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(54) Title: DEUTERATED SACUBITRIL

(57) Abstract: This invention relates to deuterium substituted analogs of sacubitril and pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering sacubitril. The invention also relates to compositions comprising a combination of a deuterated sacubitril analog and an angiotensin receptor antagonist. Such combinations are useful, for example, for treating patients with heart failure to reduce the risk of death from cardiovascular causes or hospitalization for heart failure.



DEUTERATED SACUBITRIL**CROSS REFERENCE TO RELATED APPLICATIONS**

[1] This application claims the benefit of U.S. Provisional Serial No. 62/046,061 filed September 4, 2014. This disclosure of the prior application is considered part of (and is incorporated by reference in) the disclosure of this application.

BACKGROUND OF THE INVENTION

[2] Heart failure is a disease in which the heart cannot pump enough blood to the body's organs, resulting in shortness of breath, fatigue and retention of fluids. Five million to six million Americans, and an estimated 26 million people globally, have heart failure, and it is the leading cause of hospitalization in the United States and Europe, according to a recent paper in the Journal of the American College of Cardiology.

[3] Sacubitril, also known as AHU377, and chemically as 5-(biphenyl-4-yl)-4(*S*)-(3-carboxypropionamido)-2(*R*)-methylbutyric acid ethyl ester, is an inhibitor of neprilysin, also known as enkephalinase or neutral endopeptidase (NEP). Sacubitril has been approved as part of a fixed dose combination with valsartan, an angiotensin II receptor antagonist, for reducing the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure. The combination, known by the code name LCZ696, and marketed as Entresto, was found to have efficacy in prolonging the lives of people with heart failure. The efficacy of LCZ696 in comparison to enalapril was shown in a phase 3 clinical trial in patients who had heart failure with a reduced ejection fraction of 40% or less. The clinical trial showed an overwhelming benefit for patients who received LCZ696 at a dose of 200 mg twice daily versus enalapril at a dose of 10 mg twice daily. See John J.V. McMurray, et al. for the PARADIGM-HF Investigators and Committees (August 30, 2014). "Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure". N Eng J Med 371.

[4] Sacubitril is described in US patent 5,217,996. Despite its promising activity, sacubitril is administered as a fixed dose combination with another active ingredient. The selection of a suitable fixed dose combination is often limited by the pharmacokinetics and pharmacodynamics of each active ingredient. For LCZ696, the pharmacokinetics and pharmacodynamics have been described by J. Gu, et al. J. Clin. Pharmacol. 2010;

50:401-414 (2010). It would be desirable to have new analogs of sacubitril with improved pharmacokinetic properties, especially new analogs that provide greater options for use with a second therapeutic agent.

SUMMARY OF THE INVENTION

[5] This invention relates to deuterium substituted analogs of sacubitril and pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering sacubitril. The invention also relates to compositions comprising a combination of a deuterated sacubitril analog and an angiotensin receptor antagonist. Such combinations are useful, for example, for treating patients with heart failure to reduce the risk of death from cardiovascular causes or hospitalization for heart failure.

DETAILED DESCRIPTION OF THE INVENTION

[6] The compounds of this invention are deuterium substituted analogs of sacubitril that are useful for treating subjects who had heart failure. In particular, the compounds of this invention are useful when combined with an angiotensin receptor antagonist such as valsartan.

[7] In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as “H” or “hydrogen”, the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as “D” or “deuterium”, the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

[8] The term “isotopic enrichment factor” as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

[9] In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium

incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[10] The term “isotopologue” refers to a species in which the chemical structure differs from a specific compound of this invention only in the isotopic composition thereof.

[11] It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of Compound 1 will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada, E et al., *Seikagaku*, 1994, 66:15; Gannes, LZ et al., *Comp Biochem Physiol Mol Integr Physiol*, 1998, 119:725.

[12] The term “compound,” when referring to a compound of this invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues *in toto* will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues *in toto* will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

[13] The invention also provides salts of the compounds of the invention.

[14] A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

[15] The term “pharmaceutically acceptable,” as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A

“pharmaceutically acceptable salt” means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A “pharmaceutically acceptable counterion” is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

[16] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and

hydrobromic acid, and especially those formed with organic acids such as maleic acid.

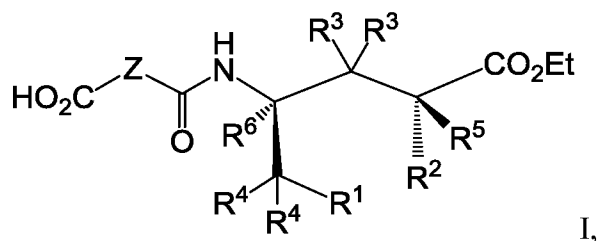
[17] The pharmaceutically acceptable salt may also be a salt of a compound of the present invention having an acidic functional group, such as a carboxylic acid functional group, and a base. Exemplary bases include, but are not limited to, hydroxide of alkali metals including sodium, potassium, and lithium; hydroxides of alkaline earth metals such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, organic amines such as unsubstituted or hydroxyl-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-(C₁-C₆)-alkylamine), such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; morpholine; thiomorpholine; piperidine; pyrrolidine; and amino acids such as arginine, lysine, and the like.

[18] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

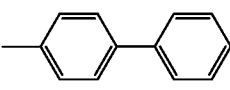
[19] “D” and “d” both refer to deuterium. “Stereoisomer” refers to both enantiomers and diastereomers. “Tert” and “t-” each refer to tertiary. “US” refers to the United States of America.

“Substituted with deuterium” refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms.

[20] The present invention provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is , optionally substituted by one or more deuterium;

R² is methyl, optionally substituted by one or more deuterium;

Z is $-\text{C}(\text{R}^7)_2\text{C}(\text{R}^8)_2-$, wherein each R^7 and each R^8 are independently hydrogen or deuterium;

Each R^3 is independently hydrogen or deuterium;

Each R^4 is independently hydrogen or deuterium;

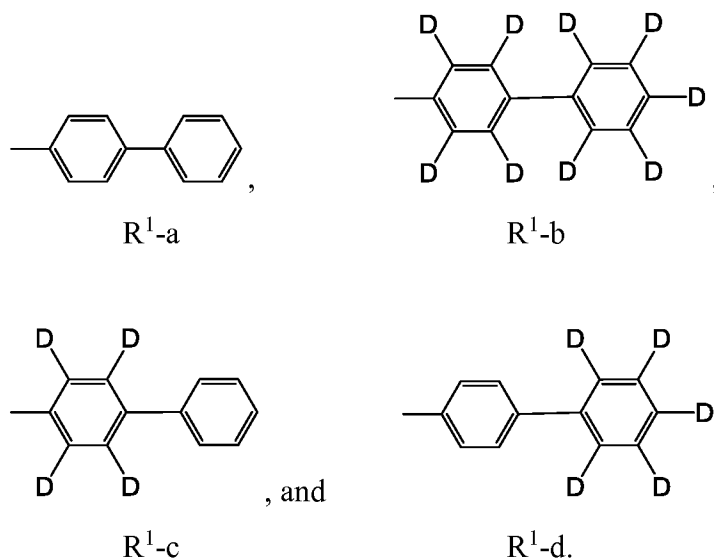
R^5 is hydrogen or deuterium; and

R^6 is hydrogen or deuterium; provided that R^6 is deuterium when neither R^1 nor R^2 are substituted by deuterium and each of R^3 , R^4 , R^5 , R^7 and R^8 are hydrogen.

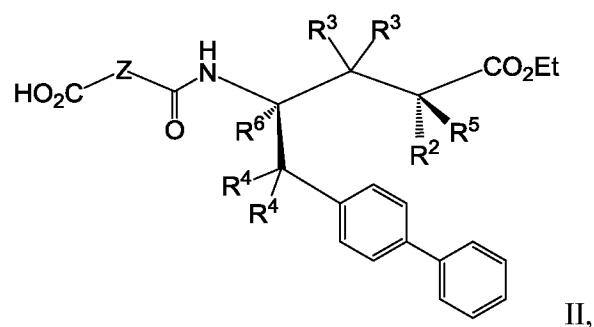
[21] One embodiment relates to a compound of Formula I where R^2 is $-\text{CH}_3$ or $-\text{CD}_3$, each R^3 is the same, each R^4 is the same, each R^7 is the same and each R^8 is the same.

[22] Another embodiment relates to compound of Formula I where Z is $-\text{CH}_2\text{CH}_2-$; $-\text{CD}_2\text{CD}_2-$; $-\text{CD}_2\text{CH}_2-$; or $-\text{CH}_2\text{CD}_2-$. In one aspect, Z is $-\text{CH}_2\text{CH}_2-$; $-\text{CD}_2\text{CD}_2-$; $-\text{CD}_2\text{CH}_2-$; or $-\text{CH}_2\text{CD}_2-$, R^2 is $-\text{CH}_3$ or $-\text{CD}_3$, each R^3 is the same, each R^4 is the same, each R^7 is the same and each R^8 is the same.

[23] Preferred R^1 groups are the following:



[24] One embodiment relates to compounds of Formula I where R^1 is $\text{R}^1\text{-a}$, which are referred to as compounds of Formula II:



or a pharmaceutically acceptable salt thereof, where Z, R², R³, R⁴, R⁵, and R⁶ are as described above.

[25] In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

[26] Examples of specific compounds of Formula II are shown in Table 1a and Table 1b below. In these compounds, all atoms not designated as deuterium are present at their natural abundance.

Table 1a. Examples of Specific Compounds of Formula II

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
II-1	-CD ₂ CD ₂ -	-CH ₃	H	H	H	H
II-2	-CD ₂ CD ₂ -	-CD ₃	D	D	D	D
II-3	-CD ₂ CD ₂ -	-CD ₃	D	D	H	H
II-4	-CD ₂ CD ₂ -	-CD ₃	D	H	H	H
II-5	-CD ₂ CD ₂ -	-CD ₃	H	H	H	H
II-6	-CD ₂ CD ₂ -	-CH ₃	D	D	H	H
II-7	-CD ₂ CD ₂ -	-CH ₃	D	D	D	H
II-8	-CD ₂ CD ₂ -	-CH ₃	H	D	H	H
II-9	-CH ₂ CH ₂ -	-CD ₃	D	D	D	D

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
II-10	-CH ₂ CH ₂ -	-CD ₃	D	D	H	H
II-11	-CH ₂ CH ₂ -	-CD ₃	D	H	H	H
II-12	-CH ₂ CH ₂ -	-CD ₃	H	H	H	H
II-13	-CH ₂ CH ₂ -	-CH ₃	D	D	H	H
II-14	-CH ₂ CH ₂ -	-CH ₃	D	D	D	H
II-15	-CH ₂ CH ₂ -	-CH ₃	H	D	H	H

or a pharmaceutically acceptable salt thereof.

Table 1b. Examples of Specific Compounds of Formula II

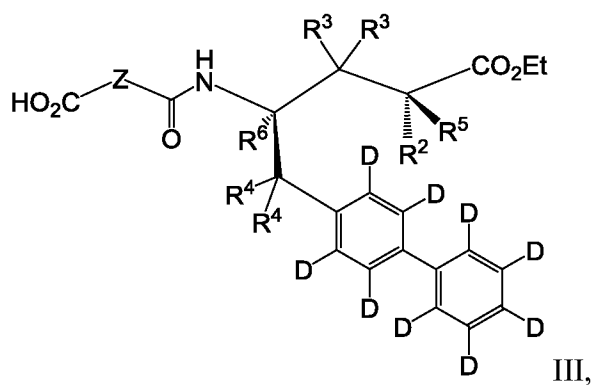
Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
II-16	-CD ₂ CD ₂ -	-CH ₃	D	H	H	H
II-17	-CD ₂ CD ₂ -	-CH ₃	H	H	D	H
II-18	-CD ₂ CD ₂ -	-CH ₃	H	H	H	D
II-19	-CD ₂ CD ₂ -	-CH ₃	H	D	D	H
II-20	-CD ₂ CD ₂ -	-CH ₃	H	H	D	D
II-21	-CD ₂ CD ₂ -	-CH ₃	D	H	H	D
II-22	-CD ₂ CD ₂ -	-CH ₃	D	H	D	H
II-23	-CD ₂ CD ₂ -	-CH ₃	H	D	H	D
II-24	-CD ₂ CD ₂ -	-CH ₃	H	D	D	D
II-25	-CD ₂ CD ₂ -	-CH ₃	D	H	D	D
II-26	-CD ₂ CD ₂ -	-CH ₃	D	D	H	D
II-27	-CD ₂ CD ₂ -	-CH ₃	D	D	D	D

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
II-28	-CD ₂ CD ₂ -	-CD ₃	H	D	H	H
II-29	-CD ₂ CD ₂ -	-CD ₃	H	H	D	H
II-30	-CD ₂ CD ₂ -	-CD ₃	H	H	H	D
II-31	-CD ₂ CD ₂ -	-CD ₃	H	D	D	H
II-32	-CD ₂ CD ₂ -	-CD ₃	H	H	D	D
II-33	-CD ₂ CD ₂ -	-CD ₃	D	H	H	D
II-34	-CD ₂ CD ₂ -	-CD ₃	D	H	D	H
II-35	-CD ₂ CD ₂ -	-CD ₃	H	D	H	D
II-36	-CD ₂ CD ₂ -	-CD ₃	D	D	D	H
II-37	-CD ₂ CD ₂ -	-CD ₃	H	D	D	D
II-38	-CD ₂ CD ₂ -	-CD ₃	D	H	D	D
II-39	-CD ₂ CD ₂ -	-CD ₃	D	D	H	D
II-40	-CH ₂ CH ₂ -	-CH ₃	D	H	H	H
II-41	-CH ₂ CH ₂ -	-CH ₃	H	H	D	H
II-42	-CH ₂ CH ₂ -	-CH ₃	H	H	H	D
II-43	-CH ₂ CH ₂ -	-CH ₃	H	D	D	H
II-44	-CH ₂ CH ₂ -	-CH ₃	H	H	D	D
II-45	-CH ₂ CH ₂ -	-CH ₃	D	H	H	D
II-46	-CH ₂ CH ₂ -	-CH ₃	D	H	D	H
II-47	-CH ₂ CH ₂ -	-CH ₃	H	D	H	D
II-48	-CH ₂ CH ₂ -	-CH ₃	H	D	D	D

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
II-49	-CH ₂ CH ₂ -	-CH ₃	D	H	D	D
II-50	-CH ₂ CH ₂ -	-CH ₃	D	D	H	D
II-51	-CH ₂ CH ₂ -	-CH ₃	D	D	D	D
II-52	-CH ₂ CH ₂ -	-CD ₃	H	D	H	H
II-53	-CH ₂ CH ₂ -	-CD ₃	H	H	D	H
II-54	-CH ₂ CH ₂ -	-CD ₃	H	H	H	D
II-55	-CH ₂ CH ₂ -	-CD ₃	H	D	D	H
II-56	-CH ₂ CH ₂ -	-CD ₃	H	H	D	D
II-57	-CH ₂ CH ₂ -	-CD ₃	D	H	H	D
II-58	-CH ₂ CH ₂ -	-CD ₃	D	H	D	H
II-59	-CH ₂ CH ₂ -	-CD ₃	H	D	H	D
II-60	-CH ₂ CH ₂ -	-CD ₃	D	D	D	H
II-61	-CH ₂ CH ₂ -	-CD ₃	H	D	D	D
II-62	-CH ₂ CH ₂ -	-CD ₃	D	H	D	D
II-63	-CH ₂ CH ₂ -	-CD ₃	D	D	H	D

or a pharmaceutically acceptable salt thereof.

[27] Another embodiment relates to compounds of Formula I where R¹ is R¹-b, which are referred to as compounds of Formula III,



or a pharmaceutically acceptable salt thereof, where Z, R², R³, R⁴, R⁵, and R⁶ are as described above.

[28] Examples of specific compounds of Formula III are shown in Table 2a and Table 2b below. In these compounds, all atoms not designated as deuterium are present at their natural abundance.

Table 2a. Examples of Specific Compounds of Formula III

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-1	-CD ₂ CD ₂ -	-CH ₃	H	H	H	H
III-2	-CD ₂ CD ₂ -	-CD ₃	D	D	D	D
III-3	-CD ₂ CD ₂ -	-CD ₃	D	D	H	H
III-4	-CD ₂ CD ₂ -	-CD ₃	D	H	H	H
III-5	-CD ₂ CD ₂ -	-CD ₃	H	H	H	H
III-6	-CD ₂ CD ₂ -	-CH ₃	D	D	H	H
III-7	-CD ₂ CD ₂ -	-CH ₃	D	D	D	H
III-8	-CD ₂ CD ₂ -	-CH ₃	H	D	H	H
III-9	-CH ₂ CH ₂ -	-CD ₃	D	D	D	D
III-10	-CH ₂ CH ₂ -	-CD ₃	D	D	H	H

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-11	-CH ₂ CH ₂ -	-CD ₃	D	H	H	H
III-12	-CH ₂ CH ₂ -	-CD ₃	H	H	H	H
III-13	-CH ₂ CH ₂ -	-CH ₃	D	D	H	H
III-14	-CH ₂ CH ₂ -	-CH ₃	D	D	D	H
III-15	-CH ₂ CH ₂ -	-CH ₃	H	D	H	H

or a pharmaceutically acceptable salt thereof.

Table 2b. Examples of Specific Compounds of Formula III

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-16	-CD ₂ CD ₂ -	-CH ₃	D	H	H	H
III-17	-CD ₂ CD ₂ -	-CH ₃	H	H	D	H
III-18	-CD ₂ CD ₂ -	-CH ₃	H	H	H	D
III-19	-CD ₂ CD ₂ -	-CH ₃	H	D	D	H
III-20	-CD ₂ CD ₂ -	-CH ₃	H	H	D	D
III-21	-CD ₂ CD ₂ -	-CH ₃	D	H	H	D
III-22	-CD ₂ CD ₂ -	-CH ₃	D	H	D	H
III-23	-CD ₂ CD ₂ -	-CH ₃	H	D	H	D
III-24	-CD ₂ CD ₂ -	-CH ₃	H	D	D	D
III-25	-CD ₂ CD ₂ -	-CH ₃	D	H	D	D
III-26	-CD ₂ CD ₂ -	-CH ₃	D	D	H	D
III-27	-CD ₂ CD ₂ -	-CH ₃	D	D	D	D
III-28	-CD ₂ CD ₂ -	-CD ₃	H	D	H	H

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-29	-CD ₂ CD ₂ -	-CD ₃	H	H	D	H
III-30	-CD ₂ CD ₂ -	-CD ₃	H	H	H	D
III-31	-CD ₂ CD ₂ -	-CD ₃	H	D	D	H
III-32	-CD ₂ CD ₂ -	-CD ₃	H	H	D	D
III-33	-CD ₂ CD ₂ -	-CD ₃	D	H	H	D
III-34	-CD ₂ CD ₂ -	-CD ₃	D	H	D	H
III-35	-CD ₂ CD ₂ -	-CD ₃	H	D	H	D
III-36	-CD ₂ CD ₂ -	-CD ₃	D	D	D	H
III-37	-CD ₂ CD ₂ -	-CD ₃	H	D	D	D
III-38	-CD ₂ CD ₂ -	-CD ₃	D	H	D	D
III-39	-CD ₂ CD ₂ -	-CD ₃	D	D	H	D
III-40	-CH ₂ CH ₂ -	-CH ₃	D	H	H	H
III-41	-CH ₂ CH ₂ -	-CH ₃	H	H	D	H
III-42	-CH ₂ CH ₂ -	-CH ₃	H	H	H	D
III-43	-CH ₂ CH ₂ -	-CH ₃	H	D	D	H
III-44	-CH ₂ CH ₂ -	-CH ₃	H	H	D	D
III-45	-CH ₂ CH ₂ -	-CH ₃	D	H	H	D
III-46	-CH ₂ CH ₂ -	-CH ₃	D	H	D	H
III-47	-CH ₂ CH ₂ -	-CH ₃	H	D	H	D
III-48	-CH ₂ CH ₂ -	-CH ₃	H	D	D	D
III-49	-CH ₂ CH ₂ -	-CH ₃	D	H	D	D

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-50	-CH ₂ CH ₂ -	-CH ₃	D	D	H	D
III-51	-CH ₂ CH ₂ -	-CH ₃	D	D	D	D
III-52	-CH ₂ CH ₂ -	-CD ₃	H	D	H	H
III-53	-CH ₂ CH ₂ -	-CD ₃	H	H	D	H
III-54	-CH ₂ CH ₂ -	-CD ₃	H	H	H	D
III-55	-CH ₂ CH ₂ -	-CD ₃	H	D	D	H
III-56	-CH ₂ CH ₂ -	-CD ₃	H	H	D	D
III-57	-CH ₂ CH ₂ -	-CD ₃	D	H	H	D
III-58	-CH ₂ CH ₂ -	-CD ₃	D	H	D	H
III-59	-CH ₂ CH ₂ -	-CD ₃	H	D	H	D
III-60	-CH ₂ CH ₂ -	-CD ₃	D	D	D	H
III-61	-CH ₂ CH ₂ -	-CD ₃	H	D	D	D
III-62	-CH ₂ CH ₂ -	-CD ₃	D	H	D	D
III-63	-CH ₂ CH ₂ -	-CD ₃	D	D	H	D
III-64	-CH ₂ CH ₂ -	-CH ₃	H	H	H	H

or a pharmaceutically acceptable salt thereof.

[29] Another embodiment relates to compounds of Formula I where R¹ is R¹-c, which are referred to as compounds of Formula IV, or a pharmaceutically acceptable salt thereof, where Z, R², R³, R⁴, R⁵, R⁶ and R⁷ are as described above.

[30] Another embodiment relates to compounds of Formula I where R¹ is R¹-d, which are referred to as compounds of Formula V, or a pharmaceutically acceptable salt thereof, where Z, R², R³, R⁴, R⁵, and R⁶ are as described above.

[31] Examples of specific compounds of Formulae IV and V are those compounds of each formula where Z, R², R³, R⁴, R⁵, and R⁶ are as described in Tables 2a and 2b above.

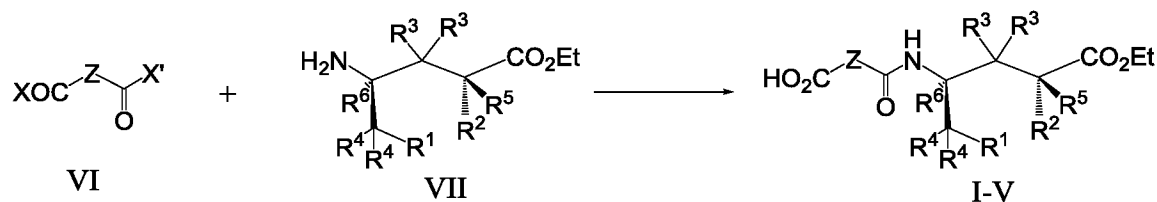
[32] Compounds of Formula I, II, III, IV and V are deuterium-substituted analogs of sacubitril, which is 5-(biphenyl-4-yl)-4(*S*)-(3-carboxypropionamido)-2(*R*)-methylbutyric acid ethyl ester. Compounds of Formula I-V predominantly have the same stereochemistry as sacubitril at the corresponding 2(*R*) and 4(*S*) positions. The compounds and compositions of this invention may include small amounts of other stereoisomers. Preferably, for the compounds of Formula I-V, the percentage of compounds having the (*R*) configuration at the 2 position is greater than 80%, greater than 90%, greater than 95% and greater than 99% and the percentage of compounds having the (*S*) configuration at the 4 position is greater than 80%, greater than 90%, greater than 95% and greater than 99%.

Exemplary Synthesis

[33] The synthesis of compounds of Formula I-V may be achieved by synthetic chemists of ordinary skill by reference to known methods for making sacubitril, the use of deuterated intermediates and reagents that are available, and the description of synthetic schemes and examples disclosed herein.

US Patent 5,217,996 describes the synthesis of sacubitril. The synthetic approaches described in this patent may be adapted to prepare compounds of this invention. These approaches may be used to provide compounds of Formula I-V, wherein each atom designated as D has deuterium incorporation of at least 90%, at least 95%, or at least 99%. By an analogous manner, compounds of Formula I-V may be prepared by condensing a compound of Formula VI with a compound of Formula VII as shown in Scheme I below.

Scheme I

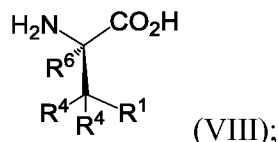


[34] In starting compound VI, COX is a carboxyl or carboxyl derivatized in the form

of a pharmaceutically acceptable ester or amide, and X' is a leaving group suitable for condensing a carboxylic acid with an amine to form an amide. Deuterated versions of the intermediate VI are readily available by methods known in the art. For example, compounds where Z is $-\text{CD}_2\text{CD}_2-$ may be prepared from succinic acid using deuterium-hydrogen exchange reactions under acid or base catalysis in the presence of a deuterated solvent. Suitable deuterated solvents include, for example, deuterium oxide, a deuterated alcohol such as EtOD or MeOD, or a combination thereof. Compounds where Z is $-\text{CHD}-\text{CHD}-$ can be prepared from fumaric acid by hydrogenation with deuterium. Intermediate VI can be prepared by known methods where the percent incorporation of each deuterium is at least 90%, at least 95% and at least 99%. Thus, compounds of Formula I may be prepared where each of R^6 and R^7 have deuterium incorporation that is at least 90%, at least 95% and at least 99%.

[35] Intermediate VII used in Scheme I above may be prepared by:

(a) reducing the carboxylic acid of a biarylamine of Formula VIII

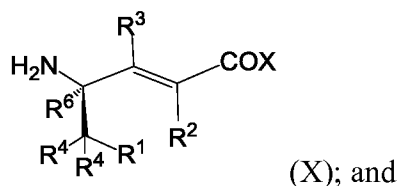


in a temporarily protected form if required, to yield the respective aldehyde;

(b) subsequently reacting said aldehyde with a triphenylphosphonium compound of Formula IX



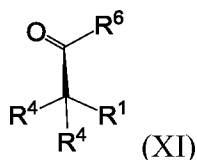
to provide a compound of Formula X



(c) hydrogenating the compound of Formula X with hydrogen or deuterium to provide intermediate VII.

[36] Hydrogenating the compound of Formula X used in Scheme I above may be performed according to the asymmetric hydrogenation procedures provided in US 2009/0326066. Asymmetric deuteration using D₂ gas and any of the catalysts detailed in US 2009/0326066, for example, diiodo(p-cymene)ruthenium(II) dimer and (αR,αR)-2,2'-bis(α-N,N-dimethylaminophenylmethyl)-(S,S)-1, 1'-bis[di(3,5-dimethyl-4-methoxyphenyl)phosphine]ferrocene (Mandyphos SL-M004-1) in ethanol can afford isotopically enriched intermediate VII with deuteration at R³ and/or R⁵. Using such methods, R³ and/or R⁵ in intermediate VII can be prepared having deuterium incorporation of at least 90%, at least 95% and at least 99% at each deuterium of the R³ and/or R⁵ group. Additionally, using such methods affords high diastereomeric purity of wherein the percentage of compounds having the (R) configuration at the 2 position is greater than 80%, greater than 90%, greater than 95% or greater than 99% and the percentage of compounds having the (S) configuration at the 4 position is greater than 80%, greater than 90%, greater than 95% or greater than 99%

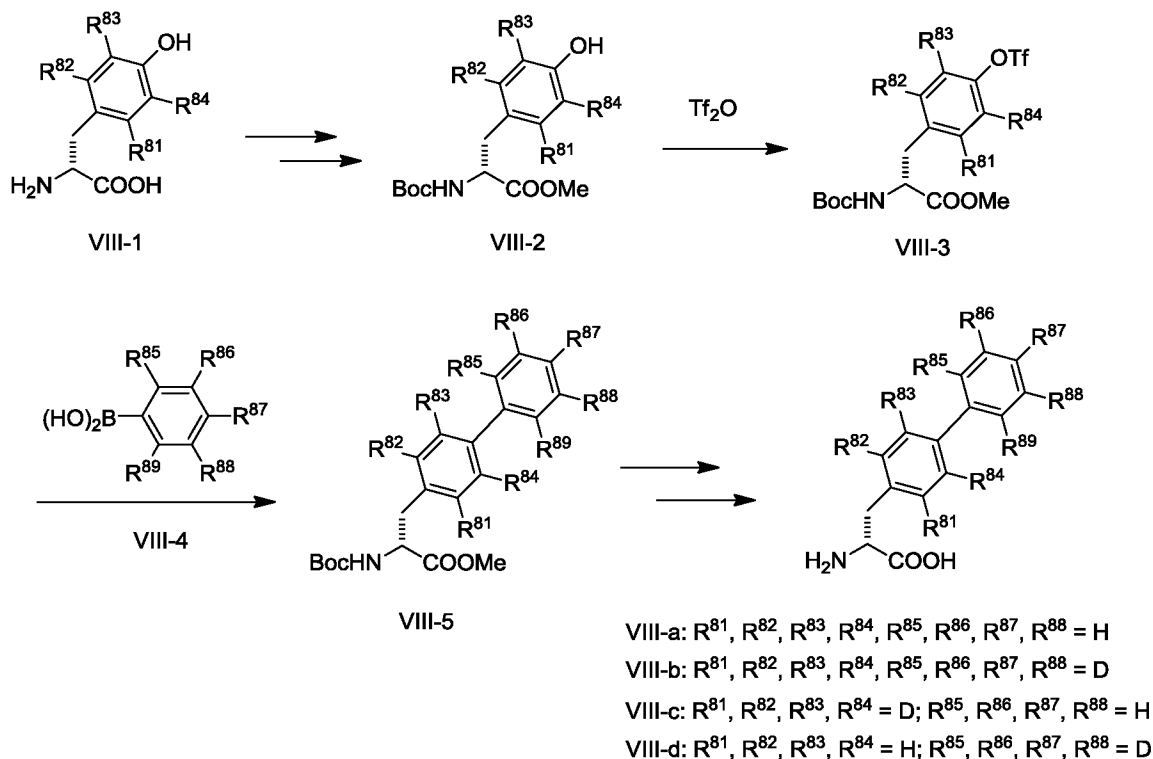
[37] Intermediate VIII is an amino acid that can be prepared by known methods for preparing α-amino acids such as a Strecker synthesis. Such methods are amenable to incorporation of deuterium at high levels of isotopic purity. For example, the amino acid VII can be prepared a Strecker synthesis from the corresponding aldehyde XI:



[38] A non-limiting example of a general synthesis of intermediate VIII is shown in Scheme II. Methods for the synthesis of chiral 2-acylamino-3-diphenylpropanoic acid are known in the art, for example, as described in US 2012/0016151 and in Ksander, G. M. et al. *Journal of Medicinal Chemistry* **1995**, 38 (10), 1689-1700. Many of the corresponding amino acids VIII-1 are commercially available, for example, H-tyrosine (R⁸¹, R⁸², R⁸³, R⁸⁴ = H) and d₄-D-tyrosine (R⁸¹, R⁸², R⁸³, R⁸⁴ = D). Protecting group chemistry known in the art leads to protected amino ester VIII-2, which can then be converted to triflate VIII-3, and coupled under transition-metal catalyzed conditions with boronic acid VIII-4 to afford protected biphenyl amino esters VIII-5, which can be deprotected under standard conditions to give intermediates VIII-a through VIII-d. Some corresponding boronic

acids VIII-4, for example, phenylboronic acid ($R^{85}, R^{86}, R^{87}, R^{88}, R^{89} = H$) and d_5 -phenylboronic acid ($R^{85}, R^{86}, R^{87}, R^{88}, R^{89} = D$), are commercially available. It is expected that compounds VIII-a through VIII-d can be readily prepared with %-atom d incorporation values of 95% or greater under these conditions.

Scheme II



[39] Compounds having deuterium at R^4 can be prepared from intermediate XI or a precursor thereof where R^4 is hydrogen by hydrogen-deuterium exchange reactions in deuterated solvents as described above. Compounds having deuterium at R^6 can be prepared from the analogous carboxylic acid or ester by reduction to the aldehyde using a deuterated reducing agent. These methods may provide high levels of deuterium incorporation where the percent incorporation of each deuterium at R^4 or at R^6 is at least 90%, at least 95% and at least 99%. Thus, compounds of Formula I-V may be prepared where each R^4 and R^6 have deuterium incorporation that is at least 90%, at least 95% and at least 99%. The starting aldehyde (XI) may be obtained where R^1 is a biphenyl moiety that is optionally substituted with deuterium, and in particular where the phenyl rings of the biphenyl are independently perdeuterated. In step (b) above, other Wittig reagents

may be used in place of intermediate IX and may be prepared where R² is a methyl group or a deuterated methyl group having deuterium incorporation of at least 90%, at least 95% and at least 99% at each deuterium of the R² group.

[40] The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., R¹, R², R³, etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

[41] Additional methods of synthesizing compounds of Formula I-V and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene, TW et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser, L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette, L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

Compositions

[42] The invention also provides pharmaceutical compositions comprising an effective amount of a compound of Formula I-V (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and a pharmaceutically acceptable carrier. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

[43] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum

albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[44] In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

[45] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[46] Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

[47] Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid

carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

[48] In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any angiotensin II receptor antagonist, also known as an angiotensin receptor blocker or ARB. Preferably the ARB has a high affinity for the type I angiotensin receptor. Examples of suitable ARBs include valsartan, losartan, irbesartan, olmesartan, telmisartan and candesartan.

[49] In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term “effective amount” refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat the target disorder. For the treatment of a subject who has had heart failure, the amount of compound of Formula I-V administered is in the range of 10 mg to 400 mg per day, 20 mg to 300 mg per day, 25 mg to 200 mg per day, 30 mg to 200 mg per day, 40 mg to 200 mg per day or 50 to 200 mg per day. The compound may be administered once per day or twice per day.

[50] When the compound of Formula I-V is administered in combination with an ARB, the molar ratio of compound of Formula I-V to the ARB will be in the range of 1:2, 5:8, 3:4, 7:8, or 1:1. For the treatment of a subject who has had heart failure, wherein the compound of Formula I-V is administered in combination with an ARB such as valsartan, the amount of compound of Formula I-V administered is in the range of 10 mg to 400 mg per day, 20 mg to 300 mg per day, 25 mg to 200 mg per day, 30 mg to 200 mg per day, 40 mg to 200 mg per day and 50 to 200 mg per day. The compound may be administered in combination with an ARB such as valsartan once per day or twice per day.

[51] Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician.

Methods of Treatment

[52] In one embodiment the invention provides a method of inhibiting the activity of neprilysin or neutral endopeptidase (NEP) in a cell, *in vitro* or *in vivo*, comprising contacting the cell with one or more compounds of Formula I-V herein, or a pharmaceutically acceptable salt thereof.

[53] According to another embodiment, the invention provides a method of treating a disease that is beneficially treated by LCZ696 in a subject in need thereof, comprising the step of administering to the subject an effective amount of a compound or a composition of this invention and, in particular a combination of a compound of this invention with a suitable ARB.

[54] The compounds of this invention are useful for treating subjects who have had heart failure. The compound is administered to reduce the risk of death or the need for hospitalization due to cardiovascular causes in said subjects. The compounds of this invention are also useful for treating hypertension, renal insufficiency including edema and salt retention, pulmonary edema and congestive heart failure.

[55] In another embodiment, any of the above methods of treatment comprises the further step of co-administering to the subject in need thereof one or more second therapeutic agents. The second therapeutic agent may be selected from any angiotensin II receptor antagonist, also known as an angiotensin receptor blocker or ARB. Preferably the ARB has a high affinity for the type I angiotensin receptor. Examples of suitable ARBs include valsartan, losartan, irbesartan, olmesartan, telmisartan and candesartan.

[56] Thus, the invention also relates to method of treating a subject who had heart failure by administering a compound of Formula I-V in combination with an angiotensin receptor antagonist. In various embodiments of this method, the amount of compound of Formula I-V administered is in the range of 10 mg to 400 mg per day, 20 mg to 300 mg per day, 25 mg to 200 mg per day, 30 mg to 200 mg per day, 40 mg to 200 mg per day or 50 to 200 mg per day. The compound may be administered once per day or twice per day. In other embodiments of this method, the compound of Formula I-V and the ARB are administered in a molar ratio that is in the range of 1:2, 5:8, 3:4, 7:8, or 1:1.

[57] In yet another aspect, the invention provides the use of a compound of Formula I-V alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I-V for use in the treatment in a subject of a disease, disorder or symptom thereof delineated herein.

Evaluation of Metabolic Stability

[58] **Microsomal Assay:** Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, KS). β -nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride (MgCl_2), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

[59] **Determination of Metabolic Stability:** 7.5 mM stock solutions of test compounds are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5-50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM MgCl_2 . The diluted microsomes are added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 12.5-50 μM test compound is added to the microsomes and the mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25-1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM MgCl_2 . The reaction mixtures are incubated at 37 °C, and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4 °C for 20 minutes after which 100 μL of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for the non-deuterated counterpart of the compound of Formula I-V and the positive control, 7-ethoxycoumarin (1 μM). Testing is done in triplicate.

[60] **Data analysis:** The *in vitro* $t_{1/2}$ s for test compounds are calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.

$$\text{in vitro } t_{1/2} = 0.693/k$$

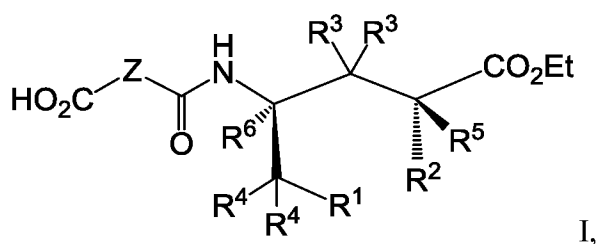
$$k = -[\text{slope of linear regression of \% parent remaining (ln) vs incubation time}]$$

[61] Data analysis is performed using Microsoft Excel Software.

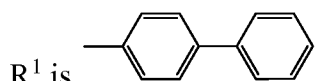
Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

We claim:

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:



R^1 is , optionally substituted by one or more deuterium;

R^2 is methyl, optionally substituted by one or more deuterium;

Z is $-C(R^7)_2C(R^8)_2-$, wherein each R^7 and each R^8 are independently hydrogen or deuterium;

Each R^3 is independently hydrogen or deuterium;

Each R^4 is independently hydrogen or deuterium;

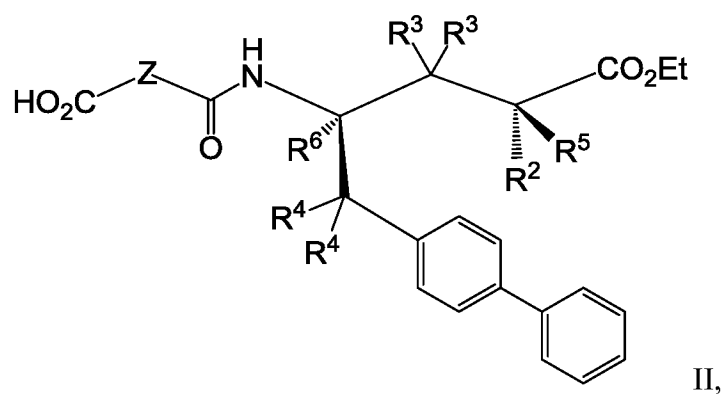
R^5 is hydrogen or deuterium; and

R^6 is hydrogen or deuterium; provided that R^6 is deuterium when neither R^1 nor R^2 are substituted by deuterium and each of R^3 , R^4 , R^5 , R^7 and R^8 are hydrogen.

2. The compound of claim 1 wherein R^2 is $-CH_3$ or $-CD_3$, each R^3 is the same, each R^4 is the same, each R^7 is the same and each R^8 is the same.

3. The compound of claim 1 or 2 wherein Z is $-CH_2CH_2-$; $-CD_2CD_2-$; $-CD_2CH_2-$; or $-CH_2CD_2-$.

4. The compound of claim 1, wherein the compound is of Formula II and is selected from the following:



Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
II-1	−CD ₂ CD ₂ −	−CH ₃	H	H	H	H
II-2	−CD ₂ CD ₂ −	−CD ₃	D	D	D	D
II-3	−CD ₂ CD ₂ −	−CD ₃	D	D	H	H
II-4	−CD ₂ CD ₂ −	−CD ₃	D	H	H	H
II-5	−CD ₂ CD ₂ −	−CD ₃	H	H	H	H
II-6	−CD ₂ CD ₂ −	−CH ₃	D	D	H	H
II-7	−CD ₂ CD ₂ −	−CH ₃	D	D	D	H
II-8	−CD ₂ CD ₂ −	−CH ₃	H	D	H	H
II-9	−CH ₂ CH ₂ −	−CD ₃	D	D	D	D
II-10	−CH ₂ CH ₂ −	−CD ₃	D	D	H	H
II-11	−CH ₂ CH ₂ −	−CD ₃	D	H	H	H
II-12	−CH ₂ CH ₂ −	−CD ₃	H	H	H	H
II-13	−CH ₂ CH ₂ −	−CH ₃	D	D	H	H
II-14	−CH ₂ CH ₂ −	−CH ₃	D	D	D	H
II-15	−CH ₂ CH ₂ −	−CH ₃	H	D	H	H

or a pharmaceutically acceptable salt thereof, wherein all atoms not designated as deuterium are present in their natural abundance.

5. The compound of claim 1, wherein the compound is of Formula II and is selected from the following:

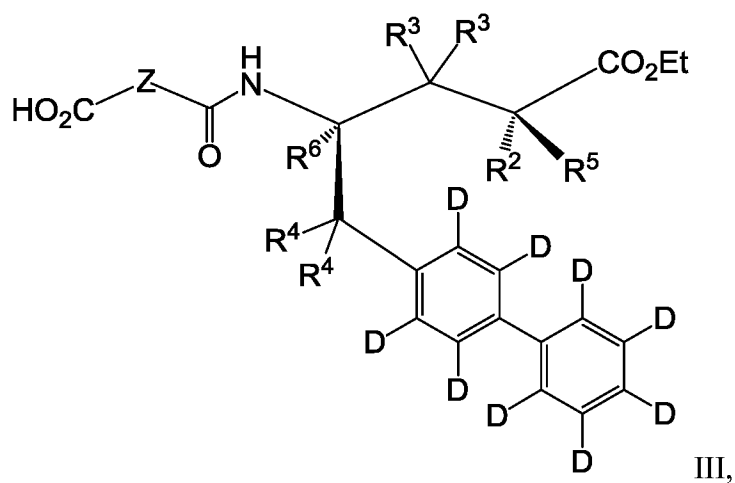
Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
II-16	-CD ₂ CD ₂ -	-CH ₃	D	H	H	H
II-17	-CD ₂ CD ₂ -	-CH ₃	H	H	D	H
II-18	-CD ₂ CD ₂ -	-CH ₃	H	H	H	D
II-19	-CD ₂ CD ₂ -	-CH ₃	H	D	D	H
II-20	-CD ₂ CD ₂ -	-CH ₃	H	H	D	D
II-21	-CD ₂ CD ₂ -	-CH ₃	D	H	H	D
II-22	-CD ₂ CD ₂ -	-CH ₃	D	H	D	H
II-23	-CD ₂ CD ₂ -	-CH ₃	H	D	H	D
II-24	-CD ₂ CD ₂ -	-CH ₃	H	D	D	D
II-25	-CD ₂ CD ₂ -	-CH ₃	D	H	D	D
II-26	-CD ₂ CD ₂ -	-CH ₃	D	D	H	D
II-27	-CD ₂ CD ₂ -	-CH ₃	D	D	D	D
II-28	-CD ₂ CD ₂ -	-CD ₃	H	D	H	H
II-29	-CD ₂ CD ₂ -	-CD ₃	H	H	D	H
II-30	-CD ₂ CD ₂ -	-CD ₃	H	H	H	D
II-31	-CD ₂ CD ₂ -	-CD ₃	H	D	D	H
II-32	-CD ₂ CD ₂ -	-CD ₃	H	H	D	D

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
II-33	-CD ₂ CD ₂ -	-CD ₃	D	H	H	D
II-34	-CD ₂ CD ₂ -	-CD ₃	D	H	D	H
II-35	-CD ₂ CD ₂ -	-CD ₃	H	D	H	D
II-36	-CD ₂ CD ₂ -	-CD ₃	D	D	D	H
II-37	-CD ₂ CD ₂ -	-CD ₃	H	D	D	D
II-38	-CD ₂ CD ₂ -	-CD ₃	D	H	D	D
II-39	-CD ₂ CD ₂ -	-CD ₃	D	D	H	D
II-40	-CH ₂ CH ₂ -	-CH ₃	D	H	H	H
II-41	-CH ₂ CH ₂ -	-CH ₃	H	H	D	H
II-42	-CH ₂ CH ₂ -	-CH ₃	H	H	H	D
II-43	-CH ₂ CH ₂ -	-CH ₃	H	D	D	H
II-44	-CH ₂ CH ₂ -	-CH ₃	H	H	D	D
II-45	-CH ₂ CH ₂ -	-CH ₃	D	H	H	D
II-46	-CH ₂ CH ₂ -	-CH ₃	D	H	D	H
II-47	-CH ₂ CH ₂ -	-CH ₃	H	D	H	D
II-48	-CH ₂ CH ₂ -	-CH ₃	H	D	D	D
II-49	-CH ₂ CH ₂ -	-CH ₃	D	H	D	D
II-50	-CH ₂ CH ₂ -	-CH ₃	D	D	H	D
II-51	-CH ₂ CH ₂ -	-CH ₃	D	D	D	D
II-52	-CH ₂ CH ₂ -	-CD ₃	H	D	H	H
II-53	-CH ₂ CH ₂ -	-CD ₃	H	H	D	H

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
II-54	-CH ₂ CH ₂ -	-CD ₃	H	H	H	D
II-55	-CH ₂ CH ₂ -	-CD ₃	H	D	D	H
II-56	-CH ₂ CH ₂ -	-CD ₃	H	H	D	D
II-57	-CH ₂ CH ₂ -	-CD ₃	D	H	H	D
II-58	-CH ₂ CH ₂ -	-CD ₃	D	H	D	H
II-59	-CH ₂ CH ₂ -	-CD ₃	H	D	H	D
II-60	-CH ₂ CH ₂ -	-CD ₃	D	D	D	H
II-61	-CH ₂ CH ₂ -	-CD ₃	H	D	D	D
II-62	-CH ₂ CH ₂ -	-CD ₃	D	H	D	D
II-63	-CH ₂ CH ₂ -	-CD ₃	D	D	H	D

or a pharmaceutically acceptable salt thereof, wherein all atoms not designated as deuterium are present in their natural abundance..

6. The compound of claim 1, wherein the compound is of Formula III and is selected from the following:



Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-1	-CD ₂ CD ₂ -	-CH ₃	H	H	H	H
III-2	-CD ₂ CD ₂ -	-CD ₃	D	D	D	D
III-3	-CD ₂ CD ₂ -	-CD ₃	D	D	H	H
III-4	-CD ₂ CD ₂ -	-CD ₃	D	H	H	H
III-5	-CD ₂ CD ₂ -	-CD ₃	H	H	H	H
III-6	-CD ₂ CD ₂ -	-CH ₃	D	D	H	H
III-7	-CD ₂ CD ₂ -	-CH ₃	D	D	D	H
III-8	-CD ₂ CD ₂ -	-CH ₃	H	D	H	H
III-9	-CH ₂ CH ₂ -	-CD ₃	D	D	D	D
III-10	-CH ₂ CH ₂ -	-CD ₃	D	D	H	H
III-11	-CH ₂ CH ₂ -	-CD ₃	D	H	H	H
III-12	-CH ₂ CH ₂ -	-CD ₃	H	H	H	H
III-13	-CH ₂ CH ₂ -	-CH ₃	D	D	H	H
III-14	-CH ₂ CH ₂ -	-CH ₃	D	D	D	H
III-15	-CH ₂ CH ₂ -	-CH ₃	H	D	H	H

or a pharmaceutically acceptable salt thereof, wherein all atoms not designated as deuterium are present at their natural abundance.

7. The compound of claim 1, wherein the compound is of Formula III and is selected from the following:

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-16	-CD ₂ CD ₂ -	-CH ₃	D	H	H	H

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-17	-CD ₂ CD ₂ -	-CH ₃	H	H	D	H
III-18	-CD ₂ CD ₂ -	-CH ₃	H	H	H	D
III-19	-CD ₂ CD ₂ -	-CH ₃	H	D	D	H
III-20	-CD ₂ CD ₂ -	-CH ₃	H	H	D	D
III-21	-CD ₂ CD ₂ -	-CH ₃	D	H	H	D
III-22	-CD ₂ CD ₂ -	-CH ₃	D	H	D	H
III-23	-CD ₂ CD ₂ -	-CH ₃	H	D	H	D
III-24	-CD ₂ CD ₂ -	-CH ₃	H	D	D	D
III-25	-CD ₂ CD ₂ -	-CH ₃	D	H	D	D
III-26	-CD ₂ CD ₂ -	-CH ₃	D	D	H	D
III-27	-CD ₂ CD ₂ -	-CH ₃	D	D	D	D
III-28	-CD ₂ CD ₂ -	-CD ₃	H	D	H	H
III-29	-CD ₂ CD ₂ -	-CD ₃	H	H	D	H
III-30	-CD ₂ CD ₂ -	-CD ₃	H	H	H	D
III-31	-CD ₂ CD ₂ -	-CD ₃	H	D	D	H
III-32	-CD ₂ CD ₂ -	-CD ₃	H	H	D	D
III-33	-CD ₂ CD ₂ -	-CD ₃	D	H	H	D
III-34	-CD ₂ CD ₂ -	-CD ₃	D	H	D	H
III-35	-CD ₂ CD ₂ -	-CD ₃	H	D	H	D
III-36	-CD ₂ CD ₂ -	-CD ₃	D	D	D	H
III-37	-CD ₂ CD ₂ -	-CD ₃	H	D	D	D

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-38	-CD ₂ CD ₂ -	-CD ₃	D	H	D	D
III-39	-CD ₂ CD ₂ -	-CD ₃	D	D	H	D
III-40	-CH ₂ CH ₂ -	-CH ₃	D	H	H	H
III-41	-CH ₂ CH ₂ -	-CH ₃	H	H	D	H
III-42	-CH ₂ CH ₂ -	-CH ₃	H	H	H	D
III-43	-CH ₂ CH ₂ -	-CH ₃	H	D	D	H
III-44	-CH ₂ CH ₂ -	-CH ₃	H	H	D	D
III-45	-CH ₂ CH ₂ -	-CH ₃	D	H	H	D
III-46	-CH ₂ CH ₂ -	-CH ₃	D	H	D	H
III-47	-CH ₂ CH ₂ -	-CH ₃	H	D	H	D
III-48	-CH ₂ CH ₂ -	-CH ₃	H	D	D	D
III-49	-CH ₂ CH ₂ -	-CH ₃	D	H	D	D
III-50	-CH ₂ CH ₂ -	-CH ₃	D	D	H	D
III-51	-CH ₂ CH ₂ -	-CH ₃	D	D	D	D
III-52	-CH ₂ CH ₂ -	-CD ₃	H	D	H	H
III-53	-CH ₂ CH ₂ -	-CD ₃	H	H	D	H
III-54	-CH ₂ CH ₂ -	-CD ₃	H	H	H	D
III-55	-CH ₂ CH ₂ -	-CD ₃	H	D	D	H
III-56	-CH ₂ CH ₂ -	-CD ₃	H	H	D	D
III-57	-CH ₂ CH ₂ -	-CD ₃	D	H	H	D
III-58	-CH ₂ CH ₂ -	-CD ₃	D	H	D	H

Compound	Z	R ²	Each R ³	Each R ⁴	R ⁵	R ⁶
III-59	-CH ₂ CH ₂ -	-CD ₃	H	D	H	D
III-60	-CH ₂ CH ₂ -	-CD ₃	D	D	D	H
III-61	-CH ₂ CH ₂ -	-CD ₃	H	D	D	D
III-62	-CH ₂ CH ₂ -	-CD ₃	D	H	D	D
III-63	-CH ₂ CH ₂ -	-CD ₃	D	D	H	D
III-64	-CH ₂ CH ₂ -	-CH ₃	H	H	H	H

or a pharmaceutically acceptable salt thereof, wherein all atoms not designated as deuterium are present at their natural abundance.

8. The compound of any one of claims 1 - 7 wherein the percentage of deuterium incorporation is at least 90% at each position designated as D.

9. A pharmaceutical composition comprising a compound of any one of claims 1 - 8 and a pharmaceutically acceptable carrier.

10. The pharmaceutical composition of claim 9 further comprising an angiotensin receptor antagonist.

11. The pharmaceutical composition of claim 10 wherein the angiotensin receptor antagonist is valsartan.

12. A method of inhibiting neprilysin in a cell, comprising contacting the cell with a compound of any one of claims 1-8.

13. A method of treating a cardiovascular disorder which comprises administering to a mammal in need of such treatment an effective amount of a compound of any one of claims 1-8 in combination with one or more pharmaceutically acceptable carriers.

14. A method of treating a cardiovascular disorder comprising administering to a mammal in need of such treatment an effective amount of a composition of any one of claims 9 - 11.

15. The method of claim 13 or 14 wherein the cardiovascular disorder is selected from hypertension, renal insufficiency including edema and salt retention, pulmonary edema and congestive heart failure.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/048626

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C233/47 C07B59/00 A61K31/192 A61P9/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07B A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/065958 A1 (NOVARTIS AG [CH]; FOO SHI YIN [US]) 24 May 2012 (2012-05-24) page 5, last paragraph page 48, last paragraph - page 49, paragraph 1 abstract	1-15
A	----- TUNG R: "The Development of Deuterium-Containing Drugs", INNOVATIONS IN PHARMACEUTICAL TECHNOLOGY, SAMEDAN LTD, GB, no. 32, 1 March 2010 (2010-03-01), pages 24-26,28, XP009148260, ISSN: 1471-7204 paragraph bridging pages 24-25 ----- -/-	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search

3 November 2015

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/048626

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	WO 03/059345 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; WEBB RANDY LEE [US]; KSAN) 24 July 2003 (2003-07-24) claim 3 -----	1-15

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