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C07D 498/10 (2006.01)

Norwegian Industrial Property Office

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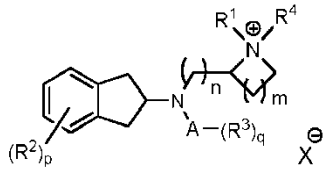
(54) Title **AMINOINDANE COMPOUNDS AND USE THEREOF IN TREATING PAIN**

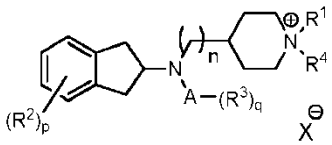
(56) References Cited: WO-A2-2006/036936, WO-A2-2007/038325, WO-A1-00/76510

Patentkrav

1. Forbindelse med formel (**I**) eller (**II**):



(I)



(II)

hvor:

A er fenyl eller monosyklisk 5- eller 6-leddet heteroaryl;

R^1 og R^4 uavhengig er C_1 til C_6 alkyl eller CH_2CH_2OH; eller

R^1 og R^4 er bundet sammen for å danne en 4- eller 6-leddet heterosyklisk ring;

R^2 uavhengig er valgt fra gruppen bestående av halogen og C_1 til C_6 alkoksy;

R^3 uavhengig er valgt fra gruppen bestående av halogen, CN, C_1 til C_6 alkyl, C_2 til C_6 alkenyl, C_2 til C_6 alkynyl, CF_3, OCF_3, SCF_3, C_1 til C_6 alkoksy, C_2 til C_6 alkynyloksy, C_1 til C_6 alkyltio, $NH(C_1$ til C_6 alkyl), $N(C_1$ til C_6 alkyl$)(C_1$ til C_6 alkyl) og $N(C_1$ til C_6 alkyl$)(C_2$ til C_6 alkenyl); eller

q er 2 og to R^3-grupper er bundet sammen for å danne en 6-leddet aryl, 5- eller 6-leddet karbosyklisk ring eller 5- eller 6-leddet heterosyklisk gruppe eller heteroaryl inneholdende 1 til 3 oksygen-, nitrogen- eller svovelatomer og 4 eller 5 karbonatomer;

m er 2 eller 3;

n er 1 til 3;

p er 0 til 2;

q er 0, 1 eller 2; og

X^- er et halogenion, trifluoracetat, sulfat, fosfat, acetat, fumarat, maleat, citrat, pyruvat, succinat, oksalat, bisulfat, malonat, xinafoat, askorbat, oleat, nikotinat, sakkarinat, adipat, formiat, glykolat, L-laktat, D-laktat, aspartat, malat, L-tartrat, D-tartrat, stearat, 2-furoat, 3-furoat, napadisylat, edisylat, isetionat, D-mandelat, L-mandelat, propionat, tartarat, ftalat, hydroklorat, hydrobromat, nitrat, metansulfonat, etansulfonat, napthalenesulfonat, benzensulfonat, toluensulfonat, mesitylenesulfonat, kamfersulfonat eller trifluormetansulfonat.

2. Forbindelse ifølge krav 1,

(b) som inneholder minst 1 kiralt senter;

(c) som er en blanding av enantiomerer;

(d) som er en *R*-enantiomer;

(e) som er en *S*-enantiomer;

(f) hvor p er 0;

(g) hvor q er 0;

(h) hvor n er 1;

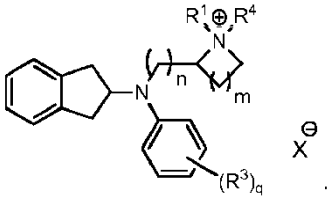
(i) hvor n er 2;

(j) hvor n er 3;

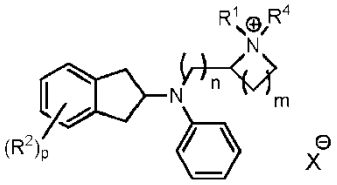
(k) hvor m er 3;

(l) hvor m er 2;

(m) som har strukturen:

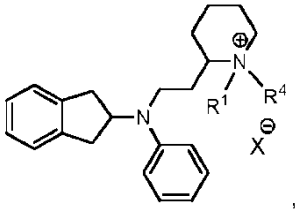


(n) som har strukturen:

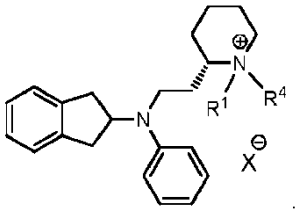


; eller

(o) som har strukturen:

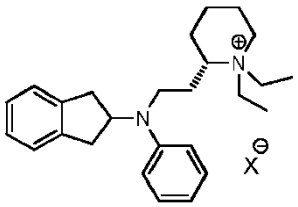


som eventuelt har strukturen:



3. Forbindelse ifølge krav 1, som er:

a)



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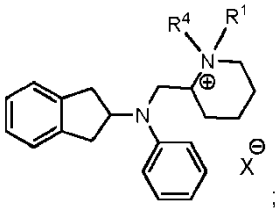
b)



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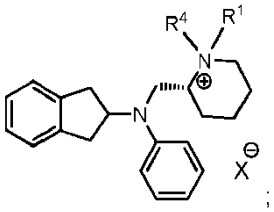
c)



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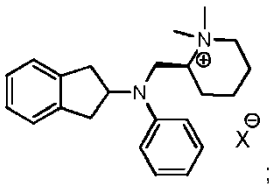
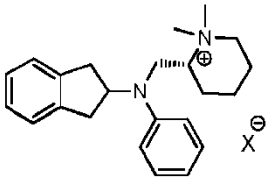
d)



;

eller

e) en racemisk blanding av



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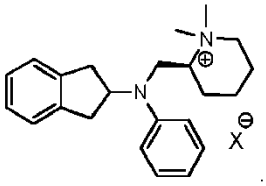

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4. Forbindelse ifølge krav 1, som er valgt fra gruppen bestående av
(S)-1,1-dimetyl-2-[2-((indan-2-yl)(fenyl)amino)etyl]piperidiniumjodid,
(R)-1,1-dimetyl-2-[2-((indan-2-yl)(fenyl)amino)etyl]piperidiniumjodid,
(S)-1,1-dietyl-2-[2-((indan-2-yl)(fenyl)amino)etyl]piperidiniumjodid,
(R)-1,1-dietyl-2-[2-((indan-2-yl)(fenyl)amino)etyl]piperidiniumjodid,
(S)-1,1-dipropyl-2-[2-((indan-2-yl)(fenyl)amino)etyl]piperidiniumjodid,
(R)-1,1-dipropyl-2-[2-((indan-2-yl)(fenyl)amino)etyl]piperidiniumjodid,
(S)-1,1-dimetyl-2-[((indan-2-yl)(fenyl)amino)metyl]piperidiniumjodid,
(R)-1,1-dimetyl-2-[((indan-2-yl)(fenyl)amino)metyl]piperidiniumjodid,
(S)-1,1-dimetyl-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumjodid,
(R)-1,1-dimetyl-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumjodid,
1,1-dimetyl-2-[((indan-2-yl)(fenyl)amino)metyl]piperidiniumjodid,
1,1-dimetyl-2-[2-((indan-2-yl)(fenyl)amino)etyl]pyrrolidiniumjodid,

1,1-dietyl-2-[((indan-2-yl)(fenyl)amino)metyl]piperidiniumjodid,
1,1-dimetyl-2-[2-((2-fluorfenyl)(indan-2-yl)amino)etyl]piperidiniumjodid,
1,1-dimetyl-2-[2-((3-fluorfenyl)(indan-2-yl)amino)etyl]piperidiniumjodid,
1,1-dimetyl-2-[2-((4-fluorfenyl)(indan-2-yl)amino)etyl]piperidiniumjodid,
1,1-dietyl-2-[2-((2-fluorfenyl)(indan-2-yl)amino)etyl]piperidiniumjodid,
1,1-dietyl-2-[2-((3-fluorfenyl)(indan-2-yl)amino)etyl]piperidiniumjodid,
1,1-dietyl-2-[2-((4-fluorfenyl)(indan-2-yl)amino)etyl]piperidiniumjodid,
1,1-dimetyl-2-[2-((indan-2-yl)(3-metylfenyl)amino)etyl]piperidiniumjodid,
1,1-dietyl-2-[2-((indan-2-yl)(3-metylfenyl)amino)etyl]piperidiniumjodid,
1,1-dimetyl-2-[2-((indan-2-yl)(4-metylfenyl)amino)etyl]piperidiniumjodid,
1,1-dietyl-2-[2-((indan-2-yl)(4-metylfenyl)amino)etyl]piperidiniumjodid,
1,1-dimetyl-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumjodid,
1,1-dietyl-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumjodid,
6-[2-((indan-2-yl)(fenyl)amino)etyl]-5-azoniaspiro[4,5]decan bromid,
1,1-dimetyl-2-[3-((indan-2-yl)(fenyl)amino)propyl]piperidiniumjodid,
1,1-dietyl-2-[3-((indan-2-yl)(fenyl)amino)propyl]piperidiniumjodid,
1,1-dimetyl-2-[((indan-2-yl)(4-metylfenyl)amino)metyl]piperidiniumjodid,
1,1-dimetyl-2-[((4-fluorfenyl)(indan-2-yl) amino)metyl]piperidiniumjodid,
1,1-dimetyl-2-[((indan-2-yl)(3-metylfenyl)amino)metyl]piperidiniumjodid,
1,1-dietyl-2-[((indan-2-yl)(4-metylfenyl)amino)metyl]piperidiniumjodid,
1,1-dimetyl-2-[((3-fluorfenyl)(indan-2-yl) amino)metyl]piperidiniumjodid,
1,1-dimetyl-2-[((indan-2-yl)(fenyl)amino)metyl]pyrrolidiniumjodid,
1,1-dietyl-2-[2-((indan-2-yl)(fenyl)amino)etyl]pyrrolidiniumjodid,
1,1-dimetyl-2-[2-((indan-2-yl)(pyridin-2-yl)amino)etyl]piperidiniumjodid,
1,1-dimetyl-2-[2-((indan-2-yl)(pyrimidin-2-yl)amino)etyl]piperidiniumjodid,
1,1-dimetyl-2-[2-((indan-2-yl)(tiazol-2-yl)amino)etyl]piperidiniumjodid,
1,1-dimetyl-4-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumbromid,
7-[2-((indan-2-yl)(2-metylfeny)amino)etyl]-3-oksa-6-azaspiro[5,5]undecan-6-iumklorid,
1,1-dimetyl-2-[2-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)(indan-2-yl)amino)etyl]piperidiniumjodid,
(R)-1,1-dimetyl-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumbromid,
(S)-1,1-dimetyl-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumklorid,
1,1-dimetyl-4-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumjodid,
1,1-bis(2-hydroksyetyl)-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumbromid,
1,1-dimetyl-2-[2-((indan-2-yl)(6-metylpyridin-2-yl)amino)etyl]piperidiniumjodid,

1,1-dimetyl-2-[2-((indan-2-yl)(6-metylpyridin-2-yl)amino)etyl]piperidiniumbromid, (S)-1,1-dietyl-2-[2-((indan-2-yl)(fenyl)amino)etyl]piperidiniumbromid, 1,1-dimetyl-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumklorid, (R)-1,1-dimetyl-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumklorid og 1,1-dimetyl-2-[2-((indan-2-yl)(2-metylfenyl)amino)etyl]piperidiniumbromid.

5. Regime omfattende:
(i) en TRPV1-reseptoraktivator; og
(ii) nevnte forbindelse med formel (**I**) eller formel (**II**) ifølge hvilket som helst av kravene 1 til 4 eller en kombinasjon derav.

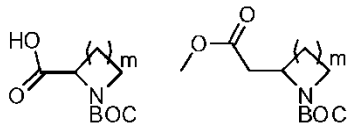
6. Regimet ifølge krav 5,
a) hvor nevnte TRPV1-reseptoraktivator er valgt fra gruppen bestående av capsaicin, dihydrocapsaicin, nordihydrocapsaicin, lidokain, artikain, prokain, tetrakain, mepivikain, bupivikain, eugenol, kamfer, clotrimazol, N-arachidonoylvanillamin, anandamid, 2-aminoetoksydifenyl borat, AM404, resiniferatoxin, forbol-12-fenylacetat-13-acetat-20-homovanillat, olvanil, N-oleoyldopamin, N-arachidonyldopamin, 6'-jodresiniferatoxin, et C_{18} N-acyletanolamin, et lipoksygenasederivat, nonivamid, et fettsyreacylamid av et tetrahydroisokinolininhibitor cysteinknutepeptid, pipelin, N-[2-(3,4-dimetylbenzyl)-3-(pivaloyloksy)propyl]-2-[4-(2-aminoetoksy)-3-metoksyfenyl]acetamid, N-[2-(3,4-dimetylbenzyl)-3-(pivaloyloksy)propyl]-N'-(4-hydroksy-3-metoksybenzyl)tiourea, hydroksy-α-sanshool, 2-aminoetoksydifenylborat, 10-shogaol, oleylgingerol, oleylshogaol, N-(4-tert-butylbenzyl)-N'-(4-hydroksy-3-metoksybenzyl)tiourea, aprindin, benzokain, butakain, kokain, dibukain, enkainid, mexiletin, oxetakain, prilokain, proparakain, prokainamid, n-acetylprokainamid, klorprokain, dyclonin, etidokain, levobupivakain, ropivakain, syklometykain, dimetokain, propoksykain, trimekain og sympokain;
b) hvor nevnte TRPV1-reseptoraktivator er lidokain;
c) som er formulert for oral, intramuskulær, rektal, kutan, subkutan, topisk, transdermal, sublingual, nasal, vaginal, epidural, intratekal, intravesical eller okulær administrering til et individ;
d) omfattende ca. 2% av nevnte TRPV1-reseptoraktivator; eller
e) omfattende ca. 0,5% av nevnte forbindelse med formel (**I**), formel (**II**) eller en kombinasjon derav.

7. Sammensetning omfattende nevnte forbindelse med formel (**I**) eller formel (**II**) ifølge hvilket som helst av kravene 1 til 4 eller en kombinasjon derav og en bærer.

8. Metode for å fremstille nevnte forbindelse (**I**) ifølge krav 1,

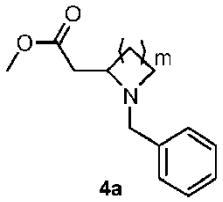
a) hvor A er fenyl, idet nevnte metode omfatter:

(i) å omdanne



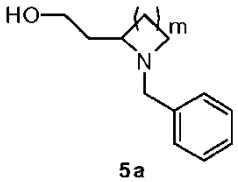
1a til **2a** ;

(ii) å omdanne nevnte forbindelse **2a** til



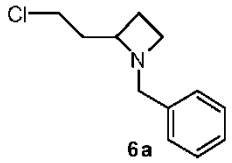
4a

(iii) å redusere nevnte forbindelse **4a** til



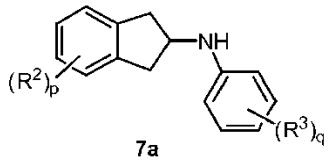
5a

(iv) å klorere nevnte forbindelse **5a** for å danne



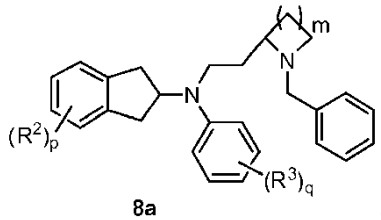
6a

(v) å koble nevnte forbindelse **6a** med



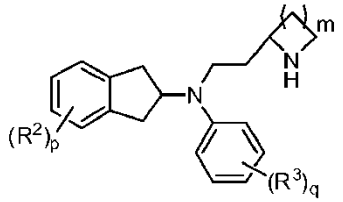
7a

for å danne



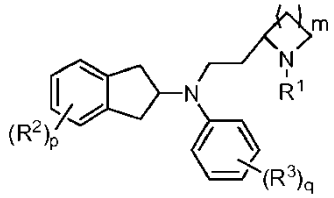
8a ;

(vi) å fjerne benzylgruppen i forbindelse **8a** via hydrogenering for å danne



9a ;

(vii) å R^1-substituere forbindelse **9a** for å danne

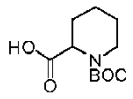


11a ;

og

(viii) å R^4-substitutere forbindelse **11a;**

eventuelt hvor nevnte forbindelse **1a** er



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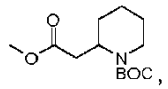
forbindelse **2a** er



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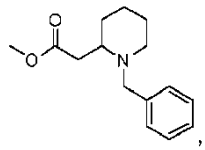
forbindelse **4a** er



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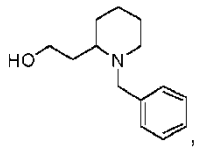
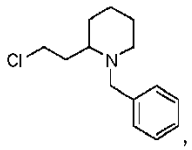
forbindelse **5a** er

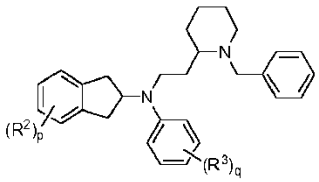


,

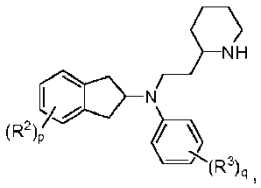
forbindelse **6a** er



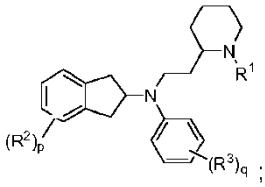
forbindelse **8a** er



forbindelse **9a** er



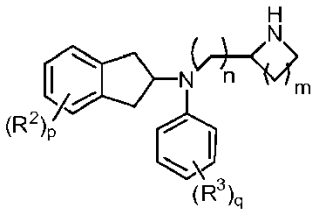
og forbindelse **11a** er



eller

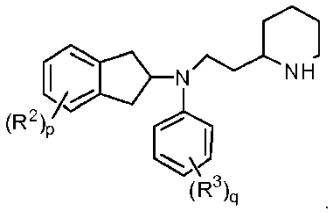
b) hvor A er fenyl, idet nevnte metode omfatter:

(vii) å R^1- og R^4-substituere forbindelse **9c:**



9c

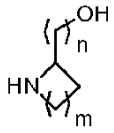
eventuelt hvor nevnte forbindelse **9c** er



9. Metode for å fremstille nevnte forbindelse (**I**) ifølge krav 1,

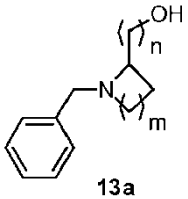
a) hvor A er fenyl, idet nevnte metode omfatter:

(i) å beskytte nitrogenatomet i



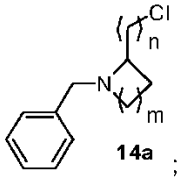
12a

for å danne



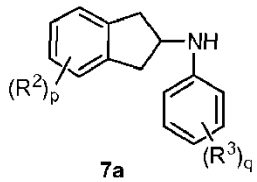
13a ;

(ii) å klorere nevnte forbindelse **13a** for å danne



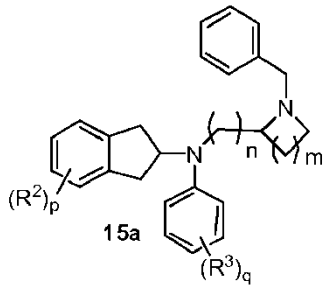
14a ;

(iii) å koble nevnte forbindelse **14a** med



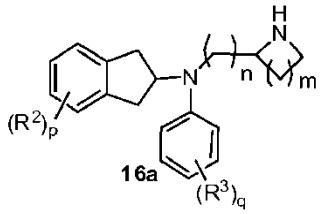
7a

for å danne



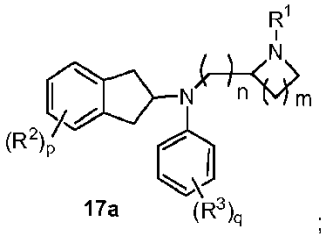
15a ;

(iv) å avbeskytte forbindelse **15a** for å danne



16a

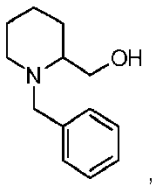
(v) å R^1-substituere nevnte forbindelse **16a** for å danne



17a ;

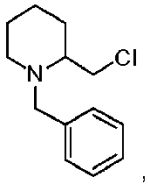
og

(vi) å R^4-substituere forbindelse **17a;** eventuelt hvor nevnte forbindelse **12a** er piperidin-2-metanol, forbindelse **13a** er



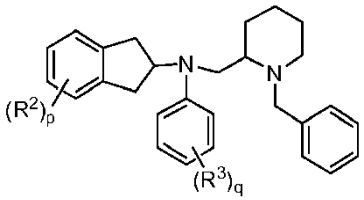
,

forbindelse **14a** er



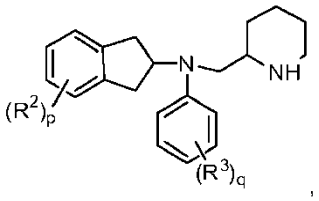
,

forbindelse **15a** er



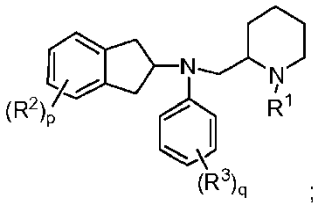
,

forbindelse **16a** er



,

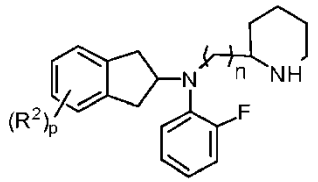
og forbindelse **17a** er



;

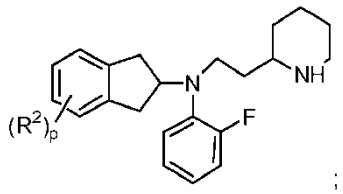
b) hvor A er fenyl, R^3 er 2-F, m er 2 og q er 1, idet nevnte metode omfatter:

(vi) å R^1- og R^4-substituere forbindelse **9d:**



9d ;

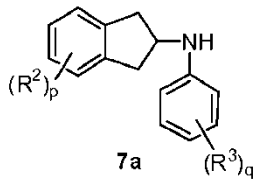
eventuelt hvor forbindelse **9d** har følgende struktur:



;

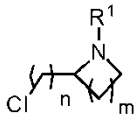
c) hvor A er fenyl, idet nevnte metode omfatter:

(i) å koble



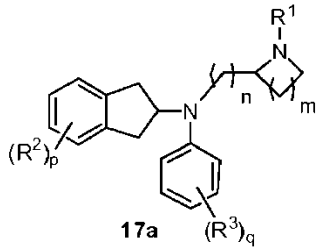
7a

og



18a

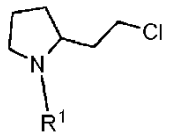
for å danne



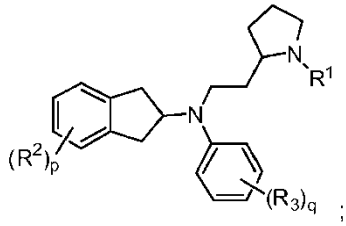
17a ;

og

(ii) å R^4-substituere forbindelse **17a;** eventuelt hvor nevnte forbindelse **18a** er



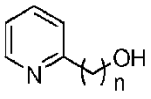
og forbindelse **17a** er



;

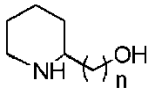
d) hvor m er 3, idet nevnte metode omfatter:

(i) å redusere



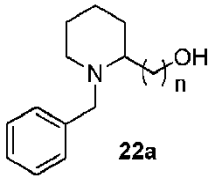
20a

ved anvendelse av en syre for å danne



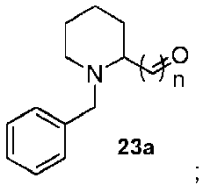
21a .HCl ;

(ii) å beskytte forbindelse **21a** med en benzylgruppe for å gi



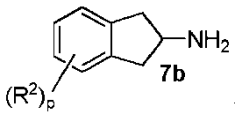
22a ;

(iii) å oksidere forbindelse **22a** for å gi



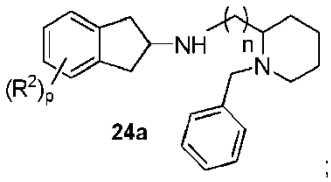
23a ;

(iv) å koble forbindelse **23a** med



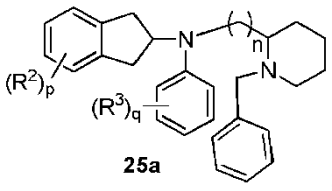
7b

for å gi



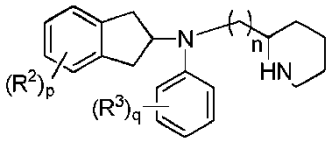
24a ;

(v) å substituere nitrogenatomet i nevnte forbindelse **24a** med en R^3-substituert fenylgruppe for å danne



25a ;

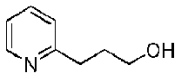
(vi) å avbeskytte nevnte forbindelse **25a** for å gi



26a ;

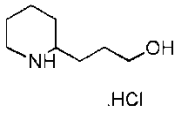
og

(vii) å R^1- og R^4-substituere nevnte forbindelse **26a;** eventuelt hvor nevnte forbindelse **20a** er



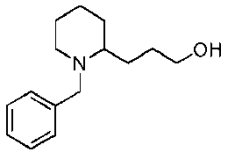
,

forbindelse **21a** er



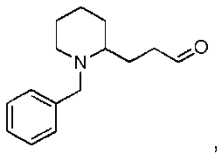
,

forbindelse **22a** er



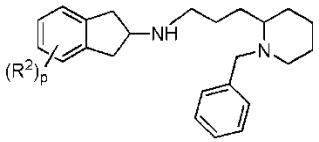
,

forbindelse **23a** er



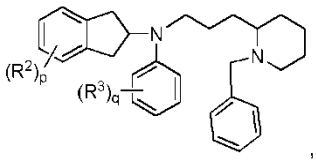
,

forbindelse **24a** er



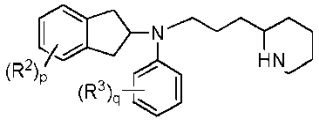
,

forbindelse **25a** er



,

og forbindelse **26a** er

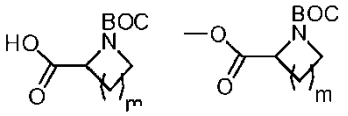


;

eller

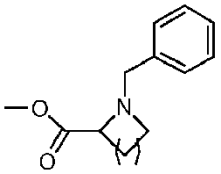
e) hvor A er fenyl, idet nevnte metode omfatter:

(i) å omdanne



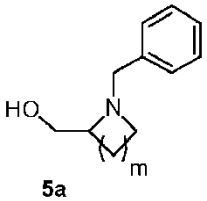
1a til **2a** ;

(ii) å omdanne nevnte forbindelse **2a** til



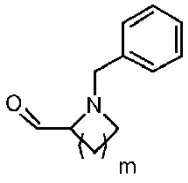
4a ;

(iii) å redusere nevnte forbindelse **4a** til



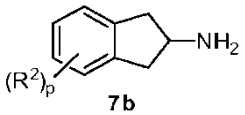
5a ;

(iv) å oksidere forbindelse **5a** for å gi



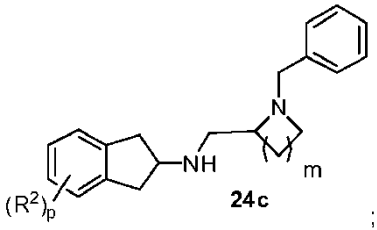
23a ;

(v) å koble nevnte forbindelse **23a** med



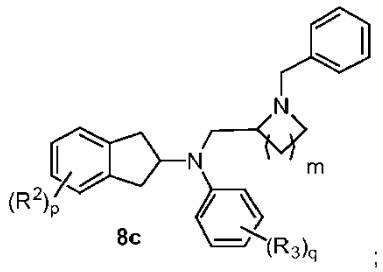
7b

for å gi



24c ;

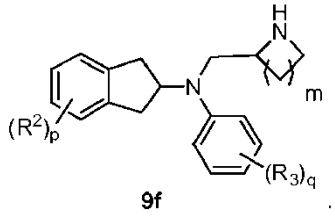
(vi) å substituere nitrogenatomet i forbindelse **24c** med en R^3-substituert fenylgruppe for å gi



;

og

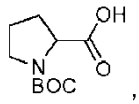
(vii) å avbeskytte forbindelse **8c** for å danne



;

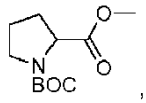
og

(viii) å R^1- og R^4-substituere nitrogenringen; eventuelt hvor nevnte forbindelse **1a** er



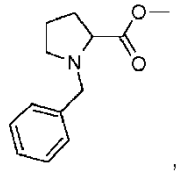
,

forbindelse **2c** er



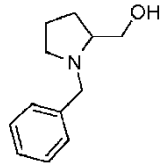
,

forbindelse **4c** er



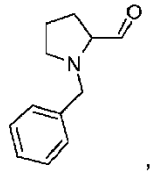
,

forbindelse **5c** er



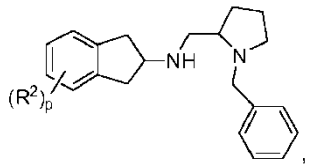
,

forbindelse **31** er

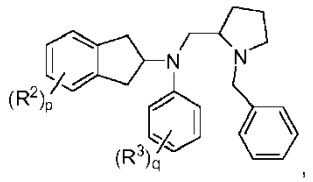


,

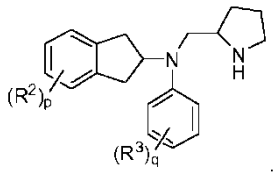
forbindelse **24c** er



forbindelse **8c** er



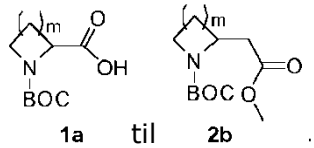
og forbindelse **9f** er



10. Metode for å fremstille nevnte forbindelse (**I**) ifølge krav 1,

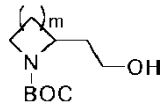
a) idet nevnte metode omfatter:

(i) å omdanne



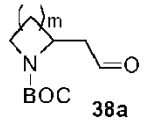
1a til **2b** ;

(ii) å redusere forbindelse **2b** til



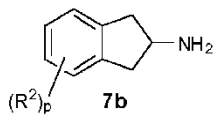
37a ;

(iii) å oksidere forbindelse **37a** til



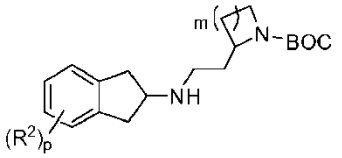
38a ;

(iv) å koble forbindelse **38a** med



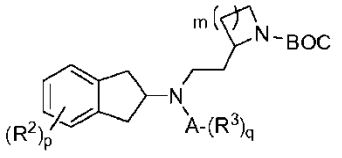
7b

til



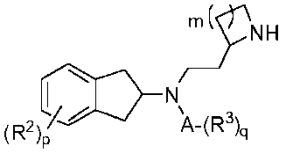
39a ;

(v) å koble forbindelse **39a** med en A-$(R^3)_q$ gruppe for å danne



40a ;

(vi) å avbeskytte forbindelse **40a** for å danne

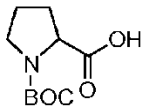


41a ;

og

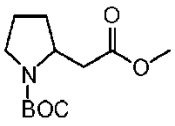
(vii) å R^1- og R^4-substituere forbindelse **41a**;

eventuelt hvor: forbindelse **1a** er



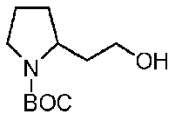
,

forbindelse **2b** er



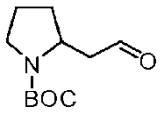
,

forbindelse **37a** er



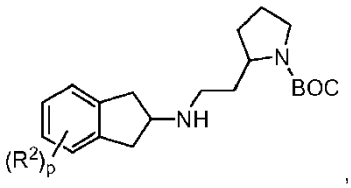
,

forbindelse **38a** er



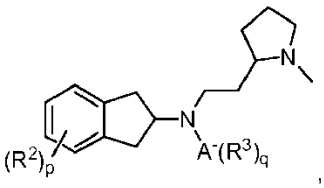
,

forbindelse **39a** er



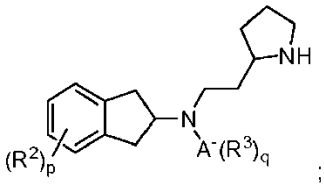
,

forbindelse **40a** er



,

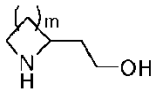
og forbindelse **41a** er



;

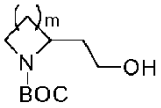
b) nevnte metode omfattende:

(i) å BOC-beskytte



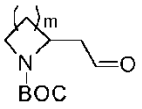
12b

for å danne



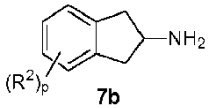
37a ;

(ii) å oksidere forbindelse **37a** for å danne



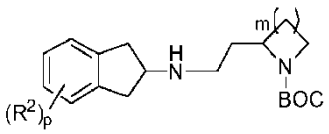
38a ;

(iii) å koble forbindelse **38a** med



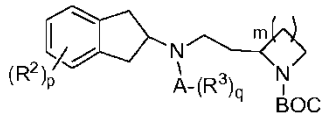
7b

for å danne



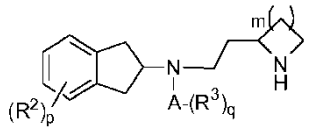
39a ;

(iv) å substituere forbindelse **39a** med A-$(R^3)_q$ for å danne



40a ;

(v) å avbeskytte forbindelse **40a** for å danne

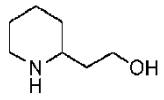


41a ;

og

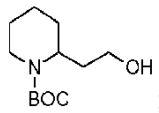
(vi) å R^1- og R^4-substituere forbindelse **41a**;

eventuelt hvor: forbindelse **12b** er



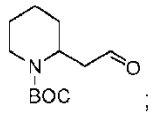
;

forbindelse **37a** er



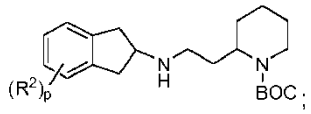
;

forbindelse **38a** er



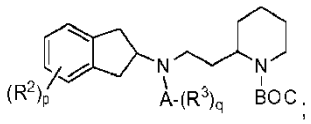
;

forbindelse **39a** er



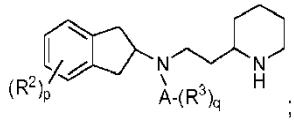
;

forbindelse **40a** er



;

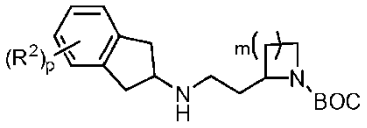
og forbindelse **41a** er



;

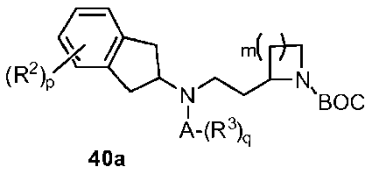
c) hvor n er 2, idet nevnte metode omfatter:

(i) å substituere



39a

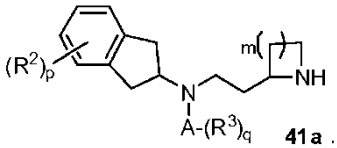
med A-$(R^3)_q$ for å danne



40a

;

(ii) å avbeskytte forbindelse **40a** for å danne

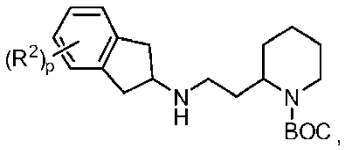


41a ;

og

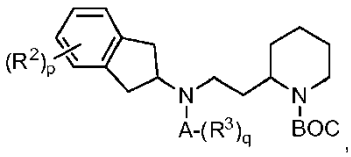
(iii) å R^1- og R^4-substituere forbindelse **41a**;

eventuelt hvor: forbindelse **39a** er



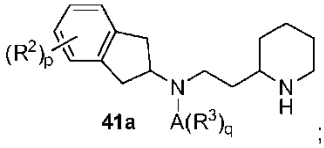
,

forbindelse **40a** er



,

og forbindelse **41a** er

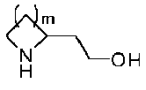


41a

;

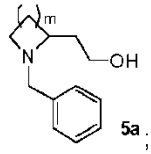
d) nevnte metode omfattende:

(i) å beskytte



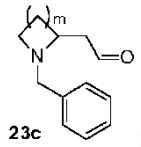
12b

for å danne



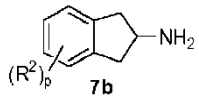
5a ;

(ii) å oksidere forbindelse **5a** for å danne



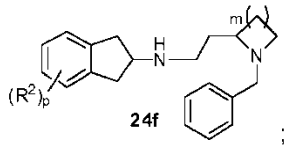
23c ;

(iii) å koble forbindelse **23a** med



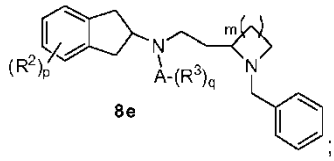
7b

for å danne



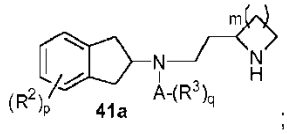
24f ;

(iv) å substituere forbindelse **24f** med A-$(R^3)_q$ for å danne



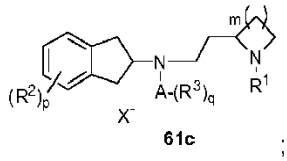
8e ;

(v) å avbeskytte forbindelse **8e** for å danne



41a ;

(vi) å R^1-substituere forbindelse **41a** for å danne

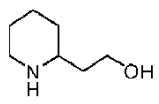


61c ;

og

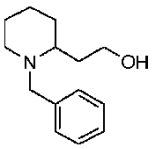
(vii) å R^4-substituere forbindelse **61c**;

eventuelt hvor: forbindelse **12b** er

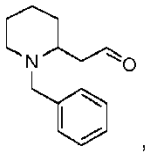


,

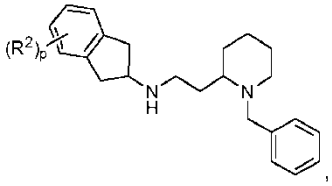
forbindelse **5a** er


,

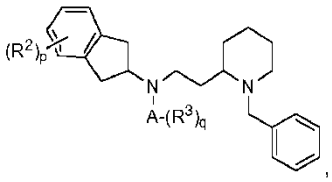
forbindelse **23c** er


,

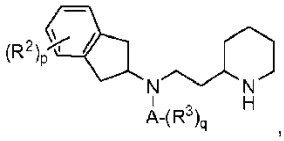
forbindelse **24f** er


,

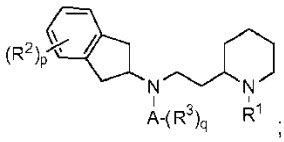
forbindelse **8e** er


,

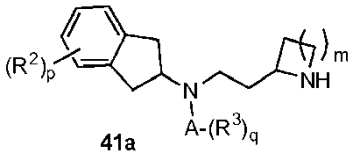
forbindelse **41a** er


,

og forbindelse **61c** er


;

e) nevnte metode omfattende å reagere


41a

med X"-$(CH_2)_r$-Y-$(CH_2)_s$-X", hvor:

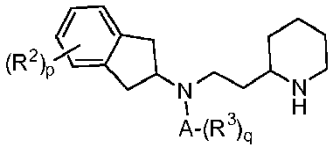
r er 1 til 4;

s er 1 til 4;

Y er CH_2, O eller S; og

X" er en utgående gruppe;

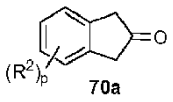
eventuelt hvor forbindelse **41a** er



og X"-$(CH_2)_r$-Y-$(CH_2)_s$-X" er $ClCH_2CH_2OCH_2CH_2Cl$;

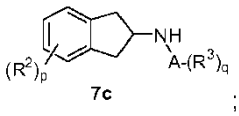
f) nevnte metode omfattende:

(i) å reagere



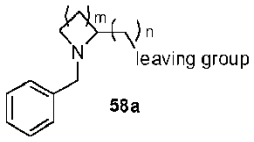
70a

med H_2N-A-$(R^3)_q$ for å danne



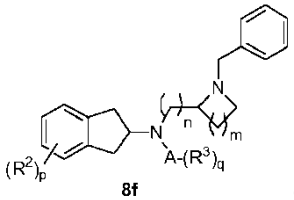
7c ;

(ii) å koble forbindelse **7c** med



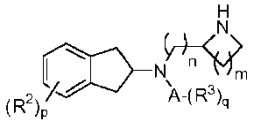
58a

for å danne



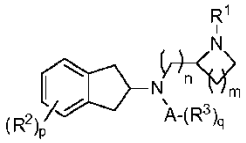
8f ;

(iii) å avbeskytte forbindelse **8f** for å danne



9h ;

(iv) R^1-substituere forbindelse **9h** for å danne

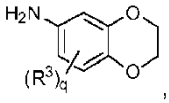


61a ;

og

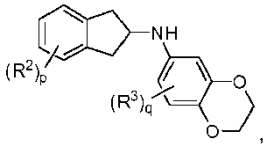
(v) R^4-substituere forbindelse **61a**;

eventuelt hvor H_2N-A-$(R^3)_q$ er



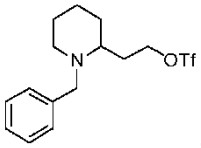
,

forbindelse **7c** er



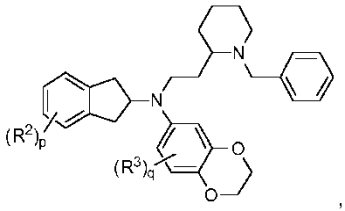
,

forbindelse **58a** er



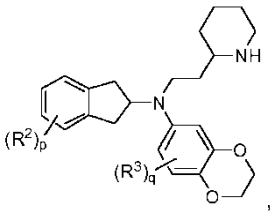
,

forbindelse **8f** er



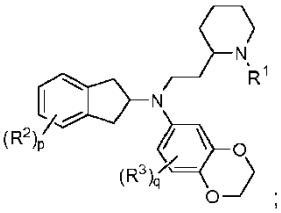
,

forbindelse **9h** er



,

og forbindelse **61a** er

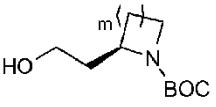


;

eller

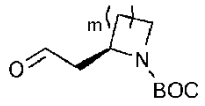
g) hvor R^4 er CH_3, idet nevnte metode omfatter:

(i) å oksidere



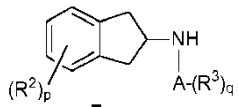
37a

for å danne



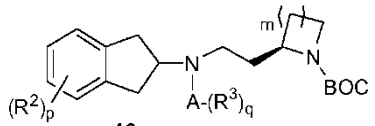
38a ;

(ii) å koble forbindelse **38a** med



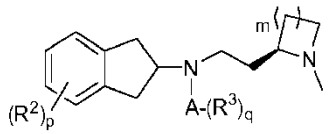
7c

for å danne



40a ;

(iii) å redusere forbindelse **40a** for å danne



41c ;

og

(iv) R^1-substituere forbindelse **41c**;

eventuelt hvor forbindelse **40a** fremstilles ved å tilsette forbindelse **38a** til en løsning som omfatter forbindelse **7c** og et mildt reduksjonsmiddel, eventuelt hvor nevnte milde reduksjonsmiddel er $Na(OAc)_3BH$;

eventuelt hvor % ee av forbindelse **40a** er minst ca. 97 % ee.

11. Forbindelse med formel (**I**) eller formel (**II**) ifølge hvilket som helst av kravene 1 til 4 eller en kombinasjon derav for bruk i behandling av smerte eller kløe i et individ.

12. Regimet ifølge hvilket som helst av kravene 5 til 6 for anvendelse i behandling av smerte eller kløe i et individ.

13. Forbindelse for anvendelse ifølge krav 11 eller regime for anvendelse ifølge krav 12, hvor

a) nevnte TRPV1-reseptor er tilstede på nociceptorer, pruriceptorer eller en kombinasjon derav;

(p) nevnte smerte er nevropatisk smerte;

(q) nevnte smerte er inflammatorisk smerte;

(r) nevnte smerte er nociceptiv smerte;

(e) nevnte smerte er prosedyrisk smerte; eller

(t) nevnte smerte er forårsaket av spiserørkreft, irritabel tarm-syndrom eller idiopatisk nevropati.

14. Regime for bruk ifølge krav 12, hvor

a) forholdet mellom TRPV1-reseptoraktivatoren og forbindelsen med formel (**I**), formel (**II**) eller en kombinasjon derav, er ca. 4:1; eller

b) forholdet mellom TRPV1-reseptoraktivatoren og forbindelsen med formel (**I**), formel (**II**), eller en kombinasjon derav, er ca. 10:1.

15. Forbindelse ifølge hvilket som helst av kravene 1 til 4 for anvendelse som et medikament.