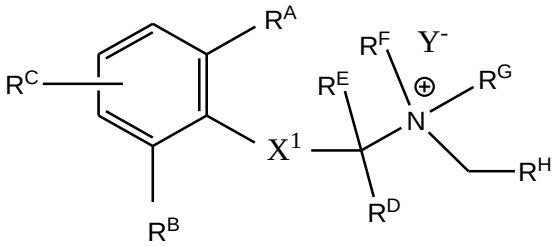
CLAIMS

What is claimed is:

1. A compound represented by Formula (**I**)



(**I**),

wherein:

Y^- is a pharmaceutically acceptable anion;

R^A~~,~~ and R^B~~, and R^C~~ are each independently selected from ~~H, D, halogen,~~ substituted or unsubstituted alkyl, ~~substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, OR^I, CN, NR^JR^K, $NR^LC(O)R^M$, $S(O)R^N$, $S(O)_2R^N$, $SO_2R^OR^P$, $SO_2NR^QR^R$, SO_3R^S,~~ or CO_2R^T~~; $C(O)R^U$, and $C(O)NR^VR^W$~~;

R^C are each independently selected from H, D, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, OR^I, CN, NR^JR^K, $NR^LC(O)R^M$, $S(O)R^N$, $S(O)_2R^N$, $SO_2R^OR^P$, $SO_2NR^QR^R$, SO_3R^S, CO_2R^T; $C(O)R^U$, and $C(O)NR^VR^W$;

each of R^I, R^J, R^K, R^L, R^M, R^N, R^O, R^P, R^Q, R^R, R^S, R^U, R^V, and R^W is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl~~; or~~, wherein R^J and R^K or R^V and R^W or R^Q and R^R ~~can be~~are optionally taken together with the nitrogen to which they are attached to form a substituted or unsubstituted 5, 6, 7, or 8 membered ring;

~~R^A, R^B, and/or R^C can be taken together with the phenyl ring to which they are attached can form a fused bicyclic or tricyclic ring system;~~

X^1 is ~~selected from CR^XR^Y, $NR^ZC(O)$, $NR^ZC(O)CR^XR^Y$, $OC(O)$, $SC(O)$, $C(O)NR^{1A}$, $C(O)O$, $(O)CS$, $NR^{1A}S(O)$, $S(O)NR^{1A}$, $NR^{1A}C(O)NR^{1A}$, $S(O)$ and $S(O)_2$~~;

~~each of R^X, R^Y, R^Z, and R^{1A}~~ is ~~independently~~ selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl;

each of R^D and R^E is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted cycloalkyl; or R^D and R^E together with the carbon to which they are attached form a substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted heterocyclic;

~~or R^D and R^Z together with the carbon and the -N-C(O)- to which they are attached form an optionally substituted 5-8-membered lactam;~~

R^F and R^G together with the N^+ to which they are attached form an optionally substituted heterocyclic ring having zero, one or more nitrogen atoms in addition to the N+;

~~or, each of R^F and R^G is independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted C_3-C_6 cycloalkyl;~~ and

R^H is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl.

2. The compound of claim 1, wherein Y^- is bromide, chloride, or iodide.

~~3. The compound of claim 1, wherein X^1 is $NHC(O)$.~~

~~4~~3. The compound of claim 1, wherein R^H is selected from a C_{6-10} aryl or a C_{5-10} heteroaryl, each optionally substituted with C_{1-6} alkane, C_3-C_6 cycloalkyl, heterocyclyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, hydroxyl, amide, ester, sulfonamide, urea, nitrile, or halogen.

~~5~~4. The compound of claim 1, wherein R^H is a C_{6-10} aryl or a 5- to 10-membered heteroaryl, each optionally substituted with a substituted or unsubstituted C_1-C_6 alkyl, halo, nitrile, hydroxyl, and alkoxy.

~~6. The compound of claim 1, wherein each of R^A and R^B is independently selected from H, halogen, C_{1-4} alkyl, and NR^JR^K; each of R^J and R^K is independently selected from H or C_{1-4} alkyl; and wherein R^C is H, halogen, C_{1-4} alkyl, or NR^JR^K.~~

~~7. The compound of claim 1, wherein R^A, R^B, and R^C are each independently selected from H, D, halogen, OR^I, substituted or unsubstituted C_1-C_4 alkyl, and NR^JR^K; wherein each of R^I, R^J and R^K is independently selected from H and substituted or unsubstituted C_1-C_4 alkyl.~~

~~8~~5. The compound of claim 1, wherein each of R^A and R^B is CH_3, and R^C is selected from the group consisting of H, CH_3, halogen, nitrile, methoxy, and ethoxy.

~~9~~6. The compound of claim 1, wherein R^D is C_{1-4} alkyl optionally substituted with halogen, oxygen, C_{3-8} cyclic alkyl, aryl, or heteroaryl, and wherein R^E is H, D, or C_{1-4} alkyl.

~~10~~7. The compound of claim 1, wherein R^D and R^E are both hydrogen.

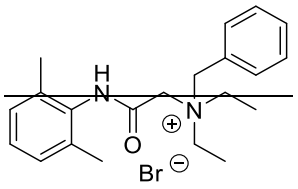
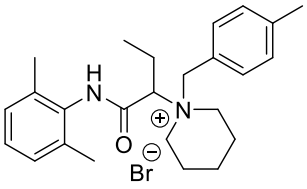
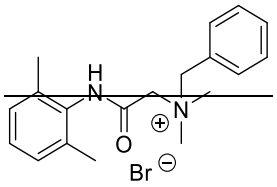
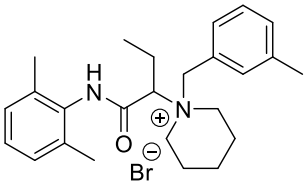
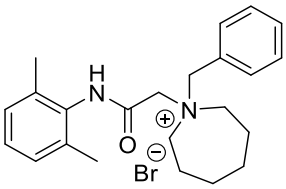
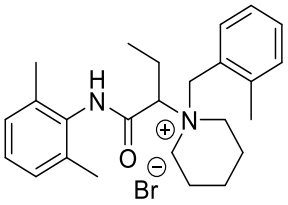
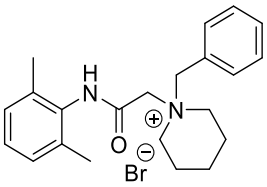
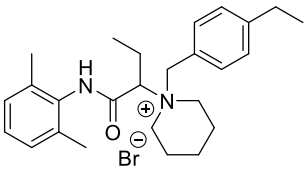
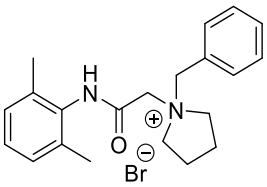
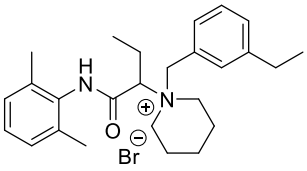
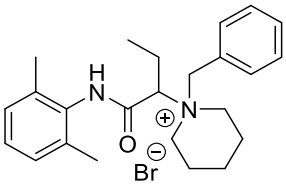
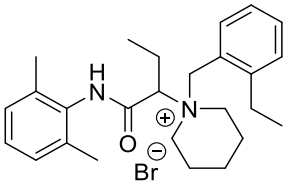
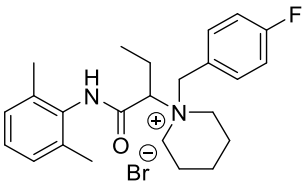
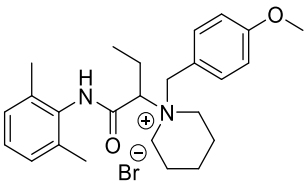
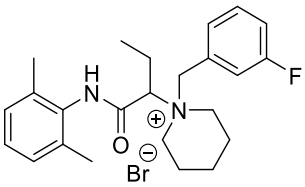
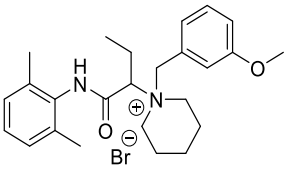
~~11~~8. The compound of claim 1, wherein R^D is hydrogen and R^E is an alkyl.

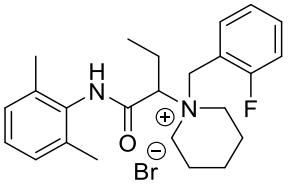
~~12~~9. The compound of claim 1, wherein R^D and R^E are taken together with the carbon to which they are attached to form a C_3-C_6 cycloalkyl.

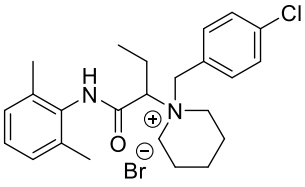
~~13~~10. The compound of claim 1, wherein R^F and R^G together with the N^+ to which they are attached form a substituted or unsubstituted five, six, seven-, or eight-membered heterocyclic ring.

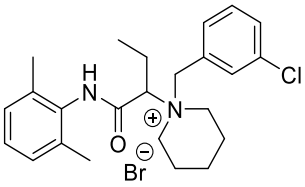
~~14. The compound of claim 1, wherein each of R^F and R^G is independently selected from unsubstituted C_1-C_4 alkyl.~~

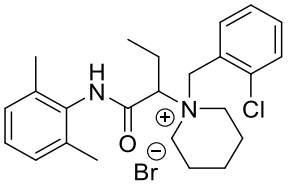
~~15~~11. The compound of claim 1, wherein the compound is selected from the Table below:

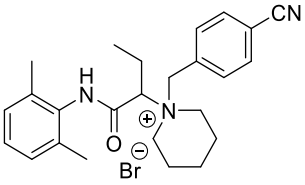
Compound #	Structure	Compound #	Structure
~~1A~~		16A	
~~2A~~		17A	
3A		18A	
4A		19A	
5A		20A	
6A		21A	
7A		22A	
8A		23A	

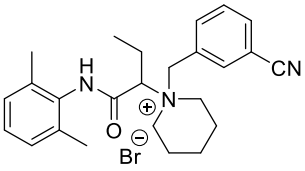
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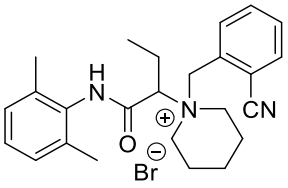
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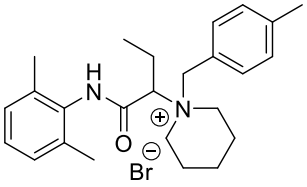
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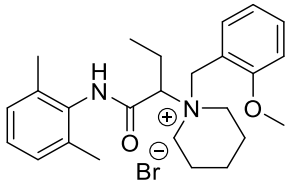
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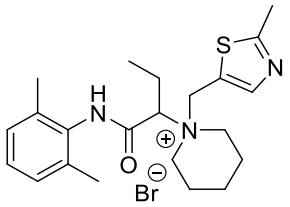
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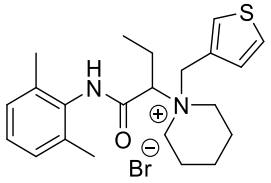
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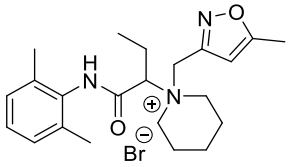
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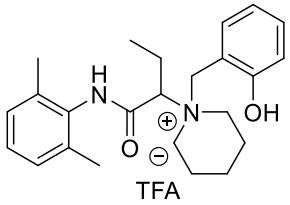
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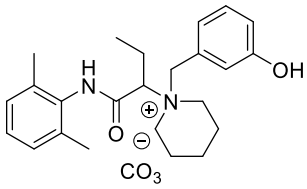
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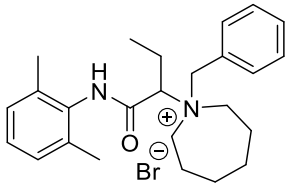
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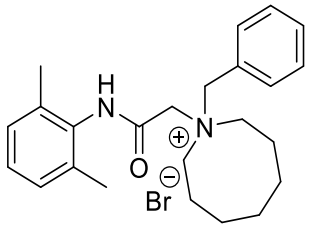
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27A 

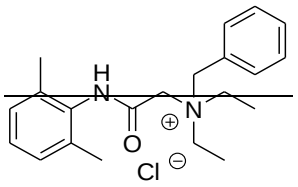
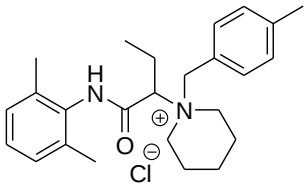
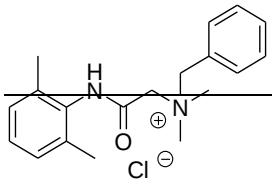
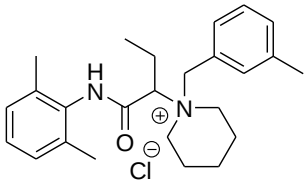
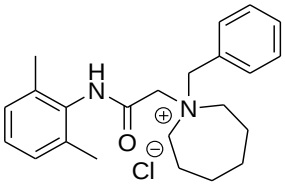
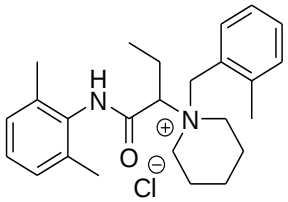
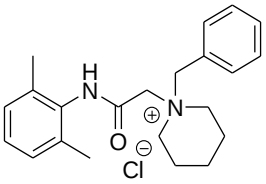
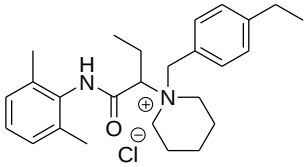
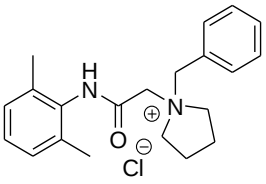
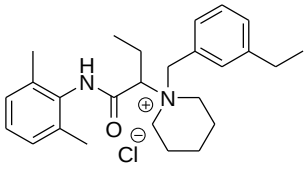
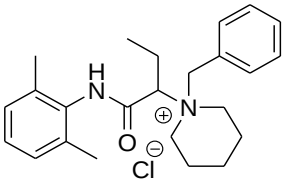
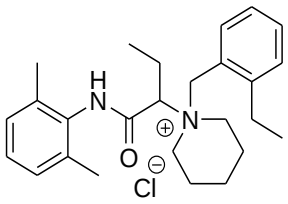
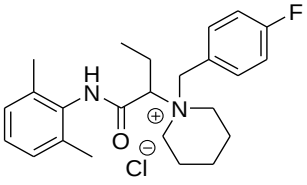
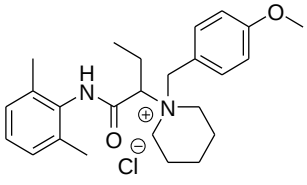
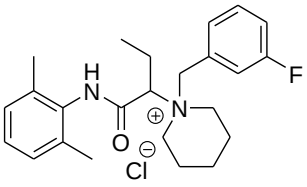
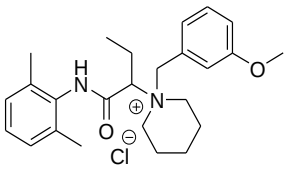
28 

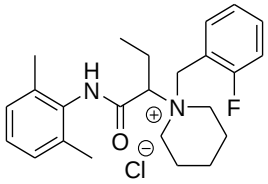
29 

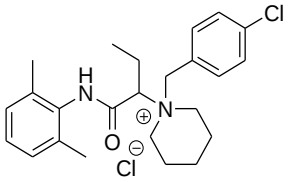
30A 

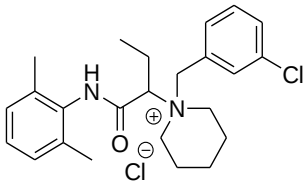
31A 

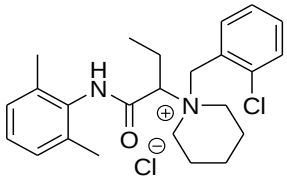
~~16~~12. The compound of claim 1, wherein the compound is selected from the Table below:

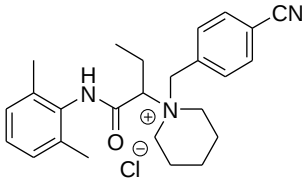
Compound #	Structure	Compound #	Structure
~~1B~~		16B	
~~2B~~		17B	
3B		18B	
4B		19B	
5B		20B	
6B		21B	
7B		22B	
8B		23B	

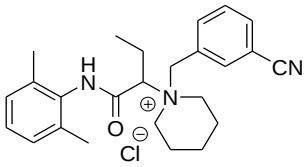
9B 

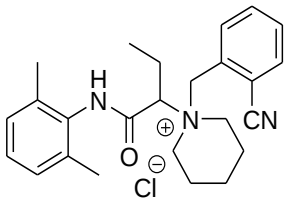
10B 

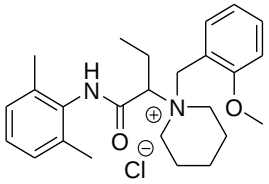
11B 

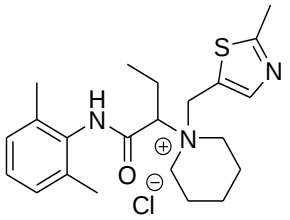
12B 

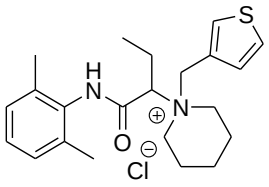
13B 

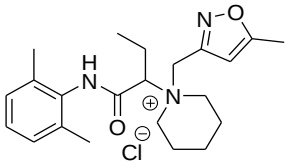
14B 

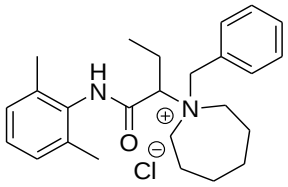
15B 

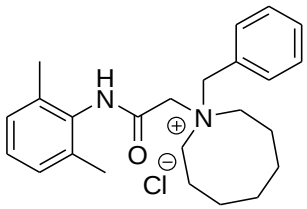
24B 

25B 

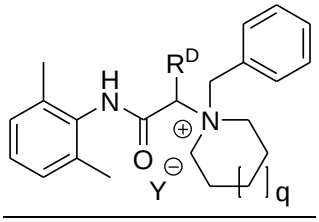
26B 

27B 

30B 

31B 

13. A compound represented by Formula (**I’**):



(I'),

wherein:

Y^- is a pharmaceutically acceptable anion;

q is 0, 1, 2, or 3; and

R^D is hydrogen, methyl, or ethyl.

14. The compound of claim 13, wherein q is 0.

15. The compound of claim 14, wherein R^D is hydrogen or ethyl.

16. The compound of claim 13, wherein q is 1.

17. The compound of claim 16, wherein R^D is hydrogen or ethyl.

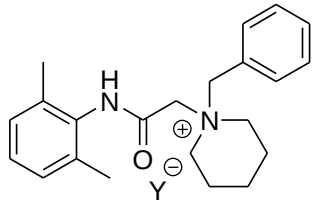
18. The compound of claim 13, wherein q is 2.

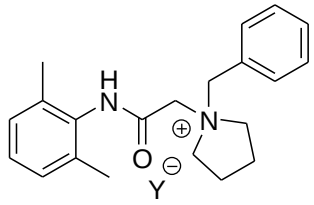
19. The compound of claim 18, wherein R^D is hydrogen or ethyl.

20. The compound of claim 13, wherein q is 3.

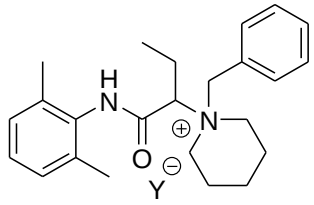
21. The compound of claim 20, wherein R^D is hydrogen or ethyl.

22. The compound of claim 13, wherein the compound is one of the following:

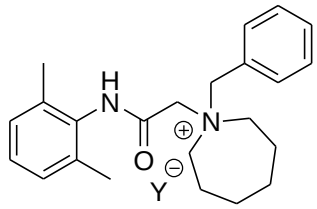

;



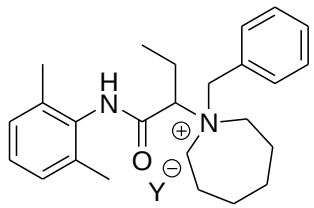
;



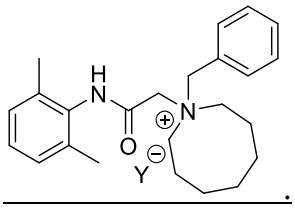
;



;



; or



.

23. The compound of claim 22, wherein Y- is bromide or chloride.

~~17~~24. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

~~18~~25. The composition of claim ~~17~~24, wherein said composition is formulated for oral, intravenous, intramuscular, rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, inhalation, vaginal, intrathecal, epidural, or ocular administration.

~~19~~26. Use of a compound of any one of claims 1 to 23 in the manufacture of a medicament for treating pain, cough, itch, or a neurogenic inflammatory disorder.

~~20~~27. The use of claim ~~19~~26, wherein said pain is selected from the group consisting of pain due to back and neck pain, lower back pain, cancer pain, gynecological and labor pain, fibromyalgia, arthritis, rheumatoid arthritis, osteoarthritis, rheumatological pains, orthopedic pains, acute and post herpetic neuralgia and other neuropathic pains (including peripheral neuropathy), sickle cell crises, vulvodynia, peri-anal pain, irritable bowel disease, irritable bowel syndrome, inflammatory bowel disease, oral mucositis, esophagitis, interstitial cystitis, urethritis and other urological pains, dental pain, headaches, trigeminal trophic syndrome, erythromelalgia, abdominal wall pain, chronic abdominal wall pain, allergic rhinitis, muscle pain, rectal pain, Levator ani syndrome, proctalgia fugax, hemorrhoid pain, stomach pain, skin ulcers, stomach ulcers, burn pain, ophthalmic irritation, conjunctivitis ~~(e.g.~~, allergic conjunctivitis~~)~~, eye redness, dry eye, dry eye syndrome (chronic ocular pain), complex regional pain syndrome, post-surgical ocular pain, postoperative pain, acute postoperative pain, and procedural pain (i.e., pain associated with injections, draining an abscess, surgery, dental procedures, ophthalmic procedures, ophthalmic irritation, conjunctivitis ~~(e.g.~~, allergic conjunctivitis~~)~~, eye redness, dry eye, arthroscopies and use of other medical instrumentation, cosmetic surgical procedures, dermatological procedures, setting fractures, and biopsies~~, and the like~~).

~~21~~28. The use of claim ~~19~~26, wherein said cough is selected from the group consisting of cough in patients with asthma, COPD, asthma-COPD overlap syndrome (ACOS),

interstitial pulmonary fibrosis (IPF), idiopathic pulmonary fibrosis, post viral cough, post-infection cough, chronic idiopathic cough and lung cancer.

~~22~~29. The use of claim ~~19~~26, wherein said itch is selected from the group consisting of itch due to pruritus, brachioradial pruritus, chronic idiopathic pruritus, genital/anal pruritus, notalgia paresthetica, scalp pruritus, allergic dermatitis, contact dermatitis, atopic dermatitis, hand eczema, poison ivy, infections, parasites, insect bites, pregnancy, metabolic disorders, liver or renal failure, drug reactions, allergic reactions, eczema, genital and anal itch, hemorrhoid itch, and cancer.

~~23~~30. The use of claim ~~19~~26, wherein said neurogenic inflammatory disorder is selected from the group consisting of allergic inflammation, asthma, chronic cough, conjunctivitis, rhinitis, psoriasis, inflammatory bowel disease, interstitial cystitis, arthritis, colitis, contact dermatitis, diabetes, eczema, cystitis, gastritis, migraine headache, rosacea, sunburn, pancreatitis, chronic rhinosinusitis, traumatic brain injury, polymicrobial sepsis, tendinopathies, chronic urticaria, rheumatic disease, acute lung injury~~, exposure to irritants, inhalation of irritants, pollutants, chemical warfare agents,~~ and atopic dermatitis.

~~24~~31. The use of any one of claims ~~19~~26 to 30, wherein ~~a~~the compound ~~represented by Formula (I)~~ is to be used in combination with one or more exogenous large pore receptor agonists.