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(54) Title IMIDAZO[4,5-D]PYRROLO[2,3-B]PYRIDINE COMPOUNDS AS INHIBITORS OF JANUS KINASES

(56) References
Cited:
WO-A1-2011/086053
WO-A1-2013/007765
MARK ZAK ET AL: "Identification of C -2 Hydroxyethyl Imidazopyrrolopyridines as Potent JAK1 Inhibitors with Favorable Physicochemical Properties and High Selectivity over JAK2", JOURNAL OF MEDICINAL CHEMISTRY, vol. 56, no. 11, 31 May 2013 (2013-05-31), pages 4764-4785, XP055462006, ISSN: 0022-2623, DOI: 10.1021/jm4004895

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Patentkrav

1. Forbindelse valgt fra gruppen bestående av

- 2-(1-((1r,4r)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)-N-(2-hydroksy-2-metylpropyl)-acetamid;
- 2-((1r,4r)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-d]pyrrolo[2,3-b]-pyridin-1(6H)-yl)cykloheksyl)acetonitril;
- 2-(1-((1r,4r)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)-N-(cyklopropylmetyl)-acetamid;
- N-(2-Cyanoethyl)-2-(1-((1r,4r)-4-(cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)acetamid;
- 2-(1-((1r,4r)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)-N-(tetrahydro-2H-pyran-4-yl)acetamid;
- 2-(1-((1r,4r)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)-N-((tetrahydro-2H-pyran-4-yl)metyl)acetamid;
- N-(2-Cyano-2-metylpropyl)-2-(1-((1r,4r)-4-(cyanometyl)-cykloheksyl)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)acetamid;
- 2-(1-((1r,4r)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)-N-((1-hydroksycyklobutyl)-metyl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-metyl-1*H*-pyrazol-4-yl)-acetamid;

5 *N*-(4-(Cyanometyl)bicyklo[2.2.1]heptan-1-yl)-2-(1-((1*r*,4*r*)-4-(cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo-[2,3-*b*]pyridin-2-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1*H*-pyrazol-3-yl)acetamid;

10 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklopropyl)-metyl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav.

2. Forbindelse ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående av

15 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid;

2-((1*r*,4*r*)-4-(2-(1*H*-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]-pyridin-1(6*H*)-yl)cykloheksyl)acetonitril;

20 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(cyklopropylmetyl)-acetamid;

N-(2-Cyanoethyl)-2-(1-((1*r*,4*r*)-4-(cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(tetrahydro-2H-pyran-4-yl)acetamid;

5 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-((1-hydroksycyklobutyl)-methyl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-((1-hydroksycyklopropyl)-methyl)acetamid; og

10 farmasøytisk akseptable salter, og kombinasjoner derav.

3. Forbindelse ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående av

15 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid;

2-((1*r*,4*r*)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6H)-yl)cykloheksyl)acetonitril;

20 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(cyklopropylmethyl)-acetamid;

N-(2-Cyanoethyl)-2-(1-((1*r*,4*r*)-4-(cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cyclonexyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(tetrahydro-2H-pyran-4-yl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav.

- 5 4. Forbindelse ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående av

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cyclonexyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid;

- 10 2-((1*r*,4*r*)-4-(2-(1*H*-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo-[2,3-*b*]pyridin-1(6*H*)-yl)cyclonexyl)acetonitril;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cyclonexyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklobutyl)metylacetamid og

- 15 farmasøytisk akseptable salter, og kombinasjoner derav,

valgfritt hvor forbindelsen er:

(a) 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cyclonexyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamido; eller

- 20 (b) 2-((1*r*,4*r*)-4-(2-(1*H*-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo-[2,3-*b*]pyridin-1(6*H*)-yl)cyclonexyl)acetonitril; eller

(c) 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklobutyl)metyl)acetamid.

5. Forbindelse ifølge krav 1, hvor forbindelsen er valgt fra
5 gruppen bestående av

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)metyl)acetamid;

10 *N*-(2-Cyano-2-metylpropyl)-2-(1-((1*r*,4*r*)-4-(cyanometyl)-cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklobutyl)-metyl)acetamid;

15 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-metyl-1*H*-pyrazol-4-yl)-acetamid;

20 *N*-(4-(Cyanometyl)bicyklo[2.2.1]heptan-1-yl)-2-(1-((1*r*,4*r*)-4-(cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo-[2,3-*b*]pyridin-2-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1*H*-pyrazol-3-yl)-acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklopropyl)-metyl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav.

- 5 6. Forbindelse ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående av

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid;

- 10 2-((1*r*,4*r*)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]-pyridin-1(6H)-yl)cykloheksyl)acetonitril;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(cyklopropylmetyl)-acetamid;

- 15 *N*-(2-Cyanoethyl)-2-(1-((1*r*,4*r*)-4-(cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(tetrahydro-2H-pyran-4-yl)acetamid;

- 20 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklobutyl)-metyl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav.

7. Forbindelse ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående av

5 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)metyl)acetamid;

10 *N*-(2-Cyano-2-metylpropyl)-2-(1-((1*r*,4*r*)-4-(cyanometyl)-cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)acetamid;

15 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklobutyl)-metyl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav.

8. Forbindelse ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående av

15 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid;

20 *N*-(4-(Cyanometyl)bicyklo[2.2.1]heptan-1-yl)-2-(1-((1*r*,4*r*)-4-(cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo-[2,3-*b*]pyridin-2-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1*H*-pyrazol-3-yl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav.

9. Forbindelse ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående av

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid;

2-((1*r*,4*r*)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6H)-yl)cykloheksyl)acetonitril;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-((1-hydroksycyklopropyl)-metyl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav, valgfritt hvor forbindelsen er valgt fra:

(a) gruppen bestående av

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid;

2-((1*r*,4*r*)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6H)-yl)cykloheksyl)acetonitril; og

farmasøytisk akseptable salter, og kombinasjoner derav; eller

20 (b) gruppen bestående av

2-((1*r*,4*r*)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6H)-yl)cykloheksyl)acetonitril;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklopropyl)-metyl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav; eller

5 (c) gruppen bestående av

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid;

10 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklopropyl)-metyl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav.

10. Forbindelse ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående av

15 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid;

2-((1*r*,4*r*)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]-pyridin-1(6H)-yl)cykloheksyl)acetonitril;

20 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(cyklopropylmetyl)-acetamid;

N-(2-Cyanoethyl)-2-(1-((1*r*,4*r*)-4-(cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)acetamid;

5 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(tetrahydro-2H-pyran-4-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(tetrahydro-2H-pyran-4-yl)methyl)acetamid;

10 *N*-(2-Cyano-2-metylpropyl)-2-(1-((1*r*,4*r*)-4-(cyanomethyl)-cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklobutyl)-methyl)acetamid;

15 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-metyl-1*H*-pyrazol-4-yl)-acetamid;

20 *N*-(4-(Cyanomethyl)bicyklo[2.2.1]heptan-1-yl)-2-(1-((1*r*,4*r*)-4-(cyanomethyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)acetamid;

2-(1-((1*r*,4*r*)-4-(Cyanomethyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1*H*-pyrazol-3-yl)acetamid;

25 2-(1-((1*r*,4*r*)-4-(Cyanomethyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklopropyl)-methyl)acetamid; og

farmasøytisk akseptable kokrystaller derav.

11. Forbindelse ifølge krav 10, valgt fra gruppen bestående av
2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-
5 metylpropyl)acetamid;
- 2-((1*r*,4*r*)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]-pyridin-1(6H)-yl)cykloheksyl)acetonitril;
- 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*((1-hydroksycyklopropyl)-
10 metyl)acetamid; og

farmasøytisk akseptable kokrystaller derav.

12. Farmasøytisk sammensetning omfattende en terapeutisk virksom mengde av minst én forbindelse ifølge krav 1.

13. Farmasøytisk sammensetning ifølge krav 12, hvor
15 forbindelsen er valgt fra gruppen bestående av
2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-
metylpropyl)acetamid;
- 2-((1*r*,4*r*)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]-pyridin-1(6H)-yl)cykloheksyl)acetonitril;
- 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo-[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*((1-hydroksycyklopropyl)-
metyl)acetamid; og

farmasøytisk akseptable salter, og kombinasjoner derav, valgfritt hvor forbindelsen er:

- (a) 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(2-hydroksy-2-metylpropyl)acetamid; eller
- 5 (b) 2-((1*r*,4*r*)-4-(2-(1H-Imidazol-4-yl)imidazo[4,5-*d*]pyrrolo-[2,3-*b*]pyridin-1(6H)-yl)cykloheksyl)acetonitril; eller
- (c) 2-(1-((1*r*,4*r*)-4-(Cyanometyl)cykloheksyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(1-hydroksycyklopropyl)metyl)acetamid.

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