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

(11) **NO/EP 2748147 B1**

NORWAY

(19) NO

(51) Int Cl.

C07D 409/04 (2006.01)
A61K 31/4725 (2006.01)
A61K 31/506 (2006.01)
C07D 401/04 (2006.01)
C07D 417/04 (2006.01)

Norwegian Industrial Property Office

(21)	Translation Published	2017.12.11
(80)	Date of The European Patent Office Publication of the Granted Patent	2017.08.02
(86)	European Application Nr.	12772470.6
(86)	European Filing Date	2012.08.24
(87)	The European Application's Publication Date	2014.07.02
(30)	Priority	2011.08.25, US, 201161527594 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
	Designated Extension States:	BA ME
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(54) Title **SUBSTITUTED 2-ALKYL-1-OXO-N-PHENYL-3-HETEROARYL-1,2,3,4-TETRAHYDROISOQUINOLINE-4-CARBOXAMIDES FOR ANTIMALARIAL THERAPIES**

(56) References Cited:

WO-A1-95/21616 WO-A1-2004/004727 WO-A1-2004/022553 WO-A2-03/044021 WO-A2-2006/104915 WO-A2-2007/105989 WO-A2-2010/055164 DE-A1- 10 312 963

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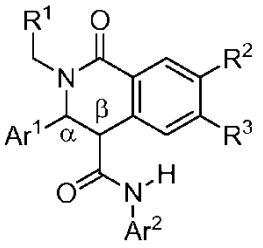
DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 23 April 2007 (2007-04-23), XP002686906, Database accession no. RN 931939-58-1

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/

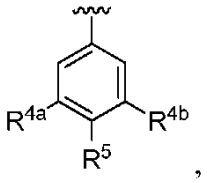
Patentkrav

1. Forbindelse med en struktur som representeres ved formel:



(II)

hvor Ar^1 er monocyklisk heteroaryl valgt fra 3-pyridinyl, 4-isoksazolyl, N-metyl-4-pyrazolyl, 4-pyrazolyl, 4-isotiazolyl, 5-tiazolyl, 5-pyrimidinyl og 4-pyridazinyl; R^1 er valgt fra hydrogen, metyl, etyl, n-propyl, i-propyl, cyklopropyl, n-butyl, i-butyl, s-butyl, t-butyl og cyklobutyl og, hvis valensen tillater det, er substituert med 0-3 grupper valgt fra fluor, klor, brom, jod, cyano, metoksyl og etoksyl; R2 og R3 er uavhengig valgt fra hydrogen, C1-C4-alkyl, C1-C4-alkoksyl, cyano, fluor, klor, brom og jod; hvor ringsubstituenter ved karbonatomene merket med α og β har *trans*-konfigurasjon; Ar^2 har en struktur som representeres ved formel:



,

hvor R^{4a} og R^{4b} er uavhengig valgt fra hydrogen, fluor, klor, brom, jod, cyano, C1-C4-alkyl, C1-C4-halogenalkyl, C1-C4-polyhalogenalkyl, C1-C4-alkoksyl, C1-C4-halogenalkoksyl og C1-C4-polyhalogenalkoksyl; R^5 er valgt fra hydrogen, fluor, klor, brom, jod, cyano, C1-C4-alkyl, C1-C4-halogenalkyl, C1-C4-polyhalogenalkyl, C1-C4-alkoksyl, C1-C4-halogenalkoksyl og C1-C4-polyhalogenalkoksyl; eller et farmasøytisk akseptabelt salt, hydrat, solvat eller en polymorf derav, samt tautomerer, geometriske isomerer, optisk aktive former derav samt tautomerer, geometriske isomerer, optisk aktive former derav for anvendelse ved forebyggelse og/eller behandling av malaria.

2. Forbindelse for anvendelse ifølge krav 1, hvor R^1 er valgt fra metyl, n-propyl, i-propyl og cyklopropyl, valgfritt substituert med 0-3 grupper valgt fra fluor og metoksyl.

3. Forbindelse for anvendelse ifølge et hvilket som helst av kravene 1 til 2, hvor R^1 er valgt fra CF_3 og $(CH_3)_2CH$.

4. Forbindelse for anvendelse ifølge et hvilket som helst av kravene 1 til 3, hvor R^2 og R^3 er uavhengig valgt fra hydrogen, C1-C4-alkyl, C1-C4-alkoksyl, cyano, fluor, klor, brom og jod.

5. Forbindelse for anvendelse ifølge et hvilket som helst av kravene 1 til 4, hvor R^2 og R^3 er uavhengig valgt fra H, OCH_3 og F.

6. Forbindelse for anvendelse ifølge et hvilket som helst av kravene 1 til 5, hvor R^{4a}, R^{4b} og R^5 er uavhengig valgt fra H, CN, F, Cl og OCF_3.

7. Forbindelse for anvendelse ifølge et hvilket som helst av kravene 1 til 6, hvor forbindelsen med formel (I) er valgt fra den følgende gruppe:

N-(3-cyano-4-fluorfenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-(cyklopropylmetyl)-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-7-fluor-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-7-metoksy-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-cyanofenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

2-isobutyl-1-okso-3-(pyridin-3-yl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-6-fluor-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-6-fluor-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-7-fluor-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-7-fluor-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

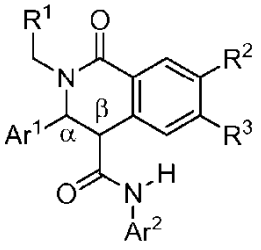
N-(3-cyano-4-fluorfenyl)-2-isobutyl-3-(isotiazol-4-yl)-1-okso-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-1-okso-3-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

og

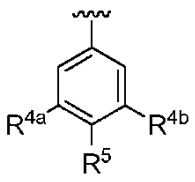
N-(3-cyano-4-fluorfenyl)-1-okso-3-(1H-pyrazol-4-yl-6,7-difluor-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid.

8. Forbindelse med en struktur som representeres ved formel:



(II)

hvor Ar^1 er valgt fra 3-pyridinyl, 4-isoksazolyl, N-metyl-4-pyrazolyl, 4-pyrazolyl, 4-isotiazolyl, 5-tiazolyl, 5-pyrimidinyl og 4-pyridazinyl; R^1 er valgt fra CF_3 og $(CH_3)_2CH$; R^2 og R^3 er uavhengig valgt fra H, OCH_3 og F; Ar^2 har en struktur som representeres ved formel:



,

hvor R^{4a}, R^{4b} og R^5 er uavhengig valgt fra H, CN, F, Cl og OCF_3, eller et farmasøytisk akseptabelt salt, hydrat, solvat eller en polymorf derav, samt tautomerer, geometriske isomerer, optisk aktive former derav, samt tautomerer, geometriske isomerer, optisk aktive former derav.

9. Forbindelse ifølge krav 8, valgt fra den følgende gruppe:

N-(3-cyano-4-fluorfenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-1-okso-3-(pyridin-3-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-(cyklopropylmetyl)-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-7-fluor-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-7-metoksy-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-cyanofenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

2-isobutyl-1-okso-3-(pyridin-3-yl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-2-isobutyl-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-6-fluor-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

2-butyl-N-(3-cyano-4-fluorfenyl)-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-6-fluor-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-1-okso-3-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-7-fluor-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyanofenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-cyano-5-fluorfenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-N-(3-(trifluormetoksy)fenyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(4-fluor-3-(trifluormetoksy)fenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-fluor-5-(trifluormetoksy)fenyl)-2-isobutyl-1-okso-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-klor-5-cyanofenyl)-7-fluor-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1-okso-1,2,3,4-tetrahydroisokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-3-(isotiazol-4-yl)-1-okso-1,2,3,4-tetrahydro-isokinolin-4-karboksamid;

N-(3-cyano-4-fluorfenyl)-2-isobutyl-1-okso-3-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid; og

N-(3-cyano-4-fluorfenyl)-1-okso-3-(1H-pyrazol-4-yl-6,7-difluor-2-(2,2,2-trifluoretyl)-1,2,3,4-tetrahydroisokinolin-4-karboksamid.

10. Forbindelse ifølge krav 8 eller 9 for anvendelse som et legemiddel.

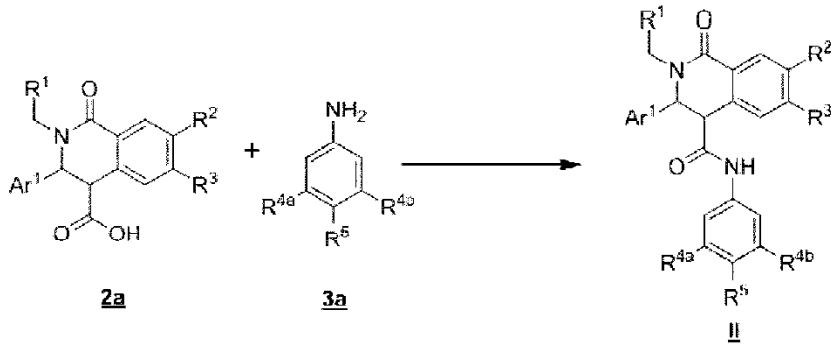
11. Farmasøytisk sammensetning omfattende minst én forbindelse ifølge krav 8 eller 9 og en farmasøytisk akseptabel bærer, et fortynningsmiddel eller en eksipiens derav.

12. Farmasøytisk formulering omfattende minst én forbindelse ifølge krav 8 eller 9, ytterligere omfattende minst ett ytterligere antimalariamiddel.

13. Farmasøytisk sammensetning ifølge krav 12 hvor det ytterligere antimalariamiddel er valgt fra artemisinin eller et artemisininderivat, klorkin, meflokin, kinin, atovakvon/proguanil, doksycyklin, hydroksyklorkin, pyronaridin, lumefantrin, pyrimetamin-sulfadoksin, kinakrin, klorkin, primakin, doksycyklin, atovakvon og proguanilhydroklorid, piperakin, ferrokin, tafenokin, arterolan, Spiro[3H-indol-3,1'-[1H]pyrido[3,4-b]indol]-2(1H)-on (CAS-registernummer: 1193314-23-6), 5,7'-diklor-6'-fluor-2',3',4',9'-tetrahydro-3'-metyl-,(1'R,3'S)-], Svovel, [4-[[2-(1,1-difluoretyl)-5-metyl[1,2,4]triazol[1,5-a]pyrimidin-7-yl]-amino]fenyl]pentafluor-] (CAS-registernummer: 1282041-94-4), Morfolin eller 4-[2-(4-cis-dispiro[cykloheksan-1,3'-[1,2,4]trioksolan-5',2"-tricyklo[3.3.1.13,7]-dekan]-4-ylfenoksy)etyl]-] (CAS-registernummer: 1029939-86-3).

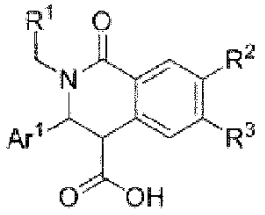
14. Fremgangsmåte for fremstilling av en forbindelse med formel (II) hvor Ar^1 er valgt fra 3-pyridinyl, 4-(1-metylpyrazolyl) og 4-pyrazolyl; R^1 er valgt fra CF_3, propyl, syklopropyl og $(CH_3)_2CH$; R^2 og R^3 er uavhengig valgt fra H, OCH_3 og F; R^{5a}, R^{5b} og R^6 er uavhengig valgt fra H, CN, F, Cl og OCF_3, omfattende et trinn med å omsette en karboksylsyre med formel 2a hvor Ar^1 er valgt fra 3-pyridinyl, 4-(1-

metylpyrazolyl) og 4-pyrazolyl; R^1 er valgt fra CF_3, propyl, syklopropyl og $(CH_3)_2CH$; R^2 og R^3 er uavhengig valgt fra H, OCH_3 og F, med et arylamin med formel 3a hvor R^{4a}, R^{4b} og R er uavhengig valgt fra H, CN, F, Cl og OCF_3:



2a 3a II

15. Mellomprodukt med formel 2a



2a

valgt fra 3-pyridinyl, 4-(1-metylpyrazolyl) og 4-pyrazolyl; R^1 er valgt fra CF_3, propyl, syklopropyl og $(CH_3)_2CH$; R^2 og R^3 er uavhengig valgt fra H, OCH_3 og F; og R^{5a}, R^{5b} og R^6 er uavhengig valgt fra H, CN, F, Cl og OCF_3, valgt fra den følgende gruppe:

1-okso-2-isobutyl-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre;

1-okso-2-(2,2,2-trifluoretyl)-3-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre;

1-okso-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre;

1-okso-2-(2,2,2-trifluoretyl)-3-(1-metyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-isokinolin-4-karboksylsyre;

1-okso-2-(2,2,2-trifluoretyl)-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre;

1-okso-2-(cyklopropylmetyl)-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre;

1-okso-2-(1-butyl)-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre;

1-okso-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-7-fluor-1,2,3,4-tetrahydro-isokinolin-4-karboksylsyre;

1-okso-2-isobutyl-3-(1-metyl-1H-pyrazol-4-yl)-6-fluor-1,2,3,4-tetrahydro-isokinolin-4-karboksylsyre;

1-okso-2-isobutyl-3-(isotiazol-4-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre;

1-okso-2-isobutyl-3-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre;

1-okso-2-(2,2,2-trifluoretyl)-3-(1-metyl-1H-pyrazol-4-yl)-7-fluor-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre;

og

2-isobutyl-7-metoksy-1-okso-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisokinolin-4-karboksylsyre.