



(12) Translation of
European patent specification

(11) NO/EP 3037424 B1

NORWAY

(19) NO
(51) Int Cl.
C07D 487/14 (2006.01)
A61K 31/519 (2006.01)
A61K 31/55 (2006.01)
A61P 35/00 (2006.01)
A61P 43/00 (2006.01)

Norwegian Industrial Property Office

(21) Translation Published 2018.02.19

(80) Date of The European Patent Office Publication of the Granted Patent 2017.11.08

(86) European Application Nr. 14837210.5

(86) European Filing Date 2014.08.22

(87) The European Application's Publication Date 2016.06.29

(30) Priority 2013.08.22, JP, 2013172746

(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 Taiho Pharmaceutical Co., Ltd., 1-27 Kandnishiki-cho, Chiyoda-kuTokyo 101-8444, JP-Japan

(72) Inventor UNO, Takao, c/o TAIHO PHARMACEUTICAL CO. LTD.3 Okubo, Tsukuba-shilbaraki 300-2611, JP-Japan
NONOSHITA, Katsumasa, c/o TAIHO PHARMACEUTICAL CO. LTD.3 Okubo, Tsukuba-shilbaraki 300-2611, JP-Japan
SHIMAMURA, Tadashi, c/o TAIHO PHARMACEUTICAL CO. LTD.3 Okubo, Tsukuba-shilbaraki 300-2611, JP-Japan

(74) Agent or Attorney BRYN AARFLOT AS, Postboks 449 Sentrum, 0104 OSLO, Norge

(54) Title **NOVEL QUINOLINE-SUBSTITUTED COMPOUND**

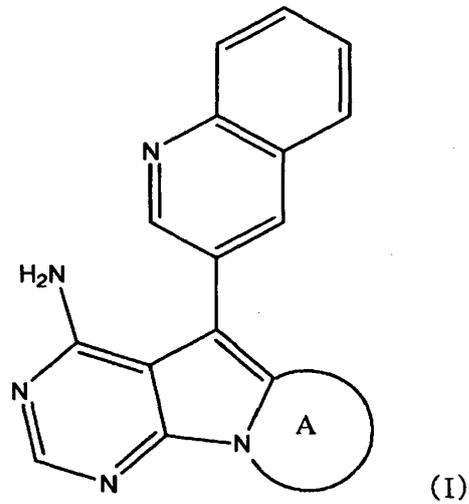
(56) References Cited: WO-A1-2013/118817, WO-A1-2013/125709, JP-A- 2008 533 172, WO-A2-2011/046964, WO-A1-2014/129596

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/>

1

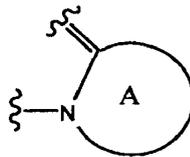
Patentkrav

1. Forbindelse representert ved formel (I) nedenfor eller et salt derav:



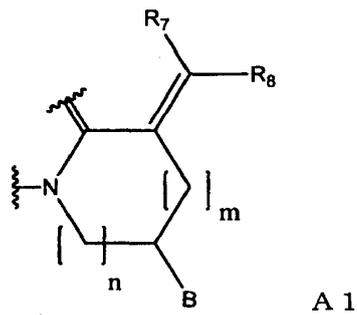
5

hvor gruppen:



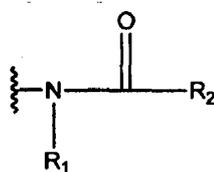
10

er (1) en gruppe representert ved Formel A1:



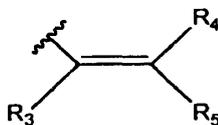
(i Formel A1 er B en gruppe representert ved:

15



2

[R₁ er et hydrogenatom eller en C1-C6 alkylgruppe; og R₂ er en gruppe representert ved:

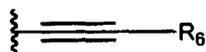


5

hvor R₃, R₄, og R₅ er like eller forskjellige, og hver representerer et hydrogenatom, et halogenatom, en C1-C6 alkylgruppe, en C6-C12 arylgruppe, en C4-C9 heteroarylgruppe, en aminometylgruppe som kan være substituert med en C1-C6 alkylgruppe, eller en 1-piperidinometylgruppe,

10

eller en gruppe representert av:

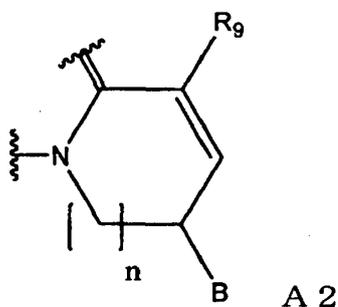


hvor R₆ representerer et hydrogenatom eller en C1-C6 alkylgruppe],

15

R₇ og R₈ er like eller forskjellige, og hver representerer et hydrogenatom eller en C1-C6 alkylgruppe; m er 0 eller 1; og n er 1 eller 2);

(2) en gruppe representert ved Formel A2:

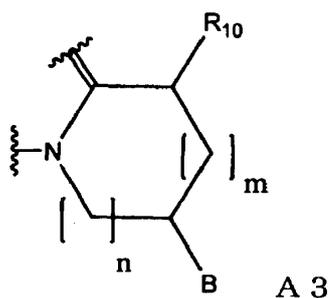


20

(i Formel A2, er B og n som definert i Formel A1; og R₉ er et hydrogenatom eller en C1-C6 alkylgruppe); eller

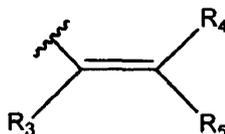
(3) en gruppe representert Formel A3:

3



(i Formel A3, er B, m og n som definert i Formel A1; og R₁₀ er en C1-C6
5 alkygruppe).

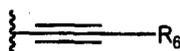
2. Forbindelse eller et salt derav ifølge krav 1, hvor R₂ er en gruppe representert ved:



10

hvor R₃, R₄, og R₅ er like eller forskjellige, og hver representerer et
hydrogenatom, et halogenatom, en C1-C6 alkygruppe, en aminometylgruppe som kan
være substituert med en C1-C6 alkygruppe eller en 1-piperidinometylgruppe,
eller en gruppe representert av:

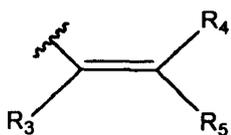
15



hvor R₆ representerer et hydrogenatom eller en C1-C6 alkygruppe.

20

3. Forbindelse eller et salt derav ifølge krav 1 eller 2, hvor R₂ er en gruppe
representert av:

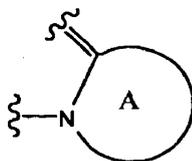


25

hvor R₃, R₄, og R₅ er like eller forskjellige, og hver representerer et
hydrogenatom, et halogenatom, en aminometylgruppe som kan være substituert med
en metylgruppe eller en 1-piperidinometylgruppe.

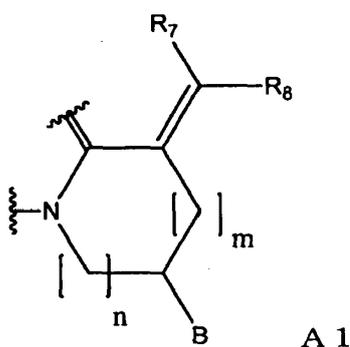
4

4. Forbindelse eller et salt derav ifølge et hvilket som helst av kravene 1 til 3, hvor gruppen:



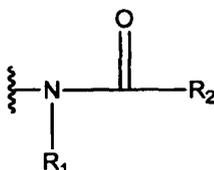
5

er (1) en gruppe representert ved Formel A1:



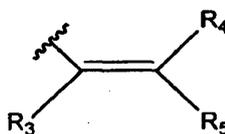
10

(i Formel A1 er B en gruppe representert ved:



15

hvor R_1 er et hydrogenatom eller en C1-C6 alkylgruppe; og R_2 er en gruppe representert ved:



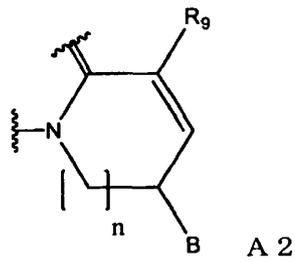
20

hvor R_3 , R_4 , og R_5 er like eller forskjellige, og hver representerer et hydrogenatom eller et halogenatom,

R_7 og R_8 er like eller forskjellige, og hver representerer et hydrogenatom eller en C1-C6 alkylgruppe; m er 0 eller 1; og n er 1); eller

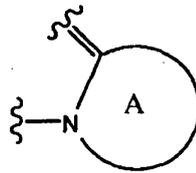
(2) en gruppe representert ved Formel A2:

5



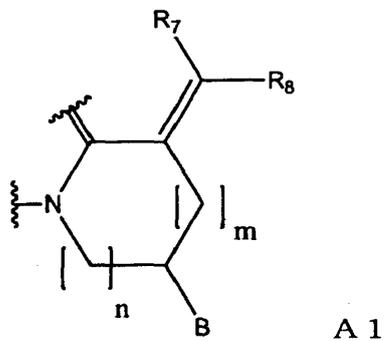
5 (i Formel A2, er B og n som definert i formel A1; og R₉ er et hydrogenatom eller en C1-C6 alkylgruppe).

5. Forbindelse eller et salt derav ifølge et hvilket som helst av kravene 1 til 4, hvor gruppen:



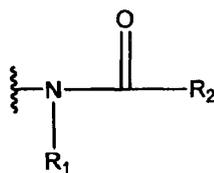
10

er (1) en gruppe representert ved Formel A1:



15

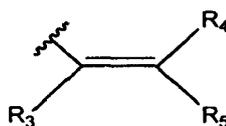
(i Formel A1 er B en gruppe representert av:



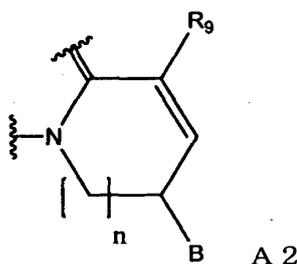
20

hvor R₁ er et hydrogenatom; og R₂ er en gruppe representert ved:

6



- 5 hvor R₃, R₄, og R₅ hver repræsenterer et hydrogenatom,
R₇ og R₈ hver repræsenterer et hydrogenatom; m er 0; og n er 1); eller
(2) en gruppe repræsenteret ved formel A2:



- 10 (i formel A2, er B og n som defineret i formel A1; og R₉ repræsenterer en C1-C6
alkylgruppe).

6. Forbindelse eller salt deraf ifølge et hvilket som helst af kravene 1 til 5, hvor
forbindelsen er valgt fra følgende gruppe af forbindelser:

- 15 (S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-
b]pyrrolizin-7-yl)acrylamide;
(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-
b]pyrrolizin-7-yl)methacrylamide;
(S) -N- (4-amino-6-metylen-5- (kinolin-3-yl) -7,8-dihydro-6H-pyrimido [5,4-b]
20 pyrrolizin-7-yl) but-2- -amid (blanding av E og Z);
(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-
b]pyrrolizin-7-yl)-4-(dimethylamino)but-2-enamide;
(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-
b]pyrrolizin-7-yl)-3-chloroacrylamide;
25 (S,Z)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-
b]pyrrolizin-7-yl)-3-chloroacrylamide;
(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-
b]pyrrolizin-7-yl)-4-(piperidin-1-yl)but-2-enamide;
(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-
30 b]pyrrolizin-7-yl)propiolamide;

- (S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)but-2-ynamide;
- (S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-4-(diethylamino)but-2-enamide;
- 5 (S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-4-(ethyl(methyl)amino)but-2-enamide;
- (S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-4-(isopropyl(methyl)amino)but-2-enamide;
- (R)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-7-yl)acrylamide;
- 10 (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;
- (S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-8-yl)acrylamide;
- 15 (R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;
- (R)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-8-yl)acrylamide;
- (S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8,9,10-tetrahydro-6H-pyrimido[5',4':4,5]pyrrolo[1,2-a]azepin-8-yl)acrylamide;
- 20 (S,E)-N-(4-amino-6-ethylidene-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-8-yl)acrylamide;
- (S)-N-(4-amino-6-isopropyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;
- 25 (S)-N-(4-amino-6-(propan-2-ylidene)-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-8-yl)acrylamide;
- (R)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-N-methylacrylamide;
- (R)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide;
- 30 (R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide;
- N-((7S)-4-amino-6-methyl-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide;
- 35 (R)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-N-methylacrylamide;

(S)-N-(4-amino-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

5 (R)-N-(4-amino-5-(quinolin-3-yl)-9,10-dihydro-8H-pyrimido[5',4':4,5]pyrrolo[1,2-a]azepin-8-yl)acrylamide;

N-((6R*,8S) -4-amino-6-metyl-5-(kinolin-3-yl)-6,7,8,9-tetrahydropyrimido [5,4-b]indolizin-8-yl) akrylamid; og

10 N-((6S*,8S)-4-amino-6-methyl-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-8-yl)acrylamide.

7. Forbindelse eller salt derav ifølge et hvilket som helst av kravene 1 til 5, hvor forbindelsen er valgt fra følgende gruppe av forbindelser:

15 (S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide;

(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide;

(S,Z)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide;

20 (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

25 (S,E)-N-(4-amino-6-ethylidene-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(R)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-N-methylacrylamide;

(R)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide;

30 (R) -N- (4-amino-6-metyl-5- (kinolin-3-yl) -8,9-dihydropyrimido [5,4-b] indolizin-8-yl) -N-metylakrylamid; og

(R)-N-(4-amino-5-(quinolin-3-yl)-9,10-dihydro-8H-pyrimido[5',4':4,5]pyrrolo[1,2-a]azepin-8-yl)acrylamide.

35 8. Forbindelse eller salt derav ifølge et hvilket som helst av kravene 6 til 7, hvor forbindelsen er (S)-N-(4-amino-6-metylen-5-(kinolin-3-yl)-7,8-dihydro-6H-

pyrimido[5,4-b] pyrrolizin-7-yl)akrylamid eller et salt derav.

5 9. Forbindelse eller salt derav ifølge et hvilket som helst av kravene 6 til 7, hvor forbindelsen er (S)-N-(4-amino-6-metyl-5-(kinolin-3-yl)-8,9-dihydropyrimido [5,4-b]indolizin-8-yl)akrylamid eller et salt derav.

10. Farmasøytisk sammensetning omfattende forbindelsen eller et salt derav ifølge et hvilket som helst av kravene 1 til 9.

10 11. Forbindelse eller salt derav som definert i et hvilket som helst av kravene 1 til 9 for anvendelse som et antitumormiddel.

12. Forbindelse eller salt derav som definert i et hvilket som helst av kravene 1 til 9 for anvendelse i forebygging eller behandling av kreft.

15