DUAL-ACTING ANTIHYPERTENSIVE AGENTS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to novel compounds having angiotensin II type 1 (AT_1) receptor antagonist activity and neprilysin-inhibition activity. The invention also relates to pharmaceutical compositions comprising such compounds, processes and intermediates for preparing such compounds and methods of using such compounds to treat diseases such as hypertension.

STATE OF THE ART

The aim of antihypertensive therapy is to lower blood pressure and prevent hypertension-related complications such as myocardial infarction, stroke, and renal disease. For patients with uncomplicated hypertension (that is, no risk factors, target organ damage, or cardiovascular disease), it is hoped that reducing blood pressure will prevent development of cardiovascular and renal comorbidities, conditions that exist at the same time as the primary condition in the same patient. For those patients with existing risk factors or comorbidities, the therapeutic target is the slowing of comorbid disease progression and reduced mortality.

Physicians generally prescribe pharmacological therapies for patients whose blood pressure cannot be adequately controlled by dietary and/or lifestyle modifications. Commonly used therapeutic classes act to promote diuresis, adrenergic inhibition, or vasodilation. A combination of drugs is often prescribed, depending upon what comorbidities are present.

There are five common drug classes used to treat hypertension: diuretics, which include thiazide and thiazide-like diuretics such as hydrochlorothiazide, loop diuretics such as furosemide, and potassium-sparing diuretics such as triamterene; β_1 adrenergic receptor blockers such as metoprolol succinate and carvedilol; calcium channel blockers such as amlodipine; angiotensin-converting enzyme (ACE) inhibitors such as captopril, benazepril, enalapril, enalaprilat, lisinopril, quinapril, and ramipril; and AT_1 receptor antagonists, also known as angiotensin II type 1 receptor blockers (ARBs), such as candesartan cilexetil,

eprosartan, irbesartan, losartan, olmesartan medoxomil, telmisartan, and valsartan. Combinations of these drugs are also administered, for example, a calcium channel blocker (amlodipine) and an ACE inhibitor (benazepril), or a diuretic (hydrochlorothiazide) and an ACE inhibitor (enalapril). All of these drugs, when used appropriately, are effective in the treatment of hypertension. Nevertheless, both efficacy and tolerability should be further improved in new drugs targeting hypertension. Despite the availability of many treatment options, the recent National Health And Nutrition Examination Survey (NHANES) demonstrated that only about 50% of all treated patients with hypertension achieve adequate blood pressure control. Furthermore, poor patient compliance due to tolerability issues with available treatments further reduces treatment success.

In addition, each of the major classes of antihypertensive agents have some drawbacks. Diuretics can adversely affect lipid and glucose metabolism, and are associated with other side effects, including orthostatic hypotension, hypokalemia, and hyperuricemia. Beta blockers can cause fatigue, insomnia, and impotence; and some beta blockers can also cause reduced cardiac output and bradycardia, which may be undesirable in some patient groups. Calcium channel blockers are widely used but it is debatable as to how effectively these drugs reduce fatal and nonfatal cardiac events relative to other drug classes. ACE inhibitors can cause coughing, and rarer side effects include rash, angioedema, hyperkalemia, and functional renal failure. AT_1 receptor antagonists are equally effective as ACE inhibitors but without the high prevalence of cough.

Neprilysin (neutral endopeptidase, EC 3.4.24.11) (NEP), is an endothelial membrane bound Zn^{2+}metallopeptidase found in many tissues, including the brain, kidney, lungs, gastrointestinal tract, heart, and peripheral vasculature. NEP is responsible for the degradation and inactivation of a number of vasoactive peptides, such as circulating bradykinin and angiotensin peptides, as well as the natriuretic peptides, the latter of which have several effects including vasodilation and diuresis. Thus, NEP plays an important role in blood pressure homeostasis. NEP inhibitors have been studied as potential therapeutics, and include thiorphan, candoxatril, and candoxatrilat. In addition, compounds have also been designed that inhibit both NEP and ACE, and include omapatrilat, gempatrilat, and sampatrilat. Referred to as vasopeptidase inhibitors, this class of compounds are described in Robl et al. (1999) *Exp. Opin. Ther. Patents* 9(12): 1665-1677.

There may be an opportunity to increase anti-hypertensive efficacy when

combining AT_1 receptor antagonism and NEP inhibition, as evidenced by AT_1 receptor antagonist/NEP inhibitor combinations described in WO 9213564 to Darrow et al (Schering Corporation); US20030144215 to Ksander et al.; Pu et al., Abstract presented at the Canadian Cardiovascular Congress (October 2004); and Gardiner et al. (2006) *JPET* 319:340-348; and WO 2007/045663 (Novartis AG) to Glasspool et al.

Recently, WO 2007/056546 (Novartis AG) to Feng et al. has described complexes of an AT_1 receptor antagonist and a NEP inhibitor, where an AT_1 receptor antagonist compound is non-covalently bound to a NEP inhibitor compound, or where the antagonist compound is linked to the inhibitor compound by a cation.

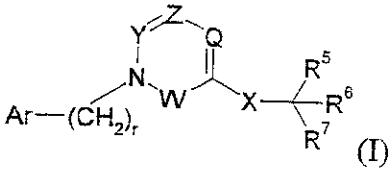
In spite of the advances in the art, there remains a need for a highly efficacious monotherapy with multiple mechanisms of action leading to levels of blood pressure control that can currently only be achieved with combination therapy. Thus, although various hypertensive agents are known, and administered in various combinations, it would be highly desirable to provide compounds having both AT_1 receptor antagonist activity and NEP inhibition activity in the same molecule. Compounds possessing both of these activities are expected to be particularly useful as therapeutic agents since they would exhibit antihypertensive activity through two independent modes of action while having single molecule pharmacokinetics.

In addition, such dual-acting compounds are also expected to have utility to treat a variety of other diseases that can be treated by antagonizing the AT_1 receptor and/or inhibiting the NEP enzyme.

SUMMARY

The present disclosure provides novel compounds that have been found to possess AT_1 receptor antagonist activity and neprilysin (NEP) enzyme inhibition activity. Accordingly, compounds of the disclosure are expected to be useful and advantageous as therapeutic agents for treating conditions such as hypertension and heart failure.

In a first aspect, there is provided a compound of formula I:

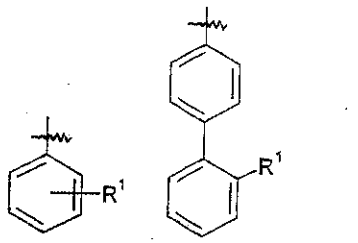


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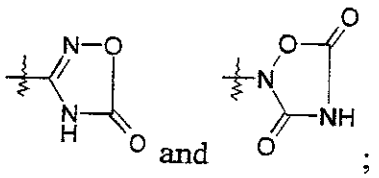
wherein:

r is 0;

Ar is selected from:

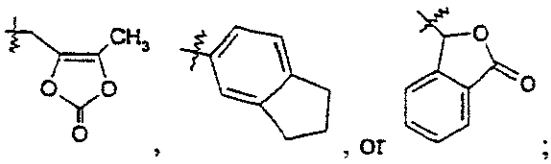


R^1 is selected from -$COOR^{1a}$, -$NHSO_2R^{1b}$, -SO_2NHR^{1d}, -SO_2OH, -$C(O)NH$-SO_2R^{1c}, -$P(O)(OH)_2$, -CN, -O-$CH(R^{1e})$-COOH, tetrazol-5-yl,



and ;

R^{1a} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(C_{1-4}alkyl)OC(O)R^{1aa}$, -$C_{0-6}$alkylenemorpholine,



, , or ;

R^{1aa} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -$NR^{1ab}R^{1ac}$, or -$CH(NH_2)CH_2COOCH_3$; R^{1ab} and R^{1ac} are independently selected from H, -C_{1-6}alkyl, and benzyl, or are taken together as -$(CH_2)_{3-6}$-; R^{1b} is R^{1c} or -$NHC(O)R^{1c}$; R^{1c} is -C_{1-6}alkyl, -C_{0-6}alkylene-O-R^{1ca}, -C_{1-5}alkylene-$NR^{1cb}R^{1cc}$, -C_{0-4}alkylenearyl or -C_{0-4}alkyleneheteroaryl; R^{1ca} is H, -C_{1-6}alkyl, or -C_{1-6}alkylene-O-C_{1-6}alkyl; R^{1cb} and R^{1cc} are independently selected from H and -C_{1-6}alkyl, or are taken together as -$(CH_2)_2$-O-$(CH_2)_2$- or -$(CH_2)_2$-N[$C(O)CH_3$]-$(CH_2)_2$-; R^{1d} is H, R^{1c}, -$C(O)R^{1c}$, or -$C(O)NHR^{1c}$; R^{1e} is -C_{1-4}alkyl or aryl;

Y is -$C(R^3)$-, Z is -N-, Q is -$C(R^2)$- and W is a bond; Y is -N-, Z is -$C(R^3)$-, Q is -$C(R^2)$- and W is a bond; Y is -$C(R^3)$-, Z is -N-, Q is -N- and W is a bond; Y is -$C(R^3)$-, Z is -CH-, Q is -N- and W is a bond; or Y is -$C(R^3)$-, Z is -CH-, Q is -$C(R^2)$- and W is -C(O)-;

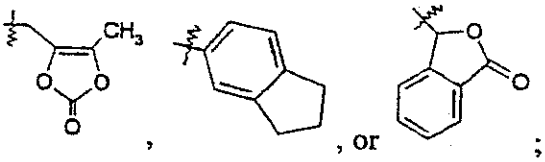
R^2 is selected from H, halo, -NO_2, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{3-6}cycloalkyl, -CN, -$C(O)R^{2a}$, -C_{0-5}alkylene-OR^{2b}, -C_{0-5}alkylene-$NR^{2c}R^{2d}$, -C_{0-3}alkylenearyl, and -C_{0-3}alkylene-heteroaryl; where R^{2a} is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, -OR^{2b} and -$NR^{2c}R^{2d}$; R^{2b} is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and -C_{0-1}alkylenearyl; and R^{2c} and R^{2d} are independently selected from H, -C_{1-4}alkyl, and -C_{0-1}alkylenearyl;

R^3 is selected from -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{3-10}alkynyl, -C_{0-3}alkylene-C_{3-7}cycloalkyl, -C_{2-3}alkenylene-C_{3-7}cycloalkyl, -C_{2-3}alkynylene-C_{3-7}cycloalkyl, -C_{0-5}alkylene-NR^{3a}-C_{0-5}alkylene-R^{3b}, -C_{0-5}alkylene-O-C_{0-5}alkylene-R^{3b}, -C_{0-5}alkylene-S-C_{1-5}alkylene-R^{3b}, and -C_{0-3}alkylenearyl; where R^{3a} is selected from H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, and -C_{0-3}alkylenearyl; and R^{3b} is selected from H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, and aryl;

X is -C_{1-12}alkylene-, where at least one -CH_2- moiety in the alkylene is replaced with a -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moiety, where R^{4a} is selected from H, -OH, and -C_{1-4}alkyl;

R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, -C_{0-2}alkylene-CHR^{5g}-COOH, -C_{0-3}alkylene-$C(O)NR^{5h}$-CHR^{5i}-COOH, and -C_{0-3}alkylene-S-SR^{5j}; R^{5a} is H or -$C(O)$-R^{5aa}; R^{5aa} is -C_{1-6}alkyl, -C_{0-6}alkylene-C_{3-7}cycloalkyl,

-C_{0-6}alkylenearyl, -C_{0-6}alkyleneheteroaryl, -C_{0-6}alkylenemorpholine, -C_{0-6}alkylenepiperazine-CH_3, -CH[$N(R^{5ab})_2$]-aa where aa is an amino acid side chain, -2-pyrrolidine, -C_{0-6}alkylene-OR^{5ab}, -O-C_{0-6}alkylenearyl, -C_{1-2}alkylene-OC(O)-C_{1-6}alkyl, -C_{1-2}alkylene-OC(O)-C_{0-6}alkylenearyl, or -O-C_{1-2}alkylene-OC(O)O-C_{1-6}alkyl; R^{5ab} is H or -C_{1-6}alkyl; R^{5b} is H, -OH, -OC(O)R^{5ba}, -CH_2COOH, -O-benzyl, -pyridyl, or -OC(S)$NR^{5bb}R^{5bc}$; R^{5ba} is H, -C_{1-6}alkyl, aryl, -OCH_2-aryl, -CH_2O-aryl, or -$NR^{5bb}R^{5bc}$; R^{5bb} and R^{5bc} are independently selected from H and -C_{1-4}alkyl; R^{5c} is H, -C_{1-6}alkyl, or -C(O)-R^{5ca}; R^{5ca} is H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, aryl, or heteroaryl; R^{5d} is H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -$NR^{5da}R^{5db}$, -CH_2SH, or -O-C_{1-6}alkyl; R^{5da} and R^{5db} are independently selected from H and -C_{1-4}alkyl; R^{5e} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(CH_3)$-O-C(O)R^{5ea},



, , or ;

R^{5ea} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -$NR^{5eb}R^{5ec}$, or -$CH(NH_2)CH_2COOCH_3$; R^{5eb} and R^{5ec} are independently selected from H, -C_{1-4}alkyl, and -C_{1-3}alkylenearyl, or are taken together as -$(CH_2)_{3-6}$-; R^{5f} is H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -C_{1-3}alkylene-$NR^{5fa}R^{5fb}$, or -C_{1-3}alkylene(aryl)-C_{0-3}alkylene-$NR^{5fa}R^{5fb}$; R^{5fa} and R^{5fb} are independently selected from H and -C_{1-4}alkyl; R^{5g} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, or -CH_2-O-$(CH_2)_2$-O-CH_3; R^{5h} is H or -C_{1-4}alkyl; R^{5i} is H, -C_{1-4}alkyl, or -C_{0-3}alkylenearyl; and R^{5j} is -C_{1-6}alkyl, aryl, or -$CH_2CH(NH_2)$COOH;

R^6 is selected from -C_{1-6}alkyl, -$CH_2O(CH_2)_2$-O-CH_3, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and

R^7 is H or is taken together with R^6 to form -C_{3-8}cycloalkyl;

wherein:

each -CH_2- group in -$(CH_2)_r$- is optionally substituted with 1 or 2 substituents independently selected from -C_{1-4}alkyl and fluoro;

each ring in Ar and each aryl and heteroaryl in R^{1-3} and R^{5-6} is optionally substituted with 1 to 3 substituents independently selected from -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, -$S(O)_2$-C_{1-4}alkyl, -phenyl, -NO_2, -NH_2, -NH-C_{1-6}alkyl and -$N(C_{1-6}alkyl)_2$, wherein each alkyl, alkenyl and alkynyl is optionally substituted with 1 to 5 fluoro atoms;

each carbon atom in X is optionally substituted with one or more R^{4b} groups and one $-CH_2-$ moiety in X may be replaced with a group selected from $-C_{4-8}$cycloalkylene-, $-CR^{4d}=CH-$, and $-CH=CR^{4d}-$; wherein R^{4b} is selected from $-C_{0-5}$alkylene-$COOR^{4c}$, $-C_{1-6}$alkyl, $-C_{0-1}$alkylene-$CONH_2$, $-C_{1-2}$alkylene-OH, $-C_{0-3}$alkylene-C_{3-7}cycloalkyl, 1H-indol-3-yl, benzyl, and hydroxybenzyl, where R^{4c} is H or $-C_{1-4}$alkyl; and R^{4d} is selected from $-CH_2$-2-thiophene and phenyl;

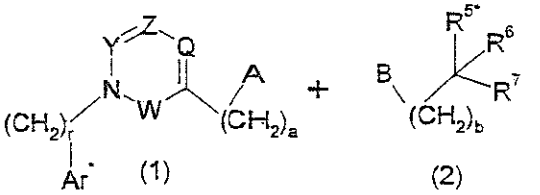
each alkyl and each aryl in R^{1-3}, R^{4a-4d}, and R^{5-6} is optionally substituted with 1 to 7 fluoro atoms;

and pharmaceutically acceptable salts thereof.

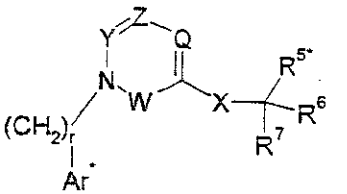
In a second aspect, there is provided a pharmaceutical composition comprising the compound as defined above and a pharmaceutically acceptable carrier.

In a third aspect, there is provided a process for preparing the compound as defined above, comprising:

(a) coupling a compound of formula 1 with a compound of formula 2:



to produce a compound having the formula:

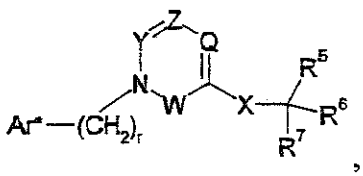
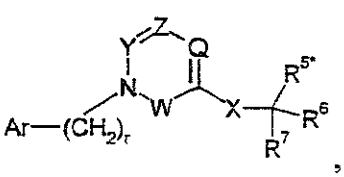
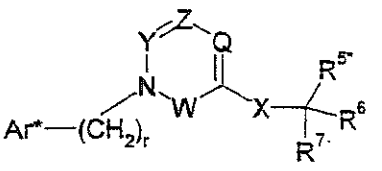


where: A is $-NH_2$ and B is -COOH or A is -COOH and B is $-NH_2$; the sum of a and b is in the range of 0 to 11; Ar* represents Ar-R^{1*}, where R^{1*} is R^1 or a protected form of R^1; and R^{5*} represents R^5 or a protected form of R^5; the carbon atoms in the $-(CH_2)_a$ and $-(CH_2)_b$ groups may be substituted with one or more R^{4b} groups; and one $-CH_2-$ group in the $-(CH_2)_a$ or the $-(CH_2)_b$ group may be replaced with $-C_{4-8}$cycloalkylene-, $-CR^{4d}=CH-$, or $-CH=CR^{4d}-$; and

(b) when R^{1*} is a protected form of R^1 and/or R^{5*} is a protected form of R^5, deprotecting the product of step (a) to produce a compound of formula I.

In a fourth aspect, there is provided a compound prepared by the process as defined above.

In a fifth aspect, there is provided an intermediate useful in the synthesis of the compound as defined above, selected from the group comprising:


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, and

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wherein: Ar* is Ar-R^{1*}; R^{1*} is selected from -C(O)O-P^2, -SO_2O-P^5, -SO_2NH-P^6, -P(O)(O-P^7)$_2$, -OCH(CH_3)-C(O)O-P^2, -OCH(aryl)-C(O)O-P^2, and tetrazol-5-yl-P^4; R^{5*} is selected from -C_{0-3}alkylene-S-P^3, -C_{0-3}alkylene-C(O)NH(O-P^5), -C_{0-3}alkylene-N(O-P^5)-C(O)R^{5d}, -C_{0-1}alkylene-NHC(O)CH_2S-P^3, -NH-C_{0-1}alkylene-P(O)(O-P^7)$_2$, -C_{0-3}alkylene-P(O)(O-P^7)-R^{5e}, -C_{0-2}alkylene-CHR^{5f}-C(O)O-P^2 and -C_{0-3}alkylene-C(O)NR^{5g}-CHR^{5h}-C(O)O-P^2; P^2 is a carboxy-protecting group selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; P^3 is a thiol-protecting group selected from ethers and esters; P^4 is a tetrazole-protecting group selected from trityl and diphenylmethyl; P^5 is a hydroxyl-protecting group selected from C_{1-6}alkyl, silyl groups, esters, and arylmethyl; P^6 is a sulfonamide-protecting group selected from *t*-butyl and acyl groups; and P^7 is a phosphate-protecting group selected from C_{1-4}alkyl, aryl, and substituted aryl; Ar, R^{5d}, R^{5e}, R^{5f}, R^{5g} and R^{5h} are as defined in claim 1; and salts thereof.

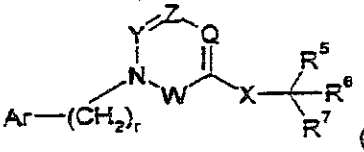
In a sixth aspect, there is provided the use of the compound as defined above for the manufacture of a medicament.

In a seventh aspect, there is provided the use of the compound as defined above for the manufacture of a medicament for treating hypertension or heart failure.

In an eighth aspect, there is provided the use of the compound as defined above for the manufacture of a medicament for antagonizing an angiotensin II type 1 receptor in a mammal.

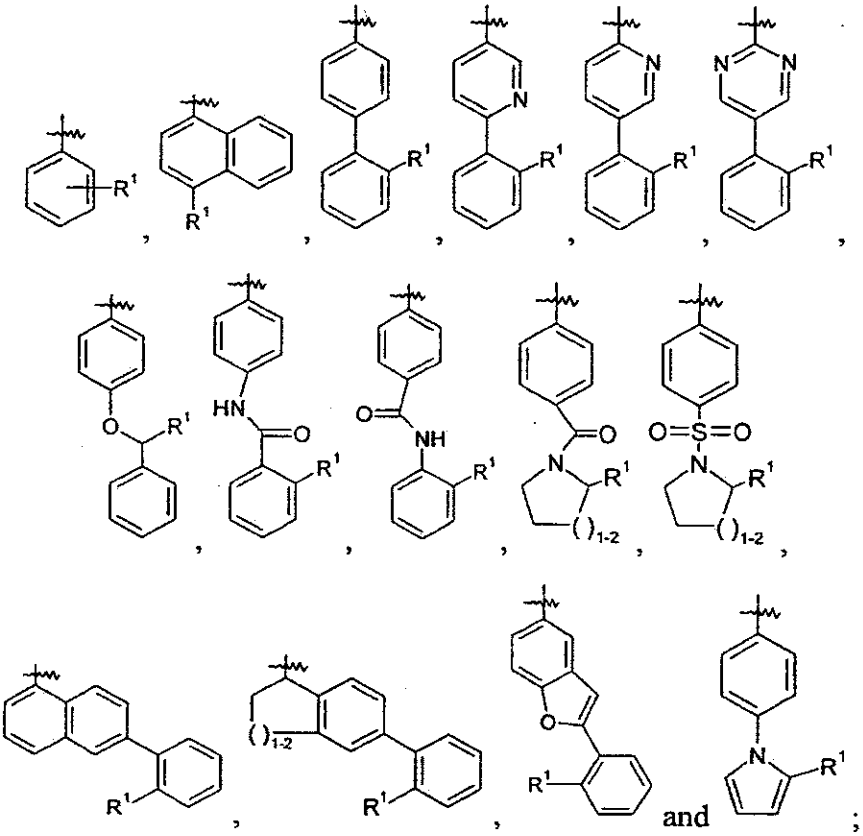
In a ninth aspect, there is provided the use of the compound as defined above for the manufacture of a medicament for inhibiting a neprilysin enzyme in a mammal.

One embodiment of the disclosure is directed to a compound of formula I:

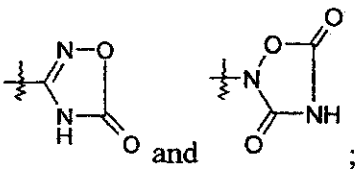

(I)

wherein: r is 0, 1 or 2;

Ar is selected from:

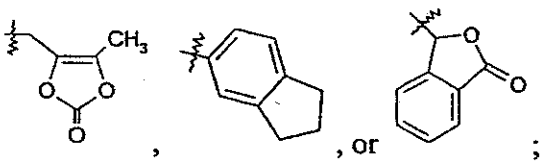


R^1 is selected from $-COOR^{1a}$, $-NHSO_2R^{1b}$, $-SO_2NHR^{1d}$, $-SO_2OH$, $-C(O)NH-SO_2R^{1c}$, $-P(O)(OH)_2$, $-CN$, $-O-CH(R^{1e})-COOH$, tetrazol-5-yl,



;

R^{1a} is H, $-C_{1-6}$alkyl, $-C_{1-3}$alkylenearyl, $-C_{1-3}$alkyleneheteroaryl, $-C_{3-7}$cycloalkyl, $-CH(C_{1-4}alkyl)OC(O)R^{1aa}$, $-C_{0-6}$alkylenemorpholine,



;

R^{1aa} is $-O-C_{1-6}$alkyl, $-O-C_{3-7}$cycloalkyl, $-NR^{1ab}R^{1ac}$, or $-CH(NH_2)CH_2COOCH_3$; R^{1ab} and R^{1ac} are independently selected from H, $-C_{1-6}$alkyl, and benzyl, or are taken together as $-(CH_2)_{3-6}-$; R^{1b} is R^{1c} or $-NHC(O)R^{1c}$; R^{1c} is $-C_{1-6}$alkyl, $-C_{0-6}$alkylene-O-R^{1ca}, $-C_{1-5}$alkylene-$NR^{1cb}R^{1cc}$, $-C_{0-4}$alkylenearyl or $-C_{0-4}$alkyleneheteroaryl; R^{1ca} is H, $-C_{1-6}$alkyl, or $-C_{1-6}$alkylene-O-C_{1-6}alkyl; R^{1cb} and R^{1cc} are independently selected from H and $-C_{1-6}$alkyl, or are taken together as $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-N[C(O)CH_3]-(CH_2)_2-$; R^{1d} is H, R^{1c}, -

$C(O)R^{1c}$, or $-C(O)NHR^{1c}$; R^{1e} is $-C_{1-4}$alkyl or aryl;

Y is $-C(R^3)-$, Z is -N-, Q is $-C(R^2)-$ and W is a bond; Y is -N-, Z is $-C(R^3)-$, Q is $-C(R^2)-$ and W is a bond; Y is $-C(R^3)-$, Z is -N-, Q is -N- and W is a bond; Y is $-C(R^3)-$, Z is -CH-, Q is -N- and W is a bond; or Y is $-C(R^3)-$, Z is -CH-, Q is $-C(R^2)-$ and W is -C(O)-;

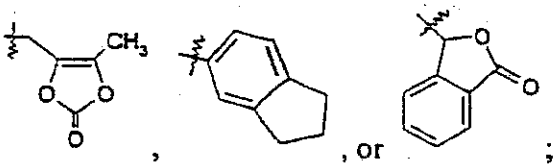
R^2 is selected from H, halo, $-NO_2$, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{3-6}$cycloalkyl, -CN, $-C(O)R^{2a}$, $-C_{0-5}$alkylene-OR^{2b}, $-C_{0-5}$alkylene-$NR^{2c}R^{2d}$, $-C_{0-3}$alkylenearyl, and $-C_{0-3}$alkyleneheteroaryl; where R^{2a} is selected from H, $-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-OR^{2b}$ and $-NR^{2c}R^{2d}$; R^{2b} is selected from H, $-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, and $-C_{0-1}$alkylenearyl; and R^{2c} and R^{2d} are independently selected from H, $-C_{1-4}$alkyl, and $-C_{0-1}$alkylenearyl;

R^3 is selected from $-C_{1-10}$alkyl, $-C_{2-10}$alkenyl, $-C_{3-10}$alkynyl, $-C_{0-3}$alkylene-C_{3-7}cycloalkyl, $-C_{2-3}$alkenylene-C_{3-7}cycloalkyl, $-C_{2-3}$alkynylene-C_{3-7}cycloalkyl, $-C_{0-5}$alkylene-NR^{3a}-C_{0-5}alkylene-R^{3b}, $-C_{0-5}$alkylene-O-C_{0-5}alkylene-R^{3b}, $-C_{0-5}$alkylene-S-C_{1-5}alkylene-R^{3b}, and $-C_{0-3}$alkylenearyl; where R^{3a} is selected from H, $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, and $-C_{0-3}$alkylenearyl; and R^{3b} is selected from H, $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, $-C_{2-4}$alkenyl, $-C_{2-4}$alkynyl, and aryl;

X is $-C_{1-12}$alkylene-, where at least one $-CH_2-$ moiety in the alkylene is replaced with a $-NR^{4a}-C(O)-$ or $-C(O)-NR^{4a}-$ moiety, where R^{4a} is selected from H, -OH, and $-C_{1-4}$alkyl;

R^5 is selected from $-C_{0-3}$alkylene-SR^{5a}, $-C_{0-3}$alkylene-$C(O)NR^{5b}R^{5c}$, $-C_{0-3}$alkylene-$NR^{5b}-C(O)R^{5d}$, $-NH-C_{0-1}$alkylene-$P(O)(OR^{5e})_2$, $-C_{0-3}$alkylene-$P(O)OR^{5e}R^{5f}$, $-C_{0-2}$alkylene-CHR^{5g}-COOH, $-C_{0-3}$alkylene-$C(O)NR^{5h}-CHR^{5i}$-COOH, and $-C_{0-3}$alkylene-S-SR^{5j}; R^{5a} is H or $-C(O)-R^{5aa}$; R^{5aa} is $-C_{1-6}$alkyl, $-C_{0-6}$alkylene-C_{3-7}cycloalkyl, $-C_{0-6}$alkylenearyl, $-C_{0-6}$alkyleneheteroaryl, $-C_{0-6}$alkylenemorpholine, $-C_{0-6}$alkylenepiperazine-CH_3, $-CH[N(R^{5ab})_2]$-aa where aa is an amino acid side chain, -2-pyrrolidine, $-C_{0-6}$alkylene-OR^{5ab}, -O-C_{0-6}alkylenearyl, $-C_{1-2}$alkylene-$OC(O)-C_{1-6}$alkyl, $-C_{1-2}$alkylene-$OC(O)-C_{0-6}$alkylenearyl, or -O-C_{1-2}alkylene-$OC(O)O-C_{1-6}$alkyl; R^{5ab} is independently H or $-C_{1-6}$alkyl; R^{5b} is H, -OH, $-OC(O)R^{5ba}$, $-CH_2COOH$, -O-benzyl, -pyridyl, or $-OC(S)NR^{5bb}R^{5bc}$; R^{5ba} is H, $-C_{1-6}$alkyl, aryl, $-OCH_2$-aryl, $-CH_2O$-aryl, or $-NR^{5bb}R^{5bc}$; R^{5bb} and R^{5bc} are independently selected from H and $-C_{1-4}$alkyl; R^{5c} is H, $-C_{1-6}$alkyl, or $-C(O)-R^{5ca}$; R^{5ca} is H, $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, aryl, or heteroaryl; R^{5d} is H, $-C_{1-4}$alkyl, $-C_{0-3}$alkylenearyl, $-NR^{5da}R^{5db}$, $-CH_2SH$, or -O-C_{1-6}alkyl; R^{5da} and R^{5db} are independently selected from H and $-C_{1-4}$alkyl; R^{5e} is H, $-C_{1-6}$alkyl, $-C_{1-3}$alkylenearyl,

-C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(CH_3)$-O-$C(O)R^{5ea}$,



; R^{5ea} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, $-NR^{5eb}R^{5ec}$, or $-CH(NH_2)CH_2COOCH_3$; R^{5eb} and R^{5ec} are independently selected from H, -C_{1-4}alkyl, and -C_{1-3}alkylenearyl, or are taken together as -$(CH_2)_{3-6}$-; R^{5f} is H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -C_{1-3}alkylene-$NR^{5fa}R^{5fb}$, or -C_{1-3}alkylene(aryl)-C_{0-3}alkylene-$NR^{5fa}R^{5fb}$; R^{5fa} and R^{5fb} are independently selected from H and -C_{1-4}alkyl; R^{5g} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, or $-CH_2$-O-$(CH_2)_2$-O-CH_3; R^{5h} is H or -C_{1-4}alkyl; R^{5i} is H, -C_{1-4}alkyl, or -C_{0-3}alkylenearyl; and R^{5j} is -C_{1-6}alkyl, aryl, or $-CH_2CH(NH_2)COOH$;

R^6 is selected from -C_{1-6}alkyl, $-CH_2O(CH_2)_2$-O-CH_3, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and

R^7 is H or is taken together with R^6 to form -C_{3-8}cycloalkyl;

wherein: each $-CH_2$- group in $-(CH_2)_r$- is optionally substituted with 1 or 2 substituents independently selected from -C_{1-4}alkyl and fluoro; each ring in Ar and each aryl and heteroaryl in R^{1-3} and R^{5-6} is optionally substituted with 1 to 3 substituents independently selected from -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, $-S(O)_2$-C_{1-4}alkyl, -phenyl, $-NO_2$, $-NH_2$, -NH-C_{1-6}alkyl and $-N(C_{1-6}alkyl)_2$, wherein each alkyl, alkenyl and alkynyl is optionally substituted with 1 to 5 fluoro atoms; each carbon atom in X is optionally substituted with one or more R^{4b} groups and one $-CH_2$- moiety in X may be replaced with a group selected from -C_{4-8}cycloalkylene-, $-CR^{4d}$=CH-, and $-CH=CR^{4d}$-; wherein R^{4b} is selected from $-C_{0-5}$alkylene-$COOR^{4c}$, -C_{1-6}alkyl, -C_{0-1}alkylene-$CONH_2$, -C_{1-2}alkylene-OH, -C_{0-3}alkylene-C_{3-7}cycloalkyl, 1H-indol-3-yl, benzyl, and hydroxybenzyl, where R^{4c} is H or -C_{1-4}alkyl; and R^{4d} is selected from $-CH_2$-thiophene and phenyl; each alkyl and each aryl in R^{1-3}, R^{4a-4d}, and R^{5-6} is optionally substituted with 1 to 7 fluoro atoms; and pharmaceutically acceptable salts thereof.

Another embodiment of the disclosure relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of the disclosure. Such compositions may optionally contain other therapeutic agents such as diuretics, β_1 adrenergic receptor blockers, calcium channel blockers, angiotensin-converting enzyme

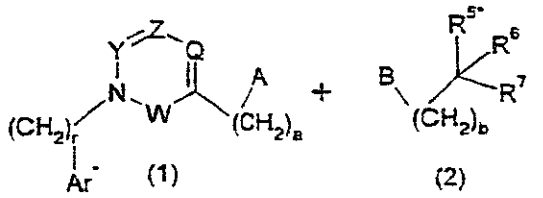
inhibitors, AT_1 receptor antagonists, neprilysin inhibitors, non-steroidal anti-inflammatory agents, prostaglandins, anti-lipid agents, anti-diabetic agents, anti-thrombotic agents, renin inhibitors, endothelin receptor antagonists, endothelin converting enzyme inhibitors, aldosterone antagonists, angiotensin-converting enzyme/neprilysin inhibitors, vasopressin receptor antagonists, and combinations thereof. Accordingly, in yet another embodiment of the disclosure, a pharmaceutical composition comprises a compound of the disclosure, a second therapeutic agent, and a pharmaceutically acceptable carrier. Another embodiment of the disclosure pertains to a combination of active agents, comprising a compound of the disclosure and a second therapeutic agent. The compound of the disclosure can be formulated together or separately from the additional agent(s). When formulated separately, a pharmaceutically acceptable carrier may be included with the additional agent(s). Thus, yet another embodiment of the disclosure relates to a combination of pharmaceutical compositions, the combination comprising: a first pharmaceutical composition comprising a compound of the disclosure and a first pharmaceutically acceptable carrier; and a second pharmaceutical composition comprising a second therapeutic agent and a second pharmaceutically acceptable carrier. The disclosure also relates to a kit containing such pharmaceutical compositions, for example where the first and second pharmaceutical compositions are separate pharmaceutical compositions.

Compounds of the disclosure possess both AT_1 receptor antagonist activity and NEP enzyme inhibition activity, and are therefore expected to be useful as therapeutic agents for treating patients suffering from a disease or disorder that is treated by antagonizing the AT_1 receptor and/or inhibiting the NEP enzyme. Thus, one embodiment of the disclosure is directed to a method of treating patients suffering from a disease or disorder that is treated by antagonizing the AT_1 receptor and/or inhibiting the NEP enzyme, comprising administering to a patient a therapeutically effective amount of a compound of the disclosure. Another embodiment of the disclosure is directed to a method of treating hypertension or heart failure, comprising administering to a patient a therapeutically effective amount of a compound of the disclosure. Still another embodiment of the disclosure pertains to a method for antagonizing an AT_1 receptor in a mammal comprising administering to the mammal, an AT_1 receptor-antagonizing amount of a compound of the disclosure. Yet another embodiment of the disclosure pertains to a method for inhibiting a NEP enzyme in a mammal comprising administering to the mammal, a NEP enzyme-inhibiting amount of a compound of the disclosure.

Compounds of formula I and pharmaceutically acceptable salts thereof, that are of particular interest include those that exhibit an inhibitory constant (pK_i) for binding to an AT_1 receptor greater than or equal to about 5.0; in particular those having a pK_i greater than or equal to about 6.0; in one embodiment those having a pK_i greater than or equal to about 7.0; more particularly those having a pK_i greater than or equal to about 8.0; and in yet another embodiment, those having a pK_i within the range of about 8.0-10.0. Compounds of particular interest also include those having a NEP enzyme inhibitory concentration (pIC_{50}) greater than or equal to about 5.0; in one embodiment those having a pIC_{50} greater than or equal to about 6.0; in particular those having a pIC_{50} greater than or equal to about 7.0; and most particularly those having a pIC_{50} within the range of about 7.0-10.0. Compounds of further interest include those having a pK_i for binding to an AT_1 receptor greater than or equal to about 7.5 and having a NEP enzyme pIC_{50} greater than or equal to about 7.0.

Since compounds of the disclosure possess AT_1 receptor antagonist activity and NEP inhibition activity, such compounds are also useful as research tools. Accordingly, one embodiment of the disclosure pertains to a method of using a compound of the disclosure as a research tool, the method comprising conducting a biological assay using a compound of the disclosure. Compounds of the disclosure can also be used to evaluate new chemical compounds. Thus another embodiment of the disclosure relates to a method of evaluating a test compound in a biological assay, comprising: (a) conducting a biological assay with a test compound to provide a first assay value; (b) conducting the biological assay with a compound of the disclosure to provide a second assay value; wherein step (a) is conducted either before, after or concurrently with step (b); and (c) comparing the first assay value from step (a) with the second assay value from step (b). Exemplary biological assays include an AT_1 receptor binding assay and a NEP enzyme inhibition assay. Still another embodiment of the disclosure is directed to a method of studying a biological system or sample comprising an AT_1 receptor, a NEP enzyme, or both, the method comprising: (a) contacting the biological system or sample with a compound of the disclosure; and (b) determining the effects caused by the compound on the biological system or sample.

The disclosure is also directed to processes and intermediates useful for preparing compounds of the disclosure. Accordingly, another embodiment of the disclosure relates to a process of preparing compounds of the disclosure comprising the step of coupling a compound of formula 1 with a compound of formula 2:



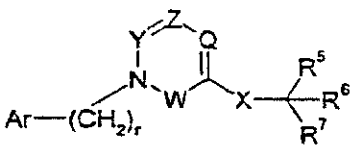
(1) (2)

where: A is $-NH_2$ and B is -COOH or A is -COOH and B is $-NH_2$; the sum of a and b is in the range of 0 to 11; Ar* represents Ar-R^{1*}, where R^{1*} is R^1 or a protected form of R^1; and R^{5*} represents R^5 or a protected form of R^5; the carbon atoms in the $-(CH_2)_a$ and $-(CH_2)_b$ groups may be substituted with one or more R^{4b} groups; and one $-CH_2-$ group in the $-(CH_2)_a$ or the $-(CH_2)_b$ group may be replaced with $-C_{4-8}$cycloalkylene-, $-CR^{4d}=CH-$, or $-CH=CR^{4d}-$; and optionally deprotecting the product when R^{1*} is a protected form of R^1 and/or R^{5*} is a protected form of R^5. Another embodiment of the disclosure relates to a process of preparing a pharmaceutically acceptable salt of a compound of formula I, comprising contacting a compound of formula I in free acid or base form with a pharmaceutically acceptable base or acid. In other embodiments, the disclosure is directed to products prepared by any of the processes described herein, as well as novel intermediates used in such process. In one embodiment of the disclosure novel intermediates have formula VIII, IX or X.

Yet another embodiment of the disclosure is directed to the use of a compound of formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament, especially for the manufacture of a medicament useful for treating hypertension or heart failure. Another embodiment of the disclosure is directed to use of a compound of the disclosure for antagonizing an AT_1 receptor or for inhibiting a NEP enzyme in a mammal. Still another embodiment of the disclosure pertains to the use of a compound of the disclosure as a research tool. Other embodiments of the disclosure are disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to compounds of formula I:



(I)

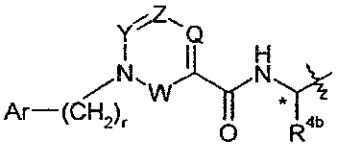
and pharmaceutically acceptable salts thereof.

As used herein, the term "compound of the invention" is intended to include compounds of formula I as well as the species embodied in formulas II-VI. In addition, the compounds of the invention may also contain several basic or acidic groups (for example, amino or carboxyl groups) and therefore, such compounds can exist as a free base, free

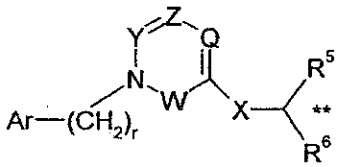
acid, or in various salt forms. All such salt forms are included within the scope of the invention. Furthermore, solvates of compounds of formula I or salts thereof are included within the scope of the invention. Finally, the compounds of the invention may also exist as prodrugs. Accordingly, those skilled in the art will recognize that reference to a compound herein, for example, reference to a "compound of the invention" includes reference to a compound of formula I as well as to pharmaceutically acceptable salts, solvates and prodrugs of that compound unless otherwise indicated. Further, the term "or a pharmaceutically acceptable salt, solvate and/or prodrug thereof" is intended to include all permutations of salts and solvates, such as a solvate of a pharmaceutically acceptable salt.

The compounds of formula I may contain one or more chiral centers and so may exist in a number of stereoisomeric forms. When such chiral centers are present, the invention is directed to racemic mixtures, pure stereoisomers (enantiomers or diastereomers), stereoisomer-enriched mixtures, and the like unless otherwise indicated. When a chemical structure is depicted without any stereochemistry, it is understood that all possible stereoisomers are encompassed by such structure. Thus, for example, the term "compound of formula I" is intended to include all possible stereoisomers of the compound. Similarly, when a particular stereoisomer is shown or named herein, it will be understood by those skilled in the art that minor amounts of other stereoisomers may be present in the compositions of the invention unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers. Individual enantiomers may be obtained by numerous methods that are well known in the art, including chiral chromatography using a suitable chiral stationary phase or support, or by chemically converting them into diastereomers, separating the diastereomers by conventional means such as chromatography or recrystallization, then regenerating the original enantiomers. Additionally, where applicable, all cis-trans or E/Z isomers (geometric isomers), tautomeric forms and topoisomeric forms of the compounds of the invention are included within the scope of the invention unless otherwise specified.

Compounds of formula I may contain one or more chiral centers. One possible chiral center could be present in the "X" portion of the compound. For example, a chiral center exists at a carbon atom in the alkylene moiety in X that is substituted with an R^{4b} group such as -C_{1-6}alkyl, for example -CH_3. This chiral center is present at the carbon atom indicated by the symbol * in the following partial formula:



Another possible chiral center could be present at the carbon on the -X-$CR^5R^6R^7$ group, when R^6 is a group such as -C_{1-6}alkyl, for example -$CH_2CH(CH_3)_2$, and R^7 is hydrogen. This chiral center is present at the carbon atom indicated by the symbol ** in the following formula:



In one embodiment of the invention, the carbon atom identified by the symbol * and/or ** has the *(R)* configuration. In this embodiment, compounds of formula I have the *(R)* configuration at the carbon atom identified by the symbol * and/or ** or are enriched in a stereoisomeric form having the *(R)* configuration at this carbon atom (or atoms). In another embodiment, the carbon atom identified by the symbol * and/or ** has the *(S)* configuration. In this embodiment, compounds of formula I have the *(S)* configuration at the carbon atom identified by the symbol * and/or ** or are enriched in a stereoisomeric form having the *(S)* configuration at this carbon atom. It is understood that a compound may have a chiral center at both the * and the ** carbon atoms. In such cases, four possible diastereomers can exist. In some cases, in order to optimize the therapeutic activity of the compounds of the invention, for example, as hypertensive agents, it may be desirable that the carbon atom identified by the symbol * and/or ** have a particular *(R)* or *(S)* configuration.

The compounds of the invention, as well as those compounds used in their synthesis, may also include isotopically-labeled compounds, that is, where one or more atoms have been enriched with atoms having an atomic mass different from the atomic mass predominately found in nature. Examples of isotopes that may be incorporated into the compounds of formula I, for example, include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{36}Cl, and ^{18}F.

The compounds of formula I have been found to possess AT_1 receptor antagonizing activity and NEP enzyme inhibition activity. Among other properties, such compounds are expected to be useful as therapeutic agents for treating diseases such as hypertension. By

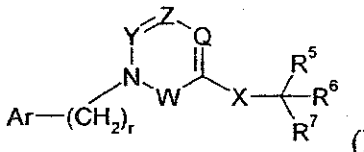
combining dual activity into a single compound, double therapy can be achieved, that is, AT_1 receptor antagonist activity and NEP enzyme inhibition activity can be obtained using a single active component. Since pharmaceutical compositions containing one active component are typically easier to formulate than compositions containing two active components, such single-component compositions provide a significant advantage over compositions containing two active components. In addition, certain compounds of the invention have also been found to be selective for inhibition of the AT_1 receptor over the angiotensin II type 2 (AT_2) receptor, a property that may have therapeutic advantages.

The nomenclature used herein to name the compounds of the invention is illustrated in the Examples herein. This nomenclature has been derived using the commercially available AutoNom software (MDL, San Leandro, California).

REPRESENTATIVE EMBODIMENTS

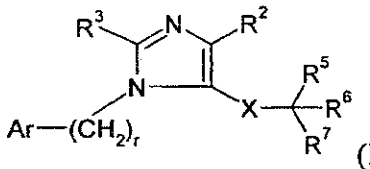
The following substituents and values are intended to provide representative examples of various aspects and embodiments of the invention. These representative values are intended to further define and illustrate such aspects and embodiments and are not intended to exclude other embodiments or to limit the scope of the invention. In this regard, the representation that a particular value or substituent is preferred is not intended in any way to exclude other values or substituents from the invention unless specifically indicated.

The invention is directed to compounds of formula I:



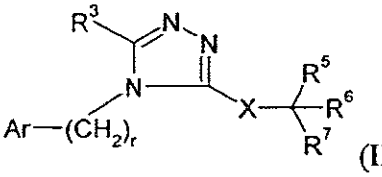
(I)

In one embodiment, Y represents $-C(R^3)-$, Z is -N-, Q is $-C(R^2)-$ and W is a bond. This embodiment of formula I can be represented by formula II:



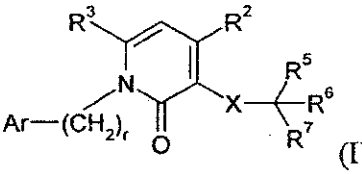
(II)

In another embodiment, Y represents $-C(R^3)-$, Z is -N-, Q is -N- and W is a bond. This embodiment of formula I can be represented by III:



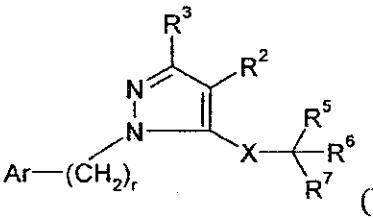
(III)

In yet another embodiment, Y represents -C(R^3)-, Z is -CH-, Q is -C(R^2)- and W is -C(O)-. This embodiment of formula I can be represented by IV:



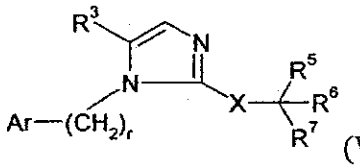
(IV)

In yet another embodiment, Y represents -N-, Z is -C(R^3)-, Q is -C(R^2)- and W is a bond. This embodiment of formula I can be represented by V:



(V)

In another embodiment, Y represents -C(R^3)-, Z is -CH-, Q is -N- and W is a bond. In this embodiment, formula I can be represented as the subgenus VI:

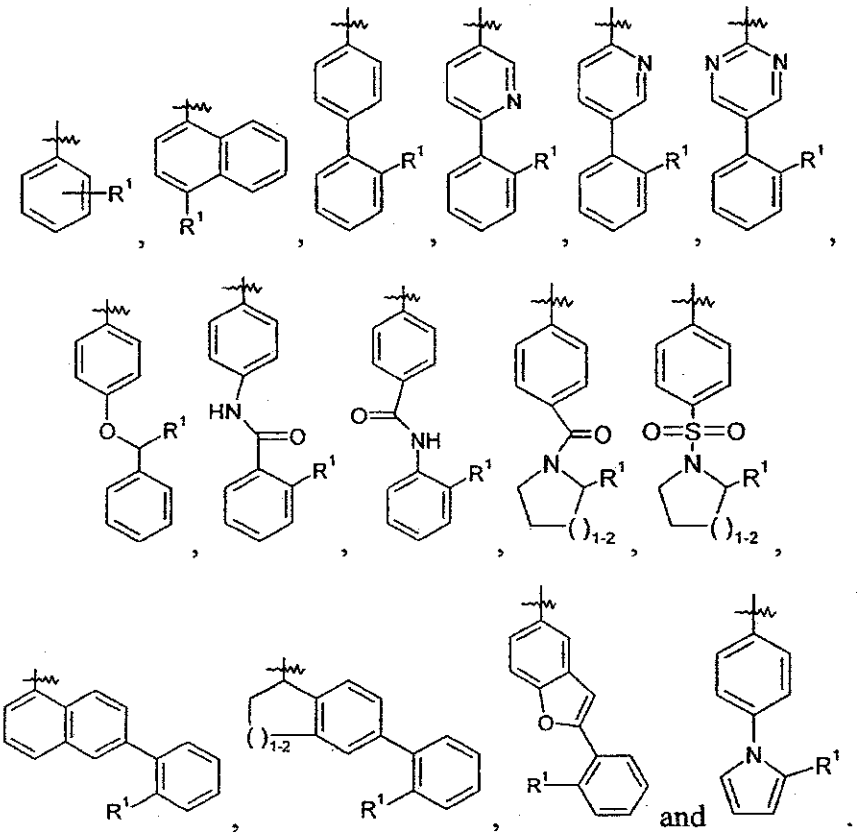


(VI)

In particular embodiments, Y represents -C(R^3)-, Z is -N-, Q is -C(R^2)- and W is a bond, or Y is -C(R^3)-, Z is -N-, Q is -N- and W is a bond.

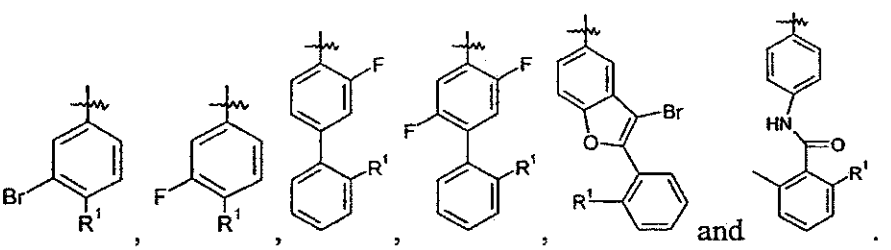
The values for r are 0, 1 or 2. In one embodiment, r is 1. Each -CH_2- group in the -$(CH_2)_r$- group may be substituted with 1 or 2 substituents independently selected from -C_{1-4}alkyl (for example, -CH_3), and fluoro. In one particular embodiment, the -$(CH_2)_r$- group is unsubstituted; in another embodiment, one or two -CH_2- groups in -$(CH_2)_r$- are substituted with a -C_{1-4}alkyl group.

Ar represents an aryl group selected from:



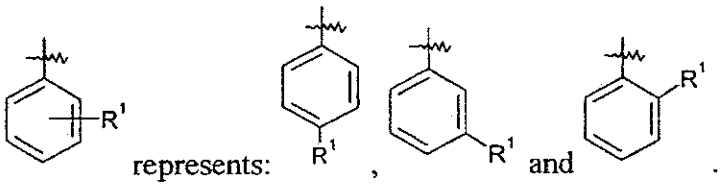
Each ring in the Ar moiety may be substituted with 1 to 3 substituents independently selected from -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, -$S(O)_2$-C_{1-4}alkyl, -phenyl, -NO_2, -NH_2, -NH-C_{1-6}alkyl and -$N(C_{1-6}alkyl)_2$. Furthermore, each of the aforementioned alkyl, alkenyl and alkynyl groups are optionally substituted with 1 to 5 fluoro atoms.

In one particular embodiment, each ring in the Ar moiety may be substituted with 1 to 2 substituents independently selected from -OH, -C_{1-4}alkyl (for example, -CH_3), halo (for example bromo, fluoro, chloro, and di-fluoro), -O-C_{1-4}alkyl (for example, -OCH_3), and -phenyl. Exemplary substituted Ar moieties include:

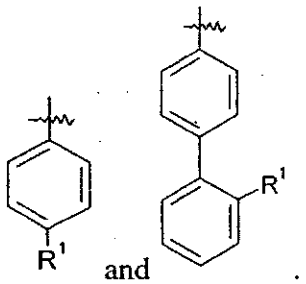


Of particular interest is where Ar is substituted with 1 or 2 halo atoms, particularly fluoro atoms.

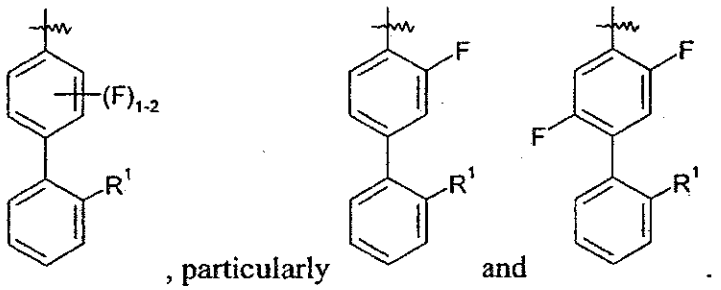
It is understood that:


represents: , , and .

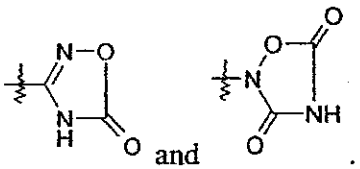
In one particular embodiment, Ar is selected from:


and .

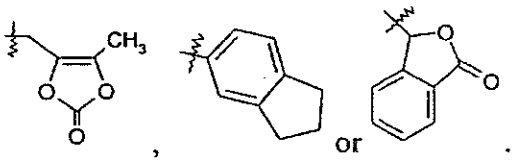
In another particular embodiment, Ar is:


, particularly and .

R^1 is selected from -$COOR^{1a}$, -$NHSO_2R^{1b}$, -SO_2NHR^{1d}, -SO_2OH, -C(O)NH-SO_2R^{1c}, -$P(O)(OH)_2$, -CN, -O-$CH(R^{1e})$-COOH, tetrazol-5-yl,


and .

The R^{1a} moiety is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(C_{1-4}alkyl)OC(O)R^{1aa}$, -$C_{0-6}$alkylenemorpholine,


, or .

R^{1aa} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -$NR^{1ab}R^{1ac}$, or -$CH(NH_2)CH_2COOCH_3$. R^{1ab} and R^{1ac} are independently selected from H, -C_{1-6}alkyl, and benzyl, or are taken together as -$(CH_2)_{3-6}$-.

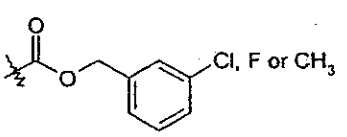
The R^{1b} moiety is R^{1c} or -$NHC(O)R^{1c}$. The R^{1c} group is -C_{1-6}alkyl, -C_{0-6}alkylene-O-R^{1ca}, -C_{1-5}alkylene-$NR^{1cb}R^{1cc}$, or -C_{0-4}alkylenearyl. The R^{1ca} moiety is H, -C_{1-6}alkyl, or

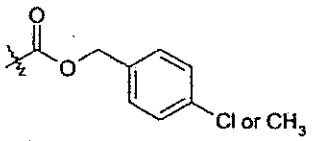
-C_{1-6}alkylene-O-C_{1-6}alkyl. The R^{1cb} and R^{1cc} groups are independently selected from H and -C_{1-6}alkyl, or are taken together as -$(CH_2)_2$-O-$(CH_2)_2$- or -$(CH_2)_2$-N[C(O)CH_3]-$(CH_2)_2$-. The R^{1d} moiety is H, R^{1c}, -C(O)R^{1c}, or -C(O)NHR^{1c}. The R^{1e} group is C_{1-4}alkyl or aryl.

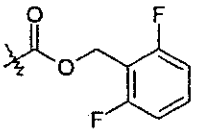
Each alkyl and each aryl in R^1 is optionally substituted with 1 to 7 fluoro atoms. In addition, the term "alkyl" is intended to include divalent alkylene groups such as those present in -C_{1-3}alkylenearyl and -C_{1-3}alkyleneheteroaryl, for example. Further, each aryl and heteroaryl group that might be present in R^1, may be substituted with 1 to 3 -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, -$S(O)_2$-C_{1-4}alkyl, -phenyl, -NO_2, -NH_2, -NH-C_{1-6}alkyl, or -N(C_{1-6}alkyl)$_2$ groups. Further, each of the aforementioned alkyl, alkenyl and alkynyl groups may be substituted with 1 to 5 fluoro atoms. It is understood that when referring to "each alkyl," "each aryl" and "each heteroaryl" group in R^1, the terms also include any alkyl, aryl and heteroaryl groups that might be present in the R^{1a} through R^{1e} moieties.

In one embodiment, R^1 is -$COOR^{1a}$ and R^{1a} is H. In another embodiment, R^1 is -$COOR^{1a}$ and R^{1a} is -C_{1-6}alkyl, examples of which include -CH_3, -CH_2CH_3, -$(CH_2)_2CH_3$, -$(CH_2)_2$-CF_3, -$CH_2CH(CH_3)_2$, -$CH(CH_3)_2$, -$CH(CH_3)$-CF_3, -$CH(CH_2F)_2$, -$C(CH_3)_3$, -$(CH_2)_3CH_3$, and -$(CH_2)_2$-CF_2CF_3. Thus, examples of R^1 include -C(O)OCH_3, -$COOCH_2CH_3$, and so forth.

In one embodiment, R^1 is -$COOR^{1a}$ and R^{1a} is -C_{1-3}alkylenearyl, for example, a benzyl group, which may be substituted such as chlorobenzyl, fluorobenzyl, difluorobenzyl, -benzyl-CH_3, -benzyl-CF_3, and-benzyl-O-CF_3. Thus, examples of R^1 include: -C(O)OCH_2-benzyl,



,


and


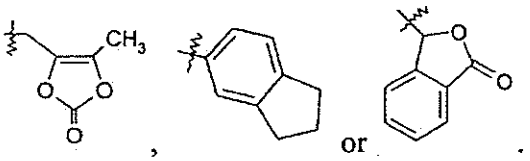
.

In one embodiment, R^1 is -$COOR^{1a}$ and R^{1a} is -C_{1-3}alkyleneheteroaryl, examples of which include -CH_2-pyridinyl. In one embodiment, R^1 is -$COOR^{1a}$ and R^{1a} is -C_{3-7}cycloalkyl, examples of which include cyclopentyl.

In yet another embodiment R^1 is -$COOR^{1a}$ and R^{1a} is -CH(C_{1-4}alkyl)OC(O)R^{1aa}, where R^{1aa} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -$NR^{1ab}R^{1ac}$, or -$CH(NH_2)CH_2COOCH_3$. R^{1ab} and R^{1ac} are independently selected from H, -C_{1-6}alkyl, and benzyl, or are taken together as -$(CH_2)_{3-6}$-. Examples of -O-C_{1-6}alkyl groups include -O-CH_2CH_3 and -O-$CH(CH_3)_2$. Exemplary -O-C_{3-7}cycloalkyl groups include -O-cyclohexyl. Thus, examples of R^1 include

-C(O)OCH(CH$_3$)OC(O)-O-CH$_2$CH$_3$, -C(O)OCH(CH$_3$)OC(O)-O-CH(CH$_3$)$_2$, and -C(O)OCH(CH$_3$)OC(O)-O-cyclohexyl.

In one embodiment, R^1 is -COOR^{1a} and R^{1a} is -C$_{0-6}$alkylenemorpholine, examples of which include -(CH$_2$)$_2$-morpholine and -(CH$_2$)$_3$-morpholine. In another embodiment, R^{1a} is



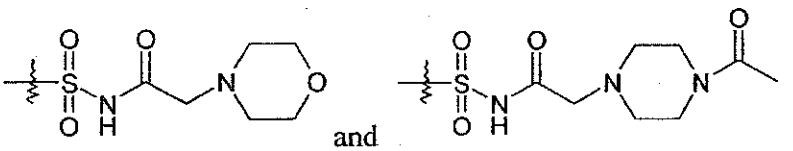
In one embodiment, R^1 is -NHSO$_2$R^{1b} and R^{1b} is R^{1c}. The R^{1c} group is -C$_{1-6}$alkyl, -C$_{0-6}$alkylene-O-R^{1ca}, -C$_{1-5}$alkylene-NR^{1cb}R^{1cc}, -C$_{0-4}$alkylenearyl or -C$_{0-4}$alkyleneheteroaryl. The R^{1ca} moiety is H, -C$_{1-6}$alkyl, or -C$_{1-6}$alkylene-O-C$_{1-6}$alkyl. The R^{1cb} and R^{1cc} groups are independently selected from H and -C$_{1-6}$alkyl, or are taken together as -(CH$_2$)$_2$-O-(CH$_2$)$_2$- or -(CH$_2$)$_2$-N[C(O)CH$_3$]-(CH$_2$)$_2$-. In one embodiment, R^{1c} is -C$_{1-6}$alkyl, such that exemplary R^1 groups include -NHSO$_2$-CH$_3$ and the fluoro-substituted group, -NHSO$_2$-CF$_3$. In another embodiment, R^{1c} is -C$_{0-4}$alkylenearyl, such that exemplary R^1 groups include -NHSO$_2$-phenyl. In another embodiment, R^{1c} is -C$_{0-4}$alkyleneheteroaryl, such that exemplary R^1 groups include -NHSO$_2$- 4,5-dimethylisoxazol-3-yl.

In another embodiment, R^1 is -NHSO$_2$R^{1b} and R^{1b} is -NHC(O)R^{1c}, where R^{1c} is defined above. In a particular embodiment, R^1 is -NHSO$_2$R^{1b}, R^{1b} is -NHC(O)R^{1c}, and R^{1c} is -C$_{1-6}$alkyl or -C$_{0-4}$alkylenearyl.

In one embodiment, R^1 is -SO$_2$NHR^{1d} and R^{1d} is H. In another embodiment, R^1 is -SO$_2$NHR^{1d} and R^{1d} is R^{1c}, where R^{1c} is defined above. In a particular embodiment, R^{1c} is -C$_{1-6}$alkyl or -C$_{0-4}$alkylenearyl. When R^{1c} is -C$_{1-6}$alkyl, exemplary R^1 groups include the fluoro-substituted groups -SO$_2$NH-CF$_3$, -SO$_2$NH-CHF$_2$, -SO$_2$NH-CF$_2$CH$_2$F and -SO$_2$NH-CF$_2$CF$_2$CF$_3$.

In another embodiment, R^1 is -SO$_2$NHR^{1d} and R^{1d} is -C(O)R^{1c}, where R^{1c} is defined above. In one embodiment of particular interest, R^{1c} is -C$_{1-6}$alkyl or -C$_{0-4}$alkylenearyl. When R^{1c} is -C$_{1-6}$alkyl, exemplary R^1 groups include -SO$_2$NHC(O)CH$_3$ and -SO$_2$NHC(O)-(CH$_2$)$_2$CH$_3$. When R^{1c} is -C$_{0-6}$alkylene-O-R^{1ca} and R^{1ca} is H, exemplary R^1 groups include -SO$_2$NHC(O)CH$_2$OH, -SO$_2$NHC(O)CH(CH$_3$)OH, and -SO$_2$NHC(O)C(CH$_3$)$_2$OH. When R^{1c} is -C$_{0-6}$alkylene-O-R^{1ca} and R^{1ca} is -C$_{1-6}$alkyl, exemplary R^1 groups include -SO$_2$NHC(O)CH$_2$-O-CH$_3$, -SO$_2$NHC(O)-O-CH$_3$, and -SO$_2$NHC(O)-O-CH$_2$CH$_3$. When R^{1c}

is -C_{0-6}alkylene-O-R^{1ca} and R^{1ca} is -C_{1-6}alkylene-O-C_{1-6}alkyl, exemplary R^1 groups include - $SO_2NHC(O)CH_2$-O-$(CH_2)_2$-O-CH_3. When R^{1c} is -C_{1-5}alkylene-$NR^{1cb}R^{1cc}$, exemplary R^1 groups include -$SO_2NHC(O)CH_2N(CH_3)_2$, -$SO_2NHC(O)$-CH_2-NH_2, and -$SO_2NHC(O)$-$CH(CH_3)$-NH_2. Another example when R^{1c} is -C_{1-5}alkylene-$NR^{1cb}R^{1cc}$ is where the R^{1cb} and R^{1cc} are taken together as -$(CH_2)_2$-O-$(CH_2)_2$- or -$(CH_2)_2$-N[$C(O)CH_3$]-$(CH_2)_2$-. Such exemplary R^1 groups include:



and

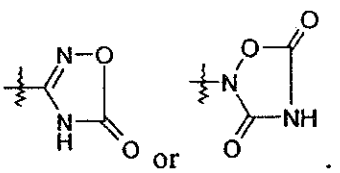
In another embodiment, R^1 is -SO_2NHR^{1d} and R^{1d} is -$C(O)NHR^{1c}$, where R^{1c} is defined above. In a particular embodiment, R^{1c} is -C_{1-6}alkyl or -C_{0-4}alkylenearyl. When R^{1c} is -C_{1-6}alkyl, exemplary R^1 groups include -$SO_2NHC(O)NH$-CH_2CH_3 and -$SO_2NHC(O)NH$-$(CH_2)_2CH_3$. When R^{1c} is -C_{0-4}alkylenearyl, exemplary R^1 groups include -$SO_2NHC(O)NH$-phenyl.

In another embodiment, R^1 is -SO_2OH, and in still another embodiment, R^1 is -$P(O)(OH)_2$. In yet another embodiment, R^1 is -CN.

In another embodiment, R^1 is -$C(O)NH$-SO_2R^{1c}, where R^{1c} is defined above. In a particular embodiment, R^{1c} is -C_{1-6}alkyl or -C_{0-4}alkylenearyl. When R^{1c} is -C_{1-6}alkyl, exemplary R^1 groups include -C(O)-NH-SO_2-CH_3, -C(O)-NH-SO_2-CH_2CH_3 and the fluoro-substituted -C(O)-NH-SO_2-CF_3 group.

In another embodiment, R^1 is -O-$CH(R^{1e})$-COOH, where R^{1e} is -C_{1-4}alkyl or aryl. Examples of such R^1 groups include, -O-$CH(CH_3)$-COOH and -O-CH(phenyl)-COOH.

In an embodiment of particular interest, R^1 is tetrazol-5-yl. In another embodiment, R^1 is:



or

R^2 is selected from H, halo, -NO_2, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{3-6}cycloalkyl, -CN, -$C(O)R^{2a}$, -C_{0-5}alkylene-OR^{2b}, -C_{0-5}alkylene-$NR^{2c}R^{2d}$, -C_{0-3}alkylenearyl, and -C_{0-3}alkyleneheteroaryl. In one particular embodiment, R^2 is selected from H, -C_{0-5}alkylene-OR^{2b}, and halo; and in another embodiment, R^2 is selected from H and halo. In one embodiment R^2 is halo such as chloro or fluoro. In another embodiment R^2 is

-C_{1-6}alkyl such as -CH_3 and -CH_2CH_3. In yet another embodiment R^2 is -C_{0-3}alkylenearyl, such as phenyl. In one embodiment, R^2 is -$C(O)R^{2a}$. The R^{2a} substituent can be H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, -OR^{2b} or -$NR^{2c}R^{2d}$. R^{2b} is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and -C_{0-1}alkylenearyl. The R^{2c} and R^{2d} groups are independently selected from H, -C_{1-4}alkyl, and -C_{0-1}alkylenearyl. In another particular embodiment, R^2 is -C_{0-5}alkylene-OR^{2b}, more particularly -C_{0-3}alkylene-OR^{2b}. In exemplary embodiments, and R^{2b} is H or -C_{1-6}alkyl, for example R^2 can be -CH_2OH, -$C(CH_3)_2OH$ or -OCH_3.

Each alkyl and each aryl in R^2 is optionally substituted with 1 to 7 fluoro atoms. It is understood that when referring to the "alkyl" in R^2, the term includes any alkyl groups that might be present in the R^{2a}, R^{2b}, R^{2c} and R^{2d} moieties. In addition, the aryl and heteroaryl in R^2, for example in -C_{0-3}alkylenearyl or -C_{0-3}alkyleneheteroaryl, may be substituted with 1 to 3 -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, -$S(O)_2$-C_{1-4}alkyl, -phenyl, -NO_2, -NH_2, -NH-C_{1-6}alkyl, or -$N(C_{1-6}alkyl)_2$ groups. Further, each of the aforementioned alkyl, alkenyl and alkynyl groups may be substituted with 1 to 5 fluoro atoms. It is understood that when referring to the "aryl" or "heteroaryl" in R^2, the term includes any aryl and heteroaryl groups that might be present in the R^{2a}, R^{2b}, R^{2c} and R^{2d} moieties.

R^3 is selected from -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{3-10}alkynyl, -C_{0-3}alkylene-C_{3-7}cycloalkyl, -C_{2-3}alkenylene-C_{3-7}cycloalkyl, -C_{2-3}alkynylene-C_{3-7}cycloalkyl, -C_{0-5}alkylene-NR^{3a}-C_{0-5}alkylene-R^{3b}, -C_{0-5}alkylene-O-C_{0-5}alkylene-R^{3b}, -C_{0-5}alkylene-S-C_{1-5}alkylene-R^{3b}, and -C_{0-3}alkylenearyl. The R^{3a} group is H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, or -C_{0-3}alkylenearyl (for example, -C_{0-1}alkylenearyl such as phenyl and benzyl). The R^{3b} group is H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, or aryl (such as phenyl).

In addition, each alkyl and each aryl in R^3 is optionally substituted with 1 to 7 fluoro atoms, where the term "alkyl" is intended to include divalent alkylene groups such as those present in -C_{0-3}alkylene-C_{3-7}cycloalkyl and -C_{0-3}alkylenearyl, for example. Each aryl in R^3, for example in -C_{0-3}alkylenearyl or aryl, may be substituted with 1 to 3 -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, -$S(O)_2$-C_{1-4}alkyl, -phenyl, -NO_2, -NH_2, -NH-C_{1-6}alkyl, or -$N(C_{1-6}alkyl)_2$ groups. Further, each of the aforementioned alkyl, alkenyl and alkynyl groups may be substituted with 1 to 5 fluoro atoms. It is understood that when referring to "each alkyl" and "each aryl" group in R^3, the terms also include any alkyl and aryl groups that might be present in the R^{3a} and R^{3b} moieties.

In one embodiment, R^3 is -C_{1-10}alkyl optionally substituted with 1 to 7 fluoro atoms such as -CF_3. In another embodiment, R^3 is -C_{2-7}alkyl; and in yet another embodiment, R^3 is -C_{2-5}alkyl, examples of which include, -CH_2CH_3, -$(CH_2)_2CH_3$, and -$(CH_2)_3CH_3$.

In another embodiment, R^3 is -C_{2-10}alkenyl such as -CH_2CH=$CHCH_3$. In yet another embodiment, R^3 is -C_{3-10}alkynyl such as -$CH_2C{\equiv}CCH_3$.

In another embodiment, R^3 is -C_{0-3}alkylene-C_{3-7}cycloalkyl such as -cyclopropyl, -CH_2-cyclopropyl, cyclopentyl, -CH_2-cyclopentyl, -$(CH_2)_2$-cyclopentyl, and -CH_2-cyclohexyl. In a particular embodiment, R^3 is -C_{0-1}alkylene-C_{3-5}cycloalkyl. In one embodiment, R^3 is -C_{2-3}alkenylene-C_{3-7}cycloalkyl such as -CH_2CH=CH-cyclopentyl; and in another embodiment, R^3 is -C_{2-3}alkynylene-C_{3-7}cycloalkyl such as -$CH_2C{\equiv}C$-cyclopentyl.

In yet another embodiment, R^3 is -C_{0-5}alkylene-NR^{3a}-C_{0-5}alkylene-R^{3b}. In one particular embodiment, R^{3a} is H and R^{3b} is -C_{1-6}alkyl. Examples of such R^3 groups include -$NHCH_2CH_3$, -$NHCH(CH_3)_2$, -$NH(CH_2)_2CH_3$, -$NH(CH_2)_3CH_3$, -$NHCH(CH_3)CH_2CH_3$, -$NH(CH_2)_4CH_3$, and -$NH(CH_2)_5CH_3$.

In one embodiment, R^3 is -C_{0-5}alkylene-O-C_{0-5}alkylene-R^{3b}. In one particular embodiment, R^{3b} is selected from H, -C_{1-6}alkyl and aryl. Examples of such R^3 groups include -OCH_3, -OCH_2CH_3, -$OCH(CH_3)_2$, -$O(CH_2)_2CH_3$, -$O(CH_2)_3CH_3$, -$OCH_2CH(CH_3)_2$, -O-phenyl, and -O-benzyl. In another embodiment, R^3 is -C_{0-5}alkylene-O-C_{0-5}alkylene-R^{3b}, where R^{3b} is -C_{1-6}alkyl, and in another embodiment, R^3 is -O-C_{1-5}alkyl.

In another embodiment, R^3 is -C_{0-5}alkylene-S-C_{1-5}alkylene-R^{3b}, and in one particular embodiment R^{3b} is H, such as when R^3 is -CH_2-S-CH_2CH_3. In another embodiment, R^3 is -C_{0-3}alkylenearyl, such as phenyl, benzyl, and -$(CH_2)_2$-phenyl.

In one particular embodiment of interest, R^3 is -C_{1-10}alkyl or -C_{0-5}alkylene-O-C_{0-5}alkylene-R^{3b}, where R^{3b} is H; and in a specific embodiment, R^3 is selected from -C_{2-5}alkyl and -C_1alkylene-O-C_{1-5}alkylene-H.

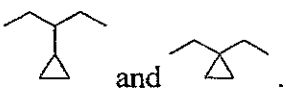
X is -C_{1-12}alkylene-, where at least one -CH_2- moiety in the alkylene is replaced with a -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moiety. Thus X can be -C_1alkylene-, -C_1alkylene-, -C_2alkylene-, -C_3alkylene-, -C_4alkylene-, -C_5alkylene-, -C_6alkylene-, -C_7alkylene-, -C_8alkylene, -C_9alkylene-, -C_{10}alkylene-, -C_{11}alkylene-, and -C_{12}alkylene-, with at least one -CH_2- moiety being replaced. R^{4a} is selected from H, -OH, and -C_{1-4}alkyl. In one embodiment, R^{4a} is H.

Each carbon atom in the -C_{1-12}alkylene- group may be substituted with one or more

R^{4b} groups. R^{4b} is selected from -C_{0-5}alkylene-$COOR^{4c}$, -C_{1-6}alkyl, -C_{0-1}alkylene-$CONH_2$, -C_{1-2}alkylene-OH, -C_{0-3}alkylene-C_{3-7}cycloalkyl, 1H-indol-3-yl, benzyl, and hydroxybenzyl, where R^{4c} is H or -C_{1-4}alkyl. In one embodiment, the carbon atoms in -C_{1-12}alkylene- are unsubstituted with R^{4b} groups. In another embodiment, 1 or 2 carbon atoms are substituted with one or two R^{4b} groups. In another embodiment, one carbon atom is substituted with one R^{4b} group. In one particular embodiment, R^{4b} is -COOH, benzyl, or -C_{1-6}alkyl, including -C_{1-3}alkyl groups such as -CH_3 and -$CH(CH_3)_2$.

In addition, one -CH_2- moiety in X may be replaced with a group selected from -C_{4-8}cycloalkylene-, -CR^{4d}=CH-, and -CH=CR^{4d}-. R^{4d} is selected from -CH_2-thiophene and phenyl. In one embodiment, none of the -CH_2- moieties are so replaced. In another embodiment, one -CH_2- moiety is replaced with -C_{4-8}cycloalkylene-, for example, cyclohexylene. In another embodiment, one -CH_2- moiety is replaced with -CH=CR^{4d}-, where R^{4d} is -CH_2-thiophene such as -CH_2-thiophen-2-yl.

Each alkyl and each aryl in R^{4a}, R^{4b}, R^{4c}, and R^{4d}, may be substituted with 1 to 7 fluoro atoms, and the term "alkyl" is intended to include divalent alkylene groups such as that present in -C_{0-5}alkylene-$COOR^{4c}$, for example. It is noted that the R^{4b} group, -C_{0-3}alkylene-C_{3-7}cycloalkyl, is intended to include a C_{3-7}cycloalkyl linked to the X -C_{1-12}alkylene- chain by a bond as well as a C_{3-7}cycloalkyl that is directly attached to the chain, as illustrated below:



In one embodiment, one to four -CH_2- moieties are replaced. In another embodiment, one -CH_2- moiety is replaced, examples of which include: -C(O)NH- and -CH_2-NHC(O)-. In one embodiment, X is -C_{2-11}alkylene- and 1, 2, or 3 -CH_2- moieties are replaced with a -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moiety. In another embodiment, X is -C_{2-5}alkylene-, where 1 or 2 -CH_2- moieties are replaced. When more than one -CH_2- moiety in C_{1-12}alkylene is replaced with a -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moiety, the replaced moieties may be contiguous or non-contiguous. Exemplary X groups include the following, which depict, examples where one or more -CH_2- moieties are replaced with -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moieties, examples where -CH_2- moieties are replaced with a group selected from -C_{4-8}cycloalkylene-, -CR^{4d}=CH-, and -CH=CR^{4d}-, as well as examples where carbon atoms in the -C_{1-12}alkylene- group are substituted with one or more R^{4b} groups:

C_1alkylene with one -CH_2- moiety replaced:

-C(O)NH-

-NHC(O)-

C_2alkylene with one -CH_2- moiety replaced:

-CH_2-NHC(O)-

-C(O)NH-CH_2-

-CH_2-C(O)NH-

-CH[$CH(CH_3)_2$]-C(O)NH-

C_2alkylene with two -CH_2- moieties replaced:

-C(O)NH-NHC(O)-

-CH=C(-CH_2-2-thiophene)-C(O)NH-

C_3alkylene with one -CH_2- moiety replaced:

-$(CH_2)_2$-NHC(O)-

-$CH(CH_3)$-CH_2-NHC(O)-

-CH[$CH(CH_3)_2$]-CH_2-NHC(O)-

-CH(COOH)-CH_2-NHC(O)-

-CH_2-CH(COOH)-NHC(O)-

C_3alkylene with two -CH_2- moieties replaced:

-NHC(O)-CH_2-NHC(O)-

C_4alkylene with one -CH_2- moiety replaced:

-$(CH_2)_3$-NHC(O)-

-C(O)NH-CH_2-CH(COOH)-CH_2-

C_4alkylene with two -CH_2- moieties replaced:

-C(O)NH-CH(benzyl)-CH_2-NHC(O)-

-C(O)NH-CH(benzyl)-CH_2-C(O)NH-

-CH_2-NHC(O)-CH_2-NHC(O)-

C_4alkylene with three -CH_2- moieties replaced:

-CH_2-NHC(O)-cyclohexylene-NHC(O)-

-CH_2-N(OH)C(O)-cyclohexylene-NHC(O)-

C_5alkylene with two -CH_2- moieties replaced:

-CH_2-NHC(O)-CH_2-CH(COOH)-NHC(O)-

-CH_2-NHC(O)-$(CH_2)_2$-NHC(O)-

-C(O)NH-$(CH_2)_2$-C(O)N(OH)-CH_2-

-C(O)NH-$(CH_2)_2$-CH(COOH)-NHC(O)-

-CH(COOH)-CH_2-NHC(O)-CH_2-NHC(O)-

-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-

C_6alkylene with two -CH_2- moieties replaced:

-C(O)NH-$(CH_2)_4$-NHC(O)-

-CH_2-NHC(O)-$(CH_2)_2$-CH(COOH)-NHC(O)-

-C(O)NH-$(CH_2)_3$-CH(COOH)-NHC(O)-

C_6alkylene with three -CH_2- moieties replaced:

-C(O)NH-$(CH_2)_2$-NHC(O)-CH_2-NHC(O)-

C_6alkylene with four -CH_2- moieties replaced:

-C(O)NH-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-

C_7alkylene with two -CH_2- moieties replaced:

-CH_2-NHC(O)-$(CH_2)_4$-NHC(O)-

-C(O)NH-$(CH_2)_4$-CH(COOH)-NHC(O)-

C_7alkylene with three -CH_2- moieties replaced:

-CH[$CH(CH_3)_2$]-C(O)NH-$(CH_2)_2$-NHC(O)-CH_2-NHC(O)-

C_7alkylene with four -CH_2- moieties replaced:

-CH_2-NHC(O)-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-

-CH_2-C(O)NH-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-

C_8alkylene with three -CH_2- moieties replaced:

-C(O)NH-$(CH_2)_4$-NHC(O)-CH_2-NHC(O)-

C_8alkylene with four -CH_2- moieties replaced:

-C(O)NH-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-

C_9alkylene with two -CH_2- moieties replaced:

-CH_2-NHC(O)-$(CH_2)_6$-NHC(O)-

C_9alkylene with four -CH_2- moieties replaced:

-CH_2-NHC(O)-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-

C_{10}alkylene with four -CH_2- moieties replaced:

-C(O)NH-$(CH_2)_6$-NHC(O)-cyclohexylene-NHC(O)-

C_{11}alkylene with three -CH_2- moieties replaced:

-CH($CH(CH_3)_2$)-C(O)NH-$(CH_2)_6$-NHC(O)-CH_2-NHC(O)-

C_{11}alkylene with four -CH_2- moieties replaced:

-CH_2-NHC(O)-$(CH_2)_6$-NHC(O)-cyclohexylene-NHC(O)-

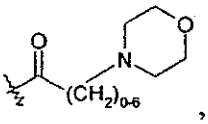
In one particular embodiment, X is -C(O)NH- or -CH_2-NHC(O)-.

R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, -C_{0-2}alkylene-CHR^{5g}-COOH, -C_{0-3}alkylene-$C(O)NR^{5h}$-CHR^{5i}-COOH, and -C_{0-3}alkylene-SR^{5j}. Each alkyl and each aryl in R^5 is optionally substituted with 1 to 7 fluoro atoms, where the term "alkyl" is intended to include divalent alkylene groups such as those present in -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, for example. Each aryl and heteroaryl in R^5 may be substituted with 1 to 3 -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, -$S(O)_2$-C_{1-4}alkyl, -phenyl, -NO_2, -NH_2, -NH-C_{1-6}alkyl, or -$N(C_{1-6}alkyl)_2$ groups. Further, each of the aforementioned alkyl, alkenyl and alkynyl groups may be substituted with 1 to 5 fluoro atoms. It is understood that when referring to "each alkyl," "each aryl" and "each heteroaryl" group in R^5, the terms also include any alkyl, aryl and heteroaryl groups that might be present in the R^{5a-5j}, R^{5aa}, R^{5ab}, R^{5ba}, R^{5bb}, R^{5bc}, R^{5ca}, R^{5da}, R^{5db}, R^{5ea}, R^{5eb}, R^{5cc}, R^{5fa}, and R^{5fb} moieties.

In one embodiment, R^5 is -C_{0-3}alkylene-SR^{5a}. R^{5a} is H or -C(O)-R^{5aa}. The R^{5aa} group is -C_{1-6}alkyl, -C_{0-6}alkylene-C_{3-7}cycloalkyl, -C_{0-6}alkylenearyl, -C_{0-6}alkyleneheteroaryl, -C_{0-6}alkylenemorpholine, -C_{0-6}alkylenepiperazine-CH_3, -$CH[N(R^{5ab})_2]$-aa where aa is an amino acid side chain, -2-pyrrolidine, -C_{0-6}alkylene-OR^{5ab}, -O-C_{0-6}alkylenearyl, -C_{1-2}alkylene-OC(O)-C_{1-6}alkyl, -C_{1-2}alkylene-OC(O)-C_{0-6}alkylenearyl, or -O-C_{1-2}alkylene-OC(O)O-C_{1-6}alkyl. The R^{5ab} group is H or -C_{1-6}alkyl. In one specific embodiment, R^{5a} is H, for example, R^5 may be -SH or -CH_2SH. In another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -C_{1-6}alkyl. Exemplary -C_{1-6}alkyl groups include -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, and -$CH_2CH(CH_3)_2$. Thus, examples of R^5 include -$SC(O)CH_3$, -$CH_2SC(O)CH_3$, -$CH_2SC(O)CH_2CH_3$, -$CH_2SC(O)CH(CH_3)_2$ and -$CH_2SC(O)C(CH_3)_3$, and -$CH_2SC(O)CH_2CH(CH_3)_2$. In one embodiment, R^{5a} is selected from H and -C(O)-C_{1-6}alkyl.

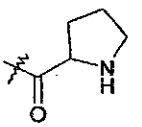
In one embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -C_{0-6}alkylene -C_{3-7}cycloalkyl. Exemplary C_{3-7}cycloalkyl groups include cyclopentyl and cyclohexyl. Thus, examples of R^5 include -$CH_2SC(O)$-cyclopentyl, -$CH_2SC(O)$-cyclohexyl, and -$CH_2SC(O)$-CH_2-cyclopentyl. In another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -C_{0-6}alkylenearyl. In one specific embodiment, the aryl is optionally substituted with 1 to 3 substituents such as -O-C_{1-6}alkyl. Exemplary aryl groups include phenyl and -phenyl-OCH_3. Thus, examples of R^5 include -$CH_2SC(O)$-phenyl and -$CH_2SC(O)$-phenyl-OCH_3.

In yet another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -C_{0-6}alkyleneheteroaryl. Exemplary heteroaryl groups include furanyl, thienyl and pyridinyl. Thus, examples of R^5 include: -CH_2SC(O)-2-pyridine, -CH_2SC(O)-3-pyridine, and -CH_2SC(O)-4-pyridine. In another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -C_{0-6}alkylenemorpholine:



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more particularly, -C_{1-3}alkylenemorpholine. Thus, examples of R^5 include -CH_2S-C(O)CH_2-morpholine and -CH_2S-C(O)$(CH_2)_2$-morpholine. In another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -C_{0-6}alkylenepiperazine-CH_3. Thus, examples of R^5 include -CH_2S-C(O)$(CH_2)_2$-piperazine-CH_3. In one embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -CH[$N(R^{5ab})_2$]-aa where aa is an amino acid side chain. For example, the amino acid side chain could be -$CH(CH_3)_2$, the valine side chain. Thus, one example of R^5 is -CH_2S-C(O)$CH(NH_2)$-$CH(CH_3)_2$. In yet another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -2-pyrrolidine:



Thus, an example of R^5 is -CH_2S-C(O)-2-pyrrolidine.

In another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -C_{0-6}alkylene-OR^{5ab}. In one embodiment, R^{5ab} is H, such that R^{5a} is -C(O)-C_{0-6}alkylene-OH. In another embodiment, R^{5ab} is -C_{1-6}alkyl, such that R^{5a} is -C(O)-C_{0-6}alkylene-O-C_{1-6}alkyl, for example, R^5 may be -CH_2SC(O)-O-CH_2CH_3.

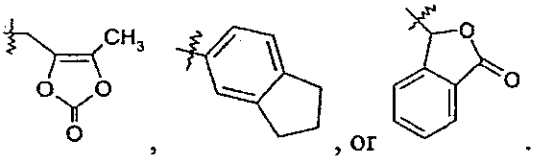
In another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -O-C_{0-6}alkylenearyl. In yet another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -C_{1-2}alkylene-OC(O)-C_{1-6}alkyl and in another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -C_{1-2}alkylene-OC(O)-C_{0-6}alkylenearyl. In yet another embodiment, R^{5a} is -C(O)-R^{5aa}, where R^{5aa} is -O-C_{1-2}alkylene-OC(O)O-C_{1-6}alkyl, for example, R^5 may be -CH_2SC(O)OCH(CH_3)-OC(O)O-$CH(CH_3)_2$.

In one embodiment, R^5 is -C_{0-3}alkylene-C(O)$NR^{5b}R^{5c}$. The R^{5b} moiety is H, -OH, -OC(O)R^{5ba}, -CH_2COOH, -O-benzyl, -pyridyl, or -OC(S)$NR^{5bb}R^{5bc}$. R^{5ba} is H, -C_{1-6}alkyl, aryl, -OCH_2-aryl (for example, -OCH_2-phenyl), -CH_2O-aryl (for example, -CH_2O-phenyl), or -$NR^{5bb}R^{5bc}$. The R^{5bb} and R^{5bc} moieties are independently selected from H and

-C_{1-4}alkyl. In one embodiment, R^{5b} is -OH or -OC(O)R^{5ba}, where -R^{5ba} is -C_{1-6}alkyl. R^{5c} is H, -C_{1-6}alkyl, or -C(O)-R^{5ca}. R^{5ca} is H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, aryl, or heteroaryl. In one particular embodiment, R^{5c} is H. In another embodiment, R^{5b} is -OH and R^{5c} is H, for example, R^5 may be -C(O)NH(OH) or -CH_2C(O)NH(OH). In another embodiment, R^{5b} is -OC(O)R^{5ba}, where -R^{5ba} is -C_{1-6}alkyl, and R^{5c} is H, for example, R^5 may be -C(O)N[OC(O)CH_3]H or -C(O)N[OC(O)C$(CH_3)_3$]H. In still another embodiment, both R^{5b} and R^{5c} are H, for example, R^5 may be -C(O)NH_2. In another embodiment, R^{5b} is -CH_2COOH and R^{5c} is H, for example, R^5 may be -C(O)N(CH_2COOH)H. In yet another embodiment, R^{5b} is -OC(O)R^{5ba}, where -R^{5ba} is -O-CH_2-aryl or -CH_2-O-aryl, for example, R^{5b} may be -OC(O)OCH_2-phenyl or -OC(O)CH_2-O-phenyl, and R^{5c} is H. Therefore, examples of R^5 include -CH_2-C(O)NH[OC(O)OCH_2-phenyl] and -CH_2-C(O)N[OC(O)-CH_2O-phenyl]H. In another embodiment, R^{5b} is -OC(S)N$R^{5bb}R^{5bc}$, where R^{5bb} and R^{5bc} are both -C_{1-4}alkyl, for example, R^{5b} may be -O-C(S)N$(CH_3)_2$. In another embodiment, R^{5b} is -OC(S)N$R^{5bb}R^{5bc}$ and R^{5c} is H, for example, R^5 may be -CH_2-C(O)N[OC(S)N$(CH_3)_2$]H.

In one embodiment, R^5 is -C_{0-3}alkylene-NR^{5b}-C(O)R^{5d}. R^{5d} is H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -N$R^{5da}R^{5db}$, -CH_2SH, or -O-C_{1-6}alkyl. The R^{5da} and R^{5db} moieties are independently selected from H and -C_{1-4}alkyl. In another embodiment, R^{5b} is -OH and R^{5d} is H, for example, R^5 may be -CH_2-N(OH)C(O)H. In another embodiment, R^{5b} is -OH and R^{5d} is -C_{1-4}alkyl, for example, R^5 may be -CH_2-N(OH)C(O)CH_3. In another embodiment, R^{5b} is H and R^{5d} is -CH_2SH, for example, R^5 may be -NHC(O)CH_2SH or -CH_2NHC(O)-CH_2SH.

In yet another embodiment, R^5 is -NH-C_{0-1}alkylene-P(O)$(OR^{5e})_2$. The R^{5e} moiety is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -C(CH_3)-O-C(O)R^{5ea},



. The R^{5ea} group is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -N$R^{5eb}R^{5ec}$, or -C$(NH_2)CH_2$COOCH_3. R^{5eb} and R^{5ec} are independently selected from H, -C_{1-4}alkyl, and -C_{1-3}alkylenearyl (for example, benzyl). R^{5eb} and R^{5ec} may also be taken together to form -$(CH_2)_{3-6}$-. In one embodiment, R^{5e} is H, for example, R^5 may be -NH-CH_2-P(O)$(OH)_2$.

In one embodiment, R^5 is -C_{0-3}alkylene-P(O)O$R^{5e}R^{5f}$. The R^{5f} moiety is H,

-C_{1-4}alkyl, -C_{0-3}alkylenearyl, -C_{1-3}alkylene-$NR^{5fa}R^{5fb}$, or -C_{1-3}alkylene(aryl)-C_{0-3}alkylene-$NR^{5fa}R^{5fb}$. The R^{5fa} and R^{5fb} groups are independently selected from H and -C_{1-4}alkyl. In one embodiment, R^{5e} is H, for example, R^5 may be -C_{0-3}alkylene-P(O)(OH)R^{5f}.

In one embodiment, R^5 is -C_{0-2}alkylene-CHR^{5g}-COOH. The R^{5g} moiety is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, or -CH_2-O-$(CH_2)_2$-OCH_3. In one embodiment, R^{5g} is -CH_2-O-$(CH_2)_2$-OCH_3, for example, R^5 may be -CH_2-C[CH_2-O-$(CH_2)_2$-OCH_3]H-COOH. In another embodiment, R^{5g} is H, for example, R^5 may be -CH_2COOH.

In one embodiment, R^5 is -C_{0-3}alkylene-C(O)NR^{5h}-CHR^{5i}-COOH. The R^{5h} moiety is H or -C_{1-4}alkyl. The R^{5i} moiety is H, -C_{1-4}alkyl, or -C_{0-3}alkylenearyl. In one embodiment, R^{5h} is H and R^{5i} is -C_{0-3}alkylenearyl, and the aryl is optionally substituted with 1 to 3 substituents such as -OH, for example, R^5 may be -C(O)NH-CH(CH_2-phenyl-OH)(COOH).

In another embodiment, R^5 is -C_{0-3}alkylene-S-SR^{5j}, and R^{5j} is selected from -C_{1-6}alkyl, aryl, and -$CH_2CH(NH_2)COOH$. Examples of such R^5 groups include -C_{0-3}alkylene-S-S-CH_3, -C_{0-3}alkylene-S-S-phenyl, and -C_{0-3}alkylene-S-S-$CH_2CH(NH_2)$-COOH.

R^6 is selected from -C_{1-6}alkyl, -$CH_2O(CH_2)_2OCH_3$, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl. In one particular embodiment, R^6 is selected from -C_{1-6}alkyl, -C_{0-3}alkylenearyl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl. Each alkyl and each aryl in R^6 is optionally substituted with 1 to 7 fluoro atoms, where the term "alkyl" is intended to include divalent alkylene groups such as those present in -C_{1-6}alkylene-O-C_{1-6}alkyl and -C_{0-3}alkylene-C_{3-7}cycloalkyl, for example. In addition, each aryl and heteroaryl in R^6 may be substituted with 1 to 3 -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, -$S(O)_2$-C_{1-4}alkyl, -phenyl, -NO_2, -NH_2, -NH-C_{1-6}alkyl, or -$N(C_{1-6}alkyl)_2$ groups. Further, each of the aforementioned alkyl, alkenyl and alkynyl groups may be substituted with 1 to 5 fluoro atoms.

In one embodiment, R^6 is -C_{1-6}alkyl, for example, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$(CH_2)_2CH_3$, -$(CH_2)_3CH_3$, -$CH(CH_3)CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH_2C(CH_3)_3$, -$(CH_2)_2CH(CH_3)_2$, or -$(CH_2)_4CH_3$. As noted above, each alkyl in R^6 is optionally substituted with 1 to 7 fluoro atoms. Examples of such fluoro-substituted R^6 groups include -$(CH_2)_2CF_3$ and -$(CH_2)_3CF_3$.

In another embodiment, R^6 is -$CH_2O(CH_2)_2OCH_3$. In still another one

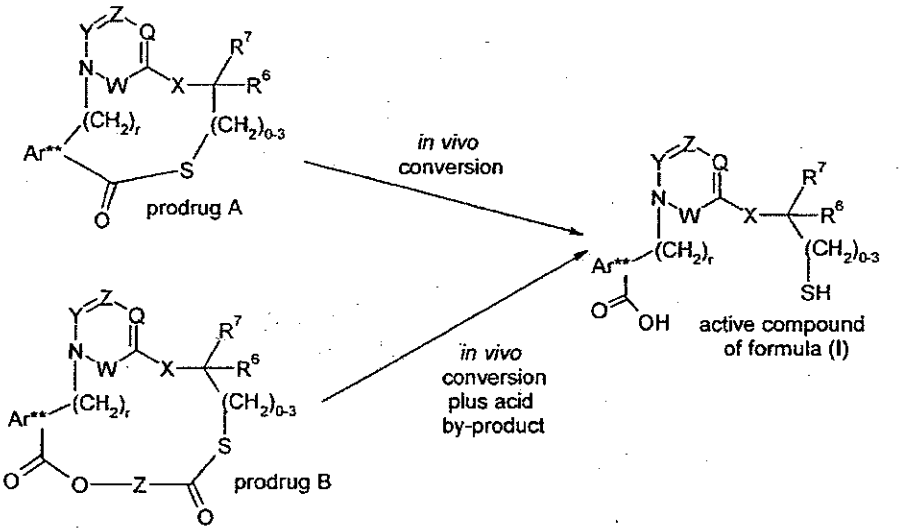
embodiment, R^6 is -C_{1-6}alkylene-O-C_{1-6}alkyl, for example, -OCH_3 and -CH_2OCH_3.

In one embodiment, R^6 is -C_{0-3}alkylenearyl, for example, phenyl, benzyl, -CH_2-biphenyl, -$(CH_2)_2$-phenyl and -CH_2-naphthalen-1-yl. The aryl may be substituted with 1 to 3 substituents. Thus, other examples of R^6 include mono-substituted groups such as, methylbenzyl, chlorobenzyl, fluorobenzyl, fluorophenyl, bromobenzyl, iodobenzyl, -benzyl-CF_3, 2-trifluoromethyl-benzyl, -benzyl-CN, and -benzyl-NO_2; and di-substituted groups such as di-chlorobenzyl and di-fluorobenzyl. Each aryl may also be substituted with 1 to 7 fluoro atoms. Thus, other examples of R^6 include penta-fluorobenzyl.

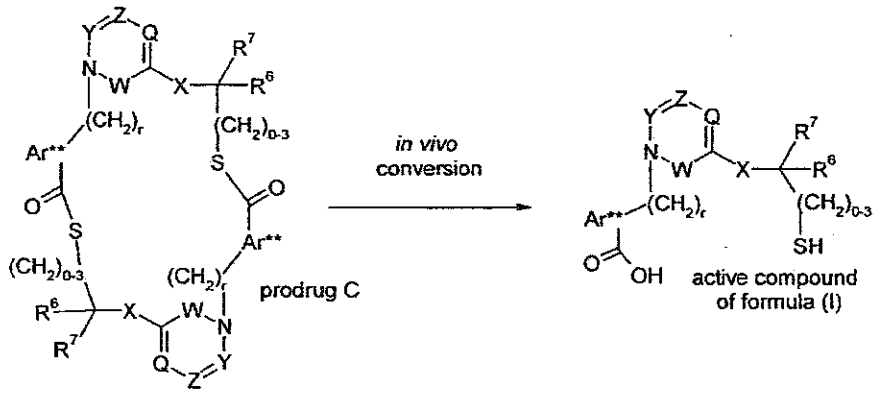
In one embodiment, R^6 is -C_{0-3}alkyleneheteroaryl, for example, -CH_2-pyridyl, -CH_2-furanyl, -CH_2-thienyl, and -CH_2-thiophenyl. In another embodiment, R^6 is -C_{0-3}alkylene-C_{3-7}cycloalkyl, for example, -CH_2-cyclopropyl, cyclopentyl, -CH_2-cyclopentyl, -cyclohexyl, and -CH_2-cyclohexyl.

R^7 is H or is taken together with R^6 to form -C_{3-8}cycloalkyl. In one embodiment, R^7 is H. In another embodiment, R^7 is taken together with R^6 to form -C_{3-8}cycloalkyl, for example cyclopentyl.

One particular embodiment of the invention provides for an active compound of formula I where Ar**-COOH represents Ar-R^1 and R^5 is -C_{0-3}alkylene-SH. One corresponding prodrug (prodrug A) can contain a thioester linkage, which can be cleaved *in vivo* to form the -COOH (R^1) and -C_{0-3}alkylene-SH (R^5) moieties. Another corresponding prodrug (prodrug B, where Z is -C_{1-6}alkylene, optionally substituted with one or more moieties such as hydroxyl, phenyl, carboxyl, and so forth), contains both an ester and a thioester group, which can be similarly cleaved *in vivo*, but which also releases a physiologically acceptable acid such as α-hydroxy acid (Z is -CH_2-), β-hydroxy acid (Z is -$(CH_2)_2$-), *(R)*-2-hydroxypropionic or lactic acid (Z is -$CH(CH_3)$-), *(R)*-hydroxyphenyl acetic or mandelic acid (Z is -CH(phenyl)-), salicylic acid (Z is -phenylene-), 2,3-dihydroxysuccinic or tartaric acid (Z is -CH[CH(OH)(COOH)]-), citric acid (Z is -$C[CH_2COOH]_2$-), hydroxy bis- and hydroxy-tris acids, and so forth.

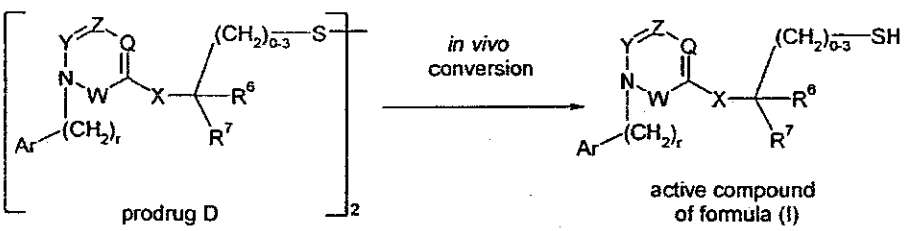


Yet another corresponding prodrug (prodrug C) is a dimer form of prodrug A, thus containing two thioester linkages, which can both be cleaved *in vivo* to form two active moieties, each containing the -COOH (R^1) and -C_{0-3}alkylene-SH (R^5) moieties.



Examples of prodrug A and C are described in Example 33.

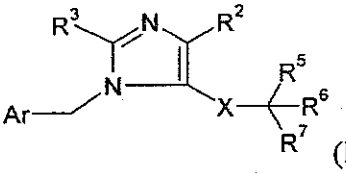
Another embodiment of the invention provides for an active compound of formula I where R^5 is -C_{0-3}alkylene-SH, and the prodrug (prodrug D) is a dimer form of the compound:



One example of prodrug D is the dimer form of the compound of Example 19(c). MS *m/z*: [M + H^+] calcd for$C_{56}H_{66}F_2N_6O_8S_2$, 1053.44; found 1053.6.

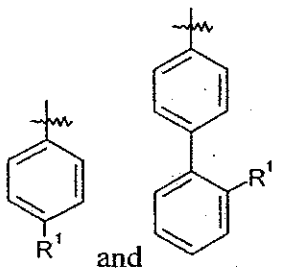
In one embodiment of the invention, the compound of formula I is the species

embodied in formula IIa:



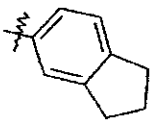
(IIa)

where Ar, R^{2-3}, X, and R^{5-7} are as defined for formula I; and pharmaceutically acceptable salts thereof. In one particular embodiment, Ar is selected from:



and

R^1 is selected from $-COOR^{1a}$, $-NHSO_2R^{1b}$, $-SO_2NHR^{1d}$, $-SO_2OH$, $-O-CH(R^{1e})-COOH$, and tetrazol-5-yl; where R^{1a} is H, $-C_{1-6}$alkyl, $-C_{1-3}$alkylenearyl, $-C_{1-3}$alkyleneheteroaryl, $-C_{3-7}$cycloalkyl, $-CH(C_{1-4}alkyl)OC(O)R^{1aa}$, or



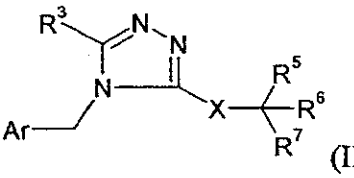
;

R^{1aa} is $-O-C_{1-6}$alkyl or $-O-C_{3-7}$cycloalkyl; R^{1b} is R^{1c}; R^{1c} is $-C_{1-6}$alkyl or $-C_{0-4}$alkylenearyl; R^{1d} is H, $-C(O)R^{1c}$, or $-C(O)NHR^{1c}$; R^{1e} is $-C_{1-4}$alkyl; R^2 is selected from H, halo, $-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, and $-C_{0-5}$alkylene-OR^{2b}; where R^{2b} is selected from H and $-C_{1-6}$alkyl; R^3 is selected from $-C_{1-10}$alkyl and $-C_{0-5}$alkylene-O-C_{0-5}alkylene-C_{1-6}alkyl; X is $-C_{1-11}$alkylene-, where 1 to 4 $-CH_2-$ moieties in the alkylene are replaced with a $-NR^{4a}-C(O)-$ or $-C(O)-NR^{4a}-$ moiety, where R^{4a} is selected from H and -OH; R^5 is selected from $-C_{0-3}$alkylene-SR^{5a}, $-C_{0-3}$alkylene-$C(O)NR^{5b}R^{5c}$, $-NH-C_{0-1}$alkylene-$P(O)(OR^{5e})_2$, $-C_{0-2}$alkylene-CHR^{5g}-COOH and $-C_{0-3}$alkylene-$C(O)NR^{5h}-CHR^{5i}$-COOH; R^{5a} is H or $-C(O)-R^{5aa}$; R^{5aa} is $-C_{1-6}$alkyl, $-C_{0-6}$alkylene-C_{3-7}cycloalkyl, $-C_{0-6}$alkylenearyl, or $-C_{0-6}$alkylenemorpholine; R^{5b} is H, -OH, $-OC(O)R^{5ba}$, $-CH_2COOH$, or $-OC(S)NR^{5bb}R^{5bc}$; R^{5ba} is $-OCH_2$-aryl or $-CH_2O$-aryl; R^{5bb} and R^{5bc} are independently $-C_{1-4}$alkyl; R^{5c} is H; R^{5e} is H; R^{5g} is $-CH_2-O-(CH_2)_2-O-CH_3$; R^{5h} is H; and R^{5i} is $-C_{0-3}$alkylenearyl; R^6 is selected from $-C_{1-6}$alkyl, $-C_{0-3}$alkylenearyl, $-C_{0-3}$alkyleneheteroaryl, and $-C_{0-3}$alkylene-C_{3-7}cycloalkyl; and R^7 is H or is taken together with R^6 to form -cyclopentyl. In one embodiment, each ring in Ar and each aryl in R^{1-3} and R^{5-6}, each carbon atom in X, and

each alkyl and each aryl in R^{1-3}, R^{4a-4d}, and R^{5-6} are optionally substituted as defined for formula I. In yet another embodiment, each ring in Ar and each aryl in R^1 and R^{5-6} is optionally substituted with 1 to 2 substituents independently selected from -C_{1-6}alkyl, -CN, halo, -O-C_{1-6}alkyl, and -NO_2, wherein each alkyl is optionally substituted with 1 to 5 fluoro atoms; each carbon atom in X is optionally substituted with one R^{4b} group and one -CH_2- moiety in X may be replaced with a group selected from -C_{4-8}cycloalkylene-, -CR^{4d}=CH-, and -CH=CR^{4d}-; wherein R^{4b} is -C_{0-5}alkylene-$COOR^{4c}$ or benzyl; R^{4c} is H; and R^{4d} is -CH_2-thiophene; and each alkyl and each aryl in R^1 and R^6 is optionally substituted with 1 to 7 fluoro atoms. In yet another embodiment, one ring in Ar is substituted with 1 or 2 fluoro atoms.

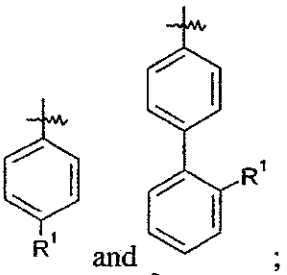
In one particular embodiment of compounds of formula IIa, R^1 is selected from -COOH, -CO(O)(C_{1-6}alkyl), -$NHSO_2$(C_{1-6}alkyl), and -SO_2NH[-C(O)(C_{1-6}alkyl)]; R^2 is selected from H, halo, -C_{1-6}alkyl, -C_{3-6}cycloalkyl and -C_{0-5}alkylene-OH; R^3 is -C_{0-5}alkylene-O-C_{0-5}alkylene-C_{1-6}alkyl; X is -C_{1-11}alkylene-, where 1 to 4 -CH_2- moieties in the alkylene are replaced with -NHC(O)- or -C(O)NH-; R^5 is -C_{0-3}alkylene-SR^{5a} or -C_{0-3}alkylene-C(O)NH(OH); R^{5a} is H or -C(O)-R^{5aa}; R^{5aa} is -C_{1-6}alkyl, -C_{0-6}alkylenearyl, or -C_{0-6}alkylenemorpholine; R^6 is selected from -C_{1-6}alkyl, -C_{0-3}alkylenearyl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and R^7 is H. In one embodiment, each ring in Ar and each aryl in R^1 and R^6 is optionally substituted with 1 to 2 halo groups; and each alkyl and each aryl in R^1 and R^6 is optionally substituted with 1 to 7 fluoro atoms. In yet another embodiment, one ring in Ar is substituted with 1 or 2 fluoro atoms. In one particular embodiment, X is -C_{1-5}alkylene-, and in another embodiment, X is selected from -C(O)NH- and -CH_2-NHC(O)-.

In one embodiment of the invention, the compound of formula I is the species embodied in formula IIIa:



(IIIa)

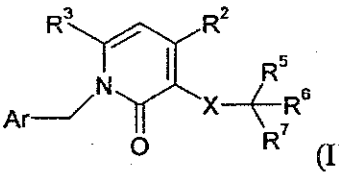
where Ar, R^3, X, and R^{5-7} are as defined for formula I; and pharmaceutically acceptable salts thereof. In one particular embodiment, Ar is selected from:



and ;

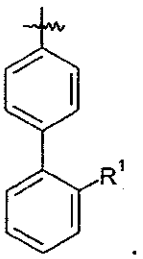
R^1 is -$COOR^{1a}$, where R^{1a} is H or -C_{1-6}alkyl; R^3 is -C_{1-10}alkyl; X is -CH_2-NHC(O)-; R^5 is selected from -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-C(O)N(OH)H; R^{5a} is H or -$C(O)C_{1-6}$alkyl; R^6 is selected from -C_{1-6}alkyl and -C_{0-3}alkylenearyl; and R^7 is H. In one embodiment, each ring in Ar and the aryl in R^6, the carbon atom in X, and each alkyl and each aryl in R^1, R^3, and R^{5-6} are optionally substituted as defined for formula I.

In one embodiment of the invention, the compound of formula I is the species embodied in formula IVa:



(IVa)

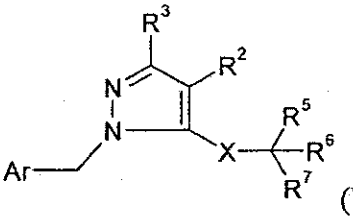
where Ar, R^{2-3}, X, and R^{5-7} are as defined for formula I; and pharmaceutically acceptable salts thereof. In one particular embodiment, Ar is:



;

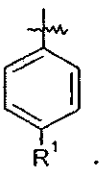
R^1 is -$COOR^{1a}$, where R^{1a} is H or -C_{1-6}alkyl; R^2 is H; R^3 is -C_{1-10}alkyl; X is -CH_2-NHC(O)-; R^5 is selected from -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-C(O)N(OH)H; R^{5a} is H or -$C(O)C_{1-6}$alkyl; R^6 is selected from -C_{1-6}alkyl and -C_{0-3}alkylenearyl; and R^7 is H. In one embodiment, each ring in Ar and the aryl in R^6, the carbon atom in X, and each alkyl and each aryl in R^1, R^3, and R^{5-6} are optionally substituted as defined for formula I.

In one embodiment of the invention, the compound of formula I is the species embodied in formula Va:



(Va)

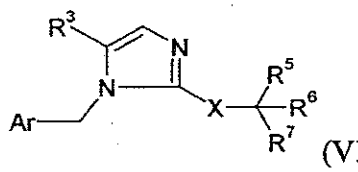
where Ar, R^{2-3}, X, and R^{5-7} are as defined for formula I; and pharmaceutically acceptable salts thereof. In one particular embodiment, Ar is:



;

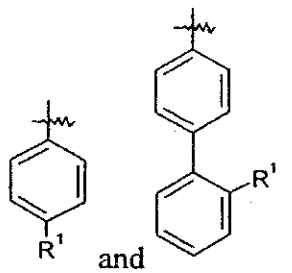
R^1 is -$COOR^{1a}$, where R^{1a} is H or -C_{1-6}alkyl; R^2 is H; R^3 is -C_{1-10}alkyl; X is -C(O)NH-; R^5 is selected from -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-C(O)N(OH)H; R^{5a} is H or -C(O)C_{1-6}alkyl; R^6 is -C_{0-3}alkylenearyl; and R^7 is H. In one embodiment, the ring in Ar and the aryl in R^6, and each alkyl and each aryl in R^1, R^3, and R^{5-6} are optionally substituted as defined for formula I.

In one embodiment of the invention, the compound of formula I is the species embodied in formula VIa:



(VIa)

where Ar, R^3, X, and R^{5-7} are as defined for formula I; and pharmaceutically acceptable salts thereof. In one particular embodiment, Ar is selected from:

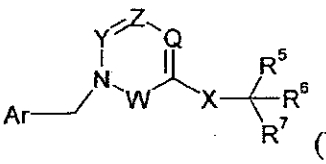


and

R^1 is -$COOR^{1a}$, where R^{1a} is H or -C_{1-6}alkyl; R^3 is -C_{1-10}alkyl; X is -C(O)NH- or -CH_2-NHC(O)-; R^5 is selected from -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-C(O)N(OH)H; R^{5a} is H or -C(O)C_{1-6}alkyl; R^6 is selected from -C_{1-6}alkyl and -C_{0-3}alkylenearyl; and R^7 is H. In one embodiment, each ring in Ar and the aryl in R^6, the carbon atom in X, and each alkyl and each aryl in R^1, R^3, and R^{5-6} are optionally substituted as defined for formula I.

In one embodiment of the invention, the compound of formula I is the species

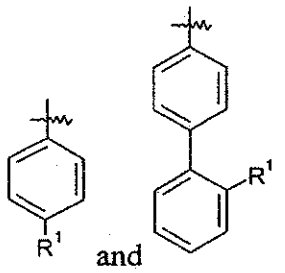
embodied in formula VII:



(VII)

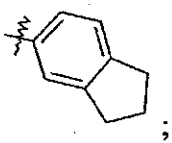
where Y is -C(R^3)-, Z is -N-, Q is -C(R^2)- and W is a bond; Y is -N-, Z is -C(R^3)-, Q is -C(R^2)- and W is a bond; Y is -C(R^3)-, Z is -N-, Q is -N- and W is a bond; or Y is -C(R^3)-, Z is -CH-, Q is -C(R^2)- and W is -C(O)-; and R^{2-3}, Ar, X, and R^{5-7} are as defined for formula I; and pharmaceutically acceptable salts thereof.

In another particular embodiment, Ar is selected from:



and

R^1 is selected from -COOR^{1a}, -NHSO_2R^{1b}, -SO_2NHR^{1d}, -SO_2OH, -O-CH(R^{1e})-COOH, and tetrazol-5-yl; where R^{1a} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -CH(C_{1-4}alkyl)OC(O)R^{1aa}, or



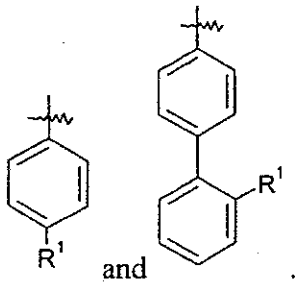
;

R^{1aa} is -O-C_{1-6}alkyl or -O-C_{3-7}cycloalkyl; R^{1b} is R^{1c}; R^{1c} is -C_{1-6}alkyl or -C_{0-4}alkylenearyl; R^{1d} is H, -C(O)R^{1c}, or -C(O)NHR^{1c}; R^{1e} is -C_{1-4}alkyl; R^2 is selected from H, halo, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and -C_{0-5}alkylene-OR^{2b}; where R^{2b} is selected from H and -C_{1-6}alkyl; R^3 is selected from -C_{1-10}alkyl and -C_{0-5}alkylene-O-C_{0-5}alkylene-R^{3b}; where R^{3b} is -C_{1-6}alkyl; X is -C_{1-11}alkylene-, where 1 to 4 -CH_2- moieties in the alkylene are replaced with a -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moiety, where R^{4a} is selected from H and -OH; R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-C(O)N$R^{5b}R^{5c}$, -NH-C_{0-1}alkylene-P(O)(OR^{5e})$_2$, -C_{0-2}alkylene-CHR^{5g}-COOH and -C_{0-3}alkylene-C(O)NR^{5h}-CHR^{5i}-COOH; R^{5a} is H or -C(O)-R^{5aa}; R^{5aa} is -C_{1-6}alkyl, -C_{0-6}alkylene-C_{3-7}cycloalkyl, -C_{0-6}alkylenearyl, or -C_{0-6}alkylenemorpholine; R^{5b} is H, -OH, -OC(O)R^{5ba}, -CH_2COOH, or -OC(S)N$R^{5bb}R^{5bc}$; R^{5ba} is -OCH_2-aryl or -CH_2O-aryl; R^{5bb} and R^{5bc} are independently -C_{1-4}alkyl; R^{5c} is H; R^{5e} is H; R^{5g} is -CH_2-O-$(CH_2)_2$-O-CH_3; R^{5h} is H; and R^{5i} is -C_{0-3}alkylenearyl; R^6 is selected

from -C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and R^7 is H or is taken together with R^6 to form -C_{3-8}cycloalkyl. In one embodiment, each ring in Ar and each aryl in R^{1-3} and R^{5-6}, each carbon atom in X, and each alkyl and each aryl in R^{1-3}, R^{4a-4d}, and R^{5-6} are optionally substituted as defined for formula I. In yet another embodiment, each ring in Ar and each aryl in R^1 and R^{5-6} is optionally substituted with 1 to 2 substituents independently selected from -C_{1-6}alkyl, -CN, halo, -O-C_{1-6}alkyl, and -NO_2, wherein each alkyl is optionally substituted with 1 to 5 fluoro atoms; each carbon atom in X is optionally substituted with one R^{4b} group and one -CH_2- moiety in X may be replaced with a group selected from -C_{4-8}cycloalkylene-, -CR^{4d}=CH-, and -CH=CR^{4d}-; wherein R^{4b} is -C_{0-5}alkylene-$COOR^{4c}$ or benzyl; R^{4c} is H; and R^{4d} is -CH_2-thiophene; and each alkyl and each aryl in R^1 and R^6 is optionally substituted with 1 to 7 fluoro atoms. In another aspect, these embodiments have formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

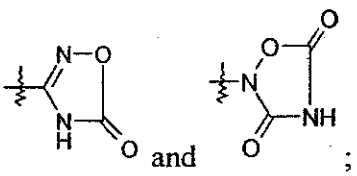
In another particular embodiment, X is selected from the group: -C(O)NH-; -CH_2-NHC(O)-; -C(O)NH-CH_2-; -C(O)NH-NHC(O)-; -CH=C(-CH_2-2-thiophene)-C(O)NH-; -$(CH_2)_2$-NHC(O)-; -C(O)NH-CH_2-CH(COOH)-CH_2-; -C(O)NH-CH(benzyl)-CH_2-NHC(O)-; -C(O)NH-CH(benzyl)-CH_2-C(O)NH-; -CH_2-NHC(O)-CH_2-NHC(O)-; -CH_2-NHC(O)-cyclohexylene-NHC(O)-; -CH_2-N(OH)C(O)-cyclohexylene-NHC(O)-; -CH_2-NHC(O)-CH_2-CH(COOH)-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_2$-NHC(O)-; -C(O)NH-$(CH_2)_2$-C(O)N(OH)-CH_2-; -C(O)NH-$(CH_2)_2$-CH(COOH)-NHC(O)-; -C(O)NH-$(CH_2)_4$-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_2$-CH(COOH)-NHC(O)-; -C(O)NH-$(CH_2)_3$-CH(COOH)-NHC(O)-; -C(O)NH-$(CH_2)_2$-NHC(O)-CH_2-NHC(O)-; -C(O)NH-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_4$-NHC(O)-; -C(O)NH-$(CH_2)_4$-CH(COOH)-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-; -CH_2-C(O)NH-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-; -C(O)NH-$(CH_2)_4$-NHC(O)-CH_2-NHC(O)-; -C(O)NH-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_6$-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-; -C(O)NH-$(CH_2)_6$-NHC(O)-cyclohexylene-NHC(O)-; and -CH_2-NHC(O)-$(CH_2)_6$-NHC(O)-cyclohexylene-NHC(O)-. In another aspect, this embodiment has formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

In one particular embodiment, Ar is selected from:



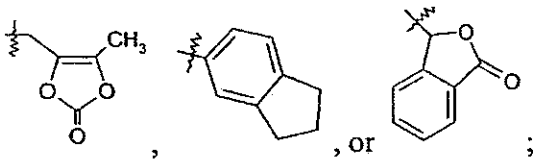
In another aspect, this embodiment has formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

In another particular embodiment, R^1 is selected from -COOH, $-NHSO_2R^{1b}$, $-SO_2NHR^{1d}$, $-SO_2OH$, $-C(O)NH-SO_2R^{1c}$, $-P(O)(OH)_2$, -CN, $-O-CH(R^{1e})-COOH$, tetrazol-5-yl,



where R^{1b}, R^{1c}, R^{1d}, and R^{1e}, are as defined for formula I. In one particular embodiment, R^1 is selected from $-COOR^{1a}$, $-SO_2NHR^{1d}$, and tetrazol-5-yl. In another embodiment, R^1 is selected from -COOH, $-SO_2NHC(O)-C_{1-6}$alkyl, and tetrazol-5-yl. In another aspect, these embodiments have formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

In one particular embodiment, R^1 is $-COOR^{1a}$, where R^{1a} is $-C_{1-6}$alkyl, $-C_{1-3}$alkylenearyl, $-C_{1-3}$alkyleneheteroaryl, $-C_{3-7}$cycloalkyl, $-CH(C_{1-4}$alkyl$)OC(O)R^{1aa}$, $-C_{0-6}$alkylenemorpholine,

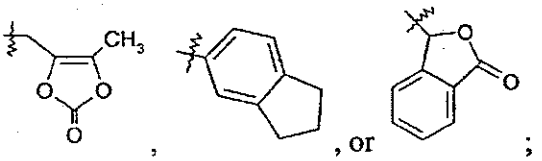


where R^{1aa} is as defined for formula I. In one aspect of the invention, these compounds may find particular utility as prodrugs or as intermediates in the synthetic procedures described herein. In one particular embodiment, R^1 is $-COOR^{1a}$ and R^{1a} is $-C_{1-6}$alkyl. In another aspect, these embodiments have formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

In one particular embodiment, R^1 is selected from $-COOR^{1a}$ and tetrazol-5-yl, where R^{1a} is H or $-C_{1-6}$alkyl. In another aspect, this embodiment has formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

In one embodiment, R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, and -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, -C_{0-2}alkylene-CHR^{5g}-COOH, and -C_{0-3}alkylene-$C(O)NR^{5h}$-CHR^{5i}-COOH; where R^{5a} is H, R^{5b} is -OH, R^{5c} is H, R^{5d} is H, R^{5e} is H; and R^{5f}, R^{5g}, R^{5h}, R^{5i} are as defined for formula I. More particularly, in one embodiment, R^5 is selected from -C_{0-1}alkylene-SH, -C_{0-1}alkylene-C(O)-N(OH)H, and -C_{0-3}alkylene-N(OH)-C(O)H. In another embodiment, R^5 is selected from -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, where R^{5a} is H; R^{5b} is -OH. In one particular embodiment, R^{5c} is H. In another aspect, these embodiments have formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

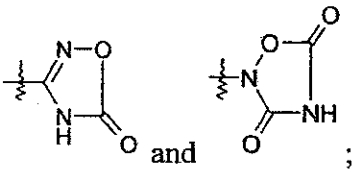
In yet another embodiment, R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, and -C_{0-3}alkylene-S-SR^{5j}; where R^{5a} is -$C(O)$-R^{5aa}; R^{5b} is H, -$OC(O)R^{5ba}$, -CH_2COOH, -O-benzyl, -pyridyl, or -$OC(S)NR^{5bb}R^{5bc}$; R^{5e} is -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(CH_3)$-O-$C(O)R^{5ea}$,



and where R^{5aa}, R^{5ba}, R^{5bb}, R^{5bc}, R^{5c}, R^{5d}, R^{5ea}, R^{5f}, and R^{5j} are as defined for formula I. In one aspect of the invention, these compounds may find particular utility as prodrugs or as intermediates in the synthetic procedures described herein. In another aspect, these embodiments have formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

In one particular embodiment, R^5 is selected from -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$; where R^{5a} is selected from H and -$C(O)$-C_{1-6}alkyl; R^{5b} is selected from H, -OH, and -$OC(O)$-C_{1-6}alkyl; and R^{5c} is selected from H and -C_{1-6}alkyl. In another aspect, this embodiment has formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

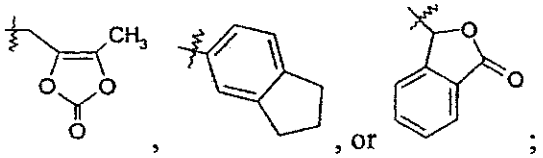
In another embodiment, R^1 is selected from -$COOR^{1a}$ where R^{1a} is H, -$NHSO_2R^{1b}$, -SO_2NHR^{1d}, -SO_2OH, -C(O)NH-SO_2R^{1c}, -$P(O)(OH)_2$, -CN, -O-$CH(R^{1e})$-COOH, tetrazol-5-yl,



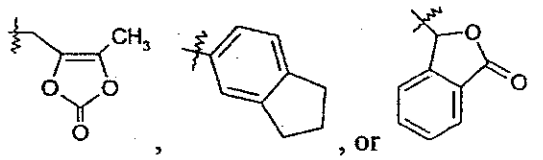
and ;

R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, and -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, -C_{0-2}alkylene-CHR^{5g}-COOH, and -C_{0-3}alkylene-$C(O)NR^{5h}$-CHR^{5i}-COOH; R^{5a} is H, R^{5b} is -OH, R^{5c} is H, R^{5d} is H, R^{5e} is H; and R^{5f}, R^{5g}, R^{5h}, R^{5i} are as defined for formula I. In one particular embodiment, R^1 is selected from -COOH, -SO_2NHR^{1d}, and tetrazol-5-yl; and R^5 is selected from -C_{0-3}alkylene-SH, and -C_{0-3}alkylene-C(O)N(OH)H. In another aspect, these embodiments have formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

In another embodiment, R^1 is -$COOR^{1a}$, where R^{1a} is -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(C_{1-4}alkyl)OC(O)R^{1aa}$, -$C_{0-6}$alkylenemorpholine,

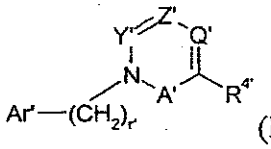


; R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, and -C_{0-3}alkylene-S-SR^{5j}; where R^{5a} is -$C(O)$-R^{5aa}; R^{5b} is H, -$OC(O)R^{5ba}$, -CH_2COOH, -O-benzyl, -pyridyl, or -$OC(S)NR^{5bb}R^{5bc}$; R^{5e} is -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(CH_3)$-O-$C(O)R^{5ea}$,



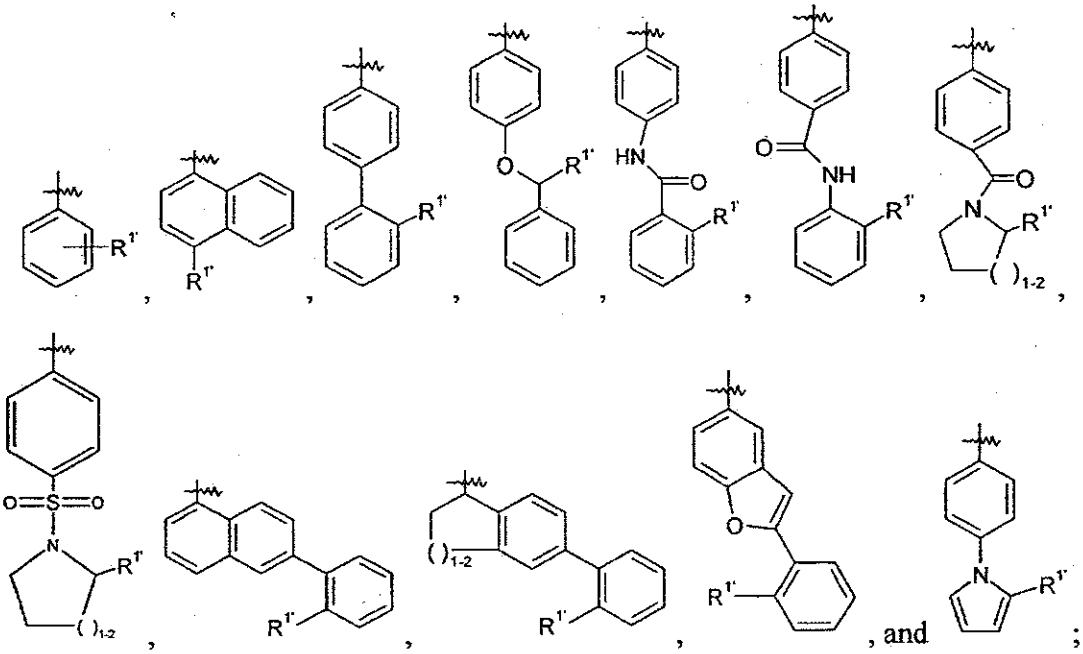
; and where R^{5aa}, R^{5ba}, R^{5bb}, R^{5bc}, R^{5c}, R^{5d}, R^{5ea}, R^{5f}, and R^{5j} are as defined for formula I. In another aspect, this embodiment has formula II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa or VII.

A particular group of compounds of formula I are those disclosed in U.S. Provisional Application No. 60/925,931, filed on April 24, 2007. This group includes compounds of formula (I'):

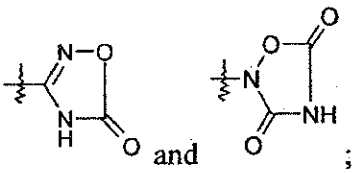


(I')

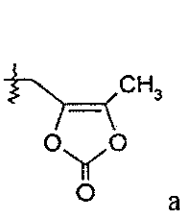
wherein: Y' is -C($R^{3'}$)-, Z' is -N-, Q' is -C($R^{2'}$)- and A' is a bond; Y' is -N-, Z' is -C($R^{3'}$)-, Q' is -C($R^{2'}$)- and A' is a bond; Y' is -C($R^{3'}$)-, Z' is -N-, Q' is -N- and A' is a bond; Y' is -C($R^{3'}$)-, Z' is -CH-, Q' is -N- and A' is a bond; or Y' is -C($R^{3'}$)-, Z' is -CH-, Q' is -C($R^{2'}$)- and A' is -C(O)-; r' is 0, 1 or 2; Ar' is an aryl group selected from:

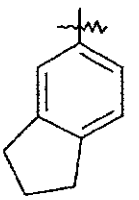


; $R^{1'}$ is selected from -COO$R^{1a'}$, -NHSO$_2$-C$_{1-6}$alkyl, -NHSO$_2$aryl, -NHSO$_2$NHC(O)-C$_{1-6}$alkyl, -NHSO$_2$NHC(O)-aryl, -SO$_2$NHC(O)-C$_{1-6}$alkyl, -SO$_2$NHC(O)-aryl, -SO$_2$NHC(O)NH-C$_{1-6}$alkyl, -SO$_2$NHC(O)NH-aryl, -SO$_2$OH, -SO$_2$NH$_2$, -SO$_2$NH-C$_{1-6}$alkyl, -SO$_2$NH-aryl, -C(O)NH-SO$_2$-C$_{1-6}$alkyl, -C(O)NH-SO$_2$-aryl, -P(O)(OH)$_2$, -CN, -OCH(CH$_3$)-COOH, -OCH(aryl)-COOH, tetrazol-5-yl,



; where $R^{1a'}$ is selected from H, -C$_{1-6}$alkyl, benzyl, -C$_{1-3}$alkyleneheteroaryl, cycloalkyl, -CH(CH$_3$)OC(O)$R^{1b'}$,

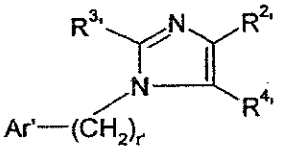


and  ;

$R^{1b'}$ is selected from -O-C_{1-6}alkyl, -O-cycloalkyl, -$NR^{1c'}R^{1d'}$, -$CH(NH_2)CH_2COOCH_3$; and $R^{1c'}$ and $R^{1d'}$ are independently selected from H, -C_{1-6}alkyl, and benzyl, or are taken together as -$(CH_2)_{3-6}$-; $R^{2'}$ is selected from H, -CH_2OH, halo, -NO_2, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{3-6}cycloalkyl, -CN, -$C(O)R^{2a'}$, and -C_{0-3}alkylenearyl; where $R^{2a'}$ is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, -C_{0-3}alkylene-phenyl, -$OR^{2b'}$ and -$NR^{2c'}R^{2d'}$; $R^{2b'}$ is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, phenyl and benzyl; and $R^{2c'}$ and $R^{2d'}$ are independently selected from H, -C_{1-4}alkyl, and -C_{0-1}alkylene-phenyl; $R^{3'}$ is selected from -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{3-10}alkynyl, -C_{3-7}cycloalkyl, -C_{0-3}alkylene-C_{3-7}cycloalkyl, -C_{0-3}alkenylene-C_{3-7}cycloalkyl, -C_{0-3}alkynylene-C_{3-7}cycloalkyl, -$(CH_2)_{0-5}NR^{3a'}(CH_2)_{0-5}R^{3b'}$, -$(CH_2)_{0-5}O(CH_2)_{1-5}R^{3b'}$, -$(CH_2)_{1-5}S(CH_2)_{1-5}R^{3b'}$, and -$C_{0-3}$alkylenearyl; where $R^{3a'}$ is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and -C_{0-1}alkylene-phenyl; and $R^{3b'}$ is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, and phenyl; $R^{4'}$ is -X'-$CR^{5'}R^{6'}R^{7'}$; X' is C_{1-12}alkylene, where at least one -CH_2- moiety in the alkylene is replaced with a -$NR^{4a'}$-C(O)- or -C(O)-$NR^{4a'}$- moiety, where $R^{4a'}$ is selected from H, -OH, and -C_{1-4}alkyl; $R^{5'}$ is selected from -C_{0-3}alkylene-$SR^{5a'}$, -C_{0-3}alkylene-$C(O)NR^{5b'}R^{5c'}$, -C_{0-3}alkylene-$NR^{5b'}$-$C(O)R^{5d'}$, -C_{0-1}alkylene-$NHC(O)CH_2SH$, -NH-C_{0-1}alkylene-$P(O)(OH)_2$, -C_{0-3}alkylene-P(O)OH-$R^{5e'}$, -C_{0-2}alkylene-$CHR^{5f'}$-COOH and -C_{0-3}alkylene-$C(O)NR^{5g'}$-$CHR^{5h'}$-COOH; where $R^{5a'}$ is selected from H, -C(O)-C_{1-6}alkyl, -C(O)-C_{0-6}alkylene-C_{3-7}cycloalkyl, -C(O)-C_{0-6}alkylenearyl, and -C(O)-C_{0-6}alkyleneheteroaryl; $R^{5b'}$ is selected from H, -OH, -$OC(O)C_{1-6}$alkyl, -CH_2COOH, -O-benzyl, -pyridyl, -$OC(O)OCH_2$-phenyl, -$OC(O)CH_2O$-phenyl, -$OC(O)N(CH_3)_2$, and -$OC(S)N(CH_3)_2$; $R^{5c'}$ is selected from H, -C_{1-6}alkyl, and -C(O)-$R^{5c''}$, where $R^{5c''}$ is selected from -C_{1-6}alkyl, -C_{3-7}cycloalkyl, aryl, and heteroaryl; $R^{5d'}$ is selected from H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -$NR^{5d''}R^{5d'''}$, and -O-C_{1-6}alkyl, where $R^{5d''}$ and $R^{5d'''}$ are independently selected from H and -C_{1-4}alkyl; $R^{5e'}$ is selected from H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -C_{1-3}alkylene-$NR^{5e''}R^{5e'''}$, and -C_{1-3}alkylene(aryl)-C_{0-3}alkylene-$NR^{5e''}R^{5e'''}$, where $R^{5e''}$ and $R^{5e'''}$ are independently selected from H and -C_{1-4}alkyl; $R^{5f'}$ is selected from H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, and -CH_2-O-$(CH_2)_2$-OCH_3; $R^{5g'}$ is selected from H and -C_{1-4}alkyl; and $R^{5h'}$ is selected from H,

-C_{1-4}alkyl, and -C_{0-3}alkylenearyl; $R^{6'}$ is selected from -C_{1-6}alkyl, -$CH_2O(CH_2)_2OCH_3$, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and $R^{7'}$ is H or is taken together with $R^{6'}$ to form -C_{3-8}cycloalkyl; wherein: each -CH_2- group in -$(CH_2)_r$- is optionally substituted with 1 or 2 substituents independently selected from -C_{1-4}alkyl and fluoro; each alkyl and each aryl in $R^{1'-4'}$ is optionally substituted with 1 to 7 fluoro atoms; each ring in Ar' and each aryl in $R^{1'-4'}$ is optionally substituted with 1 to 3 substituents independently selected from -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O(C_{1-6}alkyl), -S(C_{1-6}alkyl), -S(O)(C_{1-6}alkyl), -$S(O)_2$(C_{1-4}alkyl), -phenyl, -NO_2, -NH_2, -NH(C_{1-6}alkyl) and -N(C_{1-6}alkyl)$_2$, wherein each alkyl, alkenyl and alkynyl is optionally substituted with 1 to 5 fluoro atoms; and each carbon atom in the alkylene moiety in X' is optionally substituted with one more $R^{4b'}$ groups and one -CH_2- moiety in X' may be replaced with -C_{4-8}cycloalkylene; wherein $R^{4b'}$ is selected from -C_{0-5}alkylene-COOH, -C_{1-6}alkyl, -C_{0-1}alkylene-$CONH_2$, -C_{1-2}alkylene-OH, -C_{0-3}alkylene-C_{3-7}cycloalkyl, and benzyl; and pharmaceutically acceptable salts thereof.

In one particular embodiment of the compound of formula (I'), Y' represents -$C(R^{3'})$-, Z' is -N-, Q' is -$C(R^{2'})$- and A' is a bond, which can be represented as:



In addition, particular compounds of formula I that are of interest include those set forth in the Examples below, as well as the pharmaceutically acceptable salts thereof.

DEFINITIONS

When describing the compounds, compositions, methods and processes of the invention, the following terms have the following meanings unless otherwise indicated. Additionally, as used herein, the singular forms "a," "an," and "the" include the corresponding plural forms unless the context of use clearly dictates otherwise. The terms "comprising", "including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

The term "pharmaceutically acceptable" refers to a material that is not biologically or otherwise undesirable. For example, the term "pharmaceutically acceptable carrier" refers to a material that can be incorporated into a composition and administered to a patient without causing undesirable biological effects or interacting in a deleterious manner

with other components of the composition. Such pharmaceutically acceptable materials typically have met the required standards of toxicological and manufacturing testing, and include those materials identified as suitable inactive ingredients by the U.S. Food and Drug administration.

The term "pharmaceutically acceptable salt" means a salt prepared from a base or an acid which is acceptable for administration to a patient, such as a mammal (for example, salts having acceptable mammalian safety for a given dosage regime). However, it is understood that the salts covered by the invention are not required to be pharmaceutically acceptable salts, such as salts of intermediate compounds that are not intended for administration to a patient. Pharmaceutically acceptable salts can be derived from pharmaceutically acceptable inorganic or organic bases and from pharmaceutically acceptable inorganic or organic acids. In addition, when a compound of formula I contains both a basic moiety, such as an amine, pyridine or imidazole, and an acidic moiety such as a carboxylic acid or tetrazole, zwitterions may be formed and are included within the term "salt" as used herein. Salts derived from pharmaceutically acceptable inorganic bases include ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, and zinc salts, and the like. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperadine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. Salts derived from pharmaceutically acceptable inorganic acids include salts of boric, carbonic, hydrohalic (hydrobromic, hydrochloric, hydrofluoric or hydroiodic), nitric, phosphoric, sulfamic and sulfuric acids. Salts derived from pharmaceutically acceptable organic acids include salts of aliphatic hydroxyl acids (for example, citric, gluconic, glycolic, lactic, lactobionic, malic, and tartaric acids), aliphatic monocarboxylic acids (for example, acetic, butyric, formic, propionic and trifluoroacetic acids), amino acids (for example, aspartic and glutamic acids), aromatic carboxylic acids (for example, benzoic, p-chlorobenzoic, diphenylacetic, gentisic, hippuric, and triphenylacetic acids), aromatic hydroxyl acids (for

example, o-hydroxybenzoic, p-hydroxybenzoic, 1-hydroxynaphthalene-2-carboxylic and 3-hydroxynaphthalene-2-carboxylic acids), ascorbic, dicarboxylic acids (for example, fumaric, maleic, oxalic and succinic acids), glucoronic, mandelic, mucic, nicotinic, orotic, pamoic, pantothenic, sulfonic acids (for example, benzenesulfonic, camphosulfonic, edisylic, ethanesulfonic, isethionic, methanesulfonic, naphthalenesulfonic, naphthalene-1,5-disulfonic, naphthalene-2,6-disulfonic and p-toluenesulfonic acids), xinafoic acid, and the like.

As used herein, the term "prodrug" is intended to mean an inactive (or significantly less active) precursor of a drug that is converted into its active form in the body under physiological conditions, for example, by normal metabolic processes. The term is also intended to include certain protected derivatives of compounds of formula I that may be made prior to a final deprotection stage. Such compounds may not possess pharmacological activity at AT_1 and/or NEP, but may be administered orally or parenterally and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active at AT_1 and/or NEP. Thus, all protected derivatives and prodrugs of compounds formula I are included within the scope of the invention. Prodrugs of compounds of formula I having a free carboxyl, sulfhydryl or hydroxy group can be readily synthesized by techniques that are well known in the art. These prodrug derivatives are then converted by solvolysis or under physiological conditions to be the free carboxyl, sulfhydryl and/or hydroxy compounds. Exemplary prodrugs include: esters including C_{1-6}alkylesters and aryl-C_{1-6}alkylesters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals, ketals, and disulfides. In one embodiment, the compounds of formula I have a free sulfhydryl or a free carboxyl and the prodrug is an ester derivative.

The term "solvate" means a complex or aggregate formed by one or more molecules of a solute, for example, a compound of formula I or a pharmaceutically acceptable salt thereof, and one or more molecules of a solvent. Such solvates are typically crystalline solids having a substantially fixed molar ratio of solute and solvent. Representative solvents include, by way of example, water, methanol, ethanol, isopropanol, acetic acid and the like. When the solvent is water, the solvate formed is a hydrate.

The term "therapeutically effective amount" means an amount sufficient to effect treatment when administered to a patient in need thereof, that is, the amount of drug needed to obtain the desired therapeutic effect. For example, a therapeutically effective

amount for treating hypertension could be the amount of drug needed to reduce blood pressure or the amount of drug needed to maintain normal blood pressure. On the other hand, the term "effective amount" means an amount sufficient to obtain a desired result, which may not necessary be a therapeutic result. For example, when studying a system comprising an AT_1 receptor, an "effective amount" may be the amount needed to antagonize the receptor.

The term "treating" or "treatment" as used herein means the treating or treatment of a disease or medical condition (such as hypertension) in a patient, such as a mammal (particularly a human) that includes: (a) preventing the disease or medical condition from occurring, that is, prophylactic treatment of a patient; (b) ameliorating the disease or medical condition such as by eliminating or causing regression of the disease or medical condition in a patient; (c) suppressing the disease or medical condition such as by slowing or arresting the development of the disease or medical condition in a patient; or (d) alleviating the symptoms of the disease or medical condition in a patient. For example, the term "treating hypertension" would include preventing hypertension from occurring, ameliorating hypertension, suppressing hypertension, and alleviating the symptoms of hypertension (for example, lowering blood pressure). The term "patient" is intended to include those mammals, such as humans, that are in need of treatment or disease prevention or that are presently being treated for disease prevention or treatment of a specific disease or medical condition. The term "patient" also includes test subjects in which compounds of the invention are being evaluated or test subjects being used in a assay, for example an animal model.

The term "alkyl" means a monovalent saturated hydrocarbon group which may be linear or branched. Unless otherwise defined, such alkyl groups typically contain from 1 to 10 carbon atoms and include, for example, -C_{1-4}alkyl, -C_{1-6}alkyl, and -C_{1-10}alkyl. Representative alkyl groups include, by way of example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, isobutyl, *t*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

When a specific number of carbon atoms is intended for a particular term used herein, the number of carbon atoms is shown preceding the term as subscript. For example, the term "-C_{1-6}alkyl" means an alkyl group having from 1 to 6 carbon atoms, and the term "-C_{3-6}cycloalkyl" means a cycloalkyl group having from 3 to 6 carbon atoms, where the carbon atoms are in any acceptable configuration.

The term "alkylene" means a divalent saturated hydrocarbon group that may be linear or branched. Unless otherwise defined, such alkylene groups typically contain from 0 to 10 carbon atoms and include, for example, -C_{0-1}alkylene-, -C_{0-2}alkylene-, -C_{0-3}alkylene-, -C_{0-5}alkylene-, -C_{0-6}alkylene-, -C_{1-2}alkylene- and -C_{1-12}alkylene-. Representative alkylene groups include, by way of example, methylene, ethane-1,2-diyl ("ethylene"), propane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl and the like. It is understood that when the alkylene term include zero carbons such as -C_{0-1}alkylene- or -C_{0-5}alkylene-, such terms are intended to include a single bond.

The term "alkylthio" means a monovalent group of the formula -S-alkyl, where alkyl is as defined herein. Unless otherwise defined, such alkylthio groups typically contain from 1 to 10 carbon atoms and include, for example, -S-C_{1-4}alkyl and -S-C_{1-6}alkyl. Representative alkylthio groups include, by way of example, ethylthio, propylthio, isopropylthio, butylthio, *s*-butylthio and *t*-butylthio.

The term "alkenyl" means a monovalent unsaturated hydrocarbon group which may be linear or branched and which has at least one, and typically 1, 2 or 3, carbon-carbon double bonds. Unless otherwise defined, such alkenyl groups typically contain from 2 to 10 carbon atoms and include, for example, -C_{2-4}alkenyl and -C_{2-10}alkenyl. Representative alkenyl groups include, by way of example, ethenyl, *n*-propenyl, isopropenyl, *n*-but-2-enyl, *n*-hex-3-enyl and the like. The term "alkenylene" means a divalent alkenyl group, and includes groups such as -C_{2-3}alkenylene-.

The term "alkoxy" means a monovalent group of the formula -O-alkyl, where alkyl is as defined herein. Unless otherwise defined, such alkoxy groups typically contain from 1 to 10 carbon atoms and include, for example, -O-C_{1-4}alkyl and -O-C_{1-6}alkyl. Representative alkoxy groups include, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy, *t*-butoxy and the like.

The term "alkynyl" means a monovalent unsaturated hydrocarbon group which may be linear or branched and which has at least one, and typically 1, 2 or 3, carbon-carbon triple bonds. Unless otherwise defined, such alkynyl groups typically contain from 2 to 10 carbon atoms and include, for example, -C_{2-4}alkynyl and -C_{3-10}alkynyl. Representative alkynyl groups include, by way of example, ethynyl, *n*-propynyl, *n*-but-2-ynyl, *n*-hex-3-ynyl and the like. The term "alkynylene" means a divalent alkynyl group and includes groups such as -C_{2-3}alkynylene.

Amino acid residues are often designated as -C(O)-CHR-NH-, where the R moiety

is referred to as the "amino acid side chain." Thus, for the amino acid valine, HO-C(O)-CH[-CH(CH_3)$_2$]-NH_2, the side chain is -CH(CH_3)$_2$. Ther term "amino acid side chain" is intended to include side chains of the twenty common naturally occurring amino acids: alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. Of particular interest are the side chains of non-polar amino acids such as isoleucine, leucine, and valine.

The term "aryl" means a monovalent aromatic hydrocarbon having a single ring (for example, phenyl) or fused rings. Fused ring systems include those that are fully unsaturated (for example, naphthalene) as well as those that are partially unsaturated (for example, 1,2,3,4-tetrahydronaphthalene). Unless otherwise defined, such aryl groups typically contain from 6 to 10 carbon ring atoms and include, for example, -C_{6-10}aryl. Representative aryl groups include, by way of example, phenyl and naphthalene-1-yl, naphthalene-2-yl, and the like. The term "arylene" means a divalent aryl group such as phenylene.

The term "cycloalkyl" means a monovalent saturated carbocyclic hydrocarbon group. Unless otherwise defined, such cycloalkyl groups typically contain from 3 to 10 carbon atoms and include, for example, -C_{3-5}cycloalkyl, -C_{3-6}cycloalkyl and -C_{3-7}cycloalkyl. Representative cycloalkyl groups include, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The term "cycloalkylene" means a divalent aryl group such as -C_{4-8}cycloalkylene.

The term "halo" means fluoro, chloro, bromo and iodo.

The term "heteroaryl" means a monovalent aromatic group having a single ring or two fused rings and containing in the ring(s) at least one heteroatom (typically 1 to 3) selected from nitrogen, oxygen or sulfur. Unless otherwise defined, such heteroaryl groups typically contain from 5 to 10 total ring atoms and include, for example, -C_{2-9}heteroaryl. Representative heteroaryl groups include, by way of example, monovalent species of pyrrole, imidazole, thiazole, oxazole, furan, thiophene, triazole, pyrazole, isoxazole, isothiazole, pyridine, pyrazine, pyridazine, pyrimidine, triazine, indole, benzofuran, benzothiophene, benzoimidazole, benzthiazole, quinoline, isoquinoline, quinazoline, quinoxaline and the like, where the point of attachment is at any available carbon or nitrogen ring atom.

The term "optionally substituted" means that group in question may be

unsubstituted or it may be substituted one or several times, such as 1 to 3 times or 1 to 5 times. For example, an alkyl group that is "optionally substituted" with 1 to 5 fluoro atoms, may be unsubstituted, or it may contain 1, 2, 3, 4, or 5 fluoro atoms.

The term "protected derivatives thereof" means a derivative of the specified compound in which one or more functional groups of the compound are protected or blocked from undergoing undesired reactions with a protecting or blocking group. Functional groups that may be protected include, by way of example, carboxy groups, amino groups, hydroxyl groups, thiol groups, carbonyl groups and the like. Representative protecting groups for carboxy groups include esters (such as a *p*-methoxybenzyl ester), amides and hydrazides; for amino groups, carbamates (such as *t*-butoxycarbonyl) and amides; for hydroxyl groups, ethers and esters; for thiol groups, thioethers and thioesters; for carbonyl groups, acetals and ketals; and the like. Such protecting groups are well-known to those skilled in the art and are described, for example, in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

All other terms used herein are intended to have their ordinary meaning as understood by those of ordinary skill in the art to which they pertain.

General Synthetic Procedures

Compounds of the invention can be prepared from readily available starting materials using the following general methods, the procedures set forth in the Examples, or by using other methods, reagents, and starting materials that are known to those of ordinary skill in the art. Although the following procedures may illustrate a particular embodiment of the invention, it is understood that other embodiments of the invention can be similarly prepared using the same or similar methods or by using other methods, reagents and starting materials known to those of ordinary skill in the art. It will also be appreciated that where typical or preferred process conditions (for example, reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. While optimum reaction conditions will typically vary depending on various reaction parameters such as the particular reactants, solvents and quantities used, those of ordinary skill in the art can readily determine suitable reaction conditions using routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary or desired to prevent certain functional groups from undergoing

undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions and reagents for protection and deprotection of such functional groups are well-known in the art. Protecting groups other than those illustrated in the procedures described herein may be used, if desired. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein. More specifically, the following abbreviations and reagents are used in the schemes presented below:

P^1 represents an "amino-protecting group," a term used herein to mean a protecting group suitable for preventing undesired reactions at an amino group. Representative amino-protecting groups include, but are not limited to, *t*-butoxycarbonyl (BOC), trityl (Tr), benzyloxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), formyl, trimethylsilyl (TMS), *t*-butyldimethylsilyl (TBDMS), and the like. Standard deprotection techniques are used to remove the P^1 group. For example, deprotection of an N-BOC group can involve reagents such as TFA in DCM or HCl in 1,4-dioxane, while a Cbz group can be removed by employing catalytic hydrogenation conditions such as H_2 (1 atm), 10% Pd/C in an alcoholic solvent.

P^2 represents a "carboxy-protecting group," a term used herein to mean a protecting group suitable for preventing undesired reactions at a carboxy group. Representative carboxy-protecting groups include, but are not limited to, methyl, ethyl, *t*-butyl, benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), trimethylsilyl (TMS), *t*-butyldimethylsilyl (TBDMS), diphenylmethyl (benzhydryl, DPM) and the like. Standard deprotection techniques and reagents are used to remove the P^2 group, and may vary depending upon which group is used. For example, NaOH is commonly used when P^2 is methyl, an acid such as TFA or HCl is commonly used when P^2 is *t*-butyl, and catalytic hydrogenation condition such as H_2 (1 atm) and 10% Pd/C in alcoholic solvent ("H_2/Pd/C") may be used when P^2 is benzyl.

P^3 represents a "thiol-protecting group," a term used herein to mean a protecting group suitable for preventing undesired reactions at a thiol group. Representative thiol-protecting groups include, but are not limited to, ethers, esters such as $-C(O)CH_3$, and the like. Standard deprotection techniques and reagents such as NaOH, primary alkylamines, and hydrazine, may be used to remove the P^3 group.

P^4 represents a "tetrazole-protecting group," a term used herein to mean a

protecting group suitable for preventing undesired reactions at a tetrazole group. Representative tetrazole-protecting groups include, but are not limited to trityl and diphenylmethyl. Standard deprotection techniques and reagents such as TFA in DCM or HCl in 1,4-dioxane may be used to remove the P^4 group.

P^5 represents a "hydroxyl-protecting group," a term that is used herein to mean a protecting group suitable for preventing undesired reactions at a hydroxyl group. Representative hydroxyl-protecting groups include, but are not limited to C_{1-6}alkyls, silyl groups including triC_{1-6}alkylsilyl groups, such as trimethylsilyl (TMS), triethylsilyl (TES), and *tert*-butyldimethylsilyl (TBDMS); esters (acyl groups) including C_{1-6}alkanoyl groups, such as formyl, acetyl, and pivaloyl, and aromatic acyl groups such as benzoyl; arylmethyl groups such as benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), and diphenylmethyl (benzhydryl, DPM); and the like. Standard deprotection techniques and reagents are used to remove the P^5 group, and may vary depending upon which group is used. For example, H_2/Pd/C is commonly used when P^5 is benzyl, while NaOH is commonly used when P^5 is an acyl group.

P^6 represents a "sulfonamide-protecting group," a term that is used herein to mean a protecting group suitable for preventing undesired reactions at a sulfonamide group. Representative sulfonamide-protecting groups include, but are not limited to *t*-butyl and acyl groups. Exemplary acyl groups include aliphatic lower acyl groups such as the formyl, acetyl, phenylacetyl, butyryl, isobutyryl, valeryl, isovaleryl and pivaloyl groups, and aromatic acyl groups such as the benzoyl and 4-acetoxybenzoyl. Standard deprotection techniques and reagents are used to remove the P^6 group, and may vary depending upon which group is used. For example, HCl is commonly used when P^6 is *t*-butyl, while NaOH is commonly used when P^6 is an acyl group.

P^7 represents a "phosphate-protecting group or phosphinate-protecting group," a term used herein to mean a protecting group suitable for preventing undesired reactions at a phosphate or phosphinate group. Representative phosphate and phosphinate protecting groups include, but are not limited to C_{1-4}alkyls, aryl (for example, phenyl) and substituted aryls (for example, chlorophenyl and methylphenyl). The protected group can be represented by -P(O)$(OR)_2$, where R is a group such as a C_{1-6}alkyl or phenyl. Standard deprotection techniques and reagents such as TMS-I/2,6-lutidine, and H_2/Pd/C are used to remove the P^7 group such as ethyl, and benzyl, respectively.

In addition, L is used to designate a "leaving group," a term used herein to mean a

functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, triflate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

Suitable bases for use in these schemes include, by way of illustration and not limitation, potassium carbonate, calcium carbonate, sodium carbonate, triethylamine, pyridine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), N,N-diisopropylethylamine (DIPEA), sodium hydroxide, potassium hydroxide, potassium *t*-butoxide, and metal hydrides.

Suitable inert diluents or solvents for use in these schemes include, by way of illustration and not limitation, tetrahydrofuran (THF), acetonitrile (MeCN), *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), toluene, dichloromethane (DCM), chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), 1,4-dioxane, methanol, ethanol, water, and the like.

Suitable carboxylic acid/amine coupling reagents include benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), *O*-(7-azabenzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), dicyclohexylcarbodiimide (DCC), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC), carbonyldiimidazole (CDI), and the like. Coupling reactions are conducted in an inert diluent in the presence of a base, and are performed under conventional amide bond-forming conditions.

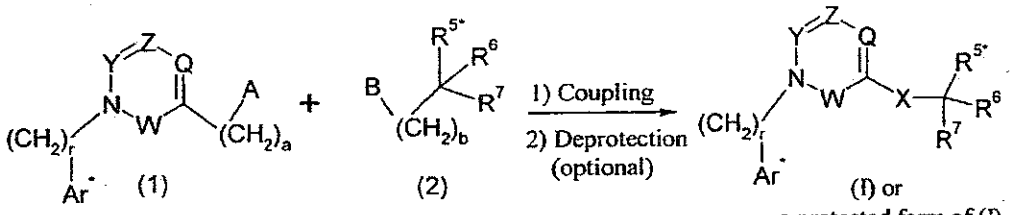
All reactions are typically conducted at a temperature within the range of about -78 °C to 100 °C, for example at room temperature. Reactions may be monitored by use of thin layer chromatography (TLC), high performance liquid chromatography (HPLC), and/or LCMS until completion. Reactions may be complete in minutes, or may take hours, typically from 1-2 hours and up to 48 hours. Upon completion, the resulting mixture or reaction product may be further treated in order to obtain the desired product. For example, the resulting mixture or reaction product may be subjected to one or more of the following procedures: concentrating or partitioning (for example, between EtOAc and water or between 5% THF in EtOAc and 1M phosphoric acid); extraction (for example, with EtOAc, $CHCl_3$, DCM, HCl); washing (for example, with saturated aqueous NaCl, saturated $NaHCO_3$, Na_2CO_3 (5%), $CHCl_3$ or 1M NaOH); drying (for example, over

$MgSO_4$, over Na_2SO_4, or *in vacuo*); filtering; crystallizing (for example, from EtOAc and hexane); and/or being concentrated (for example, *in vacuo*).

By way of illustration, compounds of formula I, as well as their salts, solvates, and prodrugs can be prepared by one or more of the following exemplary processes.

Scheme I: Peptide Coupling Reaction and Optional Deprotection

The X moiety contains one or more amide groups, and therefore the compounds of the invention may be formed by a coupling reaction under conventional amide bond-forming conditions, followed by a deprotection step if needed. In Scheme I, the A and B moieties couple to form X, and the sum of a and b is in the range of 0 to 11. Thus, one moiety comprises an amine group and one moiety comprises a carboxylic acid group, i.e., A is $-NH_2$ and B is -COOH or A is -COOH and B is $-NH_2$.



Scheme I

For example, to synthesize a compound of formula I where X is -CONH-, A would be -COOH and B would be $-NH_2$. Similarly, A as $-NH_2$ and B as -COOH would couple to form -NHCO- as the X moiety. A and B can be readily modified if a longer X is desired, whether it contains an alkylene portion or additional amide groups. For example, A as $-CH_2NH_2$ and B as -COOH would couple to form $-CH_2NHCO-$ as the X moiety.

It is understood that the carbon atoms in the $-(CH_2)_a$ and $-(CH_2)_b$ groups make up the "X" linker. Therefore, these carbon atoms may be substituted with one or more R^{4b} groups. Furthermore, one $-CH_2-$ group in the $-(CH_2)_a$ or the $-(CH_2)_b$ group may be replaced with a $-C_{4-8}$cycloalkylene-, $-CR^{4d}=CH-$, or $-CH=CR^{4d}-$ group.

Ar* represents Ar-R^{1*}, where R^{1*} may represent R^1 as defined herein, or a protected form of R^1 (for example, -tetrazol-5-yl-P^4 or $-C(O)O-P^2$ such as $-C(O)O-C_{1-6}$alkyl), or a precursor of R^1 (for example, -CN that is then converted to tetrazole, or nitro that is then converted to amino from which the desired R^1 is prepared). R^{5*} represents R^5 as defined herein, or a protected form of R^5. Therefore, when R^{1*} represents R^1 and R^{5*} represents R^5, the reaction is complete after the coupling step.

On the other hand, when R^{1*} represents a protected form of R^1 and/or R^{5*} represents a protected form of R^5, a subsequent global or sequential deprotection step would yield the

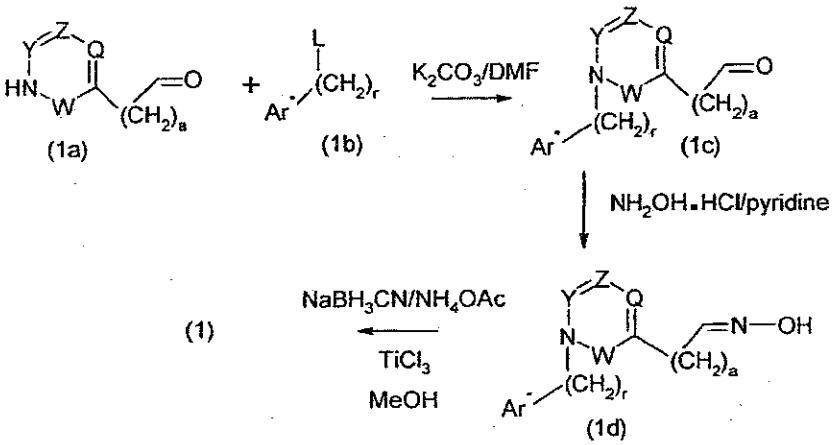
non-protected compound. Similarly, when R^1* represents a precursor of R^1, a subsequent conversion step would yield the desired compound. Reagents and conditions for the deprotection vary with the nature of protecting groups in the compound. Typical deprotection conditions when R^5* represents C_{0-3}alkylene-S-P^3, include treating the compound with NaOH in an alcoholic solvent at 0 °C or room temperature to yield the non-protected compound. Typical deprotection conditions when R^1* represents C(O)O-P^2 where P^2 refers to *t*-butyl include treating the compound with TFA in DCM at room temperature to yield the non-protected compound. Thus, one method of preparing compounds of the invention involves coupling compounds (1) and (2), with an optional deprotection step when R^1* is a protected form of R^1 and/or R^5* is a protected form of R^5, thus forming a compound of formula I or a pharmaceutically acceptable salt thereof.

Examples of compound (1) include: 4'-(5-aminomethyl-2-butyl-4-chloroimidazol-1-ylmethyl)biphenyl-2-carboxylic acid *t*-butyl ester; 2-butyl-3-(4-methoxycarbonylbenzyl)-3H-imidazole-4-carboxylic acid; 4-(5-aminomethyl-2-butyl-imidazol-1-ylmethyl)-2,3-difluorobenzoic acid methyl ester; C-{2-butyl-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-yl}methylamine; 4'-(3-aminomethyl-5-propyl[1,2,4]triazol-4-ylmethyl)biphenyl-2-carboxylic acid; 4'-(3-aminomethyl-6-butyl-2-oxo-2H-pyridin-1-ylmethyl)biphenyl-2-carboxylic acid; 4'-(5-aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)biphenyl-2-carboxylic acid *t*-butyl ester; 4'-(5-aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester; 4'-(5-aminomethyl-2-propoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester; and 4'-(5-aminomethyl-4-chloro-2-ethoxyimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester.

Examples of compound (2) include: *(R)*-1-benzyl-2-hydroxycarbamoylethyl)-carbamic acid; *(R)*-2-((*R*)-2-amino-3-phenylpropyldisulfanyl)-1-benzylethylamine; *(S)*-2-acetylsulfanyl-4-methylpentanoic acid; 2-acetylsulfanylmethyl-4-methyl-pentanoic acid and *(S)*-2-acetylsulfanylmethyl-4-methylpentanoic acid; and *(R)*-2-(2-benzyloxycarbamoyl-3-phenypropionylamino)succinic acid 1-methyl ester.

Compound (1)

Compound (1) can be prepared by the following reaction:

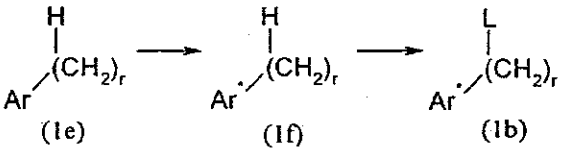


Compounds (1a) and (1b) are combined with K_2CO_3 in a solvent such as DMF to form intermediate (1c), which then undergoes oxime formation by reaction with hydroxylamine hydrochloride (NH_2OH•HCl) in pyridine to form intermediate (1d). Intermediate (1d) is reacted with $NaBH_3CN$, NH_4OAc, and $TiCl_3$, in a solvent such as MeOH, to form Compound (1) where A is -NH(R^{4a}). Compound (1) where A is -COOH can be formed by reacting intermediate (1c) with 2-methyl-2-butene, sodium dihydrogen phosphate and sodium chlorite.

Compound (1a)

Compound (1a) can be readily prepared by techniques that are well known in the art and/or is commercially available. Examples of compound (1a) include 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde, 5-bromo-2-butyl-3H-imidazole-4-carbaldehyde, 5-bromo-2-ethoxy-3H-imidazole-4-carbaldehyde, bromo-2-propoxy-3H-imidazole-4-carbaldehyde, and 5-chloro-2-ethoxy-3H-imidazole-4-carbaldehyde, all of which are either commercially available or are readily synthesized by techniques that are well known in the art. For example: 5-bromo-2-butyl-3H-imidazole-4-carbaldehyde can be made reacting 2-butyl-3H-imidazole-4-carbaldehyde with *N*-bromosuccinimide in a suitable solvent such as DMF; 5-bromo-2-ethoxy-3H-imidazole-4-carbaldehyde can be prepared by reacting 2,4,5-tribromo-1H-imidazole with [β-(trimethylsilyl)ethoxy]methyl chloride, followed by reaction with potassium *t*-butoxide in ethanol, then *n*-butyllithium and DMF, with a final deprotection step; and 5-chloro-2-ethoxy-3H-imidazole-4-carbaldehyde can be prepared by reacting 4,5-dibromo-2-ethoxy-1-(2-trimethylsilanylethoxymethyl)-1H-imidazole and hexachloroethane then DMF, both steps conducted with *n*-butyllithium, N,N,N',N'-tetramethylethylenediamine, and appropriate solvents, with a final deprotection step.

Compound (1b)

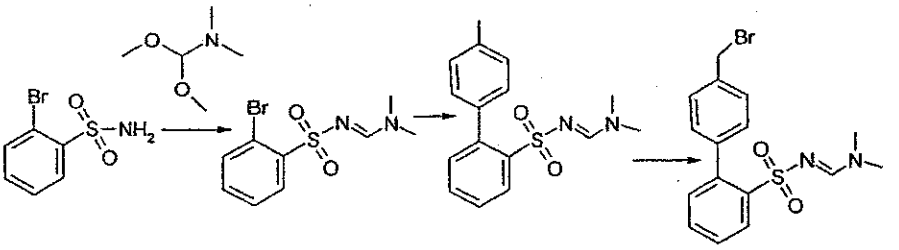


The starting material (1e) can be prepared using synthetic methods that are reported in the literature, for example Duncia et al. (1991) *J. Org. Chem.* 56: 2395-400, and references cited therein. Alternatively, the starting material in a protected form (1f) may be commercially available. Using a commercially available non-protected starting material (1e), the R^1 group is first protected to form protected intermediate (1f), then the leaving group (L) is added to form compound (1b), for example, by a halogenation reaction. For example, a bromination reaction of a methyl group of *N*-triphenylmethyl-5-[4'-methylbiphenyl-2-yl]tetrazole is described in Chao et al. (2005) *J. Chinese Chem. Soc.* 52:539-544. In addition, when Ar* has a -CN group, it can be subsequently converted to the desired tetrazolyl group, which may be protected. Conversion of the nitrile group is readily achieved by reaction with a suitable azide such as sodium azide, trialkyltin azide (particularly tributyltin azide) or triaryltin azide. Compound (1b) when Ar has one of the remaining formulas is readily synthesized using similar techniques or other methods as are well known in the art.

Exemplary methods of preparing compound (1b) include the following. A solution of the starting material (1e) and thionyl chloride are stirred at room temperature. After completion, the reaction is concentrated *in vacuo* to afford a solid, which is dissolved in a solvent such as THF and cooled to 0 °C. Potassium *t*-butoxide is then added. Upon completion, the reaction is partitioned between EtOAc and water. The organic layer is washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to afford compound (1f). Alternately, HCl is added to a solution of the starting material (1e) and a solvent such as methanol. The reaction is heated to reflux and stirred until completion (~48 hours), then cooled and concentrated. The recovered material is dried *in vacuo* to obtain intermediate (1f). Intermediate (1f), benzoyl peroxide, and *N*-bromosuccinimide are dissolved in CCl_4 or benzene, and heated to reflux. The reaction is stirred to completion, cooled to room temperature, filtered, and concentrated *in vacuo*. The resulting residue is crystallized from diethyl ether and hexane or flash chromatographed to give compound (1b). Examples of compound (1e) include: 4'-methylbiphenyl-2-carboxylic acid; 2,3-difluoro-4-methyl-benzoic acid; and 2-fluoro-4-methylbenzoic acid.

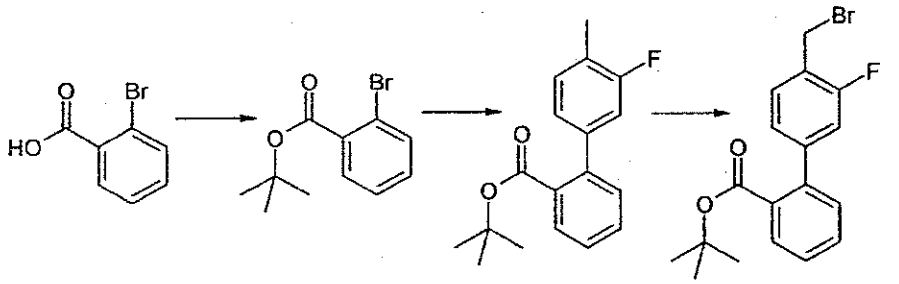
Examples of compound (1f) include *N*-triphenylmethyl-5-[4'-methylbiphenyl-2-yl]tetrazole.

Compound (1b) where R^1 is $-SO_2NHR^{1d}$ may be synthesized as follows:



The starting material, 2-bromobenzene-1-sulfonamide, is commercially available. Reaction of 2-bromobenzene-1-sulfonamide in a solvent such as DMF, with 1,1-dimethoxy-N,N-dimethylmethanamine, followed by the addition of sodium hydrogen sulfate in water, yields 2-bromo-N-[1-dimethylaminometh-*(E)*-ylidene]benzenesulfonamide. This compound is reacted with 4-methylphenylboronic acid to yield 4'-methylbiphenyl-2-sulfonic acid 1-dimethylaminometh-*(E)*-ylideneamide, then the $-(CH_2)_r-L^1$ moiety is added, for example, by a halogenation reaction, to form compound (1b).

Compound (1b) where the Ar moiety is substituted may be synthesized as follows:



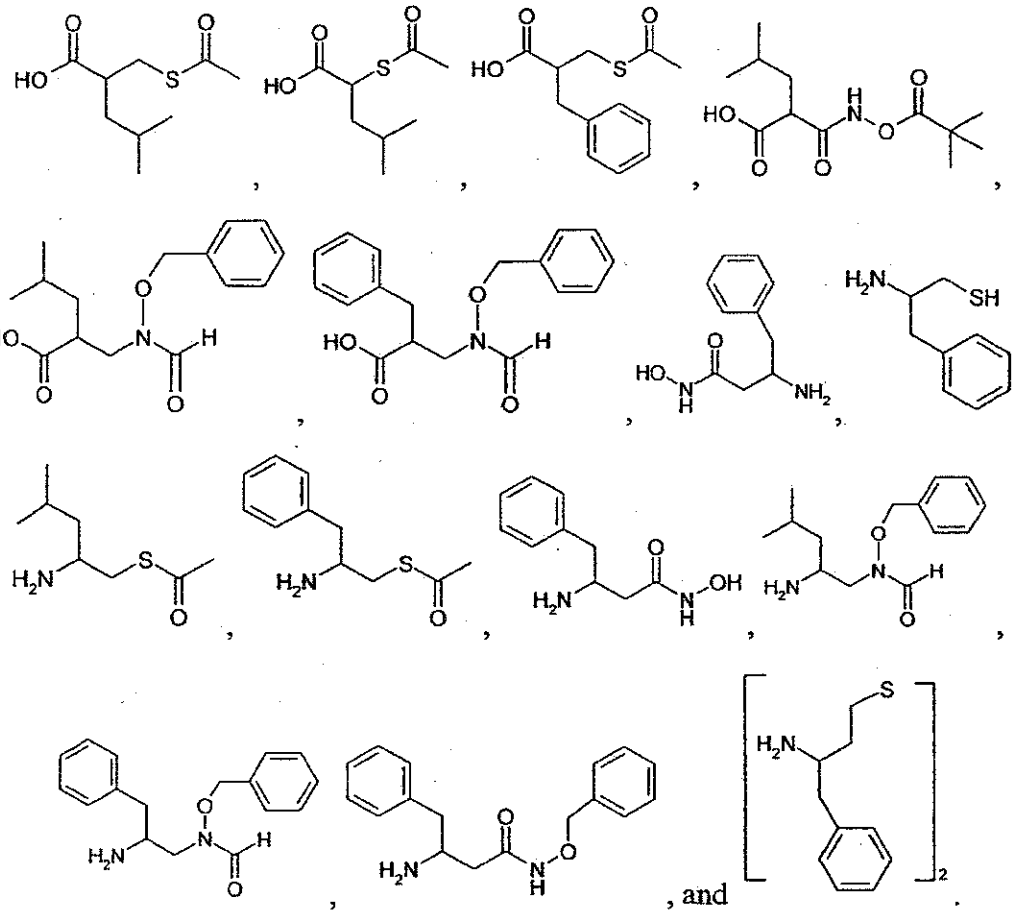
The starting material, 2-bromobenzoic acid, is commercially available. Reaction of 2-bromobenzoic acid in a suitable solvent, with *t*-butyl alcohol, DCC and DMAP, yields 2-bromo-benzoic acid *t*-butyl ester. This compound is reacted with 3-fluoro-4-methylphenylboronic acid to yield 3'-fluoro-4'-methyl-biphenyl-2-carboxylic acid *t*-butyl ester, then the $-(CH_2)_r-L^1$ moiety is added, for example, by a halogenation reaction, to form compound (1b).

Examples of compound (1b) include 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole; 4'-bromomethylbiphenyl-2-carboxylic acid *t*-butyl ester; 4-bromomethylbenzoic acid methyl ester; 4-bromomethyl-2,3-difluorobenzoic acid methyl ester; 4'-formyl-biphenyl-2-sulfonic acid *t*-butylamide; 4'-aminomethylbiphenyl-2-carboxylic acid *t*-butyl

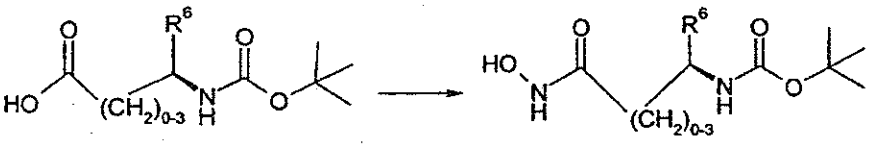
ester; and 4'-bromomethyl-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester.

Compound (2)

Compound (2) is readily synthesized by following the techniques described in the literature, for example, Neustadt et al (1994) *J. Med. Chem.* 37:2461-2476 and Moree et al. (1995) *J. Org. Chem.* 60: 5157-69, as well as by using the exemplary procedures described below. Examples of Compound (2), depicted without chirality, include:



Preparation of chiral amino hydroxamate compound (2^i)

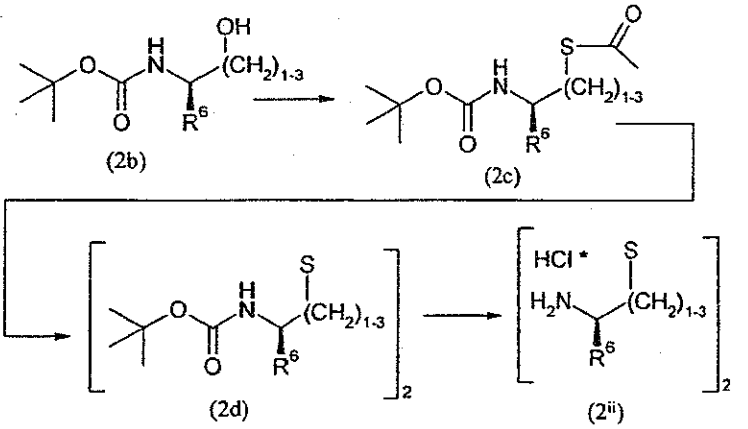


(2a) (2^i)

A base such as DIPEA and a coupling agent such as EDC are added to a solution of compound (2a) in DMF containing HOBt and hydroxylamine hydrochloride. The mixture is stirred at room temperature until completion (~12 hours), then concentrated *in vacuo*.

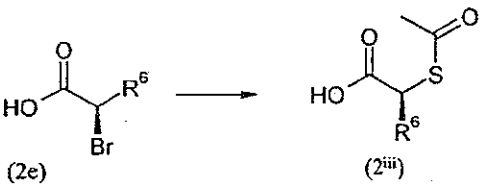
The resulting material is distributed between 5% THF in EtOAc and 1M phosphoric acid. The organic layer is collected and washed with a base such as 1M NaOH. The alkaline aqueous layer is then acidified, for example with 1M phosphoric acid, and extracted with EtOAc. The organic layer is evaporated and the residue purified by silica gel chromatography to afford compound (2^{i}). Examples of compound (2a) include *(R)*-3-*t*-butoxycarbonylamino-4-phenylbutyric acid.

Preparation of chiral amino sulfhydryl dimer compound (2^{ii})



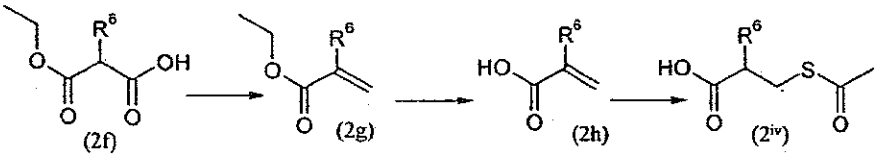
Diisopropyl azodicarboxylate is added to a solution of triphenylphosphine in a solvent such as THF, cooled in an ice bath. The solution is stirred and compound (2b) and thioacetic acid are added. The mixture is stirred at 0 °C for 1 hour, then stirred at room temperature until completion (~12 hours). The mixture is stripped, diluted with EtOAc, and washed with a cold saturated $NaHCO_3$ solution. The organic layer is dried over $MgSO_4$, and the filtrate evaporated to dryness. The resulting material is flash chromatographed to provide compound (2c). Compound (2c) is dissolved in solvent, followed by the addition of a base such as 1M LiOH. Air is bubbled through the solution for 1 hour followed by the addition of solvent. The reaction is stirred at room temperature until completion (~24 hours). The solution is then acidified to pH~5, for example with acetic acid. The precipitate is filtered and rinsed with deionized water, producing the compound (2d) dimer. The solid is suspended in MeCN, then concentrated under reduced pressure. The recovered material is dissolved in 4M HCl in 1,4-dioxane and stirred at room temperature until the reaction is complete (~2 hours). The reaction is then concentrated under reduced pressure, and triturated with EtOAc. The product is filtered, washed with EtOAc, and dried *in vacuo* to provide compound (2^{ii}). Examples of compound (2b) include ((*R*)-1-benzyl-2-hydroxyethyl)carbamic acid *t*-butyl ester.

Preparation of chiral sulfanyl acid compound (2^{iii})



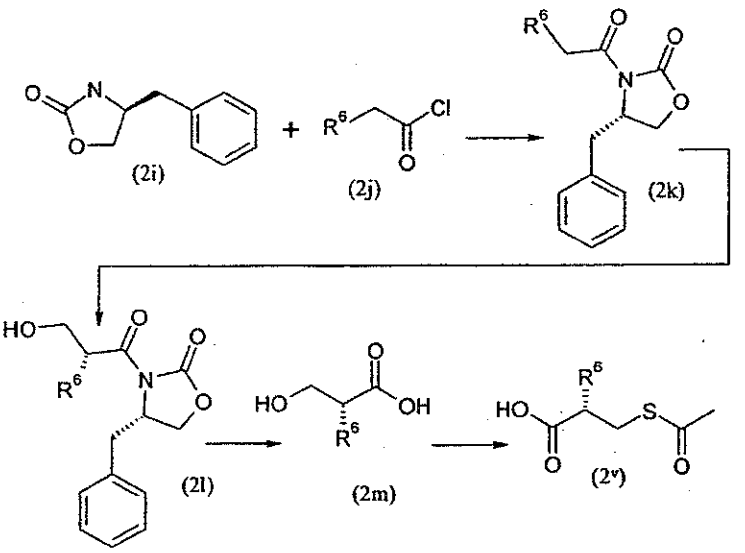
Compound (2e) is formed by dissolving a compound such as D-leucine (for R^6 = isobutyl, for example) in 3M HBr (aqueous) and cooled to 0 °C. A solution of $NaNO_2$ in water is added, and the reaction stirred at 0 °C until completion (~ 2.5 hours). The reaction is then extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to afford compound (2e). Compound (2e) is combined with potassium thioacetate or sodium thioacetate and DMF, and the reaction stirred at room temperature until completion (~ 1 hour). Water is added. The reaction is then extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to provide compound (2^{iii}). The product is purified by silica gel chromatography. Examples of compound (2e) include *(R)*-2-bromo-4-methylpentanoic acid. Examples of compound (2^{iii}) include *(S)*-2-acetylsulfanyl-4-methylpentanoic acid.

Preparation of sulfanyl acid compound (2^{iv})



Compound (2f) is mixed with diethylamine and cooled in an ice bath. An aqueous formaldehyde solution (37%) is then added, and the mixture stirred at 0 °C for approximately 2 hours, warmed to room temperature and stirred overnight. The mixture is then extracted with ether, washed, dried, and evaporated to dryness, to provide compound (2g). Compound (2g) is then dissolved in 1,4-dioxane, and a 1M NaOH solution is added. The mixture is stirred at room temperature until completion (approximately 2 days). The organic solvent is removed *in vacuo*, and the aqueous residue is rinsed with EtOAc and acidified to approximately pH 1 with concentrated HCl. The product is extracted with EtOAc, dried, and evaporated to dryness to yield compound (2h). Compound (2h) is combined with thiolacetic acid (10 mL), and the mixture is stirred at 80 °C until completion (approximately 2 hours), then concentrated to dryness to yield compound (2^{iv}), which is dissolved in toluene and concentrated to remove any trace of thiolacetic acid. Examples of compound (2f) include 2-benzylmalonic acid monoethyl ester (R^6 = benzyl) and 2-isobutylmalonic acid monoethyl ester (R^6 = isobutyl).

Preparation of chiral sulfanyl acid compound (2^v)



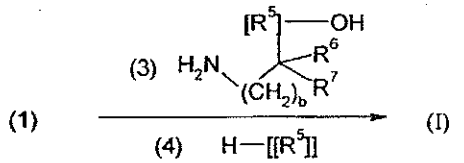
Compound (2i), *(S)*-4-benzyl-2-oxazolidinone, is commercially available. Compound (2j) is also typically commercially available or can be readily synthesized. For example, R^6-CH_2-COOH (for example, isocaproic acid or 3-phenylpropionic acid) is dissolved in methylene chloride and thionyl chloride is added. The mixture is stirred at room temperature until the reaction is complete (for example, overnight), and then concentrated to provide (2j). Examples of compound (2j) include 4-methylpentanoyl chloride and 3-phenylpropionyl chloride.

Compound (2i) is dissolved in a suitable solvent and cooled (-78 °C) under nitrogen. *n*-Butyllithium in hexanes is added dropwise and stirred, followed by the addition of (2j) dropwise. The mixture is stirred at -78 °C, then warmed to 0 °C. Saturated $NaHCO_3$ is added and the mixture warmed to room temperature. The mixture is extracted, washed, dried, filtered, and concentrated to afford (2k). Compound (2k) is dissolved in DCM and stirred at 0 °C under nitrogen. 1M Titanium tetrachloride is added, followed by 1,3,5-trioxane, all in appropriate solvents. A second equivalent of 1M titanium tetrachloride is added and the mixture stirred at 0 °C until the reaction is complete. The reaction is then quenched with saturated ammonium chloride. Appropriate solvents are added, the aqueous phase is extracted, and the organic layers are combined, dried, filtered, and concentrated to provide (2l), which can then be purified by silica gel chromatography or used in the next step without further purification. Compound (2l) is dissolved in a solvent, to which is added 9 M hydrogen peroxide in water, followed by the dropwise addition of 1.5 M lithium hydroxide monohydrate in water. The mixture is warmed to

room temperature and stirred. Optionally, potassium hydroxide may be added and the mixture heated at 60 °C then cooled at room temperature. To this is added an aqueous solution of sodium sulfite followed by water and chloroform. The aqueous layer is extracted, acidified and extracted again. The organic layer is washed, dried, filtered, and rotovaped to provide (2m). Triphenylphosphine is dissolved in an appropriate solvent and cooled at 0 °C (ice bath). Diisopropyl azodicarboxylate is added dropwise and the mixture stirred. Compound (2m) and thioacetic acid, dissolved in an appropriate solvent, are added dropwise to the mixture. After the addition, the mixture is removed from the ice bath and stirred at room temperature until the reaction is complete (approximately 3.5 hours), concentrated, and then partitioned. The organic layer is extracted and the combined aqueous extracts washed, acidified and extracted. The organic layer is washed again, dried, filtered, and rotovaped to provide compound (2^v). Examples of compound (2^v) include *(S)*-2-acetylsulfanylmethyl-4-methylpentanoic acid.

Scheme II: Peptide Coupling Reaction

Compounds of formula I can also be prepared by coupling compound (3) and compound (1) where A is -COOH, followed by reaction with compound (4). In compounds (1) and (3), the sum of a and b is in the range of 0 to 11. In compounds (3) and (4), the $[R^5]$ and $[[R^5]]$ moieties represent portions of the R^5 moiety. For example, if R^5 is $-CH_2C(O)N(OH)H$, then $[R^5]$ would be $-CH_2C(O)-$ and $[[R^5]]$ would be -N(OH)H.



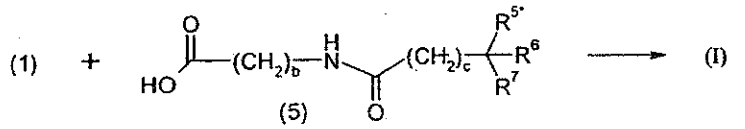
Scheme II

The amide coupling of compounds (1) and (3) is typically conducted at room temperature with coupling reagents such as pentafluorophenol combined with EDC and DIPEA in solvents such as DMF. Compounds (3) and (4) are available commercially or can be readily synthesized by techniques that are well known in the art. Examples of compound (3) include 3-amino-4-(3-chlorophenyl)butyric acid. Examples of compound (4) include H_2NOH, H_2NO-benzyl, and H_2NO-*t*-butyl.

Scheme III: Peptide Coupling Reaction

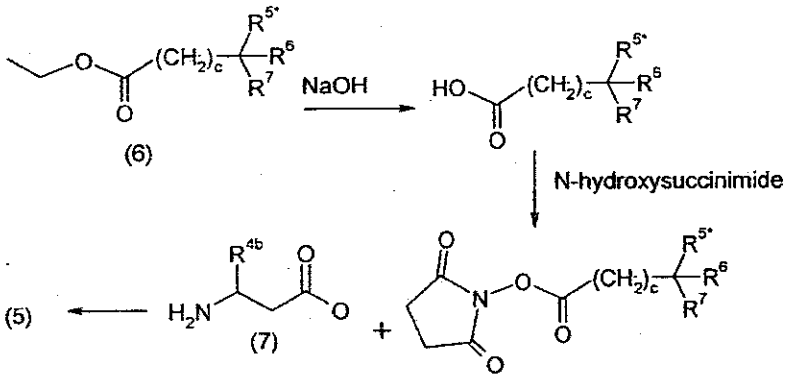
Compounds of formula I can also be prepared by coupling compounds (1) and (5) under conventional amide bond-forming conditions. This synthesis is particularly useful

for preparing compounds of formula I where more than one -CH_2- moiety in the alkylene is replaced with -NR^{4a}-C(O)- or -C(O)-NR^{4a}-. In the compounds depicted below, b will typically be at least 1 and the sum of a, b and c is in the range of 1 to 10.



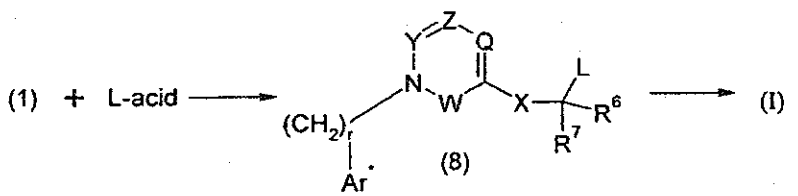
Scheme III

Compound (5) is formed by converting the ester compound (6) to the acid with a base, converting the acid to the dioxopyrrolidinyl ester with N-hydroxysuccinimide, then converting the dioxopyrrolidinyl ester with compound (7) to form compound (5). Compound (5) may have one or more R^{4b} substituents on the carbon atoms in the -$(CH_2)_b$- and/or -$(CH_2)_c$- portions.



Compound (6) can be readily synthesized by following the techniques described in the literature, for example, Fournie-Zaluski et al. (1985) *J. Med. Chem.* *28*(9):1158-1169). Examples of compound (6) include 2-benzyl-N-benzyloxymalonamic acid ethyl ester. Compound (7) is available commercially or can be readily synthesized by techniques that are well known in the art. This reactant is particularly useful where a carbon atom in the alkylene moiety in X is substituted with an R^{4b} group. For example, 2-aminosuccinic acid 1-methyl ester is an example of compound (7) that is useful for preparing compounds where R^{4b} is -COOH, where the R^{4b} moiety is in a protected form, -COOMe.

Scheme IV: Two-Step Reaction



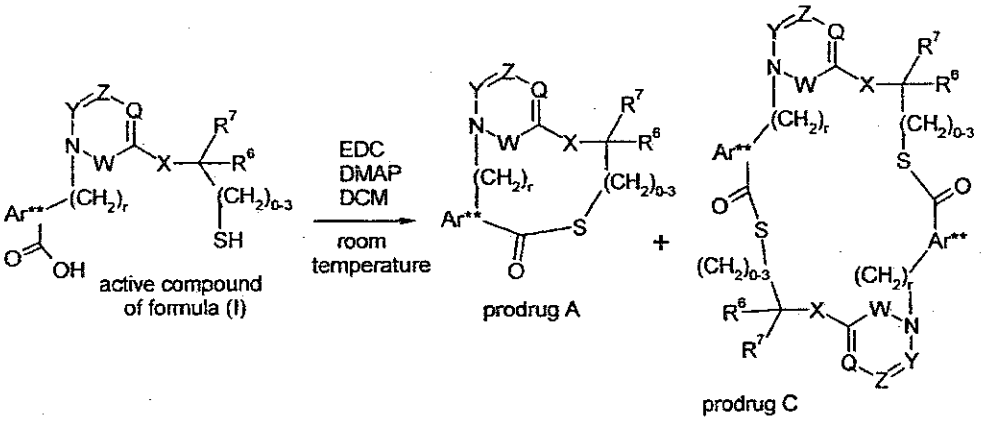
Scheme IV

Compounds of formula I can also be prepared by a two-step method, where the first step involves the addition of a halogen-substituted alkanoic acid ("L-acid") such as α-bromoisocaproic acid to compound (1), to provide Intermediate (8), where L is a leaving group such as bromo. Intermediate (8) is then reacted with a thiol or sulfur-containing nucleophilic reactant that contains the desired R^{5*} group, for example, potassium thioacetate or thiourea.

If desired, pharmaceutically acceptable salts of the compounds of formula I can be prepared by contacting the free acid or base form of a compound of formula I with a pharmaceutically acceptable base or acid.

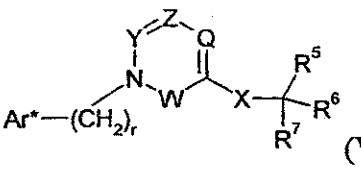
Scheme V: Pro-drug Synthesis

Prodrugs can be readily synthesized using the techniques described above. In addition, prodrugs can be formed by further modifying active compounds of formula I where Ar**-COOH represents Ar-R^1 and R^5 is -C_{0-3}alkylene-SH, as shown below:



Thus, both prodrug A and prodrug C can be readily synthesized from the corresponding active prodrug.

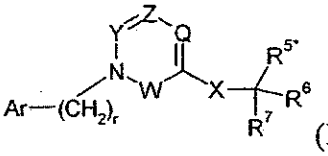
Certain intermediates described herein are believed to be novel and accordingly, such compounds are provided as further aspects of the invention including, for example, the compounds of formulas VIII, IX and X, and salts thereof:



(VIII)

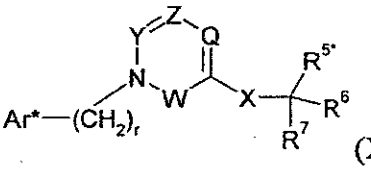
Where Ar* is Ar-R^1*; Ar, r, Y, Z, Q, W, X, and R^{5-7} are as defined for formula I; and R^1* is selected from -C(O)O-P^2, -SO_2O-P^5, -SO_2NH-P^6, -P(O)(O-P^7)$_2$, -OCH(CH_3)-C(O)O-P^2, -OCH(aryl)-C(O)O-P^2, and tetrazol-5-yl-P^4; where P^2 is a carboxy-protecting group, P^4 is a

tetrazole-protecting group, P^5 is a hydroxyl-protecting group, P^6 is a sulfonamide-protecting group, and P^7 is a phosphate-protecting group;



(IX)

Where Ar, r, Y, Z, Q, W, X, and R^{6-7} are as defined for formula I; R^{5*} is selected from $-C_{0-3}$alkylene-S-P^3, $-C_{0-3}$alkylene-C(O)NH(O-P^5), $-C_{0-3}$alkylene-N(O-P^5)-C(O)R^{5d}, $-C_{0-1}$alkylene-NHC(O)CH_2S-P^3, -NH-C_{0-1}alkylene-P(O)(O-P^7)$_2$, $-C_{0-3}$alkylene-P(O)(O-P^7)-R^{5e}, $-C_{0-2}$alkylene-CHR^{5f}-C(O)O-P^2 and $-C_{0-3}$alkylene-C(O)NR^{5g}-CHR^{5h}-C(O)O-P^2; and R^{5d-h} are as defined for formula I; where P^2 is a carboxy-protecting group, P^3 is a thiol-protecting group, P^5 is a hydroxyl-protecting group, and P^7 is a phosphate-protecting group; and



(X)

Where Ar* is Ar-R^1*; Ar, r, Y, Z, Q, W, X, and R^{6-7} are as defined for formula I; R^1* is selected from -C(O)O-P^2, $-SO_2$O-P^5, $-SO_2$NH-P^6, -P(O)(O-P^7)$_2$, $-OCH(CH_3)$-C(O)O-P^2, -OCH(aryl)-C(O)O-P^2, and tetrazol-5-yl-P^4; R^{5*} is selected from is selected from $-C_{0-3}$alkylene-S-P^3, $-C_{0-3}$alkylene-C(O)NH(O-P^5), $-C_{0-3}$alkylene-N(O-P^5)-C(O)R^{5d}, $-C_{0-1}$alkylene-NHC(O)CH_2S-P^3, -NH-C_{0-1}alkylene-P(O)(O-P^7)$_2$, $-C_{0-3}$alkylene-P(O)(O-P^7)-R^{5e}, $-C_{0-2}$alkylene-CHR^{5f}-C(O)O-P^2 and $-C_{0-3}$alkylene-C(O)NR^{5g}-CHR^{5h}-C(O)O-P^2; and R^{5d-h} are as defined for formula I; where P^2 is a carboxy-protecting group, P^3 is a thiol-protecting group, P^4 is a tetrazole-protecting group, P^5 is a hydroxyl-protecting group, P^6 is a sulfonamide-protecting group, and P^7 is a phosphate-protecting group. Thus, another method of preparing compounds of the invention involves deprotecting a compound of formula VIII, IX, or X.

Further details regarding specific reaction conditions and other procedures for preparing representative compounds of the invention or intermediates thereof are described in the Examples set forth below.

UTILITY

Compounds of the invention possess angiotensin II type 1 (AT_1) receptor antagonist activity. In one embodiment, compounds of the invention are selective for inhibition of the

AT_1 receptor over the AT_2 receptor. Compounds of the invention also possess neprilysin (NEP) inhibition activity, that is, the compounds are able to inhibit enzyme-substrate activity. In another embodiment, the compounds do not exhibit significant inhibitory activity of the angiotensin-converting enzyme. Compounds of formula I may be active drugs as well as prodrugs. Thus, when discussing the activity of compounds of the invention, it is understood that any such prodrugs have the expected activity once metabolized.

One measure of the affinity of a compound for the AT_1 receptor is the inhibitory constant (K_i) for binding to the AT_1 receptor. The pK_i value is the negative logarithm to base 10 of the K_i. One measure of the ability of a compound to inhibit NEP activity is the inhibitory concentration (IC_{50}), which is the concentration of compound that results in half-maximal inhibition of substrate conversion by the NEP enzyme. The pIC_{50} value is the negative logarithm to base 10 of the IC_{50}. Compounds of formula I and pharmaceutically acceptable salts thereof that have both AT_1 receptor-antagonizing activity and NEP enzyme-inhibiting activity are of particular interest, including those that exhibit a pK_i at the AT_1 receptor greater than or equal to about 5.0, and exhibit a pIC_{50} for NEP greater than or equal to about 5.0.

In one embodiment, compounds of interest have a pK_i at the AT_1 receptor $\geq$ about 6.0, a pK_i at the AT_1 receptor $\geq$ about 7.0, or a pK_i at the AT_1 receptor $\geq$ about 8.0. Compounds of interest also include those having a pIC_{50} for NEP $\geq$ about 6.0 or a pIC_{50} for NEP $\geq$ about 7.0. In another embodiment, compounds of interest have a pK_i at the AT_1 receptor within the range of about 8.0-10.0 and a pIC_{50} for NEP within the range of about 7.0-10.0.

In another embodiment, compounds of particular interest have a pK_i for binding to an AT_1 receptor greater than or equal to about 7.5 and a NEP enzyme pIC_{50} greater than or equal to about 7.0. In another embodiment, compounds of interest have a pK_i greater than or equal to about 8.0 and a pIC_{50} greater than or equal to about 8.0.

It is noted that in some cases, compounds of the invention, while still having dual activity, may possess either weak AT_1 receptor antagonist activity or weak NEP inhibition activity. In such cases, those of skill in the art will recognize that these compounds still have utility as primarily either a NEP inhibitor or a AT_1 receptor antagonist, respectively, or have utility as research tools.

Exemplary assays to determine properties of compounds of the invention, such as

the AT_1 receptor binding and/or NEP inhibiting activity, are described in the Examples and include by way of illustration and not limitation, assays that measure AT_1 and AT_2 binding (described in Assay 1), and NEP inhibition (described in Assay 2). Useful secondary assays include assays to measure ACE inhibition (also described in Assay 2) and aminopeptidase P (APP) inhibition (described in Sulpizio et al. (2005) *JPET* 315:1306-1313). A pharmacodynamic assay to assess the *in vivo* inhibitory potencies for ACE, AT_1, and NEP in anesthetized rats is described in Assay 3 (see also Seymour et al. *Hypertension* 7(Suppl I):I-35-I-42, 1985 and Wigle et al. *Can. J. Physiol. Pharmacol.* 70:1525-1528, 1992), where AT_1 inhibition is measured as the percent inhibition of the angiotensin II pressor response, ACE inhibition is measured as the percent inhibition of the angiotensin I pressor response, and NEP inhibition is measured as increased urinary cyclic guanosine 3', 5'-monophosphate (cGMP) output. Useful *in vivo* assays include the conscious spontaneously hypertensive rat (SHR) model, which is a renin dependent hypertension model useful for measuring AT_1 receptor blocking (described in Assay 4; see also Intengan et al. (1999) *Circulation* 100(22):2267-2275 and Badyal et al. (2003) *Indian Journal of Pharmacology* 35:349-362), and the conscious desoxycorticosterone acetate-salt (DOCA-salt) rat model, which is a volume dependent hypertension model useful for measuring NEP activity (described in Assay 5; see also Trapani et al. (1989) *J. Cardiovasc. Pharmacol.* 14:419-424, Intengan et al. (1999) *Hypertension* 34(4):907-913, and Badyal et al. (2003) *supra*). Both the SHR and DOCA-salt models are useful for evaluating the ability of a test compound to reduce blood pressure. The DOCA-salt model is also useful to measure a test compound's ability to prevent or delay a rise in blood pressure. Compounds of the invention are expected to antagonize the AT_1 receptor and/or inhibit the NEP enzyme in any of the assays listed above, or assays of a similar nature. Thus, the aforementioned assays are useful in determining the therapeutic utility of compounds of the invention, for example, their utility as antihypertensive agents. Other properties and utilities of compounds of the invention can be demonstrated using other *in vitro* and *in vivo* assays well-known to those skilled in the art.

Compounds of the invention are expected to be useful for the treatment and/or prevention of medical conditions responsive to AT_1 receptor antagonism and/or NEP inhibition. Thus it is expected that patients suffering from a disease or disorder that is treated by antagonizing the AT_1 receptor and/or by inhibiting the NEP enzyme can be treated by administering a therapeutically effective amount of a compound of the

invention. For example, by antagonizing the AT_1 receptor and thus interfering with the action of angiotensin II on its receptors, these compounds are expected to find utility in preventing the increase in blood pressure produced by angiotensin II, a potent vasopressor. In addition, by inhibiting NEP, the compounds are also expected to potentiate the biological effects of endogenous peptides that are metabolized by NEP, such as the natriuretic peptides, bombesin, bradykinins, calcitonin, endothelins, enkephalins, neurotensin, substance P and vasoactive intestinal peptide. For example, by potentiating the effects of the natriuretic peptides, compounds of the invention are expected to be useful to treat glaucoma. These compounds are also expected to have other physiological actions, for example, on the renal, central nervous, reproductive and gastrointestinal systems.

Compounds of the invention are expected to find utility in treating and/or preventing medical conditions such as cardiovascular and renal diseases. Cardiovascular diseases of particular interest include heart failure such as congestive heart failure, acute heart failure, chronic heart failure, and acute and chronic decompensated heart failure. Renal diseases of particular interest include diabetic nephropathy and chronic kidney disease. One embodiment of the invention is directed to a method for treating hypertension, comprising administering to a patient a therapeutically effective amount of a compound of the invention. Typically, the therapeutically effective amount is the amount that is sufficient to lower the patient's blood pressure. In one embodiment, the compound is administered as an oral dosage form.

Another embodiment of the invention is directed to a method for treating heart failure, comprising administering to a patient a therapeutically effective amount of a compound of the invention. Typically, the therapeutically effective amount is the amount that is sufficient to lower blood pressure and/or improve renal functions. In one embodiment, the compound is administered as an intravenous dosage form. When used to treat heart failure, the compound may be administered in combination with other therapeutic agents such as diuretics, natriuretic peptides, and adenosine receptor antagonists.

Compounds of the invention are also expected to be useful in preventative therapy, for example in preventing the progression of cardiac insufficiency after myocardial infarction, preventing arterial restenosis after angioplasty, preventing thickening of blood vessel walls after vascular operations, preventing atherosclerosis, and preventing diabetic angiopathy.

In addition, as NEP inhibitors, compounds of the invention are expected to inhibit enkephalinase, which will inhibit the degradation of endogenous enkephalins and thus such compounds may also find utility as analgesics. Due to their NEP inhibition properties, compounds of the invention are also expected to be useful as antitussive agents and antidiarrheal agents (for example, for the treatment of watery diarrhea), as well as find utility in the treatment of menstrual disorders, preterm labor, pre-eclampsia, endometriosis, reproductive disorders (for example, male and female infertility, polycystic ovarian syndrome, implantation failure), and male and female sexual dysfunction, including male erectile dysfunction and female sexual arousal disorder. More specifically, the compounds of the invention are expected to be useful in treating female sexual dysfunction, which is often defined as a female patient's difficulty or inability to find satisfaction in sexual expression. This covers a variety of diverse female sexual disorders including, by way of illustration and not limitation, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder. When used to treat such disorders, especially female sexual dysfunction, compounds of the invention may be combined with one or more of the following secondary agents: PDE5 inhibitors, dopamine agonists, estrogen receptor agonists and/or antagonists, androgens, and estrogens.

The amount of the compound of the invention administered per dose or the total amount administered per day may be predetermined or it may be determined on an individual patient basis by taking into consideration numerous factors, including the nature and severity of the patient's condition, the condition being treated, the age, weight, and general health of the patient, the tolerance of the patient to the active agent, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the compound and any secondary agents being administered, and the like. Treatment of a patient suffering from a disease or medical condition (such as hypertension) can begin with a predetermined dosage or a dosage determined by the treating physician, and will continue for a period of time necessary to prevent, ameliorate, suppress, or alleviate the symptoms of the disease or medical condition. Patients undergoing such treatment will typically be monitored on a routine basis to determine the effectiveness of therapy. For example, in treating hypertension, blood pressure measurements may be used to determine the effectiveness of treatment. Similar indicators for other diseases and conditions described herein, are well known and are readily available to the treating physician. Continuous monitoring by the physician will

insure that the optimal amount of the compound of the invention will be administered at any given time, as well as facilitating the determination of the duration of treatment. This is of particular value when secondary agents are also being administered, as their selection, dosage, and duration of therapy may also require adjustment. In this way, the treatment regimen and dosing schedule can be adjusted over the course of therapy so that the lowest amount of active agent that exhibits the desired effectiveness is administered and, further, that administration is continued only so long as is necessary to successfully treat the disease or medical condition.

Since compounds of the invention possess AT_1 receptor antagonist activity and/or NEP enzyme inhibition activity, such compounds are also useful as research tools for investigating or studying biological systems or samples having AT_1 receptors or a NEP enzyme, for example to study diseases where the AT_1 receptor or NEP enzyme plays a role. Any suitable biological system or sample having AT_1 receptors and/or a NEP enzyme may be employed in such studies which may be conducted either *in vitro* or *in vivo*. Representative biological systems or samples suitable for such studies include, but are not limited to, cells, cellular extracts, plasma membranes, tissue samples, isolated organs, mammals (such as mice, rats, guinea pigs, rabbits, dogs, pigs, humans, and so forth), and the like, with mammals being of particular interest. In one particular embodiment of the invention an AT_1 receptor in a mammal is antagonized by administering an AT_1-antagonizing amount of a compound of the invention. In another particular embodiment, NEP enzyme activity in a mammal is inhibited by administering a NEP-inhibiting amount of a compound of the invention. Compounds of the invention can also be used as research tools by conducting biological assays using such compounds.

When used as a research tool, a biological system or sample comprising an AT_1 receptor and/or a NEP enzyme is typically contacted with an AT_1 receptor-antagonizing or NEP enzyme-inhibiting amount of a compound of the invention. After the biological system or sample is exposed to the compound, the effects of antagonizing the AT_1 receptor and/or inhibiting the NEP enzyme are determined using conventional procedures and equipment, such as by measuring receptor binding in a binding assay or measuring ligand-mediated changes in a functional assay. Exposure encompasses contacting cells or tissue with the compound, administering the compound to a mammal, for example by *i.p.*, *i.v.* or *s.c.* administration, and so forth. This determining step can involve measuring a response (a quantitative analysis) or can involve making an observation (a qualitative analysis).

Measuring a response involves, for example, determining the effects of the compound on the biological system or sample using conventional procedures and equipment, such as radioligand binding assays and measuring ligand-mediated changes in functional assays. The assay results can be used to determine the activity level as well as the amount of compound necessary to achieve the desired result, that is, an AT_1 receptor-antagonizing and/or a NEP enzyme-inhibiting amount. Typically, the determining step will involve determining the AT_1 receptor ligand-mediated effects and/or determining the effects of inhibiting the NEP enzyme.

Additionally, compounds of the invention can be used as research tools for evaluating other chemical compounds, and thus are also useful in screening assays to discover, for example, new compounds having AT_1 receptor-antagonizing activity and/or NEP-inhibiting activity. In this manner, a compound of the invention is used as a standard in an assay to allow comparison of the results obtained with a test compound and with compounds of the invention to identify those test compounds that have about equal or superior activity, if any. For example, K_i data (as determined, for example, by a binding assay) for a test compound or a group of test compounds is compared to the K_i data for a compound of the invention to identify those test compounds that have the desired properties, for example, test compounds having a K_i value about equal or superior to a compound of the invention, if any. This aspect of the invention includes, as separate embodiments, both the generation of comparison data (using the appropriate assays) and the analysis of test data to identify test compounds of interest. Thus, a test compound can be evaluated in a biological assay, by a method comprising the steps of: (a) conducting a biological assay with a test compound to provide a first assay value; (b) conducting the biological assay with a compound of the invention to provide a second assay value; wherein step (a) is conducted either before, after or concurrently with step (b); and (c) comparing the first assay value from step (a) with the second assay value from step (b). Exemplary biological assays include an AT_1 receptor binding assay and a NEP enzyme inhibition assay.

PHARMACEUTICAL COMPOSITIONS AND FORMULATIONS

Compounds of the invention are typically administered to a patient in the form of a pharmaceutical composition or formulation. Such pharmaceutical compositions may be administered to the patient by any acceptable route of administration including, but not limited to, oral, rectal, vaginal, nasal, inhaled, topical (including transdermal), ocular, and

parenteral modes of administration. Further, the compounds of the invention may be administered, for example orally, in multiple doses per day (for example, two, three, or four times daily), in a single daily dose or a single weekly dose. It will be understood that any form of the compounds of the invention, (that is, free base, free acid, pharmaceutically acceptable salt, solvate, etc.) that is suitable for the particular mode of administration can be used in the pharmaceutical compositions discussed herein.

Accordingly, in one embodiment, the invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the invention. The compositions may contain other therapeutic and/or formulating agents if desired. When discussing compositions, the "compound of the invention" may also be referred to herein as the "active agent, " to distinguish it from other components of the formulation, such as the carrier. Thus, it is understood that the term "active agent" includes compounds of formula I as well as pharmaceutically acceptable salts, solvates and prodrugs of that compound.

The pharmaceutical compositions of the invention typically contain a therapeutically effective amount of a compound of the invention. Those skilled in the art will recognize, however, that a pharmaceutical composition may contain more than a therapeutically effective amount, such as in bulk compositions, or less than a therapeutically effective amount, that is, individual unit doses designed for multiple administration to achieve a therapeutically effective amount. Typically, the composition will contain from about 0.01-95 wt% of active agent, including, from about 0.01-30 wt%, such as from about 0.01- 10 wt%, with the actual amount depending upon the formulation itself, the route of administration, the frequency of dosing, and so forth. In one embodiment, a composition suitable for an oral dosage form, for example, may contain about 5-70 wt%, or from about 10-60 wt% of active agent.

Any conventional carrier or excipient may be used in the pharmaceutical compositions of the invention. The choice of a particular carrier or excipient, or combinations of carriers or excipients, will depend on the mode of administration being used to treat a particular patient or type of medical condition or disease state. In this regard, the preparation of a suitable composition for a particular mode of administration is well within the scope of those skilled in the pharmaceutical arts. Additionally, carriers or excipients used in such compositions are commercially available. By way of further illustration, conventional formulation techniques are described in *Remington: The Science*

and Practice of Pharmacy, 20th Edition, Lippincott Williams & White, Baltimore, Maryland (2000); and H. C. Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7th Edition, Lippincott Williams & White, Baltimore, Maryland (1999).

Representative examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, the following: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, such as microcrystalline cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; compressed propellant gases, such as chlorofluorocarbons and hydrofluorocarbons; and other non-toxic compatible substances employed in pharmaceutical compositions.

Pharmaceutical compositions are typically prepared by thoroughly and intimately mixing or blending the active agent with a pharmaceutically acceptable carrier and one or more optional ingredients. The resulting uniformly blended mixture may then be shaped or loaded into tablets, capsules, pills, canisters, cartridges, dispensers and the like using conventional procedures and equipment.

In formulations where the compound of the invention contains a thiol group, additional consideration may be given to minimize or eliminate oxidation of the thiol to form a disulfide. In solid formulations, this may be accomplished by reducing the drying time, decreasing the moisture content of the formulation, and including materials such as ascorbic acid, sodium ascorbate, sodium sulfite and sodium bisulfite, as well as materials such as a mixture of lactose and microcrystalline cellulose. In liquid formulations, stability of the thiol may be improved by the addition of amino acids, antioxidants, or a combination of disodium edetate and ascorbic acid.

In one embodiment, the pharmaceutical compositions are suitable for oral administration. Suitable compositions for oral administration may be in the form of capsules, tablets, pills, lozenges, cachets, dragees, powders, granules; solutions or suspensions in an aqueous or non-aqueous liquid; oil-in-water or water-in-oil liquid

emulsions; elixirs or syrups; and the like; each containing a predetermined amount of the active agent.

When intended for oral administration in a solid dosage form (capsules, tablets, pills and the like), the composition will typically comprise the active agent and one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate. Solid dosage forms may also comprise: fillers or extenders, such as starches, microcrystalline cellulose, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and/or sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as cetyl alcohol and/or glycerol monostearate; absorbents, such as kaolin and/or bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and/or mixtures thereof; coloring agents; and buffering agents.

Release agents, wetting agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may also be present in the pharmaceutical compositions. Exemplary coating agents for tablets, capsules, pills and like, include those used for enteric coatings, such as cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymers, cellulose acetate trimellitate, carboxymethyl ethyl cellulose, hydroxypropyl methyl cellulose acetate succinate, and the like. Examples of pharmaceutically acceptable antioxidants include: water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfate sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, lecithin, propyl gallate, alpha-tocopherol, and the like; and metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid, sorbitol, tartaric acid, phosphoric acid, and the like.

Compositions may also be formulated to provide slow or controlled release of the active agent using, by way of example, hydroxypropyl methyl cellulose in varying proportions or other polymer matrices, liposomes and/or microspheres. In addition, the pharmaceutical compositions of the invention may contain opacifying agents and may be formulated so that they release the active agent only, or preferentially, in a certain portion

of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active agent can also be in micro-encapsulated form, optionally with one or more of the above-described excipients.

Suitable liquid dosage forms for oral administration include, by way of illustration, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. Liquid dosage forms typically comprise the active agent and an inert diluent, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (for example, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Suspensions may contain suspending agents such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

When intended for oral administration, the pharmaceutical compositions of the invention may be packaged in a unit dosage form. The term "unit dosage form" refers to a physically discrete unit suitable for dosing a patient, that is, each unit containing a predetermined quantity of the active agent calculated to produce the desired therapeutic effect either alone or in combination with one or more additional units. For example, such unit dosage forms may be capsules, tablets, pills, and the like.

In another embodiment, the compositions of the invention are suitable for inhaled administration, and will typically be in the form of an aerosol or a powder. Such compositions are generally administered using well-known delivery devices, such as a nebulizer, dry powder, or metered-dose inhaler. Nebulizer devices produce a stream of high velocity air that causes the composition to spray as a mist that is carried into a patient's respiratory tract. An exemplary nebulizer formulation comprises the active agent dissolved in a carrier to form a solution, or micronized and combined with a carrier to form a suspension of micronized particles of respirable size. Dry powder inhalers administer the active agent as a free-flowing powder that is dispersed in a patient's air-stream during inspiration. An exemplary dry powder formulation comprises the active agent dry-blended with an excipient such as lactose, starch, mannitol, dextrose, polylactic acid, polylactide-co-glycolide, and combinations thereof. Metered-dose inhalers discharge a measured

amount of the active agent using compressed propellant gas. An exemplary metered-dose formulation comprises a solution or suspension of the active agent in a liquefied propellant, such as a chlorofluorocarbon or hydrofluoroalkane. Optional components of such formulations include co-solvents, such as ethanol or pentane, and surfactants, such as sorbitan trioleate, oleic acid, lecithin, glycerin, and sodium lauryl sulfate. Such compositions are typically prepared by adding chilled or pressurized hydrofluoroalkane to a suitable container containing the active agent, ethanol (if present) and the surfactant (if present). To prepare a suspension, the active agent is micronized and then combined with the propellant. Alternatively, a suspension formulation can be prepared by spray drying a coating of surfactant on micronized particles of the active agent. The formulation is then loaded into an aerosol canister, which forms a portion of the inhaler.

Compounds of the invention can also be administered parenterally (for example, by subcutaneous, intravenous, intramuscular, or intraperitoneal injection). For such administration, the active agent is provided in a sterile solution, suspension, or emulsion. Exemplary solvents for preparing such formulations include water, saline, low molecular weight alcohols such as propylene glycol, polyethylene glycol, oils, gelatin, fatty acid esters such as ethyl oleate, and the like. Parenteral formulations may also contain one or more anti-oxidants, solubilizers, stabilizers, preservatives, wetting agents, emulsifiers, and dispersing agents. Surfactants, additional stabilizing agents or pH-adjusting agents (acids, bases or buffers) and anti-oxidants are particularly useful to provide stability to the formulation, for example, to minimize or avoid hydrolysis of ester and amide linkages, or dimerization of thiols that may be present in the compound. These formulations may be rendered sterile by use of a sterile injectable medium, a sterilizing agent, filtration, irradiation, or heat. In one particular embodiment, the parenteral formulation comprises an aqueous cyclodextrin solution as the pharmaceutically acceptable carrier. Suitable cyclodextrins include cyclic molecules containing six or more α-D-glucopyranose units linked at the 1,4 positions by a linkages as in amylase, β-cyclodextrin or cycloheptaamylose. Exemplary cyclodextrins include cyclodextrin derivatives such as hydroxypropyl and sulfobutyl ether cyclodextrins such as hydroxypropyl-β-cyclodextrin and sulfobutyl ether β-cyclodextrin. Exemplary buffers for such formulations include carboxylic acid-based buffers such as citrate, lactate and maleate buffer solutions.

Compounds of the invention can also be administered transdermally using known transdermal delivery systems and excipients. For example, the compound can be admixed

with permeation enhancers, such as propylene glycol, polyethylene glycol monolaurate, azacycloalkan-2-ones and the like, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers and buffers, may be used in such transdermal compositions if desired.

If desired, the compounds of the invention may be administered in combination with one or more other therapeutic agents. Thus, in one embodiment, pharmaceutical compositions of the invention contain other drugs that are co-administered with a compound of the invention. For example, the composition may further comprise one or more drugs (also referred to as "secondary agents(s)") selected from the group of diuretics, β_1 adrenergic receptor blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, AT_1 receptor antagonists, neprilysin inhibitors, non-steroidal anti-inflammatory agents, prostaglandins, anti-lipid agents, anti-diabetic agents, anti-thrombotic agents, renin inhibitors, endothelin receptor antagonists, endothelin converting enzyme inhibitors, aldosterone antagonists, angiotensin-converting enzyme/neprilysin inhibitors, and combinations thereof. Such therapeutic agents are well known in the art, and examples are described below. By combining a compound of the invention with a secondary agent, triple therapy can be achieved; AT_1 receptor antagonist activity, NEP inhibition activity, and activity associated with the secondary agent (for example, β_1 adrenergic receptor blocker) can be achieved using only two active components. Since compositions containing two active components are typically easier to formulate than compositions containing three active components, such two-component compositions provide a significant advantage over compositions containing three active components. Accordingly, in yet another aspect of the invention, a pharmaceutical composition comprises a compound of the invention, a second active agent, and a pharmaceutically acceptable carrier. Third, fourth etc. active agents may also be included in the composition. In combination therapy, the amount of compound of the invention that is administered, as well as the amount of secondary agents, may be less than the amount typically administered in monotherapy.

Compounds of the invention may be physically mixed with the second active agent to form a composition containing both agents; or each agent may be present in separate and distinct compositions which are administered to the patient simultaneously or at separate times. For example, a compound of the invention can be combined with a second active agent using conventional procedures and equipment to form a combination

of active agents comprising a compound of the invention and a second active agent. Additionally, the active agents may be combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition comprising a compound of the invention, a second active agent and a pharmaceutically acceptable carrier. In this embodiment, the components of the composition are typically mixed or blended to create a physical mixture. The physical mixture is then administered in a therapeutically effective amount using any of the routes described herein.

Alternatively, the active agents may remain separate and distinct before administration to the patient. In this embodiment, the agents are not physically mixed together before administration but are administered simultaneously or at separate times as separate compositions. Such compositions can be packaged separately or may be packaged together in a kit. When administered at separate times, the secondary agent will typically be administered less than 24 hours after administration of the compound of the invention, ranging anywhere from concurrent with administration of the compound of the invention to about 24 hours post-dose. This is also referred to as sequential administration. Thus, a compound of the invention can be orally administered simultaneously or sequentially with another active agent using two tablets, with one tablet for each active agent, where sequential may mean being administered immediately after administration of the compound of the invention or at some predetermined time later (for example, one hour later or three hours later). Alternatively, the combination may be administered by different routes of administration, that is, one orally and the other by inhalation.

In one embodiment, the kit comprises a first dosage form comprising a compound of the invention and at least one additional dosage form comprising one or more of the secondary agents set forth herein, in quantities sufficient to carry out the methods of the invention. The first dosage form and the second (or third, etc,) dosage form together comprise a therapeutically effective amount of active agents for the treatment or prevention of a disease or medical condition in a patient.

Secondary agent(s), when included, are present in a therapeutically effective amount such that they are typically administered in an amount that produces a therapeutically beneficial effect when co-administered with a compound of the invention. The secondary agent can be in the form of a pharmaceutically acceptable salt, solvate, optically pure stereoisomer, and so forth. The secondary agent may also be in the form of a prodrug, for example, a compound having a carboxylic acid group that has been

esterified. Thus, secondary agents listed below are intended to include all such forms, and are commercially available or can be prepared using conventional procedures and reagents.

In one embodiment, a compound of the invention is administered in combination with a diuretic. Representative diuretics include, but are not limited to: carbonic anhydrase inhibitors such as acetazolamide and dichlorphenamide; loop diuretics, which include sulfonamide derivatives such as acetazolamide, ambuside, azosernide, bumetanide, butazolamide, chloraminophenamide, clofenamide, clopamide, clorexolone, disulfamide, ethoxolamide, 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 a β_1 adrenergic receptor blocker. Representative β_1 adrenergic receptor blockers include, but are not limited to, acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, bubridine, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetolol, levobunolol, mepindolol, metipranolol, metoprolol such as metoprolol succinate and metoprolol tartrate, moprolol, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, penbutolol, perbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sufinalol, talindol, tertatolol, tilisolol,

timolol, toliprolol, xibenolol, and combinations thereof. In one particular embodiment, the β_1 adrenergic receptor blocker is selected from atenolol, bisoprolol, metoprolol, propranolol, sotalol, and combinations thereof.

In one embodiment, a compound of the invention is administered in combination with a calcium channel blocker. Representative calcium channel blockers include, but are not limited to, amlodipine, anipamil, aranipine, barnidipine, bencyclane, benidipine, bepridil, clentiazem, cilnidipine, cinnarizine, diltiazem, efonidipine, elgodipine, etafenone, felodipine, fendiline, flunarizine, gallopamil, isradipine, lacidipine, lercanidipine, lidoflazine, lomerizine, manidipine, mibefradil, nicardipine, nifedipine, niguldipine, niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, perhexiline, prenylamine, ryosidine, semotiadil, terodiline, tiapamil, verapamil, and combinations thereof. In a particular embodiment, the calcium channel blocker is selected from amlodipine, bepridil, diltiazem, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, ryosidine, verapamil, and combinations thereof.

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, 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, enalapril, lisinopril, ramipril, and combinations thereof.

In one embodiment, a compound of the invention is 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, benzyllosartan, candesartan, candesartan cilexetil, elisartan, embusartan, enoltasosartan, eprosartan, fonsartan, forasartan, glycyllosartan, irbesartan, isoteoline, losartan, medoximil, milfasartan, olmesartan, opomisartan, pratosartan, ripisartan, saprisartan, saralasin, sarmesin, tasosartan, telmisartan, valsartan, zolasartan, and combinations thereof. In a particular embodiment, the ARB is selected from candesartan, eprosartan, irbesartan, losartan, olmesartan, irbesartan, saprisartan, tasosartan, telmisartan, and combinations thereof. Exemplary salts include 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 day.

In another embodiment, a compound of the invention is administered in combination with a neprilysin (NEP) inhibitor. Representative NEP inhibitors include, but are not limited to: candoxatril; candoxatrilat; dexecadotril ((+)-N-[2*(R)*-(acetylthiomethyl)-3-phenylpropionyl]glycine benzyl ester); CGS-24128 (3-[3-(biphenyl-4-yl)-2-(phosphonomethylamino)propionamido]propionic acid); CGS-24592 (*(S)*-3-[3-(biphenyl-4-yl)-2-(phosphonomethylamino)propionamido]propionic acid); CGS-25155 (N-[9*(R)*-(acetylthiomethyl)-10-oxo-1-azacyclodecan-2*(S)*-ylcarbonyl]-4*(R)*-hydroxy-L-proline benzyl ester); 3-(1-carbamoylcyclohexyl)propionic acid derivatives described in WO 2006/027680 to Hepworth et al. (Pfizer Inc.); JMV-390-1 (2*(R)*-benzyl-3-(N-hydroxycarbamoyl)propionyl-L-isoleucyl-L-leucine); ecadotril; phosphoramidon; retrothiorphan; RU-42827 (2-(mercaptomethyl)-N-(4-pyridinyl)benzenepropionamide); RU-44004 (N-(4-morpholinyl)-3-phenyl-2-(sulfanylmethyl)propionamide); SCH-32615 (*(S)*-N-[N-(1-carboxy-2-phenylethyl)-L-phenylalanyl]-β-alanine) and its prodrug SCH-34826 (*(S)*-N-[N-[1-[[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine); sialorphin; SCH-42495 (N-[2*(S)*-(acetylsulfanylmethyl)-3-(2-methylphenyl)propionyl]-L-methionine ethyl ester); spinorphin; SQ-28132 (N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]leucine); SQ-28603 (N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-β-alanine); SQ-29072 (7-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]heptanoic acid); thiorphan and its prodrug racecadotril; UK-69578 (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]cyclopentyl]carbonyl]amino] cyclohexanecarboxylic acid); UK-447,841 (2-{1-[3-(4-chlorophenyl)propylcarbamoyl]-cyclopentylmethyl}-4-methoxybutyric acid); UK-505,749 (*(R)*-2-methyl-3-{1-[3-(2-methylbenzothiazol-6-yl)propylcarbamoyl]cyclopentyl}propionic acid); 5-biphenyl-4-yl-4-(3-carboxypropionylamino)-2-methylpentanoic acid and 5-biphenyl-4-yl-4-(3-carboxypropionylamino)-2-methylpentanoic acid ethyl ester (WO 2007/056546); daglutril [*(3S,2'R)*-3-{1-[2'-(ethoxycarbonyl)-4'-phenylbutyl]-cyclopentan-1-carbonylamino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid] described in WO 2007/106708 to Khder et al. (Novartis AG); and combinations thereof. In a particular embodiment, the NEP inhibitor is selected from candoxatril, candoxatrilat, CGS-24128, phosphoramidon, SCH-32615, SCH-34826, SQ-28603, thiorphan, and combinations

thereof. The NEP inhibitor will be administered in an amount sufficient to provide from about 20-800 mg per day, with typical daily dosages ranging from 50-700 mg per day, more commonly 100-600 or 100-300 mg per day.

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

In yet another embodiment, a compound of the invention is administered in combination with an anti-diabetic agent. Representative anti-diabetic agents include, but are not limited to: injectable drugs such as insulin and insulin derivatives; orally effective drugs including biguanides such as metformin, glucagon antagonists, α-glucosidase inhibitors such as acarbose and miglitol, meglitinides such as repaglinide, oxadiazolidinediones, sulfonylureas such as chlorpropamide, glimepiride, glipizide, glyburide, and tolazamide, thiazolidinediones such as pioglitazone and rosiglitazone; and combinations thereof.

In one embodiment, a compound of the invention is administered in combination with an anti-thrombotic agent. Representative anti-thrombotic agents include, but are not

limited to, aspirin, anti-platelet agents, heparin, and combinations thereof. 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, a compound of the invention is administered in combination with an endothelin receptor antagonist, representative examples of which include, but are not limited to, bosentan, darusentan, tezosentan, and combinations thereof. Compounds of the invention may also be administered in combination with an endothelin converting enzyme inhibitor, examples of which include, but are not limited to, phosphoramidon, CGS 26303, and combinations thereof. In yet another embodiment, a compound of the invention is administered in combination with an aldosterone antagonist, representative examples of which include, but are not limited to, eplerenone, spironolactone, and combinations thereof.

Combined therapeutic agents may also be helpful in further combination therapy with compounds of the invention. For example, a combination of the ACE inhibitor enalapril (in the maleate salt form) and the diuretic hydrochlorothiazide, which is sold under the mark Vaseretic®, or a combination of the calcium channel blocker amlodipine (in the besylate salt form) and the ARB olmesartan (in the medoxomil prodrug form), or a combination of a calcium channel blocker and a statin, all may also be used with the compounds of the invention. Dual-acting agents may also be helpful in combination therapy with compounds of the invention. For example, angiotensin-converting enzyme/neprilysin (ACE/NEP) inhibitors such as: 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-26303 ([N-[2-(biphenyl-4-yl)-1*(S)*-(1H-tetrazol-5-yl)ethyl]amino]methylphosphonic acid); CGS-35601 (N-[1-[4-methyl-2*(S)*-sulfanylpentanamido]cyclopentylcarbonyl]-L-tryptophan); fasidotril; fasidotrilate; enalaprilat; ER-32935 ((3R,6S,9aR)-6-[3*(S)*-methyl-2*(S)*-sulfanylpentanamido]-5-oxoperhydrothiazolo[3,2-a]azepine-3-carboxylic acid); gempatrilat; MDL-101264 ((4S,7S,12bR)-7-[2*(S)*-(2-morpholinoacetylthio)-3-phenylpropionamido]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylic acid); MDL-101287 ([4S-[4α,7α(R*),12bβ]]-7-[2-(carboxymethyl)-3-phenylpropionamido]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylic acid); omapatrilat;

RB-105 (N-[2*(S)*-(mercaptomethyl)-3*(R)*-phenylbutyl]-L-alanine); sampatrilat; SA-898 ((2R,4R)-N-[2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)thiazolidin-4-ylcarbonyl]-L-phenylalanine); Sch-50690 (N-[1*(S)*-carboxy-2-[N2-(methanesulfonyl)-L-lysylamino]ethyl]-L-valyl-L-tyrosine); and combinations thereof, may also be included. In one particular embodiment, the ACE/NEP inhibitor is selected from: AVE-7688, enalaprilat, fasidotril, fasidotrilate, omapatrilat, sampatrilat, and combinations thereof.

Other therapeutic agents such as α_2-adrenergic receptor agonists and vasopressin receptor antagonists may also be helpful in combination therapy. Exemplary α_2-adrenergic receptor agonists include clonidine, dexmedetomidine, and guanfacine. Exemplary vasopressin receptor antagonists include tolvaptan.

The following formulations illustrate representative pharmaceutical compositions of the invention.

Exemplary Hard Gelatin Capsules For Oral Administration

A compound of the invention (50 g), 440 g spray-dried lactose and 10 g magnesium stearate are thoroughly blended. The resulting composition is then loaded into hard gelatin capsules (500 mg of composition per capsule). Alternately, a compound of the invention (20 mg) is thoroughly blended with starch (89 mg), microcrystalline cellulose (89 mg) and magnesium stearate (2 mg). The mixture is then passed through a No. 45 mesh U.S. sieve and loaded into a hard gelatin capsule (200 mg of composition per capsule).

Exemplary Gelatin Capsule Formulation For Oral Administration

A compound of the invention (100 mg) is thoroughly blended with polyoxyethylene sorbitan monooleate (50 mg) and starch powder (250 mg). The mixture is then loaded into a gelatin capsule (300 mg of composition per capsule).

Alternately, a compound of the invention (40 mg) is thoroughly blended with microcrystalline cellulose (Avicel PH 103; 260 mg) and magnesium stearate (0.8 mg). The mixture is then loaded into a gelatin capsule (Size #1, White, Opaque) (300 mg of composition per capsule).

Exemplary Tablet Formulation For Oral Administration

A compound of the invention (10 mg), starch (45 mg) and microcrystalline cellulose (35 mg) are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The granules so produced are dried at 50-60 °C and passed through a No. 16 mesh U.S. sieve. A solution of polyvinylpyrrolidone (4 mg as a 10 % solution in sterile water) is mixed with

sodium carboxymethyl starch (4.5 mg), magnesium stearate (0.5 mg), and talc (1 mg), and this mixture is then passed through a No. 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc are then added to the granules. After mixing, the mixture is compressed on a tablet machine to afford a tablet weighing 100 mg.

Alternately, a compound of the invention (250 mg) is thoroughly blended with microcrystalline cellulose (400 mg), silicon dioxide fumed (10 mg), and stearic acid (5 mg). The mixture is then compressed to form tablets (665 mg of composition per tablet).

Alternately, a compound of the invention (400 mg) is thoroughly blended with cornstarch (50 mg), croscarmellose sodium (25 mg), lactose (120 mg), and magnesium stearate (5 mg). The mixture is then compressed to form a single-scored tablet (600 mg of composition per tablet).

Alternately, a compound of the invention (100 mg) is thoroughly blended with cornstarch (100 mg) with an aqueous solution of gelatin (20 mg). The mixture is dried and ground to a fine powder Microcrystalline cellulose (50 mg) and magnesium stearate (5 mg) are the admixed with the gelatin formulation, granulated and the resulting mixture compressed to form tablets (100 mg of active per tablet).

Exemplary Suspension Formulation For Oral Administration

The following ingredients are mixed to form a suspension containing 100 mg of active agent per 10 mL of suspension:

Ingredients	Amount
Compound of the invention	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum® K (magnesium aluminum silicate)	1.0 g
Flavoring	0.035 mL
Colorings	0.5 mg
Distilled water	q.s. to 100 mL

Exemplary Liquid Formulation For Oral Administration

A suitable liquid formulation is one with a carboxylic acid-based buffer such as citrate, lactate and maleate buffer solutions. For example, a compound of the invention (which may be pre-mixed with DMSO) is blended with a 100 mM ammonium citrate buffer and the pH adjusted to pH 5, or with is blended with a 100 mM citric acid solution

and the pH adjusted to pH 2. Such solutions may also include a solubilizing excipient such as a cyclodextrin, for example the solution may include 10 wt% hydroxypropyl-β-cyclodextrin.

Other suitable formulations include a 5% $NaHCO_3$ solution, with or without cyclodextrin.

Exemplary Injectable Formulation For Administration By Injection

A compound of the invention (0.2 g) is blended with 0.4 M sodium acetate buffer solution (2.0 mL). The pH of the resulting solution is adjusted to pH 4 using 0.5 N aqueous hydrochloric acid or 0.5 N aqueous sodium hydroxide, as necessary, and then sufficient water for injection is added to provide a total volume of 20 mL. The mixture is then filtered through a sterile filter (0.22 micron) to provide a sterile solution suitable for administration by injection.

Exemplary Compositions For Administration By Inhalation

A compound of the invention (0.2 mg) is micronized and then blended with lactose (25 mg). This blended mixture is then loaded into a gelatin inhalation cartridge. The contents of the cartridge are administered using a dry powder inhaler, for example.

Alternately, a micronized compound of the invention (10 g) is dispersed in a solution prepared by dissolving lecithin (0.2 g) in demineralized water (200 mL). The resulting suspension is spray dried and then micronized to form a micronized composition comprising particles having a mean diameter less than about 1.5 μm. The micronized composition is then loaded into metered-dose inhaler cartridges containing pressurized 1,1,1,2-tetrafluoroethane in an amount sufficient to provide about 10 μg to about 500 μg of the compound of the invention per dose when administered by the inhaler.

Alternately, a compound of the invention (25 mg) is dissolved in citrate buffered (pH 5) isotonic saline (125 mL). The mixture is stirred and sonicated until the compound is dissolved. The pH of the solution is checked and adjusted, if necessary, to pH 5 by slowly adding aqueous IN sodium hydroxide. The solution is administered using a nebulizer device that provides about 10 μg to about 500 μg of the compound of the invention per dose.

EXAMPLES

The following Preparations and Examples are provided to illustrate specific embodiments of the invention. These specific embodiments, however, are not intended to limit the scope of the invention in any way unless specifically indicated.

The following abbreviations have the following meanings unless otherwise indicated and any other abbreviations used herein and not defined have their standard, generally accepted meaning:

ACE	angiotensin converting enzyme
APP	aminopeptidase P
AT_1	angiotensin II type 1 (receptor)
AT_2	angiotensin II type 2 (receptor)
BSA	bovine serum albumin
DCM	dichloromethane or methylene chloride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
Dnp	2,4-dinitrophenyl
DOCA	deoxycorticosterone acetate
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
EDTA	ethylenediaminetetraacetic acid
EGTA	ethylene glycol *bis*(β-aminoethyl ether)-N,N,N'N'-tetraacetic acid
EtOAc	ethyl acetate
HATU	*N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate
Mca	(7-methoxycoumarin-4-yl)acyl
MeCN	acetonitrile
MeOH	methanol
$NaBH_3CN$	sodium cyanoborohydride
NBS	*N*-bromosuccinimide
NEP	neprilysin (EC 3.4.24.11)
PBS	phosphate buffered saline
SHR	spontaneously hypertensive rat
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tris	tris(hydroxymethyl)aminomethane

Tween-20 polyethylene glycol sorbitan monolaurate

Unless noted otherwise, all materials, such as reagents, starting materials and solvents, were purchased from commercial suppliers (such as Sigma-Aldrich, Fluka Riedel-de Haën, and the like) and were used without further purification.

Reactions were run under nitrogen atmosphere, unless noted otherwise. The progress of reactions were monitored by thin layer chromatography (TLC), analytical high performance liquid chromatography (anal. HPLC), and mass spectrometry, the details of which are given in specific examples. Solvents used in analytical HPLC were as follows: solvent A was 98% water/2% MeCN /1.0 mL/L TFA; solvent B was 90% MeCN/10% water/1.0 mL/L TFA.

Reactions were worked up as described specifically in each preparation or example; commonly reaction mixtures were purified by extraction and other purification methods such as temperature-, and solvent-dependent crystallization, and precipitation. In addition, reaction mixtures were routinely purified by preparative HPLC, typically using Microsorb C18 and Microsorb BDS column packings and conventional eluents. Characterization of reaction products was routinely carried out by mass and ^{1}H-NMR spectrometry. For NMR measurement, samples were dissolved in deuterated solvent (CD_3OD, $CDCl_3$, or DMSO-d_6), and ^{1}H-NMR spectra were acquired with a Varian Gemini 2000 instrument (400 MHz) under standard observation conditions. Mass spectrometric identification of compounds was typically conducted using an electrospray ionization method (ESMS) with an Applied Biosystems (Foster City, CA) model API 150 EX instrument or an Agilent (Palo Alto, CA) model 1200 LC/MSD instrument.

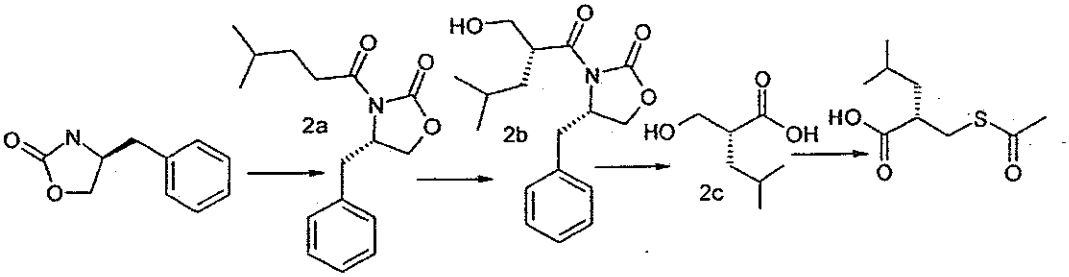
PREPARATION 1

4-Methylpentanoyl Chloride

Isocaproic acid (10.0 g, 86.1 mmol) was dissolved in methylene chloride (30.0 mL, 468.0 mmol), and thionyl chloride (18.8 mL, 258 mmol) was added. The mixture was stirred at room temperature overnight, then rotovaped to provide the title compound, which was used immediately in the next reaction.

PREPARATION 2

(S)-2-Acetylsulfanylmethyl-4-methylpentanoic Acid



(S)-4-Benzyl-3-(4-methylpentanoyl)oxazolidin-2-one (2a): *(S)*-4-Benzyl-2-oxazolidinone (15.1 g, 85.0 mmol) was dissolved in THF (200 mL, 2.5 mol), cooled at -78 °C under nitrogen, and stirred for 10 minutes. 1.6 M of *n*-butyllithium in hexane (53.1 mL) was added dropwise and stirred for 15 minutes. 4-Methylpentanoyl chloride (12.6 g, 93.5 mmol) was added dropwise, stirred for 30 minutes at -78 °C, then warmed to 0 °C for 2 hours. 150 mL of saturated $NaHCO_3$ was added and the mixture was warmed to room temperature for 30 minutes. The mixture was extracted with DCM, washed with Na_2CO_3 (5%) and saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. Excess oxazolidinone was removed using hexanes to provide intermediate (2a) (14.5 g).

(S)-4-Benzyl-3-(*(R)*-2-hydroxymethyl-4-methylpentanoyl)oxazolidin-2-one (2b): Intermediate (2a) (14.5 g, 46.3 mmol) was dissolved in DCM (151 mL, 2.4 mol) and stirred at 0 °C under nitrogen. 1 M titanium tetrachloride in DCM (48.6 mL) was added and stirred for 15 minutes. DIPEA (8.9 mL, 51.0 mmol) was added dropwise at 0 °C and the mixture was stirred for 75 minutes. 1,3,5-Trioxane (4.6 g, 51.0 mmol) in DCM (30 mL) was then added. After 10 minutes a second equivalent of 1 M titanium tetrachloride in DCM (48.6 mL) was added and the mixture stirred at 0 °C for 5 hours. The reaction was then quenched with 250 mL of saturated ammonium chloride. Water and DCM were added, and the aqueous phase was extracted twice more with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The resulting material was purified by silica gel chromatography (0-60% EtOAc:hexanes) to provide intermediate (2b) (13.9 g).

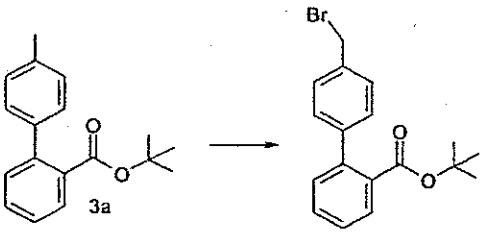
(R)-2-Hydroxymethyl-4-methylpentanoic acid (2c): Intermediate (2b) (13.9 g, 40.8 mmol) was dissolved in THF (200 mL, 2 mol) and stirred at 0 °C. 9 M hydrogen peroxide in water (46.3 mL) was added, followed by dropwise addition of 1.5 M lithium hydroxide monohydrate in water (54.4 mL). The mixture was then warmed to room temperature and

stirred for 2.5 hours. Potassium hydroxide (4.6 g, 81.6 mmol) was added and the mixture was heated at 60 °C for 30 minutes and then cooled at room temperature. To this was added a solution of sodium sulfite (10 g in 200 mL water) followed by water and chloroform (200 mL of each). The aqueous layer was extracted twice more with $CHCl_3$ (150 mL), acidified and extracted with EtOAc. The organic layer was then washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and rotovaped to provide intermediate (2c) (5.4 g).

Triphenylphosphine (19.5 g, 74.3 mmol) was dissolved in THF (200 mL, 2 mol) and cooled at 0 °C. Diisopropyl azodicarboxylate (14.6 mL, 74.3 mmol) was added dropwise and the mixture stirred for 10 minutes at 0 °C. Intermediate (2c) (5.4 g, 37.1 mmol) and thioacetic acid (8.0 mL, 111 mmol) were dissolved in THF (20 mL) and added dropwise to the reaction. After the addition, the mixture was removed from the ice bath and stirred at room temperature. The mixture was stirred for 3.5 hours, concentrated to approximately a third of the volume, and then partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was extracted three times more with saturated $NaHCO_3$ and the combined aqueous extracts were washed twice with $CHCl_3$, acidified with 1N HCl and extracted three times with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and rotovaped to provide the title compound (33% yield).

PREPARATION 3

4'-Bromomethylbiphenyl-2-carboxylic Acid *t*-Butyl Ester



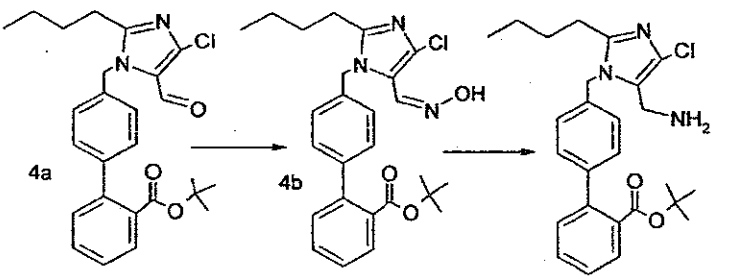
4'-Methylbiphenyl-2-carboxylic acid *t*-butyl ester (3a): A solution of 4'-methylbiphenyl-2-carboxylic acid (48.7 g, 230 mmol) and thionyl chloride (150 mL) was stirred at room temperature. After 5.5 hours, the mixture was concentrated *in vacuo*. Excess thionyl chloride was removed by co-distillation with toluene to afford a yellow solid (52.6 g). The material was then dissolved in THF (500 mL) and cooled to 0 °C. Potassium *t*-butoxide (15.0 g, 130 mmol) was added portion wise, followed by addition of 1M solution of potassium *t*-butoxide in THF (250 mL). Additional solid potassium

t-butoxide (21.4 g, 100 mmol) was added and the mixture was stirred at 0 °C for 1.5 hours. The mixture was then partitioned between EtOAc and water, and the organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated to afford intermediate (3a) as a yellow oil (62.3 g), which was used directly in the next step.

Benzoyl peroxide (3.9 g, 16.0 mmol) was added to a solution of intermediate (3a) (62 g, 230 mmol) and NBS (41.2 g, 230 mmol) in benzene (800 mL). The mixture was then heated at reflux. After 4.5 hours, benzoyl peroxide (1 g) was added, followed by NBS (16 g, 66.0 mmol) 30 minutes later. The mixture was stirred for a total of 6 hours, cooled, filtered, and concentrated *in vacuo*. The resulting residue was then crystallized from diethyl ether and hexane at 4 °C overnight to give the title compound as a pale yellow solid (40.7 g). ^{1}H-NMR (DMSO): δ (ppm) 1.1 (s, 9H), 4.6 (s, 2H), 7.1-7.6 (m, 8H).

PREPARATION 4

4'-(5-Aminomethyl-2-butyl-4-chloroimidazol-1-ylmethyl) biphenyl-2-carboxylic Acid *t*-Butyl Ester



4'-(2-Butyl-4-chloro-5-formylimidazol-1-ylmethyl)biphenyl-2-carboxylic acid *t*-butyl ester (4a): 2-Butyl-5-chloro-3H-imidazole-4-carbaldehyde (9.9 g, 53.3 mmol), 4'-bromomethylbiphenyl-2-carboxylic acid *t*-butyl ester (18.5 g, 53.3 mmol), and K_2CO_3 (7.4 g, 53.3 mmol) were combined in DMF (200 mL) and stirred at room temperature overnight. The reaction was quenched with water, extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash chromatography (0-40% EtOAc:hexanes) to yield 21.5 g of intermediate (4a).

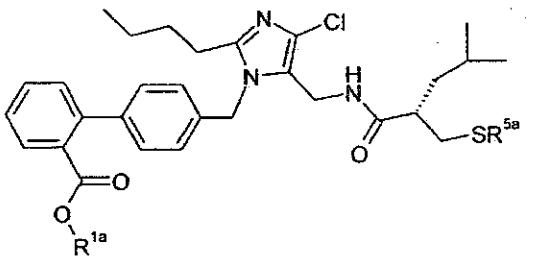
4'-[2-Butyl-4-chloro-5-(hydroxyiminomethyl)imidazol-1-ylmethyl]biphenyl-2-carboxylic acid *t*-butyl ester (4b): Intermediate (4a) (12.1 g, 26.7 mmol) and NH_2OH•HCl (2.4 g, 34.7 mmol) were combined in 80 mL water and 160 mL pyridine and stirred at room temperature overnight. Water (80 mL) was added and the mixture was stirred for 1 hour. The precipitate was filtered and dried to yield 11.7 g of intermediate (4b), which was

used in the next step without further purification.

Intermediate (4b) (8.8 g, 19 mmol), $NaBH_3CN$ (5.3 g, 84.6 mmol) and NH_4OAc (3.2 g, 41.4 mmol) were dissolved in MeOH (100 mL) and cooled to 0 °C. After 15 minutes, $TiCl_3$ (8.70 g, 56.4 mmol) was added in three portions, and the mixture was stirred at 0 °C for 10 minutes. The mixture was then removed from the ice bath and allowed to warm to room temperature, while stirring, for 3 hours. The mixture was cooled to 0 °C, the reaction quenched with NH_4OH (100 mL), and the mixture stirred for 15 minutes. The resulting titanium salt precipitant was filtered off and rinsed with MeOH multiple times. The filtrate was concentrated. The resulting residue was taken up in a 3:1 mixture of $CHCl_3$ and isopropanol. Saturated aqueous NaCl and saturated aqueous $NaHCO_3$ were added. The product was extracted twice with a 3:1 mixture of $CHCl_3$ and isopropanol, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated to yield 8.2 g of the title compound.

EXAMPLE 1

4'-5-[((*S*)-2-Acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butyl-4-chloroimidazol-1-ylmethylbiphenyl-2-carboxylic Acid *t*-Butyl Ester (1a; R^{1a} = *t*-butyl; R^{5a} = $-C(O)CH_3$); 4'-5-[((*S*)-2-Acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butyl-4-chloroimidazol-1-ylmethylbiphenyl-2-carboxylic Acid (1b; R^{1a} = H; R^{5a} = $-C(O)CH_3$); and 4'-2-Butyl-4-chloro-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]imidazol-1-ylmethylbiphenyl-2-carboxylic Acid (1c; R^{1a} = H; R^{5a} = H)

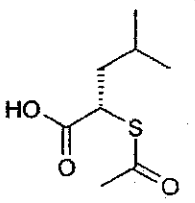


(*S*)-2-Acetylsulfanylmethyl-4-methylpentanoic acid (371 mg, 1.8 mmol) and HATU (691 mg, 1.8 mmol) was dissolved in DMF (5 mL, 60 mmol) and stirred at room temperature for 15 minutes. DIPEA (0.3 mL, 2 mmol) was then added and the mixture was stirred for 1 hour. 4'-(5-Aminomethyl-2-butyl-4-chloroimidazol-1-ylmethyl)biphenyl-2-carboxylic acid *t*-butyl ester (750 mg, 1.7 mmol) and DIPEA (0.3 mL, 2 mmol) in DMF (2 mL) was added and the mixture was stirred at room temperature for 4 hours. The reaction was quenched with water and the mixture extracted with EtOAc. The organic

layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. The reaction was purified by silica gel chromatography (1:1 EtOAc:hexanes) to obtain the acetylsulfanyl ester intermediate (1a). This intermediate was dissolved in DCM:TFA (1:1) (3 mL each) and stirred at room temperature for 3.5 hours and then concentrated to obtain the acetylsulfanyl acid intermediate (1b). This intermediate was redissolved in 1:1 MeOH:NaOH (1N) (2 mL each) and was stirred at room temperature under nitrogen for 1 hour, the reaction quenched with acetic acid, and the mixture concentrated. The resulting material was purified by preparative HPLC (30-70%) to yield 360 mg of the final product (1c). MS *m/z*: $[M + H^+]$ calcd for $C_{29}H_{36}ClN_3O_3S$, 542.22; found, 542.4. ^{1}H-NMR (DMSO): 8.4 (1H, t), 7.69 (1H, d), 7.53 (1H, t), 7.42 (1H, t), 7.33 (1H, d), 7.27 (2H, d), 7.01 (2H, d), 5.23 (2H, s), 4.18 (2H, m), 2.35 (1H, m), 2.05 (1H, t), 1.45 (2H, m) 1.38 (2H, m) 1.2 (3H, m), 0.77 (9H, m).

PREPARATION 5

(S)-2-Acetylsulfanyl-4-methylpentanoic Acid



(R)-2-Bromo-4-methylpentanoic acid (5a): D-Leucine (9.9 g, 75.2 mmol) was dissolved in 3.0 M of HBr in water (120 mL) and cooled to 0 °C. A solution of $NaNO_2$ (8.3 g, 120 mmol) in water (20 mL, 100 mmol) was added. The reaction was stirred at 0 °C for 2.5 hours and then extracted twice with EtOAc, washed twice with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to afford 12.6 g of intermediate (5a) as a pale yellow oil. This was taken on to the next step without further purification. ^{1}H-NMR (DMSO): 4.31 (1H, t), 1.75 (2H, m) 1.65 (1H, m) 0.82 (6H, dd).

Intermediate (5a) (12.5 g, 64.1 mmol), potassium thioacetate (11.0 g, 96.1 mmol), and DMF (100 mL, 1.0 mol) were combined and the mixture stirred at room temperature for 1 hour. Water (100 mL) was then added, and the mixture was extracted three times with EtOAc, washed twice with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated. The product was purified by silica gel chromatography (0-40% EtOAc:hexanes with 5% acetic acid) to yield 6.8 g of the title compound as a pale yellow oil. ^{1}H-NMR (DMSO): 3.96 (1H, t), 2.45 (3H, s), 1.70 (1H, m), 1.55 (1H, m), 1.42 (1H, m), 0.84 (6H, dd).

Alternate Synthesis of Title Compound

(R)-2-Bromo-4-methylpentanoic acid (5a): While stirring, D-leucine (76.6 g, 584 mmol, 1.0 eq) was dissolved into 920 mL of aq. 3.0 M HBr (2.8 mol, 4.7 eq) and cooled to 0 °C. A solution of $NaNO_2$ (64.5 g, 934 mmol, 1.6 eq) in 200 mL water was slowly added over 20 minutes and the mixture was stirred at 0 °C for 3 hours. The mixture was extracted 2x with 500 mL EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure, to yield *(R)*-2-bromo-4-methylpentanoic acid as a yellow oil (103 g). ^{1}H-NMR (DMSO) δ (ppm): 0.9 (m, 6H), 1.6-1.7 (m, 1H), 1.7-1.9 (m, 2H), 4.3 (t, 1H).

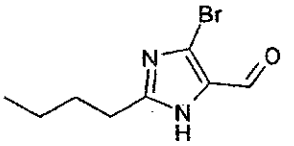
Intermediate (5a) (103 g, 528 mmol, 1.0 eq) was dissolved into 800 mL DMF and cooled to 0 °C. Potassium thioacetate (90.5 g, 792 mmol, 1.5 eq) was added slowly and the mixture was allowed to slowly warm to room temperature. After 8 hours, the reaction was quenched with 600 mL water, extracted 3x with 500 mL EtOAc, washed with saturated aqueous NaCl and dried over $MgSO_4$. The organic was filtered and concentrated under reduced pressure producing the crude title compound as a brown oil. The crude product (85 g) was dissolved into 350 mL diisopropyl ether and chilled at 0 °C in ice. 1.0 eq. of diisopropyl amine was added slowly and the resulting mixture was stirred for 1 hour. The solution was filtered and the solid was washed with 250 mL cold diisopropyl ether. The solid was then suspended in 500 mL EtOAc and washed with 900 mL 5% $KHSO_4$ (aq.). The organic was dried over $MgSO_4$ and concentrated under reduced pressure to yield the title compound as a yellow oil (39.6 g). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.9 (m, 6H), 1.6 (m, 1H), 1.7 (m, 1H), 1.8 (m, 1H), 2.3 (s, 3H), 4.2 (t, 1H).

Alternately, thioacetic acid (13.7 g, 180 mmol) and DMF (300 mL) were combined, and the mixture cooled in an ice bath. Sodium carbonate (19.0 g, 180 mmol) was added. After 30 minutes, Intermediate (5a) (33.4 g, 171 mmol) in 20 mL DMF was added dropwise and the mixture was stirred at 0 °C to room temperature over 7 hours. The reaction was diluted with 200 mL EtOAc and washed with 200 mL of a 1:1 saturated aqueous NaCl:1N HCl solution. The layers were separated and the aqueous phase was extracted again with 200 mL EtOAc. The organics were combined, washed with saturated aqueous NaCl, dried over MgSO4, filtered, and concentrated under reduced pressure. The recovered oil was dissolved into diisopropyl ether (150 mL, 1.1 mol) and chilled at 0 °C. Dicyclohexylamine (33.4 mL, 168 mmol) was added dropwise and the solid was allowed to crash out of solution. After stirring for an additional 30 minutes the material was

filtered and washed with 150 mL cold diisopropyl ether. The recovered solid (41 g) was suspended in 300 mL EtOAc. 500mL of 5% $KHSO_4$ was added and the layers were separated. The organic was washed with saturated aqueous NaCl, dried over MgSO4, filtered, and concentrated under reduced pressure o yield the title compound as a yellow oil (20.7 g). ^{1}H NMR ($CDCl_3$) δ (ppm): 0.9 (m, 6H), 1.6 (m, 1H), 1.7 (m, 1H), 1.8 (m, 1H), 2.3 (s, 3H), 4.2 (t, 1H).

PREPARATION 6

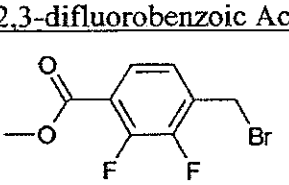
5-Bromo-2-butyl-3H-imidazole-4-carbaldehyde



2-Butyl-3H-imidazole-4-carbaldehyde (30.0 g, 197 mmol) was dissolved in DMF (220 mL, 2.8 mol). NBS (36.8 g, 207 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was then concentrated and taken up in EtOAc and water. The aqueous layer was extracted three times with EtOAc, and the combined organic extracts washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated. The mixture was purified by silica gel chromatography (0-50% EtOAc:hexanes) to obtain 7.8 g of the title compound as a gray solid. MS *m/z*: [M + H^+] calcd for $C_8H_{11}BrN_2O$, 232.09; found 233.0. ^{1}H-NMR (DMSO): 13.3 (1H, br), 9.48 (1H, s), 2.66 (2H, t), 1.59 (2H, m), 1.25 (2H, m), 0.85 (3H, t).

PREPARATION 7

4-Bromomethyl-2,3-difluorobenzoic Acid Methyl Ester



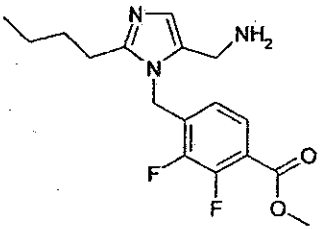
2,3-Difluoro-4-methyl-benzoic acid methyl ester (7a): 2,3-Difluoro-4-methyl-benzoic acid (10.0 g, 58.1 mmol) was dissolved in MeOH (200 mL, 6.0 mol) and sulfuric acid (1.00 mL, 19.0 mmol), and was heated at reflux overnight. The mixture was then cooled and concentrated under reduced pressure. The resulting residue was taken up in EtOAc and washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated to yield 9.0 g of intermediate (7a) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.61 (1H, t), 7.00 (1H, t), 3.93 (3H, s), 2.35 (3H, s).

Intermediate (7a) (9.0 g, 48.4 mmol), NBS (8.6 g, 48.4 mmol), and benzoyl

peroxide (100 mg, 0.5 mmol) were dissolved in benzene (200 mL, 2.0 mol) and the mixture was heated at reflux overnight. The mixture was then cooled and concentrated under reduced pressure. The resulting residue was taken up in EtOAc and washed with water and saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. The crude reaction was purified by silica gel chromatography (0-10% EtOAc:hexanes) to obtain 4.6 g of the title compound as a light yellow solid. MS *m/z*: [M + H^+] calcd for $C_9H_7BrF_2O_2$, 266.05; found 267.1. ^{1}H-NMR ($CDCl_3$): 7.70 (1H, t), 7.28 (1H, t), 4.48 (2H, s), 3.95 (3H, s).

PREPARATION 8

4-(5-Aminomethyl-2-butyl-imidazol-1-ylmethyl)-2,3-difluorobenzoic Acid Methyl Ester Dihydrochloride Salt



4-(4-Bromo-2-butyl-5-formyl-imidazol-1-ylmethyl)-2,3-difluorobenzoic acid methyl ester (8a): 4-bromomethyl-2,3-difluorobenzoic acid methyl ester (3.5 g, 13.2 mmol), 5-bromo-2-butyl-3H-imidazole-4-carbaldehyde (3.1 g, 13.2 mmol) and potassium carbonate (1.8 g, 13.2 mmol) were combined and dissolved in DMF (20 mL, 300 mmol). The mixture was stirred at room temperature overnight. The mixture was then diluted with water and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated. The crude reaction was purified by silica gel chromatography (0-50% EtOAc:hexanes) to obtain 4.16 g of intermediate (8a) as a yellow solid. MS *m/z*: [M + H^+] calcd for $C_{17}H_{17}BrF_2N_2O_3$, 416.23; found 417.1. ^{1}H-NMR ($CDCl_3$): 9.68 (1H, s), 7.64 (1H, t), 6.55 (1H, t), 5.64 (2H, s), 3.95 (3H, s), 2.63 (2H, t), 1.69 (2H, m), 1.36 (2H, m) 0.90 (3H, t).

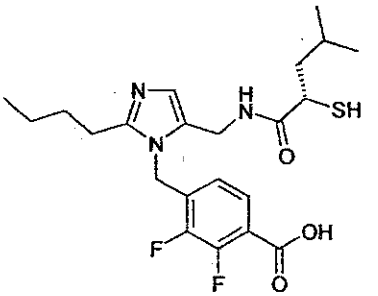
4-[4-Bromo-2-butyl-5-(hydroxyiminomethyl)imidazol-1-ylmethyl]-2,3-difluorobenzoic acid methyl ester (8b): Intermediate (8a) (4.1 g, 10 mmol) was dissolved in pyridine (20 mL, 200 mmol), and water (10 mL, 600 mmol). NH_2OH•HCl (898 mg, 12.9 mmol) was added and the mixture was stirred at room temperature overnight. The reaction was quenched by the addition of water (20 mL) and the mixture stirred for 20 minutes. The resulting solid was filtered and dried to yield 3.6 g of intermediate (8b) as a light

yellow solid. MS *m/z*: [M + H^+] calcd for $C_{17}H_{18}BrF_2N_3O_3$, 431.24; found 432.2.

Intermediate (8b) (3.6 g, 8.2 mmol), palladium hydroxide (0.58 g, 4.1 mmol), 1 M of HCl in water (16.5 mL), and MeOH (190 mL, 4.7 mol) were combined. The mixture was degassed and then stirred under hydrogen for 4 hours. The palladium was filtered and then the solute was concentrated to yield 3.3 g of the title compound as a yellow-orange solid. MS *m/z*: [M + H^+] calcd for $C_{17}H_{21}F_2N_3O_2$, 338.16; found 338.2. ^{1}H-NMR (DMSO): 9.69 (2H, br), 7.84 (1H, s), 7.67 (1H, m), 6.94 (1H, m) 5.80 (2H, s), 4.10 (2H, d), 3.88 (3H, s), 2.98 (2H, t), 1.56 (2H, m), 1.29 (2H, m), 0.84 (3H, t).

EXAMPLE 2

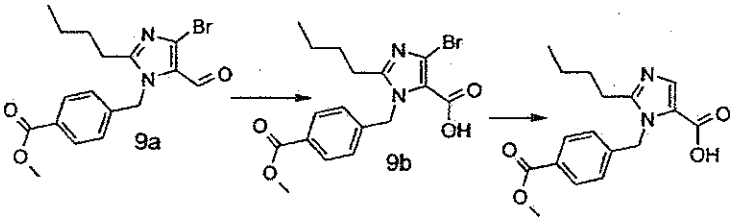
4-{2-Butyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2,3-difluorobenzoic Acid



(S)-2-Acetylsulfanyl-4-methylpentanoic acid (205 mg, 1.1 mmol) was dissolved in DMF (8.1 mL, 104 mmol). HATU (409 mg, 1.1 mmol) and DIPEA (170 µL, 1.0 mmol) were added and the mixture was stirred at room temperature for 30 minutes. 4-(5-Aminomethyl-2-butyl-imidazol-1-ylmethyl)-2,3-difluorobenzoic acid methyl ester dihydrochloride salt (401 mg, 1.0 mmol) was dissolved in DMF (1 ml) with DIPEA (170 µL, 1.0 mmol) and added to the mixture. The mixture was stirred at room temperature for 2 hours. The reaction was then quenched with water, and the mixture extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. The crude residue was then redissolved in 1:1 MeOH:NaOH (4 mL) and stirred at room temperature under nitrogen for 1 hour. The reaction was quenched with acetic acid and the mixture was concentrated. The product was purified by preparative HPLC (2-90%) to yield 108 mg of the title compound as a white solid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{29}F_2N_3O_3S$, 454.19; found 454.2. ^{1}H-NMR (DMSO): 8.44 (1H, t), 7.59 (1H, t), 7.25 (1H, s), 6.62 (1H, t), 5.56 (2H, s), 4.24 (2H, m), 3.14 (2H, q), 2.79 (2H, t), 2.72 (1H, d), 1.2-1.6 (7H, m), 0.78 (6H, d), 0.71 (3H, d).

PREPARATION 9

2-Butyl-3-(4-methoxycarbonylbenzyl)-3H-imidazole-4-carboxylic Acid (TFA Salt)



4-(4-Bromo-2-butyl-5-formyl-imidazol-1-ylmethyl)benzoic acid methyl ester (9a): 5-Bromo-2-butyl-3H-imidazole-4-carbaldehyde (38 g, 160 mmol) was dissolved in DMF (400 mL, 5 mol). Potassium carbonate (27 g, 200 mmol) was added followed by methyl 4-bromomethylbenzoate (38 g, 160 mmol) and the solution was stirred at room temperature overnight. The mixture was then concentrated and purified by silica gel chromatography (0-50% EtOAc:hexanes) to yield intermediate (9a) (32.2 g, 62.2 mmol). MS *m/z*: [M + H^+] calcd for $C_{17}H_{19}N_2O_3Br$, 379.3; found 379.1. ^{1}H-NMR (400 Mz, CD_3OD) δ (ppm): 0.82 (t, 3H, *J* = 5 Hz), 1.28 (m, 2H), 1.54 (q, 2H, *J* = 5 Hz), 2.70 (t, 2H, *J* = 5 Hz), 5.69 (s, 2H), 7.15 (d, 2H, *J* = 5 Hz), 7.96 (d, 2H, *J* = 5 Hz), 9.66 (s, 1H).

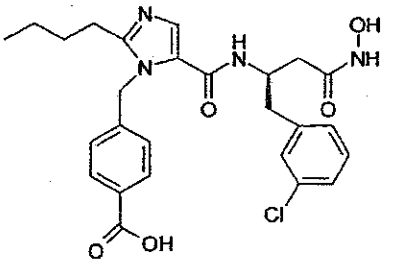
5-Bromo-2-butyl-3-(4-methoxycarbonylbenzyl)-3H-imidazole-4-carboxylic acid (9b): Intermediate (9a) (20 g, 50 mmol) was dissolved in 1-butanol (580 mL, 6.3 mol). To this was added 2.0 M 2-methyl-2-butene in THF (295 mL), sodium dihydrogen phosphate (50.6 g, 422 mmol), and sodium chlorite (50.6 g, 559 mmol) in water (780 mL, 43 mol). The mixture was stirred at room temperature overnight then extracted with 500 mL EtOAc and washed twice with 250 mL of saturated sodium sulfite solution. The organic extract was dried over $MgSO_4$, concentrated, then purified by silica gel chromatography (0-50% EtOAc:hexanes) to yield intermediate (9b) (20 g, 50 mol). MS *m/z*: [M + H^+] calcd for $C_{17}H_{19}N_2O_4Br$, 395.3; found 397.2. ^{1}H-NMR (400 Mz, CD_3OD): δ (ppm) 0.82 (t, 3H, *J* = 5 Hz), 1.27 (m, 2H), 1.53 (q, 2H, *J* = 5 Hz), 2.64 (t, 2H, J = 5 Hz), 5.71 (s, 2H), 7.10 (d, 2H, *J* = 5 Hz), 7.96 (d, 2H, *J* = 5 Hz).

Intermediate (9b) (20 g, 50 mmol) was dissolved in MeOH (390 mL, 9.6 mol). TFA (4.33 mL, 56.2 mmol) was added to solubilize the material. The mixture was degassed under nitrogen and palladium 10% on carbon wt (0.54g, 5 mmol) was added. The mixture was placed under hydrogen and stirred at room temperature for 4 hours. The mixture was then filtered through a pad of Celite® and concentrated. The resulting residue was triturated with EtOAc and filtered to recover the title compound as a TFA salt (15.9 g,

36.9 mmol). MS *m/z*: [M + H^+] calcd for $C_{17}H_{20}N_2O_4$, 316.4; found 317.3. ^{1}H-NMR (400 Mz, CD_3OD): δ (ppm) 0.85 (t, 3H, *J* = 5 Hz), 1.32 (m, 2H), 1.55 (q, 2H, *J* = 5 Hz), 2.96 (t, 2H, *J* = 5 Hz), 5.92 (s, 2H), 7.26 (d, 2H, *J* = 5 Hz), 8.00 (d, 2H, *J* = 5 Hz), 8.2 (s, 1H).

EXAMPLE 3

4-{2-Butyl-5-[*(R)*-1-(3-chlorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic Acid (TFA salt)



2-Butyl-3-(4-methoxycarbonylbenzyl)-3H-imidazole-4-carboxylic acid TFA salt (2.7 g, 6.3 mmol) was dissolved in DMF (30 mL). The solution was stirred at room temperature and pentafluorophenol (1.2 g, 6.3 mmol), EDC (1.2 g, 6.3 mmol), and DIPEA (1.1 mL, 6.3 mmol) were added. The solution was allowed to stir at room temperature overnight. To this was added *(R)*-3-amino-4-(3-chlorophenyl)butyric acid HCl salt (0.8 g, 6.3 mmol) and DIPEA (1.1 mL, 6.3 mmol), and the solution was stirred at 60 °C for 4 hours. The crude reaction mixture was then allowed to cool to room temperature, concentrated under reduced pressure, then diluted with EtOAc. The organic solution was washed with 1M phosphoric acid, a saturated solution of NaCl, then dried over $MgSO_4$. After filtration, the organic solution was concentrated under reduced pressure to afford the crude acid.

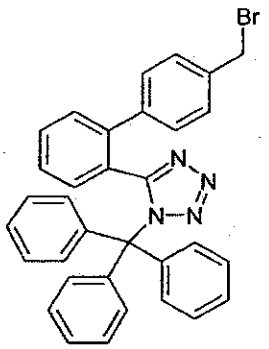
The crude acid was then dissolved in DMF (30 mL). The solution was stirred at room temperature and pentafluorophenol (1.2g, 6.3 mmol), EDC (1.2 g, 6.3 mmol), and DIPEA (1.1 mL, 6.3 mmol) were added. The resulting solution was allowed to stir at room temperature overnight. To this was added hydroxylamine HCl salt (450 mg, 6.3 mmol) and DIPEA (1.1 mL, 6.3 mmol), and the solution was stirred at 40 °C for 4 hours. The crude reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure, and diluted with EtOAc. The organic layer was then washed with 1M phosphoric acid, a saturated solution of NaCl, and then dried over $MgSO_4$. After filtration, the mixture was concentrated under reduced pressure to afford the crude hydroxamate.

The crude hydroxamate was dissolved in THF (10 mL) followed by addition of 1M NaOH (31.6 mL, 31.6 mmol). The mixture was stirred at 40 °C for 4 hours and then

acidified to pH 4 with 1 M HCl. The aqueous solution was extracted three times with EtOAc, and the combined organic extracts were concentrated under reduced pressure to afford the crude material which was purified by reverse phase chromatography (1:1 water:MeCN with 0.1% TFA) to obtain the title compound as a TFA salt (279 mg, 0.23 mmol). MS *m/z*: $[M + H^+]$ calcd for $C_{26}H_{29}ClN_4O_5$, 513.18; found 513.5. ^{1}H-NMR (400 Mz, $(CD_3)_2SO$): δ (ppm) 0.74 (t, 3H, J = 5 Hz), 1.18 (q, 2H, J = 5 Hz), 1.41 (m, 2H), 2.20 (d, 2H, J = 5 Hz), 2.68 (m, 3H), 4.36 (m, 2H), 5.71 (m, 2H), 7.11 (m, 5H, J = 5 Hz), 7.86 (m, 2H), 8.00 (s, 1H), 8.59 (s, 1H).

PREPARATION 10

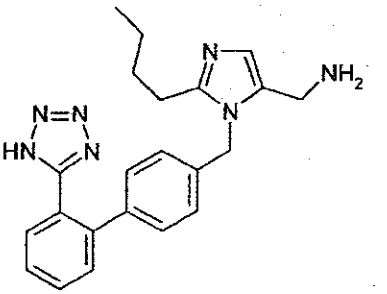
5-(4'-Bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole



To a nitrogen-saturated suspension of *N*-triphenylmethyl-5-[4'-methylbiphenyl-2-yl]tetrazole (10 g, 20.9 mmol) in DCM was added NBS (3.7 g, 20.9 mmol) and a catalytic amount of benzoyl peroxide (60 mg, 0.24 mmol). The mixture was stirred at reflux for 15 hours. After cooling to room temperature, the precipitate was filtered and the organic solution was concentrated *in vacuo*. Silica gel chromatography (EtOAc:hexanes) gave the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 4.61 (s, 2H), 6.80 (d, 6H), 7.01 (d, 2H), 7.24 (d, 2H), 7.28-7.35 (m, 9H), 7.43-7.45 (dd, 1H), 7.50-7.56 (td, 1H), 7.58-7.60 (td, 1H), 7.77-7.79 (dd, 1H).

PREPARATION 11

C-{2-Butyl-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-yl}methylamine•2[$C_2HF_3O_2$]



2-Butyl-5-chloro-3-[2'-(1-trityl-1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazole-4-carbaldehyde (11a): To a DMF (150 mL) solution of 5-(4'-bromomethyl-biphenyl-2-yl)-1-trityl-1H-tetrazole (30 g, 53.8 mmol) was added 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde (10 g, 53.8 mmol) and K_2CO_3 (7.4 g, 53.8 mmol). The mixture was stirred at room temperature overnight. EtOAc (500 mL) was added and the organic was washed three times with a $NaHCO_3$ solution (200 mL) followed by saturated aqueous NaCl (200 mL). Solvent was removed and purification was achieved by silica gel chromatography (50:50 EtOAc:hexanes) using an isocratic gradient to provide intermediate (11a) a white solid (41 g). MS *m/z*: [M + H^+] calcd for $C_{41}H_{35}ClN_6O$, 663.26; found 663.4. ^{1}H-NMR (d_4-MeOH): 0.83 (m, 3H), 1.26 (m, 2H), 1.53 (m, 2H), 2.53 (m, 2H), 5.56 (s, 2H), 6.87-6.96 (m, 8H), 7.05 (m, 2H), 7.25-7.43 (m, 10H), 7.53-7.58 (m, 2H), 7.84 (d, 1H), 9.73 (s, 1H).

{2-Butyl-5-chloro-3-[2'-(1-trityl-1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-yl}-methanol (11b): To an EtOH (500 mL) solution of intermediate (11a) (41.0 g, 61.8 mmol) was added solid $NaBH_4$ (2.8 g, 74.1 mmol). The mixture was stirred at room temperature for 1 hour. After cooling to 0 °C, the reaction was quenched by dropwise addition of a 50/50 solution of acetic acid/water until no effervescence was observed. EtOAc (500 mL) was added and the organic was washed three times with saturated aqueous NaCl (100 mL). Solvent was removed and purification was achieved by silica gel chromatography (50:50 EtOAc:hexanes) using an isocratic gradient to provide intermediate (11b) as a white solid (37 g). MS *m/z*: [M + H^+] calcd for $C_{41}H_{37}ClN_6O$, 665.28; found 665.3. ^{1}H-NMR (d_4-MeOH): 0.79 (m, 3H), 1.20 (m, 2H), 1.46 (m, 2H), 2.45 (m, 2H), 4.30 (s, 2H), 5.19 (s, 2H), 6.83-6.90 (m, 8H), 7.05 (d, 2H), 7.23-7.33 (m, 10H), 7.53 (m, 2H), 7.81 (d, 1H).

Methanesulfonic acid 2-butyl-5-chloro-3-[2'-(1-trityl-1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl ester (11c): To a DCM (200 mL) solution of intermediate (11b) (13.6 g, 20.4 mmol), cooled to -78 °C, was added methane sulfonyl chloride (6.3 mL, 81.6 mmol). The mixture was stirred at -78 °C for 15 minutes. A saturated $NaHCO_3$ solution (100 mL) and EtOAc (500 mL) were added to the cooled mixture, which was then allowed to reach room temperature. The organic was washed an additional three times with saturated aqueous NaCl (100 mL). After drying over sodium sulfate and filtration, the removal of solvent provided intermediate (11c) as a yellow oil (15 g) which was used directly in the next step. MS *m/z*: $[M + H^+]$ calcd for $C_{42}H_{39}ClN_6O_3S$, 743.26; due to the reactive nature of intermediate (11c), only the methanol substituted product was observed upon running a mass spectrum of the sample when dissolved in methanol; methanol substituted product $[M + H^+] = 679.6$.

5-[4'-(5-Azidomethyl-2-butyl-4-chloro-imidazol-1-ylmethyl)-biphenyl-2-yl]-1-trityl-1H-tetrazole (11d): To a dimethyl sulfoxide (100 mL) solution of intermediate (11c) (15 g, 20 mmol) was added sodium azide (3.9 g, 60 mmol). The mixture was stirred at room temperature for 20 minutes. EtOAc (500 mL) and saturated aqueous NaCl (100 mL) were added and the layers were separated, retaining the organic layer. The organic was washed an additional three times with saturated aqueous NaCl (100 mL). After drying over sodium sulfate and filtration, the removal of solvent provided intermediate (11d) as a yellow solid (12 g), which was used directly in the next step. MS *m/z*: $[M + H^+]$ calcd for $C_{41}H_{36}ClN_9$, 690.29; found 690.5.

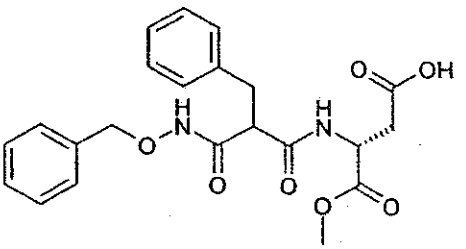
C-{2-Butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-yl}methylamine•2$[C_2HF_3O_2]$ (11e): To a MeOH (150 mL) solution of intermediate (11d) (12 g, 17 mmol), was added palladium on carbon (6.0 g; 10% Pd w/w). The solution was first degassed and backfilled with nitrogen gas (1 atm) followed by additional degassing and backfilling with hydrogen gas (1 atm). The solution was then stirred at room temperature for 2-3 hours at which the azide reduction was 50% complete. Additional palladium on carbon (1.0 g; 10% Pd w/w) was added and the solution stirred under hydrogen. After 1.5 hours the reaction was complete, the mixture was degassed and backfilled with nitrogen prior to filtration through Celite. The filtrate was reduced to a volume of 50 mL. Into the filtrate was slowly added 6N HCl (150 mL) and the solution was stirred for 4 hours and then evaporated to dryness. Purification was accomplished by preparative HPLC (reverse phase) to provide intermediate (11e) as a white solid bis-TFA

salt (4.0 g). MS *m/z*: [M + H$^+$] calcd for $C_{22}H_{24}ClN_7$, 422.19; found. 422.0. ^{1}H-NMR (d_4-MeOH): 0.89 (m, 3H), 1.35 (m, 2H), 1.59 (m, 2H), 2.88 (m, 2H), 4.20 (s, 2H), 5.58 (s, 2H), 7.10 (d, 2H), 7.19 (d, 2H), 7.52-7.67 (m, 4H).

To a MeOH (195 mL) solution of intermediate (11e) (2.34 g, 5.5 mmol), was added 1N NaOH (58 mL) and palladium on carbon (1.9 g; 10% Pd w/w). The solution was first degassed and backfilled with nitrogen gas (1 atm) followed by additional degassing and backfilling with hydrogen gas (1 atm). The solution was then stirred at room temperature for 2-3 hours. The solution was degassed and backfilled with nitrogen prior to filtration through Celite. Into the filtrate was slowly added 1N HCl (58 mL) and the neutralized solution was evaporated to dryness. Purification was accomplished by preparative HPLC (reverse phase) to provide the title compound as a white solid bis-TFA salt (1.90 g). MS *m/z*: [M + H$^+$] calcd for $C_{22}H_{25}N_7$ 388.22; found 388.2. ^{1}H-NMR (d_4-MeOH): 0.91 (m, 3H), 1.38 (m, 2H), 1.63 (m, 2H), 3.00 (m, 2H), 4.21 (s, 2H), 5.61 (s, 2H), 7.10 (d, 2H), 7.19 (d, 2H), 7.52-7.67 (m, 4H), 7.74 (s, 1H).

PREPARATION 12

(R)-2-(2-Benzyloxycarbamoyl-3-phenypropionylamino)succinic Acid 1-Methyl Ester



2-Benzyl-N-benzyloxy-malonamic acid ethyl ester was prepared as described in Fournie-Zaluski et al. (1985) *J. Med. Chem.* 28(9):1158-1169).

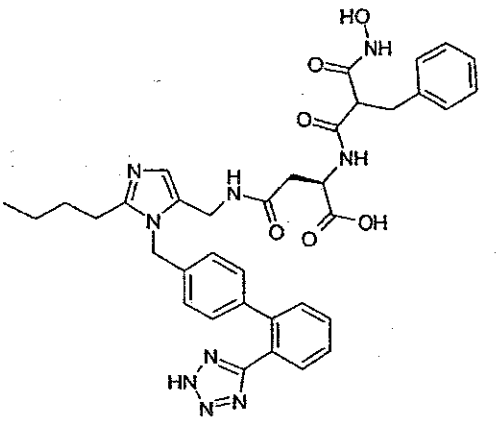
2-Benzyl-N-benzyloxy-malonamic acid (12a): To a solution of the 2-benzyl-N-benzyloxy-malonamic acid ethyl ester (19 g, 58.1 mmol) dissolved in a mixture of THF (70 mL) and MeOH (200 mL) was added a solution of NaOH (5.4 g, 135 mmol) in water (100 mL). The mixture was stirred at room temperature for 24 hours, and evaporated to remove volatile organic solvents. The aqueous residue was diluted with water (200 mL), and washed with DCM (200 mL). The aqueous layer was saved and acidified to pH~4 by adding concentrated HCl. The desired product was precipitated, washed with water, dissolved in acetone (200 mL), and evaporated to dryness, affording intermediate (12a) as a white solid (14.2 g). ^{1}H-NMR (CD_3OD, 300 MHz) δ (ppm) 7.20-7.06 (m, 5H), 4.60-4.56 (d, 1H), 4.42-4.38 (d, 1H), 3.10-2.98 (m, 2H).

2-Benzyl-N-benzyloxy-malonamic acid 2,5-dioxo-pyrrolidin-1-yl ester (12b): Intermediate (12a) (0.5 g, 1.7 mmol) was added to N-hydroxysuccinimide (290 mg, 2.6 mmol) and EDC (320 mg, 1.7 mmol) and dissolved in MeCN (6 mL). The mixture was stirred overnight at room temperature and then partitioned between EtOAc and 10% aqueous citric acid. The organic layer was separated, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated to provide intermediate (12b) as a foam (0.8 g, 2 mmol).

Intermediate (12b) (170 mg, 420 μmol) was dissolved in MeCN (4 mL) and H-D-Asp-OMe (0.09 g, 0.63 mmol) was added followed by solid $NaHCO_3$ (110 mg, 1.3 mmol) and water (1 mL). The reaction was stirred at room temperature overnight and then partitioned with EtOAc and aqueous HCl (0.01 N). The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, concentrated, and then purified by preparative HPLC to provide the title compound (80 mg, 190 μmol).

EXAMPLE 4

(R)-N-{2-Butyl-3-[2'-(2H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}-2-(2-hydroxycarbamoyl-3-phenyl-propionylamino)succinamic Acid

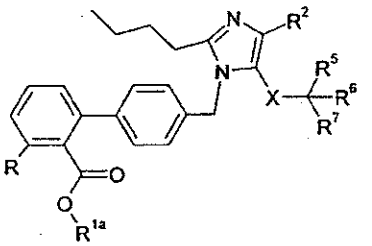


(R)-2-(2-Benzyloxycarbamoyl-3-phenylpropionylamino)succinic acid 1-methyl ester (70 mg, 160 μmol) was mixed with DMF (1 mL). To this solution was added HATU (60 mg, 160 μmol) and the solution was stirred for 20 minutes. {2-Butyl-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-yl}methylamine (60 mg, 160 μmol) was then added followed by triethylamine (70 μL, 480 μmol). After approximately 5 hours the reaction was partitioned between EtOAc and 0.01 N HCl. The aqueous layer was separated and extracted with EtOAc and the combined organic layers were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated to yield 140 mg of a clear oil. The resulting oil was dissolved in MeOH (10 mL) and 1 N NaOH was added (0.5

mL). The mixture was then stirred at room temperature overnight and then briefly heated to 45 °C for 90 minutes. The mixture was then cooled and acetic acid (20 drops) was added followed by 10% palladium on carbon (25 mg) under an inert atmosphere. The reaction was then charged with hydrogen (1 atm) and stirred for 29 hours. The solution was then filtered, concentrated, and purified by preparative HPLC (reverse phase) to give the title compound as the TFA salt (18 mg, 20 μmol). MS *m/z*: $[M + H^+]$ calcd for $C_{36}H_{39}N_9O_6$, 694.30; found 694.4.

EXAMPLE 5

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 5-1 to 5-42, having the following formula where R is an optional substituent, were also prepared:



Ex.	R^{1a}	R^2	-X	R^5	R^6	R^7	R
5-1	H	Cl	-C(O)NH-$(CH_2)_6$-NHC(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R6 and R7 taken together to form cyclopentyl		-
5-2	H	Cl	-C(O)NH-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl		-
5-3	H	Cl	-C(O)NH-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl		-
5-4	H	Cl	-C(O)NH-$(CH_2)_4$-NHC(O)-	-SH	benzyl	H	-
5-5	H	Cl	-C(O)NH-$(CH_2)_2$-NHC(O)-CH_2-NHC(O)-	-C(O)N(OH)H	benzyl	H	-
5-6	H	Cl	-C(O)NH-$(CH_2)_4$-NHC(O)-CH_2-NHC(O)-	-C(O)N(OH)H	benzyl	H	-
5-6	H	Cl	-CH_2-NHC(O)-$(CH_2)_2$-NHC(O)-	-CH_2SH	benzyl	H	-
5-8	H	Cl	-CH_2-NHC(O)-$(CH_2)_2$-NHC(O)-	-SH	benzyl	H	-

Ex.	R^{1a}	R^2	-X	R^5	R^6	R^7	R
5-9	H	Cl	$-CH_2$-NHC(O)-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-	$-CH_2$-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl		-
5-10	H	Cl	$-CH_2$-NHC(O)-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-	$-CH_2$-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl		-
5-11	H	Cl	$-CH_2$-NHC(O)-$(CH_2)_6$-NHC(O)-cyclohexylene-NHC(O)-	$-CH_2$-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl		-
5-12	H	Cl	$-CH_2$-NHC(O)-	-SH	benzyl	H	-
5-13	H	Cl	$-CH_2$-NHC(O)-	$-SC(O)CH_3$	$-CH(CH_3)CH_2CH_3$	H	-
5-14	H	H	$-CH_2$-NHC(O)-	-SH	$-CH(CH_3)CH_2CH_3$	H	-
5-15	H	H	$-CH_2$-NHC(O)-	-C(O)N(OH)H	$-CH_2CH-(CH_3)_2$	H	-
5-16	H	H	$-CH_2$-NHC(O)-	$-SC(O)CH_3$	$-CH_2CH-(CH_3)_2$	H	-
5-17	H	Cl	$-CH_2$-NHC(O)-	-C(O)N(OH)H	$-CH(CH_3)CH_2CH_3$	H	-
5-18	H	Cl	$-CH_2$-NHC(O)-	-C(O)N[OC(O)CH_3]H	$-CH_2CH-(CH_3)_2$	H	-
5-19	H	H	-C(O)NH-	$-CH_2C(O)$-N(OH)H	benzyl	H	-
5-20	H	H	-C(O)NH-	$-CH_2C(O)$-N(OH)H	$-CH_2CH-(CH_3)_2$	H	-
5-21	H	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH-(CH_3)_2$	H	-
5-22	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH-(CH_3)_2$	H	-
5-23	H	H	$-CH_2$-NHC(O)-	-NHC(O)-CH_2SH	$-CH_2CH-(CH_3)_2$	H	-
5-24	H	Cl	$-CH_2$-NHC(O)-	-C(O)N(OH)H	cyclopentyl	H	-
5-25	H	H	$-CH_2$-NHC(O)-	-C(O)N(OH)H	cyclopentyl	H	-
5-26	H	$-CH_2$-OH	-C(O)NH-	$-CH_2C(O)$-N(OH)H	benzyl	H	-
5-27	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2$-cyclopropyl	H	-
5-28	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH-(CH_3)_2$	H	-
5-29	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	benzyl	H	F
5-30	H	Cl	$-CH_2$-NHC(O)-	-C(O)N(OH)H	$-CH_2CH-(CH_3)_2$	H	F
5-31	$-CH_3$	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH-(CH_3)_2$	H	-
5-32	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-(CH_2)_3CH_3$	H	-
5-33	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-(CH_2)_2-CH(CH_3)_2$	H	-

Ex.	R^{1a}	R^2	-X	R^5	R^6	R^7	R
5-34	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH(CH_3)-CH_2CH_3$	H	-
5-35	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2$-cyclopentyl	H	-
5-36	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2$-cyclohexyl	H	-
5-37	H	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2$-naphthyl	H	-
5-38	H	$-CH_2-CH_3$	$-CH_2$-NHC(O)-	-SH	$-CH_2CH-(CH_3)_2$	H	-
5-39	H	$-CH_2-CH_3$	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH-(CH_3)_2$	H	-
5-40	H	cyclo-propyl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH-(CH_3)_2$	H	-
5-41	H	cyclo-propyl	$-CH_2$-NHC(O)-	-SH	$-CH_2$-cyclopropyl	H	-
5-42	H	$-O-CH_3$	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH-(CH_3)_2$	H	-

(5-1) 4'-[2-butyl-5-(6-{[4-({1-[2-carboxy-3-(2-methoxyethoxy)propyl] cyclopentanecarbonyl}amino)cyclohexanecarbonyl]amino}hexylcarbamoyl)-4-chloroimidazol-1-ylmethyl]biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{48}H_{66}ClN_5O_9$, 892.46; found 892.2.

(5-2) 4'-[2-butyl-5-(4-{[4-({1-[2-carboxy-3-(2-methoxyethoxy)propyl] cyclopentanecarbonyl}amino)cyclohexanecarbonyl]amino} butylcarbamoyl)-4-chloroimidazol-1-ylmethyl]biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{46}H_{62}ClN_5O_9$, 864.42; found 864.4.

(5-3) 4'-[2-butyl-5-(2-{[4-({1-[2-carboxy-3-(2-methoxyethoxy)propyl] cyclopentanecarbonyl}amino)cyclohexanecarbonyl]-amino}-ethylcarbamoyl)-4-chloroimidazol-1-ylmethyl]biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{44}H_{58}ClN_5O_9$, 836.39; found 836.4.

(5-4) 4'-{2-butyl-4-chloro-5-[4-(*(S)*-2-mercapto-3-phenylpropionylamino) butylcarbamoyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{35}H_{39}ClN_4O_4S$, 647.24; found 648.2.

(5-5) 4'-(2-butyl-4-chloro-5-{2-[2-(2-hydroxycarbamoyl-3-phenylpropionylamino) acetylamino]ethylcarbamoyl}imidazol-1-ylmethyl)biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{36}H_{39}ClN_6O_7$, 703.26; found 704.2.

(5-6) 4'-(2-butyl-4-chloro-5-{4-[2-(2-hydroxycarbamoyl-3-phenylpropionylamino) acetylamino]butylcarbamoyl}imidazol-1-ylmethyl)biphenyl-2-carboxylic acid. MS *m/z*:

[M + H^+] calcd for $C_{38}H_{43}ClN_6O_7$, 731.29; found 732.2.

(5-7) 4'-(5-{[3-(2-benzyl-3-mercapto-propionylamino)propionylamino]methyl}-2-butyl-4-chloroimidazol-1-ylmethyl)biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{35}H_{39}ClN_4O_4S$, 647.24; found 647.2.

(5-8) 4'-(2-butyl-4-chloro-5-{[3-((s)-2-mercapto3-phenylpropionylamino) propionylamino]methyl}-imidazol-1-ylmethyl)biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{34}H_{37}ClN_4O_4S$, 633.22; found 633.2.

(5-9) 4'-{2-butyl-5-[(3-{[4-({1-[2-carboxy-3-(2-methoxyethoxy)propyl] cyclopentanecarbonyl}amino)-cyclohexanecarbonyl]amino}propionylamino)methyl]-4-chloroimidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{45}H_{60}ClN_5O_9$, 850.41; found 850.4.

(5-10) 4'-{2-butyl-5-[(5-{[4-({1-[2-carboxy-3-(2-methoxyethoxy)propyl] cyclopentanecarbonyl}amino)cyclohexanecarbonyl]amino}pentanoylamino)methyl]-4-chloroimidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{47}H_{64}ClN_5O_9$, 878.44; found 878.4.

(5-11) 4'-{2-butyl-5-[(7-{[4-({1-[2-carboxy-3-(2-methoxyethoxy)propyl] cyclopentanecarbonyl}amino)cyclohexanecarbonyl]amino} heptanoylamino)methyl]-4-chloroimidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{49}H_{68}ClN_5O_9$, 906.47; found 906.4.

(5-12) 4'-{2-butyl-4-chloro-5-[((s)-2-mercapto-3-phenylpropionylamino)methyl] imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{31}H_{32}ClN_3O_3S$, 562.19; found 562.3.

(5-13) 4'-{5-[(2-acetylsulfanyl-3-methylpentanoylamino)methyl]-2-butyl-4-chloroimidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{36}ClN_3O_4S$, 570.21; found 570.3.

(5-14) 4'-{2-butyl-5-[(2-mercapto-3-methylpentanoylamino)methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{28}H_{35}N_3O_3S$, 494.24; found 494.2.

(5-15) 4'-{2-butyl-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}N_4O_5$, 521.27; found 521.2. ^{1}H-NMR (DMSO) 10.6 (1H, s), 8.28 (1H, t), 7.71 (1H, d), 7.56 (1H, t), 7.44 (1H, d), 7.41 (1H, d), 7.31 (3H, t), 7.15 (2H, d), 5.49 (2H, s), 4.24 (2H, d), 2.98 (1H, t), 2.89, 2H, t), 1.45, (5H, m), 1.2 (2H, q), 0.77 (9H, m).

(5-16) 4'-{5-[(2-acetylsulfanyl-3-methylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{37}N_3O_4S$, 536.25; found 536.5.

(5-17) 4'-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{35}ClN_4O_5$, 555.23; found 555.4.

(5-18) 4'-{5-[(2-acetoxycarbamoyl-4-methyl-pentanoylamino)-methyl]-2-butyl-4-chloroimidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{31}H_{37}ClN_4O_6$, 597.24; found 597.2.

(5-19) 4'-[2-butyl-5-(1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl)imidazol-1-ylmethyl]biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{32}H_{34}N_4O_5$, 555.25; found 556.4.

(5-20) 4'-[2-butyl-5-(1-hydroxycarbamoylmethyl-3-methylbutylcarbamoyl)imidazol-1-ylmethyl]biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}N_4O_5$, 521.27; found 522.4.

(5-21) 4'-{2-butyl-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{37}N_3O_3S$, 508.26; found 508.2.

(5-22) 4'-{2-butyl-4-chloro-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}ClN_3O_3S$, 542.22; found 542.4. ^{1}H-NMR (DMSO) 8.4 (1H, t), 7.69 (1H, d), 7.53 (1H, t), 7.42 (1H, t), 7.33 (1H, d), 7.27 (2H, d), 7.01 (2H, d), 5.23 (2H, s), 4.18 (2H, m), 2.35 (1H, m), 2.05 (1H, t), 1.45 (2H, m) 1.38 (2H, m) 1.2 (3H, m), 0.77 (9H, m).

(5-23) 4'-(2-butyl-5-{[2-(2-mercapto-acetylamino)-4-methylpentanoylamino]methyl} imidazol-1-ylmethyl)biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{38}N_4O_4S$, 551.26; found 551.3.

(5-24) 4'-{2-butyl-4-chloro-5-[(2-cyclopentyl-2-hydroxycarbamoylacetylamino) methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{35}ClN_4O_5$, 567.23; found 567.3.

(5-25) 4'-{2-butyl-5-[(2-cyclopentyl-2-hydroxycarbamoylacetylamino)methyl] imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{36}N_4O_5$, 533.27; found 533.3.

(5-26) 4'-[2-butyl-5-(1-hydroxycarbamoylmethyl-2-pheny-ethylcarbamoyl)-4-

hydroxymethylimidazol-1-ylmethyl]biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{33}H_{36}N_4O_6$, 585.26; found 585.2.

(5-27) 4'-{2-butyl-4-chloro-5-[(2-cyclopropylmethyl-3-mercaptopropionylamino) methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{34}ClN_3O_3S$, 540.20; found 540.0.

(5-28) 4'-{2-butyl-4-chloro-5-[((r)-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}ClN_3O_3S$, 542.22; found 542.4. ^{1}H-NMR (DMSO) 8.4 (1H, t), 7.69 (1H, d), 7.53 (1H, t), 7.42 (1H, t), 7.33 (1H, d), 7.27 (2H, d), 7.01 (2H, d), 5.23 (2H, s), 4.18 (2H, m), 2.35 (1H, m), 2.05 (1H, t), 1.45 (2H, m) 1.38 (2H, m) 1.2 (3H, m), 0.77 (9H, m).

(5-29) 4'-{5-[(2-benzyl-3-mercapto-propionylamino)methyl]-2-butyl-4-chloroimidazol-1-ylmethyl}-3-fluorobiphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{32}H_{33}ClFN_3O_3S$, 594.19; found 594.4.

(5-30) 4'-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}-3-fluorobiphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{34}ClFN_4O_5$, 573.22; found 574.

(5-31) 4'-{2-butyl-4-chloro-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{30}H_{38}ClN_3O_3S$, 556.23; found 556.2.

(5-32) 4'-{2-butyl-4-chloro-5-[(2-mercaptomethylhexanoylamino)methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}ClN_3O_3S$, 542.22; found 542.2.

(5-33) 4'-{2-butyl-4-chloro-5-[(2-mercaptomethyl-5-methylhexanoylamino)methyl] imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{38}ClN_3O_3S$, 556.23; found 556.2.

(5-34) 4'-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-methylpentanoylamino)methyl] imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}ClN_3O_3S$, 542.22; found 542.2.

(5-35) 4'-{2-butyl-4-chloro-5-[(3-cyclopentyl-2-mercaptomethylpropionylamino) methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{31}H_{38}ClN_3O_3S$, 568.23; found 568.2.

(5-36) 4'-{2-butyl-4-chloro-5-[(3-cyclohexyl-2-mercaptomethylpropionylamino) methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for

$C_{32}H_{40}ClN_3O_3S$, 582.25; found 582.2.

(5-37) 4'-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-naphthalen-1-ylpropionylamino) methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{36}H_{36}ClN_3O_3S$, 626.22; found 626.2.

(5-38) 4'-{2-butyl-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H^+] calcd for $C_{30}H_{39}N_3O_3S$, 522.27; found 522.4.

(5-39) 4'-{2-butyl-4-ethyl-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H^+] calcd for $C_{31}H_{41}N_3O_3S$, 536.29; found 536.4.

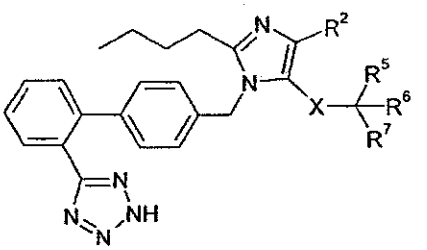
(5-40) 4'-{2-butyl-4-cyclopropyl-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H^+] calcd for $C_{32}H_{41}N_3O_3S$, 548.29; found 548.4.

(5-41) 4'-{2-butyl-4-cyclopropyl-5-[(*(S)*-3-cyclopropyl-2-mercapto-propionylamino)methyl]-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H^+] calcd for $C_{31}H_{37}N_3O_3S$, 532.26; found 532.2.

(5-42) 4'-{2-butyl-5-[(*(R)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-4-methoxy-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H^+] calcd for $C_{30}H_{39}N_3O_4S$, 538.27; found 538.6.

EXAMPLE 6

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 6-1 to 6-44, having the following formula, were also prepared:



Ex.	R^2	-X	R^5	R^6	R^7
6-1	Cl	-CH_2-NHC(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-(CH_2)$_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl	
6-2	Cl	-C(O)NH-(CH_2)$_2$-NHC(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-(CH_2)$_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl	

Ex.	R^2	-X	R^5	R^6	R^7
6-3	Cl	-C(O)NH-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl	
6-4	Cl	-C(O)NH-$(CH_2)_6$-NHC(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl	
6-5	Cl	-C(O)NH-$(CH_2)_4$-NHC(O)-	-CH_2SH	benzyl	H
6-6	Cl	-C(O)NH-$(CH_2)_4$-NHC(O)-	-SH	benzyl	H
6-7	Cl	-CH_2-NHC(O)-$(CH_2)_2$-NHC(O)-	-CH_2SH	benzyl	H
6-8	Cl	-CH_2-NHC(O)-$(CH_2)_4$-NHC(O)-	-CH_2SH	benzyl	H
6-9	Cl	-CH_2-NHC(O)-$(CH_2)_6$-NHC(O)-	-CH_2SH	benzyl	H
6-10	Cl	-C(O)NH-$(CH_2)_2$-C(O)N(OH)-CH_2-	-C(O)NH-(CH_2COOH)	benzyl	H
6-11	Cl	-C(O)NH-$(CH_2)_4$-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl	H
6-12	Cl	-C(O)NH-$(CH_2)_4$-CH(COOH)-NHC(O)-	-CH_2SH	benzyl	H
6-13	Cl	-CH_2-C(O)NH-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl	
6-14	Cl	-CH_2-NHC(O)-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl	
6-15	Cl	-CH_2-N(OH)C(O)-cyclohexylene-NHC(O)-	-CH_2-CH-[CH_2-O-$(CH_2)_2$-OCH_3]-COOH	R^6 and R^7 taken together to form cyclopentyl	
6-16	Cl	-C(O)NH-CH_2-CH(COOH)-CH_2-	-C(O)NH-(CH_2COOH)	R^6 and R^7 taken together to form cyclopentyl	
6-17	Cl	-CH_2-NHC(O)-CH_2-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl	H
6-18	H	-CH_2-NHC(O)-CH_2-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl	H
6-19	Cl	-CH_2-NHC(O)-$(CH_2)_2$-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl	H
6-20	Cl	-C(O)NH-CH_2-CH(COOH)-CH_2-	-C(O)NH-CH(CH_2-phenyl-OH)(COOH)	R^6 and R^7 taken together to form cyclopentyl	

Ex.	R^2	-X	R^5	R^6	R^7
6-21	Cl	-C(O)NH-$(CH_2)_3$-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl	H
6-22	Cl	-C(O)NH-$(CH_2)_2$-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl	H
6-23	Cl	-C(O)NH-$(CH_2)_4$-CH(COOH)-NHC(O)-	-CH_2SH	-CH_2-biphenyl	H
6-24	Cl	-C(O)NH-$(CH_2)_4$-CH(COOH)-NHC(O)-	-C(O)N(OH)H	-CH_2-biphenyl	H
6-25	H	-C(O)NH-$(CH_2)_2$-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl	H
6-26	H	-CH_2-NHC(O)-CH_2-CH(COOH)-NHC(O)-	-NH-CH_2-P(O)$(OH)_2$	-CH_2-biphenyl	H
6-27	H	-C(O)NH-$(CH_2)_4$-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl	H
6-28	H	-CH_2-NHC(O)-CH_2-CH(COOH)-NHC(O)-	-C(O)NH_2	benzyl	H
6-29	Cl	-CH_2-NHC(O)-	-SC(O)CH_3	benzyl	H
6-30	Cl	-CH_2-NHC(O)-	-CH_2SC(O)CH_3	-$CH(CH_3)_2$	H
6-31	Cl	-CH_2-NHC(O)-	-C(O)N(OH)H	-$CH_2CH(CH_3)_2$	H
6-32	Cl	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl	H
6-33	H	-C(O)NH-	-CH_2C(O)N(OH)H	-$CH_2CH(CH_3)_2$	H
6-34	Cl	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$	H
6-35	H	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl	H
6-36	H	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$	H
6-37	H	-CH_2-NHC(O)-	-C(O)N(OH)H	-$CH_2CH(CH_3)_2$	H
6-38	Cl	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$	H
6-39	H	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$	H
6-40	H	-C(O)NH-	-CH_2C(O)N(OH)H	2-trifluoro-methylbenzyl	H
6-41	H	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$	H
6-42	Cl	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$	H
6-43	H	-C(O)NH-	-CH_2SH	-$CH_2CH(CH_3)_2$	H
6-44	Cl	-CH_2-NHC(O)-	-SH	$CH_2CH(CH_3)_2$	H

(6-1) 3-{1-[4-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}carbamoyl)cyclohexylcarbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propionic acid. MS *m/z*: $[M + H^+]$ calcd for $C_{42}H_{55}ClN_8O_6$, 803.39; found 803.0.

(6-2) 3-(1-{4-[2-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}-amino)-ethylcarbamoyl]-cyclohexylcarbamoyl}-cyclopentyl)-2-

(2-methoxy-ethoxymethyl)-propionic acid. MS *m/z*: [M + H^+] calcd for $C_{44}H_{58}ClN_9O_7$, 860.42; found 860.2.

(6-3) 3-(1-{4-[4-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)butylcarbamoyl] cyclohexylcarbamoyl}cyclopentyl)-2-(2-methoxyethoxymethyl)propionic acid. MS *m/z*: [M + H^+] calcd for $C_{46}H_{62}ClN_9O_7$, 888.45; found 888.4.

(6-4) 3-(1-{4-[6-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)hexylcarbamoyl]cyclohexylcarbamoyl}cyclopentyl)-2-(2-methoxyethoxymethyl)propionic acid. MS *m/z*: [M + H^+] calcd for $C_{48}H_{66}ClN_9O_7$, 916.48; found 916.4.

(6-5) 2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carboxylic acid [4-(2-benzyl-3-mercaptopropionylamino)butyl]amide. MS *m/z*: [M + H^+] calcd for $C_{36}H_{41}ClN_8O_2S$, 685.28; found 685.2.

(6-6) 2-butyl-5-chloro-3-[2'-(2H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carboxylic acid [4-(*(R)*-2-mercapto-3-phenylpropionylamino)butyl]amide. MS *m/z*: [M + H^+] calcd for $C_{35}H_{39}ClN_8O_2S$, 671.26; found 671.2.

(6-7) N-[2-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}carbamoyl)ethyl]-2-mercaptomethyl-3-phenylpropionamide. MS *m/z*: [M + H^+] calcd for $C_{35}H_{39}ClN_8O_2S$, 671.26; found 671.2.

(6-8) 5-(2-mercaptomethyl-3-phenylpropionylamino)pentanoic acid {2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS *m/z*: [M + H^+] calcd for $C_{37}H_{43}ClN_8O_2S$, 699.29; found 699.2.

(6-9) 7-(2-mercaptomethyl-3-phenylpropionylamino)heptanoic acid {2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS *m/z*: [M + H^+] calcd for $C_{39}H_{47}ClN_8O_2S$, 727.32; found 727.2.

(6-10) [2-({[3-({2-butyl-5-chloro-3-[2'-(2H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)propionyl]hydroxyamino}methyl)-3-phenylpropionylamino] acetic acid. MS *m/z*: [M + H^+] calcd for $C_{37}H_{40}ClN_9O_6$, 742.28; found 742.2.

(6-11) *(S)*-6-({2-butyl-5-chloro-3-[2'-(2H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)-2-(2-hydroxycarbamoyl-3-phenylpropionylamino)hexanoic acid. MS *m/z*: [M + H^+] calcd for $C_{38}H_{42}ClN_9O_6$, 756.30; found 756.2.

(6-12) *(S)*-2-(2-benzyl-3-mercapto-propionylamino)-6-({2-butyl-5-chloro-3-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)hexanoic acid. MS

m/z: [M + H^+] calcd for $C_{38}H_{43}ClN_8O_4S$, 743.28; found 743.2.

(6-13) 3-(1-{4-[2-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}carbamoyl)ethylcarbamoyl]cyclohexylcarbamoyl}cyclopentyl)-2-(2-methoxy-ethoxymethyl)propionic acid. MS *m/z*: [M + H^+] calcd for $C_{45}H_{60}ClN_9O_7$, 874.43; found 874.6.

(6-14) 3-(1-{4-[4-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}carbamoyl)butylcarbamoyl]cyclohexylcarbamoyl}cyclopentyl)-2-(2-methoxyethoxymethyl)propionic acid. MS *m/z*: [M + H^+] calcd for $C_{47}H_{64}ClN_9O_7$, 902.46; found 902.5

(6-15) 3-{1-[4-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}hydroxycarbamoyl)cyclohexylcarbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propionic acid. MS *m/z*: [M + H^+] calcd for $C_{42}H_{55}ClN_8O_7$, 819.39; found 819.5.

(6-16) 2-[({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)methyl]-3-[1-(carboxymethylcarbamoyl)cyclopentyl] propionic acid. MS *m/z*: [M + H^+] calcd for $C_{34}H_{39}ClN_8O_6$, 691.27; found 692.2.

(6-17) *(R)*-N-{2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}-2-(2-hydroxycarbamoyl-3-phenylpropionylamino)succinamic acid. MS *m/z*: [M + H^+] calcd for $C_{36}H_{38}ClN_9O_6$, 728.26; found 728.5.

(6-18) *(S)*-N-{2-butyl-3-[2'-(2H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}-2-(2-hydroxycarbamoyl-3-phenylpropionylamino)succinamic acid. MS *m/z*: [M + H^+] calcd for $C_{36}H_{39}N_9O_6$, 694.30; found 694.5.

(6-19) *(R)*-4-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}carbamoyl)-2-(2-hydroxycarbamoyl-3-phenylpropionylamino)butyric acid. MS *m/z*: [M + H^+] calcd for $C_{37}H_{40}ClN_9O_6$, 742.28; found 742.5.

(6-20) 2-[({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)methyl]-3-{1-[*(S)*-1-carboxy-2-(4-hydroxyphenyl) ethylcarbamoyl]cyclopentyl}propionic acid. MS *m/z*: [M + H^+] calcd for $C_{41}H_{45}ClN_8O_7$, 797.31; found 797.2.

(6-21) *(S)*-5-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)-2-(2-hydroxycarbamoyl-3-phenylpropionylamino)pentanoic acid. MS *m/z*: [M + H^+] calcd for $C_{37}H_{40}ClN_9O_6$, 742.28; found 742.5.

(6-22) *(S)*-4-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-

imidazole-4-carbonyl}amino)-2-(2-hydroxycarbamoyl-3-phenylpropionylamino)butyric acid. MS *m/z*: [M + H^+] calcd for $C_{36}H_{38}ClN_9O_6$, 728.26; found 728.5.

(6-23) *(S)*-2-(2-biphenyl-4-ylmethyl-3-mercaptopropionylamino)-6-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino) hexanoic acid. MS *m/z*: [M + H^+] calcd for $C_{44}H_{47}ClN_8O_4S$, 819.31; found 819.7.

(6-24) *(S)*-2-(3-biphenyl-4-yl-2-hydroxycarbamoylpropionylamino)-6-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino) hexanoic acid. MS *m/z*: [M + H^+] calcd for $C_{44}H_{46}ClN_9O_6$, 832.33; found 832.7.

(6-25) *(S)*-4-({2-butyl-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)-2-(2-hydroxycarbamoyl-3-phenylpropionylamino)butyric acid. MS *m/z*: [M + H^+] calcd for $C_{36}H_{39}N_9O_6$, 694.30; found 694.5.

(6-26) *(S)*-2-[*(S)*-3-biphenyl-4-yl-2-(phosphonomethylamino)propionylamino]-N-{2-butyl-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}succinamic acid. MS *m/z*: [M + H^+] calcd for $C_{42}H_{46}N_9O_7P$, 820.33; found 820.3.

(6-27) *(S)*-6-({2-butyl-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carbonyl}amino)-2-(2-hydroxycarbamoyl-3-phenylpropionylamino)hexanoic acid. MS *m/z*: [M + H^+] calcd for $C_{38}H_{43}N_9O_6$, 722.33; found 722.3.

(6-28) *(R)*-N-{2-butyl-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}-2-(2-carbamoyl-3-phenylpropionylamino)succinamic acid. MS *m/z*: [M + H^+] calcd for $C_{36}H_{39}N_9O_5$, 678.31; found 679.4.

(6-29) thioacetic acid S-[1-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}carbamoyl)-2-phenylethyl]ester. MS *m/z*: [M + H^+] calcd for $C_{33}H_{34}ClN_7O_2S$, 628.22; found 628.5.

(6-30) thioacetic acid S-[2-({2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}carbamoyl)-3-methylbutyl]ester. MS *m/z*: [M + H^+] calcd for $C_{30}H_{36}ClN_7O_2S$, 594.23; found 594.5.

(6-31) N-{2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}-N'-hydroxy-2-isobutylmalonamide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{35}ClN_8O_3$, 579.25; found 579.4.

(6-32) 2-butyl-5-chloro-3-[2'-(2H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carboxylic acid (1-hydroxycarbamoylmethyl-2-phenylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{32}H_{33}ClN_8O_3$, 613.24; found 614.4.

(6-33) 2-butyl-3-[2'-(2H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-

carboxylic acid (1-hydroxycarbamoylmethyl-3-methylbutyl)amide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}N_8O_3$, 545.29; found 545.4.

(6-34) 2-mercaptomethyl-4-methylpentanoic acid {2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}ClN_7OS$, 566.24; found 566.4.

(6-35) 2-butyl-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carboxylic acid (*(R)*-1-hydroxycarbamoylmethyl-2-phenylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{32}H_{34}N_8O_3$, 579.28; found 580.0.

(6-36) 2-mercaptomethyl-4-methylpentanoic acid {2-butyl-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{37}N_7OS$, 532.28; found 532.2.

(6-37) N-{2-butyl-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}-N'-hydroxy-2-isobutylmalonamide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}N_8O_3$, 545.29; found 545.5.

(6-38) *(R)*-2-mercaptomethyl-4-methylpentanoic acid {2-butyl-5-chloro-3-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}ClN_7OS$, 566.24; found 567.

(6-39) *(R)*-2-mercaptomethyl-4-methylpentanoic acid {2-butyl-3-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{37}N_7OS$, 532.28; found 532.

(6-40) 2-butyl-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carboxylic acid [*(R)*-1-hydroxycarbamoylmethyl-2-(2-trifluoromethylphenyl)ethyl]amide. MS *m/z*: [M + H^+] calcd for $C_{33}H_{33}F_3N_8O_3$, 647.26; found 647.4.

(6-41) *(S)*-2-mercaptomethyl-4-methylpentanoic acid {2-butyl-3-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{37}N_7OS$, 532.28; found 533.

(6-42) *(S)*-2-mercaptomethyl-4-methylpentanoic acid {2-butyl-5-chloro-3-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}ClN_7OS$, 566.24; found 567.

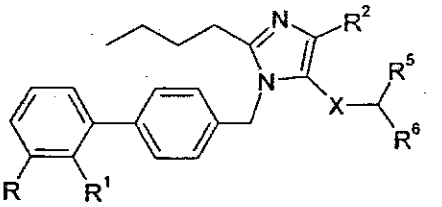
(6-43) 2-butyl-3-[2'-(2H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazole-4-carboxylic acid (*(R)*-1-mercaptomethyl-3-methylbutyl)amide. MS *m/z*: [M + H^+] calcd for $C_{28}H_{35}N_7OS$, 518.26; found 518.4.

(6-44) *(S)*-2-mercapto-4-methyl-pentanoic acid {2-butyl-5-chloro-3-[2'-(1H-tetrazol-5-

yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS m/z: [M+H$^+$] calcd for $C_{28}H_{34}ClN_7OS$, 552.22; found 552.4.

EXAMPLE 7

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 7-1 to 7-8, having the following formula where R is an optional substituent, were also prepared:



Ex.	R^1	R^2	-X	R^5	R^6	R
7-1	-COOH	Cl	-CH_2-NHC(O)-	-SH	-CH(CH_3)-CH_2CH_3	-
7-2	-C(O)OC(CH_3)$_3$	Cl	-CH_2-NHC(O)-	-SC(O)CH_3	-CH(CH_3)-CH_2CH_3	-
7-3	-SO_2NH-C(O)NH-$(CH_2)_2CH_3$	H	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl	-
7-4	-NHSO_2-CF_3	H	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl	-
7-5	-SO_2NH-C(O)CH_3	H	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl	-
7-6	-SO_2NH-C(O)NH-$(CH_2)_2CH_3$	H	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl	-
7-7	-SO_2NH-C(O)CH_3	H	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl	-
7-8	-COOH	Cl	-CH_2-NHC(O)-	-CH_2SH	-CH_2-$CH(CH_3)_2$	F

(7-1) 4'-{2-butyl-4-chloro-5-[(2-mercapto-3-methylpentanoylamino)methyl] imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H$^+$] calcd for $C_{28}H_{34}ClN_3O_3S$, 528.20; found 528.3.

(7-2) 4'{5-[(2-acetylsulfanyl-3-methyl-pentanoylamino)methyl]-2-butyl-4-chloroimidazol-1-ylmethyl}biphenyl-2-carboxylic acid *t*-butyl ester. MS *m/z*: [M + H$^+$] calcd for $C_{34}H_{44}ClN_3O_4S$, 626.27; found 626.5.

(7-3) 2-butyl-N-(4-(hydroxyamino)-4-oxo-1-phenylbutan-2-yl)-1-((2'-(N-(propylcarbamoyl)sulfamoyl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxamide. MS *m/z*: [M + H$^+$] calcd for $C_{35}H_{42}N_6O_6S$, 675.29; found 675.2.

(7-4) 2-butyl-3-(2'-trifluoromethanesulfonylaminobiphenyl-4-ylmethyl)-3H-imidazole-4-carboxylic acid (*(R)*-1-benzyl-2-hydroxycarbamoylethyl)amide. MS *m/z*: [M +

H^+] calcd for $C_{32}H_{34}F_3N_5O_5S$, 658.22; found 658.2.

(7-5) 3-(2'-acetylsulfamoylbiphenyl-4-ylmethyl)-2-butyl-3H-imidazole-4-carboxylic acid *(R)*-1-benzyl-2-hydroxycarbamoylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{33}H_{37}N_5O_6S$, 632.25; found 632.4.

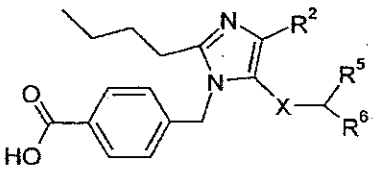
(7-6) *(R)*-2-butyl-N-(4-(hydroxyamino)-4-oxo-1-phenylbutan-2-yl)-1-((2'-(N-(propylcarbamoyl)sulfamoyl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxamide. MS *m/z*: [M + H^+] calcd for $C_{35}H_{42}N_6O_6S$, 675.29; found 675.4.

(7-7) 3-(2'-Acetylsulfamoylbiphenyl-4-ylmethyl)-2-butyl-3H-imidazole-4-carboxylic acid *(S)*-1-benzyl-2-hydroxycarbamoylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{33}H_{37}N_5O_6S$, 632.25; found 632.4.

(7-8) 4'-{2-butyl-4-chloro-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-3-fluorobiphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{35}ClFN_3O_3S$, 560.21; found 561.

EXAMPLE 8

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 8-1 to 8-77, having the following formula, were also prepared:



Ex.	R^2	-X	R^5	R^6
8-1	Cl	-C(O)NH-$(CH_2)_4$-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl
8-2	Cl	-C(O)NH-$(CH_2)_2$-CH(COOH)-NHC(O)-	-C(O)N(OH)H	benzyl
8-3	Cl	-CH_2-NHC(O)-	-SH	-$CH(CH_3)$-CH_2CH_3
8-4	Cl	-CH_2-NHC(O)-	-C(O)N(OH)H	-$CH_2CH(CH_3)_2$
8-5	H	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl
8-6	H	-C(O)NH-	-CH_2C(O)N(OH)H	-$CH_2CH(CH_3)_2$
8-7	Cl	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl
8-8	H	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl
8-9	H	-C(O)NH-	-CH_2C(O)N(OH)H	benzyl
8-10	Cl	-CH_2-NHC(O)-	-CH_2SH	benzyl
8-11	Cl	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$
8-12	Cl	-CH_2-NHC(O)-	-NHC(O)CH_2SH	benzyl
8-13	Cl	-CH_2-NHC(O)-	-CH_2SH	-$CH(CH_3)_2$
8-14	Cl	-CH_2-NHC(O)-	-CH_2SH	-CH_3
8-15	Cl	-CH_2-NHC(O)-CH_2-NHC(O)-	-CH_2SH	benzyl

Ex.	R^2	-X	R^5	R^6
8-16	Cl	$-CH_2$-NHC(O)-	$-CH_2C(O)N(OH)H$	$-CH_2CH(CH_3)_2$
8-17	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-methylbenzyl
8-18	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	3,4-difluorobenzyl
8-19	H	-C(O)NH-CH_2-	-C(O)N(OH)H	benzyl
8-20	Cl	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2$-pyridin-4-yl
8-21	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2$-naphthalen-2-yl
8-22	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-methylbenzyl
8-23	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-chlorobenzyl
8-24	H	-C(O)NH-	$-CH_2$-C(O)NH[OC(O)OCH_2-phenyl]	benzyl
8-25	H	-C(O)NH-	$-CH_2$-C(O)N[OC(O)CH_2O-phenyl]H	benzyl
8-26	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
8-27	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-(CH_2)_2$-phenyl
8-28	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2$-thiophen-3-yl
8-29	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2$-furan-2-yl
8-30	H	$-CH_2$-NHC(O)-	-C(O)N(OH)H	$-CH_2CH(CH_3)_2$
8-31	H	$-CH_2$-NHC(O)-	-C(O)N(OH)H	benzyl
8-32	H	-C(O)NH-	$-CH_2$-C(O)N[OC(S)N$(CH_3)_2$]H	benzyl
8-33	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-trifluoromethyl-benzyl
8-34	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2$-naphthalen-2-yl
8-35	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-fluorobenzyl
8-36	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	3-fluorobenzyl
8-37	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-bromobenzyl
8-38	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	2-bromobenzyl
8-39	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-nitrobenzyl
8-40	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	2-methylbenzyl
8-41	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	3-methylbenzyl
8-42	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	pentafluorobenzyl
8-43	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	2,4-dichlorobenzyl
8-44	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	2,4-dichlorobenzyl
8-45	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	3,4-dichlorobenzyl
8-46	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-iodobenzyl
8-47	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-iodobenzyl
8-48	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	2-trifluoro-methylbenzyl
8-49	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	3-trifluoro-methylbenzyl
8-50	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	2-cyanobenzyl
8-51	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	3,4-difluorobenzyl
8-52	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	2-chlorobenzyl
8-53	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	2-fluorobenzyl
8-54	H	-C(O)NH-CH(benzyl)-CH_2-NHC(O)-	-C(O)N(OH)H	benzyl
8-55	H	-C(O)NH-CH(benzyl)-CH_2-NHC(O)-	$-CH_2SH$	benzyl

Ex.	R^2	-X	R^5	R^6
8-56	H	-C(O)NH-CH(benzyl)-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$
8-57	H	-C(O)NH-CH(benzyl)-CH_2-NHC(O)-	-CH_2SH	-$CH(CH_3)_2$
8-58	Cl	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$
8-59	H	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$
8-60	H	-C(O)NH-CH(benzyl)-CH_2-C(O)NH-	-$CH_2C(O)N(OH)H$	benzyl
8-61	H	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$
8-62	H	-C(O)NH-CH(benzyl)-CH_2-C(O)NH-	-CH_2SH	benzyl
8-63	H	-C(O)NH-	-CH_2SH	benzyl
8-64	Cl	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$
8-65	H	-CH_2-NHC(O)-	-SH	-CH_2CH_3
8-66	H	-C(O)NH-	-CH_2SH	-$CH_2CH(CH_3)_2$
8-67	H	-C(O)NH-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$
8-68	H	-C(O)NH-NHC(O)-	-CH_2SH	benzyl
8-69	Cl	-$(CH_2)_2$-NHC(O)-	-CH_2SH	benzyl
8-70	H	-CH_2-NHC(O)-	-CH_2SH	-$(CH_2)_3CH_3$
8-71	H	-CH_2-NHC(O)-	-CH_2SH	-$(CH_2)_2$ $CH(CH_3)_2$
8-72	H	-CH_2-NHC(O)-	-CH_2SH	-$CH(CH_3)$-CH_2CH_3
8-73	H	-CH_2-NHC(O)-	-CH_2SH	-CH_2-cyclopentyl
8-74	H	-CH_2-NHC(O)-	-CH_2SH	-CH_2-cyclohexyl
8-75	H	-CH_2-NHC(O)-	-CH_2SH	-CH_2-naphthalen-3-yl
8-76	H	-CH=C(-CH_2-2-thiophene)-C(O)NH-	-$CH_2C(O)N(OH)H$	benzyl
8-77	H	-CH=C(-CH_2-2-thiophene)-C(O)NH-	-$CH_2SC(O)CH_3$	benzyl

(8-1) 4-{2-butyl-5-[*(S)*-5-carboxy-5-(2-hydroxycarbamoyl-3-phenylpropionylamino) pentylcarbamoyl]-4-chloroimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{32}H_{38}ClN_5O_8$, 656.24; found 656.2.

(8-2) 4-{2-butyl-5-[*(S)*-3-carboxy-3-(2-hydroxycarbamoyl-3-phenylpropionylamino) propylcarbamoyl]-4-chloroimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{34}ClN_5O_8$, 628.21; found 629.2.

(8-3) 4-{2-butyl-4-chloro-5-[(2-mercapto-3-methyl-pentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}ClN_3O_3S$, 452.17; found 452.2.

(8-4) 4-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-4-methyl-pentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{31}ClN_4O_5$, 479.20; found 479.2.

(8-5) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}N_4O_5$, 479.22; found 479.3.

(8-6) 4-[2-butyl-5-(1-hydroxycarbamoylmethyl-3-methyl-butylcarbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}N_4O_5$, 445.24; found 445.2.

(8-7) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butyl-4-chloroimidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}ClN_4O_5$, 513.18; found 513.3.

(8-8) 4-[5-(*(R)*-1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}N_4O_5$, 479.22; found 479.4.

(8-9) 4-[5-(*(S)*-1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}N_4O_5$, 479.22; found 479.3. For the TFA salt: ^{1}H-NMR (400 Mz, $(CD_3)_2SO$): δ (ppm) 0.74 (t, 3H, *J* = 5 Hz), 1.20 (q, 2H, *J* = 5 Hz), 1.41 (m, 2H), 2.19 (d, 2H, *J* = 5 Hz), 2.73 (m, 3H), 5.69 (m, 4H), 7.11 (m, 7H, *J* = 5 Hz), 7.85 (m, 2H), 8.50 (s, 1H).

(8-10) 4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-phenylpropionylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}ClN_3O_3S$, 500.17; found 501.

(8-11) 4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-4-methyl-pentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}ClN_3O_3S$, 466.19; found 467.

(8-12) 4-(2-butyl-4-chloro-5-{[2-(2-mercapto-acetylamino)-3-phenylpropionylamino]-methyl}imidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{31}ClN_4O_4S$, 543.18; found 544.

(8-13) 4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-methyl-butyrylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}ClN_3O_3S$, 452.17; found 453.

(8-14) 4-{2-butyl-4-chloro-5-[(*(S)*-3-mercapto-2-methylpropionylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{20}H_{26}ClN_3O_3S$, 424.14; found 425.

(8-15) 4-(5-{[2-(2-benzyl-3-mercaptopropionylamino)acetylamino]methyl}-2-butyl-4-chloroimidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{28}H_{33}ClN_4O_4S$, 557.19; found 558.

(8-16) 4-{2-butyl-4-chloro-5-[(2-hydroxycarbamoylmethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{33}ClN_4O_5$, 493.21; found 494.

(8-17) 4-{2-butyl-5-[*(S)*-2-hydroxycarbamoyl-1-(4-methylbenzyl)ethylcarbamoyl]

imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{32}N_4O_5$, 493.24; found 493.4.

(8-18) 4-{2-butyl-5-[*(S)*-1-(3,4-difluorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{28}F_2N_4O_5$, 515.20; found 515.2.

(8-19) 4-[2-butyl-5-(2-hydroxycarbamoyl-3-phenyl-propylcarbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}N_4O_5$, 479.22; found 480.2.

(8-20) 4-[2-butyl-4-chloro-5-(*(R)*-2-hydroxycarbamoyl-1-pyridin-4-ylmethylethylcarbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{28}ClN_5O_5$, 514.18; found 515.2.

(8-21) 4-[2-butyl-5-(*(R)*-2-hydroxycarbamoyl-1-naphthalen-2-ylmethylethylcarbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{32}N_4O_5$, 529.24; found 529.4.

(8-22) 4-{2-butyl-5-[*(R)*-2-hydroxycarbamoyl-1-(4-methylbenzyl)ethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{32}N_4O_5$, 493.24; found 493.4.

(8-23) 4-{2-butyl-5-[*(R)*-1-(4-chlorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}ClN_4O_5$, 513.18; found 514.2.

(8-24) *(S)*-4-((5-(4-(benzyloxycarbonyloxyamino)-4-oxo-1-phenylbutan-2-ylcarbamoyl)-2-butyl-1H-imidazol-1-yl)methyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{34}H_{36}N_4O_7$, 613.26; found 613.2.

(8-25) 4-(2-butyl-5-{*(S)*-1-[(2-phenoxyacetoxycarbamoyl)methyl]-2-phenylethylcarbamoyl}imidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{34}H_{36}N_4O_7$, 613.26; found 613.4.

(8-26) 4-{2-butyl-5-[(2-mercaptomethyl-4-methyl-pentanoylamino)methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{33}N_3O_3S$, 432.22; found 433. ^{1}H-NMR (DMSO) 8.07 (2H, d), 7.6 (1H, s), 7.2 (2H, d), 5.6 (2H, s), 4.45 (1H, d), 4.32 (1H, d), 2.9 (2H, t), 2.55 (2H, m), 2.4 (1H, m), 1.58 (2H, m), 1.35 (5H, m), 0.83 (9H, m).

(8-27) 4-[2-butyl-5-(*(R)*-1-hydroxycarbamoylmethyl-3-phenylpropylcarbamoyl) imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{32}N_4O_5$, 493.24; found 493.5.

(8-28) 4-[2-butyl-5-(*(R)*-2-hydroxycarbamoyl-1-thiophen-3-ylmethyl-ethylcarbamoyl)

imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{28}N_4O_5S$, 485.18; found 485.5.

(8-29) 4-[2-butyl-5-*((R)*-1-furan-2-ylmethyl-2-hydroxycarbamoylethylcarbamoyl) imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{28}N_4O_6$, 469.20; found 469.5.

(8-30) 4-{2-butyl-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}N_4O_5$, 445.24; found 445.2. ^{1}H-NMR (DMSO) 10.6 (1H, s), 8.92 (1H, s), 8.15 (1H, t), 7.91 (2H, d), 7.41 (1H, s), 7.15 (2H, d), 5.53 (2H, s), 4.19 (2H, d), 2.89 (1H, t), 2.81 (2H, t), 1.48 (3H, m), 1.21, 4H, m), 0.74 (9H, m).

(8-31) 4-{2-butyl-5-[(2-hydroxycarbamoyl-3-phenylpropionylamino)methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}N_4O_5$, 479.22; found 479.0.

(8-32) *(S)*-4-((2-butyl-5-(4-(dimethylcarbamothioyloxyamino)-4-oxo-1-phenylbutan-2-ylcarbamoyl)-1H-imidazol-1-yl)methyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{35}N_5O_5S$, 566.24; found 566.2.

(8-33) 4-{2-butyl-5-[*(R)*-2-hydroxycarbamoyl-1-(4-trifluoromethylbenzyl)ethyl-carbamoyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{29}F_3N_4O_5$, 547.21; found 547.7.

(8-34) 4-[2-butyl-5-*((R)*-2-hydroxycarbamoyl-1-naphthalen-2-ylmethylethyl-carbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{32}N_4O_5$, 529.24; found 529.7.

(8-35) 4-{2-butyl-5-[*(R)*-1-(4-fluorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}FN_4O_5$, 497.21; found 497.6.

(8-36) 4-{2-butyl-5-[*(R)*-1-(3-fluorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}FN_4O_5$, 497.21; found 497.7.

(8-37) 4-{5-[*(R)*-1-(4-bromobenzyl)-2-hydroxycarbamoylethylcarbamoyl]-2-butylimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}BrN_4O_5$, 557.13; found 558.5.

(8-38) 4-{5-[*(R)*-1-(2-bromobenzyl)-2-hydroxycarbamoylethylcarbamoyl]-2-butylimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}BrN_4O_5$, 557.13; found 558.4.

(8-39) 4-{2-Butyl-5-[*(R)*-2-hydroxycarbamoyl-1-(4-nitrobenzyl)ethylcarbamoyl]-imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}N_5O_7$, 524.212; found 524.7.

(8-40) 4-{2-butyl-5-[*(R)*-2-hydroxycarbamoyl-1-(2-methylbenzyl)ethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{32}N_4O_5$, 493.24; found 493.8.

(8-41) 4-{2-butyl-5-[*(R)*-2-hydroxycarbamoyl-1-(3-methylbenzyl)ethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{32}N_4O_5$, 493.24; found 493.7.

(8-42) 4-[2-butyl-5-(*(R)*-2-hydroxycarbamoyl-1-pentafluorophenylmethylethyl-carbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{25}F_5N_4O_5$, 569.17; found 569.7.

(8-43) 4-{2-butyl-5-[*(S)*-1-(2,4-dichlorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{28}Cl_2N_4O_5$, 547.14 ; found 548.4.

(8-44) 4-{2-butyl-5-[*(R)*-1-(2,4-dichlorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{28}Cl_2N_4O_5$, 547.14; found 548.5.

(8-45) 4-{2-butyl-5-[*(R)*-1-(3,4-dichlorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{28}Cl_2N_4O_5$, 547.14; found 548.6.

(8-46) 4-{2-butyl-5-[*(S)*-2-hydroxycarbamoyl-1-(4-iodobenzyl)ethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}IN_4O_5$, 605.12; found 605.5.

(8-47) 4-{2-butyl-5-[*(R)*-2-hydroxycarbamoyl-1-(4-iodobenzyl)ethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}IN_4O_5$, 605.12; found 605.5.

(8-48) 4-{2-butyl-5-[*(R)*-2-hydroxycarbamoyl-1-(2-trifluoromethylbenzyl)ethyl-carbamoyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{29}F_3N_4O_5$, 547.21; found 547.6.

(8-49) 4-{2-butyl-5-[*(R)*-2-hydroxycarbamoyl-1-(3-trifluoromethylbenzyl)ethyl-carbamoyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{29}F_3N_4O_5$, 547.21; found 547.6.

(8-50) 4-{2-butyl-5-[*(R)*-1-(2-cyanobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{29}N_5O_5$, 504.22; found 504.7.

(8-51) 4-{2-butyl-5-[*(R)*-1-(3,4-difluorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{28}F_2N_4O_5$, 515.20; found 515.8.

(8-52) 4-{2-butyl-5-[*(R)*-1-(2-chlorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}ClN_4O_5$, 513.18; found 514.3.

(8-53) 4-{2-butyl-5-[*(R)*-1-(2-fluorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}FN_4O_5$, 497.21; found 497.5.

(8-54) 4-(2-butyl-5-{*(S)*-1-[(2-hydroxycarbamoyl-3-phenylpropionylamino)methyl]-2-phenylethylcarbamoyl}imidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{35}H_{39}N_5O_6$, 626.29; found 626.4.

(8-55) 4-(2-butyl-5-{*(S)*-1-[(2-mercaptomethyl-3-phenylpropionylamino)methyl]-2-phenylethylcarbamoyl}imidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{35}H_{40}N_4O_4S$, 613.28; found 613.4.

(8-56) 4-(2-butyl-5-{*(S)*-1-[(2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-phenylethylcarbamoyl}imidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{32}H_{42}N_4O_4S$, 579.29; found 579.4.

(8-57) 4-(2-butyl-5-{*(S)*-1-[(2-mercaptomethyl-3-methylbutyrylamino)methyl]-2-phenylethylcarbamoyl}imidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{31}H_{40}N_4O_4S$, 565.28; found 565.2.

(8-58) 4-{2-butyl-4-chloro-5-[(*(R)*-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}ClN_3O_3S$, 466.19; found 466.3.

(8-59) 4-{2-butyl-5-[(*(R)*-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{33}N_3O_3S$, 432.22; found 432.3. ^{1}H-NMR (DMSO) 8.52 (1H, t), 7.92 (2H, d), 7.48 (1H, s), 7.18 (2H, d), 5.55 (2H, s), 4.21 (2H, m), 2.84 (2H, t), 2.16 (1H, t), 1.46 (2H, m), 1.22 (5 H, m), 0.76 (9H, m).

(8-60) 4-{5-[*(S)*-1-benzyl-2-(*(R)*-1-benzyl-2-hydroxycarbamoylethylcarbamoyl) ethylcarbamoyl]-2-butylimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for

$C_{36}H_{41}N_5O_6$, 640.31; found 640.3.

(8-61) 4-{2-butyl-5-[((*S*)-2-mercaptomethyl-4-methyl-pentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{33}N_3O_3S$, 432.22; found 432.

(8-62) 4-{5-[(*S*)-1-benzyl-2-((*R*)-1-mercaptomethyl-2-phenylethylcarbamoyl) ethylcarbamoyl]-2-butylimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{35}H_{40}N_4O_4S$, 613.28; found 613.4.

(8-63) 4-[5-((*R*)-1-benzyl-2-mercaptoethylcarbamoyl)-2-butylimidazol-1-ylmethyl] benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{29}N_3O_3S$, 452.19; found 452.2.

(8-64) 4-{2-butyl-4-chloro-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}ClN_3O_3S$, 466.19; found 467.2.

(8-65) 4-{2-butyl-5-[(2-mercaptobutyrylamino)methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{20}H_{27}N_3O_3S$, 390.18; found 390.2.

(8-66) 4-[2-butyl-5-((*R*)-1-mercaptomethyl-3-methylbutylcarbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{31}N_3O_3S$, 418.21; found 418.2.

(8-67) 4-{2-butyl-5-[N'-(2-mercaptomethyl-4-methylpentanoyl)hydrazinocarbonyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}N_4O_4S$, 461.21; found 461.4.

(8-68) 4-{5-[N'-(2-benzyl-3-mercapto-propionyl)hydrazinocarbonyl]-2-butylimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}N_4O_4S$, 495.20; found 495.4.

(8-69) 4-{5-[2-(2-benzyl-3-mercaptopropionylamino)ethyl]-2-butyl-4-chloroimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{32}ClN_3O_3S$, 514.19; found 514.2.

(8-70) 4-{2-butyl-5-[(2-mercaptomethylhexanoylamino)methyl]imidazol-1-ylmethyl} benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{33}N_3O_3S$, 432.22; found 432.2.

(8-71) 4-{2-butyl-5-[(2-mercaptomethyl-5-methylhexanoylamino)methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{35}N_3O_3S$, 446.24; found 446.2.

(8-72) 4-{2-butyl-5-[(2-mercaptomethyl-3-methyl-pentanoylamino)methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{33}N_3O_3S$, 432.22; found 432.2.

(8-73) 4-{2-butyl-5-[(3-cyclopentyl-2-mercaptomethylpropionylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{35}N_3O_3S$, 458.24; found 458.2.

(8-74) 4-{2-butyl-5-[(3-cyclohexyl-2-mercaptomethylpropionylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{37}N_3O_3S$, 472.26; found 472.2.

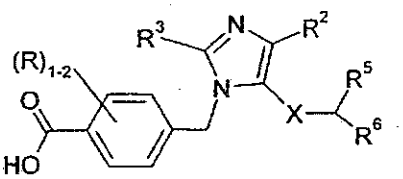
(8-75) 4-{2-butyl-5-[(2-mercaptomethyl-3-naphthalen-1-ylpropionylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{33}N_3O_3S$, 516.22; found 517.2.

(8-76) 4-{5-[(E)-2-(*(R)*-1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-3-thiophen-2-ylpropenyl]-2-butylimidazol-1-ylmethyl}benzoic acid. MS m/z: [M+H^+] calcd for $C_{33}H_{36}N_4O_5S$, 601.24; found 602.5.

(8-77) 4-{5-[(E)-2-(*(R)*-2-acetylsulfanyl-1-benzylethylcarbamoyl)-3-thiophen-2-ylpropenyl]-2-butylimidazol-1-ylmethyl}benzoic acid. MS m/z: [M+H^+] calcd for $C_{34}H_{37}N_3O_4S_2$, 616.22; found 616.4.

EXAMPLE 9

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 9-1 to 9-63, having the following formula where one or two R groups are optionally present, were also prepared. For Compounds 9-1 to 9-60, R^3 is $-(CH_2)_3CH_3$. For Compounds, 9-61 to 9-63, R^3 is $-(CH_2)_2CH_3$.



Ex.	R	R^2	-X	R^5	R^6
9-1	3-methoxy	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-2	3-methoxy	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	benzyl
9-3	3-methoxy	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH(CH_3)_2$
9-4	3-methoxy	Cl	$-CH_2$-NHC(O)-CH_2-NHC(O)-	$-CH_2SH$	benzyl
9-5	3-methoxy	Cl	$-CH_2$-NHC(O)-	-C(O)N(OH)H	$-CH_2CH(CH_3)_2$
9-6	3-methoxy	Cl	$-CH_2$-NHC(O)-	-C(O)N(OH)H	benzyl
9-7	2-bromo	Cl	$-CH_2$-NHC(O)-	-C(O)N(OH)H	$-CH_2CH(CH_3)_2$
9-8	2-bromo	Cl	$-CH_2$-NHC(O)-	-C(O)N(OH)H	benzyl
9-9	2-bromo	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-10	2-phenyl	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-11	2-bromo	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-12	2-bromo	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-13	2-fluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-14	2-bromo	H	-C(O)NH-	$-CH_2$-C(O)N(OH)H	2-bromobenzyl

Ex.	R	R^2	-X	R^5	R^6
9-15	2-bromo	H	-C(O)NH-	$-CH_2$-C(O)N(OH)H	2-methylbenzyl
9-16	3-fluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-17	2,6-difluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-18	3-fluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-19	2,6-difluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-20	2-bromo	H	$-CH_2$-NHC(O)-	$-CH_2SC(O)$-phenyl-OCH_3	$-CH_2CH(CH_3)_2$
9-21	2-bromo	H	$-CH_2$-NHC(O)-	$-CH_2SC(O)-CH_3$	$-CH_2CH(CH_3)_2$
9-22	2-bromo	H	$-CH_2$-NHC(O)-	$-CH_2SC(O)-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
9-23	2-bromo	H	$-CH_2$-NHC(O)-	$-CH_2SC(O)-C(CH_3)_2$	$-CH_2CH(CH_3)_2$
9-24	2-bromo	H	$-CH_2$-NHC(O)-	$-CH_2SC(O)CH_2-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
9-25	2-bromo	H	$-CH_2$-NHC(O)-	$-CH_2$-SC(O)-cyclohexyl	$-CH_2CH(CH_3)_2$
9-26	2-bromo	H	$-CH_2$-NHC(O)-	$-CH_2SC(O)$-phenyl	$-CH_2CH(CH_3)_2$
9-27	2-bromo	H	-C(O)NH-	$-CH_2SH$	benzyl
9-28	2-bromo	H	-C(O)NH-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-29	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_3$
9-30	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2CH_3$
9-31	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-(CH_2)_2CH_3$
9-32	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-(CH_2)_3CH_3$
9-33	2-fluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-34	2-methyl	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-35	2-methoxy	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-36	2-chloro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-37	3-bromo	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-38	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH(CH_3)-CH_2CH_3$
9-39	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2CH(CH_3)_2$
9-40	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-(CH_2)_4CH_3$
9-41	3-chloro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-42	2-chloro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-43	2,5-difluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-44	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	phenyl
9-45	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	4-fluorophenyl
9-46	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2C(CH_3)_3$
9-47	2,5-difluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-48	2,3-difluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-49	2,3-difluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-50	2-fluoro	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-51	2-fluoro	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-52	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2CH(CH_3)_2$
9-53	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	benzyl
9-54	2,3-difluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2C(CH_3)_3$
9-55	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2CH(CH_3)_2$
9-56	2,3-difluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2CH(CH_3)_2$

Ex.	R	R^2	-X	R^5	R^6
9-57	2,3-difluoro	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH(CH_3)-CH_2CH_3$
9-58	2-fluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2CF_3$
9-59	2,3-difluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2C(CH_3)_3$
9-60	2,3-difluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2C(CH_3)_3$
9-61	2,3-difluoro	$-CH_2CH_3$	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
9-62	2,3-difluoro	$-CH_2CH_3$	$-CH_2$-NHC(O)-	-SH	$-CH_2CH(CH_3)_2$
9-63	2,3-difluoro	H	$-CH_2$-NHC(O)-	-SH	$-CH_2CH(CH_3)_2$

(9-1) 4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-3-methoxybenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{34}ClN_3O_4S$, 496.20; found 497.2.

(9-2) 4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-phenylpropionylamino)methyl] imidazol-1-ylmethyl}-3-methoxybenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{32}ClN_3O_4S$, 530.18; found 531.2.

(9-3) 4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-methylbutyrylamino)methyl] imidazol-1-ylmethyl}-3-methoxybenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}ClN_3O_4S$, 482.18; found 483.2.

(9-4) 4-(5-{[2-(2-benzyl-3-mercaptopropionylamino)-acetylamino]methyl}-2-butyl-4-chloroimidazol-1-ylmethyl)-3-methoxybenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{35}ClN_4O_5S$, 587.20; found 588.2.

(9-5) 4-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-3-methoxybenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{33}ClN_4O_6$, 509.21; found 509.6.

(9-6) 4-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-3-phenylpropionylamino)methyl] imidazol-1-ylmethyl}-3-methoxybenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{31}ClN_4O_6$, 543.19; found 543.6.

(9-7) 2-bromo-4-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-4-methylpentanoyl-amino)methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{30}BrClN_4O_5$, 557.11; found 558.2.

(9-8) 2-bromo-4-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-3-phenylpropionyl-amino)methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{28}BrClN_4O_5$, 591.09; found 593.2.

(9-9) 2-bromo-4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-4-methylpentanoylamino)

methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{31}BrClN_3O_3S$, 544.10; found 546.2.

(9-10) 5-{2-butyl-4-chloro-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}ClN_3O_3S$, 542.22; found 543.2.

(9-11) 2-bromo-4-{2-butyl-5-[*((S)*-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}BrN_3O_3S$, 510.13; found 510.4. ^{1}H-NMR (DMSO) 8.53 (1H, t), 7.72 (1H, d), 7.48 (2H, d), 7.07 (1H, d), 5.51 (2H, s), 4.23 (2H, m), 2.86 (2H, t), 2.34 (1H, m), 2.17 (1H, t), 1.44, (2H, m), 1.25 (5H, m), 0.76 (9H, m).

(9-12) 2-bromo-4-{2-butyl-5-[*((R)*-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}BrN_3O_3S$, 510.13; found 510.4. ^{1}H-NMR (DMSO) 8.53 (1H, t), 7.72 (1H, d), 7.48 (2H, d), 7.07 (1H, d), 5.51 (2H, s), 4.23 (2H, m), 2.86 (2H, t), 2.34 (1H, m), 2.17 (1H, t), 1.44, (2H, m), 1.25 (5H, m), 0.76 (9H, m).

(9-13) 4-{2-butyl-5-[*((S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}FN_3O_3S$, 450.22; found 451.2. ^{1}H-NMR (DMSO) 8.48 (1H, t), 7.83 (1H, t), 7.38 (1H, s), 6.95 (2H, d), 5.48 (2H, s), 4.19 (2H, m), 2.75 (2H, t), 2.30 (1H, m), 2.14 (1H, t), 1.46 (2H, m), 1.23 (5H, m), 0.76 (9H, m).

(9-14) 2-bromo-4-{5-[*(R)*-1-(2-bromobenzyl)-2-hydroxycarbamoylethylcarbamoyl]2-butylimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{28}Br_2N_4O_5$, 635.04; found 636.0.

(9-15) 2-bromo-4-{2-butyl-5-[*(R)*-2-hydroxycarbamoyl-1-(2-methylbenzyl) ethylcarbamoyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{31}BrN_4O_5$, 571.15; found 572.2.

(9-16) 4-{2-butyl-5-[*((R)*-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-3-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}FN_3O_3S$, 450.22; found 451.2. ^{1}H-NMR (DMSO) 8.48 (1H, t), 7.73 (2H, m), 7.46 (1H, s), 5.59 (2H, s), 4.22 (2H, m), 2.85 (2H, t), 2.3 (1H, t), 2.16 (1H, t), 1.47 (2H, m), 1.22 (5H, m), 0.75 (9H, m).

(9-17) 4-{2-butyl-5-[*((R)*-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2,6-difluorobenzoic acid. MS *m/z*: [M + H^+] calcd for

$C_{23}H_{31}F_2N_3O_3S$, 468.21; found 469.2. ^{1}H-NMR (DMSO) 8.49 (1H, t), 7.38 (1H, s), 6.93 (2H, d), 5.46 (2H, s), 4.21 (2H, m), 2.77 (2H, t), 2.31 (1H, m), 2.18 (1H, t), 1.47 (2H, m), 1.23 (5H, m), 0.78 (9H, m).

(9-18) 4-{2-butyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-3-fluorobenzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{23}H_{32}FN_3O_3S$, 450.22; found 451.2. ^{1}H-NMR (DMSO) 8.48 (1H, t), 7.73 (2H, m), 7.46 (1H, s), 5.59 (2H, s), 4.22 (2H, m), 2.85 (2H, t), 2.3 (1H, t), 2.16 (1H, t), 1.47 (2H, m), 1.22 (5H, m), 0.75 (9H, m).

(9-19) 4-{2-butyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2,6-difluorobenzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{23}H_{31}F_2N_3O_3S$, 468.21; found 469. ^{1}H-NMR (DMSO) 8.49 (1H, t), 7.38 (1H, s), 6.93 (2H, d), 5.46 (2H, s), 4.21 (2H, m), 2.77 (2H, t), 2.31 (1H, m), 2.18 (1H, t), 1.47 (2H, m), 1.23 (5H, m), 0.78 (9H, m).

(9-20) 2-bromo-4-(2-butyl-5-{[2-(4-methoxybenzoylsulfanylmethyl)-4-methylpentanoylamino]methyl}imidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{31}H_{38}BrN_3O_5S$, 644.17; found 645.2.

(9-21) 4-{5-[(2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-bromobenzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{25}H_{34}BrN_3O_4S$, 552.15; found 553.2.

(9-22) 2-bromo-4-{2-butyl-5-[(2-isobutyrylsulfanylmethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{27}H_{38}BrN_3O_4S$, 580.18; found 581.2.

(9-23) 2-bromo-4-(2-butyl-5-{[2-(2,2-dimethylpropionylsulfanylmethyl)-4-methyl-pentanoylamino]methyl}imidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{28}H_{40}BrN_3O_4S$, 594.19; found 595.2.

(9-24) 2-bromo-4-(2-butyl-5-{[4-methyl-2-(3-methylbutyrylsulfanylmethyl) pentanoylamino]methyl}imidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{28}H_{40}BrN_3O_4S$, 594.19; found 595.2.

(9-25) 2-bromo-4-{2-butyl-5-[(2-cyclohexanecarbonylsulfanylmethyl-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{30}H_{42}BrN_3O_4S$, 620.21; found 621.2.

(9-26) 4-{5-[(2-benzoylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-bromobenzoic acid. MS *m/z*: [M + H$^+$] calcd for

$C_{30}H_{36}BrN_3O_4S$, 614.16; found 615.2.

(9-27) 4-[5-((*R*)-1-benzyl-2-mercaptoethylcarbamoyl)-2-butylimidazol-1-ylmethyl]-2-bromobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{28}BrN_3O_3S$, 530.10; found 530.2.

(9-28) 2-bromo-4-[2-butyl-5-((*R*)-1-mercaptomethyl-3-methylbutylcarbamoyl) imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}BrN_3O_3S$, 496.12; found 496.4.

(9-29) 4-{2-butyl-5-[(2-mercaptopropionylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{19}H_{24}FN_3O_3S$, 394.15; found 394.2.

(9-30) 4-{2-butyl-5-[(2-mercaptobutyrylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{20}H_{26}FN_3O_3S$, 408.17; found 408.2.

(9-31) 4-{2-butyl-5-[(2-mercaptopentanoylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{21}H_{28}FN_3O_3S$, 422.18; found 422.2.

(9-32) 4-{2-butyl-5-[(2-mercaptohexanoylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}FN_3O_3S$, 436.20; found 436.2.

(9-33) 4-{2-butyl-5-[((*R*)-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}FN_3O_3S$, 450.22; found 450.2. ^{1}H-NMR (DMSO) 8.48 (1H, t), 7.83 (1H, t), 7.38 (1H, s), 6.95 (2H, d), 5.48 (2H, s), 4.19 (2H, m), 2.75 (2H, t), 2.30 (1H, m), 2.14 (1H, t), 1.46 (2H, m), 1.23 (5H, m), 0.76 (9H, m).

(9-34) 4-{2-butyl-5-[((*R*)-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2-methylbenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{35}N_3O_3S$, 446.24; found 446.6.

(9-35) 4-{2-butyl-5-[((*R*)-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2-methoxybenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{35}N_3O_4S$, 462.24; found 462.6.

(9-36) 4-{2-butyl-5-[((*R*)-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2-chlorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}ClN_3O_3S$, 466.19; found 466.2.

(9-37) 3-bromo-4-{2-butyl-5-[((*R*)-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}BrN_3O_3S$, 510.13; found 510.4.

(9-38) 4-{2-butyl-5-[(2-mercapto-3-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}FN_3O_3S$, 436.20; found

436.2.

(9-39) 4-{2-butyl-5-[(2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}FN_3O_3S$, 436.20; found 436.2.

(9-40) 4-{2-butyl-5-[(2-mercaptoheptanoylamino)methyl]-imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}FN_3O_3S$, 450.22; found 450.2.

(9-41) 4-{2-butyl-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3-chlorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}ClN_3O_3S$, 466.19; found 466.4.

(9-42) 4-{2-butyl-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2-chlorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}ClN_3O_3S$, 466.19; found 466.4.

(9-43) 4-{2-butyl-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2,5-difluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{31}F_2N_3O_3S$, 468.21; found 468.3. ^{1}H-NMR (DMSO) 8.50 (1H, t), 7.70 (1H, m), 7.46 (1H, s), 6.86 (1H, m), 5.55 (2H, s), 4.24 (2H, m), 2.83 (2H, t), 2.30 (1H, m), 2.16 (1H, m), 1.52 (2H, m), 1.23 (5H, m), 0.76 (9H, m).

(9-44) 4-{2-butyl-5-[(2-mercapto-2-phenylacetylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{26}FN_3O_3S$, 456.17; found 456.2.

(9-45) 4-(2-butyl-5-{[2-(4-fluorophenyl)-2-mercaptoacetylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{24}H_{25}F_2N_3O_3S$, 474.16; found 474.2.

(9-46) 4-{2-butyl-5-[(2-mercapto-4,4-dimethylpentanoylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}FN_3O_3S$, 450.22; found 450.2.

(9-47) 4-{2-butyl-5-[(*(R)*-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2,5-difluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{31}F_2N_3O_3S$, 468.21; found 468.4.

(9-48) 4-{2-butyl-5-[(*(R)*-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{31}F_2N_3O_3S$, 468.21; found 468.4.

(9-49) 4-{2-butyl-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS *m/z*: [M + H^+] calcd for

$C_{23}H_{31}F_2N_3O_3S$, 468.21; found 468.4. ^{1}H-NMR (DMSO) 8.45 (1H, m), 7.62 (1H, t), 7.42 (1H, s), 6.71 (1H, t), 5.59 (2H, s), 4.21 (2H, m), 2.83 (2H, t), 2.28 (1H, m), 2.16 (1H, t), 2.51 (2H, m), 1.24 (5H, m), 0.75 (9H, m).

(9-50) 4-{2-butyl-4-chloro-5-[(*(R)*-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{31}ClFN_3O_3S$, 484.18; found 484.4.

(9-51) 4-{2-butyl-4-chloro-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{31}ClFN_3O_3S$, 484.18; found 484.4.

(9-52) 4-{2-butyl-5-[(*(R)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}FN_3O_3S$, 436.20; found 436.2. ^{1}H-NMR (DMSO) 8.50 (1H, t), 7.83 (1H, t), 7.42 (1H, s), 6.96 (2H, t), 5.45 (2H, s), 4.23 (2H, m), 3.18 (2H, m), 2.75 (1H, m), 1.18-1.50 (7H, m), 0.74 (9H, m).

(9-53) 4-{2-butyl-5-[(*(S)*-2-mercapto-3-phenylpropionylamino)methyl]imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{28}FN_3O_3S$, 470.18; found 470.4.

(9-54) 4-{2-butyl-5-[(2-mercapto-4,4-dimethylpentanoylamino)methyl]imidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{31}F_2N_3O_3S$, 468.21; found 468.3.

(9-55) 4-{2-butyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS m/z: [M+H^+] calcd for $C_{22}H_{30}FN_3O_3S$, 436.20; found 436.4.

(9-56) 4-{2-butyl-5-[(*(R)*-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS m/z: [M+H^+] calcd for $C_{22}H_{29}F_2N_3O_3S$, 454.19; found 454.2.

(9-57) 4-{2-butyl-5-[(2-mercaptomethyl-3-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS m/z: [M+H^+] calcd for $C_{23}H_{31}F_2N_3O_3S$, 468.21; found 468.2.

(9-58) 4-{2-butyl-5-[(4,4,4-trifluoro-2-mercaptobutyrylamino)methyl]-imidazol-1-ylmethyl}-2-fluorobenzoic acid. MS m/z: [M+H^+] calcd for $C_{20}H_{23}F_4N_3O_3S$, 462.14; found 462.4.

(9-59) 4-{2-butyl-5-[(*(S)*-2-mercapto-4,4-dimethylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS m/z: [M+H^+] calcd for $C_{23}H_{31}F_2N_3O_3S$, 468.21;

found 468.5.

(9-60) 4-{2-butyl-5-[((*R*)-2-mercapto-4,4-dimethylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS m/z: [M+H$^+$] calcd for $C_{23}H_{31}F_2N_3O_3S$, 468.21; found 468.5.

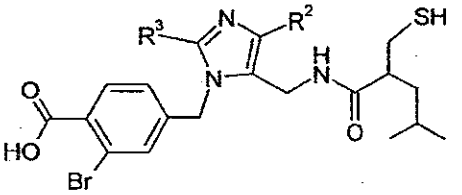
(9-61) 4-{4-ethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propylimidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS m/z: [M+H$^+$] calcd for $C_{24}H_{33}F_2N_3O_3S$, 482.22; found 482.3.

(9-62) -{4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propylimidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS m/z: [M+H$^+$] calcd for $C_{23}H_{31}F_2N_3O_3S$, 468.21; found 468.4.

(9-63) 2,3-difluoro-4-{5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propyl-imidazol-1-ylmethyl}benzoic acid. MS m/z: [M+H$^+$] calcd for $C_{21}H_{27}F_2N_3O_3S$, 440.17; found 440.2.

EXAMPLE 10

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 10-1 to 10-5, having the following formula, were also prepared:



Ex.	R^2	R^3
10-1	H	$-(CH_2)_2CH_3$
10-2	H	$-(CH_2)_2CH_3$
10-3	H	$-CH_2CH_3$
10-4	H	$-CH_2CH_3$
10-5	Cl	$-CH_2CH_3$

(10-1) 2-bromo-4-{5-[((*R*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propylimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{22}H_{30}BrN_3O_3S$, 496.12; found 497.2.

(10-2) 2-bromo-4-{5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propylimidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{22}H_{30}BrN_3O_3S$, 496.12; found 497.2.

(10-3) 2-bromo-4-{2-ethyl-5-[((*R*)-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{21}H_{28}BrN_3O_3S$,

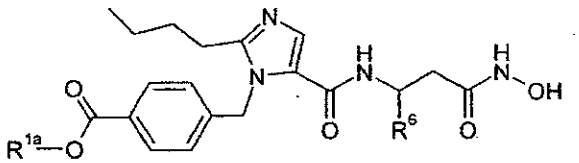
482.10; found 483.2.

(10-4) 2-bromo-4-{2-ethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{21}H_{28}BrN_3O_3S$, 482.10; found 483.2. ^{1}H-NMR (MeOH) 8.67 (1H, t), 7.83 (1H, d), 7.51 (2H, d), 7.10 (1H, d), 5.57 (2H, d), 4.47 (1H, dd), 4.61 (1H, dd), 2.93 (2H, q), 2.56 (2H, m), 2.38 (1H, m), 1.36 (7H, m), 0.83 (6H, dd).

(10-5) 2-bromo-4-{4-chloro-2-ethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H$^+$] calcd for $C_{21}H_{27}BrClN_3O_3S$, 516.06; found 518.0.

EXAMPLE 11

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 11-1 to 11-20, having the following formula, were also prepared:



Ex.	R^{1a}	R^6
11-1	-CH(CH$_3$)-O-C(O)O-CH$_2$CH$_3$	benzyl
11-2	-CH$_3$	-(CH$_2$)$_2$-phenyl
11-3	-CH$_3$	-CH$_2$-thiophen-3-yl
11-4	-CH$_3$	-CH$_2$-furan-2-yl
11-5	-CH$_3$	benzyl
11-6	-CH$_2$CH$_3$	benzyl
11-7	-(CH$_2$)$_2$CH$_3$	benzyl
11-8	-CH(CH$_3$)-CF$_3$	benzyl
11-9	-(CH$_2$)$_2$-CF$_2$CF$_3$	benzyl
11-10	-CH(CH$_2$F)$_2$	benzyl
11-11	-CH(CH$_3$)-O-C(O)O-CH(CH$_3$)$_2$	benzyl
11-12	-CH(CH$_3$)-O-C(O)O-cyclohexyl	benzyl
11-13	cyclopentyl	benzyl
11-14	-CH(CH$_3$)$_2$	benzyl
11-15	-CH$_2$-pyridin-4-yl	benzyl
11-16	benzyl	benzyl
11-17	4-fluorobenzyl	benzyl
11-18	4-trifluoromethylbenzyl	benzyl
11-19	4-trifluoromethoxybenzyl	benzyl
11-20	indan-5-yl	benzyl

(11-1) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butyl-imidazol-1-ylmethyl]benzoic acid 1-ethoxycarbonyloxyethyl ester. MS *m/z*: [M + H$^+$] calcd for

$C_{31}H_{38}N_4O_8$, 595.27; found 595.5.

(11-2) 4-[2-butyl-5-((*R*)-1-hydroxycarbamoylmethyl-3-phenylpropylcarbamoyl) imidazol-1-ylmethyl]benzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{28}H_{34}N_4O_5$, 507.25; found 508.1.

(11-3) 4-[2-butyl-5-((*R*)-2-hydroxycarbamoyl-1-thiophen-3-ylmethylethylcarbamoyl) imidazol-1-ylmethyl]benzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{25}H_{30}N_4O_5S$, 499.19; found 500.1.

(11-4) 4-[2-butyl-5-((*R*)-1-furan-2-ylmethyl-2-hydroxycarbamoylethylcarbamoyl) imidazol-1-ylmethyl]benzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{25}H_{30}N_4O_6$, 483.22; found 483.9.

(11-5) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{27}H_{32}N_4O_5$, 493.24; found 493.2.

(11-6) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid ethyl ester. MS *m/z*: [M + H^+] calcd for $C_{28}H_{34}N_4O_5$, 507.25; found 507.2.

(11-7) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid propyl ester. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}N_4O_5$, 521.27; found 521.2.

(11-8) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid 2,2,2-trifluoro-1-methylethyl ester. MS *m/z*: [M + H^+] calcd for $C_{29}H_{33}F_3N_4O_5$, 575.24; found 575.

(11-9) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid 3,3,4,4,4-pentafluorobutyl ester. MS *m/z*: [M + H^+] calcd for $C_{30}H_{33}F_5N_4O_5$, 625.24; found 625.

(11-10) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid 2-fluoro-1-fluoromethylethyl ester. MS *m/z*: [M + H^+] calcd for $C_{29}H_{34}F_2N_4O_5$, 557.25; found 557.

(11-11) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid 1-isopropoxycarbonyloxyethyl ester. MS *m/z*: [M + H^+] calcd for $C_{32}H_{40}N_4O_8$, 609.28; found 609.4.

(11-12) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid 1-cyclohexyloxycarbonyloxyethyl ester. MS *m/z*: [M + H^+] calcd for

$C_{35}H_{44}N_4O_8$, 649.32; found 649.4.

(11-13) 4-[2-butyl-5-(1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl)imidazol-1-ylmethyl]benzoic acid cyclopentyl ester. MS *m/z*: [M + H^+] calcd for $C_{31}H_{38}N_4O_5$, 547.28; found 547.

(11-14) 4-[2-butyl-5-(1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl)imidazol-1-ylmethyl]benzoic acid isopropyl ester. MS *m/z*: [M + H^+] calcd for $C_{29}H_{36}N_4O_5$, 521.27; found 521.

(11-15) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid pyridin-4-ylmethyl ester. MS *m/z*: [M + H^+] calcd for $C_{32}H_{35}N_5O_5$, 570.26; found 570.6.

(11-16) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid benzyl ester. MS *m/z*: [M + H^+] calcd for $C_{33}H_{36}N_4O_5$, 569.27; found 569.4.

(11-17) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid 4-fluorobenzyl ester. MS *m/z*: [M + H^+] calcd for $C_{33}H_{35}FN_4O_5$, 587.26; found 587.0.

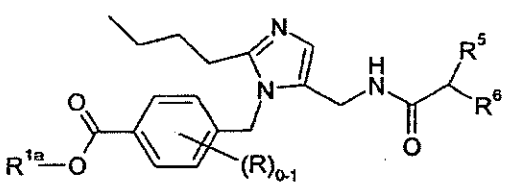
(11-18) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid 4-trifluoromethylbenzyl ester. MS *m/z*: [M + H^+] calcd for $C_{34}H_{35}F_3N_4O_5$, 637.26; found 638.0.

(11-19) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid 4-trifluoromethoxybenzyl ester. MS *m/z*: [M + H^+] calcd for $C_{34}H_{35}F_3N_4O_6$, 653.25; found 653.2.

(11-20) 4-[2-butyl-5-(1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl)imidazol-1-ylmethyl]benzoic acid indan-5-yl ester. MS *m/z*: [M + H^+] calcd for $C_{35}H_{38}N_4O_5$, 595.28; found 595.2.

EXAMPLE 12

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 12-1 to 12-20, having the following formula where R is an optional substituent, were also prepared:



Ex.	R^{1a}	R	R^5	R^6
12-1	$-CH_3$	-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
12-2	H	2-bromo	$-CH_2SH$	$-CH_2CH(CH_3)_2$
12-3	$-CH_3$	2-bromo	$-CH_2SH$	$-CH_2CH(CH_3)_2$
12-4	$-CH_3$	2-bromo	$-CH_2SC(O)CH_3$	$-CH_2CH(CH_3)_2$
12-5	$-CH_2CH_3$	2-bromo	$-CH_2SH$	$-CH_2CH(CH_3)_2$
12-6	$-CH(CH_3)_2$	2-bromo	$-CH_2SH$	$-CH_2CH(CH_3)_2$
12-7	$-(CH_2)_3CH_3$	2-bromo	$-CH_2SH$	$-CH_2CH(CH_3)_2$
12-8	$-CH_3$	2-fluoro	$-CH_2SC(O)CH_3$	$-CH_2CH(CH_3)_2$
12-9	$-CH_3$	2-methyl	$-CH_2SC(O)CH_3$	$-CH_2CH(CH_3)_2$
12-10	$-CH_3$	2-methoxy	$-CH_2SC(O)CH_3$	$-CH_2CH(CH_3)_2$
12-11	$-CH_3$	2-chloro	$-CH_2SC(O)CH_3$	$-CH_2CH(CH_3)_2$
12-12	$-CH_3$	3-chloro	$-CH_2SC(O)CH_3$	$-CH_2CH(CH_3)_2$
12-13	$-CH_3$	2-chloro	$-CH_2SC(O)CH_3$	$-CH_2CH(CH_3)_2$
12-14	$-CH_3$	2-fluoro	$-SC(O)CH_3$	phenyl
12-15	$-CH_3$	2-fluoro	$-SC(O)CH_3$	2-chlorophenyl
12-16	$-CH_3$	2-fluoro	$-SC(O)CH_3$	4-fluorophenyl
12-17	$-CH_3$	2-fluoro	$-SC(O)CH_3$	4-chlorophenyl
12-18	$-CH_3$	2-fluoro	$-SC(O)CH_3$	$-CH_2CH(CH_3)_2$
12-19	$-CH_3$	2-fluoro	$-SC(O)CH_3$	$-CH(CH_3)_2$
12-20	$-CH_3$	2-fluoro	$-SC(O)CH_3$	$-CH_2C(CH_3)_3$

(12-1) 4-{2-butyl-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}benzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{24}H_{35}N_3O_3S$, 446.24; found 446.3.

(12-2) 2-bromo-4-{2-butyl-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}BrN_3O_3S$, 510.13; found 511.

(12-3) 2-bromo-4-{2-butyl-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{24}H_{34}BrN_3O_3S$, 524.15; found 524.4.

(12-4) 4-{5-[(2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-bromobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{26}H_{36}BrN_3O_4S$, 566.16; found 566.1.

(12-5) 2-bromo-4-{2-butyl-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid ethyl ester. MS *m/z*: [M + H^+] calcd for $C_{25}H_{36}BrN_3O_3S$, 538.17; found 539.2.

(12-6) 2-bromo-4-{2-butyl-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid isopropyl ester. MS *m/z*: [M + H^+] calcd for $C_{26}H_{38}BrN_3O_3S$, 552.18; found 553.2.

(12-7) 2-bromo-4-{2-butyl-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl]

imidazol-1-ylmethyl}benzoic acid butyl ester. MS *m/z*: [M + H^+] calcd for $C_{27}H_{40}BrN_3O_3S$, 566.20; found 567.2.

(12-8) 4-{5-[((*R*)-2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butyl-imidazol-1-ylmethyl}-2-fluorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{26}H_{36}FN_3O_4S$, 506.24; found 506.2.

(12-9) 4-{5-[((*R*)-2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-methylbenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{27}H_{39}N_3O_4S$, 502.27; found 502.2.

(12-10) 4-{5-[((*R*)-2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-methoxybenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{27}H_{39}N_3O_5S$, 518.26; found 518.2.

(12-11) 4-{5-[((*R*)-2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-chlorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{26}H_{36}ClN_3O_4S$, 522.21; found 522.1.

(12-12) 4-{5-[((*S*)-2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}-3-chlorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{26}H_{36}ClN_3O_4S$, 522.21; found 523.2.

(12-13) 4-{5-[((*S*)-2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-chlorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{26}H_{36}ClN_3O_4S$, 522.21; found 523.2.

(12-14) 4-{5-[(2-acetylsulfanyl-2-phenylacetylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-fluorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{27}H_{30}FN_3O_4S$, 512.19; found 512.2.

(12-15) 4-(5-{[2-acetylsulfanyl-2-(2-chlorophenyl)-acetylamino]methyl}-2-butylimidazol-1-ylmethyl)-2-fluorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{27}H_{29}ClFN_3O_4S$, 546.16; found 546.2.

(12-16) 4-(5-{[2-acetylsulfanyl-2-(4-fluorophenyl)-acetylamino]methyl}-2-butylimidazol-1-ylmethyl)-2-fluorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{27}H_{29}F_2N_3O_4S$, 530.18; found 530.2.

(12-17) 4-(5-{[2-acetylsulfanyl-2-(4-chlorophenyl)-acetylamino]methyl}-2-butylimidazol-1-ylmethyl)-2-fluorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{27}H_{29}ClFN_3O_4S$, 546.16; found 546.2.

(12-18) 4-{5-[(2-acetylsulfanyl-4-methylpentanoylamino)methyl]-2-butylimidazol-1-

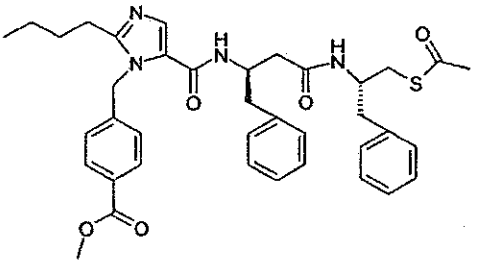
ylmethyl}-2-fluorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{25}H_{34}FN_3O_4S$, 492.23; found 492.2.

(12-19) 4-{5-[(2-acetylsulfanyl-3-methylbutyrylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-fluorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{24}H_{32}FN_3O_4S$, 478.21; found 478.2.

(12-20) 4-{5-[(2-acetylsulfanyl-4,4-dimethylpentanoylamino)methyl]-2-butylimidazol-1-ylmethyl}-2-fluorobenzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{26}H_{36}FN_3O_4S$, 506.24; found 506.2.

EXAMPLE 13

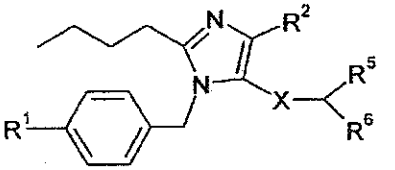
Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, the following compound was also prepared:



4-{5-[*(R)*-2-(*(S)*-2-Acetylsulfanyl-1-benzylethylcarbamoyl)-1-benzylethylcarbamoyl]-2-butylimidazol-1-ylmethyl}benzoic acid methyl ester. MS *m/z*: [M + H^+] calcd for $C_{38}H_{44}N_4O_5S$, 669.30; found 669.5.

EXAMPLE 14

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 14-1 to 14-24, having the following formula, were also prepared:



Ex.	R^1	R^2	X	R^5	R^6
14-1	-O-CH(CH_3)-COOH	Cl	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2CH(CH_3)_2$
14-2	$-NHSO_2-CF_3$	Cl	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-3	$-NHSO_2-CF_3$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-4	$-SO_2-NHC(O)CH_3$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl

Ex.	R^1	R^2	X	R^5	R^6
14-5	$-SO_2$-NH-C(O)NH-$(CH_2)_2$-CH_3	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-6	$-SO_2$-NH-C(O)NH-$(CH_2)_2$-CH_3	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-chlorobenzyl
14-7	$-NHSO_2-CF_3$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2CH(CH_3)_2$
14-8	$-NHSO_2-CF_3$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-9	-O-CH(CH_3)-COOH	Cl	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-10	-O-CH(CH_3)-COOH	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2CH(CH_3)_2$
14-11	-C(O)O-$(CH_2)_2$-CF_3	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-12	$-SO_2OH$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-13	$-SO_2OH$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-14	$-SO_2OH$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2CH(CH_3)_2$
14-15	$-SO_2OH$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	4-chlorobenzyl
14-16	$-SO_2OH$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-17	$-NHSO_2-CF_3$	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-18	tetrazolyl	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	2-bromobenzyl
14-19	tetrazolyl	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
14-20	tetrazolyl	H	-C(O)NH-	$-CH_2COOH$	benzyl
14-21	tetrazolyl	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2CH(CH_3)_2$
14-22	tetrazolyl	H	-C(O)NH-	$-CH_2SH$	benzyl
14-23	tetrazolyl	H	-C(O)NH-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
14-24	$-SO_2$NHC(O)-phenyl	H	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$

(14-1) 2-{4-[2-butyl-4-chloro-5-(1-hydroxycarbamoylmethyl-3-methylbutyl-carbamoyl)imidazol-1-ylmethyl]phenoxy}propionic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{35}ClN_4O_6$, 523.22; found 523.4.

(14-2) 2-butyl-5-chloro-3-(4-trifluoromethanesulfonylaminobenzyl)-3H-imidazole-4-carboxylic acid (1-hydroxycarbamoylmethyl-2-phenylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}ClF_3N_5O_5S$, 616.15; found 616.4.

(14-3) 2-butyl-3-(4-trifluoromethanesulfonylaminobenzyl)-3H-imidazole-4-carboxylic acid (1-hydroxycarbamoylmethyl-2-phenylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}F_3N_5O_5S$, 582.19; found 582.4.

(14-4) 3-(4-acetylsulfamoylbenzyl)-2-butyl-3H-imidazole-4-carboxylic acid (1-hydroxycarbamoylmethyl-2-phenylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{27}H_{33}N_5O_6S$, 556.22; found 556.3.

(14-5) 2-butyl-N-(4-(hydroxyamino)-4-oxo-1-phenylbutan-2-yl)-1-(4-(N-(propylcarbamoyl)sulfamoyl)benzyl)-1H-imidazole-5-carboxamide. MS *m/z*: [M + H^+]

calcd for $C_{29}H_{38}N_6O_6S$, 599.26; found 599.4.

(14-6) *(S)*-2-butyl-N-(1-(4-chlorophenyl)-4-(hydroxyamino)-4-oxobutan-2-yl)-1-(4-(N-(propylcarbamoyl)sulfamoyl)benzyl)-1H-imidazole-5-carboxamide. MS *m/z*: [M + H^+] calcd for $C_{29}H_{37}ClN_6O_6S$, 633.22; found 634.2.

(14-7) 2-butyl-3-(4-trifluoromethanesulfonylaminobenzyl)-3H-imidazole-4-carboxylic acid *((S)*-1-hydroxycarbamoylmethyl-3-methylbutyl)amide. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}F_3N_5O_5S$, 548.21; found 548.3.

(14-8) 2-butyl-3-(4-trifluoromethanesulfonylamino-benzyl)-3H-imidazole-4-carboxylic acid *((S)*-1-benzyl-2-hydroxycarbamoylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}F_3N_5O_5S$, 582.19; found 582.3.

(14-9) 2-{4-[2-butyl-4-chloro-5-(1-hydroxycarbamoylmethyl-2-phenylethyl-carbamoyl)imidazol-1-ylmethyl]phenoxy}propionic acid. MS *m/z*: [M + H^+] calcd for $C_{28}H_{33}ClN_4O_6$, 557.21; found 557.0.

(14-10) 2-{4-[2-butyl-5-*((S)*-1-hydroxycarbamoylmethyl-3-methylbutylcarbamoyl) imidazol-1-ylmethyl]phenoxy}propionic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{36}N_4O_6$, 489.26; found 489.4.

(14-11) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzoic acid 3,3,3-trifluoropropyl ester. MS *m/z*: [M + H^+] calcd for $C_{29}H_{33}F_3N_4O_5$, 575.24; found 575.4.

(14-12) 4-[5-(1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzenesulfonic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{30}N_4O_6S$, 515.19; found 515.5.

(14-13) 4-[5-*((S)*-1-benzyl-2-hydroxycarbamoylethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzenesulfonic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{30}N_4O_6S$, 515.19; found 515.5.

(14-14) 4-[2-butyl-5-(1-hydroxycarbamoylmethyl-3-methylbutylcarbamoyl)imidazol-1-ylmethyl]benzenesulfonic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{32}N_4O_6S$, 481.20; found 481.2.

(14-15) 4-{2-butyl-5-[*(S)*-1-(4-chlorobenzyl)-2-hydroxycarbamoylethylcarbamoyl] imidazol-1-ylmethyl}benzenesulfonic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{29}ClN_4O_6S$, 549.15; found 550.2.

(14-16) 4-[5-*((R)*-1-benzyl-2-hydroxycarbamoyl-ethylcarbamoyl)-2-butylimidazol-1-ylmethyl]benzenesulfonic acid. MS *m/z*: [M + H^+] calcd for $C_{25}H_{30}N_4O_6S$, 515.19; found

515.2.

(14-17) 2-butyl-3-(4-trifluoromethanesulfonylaminobenzyl)-3H-imidazole-4-carboxylic acid *(R)*-1-benzyl-2-hydroxycarbamoylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}F_3N_5O_5S$, 582.19; found 582.2.

(14-18) 2-butyl-3-[4-(1H-tetrazol-5-yl)benzyl]-3H-imidazole-4-carboxylic acid [*(R)*-2-(2-bromophenyl)-1-hydroxycarbamoylmethylethyl]amide. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}BrN_8O_3$, 581.15; found 583.3.

(14-19) 2-butyl-3-[4-(1H-tetrazol-5-yl)benzyl]-3H-imidazole-4-carboxylic acid *(R)*-1-hydroxycarbamoylmethyl-2-phenylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}N_8O_3$, 503.24; found 503.5.

(14-20) *(R)*-3-({2-butyl-3-[4-(1H-tetrazol-5-yl)benzyl]-3H-imidazole-4-carbonyl} amino)-4-phenylbutyric acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}N_7O_3$, 488.23; found 488.3.

(14-21) 2-butyl-3-[4-(1H-tetrazol-5-yl)benzyl]-3H-imidazole-4-carboxylic acid *(R)*-1-hydroxycarbamoylmethyl-3-methylbutyl)amide. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}N_8O_3$, 469.26; found 469.2.

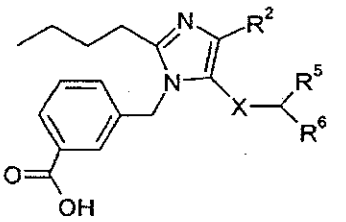
(14-22) 2-butyl-3-[4-(2H-tetrazol-5-yl)benzyl]-3H-imidazole-4-carboxylic acid *(R)*-1-mercaptomethyl-2-phenylethyl)amide. MS *m/z*: [M + H^+] calcd for $C_{25}H_{29}N_7OS$, 476.22; found 476.4.

(14-23) 2-butyl-3-[4-(2H-tetrazol-5-yl)benzyl]-3H-imidazole-4-carboxylic acid *(R)*-1-mercaptomethyl-3-methylbutyl)amide. MS *m/z*: [M + H^+] calcd for $C_{22}H_{31}N_7OS$, 442.23; found 442.4.

(14-24) 2-mercaptomethyl-4-methylpentanoic acid [3-(4-benzoylsulfamoylbenzyl)-2-butyl-3H-imidazol-4-ylmethyl]amide. MS m/z: [M+H^+] calcd for $C_{29}H_{38}N_4O_4S_2$, 571.23; found 571.2.

EXAMPLE 15

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 15-1 to 15-12, having the following formula, were also prepared:



Ex.	R^2	X	R^5	R^6
15-1	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	$-CH_2CH(CH_3)_2$
15-2	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH_2CH(CH_3)_2$
15-3	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	benzyl
15-4	Cl	$-CH_2$-NHC(O)-	$-CH_2SH$	$-CH(CH_3)_2$
15-5	Cl	$-CH_2$-NHC(O)-	-SH	$-CH(CH_3)$-CH_2CH_3
15-6	Cl	$-CH_2$-NHC(O)-CH_2-NHC(O)-	$-CH_2SH$	benzyl
15-7	Cl	$-CH_2$-NHC(O)-	-C(O)N(OH)H	$-CH_2CH(CH_3)_2$
15-8	Cl	$-CH_2$-NHC(O)-	-C(O)N(OH)H	benzyl
15-9	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
15-10	H	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
15-11	Cl	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl
15-12	Cl	-C(O)NH-	$-CH_2C(O)N(OH)H$	benzyl

(15-1) 3-[2-butyl-5-(1-hydroxycarbamoylmethyl-3-methylbutylcarbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}N_4O_5$, 445.24; found 445.2.

(15-2) 3-{2-butyl-4-chloro-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}ClN_3O_3S$, 466.19; found 466.2.

(15-3) 3-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-phenylpropionylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}ClN_3O_3S$, 500.17; found 500.2.

(15-4) 3-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-methylbutyrylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}ClN_3O_3S$, 452.17; found 452.2.

(15-5) 3-{2-butyl-4-chloro-5-[(2-mercapto-3-methylpentanoylamino)methyl]imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}ClN_3O_3S$, 452.17; found 452.2.

(15-6) 3-(5-{[2-(2-benzyl-3-mercaptopropionylamino)acetylamino]methyl}-2-butyl-4-chloroimidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{28}H_{33}ClN_4O_4S$, 557.19; found 557.2.

(15-7) 3-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino)methyl]

imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{31}ClN_4O_5$, 479.20; found 479.2.

(15-8) 3-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-3-phenylpropionylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}ClN_4O_5$, 513.18; found 513.2.

(15-9) 3-[2-butyl-5-(1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}N_4O_5$, 479.22; found 479.4.

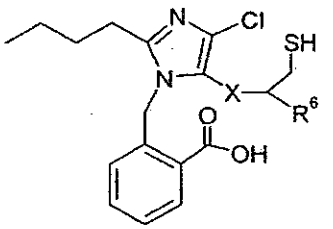
(15-10) 3-[2-butyl-5-(*(R)*-1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl) imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}N_4O_5$, 479.22; found 479.4.

(15-11) 3-[2-butyl-4-chloro-5-(*(R)*-1-hydroxycarbamoylmethyl-2-phenylethyl-carbamoyl)imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}ClN_4O_5$, 513.18; found 514.2.

(15-12) 3-[2-butyl-4-chloro-5-(1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl) imidazol-1-ylmethyl]benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{29}ClN_4O_5$, 513.18; found 514.2.

EXAMPLE 16

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 16-1 to 16-4, having the following formula, were also prepared:



Ex.	-X	R^6
16-1	$-CH_2-NHC(O)-$	$-CH_2CH(CH_3)_2$
16-2	$-CH_2-NHC(O)-$	benzyl
16-3	$-CH_2-NHC(O)-$	$-CH(CH_3)_2$
16-4	$-CH_2-NHC(O)-CH_2-NHC(O)-$	benzyl

(16-1) 2-{2-butyl-4-chloro-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{23}H_{32}ClN_3O_3S$, 466.19; found 467.

(16-2) 2-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-phenylpropionylamino)methyl]

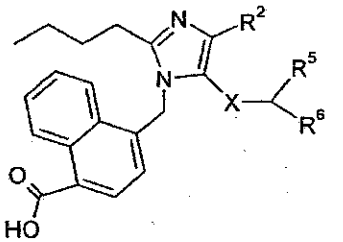
imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{30}ClN_3O_3S$, 500.17; found 501.

(16-3) 2-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-methylbutyrylamino)methyl] imidazol-1-ylmethyl}benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{22}H_{30}ClN_3O_3S$, 452.17; found 453.

(16-4) 2-(5-{[2-(2-benzyl-3-mercaptopropionylamino)acetylamino]methyl}-2-butyl-4-chloroimidazol-1-ylmethyl)benzoic acid. MS *m/z*: [M + H^+] calcd for $C_{28}H_{33}ClN_4O_4S$, 557.19; found 558.

EXAMPLE 17

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 17-1 to 17-14, having the following formula, were also prepared:



Ex.	R^2	-X	R^5	R^6
17-1	Cl	-CH_2-NHC(O)-	-CH_2SH	-$CH_2CH(CH_3)_2$
17-2	Cl	-CH_2-NHC(O)-	-CH_2SH	benzyl
17-3	Cl	-CH_2-NHC(O)-	-CH_2SH	-$CH(CH_3)_2$
17-4	Cl	-CH_2-NHC(O)-CH_2 -NHC(O)-	-CH_2SH	benzyl
17-5	Cl	-CH_2-NHC(O)-	-C(O)N(OH)H)	-$CH_2CH(CH_3)_2$
17-6	Cl	-CH_2-NHC(O)-	-C(O)N(OH)H)	-$CH(CH_3)_2$
17-7	H	-C(O)NH-	-CH_2C(O)N(OH)H)	-$CH_2CH(CH_3)_2$
17-8	Cl	-C(O)NH-	-C(O)N(OH)H)	benzyl
17-9	H	-C(O)NH-	-CH_2C(O)N(OH)H)	benzyl
17-10	Cl	-C(O)NH-	-CH_2C(O)N(OH)H)	benzyl
17-11	H	-C(O)NH-	-CH_2C(O)N(OH)H)	benzyl
17-12	H	-C(O)NH-	-CH_2C(O)N(OH)H)	2-bromobenzyl
17-13	H	-C(O)NH-	-CH_2COOH	benzyl
17-14	H	-CH_2-NHC(O)-	-C(O)N(OH)H)	-$CH_2CH(CH_3)_2$

(17-1) 4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{34}ClN_3O_3S$, 516.20; found 517.2.

(17-2) 4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-phenylpropionylamino)methyl] imidazol-1-ylmethyl}-naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for

$C_{30}H_{32}ClN_3O_3S$, 550.19; found 551.2.

(17-3) 4-{2-butyl-4-chloro-5-[(2-mercaptomethyl-3-methylbutyrylamino)methyl] imidazol-1-ylmethyl}-naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{32}ClN_3O_3S$, 502.19; found 502.2.

(17-4) 4-(5-{[2-(2-benzyl-3-mercaptopropionylamino)acetylamino]methyl}-2-butyl-4-chloroimidazol-1-ylmethyl)naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{32}H_{35}ClN_4O_4S$, 607.21; found 607.2.

(17-5) 4-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{33}ClN_4O_5$, 529.21; found 529.2.

(17-6) 4-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-3-methylbutyrylamino)methyl] imidazol-1-ylmethyl}naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{26}H_{31}ClN_4O_5$, 515.20; found 515.2.

(17-7) 4-[2-butyl-5-(1-hydroxycarbamoylmethyl-3-methylbutylcarbamoyl)imidazol-1-ylmethyl]naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{27}H_{34}N_4O_5$, 495.25; found 495.4.

(17-8) 4-[2-butyl-4-chloro-5-(*(S)*-1-hydroxycarbamoyl-2-phenylethylcarbamoyl) imidazol-1-ylmethyl]naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{29}H_{29}ClN_4O_5$, 549.18; found 549.2.

(17-9) 4-[2-butyl-5-(1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl)imidazol-1-ylmethyl]naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{32}N_4O_5$, 529.24; found 529.4.

(17-10) 4-[2-butyl-4-chloro-5-(1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl) imidazol-1-ylmethyl]naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{31}ClN_4O_5$, 563.20; found 563.4.

(17-11) 4-[2-butyl-5-(*(R)*-1-hydroxycarbamoylmethyl-2-phenylethylcarbamoyl) imidazol-1-ylmethyl]naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{32}N_4O_5$, 529.24; found 529.5.

(17-12) 4-{5-[*(R)*-2-(2-bromophenyl)-1-hydroxycarbamoylmethylethylcarbamoyl]-2-butylimidazol-1-ylmethyl}naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{31}BrN_4O_5$, 607.15; found 608.2.

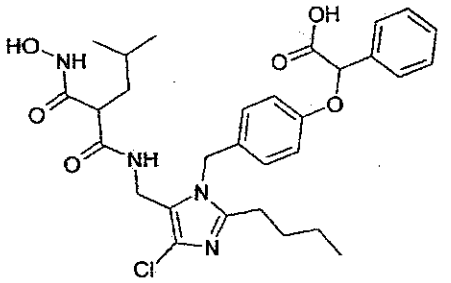
(17-13) 4-[2-butyl-5-(*(R)*-1-carboxymethyl-2-phenylethylcarbamoyl)imidazol-1-ylmethyl]naphthalene-1-carboxylic acid. MS *m/z*: [M + H^+] calcd for $C_{30}H_{31}N_3O_5$, 514.23;

found 514.2.

(17-14) 4-{2-butyl-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}naphthalene-1-carboxylic acid. MS *m/z*: [M + H$^+$] calcd for $C_{27}H_{34}N_4O_5$ 495.25; found 495.2.

EXAMPLE 18

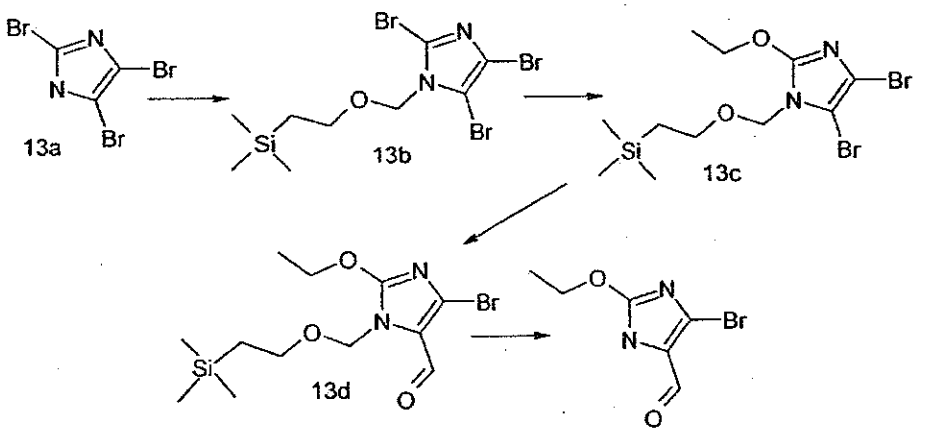
Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, the following compound was also prepared:



(4-{2-butyl-4-chloro-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}phenoxy)phenylacetic acid. MS *m/z*: [M + H$^+$] calcd for $C_{30}H_{37}ClN_4O_6$, 585.24; found 585.4.

PREPARATION 13

5-Bromo-2-ethoxy-3H-imidazole-4-carbaldehyde



2,4,5-Tribromo-1H-imidazole (13a) (98.7 g, 324 mmol, 1.0 eq) was dissolved into 1.20 L of methylene chloride and cooled to 0 °C. To this was added DIPEA (62 mL, 360 mmol, 1.1 eq) followed by the slow addition of [β-(trimethylsilyl)ethoxy]methyl chloride (60.2 mL, 340 mmol, 1.05 eq). The solution was slowly warmed to room temperature. After 2 hours the mixture was washed 2x with 600mL of 1M H_3PO_4/saturated aqueous NaCl (1/10 mL). The organic layer was dried over $MgSO_4$, and evaporated to dryness, yielding intermediate (13b) as faint yellow liquid that solidified on standing (137 g).

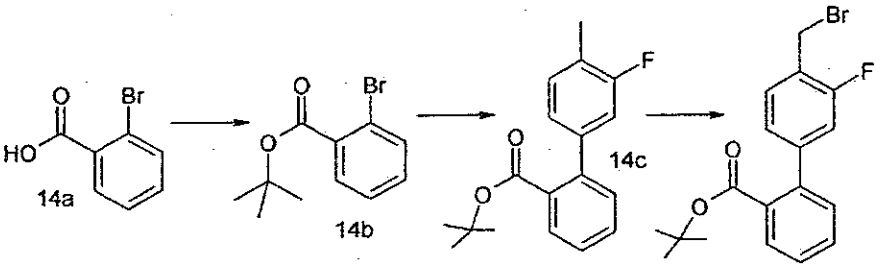
Intermediate (13b) (130 g, 290 mmol, 1.0 eq) was dissolved into 650 mL anhydrous ethanol. To this was slowly added potassium tert-butoxide (98.6 g, 879 mmol, 3.0 eq) and the mixture was heated to reflux for 16 hours. The mixture was then cooled to room temperature, filtered and concentrated. The resulting oil was dissolved into 800 mL EtOAc and washed with 400 mL saturated $NaHCO_3$. The layers were separated and the organic was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated, yielding intermediate (13c) as a brown oil (115.3 g). MS *m/z*: $[M + H^+]$ calcd for $C_{11}H_{20}Br_2N_2O_2Si$, 401.9 found 401.2.

Intermediate (13c) (69.5 g, 174 mmol, 1.0 eq) was dissolved in 600 mL of anhydrous THF and cooled to -78 °C under nitrogen. A 2.5 M solution of n-butyllithium in hexanes (72.9 mL, 180 mmol, 1.05 eq) was added dropwise and the mixture was stirred at -78 °C for 10 minutes. DMF (40 mL, 520 mmol, 3.0 eq) was then added and the mixture was stirred at -78 °C for 15 minutes and was then warmed to room temperature. The reaction was quenched with 10 mL water, diluted with 600 mL EtOAc and was washed with 100mL water, saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The recovered material was purified by silica gel chromatography (15-30% EtOAc:hexanes) to produce intermediate (13d) as a pale yellow oil (45 g).

Intermediate (13d) (105.8 g, 303 mmol, 1.0 eq) was cooled at 0 °C in ice. TFA (300 mL) was added and the mixture was stirred at 0 °C for 15 minutes, then warmed to room temperature. After 90 minutes the mixture was concentrated under reduced pressure and redissolved in 700 mL EtOAc. The organic was washed 2x 600 mL saturated bicarbonate, saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to produce a yellow solid. The material was suspended in 300 mL hexane and stirred at 0 °C for 30 minutes. The material was filtered and the solid was washed with 150 mL of cold hexane to yield the title compound as a pale white solid (61.2 g). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.4 (m, 3H), 4.5 (m, 2H), 5.2 (s, 1H), 9.2 (d, 1H).

PREPARATION 14

4'-Bromomethyl-3'-fluorobiphenyl-2-carboxylic Acid *t*-Butyl Ester



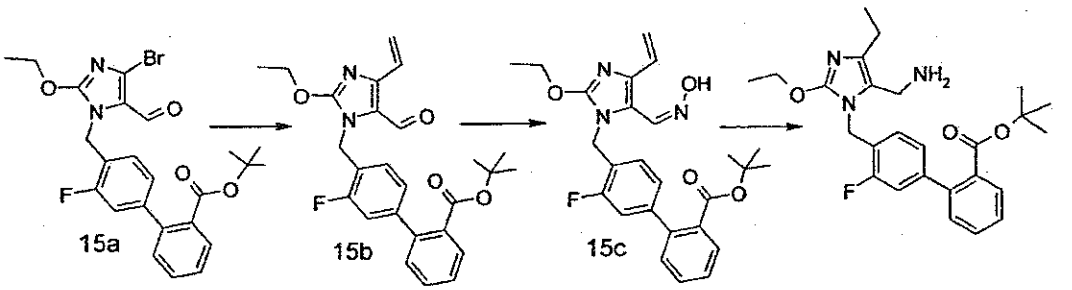
To a solution of 1.0 M DCC in methylene chloride (505 mL, 505 mmol, 1.0 eq) cooled at 0°C was added 2-bromobenzoic acid (14a) (101.6 g, 505 mmol, 1.0 eq) followed by DMAP (5.7 g, 470 mmol, 0.09 eq) and *t*-butyl alcohol (53.2 mL, 560 mmol, 1.1 eq). The mixture was stirred at room temperature for 18 hours and was then filtered. The organic was washed with 400 mL saturated $NaHCO_3$, saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated to produce the crude intermediate (14b) as an oil (141.8 g).

The crude intermediate (14b) (111.2 g, 433 mmol 1.0 eq) and 3-fluoro-4-methylphenylboronicacid (73.2 g, 476 mmol, 1.1 eq) were suspended in isopropyl alcohol (370 mL). A 2.0 M solution of sodium carbonate in water (370 mL) was added and the mixture was degassed under nitrogen. Tetrakis(triphenylphosphine)palladium(0) (5.0 g, 4.3 mmol, 0.01 eq) was then added and the mixture was stirred at 90 °C for 46 hours. The mixture was cooled to room temperature, diluted with 800 mL EtOAc, and the layers were separated. The organic was washed with saturated aqueous NaCl and concentrated under reduced pressure. The recovered oil was purified by silica gel chromatography (4-6% EtOAc:hexanes) to yield intermediate (14c) as an oil (97.4 g).

Intermediate (14c) (89.8 g, 314 mmol, 1.0 eq) was dissolved in CCl_4 (620 mL) and was degassed under nitrogen. NBS (55.8 g, 314 mmol, 1.0 eq) was added, followed by benzoyl peroxide (1.5 g, 6.3 mmol, 0.02 eq) and the mixture was heated at 90 °C under nitrogen for 16 hours. The reaction was cooled in an ice bath, filtered, and concentrated under reduced pressure. The recovered oil was triturated with 150 mL of 3% EtOAc:hexanes. The solution was chilled at -20 °C for 2 hours, then filtered and washed with 200 mL cold 3% EtOAc:hexanes solution to yield the title compound as an off white solid (88.9 g). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.3 (m, 9H), 4.6 (s, 2H), 7.0-7.1 (m, 2H), 7.3 (dd, 1H), 7.4 (m, 1H), 7.5 (m, 1H), 7.8 (dd, 1H).

PREPARATION 15

4'-(5-Aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic Acid *t*-Butyl Ester



4'-(4-Bromo-2-ethoxy-5-formylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid t-butyl ester (15a): 5-Bromo-2-ethoxy-3H-imidazole-4-carbaldehyde (15.0 g, 68.5 mmol), 4'-bromomethyl-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (25.0 g, 68.5 mmol) and potassium carbonate (9.5 g, 68.5 mmol) were dissolved in DMF (958 mL, 12.4 mol) and was stirred at room temperature for 2 hours. The reaction was quenched with water, and the mixture extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified by silica gel chromatography (0-30% EtOAc:hexanes) to yield intermediate (15a) (25g). MS m/z: $[M+H^+]$ calcd for $C_{24}H_{24}BrFN_2O_4$, 503.3; found 503.2. ^{1}H-NMR ($CDCl_3$): 9.57 (1H, s), 7.80 (1H, d), 7.48 (2H, m), 7.27 (1H, s), 7.11 (1H, t), 7.01 (2H, d), 5.47 (2H, s), 4.33 (2H, q), 1.41 (3H, t), 1.24 (9H, s).

4'-(2-Ethoxy-5-formyl-4-vinylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (15b): Intermediate (15a) (11.0 g, 21.8 mmol) was dissolved in 1,2-dimethoxyethane (100 mL, 1 mol). Tetrakis(triphenylphosphine)palladium(0) (252 mg, 218 μmol) was added and the mixture was stirred under nitrogen for 20 minutes. Water (48 mL, 2.6 mol), 2,4,6-trivinylcyclotriboroxane pyridine complex (2.1 g, 8.7 mmol) and potassium carbonate (3.0 g, 21.8 mmol) were then added and the mixture was heated at 90 °C under nitrogen. After 2 hours, the mixture was cooled to room temperature, diluted with EtOAc, washed with water and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The mixture was purified by silica gel chromatography (0-50% EtOAc:hexanes) to yield intermediate (15b) (9.8 g). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{27}FN_2O_4$, 451.2; found 451.0. ^{1}H-NMR ($CDCl_3$): 8.17 (1H, s), 7.79 (1H, d), 7.48 (1H, t), 7.40 (1H, t), 7.28 (1H, s), 7.01(2H, m), 6.86 (1H, t), 6.67 (1H, m), 5.95 (1H, d), 5.41 (2H, s), 5.27 (1H, d), 4.48 (2H, q), 1.38 (3H, t), 1.25 (9H, s).

4'-[2-Ethoxy-5-(hydroxyiminomethyl)-4-vinylimidazol-1-ylmethyl]-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (15c): Intermediate (15b) (19.5 g, 43.4 mmol) was dissolved in pyridine (100 mL, 1 mol). Hydroxylamine hydrochloride (9.0 g, 130 mmol) was added, followed by water (50 mL, 3 mol), and the mixture was stirred at room temperature overnight. Water (100 mL) was then added and the mixture was stirred for 20 minutes. The precipitant was filtered off and dried to yield intermediate (15c) (13.5 g). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{28}FN_3O_4$, 466.2; found 466.4. ^{1}H-NMR ($CDCl_3$): 9.78 (1H, s), 7.81 (1H, d), 7.48 (2H, m), 7.26 (1H, s), 7.0 (4H, m), 6.20 (1H, d), 5.53 (1H, d), 5.50 (2H, s), 4.55 (2H, q), 1.43 (3H, t), 1.25 (9H, s).

Intermediate (15c) (4.0 g, 8.6 mmol) was dissolved in ethanol (250 mL, 4.3 mol) and sulfuric acid (0.50 mL, 9.4 mmol), and subjected to sonication. Once fully dissolved, the mixture was added to 10% Pd/C, Degussa type, wet 50% (0.05:0.45:0.5, palladium:carbon black:water, 3.0 g, 1.4 mmol) in 20 ml of ethanol. The solution was degassed and stirred at room temperature under hydrogen for 5 hours. The palladium was filtered off and the mixture was concentrated to yield the title compound (3.3 g). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{32}FN_3O_3$, 454.3; found 454.2. ^{1}H-NMR ($CDCl_3$): 7.82 (1H, d), 7.50 (1H, t), 7.42 (1H, t) 7.35 (1H, d), 7.27 (1H, d), 7.12 (1H, s), 7.04 (1H, d), 5.34 (1H, b), 4.65 (2H, s), 4.40 (2H, q), 4.12 (2H, q), 2.70 (1H, b), 1.50 (3H, t), 1.28 (9H, s), 1.17 (3H, t).

Alternate Synthesis of Intermediate (15a)

5-Bromo-2-ethoxy-3H-imidazole-4-carbaldehyde (19.8 g, 90.6 mmol), and 4'-bromomethyl-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (33.1 g, 90.6 mmol) were dissolved in DMF (400 mL). The mixture was cooled in an ice bath and potassium carbonate (12.5 g, 90.6 mmol) was added over 5 minutes. The temperature was slowly warmed overnight. The reaction was then quenched with water. The mixture was extracted with 300 mL EtOAc, washed with saturated aqueous NaCl, dried over MgSO4, filtered, and concentrated. The product was purified by silica gel chromatography (0-30% EtOAc:hexanes) to obtain intermediate (15a) as a white solid (34.2 g). MS m/z: $[M+H^+]$ calc'd for $C_{24}H_{24}BrFN_2O_4$, 503.3; found 503.2. ^{1}H NMR ($CDCl_3$) 9.57 (1H, s), 7.80 (1H, d), 7.48 (2H, m), 7.27 (1H, s), 7.11 (1H, t), 7.01 (2H, d), 5.47 (2H, s), 4.33 (2H, q), 1.41 (3H, t), 1.24 (9H, s).

Alternate Synthesis of Title Compound

Intermediate (15c) (4.5 g, 9.7 mmol) was dissolved in acetic acid (100 mL, 2000 mmol) and stirred for 10 minutes at room temperature. Zinc dust (5.9 g, 90.2 mmol) was

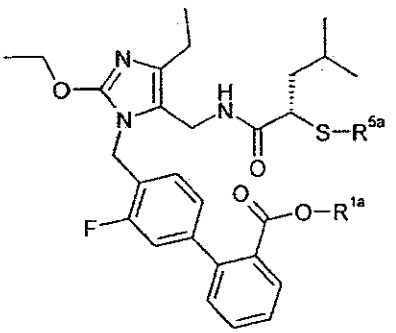
then added and the mixture was stirred for 45 minutes. The zinc was filtered off and the acetic acid was concentrated. The residue was taken up in EtOAc and washed with sodium bicarbonate and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was added to 10% Pd/C, Degussa type, wet 50% (0.05:0.45:0.5, palladium:carbon black:water, 400 mg, 0.2 mmol) in ethanol (200 mL, 3 mol). The mixture was degassed and stirred under hydrogen for 1.5 hours. The palladium was filtered off and the solvent was concentrated to obtain the title compound (4.6 g). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{32}FN_3O_3$, 454.3; found 454.2. ^{1}H-NMR ($CDCl_3$): 7.82 (1H, d), 7.50 (1H, t), 7.42 (1H, t) 7.35 (1H, d), 7.27 (1H, d), 7.12 (1H, s), 7.04 (1H, d), 5.34 (1H, b), 4.65 (2H, s), 4.40 (2H, q), 4.12 (2H, q), 2.70 (1H, b), 1.50 (3H, t), 1.28 (9H, s), 1.17 (3H, t).

Alternate Synthesis of Title Compound

Intermediate (15c) (5.1 g, 11 mmol) was dissolved in acetic acid (100 mL) and sulfuric acid (640 µL, 12 mmol). The mixture was degassed under nitrogen and 10% Pd/C, Degussa type, wet 50% (0.05:0.45:0.5, palladium:carbon black:water, 1.5 g, 723 µmol) was added. The mixture was then degassed under hydrogen at 50 psi on a Parr shaker and shaken at room temperature. After 12 hours, the mixture was filtered and concentrated under reduced pressure. The recovered material was dissolved into 50 mL EtOAc, washed with 50 mL saturated bicarbonate, saturated aqueous NaCl, and evaporated. The material was purified by silica gel chromatography (0-10% MeOH:DCM) to yield the title compound as a clear oil (4.6 g). MS m/z: $[M+H^+]$ calc'd for $C_{26}H_{32}FN_3O_3$, 454.3; found 454.2. ^{1}H NMR ($CDCl_3$) 7.82 (1H, d), 7.50 (1H, t), 7.42 (1H, t) 7.35 (1H, d), 7.27 (1H, d), 7.12 (1H, s), 7.04 (1H, d), 5.34 (1H, b), 4.65 (2H, s), 4.40 (2H, q), 4.12 (2H, q), 2.70 (1H, b), 1.50 (3H, t), 1.28 (9H, s), 1.17 (3H, t).

EXAMPLE 19

4'-{5-[((*S*)-2-Acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid *t*-Butyl Ester (19a; R^{1a} = *t*-butyl; R^{5a} = -C(O)CH_3); 4'-{5-[((*S*)-2-Acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid (19b; R^{1a} = H; R^{5a} = -C(O)CH_3); and 4'-{2-Ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid (19c; R^{1a} = H; R^{5a} = H)



(*S*)-2-Acetylsulfanyl-4-methylpentanoic acid (877 mg, 4.6 mmol) was dissolved in DMF (20 mL, 300 mmol). HATU (1.8 g, 4.6 mmol) and DIPEA (0.8 mL, 4.6 mmol) were added and the mixture was stirred at room temperature for 30 minutes. 4'-(5-Aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (1.9 g, 4.2 mmol) in DMF (20 mL, 300 mmol) with DIPEA (0.8 mL, 4.6 mmol) was added, and the mixture was stirred at room temperature for 2 hours. The reaction was quenched with water, extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. The mixture was purified by silica gel chromatography (0-50% EtOAc:hexanes) to obtain to obtain the acetylsulfanyl ester intermediate (19a) (2.4 g). MS m/z: [M+H^+] calcd for $C_{34}H_{44}FN_3O_5S$, 626.3; found 626.2. ^{1}H-NMR ($CDCl_3$): 7.80 (1H, d), 7.48 (1H, t), 7.40 (1H, t), 7.25 (1H, d), 7.06 (2H, d), 6.88 (1H, t), 6.08 (1H, t), 4.96 (2H, s), 4.38 (2H, q), 4.22 (2H, m), 3.86 (1H, t), 2.50 (2H, q), 2.32 (3H, s), 1.82 (1H, m), 1.64 (1H, m), 1.52 (1H, m), 1.34 (3H, t), 1.26 (9H, s), 1.18 (3H, t), 0.87 (6H, dd).

Intermediate (19a) was dissolved in DCM:TFA (1:1) (5 mL each) and stirred at room temperature for 3 hours, then concentrated and carried forward to provide the acetylsulfanyl acid intermediate (19b). MS m/z: [M+H^+] calcd for $C_{30}H_{36}FN_3O_5S$, 570.2; found 570.4. ^{1}H-NMR (DMSO): 8.64 (1H, b), 7.72 (1H, d), 7.55 (1H, t), 7.44 (1H, t), 7.33

(1H, d), 7.16 (1H, d), 7.07 (1H, d), 6.95 (1H, b), 5.05 (2H, s), 4.35 (2H, d), 4.12 (2H, t), 40.5 (2H, t), 2.26 (3H, s), 1.64 (1H, m), 1.40 (2H, m), 1.28 (3H, t), 1.10 (3H, t), 0.80 (6H, dd).

Intermediate (19b) was dissolved in MeOH (20 ml), and 10N NaOH (2ml) was added. The mixture was stirred at room temperature for 25 minutes under nitrogen before the reaction was quenched with acetic acid and the mixture concentrated. The resulting material was purified by preparative HPLC (10-70%) to obtain the final product (19c) as a TFA salt (1.6 g; 98% pure). MS m/z: $[M+H^+]$ calcd for $C_{28}H_{34}FN_3O_4S$, 528.2; found 528.2. ^{1}H-NMR (DMSO): 8.40 (1H, s), 7.74 (1H, d), 7.57 (1H, t), 7.47 (1H, t), 7.35 (1H, d), 7.18 (1H, d), 7.09 (1H, d), 7.02 (2H, b), 5.11 (2H, s), 4.40 (2H, d), 4.18 (2H, d), 3.28 (1H, q), 2.68 (1H, d), 2.48 (1H, d), 1.58 (2H, m), 1.44 (1H, m), 1.26 (3H, t), 1.14 (3H, t), 0.79 (6H, dd).

Alternate Synthesis of Title Compound (19c)

Alternately, intermediate (19a) was obtained by the following procedure: To a cold solution of 4'-(5-aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (1.2 g, 2.7 mmol) dissolved in DCM (45 mL) cooled with an ice-salt bath (-5 °C) was added *(S)*-2-acetylsulfanyl-4-methylpentanoic acid (chiral purity 97.3% S: 531 mg, 2.8 mmol) in 5 mL of DCM and EDC (535 mg, 2.8 mmol). The mixture was stirred at -5 °C for 1 hour under nitrogen. The reaction was quenched by adding a mixture of 1M H_3PO_4 and saturated aqueous NaCl (1:3; 50 mL), and diluted with DCM (200 mL). After shaking in a separatory funnel, the organic layer was collected and washed with sat $NaHCO_3$. After drying over $MgSO_4$, the organic layer was evaporated to dryness, yielding intermediate (19a) as a pale yellow oil. The crude product (2.1g) was used in next step without further purification. ESMS $[M+H^+]$ calcd for $C_{34}H_{44}FN_3O_5S$, 626.31; found 626.4. Anal. HPLC retention time = 3.62 min; gradient conditions = 25-95% MeCN/H_2O over 5 min. Full deprotection of both the *t*-butyl ester and mercaptoacetyl group by treating with TFA/DCM (2:1), for 1 hour at room temperature and 1M NaOH in MeOH, for 5 minutes at room temperature in two separate steps afforded the final product (19c) as a TFA salt. Its chiral purity was determined to be 97.1% S single isomer by anal. HPLC on chiral stationary phase.

Alternate Synthesis of Title Compound (19c)

4'-(5-Aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (4.0 g, 8.8 mmol), *(S)*-2-acetylsulfanyl-4-methylpentanoic acid

(1.7 g, 8.8 mmol), 4-methylmorpholine (970 μL, 8.82 mmol), and 1-hydroxy-7-azabenzotriazole (1.2 g, 8.8 mmol) were combined in a flask and dissolved in DMF (100 mL, 1.300 mol) and was cooled at 0 °C for 10 minutes. Then EDC (1.6 mL, 8.8 mmol) was added and the mixture was stirred at 0 °C for 1 hour and then at room temperature for 1 hour and 15 minutes. The reaction was quenched with water (100 mL) and extracted with EtOAc (100 mL) and was concentrated. The mixture was purified by column chromatography (0-50% EtOAc:hexanes) to obtain 4.2 g of intermediate (19a). Intermediate (19a) was dissolved in DCM:TFA (10 mL each) and the mixture was stirred at room temperature for 3 hours, and then concentrated. The residue was taken up in EtOAc, washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated to yield 3.7 g of intermediate (19b). Intermediate (19b) was dissolved in 30 mL of MeOH. The solution was degassed, stirred under nitrogen, and cooled at 0 °C. 25 mL of 0.5 M sodium methoxide in MeOH (2 eq.) was added and the mixture was stirred at 0 °C under nitrogen for 20 minutes. The mixture was then acidified with 1N HCl (15 mL). The mixture was concentrated, dissolved in EtOAc, washed with water, dried over $MgSO_4$, filtered, and then concentrated. The product was purified by preparative HPLC 10-70% MeCN:water with 0.5% TFA (70 minute method). The product was dissolved in ~ 4 mL of MeCN, 3 mL of water and 0.5 mL of TFA to be injected on the column. 2 g of the final product (19c) was isolated as 98% pure, 93.6 % ee.

Synthesis of Title Compound (19c) as a HCl Salt

The title compound (19c) was also obtained as an HCl salt as follows. Preparation of ion exchange column: Forty grams of amberlite IRA-900 resin (Aldrich) was suspended in 400 mL of 1M HCl. The mixture was shaken for 60 minutes and the bulk of the supernatant was decanted to afford wet resins, which were then transferred to a 100 mL plastic column. A small amount of sand was added to the top layer of the resin. The column was washed by elution with water (200 mL) and 50% aq. MeCN (200 mL) until the pH of the passed eluant was ~5. The TFA salt of 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoyl-amino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid (945 mg) was dissolved in 50% aq. MeCN (5 mL), and loaded onto the prepared column. The compound was eluted with 50% aq. MeCN under gravity. Fractions were collected in 5 mL volume, and analyzed by HPLC, and LCMS. Fractions having the desired mass were combined and lyophilized, affording the title compound (19c) as a HCl salt (700 mg). Analysis of the ion content of the salt using ion chromatography gave 7.1%

Cl (w/w).

Preparation of the (R) Enantiomer of Title Compound (19c)

The *(R)* enantiomer of the title compound (19c) was obtained by the following procedure.

4'-{5-[(*(R)*-2-Acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (19a'): 4'-(5-Aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (128 mg, 282 μmol), *(R)*-2-acetylsulfanyl-4-methylpentanoic acid (53.7 mg, 282 μmol), 1-hydroxy-7-azabenzotriazole (38.4 mg, 282 μmol), and 4-methylmorpholine (31.0 μL, 282 μmol) were combined and dissolved in DMF (2.5 mL, 32.3 mmol) and cooled at 0 °C for 10 minutes. EDC (50.0 μL, 282 μmol) was added. After 20 minutes, the mixture was warmed to room temperature. The reaction was complete after 90 minutes, as determined by HPLC and LCMS, and water (5 mL) was added. The mixture was extracted 2X with EtOAc, washed with 1N HCl (10 mL), water, and saturated aqueous NaCl, dried over MgSO4, filtered, and concentrated to yield a yellow oil (164 mg). This material was purified by silica gel chromatography (12 g, 0-100% EtOAc:hexanes) to yield a first lot of the acetylsulfanyl ester intermediate (19a') as a colorless oil (46 mg).

4'-(5-Aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (120.0 mg, 265 μmol) and *(R)*-2-acetylsulfanyl-4-methylpentanoic acid (50.3 mg, 264 μmol) were dissolved in methylene chloride (2.0 mL, 31.2 mmol) and cooled at 0 °C for 10 minutes. EDC (46.8 μL, 264 μmol) was added. The mixture was warmed to room temperature over 2 hours. The mixture was then cooled at 0 °C and DIPEA (46.1 μL, 264 μmol) was added. This mixture was stirred at 0 °C for 5 minutes then warmed to room temperature. After 30 minutes, water (5 mL) was added. The mixture was extracted 2X with DCM, washed with saturated aqueous NaCl, dried over MgSO4, filtered, and concentrated to yield a yellow oil (164 mg). This material was purified by silica gel chromatography (12 g, 0-100% EtOAc:hexanes) to provide a second lot of the acetylsulfanyl ester intermediate (19a') as a colorless oil (68 mg).

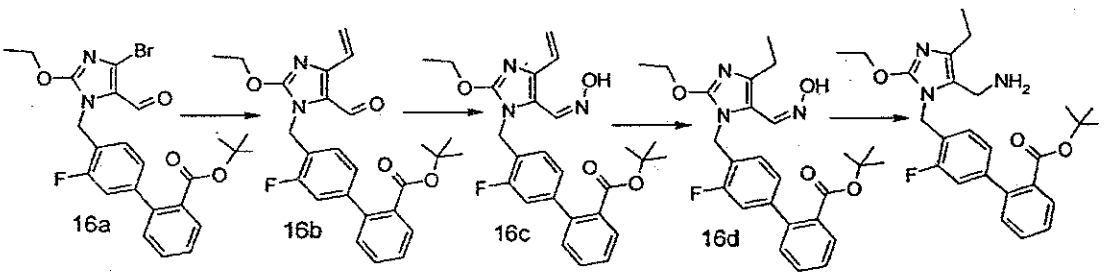
4'-{5-[(*(R)*-2-acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid (19b'): The combined lots of Intermediate (19a') (114 mg, 182 μmol) were dissolved in methylene chloride (2.0 mL, 31 mmol). TFA (2.0 mL, 26 mmol) was added. After 60 minutes, the mixture was concentrated. Sat. bicarbonate (5 mL) was added and the mixture was extracted 3X with

EtOAc, washed with saturated aqueous NaCl, dried over MgSO4, filtered, and concentrated to provide 90 mg of the crude the acetylsulfanyl acid intermediate (19b').

Intermediate (19b') was taken up in MeOH (2.0 mL) and cooled at 0 °C under nitrogen. 0.50 M of Sodium methoxide in MeOH (729 µL, 364 µmol) was added. After 30 minutes, the mixture was acidified with 6N HCl (90 µL) and concentrated. The product was purified by preparative HPLC to yield 4'-{2-ethoxy-4-ethyl-5-[((*R*)-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid as a white solid TFA salt (59.4 mg; 96.0% purity). The product was analyzed for chiral purity and found to be 99% ee. MS m/z: $[M+H^+]$ calcd for $C_{28}H_{34}FN_3O_4S$, 528.23; found 528.2.

PREPARATION 16

4'-(5-Aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic Acid *t*-Butyl Ester



4'-(4-Bromo-2-ethoxy-5-formylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (16a): 5-Bromo-2-ethoxy-3H-imidazole-4-carbaldehyde (6.0 g, 27.4 mmol), 4'-bromomethyl-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (10.0 g, 27.4 mmol), and potassium carbonate (3.8 g, 27.4 mmol) were dissolved in DMF (383 mL, 4950 mmol) and the mixture was stirred at room temperature for 2 hours. The reaction was quenched with water, and the mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated. The resulting material was purified by silica gel chromatography (0-30% EtOAc:hexanes) to yield intermediate (16a) (9.5 g). MS m/z: $[M+H^+]$ calcd for $C_{24}H_{24}BrFN_2O_4$, 503.3; found 503.2. ^{1}H-NMR ($CDCl_3$): 9.57 (1H, s), 7.80 (1H, d), 7.48 (2H, m), 7.27 (1H, s), 7.11 (1H, t), 7.01 (2H, d), 5.47 (2H, s), 4.33 (2H, q), 1.41 (3H, t), 1.24 (9H, s).

4'-(2-Ethoxy-5-formyl-4-vinylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (16b): Intermediate (16a) (9.5 g, 18.9 mmol), tetrakis(triphenylphosphine) palladium(0) (1.0 g, 0.9 mmol), (2-ethenyl)tri-n-butyltin (11.0 mL, 37.8 mmol) were

dissolved in DMF (70 mL, 900 mmol), and heated at 90 °C for 1.5 hours. The mixture was cooled to room temperature and 300 mL of EtOAc was added. The organic layer was washed using a 20% potassium fluoride solution (2 x 100 mL) and saturated aqueous NaCl. The resulting material was purified by silica gel chromatography (0-60% EtOAc:hexanes) to yield intermediate (16b) (7.7 g). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{27}FN_2O_4$, 451.2; found 451.0. ^{1}H-NMR ($CDCl_3$): 8.17 (1H, s), 7.79 (1H, d), 7.48 (1H, t), 7.40 (1H, t), 7.28 (1H, s), 7.01(2H, m), 6.86 (1H, t), 6.67 (1H, m), 5.95 (1H, d), 5.41 (2H, s), 5.27 (1H, d), 4.48 (2H, q), 1.38 (3H, t), 1.25 (9H, s).

4'-[2-Ethoxy-5-(hydroxyiminomethyl)-4-vinylimidazol-1-ylmethyl]-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (16c): Intermediate (16b) (7.7 g, 17.2 mmol) was dissolved in pyridine (40 mL, 500 mmol). Hydroxylamine hydrochloride (3.6 g, 51.5 mmol) was added, followed by the addition of water (20 mL, 1 mol). The mixture was stirred at room temperature overnight. Water (50 ml) was added and the mixture was stirred for 20 minutes. The precipitant was filtered off and dried to yield intermediate (16c) (7.8 g). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{28}FN_3O_4$, 466.2; found 466.4. ^{1}H-NMR ($CDCl_3$): 9.78 (1H, s), 7.81 (1H, d), 7.48 (2H, m), 7.26 (1H, s), 7.0 (4H, m), 6.20 (1H, d), 5.53 (1H, d), 5.50 (2H, s), 4.55 (2H, q), 1.43 (3H, t), 1.25 (9H, s).

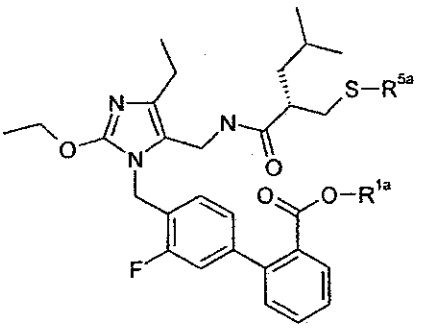
4'-[2-Ethoxy-4-ethyl-5-(hydroxyiminomethyl)imidazol-1-ylmethyl]-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (16d): Intermediate (16c) (7.8 g, 16.6 mmol) was dissolved in ethanol (420 mL, 7.2 mol). Pearlman's Catalyst, wet (0.1:0.4:0.5, palladium hydroxide:carbon black:water, 6 g, 4 mmol) was added. The mixture was degassed and stirred under hydrogen for 2 hours. The palladium was filtered off and the solvent was concentrated to yield intermediate (16d) (7.7 g). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{30}FN_3O_4$, 468.2; found 468.4.

Intermediate (16d) (7.9 g, 16.8 mmol), $NaBH_3CN$ (4.8 g, 75.7 mmol) and ammonium acetate (2.9 g, 37.0 mmol) were dissolved in MeOH. The mixture was cooled to 0 °C and stirred for 15 minutes before titanium(III) chloride (7.8 g, 50.4 mmol) was added. The mixture was stirred at 0 °C for 10 minutes then warmed to room temperature and stirred for 4 hours. Ammonium hydroxide (75 mL) was added to quench the reaction and the mixture was stirred at room temperature overnight. 75 ml of saturated sodium bicarbonate was then added. The resulting mixture was extracted 4 times with DCM, dried over $MgSO_4$, filtered, and concentrated. The resulting material was purified by silica gel chromatography (0-10% MeOH in DCM) to obtain the title compound (4.7 g). MS m/z:

[M+H$^+$] calcd for $C_{26}H_{32}FN_3O_3$, 454.3; found 454.4. ^{1}H-NMR ($CDCl_3$): 7.82 (1H, d), 7.50 (1H, t), 7.42 (1H, t) 7.35 (1H, d), 7.27 (1H, d), 7.12 (1H, s), 7.04 (1H, d), 5.34 (1H, b), 4.65 (2H, s), 4.40 (2H, q), 4.12 (2H, q), 2.70 (1H, b), 1.50 (3H, t), 1.28 (9H, s), 1.17 (3H, t).

EXAMPLE 20

4'-{5-[((*S*)-2-Acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid *t*-Butyl Ester (20a; R^{1a} = *t*-butyl; R^{5a} = -C(O)CH_3); 4'-{5-[((*S*)-2-Acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid (20b; R^{1a} = H; R^{5a} = -C(O)CH_3); 4'-{2-Ethoxy-4-ethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid (20c; R^{1a}=H; R^{5a}=H)

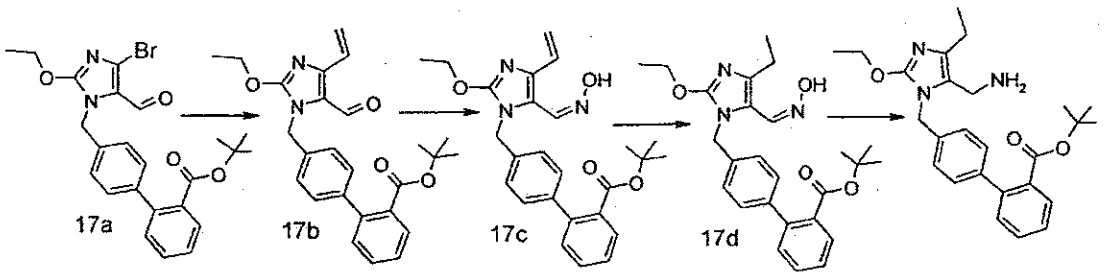


(S)-2-Acetylsulfanylmethyl-4-methylpentanoic acid (2 g, 9.7 mmol) was dissolved in DMF (100 mL, 1000 mmol). HATU (3.7 g, 9.7 mmol) and DIPEA (1.5 mL, 8.8 mmol) were added and the mixture was stirred at room temperature for 20 minutes. 4'-(5-Aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (4.0 g, 8.8 mmol) in DMF (20 mL, 200 mmol) with DIPEA (1.5 mL, 8.8 mmol) was added and the mixture was stirred at room temperature overnight. The reaction was quenched with water, and the mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to yield the acetylsulfanyl ester intermediate (20a). This intermediate was taken up in DCM:TFA (4 mL each), stirred at room temperature for 4 hours, and then concentrated to yield the acetylsulfanyl acid intermediate (20b). This intermediate was dissolved in 1:1 MeOH:1N NaOH (4 mL each) and stirred at room temperature under nitrogen for 1 hour before the reaction was quenched with acetic acid and the mixture concentrated. The residue was purified by preparative HPLC (10-70% MeCN in water w/ 0.05% TFA) to obtain the final product (20c) (2.8 g; 98% pure). MS m/z: [M+H$^+$] calcd for $C_{29}H_{36}FN_3O_4S$, 542.2; found 542.4. ^{1}H-NMR

(DMSO): 8.39 (1H, s), 7.75 (1H, d), 7.58 (1H, t), 7.45 (1H, t), 7.34 (1H, d), 7.19 (1H, d), 7.10 (2H, m), 5.16 (2H, s), 4.43 (2H, m), 4.18 (2H, m), 2.58 (2H, m), 2.41 (1H, m), 2.32 (2H, m), 2.10 (1H, t), 1.24 (8H, m), 0.78 (6H, dd).

PREPARATION 17

4'-(5-Aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-biphenyl-2-carboxylic Acid *t*-Butyl Ester



4'-(4-Bromo-2-ethoxy-5-formylimidazol-1-ylmethyl)biphenyl-2-carboxylic acid *t*-butyl ester (17a): 5-Bromo-2-ethoxy-3H-imidazole-4-carbaldehyde (3.0 g, 13.7 mmol), 4'-bromomethylbiphenyl-2-carboxylic acid *t*-butyl ester (4.8 g, 13.7 mmol), and potassium carbonate (1.9 g, 13.7 mmol), were dissolved in DMF (60 mL, 780 mmol), and the mixture was stirred at room temperature overnight. The reaction was quenched with water, and the mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated. The resulting material was purified by silica gel chromatography (0-30% EtOAc:hexanes) to yield intermediate (17a) (5.6 g). MS m/z: $[M+H^+]$ calcd for $C_{24}H_{25}BrN_2O_4$, 485.1; found 485.3. ^{1}H-NMR ($CDCl_3$): 9.58 (1H, s), 7.80 (1H, d), 7.50 (1H, t), 7.40 (1H, t), 7.30 (5H, m), 5.42 (2H, s), 4.57 (2H, q), 1.46 (3H, t), 1.18 (9H, s).

4'-(2-Ethoxy-5-formyl-4-vinylimidazol-1-ylmethyl)biphenyl-2-carboxylic acid *t*-butyl ester (17b): Intermediate (17a) (5.6 g, 11.5 mmol), tetrakis(triphenylphosphine) palladium(0) (2.1 g, 1.8 mmol), and (2-ethenyl)tri-n-butyltin (13.5 mL, 46.2 mmol) were dissolved in DMF (70 mL, 900 mmol), and heated at 90 °C for 1.5 hours. The mixture was cooled to room temperature and 300 mL of EtOAc was added. The organic layer was washed using a 20% potassium fluoride solution (2 x 100 mL) and saturated aqueous NaCl. The resulting material was purified by silica gel chromatography (0-60% EtOAc:hexanes) to yield intermediate (17b) (4.3 g). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{28}N_2O_4$, 433.2; found 433.4.

4'-[2-Ethoxy-5-(hydroxyiminomethyl)-4-vinylimidazol-1-ylmethyl]biphenyl-2-

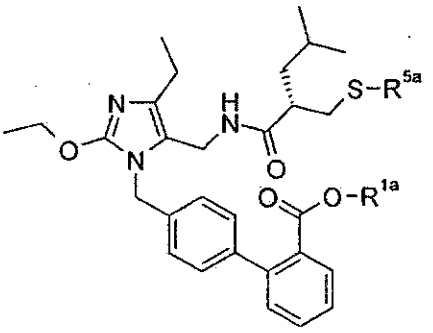
carboxylic acid *t*-butyl ester (17c): Intermediate (17b) (4.3 g, 10 mmol) was dissolved in pyridine (40 mL, 500 mmol). Hydroxylamine hydrochloride (1.7 g, 25 mmol) was added, followed by the addition of water (20 mL, 1000 mmol). The mixture was stirred at room temperature overnight. Water (30 mL) was added and the mixture was stirred for 20 minutes. The precipitant was filtered off and dried to yield intermediate (17c) (3.5 g). MS m/z: [M+H+] calcd for $C_{26}H_{29}N_3O_4$, 448.2; found 448.3.

4'-[2-Ethoxy-4-ethyl-5-(hydroxyiminomethyl)imidazol-1-ylmethyl]biphenyl-2-carboxylic acid *t*-butyl ester (17d): Intermediate (17c) (3.5 g, 7.7 mmol) was dissolved in ethanol (100 mL, 2 mol). Pearlman's Catalyst, wet (0.1:0.4:0.5, palladium hydroxide:carbon black:water, 660 mg) was added. The mixture was degassed and stirred at room temperature under hydrogen for 3 hours. The palladium was filtered off and the solute was concentrated to yield intermediate (17d) (3.3 g). MS m/z: [M+H+] calcd for $C_{26}H_{31}N_3O_4$, 450.2; found 450.3.

Intermediate (17d) (3.5 g, 7.7 mmol), $NaBH_3CN$ (1.9 g, 30.5 mmol) and ammonium acetate (1150 mg, 14.9 mmol) were dissolved in MeOH (30 mL, 700 mmol). The mixture was cooled at 0 °C and stirred for 15 minutes before titanium(III) chloride (3.1 g, 20.3 mmol) was added. The mixture was stirred at 0 °C for 10 minutes then warmed to room temperature and stirred for 3 hours. Ammonium hydroxide (75 ml) was added and the mixture was stirred at room temperature overnight. 75 ml of saturated sodium bicarbonate was then added. The resulting mixture was extracted with DCM, and the organic layer was dried over $MgSO_4$, filtered, and concentrated to obtain the title compound (2.5 g). MS m/z: [M+H+] calcd for $C_{26}H_{33}N_3O_3$, 436.3; found 436.6.

EXAMPLE 21

4'-{5-[((*S*)-2-Acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}biphenyl-2-carboxylic Acid *t*-Butyl Ester (21a; R^{1a} = *t*-butyl; R^{5a} = -C(O)CH_3); 4'-{5-[((*S*)-2-Acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}biphenyl-2-carboxylic Acid (21b; R^{1a} = H; R^{5a} = -C(O)CH_3); 4'-{2-Ethoxy-4-ethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino) methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic Acid (21c; R^{1a}=H; R^{5a}=H)

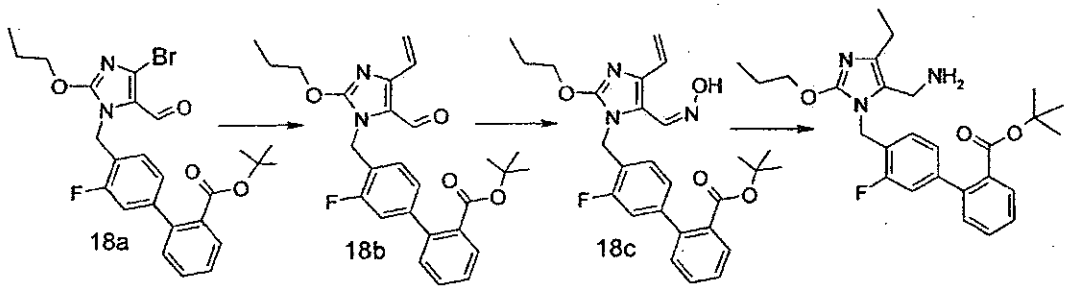


(S)-2-Acetylsulfanylmethyl-4-methylpentanoic acid (1.0 g, 5.1 mmol) was dissolved in DMF (50 mL, 600 mmol). HATU (1.8 g, 4.8 mmol) and DIPEA (800 µL, 4.6 mmol) were added and the mixture was stirred at room temperature for 20 minutes. 4'-(5-Aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)biphenyl-2-carboxylic acid *t*-butyl ester (2.0 g, 4.6 mmol) in DMF (25 mL, 300 mmol) with DIPEA (800 µL, 4.6 mmol) was added and the mixture was stirred at room temperature overnight. The reaction was quenched with water, and the mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to yield the acetylsulfanyl ester intermediate (21a). This intermediate was taken up in DCM:TFA (4 mL each), stirred at room temperature for 4 hours, then concentrated to yield the acetylsulfanyl acid intermediate (21b). This intermediate was dissolved in 1:1 MeOH:1N NaOH (5 mL each) and stirred at room temperature under nitrogen for 1 hour before the reaction was quenched with acetic acid and the mixture concentrated. The residue was purified by preparative HPLC (10-70% MeCN in water w/ 0.05% TFA) to obtain the final product (20c) (822 mg). MS m/z: [M+H+] calcd for $C_{29}H_{37}N_3O_4S$, 524.6; found 524.4. ^{1}H-NMR (DMSO): 8.33 (1H, s), 7.65 (1H, d), 7.49 (1H, t), 7.38 (1H, t), 7.24 (3H, m), 7.16 (2H, d), 5.05 (2H, s), 4.41 (2H, d), 4.10 (2H, m), 2.41 (3H, m), 2.29 (1H, m), 2.06 (1H, t), 1.20 (8H, m), 0.74 (6H, dd).

PREPARATION 18

4'-(5-Aminomethyl-2-propoxy-4-ethylimidazol-1-ylmethyl)

-3'-fluorobiphenyl-2-carboxylic acid *t*-Butyl Ester



4'-(4-Bromo-2-propoxy-5-formylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid t-butyl ester (18a): Bromo-2-propoxy-3H-imidazole-4-carbaldehyde (4.5 g, 19.3 mmol), 4'-bromomethyl-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (7.1 g, 19.5 mmol) and potassium carbonate (8.0 g, 57.9 mmol) were dissolved in DMF (100 mL). The solution was stirred at room temperature overnight. The reaction was quenched with water, extracted with 200 mL EtOAc, washed with 4 x 100 mL saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield intermediate (18a) as a colorless oil (10 g), which was used without further purification. Anal. HPLC retention time = 5.0 minutes. Gradient conditions: 25% solvent B/75% solvent A to 95% solvent B/5% solvent A over 6 minutes. MS m/z: $[M+H^+]$ calcd for $C_{25}H_{26}BrFN_2O_4$, 517.11; found 555.2. $[M+K^+]$ ^{1}H-NMR ($CDCl_3$) 9.55 (1H, s), 7.77 (1H, d), 7.46 (2H, m), 7.41 (2H, m), 7.12 (1H, t), 6.99 (2H, d), 5.45 (2H, s), 1.78 (2H, m), 1.28 (2H, m), 1.24 (9H, s), 0.98 (3H, s).

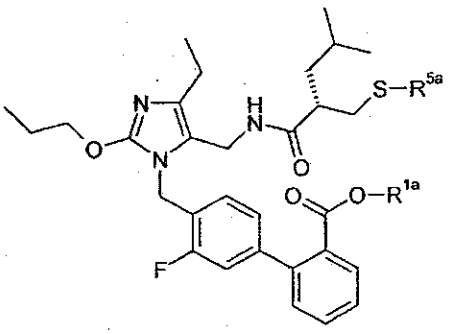
4'-(2-Propoxy-5-formyl-4-vinylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (18b): Intermediate (18a) (10.0 g, 19.3 mmol) was dissolved in DMF (100 mL). Tetrakis(triphenylphosphine)palladium(0) (400 mg, 0.4 mmol) was added, followed by (2-ethenyl)tri-n-butyltin (8.5 mL, 29.0 mmol). The reaction vessel was fitted with a reflux condenser and was heated to 110 °C with stirring for 1 hour, under nitrogen. The mixture was cooled and 200 mL EtOAc was added. The organic layer was washed with a 20% solution of potassium fluoride (2 x 50 mL) followed by saturated aqueous NaCl (100 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting material was purified by silica gel chromatography (0-80% EtOAc:hexanes) to yield intermediate (18b) as a colorless oil (7.2 g). Anal. HPLC retention time = 4.9 minutes. Gradient conditions: 25% solvent B/75% solvent A to 95% solvent B/5% solvent A over 6 minutes. MS m/z: $[M+H^+]$ calcd for $C_{27}H_{29}FN_2O_4$, 465.22; found 465.6.

4'-[2-Propoxy-5-(hydroxyiminomethyl)-4-vinylimidazol-1-ylmethyl]-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (18c): Intermediate (18b) (7.2 g, 15.5 mmol) was dissolved in pyridine (30 mL). Hydroxylamine hydrochloride (4.0 g, 57.9 mmol) was added followed by water (20 mL) and the mixture was stirred at 40 °C for 2 hours. The reaction was quenched with water, extracted with 200 mL EtOAc, washed with 3 x 100mL 1M phosphoric acid, 1 x 100mL saturated sodium bicarbonate solution, and 2 x 100 mL saturated aqueous NaCl, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (0-80% EtOAc:hexanes) to yield intermediate (18c) as a white solid (7.4 g). Anal. HPLC retention time = 4.9 minutes. Gradient conditions: 25% solvent B/75% solvent A to 95% solvent B/5% solvent A over 6 minutes. MS m/z: $[M+H^+]$ calcd for $C_{27}H_{30}FN_3O_4$, 480.23; found 480.4. ^{1}H-NMR (DMSO-d_6) 10.99 (1H, s), 8.21 (1H, s), 7.67 (1H, d), 7.54 (1H, m), 7.44 (1H, s), 7.34 (1H, m), 7.11 (2H, m), 6.81 (2H, m), 5.73 (1H, d), 5.36 (2H, s), 5.10 (1H, d), 1.66 (2H, m), 1.13 (9H, s), 0.85 (4H, m).

Intermediate (18c) (7.4 g, 15.0 mmol) was dissolved in EtOAc (200 mL), followed by the addition of sulfuric acid (1.50 mL). 10% Pd/C, Degussa type, wet 50% (0.05:0.45:0.5, palladium:carbon black:water, 16.0 g) was then added and the mixture was degassed with nitrogen and then stirred at room temperature under hydrogen for 2 hours. The mixture was then degassed with nitrogen, the palladium was filtered off under nitrogen and the resulting material was concentrated to obtain the title compound as a pale yellow oil (6.5 g). Anal. HPLC retention time = 3.2 minutes. Gradient conditions: 10% solvent B/90% solvent A to 90% solvent B/10% solvent A over 6 minutes. MS m/z: $[M+H^+]$ calcd for $C_{27}H_{34}FN_3O_3$, 468.27; found 468.4. ^{1}H-NMR (DMSO-d_6) 7.67 (1H, d), 7.54 (1H, t), 7.33 (1H, t) 7.10 (1H, d), 7.03 (2H, d), 6.87 (1H, s), 5.08 (1H, s), 4.12 (2H, m), 4.00 (2H, s), 3.99 (2H, s), 3.48 (2H, s), 2.32 (2H, m), 1.62 (3H, m), 1.14 (9H, s), 0.85(3H, t).

EXAMPLE 22

4'-{5-[((*S*)-2-Acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-4-ethyl-2-propoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid *t*-Butyl Ester (22a; R^{1a} = *t*-butyl; R^{5a} = -C(O)CH_3); 4'-{5-[((*S*)-2-Acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-4-ethyl-2-propoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid (22b; R^{1a} = H; R^{5a} = -C(O)CH_3); 4'-{4-Ethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid • $C_2HF_3O_2$ (22c; R^{1a}=H; R^{5a}=H)



HATU (3.1 g, 8.2 mmol) was added to a solution of *(S)*-2-acetylsulfanylmethyl-4-methylpentanoic acid (1.7 g, 8.2 mmol) in DMF (60 mL), and stirred for 5 minutes at room temperature. 4'-(5-Aminomethyl-2-propoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (3.5 g, 7.5 mmol) was added as a DMF solution (5 mL), followed by the addition of DIPEA (2.6 mL, 15.0 mmol). The mixture was stirred for 15 minutes, then 200 mL EtOAc was added. The organic layer was washed with 4 x 100 mL saturated aqueous NaCl, dried over $MgSO_4$ for 10 minutes, filtered and evacuated to dryness *in vacuo*. The material was then concentrated and the resulting crude solid was purified by silica gel chromatography (EtOAc/hexanes, 10-70% EtOAc) to yield the acetylsulfanyl ester intermediate (22a). Anal. HPLC retention time = 4.4 minutes. Gradient conditions: 10% solvent B/90% solvent A to 90% solvent B/10% solvent A over 6 minutes. MS m/z: [M+H$^+$] calcd for $C_{36}H_{48}FN_3O_5S$, 654.34; found 654.5.

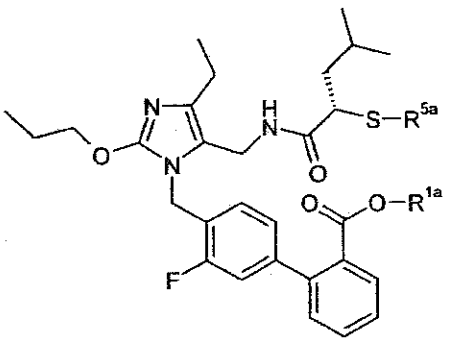
4N HCl in dioxane (10mL) was added to intermediate (22a), and the mixture was stirred overnight at room temperature. Volatiles were removed *in vacuo* to yield the acetylsulfanyl acid intermediate (22b) as an orange oil, which was used without further purification. Anal. HPLC retention time = 3.9 minutes. Gradient conditions: 10% solvent B/90% solvent A to 90% solvent B/10% solvent A over 6 minutes. MS m/z: [M+H$^+$] calcd for $C_{32}H_{40}FN_3O_5S$, 598.28; found 598.5.

10 N NaOH (2.0 mL) was added to a methanolic (50 mL) solution of intermediate (22b). The solution was stirred at room temperature for 30 minutes under nitrogen after which acetic acid (2.0 mL) was added. The solution was concentrated and purified by preparative HPLC (reverse phase): gradient of 20-65% (over 60 minutes); flow rate 15mL/min; detection at 280 nm. Pure fractions were combined and lyophilized in 50/50 water/MeCN to give the final product (22c) as a white solid TFA salt (1.4 g). Anal. HPLC retention time = 3.9 minutes. Gradient conditions: 10% solvent B/90% solvent A to 90%

solvent B/10% solvent A over 6 minutes. MS m/z: [M+H$^+$] calcd for $C_{30}H_{38}FN_3O_4S$, 556.26; found 556.2. ^{1}H-NMR (d_4-MeOH) 8.57 (1H, t), 7.86 (1H, d), 7.55 (1H, t), 7.46 (1H, t) 7.32 (1H, d), 7.22 (2H, t), 7.12 (2H, m), 5.32 (1H, s), 4.42 (2H, m), 4.3-4.4 (1H, m), 2.73 (2H, m), 2.55 (2H, m), 2.42 (1H, m), 1.80 (2H, m), 1.48 (2H, m), 1.26 (2H, m), 0.94 (3H, t), 0.86 (3H, m).

EXAMPLE 23

4'-{5-[((*S*)-2-Acetylsulfanyl-4-methylpentanoylamino)methyl]-4-ethyl-2-propoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid *t*-Butyl Ester (23a; R^{1a} = *t*-butyl; R^{5a} = -C(O)CH_3); 4'-{5-[((*S*)-2-Acetylsulfanyl-4-methylpentanoylamino)methyl]-4-ethyl-2-propoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid (23b; R^{1a} = H; R^{5a} = -C(O)CH_3); 4'-{4-Ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid • $C_2HF_3O_2$ (23c; R^{1a}=H; R^{5a}=H)



HATU (4.3 g, 11.3 mmol) was added to a solution of *(S)*-2-acetylsulfanyl-4-methylpentanoic acid (2.2 g, 11.3 mmol) in DMF (80 mL), and stirred for 5 minutes at room temperature. 4'-(5-Aminomethyl-2-propoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (4.8 g, 10.3 mmol) was added as a DMF solution (5 mL) followed by DIPEA (3.6 mL, 20.5 mmol). The mixture was stirred for 15 minutes, then 200 mL EtOAc was added. The organic layer was washed with 4 x 100 mL saturated aqueous NaCl, dried over $MgSO_4$ for 10 minutes, filtered and evacuated to dryness. The mixture was concentrated and the resulting crude solid was purified by flash chromatography (EtOAc/hexanes, 10-70% EtOAc) to yield the acetylsulfanyl ester intermediate (23a). Anal. HPLC retention time = 3.4 minutes. Gradient conditions: 25% solvent B/75% solvent A to 95% solvent B/5% solvent A over 6 minutes. MS m/z: [M+H$^+$] calcd for $C_{35}H_{46}FN_3O_5S$, 640.32; found 640.0.

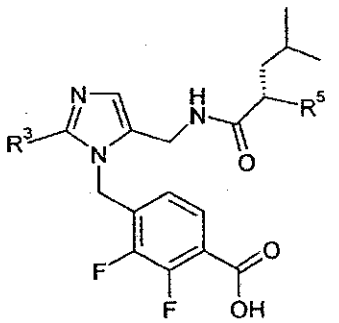
4N HCl in dioxane (10mL) was added to intermediate (23a), and the mixture was

stirred overnight at room temperature. Volatiles were removed *in vacuo* to yield the acetylsulfanyl acid intermediate (23b) as an orange oil, which was used without further purification. Anal. HPLC retention time = 2.9 minutes. Gradient conditions: 25% solvent B/75% solvent A to 95% solvent B/5% solvent A over 6 minutes. MS m/z: $[M+H^+]$ calcd for $C_{31}H_{38}FN_3O_5S$, 584.26; found 584.0.

10 N NaOH (2.0 mL) was added to a methanolic (50 mL) solution of intermediate (23b). The solution was stirred at room temperature for 30 minutes under nitrogen after which acetic acid (2.0 mL) was added. The solution was concentrated and purified by preparative HPLC (reverse phase): gradient of 20-65% (over 60 minutes); flow rate 15mL/min; detection at 280 nm. Pure fractions were combined and lyophilized in 50/50 water/MeCN to give the final product (23c) as a white solid TFA salt (1.0 g). Anal. HPLC retention time = 3.9 minutes. Gradient conditions: 10% solvent B/90% solvent A to 90% solvent B/10% solvent A over 6 minutes. MS m/z: $[M+H^+]$ calcd for $C_{29}H_{36}FN_3O_4S$, 542.25; found 542.6. ^{1}H-NMR (d_4-MeOH) 8.53 (1H, t), 7.86 (1H, d), 7.56 (1H, t), 7.46 (1H, t) 7.32 (1H, d), 7.20 (2H, t), 7.12 (2H, m), 5.29 (1H, s), 4.42 (2H, m), 4.3-4.4 (1H, m), 2.73 (2H, m), 2.55 (2H, m), 1.80 (2H, m), 1.48 (2H, m), 1.26 (2H, m), 0.94 (3H, t), 0.86 (3H, m).

EXAMPLE 24

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 24-1 to 24-3, having the following formula, were also prepared:



Ex.	R^3	R^5
24-1	-O-$(CH_2)_2CH_3$	-SH
24-2	-O-CH_2CH_3	-CH_2SH
24-3	-O-$(CH_2)_2CH_3$	-CH_2SH

(24-1) 2,3-difluoro-4-{5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}benzoic acid. MS m/z: $[M+H^+]$ calcd for $C_{21}H_{27}F_2N_3O_4S$,

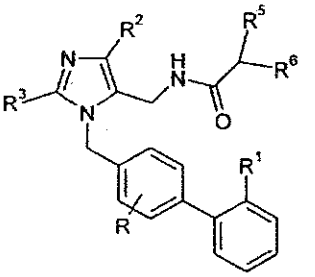
456.17; found 456.2.

(24-2) 4-{2-ethoxy-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2,3-difluorobenzoic acid. MS m/z: [M+H$^+$] calcd for $C_{21}H_{27}F_2N_3O_4S$, 456.17; found 456.2.

(24-3) 2,3-difluoro-4-{5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}benzoic acid. MS m/z: [M+H$^+$] calcd for $C_{22}H_{29}F_2N_3O_4S$, 470.18; found 470.4.

EXAMPLE 25

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 25-1 to 25-70 having the following formula where one or two R groups are optionally present, were also prepared.



Ex.	R	R^1	R^2	R^3	R^5	R^6
25-1	-	-COOH	H	-O-$(CH_2)_2CH_3$	-CH_2SH	-CH_2-$CH(CH_3)_2$
25-2	-	-COOH	H	-O-CH_2CH_3	-CH_2SH	-CH_2-$CH(CH_3)_2$
25-3	-	-COOH	-CH_2CH_3	-O-$(CH_2)_2CH_3$	-CH_2SH	-CH_2-$CH(CH_3)_2$
25-4	-	-COOH	-CH_2CH_3	-O-$(CH_2)_2CH_3$	-SH	-CH_2-$CH(CH_3)_2$
25-5	-	-COOH	-CH_2CH_3	O-CH_2CH_3	-SH	-CH_2-$CH(CH_3)_2$
25-6	-	-SO_2-NH-C(O)CH_3	H	-O-$(CH_2)_2CH_3$	-CH_2SH	-CH_2-$CH(CH_3)_2$
25-7	-	-SO_2-NH-C(O)CH_3	-CH_2CH_3	-O-$(CH_2)_2CH_3$	-CH_2SH	-CH_2-$CH(CH_3)_2$
25-8	-	-SO_2-NHC(O)-CH_2CH_3	H	-O-$(CH_2)_2CH_3$	-CH_2SH	-CH_2-$CH(CH_3)_2$
25-9	2'-F	-COOH	-CH_2CH_3	-O-$(CH_2)_2CH_3$	-SH	-CH_2-$CH(CH_3)_2$
25-10	2'-F	-COOH	-CH_2CH_3	-O-$(CH_2)_2CH_3$	-CH_2SH	-CH_2-$CH(CH_3)_2$
25-11	2'-F	-COOH	-CH_2CH_3	-O-$(CH_2)_2CH_3$	-SH	-CH_2-$CH(CH_3)_2$
25-12	2'-F	-COOH	-CH_2CH_3	-O-$(CH_2)_2CH_3$	-CH_2SH	-CH_2-$CH(CH_3)_2$

Ex.	R	R^1	R^2	R^3	R^5	R^6
25-13	2'-Cl	-COOH	$-CH_2CH_3$	$-O-(CH_2)_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-14	3'-Cl	-COOH	$-CH_2CH_3$	$-O-(CH_2)_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-15	-	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-CH_2-SC(O)CH_3$	$-CH_2-CH(CH_3)_2$
25-16	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-SC(O)-CH_3$	$-CH_2-CH(CH_3)_2$
25-17	2'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-18	2'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-19	3'-F	-COOH	$-CH_2CH_3$	$-O-(CH_2)_2CH_3$	$-SC(O)-CH_3$	$-CH_2-CH(CH_3)_2$
25-20	3'-F	-COOH	$-CH_2CH_3$	$-OCH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-21	3'-F	-COOH	$-CH_2CH_3$	$-OCH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-22	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-SC(O)-CH_3$	$-CH_2-CH(CH_3)_2$
25-23	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-CH_2S-C(O)CH_3$	$-CH_2-CH(CH_3)_2$
25-24	-	-COOH	cyclo-propyl	$-O-(CH_2)_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-25	-	-COOH	cyclo-propyl	$-O-(CH_2)_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-26	-	-COOH	cyclo-propyl	$-O-CH_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-27	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2$-cyclo-propyl
25-28	3'-F	-COOH	cyclo-propyl	$-O-(CH_2)_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-29	3'-F	$-NHSO_2CF_3$	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-30	-	$-SO_2NH-C(O)CH_3$	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-31	3-F	$-SO_2NH-C(O)CH_3$	$-CH_2CH_3$	$-OCH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-32	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-(CH_2)_2CH_3$
25-33	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-34	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2C(CH_3)_3$
25-35	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SC(O)-phenyl	$-CH_2-CH(CH_3)_2$
25-36	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-SC(O)-CH_2-$morpholine	$-CH_2-CH(CH_3)_2$
25-37	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-SC(O)-(CH_2)_2-$morpholine	$-CH_2-CH(CH_3)_2$

Ex.	R	R^1	R^2	R^3	R^5	R^6
25-38	-	-COOH	$-CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-39	-	-COOH	$-CH_3$	$-O-CH_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-40	-	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2CH_3$
25-41	-	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH(CH_3)-CH_2CH_3$
25-42	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-SC(O)-CH_2CH_3$	$-CH_2-CH(CH_3)_2$
25-43	3'-F	-COOH	$-CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-44	3'-F	-COOH	$-CH_3$	$-O-CH_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-45	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2$-cyclo-propyl
25-46	-	-COOH	cyclo-propyl	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-47	3'-F	-COOH	$-O-CH_3$	$-(CH_2)_3CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-48	3'-F	-COOH	$-O-CH_3$	$-(CH_2)_3CH$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-49	3'-F	-COOH	$-O-CH_3$	$-(CH_2)_3CH$	-SH	$-CH(CH_3)-CH_2CH_3$
25-50	2'-F	-COOH	-Cl	$-(CH_2)_3CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-51	3'-F	-COOH	cyclo-propyl	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-52	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-CH_2-N(OH)-CHO$	$-CH_2-CH(CH_3)_2$
25-53	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-CH_2-N(OH)-CHO$	benzyl
25-54	3'-F	-COOH	-Cl	$-(CH_2)_3CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-55	3'-F	-COOH	-Cl	$-(CH_2)_3CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-56	3'-F	-COOH	$-CH_2OH$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-57	3'-F	-COOH	$-CH_2OH$	$-O-CH_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-58	-	tetrazol-5-yl	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-59	3'-F	-COOH	$-C(CH_3)_2-OH$	$-(CH_2)_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-60	3'-F	-COOH	$-C(CH_3)_2-OH$	$-(CH_2)_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-61	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-(CH_2)_2$-phenyl
25-62	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH(CH_3)-CH_2CH_3$

Ex.	R	R^1	R^2	R^3	R^5	R^6
25-63	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	phenyl
25-64	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	2-chlorophenyl
25-65	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2$-cyclohexyl
25-66	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	cyclopropyl
25-67	3'-F	-COOH	Cl	$-O-CH_2CH_3$	$-SC(O)CH_3$	$-CH_2-CH(CH_3)_2$
25-68	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-C(O)-NH(OH)	benzyl
25-69	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-C(O)-NH(OH)	$-CH_2-CH(CH_3)_2$
25-70	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2$-cyclobutyl

(25-1) 4'-{5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{28}H_{35}N_3O_4S$, 510.24; found 510.5.

(25-2) 4'-{2-ethoxy-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{27}H_{33}N_3O_4S$, 496.22; found 496.3.

(25-3) 4'-{4-ethyl-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{30}H_{39}N_3O_4S$, 538.27; found 538.5.

(25-4) 4'-{4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{29}H_{37}N_3O_4S$, 524.25; found 524.6.

(25-5) 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{28}H_{35}N_3O_4S$, 510.24; found 510.5.

(25-6) *(S)*-2-mercaptomethyl-4-methylpentanoic acid [3-(2'-acetylsulfamoyl-biphenyl-4-ylmethyl)-2-propoxy-3H-imidazol-4-ylmethyl]amide. MS m/z: $[M+H^+]$ calcd for $C_{29}H_{38}N_4O_5S_2$, 587.23; found 587.5.

(25-7) *(S)*-2-mercaptomethyl-4-methylpentanoic acid [3-(2'-acetylsulfamoyl-biphenyl-4-ylmethyl)-5-ethyl-2-propoxy-3H-imidazol-4-ylmethyl]amide. MS m/z: $[M+H^+]$ calcd for $C_{31}H_{42}N_4O_5S_2$, 615.26; found 615.4.

(25-8) *(S)*-N-((1-((2'-(N-(ethylcarbamoyl)sulfamoyl)biphenyl-4-yl)methyl)-2-propoxy-1H-imidazol-5-yl)methyl)-2-(mercaptomethyl)-4-methylpentanamide. MS m/z: $[M+H^+]$

calcd for $C_{30}H_{41}N_5O_5S_2$, 616.26; found 616.4.

(25-9) 4'-{4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-2'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{36}FN_3O_4S$, 542.24; found 542.6.

(25-10) 4'-{4-ethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-2'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{38}FN_3O_4S$, 556.26; found 556.2.

(25-11) 4'-{4-ethyl-5-[((*R*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-2'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{36}FN_3O_4S$, 542.24; found 542.6.

(25-12) 4'-{4-ethyl-5-[((*R*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-2'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{38}FN_3O_4S$, 556.26; found 556.2.

(25-13) 2'-chloro-4'-{4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{36}ClN_3O_4S$, 558.21; found 558.2.

(25-14) 3'-chloro-4'-{4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{36}ClN_3O_4S$, 558.21; found 558.4.

(25-15) 4'-{5-[((*S*)-2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethyl-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{31}H_{39}N_3O_5S$, 566.26; found 566.6.

(25-16) 4'-{5-[((*S*)-2-acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethyl-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{36}FN_3O_5S$, 570.24; found 570.4.

(25-17) 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{36}FN_3O_4S$, 542.24; found 542.6.

(25-18) 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{34}FN_3O_4S$, 528.23; found 528.4.

(25-19) 4'-{5-[((*S*)-2-acetylsulfanyl-4-methylpentanoylamino)methyl]-4-ethyl-2-propoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$]

calcd for $C_{31}H_{38}FN_3O_5S$, 584.25; found 584.0.

(25-20) 4'-{4-ethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-methoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{34}FN_3O_4S$, 528.23; found 528.4.

(25-21) 4'-{4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-methoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{27}H_{32}FN_3O_4S$, 514.21; found 514.6.

(25-22) 4'-{5-[(2-acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{36}FN_3O_5S$, 570.24; found 570.4.

(25-23) 4'-{5-[((*S*)-2-acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{31}H_{38}FN_3O_5S$, 584.25; found 584.5.

(25-24) 4'-{4-cyclopropyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{37}N_3O_4S$, 536.25; found 536.4.

(25-25) 4'-{4-cyclopropyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{31}H_{39}N_3O_4S$, 550.27; found 550.4.

(25-26) 4'-{4-cyclopropyl-2-ethoxy-5-[((*S*)-2-mercaptomethyl-4-methylpentanoyl-amino)methyl]-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{37}N_3O_4S$, 536.25; found 536.4.

(25-27) 4'-{5-[((*S*)-3-cyclopropyl-2-mercapto-propionylamino)methyl]-2-ethoxy-4-ethyl-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{32}FN_3O_4S$, 526.21; found 526.4.

(25-28) 4'-{4-cyclopropyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{36}FN_3O_4S$, 554.24; found 554.2.

(25-29) (*S*)-2-mercapto-4-methylpentanoic acid [2-ethoxy-5-ethyl-3-(3-fluoro-2'-trifluoromethanesulfonylamino-biphenyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]amide. MS m/z: [M+H$^+$] calcd for $C_{28}H_{34}F_4N_4O_4S_2$, 631.20; found 631.4.

(25-30) (*S*)-2-mercapto-4-methylpentanoic acid [3-(2'-acetylsulfamoyl-biphenyl-4-ylmethyl)-2-ethoxy-5-ethyl-3H-imidazol-4-ylmethyl]amide. MS m/z: [M+H$^+$] calcd for

$C_{29}H_{38}N_4O_5S_2$, 587.23; found 587.2.

(25-31) *(S)*-2-mercaptomethyl-4-methylpentanoic acid [3-(2'-acetylsulfamoyl-3-fluorobiphenyl-4-ylmethyl)-5-ethyl-2-methoxy-3H-imidazol-4-ylmethyl]amide. MS m/z: [M+H$^+$] calcd for $C_{29}H_{37}FN_4O_5S_2$, 605.22; found 605.4.

(25-32) 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercaptopentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{27}H_{32}FN_3O_4S$, 514.21; found 514.4.

(25-33) 4'-{2-ethoxy-4-ethyl-5-[(2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{34}FN_3O_4S$, 528.23; found 529.0.

(25-34) 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4,4-dimethylpentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{36}FN_3O_4S$, 542.24; found 542.4.

(25-35) 4'-{5-[(*(S)*-2-benzoylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{35}H_{38}FN_3O_5S$, 632.25; found 632.4.

(25-36) 4'-(2-ethoxy-4-ethyl-5-{[*(S)*-4-methyl-2-(2-morpholin-4-yl-acetylsulfanyl)-pentanoylamino]-methyl}-imidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{34}H_{43}FN_4O_6S$, 655.29; found 655.6.

(25-37) 4'-(2-ethoxy-4-ethyl-5-{[*(S)*-4-methyl-2-(3-morpholin-4-yl-propionylsulfanyl)-pentanoylamino]methyl}-imidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{35}H_{45}FN_4O_6S$, 669.30; found 669.5.

(25-38) 4'-{2-ethoxy-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]-4-methyl-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{27}H_{33}N_3O_4S$, 496.22; found 496.6.

(25-39) 4'-{2-ethoxy-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-4-methyl-imidazol-1-ylmethyl}-biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{35}N_3O_4S$, 510.24; found 510.6.

(25-40) 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercaptobutyrylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{26}H_{30}FN_3O_4S$, 500.19; found 500.4.

(25-41) 4'-{2-ethoxy-4-ethyl-5-[((2S,3S)-2-mercapto-3-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for

$C_{28}H_{34}FN_3O_4S$, 528.23; found 528.4.

(25-42) 4'-{2-ethoxy-4-ethyl-5-[((*S*)-4-methyl-2-propionylsulfanylpentanoylamino)-methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{31}H_{38}FN_3O_5S$, 584.25; found 584.2.

(25-43) 4'-{2-ethoxy-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-4-methyl-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{27}H_{32}FN_3O_4S$, 514.21; found 514.6.

(25-44) 4'-{2-ethoxy-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-4-methyl-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{34}FN_3O_4S$, 528.23; found 528.2.

(25-45) 4'-{5-[((*S*)-3-cyclopentyl-2-mercaptopropionylamino)methyl]-2-ethoxy-4-ethyl-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{36}FN_3O_4S$, 554.24; found 554.4.

(25-46) 4'-{4-cyclopropyl-2-ethoxy-5-[((*S*)-2-mercapto-4-methylpentanoylamino)-methyl]imidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{35}N_3O_4S$, 522.24; found 522.4.

(25-47) 4'-{2-butyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-4-methoxy-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{36}FN_3O_4S$, 542.24; found 542.2.

(25-48) 4'-{2-butyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-4-methoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{38}FN_3O_4S$, 556.26; found 556.2.

(25-49) 4'-{2-butyl-5-[((2S,3S)-2-mercapto-3-methylpentanoylamino)methyl]-4-methoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{36}FN_3O_4S$, 542.24; found 542.2.

(25-50) 4'-{2-butyl-4-chloro-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)-methyl]imidazol-1-ylmethyl}-2'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{35}ClFN_3O_3S$, 560.21; found 560.2.

(25-51) 4'-{4-cyclopropyl-2-ethoxy-5-[((*S*)-2-mercapto-4-methylpentanoylamino)-methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{34}FN_3O_4S$, 540.23; found 540.4.

(25-52) 4'-[2-ethoxy-4-ethyl-5-({2-[(formylhydroxyamino)methyl]-4-methylpentanoyl-amino}methyl)imidazol-1-ylmethyl]-3'-fluorobiphenyl-2-carboxylic acid. MS m/z:

[M+H$^+$] calcd for $C_{30}H_{37}FN_4O_6$, 569.27; found 569.6.

(25-53) 4'-(5-{[2-benzyl-3-(formylhydroxyamino)propionylamino]methyl}-2-ethoxy-4-ethyl-imidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{33}H_{35}FN_4O_6$, 603.25; found 603.4.

(25-54) 4'-{2-butyl-4-chloro-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{33}ClFN_3O_3S$, 546.19; found 546.6.

(25-55) 4'-{2-butyl-4-chloro-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)-methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{35}ClFN_3O_3S$, 560.21; found 560.2.

(25-56) 4'-{2-ethoxy-4-hydroxymethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)-methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{27}H_{32}FN_3O_5S$, 530.20; found 530.4.

(25-57) 4'-{2-ethoxy-4-hydroxymethyl-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoyl-amino)-methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{34}FN_3O_5S$, 544.22; found 544.4.

(25-58) *(S)*-2-mercapto-4-methyl-pentanoic acid {2-ethoxy-5-ethyl-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide. MS m/z: [M+H$^+$] calcd for $C_{28}H_{35}N_7O_2S$, 534.26; found 534.4.

(25-59) 3'-fluoro-4'-{4-(1-hydroxy-1-methylethyl)-5-[(*(S)*-2-mercapto-4-methyl-pentanoylamino)methyl]-2-propylimidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{38}FN_3O_4S$, 556.26; found 556.4.

(25-60) 3'-fluoro-4'-{4-(1-hydroxy-1-methylethyl)-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propylimidazol-1-ylmethyl}biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{31}H_{40}FN_3O_4S$, 570.27; found 570.4.

(25-61) 4'-{2-ethoxy-4-ethyl-5-[(2-mercapto-4-phenylbutyrylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{32}H_{34}FN_3O_4S$, 576.23; found 576.4.

(25-62) 4'-{2-ethoxy-4-ethyl-5-[(*(2S,3R)*-2-mercapto-3-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{34}FN_3O_4S$, 528.23; found 528.4.

(25-63) 4'-{2-ethoxy-4-ethyl-5-[(2-mercapto-2-phenylacetylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{30}FN_3O_4S$,

548.19; found 548.4.

(25-64) 4'-(5-{[2-(2-chloro-phenyl)-2-mercaptoacetylamino]methyl}-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{29}ClFN_3O_4S$, 582.16; found 582.2.

(25-65) 4'-{5-[(*(S)*-3-cyclohexyl-2-mercaptopropionylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{31}H_{38}FN_3O_4S$, 568.26; found 568.4.

(25-66) 4'-{5-[(*(S)*-2-cyclopentyl-2-mercaptoacetylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{34}FN_3O_4S$, 540.23; found 540.4.

(25-67) 4'-{5-[(*(S)*-2-acetylsulfanyl-4-methylpentanoylamino)methyl]-4-chloro-2-ethoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{28}H_{31}ClFN_3O_5S$, 576.17; found 576.4.

(25-68) 4'-{2-ethoxy-4-ethyl-5-[(2-hydroxycarbamoyl-3-phenylpropionylamino)-methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{32}H_{33}FN_4O_6$, 589.24; found 589.4.

(25-69) 4'-{2-ethoxy-4-ethyl-5-[(2-hydroxycarbamoyl-4-methylpentanoylamino)-methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{35}FN_4O_6$, 555.25; found 555.2.

(25-70) 4'-{5-[(*(S)*-3-cyclobutyl-2-mercaptopropionylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{34}FN_3O_4S$, 540.23; found 540.5.

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 25-71- to 25-95 can also readily be prepared.

Ex.	R	R^1	R^2	R^3	R^5	R^6
25-71	3'-F	-COOH	Cl	$-(CH_2)_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-72	3'-F	-COOH	Cl	$-(CH_2)_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-73	2',5'-diF	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-74	2',5'-diF	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-75	3'-F	-COOH	$-CH_2F$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$

Ex.	R	R^1	R^2	R^3	R^5	R^6
25-76	3'-F	-COOH	$-CH_2F$	$-O-CH_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-77	-	-COOH	$-CF_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-78	-	-COOH	Br	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-79	-	tetrazol-5-yl	$-CH_2CH_3$	$-O-CH_2CH_3$	$-SC(O)CH_3$	$-CH_2-CH(CH_3)_2$
25-80	3'-F	tetrazol-5-yl	Cl	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-81	3'-F	tetrazol-5-yl	cyclo-propyl	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-82	3'-F	-COOH	Cl	$-OCH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-83	3'-F	-COOH	Cl	$-O-(CH_2)_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-84	3'-F	-COOH	Cl	$-OCH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-85	3'-F	-COOH	Cl	$-O-(CH_2)_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
25-86	3'-F	$-C(O)OCH_3$	$-CH_2CH_3$	$-O-CH_2CH_3$	$-SC(O)CH_3$	$-CH_2-CH(CH_3)_2$
25-87	3'-F	$-C(O)OCH_3$	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-88	3'-F	$-C(O)-NHSO_2CF_3$	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CH(CH_3)_2$
25-89	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	benzyl
25-90	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-CH_2-CF_3$
25-91	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	$-(CH_2)_2-CF_3$
25-92	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	2-fluorophenyl
25-93	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	4-chlorobenzyl
25-94	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	2-fluorobenzyl
25-95	3'-F	-COOH	$-CH_2CH_3$	$-O-CH_2CH_3$	-SH	3-fluorobenzyl

(25-71) 4'-{4-chloro-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)-methyl]-2-propyl-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-72) 4'-{4-chloro-5-[(*(S)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-propylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-73) 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-2',5'-difluorobiphenyl-2-carboxylic acid.

(25-74) 4'-{2-ethoxy-4-ethyl-5-[*((S)*-2-mercaptomethyl-4-methylpentanoylamino)-methyl]imidazol-1-ylmethyl}-2',5'-difluorobiphenyl-2-carboxylic acid.

(25-75) 4'-{2-ethoxy-4-fluoromethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)-methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-76) 4'-{2-ethoxy-4-fluoromethyl-5-[((*S*)-2-mercaptomethyl-4-methylpentanoyl-amino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-77) 4'-{2-ethoxy-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-4-trifluoro-methylimidazol-1-ylmethyl}biphenyl-2-carboxylic acid.

(25-78) 4'-{4-bromo-2-ethoxy-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}biphenyl-2-carboxylic acid.

(25-79) thioacetic acid S-[(*S*)-1-({2-ethoxy-5-ethyl-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}carbamoyl)-3-methylbutyl] ester.

(25-80) (*S*)-2-mercapto-4-methylpentanoic acid {5-chloro-2-ethoxy-3-[3-fluoro-2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide.

(25-81) (*S*)-2-mercapto-4-methylpentanoic acid {5-cyclopropyl-2-ethoxy-3-[3-fluoro-2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3H-imidazol-4-ylmethyl}amide.

(25-82) 4'-{4-chloro-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-methoxy-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-83) 4'-{4-chloro-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-2-propoxy-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-84) 4'-{4-chloro-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-methoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-85) 4'-{4-chloro-5-[((*S*)-2-mercaptomethyl-4-methylpentanoylamino)methyl] -2-propoxyimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-86) 4'-{5-[((*S*)-2-acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethyl-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid methyl ester.

(25-87) 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid methyl ester.

(25-88) (*S*)-2-mercapto-4-methyl-pentanoic acid [2-ethoxy-5-ethyl-3-(3-fluoro-2'-trifluoromethanesulfonylaminocarbonylbiphenyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-amide.

(25-89) 4'-{2-ethoxy-4-ethyl-5-[((*R*)-2-mercapto-3-phenylpropionylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-90) 4'-{2-ethoxy-4-ethyl-5-[(4,4,4-trifluoro-2-mercaptobutyrylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

(25-91) 4'-{2-ethoxy-4-ethyl-5-[(5,5,5-trifluoro-2-mercaptopentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

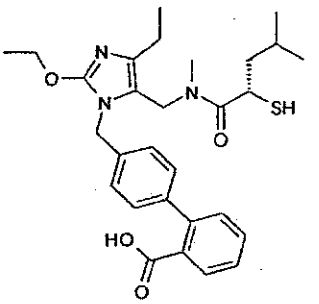
(25-92) 4'-(2-ethoxy-4-ethyl-5-{[2-(2-fluorophenyl)-2-mercaptoacetylamino]methyl}-imidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid.

(25-93) 4'-(5-{[3-(4-chlorophenyl)-2-mercaptopropionylamino]methyl}-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid.

(25-94) 4'-(2-ethoxy-4-ethyl-5-{[3-(2-fluorophenyl)-2-mercaptopropionylamino]-methyl}-imidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid.

(25-95) 4'-(2-ethoxy-4-ethyl-5-{[3-(3-fluorophenyl)-2-mercaptopropionylamino]-methyl}imidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid.

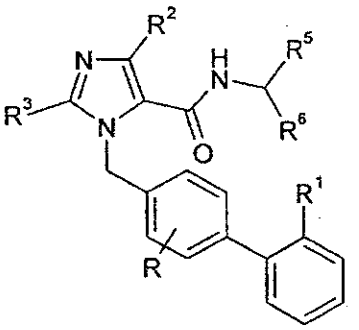
Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compound 25-96 can also readily be prepared:



(25-96) 4'-(2-ethoxy-4-ethyl-5-{[(*(S)*-2-mercapto-4-methylpentanoyl)methylamino]-methyl}-imidazol-1-ylmethyl)biphenyl-2-carboxylic acid.

EXAMPLE 26

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 26-1 to 26-10, having the following formula, were also prepared:



Ex.	R	R^1	R^2	R^3	R^5	R^6
26-1	3-fluoro	$-SO_2-NHC(O)-CH_3$	H	$-O-CH_2CH_3$	$-CH_2SH$	benzyl
26-2	3'-fluoro	-COOH	H	$-O-CH_2CH_3$	$-CH_2SH$	3,5-difluoro-benzyl
26-3	3'-fluoro	-COOH	H	$-O-CH_2CH_3$	$-CH_2SH$	2-fluorobenzyl
26-4	3'-fluoro	-COOH	H	$-O-CH_2CH_3$	$-CH_2SH$	3-fluorobenzyl
26-5	3'-fluoro	-COOH	H	$-O-CH_2CH_3$	$-CH_2SH$	2-chloro-benzyl
26-6	3'-fluoro	-COOH	H	$-O-CH_2CH_3$	$-CH_2SH$	3-chloro-benzyl
26-7	3'-fluoro	-COOH	H	$-O-CH_2CH_3$	$-CH_2SH$	4-fluorobenzyl
26-8	3'-fluoro	-COOH	H	$-O-CH_2CH_3$	$-CH_2SH$	$-CH_2-CH(CH_3)_2$
26-9	3'-fluoro	-COOH	$-C(CH_3)_2-OH$	$-(CH_2)_2CH_3$	$-CH_2SH$	benzyl
26-10	3'-fluoro	-COOH	$-C(CH_3)_2-OH$	$-(CH_2)_2CH_3$	$-CH_2SH$	2-methyl-benzyl

(26-1) 3-(2'-acetylsulfamoyl-3-fluorobiphenyl-4-ylmethyl)-2-ethoxy-3H-imidazole-4-carboxylic acid ((*R*)-1-benzyl-2-mercaptoethyl)-amide. MS m/z: $[M+H^+]$ calcd for $C_{30}H_{31}FN_4O_5S_2$, 611.17; found 611.4.

(26-2) 4'-{5-[(*R*)-1-(3,5-difluorobenzyl)-2-mercapto-ethylcarbamoyl]-2-ethoxy-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{29}H_{26}F_3N_3O_4S$, 570.16; found 570.6.

(26-3) 4'-{2-ethoxy-5-[(*R*)-1-(2-fluorobenzyl)-2-mercapto-ethylcarbamoyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{29}H_{27}F_2N_3O_4S$, 552.17; found 552.8.

(26-4) 4'-{2-ethoxy-5-[(*R*)-1-(3-fluorobenzyl)-2-mercapto-ethylcarbamoyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{29}H_{27}F_2N_3O_4S$, 552.17; found 552.8.

(26-5) 4'-{5-[(*R*)-1-(2-chlorobenzyl)-2-mercaptoethylcarbamoyl]-2-ethoxy-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{29}H_{27}ClFN_3O_4S$, 568.14; found 568.3.

(26-6) 4'-{5-[(*R*)-1-(3-chlorobenzyl)-2-mercaptoethylcarbamoyl]-2-ethoxy-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: $[M+H^+]$ calcd for $C_{29}H_{27}ClFN_3O_4S$, 568.14; found 568.2.

(26-7) 4'-{2-ethoxy-5-[*(R)*-2-(4-fluorophenyl)-1-mercaptomethylethylcarbamoyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{29}H_{27}F_2N_3O_4S$, 552.17; found 552.8.

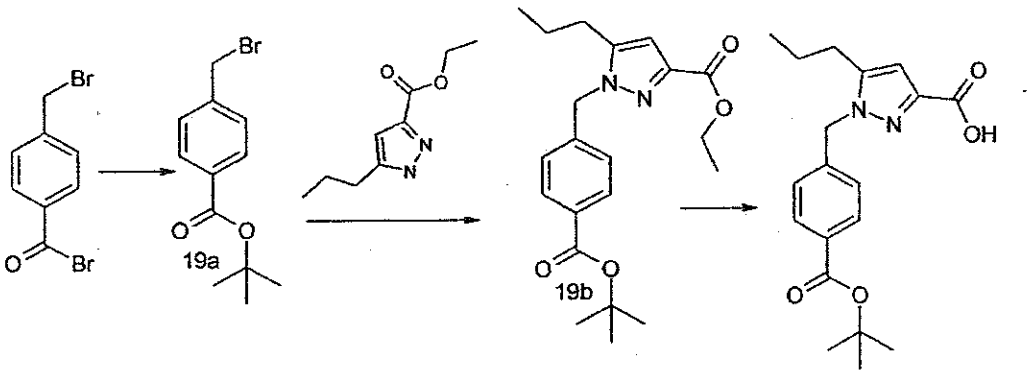
(26-8) 4'-[2-ethoxy-5-(*(R)*-1-mercaptomethyl-2-*o*-tolylethylcarbamoyl)-imidazol-1-ylmethyl]-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{30}FN_3O_4S$, 548.19; found 548.6.

(26-9) 4'-[5-(*(R)*-1-benzyl-2-mercapto-ethylcarbamoyl)-4-(1-hydroxy-1-methylethyl)-2-propylimidazol-1-ylmethyl]-3'-fluorobiphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{33}H_{36}FN_3O_4S$, 590.24; found 590.4.

(26-10) 3'-fluoro-4'-[4-(1-hydroxy-1-methyl-ethyl)-5-(*(R)*-1-mercaptomethyl-3-methylbutylcarbamoyl)-2-propylimidazol-1-ylmethyl]-biphenyl-2-carboxylic acid. MS m/z: [M+H$^+$] calcd for $C_{30}H_{38}FN_3O_4S$, 556.26; found 556.4.

PREPARATION 19

1-(4-*t*-Butoxycarbonylbenzyl)-5-propyl-1H-pyrazole-3-carboxylic Acid



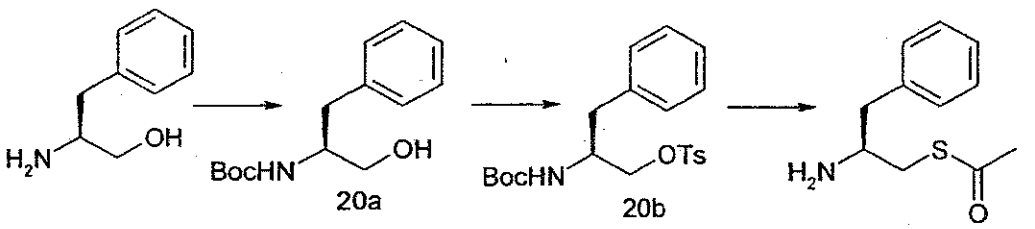
4-Bromomethylbenzoic acid *t*-butyl ester (19a): 4-Bromomethylbenzoyl bromide (13.9 g, 50 mmol, 1.0 eq) was added to 50 mL of DCM, followed by *t*-butanol (9.6 mL, 100 mmol, 2.0 eq) and the mixture was slowly warmed to room temperature. After 20 hours, the reaction was concentrated under reduced pressure, dissolved into 350 mL EtOAc, washed with 400 mL sat. bicarbonate and 200 mL saturated aqueous NaCl. The organic was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield intermediate (19a) as a semisolid (7.3 g).

1-(4-*t*-Butoxycarbonyl-benzyl)-5-propyl-1H-pyrazole-3-carboxylic acid ethyl ester (19b): To the recovered intermediate (19a) (1.4 g, 5 mmol, 1.0 eq) dissolved into 15 mL DMF, was added 5-propyl-1H-pyrazole-3-carboxylic acid ethyl ester (910 mg, 5.0 mmol, 1.0 eq) and potassium carbonate (0.8 g, 5.5 mmol, 1.1 eq) and the mixture was stirred at

room temperature for 16 hours. The mixture was then added to 50 mL of 10% aq. LiCl solution and extracted with 50 mL EtOAc. The organic was dried over $MgSO_4$, and concentrated under reduced pressure to yield intermediate (19b) and its regioisomer in a 1:1 ratio. The recovered regioisomers were dissolved into 25 mL MeOH. To this was added 10mL of 1M NaOH and the mixture was stirred at room temperature over night. The mixture was acidified with acetic acid and concentrated under reduced pressure. The recovered oil was purified by preparatory HPLC, producing the desired regioisomer of the title compound as a white solid TFA salt after lyophilization (230 mg). ^{1}H NMR (DMSO) 0.89 (t, 3H), 1.52 (s, 9H), 5.71 (s, 2H), 6.71 (s, 1H), 7.15 (d, 2H), 7.83 (d, 2H), 13.28 (br s, 1H).

PREPARATION 20

Thioacetic acid S-(*(S)*-2-amino-3-phenylpropyl) Ester



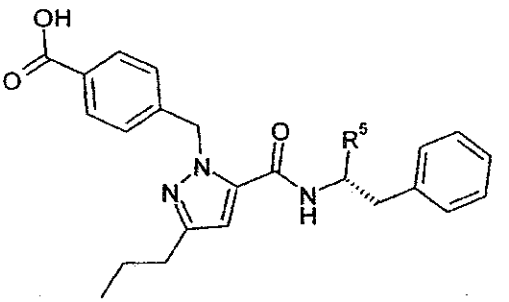
(*(S)*-1-Benzyl-2-hydroxyethyl)carbamic acid *t*-butyl ester (20a): *(S)*-2-Amino-3-phenyl-propan-1-ol (5 g, 33 mmol, 1.0 eq) was dissolved into 100 mL MeOH. To this was added di-*t*-butyldicarbonate (7.6 g, 35 mmol, 1.1 eq) and the mixture was stirred at room temperature for 4 hours. The mixture was then concentrated under reduced pressure, dissolved into EtOAc, and washed with 1M H_3PO_4 and saturated aqueous NaCl. After drying over $MgSO_4$, the organic was filtered and concentrated under reduced pressure to yield crude intermediate (20a) (8.5 g).

Toluene-4-sulfonic acid *(S)*-2-*t*-butoxycarbonylamino-3-phenylpropyl ester (20b): The recovered intermediate (20a) (8.5 g, 33 mmol, 1.0 eq) was dissolved into 70 mL pyridine containing potassium hydroxide (2.1 g, 37 mmol, 1.1 eq) and the mixture was chilled in an ice bath. Tosyl chloride (7.1 g, 37 mmol, 1.1 eq) was added and the mixture was stirred at 0 °C for 2 hours then refrigerated overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure. The recovered residue was dissolved into 300 mL EtOAc, washed with 2x200 mL 1M H_3PO_4, saturated bicarbonate, and saturated aqueous NaCl. The organic was dried over $MgSO_4$ and concentrated under reduced pressure to yield intermediate (20b) (10.3 g) as a pale brown oil.

Intermediate (20b) (10.3 g, 25 mmol, 1.0 eq) was added to a solution of thioacetic acid (2.2 mL, 30 mmol, 1.2 eq) and KOH (1.7 g, 30 mmol, 1.2 eq) in 80 mL DMF cooled to 0 °C. The mixture was stirred at 0 °C for 2 hours, slowly warmed to room temperature, then stirred for 48 hours. The mixture was diluted with water and extracted with EtOAc. The material was washed 2x with sat. bicarbonate and saturated aqueous NaCl , then dried over $MgSO_4$. The organic was filtered and concentrated under reduced pressure to yield an oil (7.1 g). This oil was then dissolved into 30 mL of 1:1 TFA:DCM and stirred at room temperature for 1 hour. The mixture was concentrated to produce the title compound in a quantitative yield.

EXAMPLE 27

4-[5-((*S*)-1-Benzyl-2-mercaptoethylcarbamoyl)-3-propylpyrazol-1-ylmethyl] benzoic acid (compound 27-1; $R^5 = -CH_2SH$)

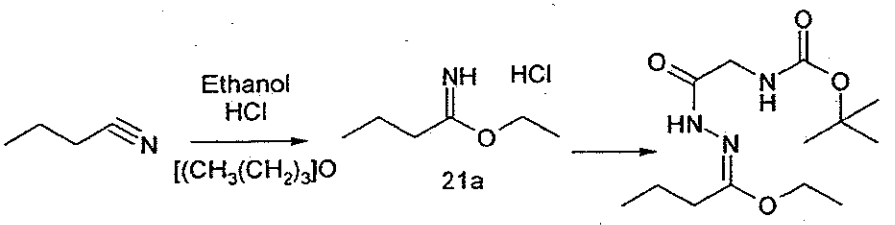


1-(4-*t*-Butoxycarbonylbenzyl)-5-propyl-1H-pyrazole-3-carboxylic acid (460 mg, 0.1 mmol, 1.0 eq) was dissolved into 1.0 mL DMF. To this was added HATU and the mixture was shaken for 10 minutes. Thioacetic acid S-((*S*)-2-amino-3-phenylpropyl) ester (320 mg, 0.1 mmol, 1.0 eq) was added, followed by DIPEA (520 µL, 0.3 mmol, 3.0 eq). The mixture was shaken over night, concentrated under reduced pressure, and the residue redissolved into 3 mL of 4N HCl in dioxane and shaken for 4 hours. The mixture was again concentrated under reduced pressure, and dissolved into 2.0 mL MeOH. The mixture was purged with nitrogen, 1.0 mL of 3M NaOH was added, and the mixture was stirred at room temperature for 2 hours. The mixture was acidified with 0.5 mL acetic acid and concentrated under reduced pressure. The recovered oil was purified by reverse HPLC to yield compound 27-1 as a white solid (1.3 mg). MS m/z: $[M+H^+]$ calc'd for $C_{24}H_{27}N_3O_3S$, 438.2; found 438.

Compound (27-2) was prepared in a similar manner: 4-[5-((*S*)-1-hydroxycarbamoyl-2-phenylethylcarbamoyl)-3-propylpyrazol-1-ylmethyl]benzoic acid ($R^5 = -C(O)N(OH)H$). MS *m/z*: $[M + H^+]$ calcd for $C_{24}H_{26}N_4O_5$, 451.19; found 451.

PREPARATION 21

[1-Ethoxy-but-(E)-ylidene-hydrazinocarbonylmethyl]carbamic acid *t*-Butyl Ester

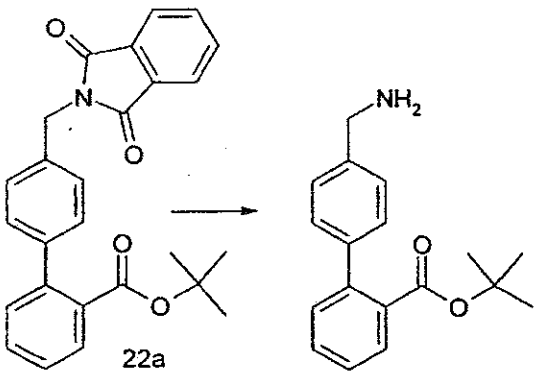


Ethyl butyrimidate•HCl (21a): 1-cyanopropane (20 g, 290 mmol) was mixed with butylether (250 mL) and cooled to 0 °C. Ethanol (18.6 mL, 320 mmol) was added and HCl gas was bubbled through the mixture for 45 minutes. The mixture was then sealed and stored at 5 °C overnight. A 100 mL aliquot of the mixture was withdrawn and concentrated to give an oil which was dissolved in MeCN and concentrated until crystallization was initiated. EtOAc was added and the mixture was maintained at -20 °C overnight. The resulting solidified mixture was diluted with EtOAc, filtered, and washed with diethyl ether under nitrogen to give 7.8 g of compound (21a) as a white solid. ^{1}H-NMR (DMSO): 11.5 ppm (bs, 2H), 4.45 ppm (q, 2H), 2.6 ppm (t, 2H), 1.65 ppm (m, 2H), 1.3 ppm (t, 3H), 0.9 ppm (t, 3H).

Compound (21a) (3.0 g, 19.9 mmol) was dissolved in ethanol (10 mL) and cooled to -78° C. Hydrazinocarbonylmethylcarbamic acid *t*-butyl ester in ethanol (10 mL) was added dropwise over 20 minutes. The mixture was then capped and stored at 4 °C for 4 days. The precipitant was filtered off and the solvent was concentrated to obtain the title compound (4.0 g).

PREPARATION 22

4'-Aminomethylbiphenyl-2-carboxylic Acid *t*-Butyl Ester



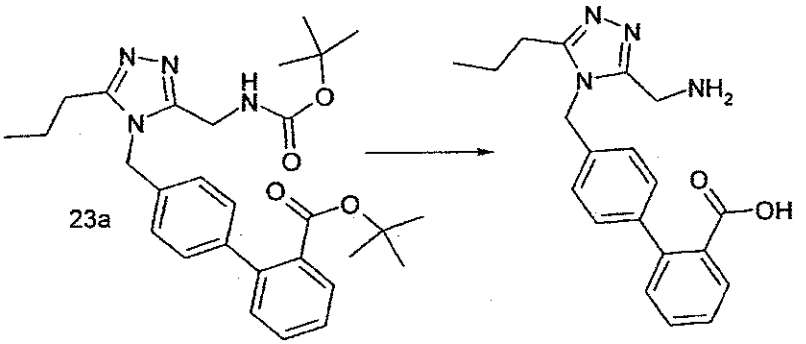
4'-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)biphenyl-2-carboxylic Acid *t*-Butyl Ester (22a): 4'-Bromomethylbiphenyl-2-carboxylic acid *t*-butyl ester (4.0 g, 11.5 mmol)

and potassium phthalimide were combined and dissolved in DMF (30 mL), and the mixture was heated at 50 °C for two days. The mixture was then cooled to room temperature and the reaction quenched with water (30 mL). The mixture was then extracted with EtOAc, and washed with a 10% aqueous lithium chloride solution. The organic layer was dried over $MgSO_4$, filtered and concentrated to obtain intermediate (22a) (4.8 g). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{23}NO_4$, 414.5; found 414.3.

Intermediate (22a) (4.8 g, 11.5 mmol) and hydrazine (5.0 mL, 100 mmol) were dissolved in ethanol (50 mL) and heated at 80 °C for 5 hours. The mixture was then cooled to room temperature, the precipitant was filtered off and the solvent was concentrated to obtain the title compound (3.4 g). MS m/z: $[M+H^+]$ calcd for $C_{18}H_{21}NO_2$, 284.4; found 284.3.

PREPARATION 23

4'-(3-Aminomethyl-5-propyl[1,2,4]triazol-4-ylmethyl)biphenyl-2-carboxylic Acid

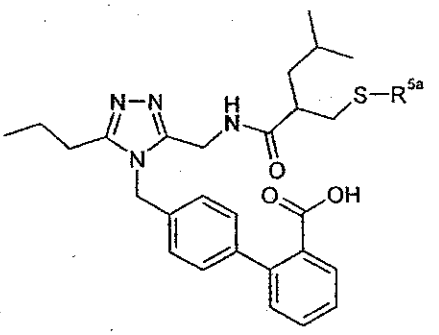


4'-[3-(*t*-Butoxycarbonylaminomethyl)-5-propyl-[1,2,4]triazol-4-ylmethyl]biphenyl-2-carboxylic acid *t*-butyl ester (23a): 4'-Aminomethylbiphenyl-2-carboxylic acid *t*-butyl ester (1.5 g, 5.2 mmol) and [1-ethoxy-but-(E)-ylidene-hydrazinocarbonylmethyl] carbamic acid *t*-butyl ester (1.0 g, 3.5 mmol) were combined and dissolved in ethanol (50 mL). The mixture was heated at 50 °C for 2 hours and then 70 °C overnight. The mixture was then cooled and concentrated. The product was purified by silica gel chromatography (0-20% MeOH:DCM) to obtain intermediate (23a) (400 g). MS m/z: $[M+H^+]$ calcd for $C_{29}H_{38}N_4O_4$, 507.6; found 507.3.

Intermediate (23a) (400 mg, 790 μmol) was dissolved in a mixture of TFA (1 mL) and DCM (2 mL). The mixture was stirred at room temperature for 4 hours and was then concentrated. The product was purified by preparative HPLC (10-50% MeCN in water w/ 0.05% TFA) to obtain the title compound (120 mg). MS m/z: $[M+H^+]$ calcd for $C_{20}H_{22}N_4O_2$, 351.4; found 351.2.

EXAMPLE 28

4'-{3-[(2-Acetylsulfanylmethyl-4-methylpentanoylamino)methyl]-5-propyl[1,2,4]triazol-4-ylmethyl}biphenyl-2-carboxylic Acid (28a; R^{5a} = -C(O)CH_3) and 4'-{3-[(2-Mercaptomethyl-4-methylpentanoylamino)methyl]-5-propyl[1,2,4] triazol-4-ylmethyl}biphenyl-2-carboxylic Acid (28b; R^{5a}=H)



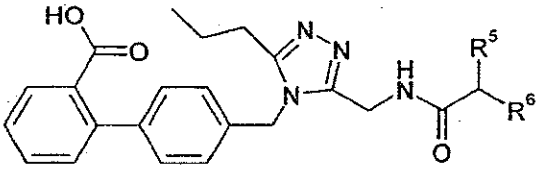
2-Acetylsulfanylmethyl-4-methylpentanoic acid (66.0 mg, 0.314 mmol) and HATU (119 mg, 314 μmol) were combined and dissolved in DMF (2 mL) and stirred for 15 minutes. DIPEA (50 μL, 290 μmol) was then added and the mixture stirred at room temperature for 30 minutes. 4'-(3-Aminomethyl-5-propyl-1,2,4-triazol-4-ylmethyl)biphenyl-2-carboxylic acid (100 mg, 290 μmol) in DMF (1 mL) was added to the mixture, followed by the addition of a second equivalent of DIPEA (50 μL, 290 μmol). The mixture was stirred at room temperature overnight. Water (5 mL) was added to quench the reaction, and the mixture was then extracted with EtOAc and washed with a 10% aqueous lithium chloride solution. The organic layer was dried over $MgSO_4$, filtered and concentrated to obtain intermediate (28a) (50 mg) which was carried directly on to the next reaction. MS m/z: [M+H^+] calcd for $C_{29}H_{36}N_4O_4S$, 537.7; found 537.3.

Intermediate (28a) (50 mg, 930 μmol) was dissolved in MeOH (2 mL) and 1 N sodium bicarbonate (2 mL), and stirred at room temperature under nitrogen for 30 minutes. The reaction was quenched with acetic acid and the resulting mixture concentrated. The product was purified by preparative HPLC (30-70% MeCN in water w/ 0.05% TFA) to obtain the title compound (9 mg). MS m/z: [M+H^+] calcd for $C_{27}H_{34}N_4O_3S$, 494.7; found 494.4.

EXAMPLE 29

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 29-1 to 29-4, having the following

formula, were also prepared:



(29-1) 4'-{3-[(2-hydroxycarbamoyl-4-methylpentanoylamino)methyl]-5-propyl[1,2,4] triazol-4-ylmethyl}biphenyl-2-carboxylic acid (R^5 = -C(O)N(OH)H; R^6 = $-CH_2CH(CH_3)_2$). MS *m/z*: [M + H^+] calcd for $C_{27}H_{33}N_5O_5$, 508.25; found 508.4.

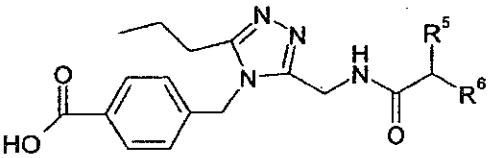
(29-2) 4'-{3-[(2-hydroxycarbamoyl-3-phenylpropionylamino)methyl]-5-propyl[1,2,4] triazol-4-ylmethyl}biphenyl-2-carboxylic acid (R^5 = -C(O)N(OH)H; R^6 = benzyl). MS *m/z*: [M + H^+] calcd for $C_{30}H_{31}N_5O_5$, 542.23; found 542.2.

(29-3) 4'-{3-[(2-mercaptomethyl-3-phenylpropionylamino)methyl]-5-propyl[1,2,4] triazol-4-ylmethyl}biphenyl-2-carboxylic acid (R^5 = $-CH_2SH$; R^6 = benzyl). MS *m/z*: [M + H^+] calcd for $C_{30}H_{32}N_4O_3S$, 529.22; found 529.

(29-4) 4'-{3-[(*(R)*-2-mercaptomethyl-4-methylpentanoylamino)methyl]-5-propyl [1,2,4]triazol-4-ylmethyl}biphenyl-2-carboxylic acid (R^5 = $-CH_2SH$; R^6 = $-CH_2CH(CH_3)_2$). MS *m/z*: [M + H^+] calcd for $C_{27}H_{34}N_4O_3S$, 495.24; found 495.2.

EXAMPLE 30

Following the procedures described in the examples above, and substituting the appropriate starting materials and reagents, compounds 30-1 to 30-4, having the following formula, were also prepared:



(30-1) 4-{3-[(2-mercaptomethyl-4-methylpentanoylamino)methyl]-5-propyl[1,2,4] triazol-4-ylmethyl}benzoic acid (R^5 = $-CH_2SH$; R^6 = $-CH_2CH(CH_3)_2$). MS *m/z*: [M + H^+] calcd for $C_{21}H_{30}N_4O_3S$, 419.20; found 419.2.

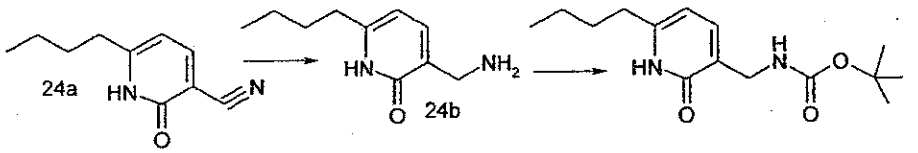
(30-2) 4-{3-[(2-mercaptomethyl-3-phenylpropionylamino)methyl]-5-propyl[1,2,4] triazol-4-ylmethyl}benzoic acid (R^5 = $-CH_2SH$; R^6 = benzyl). MS *m/z*: [M + H^+] calcd for $C_{24}H_{28}N_4O_3S$, 453.19; found 453.2.

(30-3) 4-{3-[(2-hydroxycarbamoyl-4-methylpentanoylamino)methyl]-5-propyl[1,2,4] triazol-4-ylmethyl}benzoic acid (R^5 = -C(O)N(OH)H; R^6 = $-CH_2CH(CH_3)_2$). MS *m/z*: [M + H^+] calcd for $C_{21}H_{29}N_5O_5$, 432.22; found 432.2.

(30-4) 4-{3-[(2-hydroxycarbamoyl-3-phenylpropionylamino)methyl]-5-propyl[1,2,4] triazol-4-ylmethyl}benzoic acid (R^5 = -C(O)N(OH)H; R^6 = benzyl). MS *m/z*: [M + H^+] calcd for $C_{24}H_{27}N_5O_5$, 466.20; found 466.2.

PREPARATION 24

(6-Butyl-2-oxo-1,2-dihydropyridin-3-ylmethyl)carbamic Acid *t*-Butyl Ester



6-Butyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (24a): A solution of diisopropylamine (20.5 mL, 2 eq) in THF (200 mL) was cooled to -5 °C. *n*-Butyllithium (53.5 mL, 2.9 M in hexanes, 2 eq) was added over 10 minutes. The solution was allowed to rise to 0 °C, stirred for 0.5 hours, then cooled again to -30 °C. 3-Cyano-6-methyl-2(1H)pyridinone (10 g, 75 mmol) was added portionwise, and the mixture was allowed to warm to room temperature and stirred for 2 hours. The solution was then cooled to -50 °C, and 1-bromopropane (6.8 mL, 1 eq) was added. The solution was allowed to warm to room temperature, stirred for 1 hour, and then quenched with a saturated ammonium chloride solution. The THF was evaporated and the aqueous phase extracted with DCM (2 x 100 mL). The organics were washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated to yield intermediate (24a) as an orange solid (10.8 g, 61 mmol), which was used without further purification. MS m/z: [M+H^+] calcd for $C_{10}H_{12}N_2O$, 177.2; found 177.0. ^{1}H-NMR (DMSO) 7.87 (1H, d), 6.05 (1H, d), 2.38 (2H, t), 1.41 (2H, m), 1.15 (2H, m), 0.93 (1H, d), 0.73 (3H, t).

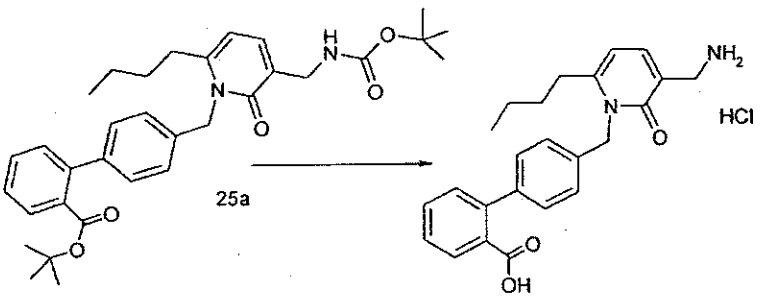
3-Aminomethyl-6-butyl-1H-pyridin-2-one (24b): intermediate (24a) (180 mg, 1 mmol) was dissolved in MeOH (10 mL). Aqueous ammonia (1 mL) was added, followed by wet Raney Nickel (100 mg). The mixture was stirred at room temperature under hydrogen for 3 hours. The mixture was then filtered and the filtrate evaporated to yield intermediate (24b) (157 mg, 870 µmol, which was used without further purification. MS m/z: [M+H^+] calcd for $C_{10}H_{17}N_2O$, 181.3; found 181.3.

Intermediate (24b) (157 mg, 0.87 mmol) was dissolved in DCM (10 mL). Triethylamine (121 µL, 1 eq) was added, followed by di-*tert*-butyl dicarbonate (189 mg, 1 eq). The mixture was stirred at room temperature for 16 hours. The solvent was then evaporated and the residue purified by silica gel chromatography (1:1 EtOAc:hexane) to

afford the title compound (200 mg, 710 μmol). MS m/z: [M+H$^+$] calcd for $C_{15}H_{25}N_2O_3$, 281.4; found 281.3.

PREPARATION 25

4'-(3-Aminomethyl-6-butyl-2-oxo-2H-pyridin-1-ylmethyl)biphenyl-2-carboxylic Acid•HCl

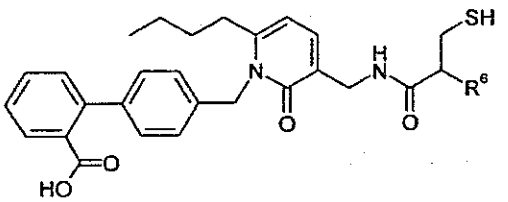


4'-[3-(*t*-Butoxycarbonylaminomethyl)-6-butyl-2-oxo-2H-pyridin-1-ylmethyl]biphenyl-2-carboxylic Acid *t*-Butyl Ester (25a): (6-Butyl-2-oxo-1,2-dihydropyridin-3-ylmethyl)carbamic acid *t*-butyl ester (200 mg, 0.71 mmol) was dissolved in THF (5 mL) and cooled to -5 °C. *n*-Butyllithium (285 μL, 2.5M solution in hexanes, 1 eq) was added, and the mixture was stirred at -5 °C for 5 minutes. 4'-Bromomethylbiphenyl-2-carboxylic acid *t*-butyl ester (247 mg, 1 eq) was added, and solution was warmed to reflux and stirred for 72 hours. The solution was allowed to cool, the solvent evaporated and the residue purified by silica gel chromatography (3:1 hexanes:EtOAc) to yield intermediate (25a) as a white solid (180 mg, 330 μmol). MS m/z: [M+H$^+$] calcd for $C_{33}H_{43}N_2O_5$, 547.7; found 547.3.

Intermediate (25a) (180 mg, 0.33 mmol) was dissolved in DCM (3 mL) and TFA (3 mL). The mixture was stirred at room temperature for 16 hours, and then evaporated to dryness. The residue was dissolved in MeCN and water, and HCl (1M, 0.5mL) was added. The solution was lyophilized to yield the title compound (133 mg, 310 μmol) as a white solid, which was used without further purification. MS m/z: [M+H$^+$] calcd for $C_{24}H_{27}N_2O_3$, 391.5; found 391.3.

EXAMPLE 31

4'-{6-Butyl-3-[(2-mercaptomethyl-4-methylpentanoylamino)methyl]-2-oxo-2H-pyridin-1-ylmethyl}biphenyl-2-carboxylic Acid (compound 31-1; $R^6 = -CH_2CH(CH_3)_2$)

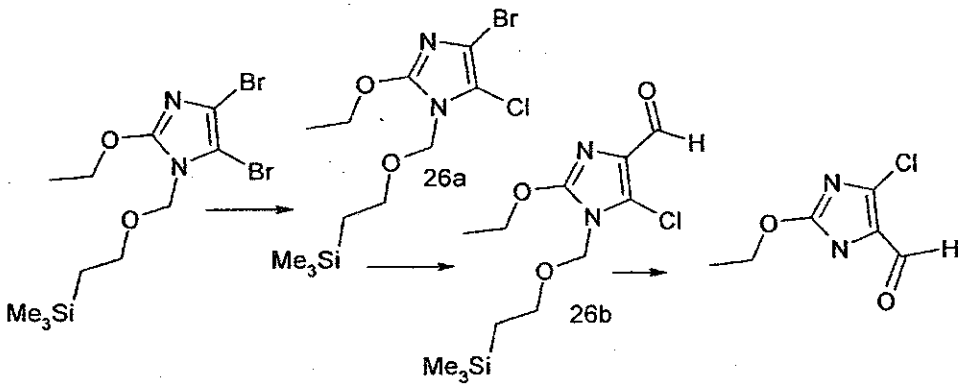


2-Acetylsulfanylmethyl-4-methyl-pentanoic acid (24 mg, 1.1 eq) and HATU (44 mg, 1.1 eq) were dissolved in DMF (2 mL). DIPEA (740 μL, 4 eq) was added, and the mixture was stirred at room temperature for 15 minutes. 4'-(3-Aminomethyl-6-butyl-2-oxo-2H-pyridin-1-ylmethyl)biphenyl-2-carboxylic acid HCl (45 mg, 0.1 mmol) was added, and the solution was stirred at room temperature for 4 hours. The reaction was quenched with water (8 mL) and concentrated HCl (3 drops), and the mixture extracted with EtOAc (10 mL). The organic layer was dried over Na_2SO_4, and evaporated. The residue was dissolved in MeOH (1 mL) and 1M NaOH (3 mL). The solution was stirred under nitrogen for 20 minutes, and the reaction was then quenched with acetic acid (2 mL). The MeOH was evaporated, and the aqueous component extracted with EtOAc (10 mL). The solvent was evaporated and the residue purified by reverse phase chromatography to afford the title compound (7.5 mg, 140 μmol). MS m/z: $[M+H^+]$ calcd for $C_{31}H_{39}N_2O_4S$, 535.7; found 535.2.

Compound (31-2) was prepared in a similar manner: 4'-{3-[(2-benzyl-3-mercaptopropionylamino)methyl]-6-butyl-2-oxo-2H-pyridin-1-ylmethyl}biphenyl-2-carboxylic acid (R^6 = benzyl). MS *m/z*: $[M + H^+]$ calcd for $C_{34}H_{36}N_2O_4S$, 569.24; found 570.2.

PREPARATION 26

4-chloro-2-ethoxyimidazole-5-carboxaldehyde



4-Bromo-5-chloro-2-ethoxy-1-(2-trimethylsilanylethoxymethyl)-1H-imidazole (26a): n-Butyllithium (2.5M in hexanes, 3.3 mL) was added to a solution of 4,5-dibromo-2-ethoxy-1-(2-trimethylsilanylethoxymethyl)-1H-imidazole (3.0 g, 7.5 mmol) and N,N,N',N'-tetramethylethylenediamine (1.2 mL, 8.3 mmol) in THF (20 mL) at -78 °C. After 3 minutes, a solution of hexachloroethane (2.3 g, 9.7 mmol) in THF (8 mL) was added at -78 °C. The mixture was stirred at -78 °C for 1 hour and was then allowed to warm to room

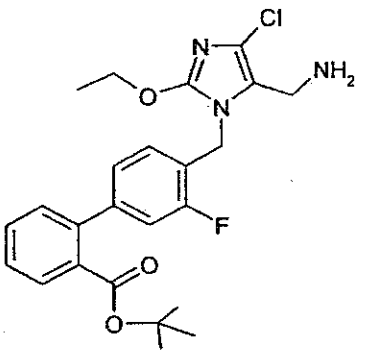
temperature. Saturated aq. NH_4Cl (3 mL) was added and the mixture was concentrated *in vacuo*. The mixture was extracted with EtOAc (2x100 mL) and sat. aq. $NaHCO_3$ (30 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography (EtOAc:hexane) afforded intermediate (26a) (2.3 g).

5-Chloro-2-ethoxy-1-(2-trimethylsilanylethoxymethyl)-1H-imidazole-4-carbaldehyde (26b): n-Butyllithium (2.5M in hexanes,1.2 mL) was added to a solution of intermediate (26a) (1.0 g, 2.8 mmol) and N,N,N',N'-tetramethylethylenediamine (0.5 mL, 3.1 mmol) in THF (8 mL) at -78 °C. DMF (0.3 mL, 3.4 mmol) was added after 3 minutes. The mixture was stirred at -78 °C for 1 hour. The mixture was allowed to warm to room temperature over 30 minutes. Saturated aq. NH_4OH (1 mL) was added and the mixture was concentrated *in vacuo*. The mixture was extracted with DCM (2x30 mL) and 0.5M PO_3H_4 (10 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography (EtOAc:hexane) afforded intermediate (26b) (600 mg).

A solution of intermediate (26b) (500 mg, 2.0 mmol) in DCM (2 mL) and TFA (4 mL) was stirred at room temperature for 3 hours. The mixture was concentrated *in vacuo*. The concentrate was extracted with DCM (2x8 mL) and sat. aq. $NaHCO_3$ (5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude title compound (298 mg).

PREPARATION 27

4'-(5-Aminomethyl-4-chloro-2-ethoxyimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-Butyl Ester



4'-(4-Chloro-2-ethoxy-5-formyl-imidazol-1-ylmethyl)-3'-fluoro-biphenyl-2-carboxylic acid tert-butyl ester (27a): A solution of 4-chloro-2-ethoxyimidazole-5-carboxaldehyde (295.0 mg, 1.7 mmol), 4'-bromomethyl-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (617 mg, 1.7 mmol) and potassium carbonate (467 mg, 3.4 mmol) in

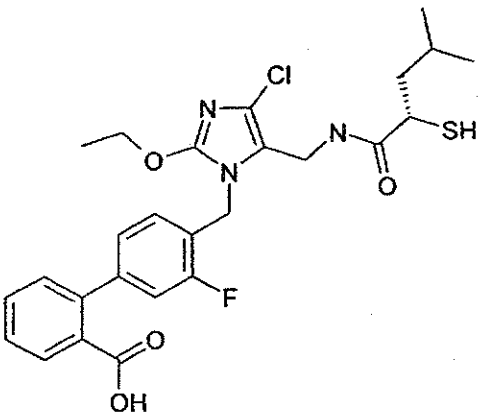
DMF (6 mL) was stirred overnight. The mixture was filtered and concentrated *in vacuo*. Silica gel chromatography (hexane:EtOAc) afforded intermediate (27a) (598 mg).

4'-[4-Chloro-2-ethoxy-5-(hydroxyiminomethyl)imidazol-1-ylmethyl]-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (27b): Hydroxylamine hydrochloride (185 mg) was added to a solution of intermediate (27) (610.0 mg, 1.3 mmol) in pyridine (8 mL) and water (3 mL). After 1 hour, water (20 mL) was added and the resulting precipitate was filtered. The solid was dried *in vacuo* to afford crude intermediate (27b) (468 mg).

Titanium(III) chloride (448 mg, 2.90 mmol) was added to a solution of intermediate (27b) (459.0 mg, 1.0 mmol), $NaBH_3CN$ (274 mg, 4.4 mmol) and ammonium acetate (164 mg, 2.1 mmol) in MeOH (8 mL) at 0 °C. The mixture was stirred at room temperature for 3 hours. The mixture was added to a solution of sat. aq. ammonia (15 mL) and MeOH (15 mL). The solution was filtered, and concentrated *in vacuo*. The concentrate was extracted with DCM (2x80 mL) and sat. aq. $NaHCO_3$ (50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel chromatography [DCM:MeOH (5% triethylamine)] afforded the title compound (85 mg).

EXAMPLE 32

4'-{4-Chloro-2-ethoxy-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic Acid• $C_2HF_3O_2$

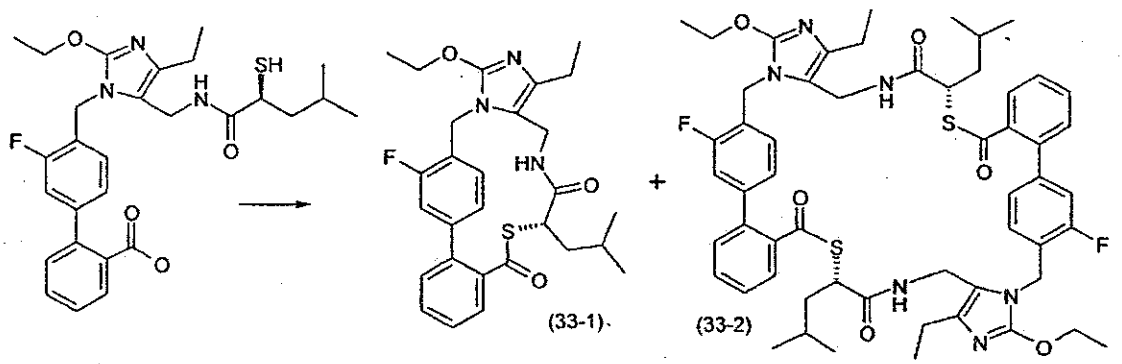


EDC (30 µL, 0.2 mmol) was added to a solution of 4'-(5-aminomethyl-4-chloro-2-ethoxyimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (80.0 mg, 0.2 mmol), *(S)*-2-acetylsulfanyl-4-methylpentanoic acid (33.1 mg, 0.2 mmol), 1-Hydroxy-7-azabenzotriazole (23.7 mg, 0.2 mmol), and 4-methylmorpholine (19.1 µL, 0.2 mmol) in DMF (1 mL) at 0 °C. The mixture was stirred overnight at room temperature. The mixture was extracted with EtOAc (2x10mL) and 0.5M aq. HCl (10mL). The combined organic fractions were dried over sodium sulfate and concentrated *in vacuo* to afford an oil. A

solution of the oil in DCM (2 mL) and TFA (4 mL) was stirred at room temperature. After 2 hours, the mixture was concentrated *in vacuo* to afford an oil. A solution of the oil in MeOH (2 mL) and 1M aq. NaOH (3 mL) was stirred under nitrogen for 1.5 hours. The mixture was neutralized with 6M aq. HCl and was concentrated *in vacuo*. Reverse phase HPLC afforded the title compound (9.7 mg). MS m/z: $[M+H^+]$ calcd for $C_{26}H_{29}ClFN_3O_4S$, 534.16; found: 534.0.

EXAMPLE 33

Cyclization of 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]-imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid to form cyclic prodrugs (33-1) and (33-2)



To a solution of 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoyl-amino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid•$C_2HF_3O_2$ (138 mg, 215 μmol) in methylene chloride (20 mL, 0.3 mol) was added DMAP (27.6 mg, 0.226 mmol) and EDC (43.3 mg, 0.226 mmol). The mixture was stirred at room temperature overnight. After evaporation of volatile solvents, the residue was purified by preparative HPLC, to yield the cyclic thioesters as monomer (33-1) and dimer (33-2) in a pure form (>95%).

(33-1) ESMS $[M+H^+]$ calcd for $C_{28}H_{32}FN_3O_3S$, 510.22; found 510.6. Anal. HPLC retention time = 3.86 min; gradient conditions = 25-95% MeCN/H_2O over 5 min. ^{1}H-NMR (CD_3OD, 300 MHz) δ (ppm) 7.60 (m, 1H), 7.54 (m, 1H), 7.52-7.48 (m, 2H), 7.40 (m, 1H), 7.36-7.38 (m, 1H), 6.89-6.92 (d, 1H), 4.71 (m, 2H), 4.30-4.35 (br d, 1H), 4.20 (br d, 1H), 4.05 (t, 1H), 2.60-2.68 (m, 2H), 1.60-1.75 (m, 1H), 1.55-1.60 (m, 4H), 1.43 (m, 1H), 1.23 (t, 3H), 0.90 (d, 6H).

(33-2) ESMS $[M+H^+]$ calcd for $C_{56}H_{64}F_2N_6O_6S_2$, 1019.44; found 1019.8. Anal. HPLC retention time = 4.19 min; gradient conditions 25-95% MeCN/H_2O over 5 min.

ASSAY 1

AT_1 and AT_2 Radioligand Binding Assays

These *in vitro* assays were used to assess the ability of test compounds to bind to the AT_1 and the AT_2 receptors.

Membrane Preparation From Cells Expressing Human AT_1 or AT_2 Receptors

Chinese hamster ovary (CHO-K1) derived cell lines stably expressing the cloned human AT_1 or AT_2 receptors, respectively, were grown in HAM's-F12 medium supplemented with 10% fetal bovine serum, 10 μg/ml penicillin/streptomycin, and 500 μg/ml geneticin in a 5% CO_2 humidified incubator at 37 °C. AT_2 receptor expressing cells were grown in the additional presence of 100 nM PD123,319 (AT_2 antagonist). When cultures reached 80-95% confluence, the cells were washed thoroughly in PBS and lifted with 5 mM EDTA. Cells were pelleted by centrifugation and snap frozen in MeOH-dry ice and stored at -80 °C until further use.

For membrane preparation, cell pellets were resuspended in lysis buffer (25 mM Tris/HCl pH 7.5 at 4 °C, 1 mM EDTA, and one tablet of Complete Protease Inhibitor Cocktail Tablets with 2 mM EDTA per 50 mL buffer (Roche cat.# 1697498, Roche Molecular Biochemicals, Indianapolis, IN)) and homogenized using a tight-fitting Dounce glass homogenizer (10 strokes) on ice. The homogenate was centrifuged at 1000 x g, the supernatant was collected and centrifuged at 20,000 x g. The final pellet was resuspended in membrane buffer (75 mM Tris/HCl pH 7.5, 12.5 mM $MgCl_2$, 0.3 mM EDTA, 1 mM EGTA, 250 mM sucrose at 4 °C) and homogenized by extrusion through a 20G gauge needle. Protein concentration of the membrane suspension was determined by the method described in Bradford (1976) *Anal Biochem.* 72:248-54. Membranes were snap frozen in MeOH-dry ice and stored at -80 °C until further use.

Ligand Binding Assay to Determine Compound Affinities for the Human AT_1 and AT_2 Angiotensin Receptors

Binding assays were performed in 96-well Acrowell filter plates (Pall Inc., cat.# 5020) in a total assay volume of 100 μL with 0.2 μg membrane protein for membranes containing the human AT_1 receptor, or 2 μg membrane protein for membranes containing the human AT_2 receptor in assay buffer (50 mM Tris/HCl pH 7.5 at 20 °C, 5 mM $MgCl_2$, 25 μM EDTA, 0.025% BSA). Saturation binding studies for determination of K_d values of the ligand were done using N-terminally Europium-labeled angiotensin-II ([Eu]AngII, H-(Eu-N^1)-Ahx-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-OH; PerkinElmer, Boston, MA) at 8

different concentrations ranging from 0.1 nM to 30 nM. Displacement assays for determination of pK_i values of test compounds were done with [Eu]AngII at 2 nM and 11 different concentrations of drug ranging from 1 pM to 10 μM. Drugs were dissolved to a concentration of 1 mM in DMSO and from there serially diluted into assay buffer. Non-specific binding was determined in the presence of 10 μM unlabeled angiotensin-II. Assays were incubated for 120 minutes in the dark, at room temperature or 37 °C, and binding reactions were terminated by rapid filtration through the Acrowell filter plates followed by three washes with 200 μL ice cold wash buffer (50 mM Tris/HCl pH 7.5 at 4 °C, 5 mM $MgCl_2$) using a Waters filtration manifold. Plates were tapped dry and incubated with 50 μl DELFIA Enhancement Solution (PerkinElmer cat.# 4001-0010) at room temperature for 5 minutes on a shaker. Filter-bound [Eu]AngII was quantitated immediately on a Fusion plate reader (PerkinElmer) using Time Resolved Fluorescence (TRF). Binding data were analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the 3-parameter model for one-site competition. The BOTTOM (curve minimum) was fixed to the value for nonspecific binding, as determined in the presence of 10 μM angiotensin II. K_i values for drugs were calculated from observed IC_{50} values and the K_d value of [Eu]AngII according to the Cheng-Prusoff equation described in Cheng et al. (1973) *Biochem Pharmacol.* 22(23):3099-108. Selectivities of test compounds for the AT_1 receptor over the AT_2 receptor were calculated as the ratio of AT_2K_i/AT_1K_i. Binding affinities of test compounds were expressed as negative decadic logarithms of the K_i values (pK_i).

In this assay, a higher pK_i value indicates that the test compound has a higher binding affinity for the receptor tested. Exemplary compounds of the invention that were tested in this assay, typically were found to have a pK_i at the AT_1 receptor greater than or equal to about 5.0. For example, the compound of Example 1 was found to have a pK_i value greater than about 7.0.

ASSAY 2

In vitro Assays for the Quantitation of Inhibitor Potencies (IC_{50}) at Human and Rat NEP, and Human ACE

The inhibitory activities of compounds at human and rat NEP and human ACE were determined using *in vitro* assays as described below.

Extraction of NEP Activity from Rat Kidneys

Rat NEP was prepared from the kidneys of adult Sprague Dawley rats. Whole

kidneys were washed in cold PBS and brought up in ice-cold lysis buffer (1% Triton X-114, 150 mM NaCl, 50 mM Tris pH 7.5; Bordier (1981) *J. Biol. Chem.* 256: 1604-1607) in a ratio of 5 mL of buffer for every gram of kidney. Samples were homogenized using a polytron hand held tissue grinder on ice. Homogenates were centrifuged at 1000 x g in a swinging bucket rotor for 5 minutes at 3 °C. The pellet was resuspended in 20 mL of ice cold lysis buffer and incubated on ice for 30 minutes. Samples (15-20 mL) were then layered onto 25 mL of ice-cold cushion buffer (6% w/v sucrose, 50 mM pH 7.5 Tris, 150 mM NaCl, 0.06%, Triton X-114), heated to 37 °C for 3-5 minutes and centrifuged at 1000 x g in a swinging bucket rotor at room temperature for 3 minutes. The two upper layers were aspirated off, leaving a viscous oily precipitate containing the enriched membrane fraction. Glycerol was added to a concentration of 50% and samples were stored at -20 °C. Protein concentrations were quantitated using a BCA detection system with BSA as a standard.

Enzyme Inhibition Assays

Recombinant human NEP and recombinant human ACE were obtained commercially (R&D Systems, Minneapolis, MN, catalog numbers 1182-ZN and 929-ZN, respectively). The fluorogenic peptide substrate Mca-BK2 (Mca-Arg-Pro-Pro-Gly-Phe-Ser-Ala-Phe-Lys(Dnp)-OH; Johnson et al. (2000) *Anal. Biochem.* 286: 112-118) was used for the human NEP and ACE assays, and Mca-RRL (Mca-DArg-Arg-Leu-(Dnp)-OH; Medeiros et al. (1997) *Braz. J. Med. Biol. Res.* 30:1157-1162) was used for the rat NEP assay (both from Anaspec, San Jose, CA).

The assays were performed in 384-well white opaque plates at room temperature using the respective fluorogenic peptides at a concentration of 10 μM in assay buffer (50 mM Tris/HCL at 25 °C, 100 mM NaCl, 0.01% Tween-20, 1 μM Zn, 0.025% BSA). Human NEP and human ACE were used at concentrations that resulted in quantitative proteolysis of 5 μM of Mca-BK2 within 20 minutes at room temperature. The rat NEP enzyme preparation was used at a concentration that yielded quantitative proteolysis of 3 μM of Mca-RRL within 20 minutes at room temperature.

Assays were started by adding 25 μL of enzyme to 12.5 μL of test compound at 12 concentrations (10 μM to 20 pM). Inhibitors were allowed to equilibrate with the enzyme for 10 minutes before 12.5 μL of the fluorogenic substrates were added to initiate the reaction. Reactions were terminated by the addition of 10 μL of 3.6% glacial acetic acid after 20 minutes of incubation. Plates were read on a fluorometer with excitation and

emission wavelengths set to 320 nm and 405 nm, respectively.

Raw data (relative fluorescence units) were normalized to % activity from the average high readings (no inhibition, 100% enzyme activity) and average low readings (full inhibition, highest inhibitor concentration, 0% enzyme activity) using three standard NEP and ACE inhibitors, respectively. Nonlinear regression of the normalized data was performed using a one site competition model (GraphPad Software, Inc., San Diego, CA). Data were reported as pIC_{50} values.

Exemplary compounds of the invention that were tested in this assay, typically were found to have a pIC_{50} for the NEP enzyme greater than or equal to about 5.0. For example, the compound of Example 1 has a pIC_{50} value greater than or equal to about 7.0.

ASSAY 3

Pharmacodynamic (PD) assay for ACE, AT_1, and NEP Activity in Anesthetized Rats

Male, Sprague Dawley, normotensive rats are anesthetized with 120 mg/kg (i.p.) of inactin. Once anesthetized, the jugular vein, carotid artery (PE 50 tubing) and bladder (URI-1 urinary silicone catheter) are cannulated and a tracheotomy is performed (Teflon Needle, size 14 gauge) to faciliate spontaneous respiration. The animals are then allowed a 60 minute stablization period and kept continuously infused with 5mL/kg/h of saline (0.9%) throughout, to keep them hydrated and ensure urine production. Body temperature is maintained throughout the experiment by use of a heating pad. At the end of the 60 minute stabilization period, the animals are dosed intravenously (i.v.) with two doses of angiotensin (AngI, 1.0 μg/kg, for ACE inhibitor activity; AngII, 0.1 μg/kg, for AT_1 receptor antagonist activity) at 15 minutes apart. At 15 minutes post-second dose of angiotensin (AngI or AngII), the animals are treated with vehicle or test compound. Five minutes later, the animals are additionally treated with a bolus i.v. injection of atrial natriuretic peptide (ANP; 30 μg/kg). Urine collection (into pre-weighted eppendorf tubes) is started immediately after the ANP treatment and continued for 60 minutes. At 30 and 60 minutes into urine collection, the animals are re-challenged with angiotensin (AngI or AngII). Blood pressure measurements are done using the Notocord system (Kalamazoo, MI). Urine samples are frozen at -20 °C until used for the cGMP assay. Urine cGMP concentrations are determined by Enzyme Immuno Assay using a commercial kit (Assay Designs, Ann Arbor, Michigan, Cat. No. 901-013). Urine volume is determined gravimetrically. Urinary cGMP output is calculated as the product of urine output and urine cGMP concentration. ACE inhibition or AT_1 antagonism is assessed by quantifying

the % inhibition of pressor response to AngI or AngII, respectively. NEP inhibition is assessed by quantifying the potentiation of ANP-induced elevation in urinary cGMP output.

ASSAY 4

In Vivo Evaluation of Antihypertensive Effects in the Conscious SHR Model of Hypertension

Spontaneously hypertensive rats (SHR, 14-20 weeks of age) are allowed a minimum of 48 hours acclimation upon arrival at the testing site. Seven days prior to testing, the animals are either placed on a restricted low-salt diet with food containing 0.1% of sodium for sodium depleted SHRs (SD-SHR) or are placed on a normal diet for sodium repleted SHRs (SR-SHR). Two days prior to testing, the animals are surgically implemented with catheters into a carotid artery and the jugular vein (PE50 polyethylene tubing) connected via a PE10 polyethylene tubing to a selected silicone tubing (size 0.020 ID x 0.037 OD x 0.008 wall) for blood pressure measurement and test compound delivery, respectively. The animals are allowed to recover with appropriate post operative care.

On the day of the experiment, the animals are placed in their cages and the catheters are connected via a swivel to a calibrated pressure transducer. After 1 hour of acclimation, a baseline measurement is taken over a period of at least five minutes. The animals are then dosed i.v. with vehicle or test compound in ascending cumulative doses every 60 minutes followed by a 0.3 mL saline to clear the catheter after each dose. Data is recorded continuously for the duration of the study using Notocord software (Kalamazoo, MI) and stored as electronic digital signals. In some studies, the effects of a single intravenous or oral (gavage) dose are monitored for at least 6 hours after dosing. Parameters measured are blood pressure (systolic, diastolic and mean arterial pressure) and heart rate.

ASSAY 5

In Vivo Evaluation of Antihypertensive Effects in the Conscious DOCA-Salt Rat Model of Hypertension

CD rats (male, adult, 200-300 grams, Charles River Laboratory, USA) are allowed a minimum of 48 hours acclimation upon arrival at the testing site before they are placed on a high salt diet.

One week after the start of the high salt diet, a DOCA-salt pellet (100 mg, 21 days

release time, Innovative Research of America, Sarasota, FL) is implanted subcutaneously and unilateral nephrectomy is performed. On 16 or 17 days post DOCA-salt pellet implantation, animals are implanted surgically with catheters into a carotid artery and the jugular vein with a PE50 polyethylene tubing, which in turn was connected via a PE10 polyethylene tubing to a selected silicone tubing (size 0.020 ID x 0.037 OD x 0.008 wall) for blood pressure measurement and test compound delivery, respectively. The animals are allowed to recover with appropriate post operative care.

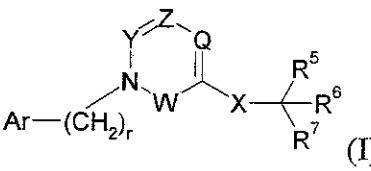
On the day of the experiment, each animal is kept in its cage and connected via a swivel to a calibrated pressure transducer. After 1 hour of acclimation, a baseline measurement is taken over a period of at least five minutes. The animals are then dosed i.v. with a vehicle or test compound in escalating cumulative doses every 60 minutes followed by 0.3 mL of saline to flush the catheter after each dose. In some studies, the effects of a single intravenous or oral (gavage) dose is tested and monitored for at least 6 hours after dosing. Data is recorded continuously for the duration of the study using Notocord software (Kalamazoo, MI) and stored as electronic digital signals. Parameters measured are blood pressure (systolic, diastolic and mean arterial pressure) and heart rate. For cumulative and single dosing, the percentage change in mean arterial pressure (MAP, mmHg) or heart rate (HR, bpm) is determined as described for Assay 4.

While the present invention has been described with reference to specific aspects or embodiments thereof, it will be understood by those of ordinary skilled in the art that various changes can be made or equivalents can be substituted without departing from the true spirit and scope of the invention. Additionally, to the extent permitted by applicable patent statues and regulations, all publications, patents and patent applications cited herein are hereby incorporated by reference in their entirety to the same extent as if each document had been individually incorporated by reference herein.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula I:

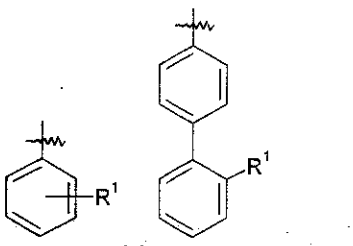


(I)

wherein:

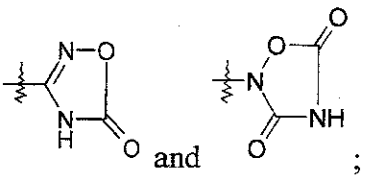
r is 0;

Ar is selected from:



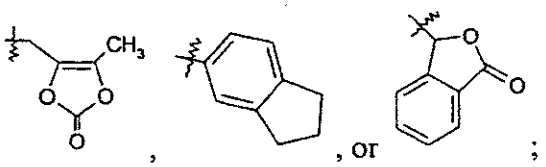
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R^1 is selected from -$COOR^{1a}$, -$NHSO_2R^{1b}$, -SO_2NHR^{1d}, -SO_2OH, -C(O)NH-SO_2R^{1c}, -$P(O)(OH)_2$, -CN, -O-$CH(R^{1e})$-COOH, tetrazol-5-yl,



and ;

R^{1a} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(C_{1-4}alkyl)OC(O)R^{1aa}$, -$C_{0-6}$alkylenemorpholine,



R^{1aa} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -$NR^{1ab}R^{1ac}$, or -$CH(NH_2)CH_2COOCH_3$; R^{1ab} and R^{1ac} are independently selected from H, -C_{1-6}alkyl, and benzyl, or are taken together as -$(CH_2)_{3-6}$-; R^{1b} is R^{1c} or -$NHC(O)R^{1c}$; R^{1c} is -C_{1-6}alkyl, -C_{0-6}alkylene-O-R^{1ca}, -C_{1-5}alkylene-$NR^{1cb}R^{1cc}$, -C_{0-4}alkylenearyl or -C_{0-4}alkyleneheteroaryl; R^{1ca} is H, -C_{1-6}alkyl, or -C_{1-6}alkylene-O-C_{1-6}alkyl; R^{1cb} and R^{1cc} are independently selected from H and -C_{1-6}alkyl, or are taken together as -$(CH_2)_2$-O-$(CH_2)_2$- or -$(CH_2)_2$-$N[C(O)CH_3]$-$(CH_2)_2$-; R^{1d} is H, R^{1c}, -$C(O)R^{1c}$, or -$C(O)NHR^{1c}$; R^{1e} is -C_{1-4}alkyl or aryl;

Y is -$C(R^3)$-, Z is -N-, Q is -$C(R^2)$- and W is a bond; Y is -N-, Z is -$C(R^3)$-, Q is -$C(R^2)$- and W is a bond; Y is -$C(R^3)$-, Z is -N-, Q is -N- and W is a bond; Y is -$C(R^3)$-, Z is -CH-, Q is -N- and W is a bond; or Y is -$C(R^3)$-, Z is -CH-, Q is -$C(R^2)$- and W is -C(O)-;

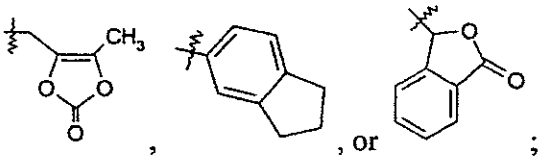
R^2 is selected from H, halo, -NO_2, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{3-6}cycloalkyl, -CN, -$C(O)R^{2a}$, -C_{0-5}alkylene-OR^{2b}, -C_{0-5}alkylene-$NR^{2c}R^{2d}$, -C_{0-3}alkylenearyl, and -C_{0-3}alkylene-heteroaryl; where R^{2a} is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, -OR^{2b} and -$NR^{2c}R^{2d}$; R^{2b} is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and -C_{0-1}alkylenearyl; and R^{2c} and R^{2d} are independently selected from H, -C_{1-4}alkyl, and -C_{0-1}alkylenearyl;

R^3 is selected from -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{3-10}alkynyl, -C_{0-3}alkylene-C_{3-7}cycloalkyl, -C_{2-3}alkenylene-C_{3-7}cycloalkyl, -C_{2-3}alkynylene-C_{3-7}cycloalkyl, -C_{0-5}alkylene-NR^{3a}-C_{0-5}alkylene-R^{3b}, -C_{0-5}alkylene-O-C_{0-5}alkylene-R^{3b}, -C_{0-5}alkylene-S-C_{1-5}alkylene-R^{3b}, and -C_{0-3}alkylenearyl; where R^{3a} is selected from H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, and -C_{0-3}alkylenearyl; and R^{3b} is selected from H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, and aryl;

X is -C_{1-12}alkylene-, where at least one -CH_2- moiety in the alkylene is replaced with a -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moiety, where R^{4a} is selected from H, -OH, and -C_{1-4}alkyl;

R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, -C_{0-2}alkylene-CHR^{5g}-COOH, -C_{0-3}alkylene-$C(O)NR^{5h}$-CHR^{5i}-COOH, and -C_{0-3}alkylene-S-SR^{5j}; R^{5a} is H or -$C(O)$-R^{5aa}; R^{5aa} is -C_{1-6}alkyl, -C_{0-6}alkylene-C_{3-7}cycloalkyl,

-C_{0-6}alkylenearyl, -C_{0-6}alkyleneheteroaryl, -C_{0-6}alkylenemorpholine, -C_{0-6}alkylenepiperazine-CH_3, -CH[$N(R^{5ab})_2$]-aa where aa is an amino acid side chain, -2-pyrrolidine, -C_{0-6}alkylene-OR^{5ab}, -O-C_{0-6}alkylenearyl, -C_{1-2}alkylene-OC(O)-C_{1-6}alkyl, -C_{1-2}alkylene-OC(O)-C_{0-6}alkylenearyl, or -O-C_{1-2}alkylene-OC(O)O-C_{1-6}alkyl; R^{5ab} is H or -C_{1-6}alkyl; R^{5b} is H, -OH, -$OC(O)R^{5ba}$, -CH_2COOH, -O-benzyl, -pyridyl, or -$OC(S)NR^{5bb}R^{5bc}$; R^{5ba} is H, -C_{1-6}alkyl, aryl, -OCH_2-aryl, -CH_2O-aryl, or -$NR^{5bb}R^{5bc}$; R^{5bb} and R^{5bc} are independently selected from H and -C_{1-4}alkyl; R^{5c} is H, -C_{1-6}alkyl, or -C(O)-R^{5ca}; R^{5ca} is H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, aryl, or heteroaryl; R^{5d} is H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -$NR^{5da}R^{5db}$, -CH_2SH, or -O-C_{1-6}alkyl; R^{5da} and R^{5db} are independently selected from H and -C_{1-4}alkyl; R^{5e} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(CH_3)$-O-C(O)R^{5ea},



; R^{5ea} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -$NR^{5eb}R^{5ec}$, or -$CH(NH_2)CH_2COOCH_3$; R^{5eb} and R^{5ec} are independently selected from H, -C_{1-4}alkyl, and -C_{1-3}alkylenearyl, or are taken together as -$(CH_2)_{3-6}$-; R^{5f} is H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -C_{1-3}alkylene-$NR^{5fa}R^{5fb}$, or -C_{1-3}alkylene(aryl)-C_{0-3}alkylene-$NR^{5fa}R^{5fb}$; R^{5fa} and R^{5fb} are independently selected from H and -C_{1-4}alkyl; R^{5g} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, or -CH_2-O-$(CH_2)_2$-O-CH_3; R^{5h} is H or -C_{1-4}alkyl; R^{5i} is H, -C_{1-4}alkyl, or -C_{0-3}alkylenearyl; and R^{5j} is -C_{1-6}alkyl, aryl, or -$CH_2CH(NH_2)COOH$;

R^6 is selected from -C_{1-6}alkyl, -$CH_2O(CH_2)_2$-O-CH_3, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and

R^7 is H or is taken together with R^6 to form -C_{3-8}cycloalkyl;

wherein:

each -CH_2- group in -$(CH_2)_r$- is optionally substituted with 1 or 2 substituents independently selected from -C_{1-4}alkyl and fluoro;

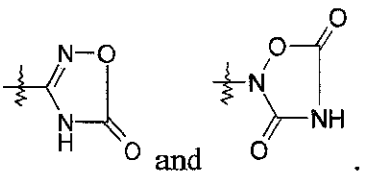
each ring in Ar and each aryl and heteroaryl in R^{1-3} and R^{5-6} is optionally substituted with 1 to 3 substituents independently selected from -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, -$S(O)_2$-C_{1-4}alkyl, -phenyl, -NO_2, -NH_2, -NH-C_{1-6}alkyl and -$N(C_{1-6}alkyl)_2$, wherein each alkyl, alkenyl and alkynyl is optionally substituted with 1 to 5 fluoro atoms;

each carbon atom in X is optionally substituted with one or more R^{4b} groups and one $-CH_2-$ moiety in X may be replaced with a group selected from $-C_{4-8}$cycloalkylene-, $-CR^{4d}=CH-$, and $-CH=CR^{4d}-$; wherein R^{4b} is selected from $-C_{0-5}$alkylene-$COOR^{4c}$, $-C_{1-6}$alkyl, $-C_{0-1}$alkylene-$CONH_2$, $-C_{1-2}$alkylene-OH, $-C_{0-3}$alkylene-C_{3-7}cycloalkyl, 1H-indol-3-yl, benzyl, and hydroxybenzyl, where R^{4c} is H or $-C_{1-4}$alkyl; and R^{4d} is selected from $-CH_2$-2-thiophene and phenyl;

each alkyl and each aryl in R^{1-3}, R^{4a-4d}, and R^{5-6} is optionally substituted with 1 to 7 fluoro atoms;

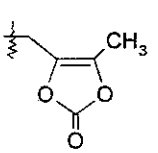
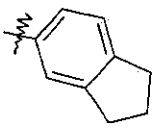
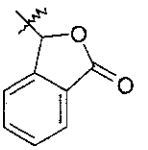
and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein R^1 is selected from -COOH, $-NHSO_2R^{1b}$, $-SO_2NHR^{1d}$, $-SO_2OH$, $-C(O)NH-SO_2R^{1c}$, $-P(O)(OH)_2$, -CN, $-O-CH(R^{1e})$-COOH, tetrazol-5-yl,

 and .

3. The compound of Claim 2, wherein R^1 is selected from -COOH, $-SO_2NHR^{1d}$, and tetrazol-5-yl.

4. The compound of Claim 1, wherein R^1 is $-COOR^{1a}$, where R^{1a} is selected from $-C_{1-6}$alkyl, $-C_{1-3}$alkylenearyl, $-C_{1-3}$alkyleneheteroaryl, $-C_{3-7}$cycloalkyl, $-CH(C_{1-4}$alkyl$)OC(O)R^{1aa}$, $-C_{0-6}$alkylenemorpholine,

, , and .

5. The compound of Claim 1, wherein Y represents $-C(R^3)-$, Z is -N-, Q is $-C(R^2)-$ and

W is a bond.

6. The compound of Claim 1, wherein Y represents -C(R^3)-, Z is -N-, Q is -N- and W is a bond.

7. The compound of Claim 1, wherein Y represents -C(R^3)-, Z is -CH-, Q is -C(R^2)- and W is -C(O)-.

8. The compound of Claim 1, wherein Y represents -N-, Z is -C(R^3)-, Q is -C(R^2)- and W is a bond.

9. The compound of Claim 1, wherein Y represents -C(R^3)-, Z is -CH-, Q is -N- and W is a bond.

10. The compound of Claim 1, wherein R^2 is selected from H, halo, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and -C_{0-5}alkylene-OR^{2b}.

11. The compound of Claim 1, wherein R^3 is selected from -C_{1-10}alkyl and -C_{0-5}alkylene-O-C_{0-5}alkylene-R^{3b}, where R^{3b} is -C_{1-6}alkyl.

12. The compound of Claim 11, wherein R^3 is selected from -C_{2-5}alkyl and -O-C_{1-5}alkyl.

13. The compound of Claim 1, wherein X is -C_{1-11}alkylene-, 1 to 4 -CH_2- moieties in the alkylene are replaced with a -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moiety, and R^{4a} is selected from H and -OH.

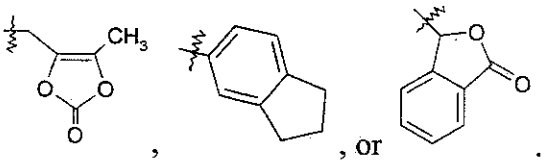
14. The compound of Claim 13 wherein X is selected from: -C(O)NH-; -CH_2-NHC(O)-; -C(O)NH-CH_2-; -C(O)NH-NHC(O)-; -CH=C(-CH_2-2-thiophene)-C(O)NH-; -$(CH_2)_2$-NHC(O)-; -C(O)NH-CH_2-CH(COOH)-CH_2-; -C(O)NH-CH(benzyl)-CH_2-NHC(O)-; -C(O)NH-CH(benzyl)-CH_2-C(O)NH-; -CH_2-NHC(O)-CH_2-NHC(O)-; -CH_2-NHC(O)-cyclohexylene-NHC(O)-; -CH_2-N(OH)C(O)-cyclohexylene-NHC(O)-; -CH_2-NHC(O)-CH_2-CH(COOH)-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_2$-NHC(O)-; -C(O)NH-$(CH_2)_2$-C(O)N(OH)-CH_2-; -C(O)NH-$(CH_2)_2$-CH(COOH)-NHC(O)-; -C(O)NH-$(CH_2)_4$-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_2$-CH(COOH)-NHC(O)-; -C(O)NH-$(CH_2)_3$-CH(COOH)-NHC(O)-; -C(O)NH-$(CH_2)_2$-NHC(O)-CH_2-NHC(O)-; -C(O)NH-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_4$-NHC(O)-; -C(O)NH-$(CH_2)_4$-CH(COOH)-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-; -CH_2-C(O)NH-$(CH_2)_2$-NHC(O)-cyclohexylene-NHC(O)-; -C(O)NH-$(CH_2)_4$-NHC(O)-CH_2-NHC(O)-; -C(O)NH-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_6$-NHC(O)-; -CH_2-NHC(O)-$(CH_2)_4$-NHC(O)-cyclohexylene-NHC(O)-; -C(O)NH-$(CH_2)_6$-NHC(O)-cyclohexylene-NHC(O)-; and

-CH_2-NHC(O)-$(CH_2)_6$-NHC(O)-cyclohexylene-NHC(O)-.

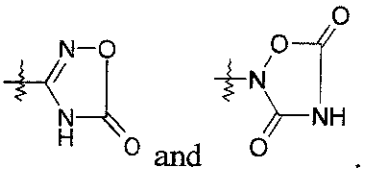
15. The compound of Claim 14, wherein X is selected from -C(O)NH- and -CH_2-NHC(O)-.

16. The compound of Claim 1, wherein R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, -C_{0-2}alkylene-CHR^{5g}-COOH, and -C_{0-3}alkylene-$C(O)NR^{5h}$-CHR^{5i}-COOH; R^{5a} is H, R^{5b} is -OH, R^{5c} is H, R^{5d} is H, R^{5e} is H.

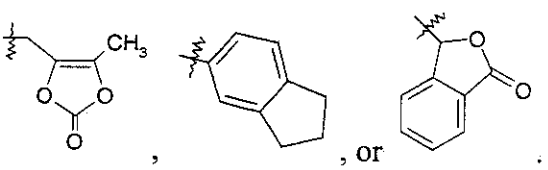
17. The compound of Claim 1, wherein R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, and -C_{0-3}alkylene-S-SR^{5j}; where R^{5a} is -C(O)-R^{5aa}; R^{5b} is H, -$OC(O)R^{5ba}$, -CH_2COOH, -O-benzyl, -pyridyl, or -$OC(S)NR^{5bb}R^{5bc}$; R^{5e} is -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(CH_3)$-O-$C(O)R^{5ea}$,


, , or .

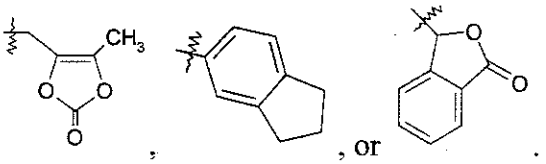
18. The compound of Claim 16, wherein R^1 is selected from -COOH, -$NHSO_2R^{1b}$, -SO_2NHR^{1d}, -SO_2OH, -C(O)NH-SO_2R^{1c}, -$P(O)(OH)_2$, -CN, -O-$CH(R^{1e})$-COOH, tetrazol-5-yl,


and .

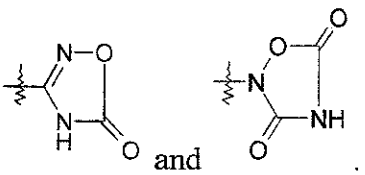
19. The compound of Claim 17, wherein R^1 is -$COOR^{1a}$, where R^{1a} is -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(C_{1-4}$alkyl$)OC(O)R^{1aa}$, -C_{0-6}alkylenemorpholine,


, , or .

20. The compound of Claim 16, wherein R^1 is -$COOR^{1a}$, and R^{1a} is -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(C_{1-4}$alkyl$)OC(O)R^{1aa}$, -C_{0-6}alkylenemorpholine,



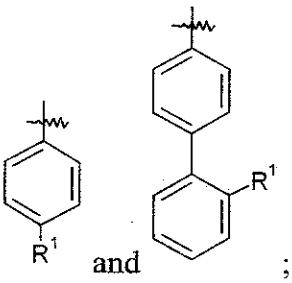
21. The compound of Claim 17, wherein R^1 is selected from -COOH, -$NHSO_2R^{1b}$, -SO_2NHR^{1d}, -SO_2OH, -C(O)NH-SO_2R^{1c}, -$P(O)(OH)_2$, -CN, -O-$CH(R^{1e})$-COOH, tetrazol-5-yl,



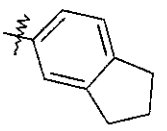
22. The compound of Claim 1, wherein R^6 is selected from -C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl.

23. The compound of Claim 1, wherein R^7 is H or is taken together with R^6 to form cyclopentyl.

24. The compound of Claim 5, wherein Ar is selected from:



R^1 is selected from -$COOR^{1a}$, -$NHSO_2R^{1b}$, -SO_2NHR^{1d}, -SO_2OH, -O-$CH(R^{1e})$-COOH, and tetrazol-5-yl; where R^{1a} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(C_{1-4}alkyl)OC(O)R^{1aa}$, or



R^{1aa} is -O-C_{1-6}alkyl or -O-C_{3-7}cycloalkyl; R^{1b} is R^{1c}; R^{1c} is -C_{1-6}alkyl or -C_{0-4}alkylenearyl; R^{1d} is H, -$C(O)R^{1c}$, or -$C(O)NHR^{1c}$; R^{1e} is -C_{1-4}alkyl;

R^2 is selected from H, halo, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and -C_{0-5}alkylene-OR^{2b}; where R^{2b} is selected from H and -C_{1-6}alkyl;

R^3 is selected from -C_{1-10}alkyl and -C_{0-5}alkylene-O-C_{0-5}alkylene-C_{1-6}alkyl;

X is -C_{1-11}alkylene-, where 1 to 4 -CH_2- moieties in the alkylene are replaced with a -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moiety, where R^{4a} is selected from H and -OH;

R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-C(O)$NR^{5b}R^{5c}$, -NH-C_{0-1}alkylene-P(O)$(OR^{5e})_2$, -C_{0-2}alkylene-CHR^{5g}-COOH and -C_{0-3}alkylene-C(O)NR^{5h}-CHR^{5i}-COOH; R^{5a} is H or -C(O)-R^{5aa}; R^{5aa} is -C_{1-6}alkyl, -C_{0-6}alkylene-C_{3-7}cycloalkyl, -C_{0-6}alkylenearyl, or -C_{0-6}alkylenemorpholine; R^{5b} is H, -OH, -$OC(O)R^{5ba}$, -CH_2COOH, or -$OC(S)NR^{5bb}R^{5bc}$; R^{5ba} is -OCH_2-aryl or -CH_2O-aryl; R^{5bb} and R^{5bc} are independently -C_{1-4}alkyl; R^{5c} is H; R^{5e} is H; R^{5g} is -CH_2-O-$(CH_2)_2$-O-CH_3; R^{5h} is H; and R^{5i} is -C_{0-3}alkylenearyl;

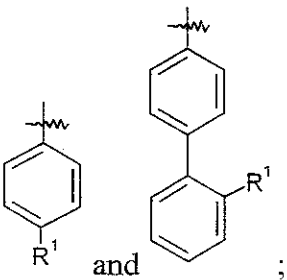
R^6 is selected from -C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and

R^7 is H or is taken together with R^6 to form cyclopentyl.

25. The compound of Claim 24, wherein R^1 is selected from -COOH, -CO(O)(C_{1-6}alkyl), -$NHSO_2$(C_{1-6}alkyl), and -SO_2NH[-C(O)(C_{1-6}alkyl)]; R^2 is selected from H, halo, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and -C_{0-5}alkylene-OH; R^3 is -C_{0-5}alkylene-O-C_{0-5}alkylene-C_{1-6}alkyl; X is -C_{1-11}alkylene-, where 1 to 4 -CH_2- moieties in the alkylene are replaced with -NHC(O)- or -C(O)NH-; R^5 is -C_{0-3}alkylene-SR^{5a} or -C_{0-3}alkylene-C(O)NH(OH); R^{5a} is H or -C(O)-R^{5aa}; R^{5aa} is -C_{1-6}alkyl, -C_{0-6}alkylenearyl, or -C_{0-6}alkylenemorpholine; R^6 is selected from -C_{1-6}alkyl, -C_{0-3}alkylenearyl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and R^7 is H.

26. The compound of Claim 25, wherein one ring in Ar is substituted with 1 or 2 fluoro atoms.

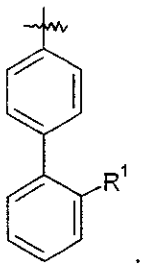
27. The compound of Claim 6, wherein Ar is selected from:



and ;

R^1 is -$COOR^{1a}$, where R^{1a} is H or -C_{1-6}alkyl; R^3 is -C_{1-10}alkyl; X is -CH_2-NHC(O)-; R^5 is selected from -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-C(O)N(OH)H; R^{5a} is H or -C(O)C_{1-6}alkyl; R^6 is selected from -C_{1-6}alkyl and -C_{0-3}alkylenearyl; and R^7 is H.

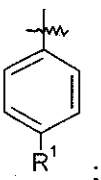
28. The compound of Claim 7, wherein Ar is:



;

R^1 is -$COOR^{1a}$, where R^{1a} is H or -C_{1-6}alkyl; R^2 is H; R^3 is -C_{1-10}alkyl; X is -CH_2-NHC(O)-; R^5 is selected from -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-C(O)N(OH)H; R^{5a} is H or -C(O)C_{1-6}alkyl; R^6 is selected from -C_{1-6}alkyl and -C_{0-3}alkylenearyl; and R^7 is H.

29. The compound of Claim 8, wherein Ar is:



;

R^1 is -$COOR^{1a}$, where R^{1a} is H or -C_{1-6}alkyl; R^2 is H; R^3 is -C_{1-10}alkyl; X is -C(O)NH-; R^5

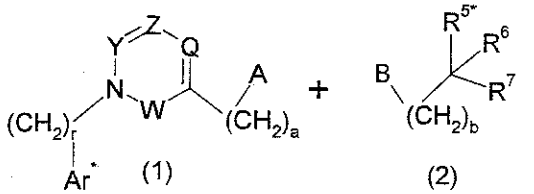
is selected from -C_{0-3}alkylene-SR^{5a} and -C_{0-3}alkylene-C(O)N(OH)H; R^{5a} is H or -C(O)C_{1-6}alkyl; R^6 is -C_{0-3}alkylenearyl; and R^7 is H.

30. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

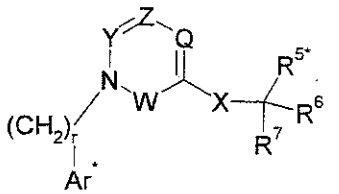
31. The pharmaceutical composition of Claim 30 further comprising a second therapeutic agent selected from the group consisting of diuretics, β_1 adrenergic receptor blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, AT_1 receptor antagonists, neprilysin inhibitors, non-steroidal anti-inflammatory agents, prostaglandins, anti-lipid agents, anti-diabetic agents, anti-thrombotic agents, renin inhibitors, endothelin receptor antagonists, endothelin converting enzyme inhibitors, aldosterone antagonists, angiotensin-converting enzyme/neprilysin inhibitors, vasopressin receptor antagonists, and combinations thereof.

32. A process for preparing the compound of Claim 1, comprising:

(a) coupling a compound of formula 1 with a compound of formula 2:



to produce a compound having the formula:



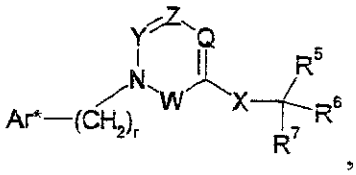
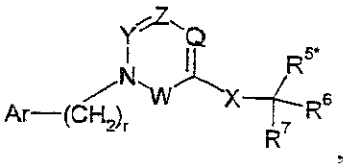
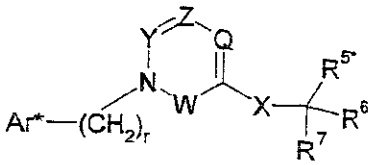
where: A is -NH_2 and B is -COOH or A is -COOH and B is -NH_2; the sum of a and b is in the range of 0 to 11; Ar* represents Ar-R^{1*}, where R^{1*} is R^1 or a protected form of R^1; and R^{5*} represents R^5 or a protected form of R^5; the carbon atoms in the -$(CH_2)_a$ and -$(CH_2)_b$ groups may be substituted with one or more R^{4b} groups; and one -CH_2- group in the -$(CH_2)_a$ or the -$(CH_2)_b$ group may be replaced with -C_{4-8}cycloalkylene-, -CR^{4d}=CH-, or -CH=CR^{4d}-; and

(b) when R^{1*} is a protected form of R^1 and/or R^{5*} is a protected form of R^5, deprotecting the product of step (a) to produce a compound of formula I.

33. A compound prepared by the process of Claim 32.

34. An intermediate useful in the synthesis of the compound of Claim 1, selected from

the group comprising:



, and


wherein: Ar* is Ar-R^{1}*; R^{1}* is selected from -C(O)O-P^{2}, -SO_2O-P^{5}, -SO_2NH-P^{6}, -P(O)(O-P^{7})$_2$, -OCH(CH_3)-C(O)O-P^{2}, -OCH(aryl)-C(O)O-P^{2}, and tetrazol-5-yl-P^{4}; R^{5*} is selected from -C_{0-3}alkylene-S-P^{3}, -C_{0-3}alkylene-C(O)NH(O-P^{5}), -C_{0-3}alkylene-N(O-P^{5})-C(O)R^{5d}, -C_{0-1}alkylene-NHC(O)CH_2S-P^{3}, -NH-C_{0-1}alkylene-P(O)(O-P^{7})$_2$, -C_{0-3}alkylene-P(O)(O-P^{7})-R^{5e}, -C_{0-2}alkylene-CHR^{5f}-C(O)O-P^{2} and -C_{0-3}alkylene-C(O)NR^{5g}-CHR^{5h}-C(O)O-P^{2}; P^{2} is a carboxy-protecting group selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; P^{3} is a thiol-protecting group selected from ethers and esters; P^{4} is a tetrazole-protecting group selected from trityl and diphenylmethyl; P^{5} is a hydroxyl-protecting group selected from C_{1-6}alkyl, silyl groups, esters, and arylmethyl; P^{6} is a sulfonamide-protecting group selected from *t*-butyl and acyl groups; and P^{7} is a phosphate-protecting group selected from C_{1-4}alkyl, aryl, and substituted aryl; Ar, R^{5d}, R^{5e}, R^{5f}, R^{5g} and R^{5h} are as defined in claim 1; and salts thereof.

35. Use of the compound of Claim 1 for the manufacture of a medicament.

36. Use of the compound of Claim 1 for the manufacture of a medicament for treating hypertension or heart failure.

37. Use of the compound of Claim 1 for the manufacture of a medicament for antagonizing an angiotensin II type 1 receptor in a mammal.

38. Use of the compound of Claim 1 for the manufacture of a medicament for inhibiting a neprilysin enzyme in a mammal.