metaproterenol, pirbuterol, salbutamol, salmefamol, salmeterol, terbutaline, vilanterol, and the like Typically, the β_2-adrenergic receptor agonist will be administered in an amount sufficient to provide from about 0.05-500 μg per dose.

In one embodiment, compounds of the invention are administered in combination with an advanced glycation end product (AGE) breaker, examples of which include, by way of illustration and not limitation, alagebrium (or ALT-711), and TRC4149.

In another embodiment, compounds of the invention are administered in combination with an aldosterone antagonist, representative examples of which include, but are not limited to, eplerenone, spironolactone, and combinations thereof. Typically, the aldosterone antagonist will be administered in an amount sufficient to provide from about 5-300 mg per day.

In one embodiment, compounds of the invention are administered in combination with an aminopeptidase N or dipeptidyl peptidase III inhibitor, examples of which include, by way of illustration and not limitation, bestatin and PC18 (2-amino-4-methylsulfonyl butane thiol, methionine thiol).

Compounds of the invention can also be administered in combination with an angiotensin-converting enzyme (ACE) inhibitor. Representative ACE inhibitors include, but are not limited to, accupril, alacepril, benazepril, benazeprilat, captopril, ceranapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, moexipril, monopril, ~~moveltopril~~moveltipril, pentopril, perindopril, quinapril, quinaprilat, ramipril, ramiprilat, saralasin acetate, spirapril, temocapril, trandolapril, zofenopril, and combinations thereof. In a particular embodiment, the ACE inhibitor is selected from: benazepril, captopril, enalapril, lisinopril, ramipril, and combinations thereof. Typically, the ACE inhibitor will be administered in an amount sufficient to provide from about 1-150 mg per day.

In another embodiment, compounds of the invention are administered in combination with a dual-acting angiotensin-converting enzyme/neprilysin (ACE/NEP) inhibitor, examples of which include, but are not limited to: AVE-0848 (*(4S,7S,12bR)*-7-[3-methyl-2*(S)*-sulfanylbutyramido]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]-benzazepine-4-carboxylic acid); AVE-7688 (ilepatril) and its parent compound; BMS-182657 (2-[2-oxo-3*(S)*-[3-phenyl-2*(S)*-sulfanylpropionamido]-2,3,4,5-tetrahydro-1H-1-benzazepin-1-yl]acetic acid); CGS-35601 (N-[1-[4-methyl-2*(S)*-sulfanylpentanamido]cyclopentylcarbonyl]-L-tryptophan); fasidotril; fasidotrilate;

combination with antidiarrheal treatments. Representative treatment options include, but are not limited to, oral rehydration solutions (ORS), loperamide, diphenoxylate, and bismuth ~~sabsalicylate~~ subsalicylate.

In yet another embodiment, a compound of the invention is administered in combination with an anti-glaucoma agent. Representative anti-glaucoma agents include, but are not limited to: α-adrenergic agonists such as brimonidine; β_1-adrenergic receptor antagonists; topical β_1-blockers such as betaxolol, levobunolol, and timolol; carbonic anhydrase inhibitors such as acetazolamide, brinzolamide, or dorzolamide; cholinergic agonists such as cevimeline and DMXB-anabaseine; epinephrine compounds; miotics such as pilocarpine; and prostaglandin analogs.

In yet another embodiment, compounds of the invention are administered in combination with an anti-lipid agent. Representative anti-lipid agents include, but are not limited to: cholesteryl ester transfer protein inhibitors (CETPs) such as anacetrapib, dalcetrapib, and torcetrapib; statins such as atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin; and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with an anti-thrombotic agent. Representative anti-thrombotic agents include, but are not limited to: aspirin; anti-platelet agents such as clopidogrel, prasugrel, and ticlopidine; heparin, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with an AT_1 receptor antagonist, also known as angiotensin II type 1 receptor blockers (ARBs). Representative ARBs include, but are not limited to, abitesartan, azilsartan (e.g., azilsartan medoxomil), benzyllosartan, candesartan, candesartan cilexetil, elisartan, embusartan, enoltasosartan, eprosartan, EXP3174, fonsartan, forasartan, glycyllosartan, irbesartan, isoteoline, losartan, medoximil, milfasartan, olmesartan (e.g., olmesartan medoxomil), opomisartan, pratosartan, ripisartan, saprisartan, saralasin, sarmesin, TAK-591, tasosartan, telmisartan, valsartan, zolasartan, and combinations thereof. In a particular embodiment, the ARB is selected from azilsartan medoxomil, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan medoxomil, ~~irbesartan,~~ saprisartan, tasosartan, telmisartan, valsartan, and combinations thereof. Exemplary salts and/or prodrugs include candesartan cilexetil, eprosartan mesylate, losartan potassium salt, and olmesartan medoxomil. Typically, the ARB will be administered in an amount sufficient to provide from about 4-600 mg per dose, with exemplary daily dosages ranging from 20-320 mg per

inhibitors such as acetazolamide and dichlorphenamide; loop diuretics, which include sulfonamide derivatives such as acetazolamide, ambuside, ~~azosernide~~azosemide, bumetanide, butazolamide, chloraminophenamide, clofenamide, clopamide, clorexolone, disulfamide, ~~ethoxolamide~~ethoxzolamide, furosemide, mefruside, methazolamide, piretanide, torsemide, tripamide, and xipamide, as well as non-sulfonamide diuretics such as ethacrynic acid and other phenoxyacetic acid compounds such as tienilic acid, indacrinone and quincarbate; osmotic diuretics such as mannitol; potassium-sparing diuretics, which include aldosterone antagonists such as spironolactone, and Na^+ channel inhibitors such as amiloride and triamterene; thiazide and thiazide-like diuretics such as althiazide, bendroflumethiazide, benzylhydrochlorothiazide, benzthiazide, buthiazide, chlorthalidone, chlorothiazide, cyclopenthiazide, cyclothiazide, epithiazide, ethiazide, fenquizone, flumethiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, methylclothiazide, meticrane, metolazone, paraflutizide, polythiazide, quinethazone, teclothiazide, and trichloromethiazide; and combinations thereof. In a particular embodiment, the diuretic is selected from amiloride, bumetanide, chlorothiazide, chlorthalidone, dichlorphenamide, ethacrynic acid, furosemide, hydrochlorothiazide, hydroflumethiazide, indapamide, methylclothiazide, metolazone, torsemide, triamterene, and combinations thereof. The diuretic will be administered in an amount sufficient to provide from about 5-50 mg per day, more typically 6-25 mg per day, with common dosages being 6.25 mg, 12.5 mg or 25 mg per day.

Compounds of the invention may also be administered in combination with an endothelin converting enzyme (ECE) inhibitor, examples of which include, but are not limited to, phosphoramidon, CGS 26303, and combinations thereof.

In a particular embodiment, compounds of the invention are administered in combination with an endothelin receptor antagonist. Representative endothelin receptor antagonists include, but are not limited to: selective endothelin receptor antagonists that affect endothelin A receptors, such as avosentan, ambrisentan, atrasentan, BQ-123, clazosentan, darusentan, sitaxentan, and zibotentan; and dual endothelin receptor antagonists that affect both endothelin A and B receptors, such as bosentan, macitentan, tezosentan~~)~~.

In yet another embodiment, a compound of the invention is administered in combination with one or more HMG-CoA reductase inhibitors, which are also known as statins. Representative statins include, but are not limited to, atorvastatin, fluvastatin,

and molsidomine.

In yet another embodiment, compounds of the invention are administered in combination with a non-steroidal anti-inflammatory agent (NSAID). Representative NSAIDs include, but are not limited to: acemetacin, acetyl salicylic acid, alclofenac, alminoprofen, amfenac, amiprilose, ~~amoxiprin~~aloxiprin, anirolac, apazone, azapropazone, benorilate, benoxaprofen, bezpiperylon, broperamole, bucloxic acid, carprofen, clidanac, diclofenac, diflunisal, diftalone, enolicam, etodolac, etoricoxib, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, flufenamic acid, flufenisal, fluprofen, flurbiprofen, furofenac, ibufenac, ibuprofen, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketorolac, lofemizole, lornoxicam, meclofenamate, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, miroprofen, mofebutazone, nabumetone, naproxen, niflumic acid, oxaprozin, oxpinac, oxyphenbutazone, phenylbutazone, piroxicam, pirprofen, pranoprofen, salsalate, sudoxicam, sulfasalazine, sulindac, suprofen, tenoxicam, tiopinac, tiaprofenic acid, tioxaprofen, tolfenamic acid, tolmetin, triflumidate, zidometacin, zomepirac, and combinations thereof. In a particular embodiment, the NSAID is selected from etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, naproxen, oxaprozin, piroxicam, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with an N-methyl d-aspartate (NMDA) receptor antagonist, examples of which include, by way of illustration and not limitation, including amantadine, dextromethorphan, dextropropoxyphene, ketamine, ketobemidone, memantine, methadone, and so forth.

In still another embodiment, compounds of the invention are administered in combination with an opioid receptor agonist (also referred to as opioid analgesics). Representative opioid receptor agonists include, but are not limited to: buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levallorphan, levorphanol, meperidine, methadone, morphine, nalbuphine, nalmefene, nalorphine, naloxone, naltrexone, nalorphine, oxycodone, oxymorphone, pentazocine, propoxyphene, tramadol, and combinations thereof. In certain embodiments, the opioid receptor agonist is selected from codeine, dihydrocodeine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, tramadol, and combinations thereof.

In a particular embodiment, compounds of the invention are administered in combination with a phosphodiesterase (PDE) inhibitor, particularly a PDE-V inhibitor. Representative PDE-V inhibitors include, but are not limited to, avanafil, lodenafil,

mirodenafil, sildenafil (Revatio®), tadalafil (Adcirca®), vardenafil (Levitra®), and udenafil.

In another embodiment, compounds of the invention are administered in combination with a prostaglandin analog (also referred to as prostanoids or prostacyclin analogs). Representative prostaglandin analogs include, but are not limited to, beraprost sodium, bimatoprost, epoprostenol, iloprost, latanoprost, tafluprost, travoprost, and treprostinil, with bimatoprost, latanoprost, and tafluprost being of particular interest.

In yet another embodiment, compounds of the invention are administered in combination with a prostaglandin receptor agonist, examples of which include, but are not limited to, bimatoprost, latanoprost, travoprost, and so forth.

Compounds of the invention may also be administered in combination with a renin inhibitor, examples of which include, but are not limited to, aliskiren, enalkiren, remikiren, and combinations thereof.

In another embodiment, compounds of the invention are administered in combination with a selective serotonin reuptake inhibitor (SSRI). Representative SSRIs include, but are not limited to: citalopram and the citalopram metabolite desmethylcitalopram, dapoxetine, escitalopram (e.g., escitalopram oxalate), fluoxetine and the fluoxetine desmethyl metabolite norfluoxetine, fluvoxamine (e.g., fluvoxamine maleate), paroxetine, sertraline and the sertraline metabolite demethylsertraline, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with a 5-HT_{1D} serotonin receptor agonist, examples of which include, by way of illustration and not limitation, triptans such as almotriptan, avitriptan, eletriptan, frovatriptan, naratriptan rizatriptan, sumatriptan, and zolmitriptan.

In one embodiment, compounds of the invention are administered in combination with a sodium channel blocker, examples of which include, by way of illustration and not limitation, carbamazepine, fosphenytoin, ~~lamotrigine~~lamotrigine, lidocaine, mexiletine, oxcarbazepine, phenytoin, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with a soluble guanylate cyclase stimulator or activator, examples of which include, but are not limited to ataciguat, riociguat, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with a tricyclic antidepressant (TCA), examples of which include, by way of illustration and not limitation, amitriptyline, amitriptylinoxide, butriptyline, clomipramine,

mL) followed by the addition of 4 M of HCl in dioxane (295.0 µL). The mixture was heated and maintained at 60°C for 4 hours. The mixture was concentrated and purified by preparative HPLC to yield the title compound (10 mg; purity 95%). MS *m/z* $[M+H]^+$ calc'd for $C_{24}H_{28}N_4O_5$, 453.21; found 453.3.

E. *(2S,4S)*-5-Biphenyl-4-yl-2-hydroxymethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)-amino]-pentanoic acid 2-(2-methoxy-ethoxy)-ethyl ester (R^7 = $-(CH_2)_2O(CH_2)_2OCH_3$)

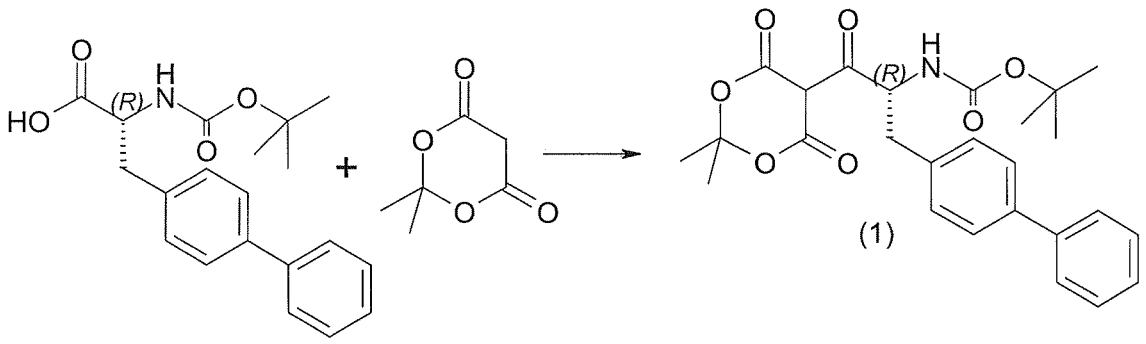
(2S,4S)-5-Biphenyl-4-yl-2-hydroxymethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)-amino]-pentanoic acid (20 mg, 39 µmol, 1.0 eq.) was dissolved in 2-(2-methoxyethoxy)-ethanol, (3 mL) followed by the addition of 4 M of HCl in dioxane (295.0 µL). The mixture was heated and maintained at 60°C for 4 hours. The mixture was concentrated and purified by preparative HPLC to yield the title compound (13 mg; purity 95%). MS *m/z* $[M+H]^+$ calc'd for $C_{26}H_{32}N_4O_6$, 497.23; found 497.6.

F. *(2S,4S)*-5-Biphenyl-4-yl-2-hydroxymethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)-amino]-pentanoic acid 1-cyclohexyloxycarbonyloxy-ethyl ester (R^7 = $-CH(CH_3)OCOO$-cyclohexyl)

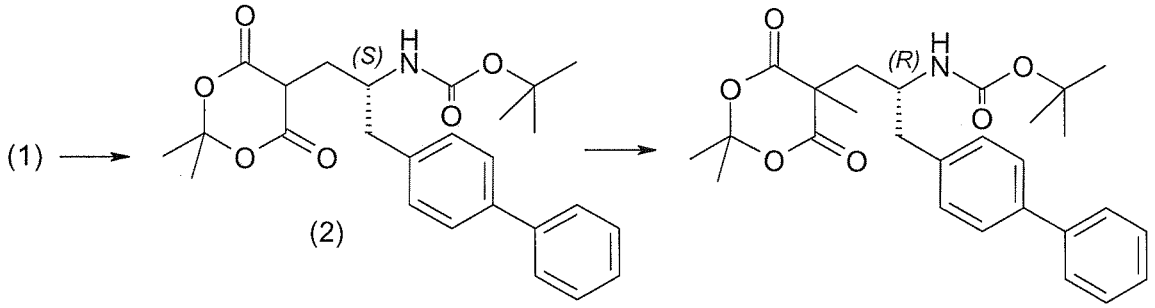
(2S,4S)-5-Biphenyl-4-yl-4-*t*-butoxycarbonylamino-2-hydroxymethyl-pentanoic acid (50 mg, 120 µmol, 1.0 eq.), DMA (1 mL), DIPEA (0.13 mL, 0.75 mmol) and 1-chloroethyl cyclohexyl carbonate (52 mg, 250 µmol, 2.0 eq.) were combined. The reaction vessel was capped and microwaved at 80°C for 2 hours. The mixture was dried under vacuum, dissolved in MeCN (2 mL), and combined with 4 M of HCl in dioxane (500 µL). The resulting mixture was stirred at room temperature for 30 minutes. The precipitate was filtered and discarded, and the filtrate containing the intermediate was concentrated down and submitted to next step. 1,2,3-triazole-4-carboxylic acid (14 mg, 120 µmol, 0.5 eq.) and HATU (48 mg, 120 µmol, 1.0 eq) were dissolved in DMF (1 mL) and the resulting solution was stirred for 5 minutes, followed by the addition of DIPEA (44 µL) and the intermediate from last step. The mixture was stirred for 5 minutes. The reaction was quenched with water and the product dried under vacuum. The product was then purified by preparative HPLC to yield the title compound (4.8 mg, 95% purity). MS *m/z* $[M+H]^+$ calc'd for $C_{30}H_{36}N_4O_7$, 565.26; found 565.4.

Preparation 4

[*(R)*-2-Biphenyl-4-yl-1-(2,2,5-trimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-ethyl]-carbamic acid *t*-butyl Ester



(R)-3-Biphenyl-4-yl-2-*t*-butoxycarbonylamino-propionic acid (5.0 g, 15 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (2.3 g, 16.1 mmol) were combined in DMAP (3.2 g, 26.4 mmol). Additional DMAP (2.0 g, 16.1 mmol) and DCM (50 mL) was added and the resulting mixture was stirred and cooled to -5°C (nitrogen purge) for 30 minutes. EDCI (HCl; (3.1 g, 16.1 mmol) was added in portions, while maintaining the internal temperature below 0°C with stirring. The mixture was then cooled to -5°C, stirred at that temperature for 3 hours, then left at -20°C overnight. The mixture was then washed with 0.4 M aqueous $KHSO_4$ (80 mL) and saturated aqueous NaCl (20 mL), then dried over $MgSO_4$ overnight. The solids were filtered off and the filtrate was then evaporated to dryness to yield crude Compound 1 (3.2 g).



AcOH (8.6 mL) was added to a solution of crude Compound 1 (6.4 g, 14 mmol, 1.0 eq.) in anhydrous MeCN (90 mL) was added AcOH (8.6 mL) at -5°C under nitrogen. The mixture was stirred at -5°C for 30minutes, then sodium borohydride (1.3 g, 34.5 mmol, 2.5 eq.) was added in small portions over 2 hours. After stirring for another 1 hour at -5°C, saturated aqueous NaCl and 1.7 M of NaCl in water (30 mL) was added. The layers were separated and the organic layer was washed with saturated aqueous NaCl (2x30mL) and water (2x30mL), dried under $MgSO_4$, filtered and evaporated, The resulting crude product

ZC. *(2S,4R)*-5-Biphenyl-4-yl-2-hydroxymethyl-2-methyl-4-[(3H-[1,2,3]triazole-4-carbonyl)-amino]-pentanoic acid *(R)*-1-cyclohexyloxycarbonyloxy-ethyl ester (R^4=H; R^7 = -$CH(CH_3)OC(O)O$-cyclohexyl)

ZD. *(2S,4R)*-5-Biphenyl-4-yl-2-hydroxymethyl-2-methyl-4-[(3H-[1,2,3]triazole-4-carbonyl)-amino]-pentanoic acid *(S)*-1-cyclohexyloxycarbonyloxy-ethyl ester (R^4=H; R^7 = -$CH(CH_3)OC(O)O$-cyclohexyl)

1-Chloroethyl cyclohexyl carbonate (240 mg, 1.2 mmol) was added to a mixture of *(2S,4R)*-5-biphenyl-4-yl-4-*t*-butoxycarbonylamino-2-hydroxymethyl-2-methyl-pentanoic acid (300 mg, 726 µmol) and Et_3N (106 µL, 762 µmol) in acetone (10 mL). The mixture was refluxed for 24 hours and the reaction monitored for completion. The individual isomers were separated (~ 1:1) and purified (Interchim reverse phase chromatography column) the solvent was removed under vacuum. MeCN (2 mL) and 4 M HCl in 1,4-dioxane (3 mL, 10 mmol) was added and the resulting mixture was stirred for 30 minutes. The solvent was evaporated under vacuum and the product was azeotroped with toluene (1x) to yield *(2S,4R)*-4-amino-5-biphenyl-4-yl-2-hydroxymethyl-2-methyl-pentanoic acid 1-cyclohexyloxycarbonyloxy-ethyl ester.

1,2,3-Triazole-4-carboxylic acid (45.2 mg, 400 µmol) , DIPEA (209 µL, 1.2 mmol) and HCTU (165 mg, 400 µmol) were combined in DMF (0.2 mL) and stirred for 5 minutes at room temperature. This was then combined with *(2S,4R)*-4-amino-5-biphenyl-4-yl-2-hydroxymethyl-2-methyl-pentanoic acid 1-cyclohexyloxycarbonyloxy-ethyl ester (193 mg, 400 µmol). The resulting mixture was stirred for 15 minutes and the reaction was quenched with AcOH. The products were purified and separated by preparative HPLC, then lyophilized to yield ~~to yield~~ compound ZC (20 mg; purity 95%), MS *m/z* $[M+H]^+$ calc'd for $C_{31}H_{38}N_4O_7$, 579.27; found 579.6, and compound ZD (15 mg; purity 95%), MS *m/z* $[M+H]^+$ calc'd for $C_{31}H_{38}N_4O_7$, 579.27; found 579.6.

ZE. *(2S,4R)*-5-Biphenyl-4-yl-2-hydroxymethyl-2-methyl-4-[(1-phosphonooxymethyl-1H-[1,2,3]triazole-4-carbonyl)-amino]-pentanoic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester (R^4= -$CH_2OP(O)(OH)_2$; R^7 = -CH_2-5-methyl-[1,3]dioxol-2-one)

To a solution of *(2S,4R)*-5-biphenyl-4-yl-2-hydroxymethyl-2-methyl-4-[(1H-[1,2,3]triazole-4-carbonyl)-amino]-pentanoic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester (200 mg, 0.4 mmol) in DMF (1.2 mL, 15.4 mmol) was added K_2CO_3 (58.4 mg, 0.423 mmol) and phosphoric acid di-*t*-butyl ester chloromethyl ester (99.4 mg, 384 µmol). The resulting mixture was stirred at room temperature until the reaction was complete