4	78.7	68.9	62.5
0.075	94.9	92.5	91.4	91.6	86.6	76.7	66.5	68.6	56.4
0.025	94.4	86.4	86.3	78.7	73.3	50	63.1	50.7	45.5
0.00834	86.7	79	70.3	75.2	58.4	53.7	24.6	31.8	25.6
0.00278	81.4	67.9	64.8	42.6	45	19.2	26.1	18.6	17.9
0.00093	74.5	49.9	41.8	52.4	31.9	36.2	3.38	12.7	1.52
0	53.9	18	29.5	14.7	17.7	0.225	18.5	9.23	-2.19

Table 16: Antiproliferative Activity of Dexamethasone (DEX) and Salmeterol against Human Multiple Myeloma Cells (EJM)

Salmeterol (μM) / DEX (μM)	0.0203	0.0101	0.00506	0.00253	0.00127	0.000633	0.000316	0.000158	0
2.03	77.2	75.6	77.9	74.9	75	73.3	76.2	74.9	10.1
0.675	79.1	78.6	74.7	77	76	78.3	73.8	75.5	4.03
0.225	77.4	76.9	77.8	74.6	76	74.7	78.1	75.2	7.36
0.075	79.5	77.7	73.7	75.5	75.4	78	71.5	73.6	-0.778
0.025	76.2	72.2	73.8	72.1	73.8	69.6	77.4	66.5	7.43
0.00834	69.4	69.7	68.7	66	63.8	68.6	58.9	64.1	-13
0.00278	61.4	54	62	56.3	57.1	49.7	60.7	55.4	4.1
0.00093	57.4	55	51.7	51.2	51.2	57.4	44.2	40.9	-18.7
0	43.6	42.8	47.9	43.2	45.4	39.4	47.7	38.1	10

Table 17: Antiproliferative Activity of Dexamethasone (DEX) and Salmeterol against Human Multiple Myeloma Cells (MM.1S)

Salmeterol (μM) / DEX (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
2.03	90.1	89.5	90.2	89.5	91	89.6	90.7	90.7	33.4
0.675	88.6	88.5	87.8	88.2	87.6	89	87.9	85.8	21.7
0.225	87.9	87.7	87.8	86.6	87.5	87.8	89.3	87.5	25.6
0.075	85.2	83.7	85.9	83.9	85	83.5	84	83.7	29.9
0.025	80.1	81.9	82.9	80	76.9	78.2	77.5	76.5	20.8
0.00834	72.9	74	72.6	69.2	66.2	74.8	69.8	68	1.81
0.00278	69.4	66.1	67	65.8	66.2	62.3	65.4	60.7	4.93
0.00093	60	60.2	58.7	60.5	61.1	62.1	60.3	60.2	6.94
0	59.6	58.1	55.9	57.8	55.1	58.1	59.7	52.9	2.79

Table 18: Antiproliferative Activity of Dexamethasone (DEX) and Salmeterol against Human Multiple Myeloma Cells (ANBL-6)

Salmeterol (μM) / DEX (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
2.03	95	94.6	94.4	94.2	94.3	93.9	90.2	88	79.2
0.675	94.4	94.8	94.8	94.6	93.6	94.3	91.7	89.1	78
0.225	94.1	94.5	95	94.6	93.8	92.5	90.2	86	76.9
0.075	93.8	94.4	95.1	94	93.1	91.2	86.2	81.1	72.3
0.025	94.1	94	94.8	93.8	90.2	83.9	74.8	68	58.1
0.00834	93	88.6	89.6	85.8	78.5	66.9	50.4	51.1	29.9
0.00278	85.8	79.4	79.3	73.5	60	48.2	38.5	26.5	15.4
0.00093	73.6	59.2	56.1	59.7	41	43.8	24.2	19.5	9.36
0	56.1	46.3	41.9	36.1	22.1	24.2	18.6	13.4	4.07

Table 19: Antiproliferative Activity of Dexamethasone (DEX) and Terbutaline against Human Multiple Myeloma Cells (MM.1S)

Terbutaline (μM) / DEX (μM)	2.03	1.01	0.506	0.253	0.127	0.0633	0.0316	0.0158	0
2.03	96	96.1	95.6	95.2	95.1	94.5	94.6	93.7	73.4
0.675	95.2	95.3	94.8	95.2	95.3	94.9	94.7	94.8	71.2
0.225	95.2	95	95.4	95.4	94.6	95	94.4	93.7	70.1
0.075	95.2	95.4	94.8	95.2	94.6	94.9	94	91.5	63.4
0.025	95.4	94.8	94.8	94.5	94.7	94	92.7	90.7	52.6
0.00834	92.5	93.3	92.6	91.2	89.3	88.5	85.5	82.7	30.5
0.00278	85.4	81.9	83.7	89.9	76.9	71.8	65.8	61.9	17.3
0.00093	72.1	72.3	70	67.3	65.3	56.8	57.8	48.7	15
0	58	55.2	53	51.1	40	35.7	38.4	30	11.5

Table 20: Antiproliferative Activity of Dexamethasone (DEX) and Salmeterol against Diffuse Large B-Cell Lymphoma Cell Line OCI-Ly10

Salmeterol (μM) / DEX (μM)	0.769	0.256333	0.085444	0.028481	0.009494	0.003165	0.001055	0.000352	0
0.101	100	96	91	80	74	71	69	71	67
0.033666667	100	95	86	62	62	56	59	52	56
0.011222222	97	87	57	42	40	41	41	45	29
0.003740741	90	63	40	27	29	21	27	22	22
0.001246914	69	38	21	14	7.5	10	9.4	8.9	9.7
0.000415638	64	33	22	19	7.6	11	6.7	12	4.5
0.000138546	50	33	13	5.5	1.7	16	13	6.2	0.78
0.000046182	57	36	21	11	14	0.6	16	9.7	12
0	71	27	6.3	-0.6	9.1	6.3	5.9	16	0.07

Strong synergy is also observed when beta adrenergic agonists are combined with either lenalidomide (Table 21), melphalan (Table 22), or doxorubicin (Table 23), three drugs that are part of standard of care for the treatment of multiple myeloma.

Table 21: Summary of Synergy Scores for the BAR Agonists Salmeterol, Formoterol, Clenbuterol, Salbutamol, and Terbutaline when Combined with Lenalidomide in the Multiple Myeloma Cell Lines MM.1S, ANBL-6, and MM.1R

Combination	MM.1S	ANBL-6	MM.1R
salmeterol × lenalidomide	4.62	5.01	n.d.
formoterol × lenalidomide	5.01	5.27	n.d.
clenbuterol × lenalidomide	n.d.	5.50	4.86
salbutamol × lenalidomide	n.d.	3.76	2.74
terbutaline × lenalidomide	0.97	5.39	4.22
broxaterol × lenalidomide	3.94	n.d.	n.d.
picumeterol × lenalidomide	2.64	n.d.	n.d.

Table 22: Summary of Synergy Scores for the BAR Agonists Salmeterol, Clenbuterol, Salbutamol, and Terbutaline when Combined with Melphalan in the Multiple Myeloma Cell Lines ANBL-6, EJM, INA-6, and MM.1R

Combination	ANBL-6	EJM	INA-6	MM.1R
salmeterol × melphalan	n.d.	2.26	1.19	4.21
clenbuterol × melphalan	n.d.	n.d.	1.76	2.46
salbutamol × melphalan	3.36	1.34	n.d.	n.d.
terbutaline × melphalan	3.84	1.22	1.88	1.81

Table 23: Summary of Synergy Scores for the BAR Agonists Salmeterol and Terbutaline when Combined with Doxorubicin in the Multiple Myeloma Cell Lines MM.1S, EJM, ANBL-6, and MM.1R

Combination	MM.1S	EJM	ANBL-6	MM.1R
salmeterol × doxorubicin	1.73	2.11	5.67	1.13
terbutaline × doxorubicin	1.23	0.76	3.28	0.84

Representative 9×9 data for BAR agonists in combination with lenalidomide (Tables 24-25), melphalan (Table 26), and doxorubicin (Table 27) are shown below.

Table 24: Antiproliferative Activity of Lenalidomide (LEN) and Salmeterol against Human Multiple Myeloma Cells (MM.1S)

Salmeterol (nM) / LEN (μM)	0.32	0.16	0. 081	0. 0405	0. 0202	0. 0101	0. 00506	0.00000253	0
4.04	88.7	84.5	85.5	78.1	75.1	70.3	61	57.4	50.2
2.02	85.3	81.4	79.6	72.8	65.7	64.7	55.7	47.9	38.2
1.01	80.2	80	77.3	73	67.9	60.7	51.6	49.1	36.3
0.253	80.8	77.9	76.3	69.1	60.1	53.6	44.4	40.1	36.7
0.126	81.2	73.6	73.9	69.4	59.9	54.5	42.9	37.3	31.2
0.0632	75.7	74.1	70.2	66	61.4	49.8	40.5	36.8	29
0.0316	75.6	71.3	66.9	67	55.5	52.5	45.5	32.8	27.3
0	74	67.1	61.4	59.9	55.8	46.5	41.5	34.4	26.4
4.04	56.5	44.7	43.7	35.2	22.1	22.6	19.2	15.1	3.71

Table 25: Antiproliferative Activity of Lenalidomide (LEN) and Salmeterol against Human Multiple Myeloma Cells (ANBL-6)

Salmeterol (μM) / LEN (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
4.04	90.7	87.3	87.7	82.7	78.5	77.1	69.9	65	61.9
2.02	87.6	83.7	84.6	81.4	78.5	72.6	68	64.2	52.8
1.01	84.7	86.7	79.6	78.7	76.4	71.4	67.8	61.8	54.3
0.505	87.3	84	81.5	79.3	73.8	67.8	65.8	60.4	53.5
0.253	87.4	82.3	79.1	79.8	74.8	68.5	65.2	58.2	51.8
0.126	84.9	80.9	78.3	75.6	74.5	67	61.4	62.1	52.5
0.0632	85	80.3	81.9	73.3	75.2	67.6	63.9	57.4	44.8
0.0316	83.2	74.6	73.5	72	70.5	61.7	60.6	54.6	34.3
0	55.7	52.9	46.7	45.9	39	33.9	34.7	21.5	-3.58

Table 26: Antiproliferative Activity of Melphalan (MELPH) and Salmeterol against Human Multiple Myeloma Cells (MM.1S)

Salmeterol (μM) / MELPH (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
20.9	92	93	92.5	92.2	92.7	92.8	92.4	92.3	93.3
10.5	90.9	90.6	89.5	88	87.3	87.4	83.2	84.2	79.6
5.23	89.3	89.2	91	88.6	83.9	85.8	81.9	87.2	74.5
2.61	87.3	83.4	85.8	84.5	79.6	78.4	78.7	72.7	62
1.31	80.8	75.4	74.6	67.9	71	60.5	63.3	58.5	52.7
0.653	72.8	64.9	63.3	56.6	57	45.7	43.7	42.1	32.1
0.327	67.2	62.2	55.2	54	39.2	33.6	34.3	21.4	23
0.163	64.8	60.4	46.7	48.4	37.9	33.3	21.7	18	8.01
0	64.5	47.2	43.1	40.7	30.9	25.9	20.8	15.3	2.99

Table 27: Antiproliferative Activity of Doxorubicin (DOX) and Salmeterol against Human Multiple Myeloma Cells (MM.1S)

Salmeterol (μM) / DOX (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
2.06	94.2	93.7	94.9	94.3	94.5	94.6	94	94.1	94.5
0.688	90.2	89.6	89.4	90.8	92	92.3	91.9	91.3	92.8
0.229	76.7	76.1	75.2	76	75.3	77.8	77.2	78.2	76.7
0.0764	77.7	79.5	77.5	79	77.6	78.8	77.3	77.4	74
0.0255	79.8	77.1	76.5	76.9	74.7	76.3	67.5	72.6	61.2
0.00849	65.4	49.7	55.9	50.4	44.4	47.9	20.3	19.5	2.23
0.00283	58	46.3	52.5	43.1	31.8	24.3	13.9	8.19	1.3
0.000943	55.3	52.8	41.2	39.3	33.3	30.6	9.49	9.3	2.23
0	58.7	44.3	36.4	32.5	26.4	16.5	16	14.9	-2.79

Synergistic combination activity was also observed when BAR agonists were used in combination with the proteosome inhibitor bortezomib (Velcade). High resolution 9×9 combination analysis of formoterol and salmeterol crossed with bortezomib in the MM.1S multiple myeloma cell line is shown in Tables 28 and 29. As seen in Table 28, the single agent activity for 0.00253 μM bortezomib is 30.8% inhibition of proliferation, and the single agent activity of 0.0000202 μM formoterol is 51%. Combination anti-proliferative activity is 78%, a value that is more than additive for combined activity of the single agents. Similar combination effects are seen with salmeterol (Table 29). For example, the single agent activity for 0.00253 nM bortezomib is 19.6%, and single agent activity for 0.00032 μM salmeterol is 42%. Combination anti-proliferative activity is 82.6%.

Table 28: Antiproliferative Activity of Bortezomib (BORT) and Formoterol against Human Multiple Myeloma Cells (MM.1S)

Formoterol (μM) / BORT(μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
0.0405	79.2	87.2	85.5	82.8	93.8	94.1	93.3	93.4	0
0.0203	87.7	93.1	93.8	93.6	92.9	94.2	93.6	93	94.6
0.0101	92.3	93.8	92.8	93.7	92.8	92.2	90.3	91.9	94.4
0.00506	92.5	93	92.3	91.4	89.2	78.8	86.4	80.8	91.8
0.00253	90.8	88.8	83.3	78.3	78	64.7	59.6	49.1	30.8
0.00127	81.6	74.8	78.2	69.2	56.1	43.2	27.9	19.5	7.32
0.000633	77.8	70	72.5	65.1	58.8	46.3	33	20.3	5.74
0.000316	75.5	69.1	68.5	65	56.8	45	37	19.5	6.04
0	72.7	69.4	65.7	57.5	51	40.7	36.2	22.4	5.51

Table 29: Antiproliferative Activity of Bortezomib (BORT) and Salmeterol against Human Multiple Myeloma Cells (MM.1S)

Salmeterol (μM) / BORT (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
0.0405		94.5	93.9	94.1	94.4	94.3	94.3	94.4	93.5
0.0203	94.2	94.3	94.1	93.7	93.5	93.7	93.7	94.9	94.7
0.0101	94.2	94	93.1	94.1	93.5	92.9	91.6	92.1	94
0.00506	92	88.1	88.7	83.8	78.9	71.6	78.2	54.3	91.6
0.00253	82.6	77.5	62.2	54.4	53.8	38.9	35.2	24.4	19.6
0.00127	61.7	43.2	43.2	30.4	26.3	16.5	14.9	4.92	2.2
0.000633	53.7	43.3	35.5	31.5	28.7	19.8	14.4	7.22	2.43
0.000316	52.7	38.5	32.4	29.9	23	18	9.37	2.56	1.9
0	42.1	35.4	31	26.5	21.9	16.9	16.9	8.95	-1.02

BAR agonists also had potent synergistic combination activity against multiple B-cell malignancies when used in combination with adenosine receptor A2A agonists (multiple myeloma, DLBCL, and Burkitt's lymphoma) or phosphodiesterase inhibitors (multiple myeloma and Burkitt's lymphoma). Representative synergy scores are shown in Table 30 and representative high resolution 9×9 combination analysis are shown in Table 31 (the adenosine receptor A2A agonist ATL 1222 crossed with Salmeterol using the multiple myeloma cell line MM.1S) and Tables 32-33 (Salmeterol combined with the PDE inhibitor trequinsin using the MM.1S and ANBL-6 multiple myeloma cell lines).

Table 30: Summary of Synergy Scores for the BAR Agonists when Combined with Adenosine Receptor Agonists ATL 1222 and Chloro-IB-MECA or the PDE Inhibitors Trequinsin and Roflumilast in MM.1S and ANBL-6 (Multiple Myeloma), GA-10 (Burkitt's Lymphoma), or OCI-ly10 (DLBCL)

Combination	MM.1S	GA-10	ANBL-6	OCI-ly10
salmeterol × ATL 1222	4.88	n.d.	1.47	1.36
formoterol × ATL 1222	2.09	n.d.	1.86	n.d.
salmeterol × chloro-IB-MECA	n.d.	1.07	n.d.	3.26
salmeterol × trequinsin	10.4	n.d.	6.84	2.99
formoterol × trequinsin	6.34	n.d.	n.d.	n.d.
salmeterol × roflumilast	n.d.	n.d.	n.d.	4.28

Table 31: Antiproliferative Activity of ATL 1222 and Salmeterol against Human Multiple Myeloma Cells (MM.1S)

Salmeterol (μM) / ATL 1222 (μM)	0.00032	0.00016	0.000081	0.0000405	0.0000202	0.0000101	0.00000506	0.00000253	0
0.0203	84.7	82.3	81.8	77.3	78.3	76.5	70.8	73.8	70.1
0.0101	82.9	81.5	79.6	77.6	77.2	73	72.5	71.8	65.9
0.00506	81.1	79	77.1	71.8	72.4	69.2	67.6	65.8	60.8
0.00253	78.9	73.6	72.6	71.2	65.2	60.9	58.4	58.3	48.6
0.00127	75.7	64.8	66.3	61.1	59.2	55.1	47.6	45.2	39.2
0.000633	68.7	62	56.4	53.8	45.4	44.2	36.7	28.8	27.9
0.000316	65.6	53.8	57	49.5	41	33	25.3	17.3	13
0.000158	59.8	50.1	46.2	42.9	33.5	32.6	18.9	7.42	8.7
0	52	36.6	34.8	26.3	20	16.6	12.2	10.9	-1.96

Table 32: Antiproliferative Activity of Salmeterol (SAL) and Trequinsin against Human Multiple Myeloma Cells (MM.1S)

Trequinsin (μM) / SAL (μM)	10.1	3.38	1.13	0.375	0.125	0.0417	0.0139	0.00464	0
0.000324	90.4	83.3	77.9	76.9	76.5	71.2	72.6	60.1	54
0.000162	90.8	77.5	74.1	73.6	64.5	64	61.5	54	46.5
0.000081	84.3	77.6	73.6	56.8	60.1	52.7	54.5	42	45.9
0.0000405	78.3	75.6	61.9	63.9	58.8	53.2	39.6	42.4	35.5
0.0000202	84.1	63.8	63.5	55.9	42.6	44.9	42.6	26.5	32.6
0.0000101	76.1	55.5	39.4	28.6	33.4	28.8	23.7	21	21.3
0.00000506	69.5	40.3	29.7	24.4	16.9	15.9	18.7	20	16.3
0.00000253	50.3	23.6	20.9	7.63	8.1	12.1	9.95	5.4	11.3
0	35.2	12.4	5.55	4.78	-4.78	2.47	1.62	3.47	-5.71

Table 33: Antiproliferative Activity of Salmeterol (SAL) and Trequinsin against Human Multiple Myeloma Cells (ANBL-6)

Trequinsin (μM) / SAL (μM)	10.1	3.38	1.13	0.375	0.125	0.0417	0.0139	0.00464	0
0.0203	94.1	88	83.3	76.5	66.8	62.7	56.6	60.2	58
0.0101	93.3	88.4	80.5	71.3	62.6	61.1	56.2	59.3	54.7
0.00506	94.2	86.3	80.6	71.7	69	59.5	60.6	58	55
0.00253	93.2	87.8	81.3	74.4	65.7	62.7	59.3	61.3	54
0.00127	92	89.5	80.1	73	65.7	60.6	61.7	63.1	55.7
0.000633	93.6	88.4	81.3	73	69.4	64	58.2	57.1	58.4
0.000316	93.6	86.9	80.1	72.2	63.9	57.5	61.8	62.1	54.8
0.000158	92.7	89	81.6	71.3	65.5	56.4	55.1	53.4	50.7
0	50.3	28.6	17.4	7.82	4.39	-4.22	-1.74	2.91	-3.34

BAR agonists also synergize with histone deacetylase (HDAC) inhibitors. The synergy scores for salmeterol in combination with the HDAC inhibitors MS-275, scriptaid, suberoylanilide hydroxamic acid (SAHA), and trichostatin A using the multiple myeloma cell line MM.1S are shown in Table 34. Representative combination data (salmeterol and SAHA) are provided in Table 35.

Table 34: Summary of Synergy Scores for the BAR Agonists Salmeterol Combined with HDAC Inhibitors in the Multiple Myeloma Cell Line MM.1S.

Combination	Synergy score
salmeterol × MS-275	1.98
salmeterol × scriptaid	2.96
salmeterol × SAHA	2.01
salmeterol × trichostatin A	4.11

Table 35: Antiproliferative Activity of Salmeterol and SAHA Against Human Multiple Myeloma Cells (MM.1S)

Salmeterol (nM) \ SAHA (μM)	7.1	3.6	1.8	0.89	0.44	0
0.011	100	100	100	90	88	78
0.0036	100	100	99	92	79	70
0.0012	100	100	99	90	82	70
0.0004	100	100	99	87	78	65
0.00013	100	100	98	86	72	48
0.000045	100	100	96	72	48	22
0	100	100	83	34	25	0.7

BAR agonists also have synergistic activity when used in combination with HSP-90 inhibitors. Data for the combination of salmeterol and 17-AAG are shown in Table 36.

Table 36: Antiproliferative Activity of Salmeterol and 17-AAG Against Human Multiple Myeloma Cells (MM.1S)

17-AAG (μM) / Salmeterol (nM)	0.31	0.15	0.077	0.039	0.019	0
0.011	89	81	74	80	75	81
0.0036	82	73	72	72	69	64
0.0012	78	69	69	67	66	65
0.0004	74	61	63	60	61	60
0.00013	62	54	56	53	49	51
0.000045	47	35	36	38	43	19
0	17	12	3.1	1.7	3	1.1

Example 3. BAR agonist drug combinations potently induce apoptosis and cell death

BAR agonists were highly synergistic and potently antiproliferative in combination with dexamethasone, melphalan, lenalidomide, and bortezomib as determined using an assay that measures ATP, a surrogate for the measurement of cell health and number. MM.1S cells were further treated with the BAR agonist salmeterol and either dexamethasone, lenalidomide, trequinsin, or bortezomib, as single agents or in combination with salmeterol. Effects on cell viability were determined by measuring the percent of cells that were annexin V positive (an early marker for apoptosis) and by measuring the percent of cells propidium iodide (PI) positive, an indicator that cellular membranes are compromised and a marker of cell death. Figure 1 shows the results for MM.1S cells treated with 0.13nM salmeterol and 20nM dexamethasone for 48 hours as single agents or in combination. While neither agent had appreciable activity (<10%), use in combination resulted in ~80% of the cells becoming annexin V positive. Combination-induction of apoptosis was also observed with salmeterol-lenalidomide and salmeterol-trequinsin (Figure 2). Treatment of cells with 0.3nM salmeterol resulted in ~40% induction of MM.1S cell apoptosis after 72 hours. In contrast, 1μM lenalidomide or 2μM trequinsin at 72 hours had negligible effects. These drugs in combination synergistically induced apoptosis; salmeterol-lenalidomide treated cells were 65% annexin V positive, while salmeterol-trequinsin treated cells were 75% annexin V positive. Finally, the activity of salmeterol and bortezomib was determined (Figure 3). MM.1S cells treated with 0.13nM salmeterol for 72 hours were 22% annexin V positive, and cells cultured in the presence of 2nM bortezomib were 50% annexin V positive. Use of these drugs in combination resulted in the cells being 71% annexin positive. In summary, BAR agonists used in combination with drugs used to treat multiple myeloma resulted in the rapid synergistic induction of apoptosis and cell death.

Example 4. BAR agonist drug combinations synergistically inhibit viability as determined using long term growth conditions (CFU assays)

BAR agonists have potent synergistic antiproliferative activities in combination with dexamethasone, lenalidomide, melphalan, and bortezomib, drugs commonly used to treat B cell malignancies. BAR agonist combinations

synergistically induce apoptosis of cells in culture. The effect of BAR agonists on cells grown in soft agar was also determined. This approach allows the measurement of long term cell viability after single agent or combination treatment. RPMI-8226 cells were treated with 2nM salmeterol, 100nM bortezomib, 200nM bortezomib, or the combinations of both drugs for 5 hours. Cells were washed and plated in soft agar. After three weeks colonies were counted to determine cell viability. For each 10,000 cells plated, 740 colonies were observed if cells had not been exposed to drugs. Exposure of cells to 2nM salmeterol reduced the colony number to 360, while exposing cells to 100nM bortezomib reduced the colony forming number to 39. The combination of both drugs reduced the colony forming number to 8. Similar effects were observed when the bortezomib concentration was increased to 200nM, where 7 colonies were observed with the number reduced to 3 by combination drug activity.

Example 5. Selectivity - combination activity in normal cells

With the observation that BAR agonists have strong synergistic antiproliferative activity across a large panel of representative B cell malignancy cell lines, combination activity was examined using non-transformed cells to question whether activity was selective. Strong combination activity with transformed cells but not normal counterparts suggests the potential for a "therapeutic window" where tumor cells are selectively killed over normal cells. Human coronary artery endothelial cells (HCAEC) were cultured in the presence of salmeterol and dexamethasone or salmeterol and lenalidomide for 72 hours using the conditions described for Table 10. The synergy scores were 0.031 for salmeterol and dexamethasone and 0.019 for salmeterol and lenalidomide. Similarly, the combination activity using PBMCs was 0.059 for Salmeterol and dexamethasone and 0.224 for salmeterol and lenalidomide. Combination activity was not observed with either drug combination using either HCAEC or PBMC.

Example 6. The beta 2 adrenergic receptor is important for activity.

BAR agonists employed in the above examples primarily target the beta 2 adrenergic receptor subtype. To determine whether a beta 1 adrenergic receptor agonist has similar activity, the beta 1 agonist dobutamine was combined with dexamethasone, and anti-proliferative activity determined using the multiple myeloma

cell lines MM.1S and EJM. Dobutamine is a beta 1 agonist with 6 to 10-fold selectivity for beta 1 vs. beta 2 receptor (J Clin Invest 1981 67(6):1703-11). The synergy score for dobutamine × dexamethasone for MM.1S was 2.61, and with EJM cells, a synergy score of 1.93 was observed. The 6×6 data for this combination are shown in Tables 41 and 42. For generation of the data in Tables 37 and 38, as with the 9×9 crosses, inhibition of proliferation was measured as described, after incubation of cells with test compound(s) for 72 hours. The effects of various concentrations of single agents or agents in combination were compared to control wells (cells not treated). The effects of agents alone and in combination are shown as percent inhibition of cell proliferation. As with beta 2 agonists, the beta 1 agonist dobutamine has potent combination activity when combined with dexamethasone.

Table 37: Antiproliferative Activity of Dexamethasone (DEX) and Dobutamine Against Human Multiple Myeloma Cells (MM.1S)

DEX (μM) \ Dobutamine (μM)	0.506	0.253	0.127	0.0633	0.0316	0
0.15	94.9	90.8	88.7	78.9	80.8	62.9
0.0502	86.6	86.8	78.8	68.7	67.5	50.5
0.0167	67	82.2	45	57.1	43.3	37.2
0.00557	59.2	42	40	14.2	33	2.23
0.00186	23.8	26.4	13	18.7	5.75	10.5
0	22.9	-0.808	18.1	-13.4	-2.04	9.46

Table 38: Antiproliferative Activity of Dexamethasone (DEX) and Dobutamine Against Human Multiple Myeloma Cells (EJM)

DEX (μM) \ Dobutamine (μM)	0.506	0.253	0.127	0.0633	0.0316	0
1.02	69.9	63.2	51.2	38.7	24.5	0.767
0.341	51.5	40.2	38.4	17.6	5.92	-11.2
0.114	52.5	43.4	24.5	18.7	6.34	4.81
0.0379	63.8	28.9	2.72	0.767	3.97	-13.6
0.0126	35.1	29.8	-1.05	-2.86	-9.27	-7.6
0	21.5	3.14	3.55	-4.11	-2.3	-9.13

To confirm that the activity of BAR agonists is beta adrenergic receptor-dependent, we examined the anti-proliferative activity of salmeterol, in the presence of increasing concentrations of the beta 1 and beta 2 adrenergic receptor antagonist CGP 12177A. As shown in Table 39, the lowest concentration of CGP 12177A tested (0.0019 μM) potently blocked salmeterol activity.

Table 39: Antiproliferative Activity of Salmeterol (SAL) on Human Multiple Myeloma Cells (MM.1S) in the Presence of CGP 12177A.

Salmeterol (μM) / CGP 12177A (μM)	0.01	0.0034	0.0011	0.00037	0.00012	0
0.3	3.3	1.1	3.6	4.9	4.3	3.3
0.150	4.5	-2.7	-3.9	4.3	-3.9	-4.5
0.076	10	2.3	2.1	4.1	5.7	0.9
0.038	18	12	3.3	2.6	6.2	-3.3
0.0019	16	4.2	-0.3	-0.77	2.7	-0.3
0	49	50	49	42	26	6.2

We have tested 13 BAR agonists and found that each synergized with dexamethasone (Table 10). Furthermore, BAR agonists synergize with lenalidomide (Table 21), melphalan (Table 22), doxorubicin (Table 23), bortezomib (Tables 28 and 29), A2A agonists and PDE inhibitors (Table 30), and HDAC inhibitors (Tables 34 and 35). All of the drugs assayed in these examples agonize the beta 2 adrenergic receptor but can be less selective at higher concentrations, activating other beta adrenergic receptor family members or possibly other cellular targets. To determine if the beta 2 receptor is necessary for the antiproliferative effects observed with B cells, we examined combination activity when BAR agonist was assayed in the presence of the highly selective beta 2 specific antagonist ICI 118,551.

Table 40 shows the potent synergy observed for the combination dexamethasone and clenbuterol in a 6×6 dose matrix format. The addition of 0.91 nM ICI 118,551 significantly reduced clenbuterol single agent activity (Table 41), while 9.2 nM ICI 118,551 (Table 42) completely blocked clenbuterol single agent activity and most of the synergy.

Table 40: Antiproliferative Activity of Clenbuterol and Dexamethasone on Human Multiple Myeloma Cells (MM.1S).

Clenbuterol (μM) / Dexamethasone (μM)	0.01	0.0051	0.0025	0.0013	0.0006	0
0.15	100	100	100	100	100	70
0.076	100	100	99	99	100	63
0.038	99	99	98	99	99	56
0.019	99	99	99	98	100	47
0.0095	99	98	96	95	98	38
0	78	61	62	57	66	13

Table 41: Antiproliferative Activity of Clenbuterol and Dexamethasone on Human Multiple Myeloma Cells (MM.1S) in the Presence of 0.91 μM ICI, 118,551

Clenbuterol (μM) / Dexamethasone (μM)	0.01	0.0051	0.0025	0.0013	0.0006	0
0.15	99	97	96	95	98	72
0.076	100	96	94	90	97	61
0.038	98	94	90	86	92	56
0.019	98	88	88	83	92	46
0.0095	94	82	74	67	84	34
0	54	15	21	7.8	28	1.5

Table 42: Antiproliferative Activity of Clenbuterol and Dexamethasone on Human Multiple Myeloma Cells (MM.1S) in the Presence of 9.2 μM ICI, 118,551

Clenbuterol (μM) / Dexamethasone (μM)	0.01	0.0051	0.0025	0.0013	0.0006	0
0.15	93	84	84	78	86	71
0.076	92	77	74	68	78	60
0.038	83	62	58	56	66	56
0.019	79	50	52	47	56	48
0.0095	86	78	66	56	41	31
0	5.2	-5.1	-7.1	4.7	6.8	3.6

When dexamethasone and dobutamine were combined, some synergy was observed but only at high concentrations of dobutamine (Table 43). The addition of 0.91 nM ICI 118,551, dramatically reduced combination activity, with residual synergy observed only at the highest concentration of dobutamine tested (Table 44).

Table 43: Antiproliferative Activity of Dobutamine and Dexamethasone on Human Multiple Myeloma Cells (MM.1S)

Dobutamine (μM) / Dexamethasone (μM)	1.0	0.51	0.25	0.13	0.063	0
0.15	98	87	87	86	81	72
0.076	96	86	81	71	70	63
0.038	94	80	72	66	68	60
0.019	91	70	66	61	63	47
0.0095	83	60	55	41	47	33
0	28	12	4.7	14	11	8.7

Table 44: Antiproliferative Activity of Dobutamine and Dexamethasone on Human Multiple Myeloma Cells (MM.1S) in the Presence of 0.91 μM ICI, 118,551

Dobutamine (μM) / Dexamethasone (μM)	1.0	0.51	0.25	0.13	0.063	0
0.15	89	79	86	76	75	71
0.076	79	70	66	63	62	63
0.038	73	52	54	54	55	54
0.019	62	44	45	44	49	43
0.0095	47	31	30	31	35	32
0	-1.8	-2.8	-5.4	2	2.2	1.9

The beta 3 agonist BRL37344 was not very active as a single agent, but some combination synergy was observed with dexamethasone when high concentrations of BRL37344 were used (20 nM, Table 45). BRL37344 is a beta 3 agonist that is 76-fold selective for beta 3 vs. beta 2 (Mol Phar 1994 46(2):357-63). The combination activity of BRL37344 and dexamethasone was inhibited in the presence of 0.91 nM of the beta 2 antagonist ICI 118,551 (Table 46).

Table 45: Antiproliferative Activity of BRL 37344 and Dexamethasone on Human Multiple Myeloma Cells (MM.1S)

BRL 37344 (μM) / Dexamethasone (μM)	0.02	0.01	0.0051	0.0025	0.0013	0
0.15	94	84	81	78	75	69
0.076	88	76	74	71	68	62
0.038	84	65	72	64	52	58
0.019	74	63	58	50	50	49
0.0095	70	47	44	38	44	33
0	10	10	8.3	7.7	4	3.9

Table 46: Antiproliferative Activity of BRL 37344 and Dexamethasone on Human Multiple Myeloma Cells (MM.1S) in the Presence of 0.92 µM ICI 118,551

BRL 37344 (µM) / Dexamethasone (µM)	0.02	0.01	0.0051	0.0025	0.0013	0
0.15	79	77	73	74	73	68
0.076	67	64	64	64	60	60
0.038	56	47	55	52	50	53
0.019	45	40	44	42	47	42
0.0095	28	32	27	33	37	32
0	-12	-8.2	-4.9	3.2	0.2	-0.3

The results obtained with the beta receptor antagonist ICI 118,551 point to the beta 2 receptor subtype as being important for the antiproliferative effect of agonists on cell growth. We also examined the antiproliferative activity of BAR agonists when the MM cell line MM.1R was transfected with siRNA targeting the beta 2 receptor or two control siRNA, one (control) designed using scrambled sequences so that cellular transcripts are not targeted and a second siRNA (A2A) that reduces expression of the A2A receptor RNA by 75% as determined by PCR analysis. Specific gene silencing was greater than 60% as determined by real time PCR analysis 48 hours post-transfection. At 48 hours post-transfection, cells were exposed to the beta 2 receptor agonist salbutamol and incubated an additional 72 hours, and the compounds were assayed for antiproliferative activity. Representative data are shown in Figure 4. Cells transfected with A2A receptor siRNA or a control siRNA had similar sensitivity to salbutamol (65-68% inhibition of proliferation). In contrast, two different siRNA that targeted the beta 2 receptor reduced salbutamol antiproliferative activity to 39-45%.

Example 7. Tumor cell resistance profiles after chronic exposure to beta adrenergic agonists

A recurrent problem in cancer therapy is that prolonged exposure of tumor cells to chemotherapeutic agents can generate cells resistant to agents that initially have antiproliferative or cell killing activity. To determine if multiple myeloma cells become resistant to the effects of BAR agonists after prolonged exposure, MM.1S cells were cultured in the presence of increasing concentrations of either salmeterol or salbutamol over a one month period such that at the end of 30 days, the concentration of drug was 64 nM for salmeterol and 150 nM for salbutamol. Cells cultured for one month in the presence of BAR agonist were washed to remove drug and put into 384 well plates for 9×9 dose matrix combination screening with BAR agonists and dexamethasone. As a control, combination screening was performed using MM.1S cells that did not have prior exposure to BAR agonists. Table 47 shows a 9×9 combination matrix for salmeterol and dexamethasone in naïve cells, the result being very similar to the data shown in Table 17 with the combination having potent synergistic antiproliferative activity. After culture in 64 nM salmeterol, cells were no longer sensitive to salmeterol when deployed as a single agent; however, some

combination synergistic activity was still observed (Table 48). For example, the combination of 0.0022 μM salmeterol (4.1% inhibition) and 0.0082 μM dexamethasone (51% inhibition) inhibited proliferation by 70% when used in combination. Chronic exposure of cells to salmeterol had a striking effect on dexamethasone single agent activity. While dexamethasone inhibited the proliferation of naïve cells ~70% at 2.0-0.23 μM (Table 47), effects on proliferation were more pronounced for cells exposed long term to salmeterol with ~96% inhibition observed at 2.0-0.23 μM dexamethasone (Table 48). This boost in dexamethasone single agent activity was not observed with cells cultured for one month in the presence of salbutamol (compare Tables 49 and 50), but salbutamol/dexamethasone synergy was still observed (Table 50).

The dose matrix results for MM.1S cells cultured in the presence of BAR agonists for one month show that the cells were insensitive to BAR agonists when used as a single agent. However, synergistic antiproliferative activity was still observed in combination with dexamethasone. Similar results were observed for BAR agonists in combination with melphalan. The BAR agonists were no longer active as single agents but synergized with melphalan (Table 51). However, unlike with dexamethasone, melphalan single agent activity was not potentiated.

The observation that cells treated for one month with salmeterol were hypersensitive to dexamethasone (compare dexamethasone single agent activity for Table 47 and 48) has interesting clinical ramifications. As an independent approach to confirm that tumor cells become hypersensitive to salmeterol, MM.1S cells treated with salmeterol or salbutamol for one month were incubated with either low (8nM) or high (80nM) dexamethasone or 250pM salmeterol. Forty eight hours later, the percent of cells positive for Annexin V and propidium iodide (PI) was determined using FACS (Figure 5). Control cells not exposed to BAR agonist for one month were sensitive to salmeterol (20% Annexin V/PI +) and both low and high concentrations of dexamethasone (8 and 45% Annexin V/PI+). As expected, cells treated for one month with salmeterol or salbutamol were not sensitive to 250pM salmeterol. However, cells exposed to salmeterol for one month were hypersensitive to dexamethasone, with 47% Annexin V/PI+ cells found with 8nM dexamethasone treatment while 80nM dexamethasone treatment resulted in 65% of the cells becoming Annexin V/PI+.

Table 47: Antiproliferative Activity of Salmeterol and Dexamethasone on Human Multiple Myeloma Cells (MM.1S)

Salmeterol (μM) / DEX (μM)	0.02	0.0066	0.0022	0.00074	0.00024	0.00008	0.000027	0.0000091	0
2.0	96	96	96	96	95	96	92	86	70
0.666	96	96	96	96	96	95	90	83	71
0.23	96	95	96	96	96	95	90	80	68
0.074	96	96	96	96	96	94	88	76	59
0.024	96	94	96	94	95	90	82	67	48
0.0082	94	94	94	92	90	79	70	48	39
0.00274	86	87	87	82	80	53	38	25	15
0.0009	72	76	71	67	62	33	31	14	11
0	59	53	56	51	44	25	7.1	4.9	3.4

Table 48: Antiproliferative Activity of Salmeterol and Dexamethasone on Human Multiple Myeloma Cells (MM.1S) Cultured in the Presence of Salmeterol for One Month (final concentration 64 nM)

Salmeterol (μM) / DEX (μM)	(1 month 64 nM Salmeterol)								
	0.02	**0.0066**	**0.0022**	**0.00074**	**0.00024**	**0.00008**	**0.000027**	**0.0000091**	**0**
2.0	97	96	96	97	96	96	96	96	96
0.666	96	96	97	97	96	95	95	96	96
0.23	97	97	96	96	96	96	96	95	96
0.074	96	95	96	96	96	95	95	94	93
0.024	91	91	92	90	93	83	88	87	81
0.0082	67	73	70	64	71	55	65	58	51
0.00274	38	41	36	36	41	23	38	37	23
0.0009	21	19	17	17	18	13	13	7.5	8.2
0	5.6	3.6	4.1	9.5	6.4	6.1	2	6.7	2.6

Table 49: Antiproliferative Activity of Salbutamol and Dexamethasone on Human Multiple Myeloma Cells (MM.1S)

DEX (μM) \ Salbutamol (μM)	0.2	0.1	0.05	0.025	0.0125	0.00625	0.00375	0.0000091	0
2.0	96	96	96	96	96	94	91	92	75
0.666	96	96	96	96	95	95	92	90	75
0.23	96	96	95	96	95	93	93	90	73
0.074	96	96	96	95	96	94	91	87	63
0.024	95	96	94	95	93	88	82	74	47
0.0082	92	92	90	87	84	74	72	67	37
0.00274	87	82	80	72	72	51	43	39	12
0.0009	76	70	66	56	53	34	24	22	13
0	58	55	51	38	39	30	15	10	2.4

Table 50: Antiproliferative Activity of Salbutamol and Dexamethasone on Human Multiple Myeloma Cells (MM.1S) Cultured in the Presence of Salbutamol for One Month (final concentration 150 nM)

Salbutamol (μM) / DEX (μM)	(1 month 150 nM Salbutamol) 0.2	0.1	0.05	0.025	0.0125	0.00625	0.00375	0.0000091	0
2.0	95	93	93	92	89	80	72	73	61
0.666	94	93	92	92	90	84	73	72	60
0.23	94	93	91	90	89	78	70	71	59
0.074	92	90	90	87	84	77	71	60	48
0.024	84	79	80	78	67	57	57	51	39
0.0082	62	66	60	47	56	37	39	34	30
0.00274	41	36	31	26	24	17	21	17	10
0.0009	16	8.8	14	8.3	14	8.8	2.9	7.5	6.5
0	6.8	11	1.5	4.6	-1.9	4.6	-5.8	-5.3	-7.8

Table 51: Summary of Synergy Scores for the BAR agonists Salmeterol and Salbutamol Combined with Dexamethasone or Melphalan in Naïve MM.1S Cells or Cells Cultured in the Presence of Salmeterol or Salbutamol for One Month

Combination	MM.1S	MM.1S/1 month Salbutamol (150nM)	MM.1S 1 month Salmeterol (64nM)
salmeterol × dexamethasone	18.05	13.27	2.26
salbutamol × dexamethasone	10.66	8.26	1.61
salmeterol × melphalan	4.17	3.5	2.02
salbutamol × melphalan	2.94	2.31	1.75

Example 8. Combinations with IL-6.

Myeloma cells migrate to bone, where they form tumors called plasmocytomas. These malignant cells express cell adhesion molecules that allow attachment and communication with cells of the bone marrow microenvironment. This communication influences myeloma cell survival and growth as MM cells secrete a number of cytokines that act on bone marrow stromal cells (BMSCs), which, in turn, secrete factors that contribute to the growth and proliferation of MM cells. One factor, IL-6, is a central regulatory cytokine in the pathogenesis of MM. This cytokine causes proliferation of MM cells and inhibits cancer drug sensitivity/apoptosis.

The protective effect of IL-6 can be observed with MM cells in culture. Other investigators have shown that MM.1S cell proliferation is stimulated by IL-6, and the cells are more resistant to chemotherapeutic agents such as dexamethasone and rapamycin. Shown in Tables 52-53 is the 6×6 analysis of salmeterol × dexamethasone (in triplicate) using MM.1S cells -/+ IL-6. Consistent with what has been described by others, the proliferation of MM.1S cells is inhibited 52% when cultured in the presence of 0.15 μM dexamethasone. In contrast, when 10ng/ml IL-6 is present in the media, the inhibitory effect of dexamethasone is approximately halved, with MM.1S proliferation inhibited only 24%. In contrast, IL-6 increased BAR agonist activity. The antiproliferative activity of salmeterol was increased at each concentration tested (compare Tables 52 and 53). Also, shown (Table 54) is an 8-point titration of salmeterol using MM.1S cells (in quadruplicate) cultured in the

presence or absence of 10ng/ml IL-6. Again, IL-6 increases the activity of the BAR agonist salmeterol. BAR agonists are a class of drugs that should be more active in the bone tumor microenvironment, having a more potent anti-tumor effect due to the presence of IL-6.

Table 52: Antiproliferative Activity of Dexamethasone (DEX) and Salmeterol Against Human Multiple Myeloma Cells (MM.1S) without IL-6.

Salmeterol (μM) / DEX (μM)	(no IL-6) 0.00051	0.000253	0.00013	0.0000633	0.000032	0
0.15	93	93	91	89	83	52
0.076	94	92	87	88	86	45
0.038	92	91	88	85	73	44
0.019	90	88	89	75	77	32
0.0096	84	81	77	73	66	27
0	46	48	38	21	21	7.1

Table 53: Antiproliferative Activity of Dexamethasone (DEX) and Salmeterol Against Human Multiple Myeloma Cells (MM.1S), 10 ng/ml IL-6

Salmeterol (μM) / DEX (μM)	(+ 10ng/ml IL-6) 0.00051	0.000253	0.00013	0.0000633	0.000032	0
0.15	90	88	86	80	72	24
0.076	88	86	80	75	69	26
0.038	85	82	79	70	59	26
0.019	82	76	72	65	65	14
0.0096	76	71	64	60	54	12
0	52	51	41	29	22	3.6

Table 54: Antiproliferative Activity of Salmeterol Against Human Multiple Myeloma Cells (MM.1S), 8 point titration -/+10 ng/ml IL-6

Condition	0.025pM	0.051pM	0.1pM	0.2pM	0.4pM	0.81pM	160pM	320pM
salmeterol (no IL-6)	5	6.7	11	25	30	43	50	59
salmeterol (10ng/mL IL-6)	2.8	8.6	19	30	36	54	59	66

Example 9. BAR agonist activity using multiple myeloma patient tumor cells

The observation that beta agonists synergize with drugs used for the treatment of multiple myeloma in multiple myeloma cell lines suggest that such a drug pairing may have value in the clinic for treatment of the disease. To address this possibility more directly, in addition to the analysis of cell lines, we examined that activity of BAR agonist (salmeterol) and dexamethasone using multiple myeloma tumor cells from patients. Tumor cells were obtained via bone marrow aspirates and affinity selected using CD138-linked magnetic beads. Purified tumor cells were incubated with salmeterol and dexamethasone using an 8×8 dose matrix format and 48 hours later, cell viability was determined using an MTT colorimetric assay. As shown in Table 55, the combination of salmeterol and dexamethasone exhibited potent synergistic activity. For example, 0.4 nM salmeterol had 38% activity, 0.063 μM dexamethasone 44% activity and the combination 92% activity.

Table 55: Reduction in Cell Viability of Dexamethasone (DEX) and Salmeterol Against Tumor Cells from a Patient with Multiple Myeloma

Salmeterol (nM) / DEX (μM)	0.8	0.4	0.2	0.1	0.05	0.025	0.0125	0
4.0	91	92	90	88	80	75	64	46
2.0	91	92	88	90	81	72	68	47
1.0	92	91	92	88	84	78	70	50
0.5	91	92	89	88	82	78	71	56
0.25	91	92	91	86	80	76	68	50
0.125	91	93	89	87	82	74	68	53
0.0625	91	92	91	87	78	72	61	44
0	44	38	40	35	13	12	-0.2	0

Figure 6 shows single agent/combination data from Table 55 (patient 1) plus the results obtained using cells for two additional patients. Synergistic salmeterol/ dexamethasone combination activity was clearly observed for patients 1 and 3. We have also examined the activity of salmeterol and bortezomib using patient tumor cells (Figure 7). While tumor cell viability was 80% after treatment with either 2nM bortezomib or 1nM salmeterol for 48 hours, the drugs in combination reduced viability to 58%.

Example 10. Combination activity in vivo (mouse model)

1. BAR agonist in combination with dexamethasone (MM.1S cells)

To further characterize combination activity, we examined the ability of salmeterol in combination with the standard of care, dexamethasone (Dex), to inhibit the growth of human multiple myeloma xenografts and prolong survival in a severe combined immune deficient (SCID) mouse model as compared to each of the single agent components (Figure 8).

The human multiple myeloma cell line MM1S was injected subcutaneously into the flanks of SCID mice. Five days following the injection of MM1S cells, animals were randomized into the following four treatment groups (n=6-7) based on tumor size.

Group 1-Vehicle (90% PBS + 10% EtOH)
Group 2-Dex (1 mg/kg)
Group 3-Salmeterol (10 mg/kg)
Group 4-Salmeterol (10 mg/kg) + Dex (1 mg/kg)

The prepared test, positive, and negative control substances were administered via subcutaneous injection daily for up to 85 Days. During the treatment period, tumor volume and animal body weights were measured 3 times per week (Monday, Wednesday and Friday). The animals were removed from the study if there was overall poor body condition, tumor volume above 3000 mm^3, body weight loss greater than or equal to 20% or ulcerated tumors.

All of the animals in the Dex (1 mg/kg) study group were removed by the 66^{th} study day. All of the animals in the salmeterol (10 mg/kg) study group were removed by the 43^{rd} study day. Five of 7 animals in study group salmeterol (10 mg/kg) + Dex

(1 mg/kg) survived until the final study day (85). The salmeterol (10 mg/kg) + Dex (1 mg/kg) study group had significantly greater survival when compared to the Dex (1 mg/kg) study group and the salmeterol (10 mg/kg) study group ($p<0.05$, ANOVA).

The percent change in tumor volume was calculated for the groups Dex (1 mg/kg), salmeterol (10 mg/kg), and salmeterol (10 mg/kg) + Dex (1 mg/kg) from study date Day 1 to Day 41. Day 41 was the last day that there was not more than one animal removed from each group. Results show that the percent change in tumor volume for each combination group was less than that of the single agent components.

The slope of the tumor volume growth of each animal was calculated from the initial study day until the day each animal was removed from the study. From these slopes the mean change in tumor volume per study day was calculated. The lowest mean change was calculated in the Salmeterol (10 mg/kg) + Dex (1 mg/kg) study group (18.36 mm^3/day). No statistical significance was calculated between these two study groups and the single agent components.

Body weight gain was observed in all study groups. Study animals gained between 1.5 and 28.5 percent over the course of the study.

The combination of Salmeterol (10 mg/kg) + Dex (1 mg/kg) significantly improved survival, and reduced the percent change in tumor volume from Day 1 to Day 41 when compared to its single agent components. It also had the lowest mean change in tumor volume per study day compared with all other groups within the study.

2. BAR agonist in combination with dexamethasone or bortezomib (RPMI 8226 cells)

The anticancer activity of the beta adrenergic agonist salmeterol was also evaluated in the RPMI-8226 multiple myeloma (MM) xenograft model (Figure 9). Salmeterol was administered alone and in combination with the standard of care (SOC) agents bortezomib and dexamethasone. Bortezomib was given at its MTD (1 mg/kg) and ½ its MTD (0.5 mg/kg). Dexamethasone was administered by intraperitoneal (IP) injection daily for thirty-six treatments (QD×36). Bortezomib was injected intravenously (IV) every third day for six treatments (Q3D×6).

Group 1-Vehicle (90% PBS + 10% EtOH)
Group 2-Dex (1 mg/kg)
Group 3- Bortezomib (0.5mg/kg)

Group 4- Bortezomib (1mg/kg)
Group 5-Salmeterol (10 mg/kg)
Group 6-Salmeterol (10 mg/kg) + Dex (1 mg/kg)
Group 7-Salmeterol (10 mg/kg) + Bortezomib (0.5 mg/kg)
Group 8-Salmeterol (10 mg/kg) + Bortezomib (0.5 mg/kg)

Significant endpoints included mean tumor growth inhibition (TGI) or regression, animal weight loss, and potential toxicity. The RPMI-8226 MM cell line was obtained from ATCC and cultured in media supplemented with 10% serum. Animals were implanted with cancer cells harvested from tissue culture and allowed to establish tumors in SCID mice. Treatment initiated when the mean tumor volume reached 137 mm^3 in size.

Some initial weight loss was observed following treatment with 1 mg/kg bortezomib alone and in combination with salmeterol. However, animal weight in these two groups was regained at the completion of the study. Notably, salmeterol was well-tolerated and did not significantly alter the weights of the animals compared to the vehicle group. The dexamethasone and 0.5 mg/kg bortezomib groups also did not induce much weight loss. Importantly, no animal deaths occurred in any group throughout the duration of the study. Both 1 mg/kg bortezomib and dexamethasone treatments dramatically inhibited tumor growth (TGIs of > 100%) in this study compared to animals that were administered the vehicle. 10 mg/kg salmeterol and 0.5 mg/kg bortezomib both exhibited moderate antitumor activity and produced TGIs of 37% and 38% respectively on Day 19 of the study. The combination of 0.5 mg/kg bortezomib and salmeterol resulted in enhanced antitumor activity yielding a TGI of 80% on Day 19. Combinations of salmeterol with 1 mg/kg bortezomib and 1mg/kg dexamethasone were also more effective at reducing tumor burden than either single agent, causing regression of tumor size (Figure 10).

Overall, Salmeterol was well-tolerated and demonstrated some anticancer activity in the RPMI-8226 MM xenograft model. Importantly, salmeterol enhanced the anticancer activity of both dexamethasone and bortezomib without adding any additional toxicity (weight loss, Figure 11). This effect was most pronounced when combined with bortezomib given at ½ its MTD. Since no toxicity was observed in terms of animal weight loss or death, an increase in the dose of salmeterol may further increase the drug's efficacy. Taken together, salmeterol possessed anticancer activity as a single agent and appears to enhance the activity of SOC agents. Salmeterol

warrants further investigation, especially in combination with SOC agents, for the treatment of MM and potentially other malignancies.

Other Embodiments

All publications, patents, and patent applications mentioned in the above specification are hereby incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific desired embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in the fields of medicine, immunology, pharmacology, endocrinology, or related fields are intended to be within the scope of the invention.

What is claimed is:

CLAIMS

1. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a beta adrenergic receptor agonist (BAR agonist) formulated for administration by a route other than inhalation, in an amount effective to treat said B-cell proliferative disorder.

2. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a BAR agonist, in an amount effective to treat said B-cell proliferative disorder, provided that, when said B-cell proliferative disorder is B-CLL, said BAR agonist is not formoterol, isoproterenol, or salmeterol, and that, when said B-cell proliferative disorder is doxorubicin resistant multiple myeloma, said BAR agonist is not salbutamol.

3. The method of claim 1 or 2, wherein said BAR agonist is administered as a monotherapy.

4. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a combination of a BAR agonist and a second compound selected from a PDE inhibitor and an A2A receptor agonist, in an amount effective to treat said B-cell proliferative disorder.

5. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a combination of a BAR agonist and an antiproliferative compound, in an amount effective to treat said B-cell proliferative disorder.

6. The method of any of claims 1, 2, 4, and 5, wherein said BAR agonist is selected from the group consisting of arbutaline, arfomoterol, bambuterol, bitolterol, broxaterol, clenbuterol, fenoterol, formoterol, hexoprenaline, indacaterol, isoetharine, isoproterenol, levalbuterol, meluadrine, metaproterenol, nylidrin, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salbutamol, salmeterol, tulobuterol, terbutaline, and xamoterol.

7. The method of any of claims 1, 2, 4, and 5, wherein said BAR agonist is selected from Table 1 or 2.

8. The method of any of claims 1, 2, 4, and 5, wherein said B-cell proliferative disorder is selected from the group consisting of autoimmune lymphoproliferative disease, B-cell chronic lymphocytic leukemia (CLL), B-cell prolymphocyte leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma, follicular lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT type), nodal marginal zone lymphoma, splenic marginal zone lymphoma, hairy cell leukemia, plasmacytoma, diffuse large B-cell lymphoma, Burkitt lymphoma, multiple myeloma, indolent myeloma, smoldering myeloma, monoclonal gammopathy of unknown significance (MGUS), B-cell non-Hodgkin's lymphoma, small lymphocytic lymphoma, monoclonal immunoglobin deposition diseases, heavy chain diseases, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, precursor B-lymphoblastic leukemia/lymphoma, Hodgkin's lymphoma (e.g., nodular lymphocyte predominant Hodgkin's lymphoma, classical Hodgkin's lymphoma, nodular sclerosis Hodgkin's lymphoma, mixed cellularity Hodgkin's lymphoma, lymphocyte-rich classical Hodgkin's lymphoma, and lymphocyte depleted Hodgkin's lymphoma), post-transplant lymphoproliferative disorder, and Waldenstrom's macroglobulinemia.

9. The method of any of claims 1, 2, 4, and 5, wherein said B-cell proliferative disorder is multiple myeloma.

10. The method any of claims 1, 2, 4, and 5, further comprising administering IL-6, a compound that increases IL-6 expression, or an IL-6 receptor agonist to said patient.

11. The method of any of claims 1, 2, 4, and 5, wherein, when said B-cell proliferative disorder is mantle cell lymphoma, said BAR agonist is not salmeterol administered with CHOP or bortezomib; when said B-cell proliferative disorder is multiple myeloma, said BAR agonist is not salbutamol administered with VAD; when said B-cell proliferative disorder is multiple myeloma, said BAR agonist is not salmeterol administered with prednisone and melphalan; when said B-cell proliferative disorder is multiple myeloma, said BAR agonist is not salbutamol administered with clodronate; or when said B-cell proliferative disorder is multiple myeloma, said BAR agonist is not salbutamol administered with melphalan, prednisone, and pamidronate for multiple myeloma.

12. The method of any of claims 1, 2, 4, and 5,wherein said patient is not suffering from asthma, bronchiolitis obliterans, COPD, or shortness of breath.

13. The method of any of claims 1, 2, 4, and 5, wherein said patient is not suffering from an immunoinflammatory disorder of the lungs.

14. The method of any of claims 1, 2, 4, and 5, wherein said patient is not suffering from an immunoinflammatory disorder.

15. The method of any of claims 1, 2, 4, and 5, wherein said patient is not preparing to undergo, undergoing, or recovering from allogenic or autologous stem cell replacement.

16. The method of any of claims 1, 2, 4, and 5, wherein said patient is not concomitantly treated with a stem cell mobilizer.

17. The method of any of claims 1, 2, 4, and 5, wherein said patient is not concomitantly treated with an mTOR inhibitor and capecitabine.

18. The method of any of claims 1, 2, 4, and 5, wherein said BAR agonist is not isoproterenol

19. The method of any of claims 2, 4, and 5, wherein said BAR agonist is formulated for oral or intravenous administration.

20. The method of any of claims 4 and 5, wherein said BAR agonist and said A2A agonist, PDE inhibitor, or antiproliferative compound are administered simultaneously.

21. The method of any of claims 4 and 5, wherein said BAR agonist and said A2A agonist, PDE inhibitor, or antiproliferative compound are administered within 14 days of one another.

22. The method of claim 4, wherein said A2A agonist is selected from Table 3 or 4, or said PDE inhibitor is selected from Table 5 or 6.

23. The method of claim 5, wherein said antiproliferative compound is selected from the group consisting of alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors, CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors, cyclin D inhibitors, NF-kB inhibitors and pathway modulators, anthracyclines, histone deacetylase inhibitors, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, AKT inhibitors, PI3K inhibitors, TRAF inhibitors, statins, mitotic kinase inhibitors, KSP inhibitors, cyclin dependent kinase inhibitors, inhibitors of anti-apoptotic proteins, immune therapies, calcineurin antagonists, and IMiDs.

24. The method of claim 5, wherein said antiproliferative compound is selected from Table 7 or 8.

25. The method of claim 5, wherein the combination of BAR agonist and antiproliferative compound is selected from Table 9.

26. The method of any of claims 1, 2, 4, and 5, wherein said BAR agonist is a beta 2 agonist.

27. A pharmaceutical composition comprising a BAR agonist in an amount effective to treat a B-cell proliferative disorder, wherein said BAR agonist is formulated for administration by a route other than inhalation.

28. The composition of claim 27, wherein said BAR agonist is formulated for oral or intravenous administration.

29. A pharmaceutical composition comprising a BAR agonist in an amount effective to treat a B-cell proliferative disorder, provided that, when said B-cell proliferative disorder is B-CLL, said BAR agonist is not formoterol, isoproterenol, or salmeterol, and that, when said B-cell proliferative disorder is doxorubicin resistant multiple myeloma, said BAR agonist is not salbutamol.

30. The composition of claim 27 or 29, wherein said BAR agonist is arbutaline, arfomoterol, bambuterol, bitolterol, broxaterol, clenbuterol, fenoterol, formoterol, hexoprenaline, indacaterol, isoetharine, isoproterenol, levalbuterol, meluadrine, metaproterenol, nylidrin, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salbutamol, salmeterol, tulobuterol, terbutaline, and xamoterol.

31. The composition of claim 27 or 29, wherein said BAR agonist is selected from Table 1 or 2.

32. A pharmaceutical composition comprising a BAR agonist and an A2A agonist, PDE inhibitor, or antiproliferative compound in an amount effective to treat a B-cell proliferative disorder.

33. The composition of claim 32, wherein said A2A agonist is selected from Table 3 or 4, or said PDE inhibitor is selected from Table 5 or 6.

34. The composition of claim 32, wherein said antiproliferative compound is selected from the group consisting of alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors, CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors, cyclin D inhibitors, NF-kB inhibitors and pathway modulators, anthracyclines, histone deacetylase inhibitors, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, AKT inhibitors, PI3K inhibitors, TRAF inhibitors, statins, mitotic kinase inhibitors, KSP inhibitors, cyclin dependent kinase inhibitors, inhibitors of anti-apoptotic proteins, immune therapies, calcineurin antagonists, and IMiDs.

35. The composition of claim 32, wherein said antiproliferative compound is selected from Table 7 or 8.

36. The composition of claim 32, wherein the combination of BAR agonist and antiproliferative compound is selected from Table 9.

37. A kit comprising a BAR agonist and an A2A agonist, PDE inhibitor, or antiproliferative compound in an amount effective to treat a B-cell proliferative disorder.

38. The kit of claim 37, wherein said BAR agonist is formulated for administration by a route other than inhalation.

39. The kit of claim 37, wherein said BAR agonist is formulated for oral or intravenous administration.

40. The kit of claim 37, wherein said BAR agonist is arbutaline, arfomoterol, bambuterol, bitolterol, broxaterol, clenbuterol, fenoterol, formoterol, hexoprenaline, indacaterol, isoetharine, isoproterenol, levalbuterol, meluadrine, metaproterenol, nylidrin, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salbutamol, salmeterol, tulobuterol, terbutaline, and xamoterol.

41. The kit of claim 37, wherein said BAR agonist is selected from Table 1 or 2.

42. The kit of claim 37, wherein said A2A agonist is selected from Table 3 or 4, or said PDE inhibitor is selected from Table 5 or 6.

43. The kit of claim 37, wherein said antiproliferative compound is selected from the group consisting of alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors, CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors,

cyclin D inhibitors, NF-kB inhibitors and pathway modulators, anthracyclines, histone deacetylase inhibitors, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, AKT inhibitors, PI3K inhibitors, TRAF inhibitors, statins, mitotic kinase inhibitors, KSP inhibitors, cyclin dependent kinase inhibitors, inhibitors of anti-apoptotic proteins, immune therapies, calcineurin antagonists, and IMiDs.

44. The kit of claim 37, wherein said antiproliferative compound is selected from Table 7 or 8.

45. The kit of claim 37, wherein the combination of BAR agonist and antiproliferative compound is selected from Table 9.

46. The kit of claim 37, further comprising instructions for administering said BAR agonist for treatment of said B-cell proliferative disorder.

47. A pharmaceutical composition comprising a BAR agonist and an IL-6 agonist in an amount effective to treat a B-cell proliferative disorder.

48. A kit comprising a BAR agonist and an IL-6 agonist in an amount effective to treat a B-cell proliferative disorder.

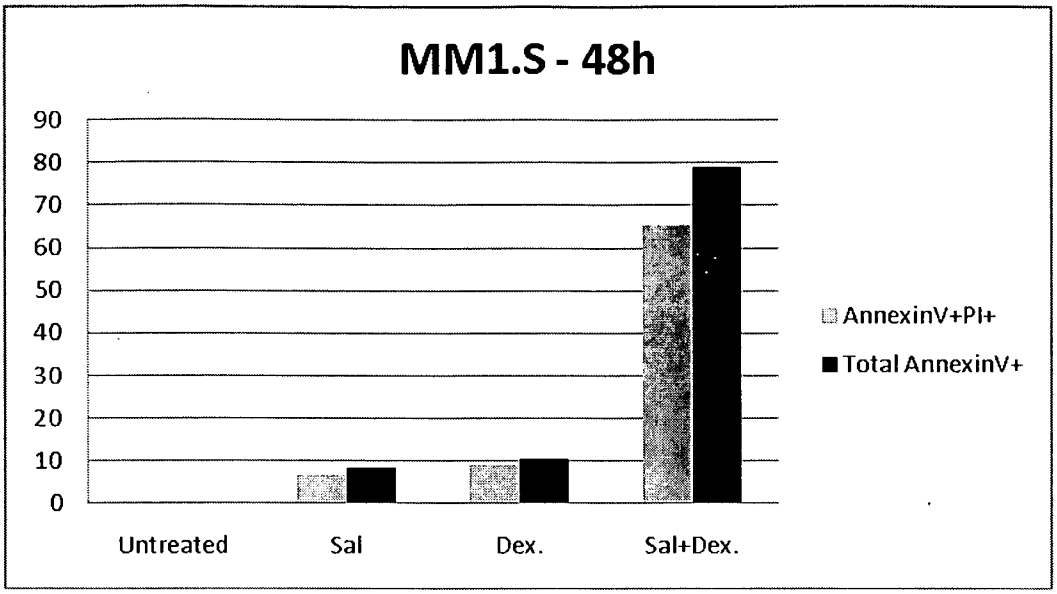


Figure 1

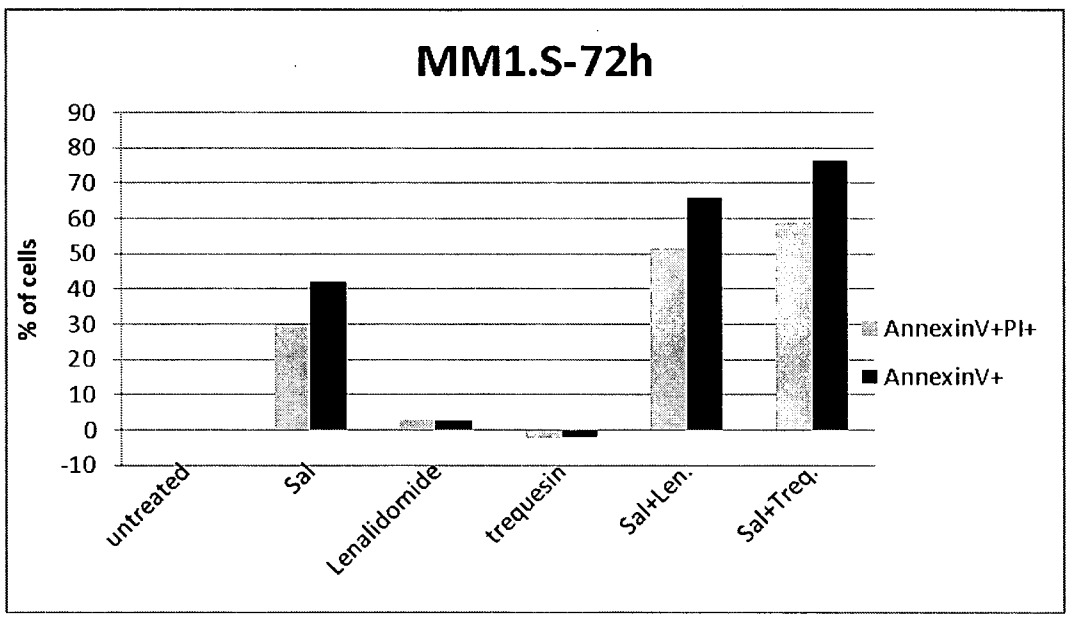


Figure 2

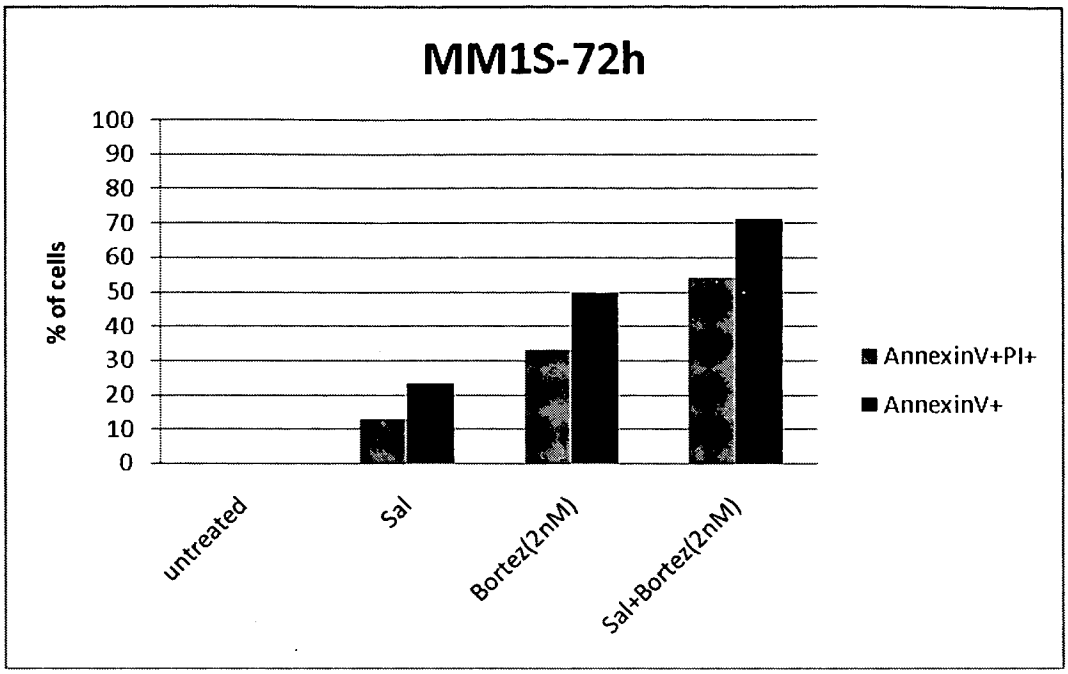


Figure 3

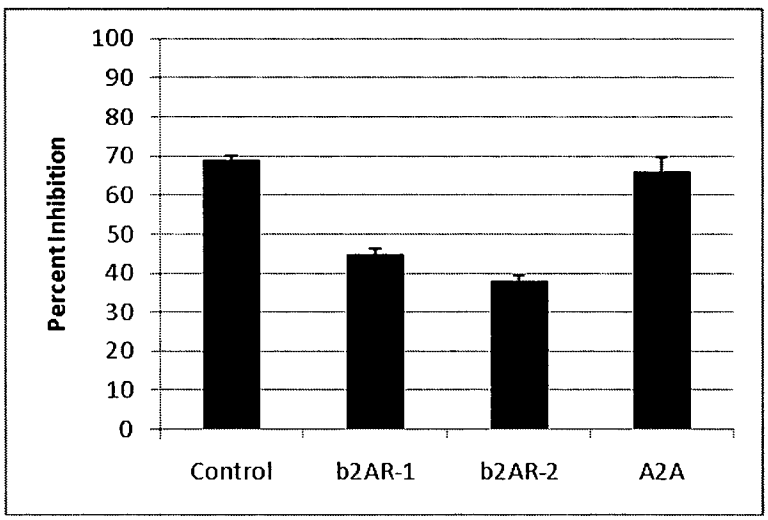


Figure 4

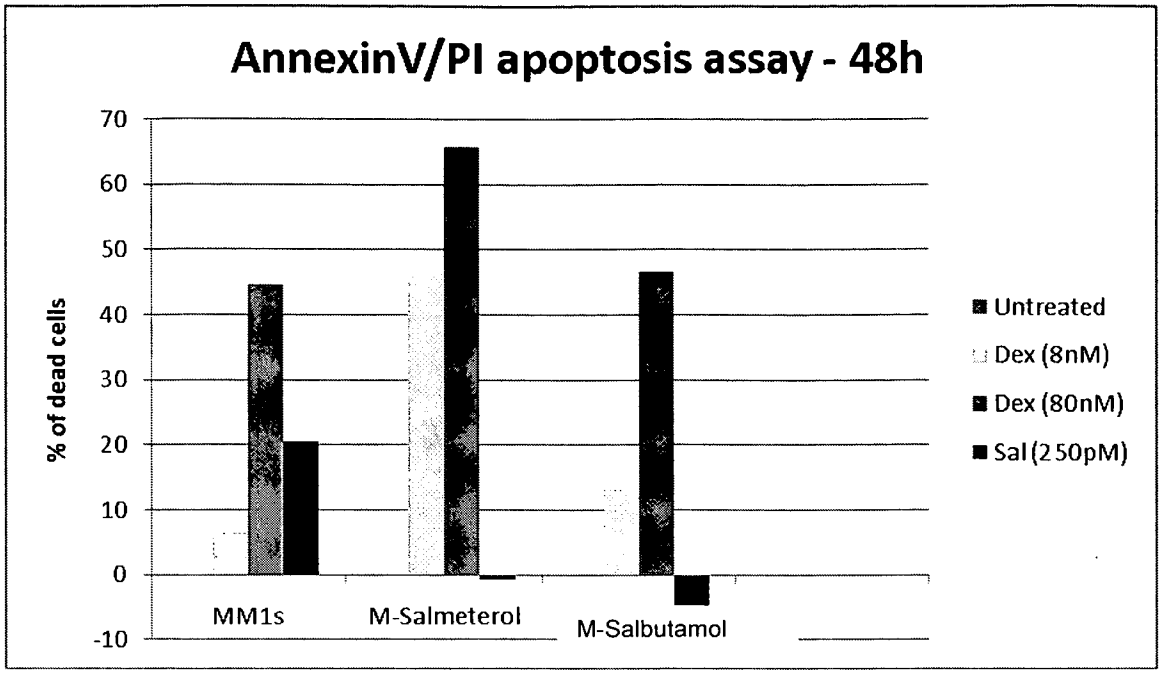


Figure 5

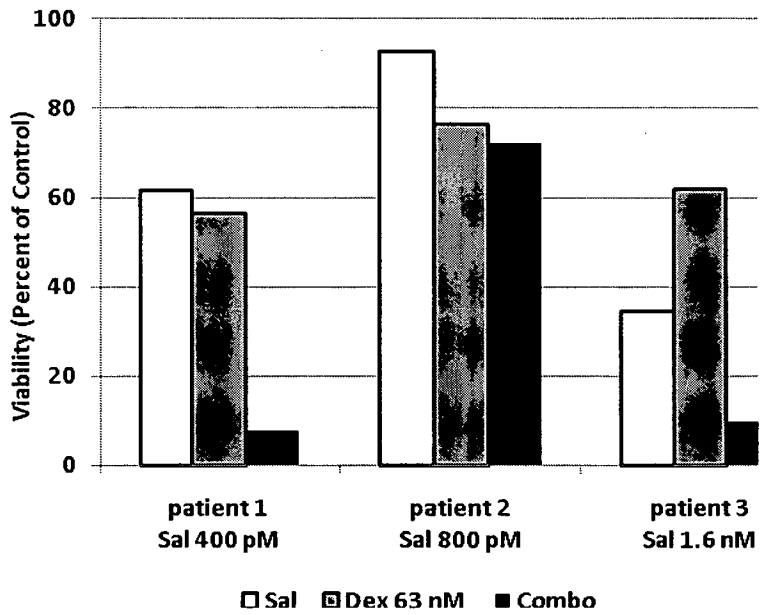


Figure 6

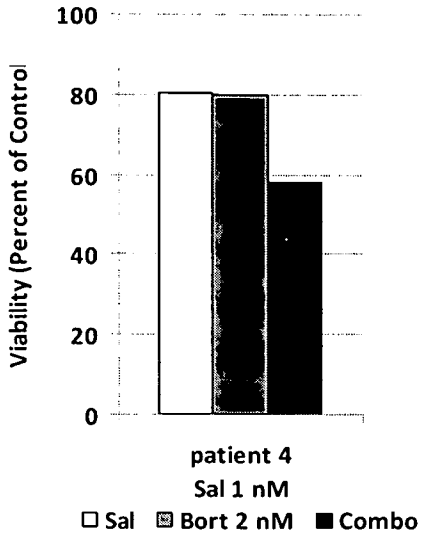


Figure 7

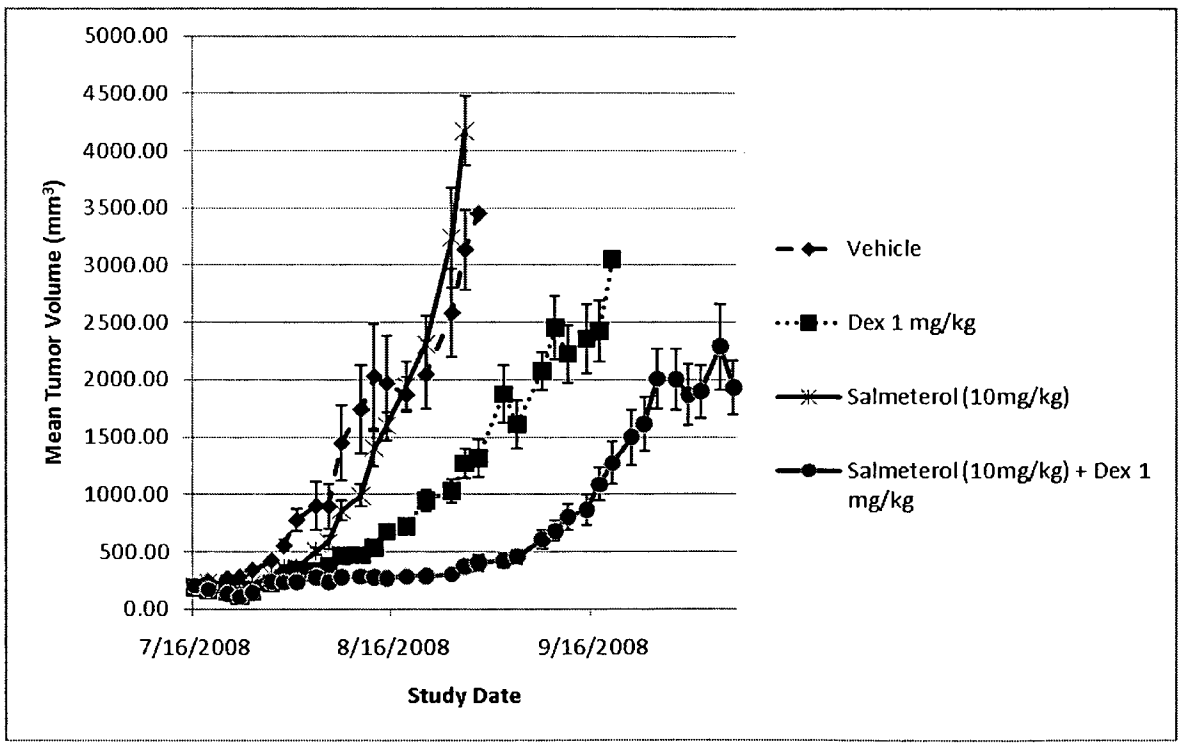


Figure 8

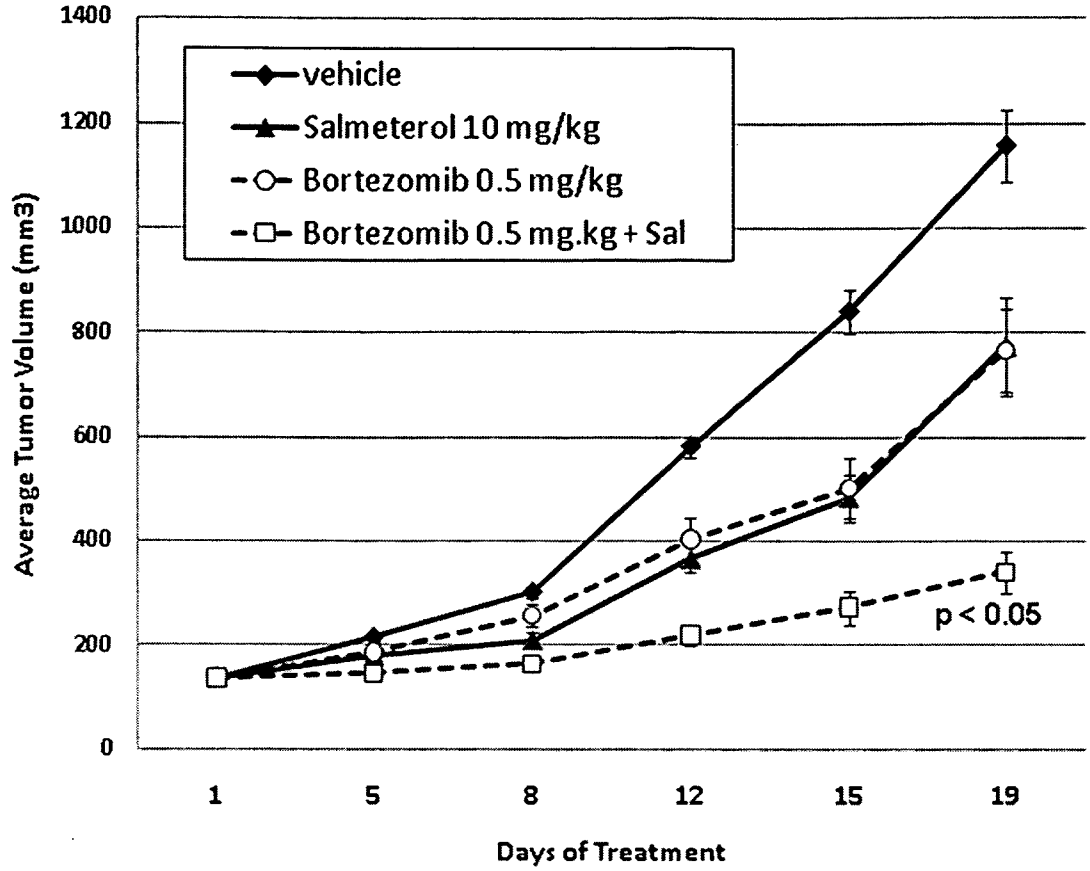


Figure 9

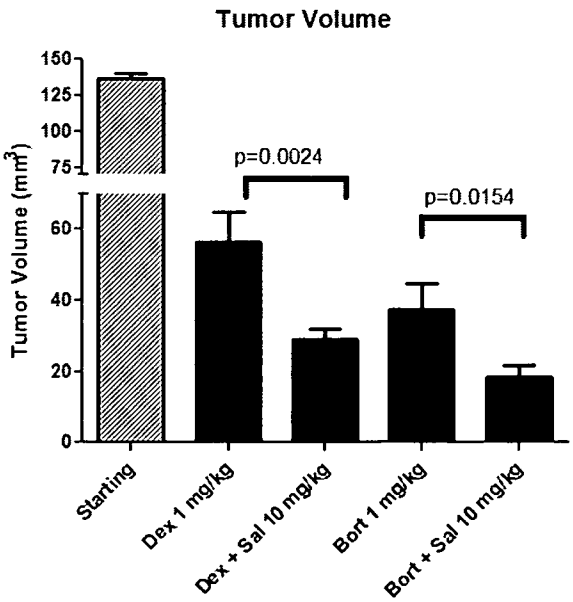


Figure 10

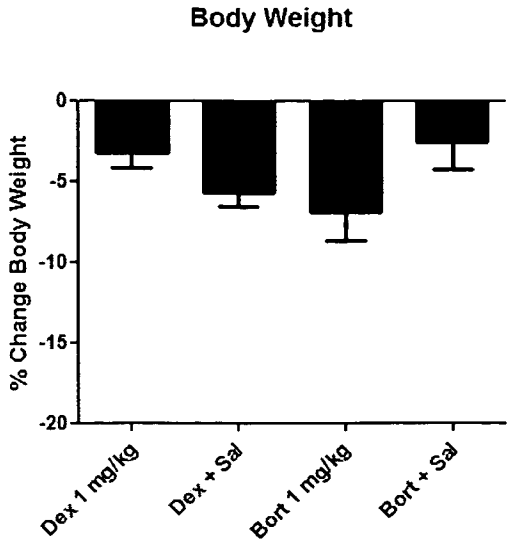

Body Weight
% Change Body Weight
0
-5
-10
-15
-20
Dex 1 mg/kg
Dex + Sal
Bort 1 mg/kg
Bort + Sal

Figure 11