(12) **Translation of European patent specification**

(11) **NO/EP 2875022 B1**

NORWAY

(19) NO

(51) Int Cl.

C07D 409/06 (2006.01)
A61K 31/4015 (2006.01)
A61K 31/4025 (2006.01)
A61P 17/14 (2006.01)
A61P 19/10 (2006.01)
A61P 25/02 (2006.01)
A61P 27/02 (2006.01)
A61P 27/06 (2006.01)
C07D 207/20 (2006.01)
C07D 207/26 (2006.01)
C07D 403/12 (2006.01)

Norwegian Industrial Property Office

(21)	Translation Published	2017.02.27
(80)	Date of The European Patent Office Publication of the Granted Patent	2016.10.12
(86)	European Application Nr.	13745744.6
(86)	European Filing Date	2013.07.19
(87)	The European Application's Publication Date	2015.05.27
(30)	Priority	2012.07.19, US, 201261673514 P 2013.03.15, US, 201361793929 P
(84)	Designated Contracting States:	AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
(73)	Proprietor	Cayman Chemical Company, Incorporated, 1180 E. Ellsworth Road, Ann Arbor, Michigan 48108, US-USA
(72)	Inventor	BARRETT, Stephen, Douglas, 2828 Fenton Road, Hartland, MI 48353, US-USA CISKE, Fred, Lawrence, 7375 Ridge Lane Circle, Dexter, MI 48130, US-USA COLOMBO, Joseph, Michael, 4290 Lake Forest Drive East, Ann Arbor, MI 48108, US-USA ENDRES, Gregory, William, 386 Huntington Drive, Saline, MI 48176, US-USA GERMAIN, Bradlee, David, 1881 Addington, Ann Arbor, MI 48108, US-USA KORNILOV, Andriy, 4816 Lakeridge Drive Apt. 1a, Ypsilanti, MI 48197, US-USA KRAMER, James, Bernard, 7726 Westbourne Court, Sylvania, OH 43560, US-USA UZIEBLO, Adam, 23147 Potomac Circle, Farmington Hills, MI 48335, US-USA MAXEY, Kirk, M., 2280 Peters Road, Ann Arbor, MI 48103, US-USA
(74)	Agent or Attorney	Tandbergs Patentkontor AS, Postboks 1570 Vika, 0118 OSLO, Norge

(54) Title **DIFLUOROLACTAM COMPOUNDS AS EP4 RECEPTOR-SELECTIVE AGONISTS FOR USE IN THE TREATMENT OF EP4-MEDIATED DISEASE AND CONDITIONS**

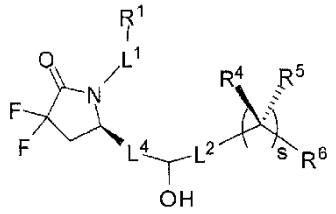
(56) References Cited:

WO-A1-2012/063207
WO-A2-02/42268
WO-A2-03/047513
LI, BIN-HUI ET AL: "Rational and practical synthesis of .alpha.,.alpha.-difluoro-.gamma.-lactams", JOURNAL OF FLUORINE CHEMISTRY , 133, 163-166 CODEN: JFLCAR; ISSN:

0022-1139, 25 October 2011 (2011-10-25), XP002713299,
FUSTERO, SANTOS ET AL: "A new tandem cross metathesis-intramolecular aza-Michael reaction for the synthesis of .alpha.,.alpha.-difluorinated lactams", SYNTHESIS , 44(12), 1863-1873 CODEN: SYNTBF; ISSN: 0039-7881, 27 April 2012 (2012-04-27), XP002713300,

Patentkrav

1. En forbindelse med formel (Ia)



(Ia)

eller et farmasøytisk akseptabelt salt derav, hvor:

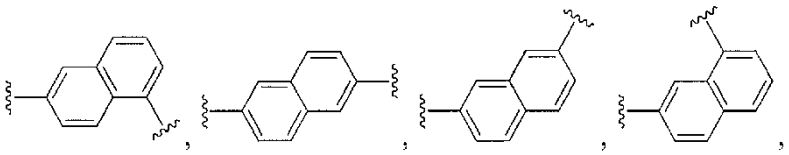
L^1 er

a) C_3-C_7alkylen, C_3-C_7alkenylen eller C_3-C_7alkynylen, hvor C_3-C_7alkylen, C_3-C_7alkenylen eller C_3-C_7alkynylen er hver eventuelt substituert med 1, 2, 3 eller 4 fluorsubstituenter;

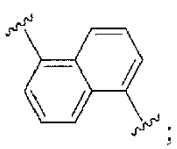
b) $-(CH_2)_t-G-(CH_2)_p-$; hvor t er 0, 1 eller 2, p er 0, 1, 2 eller 3, og t+p = 0, 1,2, 3 eller 4; eller

c) $-(CH_2)_n-G^1-(CH_2)_p-$, $-(CH_2)_n-G^2-(CH_2)_p-$, $-(CH_2)_n-C\equiv C-G^2-$ eller $-(CH_2)_n-C(R^{13})=C(R^{13})-G^2-$, hvor n er 1, 2, 3, 4 eller 5, p er 0, 1, 2 eller 3, og n+p = 1, 2, 3, 4, 5 eller 6;

Gis

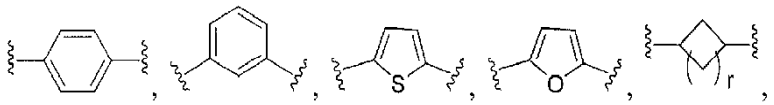


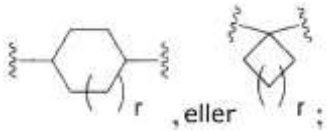
eller



G^1 er O, C(O), S, S(O), $S(O)_2$ eller NR^8; hvor R^8 er H, C_1-C_4 alkyl eller C_1-C_4alkylkarbonyl;

G^2 er





hvor G^2 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy og C_1-C_3haloalkoksy;

R^1 er $COOR^{10}$, $CONR^{10}R^{11}$, CH_2OR^{10}, SO_3R^{10}, $SO_2NR^{10}R^{11}$, $PO(OR^{10})_2$ eller tetrazol-5-yl;

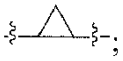
R^{10} er H, C_1-C_4 alkyl eller aryl;

R^{11} er H, C_1-C_4 alkyl, COR^{12} eller^{10} eller SO_2R^{12};

R^{12} er C_1-C_4 alkyl;

R^{13}, ved hvert tilfelle, er uavhengig H eller C_1-C_4alkyl;

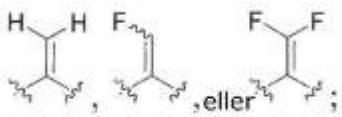
L^4 er $-C(R^2)_2-C(R^3)_2-$, $-C(R^2)=C(R^3)-$, $-C\equiv C-$ eller



hvor R^2 og R^3 er hver H, CH_3, fluor eller klor;

L^2 er $-CH_2-$ eller en binding;

R^4 og R^5 er hver uavhengig H, F, CF_3 eller C_1-C_4 alkyl; eller R^4 og R^5 sammen med karbonet til hvilket de er bundet, danner et C_3-C_5 cykloalkyl,



R^6 er aryl, heteroaryl, C_3-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_{10}haloalkyl, C_3-C_{10}haloalkenyl, C_3-C_{10}haloalkynyl eller L^3-R^7; hvor arylet og heteroarylet er eventuelt substituert med 1, 2, 3 eller 4 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, C_1-C_3haloalkoksy; og $-C_1$-C_3alkylen-C_1-C_3alkoksy; og hvor C_3-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-

C_{10}haloalkyl, C_3-C_{10}haloalkenyl og C_3-C_{10}haloalkynyl er eventuelt substituert med en substituent valgt fra gruppen bestående av $COOR^{10'}$, $CONR^{10'}R^{11'}$, $CH_2OR^{10'}$, $SO_3R^{10'}$, $SO_2NR^{10'}R^{11'}$, $PO(OR^{10'})_2$ og tetrazol-5-yl;

$R^{10'}$ er H, C_1-C_4 alkyl eller aryl;

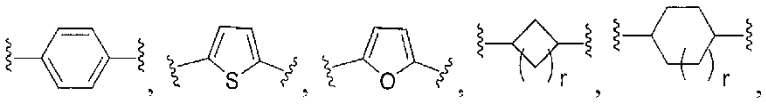
$R^{11'}$ er H, C_1-C_4 alkyl, $COR^{12'}$ eller$^{10'}$ eller $SO_2R^{12'}$;

$R^{12'}$ er C_1-C_4 alkyl;

L^3 er C_1-C_6alkylen, C_2-C_6alkenylen, C_2-C_6alkynylen, $-(CH_2)_m$-G^3-$(CH_2)_q$-, $-(CH_2)_m$-G^4-$(CH_2)_q$- eller $-G^5$-C≡C-; hvor C_1-C_6alkylen, C_2-C_6alkenylen og C_2-C_6alkynylen er eventuelt substituert med 1, 2, 3 eller 4 fluorsubstituenter; og hvor m og q er hver uavhengig 0, 1, 2 eller 3 og m + q = 0, 1, 2, 3 eller 4;

G^3 er O, C(O), S, S(O), $S(O)_2$ eller NR^9; hvor R^9 er H, C_1-C_4 alkyl eller C_1-C_4alkyl-karbonyl;

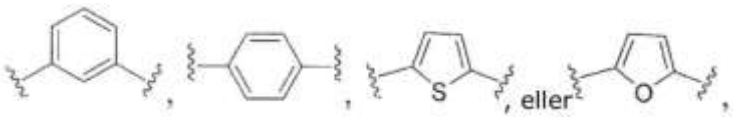
G^4 er



eller

hvor G^4 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy og C_1-C_3halo-alkoksy;

G^5 er



hvor Q^5 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy og C_1-C_3haloalkoksy;

R^7 er C_3-C_8cykloalkyl, aryl, heteroaryl eller heterocyklyl; hvor R^7 er eventuelt substituert med 1, 2, 3 eller 4 substituenter valgt fra gruppen bestående av C_1-

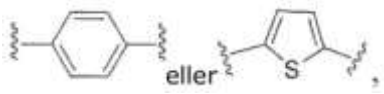
C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, C_1-C_3haloalkoksy, og -C_1-C_3alkylen-C_1-C_3alkoksy;
r er 0 eller 1; og
s er 0 eller 1.

2. Forbindelsen ifløge krav 1, eller et farmasøytisk akseptabelt salt derav, hvor:

L^1 er

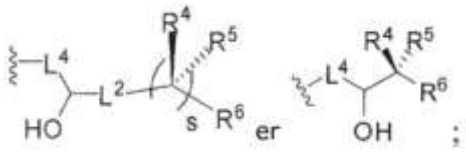
a) C_3-C_7alkylen, hvor C_3-C_7alkylen er eventuelt substituert med 1, 2, 3 eller 4 fluor-substituenter; eller
c) -$(CH_2)_n$-G^2-$(CH_2)_p$-, -$(CH_2)_n$-C≡C-G^2- eller -$(CH_2)_n$-C(H)=C(H)-G^2-, hvor n er 1, 2, 3, 4 eller 5, p er 0, 1, 2 eller 3, og n+p = 1, 2, 3, 4, 5 eller 6;

G^2 er



hvor G^2 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, og C_1-C_3halo-alkoksy;
R^1 er $COOR^{10}$; og
R^{10} er H eller C_1-C_4 alkyl.

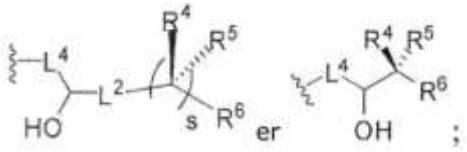
3. Forbindelse ifølge krav 1, eller et farmasøytisk akseptabelt salt derav, hvor:



L^4 er -$C(R^2)$=$C(R^3)$-;
R^2 og R^3 er hver hydrogen;
og R^5 er uavhengig H eller C_1-C_4 alkyl;
R^6 er C_3-C_{10}alkyl, C_3-C_{10}alkynyl eller L^3-R^7;
L^3 er C_1-C_6alkylen eller C_2-C_6alkynylen; hvor C_1-C_6alkylen og C_2-C_6alkynylen er eventuelt substituert med 1, 2, 3 eller 4 fluorsubstituenter; og

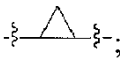
R^7 er aryl, hvor R^7 er eventuelt substituert med 1, 2, 3 eller 4 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, C_1-C_3haloalkoksy og -C_1-C_3alkylen-C_1-C_3alkoksy.

4. Forbindelse ifølge krav 2, eller et farmasøytisk akseptabelt salt derav, hvor:



;

L^4 er -$C(R^2)_2$-$C(R^3)_2$-, -$C(R^2)$=$C(R^3)$-, -C≡C- eller

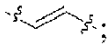


;

hvor R^2 og R^3 er hver H, CH_3, fluor eller klor;
R^4 og R^5 er hver uavhengig H, F, CF_3 eller C_1-C_4 allcyl; eller R^4 og R^5 sammen med karbonet til hvilket de er bundet, danner et C_3-C_5 cykloalkyl;
R^6 er aryl, C_3-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_{10}haloalkyl, C_3-C_{10}haloalkenyl, C_3-C_{10}haloalkynyl eller L^3-R^7;
L^3 er C_1-C_6alkylen, C_2-C_6alkenylen eller C_2-C_6alkynylen hvor C_1-C_6alkylen, C_2-C_6alkenylen og C_2-C_6alkynylen er eventuelt substituert med 1, 2, 3 eller 4 fluor-substituenter; og
R^7 er aryl, hvor R^7 er eventuelt substituert med 1, 2, 3 eller 4 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, C_1-C_3haloalkoksy og -C_1-C_3alkylen-C_1-C_3alkoksy.

5. Forbindelse ifølge krav 4, eller et farmasøytisk akseptabelt salt derav, hvor:

L^4 er



;

R^4 og R^5 er uavhengig H eller C_1-C_4 alkyl;
R^6 er C_3-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_{10}haloalkyl, C_3-C_{10}haloalkenyl, C_3-C_{10}haloalkynyl eller L^3-R^7;

L^3 er C_1-C_6alkylen, C_2-C_6alkenylen eller C_2-C_6alkynylen; hvor C_1-C_6alkylen, C_2-C_6alkenylen og C_2-C_6alkynylen er eventuelt substituert med 1, 2, 3 eller 4 fluor-substituenter; og

R^7 er aryl, hvor R^7 er eventuelt substituert med 1, 2, 3 eller 4 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, C_1-C_3haloalkoksy og -C_1-C_3alkylen-C_1-C_3alkoksy.

6. Forbindelse ifølge krav 5, eller et farmasøytisk akseptabelt salt derav, hvor:

R^4 og R^5 er uavhengig H eller CH_3;

R^6 er C_3-C_{10}alkyl, C_3-C_{10}alkynyl eller L^3-R^7;

L^3 er C_1-C_6alkylen eller C_2-C_6alkynylen; hvor C_1-C_6alkylen og C_2-C_6alkynylen er eventuelt substituert med 1, 2, 3 eller 4 fluorsubstituenter; og

R^7 er aryl, hvor R^7 er eventuelt substituert med 1, 2, 3 eller 4 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, C_1-C_3haloalkoksy og -C_1-C_3alkylen-C_1-C_3alkoksy.

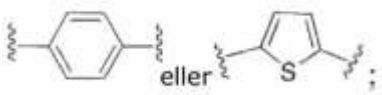
7. Forbindelse ifølge krav 6, eller et farmasøytisk akseptabelt salt derav, hvor:

L^1 er

a) C_3-C_7alkylen; eller

c) -$(CH_2)_n$-G^2-, hvor n er 2 eller 3;

G^2 er



;

R^6 er propyl, butyl, pentyl, propynyl, butynyl, pentynyl, heksynyl eller L^3-R^7;

L^3 er propylen, butylen, pentylen, propynylen eller butynylen; og

R^7 er fenyl.

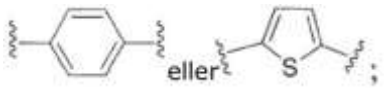
8. Forbindelse ifølge krav 7 eller et farmasøytisk akseptabelt salt derav, hvor:

L^1 er

a) n-heksylen; eller

c) $-(CH_2)_n-G^2-$, hvor n er 2 eller 3;

G^2 er



;

R^1 er $COOR^{10}$;
R^{10} er H eller CH_3;
R^6 er n-butyl, but-2-yn-1-yl, pent-2-yn-1-yl, heks-2-yn-1-yl eller L^3-R^7;
L^3 er n-propylen, n-butylen, n-pentylen eller $-CH_2-C\equiv C-$; og
R^7 er fenyl.

9. Forbindelse ifølge krav 5, eller et farmasøytisk akseptabelt salt derav, hvor:

R^6 er C_3-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{20}alkynyl, C_3-C_{10}haloalkyl, C_3-C_{10}haloalkenyl eller C_3-C_{10}haloalkynyl.

10. Forbindelse ifølge krav 5, eller et farmasøytisk akseptabelt salt derav, hvor:

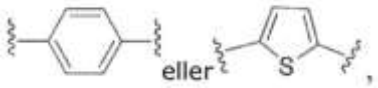
R^6 er L^3-R^7;
L^3 er C_1-C_6alkylen, C_2-C_6alkenylen eller C_2-C_6alkynylen; hvor C_1-C_6alkylen, C_2-C_6alkenylen og C_2-C_6alkynylen er eventuelt substituert med 1, 2, 3 eller 4 fluor-substituenter; og
R^7 er aryl, hvor R^7 er eventuelt substituert med 1, 2, 3 eller 4 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, C_1-C_3haloalkoksy og -C_1-C_3alkylen-C_1-C_3alkoksy.

11. Forbindelse ifølge krav 5, eller et farmasøytisk akseptabelt salt derav, hvor:

L^1 er C_3-C_7alkylen, hvor C_3-C_7alkylen er eventuelt substituert med 1, 2, 3 eller 4 fluor-substituenter.

12. Forbindelse ifølge krav 5, eller et farmasøytisk akseptabelt salt derav, hvor:

L^1 er $-(CH_2)_n-G^2-(CH_2)_p-$, $-(CH_2)_n-C\equiv C-G^2-$ eller $-(CH_2)_n-C(H)=C(H)-G^2-$, hvor n er 1, 2, 3, 4 eller 5, p er 0, 1, 2 eller 3, og n+p = 1, 2, 3, 4, 5 eller 6; og
G^2 er



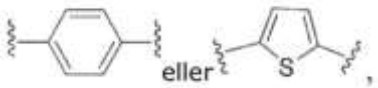
hvor G^2 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy og C_1-C_3haloalkoksy.

13. Forbindelse ifølge krav 9, eller et farmasøytisk akseptabelt salt derav, hvor:

L^1 er C_3-C_7alkylen, hvor C_3-C_7alkylen er eventuelt substituert med 1, 2, 3 eller 4 fluorsubstituenter.

14. Forbindelse ifølge krav 9, eller et farmasøytisk akseptabelt salt derav, hvor:

L^1 er $-(CH_2)_n-G^2-(CH_2)_p-$, $-(CH_2)_n-C\equiv C-G^2-$ eller $-(CH_2)_n-C(H)=C(H)-G^2-$, hvor n er 1, 2, 3, 4 eller 5, p er 0, 1, 2 eller 3, og n+p = 1, 2, 3, 4, 5 eller 6; og
G^2 er



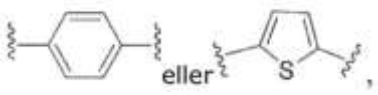
hvor G^2 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy og C_1-C_3haloalkoksy.

15. Forbindelse ifølge krav 10, eller et farmasøytisk akseptabelt salt derav, hvor:

L^1 er C_3-C_7alkylen, hvor alkylenet er eventuelt substituert med 1, 2, 3 eller 4 fluorsubstituenter.

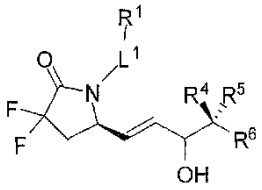
16. Forbindelse ifølge krav 10, eller et farmasøytisk akseptabelt salt derav, hvor:

L^1 er $-(CH_2)_n-G^2-(CH_2)_p-$, $-(CH_2)_n-C\equiv C-G^2-$ eller $-(CH_2)_n-C(H)=C(H)-G^2-$, hvor n er 1, 2, 3, 4 eller 5, p er 0, 1, 2 eller 3, og n+p = 1, 2, 3, 4, 5 eller 6; og
G^2 er



hvor G^2 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy og C_1-C_3haloalkoksy.

17. Forbindelse med formel (II) ifølge krav 1, eller et farmasøytisk akseptabelt salt derav, hvor:



(II)

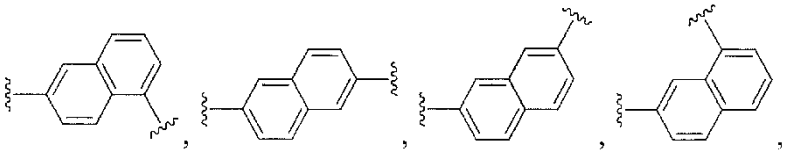
L^1 er

a) C_3-C_7alkylen, C_3-C_7alkenylen eller C_3-C_7alkynylen, hvor C_3-C_7alkylen, C_3-C_7alkenylen eller C_3-C_7alkynylen er hver eventuelt substituert med 1, 2, 3 eller 4 fluorsubstituenter;

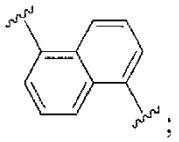
b) $-(CH_2)_t$-G-$(CH_2)_p$-; hvor t er 0, 1 eller 2, p er 0, 1, 2 eller 3, og t+p = 0, 1, 2, 3 eller 4; eller

c) $-(CH_2)_n$-G^1-$(CH_2)_p$-, $-(CH_2)_n$-G^2-$(CH_2)_p$-, $-(CH_2)_n$-C≡C-G^2- eller $-(CH_2)_n$-C(R^{13})=C(R^{13})-G^2-, hvor n er 1, 2, 3, 4 eller 5, p er 0, 1, 2 eller 3, og n+p = 1, 2, 3, 4, 5 eller 6;

G er

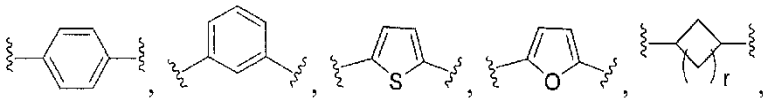


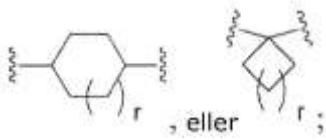
eller



G^1 er O, C(O), S, S(O), $S(O)_2$ eller NR^8; hvor R^8 er H, C_1-C_4 alkyl eller C_1-C_4alkyl-karbonyl;

G^2 er





hvor G^2 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, og C_1-C_3haloalkoksy;

R^1 er $COOR^{10}$, $CONR^{10}R^{11}$, CH_2OR^{10}, SO_3R^{10}, $SO_2NR^{10}R^{11}$, $PO(OR^{10})_2$ eller tetrazol-5-yl;

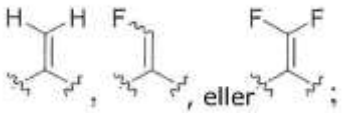
R^{10} er H, C_1-C_4 alkyl eller aryl;

R^{11} er H, C_1-C_4 alkyl, COR^{12}, OR^{10} eller SO_2R^{12};

R^{12} er C_1-C_4 alkyl;

R^{13}, ved hver forekomst, er uavhengig H eller C_1-C_4alkyl;

R^4 og R^5 er hver uavhengig H, F, CF_3 eller C_1-C_4 alkyl; eller R^4 og R^5 sammen med karbonet til hvilket de er bundet, danner et C_3-C_5 cykloalkyl,



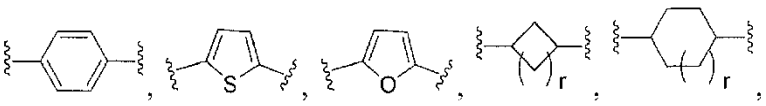
R^6 er aryl, heteroaryl, C_3-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_{10}haloalkyl, C_3-C_{10}haloalkenyl, C_3-C_{10}haloalkynyl eller L^3-R^7; hvor arylet og heteroarylet er eventuelt substituert med 1, 2, 3 eller 4 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, C_1-C_3haloalkoksy; og -C_1-C_3alkylen-C_1-C_3alkoksy; og hvor C_3-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_{10}haloalkyl, C_3-C_{10}haloalkenyl og C_3-C_{10}haloalkynyl er eventuelt substituert med en

substituent valgt fra gruppen bestående av $COOR^{10}$, $CONR^{10}R^{11}$, CH_2OR^{10}, SO_3R^{10}, $SO_2NR^{10}R^{11}$, $PO(OR^{10})_2$ og tetrazol-5-yl;

L^3 er C_1-C_6alkylen, C_2-C_6alkenylen, C_2-C_6alkynylen, $-(CH_2)_m-G^3-(CH_2)_q-$, $-(CH_2)_m-G^4-(CH_2)_q-$ eller $-G^5-C\equiv C-$; hvor C_1-C_6alkylen, C_2-C_6alkenylen og C_2-C_6alkynylen er eventuelt substituert med 1, 2, 3 eller 4 fluorsubstituenter; og hvor m og q er hver uavhengig 0, 1, 2 eller 3 og m + q = 0, 1, 2, 3 eller 4;

G^3 er O, C(O), S, S(O), $S(O)_2$ eller NR^9; hvor R^9 er H, C_1-C_4 alkyl eller C_1-C_4alkyl-karbonyl;

G^4 er

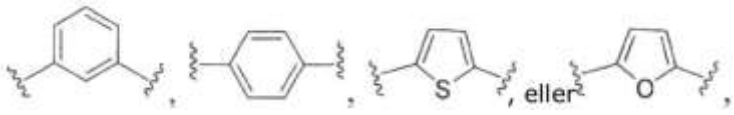


eller

;

hvor G^4 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, og C_1-C_3halo-alkoksy;

G^5 er



hvor G^5 er eventuelt substituert med 1, 2 eller 3 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy og C_1-C_3halo-alkoksy;

R^7 er C_3-C_8cykloalkyl, aryl, heteroaryl eller heterocyklyl; hvor R^7 er eventuelt substituert med 1, 2, 3 eller 4 substituenter valgt fra gruppen bestående av C_1-C_4alkyl, C_1-C_3haloalkyl, cyano, halogen, C_1-C_3alkoksy, C_1-C_3haloalkoksy og $-C_1$-C_3alkylen-C_1-C_3alkoksy; og

r er 0 eller 1.

18. Forbindelse ifølge krav 1, eller et farmasøytisk akseptabelt salt derav, valgt fra gruppen bestående av:

metyl-7-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((5*R*)-3,3-difluor-5-((3*S*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((5*R*)-3,3-difluor-5-((3*R*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((3*R*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((3*R*,4*R*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*R*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*R*,4*R*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
metyl-7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((3*R*,4*S*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*R*,4*S*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
metyl-7-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksy-4-metyldek-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyldek-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyldek-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

metyl-7-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

metyl-7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

metyl-7-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksy-4-metylokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

metyl-7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

metyl-7-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

metyl-7-((5*R*)-3,3-difluor-5-((3*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

metyl-7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

metyl-7-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

metyl-7-((5*R*)-3,3-difluor-5-((3*R*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

7-((R)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((5*R*)-3,3-difluor-5-((3*R*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

metyl-7-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksynon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

metyl-7-((5*R*)-3,3-difluor-5-((3*S*,*E*)-3-hydroksynon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

7-((5*R*)-3,3-difluor-5-((3*S*,*E*)-3-hydroksynon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

metyl-7-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksy-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;

metyl-7-((5*R*)-3,3-difluor-5-((3*S*,*E*)-3-hydroksy-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
7-((5*R*)-3,3-difluor-5-((3*S*,*E*)-3-hydroksy-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
metyl-7-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((*R*,*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
7-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((*R,E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
metyl-7-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksy-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksy-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*R*)-3,3-difluor-5-((*R,E*)-3-hydroksy-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptanoat;
7-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksy-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((*R*,*E*)-3-hydroksy-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
4-(2-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;
metyl-4-(2-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzoat;
metyl-4-(2-((*R*)-3,3-difluor-5-((3*S*,4*S,E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzoat;
metyl-4-(2-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzoat;
metyl-4-(2-((5*R*)-3,3-difluor-5-((3*R*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzoat;
4-(2-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;
4-(2-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((5R)-3,3-difluor-5-((3R,E)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyldek-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksyokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksynon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksydek-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((*S,E*)-3-hydroksy-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

metyl-4-(2-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzoat;

metyl-4-(2-((R)-3,3-difluor-5-((S,E)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzoat;

metyl-4-(2-((R)-3,3-difluor-5-((R,E)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzoat;

4-(2-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((*R*,*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

4-(2-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksy-7-fenylhept-l-en-1-yl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

metyl-5-(3-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((5*R*)-3,3-difluor-5-((3*R*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((5*R*)-3,3-difluor-5-((3*R*,*E*)-3-hydroksy-4-metylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyldek-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metylokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksyokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksynon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksydek-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksy-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
metyl-5-(3-((5*R*)-3,3-difluor-5-((*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
metyl-5-(3-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
metyl-5-(3-((*R*)-3,3-difluor-5-((*R*,*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
5-(3-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((*R*,*E*)-3-hydroksyokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksy-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

metyl-5-(3-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

5-(3-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-6-fenylheks-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-6-fenylheks-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-6-fenylheks-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-8-fenylokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-8-fenylokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-8-fenylokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

metyl-5-(3-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-8-fenyloktyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-8-fenyloktyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

5-(3-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-8-fenyloktyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

5-(3-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-8-fenyloktyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S,E*)-3-hydroksy-4-metyl-9-fenylnon-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-9-fenylnon-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-9-fenylnon-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-9-fenylnon-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

metyl-5-(3-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-9-fenylnonyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
metyl-5-(3-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-9-fenylnonyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
5-(3-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-9-fenylnonyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-9-fenylnonyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
metyl-5-(3-((*R*)-3,3-difluor-5-((3*S,*4*S,E*)-*3*-hydroksy-4-metyl-5-fenylpent-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-5-fenylpent-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-5-fenylpent-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-5-fenylpent-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
metyl-5-(3-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksy-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
metyl-5-(3-((*R*)-3,3-difluor-5-((*S*,*E*)-3-hydroksy-7-fenylhept-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
metyl-5-(3-((*S*)-3,3-difluor-5-((*S*)-3-hydroksy-7-fenylheptyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;
5-(3-((*S*)-3,3-difluor-5-((*S*)-3-hydroksy-7-fenylheptyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;
metyl-7-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)heptanoat;
7-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)heptansyre;
metyl-7-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-8-fenyloktyl)-2-oksopyrrolidin-1-yl)heptanoat;
metyl-7-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-8-fenyloktyl)-2-oksopyrrolidin-1-yl)heptanoat;
7-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-8-fenyloktyl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-8-fenyloktyl)-2-oksopyrrolidin-1-yl)heptansyre;

metyl-7-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-9-fenylnonyl)-2-oksopyrrolidin-1-yl)heptanoat;

metyl-7-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-9-fenylnonyl)-2-oksopyrrolidin-1-yl)heptanoat;

7-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-9-fenylnonyl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*S*)-3,3-difluor-5-((3*R*,4*R*)-3-hydroksy-4-metyl-9-fenylnonyl)-2-oksopyrrolidin-1-yl)heptansyre;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-8-fenylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-8-fenylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-8-fenylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

5-(3-((*R*)-3,3-ditluoro-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-8-fenylokt-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-9-fenylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

metyl-5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-9-fenylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylat;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-9-fenylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*R*,*E*)-3-hydroksy-4-metyl-9-fenylnon-1-en-6-yn-1-yl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

(*R*)-1-(6-(1*H* tetrazol-5-yl)heksyl)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)pyrrolidin-2-on;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)-*N*-etylheptanamid;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)-*N*-(metylsulfonyl)heptanamid;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*Z*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

3-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)propyl)benzosyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)hept-5-ynsyre;

(*Z*)-7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)hept-5-ensyre;

5-(3-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)prop-1-yn-1-yl)tiofen-2-karboksylsyre;

4-((2-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)etyl)tio)butansyre;

7-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)heptansyre;

5-(3-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)propyl)tiofen-2-karboksylsyre;

4-(2-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)etyl)benzosyre;

3-(3-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)propyl)benzosyre;

4-((2-((*S*)-3,3-difluor-5-((3*R*,4*S*)-3-hydroksy-4-metyl-7-fenylheptyl)-2-oksopyrrolidin-1-yl)etyl)tio)butansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*)-3-hydroksy-4-metyl-7-fenylhept-1-yn-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*R*,4*S*,*E*)-3-hydroksy-4-fenylpent-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-5-fenylpent-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-6-fenylheks-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-8-fenylokt-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-9-fenylnon-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-5-((3*S*,4*S*,*E*)-7-cykloheksyl-3-hydroksy-4-metylhept-1-en-1-yl)-3,3-difluor-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-(naftalen-2-yl)hept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-(naftalen-1-yl)hept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-7-(3-fluorfenyl)-3-hydroksy-4-metylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-7-(*m*-tolyl)hept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;

7-((*R*)-5-((3*S*,4*S*,*E*)-7-(3-klorfenyl)-3-hydroksy-4-metylhept-1-en-1-yl)-3,3-difluor-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-7-(3-metoksyfenyl)-4-metylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-7-(3-(metoksymetyl)fenyl)-4-metylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-6-(fenyltio)heks-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*S*,4*S*,*E*)-3-hydroksy-4-metyl-6-fenoksyheks-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-5-((3*S*,4*S*,*E*)-4-etyl-3-hydroksy-7-fenylhept-1-en-1-yl)-3,3-difluor-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*R*,4*R*,*E*)-3-hydroksy-4-isopropyl-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((3*R*,4*S*,*E*)-3-hydroksy-7-fenyl-4-(trifluormetyl)hept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-5-((*R*,*E*)-4,4-difluor-3-hydroksy-7-fenylhept-1-en-1-yl)-3,3-difluor-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-3,3-difluor-5-((*R*,*E*)-3-hydroksy-4-metylen-7-fenylhept-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre;
7-((*R*)-5-((*R*,*E*)-4-(difluormetylen)-3-hydroksy-7-fenylhept-1-en-1-yl)-3,3-difluor-2-oksopyrrolidin-1-yl)heptansyre; og
7-((*R*)-3,3-difluor-5-((*R*,*E*)-3-hydroksy-3-(1-(3-fenylpropyl)cyklobutyl)prop-1-en-1-yl)-2-oksopyrrolidin-1-yl)heptansyre.

19. Forbindelse ifølge hvilket som helst av kravene 1 til 18, eller et farmasøytisk akseptabelt salt derav, for anvendelse ved behandling av forhøyet intraokulært trykk, glaukom, okulær hypertensjon, tørre øyne, makulaødem, makuladegenerasjon, alopesi, ductus arteriosus eller nevropatisk smerte.

20. Forbindelse ifølge hvilket som helst av kravene 1 til 18, eller et farmasøytisk akseptabelt salt derav, for anvendelse ved behandling av forhøyet intraokulært trykk, glaukom eller okulær hypertensjon.