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C07D 471/04 (2006.01)
C07D 491/107 (2006.01)

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(54)	Title	PYRIMIDINE SULFAMIDE DERIVATIVE AND PREPARATION METHOD AND MEDICAL APPLICATION THEREOF
(56)	References Cited:	CN-A- 101 056 872 EP-A1- 1 072 597 CN-A- 1 524 079 EP-A1- 1 160 248 CN-A- 1 711 248 BOLLI MARTIN H.: "The Discovery of N-[5-(4-Bromophen- yl)-6-[2-[(5-bromo-2- pyrimidinyl)oxy]ethox y]-4-pyrimidinyl]-N' - propylsulfamide(Macitentan), an Orally Active, Potent Dual Endothelin Re- ceptor Antagonist", Journal of Medicinal Chemistry, 3 August 2012 (2012- 08-03), XP055078934,

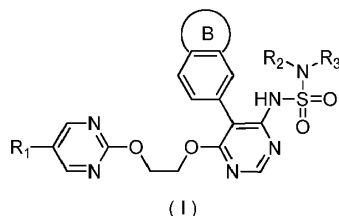
SIDHARTA P. N.: "Clinical Pharmacokinetics and Pharmacodynamics of the Endothelin Receptor Antagonist Macitentan", Clin Pharmacokinet, 10 April 2015 (2015-04-10), XP055614382,

SIDHARTA PATRICIA N.: "Macitentan: entry-into-humans study with a new endothelin receptor antagonist", Eur J Clin Pharmacol, 4 May 2011 (2011-05-04), XP019949637,

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 av formel (I), en geometrisk eller stereoisomer derav eller et farmasøytisk akseptabelt salt derav,



hvor,

R₁ er valgt fra H, F, Cl, Br, I, OH og NH₂;

R₂ er valgt fra H og C₁₋₃-alkyl, hvori C₁₋₃-alkylet er eventuelt substituert med ett, to eller tre R;

R₃ er valgt fra H, C₁₋₆-alkyl, C₁₋₆-heteroalkyl, -C₁₋₃-alkyl-C₃₋₆-sykloalkyl, C₃₋₆-sykloalkyl og -C₁₋₃-alkyl-3-7-leddet heterosykloalkyl, hvori C₁₋₆-alkylet, C₁₋₆-heteroalkylet, -C₁₋₃-alkyl-C₃₋₆-sykloalkylet, C₃₋₆-sykloalkylet eller -C₁₋₃-alkyl-3-7-leddet heterosykloalkyl er eventuelt substituert med ett, to eller tre R;

eller R₂ og R₃ er forbundet for å danne en 3-8-leddet ring eventuelt substituert med ett, to eller tre R;

ring B er valgt fra 3-7-leddet heterosykloalkyl og 5-6-leddet heteroaryl, hvori det 3-7-leddede heterosykloalkylet eller det 5-6-leddede heteroarylet er eventuelt substituert med ett, to eller tre R;

R er uavhengig valgt fra H, F, Cl, Br, I, OH, NH₂, CN, C₁₋₆-alkyl og C₁₋₆-heteroalkyl, hvori C₁₋₆-alkylet eller C₁₋₆-heteroalkylet er eventuelt substituert med ett, to eller tre R';

R' er uavhengig valgt fra F, Cl, Br, I, OH, NH₂, CN, Me, CH₂F, CHF₂, CF₃ og Et;

hvert av C₁₋₆-heteroalkylet, det 3-7-leddede heterosykloalkylet og det 5-6-leddede heteroarylet inneholder ett, to, tre eller fire heteroatomer eller heteroatomgrupper uavhengig valgt fra N, -O-, -S-, -NH-, -S(=O)₂- og -S(=O)-.

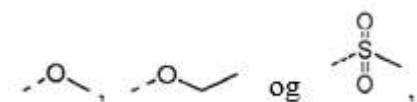
2. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i krav 1, hvori, R er valgt fra H,

F, Cl, Br, I, OH, NH₂, CN, C₁₋₃-alkyl, C₁₋₃-alkyl-S(=O)₂- og C₁₋₃-alkyl-O-, hvori C₁₋₃-alkylet, C₁₋₃-alkyl-S(=O)₂- eller C₁₋₃-alkyl-O- er eventuelt substituert med ett, to eller tre R';

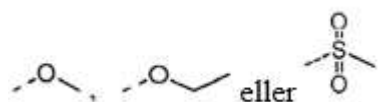
eventuelt er R₂ valgt fra H og Me;

eventuelt er R₃ valgt fra H, C₁₋₄-alkyl, C₁₋₄-alkyl-O-C₁₋₄-alkyl, syklobutyl, -C₁₋₃-alkyl-syklobutyl, -C₁₋₃-alkyl-syklopropyl, -C₁₋₃-alkyl-tetrahydrofuranyl og -C₁₋₃-alkyl-tetrahydropyranyl, hvori C₁₋₄-alkylet, C₁₋₄-alkyl-O-C₁₋₄-alkylet, syklobutylet, -C₁₋₃-alkyl-syklobutylet, -C₁₋₃-alkyl-syklopropylet, -C₁₋₃-alkyl-tetrahydrofuranylet eller -C₁₋₃-alkyl-tetrahydropyranylet er eventuelt substituert med ett, to eller tre R.

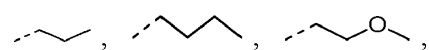
3. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i krav 2, hvori R er valgt fra H, F, Cl, Br, I, OH, NH₂, CN, Me, Et,



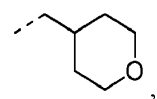
hvor Me, Et,



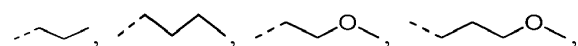
er eventuelt substituert med én, to eller tre R'; eventuelt er R₃ valgt fra H, Me, Et,



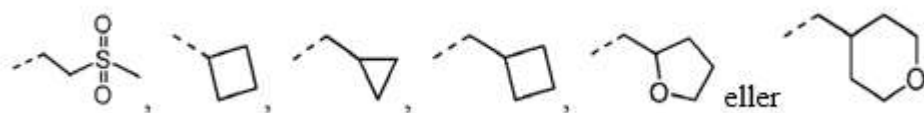
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hvor Me, Et,

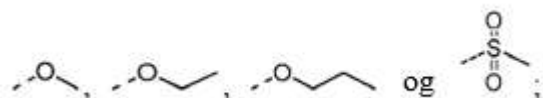


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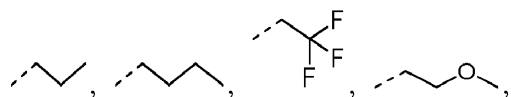


er eventuelt substituert med ett, to eller tre R.

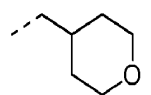
4. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i krav 3, hvori R er valgt fra H, F, Cl, Br, I, OH, NH₂, CN, Me, CH₂F, CHF₂, CF₃, Et,



eventuelt er R₃ valgt fra H, Me, Et,

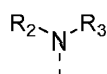


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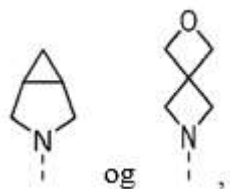
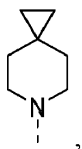


5. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i et hvilket som helst av kravene 1–4, hvori R₂ og R₃ er forbundet for å danne et 6–8-leddet heterosykloalkyl eventuelt substituert med ett, to eller tre R.

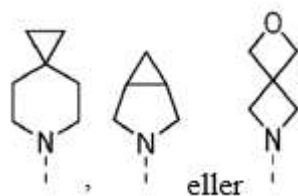
6. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i krav 5, hvori strukturenheten



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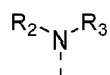


hvor

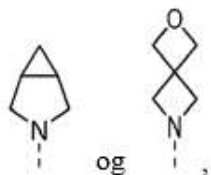
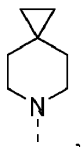


er eventuelt substituert med ett, to eller tre R.

7. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i krav 6, hvor



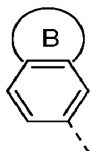
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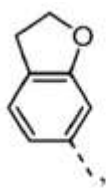
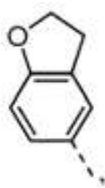
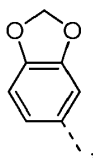
8. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i et hvilket som helst av kravene 1–4, hvor ring B er valgt fra tetrahydrofuran, tetrahydrofuran, 1,3-

dioksolanyl, pyrrolidinyl, tiazolyl, pyrazolyl og imidazolyl, hvori tetrahydrofuranylet, tetrahydrotienylet, 1,3-dioksolanylet, pyrrolidinylet, tiazolylet, pyrazolylet eller imidazolylet er eventuelt substituert med ett, to eller tre R.

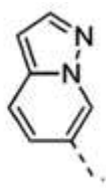
9. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i krav 8, hvori strukturenheten



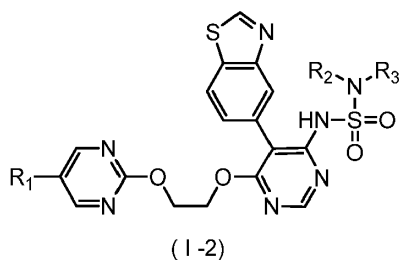
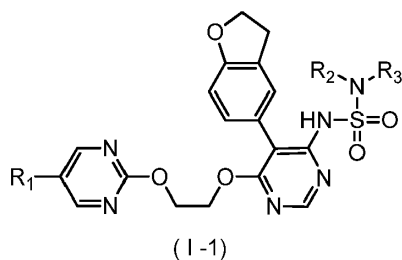
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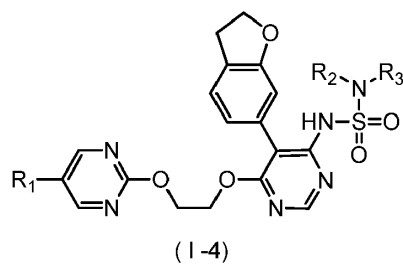
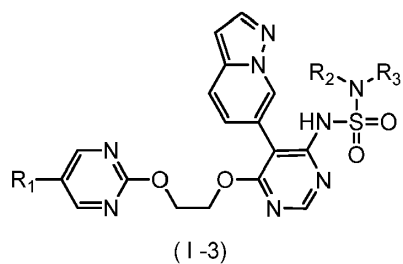
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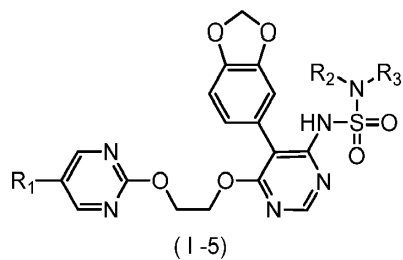
10. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i et hvilket som helst av kravene 1–7, som er valgt fra



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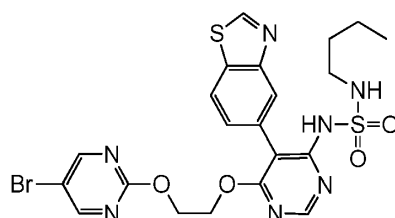
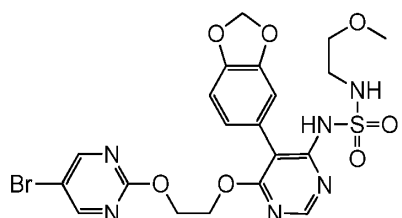
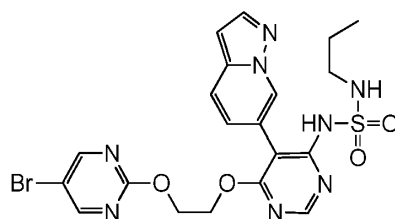
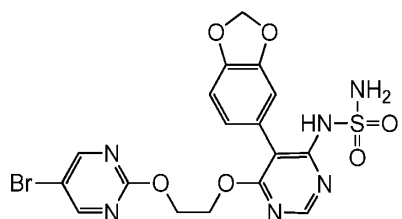
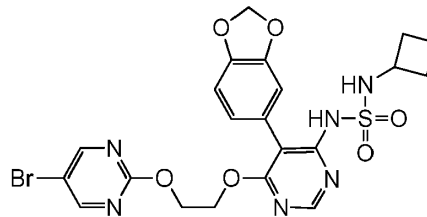
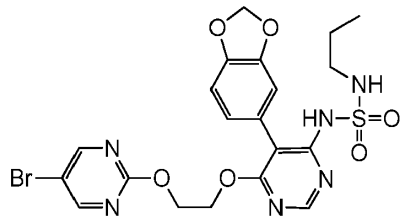
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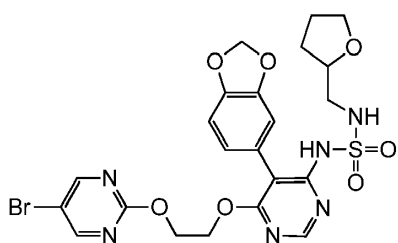
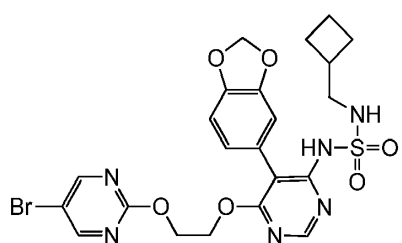
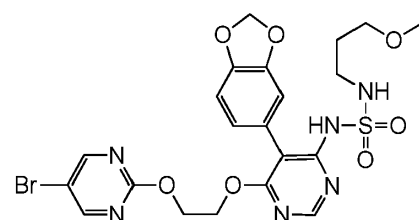
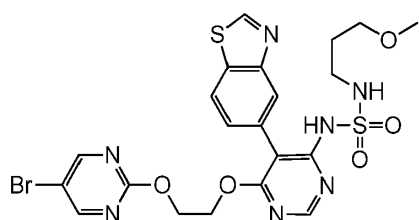
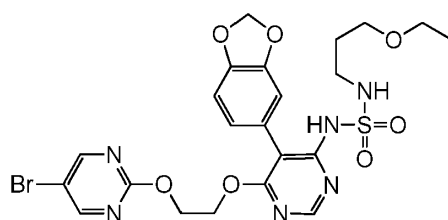
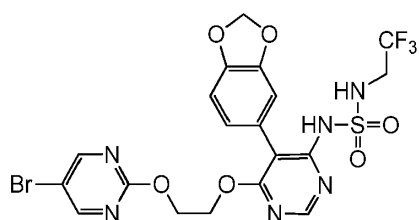
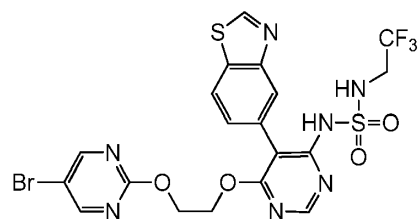
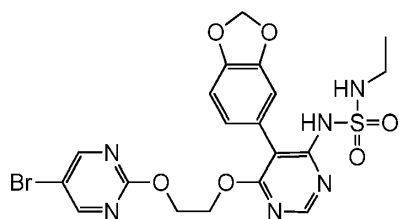
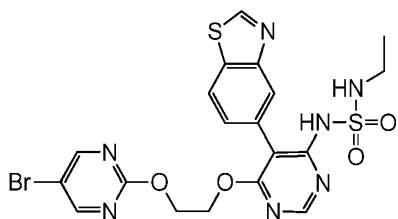
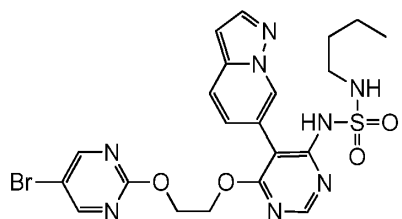
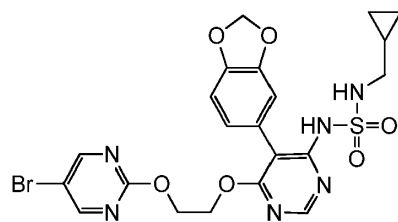
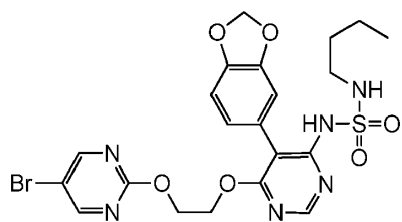


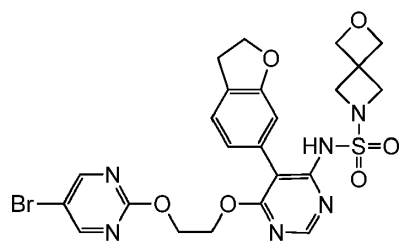
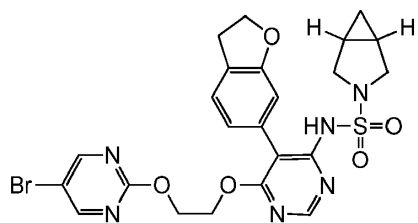
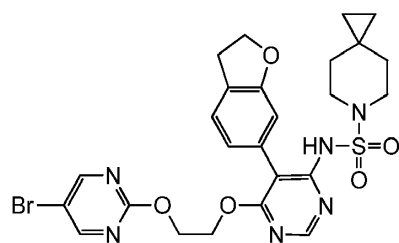
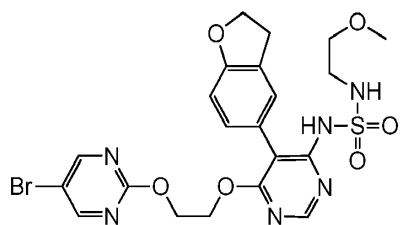
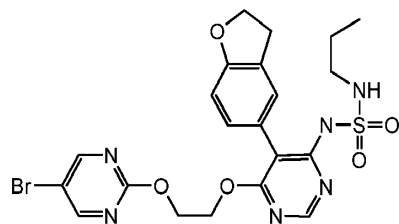
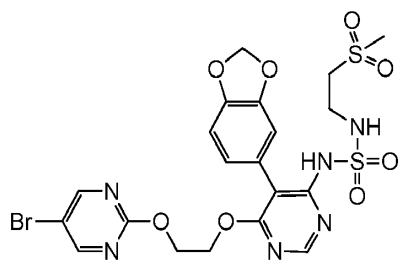
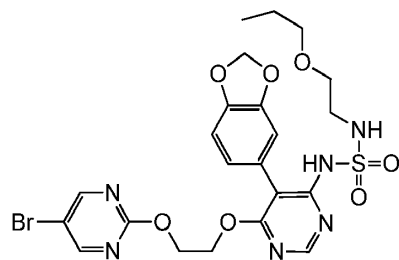
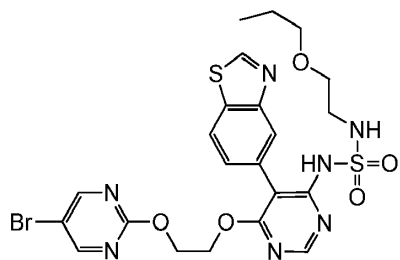
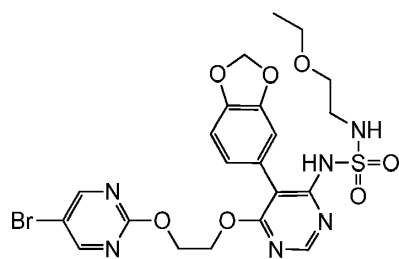
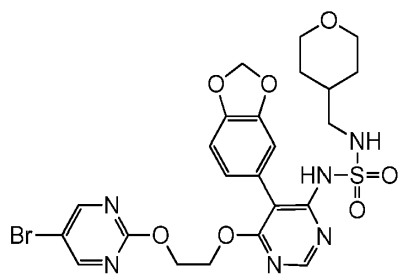
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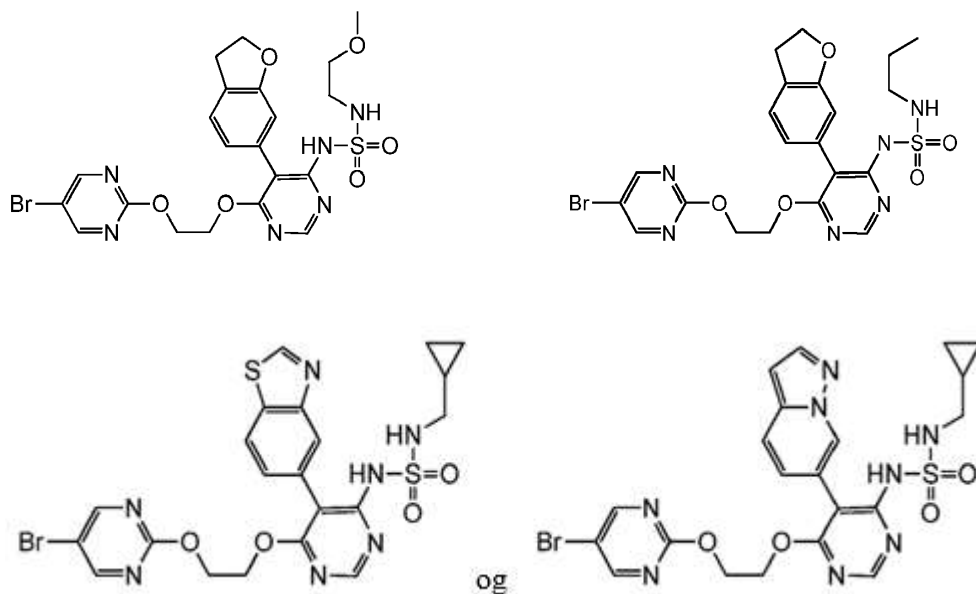
R, R₁ eller R₂ er som definert i et hvilket som helst av kravene 1–7.

11. Forbindelse ifølge krav 1, en geometrisk eller stereoisomer derav eller et farmasøytisk akseptabelt salt derav, hvori forbindelsen er valgt fra

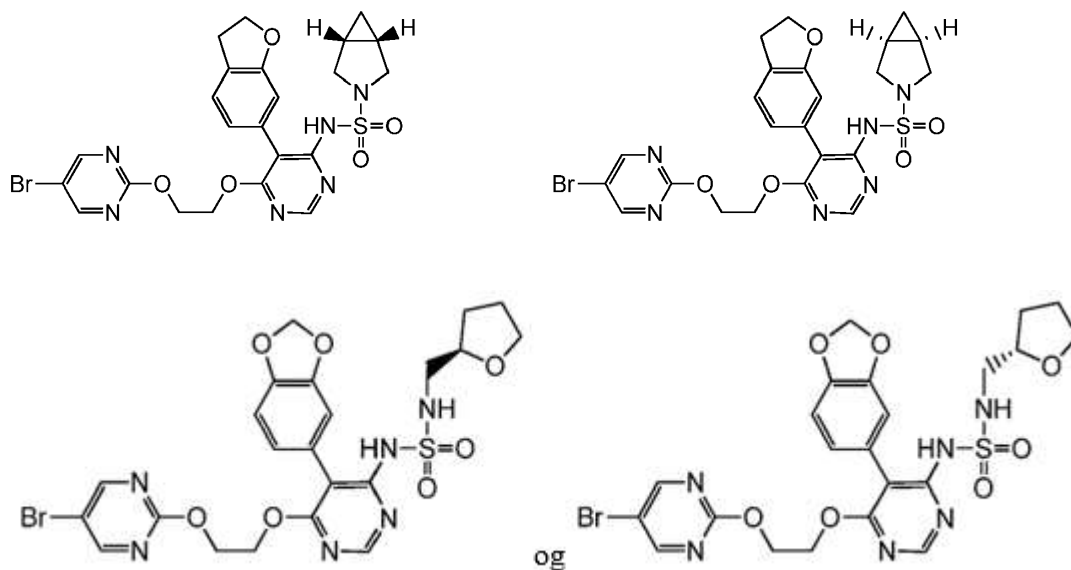








12. Forbindelsen, den geometriske eller stereoisomeren derav eller det farmasøytisk akseptable saltet derav som definert i krav 11, som er valgt fra



13. Farmasøytisk sammensetning, som omfatter en terapeutisk effektiv mengde av forbindelsen eller det farmasøytisk akseptable saltet som definert i et hvilket som helst av kravene 1–12 som en aktiv ingrediens, og en farmasøytisk akseptabel bærer.

14. Forbindelsen eller det farmasøytisk akseptable saltet som definert i et hvilket som helst av kravene 1–12 eller sammensetningen som definert i krav 13 for anvendelse som en ET_A-reseptorantagonist.

15. Forbindelsen eller det farmasøytisk akseptable saltet som definert i et hvilket som helst av kravene 1–12 eller sammensetningen som definert i krav 13 for anvendelse i behandlingen av pulmonal arteriehypertensjon, primær hypertensjon, refraktær hypertensjon, diabetisk nefropati og intrakraniell vasospasme.