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C07F 9/38 (2006.01)

Norwegian Industrial Property Office

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(54) Title **BIS(FLUOROALKYL)-1,4-BENZODIAZEPINONE COMPOUNDS AS NOTCH INHIBITORS**

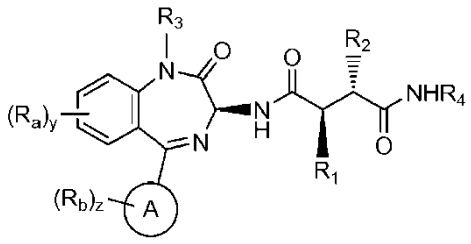
(56) References Cited:

WO-A1-00/07995
WO-A1-2014/047393
WO-A2-00/38618
WO-A2-01/60826
US-A1- 2003 134 841
US-A1- 2012 245 151
US-B1- 6 737 038

Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters concerning the validity of the patent, language of the application/patent granted at the EPO will be used as the basis for the decision. The patent documents published by the EPO are available through Espacenet (http://worldwide.espacenet.com) or via the search engine on our website here: https://search.patentstyret.no/

Patentkrav

1. En forbindelse med formel (I):



(I)

og/eller minst ett salt derav, hvor:

R_1 er $-CH_2CH_2CF_3$;

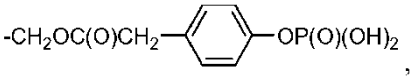
R_2 er $-CH_2CH_2CF_3$ eller $-CH_2CH_2CH_2CF_3$;

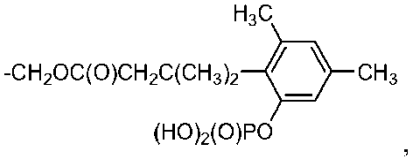
R_3 er H, $-CH_3$ eller R_x;

R_4 er H eller R_y;

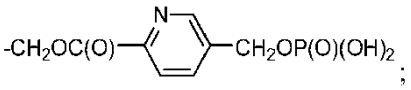
R_x er: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$,

$-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,

 ,

 ,

eller

 ;

R_y er: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$ eller $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

ring A er fenyl eller pyridinyl;

hver R_a er uavhengig av hverandre Cl, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyklopropyl, $-OCH_3$ og/eller -O(cyklopropyl);

hver R_b er uavhengig av hverandre F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyklopropyl og/eller $-OCH_3$;

y er null, 1 eller 2; og

z er null, 1 eller 2;

forutsatt at dersom ring A er fenyl, og z er null, da er y lik 1 eller 2, og minst én R_a er C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyklopropyl eller -O(cyklopropyl);

forutsatt at hvis R_3 er R_x så er R_4 lik H; og

forutsatt at hvis R_4 er R_y så er R_3 lik H eller $-CH_3$.

2. Forbindelse ifølge krav 1, og/eller minst ett salt derav, hvor:

ring A er fenyl;

R_3 er H; og

z er 1 eller 2.

3. Forbindelse ifølge krav 1, og/eller minst ett salt derav, hvor:

R_2 er $-CH_2CH_2CF_3$;

ring A er fenyl; og

z er 1 eller 2.

4. Forbindelse ifølge krav 1, og/eller minst ett salt derav, hvor:

R_2 er $-CH_2CH_2CF_3$;

ring A er fenyl;

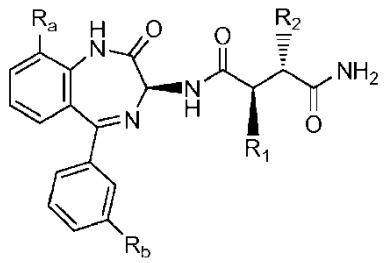
R_a er C_{1-3} alkyl eller $-CH_2OH$;

hver R_b er uavhengig av hverandre F og/eller Cl;

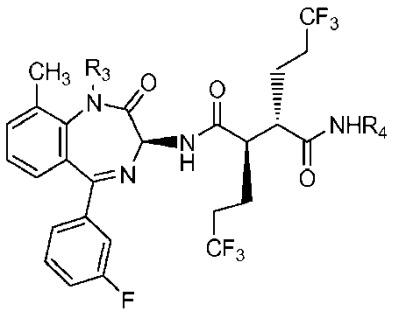
y er 1; og

z er 1 eller 2.

5. Forbindelse ifølge krav 4, som har strukturen:



6. Forbindelse ifølge krav 1, og/eller minst ett salt derav, som har strukturen:



hvor:

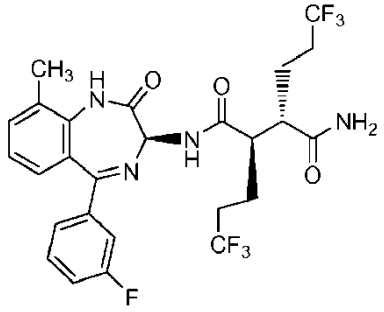
R_3 er H eller R_x;

R_4 er H eller R_y;

forutsatt at hvis R_3 er R_x så er R_4 lik H; og

forutsatt at hvis R_4 er R_y så er R_3 lik H.

7. Forbindelse ifølge krav 1, som har strukturen:



8. Forbindelse ifølge krav 1 valgt fra:(2R,3S)-N-((3S)-5-(3-fluorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (1); (2R,3S)-N-((3S)-5-(3-klorfenyl)-9-etyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (2); (2R,3S)-N-((3S)-5-(3-klorfenyl)-9-isopropyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (3); (2R,3S)-N-(9-klor-5-(3,4-dimetylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorbutyl)-2-(3,3,3-trifluorpropyl)suksinamid (4); (2R,3S)-N-(9-klor-5-(3,5-dimetylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorbutyl)-2-(3,3,3-trifluorpropyl)suksinamid (5); (2R,3S)-N-((3S)-9-etyl-5-(3-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (6); (2R,3S)-N-((3S)-5-(3-klorfenyl)-9-metyl-2-okso-2,3-

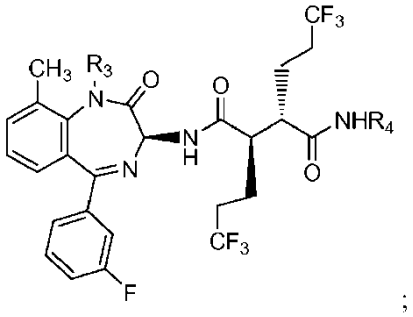
dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (7); (2R,3S)-N-((3S)-5-(3-klorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorbutyl)-2-(3,3,3-trifluorpropyl)suksinamid (8); (2R,3S)-N-((3S)-5-(3-metylfenyl)-2-okso-9-(trifluormetyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (9); (2R,3S)-N-((3S)-9-klor-5-(3,5-dimetylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (10); (2R,3S)-N-((3S)-5-(3-metylfenyl)-2-okso-9-(trifluormetyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorbutyl)-2-(3,3,3-trifluorpropyl)suksinamid (11); (2R,3S)-N-((3S)-9-isopropyl-5-(3-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (12); (2R,3S)-N-((3S)-9-isopropyl-2-okso-5-fenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (13); (2R,3S)-N-((3S)-9-(cyklopropyloksy)-5-(3-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorbutyl)-2-(3,3,3-trifluorpropyl)suksinamid (14); (2R,3S)-N-((3S)-9-(cyklopropyloksy)-5-(3-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (15); (2R,3S)-N-((3S)-9-(cyklopropyloksy)-2-okso-5-fenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorbutyl)-2-(3,3,3-trifluorpropyl)suksinamid (16); (2R,3S)-N-((3S)-9-klor-5-(3-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorbutyl)-2-(3,3,3-trifluorpropyl)suksinamid (17); (2R,3S)-N-((3S)-9-metyl-2-okso-5-(3-(trifluormetyl)fenyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorbutyl)-2-(3,3,3-trifluorpropyl)suksinamid (18); (2R,3S)-N-((3S)-9-(cyklopropyloksy)-2-okso-5-fenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (19); (2R,3S)-N-((3S)-9-metyl-2-okso-5-(3-(trifluormetyl)fenyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (20); (2R,3S)-N-((3S)-9-klor-5-(2-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (21); (2R,3S)-N-((3S)-5-(4-fluorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (22); (2R,3S)-N-((3S)-9-metyl-2-okso-5-fenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (23); (2R,3S)-N-((3S)-9-cyklopropyl-2-okso-5-fenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (24); (2R,3S)-N-((3S)-9-klor-5-(3-cyklopropylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (25); (2R,3S)-N-((3S)-5-(3-klorfenyl)-9-metoksy-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (26); (2R,3S)-N-((3S)-5-(4-klorfenyl)-9-metoksy-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (27); (2R,3S)-N-((3S)-9-klor-5-(3-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (28); (2R,3S)-N-((3S)-5-(3-metylfenyl)-9-metoksy-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-

trifluorpropyl)suksinamid (29); (2R,3S)-N-((3S)-5-(4-(hydroksymetyl)fenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (30); (2R,3S)-N-((3S)-5-(2-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (31); (2R,3S)-N-((3S)-5-(3-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (32); (2R,3S)-N-((3S)-9-metoksy-2-okso-5-(5-(trifluormetyl)-2-pyridinyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (33); (2R,3S)-N-((3S)-5-(5-klor-2-pyridinyl)-9-metoksy-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (34); (2R,3S)-N-((3S)-5-(4-metoksyfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (35); (2R,3S)-N-((3S)-5-(4-metylfenyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (36); (2R,3S)-N-((3S)-5-(3-fluorfenyl)-9-(hydroksymetyl)-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluorpropyl)suksinamid (37); ((3S)-3-(((2R,3S)-3-karbamoyl-6,6,6-trifluor-2-(3,3,3-trifluorpropyl)heksanoyl)amino)-5-(3-fluorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)metyl-L-valinat (38); ((3S)-3-(((2R,3S)-3-karbamoyl-6,6,6-trifluor-2-(3,3,3-trifluorpropyl)heksanoyl)amino)-5-(3-fluorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)metyl-L-alaninat (39); S-(((2S,3R)-6,6,6-trifluor-3-(((3S)-5-(3-fluorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)karbamoyl)-2-(3,3,3-trifluorpropyl)heksanoyl)amino)-L-cystein (40); *tert*-butyl-S-(((2S,3R)-6,6,6-trifluor-3-(((3S)-5-(3-fluorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)karbamoyl)-2-(3,3,3-trifluorpropyl)heksanoyl)amino)-L-cysteinat (41); metyl-S-(((2S,3R)-6,6,6-trifluor-3-(((3S)-5-(3-fluorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)karbamoyl)-2-(3,3,3-trifluorpropyl)heksanoyl)amino)-L-cysteinat (42); ((3S)-3-(((2R,3S)-3-karbamoyl-6,6,6-trifluor-2-(3,3,3-trifluorpropyl)heksanoyl)-amino)-5-(3-fluorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)metyl(4-(fosfonooksy)fenyl)acetat (43); ((3S)-3-(((2R,3S)-3-karbamoyl-6,6,6-trifluor-2-(3,3,3-trifluorpropyl)heksanoyl)amino)-5-(3-fluorfenyl)-9-metyl-2-okso-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)metyl-L-valyl-L-valinat (44); og salter derav.

9. En farmasøytisk sammensetning omfattende en forbindelse ifølge hvilket som helst av kravene 1 til 8, og/eller minst ett salt derav; og en farmasøytisk akseptabel bærer.

10. En sammensetning omfattende:

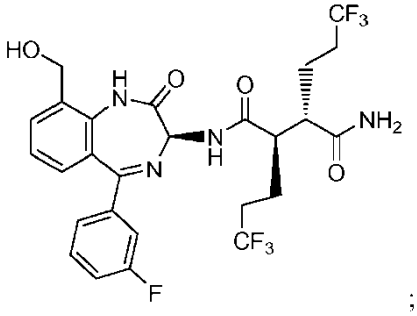
(i) minst én forbindelse med formel (I) som har strukturen:



;

og/eller minst ett salt derav;

(ii) en forbindelse med formel (I) som har strukturen:



;

eller

(iii) en blanding av (i) og (ii);

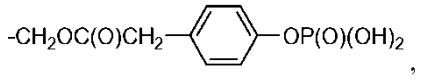
hvor:

R_3 er H eller R_x;

R_4 er H eller R_y;

R_x er: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$,

$-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



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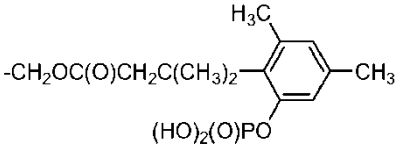
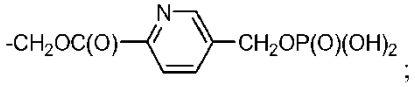


, or 

;

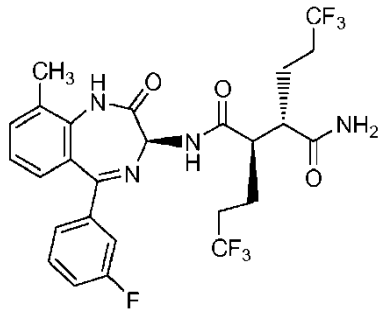
R_y er: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$ eller $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

forutsatt at hvis R_3 er R_x så er R_4 lik H; og forutsatt at hvis R_4 er R_y så er R_3 lik H.

11. Forbindelse ifølge hvilket som helst av kravene 1 til 8, eller et farmasøytisk akseptabelt salt derav, for anvendelse i terapi.

12. Forbindelse ifølge hvilket som helst av kravene 1 til 8, eller et farmasøytisk akseptabelt salt derav, for anvendelse ved behandling av kreft.

13. En forbindelse som har strukturen



eller farmasøytisk akseptable salter derav, for anvendelse ved behandling av kreft.

14. Forbindelse ifølge hvilket som helst av kravene 1 til 8, eller farmasøytisk akseptable salter derav, for anvendelse sammen med ytterligere ett eller flere midler valgt fra dasatinib, paklitaksel, tamoksifen, deksametason og karboplatin, administrert sekvensielt eller samtidig, ved behandling av kreft.