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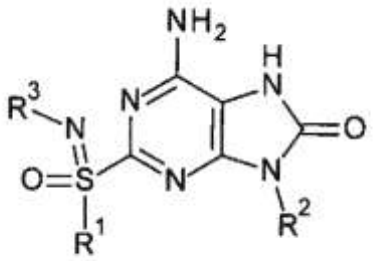
(54) Title **NOVEL SULFONIMIDOYLPURINONE COMPOUNDS AND DERIVATIVES FOR THE TREATMENT AND PROPHYLAXIS OF VIRUS INFECTION**

(56) References Cited:

WO-A1-2006/117670
JP-A- H11 193 282
US-A1- 2010 143 301

PATENTKRAV

1. Forbindelse med formel (I),



(I),

hvori

R^1 er C_{1-6}-alkyl, halogenC_{1-6}alkyl, C_{3-7}-sykloalkylC_{1-6}alkyl, C_{1-6}-alkoksyC_{1-6}alkyl eller pyrrolidinylC_{1-6}alkyl;

R^2 er C_{1-6}-alkyl, fenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl eller pyrimidinylC_{1-6}alkyl, hvor nevnte fenylC_{1-6}alkyl, pyridinylC_{1-6}-alkyl og pyrimidinylC_{1-6}-alkyl er usubstituert eller substituert med én, to eller tre substituenter uavhengig valgt blant halogen, C_{1-6}alkyl, C_{1-6}alkoksy, cyano, karboksy, karbamoyl, halogenC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkoksykarbonyl, C_{1-6}alkoksyC_{1-6}alkylaminokarbonyl, pyrrolidinylkarbonyl og piperidinylkarbonyl;

R^3 er H;

eller farmasøytisk akseptabelt salt, enantiomer eller diastereomer derav.

2. Forbindelse ifølge krav 1, hvori

R^1 er metyl, etyl, propyl, butyl, klorpropyl, sykloheksylmetyl, metoksyetyl, metoksypropyl, pyrrolidinylpropyl eller trifluoretyl;

R^2 er isobutyl, benzyl, klorbenzyl, fluorbenzyl, brombenzyl, klorfluorbenzyl, klormetylbenzyl, diklorbenzyl, difluorbenzyl, metylbenzyl, metoksybenzyl, cyanobenzyl, karbamoylbenzyl, trifluormetylbenzyl, metylsulfonylbenzyl, metoksykarbonylbenzyl, karboksybenzyl, metoksyetylaminokarbonylbenzyl, piperidinylkarbonylbenzyl, pyrrolidinylkarbonylbenzyl, pyridinylmetyl, klorpyridinylmetyl, metylpyridinylmetyl, pyrimidinylmetyl eller metylpyrimidinylmetyl;

R^3 er H;

eller farmasøytisk akseptabelt salt, enantiomer eller diastereomer derav.

3. Forbindelse ifølge krav 1, hvori R^1 er C_{1-6}alkyl, halogenC_{1-6}alkyl eller C_{1-6}alkoksyC_{1-6}alkyl.

4. Forbindelse ifølge krav 3, hvori R^1 er metyl, etyl, propyl, butyl, klorpropyl, trifluoretyl, metoksyetyl eller metoksypropyl.

5. Forbindelse ifølge krav 3, hvori R^1 er C_{1-6}alkyl.

6. Forbindelse ifølge krav 2 eller 5, hvori R^1 er metyl, etyl eller propyl.

7. Forbindelse ifølge krav 1 eller 2 valgt blant:

6-amino-9-benzyl-2-(metylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-benzyl-2-(etylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-benzyl-2-(2-metoksyetylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-benzyl-2-(propylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-benzyl-2-(butylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-benzyl-2-(3-metoksypropylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-benzyl-2-(2,2,2-trifluoretylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-benzyl-2-(sykloheksylmetylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-[(4-klorfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-[(4-metoksyfenyl)metyl]-2-(metylsulfonimidoyl)-7H-purin-8-on;

6-amino-2-(3-klorpropylsulfonimidoyl)-9-[(4-metoksyfenyl)metyl]-7H-purin-8-on;

6-amino-9-[(4-metoksyfenyl)metyl]-2-(3-pyrrolidin-1-ylpropylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-[(4-klorfenyl)metyl]-2-(metylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-[(6-klor-3-pyridyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-[(2-klorfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;

6-amino-2-(metylsulfonimidoyl)-9-(3-pyridylmetyl)-7H-purin-8-on;

3-[[6-amino-8-okso-2-(propylsulfonimidoyl)-7H-purin-9-yl]metyl]benzonitril;

3-[[6-amino-8-okso-2-(propylsulfonimidoyl)-7H-purin-9-yl]metyl]benzamid;

6-amino-2-(metylsulfonimidoyl)-9-(2-pyridylmetyl)-7H-purin-8-on;

6-amino-2-(metylsulfonimidoyl)-9-(4-pyridylmetyl)-7H-purin-8-on;

6-amino-9-isobutyl-2-(propylsulfonimidoyl)-7H-purin-8-on;

6-amino-9-[(3-klorfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;

6-amino-2-(propylsulfonimidoyl)-9-[[4-(trifluormetyl)fenyl]metyl]-7H-purin-

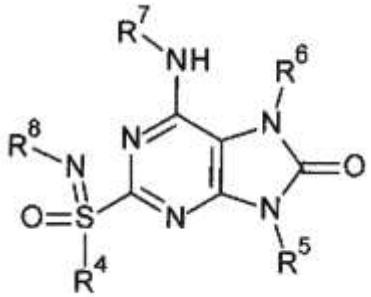
8-on;
6-amino-9-[(4-fluorfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(4-bromfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(3,4-diklorfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-(3,4-difluorfenylmetyl)-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(4-klor-3-metyl-fenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-2-(propylsulfonimidoyl)-9-(p-tolylmetyl)-7H-purin-8-on;
6-amino-9-[(4-klor-3-fluorfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(2,4-difluorfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
4-[[6-amino-8-okso-2-(propylsulfonimidoyl)-7H-purin-9-yl]metyl]benzonitril;
4-[[6-amino-8-okso-2-(propylsulfonimidoyl)-7H-purin-9-yl]metyl]benzamid;
6-amino-9-[(6-metyl-3-pyridyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(2-metyl-4-pyridyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(3-klor-4-metyl-fenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(4-metylsulfonylfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
Metyl-4-[[6-amino-8-okso-2-(propylsulfonimidoyl)-7H-purin-9-yl]metyl]benzoat;
4-[[6-amino-8-okso-2-(propylsulfonimidoyl)-7H-purin-9-yl]metyl]benzosyre;
4-[[6-amino-8-okso-2-(propylsulfonimidoyl)-7H-purin-9-yl]metyl]-N-(2-metoksyetyl)benzamid;
6-amino-9-[[4-(piperidin-1-karbonyl)fenyl]metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-2-(S-propylsulfonimidoyl)-9-[[4-(pyrrolidin-1-karbonyl)fenyl]metyl]-7H-purin-8-on;
6-metyl-2-(propylsulfonimidoyl)-9-(pyrimidin-5-ylmetyl)-7H-purin-8-on;
6-metyl-9-[(2-metylpyrimidin-5-yl)metyl]-2-(propylsulfonimidoyl)-7H-

purin-8-on;
6-amino-9-[(4-klorfenyl)metyl]-2-(etylsulfonimidoyl)-7H-purin-8-on;
6-amino-2-(etylsulfonimidoyl)-9-(p-tolylmetyl)-7H-purin-8-on; og
6-amino-2-(etylsulfonimidoyl)-9-[(4-fluorfenyl)metyl]-7H-purin-8-on.

8. Forbindelse ifølge et hvilket som helst av kravene 1, 2 eller 7, valgt blant:
6-amino-9-benzyl-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(4-klorfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(6-klor-3-pyridyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(4-fluorfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(4-bromfenyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-2-(propylsulfonimidoyl)-9-(p-tolylmetyl)-7H-purin-8-on;
6-amino-9-[(6-metyl-3-pyridyl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
Metyl-4-[[6-amino-8-okso-2-(propylsulfonimidoyl)-7H-purin-9-yl]metyl]benzoat;
4-[[6-amino-8-okso-2-(propylsulfonimidoyl)-7H-purin-9-yl]metyl]benzosyre;
6-metyl-9-[(2-metylpyrimidin-5-yl)metyl]-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-amino-9-[(4-klorfenyl)metyl]-2-(etylsulfonimidoyl)-7H-purin-8-on; og
6-amino-2-(etylsulfonimidoyl)-9-(p-tolylmetyl)-7H-purin-8-on.

9. Forbindelse ifølge et hvilket som helst av kravene 1 til 8, valgt blant:
6-amino-9-[(4-klorfenyl)metyl]-2-(etylsulfonimidoyl)-7H-purin-8-on; og
6-amino-2-(etylsulfonimidoyl)-9-(p-tolylmetyl)-7H-purin-8-on.

10. Forbindelse med formel (Ia),



(Ia),

hvori
R^4 er C_{1-6}alkyl, halogenC_{1-6}alkyl, C_{3-7}sykloalkylC_{1-6}alkyl, C_{1-6}-alkoksyC_{1-6}alkyl eller pyrrolidinylC_{1-6}alkyl;
R^5 er C_{1-6}alkyl, fenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl eller pyrimidinylC_{1-6}alkyl, hvor nevnte fenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl og pyrimidinylC_{1-6}alkyl er usubstituert eller substituert med én, to eller tre substituenter uavhengig valgt blant halogen, C_{1-6}alkyl, C_{1-6}alkoksy, cyano, karboksy, karbamoyl, halogenC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkoksykarbonyl, C_{1-6}-alkoksyC_{1-6}alkylaminokarbonyl, pyrrolidinylkarbonyl og piperidinylkarbonyl;
R^6 er H eller C_{1-6}alkyl-C(O)O-C_{1-6}alkyl−;
R^7 er H, C_{1-6}alkyl, C_{3-7}sykloalkyl eller C_{1-10}alkylkarbonyl;
R^8 er H, C_{1-6}alkylkarbonyl, karboksyC_{1-6}alkylkarbonyl, C_{1-6}-alkyoksykarbonylC_{1-6}alkylkarbonyl eller benzoyl;
forutsatt at R^6, R^7 og R^8 ikke er H på samme tid;
eller farmasøytisk akseptabelt salt, enantiomer eller diastereomer derav.

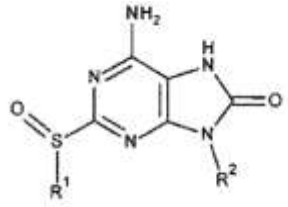
11. Forbindelse ifølge krav 10 valgt blant:
N-[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]pentanamid;
N-[[6-amino-9-[(4-klorfenyl)metyl]-8-okso-7H-purin-2-yl]-okso-propyl-λ^4-sulfanyliden]acetamid;
N-[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-metyl-okso-λ^4-sulfanyliden]acetamid;
4-[[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]amino]-4-okso-butansyre;
4-[[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]amino]-4-okso-butansyre;
4-[[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]amino]-4-okso-butansyre;
Etyl-4-[[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]amino]-3-okso-butanat;
Etyl-4-[[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]amino]-4-okso-butanat;
Etyl-4-[[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]amino]-4-okso-butanat;

N-[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]benzamid;
N-[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]benzamid;
N-[(6-amino-9-benzyl-8-okso-7H-purin-2-yl)-okso-propyl-λ^4-sulfanyliden]benzamid;
9-benzyl-6-(etylamino)-2-(propylsulfonimidoyl)-7H-purin-8-on;
6-(etylamino)-9-[(6-metyl-3-pyridyl)metyl]-2-(S-propylsulfonimidoyl)-7H-purin-8-on;
9-[(4-klorfenyl)metyl]-6-(etylamino)-2-(propylsulfonimidoyl)-7H-purin-8-on;
9-benzyl-6-(propylamino)-2-(propylsulfonimidoyl)-7H-purin-8-on;
9-benzyl-6-(isopropylamino)-2-(propylsulfonimidoyl)-7H-purin-8-on;
9-benzyl-6-(syklopropylamino)-2-(propylsulfonimidoyl)-7H-purin-8-on;
N-[9-[(4-klorfenyl)metyl]-8-okso-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-propyl-pentanamid;
N-[9-[(4-klorfenyl)metyl]-8-okso-2-(propylsulfonimidoyl)-7H-purin-6-yl]acetamid;
N-[9-benzyl-8-okso-2-(propylsulfonimidoyl)-7H-purin-6-yl]pentanamid;
N-[9-[(4-klorfenyl)metyl]-8-okso-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-etyl-
butanamid;
N-[9-[(4-klorfenyl)metyl]-8-okso-2-(propylsulfonimidoyl)-7H-purin-6-yl]-3-metyl-butanamid;
N-[9-[(4-klorfenyl)metyl]-8-okso-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-metyl-pentanamid;
N-[9-[(4-klorfenyl)metyl]-8-okso-2-(propysulfonimidoyl)-7H-purin-6-yl]-2,2-dimetyl-propanamid;
N-[9-benzyl-8-okso-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-propyl-pentanamid;
[6-amino-9-benzyl-2-(metylsulfonimidoyl)-8-okso-purin-7-yl]metylacetat;
[6-amino-9-benzyl-8-okso-2-(propylsulfonimidoyl)purin-7-yl]metylacetat;
[6-amino-9-benzyl-8-okso-2-(propylsulfonimidoyl)purin-7-yl]metyl-2,2-dimetylpropanat; og

1-[6-amino-9-benzyl-8-okso-2-(propylsulfonimidoyl)purin-7-yl]etylacetat.

12. Fremgangsmåte for fremstilling av en forbindelse ifølge et hvilket som helst av kravene 1 til 11, omfattende følgende trinn:

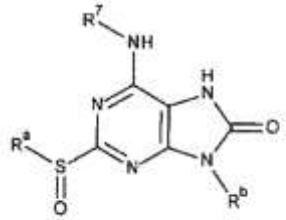
(a) å reagere en forbindelse med formel (IIa),



(IIa),

med en imineringsreagens;

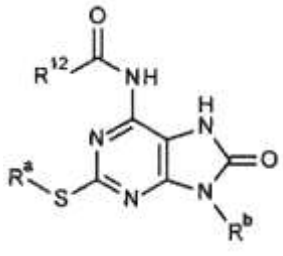
(b) å reagere en forbindelse med formel (IIb),



(IIb),

med en imineringsreagens; hvori R^a er R^1 eller R^4, R^b er R^2 eller R^5, R^7 er C_{1-6}alkyl eller C_{3-7}sykloalkyl;

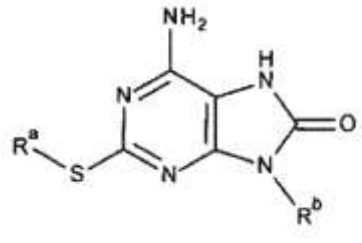
(c) å reagere en forbindelse med formel (IIIc),



(IIIc),

med en oksidant etterfulgt av en imineringsreagens, hvori R^a er R^1 eller R^4, R^b er R^2 eller R^5, R^{12} er C_{1-10}-alkyl;

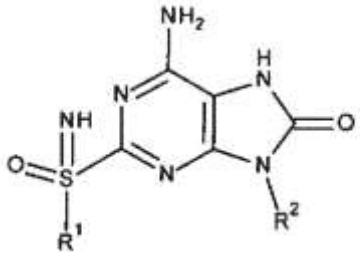
(d) å reagere en forbindelse med formel (IIIa),



(IIIa),

med en oksidant etterfulgt av en imineringsreagens, hvori R^a er R^1 eller R^4, R^b er R^2 eller R^5;

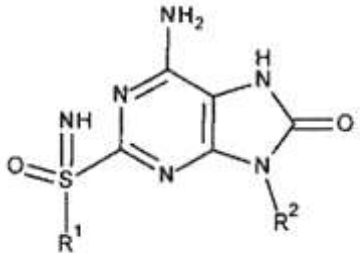
(e) å reagere en forbindelse med formel (Ie),



(Ie),

med halogenester;

(f) å reagere en forbindelse med formel (Ie),



(Ie),

med karboksylsyrenahydrid eller acylklorid;

hvori R^1, R^2, R^4 og R^5 er definert som i et hvilket som helst av kravene 1 til 29.

13. Forbindelse eller farmasøytisk akseptabelt salt, enantiomer eller diastereomer ifølge et hvilket som helst av kravene 1 til 11, for anvendelse som terapeutisk virkestoff.

14. Farmasøytisk sammensetning omfattende en forbindelse ifølge et hvilket som helst av kravene 1 til 11, og en terapeutisk inert bærer.

15. Forbindelse eller farmasøytisk akseptabelt salt, enantiomer eller diastereomer ifølge et hvilket som helst av kravene 1 til 11 for anvendelse i behandlingen eller profylaksen av hepatitt-B-virusinfeksjon.