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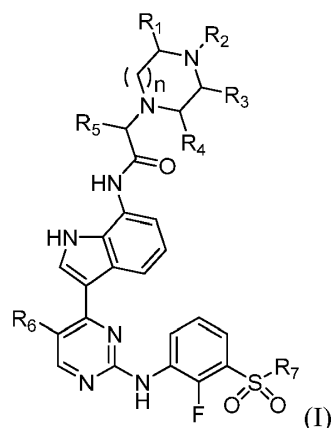
(54) Title **JAK1 SELECTIVE INHIBITORS**

(56) References
Cited: WO-A2-2009/118567
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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 på formelen (I):



5 der:

R₁, R₃ og R₄ hver er individuelt valgt blant hydrogen og metyl;

R₂ er valgt blant hydrogen, metyl og -CH₂CH₂OH;

n er 1 eller 2;

R₅ er valgt blant metyl, etyl og -CH₂OR₈;

10 R₆ er valgt blant metyl, klor og fluor;

R₇ er valgt blant metyl, etyl og syklopropyl; og

R₈ er valgt blant metyl, etyl og benzyl;

eller et farmasøytisk akseptabelt salt av dette.

15 2. Forbindelse ifølge krav 1, der hver av R₁–R₄ er uavhengig valgt blant hydrogen og metyl.

3. Forbindelse ifølge kravene 1–2, der R₁, R₃ og R₄ alle er hydrogen.

20 4. Forbindelse ifølge kravene 1–3, der R₂ er metyl.

5. Forbindelse ifølge krav 1, der R₅ er metyl eller -CH₂OR₈.

6. Forbindelse ifølge kravene 1–5, der R₈ er metyl.

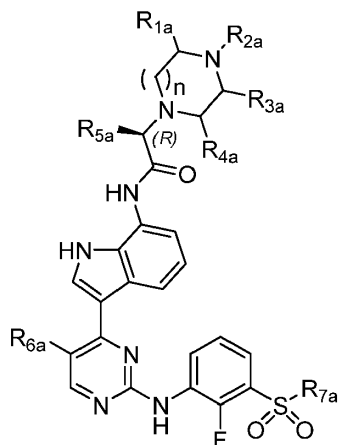
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7. Forbindelse ifølge krav 1, der R₆ er et metyl eller et fluoratom.

8. Forbindelse ifølge kravene 1–7, der R₆ er et fluoratom.

30 9. Forbindelse ifølge krav 1, der R₇ er metyl.

10. Forbindelse ifølge krav 1, som har strukturen på formelen (Ia):



formel (Ia)

5 der:

R_{1a}, R_{3a} og R_{4a} hver er individuelt valgt blant hydrogen og metyl;

R_{2a} er valgt blant hydrogen, metyl og -CH₂CH₂OH;

n er 1 eller 2;

R_{5a} er valgt blant metyl, etyl og -CH₂OR_{8a};

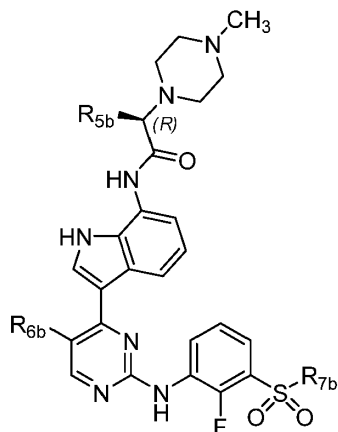
10 R_{6a} er valgt blant metyl, klor og fluor;

R_{7a} er valgt blant metyl, etyl og syklopropyl; og

R_{8a} er valgt blant metyl, etyl og benzyl;

eller et farmasøytisk akseptabelt salt av dette.

15 11. Forbindelse ifølge krav 1, som har strukturen på formelen (Ib):



formel (Ib)

der:

R_{5b} er valgt blant metyl, etyl og -CH₂OR_{8b};

20 R_{6b} er valgt blant metyl, klor og fluor;

R_{7b} er valgt blant metyl, etyl og syklopropyl; og

R_{8b} er valgt blant metyl, etyl og benzyl;
eller et farmasøytisk akseptabelt salt av dette.

12. Forbindelse ifølge krav 1, valgt blant:

- 5 (R)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-(2-hydroksyetyl)piperazin-1-yl)propanamid;
(R)-N-(3-(2-(2-fluor-3-(metylsulfonyl)fenylamino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)propanamid;
(R)-N-(3-(2-(3-(etylsulfonyl)-2-fluorfenylamino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-
10 2-(4-methylpiperazin-1-yl)propanamid;
(R)-N-(3-(2-(3-(syklopropylsulfonyl)-2-fluorfenylamino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)propanamid;
(R)-N-(3-(5-klor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)propanamid;
15 (S)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)propanamid;
(R)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-((3S, 5S)-3,4,5-trimethylpiperazin-1-yl)propanamid;
(R)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-2-((3S,5S)-3,4,5-trimethylpiperazin-1-yl)propanamid;
20 (R)-2-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)propanamid;
(S)-2-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)propanamid;
25 (R)-2-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)propanamid;
(S)-2-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)propanamid;
(S)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)butanamid;
30 (R)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)butanamid;
(S)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-methylpiperazin-1-yl)propanamid;
35 (R)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-methylpiperazin-1-yl)propanamid;
(R)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-2-(4-metyl-1,4-diazepan-1-yl)butanamid;

- (S)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-2-(4-metyl-1,4-diazepan-1-yl)butanamid;
- (S)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-((3S,5S)-3,4,5-trimetyl piperazin-1-yl)butanamid;
- 5 (R)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-((3S,5S)-3,4,5-trimetyl piperazin-1-yl)butanamid;
- (S)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-((3S,5S)-3,4,5-trimetyl piperazin-1-yl)propanamid;
- (R)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-((3S,5S)-3,4,5-trimetyl piperazin-1-yl)propanamid;
- 10 (S)-N-(3-(5-fluor-2-(2-fluor-3-(metylsulfonyl)fenylamino)pyrimidin-4-yl)-1H-indol-7-yl)-2-((3S,5S)-3,4,5-trimetyl piperazin-1-yl)butanamid;
- (R)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(piperazin-1-yl)propanamid;
- 15 (S)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(piperazin-1-yl)propanamid;
- (R)-2-((3R,5R)-3,5-dimetyl piperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- (S)-2-((3R,5R)-3,5-dimetyl piperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- 20 (S)-2-((3R,5R)-3,5-dimetyl piperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksypropanamid;
- (R)-2-((3R,5R)-3,5-dimetyl piperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksypropanamid;
- 25 (S)-2-((3R,5R)-3,5-dimetyl piperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- (R)-2-((3R,5R)-3,5-dimetyl piperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- 30 (S)-2-((3R,5R)-3,5-dimetyl piperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksypropanamid;
- (R)-2-((3R,5R)-3,5-dimetyl piperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksypropanamid;
- 35 (S)-N-(3-(5-fluor-2-(2-fluor-3-(metylsulfonyl)fenylamino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-metyl piperazin-1-yl)propanamid;
- (R)-N-(3-(5-fluor-2-(2-fluor-3-(metylsulfonyl)fenylamino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-metyl piperazin-1-yl)propanamid;

- (S)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-metyl-1,4-diazepan-1-yl)butanamid;
- (R)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-metyl-1,4-diazepan-1-yl)butanamid;
- 5 (R)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-2-(4-metyl piperazin-1-yl)butanamid;
- (S)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-2-(4-metyl piperazin-1-yl)butanamid;
- (S)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-((3S,5S)-3,4,5-trimetyl piperazin-1-yl)propanamid;
- 10 (R)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-((3S,5S)-3,4,5-trimetyl piperazin-1-yl)propanamid;
- (R)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-metyl-1,4-diazepan-1-yl)propanamid;
- 15 (S)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-metyl-1,4-diazepan-1-yl)propanamid;
- (S)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-metyl-1,4-diazepan-1-yl)propanamid;
- (R)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-metyl-1,4-diazepan-1-yl)propanamid;
- 20 (R)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-2-(4-metyl-1,4-diazepan-1-yl)propanamid;
- (S)-2-((R)-2,4-dimetyl piperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)propanamid;
- 25 (R)-2-((R)-2,4-dimetyl piperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)propanamid;
- (R)-2-((R)-2,4-dimetyl piperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)propanamid;
- (S)-2-((R)-2,4-dimetyl piperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- 30 (R)-2-((R)-2,4-dimetyl piperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- (S)-2-((R)-2,4-dimetyl piperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- 35 (R)-2-((R)-2,4-dimetyl piperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- (S)-2-((R)-2,4-dimetyl piperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksypropanamid;

- (R)-2-((R)-2,4-dimethylpiperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-3-metoksypropanamid;
- (S)-2-((R)-2,4-dimethylpiperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksypropanamid;
- 5 (R)-2-((R)-2,4-dimethylpiperazin-1-yl)-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksypropanamid;
- (R)-2-((S)-2,4-dimethylpiperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)propanamid;
- (S)-2-((S)-2,4-dimethylpiperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)propanamid;
- 10 (R)-2-((S)-2,4-dimethylpiperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- (S)-2-((S)-2,4-dimethylpiperazin-1-yl)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)butanamid;
- 15 (R)-3-etoksy-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)propanamid;
- (R)-3-etoksy-N-(3-(5-fluor-2-((2-fluor-3-(metylsulfonyl)fenyl)amino)pyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)propanamid;
- (R)-3-(benzyloksy)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)propanamid;
- 20 (S)-3-(benzyloksy)-N-(3-(2-((2-fluor-3-(metylsulfonyl)fenyl)amino)-5-metylpyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl)propanamid;
- (R)-N-(3-(5-fluor-2-(2-fluor-3-(metylsulfonyl)fenylamino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(piperazin-1-yl)propanamid; og
- 25 (S)-N-(3-(5-fluor-2-(2-fluor-3-(metylsulfonyl)fenylamino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(piperazin-1-yl)propanamid;
- eller et farmasøytisk akseptabelt salt av dette.

13. Forbindelse ifølge krav 1, som er (R)-N-(3-(5-fluor-2-(2-fluor-3-(metylsulfonyl)fenylamino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-methylpiperazin-1-yl)propanamid eller et farmasøytisk akseptabelt salt av dette.

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14. Forbindelse ifølge krav 1, som er (R)-N-(3-(5-fluor-2-(2-fluor-3-(metylsulfonyl)fenylamino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-methylpiperazin-1-yl)propanamid.

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15. Forbindelse ifølge krav 1, som er et farmasøytisk akseptabelt salt av (R)-N-(3-(5-fluor-2-(2-fluor-3-(metylsulfonyl)fenylamino)pyrimidin-4-yl)-1H-indol-7-yl)-3-metoksy-2-(4-metylpipezazin-1-yl)propanamid.
- 5 16. Farmasøytisk sammensetning som omfatter forbindelse ifølge kravene 1–15, eller et farmasøytisk akseptabelt salt av dette og et farmasøytisk akseptabelt fortynningsmiddel, hjelpestoff eller en farmasøytisk akseptabel bærer.
- 10 17. Forbindelse ifølge kravene 1-15, eller et farmasøytisk akseptabelt salt av dette, til bruk for å behandle en JAK1-relatert lidelse, der den JAK1-relaterte lidelsen er valgt blant type 1-diabetes, lupus, multippel sklerose, revmatoid artritt, psoriasis, astma, atopisk dermatitt, autoimmune tyreoidlidelser, ulcerøs kolitt, Crohns sykdom, COPD, vitiligo og alopecia areata.
- 15 18. Farmasøytisk sammensetning som omfatter forbindelse ifølge et av kravene 1–15, eller et farmasøytisk akseptabelt salt av dette, til bruk for å behandle en JAK1-relatert lidelse, der den JAK1-relaterte lidelsen er valgt blant type 1-diabetes, lupus, multippel sklerose, revmatoid artritt, psoriasis, astma, atopisk dermatitt, autoimmune tyreoidlidelser, ulcerøs kolitt, Crohns sykdom, COPD, vitiligo og alopecia areata.