PRODRUGS OF PHENOLIC TRPV1 AGONISTS

CROSS-REFERENCE

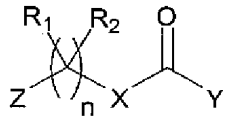
[0001] This application claims benefit of U.S. Provisional Application No. 62/084,515, filed on November 25, 2014, and is a continuation-in-part of U.S. Patent Application No. 14/743,375, filed on June 18, 2015, both of which are herein incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Described herein are compounds, pharmaceutical compositions and medicaments that include such compounds, and methods of using such compounds to modulate the transient receptor potential vanilloid 1 receptor (TRPV1) activity.

SUMMARY OF THE INVENTION

[0002a] In one aspect, there is provided a compound having the structure of Formula (I):



Formula (I);

wherein:

Y is a phenolic TRPV1 agonist, wherein the hydrogen atom of the phenolic hydroxyl group is replaced by a covalent bond to $-C(O)-X-(C(R_1)(R_2))_n-Z$;

X is $-N(R_5)-$;

n is an integer from 1 to 10;

Z is $-NR_3R_4$ or $-CO_2H$;

R_5 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl, and each R_1 and R_2 is each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted acyl, or two R_1 or R_2 groups on adjacent carbon atoms, together with the carbon atoms to which they are attached, form a substituted or unsubstituted cycloalkyl group, or R_1 and R_5 groups on adjacent atoms, together with the atoms to which they are attached, form a substituted or unsubstituted heterocycloalkyl group; and

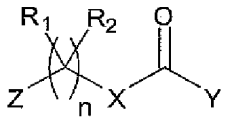
R_3 and R_4 is each independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof.

[0002b] In one aspect, there is provided a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof, as described herein, and a pharmaceutically acceptable diluent, excipient or binder.

[0002c] In one aspect, there is provided a use of a compound as described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof, for use in the manufacture of a medicament for treating pain.

[0003] In one aspect, described herein is a compound having the structure of Formula (I):



Formula (I);

wherein:

Y is a phenolic TRPV1 agonist, wherein the hydrogen atom of the phenolic hydroxyl group is replaced by a covalent bond to $-C(O)-X-(C(R_1)(R_2))_n-Z$;

X is $-C(R_1)(R_2)-$, $-O-$, $-N(R_5)-$ or $-S-$;

n is an integer from 1 to 10;

Z is $-NR_3R_4$ or $-CO_2H$;

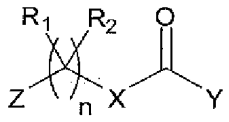
R_5 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl, and each R_1 and R_2 is each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted acyl, or two R_1 or R_2 groups on adjacent carbon atoms, together with the carbon atoms to which they are attached, form a substituted or unsubstituted cycloalkyl group, or R_1 and R_5 groups on adjacent atoms, together with the atoms to which they are attached, form a substituted or unsubstituted heterocycloalkyl group; and

R_3 and R_4 is each independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof.

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula (I):



Formula (I);

wherein:

Y is a phenolic TRPV1 agonist, wherein the hydrogen atom of the phenolic hydroxyl group is replaced by a covalent bond to $-C(O)-X-(C(R_1)(R_2))_n-Z$;

X is $-N(R_5)-$;

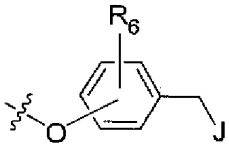
n is an integer from 1 to 10;

Z is $-NR_3R_4$ or $-CO_2H$;

R_5 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl, and each R_1 and R_2 is each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted acyl, or two R_1 or R_2 groups on adjacent carbon atoms, together with the carbon atoms to which they are attached, form a substituted or unsubstituted cycloalkyl group, or R_1 and R_5 groups on adjacent atoms, together with the atoms to which they are attached, form a substituted or unsubstituted heterocycloalkyl group; and

R_3 and R_4 is each independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl;

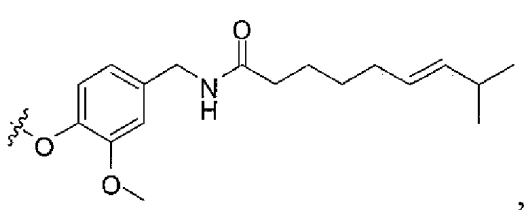
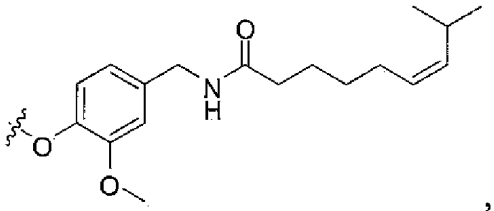
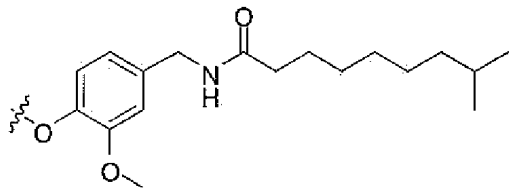
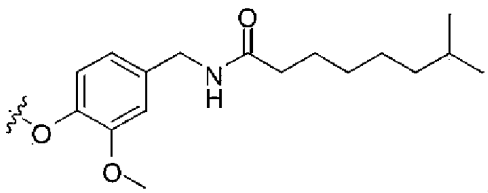
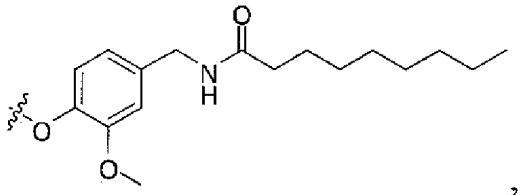
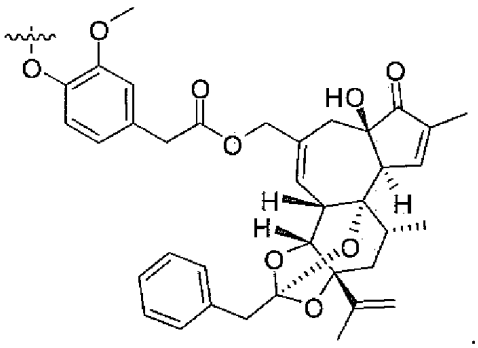
or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof.

2. The compound of claim 1, wherein Y is ; R_6 is independently selected from hydrogen, halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, $-C(=O)NH$(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone; J is $-NHC(O)R_7$ or $-C(O)OR_7$; and R_7 is substituted or unsubstituted alkyl.

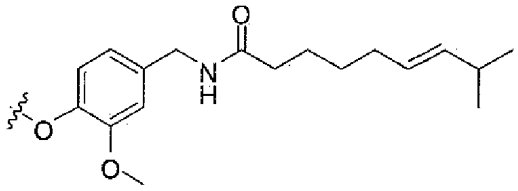
3. The compound of claim 2, wherein R_7 is unsubstituted alkyl or alkyl substituted with one or more groups selected from halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, $-C(=O)NH$(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(alkyl), $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy,

heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone.

4. The compound of any one of claims 1-3, wherein R_6 is alkoxy.
5. The compound of any one of claims 1-4, wherein R_7 is unsubstituted alkyl.
6. The compound of claim 1, wherein Y is


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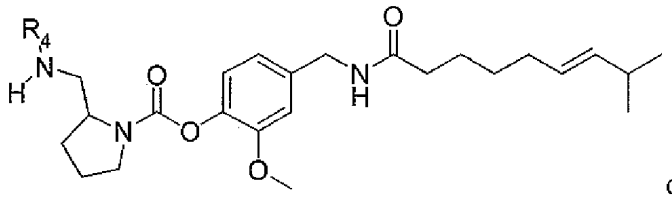
7. The compound of claim 6, wherein Y is


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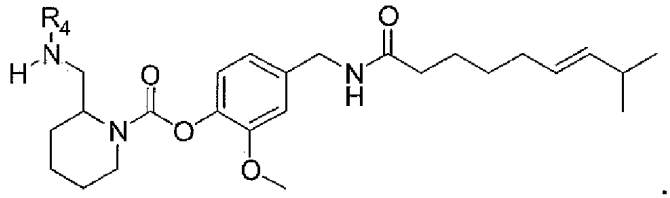
8. The compound of any one of claims 1-7, wherein Z is $-NR_3R_4$.
9. The compound of any one of claims 1-8, wherein R_3 is hydrogen and R_4 is H or substituted or unsubstituted alkyl.
10. The compound of any one of claims 1-9, wherein R_1 and R_5 groups on adjacent atoms, together with the atoms to which they are attached, form a substituted or unsubstituted heterocycloalkyl group.
11. The compound of claim 10, wherein the heterocycloalkyl group is a substituted or unsubstituted pyrrolidine ring, substituted or unsubstituted piperidine ring, or substituted or unsubstituted piperazine ring.

12. The compound of claim 10, wherein the heterocycloalkyl group is an unsubstituted pyrrolidine ring, unsubstituted piperidine ring, or unsubstituted piperazine ring.

13. The compound of claim 10, having the structure:



or



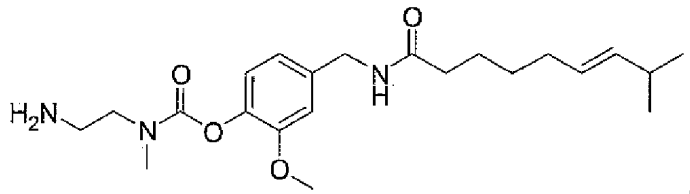
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14. The compound of any one of claims 1-9, wherein R_5 is hydrogen.

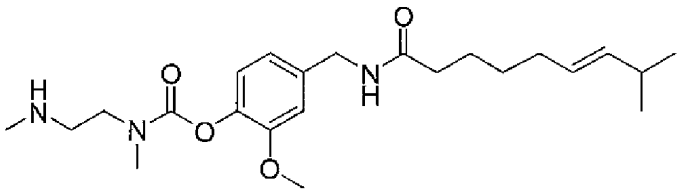
15. The compound of any one of claims 1-9, wherein R_5 is unsubstituted alkyl.

16. The compound of claims 15, wherein R_5 is $-CH_3$.

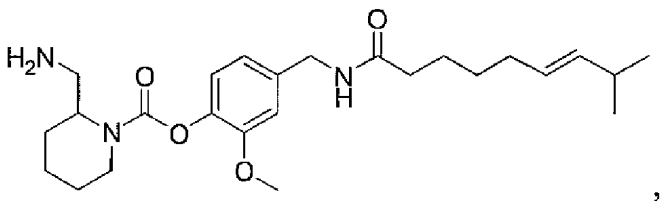
17. The compound of claim 1, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof, having the structure:



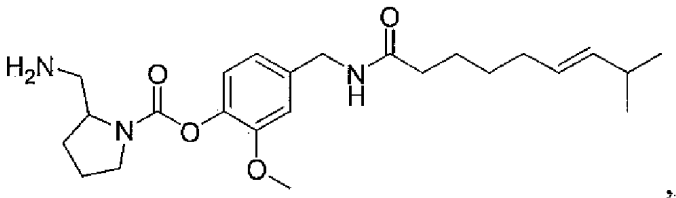
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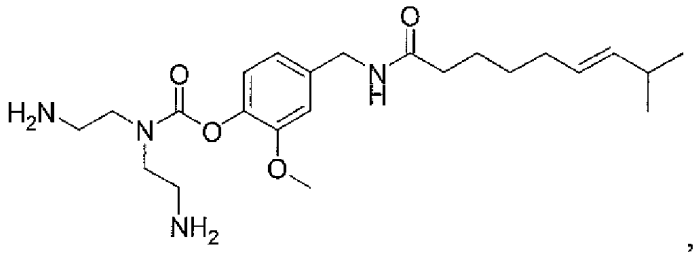
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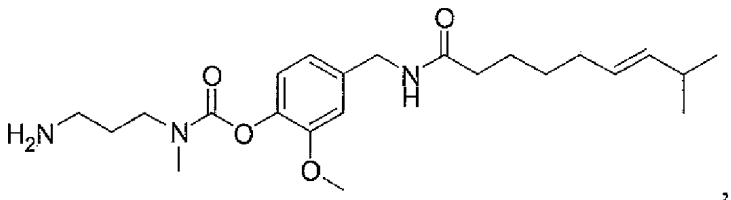
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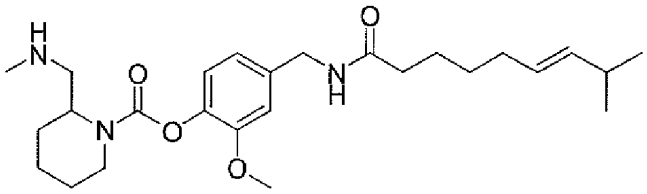
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18. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof, as claimed in any one of claims 1-17, and a pharmaceutically acceptable diluent, excipient or binder.
19. Use of a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof, for use in the manufacture of a medicament for treating pain.