PRODRUGS OF PHENOLIC TRPV1 AGONISTS

CROSS-REFERENCE

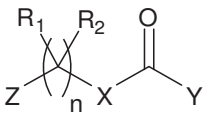
[0001] This application claims benefit of U.S. Provisional Application No. 62/084,515, filed on November 25, 2014, and is a continuation-in-part of U.S. Patent Application No. 14/743,375, filed on June 18, 2015, both of which are herein incorporated by reference in their entirety.

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.

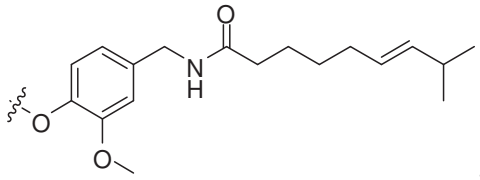
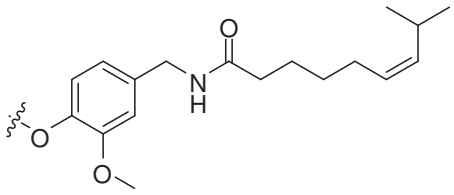
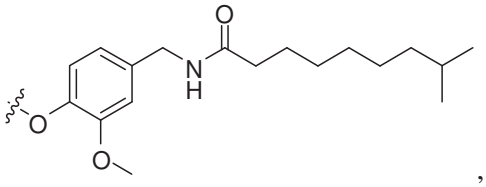
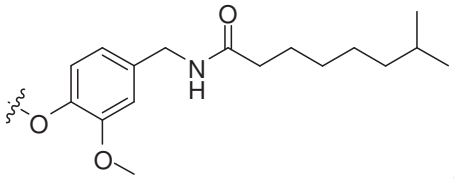
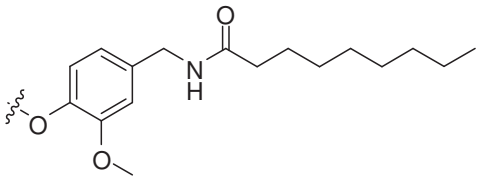
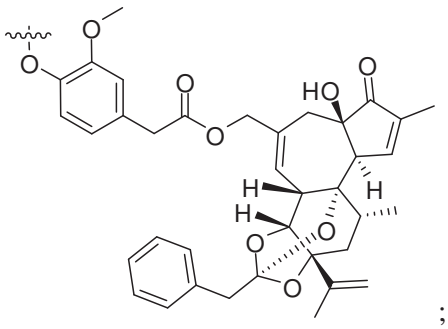
SUMMARY OF THE INVENTION

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



Formula (I);

wherein:

Y is , , , , , or ;

X is -N(R_5)-;

n is an integer from 2 to 4;

Z is -NR_3R_4;

each R_1 and R_2 is each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted acyl; and

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 wherein the heterocycloalkyl group is a substituted or unsubstituted pyrrolidine ring, substituted or unsubstituted piperidine ring, or substituted or unsubstituted piperazine ring;

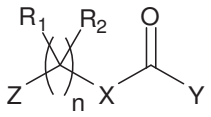
R_3 is hydrogen and R_4 is hydrogen or substituted or unsubstituted alkyl;

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, 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 $-CO_2H$;

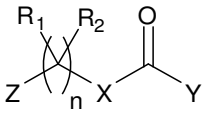
R_5 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl, and each R_1 and R_2 is each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted acyl, or two R_1 or R_2 groups on adjacent carbon atoms, 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.

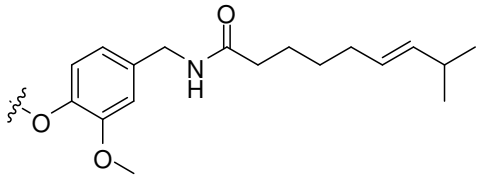
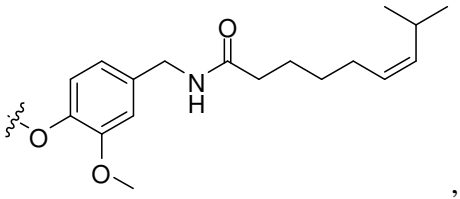
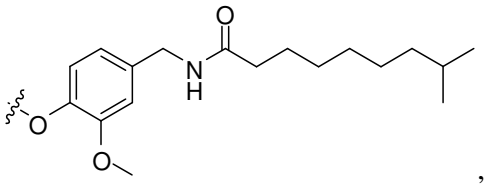
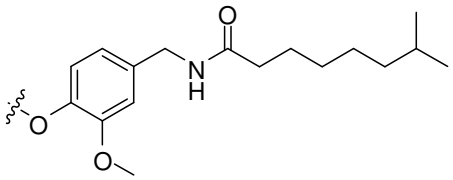
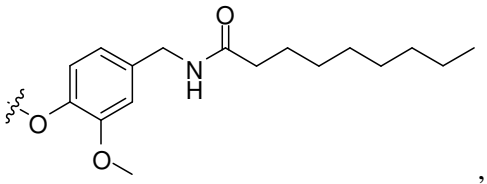
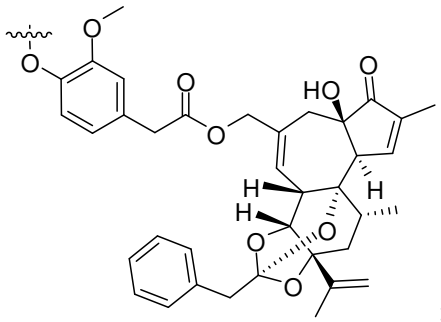
WHAT IS CLAIMED IS:

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



Formula (I);

wherein:

Y is , , , , , or ;

X is -N(R_5)-;

n is an integer from 2 to 4;

Z is -N$R_3$$R_4$;

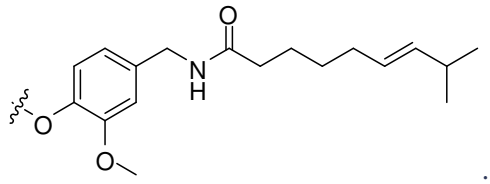
each R_1 and R_2 is each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted acyl; and

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 wherein the heterocycloalkyl group is a substituted or unsubstituted pyrrolidine ring, substituted or unsubstituted piperidine ring, or substituted or unsubstituted piperazine ring;

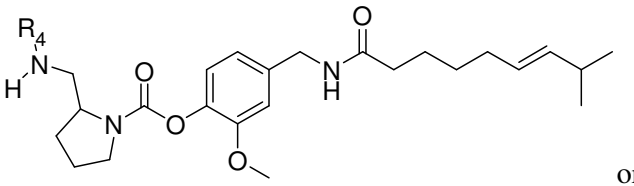
R_3 is hydrogen and R_4 is hydrogen or substituted or unsubstituted alkyl;

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

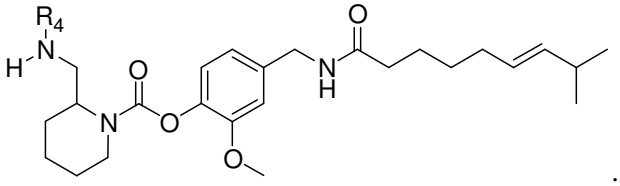
2. The compound of claim 1, wherein Y is



3. The compound of claim 1 or claim 2, wherein the R_1 and R_5 groups on adjacent atoms, together with the atoms to which they are attached, form a heterocycloalkyl group that is an unsubstituted pyrrolidine ring, unsubstituted piperidine ring, or unsubstituted piperazine ring.
4. The compound of claim 1, having the structure:

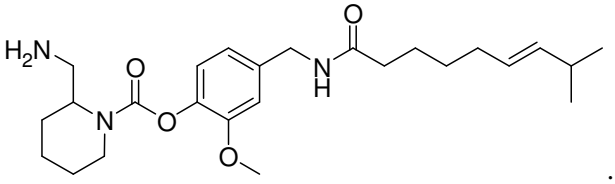


or



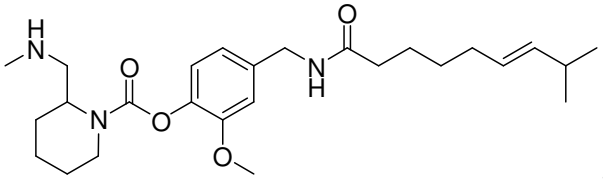
.

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



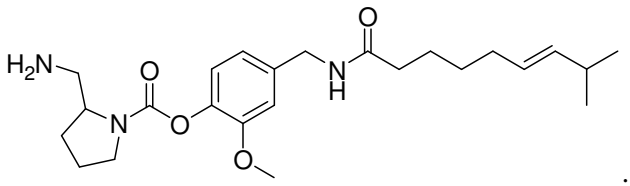
.

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



.

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



.

8. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof, as claimed in any one of claims 1-7, and a pharmaceutically acceptable diluent, excipient or binder.
9. Use of a compound of any one of claims 1-7, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or hydrate thereof, in the manufacture of a medicament for treating pain.