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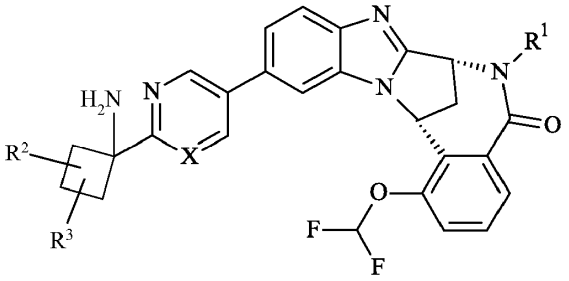
(54) Title **FUSED PENTACYCLIC IMIDAZOLE DERIVATIVES AS MODULATORS OF TNF ACTIVITY**

(56) References Cited:
US-A1- 2015 152 065
WO-A1-2016/050975

Patentkrav

1. Forbindelse av formel (I) eller et farmasøytisk akseptabelt salt derav:



(I)

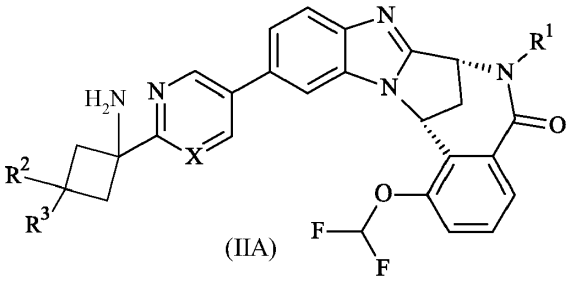
hvor

X betegner N eller C-F;

R^1 betegner hydrogen eller metyl;

R^2 betegner hydrogen, metyl eller trifluormetyl; og R^3 betegner hydrogen, cyano, hydroksy eller hydroksymetyl.

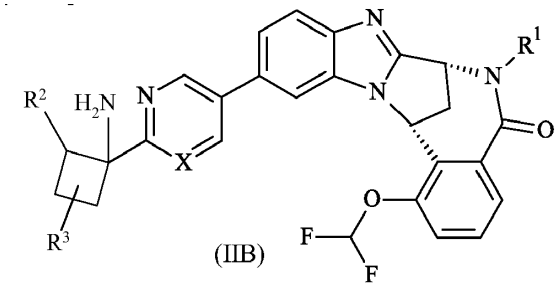
2. Forbindelse ifølge krav 1, betegnet med formel (IIA) eller et farmasøytisk akseptabelt salt derav:



(IIA)

hvor X, R^1, R^2 og R^3 er som definert i krav 1.

3. Forbindelse ifølge krav 1, betegnet med formel (IIB) eller et farmasøytisk akseptabelt salt derav:



(IIB)

hvor X, R^1, R^2 og R^3 er som definert i krav 1.

4. Forbindelse ifølge krav 1, valgt ut blant følgende:

cis-3-amino-3-{5-[(7*R*,14*R*)-1-(difluormetoksy)-6-metyl-5-okso-5,6,7,14-tetrahydro-7,14-metanobenzimidazo[1,2-*b*][2,5]benzodiazocin-11-yl]pyrimidin-2-yl}-1-metylsyklobutankarbonitril;

cis-3-amino-3-{5-[(7*R*,14*R*)-1-(difluormetoksy)-5-okso-5,6,7,14-tetrahydro-7,14-metanobenzimidazo[1,2-*b*][2,5]benzodiazocin-11-yl]pyrimidin-2-yl}-1-metylsyklobutankarbonitril;

cis-3-amino-3-{5-[(7*R*,14*R*)-1-(difluormetoksy)-6-metyl-5-okso-5,6,7,14-tetrahydro-7,14-metanobenzimidazo[1,2-*b*][2,5]benzodiazocin-11-yl]-3-fluorpyridin-2-yl}-1-metylsyklobutankarbonitril;

cis-3-amino-3-{5-[(7*R*,14*R*)-1-(difluormetoksy)-5-okso-5,6,7,14-tetrahydro-7,14-metanobenzimidazo[1,2-*b*][2,5]benzodiazocin-11-yl]-3-fluorpyridin-2-yl}-1-metylsyklobutankarbonitril;

(7*R*,14*R*)-11-{6-[(1*S*,2*R*)-1-amino-2-metylsyklobutyl]-5-fluorpyridin-3-yl}-1-(diflourmetoksy)-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]benzodiazocin-5(14*H*)-on;

(7*R*,14*R*)-11-{6-[(1*R*,2*S*)-1-amino-2-metylsyklobutyl]-5-fluorpyridin-3-yl}-1-(diflourmetoksy)-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-on;

(7*R*,14*R*)-11-[2-(1-aminosyklobutyl)pyrimidin-5-yl]-1-(difluormetoksy)-6-metyl-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]benzodiazocin-5(14*H*)-on;

(7*R*,14*R*)-11-[6-(*cis*-1-amino-3-hydroksy-3-metylsyklobutyl)-5-fluorpyridin-3-yl]-1-(difluormetoksy)-6-metyl-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-on;

(7*R*,14*R*)-11-[6-(*cis*-1-amino-3-hydroksy-3-metylsyklobutyl)-5-fluorpyridin-3-yl]-1-(difluormetoksy)-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]benzodiazocin-5(14*H*)-on;

(7*R*,14*R*)-11-{2-[*cis*-1-amino-3-(hydroksymetyl)-3-metylsyklobutyl]pyrimidin-5-yl}-1-(difluormetoksy)-6-metyl-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-on;

(7*R*,14*R*)-11-(6-[*cis*-1-amino-3-(hydroksymetyl)-3-metylsyklobutyl]-5-fluorpyridin-3-yl}-1-(difluormetoksy)-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-on;

(7*R*,14*R*)-11-(6-[*cis*-1-amino-3-hydroksy-3-(trifluormetyl)syklobutyl]-5-fluorpyridin-3-yl}-1-(difluormetoksy)-6-metyl-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-on;
(7*R,*14*R*)-11-{2-[*cis*-1-amino-3-hydroksy-3-(trifluormetyl)syklobutyl]pyrimidin-5-yl}-1-(difluormetoksy)-6-metyl-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-on;
(7*R*,14*R*)-11-(6-[*cis*-1-amino-3-hydroksy-3-(trifluormetyl)syklobutyl]-5-fluorpyridin-3-yl}-1-(difluormetoksy)-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-on;
(7*R,*14*R*)-11-(2-{*cis*-1-amino-3-[hydroksy(dideutero)metyl]-3-metylsyklobutyl}-pyrimidin-5-yl)-1-(difluormetoksy)-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]-benzodiazocin-5(14*H*)-on;
(7*R*,14*R*)-11-{2-[*cis*-1-amino-3-(hydroksymetyl)-3-metylsyklobutyl]pyrimidin-5-yl}-1-(difluormetoksy)-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*][2,5]benzodiazocin-5(14*H*)-on; og
(7*R*,14*R*)-11-(6-{*cis*-1-amino-3-[hydroksy(dideutero)metyl]-3-metylsyklobutyl}-5-fluorpyridin-3-yl)-1-(difluormetoksy)-6,7-dihydro-7,14-metanobenzimidazo[1,2-*b*]-[2,5]benzodiazocin-5(14*H*)-on.

5. Forbindelse av formel (I) ifølge krav 1 eller et farmasøytisk akseptabelt salt derav for anvendelse i terapi.

6. Forbindelse av formel (I) ifølge krav 1 eller et farmasøytisk akseptabelt salt derav for anvendelse i behandlingen og/eller forebyggingen av en inflammatorisk eller autoimmun sykdom, en nevrologisk eller nevrodegenerativ sykdom, smerte eller en nociceptiv sykdom, en kardiovaskulær sykdom, en stoffskiftesykdom, en okulær sykdom eller en onkologisk sykdom.

7. Farmasøytisk sammensetning som omfatter en forbindelse av formel (I) ifølge krav 1 eller et farmasøytisk akseptabelt salt derav i forbindelse med en farmasøytisk akseptabel bærer.

8. Farmasøytisk sammensetning ifølge krav 7, som ytterligere omfatter et farmasøytisk virkestoff.