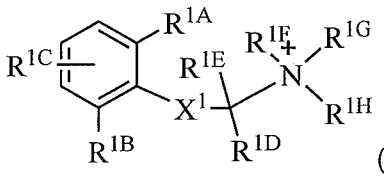
Summary

The disclosure features a quaternary amine compound having formula (I)



(I), wherein

R^{1F} and R^{1G} together complete a heterocyclic ring having at least one nitrogen atom; and wherein each of R^{1A}, R^{1B}, and R^{1C} is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OR^{1I}, $NR^{1J}R^{1K}$, $NR^{1L}C(O)R^{1M}$, $S(O)R^{1N}$, $SO_2R^{1O}R^{1P}$, $SO_2NR^{1Q}R^{1R}$, SO_3R^{1S}, CO_2R^{1T}, $C(O)R^{1U}$, and $C(O)NR^{1V}R^{1W}$; and each of R^{1I}, R^{1J}, R^{1K}, R^{1L}, R^{1M}, R^{1N}, R^{1O}, R^{1P}, R^{1Q}, R^{1R}, R^{1S}, R^{1T}, R^{1U}, R^{1V}, and R^{1W} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; wherein

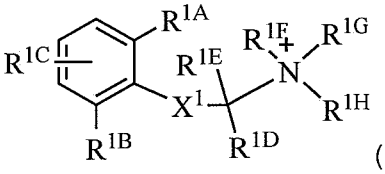
X^1 is selected from $-CR^{1X}R^{1Y}-$, $-NR^{1Z}C(O)-$, $-OC(O)-$, $-SC(O)-$, $-C(O)NR^{1AA}-$, $-CO_2-$, and $-OC(S)-$; and each of R^{1X}, R^{1Y}, R^{1Z}, and R^{1AA} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; wherein

each of R^{1D} and R^{1E} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, optionally substituted with halogen, C_{3-8} cyclic alkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl or R^{1D} and R^{1E} together form a 3-6-membered heterocyclic or heteroalkyl ring; and wherein

R^{1H} is selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, optionally substituted with halogen, C_{3-8} cyclic alkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl.

In some embodiments, X^1 is -NHC(O)-. In some embodiments, each of R^{1A} and R^{1B} is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and $NR^{1J}R^{1K}$; and each of R^{1J} and R^{1K} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; or wherein at least one R^{1C} is present. In certain other embodiments, R^{1D} is C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cyclic alkyl, aryl, or heteroaryl, R^{1E} is H and C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cyclic alkyl, aryl, or heteroaryl, or R^{1H} is C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cyclic alkyl, aryl, or heteroaryl.

In one aspect, there is provided a quaternary amine compound represented by formula (I)



(I), wherein

R^{1F} and R^{1G} together complete a heterocyclic ring having at least one nitrogen atom;

each of R^{1A}, R^{1B}, and R^{1C} is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OR^{1I}, $NR^{1J}R^{1K}$, $NR^{1L}C(O)R^{1M}$, $S(O)R^{1N}$, $SO_2R^{1O}R^{1P}$, $SO_2NR^{1Q}R^{1R}$, SO_3R^{1S}, CO_2R^{1T}, $C(O)R^{1U}$, and $C(O)NR^{1V}R^{1W}$; and each of R^{1I}, R^{1J}, R^{1K}, R^{1L}, R^{1M}, R^{1N}, R^{1O}, R^{1P}, R^{1Q}, R^{1R}, R^{1S}, R^{1T}, R^{1U}, R^{1V}, and R^{1W} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;

X^1 is selected from $-CR^{1X}R^{1Y}-$, $-NR^{1Z}C(O)-$, $-OC(O)-$, $-SC(O)-$, $-C(O)NR^{1AA}-$, $-CO_2-$, and $-OC(S)-$; and each of R^{1X}, R^{1Y}, R^{1Z}, and R^{1AA} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;

each of R^{1D} and R^{1E} is independently selected from:

H,

C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} heteroalkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl, and

C_{3-6} cycloalkyl

or R^{1D} and R^{1E} together form a 3-6-membered heterocyclic ring; and

R^{1H} is selected from:

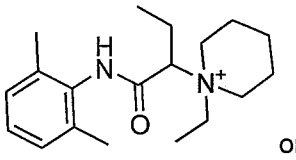
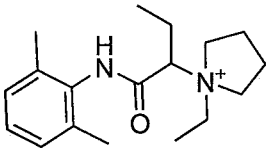
C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

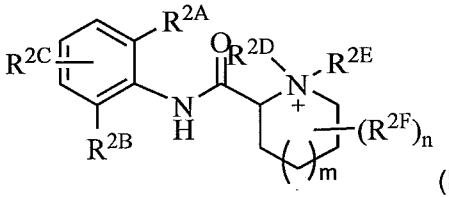
C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} heteroalkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl.

In some embodiments, the compound is a compound in Table 1. In some embodiments, the compound is:

(Compound 6)  or (Compound 3) 

The disclosure also features a quaternary amine compound having formula (II)



(II), wherein

m is 0 or 1; wherein

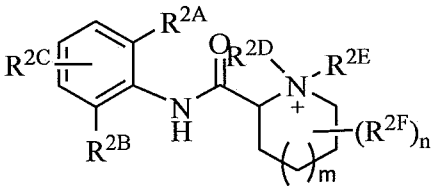
each of R^{2A}, R^{2B}, and R^{2C}, is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, CF_3, OR^{2H}, $NR^{2I}R^{2J}$, $NR^{2K}C(O)R^{2L}$, $S(O)R^{2M}$, $SO_2R^{2N}R^{2O}$, $SO_2NR^{2P}R^{2Q}$, SO_3R^{2R}, CO_2R^{2S}, $C(O)R^{2T}$, and $C(O)NR^{2U}R^{2V}$; and each of R^{2H}, R^{2I}, R^{2J}, R^{2K}, R^{2L}, R^{2M}, R^{2N}, R^{2O}, R^{2P}, R^{2Q}, R^{2R}, R^{2S}, R^{2T}, R^{2U}, and R^{2V} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;

wherein

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9 and each R^{2F} is, independently, selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, CF_3, OR^{2H}, $NR^{2I}R^{2J}$, $NR^{2K}C(O)R^{2L}$, $S(O)R^{2M}$, $SO_2R^{2N}R^{2O}$, $SO_2NR^{2P}R^{2Q}$, SO_3R^{2R}, CO_2R^{2S}, $C(O)R^{2T}$, and $C(O)NR^{2U}R^{2V}$; and each of R^{2H}, R^{2I}, R^{2J}, R^{2K}, R^{2L}, R^{2M}, R^{2N}, R^{2O}, R^{2P}, R^{2Q}, R^{2R}, R^{2S}, R^{2T}, R^{2U}, and R^{2V} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; and wherein

each of R^{2D} and R^{2E} is, independently, selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, optionally substituted with halogen, cyclic alkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl.

In another aspect, there is provided a quaternary amine compound represented by formula (II)



(II), wherein

m is 0 or 1;

each of R^{2A}, R^{2B}, and R^{2C}, is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, CF_3, OR^{2H}, $NR^{2I}R^{2J}$, $NR^{2K}C(O)R^{2L}$, $S(O)R^{2M}$, $SO_2R^{2N}R^{2O}$, $SO_2NR^{2P}R^{2Q}$, SO_3R^{2R}, CO_2R^{2S}, $C(O)R^{2T}$, and $C(O)NR^{2U}R^{2V}$;

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9; each R^{2F} is, independently, selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, CF_3, OR^{2H}, $NR^{2I}R^{2J}$, $NR^{2K}C(O)R^{2L}$, $S(O)R^{2M}$, $SO_2R^{2N}R^{2O}$, $SO_2NR^{2P}R^{2Q}$, SO_3R^{2R}, CO_2R^{2S}, $C(O)R^{2T}$, and $C(O)NR^{2U}R^{2V}$; each of R^{2H}, R^{2I}, R^{2J}, R^{2K}, R^{2L}, R^{2M}, R^{2N}, R^{2O}, R^{2P}, R^{2Q}, R^{2R}, R^{2S}, R^{2T}, R^{2U}, and R^{2V} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; and

each of R^{2D} and R^{2E} is, independently, selected from:

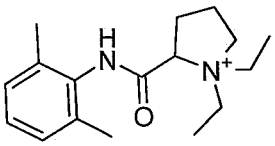
C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

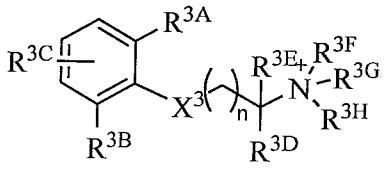
C_{2-4} heteroalkyl optionally substituted with halogen, cycloalkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl.

In some embodiments, each of R^{2D} and R^{2E} is C_{1-4} alkyl that is optionally substituted with halogen, cyclic alkyl, aryl, or heteroaryl. In another embodiment, each of R^{2A}, R^{2B}, and R^{2C} is independently selected from H, halogen, C_{1-4} alkyl, and CF_3; or wherein at least one R^{2C} is present; or wherein at least one R^{2F} is present. In certain embodiments, the compound is a compound in Table 2. In some embodiments, the compound is



(Compound 14) .

The disclosure also features a quaternary amine compound having general formula (III)



(III), wherein

n is 0, 1, 2, or 3; wherein

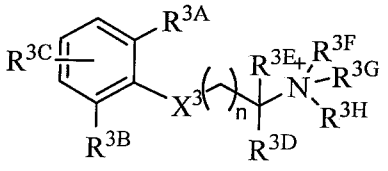
each of R^{3A}, R^{3B}, and R^{3C} is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OR^{3I}, $NR^{3J}R^{3K}$, $NR^{3L}C(O)R^{3M}$, $S(O)R^{3N}$, $SO_2R^{3O}R^{3P}$, $SO_2NR^{3Q}R^{3R}$, SO_3R^{3S}, CO_2R^{3T}, $C(O)R^{3U}$, and $C(O)NR^{3V}R^{3W}$; and each of R^{3I}, R^{3J}, R^{3K}, R^{3L}, R^{3M}, R^{3N}, R^{3O}, R^{3P}, R^{3Q}, R^{3R}, R^{3S}, R^{3T}, R^{3U}, R^{3V}, and R^{3W} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; wherein

X^3 is selected from -NHC(O)-, and -C(O)NH; wherein

each of R^{3D} and R^{3E} can, independently, be selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, optionally substituted with halogen, cyclic alkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl, or R^{1D} and R^{1E} together can form a 3-6-membered heterocyclic or heteroalkyl ring; and wherein

each of R^{3F}, R^{3G}, and R^{3H} is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, optionally substituted with halogen, cyclic alkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl.

In another aspect, there is provided a quaternary amine compound represented by formula (III)



(III), wherein

n is 0, 1, 2, or 3;

each of R^{3A}, R^{3B}, and R^{3C} is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OR^{3I}, $NR^{3J}R^{3K}$, $NR^{3L}C(O)R^{3M}$, $S(O)R^{3N}$, $SO_2R^{3O}R^{3P}$, $SO_2NR^{3Q}R^{3R}$, SO_3R^{3S}, CO_2R^{3T}, $C(O)R^{3U}$, and $C(O)NR^{3V}R^{3W}$; and each of R^{3I}, R^{3J}, R^{3K}, R^{3L}, R^{3M}, R^{3N}, R^{3O}, R^{3P}, R^{3Q}, R^{3R}, R^{3S}, R^{3T}, R^{3U}, R^{3V}, and R^{3W} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;

X^3 is selected from -NHC(O)-, and -C(O)NH;

each of R^{3D} and R^{3E} is, independently, selected from:

H,

C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} heteroalkyl optionally substituted with halogen, cycloalkyl, aryl, or heteroaryl, and

C_{3-6} cycloalkyl,

or R^{1D} and R^{1E} together form a 3-6-membered heterocyclic ring; and

each of R^{3F}, R^{3G}, and R^{3H} is independently selected from:

C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

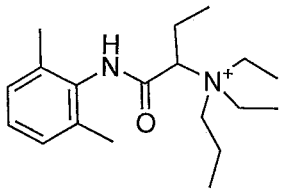
C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} heteroalkyl optionally substituted with halogen, cycloalkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl.

In particular embodiments, X^3 is –NHC(O)-. In other embodiments, n is 0 or 1. In some embodiments, each of R^{3A}, R^{3B}, and R^{3C} is independently selected from H, C_{1-4} alkyl, and $NR^{3J}R^{3K}$; and each of R^{3J} and R^{3K} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl. In yet another embodiment, each of R^{3E}, R^{3F}, and R^{3G} is independently selected from C_{1-4}

alkyl optionally substituted with halogen, cyclic alkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl. In particular embodiments, the compound is any one of Compound Nos. 21-24 in Table 3. In yet another embodiment, the compound is



(Compound 21)

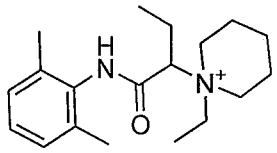
The disclosure also features a composition including the quaternary amine compound of any one of the compounds in Tables 1-3 or a compound of formulas I through III and a pharmaceutically acceptable excipient. In another aspect, there is provided a composition comprising the quaternary amine compound as defined herein and a pharmaceutically acceptable excipient. The composition can be formulated for oral, intravenous, intramuscular, rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, inhalation, vaginal, intrathecal, epidural, or ocular administration.

The disclosure also features a method for treating pain, itch, or a neurogenic inflammatory disorder in a patient, the method including administering to the patient a composition including the quaternary amine compound of any one of the compounds in Tables 1-3 or a compound of formulas I through III, wherein the compound inhibits one or more voltage-gated ion channels present in nociceptors and/or pruriceptors when applied to the internal face of the channels but does not substantially inhibit the channels when applied to the external face of the channels, and wherein the compound is capable of entering nociceptors or pruriceptors through a channel-forming receptor when the receptor is activated and inhibiting the one or more voltage-gated ion channels present in the nociceptors.

In another aspect, there is provided a quaternary amine compound as defined herein for use in a method for treating a neurogenic inflammatory disorder, itch or pain in a patient, wherein said compound inhibits one or more voltage-gated ion channels present in nociceptors and/or pruriceptors when applied to the internal face of said channels but does not substantially inhibit said channels when applied to the external face of said channels, and wherein said compound is capable of (i) entering nociceptors or pruriceptors through a channel-forming receptor when said receptor is activated and (ii) inhibiting said one or more voltage-gated ion channels present in said nociceptors and/or pruriceptors.

In certain embodiments, the channel-forming receptor is a transient receptor potential ion channel (TRP channel-forming receptor). In other embodiments, the TRP channel-forming receptor is activated by an exogenous or endogenous agonist. In yet other embodiments, the TRP channel-forming receptor is TRPA1 or TRPV1. In particular embodiments, the compound is capable of entering nociceptors or pruriceptors through the TRPA1 or TRPV1 receptor when the receptor is activated. In yet other embodiments, the compound inhibits voltage-gated sodium channels. In yet another embodiment, the pain is selected from the group consisting of neuropathic pain, inflammatory pain, nociceptive pain, pain due to infections, and procedural pain, or wherein the neurogenic inflammatory disorder is selected from the group consisting of allergic inflammation, asthma, chronic cough, conjunctivitis, rhinitis, psoriasis, inflammatory bowel disease, and interstitial cystitis, atopic dermatitis. In particular embodiments, the

compositions of the disclosure include a quaternary amine compound selected from the group consisting of: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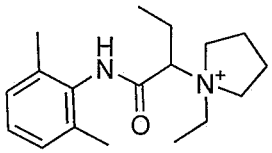
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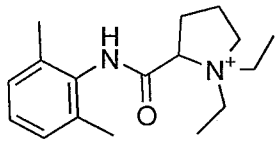
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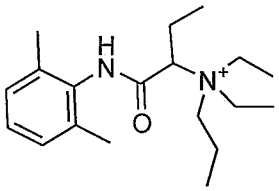
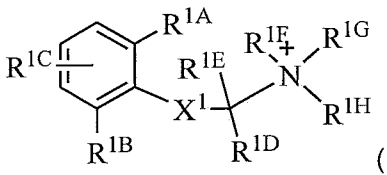


(Compound 6) (Compound 3) (Compound 14) (Compound 21).

CLAIMS

1. A quaternary amine compound represented by formula (I)



(I), wherein

R^{1F} and R^{1G} together complete a heterocyclic ring having at least one nitrogen atom;

each of R^{1A}, R^{1B}, and R^{1C} is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OR^{1I}, $NR^{1J}R^{1K}$, $NR^{1L}C(O)R^{1M}$, $S(O)R^{1N}$, $SO_2R^{1O}R^{1P}$, $SO_2NR^{1Q}R^{1R}$, SO_3R^{1S}, CO_2R^{1T}, $C(O)R^{1U}$, and $C(O)NR^{1V}R^{1W}$; and each of R^{1I}, R^{1J}, R^{1K}, R^{1L}, R^{1M}, R^{1N}, R^{1O}, R^{1P}, R^{1Q}, R^{1R}, R^{1S}, R^{1T}, R^{1U}, R^{1V}, and R^{1W} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;

X^1 is selected from $-CR^{1X}R^{1Y}-$, $-NR^{1Z}C(O)-$, $-OC(O)-$, $-SC(O)-$, $-C(O)NR^{1AA}-$, $-CO_2-$, and $-OC(S)-$; and each of R^{1X}, R^{1Y}, R^{1Z}, and R^{1AA} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;

each of R^{1D} and R^{1E} is independently selected from:

H,

C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} heteroalkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl

or R^{1D} and R^{1E} together form a 3-6-membered heterocyclic ring; and

R^{1H} is selected from:

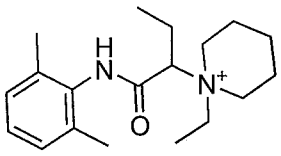
C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

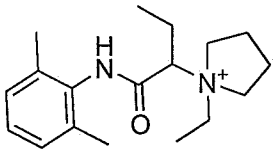
C_{2-4} heteroalkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl.

2. The compound of claim 1, wherein said compound is



(Compound 6).

3. The compound of claim 1, wherein said compound is



(Compound 3).

4. The compound of claim 1, wherein

(a) X^1 is -NHC(O)-;

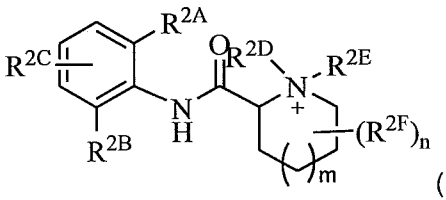
(b) each of R^{1A} and R^{1B} is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and $NR^{1J}R^{1K}$; and each of R^{1J} and R^{1K} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; or wherein at least one R^{1C} is present;

(c) R^{1D} is C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl;

(d) R^{1E} is H or C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl; and/ or

(e) R^{1H} is C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl.

5. A quaternary amine compound represented by formula (II)



(II), wherein

m is 0 or 1;

each of R^{2A}, R^{2B}, and R^{2C}, is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, CF_3, OR^{2H}, $NR^{2I}R^{2J}$, $NR^{2K}C(O)R^{2L}$, $S(O)R^{2M}$, $SO_2R^{2N}R^{2O}$, $SO_2NR^{2P}R^{2Q}$, SO_3R^{2R}, CO_2R^{2S}, $C(O)R^{2T}$, and $C(O)NR^{2U}R^{2V}$;

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9; each R^{2F} is, independently, selected from halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, CF_3, OR^{2H}, $NR^{2I}R^{2J}$, $NR^{2K}C(O)R^{2L}$, $S(O)R^{2M}$, $SO_2R^{2N}R^{2O}$, $SO_2NR^{2P}R^{2Q}$, SO_3R^{2R}, CO_2R^{2S}, $C(O)R^{2T}$, and $C(O)NR^{2U}R^{2V}$; each of R^{2H}, R^{2I}, R^{2J}, R^{2K}, R^{2L}, R^{2M}, R^{2N}, R^{2O}, R^{2P}, R^{2Q}, R^{2R}, R^{2S}, R^{2T}, R^{2U}, and R^{2V} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; and

each of R^{2D} and R^{2E} is, independently, selected from:

C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

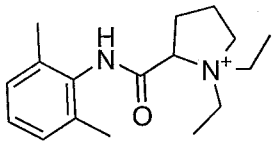
C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl, C_{2-4} heteroalkyl optionally substituted with halogen, cycloalkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl.

6. The compound of claim 5, wherein:

(a) each of R^{2D} and R^{2E} is C_{1-4} alkyl optionally substituted with halogen, cycloalkyl, aryl, or heteroaryl; and/or

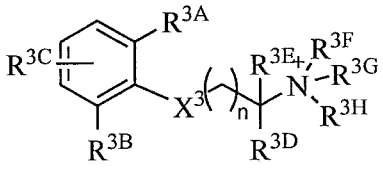
(b) each of R^{2A}, R^{2B}, and R^{2C} is independently selected from H, halogen, C_{1-4} alkyl, and CF_3; or wherein at least one R^{2C} is present; or wherein at least one R^{2F} is present.

7. The compound of claim 5, wherein said compound is



(Compound 14).

8. A quaternary amine compound represented by formula (III)



(III), wherein

n is 0, 1, 2, or 3;

each of R^{3A}, R^{3B}, and R^{3C} is independently selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OR^{3I}, $NR^{3J}R^{3K}$, $NR^{3L}C(O)R^{3M}$, $S(O)R^{3N}$, $SO_2R^{3O}R^{3P}$, $SO_2NR^{3Q}R^{3R}$, SO_3R^{3S}, CO_2R^{3T}, $C(O)R^{3U}$, and $C(O)NR^{3V}R^{3W}$; and each of R^{3I}, R^{3J}, R^{3K}, R^{3L}, R^{3M}, R^{3N}, R^{3O}, R^{3P}, R^{3Q}, R^{3R}, R^{3S}, R^{3T}, R^{3U}, R^{3V}, and R^{3W} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;

X^3 is selected from -NHC(O)-, and -C(O)NH;

each of R^{3D} and R^{3E} is, independently, selected from:

H,

C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} heteroalkyl optionally substituted with halogen, cycloalkyl, aryl, or heteroaryl, and

C_{3-6} cycloalkyl,

or R^{1D} and R^{1E} together form a 3-6-membered heterocyclic ring; and

each of R^{3F}, R^{3G}, and R^{3H} is independently selected from:

C_{1-4} alkyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkenyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} alkynyl optionally substituted with halogen, C_{3-8} cycloalkyl, aryl, or heteroaryl,

C_{2-4} heteroalkyl optionally substituted with halogen, cycloalkyl, aryl, or heteroaryl,

and C_{3-6} cycloalkyl.

9. The compound of claim 8, wherein:

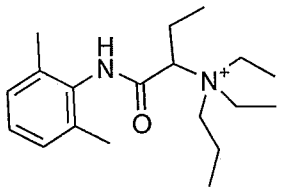
(a) X^3 is –NHC(O)-;

(b) n is 0 or 1;

(c) each of R^{3A}, R^{3B}, and R^{3C} is independently selected from H, C_{1-4} alkyl, and $NR^{3J}R^{3K}$; and each of R^{3J} and R^{3K} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; and/or

(d) each of R^{3E}, R^{3F}, and R^{3G} is independently selected from C_{1-4} alkyl optionally substituted with halogen, cycloalkyl, aryl, or heteroaryl, and C_{3-6} cycloalkyl.

10. The compound of claim 8, wherein said compound is



(Compound 21).

11. The compound of any of claims 1, 5 and 8, wherei said compound is:

(a) a compound listed in Table 1;

(b) a compound listed in Table 2; or

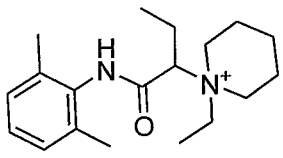
(c) any of compound Nos. 21-24 in Table 3.

12. A composition comprising the quaternary amine compound of any one of claims 1-11 and a pharmaceutically acceptable excipient.

13. The composition of claim 12, wherein said composition is formulated for oral, intravenous, intramuscular, rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, vaginal, intrathecal, epidural, or ocular administration, or wherein said compound is formulated for administration by inhalation.

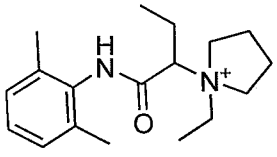
14. A quaternary amine compound of any one of claims 1-11 for use in a method for treating a neurogenic inflammatory disorder, itch or pain in a patient, wherein said compound inhibits one or more voltage-gated ion channels present in nociceptors and/or pruriceptors when applied to the internal face of said channels but does not substantially inhibit said channels when applied to the external face of said channels, and wherein said compound is capable of (i) entering nociceptors or pruriceptors through a channel-forming receptor when said receptor is activated and (ii) inhibiting said one or more voltage-gated ion channels present in said nociceptors and/or pruriceptors.

15. The compound for use of claim 14, wherein said compound is



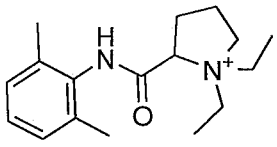
(Compound 6).

16. The compound for use of claim 14, wherein said compound is



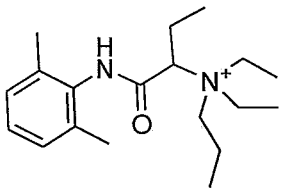
(Compound 3).

17. The compound for use of claim 14, wherein said compound is



(Compound 14).

18. The compound for use of claim 14, wherein said compound is



(Compound 21).

19. The compound for use of claim 14, wherein:

(a) said neurogenic inflammatory disorder is selected from the group consisting of allergic inflammation, asthma, chronic cough, conjunctivitis, rhinitis, psoriasis, inflammatory bowel disease, and interstitial cystitis, atopic dermatitis;

(b) said channel-forming receptor is a transient receptor potential ion channel (TRP channel-forming receptor), optionally wherein said TRP channel-forming receptor is activated by an exogenous or endogenous agonist and/ or wherein said TRP channel-forming receptor is TRPA1 or TRPV1, optionally wherein said compound is capable of entering nociceptors or pruriceptors through said TRPA1 or TRPV1 receptor when said receptor is activated;

(c) said compound inhibits voltage-gated sodium channels; and/ or

(d) said pain is selected from the group consisting of neuropathic pain, inflammatory pain, nociceptive pain, pain due to infections, and procedural pain.