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(54) Title **KINASE INHIBITORS**

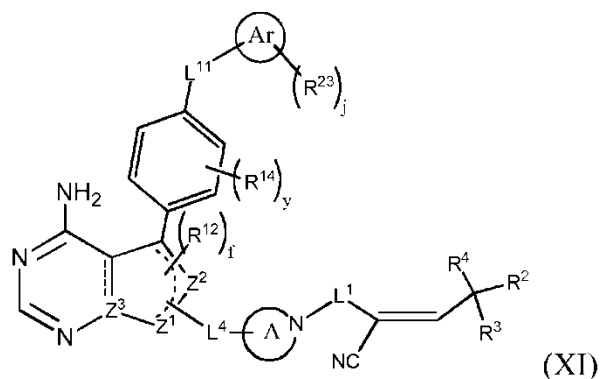
(56) References  
Cited: WO-A1-2012/158764  
WO-A1-03/051824  
WO-A2-2008/039218  
US-B1- 6 331 555

US-B1- 6 225 346  
 US-A1- 2004 006 083  
 EP-A1- 2 508 509  
 WO-A1-2012/158810  
 WO-A2-2011/046964  
 US-A1- 2010 152 143  
 US-A1- 2006 079 494  
 WO-A2-2008/005954  
 WO-A2-2011/060440  
 DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;  
 4 April 2006 (2006-04-04), XP002735876, Database accession no. 879194-65-7  
 DEEVI BASAVAIAH ET AL: "Baylis-Hillman Chemistry: A Convenient Stereoselective Synthesis  
 of (Z,Z)- and (E,E)-1,4-Diarylpiperazines", JOURNAL OF CHEMICAL RESEARCH (S), 1  
 January 2001 (2001-01-01), pages 354-355, XP055167349, & Deevi Basavaiah ET AL: "Baylis-  
 Hillman Chemistry: A Convenient Stereoselective Synthesis of (Z,Z)- and (E,E)-1,4-  
 Diallylpiperazines", , 1 January 2001 (2001-01-01), XP055167880, Retrieved from the Internet:  
 URL: <https://www.deepdyve.com/lp/wiley/chem-inform-abstract-baylis-hillman-chemistry-a-convenient-sVEQElq2Sf> [retrieved on 2015-02-06]  
 RICHARD M. JACOBSON ET AL: "Three carbon annelation reagents: unsaturated alpha  
 aminonitriles as homoenolate equivalents", TETRAHEDRON LETTERS, vol. 21, no. 13, 1  
 January 1980 (1980-01-01), pages 1205-1208, XP055167328, ISSN: 0040-4039, DOI:  
 10.1016/S0040-4039(00)71371-2  
 DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;  
 23 July 2006 (2006-07-23), XP002735875, Database accession no. 895292-61-2  
 ZHENGYING PAN ET AL.: "Discovery of Selective Irreversible Inhibitors for Bruton's Tyrosine  
 Kinase" CHEMMEDCHEM. vol. 2, no. 1, 2007, pages 58 - 61, XP008118842  
 AVIV GAZIT ET AL: "Tryphostins. 2. Heterocyclic and  $\alpha$ -Substituted Benzylidenemalononitrile  
 Tryphostins as Potent Inhibitors of EGF Receptor and ErbB2/neu Tyrosine Kinases", JOURNAL  
 OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 34, no. 6, 1 January  
 1991 (1991-01-01), pages 1896-1907, XP008155011, ISSN: 0022-2623, DOI:  
 10.1021/JM00110A022  
 NORBERT DE KIMPE ET AL: "Synthesis of [alpha]-Cyanoenamines by Cyanation of [alpha]-  
 Bromoimmonium Bromides and Dehydrobromination of [beta]-bromo-[alpha]-(dialkylamino)nitrile  
 s", CHEMISCHE BERICHTE, vol. 116, no. 12, 1 December 1983 (1983-12-01), pages 3846-  
 3857, XP055167334, ISSN: 0009-2940, DOI: 10.1002/cber.19831161208  
 H. AHLBRECHT ET AL: "3-Metallierte Enamine; IV 1 . Metallierung von 1-Cyano-enaminen, eine  
 einfache Methode zur Erzeugung von 3-Carboxy-carbanionen", SYNTHESIS, vol. 1975, no. 08,  
 1 January 1975 (1975-01-01), pages 512-516, XP055167326, ISSN: 0039-7881, DOI:  
 10.1055/s-1975-23825

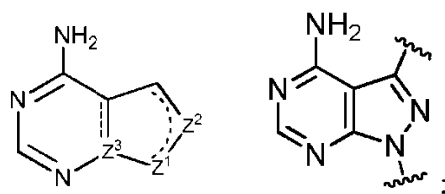
Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts,  
 section 66i the patent will receive protection in Norway only as far as there is agreement between the translation  
 and the language of the application/patent granted at the EPO. In matters 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 som har strukturen med formel (XI):



hvor:



er

y er et heltall fra 0 til 2;

j er et heltall fra 0 til 3;

f er 0;

Ar er usubstituert fenyl eller fenyl substituert i meta- og/eller para-posisjonen;

R<sup>12</sup> er fraværende;

R<sup>14</sup> er fraværende, metyl, fluor, metoksy, klor, trifluormetyl eller trifluormetoksy;

L<sup>1</sup> er -C(O)- eller SO<sub>2</sub>;

L<sup>4</sup> er en binding, -O-, -NH- eller metylen;

ring A er azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl eller piperazin-1-yl;

L<sup>11</sup> er -O-, -CO-, -CH<sub>2</sub>-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>15C</sup>-, -NR<sup>15C</sup>CO-, -CONR<sup>15C</sup>-, -NR<sup>15C</sup>SO<sub>2</sub>-, -SO<sub>2</sub>NR<sup>15C</sup>- eller -NR<sup>15C</sup>CONR<sup>15D</sup>-, hvori hvert R<sup>15C</sup> og R<sup>15D</sup> er hydrogen;

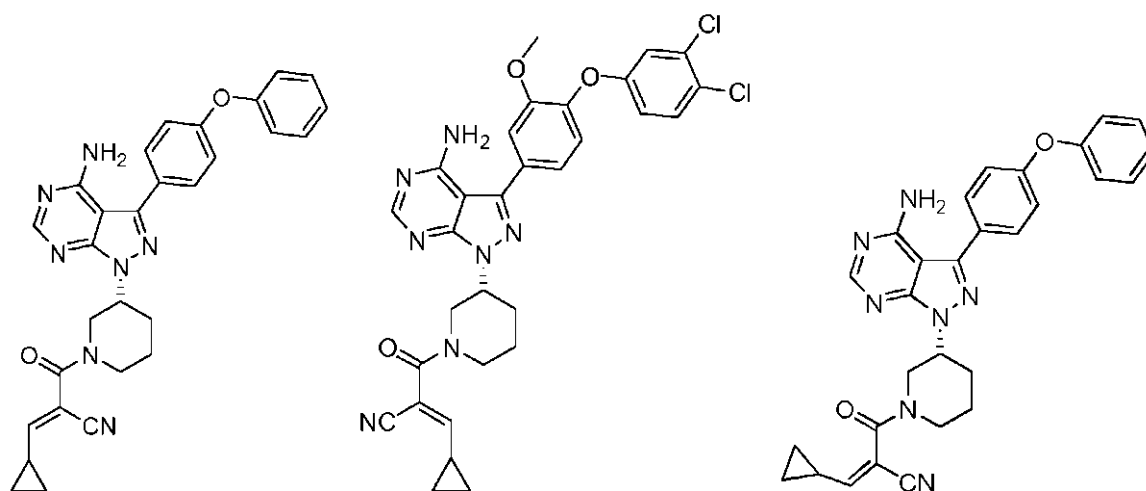
R<sup>23</sup> er fraværende, usubstituert mettet (C<sub>1</sub>-C<sub>6</sub>)alkyl, usubstituert mettet (C<sub>1</sub>-C<sub>6</sub>)alkoksy, halogen, usubstituert mettet (C<sub>1</sub>-C<sub>6</sub>)halogenalkyl, usubstituert mettet (C<sub>1</sub>-C<sub>6</sub>)halogenalkoksy eller cyano;

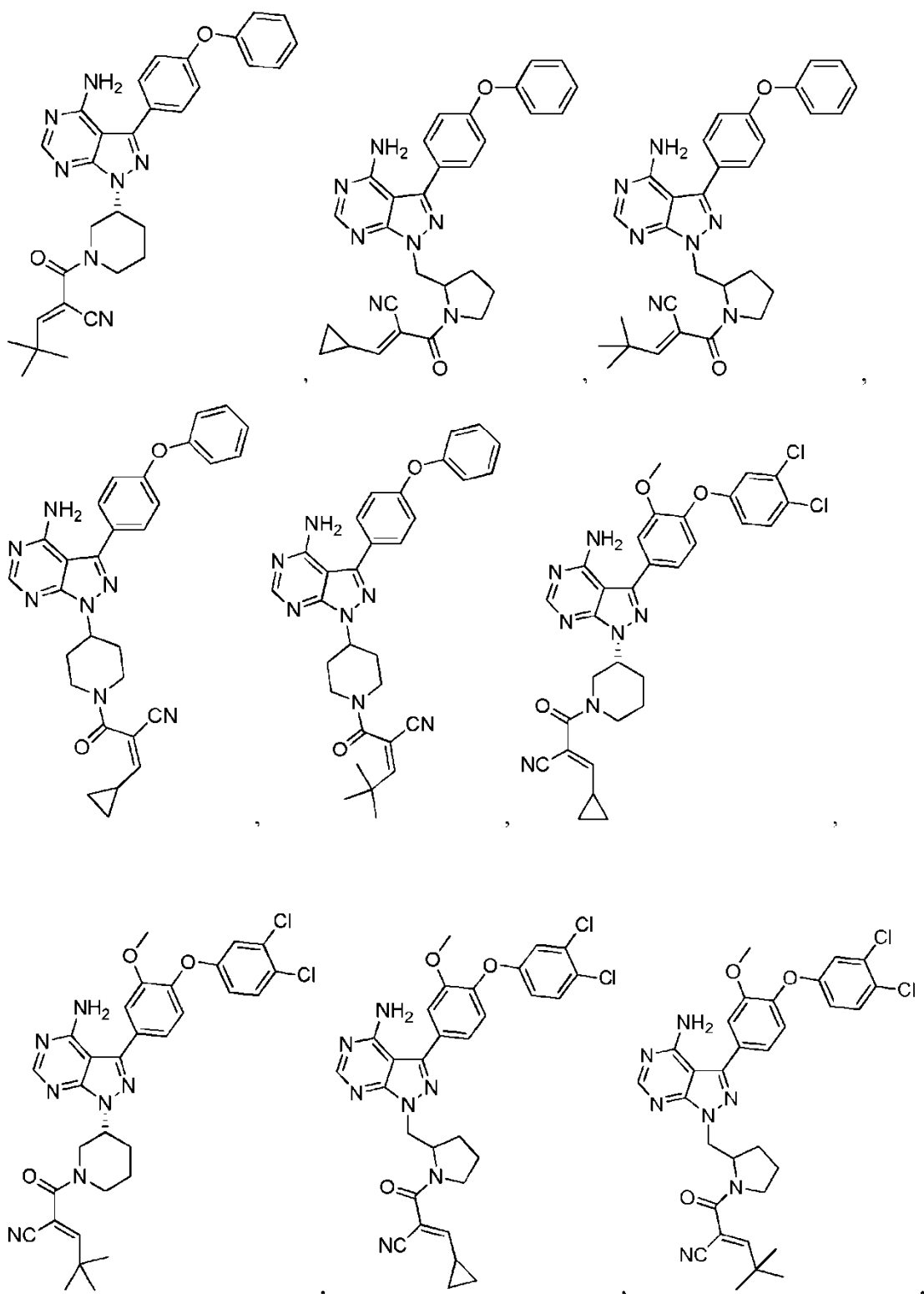
R<sup>2</sup> og R<sup>3</sup> er uavhengig usubstituert mettet C<sub>1</sub>-C<sub>6</sub>alkyl eller danner sammen (C<sub>3</sub>-C<sub>6</sub>) usubstituert mettet sykloalkyl; og

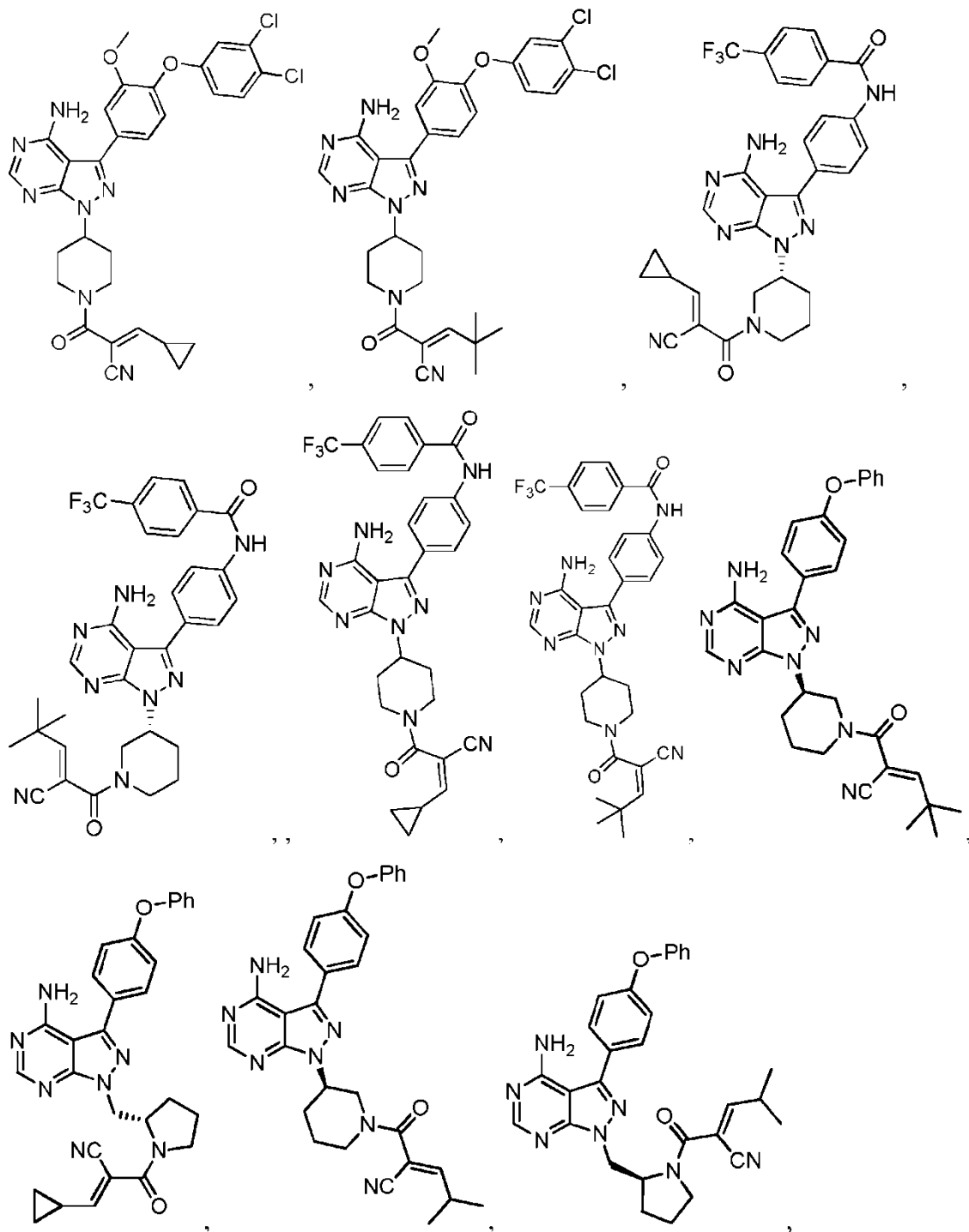
R<sup>4</sup> er hydrogen, metyl, hydroksymetyl, hydroksyetyl, 2-metylaminoetyl eller 2,2-dimetylaminoetyl; eller

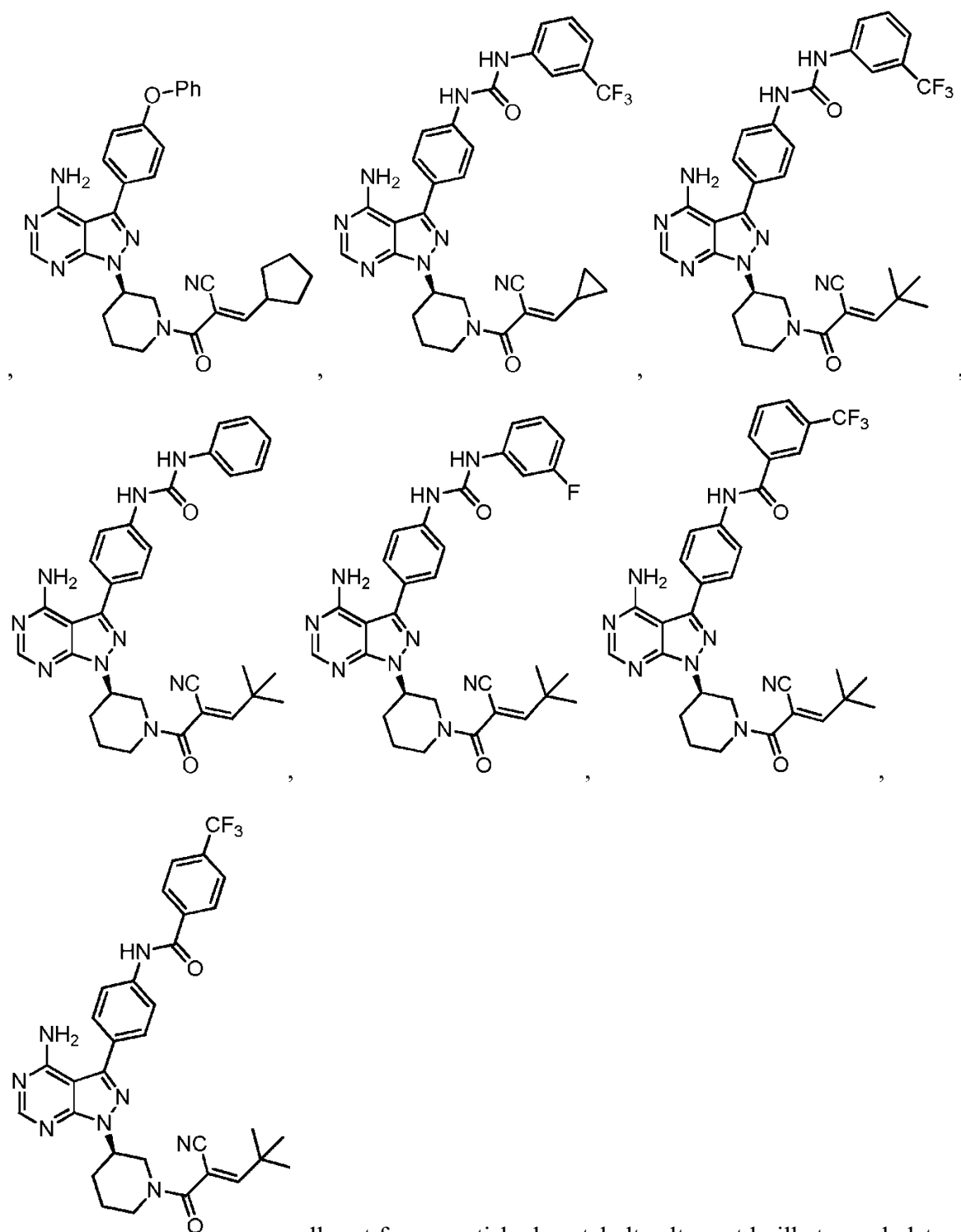
et farmasøytisk akseptabelt salt derav.

2. Forbindelsen ifølge krav 1, hvori  $L^{11}$  av forbindelsen med formel (XI) er -O-.
3. Forbindelsen ifølge krav 1, hvori  $L^4$  av forbindelsen med formel (XI) er en binding, -O- eller metylen.
4. Forbindelsen ifølge et hvilket som helst av kravene 1 til 3, hvori Ar er fenyl substituert i metaposisjonen(e) med ett eller to  $R^{23}$  som uavhengig velges fra fluor, metyl, trifluormetoksy, trifluormetyl eller metoksy.
5. Forbindelsen ifølge krav 1, hvori  $R^{23}$  er fraværende, metyl, metoksy, fluor, klor, trifluormetyl, trifluormetoksy eller cyano.
6. Forbindelsen ifølge krav 1, som er en forbindelse valgt fra









eller et farmasøytisk akseptabelt salt av et hvilket som helst av de foregående forbindelsene.

- 5 7. Farmasøytisk sammensetning omfattende en forbindelse ifølge et hvilket som helst av kravene 1 til 6, eller et farmasøytisk akseptabelt salt derav, og en farmasøytisk akseptabel eksipiens.

8. Forbindelse ifølge et hvilket som helst av kravene 1 til 6 for anvendelse i behandling av kreft, epilepsi, HIV-infeksjon, autoimmun sykdom, iskemisk sykdom, hjerneslag, nevrodegenerative sykdommer, metabolsk sykdom eller betennelse.
- 5 9. Forbindelse ifølge et hvilket som helst av kravene 1 til 6 for anvendelse ifølge krav 8 for behandling av leukemi, multippelt myelom, lymfom, ikke-småcellet lungekreft, kreft i bukspyttkjertelen eller revmatoid artritt.